IJPSR (2021), Volume 12, Issue 3 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 31 March 2020; received in revised form, 09 December 2020; accepted, 22 February 2021; published 01 March 2021

REVIEW ON DERIVING A HYPOTHESIS FOR ACHIEVING SUPERIOR BIOAVAILABILITY OF CURCUMIN AS AN ANTITUMOR AGENT

R. Manju [1] and K. Kannan [*2]

Department of Pharmaceutical Chemistry [1], Karuna College of Pharmacy, Pattambi, Palakkad - 679533, Kerala, India.
Department of Pharmacy [2], Annamalai University, Annamalai Nagar, Chidambaram - 608002, Tamil Nadu, India.

Keywords:

Synthetic curcumin, Metal complexes, Antitumor efficacy, Formulations, Ligand

Correspondence to Author:
Dr. K. Kannan

Associate Professor,
Department of Pharmacy,
Annamalai University, Annamalai Nagar, Chidambaram - 608002,
Tamil Nadu, India.

E-mail: egkkannan@yahoo.co.in

ABSTRACT: Curcumin, chemically 1,7-bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione derived from *Curcuma longa* L. is an active chemical constituent used medicinally worldwide from ancient times. Though Curcumin enjoying the reputation of many pharmacological actions, it has certain setbacks with poor bioavailability. The poor water solubility is said to be the reason for poor bioavailability, rather it is more about drug permeability and diffusion through different membranes. Curcumin as a drug candidate can be studied by considering various principal factors like rate, time, and location of the release of the drug with respect to its efficacy. It was found that the drug distribution is more at the kidney and liver than other organs due to substantial metabolism and elimination of drug at these sites. Due to its uneven, oversensitive, and non-bioavailable nature, additional clinical trials on curcumin are unwarranted. In fact, poor absorption, rapid metabolism, chemical instability, and quick systemic elimination anything could be a reason for poor bioavailability. The best possible solution for this problem is so narrow and lies somewhere around liposomal curcumin, curcumin phospholipid complexes, curcumin metal complexation and the use of structural analogs of curcumin. This review focus on compiling various scientific approaches made as the part of curcumin research to overcome the poor bioavailability and attempted in deriving a hypothesis to develop super curcumin.

INTRODUCTION:

1.1. Curcumin: Diketones are used for nearly 120 years. Many plants contain 1,3 diketone moieties as their important constituent used in the medicinal world such as pipeline, curcuminoids, cassumunin-A,B,C, ellagic acid, nomillin, limonin, flavanoids and flavones.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(3).1381-89

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(3).1381-89

From the above-mentioned compound, curcumin has a special chemical feature that it undergoes keto-enol tautomerism and intramolecular hydrogen bonding with two Michael acceptors and α, and β ketone leads to the capability of curcumin to form metal complexes and analogues.

Curcuminoids, the active chemical components present in the Indian medicinal plant turmeric (*Curcuma longa*, Linn. Zingiberaceae family) have various biological activities, including antioxidant, anti-inflammatory, anti-arthritic, and anti-tumor activities [1, 2, 3]. Further hepatoprotective, nephro-protective, and neuroprotective properties of

curcuminoids is said to be mediated by 1, 3-dicarbonyl enol substructures that form nucleophilic enolates [4, 5]. Curcumin is a homodimer of feruloyl methane containing a methoxy group and a hydroxyl group, a heptadiene along with two Michael acceptors and an *α, β*-diketone. Chemically curcumin is [diferuloylmethane, 1, 7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptddiene-3,5-dione as shown in **Structure 1**.

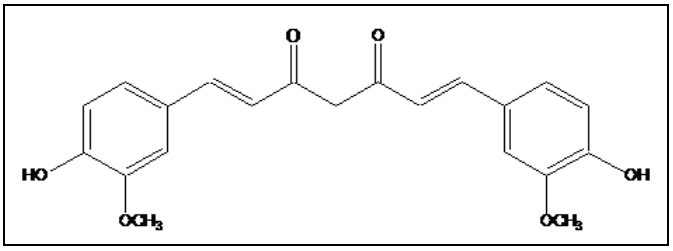


FIG. 1: STRUCTURE 1

1.2. Structure of Curcumin: The optimized structure of curcumin is planar and linear. The enol form is stable in the ground state. The crystal X-ray diffraction studies reported that enol form is the preferred tautomer, and curcumin in solid-state has a delocalized central keto-enol unit co-planar with one trans-Ar-CH=CH moiety. The characteristic structural geographies of curcumin are 2-o-methoxy phenol units, 2-enol moieties, and 1,3-diketone keto-enol system. The hydroxyl group substituted on benzene ring and diketone structure is said to be accountable for the biological activities [6]. The β-diketo moiety of curcumin undertakes keto-enol tautomerism. The strong chelating ability of diketones has widely experimented with a number of metal ions [7]. Therefore, curcumin could be of great standing in the chelating treatment of metal intoxication and overload

1.3. Natural Analogues of Curcumin from Turmeric: Turmeric contains 3 analogs called curcuminoids, which are curcumin, demethoxycurcumin (DMC), bis-demethoxycurcuminn (BDMC), which differ in the methoxy substitution on the aromatic ring. Curcumin is most abundant in turmeric [1]. Cyclo curcumin, which is another curcuminoid from turmeric differs only in the β-diketone link from curcumin. The curcuminoids are scavengers of free radicals and reactive oxygen species (ROS) such as hydroxy radicals, singlet oxygen, superoxide radicals, peroxy radicals, and peroxynitrite. Even though curcumin, DMC, and BDMC are highly reactive in scavenging reactions, curcumin is more efficient. Structures of BDMC (2) and DMC (3) were given below.

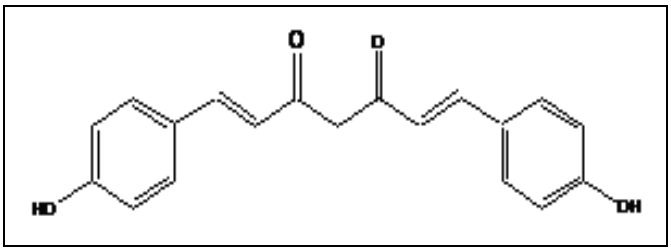


FIG. 2: STRUCTURES OF BDMC

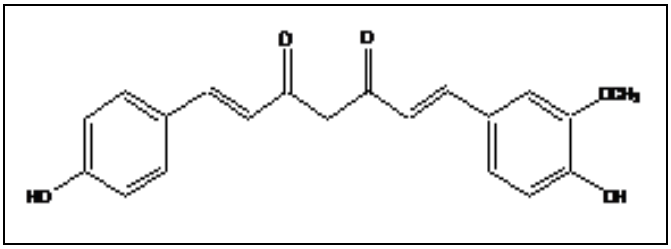


FIG. 3: STRUCTURES OF DMC

2. Various Approaches to Overcome Curcumin Poor Bioavailability:

2.1. Curcumin Scaffold Hopping; a Synthetic Approach: From a medicinal chemist's viewpoint, two scaffolds can be diverse if they are built up via different synthetic routes. Synthetic curcumin is one of such scaffolds studied and synthesized extensively in a different part of the world. Though many analogues were patented, major pitfalls in curcumin chemistry without a significant therapeutic agent require attention. The existing multidirectional studies in the last forty-plus years with diverse curcumin templates are to be analyzed to find out the most suitable scaffold among them. It is high time to investigate, test, and hypotheses *in-silico* prior to the costly random experimental implementation of synthetic curcumin. The diverse approach existed in SAR-based synthesis, and the existing numerous synthetic approaches should be streamlined for reducing the time and expense involved in bringing products to market.

Various studies have revealed that curcumin modulates abundant targets. These comprise the growth factors, growth factor receptors, transcription factors, cytokines, enzymes, and genes regulating apoptosis [8]. During the last decade, synthetic alterations of curcumin, which were meant to enhance its bioactivities, have been thoroughly measured. However, few of these investigations were paid attention to the improvement of its pharmacokinetic profiles alone.

Some of the studies suggested that the stability and bioavailability of curcumin could be enhanced by deleting the *β*-diketone moiety. G Liang *et al*., synthesized a series of mono carbonyl analogs curcumin by deleting the *β*-diketone moiety, the results in *in-vitro* stability studies and *in-vivo* pharmacokinetic studies indicated a large improvement in the bioavailability of curcumin [9]. The structure (4) of this analog is given below.

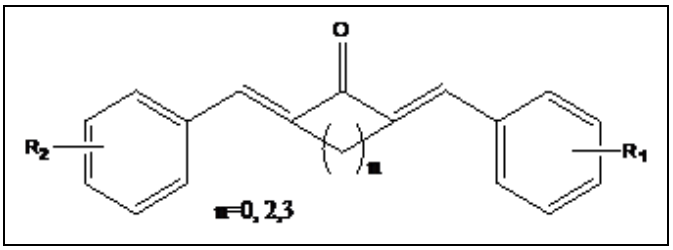


FIG. 4: STRUCTURE 4

Alteration of *β*-diketone is also performed by utilizing the high reactivity of this *β*-diketone with hydrazine, its substituted derivatives, and hydroxylamine are also in Practice. This leads to the synthesis of pyrazole and isoxazole derivatives. Mishra *et al.*, reported few derivatives in this series, and their structures (5, 6) are as follows [10].

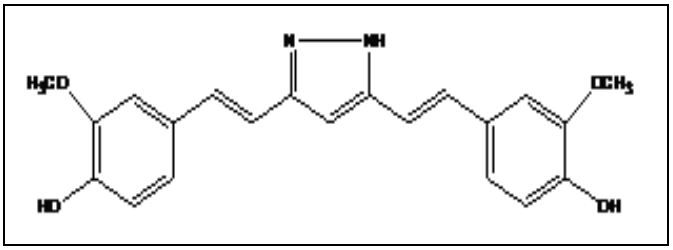


FIG. 5: STRUCTURE 5

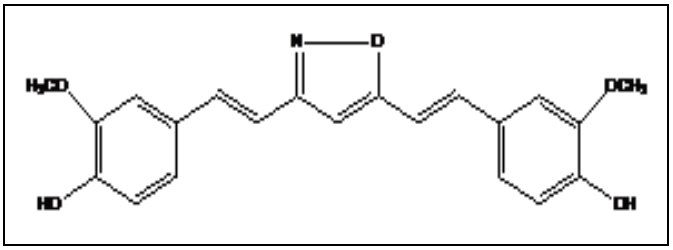


FIG. 6: STRUCTURE 6

But majority of studies on structural analogs are with different terminology of maintaining the diketone moiety as the pharmacophore and suggested structural modification at the terminal lipophilic rings and substituent methoxy groups. In South India, K. Krishnankutty *et al*., carried out extensive research on synthesis of various synthetic analogues of curcumin keeping the *β*-diketone moiety intact [11, 12]. A series of 6-aryl-5-hexene-2,4-diones and their metal complexes of ML_2 stoichiometry were synthesized by condensation of heterocyclic aldehydes with acetyl 1,3-diketone through boric anhydride mediated mechanism. Mathew Paul *et al*., reported synthesis of Metal chelates of 5-aryl-1-phenyl-4- pentene-1,3-diones and Synthesis and characterization of Co(II),Ni(II) and Cu(II) complexes of some 6-aryl-5-hexene-2,4-diones [13]. Further, V. D. John *et al*., reported antitumor studies of aluminum complexes of synthetic curcuminoids [14]. M. B. Ummathur *et al*., reported the synthesis, characterization of "metal complexes of unsaturated poly carbonyl compounds derived from benzoyl acetone and aromatic aldehydes [15]. Many works were carried out by K. L. Krishnakumar *et al*., to synthesize and characterize structural analogues of curcumin and their metal complexes based on the hypothesis that enolates of simple 1,3-diketones such as acetyl acetone and benzoyl acetone might also possess hepato protective, nephroprotective and neuro protective actions [16]. The possibility of substituting aromatic aldehydes with heterocyclic aldehydes, as they are more likely to give better pharmacological actions due to the presence of heterocyclic ring systems, are yet to be explored. Thus, these synthetic analogues will be very good candidates as drugs, as they are less likely to show side effects and adverse reactions upon a long course of treatment required for cancer-related chemotherapy. Structures of a few of these synthetic analogues (7, 8, 9, 10,) and their metal complexes (11) were given below.

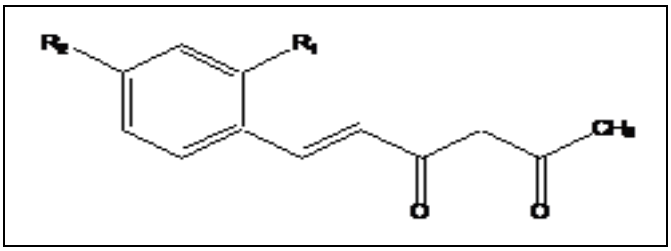


FIG. 7: STRUCTURE 7

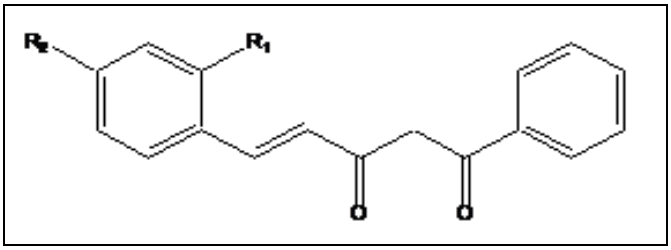


FIG. 8: STRUCTURE 8

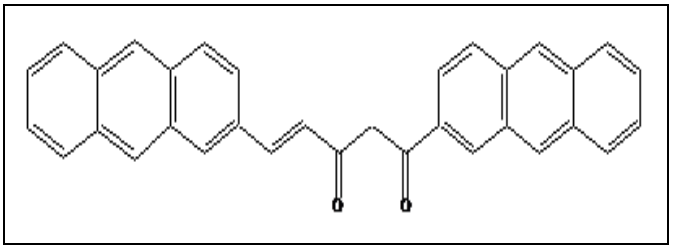


FIG. 9: STRUCTURE 9

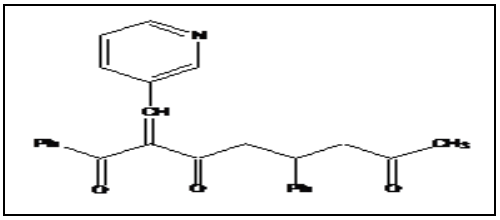


FIG. 10: STRUCTURE 10

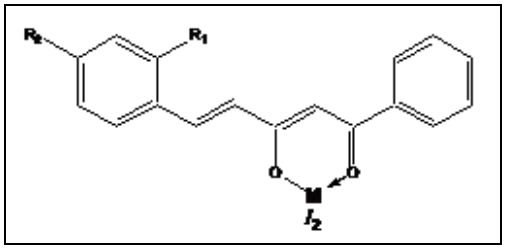


FIG. 11: STRUCTURE 11
M = Cu^{2+}, Ni^{2+}, Zn^{2+}, Pd^{2+}, Co^{2+} for n=2

Various aldehydes and diketones were used as an alternative to vanillin and acetylacetone for the synthesis of synthetic analogs. A few of them are listed in **Table 1**.

TABLE 1: ALDEHYDES & KETONES COMMON FOR SYNTHESIS OF CURCUMIN ANALOGUES

S. no.	Diketones	Aldehydes
1	2,4-pentanedione	benzaldehyde
2	1-phenyl-1,3 butanedione	cinnamaldehyde
3	3-methyl-2,4-pentanedione	furfural
4	3,3-dimethyl-2,4-pentanedione	Indole-3-carboxaldehyde
5	3-ethyl-2,4-pentanedione	Thiophene-2-carboxaldehyde
6	3-benzyl- 2,4-pentanedione	Pyrrole-3-carboxaldehyde

2.2. Curcumin as an Effective Ligand: Xue-Zhou *et al*., has done work on "Interaction of curcumin with Zn (II) and Cu(II) ions based on experiment and theoretical calculation"[17]. The result show that curcumin easily chelate with metal ions like Zn^{2+} and Cu^{2+}. This work concluded that free radical scavenging ability is stronger for Cu-curcumin complex than that for curcumin and Zn-Curcumin complex. The 1,3-diketone moiety of curcumin transformed into keto-enol tautomeric form, and it is more stable and can readily chelate the metal ions to form the complexes and scavenge the active free radicals.

K Krishnankutty *et al*., also studied the interaction of Cu(II) and Zn(II) ions with curcumin and forming a ML_2 complex models [18]. Baum *et al*., also supported the ML_2 model for the Cu(II) ion and Zn and they confirm that Zn-curcumin complex was weak in action. They suggested that Cu(II) interact with curcumin in the ML_2 model and it is more suitable for complexation [19].

The study also shows that the free radical scavenging ability of Cu(II)-curcumin complex was higher than that of the curcumin itself. The common metals used along with curcumin or its synthetic analogs with pharmacological actions are listed in **Table 2**.

TABLE 2: METALS USED COMMON FOR THE COMPLEXATION

S. no.	Metals	Pharmacological actions
1	Vanadium (V^{2+})	Anti-Alzheimer's
2	Copper (Cu^{2+})	Anti-Cancer
3	Cobalt (Co^{3+})	Anti-Inflammatory
4	Cerium (Ce^{4+})	Anti-Bacterial
5	Nickel (Ni^{2+})	Anti-Tubercular
6	Iron (Fe^{2+})	Anti-Bacterial
7	Zinc (Zn^{2+})	Anti-Neoplastic

2.3. Metal Complexes of Synthetic Curcumin as Anticancer Agent: Tumor is a mass of tissues that proliferate rapidly, spread throughout the body, and may eventually cause the death of the host. Chemotherapy is the current treatment against numerous types of cancer, either singly or in combination with surgery and or radiotherapy [20]. Yan Jiaol *et al*., reported work on "curcumin a cancer chemopreventive and chemotherapeutic agent is a biologically active iron chelator" and concluded that curcumin biologically active chelator can exhibit chemopreventive as well as chemotherapeutic agent [21]. This action is by the formation of redox-active iron complexes by iron depletion. In this study, they focused mainly on the curcumin iron complex, and they found that it is a biologically active iron chelator. Iron chelator induces iron depletion and decreases in the H and L sub-unit of the iron storage protein ferritin,

increases in the iron transport proteins transferrin receptor, and activation of iron-regulatory protein.

This study suggested that curcumin may have acted as a cancer chemo-preventive and chemo-therapeutic agent. It hinders diethylnitrosamine-induced liver tumors and has a dose-dependent chemopreventive effect in colon, duodenal, stomach, oesophageal, oral cancer, pancreatic cancer, multiple myeloma, and myelodysplasia. Curcumin prevents activation of nuclear factor-kB through blockade of 1-kB kinase and inhibits activation of cyclooxygenase 2(COX2)· Curcumin and its analogues also alter activated protein1 (AP 1) complexes and inhibit Akt. Curcumin persuades cytoprotective enzymes, including glutamate-cysteine ligase, isoforms of glutathione-S-trans-ferase as well as hemeoxygenase, and NAD (P) H: quinone oxidoreductase [1]. Curcumin possesses chemical features that may further modulate its antioxidant activity and are a good free-radical scavenger.

Marco Borsari *et al*., done work on "Curcuminoids as potential new iron-chelating agents: spectro-scopic, polarographic and potentiometric study on their Fe (III) complexing ability" [22]. In their study, they emphasis the complex formation of curcumin and diacetyl curcumin with Fe^{3+}. In this work, they mainly focused on curcumin and its derivative diacetyl curcumin as a new potential chelating agent and their complexing ability towards Fe^{3+}. Tripathi laxmi *et al*., reported on the "role of chelates in the treatment of cancer [23] that the Copper chelate of the synthetic curcuminoids shows enhanced anti-cancer activity by cytotoxic effect of these copper complexes of curcumin analogues with a hydroxyl group on the ring were found to be the most effective. *e.g.* - 2-hydroxy-naphthyl curcumin.

Garima Modi reported work on "Increased anticancer activity of curcumin-Zn (II) complex by species sensitive method" and concluded that the complexing ability of curcumin with Zn has more potent anticancer activity as compared to the parent drug [24]. Jessica *et al*., has done work on the "Transient Metals Enhance Cytotoxicity of Curcumin: Potential Involvement of the NF-kB and mTOR Signaling Pathways". This study is concerned about the metal-binding activity and cytotoxicity of curcumin in cancer treatment. This study tells that transient metals like copper-II enhances the cytotoxicity of curcumin through targeting of the NF-kB and mTOR signaling pathways [25].

Imran Ali *et al*., have done work on "Synthesis, DNA binding, hemolytic and anti-cancer assays of curcumin I-based ligands and their ruthenium(III) complexes [26]. This study indicates the complex formation of curcumin with ruthenium (III) metal ions, and their experiment shows that this metal complex showed less toxicity than the standard anticancer drug letrozole. This compound possesses potential activity against the cervical cancer cell line (HeLa) and moderate activity against liver hepatocellular carcinoma (HepG2), breast cancer (MDA-MB-231) and human colon adenocarcinoma (HT-29) cell lines. These compounds showed potential for treatment of cervical cancer in the future. The degree of ligand exchange, variety of accessible oxidation states and capability to mimic iron make ruthenium compounds good alternatives to other metal complexes in the treatment of cancer.

Monica *et al*., has done work on "Palladium complex containing Curcumin as ligand: Thermal and Spectral characterization" [27]. In this study, they report the thermal and spectral characterization of the curcumin palladium complex and evaluated the biological property. The emphasis that palladium ion binds to curcumin to the oxygen atom of the diketone group and exhibits cytotoxicity and antioxidant property.

Sheril Daniel *et al*., has done work on "Through metal binding, curcumin protects against lead-and cadmium-induced lipid peroxidation in rat brain homogenates and against lead-induced tissue damage in rat brain" [28]. The outcomes of the study display that there is an interaction between curcumin and both cadmium and lead, with the establishment of a complex between the metal and this ligand. This implies that curcumin is used intensely to chelate these toxic metals and possibly reducing their neurotoxicity and other tissue damage. According to Tomeh MA *et al*., curcumin complexes and synthetic analogues exhibiting anticancer activity; palladium, ruthenium, copper and zinc are most common among transition metals [29].

Plasma metal concentration increases in neoplastic and autoimmune diseases as an immune-mediated physiological response to these disease conditions. Treatment with metal complexes is therapeutic assistance to increase in plasma metal and the attendant distribution of metals like copper to affected tissues to enable de-novo synthesis of copper-dependent enzymes required to bring about remission by re-establishing normal tissue function. All this literature supports the virtue of complexation of curcumin or its synthetic analogs with different transition metals and hence its use as an effective cytotoxic agent. The different receptors to which curcumin analogs bind to give the various anti-neoplastic effects are enlisted in **Table 3**.

TABLE 3: RECEPTORS: CURCUMIN ANALOGUES BINDS FOR ANTI-NEOPLASTIC EFFECT

S. no.	Receptors	Anti-Neoplastic action
1	DNA polymerase	Breast cancer, Ovarian cancer
2	Focal adhesion kinase (FAK)	Breast cancer, Ovarian cancer
3	Protein Kinase (PK)	Leukemia, Renal cell carcinoma
4	Lipoxygenase (LOX)	Lung, prostrate & Colorectal cancer
5	Early growth response (Egr-1)	Prostate cancer
6	Tubulin	Skin cancer
7	Notch-1	Breast cancer
8	β-Catenin	Colon & breast cancer
9	Thioredoxin reductase	Biliary carcinoma & Lymphoma
10	Nuclear factor-kB	Epidermal neoplasia

2.4. Formulations: The strategies to enhance the biological activity of curcumin includes adjuvants, nanoparticles, liposomes, micelles, and phospho-lipid complex. Piperine is an adjuvant, which inhibit hepatic and intestinal glucuronidation, and the clearance of curcumin is decreased resulting in increase in the bioavailability [30]. Eugenol and terpeniol enhances the skin absorption of curcumin.

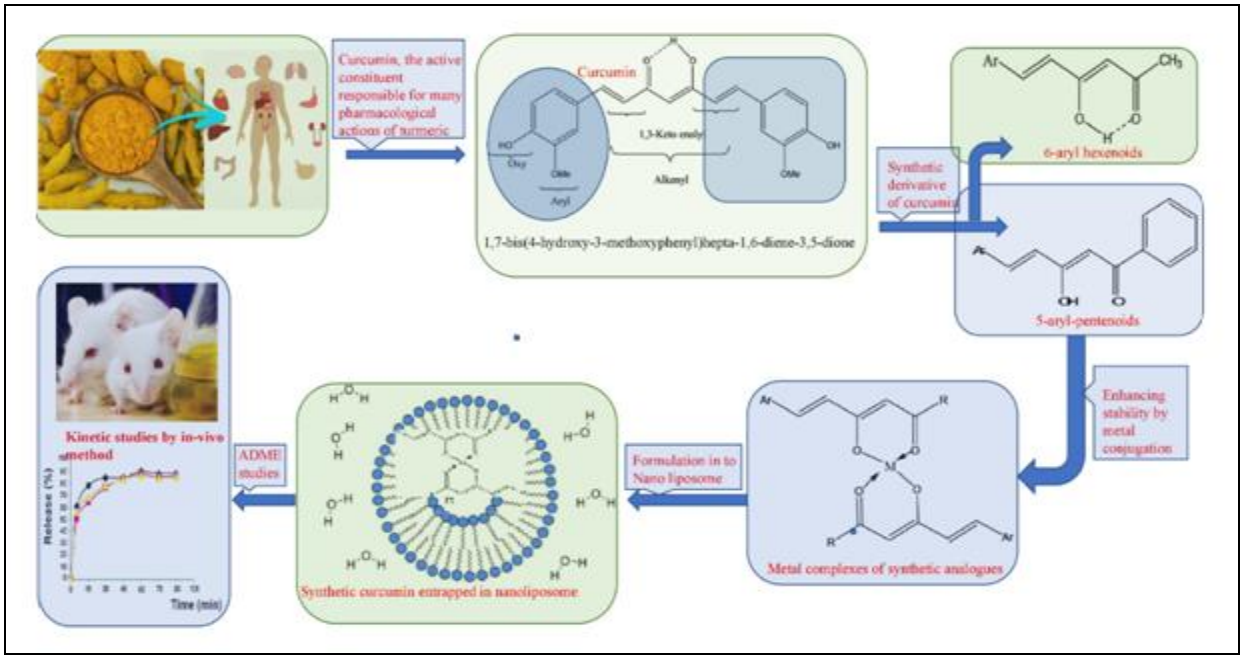
Nanoparticle technology enhances the bioavail-ability of therapeutic agents and reduces unwanted side-effects. The polymer-based nano-particle of curcumin is “nano curcumin” which is similar to free curcumin in pancreatic cancer cell lines for inhibiting the activation of transcription factors-NF-kB and reducing steady-state levels of pro-inflammatory cytokinins.

The anti-tumor activity of liposomal curcumin [31] with an excellent drug delivery system is effective against human pancreatic carcinoma cells and exhibits anti-angiogenic effects. The liposomal curcumin has greater growth-inhibitory and apoptotic effect than oxaliplatin, a standard chemotherapeutic agent for colorectal cancer. Liposomal curcumin has greater bioavailability and efficacy and less color staining effect than free curcumin. It has 10-fold higher anti-proliferative activity in human prostate cancer cells than free curcumin. The prodrug of curcumin N-maleoyl-L-valine-curcumin and N-maleoyl-glycine-curcumin is used to select the growth of bladder cancer cell lines. The activation of curcumin prodrug is because of the hydrolysis ability of cellular esterase, and thus it inhibits tumor cells' growth. PEGylation increases the solubility and decreases the degradation of the drug molecule. The solubility of curcumin is significantly increasing in a bioconjugate with PEG and cyclodextrin. Now, parallel to curcumin metal complexes for cancer treatment, curcumin nano liposomal formulations found their way in curcumin research. T. Feng *et al*., reported liposomal curcumin and its applications for the treatment of cervical cancer, prostate cancer with improved pharmacokinetic and pharmacodynamic profiles [32].

RESULTS AND DISCUSSION:

Curcumin Research: a Hypothesis: From the light of above discussion, the structural modification when applied to curcumin basic structure came out with the identification of α, β- unsaturated system as the most available pharmacophore present in the molecule. This can be further substantiated with the help of docking studies pointing to these binding sites. Various alternations are already applied to this active β diketone moiety, and scientists did many studies in order to narrate structure-activity relationships. Substitution with heterocyclic moieties at the terminal position as well the metal complexation of the final ligands was shown improved biological efficacy.

Different classes of heterocyclic compounds and other metal ions together with docking studies can be considered while framing the synthetic protocol. After the synthetic part and complexation procedures, formulation into nanoliposome can be adopted to overcome water insolubility, degradation at alkaline pH, and photodegradation, thus extremely low bioavailability in both vascular and oral administration. These synthetic curcumin-metal molecules entrapped into nanoliposomes will be a good source of curcumin and metal for meeting many nutritional requirements of the body. Further, these synthetic lipocurcumins' oxidative degradation pattern can be analyzed with *in-vivo* kinetic studies [33, 34]. The results obtained then, on comparison with the sequence of degradation of natural curcumin will definitely lay a fire in the arena of curcumin research. The proposed hypothesis is outlined below in **Scheme 1**.



SCHEME 1: PROPOSED HYPOTHESIS FOR BETTER BIOAVAILABILITY OF CURCUMIN

CONCLUSION: Anti-cancer therapies are usually long-term, so it is highly recommended to depend on such a drug that induces minimum adverse effects. So, it is safe to use synthetic curcumin analogues and their metal complexes because of its safer nature and low range adverse reactions on long-term therapy. This review suggests that synthetic curcumin analogues and their complexes do not cause retardation of body weight gain and pathological alterations in the liver and other organs. The study also suggests that metals form stable complexes with curcuminoids analogues and thus decrease the metal toxicity and enhances antitumor activity of compounds compared to natural curcuminoids.

This approach in the hypothesis focuses on establishing a balance between hydrophilicity and lipophilicity of the drug to have better passive diffusion through the cell membrane. The structural modification by deleting the terminal lipophilic groups converts the curcumin to a more hydrophilic one. This will allow the easy dissolution of the drug and make it available on the cell wall for diffusion. For permeation across the thick cell wall, the drug needs to have more lipophilic property. Curcumin loaded in the liposome form may facilitate this passage across the lipophilic cell membrane. Once it reaches inside the aqueous environment of the cell, the metal complex may get ionized.

This may prevent the reabsorption of the drug through a cell wall. Rather it is interesting to believe that synthetic curcumin in the form of the metal complex may prevent it from the chance of cell wall metabolism. Once the drug survives this stage, it can reach systemic circulation and bind with receptors to produce desired pharmacological action. But this hypothesis has to be proved with a more practical approach and trial and error method of shuffling either one or all the variables and methods in the stated hypothesis.

ACKNOWLEDGEMENT: The authors are very much grateful to the Department of Pharmacy, Annamalai University, Chidambaram, for providing the guidelines.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest.

REFERENCES:

1. Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B, Tharakan ST, Misra K, Priyadarsini IK, Rajasekharan KN and Aggarwal BB: Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. Biochemical Pharmacology 2008; 76: 1590-611.
2. Al-Kuraishy HM, Al-Gareeb AI and Rasheed HA: Antioxidant and anti-inflammatory effects of curcumin contribute into attenuation of acute gentamicin-induced nephrotoxicity in rats. Asian Journal of Pharmaceutical and Clinical Research 2019; 16: 466-68.
3. Farhood B, Mortezaee K, Goradel NH, Khanlarkhani N, Salehi E, Nashtaei MS, Najafi M and Sahebkar A: Curcumin as an anti-inflammatory agent: Implications to radiotherapy and chemotherapy. Journal of cellular Physiology 2019; 5: 5728-40.
4. Srimal RC and Dhawan BN: Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. J of Pharmacy and Pharmacology 1973; 6: 447-52.
5. Ammon HP and Wahl MA: Pharmacology of Curcuma longa. Planta Medica 1991; 1: 1-7.
6. Krishnakumar KL and Paul M: Synthesis, Characterization of some heterocyclic curcumin analogues and their copper complexes as antitubercular and antimicrobial agents. International Journal of Recent Scientific Research 2013; 4: 122-27.
7. Banerjee S and Chakravarty AR: Metal complexes of curcumin for cellular imaging, targeting, and photoinduced anticancer activity. Accounts of Chemical Research 2015; 7: 2075-83.
8. Deguchi A: Curcumin targets in inflammation and cancer. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders) 2015; 2: 88-96.
9. Liang G, Li X, Chen L, Yang S, Wu X, Studer E, Gurley E, Hylemon PB, Ye F, Li Y and Zhou H: Synthesis and anti-inflammatory activities of mono-carbonyl analogues of curcumin. Bioorganic & medicinal chemistry letters 2008; 4: 1525-29.
10. Ahsan N, Mishra S, Jain MK, Surolia A and Gupta S: Curcumin Pyrazole and its derivative (N-(3-Nitrophenyl-pyrazole) Curcumin inhibit aggregation, disrupt fibrils and modulate toxicity of Wild type and Mutant α-Synuclein. Scientific Reports 2015; 5: 9862.
11. Krishnankutty K and John VD: Synthesis, characterization, and antitumour studies of metal chelates of some synthetic curcuminoids. Synthesis and reactivity in inorganic and metal-organic chemistry 2003; 2: 343-58.
12. Paul M, Venugopalan P and Krishnankutty K: Metal chelates of 5-aryl-1-phenyl-4-pentene-1, 3-diones. Asian Journal of Chemistry 2002; 3: 1335.
13. Paul M and Krishnankutty K: Synthesis and Characterisation of Co (II), Ni (II) and Cu (II) complexes of some 6-Aryl-5-bexene-2, 4-diones. Asian Journal of Chemistry 2002; 2: 949.
14. John VD and Krishnankutty K: Antitumour studies of aluminium complexes of synthetic curcuminoids. Main Group Metal Chemistry 2010; 3: 157-66.
15. Ummathur MB, Krishnan A and Ukken M: Metal complexes of unsaturated polycarbonyl compounds derived from benzoyl acetone and aromatic aldehydes. Journal of the Iranian Chemical Research 2010; 3: 71-81
16. Krishnakumar KL and Paul M: Metal Complexes of Heterocyclic Unsaturated 1, 3-Diketones. International Journal of Pharmaceutical Sciences and Research 2013; 3: 1154-58.
17. Zhao XZ, Jiang T, Wang L, Yang H, Zhang S and Zhou P: Interaction of curcumin with Zn (II) and Cu (II) ions based on experiment and theoretical calculation. Journal of Molecular Structure 2010; 984(1-3): 316-25.
18. John VD, Kuttan G and Krishnankutty K: Anti-tumour studies of metal chelates of synthetic curcuminoids. Journal of Experimental & Clinical Cancer Research: CR 2002; 2: 219-24.
19. Baum L and Ng A: Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. Journal of Alzheimer's Disease 2004; 4: 367-77.
20. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA. A Cancer Journal for Clinicians 2019; 1: 7-34.
21. Jiao Y, Wilkinson J, Di X, Wang W, Hatcher H, Kock ND, D'Agostino R, Knovich MA, Torti FM and Torti SV: Curcumin, a cancer chemo preventive and chemo-therapeutic agent, is a biologically active iron chelator. Blood 2009; 2: 462-69.
22. Borsari M, Ferrari E, Grandi R and Saladini M: Curcuminoids as potential new iron-chelating agents: spectroscopic, polarographic and potentiometric study on their Fe (III) complexing ability. Inorganica Chimica Acta 2002; 1: 61-68.
23. Tripathi L, Kumar P and Singhai AK: Role of chelates in treatment of cancer. Indian Journal of Cancer 2007; 2: 62.
24. Modi G and Pitre KS: The role of Fe (II) in the increased medicinal potency of curcumin analyzed by electrochemical methods. Journal of Coordination Chemistry 2009; 6: 931-39.
25. Jessica RL, Xiao XZ, Jie Z and Wei QD: Transient metals enhance cytotoxicity of curcumin: potential involvement of the NF-kB and mTOR signaling pathways. Anticancer Res 2010; 30: 3249-56.
26. Ali I, Saleem K, Wesselinova D and Haque A: Synthesis, DNA binding, hemolytic, and anti-cancer assays of curcumin I-based ligands and their ruthenium (III) complexes. Medicinal Chemistry Research 2013; 3: 1386-98.
27. Rodrigues MA, Fernandes JN, Ruggiero R and Guerra W: Palladium complex containing curcumin as ligand: thermal and spectral characterization. American Journal of Chemistry 2012; 3: 157-59.
28. Daniel S, Limson JL, Dairam A, Watkins GM and Daya S: Through metal binding, curcumin protects against lead-and cadmium-induced lipid peroxidation in rat brain homogenates and against lead-induced tissue damage in rat brain. Journal of Inorganic Biochemistry 2004; 2: 266-75.
29. Tomeh MA, Hadianamrei R and Zhao X: A review of curcumin and its derivatives as anticancer agents. International Journal of Molecular Sciences 2019; 5: 1033.
30. Prado-Audelo D, María L, Caballero-Florán IH, Meza-Toledo JA, Mendoza-Muñoz N, González-Torres M, Florán B, Cortés H and Leyva-Gómez G: Formulations of curcumin nanoparticles for brain diseases. Biomolecules 2019; 2: 56.

31. Divya R, Ashok V and Rajajeyakumar M: Curcumin: the golden nutraceutical from the most powerful herb in the planet-turmeric. Chronic Complement Altern Integra Med 2019; 1: CCAIM-100004.
32. Feng T, Wei Y, Lee RJ and Zhao L: Liposomal curcumin and its application in cancer. International Journal of Nanomedicine 2017; 12: 6027.
33. Slika L and Patra D: A short review on chemical properties, stability and nano-technological advances for curcumin delivery. Expert Opinion on Drug Delivery 2020; 17(1): 61-75.
34. Li W, Jiang ZF, Tan L, Wang SX, Wang CZ, Zhang JW, Zhou LD, Zhang QH and Yuan CS: Rapid measurements of curcumin from complex samples coupled with magnetic biocompatibility molecularly imprinted polymer using electrochemical detection. Journal of Separation Science 2020; 43(6): 1173-82.

How to cite this article:
Manju R and Kannan K: Review on deriving a hypothesis for achieving superior bioavailability of curcumin as an antitumor agent. Int J Pharm Sci & Res 2021; 12(3): 1381-89. doi: 10.13040/IJPSR.0975-8232.12(3).1381-89.