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CURCUMIN: CHEMISTRY, PHARMACOLOGY, BIOAVAILABILITY AND CLINICAL PROSPECTS

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Abstract:

Curcumin is the principal yellow polyphenolic pigment of turmeric, the rhizome of Curcuma longa L. (family Zingiberaceae), and has been used for centuries in South Asian cooking and traditional medicine. In the laboratory it modulates an unusually wide range of molecular targets, including transcription factors, inflammatory enzymes, cytokines, growth-factor receptors and redox-sensitive pathways, and it has therefore been proposed for inflammatory, metabolic, neurodegenerative and malignant diseases. Its translation into medicine, however, has been limited by very low aqueous solubility, chemical instability at physiological pH, rapid metabolism and poor systemic bioavailability. This review summarises the chemistry and physicochemical properties of curcumin and the related curcuminoids, its proposed mechanisms of action, its absorption, distribution, metabolism and excretion, and the formulation strategies developed to overcome its pharmacokinetic limitations, including piperine co-administration, nanoparticles, phospholipid complexes, solid lipid particles and micellar systems. Clinical evidence in osteoarthritis, prediabetes, cancer, neurodegeneration and depression is summarised in tables, together with safety data. Finally, the review discusses scientific criticisms that curcumin behaves as a pan-assay interference compound, which complicates interpretation of in vitro findings. Curcumin is generally well tolerated, and improved formulations produce meaningfully higher plasma exposure, but robust evidence of clinical efficacy remains limited to a few conditions and requires larger, well-controlled trials with standardised, bioavailable preparations.

Keywords: *Curcumin; curcuminoids; turmeric; Curcuma longa; bioavailability; NF-kappa B; nanoformulations; piperine; clinical trials*

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INTRODUCTION:

Turmeric has been part of Ayurvedic, Unani and traditional Chinese medicine for several thousand years, where it has been applied to wounds, digestive complaints, inflammatory conditions and skin disease, and it remains a staple spice and food colourant throughout Asia [1]. The biological activity of turmeric is attributed mainly to a group of diarylheptanoid pigments called curcuminoids, of which curcumin (diferuloylmethane) is the most abundant and the most studied [1, 2]. Interest in curcumin has grown rapidly because it appears to act on many targets at once, and because it is inexpensive, derived from a food, and has a long history of human consumption [3].

The reported pharmacological properties of curcumin include anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, neuroprotective, anti-diabetic and anticancer effects, based on thousands of cell-culture and animal studies [2, 3]. Despite this, curcumin has not yet become an approved drug for any indication. The main reasons are pharmaceutical rather than purely pharmacological: curcumin is almost insoluble in water at acidic and neutral pH, degrades quickly in neutral and alkaline solution, is extensively conjugated in the intestine and liver, and reaches only trace concentrations in blood after oral dosing in humans. A second difficulty is that its chemical reactivity can produce false-positive results in screening assays.

This article reviews the chemistry, mechanisms; pharmacokinetics, formulation approaches, clinical evidence and safety of curcumin, and discusses current challenges and future directions.

Source, Chemistry and Physicochemical Properties

Source and composition

Curcumin is obtained from the dried rhizomes of *Curcuma longa*, which typically contain about 2 to 5% curcuminoids by weight together with volatile oils, resins and carbohydrates [4]. Commercial curcumin extracts are mixtures of three principal curcuminoids: curcumin (about 75 to 80%), demethoxycurcumin (about 15 to 20%) and bisdemethoxycurcumin (about 3 to 5%), and so many products labelled as curcumin are actually curcuminoid mixtures [4]. Extraction is usually carried out with organic solvents such as ethanol, acetone or ethyl acetate, followed by crystallisation or chromatographic purification, and newer methods include supercritical carbon dioxide, ultrasound-assisted and microwave-assisted extraction [4]. Principal curcuminoids of turmeric included in the table 1.

Table 1. Principal curcuminoids of turmeric

Compound	Molecular formula	Molecular weight (g/mol)	Methoxy groups on the aromatic rings	Approximate share in extracts
Curcumin (diferuloylmethane)	$C_{21}H_{20}O_6$	368.38	Two	75-80%
Demethoxycurcumin	$C_{20}H_{18}O_5$	338.35	One	15-20%
Bisdemethoxycurcumin	$C_{19}H_{16}O_4$	308.33	None	3-5%

Chemical structure

Curcumin is chemically (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione. Its structure comprises three parts: two ortho-methoxyphenol (guaiacyl) rings, two alpha,beta-unsaturated carbonyl (enone) linkers, and a central seven-carbon chain bearing a beta-diketone unit and shown in figure 1.

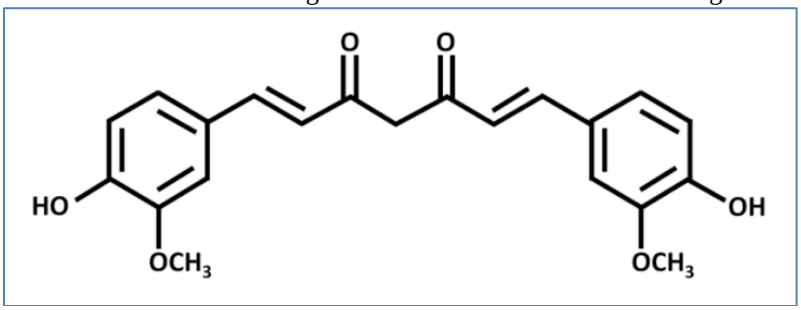


Figure 01: Chemical structure of curcumin

A simplified linear representation is:
Ar-CH=CH-C(=O)-CH2-C(=O)-CH=CH-Ar,
where Ar is 4-hydroxy-3-methoxyphenyl.

The beta-diketone moiety exists in equilibrium between a diketo form and a cis-enol form. The enol tautomer, stabilised by an intramolecular hydrogen bond and extended conjugation, predominates in the solid state and in most solvents, whereas the diketo form becomes more important in acidic aqueous solution [4]. Three

acidic protons (one enolic and two phenolic) give rise to several ionisation states with pKa values in the range of about 7.5 to 9, which explains the pH-dependent colour, solubility and stability of the compound [4]. The phenolic hydroxyl groups and the enolised beta-diketone are responsible for the radical-scavenging and metal-chelating activity, while the enone groups are electrophilic Michael acceptors that can react with nucleophilic thiols in proteins [5]. This reactivity partly explains the diversity of its biological effects, but also its promiscuity in biochemical assays.

Physicochemical properties and stability

Curcumin is a hydrophobic, orange-yellow crystalline powder. It dissolves readily in dimethyl sulfoxide, ethanol, methanol and acetone but is practically insoluble in water at acidic and neutral pH [4]. It is unstable at neutral to alkaline pH, where it undergoes hydrolytic degradation to ferulic acid, feruloylmethane and vanillin, and a large fraction decomposes within about 30 minutes in buffer at pH 7 to 8 [6]. It is also sensitive to light, which causes photodegradation, and it is more stable in acidic media and in the presence of serum proteins or other solubilising agents [6]. Physicochemical properties of curcumin included in the below table 2.

Table 2. Selected physicochemical properties of curcumin [4, 6]

Property	Description
Appearance	Orange-yellow crystalline powder
Melting point	About 183 ^{0}C
Lipophilicity	Lipophilic;
log P	Around 3
pKa	7.5-9
Solubility	Practically insoluble in water at pH below 7; soluble in DMSO, ethanol, acetone
Absorption maximum	About 420-430 nm in organic solvents (yellow); red at alkaline pH
Acid-base behaviour	Three ionisable protons (enolic and two phenolic);
Stability	Degrades at pH 7 or higher and on light exposure; stable in acid
Reactive groups	Phenolic OH, beta-diketone, two Michael-acceptor enones

3. Mechanisms of Action

Curcumin is described as a multi-target agent that modulates numerous signalling molecules rather than binding a single receptor with high affinity [7]. The principal pathways reported are summarised in Table 3.

Anti-inflammatory activity: The best-characterised mechanism is inhibition of nuclear factor kappa B (NF-kB). Curcumin was shown to suppress tumour necrosis factor-induced NF-kB activation in human cells by blocking the degradation of its inhibitor IkB-alpha, thereby preventing nuclear translocation of the transcription factor [8]. Because NF-kB controls expression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase, tumour necrosis factor, interleukins 1 and 6 and adhesion molecules, its inhibition reduces production of many pro-inflammatory mediators [7, 9]. Curcumin has also been reported to inhibit COX-2 and 5-lipoxygenase activity directly.

Antioxidant activity: Curcumin scavenges reactive oxygen and nitrogen species through as inhibition of histone-modifying enzymes [7, 11]. hydrogen donation from its phenolic and enolic groups, chelates redox-active metals and reduces lipid peroxidation [10]. In addition to direct scavenging, it can activate the Nrf2 pathway, which induces antioxidant enzymes such as heme oxygenase-1, and this indirect effect is likely to be more relevant at the low concentrations reached in tissues [10, 11].

Anticancer activity: In cell models, curcumin arrest the cell cycle, induce apoptosis through modulation of Bcl-2 family proteins and caspases, and inhibits proliferative and survival signalling including STAT3, PI3K/Akt and growth-factor receptor pathways. It has also been reported to reduce angiogenesis and metastasis-related factors such as vascular endothelial growth factor and matrix metalloproteinases [7, 11].

Other effects: Reported activities include inhibition of amyloid-beta aggregation, modulation of lipid and glucose metabolism, antimicrobial activity and epigenetic effects such

Table 3. Principal molecular targets and reported consequences [7, 9-11].

Target or pathway	Reported effect of curcumin	Biological consequence
NF-kB	Inhibits activation and nuclear translocation	Reduced COX-2, TNF, IL-1, IL-6 and adhesion molecule expression
COX-2 and 5-LOX	Reduced expression and activity	Lower prostaglandin and leukotriene synthesis
Nrf2 / ARE	Activates	Increased heme oxygenase-1 and antioxidant enzymes
Free radicals	Direct scavenging; metal	Reduced oxidative damage and lipid peroxidation

Target or pathway	Reported effect of curcumin	Biological consequence
	chelation	
STAT3, PI3K/Akt	Reduced signalling	Decreased proliferation and survival of tumour cells
Bcl-2 family, caspases, p53	Modulates expression	Induction of apoptosis in cancer cells
VEGF, MMPs	Downregulated	Reduced angiogenesis and invasion
Amyloid-beta	Interferes with aggregation	Potential neuroprotection

Pharmacokinetics and Bioavailability

The pharmacokinetic profile of curcumin is the major obstacle to its clinical use [12, 13].

Absorption: After oral administration, curcumin is poorly absorbed because of its low solubility and instability in the intestinal lumen. In a classical rat study, most of an oral dose was recovered in the faeces, with negligible amounts in urine and only traces in blood [12]. Poor absorption, rapid metabolism and rapid elimination together produce very low systemic bioavailability [13].

Metabolism: Curcumin undergoes extensive first-pass conjugation in enterocytes and the liver. The major metabolites are curcumin glucuronide and curcumin sulphate, and a reductive pathway generates dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin [14]. Conjugates and reduced metabolites often have lower biological activity than the parent compound, although tetrahydrocurcumin retains antioxidant activity.

Distribution and elimination: Absorbed curcumin circulates bound to albumin and has a short half-life, and elimination occurs mainly through biliary excretion and faeces [12,13].

Human data: In a phase I study in patients with high-risk or pre-malignant lesions, daily doses from 500 mg to 8 g for three months were tolerated, but serum curcumin was undetectable at the lower doses and reached only submicromolar to low micromolar concentrations at the highest doses [15]. A separate dose-escalation study found that doses of 3.6 g per day produced only nanomolar plasma concentrations of the parent compound, with most of the compound detected as conjugates or in faeces [16]. A further study reported tolerance of up to 12 g per day of a curcuminoid preparation, although bulky dosing was limited by the volume of powder [17]. Collectively, these findings show that high oral doses of unformulated curcumin result in plasma exposure far below the concentrations commonly used in cell-culture experiments.

Strategies to Improve Bioavailability

Several approaches have been developed to improve the solubility, stability and absorption of curcumin (Table 4).

Adjuvants: Piperine, the alkaloid of black pepper, inhibits hepatic and intestinal glucuronidation and may inhibit efflux transporters. In human volunteers, co-administration of 20 mg piperine with 2 g curcumin was reported to increase relative bioavailability by about twenty-fold, while in rats the increase was about 154% [18].

Nanoformulations: Encapsulation of curcumin in polymeric nanoparticles, liposomes, nanoemulsions, micelles and cyclodextrin or albumin complexes increases apparent solubility, protects the compound from degradation and prolongs circulation [19]. Polymeric nanoparticles based on poly (lactic-co-glycolic acid) and polyethylene glycol, known as nanocurcumin, showed in vitro activity comparable to free curcumin in pancreatic cancer cells and increased cellular uptake [20].

Dispersed and surface-controlled particles: Theracurmin, a colloidal dispersion of submicron particles made with gum ghatti, increased plasma concentration of curcumin in rats and in human volunteers compared with ordinary curcumin powder [21].

Phospholipid complexes: Complexation of curcuminoids with soy phosphatidylcholine (a phytosome, marketed as Meriva) produced substantially higher absorption of total curcuminoids in healthy volunteers than a standard curcuminoid mixture [22].

Solid lipid particles: A solid lipid curcumin particle formulation was safe and gave higher plasma levels than unformulated curcumin in healthy subjects and in patients with osteosarcoma [23].

Comparative studies: A head-to-head study in healthy adults compared several commercial formulations and found that all of them provided greater absorption of curcuminoids than standard curcumin extract, though they differed substantially from each other [24].

Table 4. Formulation strategies for curcumin

Strategy	Principle	Reported outcome	Reference
Piperine co-administration	Inhibits glucuronidation of curcumin	Markedly higher bioavailability in humans	[18]
Polymeric nanoparticles (PLGA-PEG)	Encapsulation; improved dispersion and uptake	Improved cellular uptake and activity in cancer cells	[19,20]

Strategy	Principle	Reported outcome	Reference
Colloidal submicron dispersion (Theracurmin)	Smaller particle size; improved dispersibility	Higher plasma levels than powder	[21]
Phospholipid complex (Meriva)	Amphiphilic complex improves membrane passage	Greater absorption of total curcuminoids	[22]
Solid lipid curcumin particle	Lipid matrix with enhanced dissolution	Higher plasma levels in volunteers and patients	[23]
Commercial formulation comparison	Various technologies	All tested formulations absorbed better than standard extract	[24]

An important caveat is that higher plasma levels of total curcuminoids measured after enzymatic hydrolysis mostly represent conjugated metabolites, and so improved exposure has not necessarily translated into proportional gains in clinical efficacy.

Therapeutic Applications and Clinical Evidence

A large number of clinical trials of curcumin and turmeric extracts have been reported, covering inflammatory, metabolic, neurological, psychiatric and malignant disorders [25]. Key studies are listed in Table 5.

Osteoarthritis: The most consistent evidence concerns joint pain. A meta-analysis of randomised trials in arthritis concluded that turmeric extracts and curcumin at 1000 mg per day or less, taken for 8 to 12 weeks, reduced pain and improved function, with effects comparable to those of anti-inflammatory drugs in some trials, although the quality of the studies and the heterogeneity of the preparations limit confidence [26]. In a multicentre trial in knee osteoarthritis, a Curcuma extract was found to be comparable to ibuprofen in improving pain and function with fewer gastrointestinal adverse events [27].

Prediabetes and metabolic disease: In a nine-month randomised trial of adults with prediabetes, none of the participants taking curcumin progressed to type 2 diabetes, compared with a minority of those on placebo, and the curcumin group showed improved beta-cell function [28].

Cancer: Clinical results in oncology have been modest. A phase II study of curcumin in advanced pancreatic cancer reported poor systemic bioavailability and limited anti-tumour activity, with only a small number of patients showing clinical benefit [29]. Curcumin is therefore currently investigated mainly as an adjunct to chemotherapy and in chemoprevention, rather than as a stand-alone therapy.

Neurodegeneration: Small randomised trials in Alzheimer disease found no significant difference from placebo in cognitive outcomes over 6 to 24 weeks, which was attributed in part to poor brain exposure to unformulated curcumin [30,31].

Depression; A randomised trial in major depressive disorder reported that curcumin improved depressive symptoms to a degree comparable to fluoxetine over six weeks, although the trial was small and short [32].

Table 5. Selected clinical studies of curcumin and curcuminoid preparations

Condition	Design and duration	Main finding	Reference
Mixed pre-malignant lesions	Phase I dose escalation (0.5-8 g/day, 3 months)	Well tolerated; very low serum curcumin	[15]
Arthritis	Meta-analysis of randomised trials	Reduced pain and improved function; evidence of limited quality	[26]
Knee osteoarthritis	Randomised, active-controlled, multicentre	Efficacy similar to ibuprofen; fewer GI adverse events	[27]
Prediabetes	Randomised, placebo-controlled, 9 months	Lower progression to type 2 diabetes	[28]
Advanced pancreatic cancer	Phase II, 8 g/day	Poor bioavailability; limited activity	[29]
Alzheimer disease	Randomised, placebo-controlled pilot trials (6 to 24 weeks)	No significant cognitive benefit	[30,31]
Major depression	Randomised, controlled, 6 weeks	Improvement comparable to fluoxetine in a small trial	[32]

Safety and Toxicity

Curcumin has a good overall safety record in humans. The European Food Safety Authority evaluated curcumin as a food additive (E100) and set an acceptable daily intake of 3 mg per kg body weight per day [33]. Clinical trials using doses of several grams per day for months have reported mainly mild adverse effects, most commonly nausea, diarrhoea, abdominal discomfort and headache [15,17,34].

Areas of concern include the following. First, rare cases of liver injury, including autoimmune-type hepatitis, have been reported in people taking turmeric or curcumin supplements, and these preparations frequently contain piperine or other bioavailability enhancers that increase exposure [35]. Second, curcumin has iron-chelating properties and may contribute to iron deficiency in susceptible individuals. Third, because piperine and curcumin may inhibit drug-metabolising enzymes and transporters, interactions with anticoagulants, antiplatelet agents, antidiabetic drugs and chemotherapeutic agents are theoretically possible, and caution is advised in patients on such treatments. Finally, curcumin should be used with care in people with gallstones or biliary obstruction because it stimulates bile secretion.

Limitations and Challenges

Pharmacokinetic limitations: As discussed above, extensive metabolism and low solubility prevent systemic concentrations in the range used in vitro, and so many mechanistic observations from cell culture may not be reproduced in the body [13].

Chemical instability and assay interference: Medicinal chemistry analyses have classified curcumin as both a pan-assay interference compound (PAINS) and an invalid metabolic panacea (IMP) candidate. The reasons are its chemical instability, its reactivity as a Michael acceptor toward thiols, its tendency to form aggregates, its intrinsic colour and fluorescence, its metal-chelating behaviour and its binding to many unrelated proteins [5]. These properties can generate apparent activity in screening assays that does not reflect specific target engagement [5, 36]. The same review concluded that no clinical trial had unequivocally demonstrated efficacy of curcumin for a defined disease [5].

Variability of preparations: Commercial products differ greatly in curcuminoid content, purity and formulation, and in many trials the curcuminoid mixture, rather than pure curcumin, was administered. This makes comparison across studies difficult and complicates meta-analysis.

Study quality: Many clinical trials are small, short, open-label or insufficiently powered, and publication bias favours positive results.

Regulatory status: Curcumin is marketed mostly as a dietary supplement or food additive, which means that products do not undergo the full efficacy and quality evaluation required of drugs.

Future Perspectives

Future work is likely to focus on four areas. First, rational design of delivery systems that increase tissue exposure to unconjugated curcumin, including nanocarriers, targeted systems and local or topical delivery to sites such as the joints, skin, gut and oral mucosa. Second, development of more stable curcumin analogues and derivatives, as well as the study of active metabolites such as tetrahydrocurcumin. Third, better-designed clinical trials with standardised, pharmacokinetically characterised preparations, appropriate biomarkers and adequate power, with attention to well-defined conditions such as osteoarthritis. Fourth, careful validation of molecular targets using orthogonal assays and proper controls for assay interference [5,36].

CONCLUSION:

Curcumin is a well-tolerated natural product with a rich pharmacology, including anti-inflammatory, antioxidant and anticancer effects demonstrated in laboratory systems. Its clinical development has been constrained by poor solubility, instability, rapid metabolism and low systemic bioavailability, along with its tendency to interfere with biochemical assays. Formulation technologies, such as piperine co-administration, phospholipid complexes, solid lipid particles and nanocarriers, have increased plasma exposure considerably, and the best clinical support so far is for symptom relief in osteoarthritis and for some metabolic outcomes. Evidence in cancer and neurodegeneration remains inconclusive. Progress will depend on high-quality trials of well-characterised, bioavailable formulations and on critical, assay-aware mechanistic research. Until then, curcumin is best regarded as a promising but incompletely validated therapeutic candidate rather than an established drug.

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