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Review Article

BIOAVAILABILITY ENHANCEMENT TECHNIQUES OF HERBAL MEDICINE: A CASE EXAMPLE OF CURCUMIN

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ABSTRACT

Curcumin was characterized as an excellent molecule among many naturally occurring compounds for treatment and prevention of a wide variety of human diseases especially for cancer therapeutics. It was proved to be safe even used at very high dose. However, due to its very low bioavailability, curcumin has not yet been approved as a therapeutic agent. Many attempts have been made to increase curcumin bioavailability *via* the increase of its solubility, stability, and permeability by using several techniques. This review presents the bioavailability enhancement techniques of curcumin, covering the recent progress on chemical and pharmaceutical technology techniques, the use of new materials for formulation preparation, and the use of natural compound enhancers. In addition, the recent developed transdermal curcumin delivery is also presented.

Keywords: Curcumin, Herbal medicine, Bioavailability, Curcumin derivatives, Pharmaceutical technology, Natural enhancer, Transdermal delivery

INTRODUCTION

Curcumin: benefits and problems

Curcumin is a yellow color polyphenolic compound derived from the turmeric of the herb *Curcuma longa* L. Its chemical name is bis-α,β-unsaturated β-diketone or commonly called diferuloylmethane (Fig. 1), which exhibits keto-enol tautomerism having a predominant keto form in acidic and neutral media and stable enol form in alkaline medium [1]. Turmeric is widely cultivated in India and Asian countries for used in cooking. It has been also used as traditional medicine for many aliments particularly as an anti-inflammatory agent. Commercial curcumin extract typically contains approximately 77% curcumin, 17% demethoxycurcumin, and 6% bisdemethoxycurcumin, and altogether are called curcuminoids. Curcumin has been identified as the therapeutic active principle of turmeric [2,3].

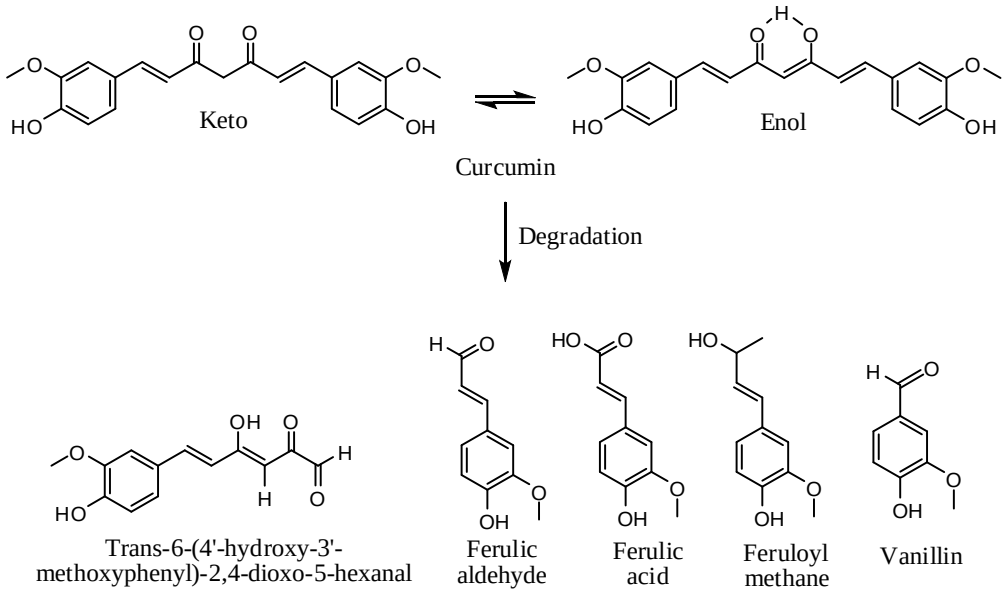

Fig. 1: Chemical structure of curcumin, where the α,β-unsaturated β-diketone (heptadiene-dione) moiety, undergoing keto-enol tautomerism and its degradation products.

In recent years, a wide biological and pharmacological property of curcumin has been extensively studied such as antioxidant, anti-inflammatory, antimicrobial, antimalarial, and anticarcinogenic activities [4-7].

Curcumin was characterized as an excellent molecule among many naturally occurring compounds for cancer therapeutics. The hepato- and nephro-protective, thrombosis suppressing, myocardial infarction protective, hypoglycemic, and antirheumatic effects of curcumin are also reported [8-10]. Curcumin has been shown in various animal models and human studies to be safe even used at very high doses (12 g/day) [11-13]. The pharmacological efficacy and safety 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. The major problem is related with the low bioavailability which poses significant pharmacological barriers for clinical application.

The pharmacodynamics and pharmacokinetics of drug are very important for therapeutic outcome, and the effective pharmacokinetics is a surrogate for pharmacodynamics. Although curcumin showed potential pharmacodynamics, it has poor pharmacokinetic characteristics, thus leading to give very low bioavailability. Curcumin is a hydrophobic compound, so having very poor solubility and low absorption. It also possesses rapid metabolism and rapid systemic

elimination. The solubility of curcumin in water especially at acidic and physiological pH is extremely low (11 ng/mL). It is hydrolyzed rapidly in alkaline solutions and readily decomposed when exposed to bright light, high temperature or oxidative conditions [14]. Based on its poor aqueous solubility and permeability, curcumin can be classified as a BCS class IV molecule [15]. Many attempts have been made to increase solubility, absorption (permeability) and stability of curcumin in order to increase bioavailability. Those were generally by using pharmaceutical technology techniques, chemical techniques or the use of enhancers. The aim of this review is to systematically present the bioavailability enhancement techniques of curcumin, covering the recent progress on chemical and pharmaceutical technology techniques, the use of new materials for formulation preparation, and the use of natural compound enhancers. The recent developed curcumin delivery focusing on transdermal delivery is also presented.

Bioavailability enhancement techniques of curcumin

Synthesis of curcumin derivatives

Several approaches in synthesis of curcumin derivatives for improve the chemical stability, solubility and permeability of curcumin have been taken in order to enhance the bioavailability of curcumin. Curcumin molecule contains chemically labile phenolic hydroxyl and β-diketone moieties make it susceptible to rapid hydrolysis followed by molecular fragmentation at physiological pH. The structure of degradation products are presented in Fig. 1. The highly reactive β-diketone moiety in the structure of curcumin causes it to be unstable at pH above 6.5. The half life ($t_{1/2}$) time of curcumin in phosphate buffered saline (PBS) at pH 7.2 was less than 10 min [16]. The β-diketone moiety also appears to be a specific substrate of a series of aldo-keto reductases and can be decomposed in human body rapidly. Moreover, the present of phenolic hydroxyl group causes curcumin has rapid metabolism since the glucuronidation is easily occurred [17]. Therefore, curcumin with its phenolic hydroxyl group capped or chemically labile moiety removed would become much more stable. Curcumin polymer or called polycurcumin synthesized by condensation polymerization of curcumin, two hydroxyl group capped (Fig. 2A), was stable at pH 7.4 for at least 48 h [18]. It was then expected to be stable at neutral conditions such as in the blood circulation and normal tissues. Acetal bonds of polycurcumin can be easily hydrolyzed at acidic pH producing oligomers and finally releasing curcumin. According to high molecular weight of polycurcumin, it could be prolonged in blood circulation and therefore has better chance to be passively accumulated in tissues *via* enhanced permeability and retention effects.

Although the remove of β-diketone moiety made curcumin more stable, β-diketone may be necessary for the biological activities of curcumin for some treatments. Some previous studies suggested that the presence of the β-diketone moiety may be necessary for the biological activities of curcumin, but from several recent studies demonstrated that some curcumin analogues containing a 5-carbon enone spacer without β-diketone either retained or increased growth suppressive activities against several cancer cells [19]. The structure activity relationships (SARs) study of curcumin for specific cancer therapy would be therefore evaluated before chemical structural modification. Some mono-carbonyl analogues of curcumin without the β-diketone moiety exhibited better antibacterial and anti-inflammatory activities than those of curcumin. The analogues lacking the β-diketone moiety (Fig. 2B) were much more stable in the pH 7.4 situation. Their contents still retained more than 90% of the original content after 75 h in pH 7.4 buffer [19]. It could be postulated that the hydrolytic degradation starts with an attack from the nucleophilic OH^- ion on the carbonyl carbon in the keto-enol form of the β-diketone moiety in curcumin.

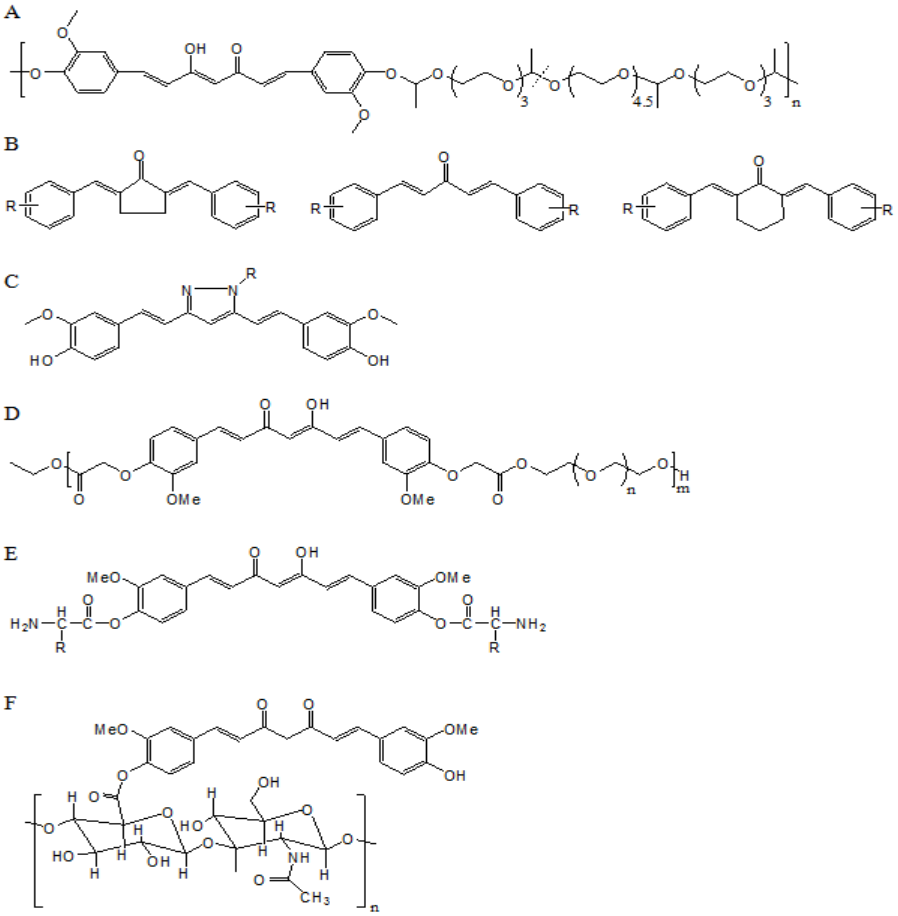

Fig. 2: Structures of synthesized curcumin derivatives: (A) polycurcumin; (B) the analogues lacking the β-diketone moiety; (C) the analogues replacing the 1,3-dicarbonyl moiety of curcumin with differently functionalized isosteric pyrazole rings; (D) PEGylated curcumin; (E) curcumin-amino acid conjugates; (F) curcumin conjugated hyaluronic acid.

Curcumin derivatives without labile β-diketone moiety and, at the same time, adding some hydrophilic functional groups would not only improve stability, but also increase water solubility of curcumin. Curcumin derivatives with high chemical stability, water solubility and high affinity to the β-amyloid peptides (Aβ) for the treatment of Alzheimer's disease had been synthesized by Airoldi et al. [20] From the SARs study of Aβ aggregation inhibitors based on curcumin pointed out the predominant features affecting inhibition of amyloid aggregation are the coplanarity of the two aromatic rings and the distance between them. Airoldi et al. then synthesized the series of compounds replacing the 1,3-dicarbonyl moiety of curcumin with differently functionalized isosteric pyrazole rings (Fig. 2C), in order to guarantee the coplanarity and to improve solubility and stability in physiological conditions. The synthesized curcumin derivatives presented an improved solubility, showing solubility higher than 1 mM in PBS, pH 7.4, which was significant compared to curcumin showing complete insoluble in water. The formation of the pyrazole moiety locks the keto-enol tautomerism in an enol-type arrangement, important for its Aβ-binding capability, and, at the same time, removes the chemically labile β-diketone moiety. From NMR experiments it carried out some hours after synthesized compound dissolution in PBS, pH 7.4, and incubation at 37 °C, afforded spectra identical to those recorded immediately after their dissolution. In contrast, curcumin was described to undergo degradation few minutes after dissolution in PBS buffer, about 90% decomposed within 30 min.

Conjugation of drugs to the chain ends or side chains of water-soluble polymers, namely polymer-drug conjugates, is one of the general approaches to increase the drugs' water solubility. Polyethylene glycol (PEG) is one of the most employed compounds. It has several advantages including biocompatible and can solubilize in both organic and aqueous media providing more room for modifications. PEGylate the curcumin as PEGylation is not only enhances the aqueous solubility but also prolongs the bioavailability [21,22]. Pandey et al. synthesized PEGylated curcumins (Fig. 2D) as water soluble drug candidates as Nrf2 activator (for chemotherapy) with enhanced aqueous solubility and bioavailability [23]. Curcumin was judiciously converted to diester using ethyl α-bromoacetate and potassium carbonate. The diester in subsequent step was copolymerized with PEG using Candida antarctica lipase under solventless condition. The enhanced affect of PEGylated curcumin analogs as Nrf2 activator than the free curcumin was observed and was attributed due to higher aqueous solubility and that could enhance bioavailability may be by enhanced membrane permeability. The PEGylation effect on some other drugs has recently been documented and justified how PEGylation changes the in vivo efficacy of drugs by modulating the balance between their pharmacodynamic and pharmacokinetic properties.

Curcumin conjugate with other water soluble compounds such as amino acid or hyaluronic acid in order to increase curcumin's water solubility were also reported. Curcumin-amino acid conjugates especially with glycine and proline (Fig. 2E) had high water solubility (10 mg/mL) [24]. The hyaluronic acid (HA), a naturally occurring polysaccharide has a strong affinity with cell specific surface markers such as CD44 and RHAMM. Thus, malignant cells with high metastatic activities often exhibit enhanced binding and uptake of HA. Conjugation of curcumin onto hyaluronic acid (Fig. 2F) could enhance its aqueous solubility and also site-specific of action. A significant increase in its solubility was observed over 7.5 mg/mL, corresponds to 95.5 μg/mL of curcumin [25]. Moreover, curcumin-hyaluronic acid conjugate had high stability at physiological pH. The high stability of the conjugate comparing to curcumin can be from the formation of micelles. In the micelle, the conjugated curcumin exist in the inner core due to its hydrophobicity. The hydrophilic HA molecules, on the other hand, protrude outwardly. The micelle formation thus protects curcumin from the deprotonation and subsequent fragmentation in the alkaline media. The conjugation of curcumin to HA advantageously stabilizes curcumin against hydrolysis and hence enhance its aqueous stability.

The increase solubility and stability of curcumin was also tried by complexation with cyclodextrins (CyDs) and soy protein isolate. The curcumin-CyD inclusion complexes could be prepared by several methods such as solvent evaporation, precipitation, and freeze drying methods [26-28]. Complex formation resulted in an increase in water solubility at pH 5 by a factor of at least 10^4. The hydrolytic stability of curcumin under alkaline conditions was strongly improved by complex formation, while the photodecomposition rate was increased compared to a curcumin solution in organic solvents [29]. The cavity size and the charge and bulkiness of the cyclodextrin side chains influenced the stability constant for complexation and the degradation rate of the curcumin molecule. For using soy protein isolate, Tapal et al. found that soy protein isolate can form a complex with the curcumin through hydrophobic interactions [30]. Upon complexation, curcumin showed increased water solubility, stable under UV and in simulated gastric and intestinal fluids for 12 h, which would provide sufficient time for intestinal absorption.

Pharmaceutical technology

Many attempts have been made to enhance bioavailability of curcumin by preparing it in novel formulations. Nanoparticles, liposomes, micelles, and phospholipid complexes are promising novel formulations, which appear to provide better permeability, longer circulation, and resistance to metabolic processes. Various types of curcumin nanoparticles such as curcumin nanocrystals and conjugates, curcumin encapsulated polymer nanoparticles, curcumin self-assemblies and nanogel, and so on, have been reviewed systematically elsewhere [31]. Therefore, the focus of this topic is to present the recent advance of curcumin formulations which were objected to improve pharmacokinetics and/or bioavailability of curcumin. Some interesting materials used in formulation preparation and the reason of their bioavailability improvement are also presented.

Nanoparticles

Nano-formulation of curcumin was developed to overcome major obstacles associated with curcumin's bioavailability like poor solubility, stability and absorption, and rapid systemic metabolism. The size distribution and surface charge of nanoparticles (NPs) are important. As we know that small size of particles are advantageous for passive targeting to tumor tissue by enhanced permeability and retention effect [32,33] and higher zeta potential influence the particle stability, cellular uptake and intracellular trafficking [34]. Choi et al. have found that the cutoff size for renal filtration is about 5.5 nm [35], particle size larger could not pass the renal filtration to excretion. Accordingly, reduced liver metabolism and renal excretion of curcumin could extend the retention time of curcumin in blood when intravenously administered. The selection of a nanoparticle preparation method for effective encapsulation of active agents involves choosing the right polymer composition, stabilizer, solvent, drug solubility and preparation technique [36]. The size, polydispersity index and entrapment efficiency are also depended on composition materials used [37].

Many materials have been explored to use as nanoparticle carriers such as poly lactic-co-glycolic acid (PLGA), human serum albumin (HSA), chitosan, poly(ε-caprolactone) (PCL), glycerol monooleate (GMO), etc. PLGA is the most generally used, because of its solid state solubility, compatibility, biodegradability, and versatile degradation kinetics. The curcumin encapsulated nanoparticles in these materials could be prepared by several techniques such as emulsion, precipitation and solvent evaporation techniques [37-40]. In general, PLGA NPs exhibit negative zeta potential. The curcumin-PLGA NPs are highly soluble in water, i.e., 1.23-1.76 mg of curcumin equivalent. The high solubility characteristics of curcumin-PLGA NPs may be a result of compatibility between polymer NP and curcumin compounds. The drug release from PLGA nanoparticles occurs by diffusion followed by degradation and is molecular weight/copolymer ratio dependent [40]. Curcumin loaded PLGA nanoparticles were considered to improve the oral bioavalability of curcumin. Blood levels after oral administration of nanoparticulate formulation were compared with oral curcumin suspension and suspension of curcumin with piperine as absorption enhancer (Fig. 3). The encapsulated curcumin into PLGA nanoparticles demonstrate at least 9-fold increase in oral bioavailability when compared to curcumin administration with piperine as absorption enhancer. The plasma concentration of curcumin from suspension formulations decreased rapidly, indicating rapid metabolism of curcumin. Whereas, a sustained release of curcumin over 48 h was observed in the nanoparticle form.

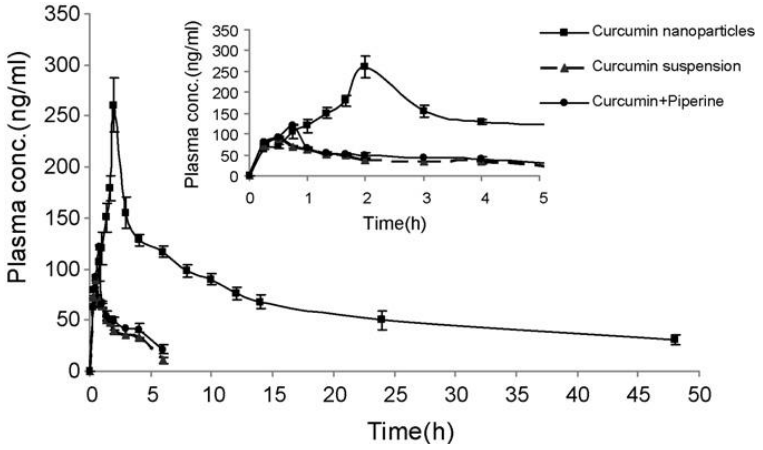

Fig. 3: Comparative *in vivo* plasma concentration *vs.* time profiles of different curcumin formulations. All values reported are mean±S.E.M. (n=5) [40].

Human serum albumin (HSA) is another excellent nanoparticle carrier because it is non-toxic and non-immunogenic. Furthermore, albumin bound nanoparticle technology does not require surfactants or polymeric materials for preparation. Accordingly, it is believed that HSA nanoparticles are likely to be well tolerated *in vivo*. Curcumin-HSA-NPs showed much greater water solubility (300-fold) than free curcumin. Amounts of curcumin in tumors after treatment with curcumin-HSA-NPs were about 14 times higher at 1 h after injection than that achieved by curcumin [41].

Recently much attention was given for bioadhesive delivery systems to enhance the drugs bioavailability by increasing the residence time which subsequently facilitate the absorption of drug through adhesion with the cellular surface. Chitosan as a cationic polysacharide has gained much attention in this field because of its nontoxic, biocompatible, and biodegradable nature. The strong mucoadhesive property of chitosan along with its interaction with tight junction facilitates the paracellular transport of macromolecules by opening the tight junction of the mucosal barriers [42]. As a cationic ligand, chitosan can facilitate the active transport of nanoparticles *via* absorptive mediated transcytosis. Chitosan based nanoparticle formulations have been employed for loading and delivering different drugs and vaccines. Curcumin loaded chitosan nanoparticles when delivered orally improved the bioavalability of curcumin in the plasma and red blood cell. Moreover, curcumin bound to chitosan nanoparticles can improve its chemical stability studied in mouse plasma [43]. A novel formulation of curcumin loaded poly(ε-caprolactone) (PCL) plus chitosan was developed recently by Liu et al. to obtain cationic nanoparticles of curcumin [38]. PCL as a non-toxic degradation product has been approved by FDA for various biomedical applications. There are numerous literatures on the synthesis of PCL micro/nanoparticles for drug delivery applications. Curcumin-PCL nanoparticles with appropriate surface modifications with chitosan to obtain cationic nanoparticles can improve the cell uptake of curcumin as compared to unmodified curcumin [38].

Liposomes, Micelles, and Phospholipid complexes

Liposme is one very promising delivery system because it has a phospholipid bilayer structure, which is similar to that of biological membrane, allowing for both stabilization of the compound in physiological pH and increasing its solubility in aqueous environment. A comparison of the stability of free curcumin and liposomal curcumin in phosphate buffered saline (PBS) was studied and the result found that liposomal curcumin can enhance curcumin stability in PBS. The high-lipo-curcumin formulation (DMPC:DMPG:cholesterol:curcumin = 70:10:80:0.5, molar ratio) can protect curcumin 100% after incubation in PBS (pH 7.4) at 37˚C for 180 min [44]. Curcumin enhanced the gastrointestinal absorption by liposomes encapsulation. Takahashi et al. prepared liposome encapsulated curcumin from commercially available lecithins (SLP-WHITE and SLP-PC70). Pharmacokinetic parameters after oral administration of liposome encapsulated curcumin were compared to curcumin and a mixture of curcumin and lecithin. High bioavailability of curcumin was evident in the case of oral liposome encapsulated curcumin; a faster rate and better absorption of curcumin were observed as compared to the other forms [45].

Micelles are aggregates of amphiphilic molecules that form at a concentration referred to as critical micelle concentration (CMC). One of the unique and very useful properties of micelles is their capacity to solubilize solute molecules that are otherwise insoluble in aqueous solutions [46]. Many methods (e.g., direct dissolution, solid dispersion, dialysis, and co-solvent evaporation) have been used for preparing micelles. Beta-casein (B-CN), an amphiphilic self-assembling protein that can form micellar nanostructures, could be used as a carrier system for hydrophobic therapeutic agents such as curcumin. Camel B-CN was used for curcumin encapsulation in the study of Esmaili et al. It was shown that camel B-CN increased the solubility of curcumin at least 2500-fold. Antioxidant activity of curcumin encapsulated in B-CN was also investigated and found that having higher than that of both free B-CN and curcumin [47]. Song et al. prepared polymeric micelles of curcumin using amphiphilic methoxypoly(ethylene glycol)-b-poly(ε-caprolactone-co-p-dioxanone) [MPEG-P(CL-co-PDO)] copolymers as micelle carrier and lyophilized without any lyoprotective agents. The lyophilized curcumin loaded micelles were easy to reconstitute and completely dispersed in water by simple shaking. The reconstituted curcumin loaded micelles was stable at least 24 h at the room temperature [48]. Song et al. also developed new triblock copolymeric micelles (PLGA-PEG-PLGA) to modify the pharmacokinetics and tissue distribution of curcumin [49]. The curcumin loaded PLGA-PEG-PLGA micelles were prepared by dialysis method. The plasma $AUC_{0-\infty}$, $t_{1/2\alpha}$ and $t_{1/2\beta}$ of curcumin micelles were increased by 1.31-, 2.48-, and 4.54-fold, respectively compared to the curcumin solution. The micelles decreased drug uptake by liver and spleen and enhanced drug distribution in lung and brain. These results suggested that PLGA-PEG-PLGA micelles would be potential carrier for curcumin.

Phospholipid complex is a common try to increase drugs' bioavailability since it can improve the gastrointestinal absorption to achieve higher drug concentration in plasma and lower kinetic elimination, and the technique is easy to prepare by using suitable solvent treatment. Several studies have indicated the beneficial role of phospholipids in enhancing the oral bioavailability of some natural drugs having poor oral absorption such as silybin, quercetin, silymarin, dolichol, saponins from *Centella asiatica* [50], and also curcumin [51]. Curcumin-phospholipid complex has much higher solubility in water or *n*-octanol than curcumin or physical mixture of curcumin and phospholipid. The complex significantly increased the rate of absorption which serum concentration of curcumin obtained from the complex (equivalent to 1.0 g/kg of curcumin) was higher (C_{max} 1.2 μg/mL) than pure curcumin (1.0 g/kg) (C_{max} 0.5 μg/mL) and the complex maintained effective concentration of curcumin for a longer period of time in rat serum. Accordingly, curcumin-phospholipid complex has better hepatoprotective activity, owe to its superior antioxidant property, than free curcumin at the same dose level [51].

Natural Compound Enhancer

The popularity of herbal medicines has risen worldwide with believe that the risk associate with herbal drugs is less than that with synthetic drugs. In traditional disease therapy with herbal medicines, several herbs are used in combination in order to obtain better therapeutic effect than just one herb used due to the synergistic effect or treatment the disease with different mechanism. It was suggested that curcumin may be administered with other lipophilic vehicles such as corn oil to increase absorption [52]. The permeation of curcumin was more from turmeric than from plain curcumin. Accordingly co-existing curcuminoids (the mixture of curcumin and two other curcuminoids) may improve the bioavailability of curcumin [52]. Since the increase of drug absorption and bioavailability is very important issue within the pharmaceutical industries, the use of absorption enhancers is one promising way. In Ayurveda, black paper (*Piper nigrum* L.), long pepper (*Piper longum* L.) and ginger (*Zingiber officinalis* L.) are mentioned as essential ingredients of many prescription and formulations used for a wide range of diseases. It was revealed that these three herbs have important role to play in increasing drugs' bioavailability when given orally although the mechanisms by which it enhances the bioavailability is not clearly understood [53]. For using herbal medicines, the safety is very important. Some natural compounds have demonstrated to increase the absorption and bioavailability of co-administered drugs. Bioavailability and absorption enhancement through co-administration of drugs with naturally occurring compounds from plants are considered to be very simple and relatively safe. Several natural compounds are reported recently as bioenhancer of curcumin's oral bioavailability. These include piperine, quercetin, and epigallocatechin-3-gallate.

Piperine (1-piperoyl piperidine) is a major alkaloidal component of *Piper nigrum* L. or *Piper longum* L. The mechanism of enhancing the drug bioavailability may be from 1) increased blood supply to the gastrointestinal tract, 2) inhibited hepatic enzymes and intestinal glucuronidation, and 3) related to alteration of the lipid fluidity on the cell membrane [53]. Shoba et al. combined piperine with curcumin and administered in rat and healthy human volunteers. When curcumin was given alone, in the dose 2 g/kg to rats, moderate serum concentrations were achieved over a period of 4 h. Concomitant administration of piperine 20 mg/kg increased the serum concentration of curcumin for a short period of 1-2 h post drug. Time to maximum (Tmax) was significantly increased while elimination half life and clearance significantly decreased, and the bioavailability was increased by 154%. On the other hand in humans after a dose of 2 g curcumin alone, serum levels were either undetectable or very low. Concomitant administration of piperine 20 mg produced much higher concentrations from 0.25 to 1 h post drug, the increase in bioavailability was 2000%. The study showed 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 [54].

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) is a flavonoid, an aglycone form of a number of other flavonoid glycosides found in citrus fruits. The mechanism of quercetin to increase drugs' bioavailability is from the inhibition of the P-gp efflux pump and the metabolizing enzyme, CYP3A4 in the intestinal mucosa [53]. Cruz-Correa et al. evaluated the efficacy of the combination of curcumin (480 mg) and quercetin (20 mg) to regress adenomas in patients with Familialadenomatous polyposis (FAP) *via* oral 3 times a day. All patients had a decreased polyp number (60.4%) and size (50.9%) after a mean of 6 months of treatment with curcumin and quercetin without appreciable toxicity [55]. However, this study did not compare with curcumin alone.

The effect of curcumin could be increased by using in combination with other natural compound. Epigallocatechin-3-gallate (EGCG), a component polyphenol green tea, was reported to counteract certain activities assigned to curcumin [56]. Overall, this study concluded that curcumin and EGCG produce opposite antioxidant effects. That was an important consideration in the context of therapeutic antioxidant use.

Recently, a novel formulation of curcumin with an enhanced bioavailability of curcumin using galactomannan fiber derived from the spice fenugreek was reported. The formulation was prepared as dispersion microgranulates by an ultrasound mediated gel-phase dispersion technique. The enhanced bioavailability of formulation was demonstrated in both rats and human volunteers in comparison with unformulated curcumin. The authors found that the relative absorption of curcumin from the novel fiber formulation was 20 times higher in animals and 15.8 times higher in humans when supplemented orally. These results were explained from the effect of dispersion formulation and the prolonged release from the non-digestible soluble fiber matrix protected curcumin against rapid enzymatic degradation in gastrointestinal tract [57]. Other natural material applied in an enhanced bioavailability of curcumin is cashew nut tree (*Anacardium occidentale*) gum. It was used as a natural buccoadhesive polymer for buccal tablet of curcumin. The buccal resident time of developed formulation was about 8 h and the mucoadhesive strength was 13.99 g. The mucoadhesive buccal tablets evaluated represent an improved transbuccal delivery system for drug substances. It could suggest that cashew nut tree gum can be used as a polymer to produce buccoadhesive tablets of curcumin with potential to bypass the first pass metabolism and improve the bioavailability of curcumin [58].

Transdermal Curcumin Delivery

Curcumin has very poor permeability studied by using Caco-2 cell model [15]. Based on its poor aqueous solubility and intestinal permeability, curcumin can be classified as a BCS class IV molecule. Curcumin is also suspected to have high first-pass metabolism delivered by the oral route. Many attempts therefore tried to use curcumin *via* another route such as buccal or skin. Das prepared curcumin in the form of mucoadhesive buccal patches by using polyvinylpyrrolidone (PVP K-30), and found that they could heal the lesion within a short period time [59]. Transdermal delivery (skin route) represents an attractive alternative to oral delivery for local and systemic therapeutic uses. The use of curcumin for the chemoprevention and treatment of various skin diseases like scleroderma, psoriasis and skin cancer was review by Thangapszham et al. [60] Transdermal drug delivery can avoid first-pass metabolism and also is considered as a convenient route for drug administration. However, the important obstacle for transdermal drug delivery is skin barrier from stratum corneum. It was the top layer of the skin make most drugs are difficult to pass through. Many strategies have been employed to enhance transdermal delivery such as the use of chemical penetration enhancers, preparation of novel formulation such as nanoformulation, liposomes, electrically driving molecules into the skin by iontophoresis, and physically disrupting the skin structure by electroporation or sonophoresis.

Fang et al. studied the efficacy of enhancers including terpenes, flavonoids and cholestanol for percutaneous absorption of curcumin in rat [61]. They found that cyclic monoterpenes gave stronger enhancement of curcumin permeation than other enhancers. The mechanism might be from the potent of producing transepidermal water loss (TEWL). Terpineol produced the highest TEWL values among the enhancers tested as compared with control. Recently Liu et al. compared the efficacy of several terpenes on skin permeation rate of curcumin using neonate pig skin [62]. The studied terpenes included limonene, 1,8-cineole, and α-terpineol. The formulation was prepared as microemulsion. They found that curcumin permeation rates in the limonene microemulsion studies were 30- and 44-fold higher than those of 1,8-cineole and α-cineole microemulsions, respectively. Terpenes are reported to enhance drug diffusivity and partitioning into the stratum corneum by disturbing the skin lipid bilayers [63]. The content ratio of limonene/water was also affected the rate of skin permeation. The optimal content of water was 5%. The authors concluded that the small amount of water in the microemulsion may have hydrated proteins in the stratum corneum and caused a disordering of the lipid bilayers in coneous cells.

Stratum corneum is the top layer of the skin and is the obstacle for drug delivery. It is difficult for most drugs to be delivered into and

through it. Many drugs incorporated into microemulsions can efficiently penetrate the skin. From the preparation of curcumin incorporated into oil-in-water microemulsion and studied the efficacy of skin penetration by using tape stripping method to remove the stratum corneum [64]. The stranum corneum was accessible by a number of 20 tapes removed and significantly small amounts of curcumin were found on the skin surface in comparison with curcumin incorporated into amphiphilic cream. Nanotechnology was also applied for development curcumin delivery *via* skin. Curcumin loaded chitin nanogels (CCNGs) were developed by using biocompatible and biodegradable chitin with curcumin [65]. The obtained nanogels were spherical particles in a size range of 70-80 nm. The CCNGs showed a 4-fold increase in steady state transdermal flux of curcumin as compared to that of control curcumin solution. The histopathology studies of the porcine skin samples treated with the prepared materials showed loosening of the horny layer of the epidermis, facilitating penetration with no observed signs of inflammation. Recently, Li et al. developed curcumin nanoformulation loaded methoxy poly(ethylene glycol)-graft-chitosan composite film for wound healing application [66]. They prepared curcumin nanoformulation first by fabricating curcumin into MPEG-PCL nanoparticles with the absence of any stabilizers or surfactants in formulation, and then encapsulated into MPEG-chitosan film. The developed curcumin nanoformulation was spherical and monodisperse with a mean diameter of about 40 nm, and clearly dissolved in water. The curcumin-MPEG-chitosan film was proved to increase the rate of wound reduction as compared with MPEG-chitosan film treatment. Moreover, the formulation that can control the release of curcumin efficiently would increase curcumin's permeation through skin. The combination of carbopol and hydroxypropyl methylcellulose (HPMC) was found to allow curcumin diffused from the formulation with Peppas kinetic model [67].

Iontophoresis was another technique could be used for facilitating the skin permeation of many drugs and curcumin. Chang et al. was prepared liposome encapsulated curcuminoids (LEC) for transdermal delivery for breast cancer therapy with the application of formulation with iontophoresis [68]. The formulation of curcumin as LEC applied with iontophoresis could elevate the accumulation and flux with a 5-fold over that of curcuminoids without liposomal encapsulation. The authors concluded that the liposomal encapsulation could increase transdermal delivery of curcuminoids and iontophoresis could enable the transdermal delivery of liposome encapsulation during breast cancer therapy.

CONCLUSIONS

This review presents the bioavailability enhancement techniques base on chemical and pharmaceutical means for herbal medicine: curcumin. Curcumin derivatives in form of polycurcumin, the analogues lacking the β-diketone moiety, the analogues replacing the 1,3-dicarbonyl moiety of curcumin with isosteric pyrazole rings, PEGylated curcumin, curcumin-amino acid conjugates and curcumin conjugated hyaluronic acid were proved to increase stability, solubility, and/or permeability of curcumin which finally lead to enhance curcumin bioavailability. Some interesting materials e.g., poly lactic-co-glycolic acid (PLGA), human serum albumin (HAS), chitosan, poly(ε-caprolactone) (PLC), lecithins, and beta-casein can be used efficiently to prepare curcumin nanoformulation, liposomes, micelles, and/or phospholipid complexes which make curcumin high solubility and stability. The material selected for use and formulation preparation technique pay important role for bioavailability enhancement effect. Recently, attempts were paid attention to natural materials; galactomanan fiber and cashew nut tree gum showed potential to act as curcumin absorption enhancing agents. Since transdermal delivery is one of potential routes for curcumin administration, the combination of chemical and pharmaceutical technology techniques, with the use of natural enhancer to design a novel curcumin formulation for transdermal delivery would be a potential way for giving maximal curcumin bioavailability. These techniques would be also efficiently applied to other herbal medicines delivery.

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