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journal homepage: www.elsevier.com/locate/hermed**Review****Curcumin, a golden spice with a low bioavailability**

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ABSTRACT

In recent years several drugs have been developed deriving from traditional products and current drug research is actively investigating the possible therapeutic roles of many Ayurvedic and Traditional Chinese Medicinal remedies. Prominent among those being examined is turmeric. Its main active ingredient is curcumin (C). Curcumin acts as an antioxidant, anti-inflammatory, anticarcinoma, antimicrobial, antiviral, hypoglycemic and wound healer. It has shown therapeutic efficacy in numerous chronic diseases and in some kinds of cancer *in vitro* and *in vivo*. Despite much evidence of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent due to its low bioavailability, instability at physiological pH, insolubility in water, slow uptake by cells and rapid metabolism inside cells. The aim of this review is to summarize the pharmacodynamic and pharmacokinetic characteristics of curcumin and to compare the different pharmaceutical strategies employed to increase its bioavailability.

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1. Introduction

Turmeric (*Curcuma longa L.*) and several other species of curcuma genus grow wild in the forests of Southern Asia, India, Indonesia, Indochina, nearby Asian countries, and some Pacific Islands including Hawaii. In the Indian Ayurvedic system of herbal medicine, turmeric is known to be strengthening and warming to the whole body. Traditional uses in India include improving digestion, improving intestinal flora, eliminating worms, relieving flatulence, cleansing and strengthening the liver and gallbladder, regulating menstruation, relieving arthritis and swelling and purifying the blood (Bhowmik et al., 2009).

In recent years several drugs derived from natural products have been developed and current drug research is actively investigating the possible therapeutic roles of many Ayurvedic and Traditional Chinese Medicinal remedies. Prominent among those being examined is turmeric. Its main active constituent is curcumin (C), but despite much evidence of its efficacy and safety, it has not yet been approved as a therapeutic agent due to its low bioavailability, instability at physiological pH, insolubility in water, slow uptake by cells and rapid metabolism inside the cell.

The aim of this review was to summarize the pharmacodynamic and pharmacokinetic characteristics of curcumin and to compare the different pharmaceutical strategies employed to increase its oral bioavailability (Ammon and Wahl, 1991).

1.1. Methodology

A general literature search was carried out using the following databases, Pubmed, Medline, Embase and Clinicaltrials.gov. (a service of the U.S. National Institutes of Health) using the key words, Ayurveda, Curcuma Longa, turmeric, curcumin, bioavailability, bioenhancer, pharmacokinetic, piperine, phytosome, liposome and nanoparticles.

The criteria then used to find the available literature on curcumin were as follows: – pharmacokinetic data was collected from *in vitro* and *in vivo* studies using the key words (curcumin AND pharmacokinetics) OR (curcumin AND bioavailability). Pharmacodynamic data was limited to articles published after 2007 and only clinical trials that had reached phase II were considered for this review.

2. Curcumin chemistry

Rhizomes of *Curcuma Longa* contain carbohydrates (60–70%), protein (6–8%), essential (3–7%) and fixed oils (5–10%), fiber

(2–7%), minerals (3–7%) and pigments known as curcuminoids (2–6%). Phytosterols, tocopherols, and fatty acids have also been identified (Ravindran et al., 2007).

Two active components of turmeric are the volatile oil and the curcuminoids (pigments) and both are present in oleoresin extracted from the turmeric root. The essential oil is composed mainly of sesquiterpenes, many of which are specific for the *Curcuma* genus. The aroma of this spice is principally derived from α- and β-turmerones and ar-turmerone (Ravindran et al., 2007).

The curcuminoids give a yellow-orange coloration to turmeric powder due to the wide electronic delocalization inside the molecules that exhibit strong absorption between 420 and 430 nm in an organic solvent (Fig. 1).

The extraction process of curcuminoids is consecutive extraction with two different solvents. The first solvent used is hexane, in order to eliminate the oily components from the dried rhizome of turmeric. The second is a more polar solvent to recover the pigment from the residue of the first extraction (Ravindran et al., 2007).

The solvent is only partially removed; the concentrate is cooled and allowed to stand until the curcuminoids crystallize.

Curcuminoids can also be extracted from powdered rhizomes using alkaline water (pH about 9) (Ran and Zhou, 1988) and recovered by precipitation at pH 3–4.

The curcuminoids are a mixture of curcumin, chemically a diferuloylmethane [1,7-bis (4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione] mixed with its two derivates, demethoxy-curcumin (DMC) [4-hydroxycinnamoyl-(4-hydroxy-3-methoxycinnamoyl) methane], and bis-demethoxy-curcumin (BDMC) [bis-(4-hydroxy cinnamoyl) methane] (Subash et al., 2011) (Fig. 2).

They share the same structure with two benzene methoxy rings, joined by an unsaturated chain. It has three important functions: an aromatic methoxy phenolic group; α,β-unsaturated β-diketo linker; and keto-enol tautomerism. All these compounds exist in the trans-trans keto-enol form. The aromatic groups provide hydrophobicity, and the linker gives flexibility. The tautomeric structures also influence the hydrophobicity and polarity. The hydrophobicity of curcuminoids makes them poorly soluble in water. Three acidity constants (pKA) were measured for curcumin as follows, pKA₁=8.38±0.04, pKA₂=9.88±0.02 and pKA₃=10.51±0.01 (Bernabé-Pineda et al., 2004).

The relative proportion of the three curcuminoids in turmeric dye varies with the cultivar. Typical curcuminoid composition of popular Indian varieties was found to be in the range of curcumin 52–63%; DMC 19–27% and BDMC 18–28%

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