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A Short Review: Chemistry of Curcumin and Its Metal Complex Derivatives

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ABSTRACT

This review covers recent progress in the synthesis of curcumin and the bioactivity of semisynthetic and synthetic analogs of curcumin. The review also shows how curcumin is a useful intermediate for the synthesis of more complex organic molecules; historical perspective; the process of preparing the metal complexes and characterization the produced complexes using various spectral and other techniques; shows the importance of curcumin and its derivatives for their potential applications in medical devices and broad-spectrum of medical application such as antibiotic ointment, alternative therapeutics, antifungal, and antibacterial activities.

1. THE ESSENTIAL CHEMISTRY OF CURCUMIN (TURMERIC)

Curcumin compounds have been intensively explored in recent decades for their outstanding antibacterial properties. Curcumin (Cum) "golden spice" or diferuloylmethane = (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione containing a chemical formula $\mathbf{C_{21}H_{20}O_6}$. Curcumin can be obtained from the rhizome of turmeric (*Curcuma longa*) which belongs to the Zingiberaceae (ginger) family. It is a perennial herb with a yellow colored natural pigment and has a 368.38 g/mole molar mass. It was isolated for the first time in 1815 and synthesized in 1910. It is used in flavoring and coloring foods and as a traditional medicinal agent that has been extensively studied over the past several decades. These studies have been shown to exhibit many bioactivities such as metabolism-regulating, anti-bacterial, anti-viral, anti-depressant, anti-cancer, anti-septic, anti-amyloid, anti-fungal, neuroprotective , anti-proliferative, immune-modulating, tissue protective effects, anti-oxidant activities, radical scavenging properties, anti-inflammatory , anti-neoplastic, bioavailability from micronized powder and liquid micelles, anti-fertile, allergies, Parkinson's disease, Alzheimer's disease (AD), anti-hyperlipidemia, anti-insect, amyotrophic lateral sclerosis (ALS), HIV disease ,diabetes , scarring ,anti-atherosclerotic, arthritis, and other chronic diseases and immune-modulating.

Its chemical composition, which includes a polyphenol that gives turmeric color, and its quick biotransformation into inactive metabolites severely limit its utility as a health-promoting agent and dietary supplement. Furthermore, (Cum)'s shortly is anticipated to propel this intriguing natural substance to the forefront of therapeutic medicines for human illness therapy. It has been frequently used in drug-loaded microspheres and wellness potential of (Cum) continues to unfold [1-6]. We expect that future studies will continue to find new ways to deliver curcumin clinical can be supported.

2. ISOLATION OF (CUM) FROM TURMERIC RHIZOMES

Different extraction procedures from Turmeric use a Soxhlet apparatus and column chromatography, followed by crystallization purification [7]. The extraction of CUM from turmeric is not water-soluble according to several methods, hence extractions must be in acetone or benzene as nonpolar solvents. The 2% of CUM is extracted in 95% ethanol for one day, then filter and dry. Curcuma powder, a powdered, pure food color, is the result of this technique.

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- Crude extract was dissolved in alcohol and was filtered. Then was concentrated.
- Using a separating funnel. The obtained concentrate was dissolved in benzene (. KOH (0.1% w/v) added to benzene (C_6H_6) solution, (CUM) partitioned between the two layers KOH layer was taken and (CUM) was precipitated by adding dilute HCl solution and filtered using (vacuum filtration unit) and dried.[7] and purification of the extract by crystallization.

The majority of curcumin complex studies have been published in the last 20 years [2-8]. Curcumin complex has been utilized as a food additive and traditional medicine. Indicator, as well as dye [9-10].

3. CURCUMIN CHEMISTRY

Curcumin and cetylacetone, the main coloring components of curcumin, show typical keto-enol tautomerism and antioxidative capabilities. They exist in keto form in neutral and acidic pH media and as enol form in alkaline pH media and as an oil- soluble pigment. Curcumin is nearly insoluble in water at room temperature when the PH is acidic or neutral [11-13]. Is an Oil-soluble chemical that is soluble in alkali and highly vulnerable to auto-degradation.

It's water-insoluble but highly soluble in dimethyl sulfoxide, acetone, and ethanol. It is unstable in alkaline and bright environments, although it is stable at high temperatures and in acids [14].

Curcumin includes 2 feruloyl moieties, non-polar heptadiene bridge and 1,3-keto–enol or diketo moiety, a conjugated β-diketone moiety and an aromatic group that produces π-π interactions [15]. The aromatic group causes π-π interactions, while the keto-enol of phenylic hydroxyl residues and phenolic groups from hydrogen bonds with the target macromolecules. The b-dicarbonyl moiety and the phenylic hydroxyl residues have H-bond giving and receiving capacity. In aqueous media, Curcumin is essentially insoluble. However, as shown by its sequence of solubility in polar aprotic and polar protic solvents: acetone, 2-butanone, ethyl acetate, methanol, ethanol, 1,2-dichloroethane, 2-propanol, ether, benzene, hexane, and DMSO it will, at some point, come into contact with water (buffer, culture -medium, cytosol blood). For three acidic protons, the pKa_1, pKa_2, and pKa_3 value of 7.8, 8.5, and 9.0, respectively [11-14].

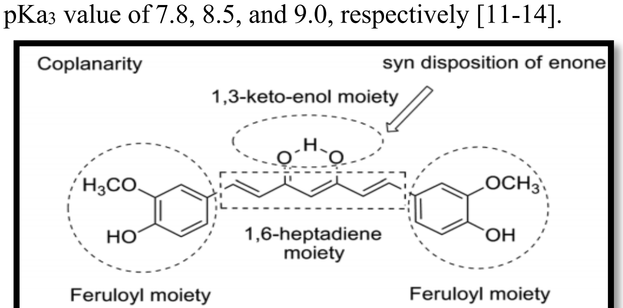

Fig.1: Curcumin chemical structure

4. COMPLEXATION OF CURCUMIN AND THEIR VARIOUS APPLICATIONS

Curcumin's clinical applications and the complexation of curcumin with metal ions have recently piqued the interest of researchers all over the world as one of the necessary ingredients for the treatment of Alzheimer's disease and *in vitro* antioxidant activity. Curcumin can be chelated with various metal ions to generate metallo-complexes of curcumin, which may have stronger benefits than free curcumin, and a better understanding of metal- curcumin biochemistry can aid in the development of new medications.

In all of our bodily fluids, many metal ions are dissolved as free ions. They are necessary for life, but they can be hazardous to the body and we need to know how to get them out medicines. Curcumin can be used as medicine in its free form but it has been to be more useful in the form of metal complexes, which are easier to remove from the body and are less poisonous.

The majority of curcumin complex studies have been published in all last 20 years. Turmeric is one of several herbs that have been utilized in traditional medical and Culinary preparations (food additives).Dye, Indicator and traditional use [17-20].

Curcumin's acetylacetonate group can combine with metallic ions under biological circumstances. In practically all studies described in the literature, curcumin complexes of type ML2 +2, and complex of type ML3 are produced when the metallic ion has an electrical charge of M^{+3} [17-20].

Thompson et al (2004) reported synthesis [$VO(acac)_2$] complexes group = (V═O) is Vanadyl with 2 equiv of Curcumin in dichloromethane solution in the presence of (2 M) NaOH which were characterized by [FT-IR, MS, magnetic moment, and (C.H.N) analysis] [21] used for their remarkable anticancer activity.

Song Y-M. et al (2009) [22] reported synthesized (CUM) and (1,10-phenanthroline-5,6-dione with Nitrates rare earth RE=Sm (III) , Eu(III), Dy(III)) complexes and characterized them using IR, UV- Vis methods. (TG) and (C.H.N) analysis, .The results demonstrated that after deprotonation, the (b-diketone) group of the (CUM) chelates with (RE) ions in a bidentate mode. However, in bidentate mode, the (1,10-phe)-5,6-dione) utilizes its (2N) atoms covenanted with (RE) ions.

Mandy et al (2011) [23] Fluorescence spectroscopy and transient absorption spectroscopy were used in a 2011 study to show that curcumin forms stable compounds with Cu(II) in methanol and sodium dodecyl sulfate. The 1:1 and 1:2 Cu(II)–curcumin complexes have two different square planar geometries [21].

Aluminum(III)– Curcumin complexes [24] were prepared tested as fluid by (^1H, ^{13}C and ^{24}Al) nuclear magnetic resonance (NMR), mass spectroscopy, (UV) spectroscopy, density functional theory (DFT)-based UV and DFT calculations to determine the possible structures of those three [Al(III)– (CUM)] complexes.

Yet, no crystalline materials form amorphous form and an amorphous consolidation of curcumin have been documented in the literature/patent, according to Sanphui and Bolla (2018) [15].Sumathi et al 2012 [25] produced (CUM)-diketimine Schiff base Scheme (1-3) and its Cu(II), Co(II), Ni(II), and Zn(II) complexes [ML] Figure (1- 11) and characterized them using spectroscopic and analytical data. elemental analysis, magnetic susceptibility, molar conductance, IR, UV-Vis, mass, NMR, and ESR spectral analysis were used to explore the structures of the complexes. all of the complexes are electrolytes, according to conductive measurements. all the complexes have octahedral or square-pyramidal geometry based on spectral and other data.

Sreelakshmi et al . (2013) [26] reported synthesis Gold nanoparticles-(CUM) molecules acting as a reducing agent application in biology and diagnosis, cancer treatment drug in medicine. Balaji et al (2014) [27] have reported synthesized [VO(phen) (CUM) Cl] complex in from react 1,10 phenonthroline with (CUM) in slope ratio (1phen :1M: 1CUM). Pi et al (2015) [28] have reported , heteroleptic zinc (II) - (CUM) complexes were synthesized from Chloro precursors and (CUM) in the presence of trimethylamine . as non-classical anticancer agents. Tukki and Akhtar (2016) [29] 2016 have reported synthesis of (CUM) - Fe(III) Complex as potential photo cytotoxic agents selectivity towards cancer cells. Reiam (2018) [30] constructed a series of mixed ligand metal complexes of M (II), and M' (III) from the (CUM) and L- phenylalaninate (L-phe) The structural features have been arrived from there, FT-IR, UV-Vis spectroscopic studies : [M (CUM)(L-Phe)$_2$] and [M'(CUM)(L-Phe)$_2$]Cl

M= VO(II), Mn(II), Co(II), Ni(II), Cu(II) Zn(II), Cd(II), Hg(II).
M'= Cr(III) & Cr(III).

Charge and adhesion properties of micro- and o-particles surfaces are also important elements in determining bio-absorption. Srivithya et al (2018) [31], have reported synthesis [Metal -(CUM)], M =Cu(II)/Ni(II)/Zn(II) binding to DNA, Figure (1-18), AFM was used to analyze their optical properties and interactions using mass spectroscopy, UV-vis, and FTIR.

Zainab (2018) [32] reported synthesized Schiff base derived from isatin and 2-aminopyridine mixed ligand complexes. (N_3^-) - curcumin. Beneduci et al (2019) [33] have studied the complexation of Fe(III) / Al(III) with curcumin derivative (HCUM,1.7-Bis(3-methoxyphenyl 4-hydroxy-Al(III). Ghaidaa and Taghreed (2019) [34], have synthesized Curcumin - Anthranilic acid [M(Anthr)$_2$(CUM)] complexes M=Mn (II), Co(II), Ni(II),Cu(II),Zn(II), Cd(II), Hg(II). Barra et al (2020) [35] , have been reported new heteroditopic receptors as Binuclear Cu(II) complexes with urea groups have a high selectivity for biologically important phosphorylated anions and act as minor groove DNA binders . Ruihao et al (2020) [36], have been reported Curcumin–boronic acid ester polymer via covalent linkages for selective killing of cancer cells. Curcumin ligands with various, d- and f- transition elements and main group have been listed in several complexes (Table 1).

Table 1: complexes of some chosen curcumin and its derivatives with various metals

Compounds	Reference
Zn(II)–curcumin	[37]
Cu (II)- –curcumin	[38] ,[39]
Cr(III)- –curcumin	[40]
Mixed ligand Schiff base with 1,10-phnanothroline, M= Co or Cu	[41]
Pd(II)–curcumin	[42]
M(diacetylcurcumin)$_2$, where M= Cu(II) and Ni(II)	[43]
Ln=Eu(III) &La(III), rare earth –curcumin	[44]
M–curcumin, M=Cr(III),Mn(II), Fe(III), Co(II), Ni(II), Cu(II) ,Zn(II)	[45]
Mixed metal (Fe (II) &Cu(II)) –curcumin	[46]
Complexes of Curcuminoid–BF$_2$	[47]
In acidic condition, Rosocyanine is produced as 2:1-complex from curcumin and boric acid	[48]
Curcumin- Fe(III)	[49]
Drug containing Rh(III) and curcumin (*Cp) ,*pentamethylcyclopentadienato	[50]
Fe(III)- curcumin	[51]
Prodrugs containing Co(III)-curcumin	[52]
Curcumin-2- aminophenol	[53]
Curcumin -Hg(II) complex in solution	[54]
Curcumin -M , M = Tc, Re	[55]
Mesoporous silica nanoparticles	[56]
Ga (III) - diketone (CUM)complex	[57]
(CUM)-based M(II) complexes as anticancer agents	[58]
DNA nanotechnology Cu(II)/Ni(II)/Zn(II)-curcumin-conjugated DNA complexes	[59]
cyclodextrins and conjugating it with silver nanoparticles	[60]
curcumin - Schiff base with various metal ions complexes ,M= Al(III), Mn(II), Fe(III), Co(II),Ni(II), Cu(II), Ag(I), Cd(II), Hg(II), and Pb(II)	[61]
Hexadentate (N_4O_2 donor) Schiff base ligands derived from curcumin with some transition and non–transition metal cations	[62]
chiff Base Derived Curcumin and L-Tyrosine with Al(III), Ag(I), and Pb(II) Metal Ions	[63]

5. THE EFFECTS OF CURCUMIN AGAINST COVID-19:

The World Health Organization clarifies that the emergence of the Corona virus 2019 called COVID-19 as a pandemic caused by the Corona virus 2 (SARS-CoV-2), it's a respiratory syndrome, then it has severe impact and difficult to bear in a clear and high way. Also, positive RNA viruses didn't find an outlet because the method of infection is limited to transmission through respiratory droplets. In addition, there is a fast-spreading epidemic in the world, its beginning was in China, and it recently appeared in December 2019 [64].

Addressing the importance of curcumin and its beneficial and positive effect in its fight against COVID-19 infection through its ability to modify molecular elements such as targets that contribute to the understanding, assimilation and also binding of SARS-CoV-2.

5.1. IN THE INTENDED AND POTENTIAL BENEFIT WHEN USING CURCUMIN AS AN AID IN FIGHTING VIRUSES:

The use of natural products as an antiviral is at the peak of its importance. Where many studies have proven that curcumin has broad-spectrum pharmacological properties, and it is also being examined for its benefit and its effect on the virus.

There are a huge number of clinical studies on curcumin, reaching 179 studies, and some of them are concerned with studying and analyzing the effect of curcumin with its anti-cancer activity, although it doesn't limit its action as an antiviral to a particular virus, but to several different viruses, including; Hepatitis, influenza and viruses such as Zika virus (ZIKV) or chikungunya virus (CHIKV) [65-66].

Front Microbiol. 2019; 10:912. Globally, COVID19 positive cases Curcumin stems from many viral activities to fight a large number of viruses, and examples of these viruses are: Human immunodeficiency virus, HSV-2, lentivirus and also influenza, ZIKA, hepatitis virus and adenovirus. pharmacological for-emulation of curcumin in nano emulsion (CR-NE) it was confirmed via the system that the applied solubility increases its bioavailability in a satisfactory manner and this indicates the compatibility of its susceptibility and also the effect related to depressurization also protected the curcumin from chemical degradation, and more stable than unencapsulated curcumin. [67]

When we look at the documents related to COVID-19, we see several substances that are similar in terms of drugs and antiviral activity. They start from CAS COVID-19 Protein Target Thesaurus, there are several documents related to CAS. We can look at these groups that have a clear effect by antiviral compounds. When referring to how the relationships are built, they are two-dimensional between the protein and its benefit and antiviral materials with correlations according to expectations graded either high, medium or low strength in the attached documents.

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إسْتِعْراض قصير: كيمياء الكركمين ومعقداتها الفلزية

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الخلاصة :

في هذا الاستعراض يتم تغطية اخر الابحاث في مجال تحضير الكركمين والفعالية الحيوية للكركمين شبه المحضر والنظائر المحضرة. كما انه في هذا الاستعراض تم بيان كيف يتم استخدام الكركمين كمركب وسطي لتحضير مركبات عضوية اكثر تعقيداً. تأريخيا، استعراض عملية تحضير المعقدات الفلزية وتشخيص المعقدات المتكونة باستخدام تقنيات طيفية وغيرها من التقنيات . ويظهر الكركمين ومشتقاته اهمية كبيرة لتطبيقاته الكثيرة في الاجهزة الطبية وطيف واسع من التطبيقات الطبية الاخرى كمضاد حيوي ، مراهم طبية ، العلاجات البديلة ، مضاد فطريات، وفعاليته كمضاد للبكتريا.

الكلمات المفتاحية: الكركمين، فعالية ضد البكتريا، مضاد حيوي ، علاجات بديلة ، معقدات فلزية ، مركبات مضادة للسرطان ، العقاقير الاولية ، و كيمياء الحيوية اللاعضوية