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Curcumin, the panacea: A review on advancement to solve pharmaco-kinetic problems

Nitika Mor and Neera Raghav*

Chemistry Department, Kurukshetra University, Kurukshetra-136119, Haryana (INDIA)
*Email: * nraghav.chem@gmail.com, mor.nitika@rediffmail.com*
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Abstract: In the wake of COVID-19 pandemic, whole human race across the globe is suffering directly or indirectly. Natural defense system of body plays a significant role in maintenance of optimum health. Therefore it is better to practice the prevalent idea that is prevention is better than cure. In India, ministry of AYUSH has issued some recommended measures. One of these is Ayurvedic immunity promoting measures and includes consumption of turmeric as golden milk. Curcumin, the active ingredient of turmeric is a molecule of immense importance as it exhibits diverse biological activities. Although curcumin displays various pharmacological activities, it has limited bioavailability due to poor aqueous solubility. The present review addresses to bioavailability of curcumin related pharmacokinetic problems and concurrent solutions.

Keywords: Curcumin, pharmacokinetic, bioavailability, sustained release.

1. Introduction

Dependency of human kind on natural products (NPs) has been aged as old as human existence. Use of NPs as medicine plays a vital role in treatment of various ailments from ancient time to contemporary medicinal system. NPs have served as lead molecules in drug discovery and development and their analogs with improved efficacy, potency, safety and purity [1-3] are in therapeutic use. Use of NPs as drugs requires knowledge of traditional medicines, detailed analysis of their pharmacological activities including understanding the molecular mechanism of action. Thereafter, new drugs as derivatives or analogues of NPs can be approved by FDA. Most of natural products used in traditional medicinal systems have been found to be safe or nontoxic with effective doses [4-5]. Over the last two decades, trends in understanding the molecular mechanism of action of natural plants that can be used as therapeutic agents has been in focus. One such molecule of great therapeutic potential

is curcumin an active ingredient of *Curcuma longifolia ver*. Turmeric.

Curcumin, a yellowish orange compound chemically known as 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxy phenyl)-(1E,6E) also called diferulolylmethane, a hydrophobic polyphenol derived from the rhizomes of herb of *Curcuma longa*, belonging to the ginger family, *Zingiberaceae*, which is the essential ingredient from Indian kitchen. In ancient times, many different cultures such as Chinese, Egypt, and Arabians have also used turmeric in medicine to cure different ailments like colds, parasitic diseases, leprosy, skin disease, inflammatory conditions including bronchitis, arthritis, inflammation of bladder, liver and kidney, urinary tract infections and diarrhea [6-9]. Curcuminoids are the diarylheptanoids, the major pharmacological active ingredients of turmeric. Curcumin, the major constituent of curcuminoids; only 3-5% of turmeric has been consumed for medicinal purpose for thousands of years. Commercial curcumin contains three components: curcumin (71.5%), demethoxycurcumin (19.4%) and bis-demethoxycurcumin (9.1%) show in fig.1 [6, 10-11].

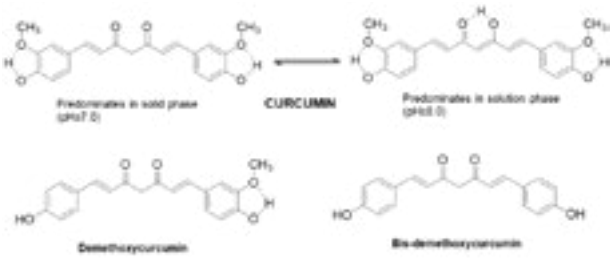

Figure1. Structures of curcuminoids

Curcumin has more probability to interact with biomolecules due to its interesting structure. Owing to its symmetrical geometry; the conjugated system of any direction can be accessible to biomolecules without any steric restriction and may be one of the reasons of its interaction with variety of molecular targets. It exhibits keto-enol tautomerism, keto form in acidic and neutral medium and stable enolic form in alkaline medium. The fact that curcumin in solution exists in its enolic form which is mainly responsible for radical-scavenging ability of curcumin [10, 12]. It exhibit diverse pharmacological activities like anti-inflammatory, antioxidant, antiviral, antifungal, anti-Alzheimer, immunomodulatory, anti-tumor, anti-diabetic and anti-rheumatic activities [13-16]. In addition, curcumin also proved to be a hepato-, cardio-, and neuro-protective molecule and thrombosis suppressing and myocardial Infarction protective molecule [17-22]. This review offers the reader an understanding about curcumin literature related to its bioavailability with pharmacokinetic problems, and concurrent solutions.

2. Pharmacokinetic and Pharmacodynamic studies of curcumin

Besides, curcumin displays multiple pharmacological activities but it has limited clinical performance due to its low bioavailability; probably because of its poor aqueous solubility, less distribution in the tissues, low serum levels, and rapid metabolism [23]. The pharmacokinetics and pharmacodynamics of curcumin has been widely investigated and found that curcumin is an excellent therapeutic agent for various ailments. However, due to low bioavailability it has limited use in clinical and therapeutics. In this section, the related issues of curcumin bioavailability such as low serum levels, fast metabolism, lesser distribution in tissues and short half-life are described extensively. The following section review the studies related to serum level, metabolism, and elimination from the body,

2.1. Serum Concentration:

Low serum level of curcumin is one of the major problems to use it as therapeutic. The first reported study to examine the uptake, distribution and elimination from the body of curcumin was found in literature in 1978 by Wahlstrom and Blennow [24] using Sprague-Dawley rats. Negligible amount of curcumin was observed in blood plasma of rats after oral administration of 1g/Kg of curcumin. The blood plasma levels and biliary excretion results indicated that curcumin was poorly absorbed from the gut. Pan et al. 1999, [25] reported that with oral administration of 1g/Kg curcumin, the low plasma level of 0.13µg/mL appeared in the plasma after 15 min. and the maximum plasma level of 0.22 µg/mL was obtained at 1h. Similarly, after *i.p.* administration of curcumin (0.1 g/kg) to mice, the plasma level of 2.25µg/mL was achieved. In another study by Yang et al. 2007, [26] showed that the *i.v.* administration of 10mg/Kg curcumin in rats, the maximum serum level of 0.36 ± 0.0525µg/mL was reached. Whereas a 50-fold higher curcumin dose administered orally gave only 0.06 ± 0.01 μg/mL maximum serum level. The results of a pharmacokinetic study in human by Sharma et al. (2004) showed that the maximum plasma level of 11.1 ± 0.6nmol/mL was obtained for orally administered curcumin [27]. The highest plasma concentration reported is 0.051µg/mL from 12g curcumin in human, 1.35µg/mL from 2g/Kg in rat, and 0.22µg/mL from 1g/kg in mice [28]. In recent study by Sun et al. (2013) showed that the *i.v.* administration of 2mg/Kg unformulated curcumin to rats exhibited better bioavailability in blood plasma [29].

The concentration was found about 6.6 µg/mL of blood plasma when administered through tail vain. In the same way, uptake and distribution of curcumin in the tissue is equally important for biological activities. The maximum curcumin concentration in the tissue was found < 3% only by i.v. administered in mice [30].

2.2. Metabolism:

Various studies have evaluated the metabolites of curcumin in human and rodents. Curcumin is subjected to conjugation and is extensively converted to its water soluble metabolites (glucuronides and sulphates), whereas reduced to dihydrocurcumin (DHC), tetrahydrocurcumin (THC), hexahydrocurcumin (HHC), and further converted to ferulic acid and dihydroferulic acid, that are excreted through urine [23]. The structures of these metabolites are shown in fig.2. Pan et al. (1999) showed that after hydrolysis of plasma samples by glucuronidase, the 99% curcumin in plasma was found as glucuronides conjugates [25]. Holder et al. (1978) examined that the major metabolites of curcumin are glucuronides of THC along with glucuronides of HHC and THC in rats; whereas the minor metabolites are dihydroferulic acid and ferulic acid in rats [25, 31]. Hoehle et al. (2006) reported that the major metabolites of curcumin in rats are THC, HHC and OHC (octahydrocurcumin); male had more OHC while female had more THC metabolites [32].

The curcumin metabolites are either less active or more active than curcumin; it is not certain till now. In one study, THC was found to exhibit better antioxidant and anti diabetic activities than curcumin in diabetic rats. Whereas Sandur et al. (2007) reported that THC exhibited much lower anti-inflammatory and antiproliferative activities compared to curcumin [33].

In another study by Iresan et al.(2001) evaluated that the metabolites of curcumin produced 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 and exhibited lesser effective biologically than curcumin [34].

The results of pharmacokinetic study of

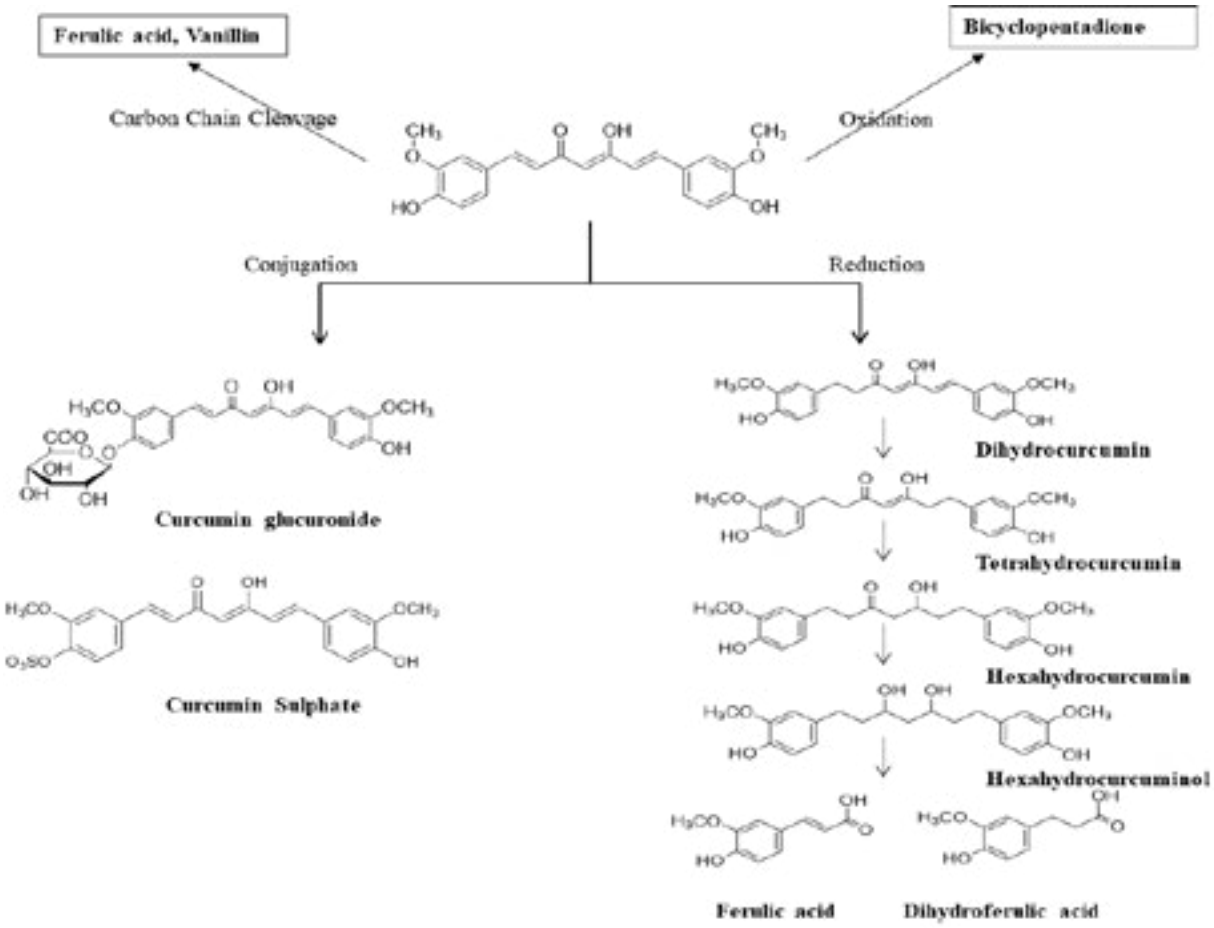

Figure2. Different metabolites of curcumin

curcumin by Andrew et al. (2019) showed that curcumin inhibited TGFβ-receptor-mediated Smad2/3 phosphorylation in all BCa cells studied (human MDA-SA, MDA-1833, MDA-2287 and murine 4T1 cells), but curcumin-glucuronide did not. In addition, curcumin blocked TGFβ-stimulated secretion of PTHrP from MDA-SA and 4T1 cells, but not curcumin-glucuronide.The study concluded with statement that compared to serum and other organs, free curcumin significantly increased in bones, also a site for enzymatic deglucuronidation activity. Thus, curcumin, but not it's-glucuronide, inhibit bone-tropic BCa cell TGFβ-signaling and to undergo site-specific activation (deconjugation) within the bone microenvironment [35].

Curcumin glucuronides were reported as the major metabolites present in the plasma after oral administration of Curcumin in rats [36].

2.3. Elimination/ Clearance from the body:

Systemic elimination or clearance of curcumin from the body is also an important factor, which determines its relative biological activity. Wahlstrom and Blennow [24] examined that when a dose of 1 g/kg curcumin was administered orally to rats, 75% of it was excreted in the feces and negligible amounts were found in the urine. Holder et al. evaluated that labeled curcumin with deuterium and tritium administered *i.v.* and *i.p*. resulted in biliary excretion from cannulated

rats and major part metabolized within 30 minutes [30].

In another study with radio labeled curcumin a dose of 400mg/rat was administered orally, similar results showed that major part of dose was excreted through feces. At lower doses 80 mg and 10 mg of [3H] 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 dosage [37-38]. 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 [26].

Sharma et al. (2001) study on 15 patients with doses between 36 and 180 mg of curcumin given orally for 4 months daily found neither curcumin nor its metabolites in urine, but curcumin was recovered from feces [39]. 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 levels of curcumin were below the detection limit [40].

3. Strategies to improve bioavailability

The pharmacokinetic study of curcumin till now suggested that the low solubility and rapid metabolism have been major issues for the poor bioavailability. It is significant to mention that the solubility of curcumin in water is about 11ng/mL [41]. There are a number of possible ways that have been designed and reported in literature to overcome this problem. To enhance the bioavailability of curcumin micelles, liposomes, solid-lipid particles, nanoparticles, phospho-lipid complexes, microencapsulation, metal complexes and bioconjugates [42-46] have been tried successfully and presented in fig.3. Adjuvants; which can block the metabolic pathway of curcumin, provide an alternative route to enhance its bioavailability [47-48]. Recent studies have incorporated the strategies to include sustained release systems as constant supplier for curcumin over a set period of time [49].

3.1. Delivery Systems

3.1.1. Nanoparticles:

Development of Drug Delivery Systems (DDSs) has emerged out as significant field in medicinal chemistry for the transportation of hydrophobic drugs at the specific site of action, prolonged release kinetics and lesser frequency of administration with reduced side effects. Nanoparticles-based delivery system is extremely useful due to their tiny size (<1000nm), can provide any delivered drug for absorption and bioavailability for a longer time [50]. Recently, Raghav et al. (2020) examined the modified polysaccharides as sustained release carriers for the delivery of curcumin *in-vitro* over a set period of time i.e. ~ 18h. Sulphated Nano Crystalline Cellulose, pectin and alginate proved better supports in comparison to phosphorylated Nano Crystalline Cellulose and carboxymethyl cellulose. Serum protein binding activities were effective for 7 h, whereas measurable anti-oxidant and anti-cathepsin activities could be observed for 3 h [49].

In another study by Rao and Khannum (2018), the nano-encapsulated curcumin was prepared using milk fat having particle size in the range of 40-250nm with the encapsulation efficiency of 91% and loading capacity was 0.9% using an optimum amount of 5% of sodium caseinate. These nanocurcumin enhanced the water solubility that was studied as antioxidant activity and was found to be more than native curcumin [51]. Ban et al. (2020) developed the solid lipid nanoparticles of curcumin using tristearin and

polyethylene glycol (PEG)ylated emulsifiers to enhance the oral bioavailability. The pharmacokinetic study in rat model showed that the oral bioavailability of curcumin increased ~12-fold using (PEG)ylated SLNs [52].

The results of pharmacokinetic study of curcumin by Zi et al. [53] showed that the solid lipid nanoparticles (SLNs) with Brij78 and TPGS can enhance the solubility and bioavailability of curcumin. The Cur-SLNs was found to have an average size of 135.3 ± 1.5nm with the entrapment efficiency of 91.09 % ± 1.23%. *In-vivo* pharmacokinetic study of these formulations was found that the AUC/ mg of these samples was 12.27-folds greater than curcumin suspension and the relative bioavailability of Cur-SLNs was 942.53%. Prakash et al. [54] formulated N-trimethyl chitosan (TMC) surface-modified SLNs to stabilize the solid lipid nanoparticles and evade the burst release. TMC-SLCNs displayed the optimal pharmacokinetic profile with Cmax of 1.21±0.12 µg/mL and $AUC_{0\text{-}8h}$ of 6.23±0.75µg/ mL, indicating that TMC coating could stabilize SLNs and prevent the burst release of curcumin from the SLNs in acidic environment.

In another study, the encapsulation of curcumin in hydrogels to form nano-microparticulate systems yielded the homogenous curcumin dispersion in aqueous solution compared to the free curcumin and in-vitro release rate of curcumin was found upto 95% [55].

Tiyaboonchai et al. (2007) developed solid lipid nanoparticles for topical purpose having the particle size of 450nm, found to be stable for six months at room temperature and effective *in-vitro* release rate was upto 12h [46]. Similarly, in-vivo study with these SLNs revealed the improved bioavailability of curcumin for topical application over free curcumin. Xie et al. [56] formulated the PLGA nanoparticles for curcumin by a (O/W) solvent evaporation technique, showed a uniform spherical shape with diameters of about 200 nm. The entrapment efficiency and loading capacity of curcumin were found to be 91.96 and 5.75%, respectively. The solubility of these curcumin nanoparticles in water was approximately 640-fold that of crude curcumin.

3.1.2. Micelles and liposomes:

Micelles and liposomes are prominent carriers for drug delivery systems due to their amphipathic in nature. The hydrophobic core can accommodate the hydrophobic drugs and hydrophilic part protects the drug from inactivation in the biological environment [57-58]. In one study, a novel proprietary curcumin liquid droplet micromicellar formulation (CLDM) formulation was prepared and the results of pharmacokinetic study performed in 12 healthy adult; showed that the area under the concentration-time curve/ mg for curcumin liquid droplet micromicellar formulation (CLDM) was 522 times greater than for the 95% curcumin. The novel CLDM formulation facilitates absorption and produces remarkably high plasma levels compared to 95% curcumin [59].

Zhao et al. designed the mixed micelles formulation composed of Pluronics P123 and F68; possessed the average particle size of 68nm. The entrapment efficiency and loading capacity were found to be 87% and 7%, respectively. The concentration of curcumin in micellar solution was about 3.02 mg/mL, which significantly increased the solubility of curcumin compared to the free drug 11ng/mL [60]. Schiborr et al. [61]

designed a comprehensive study in healthy humans (13 women, 10 men) to examine the oral bioavailability of curcumin from micronized powder and liquid micelles. The curcumin micelles were composed of 7%

curcumin powder (equivalent to 6% curcumin) and 93% Tween-80. In the crossover study, healthy volunteers were administrated a single oral dose of 500 mg curcuminoids (410 mg curcumin) as native powder, micronized powder, or liquid micelles. The results of this study showed that the intake of a single oral dose of 500 mg curcuminoids as micelles resulted in a mean plasma Cmax of 3228 nmol/L for all study subjects compared to 7nmol/L after the administration of native curcuminoids. In another study, a polymeric micellar curcumin gave a 60-fold higher biological half-life for curcumin in rats compared to native curcumin solubilized in a mixture of DMA, PEG and dextrose [62].

Another formulation considered to amplify the bioavailability is liposomal curcumin. Many studies have been found that curcumin can be successfully encapsulated in liposomes formulated from food-grade phospholipids, such as those isolated from eggs, fish, milk, or soybeans [63-65]. Chen et al. [66] formulated the curcumin liposomes coated with N-trimethyl chitosan chloride (TMC) and evaluated the *In-vivo* pharmacokinetic study in rats. The entrapment efficiency and drug loading capacity were found 86.67% and 2.33% respectively. The results revealed that the bioavailability was enhanced with *C*max of 46.13 µg/L and AUC/mg of 416.58 µg/L compared with curcumin encapsulated uncoated liposomes (*C*max = 32.12 µg/L, AUC = 263.77 µg/L) and curcumin suspension (*C*max = 35.46 µg/L, AUC = 244.77 µg/L). Li et al. (2012) designed the formulation silica-coated flexible liposomes loaded with curcumin (CUR-SLs) and curcumin loaded flexible liposomes (CUR-FLs) and found enhanced bioavailability of CUR-SLs and CUR-FLs with 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 [67]. In another study, the curcumin liposomes were prepared using commercially available lecithin. The results showed that plasma curcumin concentration was significantly higher in rats administrated liposome than in those administrated curcumin only, at all time points. The Cmax value of curcumin in the liposome group (319.2±70.4 µg/L) was higher than that obtained with curcumin only (64.6±10.7 µg/L). The AUC/mg value of curcumin after oral administration of liposome was 26502.8µg·min/L, which was 4.96-fold greater than that after curcumin-only administration and the antioxidant activity was ~2- or 3-fold higher compared to free curcumin [68]. The encapsulation of curcumin in liposomes has been shown to improve its water dispersibility, chemical stability, bioaccessibility, and bioavailability.

Figure3. Different formulations of curcumin effective in biological activities

3.1.3. Emulsions and nanoemulsion:

Oil-in-water (O/W) emulsions and nanoemulsion consist of small oil droplets dispersed within an aqueous phase [69-70]. The oil droplets are coated by a layer of emulsifier molecules that helps to prevent them from aggregating by generating repulsive colloidal interactions between them. The most

commonly used emulsifiers in the food industry are small molecule surfactants, phospholipids, proteins, and polysaccharides [71]. Joung et al.'s (2016) showed that curcumin-loaded nanoemulsions can be successfully incorporated into commercial food products, such as milk. This study demonstrated that the addition of the emulsified curcumin reduced the lipid oxidation in the milk [72].

Studies have also shown that curcumin loaded emulsions can be converted into a powdered form using spray drying [73], which would be useful for many commercial applications in foods and beverages.
Several studies have reported the potential of emulsion-based delivery systems to increase the bioavailability of curcumin [74-75].

Results of pharmacokinetic study by Yu & Haung (2012) in mice exposed that encapsulation of curcumin within nanoemulsion improves its bioavailability as compared to curcumin crystals dispersed in water. The curcumin levels in the plasma of mice were much higher after they administered curcumin in the form of nanoemulsion rather than crystals. The bioavailability in nanoemulsion was 9.3-fold higher than for the crystals [76].

Vecchione et al. (2016) formulated the curcumin loaded nanoemulsions containing lipid droplets coated with chitosan that increased curcumin levels in plasma of rats as compared to curcumin crystals. In this study, the oral bioavailability was 33-fold higher for the nanoemulsion form than in the crystalline form. In addition, including piperine in the nanoemulsions also caused further increase in curcumin bioavailability; it became 64-fold higher than crystalline curcumin, which was attributed to the ability of the piperine to block the efflux transporters in epithelial cells [77].

M.C. Bergonzi et al. [78] developed an o/w microemulsion of curcumin and investigated *in vitro* oral absorption potential using parallel artificial membrane permeability assay (PAMPA). The optimized microemulsion showed a maximum solubility of 14.57 mg/ml and permeation amount through the artificial membrane of about 17.44μg after 6 h and about 120.12 μg after 24 h, which was ~100-fold higher than free curcumin in PBS. Yu et al. [79] designed the novel curcumin organolgel based nanoemulsion formulation by selecting curcumin organolgel as oil phase and Tween 20 as emulsifier. The pharmacokinetics study was performed using Female CD-1 mice (22-26g) orally administered at the dose of 240mg/kg curcumin loaded nanoemulsion. The results indicated that the Cmax of curcumin as 29.9±5.1μg/mL in the nanoemulsion was much higher than that obtained from the unformulated curcumin (1.6±1.2μg/mL). In addition, the oral bioavailability of curcumin in the nanoemulsion exhibited 9-fold improvement compared with the unformulated crystalline.

Saipin et al. [80] developed the self-microemulsifying drug delivery systems (SMEDDS) that resulted in improved solubility and *in vivo* oral absorption of curcumin. The optimized SMEDDS used for curcumin formulations in liquid and pellet forms contained 70% mixtures of two surfactants: Cremophor EL and Labrasol (1:1), and 30% mixtures of oil: Labrafac PG and Capryol 90 (1:1). These formulations could be easily formed and very stable. Curcumin-SMEDDS liquid and pellets were found to be stable up to 6 months under intermediate and accelerated conditions. In addition, the results of pharmacokinetic studies in rats dosed with liquid and pellets SMEDDS showed 14- and 10-fold increased absorption of curcumin compared to the aqueous suspensions of curcumin, respectively.

The encapsulation of curcumin in triacylglycerol emulsions has also increased its

bioaccessibility in gastrointestinal fluids [74]. The triacylglycerols are converted into free fatty acids and monoacylglycerols and then interact with bile salts and phospholipids to form mixed micelles that can solubilize the curcumin in their hydrophobic interiors. The small micelles then transport the curcumin through the mucus layer and to the surfaces of the epithelium cells where it can be absorbed.

3.1.4. Phospholipid Complexes:

Complexation is an excellent approach to enhance absorption and bioavailability. Phospholipid complex can increase the bioavailability and absorption of curcumin due to its amphiphilic nature of complex; and increase the water and lipid solubility. Primarily, the potential formulation with silymarin has been reported to improve absorption by complexation with phospholipids [81-82]. Subsequently the phospholipid complexes of other natural drug like dolichol were also found to enhance the bioavailability [83]. Liu et al. [84] developed curcumin–phospholipid complex (CPLC) and orally administered to Sprague–Dawley male rats at dose of 100 mg/kg. CPLC showed a maximum plasma curcumin level of 600ng/mL; was much higher than for free curcumin of 267ng/mL In this study, curcumin half-life in rats was found to be increased to about 1.5-fold for CPLC over free curcumin. Maiti et al. (2007) showed a 3-fold increase in aqueous solubility and a better hepatoprotective effect for a curcumin phospholipid complex compared to free curcumin [44].

Marczylo et al. [85] explored whether formulation with phosphatidyl choline increased the oral bioavailability or affected the metabolite profile of curcumin *in-vivo*. Male Wistar rats received 340mg/kg of either unformulated curcumin or CPLC phosphatidylcholine (Meriva) by oral administration. Curcumin, the accompanying curcuminoids desmethoxycurcumin and bisdemethoxycurcumin, and the metabolites THC, HHC, 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 free curcumin. Similarly, liver levels of curcumin were higher after administration of Meriva as compared to free curcumin.

Nishant et al. [86] formulated curcumin phospholipid complex by using phosphatidyl choline and examined the *ex vivo* absorption and pharmacokinetic study in rats. In the pharmacokinetic study, curcumin was administered at a dose of 1 g/kg orally for one group. Curcumin phospholipid complex was administered to the animals of second group at a dose equivalent to 1 g/kg of curcumin. The physical mixture of curcumin and phosphatidyl choline was given to the third group at a dose equivalent to 1 g/kg of curcumin. The results of pharmacokinetic study revealed that curcumin phospholipid complex showed very high plasma concentrations, low clearance, and long half-life in rats as compared with curcumin or curcumin phospholipid complex physical mixture. The overall pharmacokinetics of curcumin has been improved after complexation with phosphatidyl choline.

3.2. Piperine:

Piperine, a major component of black pepper known as inhibitor of hepatic and intestinal glucuronidation and also exhibited an increase in absorption and bioavailability of curcumin. The effect of piperine on pharmacokinetic study of curcumin was reported to be much greater in humans than rats without any side effect**.** Shoba et al [40] reported that curcumin bioavailability in humans was enhanced 2000% in presence of piperine after administration orally, whereas in rats it might to be 154% only by concomitant

administration. Recently Raghav and Mor (2020) reported that the functional foods such as milk, CMF, and bioenhancer black pepper can serve as pharmaceutical excipients resulting into enhanced pharmacological potential and help in solubilization of biologically active compound [87].

Morgana et al. [88] designed a systematic *In-vivo* study to evaluate the effect of curcumin and piperine on periodontal repair. The samples were administered to rats daily for 15 days by oral gavage. The results showed that curcumin and piperine augmented the TGF-β level, notably improved the collagen repair, and decreased the activation of NF-kB in the periodontal tissues. Consequently, the combination of curcumin and piperine proved to be significant to stimulate tissue repair and the treatment of periodontal disease. Taiki et al. [89] supplemented the curcumin and piperine to obese mice to evaluate the effect of supplement on metabolic syndrome. The experiment was performed on 47 eight-week-old male C57BL/6 mice for 20 weeks. The mice were divided into 5 groups. Group 1 continued on high fat diet (HFD). The other 4 groups undertook CR (reduced 10% HFD intake for 10 weeks, 20% for 20 weeks) with Curcumin, Piperine, Curcumin + Piperine or none of these. The results showed that obese mice who undertook CR and received curcumin and piperine lost more fat and significantly suppressed the interleukin-1β. The authors concluded that combination of Curcumin and Piperine has the potential to suppress HFD induced inflammation and enhance CR effects for the prevention of metabolic syndrome.

3.3. Others:

Bioconjugates also enhance cellular uptake thus increase the bioavailability of curcumin. Antony et al. [90] reconstituted the Biocurcumax® (BCM-95®) combined with curcumin-lecithin-piperine capsules that enhanced the bioavailability and showed better absorption into blood and had longer retention time compared to curcumin. The results of the study showed that the relative bioavailability of BCM-95 was ~6.93-fold compared to normal curcumin and ~6.3-fold compared to curcumin-lecithin-piperine formula. BCM-95 thus, has potential for extensive application for various chronic diseases. Similarly, Curcumin C3 Complex® enhanced absorption and stimulated gastrointestinal system to prevent efflux of curcumin. Turmeric oleoresin (Curcugen™) also resulted in small incremental increases in curcumin absorption [91-95].

Another strategy to improve the biological activity of curcumin was to chelate it with metals. The presence of two phenolic groups and one active methylene group in a curcumin molecule makes it an excellent ligand for any chelation. A number of metal chelates of curcumin have been reported to possess biological activity over that of free curcumin. John et al. [96] 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. Studies by Sui et al. [97] showed that the modest activity of curcumin as an *in-vitro* inhibitor of HIV-1 and HIV-2 proteases enhanced more than 10-fold when complexed with boron.

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*. Moreover, this complex was found to be more effective as an anticancer agent, compared to uncomplexed curcumin [98]. Both *in-vitro* and *in-vivo* evaluations of a series of indium and gallium complexes of curcumin derivatives and curcumin

showed that the structural modifications and complex formation of curcumin with metal ions may yield gallium and indium curcuminoids with potential therapeutic applications [99]. Although many curcumin analogues are found to show improved biological activity over curcumin, specific evaluations of structural analogues and derivatives of curcumin to show improved tissue and plasma distribution are lacking.

4. Conclusion

The structural features of curcumin make it a very active molecule that interacts with a large number of molecular targets. In this direction, a compendium of solutions explored to overcome the problems related to bioavailability in the form of sustained release system can be useful in defining the clinical use of curcumin.

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