pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2014;46(1):2-18 http://dx.doi.org/10.4143/crt.2014.46.1.2

Review Article Open Access

Recent Developments in Delivery, Bioavailability, Absorption and Metabolism of Curcumin: the Golden Pigment from Golden Spice

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Received December 25, 2013
Accepted December 31, 2013

Curcumin (diferuloylmethane) is a yellow pigment present in the spice turmeric (*Curcuma longa*) that has been associated with antioxidant, anti-inflammatory, anticancer, antiviral, and antibacterial activities as indicated by over 6,000 citations. In addition, over one hundred clinical studies have been carried out with curcumin. One of the major problems with curcumin is perceived to be the bioavailability. How curcumin should be delivered *in vivo*, how bioavailable is it, how well curcumin is absorbed and how it is metabolized, is the focus of this review. Various formulations of curcumin that are currently available are also discussed.

Key words
Curcumin, Nano-formulation, Biological availability, Metabolism, Anticancer

Introduction

Curcumin is the major active component of turmeric, a yellow compound originally isolated from the plant *Curcuma longa*. It is a member of the curcuminoid family and has been used for centuries in traditional medicines. As a spice, it provides curry with its distinctive color and flavor. Furthermore, traditional Indian medicine has considered curcumin a drug effective for various respiratory conditions (asthma, bronchial hyperactivity, and allergy) as well as for other disorders including anorexia, coryza, cough, hepatic diseases, and sinusitis [1,2]. Extensive research over the past 30 years has shown that it plays an important role in the prevention and treatment of various pro-inflammatory chronic diseases including neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and malignant diseases.

How curcumin could exhibit these diverse effects has been a clandestine over the years. However, numerous line of

Fig. 1. Various curcumin-based products include capsules, tablets, ointments, energy drinks, soaps, and cosmetics.

evidence indicates that this agent is highly pleiotropic with anti-inflammatory [3], hypoglycemic [4,5], antioxidant [6], wound healing [7], and antimicrobial activities [8]. It has been shown to possess chemosensitization, chemotherapeutic and radiosensitization activities as well [9]. Curcumin has been studied for its chemopreventive potential in a wide variety of cancers, in both preclinical studies and in clinical trials [10]. Many clinical trials using curcumin as a therapeutic agent are underway [11]. Because of its marvelous properties, curcumin is being marketed in several countries including the United States, India, Japan, Korea, Thailand, China, Turkey, South Africa, Nepal, and Pakistan in different form such as capsules, tablets, ointments, energy drinks, soaps, and cosmetics (Fig. 1).

The molecular basis of these pleiotropic effects of curcumin is due to the modulation of various signaling molecules.

Various experimental studies have reported that curcumin has ability to inhibit proinflammatory transcription factors nuclear factor-kappaB (NF-κB) in several types of cancer [12]. Beside NF-κB, curcumin also inhibits activation of signal transducer and activator of transcription-3, and Wnt/beta-catenin, and activates peroxisome proliferator-activated receptor-gamma and Nrf2 cell-signaling pathways, thus leading to the down regulation of adipokines, including tumor necrosis factor (TNF), interleukin (IL)-6, resistin, leptin, and monocyte chemotactic protein-1, and the upregulation of adiponectin and other gene products [13]. Curcumin also modulate several inflammatory molecules along with cell survival proteins, histone acetylase, histone deacetylase, protein kinases, protein reductases, glyoxalase I, proteasome, human immunodeficiency virus type 1 (HIV1) integrase, HIV1 protease, FtsZ protofilaments, carrier proteins, DNA, RNA, and metal ions [14].

In this context, curcumin seems to offer an ideal agent because significant evidence has indicated its potential against several chronic diseases. Also, curcumin targets several of molecular pathways without any associated toxicity or resistance. In spite of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent in part perhaps because of lack of intellectual rights to it. The poor aqueous solubility, relatively low bioavailability, and intense staining color of curcumin have been highlighted as major problems [15]. However, numerous reports suggest that bioavailability could not be a concern. Various type of formulations that have been designed with curcumin are outlined in Fig. 2. In this article, we analyze the delivery, bioavailability and metabolism of curcumin and its formulation.

Delivery of Curcumin

1. Oral delivery

In most of studies curcumin has been delivered orally whether subject is human or animals. This orally delivered curcumin showed several biological effects such as antioxidant, anti-inflammatory, anticancer, antidiabetic, etc. Recently, it has been shown that curcumin (3 mg) administered orally in mice attenuate oxidative stress following downhill running-induced muscle damage [16]. Curcumin has also reported to affects exercise-induced oxidative stress in humans. In a study, oral administration of 90 mg of curcumin or the placebo 2 hours before exercise and immediately after exercise. Curcumin supplementation attenuated exercise-induced oxidative stress by increasing blood antioxidant capacity [17]. Orally administered curcumin inhibited inflammatory cytokines such as TNF, cyclooxygenase (COX)-

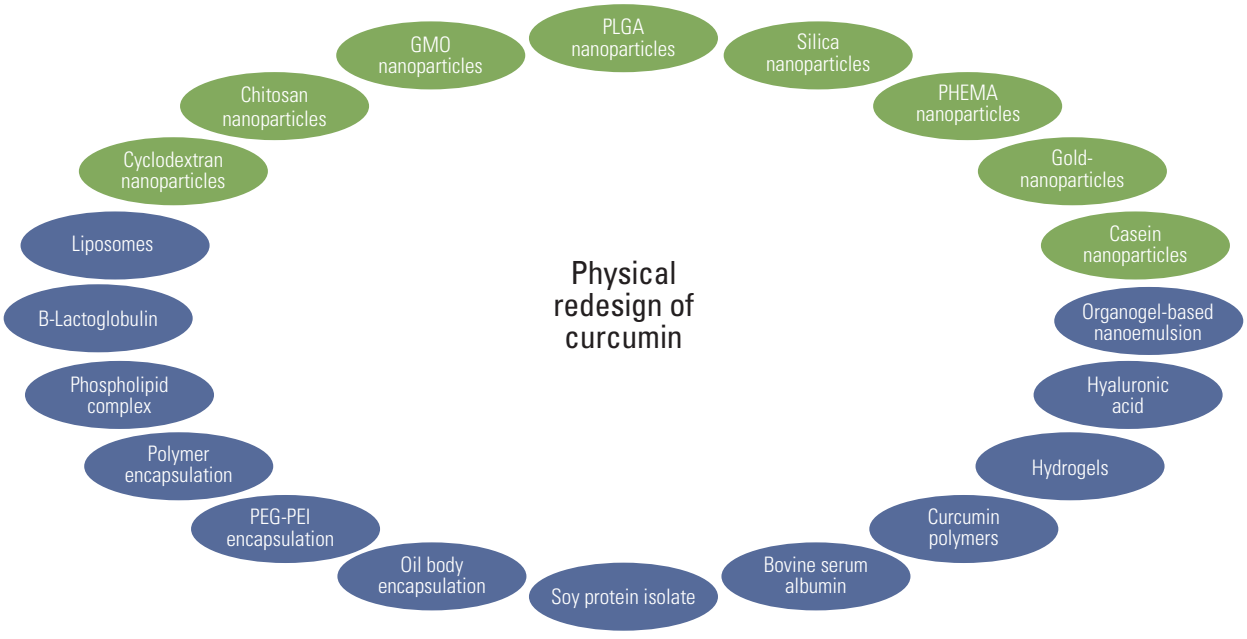

Fig. 2. Redesign of curcumin through various strategies to enhance bioavailability. GMO, glyceryl monoleate; PLGA, poly-lactic-co-glycolic acid; PHEMA, poly(2-hydroxyethyl methacrylate); PEG-PEI, polyethylene glycol-poly(ethylene imine).

2, inducible nitric oxide synthase in mice indicating its anti-inflammatory activity and further suppressing dextran sodium sulfate-induced colon carcinogenesis [18]. Clinical trials have also shown that orally delivered curcumin inhibited inflammatory molecules [12].

Curcumin showed beneficial effects in several types of cancer in patients. Recently it has been reported that oral curcumin, 6.0 g daily during radiotherapy, reduced the severity of radiation dermatitis in breast cancer patients [19]. In animal model oral administration of curcumin inhibited cancer of lung [20], skin [21], head and neck [22], oral [23], hepatocellular carcinoma [24], mammary tumors, lymphomas, leukemias [25], and familial adenomatous polyposis [26]. Oral treatment of curcumin found to effective in diabetic condtion. It attenuated high fat diet-induced glucose intolerance and elevations of oxidative stress in the skeletal muscle [27]. Curcumin also enhanced wound repair in diabetic impaired healing in mice [28]. Curcumin improves the peripheral neuropathy of R98C mice by alleviating endoplasmic reticulum stress, reducing the activation of unfolded protein response and promoting Schwann cell differentiation [29]. It also protects against the pulmonary and cardiovascular effects in mice [30].

2. Subcutaneous delivery

Subcutaneous treatment of curcumin in animals has been used to provide effective and sustained tissue concentrations. Since sustained release of subcutaneously injected unformulated curcumin in animals is likely not possible, curcumin is formulated. A single subcutaneous dose of microparticles sustained curcumin in liver for nearly a month in mice [31]. It has been also shown that the microparticle formulation of curcumin showed marked anticancer efficacy in nude mice bearing MDA-MB-231 xenografts in mice compared with controls [32].

3. Intraperitoneal (IP) delivery

IP injection is the injection of a substance into the peritoneum (body cavity). IP injection is more often applied to animals than to humans. In case of IP the bioavailability of compound is higher than gavage. Curcumin, delivered intraperitoneally, has shown inhibitory effect against lipopolysaccharide induced cardiac hypertrophy in rodents [33]. It also reduced volume of glioma tumor implanted in nude mice, and prolonged the survival of animals [34]. Another study showed that IP injection of curcumin inhibited tumorigenicity and tumor growth, decreased the percentages of myeloid-derived suppressor cells in the spleen, blood, and tumor tissues, reduced IL-6 levels in the serum and tumor tissues in a human gastric cancer xenograft model and a mouse colon cancer allograft model [35]. It has been also shown that curcumin ameliorates intracerebral hemorrhage damage by preventing matrix metalloproteinase-mediated blood-brain barrier damage and brain edema, which might provide therapeutic potential for intracerebral hemorrhage [36]. Beside these, curcumin acts against asthma. In a study it has been shown that curcumin attenuates the development of allergic airway inflammation and hyper-responsiveness, possibly through inhibition of NF-κB activation in the asthmatic lung tissue. Thus, it attenuates development of asthma by inhibition of NF-κB activation [37]. Curcumin administered IP inhibited human oral squamous cell carcinoma xenograft tumor in mice, indicating its therapeutic efficacy *in vivo* [23]. Interestingly, it has been shown that oral curcumin treatment showed no effect on important measures of bleomycin-induced injury in mice, whereas IP curcumin administration effectively inhibited inflammation and collagen deposition along with a trend toward improved survival of animals. IP curcumin also reduced fibrotic progression even when administered after the acute bleomycin-induced inflammation had subsided [38].

Intravenous Delivery

Numerous reports have been shown that intravenous injection of curcumin exhibits anticancer property in animal model. Kim et al. [39] has shown that in curcumin has in antitumor effects in xenograft mouse model of colorectal cancer. They have also shown that curcumin loaded human serum albumin (HSA) nanoparticles has greater therapeutic effect than curcumin without inducing toxicity [39]. Several other studies reported that liposomal curcumin inhibited different type of tumor growth in mouse models. It inhibited the growth of head and neck squamous cell carcinoma in xenograft mouse by the inhibition of NF-κB without affecting the expression of pAKT [40]. Liposomal formulation of curcumin also enhanced the effect of radio and chemotherapy. Shi et al. [41] showed that liposomal curcumin when combined with radiation enhanced the inhibition of tumor growth in a murine lung carcinoma (LL/2) model. It has been also reported that intravenous treatment of liposomal curcumin in combination of cisplatin significantly enhances growth inhibition of xenograft head and neck tumors in mice. The suppressive effect of curcumin was mediated through inhibition of cytoplasmic and nuclear IKKβ, resulting in inhibition of NF-κB activity [42].

Another derivative of curcumin conjugated with luteiniz-

ing hormone releasing hormone, [DLys(6)]-LHRH-curcumin, when given intravenously caused a reduction in tumor weights and volumes, and free curcumin given by gavage at an equal dose failed to cause a significant reduction in tumor weights and volumes in the nude mouse pancreatic cancer model. This bioconjugate enhanced apoptosis in tumor tissue [43]. The encapsulated curcumin with monomethoxy poly (ethylene glycol)-poly(ε-caprolactone) (MPEG-PCL) micelles also showed stronger anticancer effect than that of free curcumin. When curcumin/MPEG-PCL micelle applied intravenously inhibited the growth of subcutaneous C-26 colon carcinoma *in vivo* [44]. The intravenous administration of another curcumin derivative, curcumin-loaded HSA nanoparticles also showed greater therapeutic effect than curcumin in tumor xenograft HCT116 models without inducing toxicity [39].

1. Topical delivery

A topical treatment is a medication that is applied to body surfaces such as the skin or mucous membranes to treat ailments. Curcumin has been used topically to study its effect mostly on inflammation on target organ, wound healing, skin cancer and other. In a study it has been reported that topical use of a curcumin gel formulation strongly inhibited imiquimod-induced psoriasis-like inflammation in BALB/c mouse ear. It inhibited mRNA levels of IL-17A, IL-17F, IL-22, IL-1β, IL-6, and TNF-α cytokines in ear skin [45]. Topical curcumin is also found to be effective in CO_2 laser-induced skin wound healing. It improved re-epithelialization of wound after 7 days [46]. It has been revealed that topical treatment of curcumin and the photoinactivation of *Candida albicans* in a murine model of oral candidiasis caused a significant reduction in *C. albicans* viability. Thus, it acts photosensitizer without harming the host tissue of mice [47].

Topical treatment of curcumin also inhibited ultraviolet B (UVB)-induced tumor formation in mice. Average number of tumors formed per mouse was lesser in curcumin and UVB treated mice compared to UVB exposed animals and it also delayed the onset of tumorigenesis [21]. Beside these when curcumin applied as a noninvasive topical paste to the head and neck squamous cell carcinoma (HNSCC) xenografts tumors in mice, resulted in inhibition of its growth. Thus, it can be used as an adjuvant or chemopreventive agent in several cancer [48].

2. Nasal delivery

To increase the bioavailability and also direct nose-to-brain drug transport, nasal delivery of curcumin has been used. In a study, the pharmacokinetics results showed that the absolute bioavailability of curcumin in the microemulsion-based *in situ* ion-sensitive gelling system was 55.82% by intranasal administration. And the distribution of curcumin in brain versus blood following intranasal administration was higher than that following intravenous administration [49]. Another study also showed that the drug-targeting efficiencies of the curcumin in the cerebrum, cerebellum, hippocampus and olfactory bulb after intranasal administration of the curcumin hydrogel were 1.82, 2.05, 2.07, and 1.51 times higher than intravenous administration of the curcumin solution injection, respectively, indicating that the hydrogel and intranasal administration significantly increased the distribution of curcumin into the rat brain tissue [50].

In another study intranasal curcumin has been detected in plasma of mice after 15 minutes to 3 hours at pharmacological dose (5 mg/kg), which has shown antiasthmatic potential by inhibiting bronchoconstriction and inflammatory cell recruitment to the lungs. Thus, this study indicates that intranasal treatment of curcumin prevents airway inflammations and bronchoconstrictions in asthma without any side effect [51].

Bioavailability of Curcumin

Evidence from numerous literatures revealed that curcumin has poor absorption, biodistribution, metabolism, and bioavailability. Thus, continuous research on curcumin found some possible ways to overcome these problems. To increase the bioavailability, longer circulation, better permeability, and resistance to metabolic processes of curcumin several formulations have been prepared which include nanoparticles, liposomes, micelles, and phospholipid complexes (Table 1) [52-93].

1. Unformulated curcumin

The pharmacological studies revealed that curcumin is safe and effective which makes it a potential compound for treatment and prevention of a wide variety of human diseases. In spite of these, accumulating data revealed that curcumin has relatively low bioavailability and poor solubility in aqueous solution. First time Wahlstrom and Blennow in 1978 [94] reported that after oral administration of 1 g/kg of curcumin in Sprague-Dawley rats, negligible amounts of curcumin in blood plasma of rats was observed which could be its poor absorption from the gut. Later several studies conducted on bioavailability of curcumin and found that certain amount

Table 1. Reformulation of curcumin for enhanced bioavailability

Formulation	Reference	Formulation	Reference
Nanosuspension	[52]	PEGylated curcumin analogs	[74]
Aqueous formulation	[53]	Curcumin-loaded MPEG-PCL	[52]
Nanoemulsion	[54]	Aqueous PLGA nanoparticulate	[75]
pH-sensitive nanoparticles	[55]	Curcumin loaded cellulose nanoparticles	[76]
Microemulsion-based ion-sensitive	[49]	PLGA microparticle of curcumin	[32]
Curcumin-loaded nanoparticles	[56]	Curcumin-loaded PLGA nanospheres	[77]
Curcumin-loaded carbon nanotubes	[57]	Curcumin MPEG-PCL micelles	[78]
Curcumin co-solvent formulation	[58]	Curcumin PLGA-b-PEG-TPP	[79]
Silica-coated flexible liposomes	[59]	Curcumin PCL-PEG-PCL	[80]
Artemisinin liposomal formulations	[60]	Curcumin methoxy PEG-zein micelles	[81]
Liposomal curcumin	[61]	Curcumin-loaded alginate foams	[82]
TMC-coated liposomes	[62]	Thermosensitive poloxamer hydrogel	[50]
Liposomes-propylene glycol liposomes	[63]	Curcumin-loaded polymeric micelles	[83]
γ-Cyclodextrin liposomal nanoparticles	[64]	CSO-SA	[84]
Cationic liposome-PEG-PEI complex	[65]	Curcumin-loaded amphiphilic peptide	[85]
Curcumin-decorated nanoliposomes	[66]	Cyclodextrin-curcumin	[86]
Liposomes of DMPC and cholesterol	[67]	Dipeptide nanoparticles	[87]
Lipid-based oral formulations	[68]	Phosphatidylcholine encapsulation	[88]
Curcumin-loaded solid lipid nanoparticles	[69]	Graphene-based curcumin nanosystems	[89]
Curcumin nanoglobules/nanoemulsion	[70]	Curcumin PHEMA-NPs	[90]
Curcumin-loaded cationic liposome	[71]	Silica nanoparticles	[91]
PGL nanocapsulated curcumin	[72]	Pluronic-curcumin formulation	[92]
Curcumin TRC-NPs	[73]	EMC-curcumin	[93]

TMC, N-trimethyl chitosan chloride; PEG-PEI, polyethylene glycol-poly(ethylene imine); DMPC, dimyristoyl phosphatidyl choline; PGL, propylene glycol liposomes; TRC-NPs, thermoresponsive chitosan-g-poly(N-isopropylacrylamide) co-polymeric nanoparticles; MPEG-PCL, methoxy poly(ethylene glycol)-poly(ε-caprolactone); PLGA-b-PEG-TPP, poly(d, l-lactic-co-glycolic acid)-block (PLGA-b)-poly(ethylene glycol) (PEG)-triphenylphosphonium (TPP) polymer; PCL-PEG-PCL, poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone); CSO-SA, curcumin encapsulated in stearic acid-g-chitosan oligosaccharide; PHEMA-NPs, poly(2-hydroxyethyl methacrylate) nanoparticles; EMC, ethyl and methyl cellulose.

of curcumin are bioavailable in serum of animals. In a study, when curcumin was given orally at a dose of 2 g/kg to rats, a maximum serum concentration of 1.35±0.23 μg/mL was observed at time 0.83 hours, whereas in humans the same dose of curcumin resulted in either undetectable or extremely low (0.006±0.005 μg/mL at 1 hour) serum levels [95].

Another study conducted in freely moving rats showed that administration of curcumin (500 mg/kg, p.o.) resulted in 1% bioavailability of curcumin in rat plasma [96]. It has been also observed that oral administration of curcumin (1,000 mg/kg) in rats showed 15 ng/mL in blood plasma at 50 minutes [97]. 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 hour of dosing [98]. 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 [99].

However, it has been found that 10 mg/kg of curcumin given intravenous in rats gave a maximum serum curcumin level of 0.36 μg/mL, whereas a 50-fold higher curcumin dose administered orally gave only 0.06±0.01 μg/mL maximum serum level in rat [96]. A very recent study by Sun et al. [69] showed that intravenous administration of unformulated curcumin to rats showed better availability of curcumin in blood plasma. The concentration was 6.6 μg/mL of blood plasma when administered 2 mg/kg through tail vain [69]. These studies suggest the role of route of administration on achievable serum levels of curcumin and also the comparison of serum level in rodents and humans.

2. Nanocurcumin

To increase the bioavailability of curcumin different formulations have been made. Among them, nanoglobules

based nanoemulsion formulation has been prepared to evaluate the potential for the solubility enhancement of curcumin (Fig. 2). During *ex vivo* study, the release of curcumin from nanoemulsion was found much higher than curcumin suspension. This indicated the enhancement of solubility of curcumin in aqueous solution [70]. Another study showed an encapsulating the curcumin into the hydrogel nanoparticles yielded a homogenous curcumin dispersion in aqueous solution compared to the free form of curcumin. Also, the *in vitro* release profile showed up to 95% release of curcumin from the developed nano-microparticulate systems [100].

The pharmacokinetics of curcumin and another formulation nanoemulsion curcumin (NEC) containing up to 20% curcumin (w/w) showed a 10 fold increase in the area under the blood concentration-time curve (AUC) 24 hours and more than 40-fold increase in the C(max) in NEC compared to curcumin in mice [54]. Another curcumin-loaded apotransferrin nanoparticles (nano-curcumin), prepared by sol-oil chemistry, releases significant quantities of drug gradually over a fairly long period, ~50% of curcumin still remaining at 6 hours of time. In contrast, intracellular soluble curcumin (sol-curcumin) reaches a maximum at 2 hours followed by its complete elimination by 4 hours [101]. The colloidal nanoparticles, named as 'theracurmin' showed AUC after the oral administration more than 40-fold higher than that of curcumin powder in rats. In healthy human volunteers, theracurmin (30 mg) when administered orally resulted 27-fold higher AUC than that of curcumin powder [102]. The nanoparticle of curcumin prepared by Cheng et al. [103] produced significantly higher curcumin concentration in plasma and six times higher AUC and mean residence time in mice brain than regular curcumin. Thus, nanocurcumin enhances bioavailability of curcumin in animals as well as in humans.

3. Polylactic-co-glycolic acid (PLGA)

To improve the pharmacokinetics of curcumin with enhancing its bioavailability other effective formulation PLGA encapsulated curcumin was prepared. *In vitro* study showed that PLGA-curcumin has very rapid and more efficient cellular uptake than curcumin. Intravenous administration of either curcumin or PLGA-curcumin (2.5 mg/kg), exhibited almost twice as high serum concentration of PLGA-curcumin than curcumin [104]. Another formulation PLGA and PLGA-polyethylene glycol (PEG) (PLGA-PEG) blend nanoparticles containing curcumin were prepared. The PLGA and PLGA-PEG nanoparticles increased the curcumin mean half-life in approximately 4 and 6 hours, respectively, and the C(max) of curcumin increased 2.9- and 7.4-fold, respectively. Compared to the curcumin aqueous suspension, the PLGA and PLGA-PEG nanoparticles increased the curcumin bioavailability by 15.6- and 55.4-fold, respectively. Thus these formulations are potential carriers for the oral delivery of curcumin [105]. Other study showed that curcumin encapsulated in low and high molecular weight PLGA have relatively different oral bioavailability of curcumin. It has been found that the relative bioavailability of high molecular weight PLGA conjugated curcumin has 1.67- and 40-fold higher than that of low molecular weight PLGA conjugated curcumin and conventional curcumin, respectively [106].

In support of previous study, it has been found that after oral administration of curcumin-PLGA-nanoparticles, the relative bioavailability was increased 5.6-fold and has a longer half-life compared with that of native curcumin. This improved oral bioavailability of curcumin found to be associated with improved water solubility, higher release rate in the intestinal juice, enhanced absorption by improved permeability, inhibition of P-glycoprotein-mediated efflux, and increased residence time in the intestinal cavity [107]. It has been also observed that PLGA-curcumin enhances two and six fold increases in the cellular uptake performed in cisplatin resistant A2780CP ovarian and metastatic MDA-MB-231 breast cancer cells, respectively, compared to free curcumin [108].

4. Liposomal encapsulation

Another formulation designed for improvement of bioavailability of curcumin is liposomal curcumin. Liposomes are considered as effective drug carriers because of their ability to solubilize hydrophobic compounds and to alter their pharmacokinetic properties. In rat oral administration of liposome-encapsulated curcumin (LEC) showed high bioavailability of curcumin. In addition, a faster rate and better absorption of curcumin were observed as compared to the other forms. Oral LEC gave higher C(max) and shorter T(max) values, as well as a higher value for the AUC, at all time points [109].

The formulation silica-coated flexible liposomes loaded with curcumin (CUR-SLs) and curcumin-loaded flexible liposomes (CUR-FLs) without silica-coatings have been designed and found that the bioavailability of CUR-SLs and CUR-FLs was 7.76- and 2.35-fold higher, respectively, than that of curcumin suspensions. Silica coating markedly improved the stability of flexible liposomes, and CUR-SLs exhibited a 3.31-fold increase in bioavailability compared with CUR-FLs [59]. Another study showed that curcumin incorporated into N-trimethyl chitosan chloride (TMC)-coated liposomes exhibited different pharmacokinetic parameters and enhanced bioavailability, compared with curcumin encapsulated by uncoated liposomes and

curcumin suspension. Uncoated curcumin liposomes and TMC-coated curcumin liposomes showed a similar *in vitro* release profile [62]. In order to facilitate the intracellular delivery of curcumin, a new type of liposomes-propylene glycol liposomes (PGL) were prepared. It has been observed from cell experiment *in vitro*, PGL exhibited the highest uptake of curcumin compared with that of conventional liposomes and free curcumin solution [63]. These studies indicate that liposome conjugated curcumin increases the bioavailablity of curcumin.

5. Cyclodextrin (CD)

CD, cyclic oligosaccharides, has been also used in order to improve curcumin's delivery and bioavailability via its encapsulation with CD. It has been found that CD encapsulated curcumin (CDC) had a greater cellular uptake and longer half-life in the cancer cells compared with free curcumin indicating CDC has superior attributes compared with free curcumin for cellular uptake [86]. In addition, the improvement of CUR permeability acrossed animal skin tissue was observed in CD encapsulated curcumin and was about 1.8-fold when compared with the free curcumin [110]. Thus, these studies suggest that CDC has improved *in vitro* and *in vivo* bioavailability and chemotherapeutic efficacy compared to curcumin alone.

6. Piperine

Besides these natural compounds have been also used to increase the bioavailability of curcumin. One of them is piperine, a major component of black pepper, known as inhibitor of hepatic and intestinal glucuronidation and is also shown to increase the bioavailability of curcumin. This effect of piperine on the pharmacokinetics of curcumin has been shown to be much greater in humans than in rats. In humans, curcumin bioavailability was increased by 2,000% at 45 minutes after co-administering curcumin orally with piperine, whereas in rats, it has been found that concomitant administration of piperine 20 mg/kg with curcumin 2 g/kg increased the serum concentration of curcumin by 154% for a short period of 1-2 hours post drug. The study shows that in the dosages used, piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects [95].

Another study also showed that piperine (20 mg/kg orally) when administered with curcumin (2 g/kg orally) enhances the bioavailability of the latter up to 20-fold more in epileptic rats [111]. Enhanced bioavailability of curcumin was also evidenced by other researcher when curcumin was administered orally concomitant with piperine. Intestinal absorption of curcumin was also found relatively higher when administered concomitantly with piperine, and it stayed significantly longer in the body tissues [112]. In view of these findings, curcumin-piperine (Cu-Pi) nanoparticles has been prepared by various methods [113]. The bioavailability, cellular uptake and biological effects of this nanoparticles are being tested.

Biological Activities of Formulated Curcumin

Accumulating data evident that most, if not all, formulated curcumin have better bioavailability and biological activities than unformulated curcumin. Nanosuspension of curcumin also induces more cytotoxicity in Hela and MCF-7 cells than curcumin [44]. Curcumin-decorated nanoliposomes has shown high affinity for amyloid-β1-42 peptide and exhibit protective effects against Alzhiemer's disease [66]. LEC also suppresses HNSCC growth *in vitro* and xenograft tumor in mice [40]. Curcumin liposomes of dimyristoyl phosphatidyl choline and cholesterol inhibit proliferation of prostate cancer cell 10 times more than curcumin [67].

Beside these, PLGA encapsulated curcumin has shown more potent than curcumin in inducing apoptosis of leukemic cells and in suppressing proliferation of various tumor cell lines. It was also more active than curcumin in inhibiting TNF-induced NF-κB activation and in suppression of NF-κB-regulated proteins involved in cell proliferation, invasion, and angiogenesis [104]. PLGA nanocapsulated curcumin found to eliminate diethylnitrosamine-induced hepatocellular carcinoma in rat [72]. Doxorubicin and curcumin in a single PLGA nanoparticle formulation, curcumin facilitates the retention of doxorubicin in nucleus for a longer period of time. It also inhibits the development of drug resistance for the enhancement of antiproliferative activity of doxorubicin in K562 cells [114].

CDC is another formulation of curcumin having anti-inflammatory and antiproliferative effects. CDC was found more active than free curcumin in inhibiting TNF-induced activation of the NF-κB and in suppressing gene products regulated by NF-κB, including those involved in cell proliferation, invasion, and angiogenesis. CDC was also more active than free curcumin in inducing the death receptors DR4 and DR5 and apoptosis [86]. CD entrapped curcuminoid also induces autophagic cell death in lung cancer cells and inhibits tumor growth in nude rats [115]. Besides these, other formulations such as dipeptide nanoparticles, phosphatidylcholine encapsulated curcumin, etc. have better efficacy in their biological activities compared to free

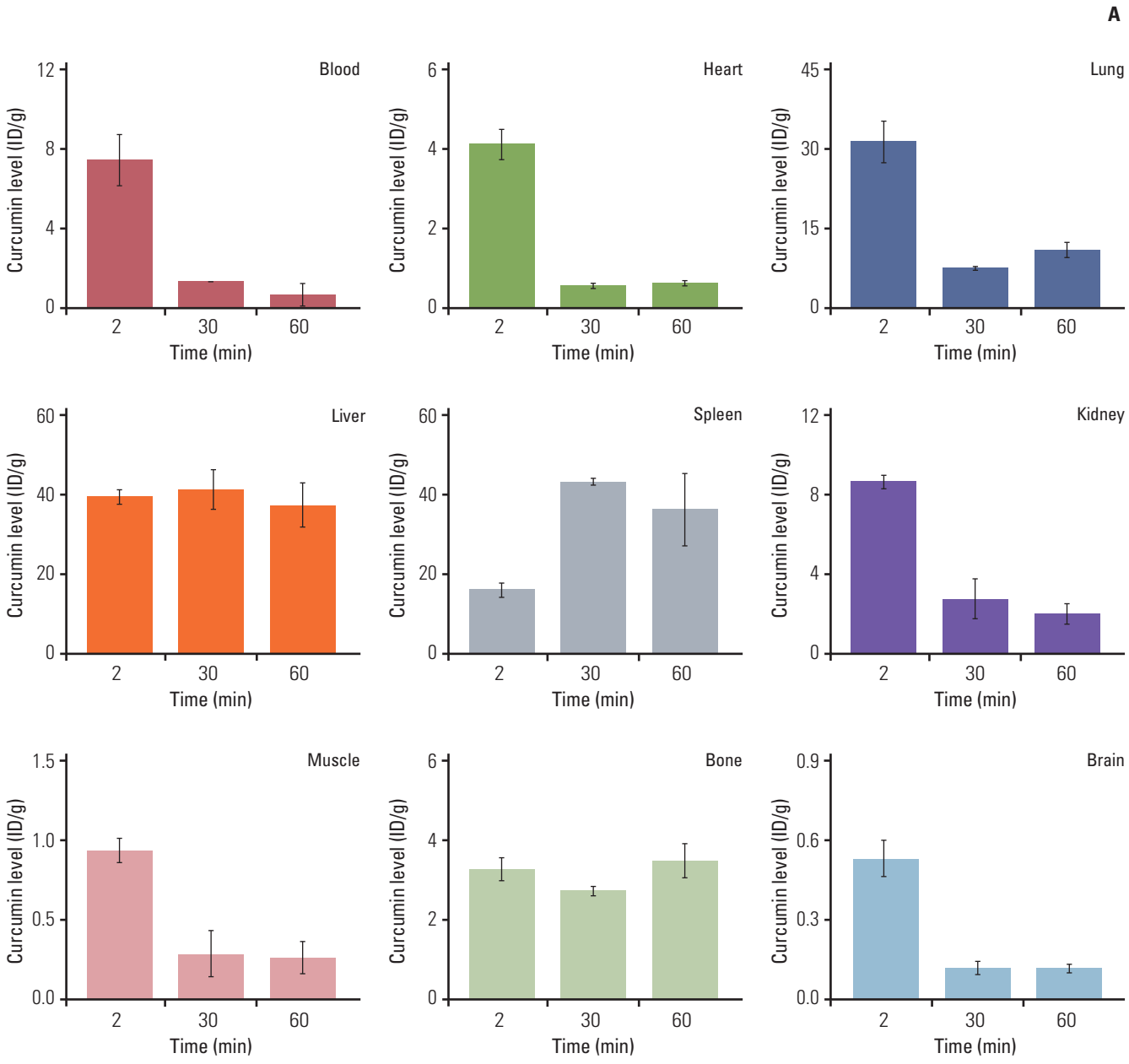

Fig. 3. Biodistribution of [^{18}F]-curcumin (A) and of [^{18}F]-curcumin co-injected with piperine (B) in mice. Adopted from Ryu et al. [117], J Med Chem. 2006;49:6111-9.

curcumin. Dipeptide nanoparticle of curcumin inhibits tumor growth in mice [87]. Phosphatidylcholine encapsulated curcumin exhibits antimalarial activity [88], inhibits vaginal inflammation [116] and induce cytotoxicity of cancer cells [81]. There are several other cucrumin formulation are synthesized having more biological activities than curcumin.

Absorption of Curcumin in Blood, Liver, Brain, Kidney, and Other Organs

Uptake and distribution of curcumin in body tissues is obviously important for its biological activity. Most of curcumin get metabolized in liver and intestine however, a small quantity is still remains detectable in the organs (Fig. 3A). Ryu et al. [117] has also shown bioavailability of

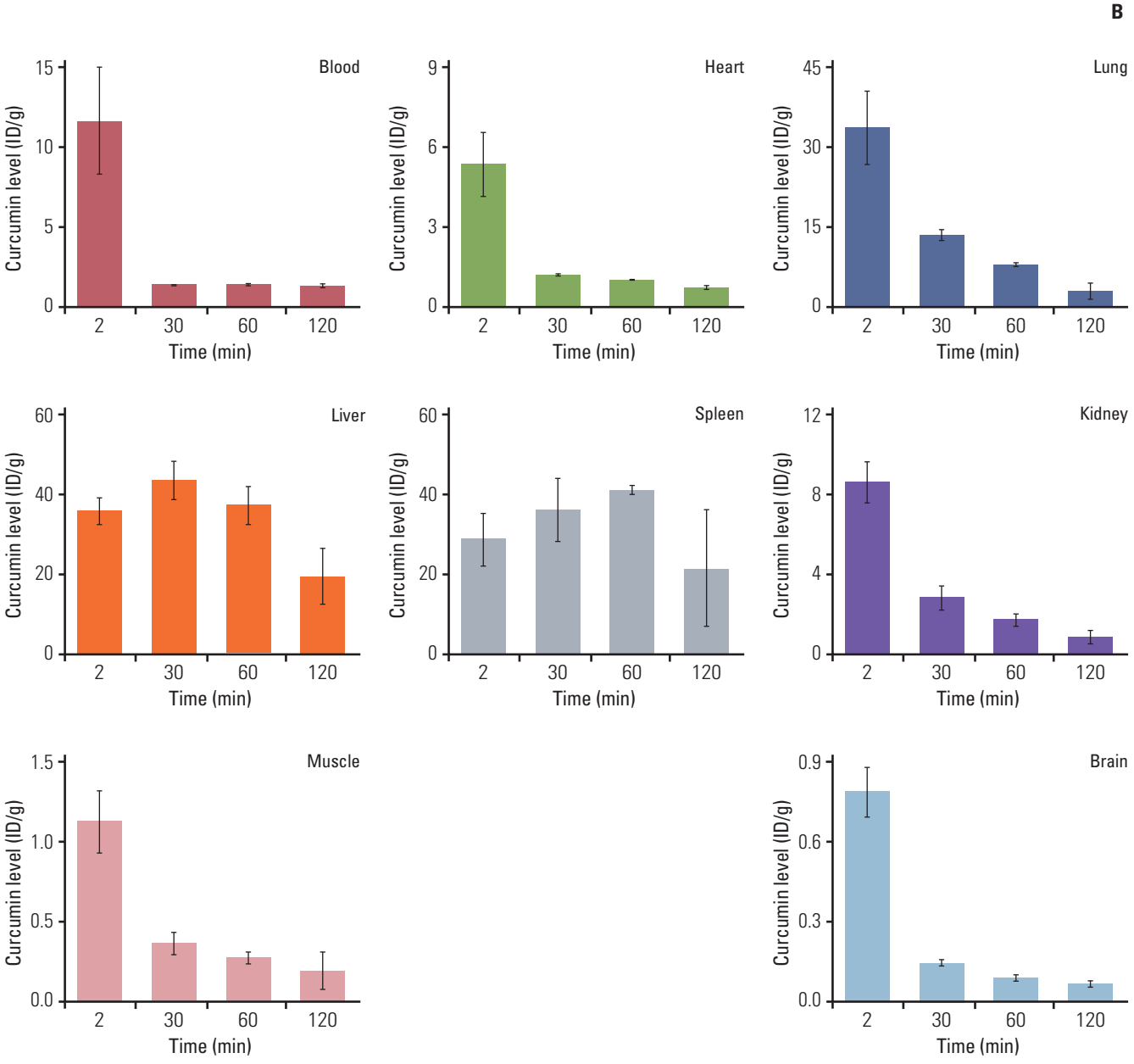

Fig. 3. Continued.

curcumin in different organ of mice. Intravenous injection of [^{18}F]-curcumin in mice found to persistently accumulated in the liver and spleen while lung uptake was found to decrease with time. Brain uptake of [^{18}F]-curcumin was at 2 minutes postinjection, and its radioactivity was rapidly washed out from the brain at 30 minutes [117]. Study by using radioactive [^{18}F]-curcumin and [^{18}F]-piperine in mice, it has been observed that initial brain uptake of [^{18}F]-curcumin was increased by 48% relative to that without piperine, although other organ uptakes were almost similar to those without piperine (Fig. 3B) [117]. These studies indicate that curcumin is bioavailable in several organs and its availability decreases with time depend on the organs.

Ravindranath and Chandrasekhara [118] showed oral administration of 400 mg curcumin to rats, about 60% of the dose was absorbed. However, very small quantities in liver and kidney (<20 μg/tissue) were observed from 15 minutes up to 24 hours after administration of curcumin [118]. Another study showed distribution of curcumin in the intestines, spleen, liver, and kidneys, which was 177.04, 26.06,

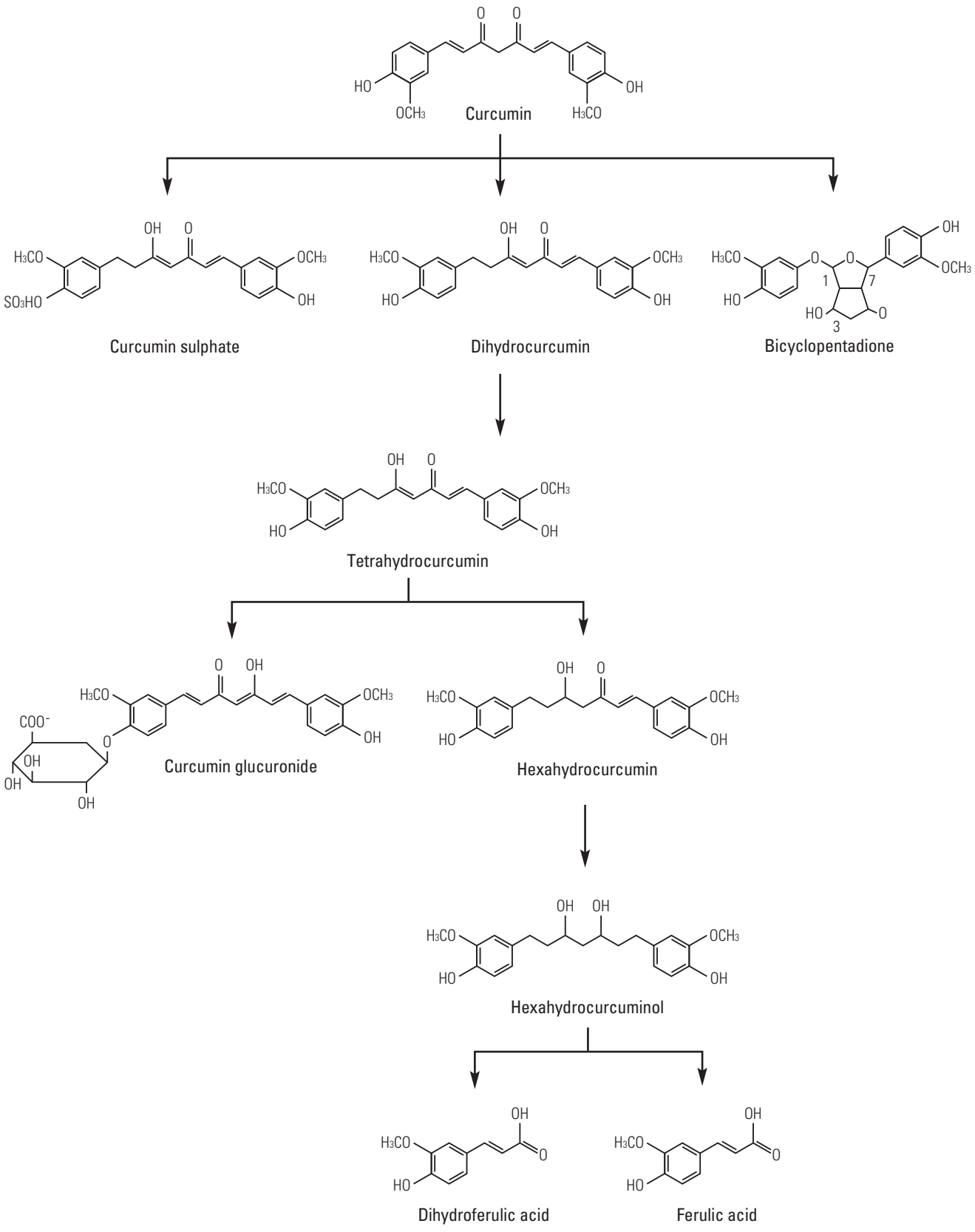

Fig. 4. Metabolism of curcumin.

26.90, and 7.51 μg/g, respectively after one hour i.p. administration of curcumin (0.1 g/kg) to mice. Only traces (0.41 μg/g) were observed in the brain at 1 hour [119]. Dietary curcumin (2%) has shown to yield low curcumin levels in the plasma, between 0 and 12 nM when given to the animals, whereas tissue concentrations of curcumin in liver and colon mucosa were 0.1-0.9 nmol/g and 0.2-1.8 μmol/g, respectively. In comparison with dietary administration, when curcumin given intragastric resulted more curcumin in the plasma but much less in the colon mucosa, indicating mode of administration play a role in distribution of curcumin [120]. In contrast, curcumin was poorly detected in patients of colorectal cancer. In a study of 12 patients with hepatic metastases from colorectal cancer, treatment of 450-3,600 mg of curcumin daily, for 1 week prior to surgery, poor availability of curcumin was observed in the peripheral or portal circulation following oral administration. While curcumin was not found in liver tissue, trace levels of products of its metabolic reduction were detected [121].

Using ultra performance liquid chromatography by Marczylo et al. [122] showed higher quantity of curcumin distribution in animals. In their experiment, rats were given oral curcumin (340 mg/kg) and after 2 hours tissue distribution was measured. Curcumin was found in plasma (16.1 ng/mL), urine (2.0 ng/mL), intestinal mucosa (1.4 mg/g), liver (3,671.8 ng/g), kidney (206.8 ng/g), and heart (807.6 ng/g) [122]. 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 amount 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 [123].

Metabolism of Curcumin

Numerous studies evaluated that curcumin undergoes metabolism in different components after oral administration in animals. Because of its metabolism, curcumin has demonstrated poorly bioavailable after p.o. dosing in animals [124], which may be related to its inadequate absorption. Curcumin bioavailability may also be poor in humans, as indicated by a pilot study of a standardized curcuma extract in colorectal cancer patients [120]. After p.o. dosing, curcumin undergoes metabolic O-conjugation to curcumin glucuronide and curcumin sulfate and bioreduction to tetrahydrocurcumin, hexahydrocurcumin, octahydrocurcumin, and hexahydrocurcuminol (Fig. 4) in rats and mice *in vivo* [119,124,125] and in suspensions of human and rat hepatocytes [124]. Reduced curcumin also subjected to glucuronidation into curcumin glucuronide, dihydro-curcumin-glucuronide, tetrahydrocurcumin-glucuronide, and curcumin sulfate [119]. Holder et al. [126] reported that the major billiary metabolites of curcumin are glucuronides of tetrahydrocurcumin and hexahydrocurcumin in rats. A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid.

Numerous studies have revealed that curcumin metabolites have antioxidative, anti-inflammatory and anticancer activities. Tetrahydrocurcumin (THC) inhibits radiation-induced lipid peroxidation [127] and induced antioxidant enzymes *in vitro* [128]. In rats, dietary administration of THC reduces aberrant crypt foci and polyps formation in azoxymethane-induced colon carcinogenesis [129]. Hexahydrocurcumin, another metabolite, has reduced ability to inhibit COX-2 expression compared to curcumin [124]. Hexahydrocurcumin also induce cell cycle arrest in human colorectal cancer SW480 cells [130]. Pan et al. [131] has shown that another metabolite, octahydrocurcumin, has very less NF-κB suppressive activity compared to curcumin. However, the free radical scavenging activity of octahydrocurcumin is higher than curcumin [132]. Beside these, we have recently showed that none of curcumin mono- or di-glucurnoid showed biological activity such as anti-inflammatory or antiproliferative activity compared to curcumin [133]. The curcumin metabolite, curcumin sulfate has shown to have less biological activities compared to curcumin. Curcumin sulfate inhibits prostaglandin E2 activity very poor than curcumin [124]. Thus these studies indicate that after metabolism of curcumin in different components, shows biological activities differ from parent curcumin.

Conclusion

Since ancient times, curcumin has been used in Asian countries against human ailments. Modern science has delineated the molecular basis for the pharmaceutical uses of curcumin. Multiple studies over the past decade have indicated the safety and efficacy of this polyphenol and have provided a solid basis for evaluating its efficacy in human clinical trials. Despite its efficacy and safety, limited curcumin bioavailability continues to be highlighted as a major concern. However in attempts to improve the bioavailability of curcumin, several strategies have been explored such as modulation of route and medium of curcumin administration, blocking of metabolic pathways by concomi-

tant administration with other agents, and conjugation and structural modifications of curcumin. Evidence from literatures indicated its increased bioavailability and efficacy in different experimental models with these strategies. In spite of these, improvements in curcumin bioavailability enhancement and efficacy have not gained significant attention in human. Therefore, further exploration in attempts to enhance the bioavailability, medicinal value, and application of this interesting molecule from Mother Nature are needed for human use.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

Dr. Aggarwal is the Ransom Horne, Jr., Professor of Cancer Research. This work was supported by a grant from Center for Targeted Therapy of MD Anderson Cancer Center.

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