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Anti-inflammatory Nutraceuticals and Chronic Diseases

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Chapter 1
Curcumin and Its Role in Chronic Diseases

A. Kunwar and K.I. Priyadarsini

Abstract Curcumin, a yellow pigment from the spice turmeric, is used in Indian and Chinese medicine since ancient times for wide range of diseases. Extensive scientific research on this molecule performed over the last 3 to 4 decades has proved its potential as an important pharmacological agent. The antioxidant, anti-inflammatory, antimicrobial and chemopreventive activities of curcumin have been extended to explore this molecule against many chronic diseases with promising results. Further, its multitargeting ability and nontoxic nature to humans even up to 12 g/day have attracted scientists to explore this as an anticancer agent in the clinic, which is in different phases of trials. With much more scope to be investigated and understood, curcumin becomes one of the very few inexpensive botanical molecules with potent therapeutic abilities.

Keywords Curcumin · Antioxidant · Anti-inflammatory · Anticancer · Turmeric · Polyphenol

1.1 Introduction

Curcumin, a natural polyphenol, is one of the most investigated biomolecules from Mother Nature. Its natural source, *Curcuma longa* or turmeric is used in Indian Ayurvedic and Siddha medicines and also in Chinese medicines since thousands of years [3, 6, 22, 107]. Turmeric is a perennial plant of the ginger family, cultivated in tropical and subtropical regions of South Asia, and India is one of the largest producers of turmeric [35]. In Ayurveda, turmeric is used to treat ailments like arthritis, sprains, open wounds, acnes, stomach upset, flatulence, dysentery, ulcers,

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jaundice, skin and eye infections. As a dietary agent, turmeric is regularly used as a spice and also as a coloring agent in Indian cuisine. Both turmeric and its active principle, curcumin, are permitted like other natural pigments and the food additive, E number for curcumin is E100. Depending on the origin and soil conditions, the percentage of curcuminoids in turmeric varies from 2 to 9 % of its dry weight. The word "curcuminoid" refers to a mixture of four polyphenols, such as curcumin, demethoxycurcumin and bis-demethoxy curcumin and cyclic curcumin. Out of these, curcumin is nearly 70 % of the total curcuminoids. In addition to these curcuminoids, turmeric also contains essential oils primarily composed of mono and sesquiterpenes, like turmerones, turmerol, etc. The strong yellow color of turmeric is mainly due to curcuminoids.

Historically, the first scientific report on isolation and chemical characteristics of curcumin was made in 1815 [115], and its molecular formula and chemical structure was published in 1910 [74]. Its first laboratory synthesis was demonstrated in 1913 [68], subsequently in 1964 a method for producing curcumin in high yields was published [80], and much later, its biosynthesis was understood [35]. Curcumin is extracted commercially from turmeric by solvent extraction with ethanol followed by column chromatography. Using high-performance liquid chromatography coupled with absorption, fluorescence and mass detectors, curcumin can be detected in nanomolar quantities in food samples and biological tissues [35, 90].

Apart from the ancient medicinal documents, early research report on therapeutic use of curcumin appears to date back to 1748; however, the first scientific document for treating human disease was reported in 1937 [79], wherein at least 67 patients were treated for chronic cholecystitis, using curcunat, which is equivalent of curcumin. In this study, oral administration for 3 weeks showed symptomatic improvement in all cases and radiologic improvement by cholecystogram in 18 patients. Interestingly, no ill effects were observed even when the treatment continued for several months. The efficacy of curcumin was attributed to its ability to cause the emptying of the gallbladder. Later in 1949, the antibacterial activity of curcumin [96] was established, since then and till 1970s there were very few reports on its biological activities [98, 106]. Initial research investigations were focused mostly on antioxidant and antibacterial activity and the first anticancer report in human participants was undertaken by Kuttan et al. [67]. However, after the report by Singh and Aggarwal [108], confirming the anti-inflammatory activity of curcumin by suppressing NF-κB activity, the pace of curcumin research has progressed systematically. With several encouraging results in rodent models, curcumin attracted researchers all over the world, to be developed as a potent anticancer drug. As per Pubmed website, (as of October 2015) there are 8247 articles reported with the word "curcumin" in the title, including 808 reviews and 141 clinical trials, out of these more than half have appeared in the last 5 years. It is well accepted by the scientific community that no other botanical molecule is as efficient and as scientifically celebrated as curcumin.

1.2 Physical, Chemical and Metabolic Reactions Influencing Curcumin Pharmacology

1.2.1 Physicochemical Properties

Curcumin is a diarylheptanoid, having three important functional moieties. It has two *o*-methoxyphenolic groups linked through a heptanoid linker consisting of an enone moiety and 1,3-diketone group in conjugation (Fig. 1.1). All these groups are involved in the biological activity of curcumin [35, 42, 88, 89]. Important physicochemical properties of curcumin are listed in Table 1.1. Like other β-diketones, curcumin exhibits keto-enol tautomerism, and in solution phase it mostly exists in the enol form [88]. Curcumin has three acidic protons two from the phenolic-OH groups (in the range 8.5–10.7) and one from the enolic OH (<8.5). Curcumin is yellow at neutral and acidic pH with absorption maximum ~420–430 nm and in alkaline solutions, it becomes red in color and the absorption maximum is shifted to 465 nm. It is practically insoluble in neutral and acidic

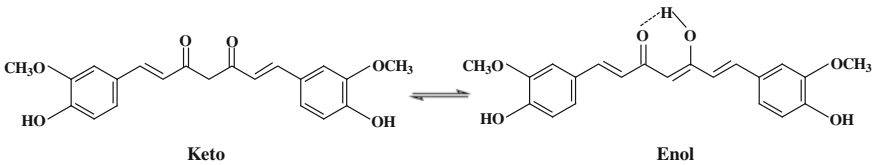

Fig. 1.1 Chemical structure of curcumin in keto and enol tautomeric forms

Table 1.1 Physico-chemical properties of curcumin

IUPAC name	(1E,6E)-1,7-bis (4-hydroxy-3-methoxy phenyl)-1,6-heptadiene 3,5-dione
Molecular formula	$C_{21}H_{20}O_6$
Molecular weight	368.39
Melting point	170–175 °C
Experimental dipole moment in dioxane	3.32 D
Absorption maximum and extinction coefficient fluorescence maximum in methanol	425 nm, 55,000 dm^3 mol^{-1} cm^{-1} 530 nm
Solubility	Insoluble in water Soluble in ethanol, methanol, chloroform, hexane, DMSO
Prototropic equilibrium constant (pKa) (three pKas)	pKa (1), Enolic proton: 7.7–8.5; pKa (2), Phenolic proton: 8.5–10.4; pKa (3), Phenolic proton: 9.5–10.7
log *P* value	~3.0
Color and odor	Yellow at neutral pH, red in alkaline pH; odorless

water, but is readily soluble in moderately polar solvents like methanol, acetonitrile, chloroform, dimethylsulfoxide (DMSO), etc. In aqueous solutions its solubility can be increased by the addition of surfactants, polymers, lipids and proteins. Because of the presence of serum albumin, clear curcumin solutions in micromolar concentration can be prepared in cell culture medium.

1.2.2 Chemical Structural Features Influencing the Biological Activity of Curcumin

Curcumin has three important functional groups, two *o*-methoxy phenolic groups, one enone moiety and an α,β-unsaturated diketone group. Each functional group has some specific role in crucial biological activity in curcumin. The *o*-methoxy phenolic-OH group of curcumin is primarily involved in direct scavenging of reactive oxygen species (ROS), where it donates an electron or hydrogen atom to the oxidizing radicals and the resultant curcumin phenoxyl radical acquires stability through the conjugation and resonating structures [87]. This phenoxyl radical is regenerated back to curcumin by water-soluble antioxidants like ascorbic acid making it an excellent chain-breaking antioxidant that has been reported to be at least ten times better than vitamin E. Curcumin binds to many biomolecules like proteins, lipids and DNA [42, 88]. The proteins that interact with curcumin include transcription factors, inflammatory molecules, kinases, tubulins, amyloid-β aggregates, adhesion molecules, growth factors, receptor proteins, protofilaments, prion proteins, etc. The experimentally reported dipole moment [84] and log *P* values (partition coefficient in octanol and water system) of curcumin (Table 1.1) indicate that the molecule has partial charge transfer character and is moderately polar to be soluble in lipid-like systems. Because of these properties and flexibility in its structure, curcumin binds to most of the biomolecules. The hydrophobic interactions and hydrogen-bonding interactions are mainly responsible for the efficient binding. It is still premature to clarify the role of any single moiety for these interactions but it appears that the orientation of the enolic group plays a crucial role.

The α,β-unsaturated β-diketo moiety of curcumin participates in nucleophilic addition reactions with molecules having functional groups like –SH, –SeH. This 1,4-addition reaction known as Michael addition reaction is of great significance in curcumin biology, like it reacts with glutathione (GSH) and depletes the GSH in cells [13]. Similarly through the reaction with the –SeH group, it inhibits thioredoxin reductase, an enzyme involved in cellular redox homeostasis [36].

Curcumin undergoes a fast chemical degradation in solution, where products like ferulic aldehyde, ferulic acid, vanillin, etc. are formed [102, 116]. The degradation occurs through the β-diketo moiety of curcumin and is increased in presence of light and decreased when solubilised in aqueous solutions along with lipids, proteins, surfactants, cyclodextrins, starch etc.

Metabolism of curcumin in mice produced varieties of products. Important products identified are curcumin glucuronide and curcumin sulfate along with reduction products like tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin [11, 37, 56]. The orally administered curcumin undergoes conjugation whereas the systemically and/or intraperionial (i.p.) administered curcumin undergoes reduction. These processes occur by phase I and phase II enzymes like for example, phenol sulfur transferase enzyme is involved in sulfonation and alcohol dehydrogenase in reduction. Other minor products identified during curcumin metabolism are ferulic acid, dihydroferulic acid, etc. It is still not confirmed how enzymatic metabolism of curcumin competes with its chemical degradation, and there is a need to investigate the role of these metabolic and degradation products in the overall bioactivity of curcumin.

1.2.3 Curcumin–Metal Interactions: Role in Curcumin Biology

Curcumin binds to many metals and metalloproteins, and the binding is through covalent interactions, as the diketo group is an excellent metal chelator [89, 90, 117]. Binding of curcumin to metals ions has several biological consequences. Its binding to Al^{3+} ions is proposed to be one of the key factors involved in its role in preventing the pathogenesis of Alzheimer's disease (AD) [58]. Zn^{2+}-curcumin complex showed anticancer activity and Au^{3+} complexes exhibit anti-arthritic activity [99]. Curcumin–metal chelation can be used to reduce toxicity of heavy metals like Hg^{2+}, Cd^{2+}, Pb^{2+} [1, 81]. Several mixed ligand complexes of curcumin with metals like Cu^{2+}, Ni^{2+}, Mn^{3+}, Pd^{2+} are also finding applications as antioxidants, superoxide dismutase mimics and anticancer agents [15, 114]. Recently curcumin derived radiopharmaceuticals are being prepared and explored as new diagnostic and therapeutic agents. For example, $^{99m}Tc^{4+}$ and $^{68}Ga^{3+}$ complexes of curcumin reported to bind to amyloid-β (Aβ) fibrils and plaques, are being explored as novel radiodiagnostic agents for AD [12, 95].

1.2.4 Curcumin Bioavailability

The major issue concerning the development of curcumin based drugs is its extremely low bioavailability [9, 86]. Due to relatively low intestinal absorption and rapid metabolism in the liver, the oral bioavailability of curcumin is very low, while most of it is excreted through the feces within 3–6 h after administration. Even after oral administration in grams, no significant curcumin was detected in the plasma, and the highest curcumin levels were found in the intestines and detectable amounts were observed in the serum, but they fall below detection limit in other tissues. However, i.p. and intravenous (i.v.) administration has shown better

Table 1.2 Examples of important formulations used to enhance in vivo bioavailability of curcumin

Formulation	Piperine (20 mg/kg) + curcumin 2 g/kg)	Curcumin–phospholipid complex (100 mg/kg)	Cyclodextrin–curcumin	Pegylated-curcumin (2.5 mg/kg)	Curcumin–phosphatidylcholine (Mervia)
Increase in bioavailability	1.5-fold in serum	2.2-fold in plasma	1.8-fold in skin	2-fold in serum	5-fold increase in plasma

bioavailability than oral administration. The maximum tissue concentrations recorded after an i.p. injection of 100 mg/kg of curcumin was 73 ± 20, 200 ± 23, 9.1 ± 1.1, 16 ± 3, 8.4 ± 6.0, 78 ± 3 and 2.9 ± 0.4 nmol/g in liver, intestine mucosa, heart, lungs, muscle, kidneys, and brain respectively [85]. At 10 mg/kg i.v., maximum serum levels were 0.36 μg/ml, while in another study 2 mg/kg through tail vain showed plasma concentration of 6.6 μg/ml [9, 86]. Increasing the dose of curcumin did not result in higher bioabsorption. Being a lipophilic molecule, curcumin is expected to cross blood–brain barrier and reach brain tissue. However, dietary supplementation did not show significant accumulation in the brain tissue, but long-term supplementation of mice for nearly 4 months at a dose of 0.5–2 g/kg showed a maximum detectable concentration of 1.5 nmol/g in the brain tissue [9, 86].

The poor bioavailability of curcumin has thus emerged as one of the major limitations for its therapeutic applications. To increase the bioavailability of curcumin, researchers have developed several novel formulations. Important among these are liposomes, nanoemulsions, pegylation, polymers, hydrogels, cyclodextrins, piperine-combined, gold and mesoporous silica nanoconjugates and curcumin–iron oxide magnetic nanoparticles [9, 65, 71, 86, 89, 90, 105, 120]. Employing them a significant improvement, not only in the bioavailability of curcumin but also in its in vivo bioactivity was reported. Most of these formulations could be dispersed in aqueous buffer medium. There are several reports describing the preparation and characterization of these nano formulations. Important formulations that showed significant improvement in curcumin bioavailability are given in Table 1.2.

1.3 Modulation of Cell Signaling Pathways by Curcumin

All the biological activities/functions of a living cell are regulated by a dense network of signal transduction pathways. The components of signal transduction pathways are growth factors and their receptors, cytokines and their receptors, protein kinases, transcription factors and gene expression. Curcumin has been shown to affect many cellular or molecular pathways in executing its crucial biological activities. Figure 1.2 gives important signaling molecules involved in biological activities of curcumin. Some important results are discussed below.