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Bioavailability of Curcumin: Problems and Promises

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Abstract: Curcumin, a polyphenolic compound derived from dietary spice turmeric, possesses diverse pharmacologic effects including anti-inflammatory, antioxidant, antiproliferative and antiangiogenic activities. Phase I clinical trials have shown that curcumin is safe even at high doses (12 g/day) in humans but exhibit poor bioavailability. Major reasons contributing to the low plasma and tissue levels of curcumin appear to be due to poor absorption, rapid metabolism, and rapid systemic elimination. To improve the bioavailability of curcumin, numerous approaches have been undertaken. These approaches involve, first, the use of adjuvant like piperine that interferes with glucuronidation; second, the use of liposomal curcumin; third, curcumin nanoparticles; fourth, the use of curcumin phospholipid complex; and fifth, the use of structural analogues of curcumin (e.g., EF-24). The latter has been reported to have a rapid absorption with a peak plasma half-life. Despite the lower bioavailability, therapeutic efficacy of curcumin against various human diseases, including cancer, cardiovascular diseases, diabetes, arthritis, neurological diseases and Crohn's disease, has been documented. Enhanced bioavailability of curcumin in the near future is likely to bring this promising natural product to the forefront of therapeutic agents for treatment of human disease.

Keywords: Curcumin; bioavailability; absorption; metabolism; formulations; adjuvants; nanoparticles; biocurcumax

A. Introduction

Curcumin, a hydrophobic polyphenol derived from the rhizome of the herb *Curcuma longa* has a wide spectrum of biological and pharmacological activities. Chemically, curcumin is a bis-α,β-unsaturated β-diketone (commonly called diferuloylmethane, Figure 1), which exhibits keto–enol tautomerism having a predominant keto form in acidic and neutral solutions and stable enol form in alkaline medium. Commercial curcumin contains approximately 77% diferuloylmethane, 17% demethoxycurcumin, and 6% bisdemethoxycurcumin. Traditionally, turmeric has been used for many ailments, particularly as an anti-inflammatory agent, and curcumin has been identified as the active principle of turmeric.[1] Curcumin has been shown to exhibit antioxidant, anti-inflammatory,[2–5] antimicrobial, and anticarcinogenic[6–10] activities. Additionally, the hepato- and nephro-protective,[11–13] thrombosis supressing,[14] myocardial infarction protective,[15–17]

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hypoglycemic,[18–21] and antirheumatic[22] effects of curcumin are also well established. Various animal models[23,24] or human studies[25–28] proved that curcumin is extremely safe even at very high doses. For example, three different phase I clinical trials indicated that curcumin, when taken as high as 12 g per day, is well tolerated.[26–28] Similarly, the efficacy of curcumin in various diseases including cancer has been well established.[29] Several clinical studies dealing with the efficacy of curcumin in humans can also be cited.[1,30] The pharmacological safety and efficacy of curcumin makes it a potential compound for treatment and prevention of a wide variety of human diseases. In spite of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent, and the relative bioavailability of curcumin has been highlighted as a major problem for this. The purpose of this review is to discuss in detail the bioavailability, factors controlling bioavailability, and means to improve the bioavailability of curcumin.

B. Problems of Curcumin Bioavailability

The reasons for reduced bioavailability of any agent within the body are low intrinsic activity, poor absorption, high rate of metabolism, inactivity of metabolic products and/or rapid elimination and clearance from the body. Studies to date have suggested a strong intrinsic activity and, hence, efficacy of curcumin as a therapeutic agent for various ailments. However, studies over the past three decades related to absorption, distribution, metabolism and excretion of curcumin have revealed poor absorption and rapid metabolism of curcumin that severely curtails its bioavailability. In this section, problems of curcumin bioavailability such as low serum levels, limited tissue distribution, apparent rapid metabolism and short half-life are described in detail.

B1. Serum Concentration. One of the major observations related to curcumin studies involves the observation of extremely low serum levels. The first reported study to examine the uptake, distribution, and excretion of curcumin was by Wahlstrom and Blennow in 1978 using Sprague–Dawley rats. Negligible amounts of curcumin in blood plasma of rats after oral administration of 1 g/kg of curcumin showed that curcumin was poorly absorbed from the gut.[31] In 1980, Ravindranath et al. showed that after oral administration of 400 mg of curcumin to rats, no curcumin was

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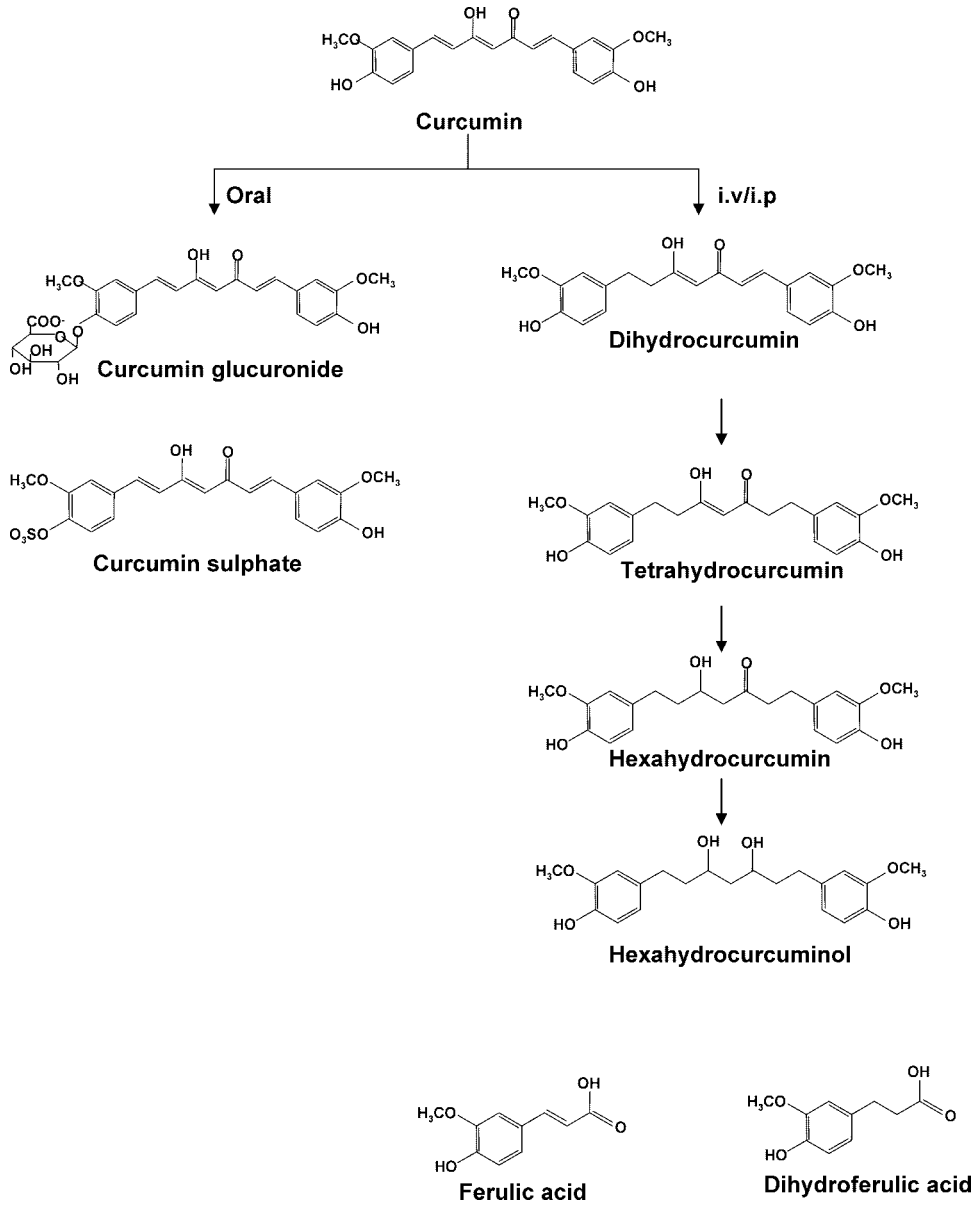

Figure 1. Structure of curcumin and its metabolites.

found in heart blood, whereas a trace amount (less than 5 μg/mL) was found in the portal blood from 15 min to 24 h after administration of curcumin.[32] In another study using tritium-labeled curcumin, the same group showed detectable amounts of curcumin in blood with doses ranging from 10 to 400 mg of curcumin per animal.[33] When curcumin was given orally at a dose of 2 g/kg to rats, a maximum serum concentration of 1.35 $\pm$ 0.23 μg/mL was observed at time 0.83 h, whereas in humans the same dose of curcumin resulted in either undetectable or extremely low (0.006 $\pm$ 0.005 μg/mL at 1 h) serum levels.[28]

Pan et al., for example, investigated the pharmacokinetic properties of curcumin administered either orally or intraperitoneal (i.p.) in mice. With oral administration of 1.0 g/kg of curcumin, low plasma levels of 0.13 μg/mL appeared in plasma after 15 min, while a maximum plasma level of 0.22 μg/mL was obtained at 1 h; plasma concentrations then declined below the detection limit by 6 h. Entirely different plasma curcumin levels were found after i.p. administration of 0.1 g/kg. Plasma curcumin levels peaked (2.25 μg/mL) within 15 min of administration and declined rapidly within 1 h.[34] Perkins and co-workers examined the pharmacokinetics of curcumin in a Min/+ mouse model of FAP using either

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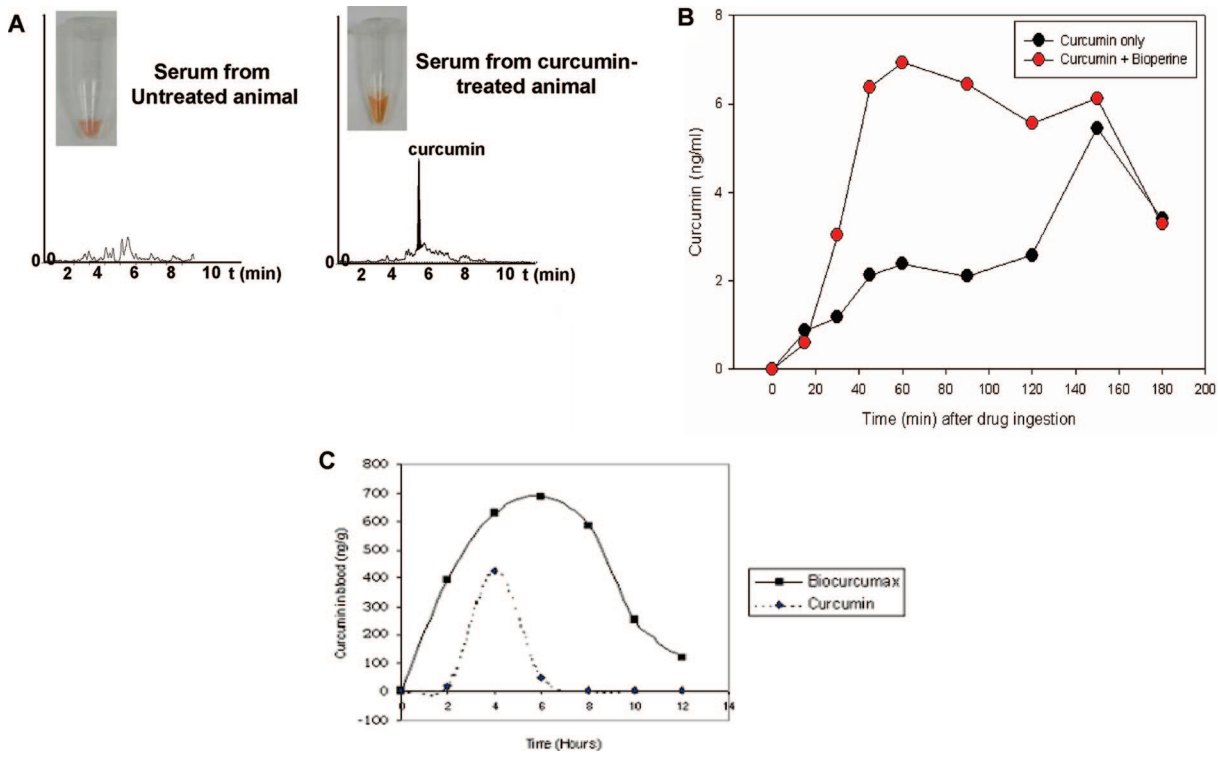

Figure 2. Bioavailability of curcumin in rodents and man. A. Bioavailability of curcumin in mice. Curcumin (1 g/kg) was administered to mice by gavage. The mice were sacrificed 1 h later by euthanasia, the blood was collected by heart puncture, and the serum was separated by centrifugation at 14000 rpm for 2 min. The physical appearance and the HPLC profiles of serum are depicted in the figure. Oral administration of curcumin leads to its appearance in the serum of mice after just 1 h. LC/MS/MS method for the detection and quantification of free curcumin in mouse serum was performed, and the amount of free curcumin detected in the serum from curcumin treated mice fell below the limit of quantification (5 ng/mL). B. Bioavailability of curcumin in human with and without piperine. Six healthy adult male human volunteers took 2 g of curcumin with or without 5 mg of piperine (as bioperine) in a cross-over design study. Three people were randomized to receive curcumin only, while the remaining three received the curcumin + piperine combination. One week following initial drug administration, volunteers were crossed over to the opposite therapies, and blood samples were again obtained for evaluation. Plasma samples were digested with combined glucuronidase + sulfatase to release curcumin from conjugated forms. Curcumin levels (determined by a validated LC/MS/MS assay) are thus reported as "total" curcumin (free drug plus drug released from conjugate forms) per milliliter of plasma. Piperine-enhanced absorption of curcumin produced a near doubling of area under the curve (AUC) (8.44 h·ng/mL for curcumin vs 15.55 h·ng/mL for curcumin + piperine). C. Turmeric oil (turmerne) enhances bioavailability of curcumin. Biocurcumax is curcumin mixed with turmeric oil. AUC was 7–8× higher when curcumin was combined with turmeric oil. For more information, visit (http://www.arjunanatural.com/HTML/biocurcumax.htm).

dietary curcumin or single doses of radiolabeled curcumin given via i.p. route[35] and showed that irrespective of the dose, traces of curcumin were present in the plasma which were at levels near the limit of detection (5 pmol/mL). Animal studies conducted in our own group showed detectable amounts of curcumin (as shown by the HPLC profiles) in serum collected from curcumin-treated nude mice, just after 1 h of treatment, as opposed to that from untreated animals (unpublished data; Figure 2a). In contrast to rodents, oral dosing of 4–8 g of curcumin in humans showed peak plasma levels of 0.41–1.75 μM after 1 h of dosing.[27] Similarly, in a human clinical trial, 3.6 g of curcumin via oral route was found to produce a plasma curcumin level of 11.1 nmol/L after an hour of dosing.[36]

A very recent study by Yang et al. showed that 10 mg/kg of curcumin given i.v. in rats gave a maximum serum curcumin level of 0.36 ± 0.05 μg/mL, whereas a 50-fold higher curcumin dose administered orally gave only 0.06 ± 0.01 μg/mL maximum serum level in rat.[37] An oral curcumin

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Table 1. Serum and Tissue Levels of Curcumin in Rodents and Human after Different Routes of Administration

species	route[a]	dose	plasma/tissue	levels	ref
mice	i.p.	100 mg/kg	plasma	2.25 μg/mL	
			intestine	117 $\pm$ 6.9 μg/g	
			spleen	26.1 $\pm$ 1.1 μg/g	34
			liver	26.9 $\pm$ 2.6 μg/g	
			kidney	7.5 $\pm$ 0.08 μg/g	
			brain	0.4 $\pm$ 0.01 μg/g	
mice	oral	100 mg/kg	plasma	0.22 μg/mL	
mice	i.p.	100 mg/kg	plasma	25 $\pm$ 2 nmol/mL	
			intestinal mucosa	200 $\pm$ 23 nmol/g	
			liver	73 $\pm$ 20 nmol/g	
			brain	2.9 $\pm$ 0.4 nmol/g	35
			heart	9.1 $\pm$ 1.1 nmol/g	
			lungs	16 $\pm$ 3 nmol/g	
			muscle	8.4 $\pm$ 6 nmol/g	
			kidney	78 $\pm$ 3 nmol/g	
rat	oral	2 g/kg	stomach	53.3 $\pm$ 5.1 (μg/g)	
			small intestine	58.6 $\pm$ 11.0 (μg/g)	32
			cecum	51.5 $\pm$ 13.5 (μg/g)	
			large intestine	5.1 $\pm$ 2.5 (μg/g)	
rat	oral	340 mg/kg	serum	6.5 $\pm$ 4.5 nM	39
rat	oral	1g/kg	serum	0.5 μg/mL	38
rat	oral	2 g/kg	serum	1.35 $\pm$ 0.23 μg/mL	28
rat	oral	500 mg/kg	plasma	0.06 $\pm$ 0.01 μg/mL	37
rat	i.v.	10 mg/kg	plasma	0.36 $\pm$ 0.05 μg/mL	
human	oral	2 g/kg	serum	0.006 $\pm$ 0.005 μg /mL	28
human	oral	4–8 g	serum	0.4–3.6 μM	27
human	oral	10 g	serum	50.5 ng/m	26
human	oral	12 g	serum	51.2 ng/mL	
human	oral	3.6 g	plasma	11.1 $\pm$ 0.6 nmol/mL	36
human	oral	0.4–3.6 g	colorectum	7–20 nmol/g	42

[a] Key: i.p., intraperitoneal; i.v., intravenous.

dose of 1 g/kg in rats produced a maximum serum curcumin level of 0.5 μg/mL after 45 min of curcumin dosing.[38] Similarly, Marczylo et al. also showed a maximum serum curcumin concentration of 6.5 $\pm$ 4.5 nM reached 0.5 h after oral dosing of curcumin.[39] These studies clearly suggest the role of route of administration on achievable serum levels of curcumin and further indicate that the serum levels of curcumin in rats and in human are not directly comparable (see Table 1).

B2. Tissue Distribution. Uptake and distribution of curcumin in body tissues is obviously important for its biological activity, yet only a limited number of studies have addressed this issue. Ravindranath et al. showed that after oral administration of 400 mg of curcumin to rats only traces of unchanged drug were found in the liver and kidney. At 30 min, 90% of curcumin was found in the stomach and small intestine, but only 1% was present at 24 h.[32] In an in vitro study, when everted sacs of rat intestine were incubated with 50–750 μg of curcumin in 10 mL of incubation medium 30–80% of the curcumin disappeared from the mucosal side and no curcumin was found in the serosal fluid. Less than 3% of the curcumin was found in the tissues at the highest curcumin concentration.[40] Another study evaluated the tissue distribution of curcumin using tritium-labeled drug. They found that radioactivity was detectable in blood, liver, and kidney following doses of 400, 80, or 10 mg of [^{3}H]curcumin. With 400 mg, considerable amounts of radio labeled products were present in tissues 12 days after dosing. The percentage of curcumin absorbed (60–66% of the given dose) remained constant regardless of the dose indicating that administration of more curcumin does not result in higher absorption.[33] That is, in rats there is a dose-dependent limitation to bioavailability.

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In a study by Pan et al. using a mouse model, a curcumin dose of 0.1 g/kg via i.p. route showed a maximum amount of curcumin in the intestine (117 μg/g) 1 h after dosing. Spleen, liver, and kidney showed moderate curcumin amounts of 26.1, 26.9, and 7.5 μg/g, respectively, whereas only a trace amount (0.4 μg/g) was found in brain tissue.[34] In a study with C57Bl/6J mice, the animals initially received curcumin (0.2%) in their diet for 1 week and were then changed to a curcumin-free diet. Levels of curcumin in gastrointestinal and hepatic tissues were analyzed for curcumin for up to 16 days after cessation of curcumin feeding. After termination of dietary curcumin intake, tissue levels of curcumin declined rapidly to unquantifiable amounts within 3–6 h. Second, in a more general analysis, mice received [^{14}C]curcumin (100 mg/kg) via the i.p. route and were then monitored for the disappearance of radioactivity associated with the curcumin molecule. Radioactivity measured in tissues after i.p. injection of [^{14}C]curcumin achieved the following peak levels, expressed as nmol/g of tissue: liver, 73 $\pm$ 20; intestinal mucosa, 200 $\pm$ 23; brain, 2.9 $\pm$ 0.4, heart, 9.1 $\pm$ 1.1; lungs, 16 $\pm$ 3; muscle 8.4 $\pm$ 6.0; kidney, 78 $\pm$ 3. Beyond the peak, radioactivity declined swiftly to reach levels between 20 and 33% of peak values at 4 h, or in the case of the small intestine, 8 h, after dosing.[35]

Similarly, the concentrations of curcumin in normal and malignant colorectal tissue of patients receiving 3600 mg of curcumin were 12.7 $\pm$ 5.7 and 7.7 $\pm$ 1.8 nmol/g, respectively, and these doses had pharmacological activity in colorectum as measured by effects on levels of M(1)G and COX-2 protein.[41] Another study by the same group showed no curcumin in liver tissues of patients, with hepatic metastases from colorectal cancer, who received 450–3600 mg of curcumin daily for 1 week prior to surgery.[42] These studies suggest that curcumin pharmacokinetics observed in tissues after i.p. administration cannot be compared directly with those observed after gavage or dietary intake. The tissue and serum distribution of curcumin reported in various animal and human studies is summarized in Table 1.

B3. Metabolites. Various studies have evaluated the metabolism of curcumin in rodents and in humans. Once absorbed, curcumin is subjected to conjugations like sulfation and glucuronidation at various tissue sites. The very first biodistribution study reported the metabolism of major part of curcumin orally administered to rats.[31] Liver was indicated as the major organ responsible for metabolism of curcumin.[31,41,43] Holder et al. reported that the major billiary metabolites of curcumin are glucuronides of tetrahydrocurcumin (THC) and hexahydrocurcumin (HHC) in rats. A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid.[44] In addition to glucuronides, sulfate conjugates were found in the urine of curcumin treated rats.[32] Hydrolysis of plasma samples with glucuronidase by Pan et al. showed that 99% of curcumin in plasma was present as glucuronide conjugates. This study also revealed curcumin–glucuronoside, dihydrocurcumin–glucuronoside, tetrahydrocurcumin (THC)–glucuronoside, and THC are major metabolites of curcumin in vivo.[34] These results are in agreement with Ireson et al. who examined curcumin metabolites in rat and human.[45] Asai et al. evaluated the absorption and metabolism of orally administered curcumin in rats. The enzymatic hydrolysis of plasma samples showed that the predominant metabolites in plasma following oral administration were glucuronides/sulfates of curcumin. The plasma concentrations of conjugated curcuminoids reached a maximum 1 h after administration. The presence of conjugative enzyme activities for glucuronidation and sulfation of curcumin in liver, kidney and intestinal mucosa suggested that orally administered curcumin is absorbed from the alimentary tract and present in the general blood circulation after largely being metabolized to the form of glucuronide/sulfate conjugates.[46] Curcumin sulfate and curcumin glucuronide were identified in the colorectal tissue of colorectal cancer patients who ingested curcumin capsules.[41] Hoehle and co-workers examined the metabolism of curcumin by rat liver tissue slices and showed the formation of reductive metabolites as THC, HHC, and octahydrocurcumin (OHC); males had more OHC, whereas females had more THC metabolites.[43] Further, the same group showed substantial contribution of gastrointestinal tract in glucuronidation of curcumin in humans, which may have important implications for their pharmacokinetic fate in vivo.[47] Thus, curcumin undergoes extensive reduction, most likely through alcohol dehdrogenase, followed by conjugation. Curcumin and its metabolites are schematically shown in Figure 1.

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Whether curcumin metabolites are as active as curcumin itself is, unfortunately, not clear. While most studies indicate that curcumin glucuronides and THC are less active than curcumin itself,[45,48] there are other studies which suggest that they may actually be more active than curcumin.[4,49–54] For example, THC was found to show better antidiabetic and antioxidant activity than curcumin in type 2 diabetic rats,[54] whereas Sandur et al. established much lower anti-inflammatory and antiproliferative activities of THC compared to curcumin.[48] Further, a study by Ireson et al. established that the metabolism of curcumin by reduction or conjugation generates species with reduced ability to inhibit COX-2 expression,[45] indicating lesser antiproliferative effects of curcumin metabolites like glucuronides and THC than curcumin. The phenolic glucuronide of curcumin and of its natural congeners, but not the parent compounds, inhibited the assembly of microtubule proteins under cell-free conditions, implying chemical reactivity of the glucuronides.[49] The difference in results is most likely due to the nature of the assays employed. The lack of availability of curcumin glucuronides and related compounds contributes to a continued lack of clear understanding of the relative pharmacologic activities of observed curucmin metabolites.

B4. Half-Life. Systemic elimination or clearance of curcumin from the body is also an important factor, which determines its relative biological activity. An early study by Wahlstrom and Blennow reported that when 1 g/kg curcumin was given orally to rats, 75% of it was excreted in the feces and negligible amounts were found in the urine. Intravenous (i.v.) and i.p. administration of curcumin resulted in biliary excretion of drug from cannulated rats.[44] Another study using radiolabeled curcumin showed that when drug was administered orally to rats at a dose of 400 mg/rat, nearly 40% of curcumin in unchanged form was found in the feces. Though no detectable amount of curcumin was found in urine, some of the derivatives like curcumin glucuronide and sulfates were observed. The major route of elimination of the radio labeled products was through feces; urinary excretion of the label was very low regardless of the dose. At lower doses of 80 mg and 10 mg of [^{3}H]curcumin, most of the label was excreted within 72 h, while with 400 mg, considerable amounts of the label was present in tissues 12 days after dosing.[33] A clinical study with 15 patients and oral curcumin doses between 36 and 180 mg of curcumin daily for up to 4 months found neither curcumin nor its metabolites in urine, but curcumin was recovered from feces.[55] The absorption and elimination half-lives of orally administered curcumin (2 g/kg) in rats were reported to be 0.31 ± 0.07 and 1.7 ± 0.5 h, respectively. But in humans, the same dose of curcumin did not allow the calculation of these half-life values because the serum curcumin levels were below the detection limit at most of the time points in most of the experimental subjects.[28] A lower curcumin dose of 1 g/kg administered orally in rats was found to have an elimination half-life value of 1.45 h,[38] which is not significantly different from the half-life reported for a higher curcumin dose and may be indicative of dose independency of curcumin elimination half-life in rats. The elimination half-life values for i.v. (10 mg/kg) and oral (500 mg/kg) curcumin in rats were reported to be 28.1 ± 5.6 and 44.5 ± 7.5 h, respectively.[37] However, the existing evidence in literature is not enough to conclude about the factors controlling in vivo elimination half-life of curcumin and future studies are warranted to address this issue.

C. Promises

The absorption, biodistribution, metabolism, and elimination studies of curcumin have, unfortunately, shown only poor absorption, rapid metabolism, and elimination of curcumin as major reasons for poor bioavailability of this interesting polyphenolic compound. Some of the possible ways to overcome these problems are discussed below. Adjuvants, which can block metabolic pathways of curcumin, are one of the major means that are being used to improve its bioavailability. Nanoparticles, liposomes, micelles, and phospholipid complexes are other promising novel formulations, which appear to provide longer circulation, better permeability, and resistance to metabolic processes.

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C1. Adjuvants. Piperine, a known inhibitor of hepatic and intestinal glucuronidation, was combined with curcumin and administered in rats and healthy human volunteers by Shoba et al. In rats, 2 g/kg of curcumin alone produced a maximum serum curcumin level of 1.35 ± 0.23 μg/mL at 0.83 h, whereas concomitant administration of piperine (20 mg/kg) increased the serum concentration of curcumin for a short period; time to maximum peak level (T_{max}) was significantly increased, while elimination half-life and clearance were significantly decreased resulting in an increase of bioavailability of 154%. In contrast, in humans receiving a dose of 2 g curcumin alone, serum levels were either undetectable or very low. Concomitant administration of piperine, however, produced 2000% increase in bioavailability.[28] Thus, the effect of piperine on bioavailability of curcumin has been shown to be much greater in humans than in rats. A human volunteer trial conducted in our group also revealed the serum curcumin level enhancing effect of piperine in human volunteers as shown in Figure 2b. Six healthy adult male human volunteers took 2 g of curcumin with or without 5 mg of piperine (as bioperine) in this crossover design study. Three people were randomized to receive curcumin only, while the remaining 3 received the curcumin + piperine combination. One week following initial drug administration, volunteers were crossed over to the opposite therapies and blood samples were again obtained for evaluation. Doubling of the absorption of curcumin was found in the presence of piperine. The effect of piperine on tissue uptake of a radio labeled fluoropropyl-substituted curcumin was evaluated in mice. Brain uptake of curcumin after 2 min was increased by 48% due to coadministration of piperine relative to that with out piperine. However, the uptake in other organs was not found to be significantly improved by piperine in this study, and the authors think this observation can be explained by the poor solubility of piperine in 10% ethanolic saline (injection medium).[56] The glucuronidation inhibiting effect of piperine[28] and the established lesser activity of curcumin glucorinides[45] will indicate that inhibition of glucuronidation by piperine may be the major mechanism by which it increases the bioavailability of curcumin.

Some other agents that showed a synergistic effect when used in combination with curcumin in various in vitro studies look promising for further evaluation of curcumin bioavailability. In a clinical study published in 2006, five familial adenomatous polyposis (FAP) patients with prior colectomy received curcumin (480 mg) and quercetin (20 mg) orally three times a day. The number and size of polyps were assessed at baseline and after therapy. All five patients had a decreased polyp number as well as size from baseline after a mean of 6 months of treatment with curcumin and quercetin. The mean percent decrease in the number and size of polyps from baseline was 60.4% and 50.9%, respectively, with minimal adverse side effects. Though the authors did not compare the combination treatment effect with the individual effect of single agents, this study throws light at least on the therapeutic value of this combination.[57]

The synergistic inhibitory effect of curcumin and genistein against pesticide induced cell growth of estrogen dependent breast carcinoma cell lines (MCF-7) have been studied by Verma et al. This *in vitro* study showed that a combination of curcumin and genistein completely inhibited the cellular proliferation induced by individual or a mixture of pesticides and the inhibitory effect was superior to the individual effects of either curcumin or genistein.[58] Curcumin uptake within rat skin after topical application of a curcumin hydrogel, with or without eugenol or terpeneol pretreatment, was evaluated in an *in vivo* study. They demonstrated the effect of eugenol and terpeniol as enhancers of skin curcumin absorption with 2.2 and 2.5-fold increases of curcumin levels in skin occurring 8 h after application. Though not strictly a bioavailability study this indicates the ability of the above agents to modulate the permeability of curcumin suggesting that these agents may also be effective as adjuvants in increasing curcumin bioavailability.[59] Other recent studies indicated that EGCG (epigallocatechin-3-gallate), a component green tea, could also counteract certain activities assigned to curcumin.[60] Thus, overall these studies indicate that the activity of curcumin can be modulated both at the cellular levels and at the organismic level, and we can expect surprising types of regulations when different agents are used simultaneously with curcumin.

C2. Nanoparticles. Recently, targeted and triggered drug delivery systems accompanied by nanoparticle technology have emerged as prominent solutions to the bioavailability of therapeutic agents. Nanoparticle-based delivery systems will probably be suitable for highly hydrophobic agents like curcumin circumventing the pitfalls of poor aqueous solubility. However, very few studies have been published citing curcumin nanoparticles. A recent study by Bisht et al. reported the synthesis, physicochemical characterization and cancer related application of a polymer-based nanoparticle of curcumin namely "nanocurcumin" with less than 100 nm size. Nanocurcumin was found to have similar *in vitro* activity as that of free curcumin in pancreatic cell lines. Like

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free curcumin, nanocurcumin also inhibits activation of the transcription factor NFκB, and reduces steady state levels of pro-inflammatory cytokines like interleukins and TNF-α. However, the authors neither determined the *in vivo* effect of nanocurcumin in mice nor its biodistribution to show any potential increase in efficacy of nanaocurcumin over free curcumin in vivo.[61] Solid lipid nanoparticles (SLNs) loaded with curcuminoids for topical application were developed and characterized by Tiyaboonchai et al. Curcuminoid loaded SLNs having 450 nm size were found to be stable for 6 months at room temperature and gave prolonged *in vitro* release of curcuminoids up to 12 h. Furthermore, the light and oxygen sensitivity of curcuminoids was strongly reduced by incorporating curcuminoids into this unique type of formulation. An *in vivo* study with healthy volunteers reveled the improved efficiency of a topical application cream containing curcuminoid loaded SLNs over that containing free curcuminoids.[62] Overall, nanoparticle based systems for curcumin delivery is still in its infancy and much progress is warranted in this area.

C3. Liposomes, Micelles, and Phospholipid Complexes. Liposomes are excellent drug delivery systems since they can carry both hydrophilic and hydrophobic molecules. Li et al. investigated the *in vitro* and *in vivo* antitumor activity of liposomal curcumin against human pancreatic carcinoma cells and demonstrated that liposomal curcumin inhibits pancreatic carcinoma growth and, in addition, exhibits antiangiogenic effects. Liposomal curcumin suppressed the pancreatic carcinoma growth in murine xenograft models and inhibited tumor angiogenesis. In the *in vivo* part of this study, the effect of liposomal curcumin was evaluated in comparison to untreated and liposomal vehicle treated mice. Comparison of effect of liposmal curcumin with free curcumin and biodistribution profiles of liposomal curcumin over free curcumin have yet to be evaluated to confirm the enhancement of curcumin bioavailability by liposomal curcumin.[63] The preclinical anticancer activity of a liposomal curcumin formulation in colorectal cancer was also recently evaluated. This study also compared the efficacy of liposomal curcumin with that of oxaliplatin, a standard chemotherapeutic agent for colorectal cancer. There was synergism between liposomal curcumin and oxaliplatin at a ratio of 4:1 in LoVo cells in vitro. In vivo, significant tumor growth inhibition was observed in Colo205 and LoVo xenografts, and the growth inhibition by liposomal curcumin was greater than that for oxaliplatin in Colo205 cells. Thus, this study established the comparable or greater growth-inhibitory and apoptotic effects of liposomal curcumin with oxaliplatin both in vitro and in vivo in colorectal cancer. This group is currently developing liposomal curcumin for introduction into the clinical setting.[64] Ruby et al. also reported the antitumor and antioxidant activities of neutral unilamellar liposomal curcuminoids in mice.[3] Nevertheless, *in vivo* preclinical studies are warranted to show the increased bioavailability of liposomal curcumin over free curcumin. Kanwar et al. evaluated the *in vitro* cellular uptake of liposomal and albumin loaded curcumin. From these studies it was found that liposomal vehicle is capable of loading more curcumin in to cells than either HSA or aqueous-DMSO, and lymphoma cells showed preferential uptake of curcumin to lymphocytes.[65]

Micelles and phospholipid complexes can improve the gastrointestinal absorption of natural drugs, thereby giving higher plasma levels and lower kinetic elimination resulting in improved bioavailability. The intestinal absorption of curcumin and micellar curcumin formulation with phospholipid and bile salt was evaluated using an *in vitro* model consisting of everted rat intestinal sacs. This study suggested biological transformation of curcumin during absorption. Further, the *in vitro* intestinal absorption of curcumin was found to increase from 47% to 56% when the same was present in micelles.[66] Pharmacokinetic studies by Ma et al. also demonstrated that a polymeric micellar curcumin gave a 60-fold higher biological half-life for curcumin in rats compared to curcumin solubilized in a mixture of DMA, PEG and dextrose.[67] Phospholipid complex formulations of several natural drugs, such as silymarin[68] and dolichol,[69] have been found to show improved bioavailability. Liu et al., for example, showed a significant improvement in curcumin bioavailability due to curcumin-phospholipid complex formation. In this study, curcumin (100 mg/kg) and curcumin–phospholipid complex (corresponding to 100 mg/kg of curcumin) were administered orally to Sprague–Dawley male rats. Curcumin–phospholipid complex showed a maximum plasma curcumin level of 600 ng/mL 2.33 h after oral administration as opposed to that of free curcumin having maximum plasma concentration of 267 ng/mL after 1.62 h of oral dosing. About a 1.5-fold increase in curcumin half-life in rats was found in this study for the curcumin phospholipid complex over free curcumin. These results indicate that the curcumin phospholipid complex can sig-

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nificantly increase circulating levels of presumably active curcumin in rats.[70] Another study conducted by Maiti et al., *showed* a 3-fold increase in aqueous solubility and a better hepatoprotective effect for a curcumin phospholipid complex compared to free curcumin. Curcumin–phospholipid complex significantly protected the liver from carbon tetrachloride induced acute liver damage in rats by restoring enzyme levels of liver glutathione system and that of superoxide dismutase, catalase and thiobarbituric acid reactive substances.[38] Marczylo et al. explored whether formulation with phosphatidylcholine increases the oral bioavailability or affects the metabolite profile of curcumin *in vivo*. Male Wistar rats received 340 mg/kg of either unformulated curcumin or curcumin formulated with phosphatidylcholine (Meriva) by oral gavage. Curcumin, the accompanying curcuminoids desmethoxycurcumin and bisdesmethoxycurcumin, and the metabolites tetrahydrocurcumin, hexahydrocurcumin, curcumin glucuronide, and curcumin sulfate were identified in plasma, intestinal mucosa, and liver of rats which had received Meriva. Peak plasma levels for parent curcumin after administration of Meriva were 5-fold higher than the equivalent values seen after unformulated curcumin dosing. Similarly, liver levels of curcumin were higher after administration of Meriva as compared to unformulated curcumin. In contrast, curcumin concentrations in the gastrointestinal mucosa after ingestion of Meriva were somewhat lower than those observed after administration of unformulated curcumin.[39] These results suggest that curcumin formulated with phosphatidylcholine furnishes higher systemic levels of parent agent than unformulated curcumin. In an attempt to increase the aqueous solubility of hydrophobic drugs, Letchford et al., showed a 13×10^5 fold increase in curcumin solubility in a polymeric micellar formulation containing methoxy poly (ethylene glycol)-block-polycaprolactone diblock copolymers (MePEG-b-PCL).[71] The enormous increase in solubility of curcumin in the above said micelle makes it a promising formulation to be explored further.

C4. Derivatives and Analogues. The chemical structure of curcumin plays a pivotal role in its biological activity. For example, isomerization has been proved to have an influence on antioxidant activity of curcumin.[72] Thus, researchers hope to achieve improved biological activity of curcumin by structural modifications. Numerous studies dealing with the enhanced biological activity of curcumin derivatives and/or analogues can be found in the literature. A review by Mosley et al.,[73] for example, systematically describes several studies dealing with the biological activity relationships of curcumin and its derivatives. A curcumin analogue designated EF-24 was reported to be a lead compound displaying increased antitumor action *in vitro* and *in vivo* in comparison to curcumin. Only one study reported the pharmacokinetics and bioavailability evaluation of a curcumin analog. In this study, the maximum tolerable dose following intravenous administration to male and female CD2F1 mice was 32 mg/kg of EF-24. EF-24 absorption was rapid after both oral and i.p. administration. The terminal elimination half-life and plasma clearance values for i.v. administration were reported to be 73.6 min and 0.482 L/min/kg, respectively. Peak plasma concentrations of nearly 1000 nM were detected 3 min after the dose was given intraperitonially and the absorption and elimination half-life values were 177 and 219 min, respectively. The bioavailability of oral and i.p. EF-24 was 60% and 35%, respectively.[74] A series of curcumin analogues including symmetrical 1,5-diarylpentadienone compounds whose aromatic rings possess two alkoxy substitutes were synthesized and screened for anticancer activity. New analogues that exhibit growth-suppressive activity 30 times that of curcumin and other commonly used anticancer drugs were identified in this study. Moreover, these analogues showed no *in vivo* toxicities.[75]

Another strategy to improve the biological activity of curcumin was to chelate it with metals. The presence of two phenolic groups and one active methelene group in a curcumin molecule makes it an excellent ligand for any chelation. Several metal chelates of curcumin are reported to possess biological activity over that of free curcumin. John et al. studied the antitumor activities of curcumin, piperonylcurcumin, 2-hydroxynaphthylcurcumin, cinnamylcurcumin, and their copper complexes. Copper complexes of curcumin and its derivatives were found to be better antitumor agents than were the parent compounds.[76] Studies by Sui et al. showed that the modest activity of curcumin as an *in vitro* inhibitor of HIV-1and HIV-2 proteases is enhanced more than 10-fold when curcumin is complexed with boron. The curcumin boron complexes were observed

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to lower the IC_{50} values significantly.[77] Further, the curcumin copper complex was equally effective as curcumin against cadmium induced oxidative damage in mice.[78] Theoretical calculation of ionization energies of curcumin and curcumin copper complexes have shown that these possess higher reactive oxygen species scavenging ability than does curcumin.[72] Similarly, it was demonstrated that curcumin-manganese complex exhibited a more potent neuroprotective activity than curcumin both *in vitro* and *in vivo* suggesting that this complex may be useful as a neuroprotective agent in the treatment of acute brain pathologies associated with NO-induced neurotoxicity and oxidative stress-induced neuronal damage such as epilepsy, stroke, and traumatic brain injury.[78–81] A vanadyl curcumin complex ($VO(cur)_2$) was reported to show a 2-fold increase in antirheumatic activity and a 4-fold increase in inhibiting smooth muscle cell proliferation as compared to free curcumin *in vitro*. Further, this complex was more effective as an anticancer agent, compared to uncomplexed curcumin.[82] Both *in vitro* and *in vivo* evaluations of a series of indium and gallium complexes of curcumin derivatives and curcumin have shown that the structural modification and/or complex formation of curcumin with metal ions may yield gallium and indium curcuminoids with potential therapeutic applications.[83] Although many curcumin analogues are found to show improved biological activity over curcumin, specific evaluations of structural analogues and/or derivatives of curcumin to show improved tissue and plasma distribution are lacking. However, the promising biological effects over curcumin showed by structural modifications throws light into the possibility of modulating bioavailability of curcumin and much needs to be done to prove that the improved biological activity of structurally modified curcumin is due to its increased bioavailability.

C5. Others. Biocongugates can increase the cellular uptake and hence better bioavailability of curcumin. For example, BCM-95 (also called Biocurcumax) curcuminoids combined with turmeric oil (turmerons) in a specific proportion enhanced the bioavailability (Figure 2c) and showed better absorption into blood and had longer retention time compared to curcumin. This product showed 700% more activity and 7–8 times more bioavailability over curcumin as confirmed by human clinical trials (unpublished data). Currently a multicenter, phase II, randomized, double-blinded, placebo controlled clinical study is ongoing to assess the efficacy and safety of BCM-95 in oral premalignant lesions/cervical cancer (www.bcm95.com). In another study, curcumin bioconjugates containing glycine, alanine, and/or piperic acid were found to show improved antimicrobial properties over curcumin, suggesting increased cellular uptake or reduced metabolism of these bioconjugates resulting in increased concentration inside the infected cells.[84]

D. Conclusions

Curcumin derived from the common food spice turmeric has been used for centuries as a remedy for many ailments. Extensive scientific research over the past decade has shown the ability of this compound to modulate multiple cellular targets and hence possesses preventive and therapeutic value against a wide variety of diseases. Curcumin has a diverse range of molecular targets like transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis. One of recent reviews from our group extensively describes the molecular targets of curcumin.[85] Despite its demonstrated efficacy and safety, limited curcumin bioavailability continues to be highlighted as a major concern. As detailed in this review, lower serum and tissue levels of curcumin irrespective of the route of administration, rapid metabolism and elimination are major factors curtailing curcumin bioavailability. Modu-

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lation of route and medium of curcumin administration, blocking of metabolic pathways by concomitant administration with other agents, and structural modifications are the main strategies now being explored in attempts to improve the bioavailability of curcumin. Attempts at enhanced *in vitro* and *in vivo* efficacies of curcumin through structural modifications of the molecule and/or new formulations have been recently reported. However, the limited literature evidence devoted to show improvements in curcumin bioavailability reveals that the curcumin bioavailability enhancement has not gained significant attention. Yet, novel delivery strategies including those of nanoparticles, liposomes, and defined phospholipid complexes offer significant promise and are worthy of further exploration in attempts to enhance the bioavailability, medicinal value, and application of this interesting molecule from Mother Nature.

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