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Review

Bioavailable curcumin formulations: A review of pharmacokinetic studies in healthy volunteers

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ABSTRACT

Curcumin is a widely studied natural compound which has shown tremendous *in vitro* therapeutic potential. Despite that, the clinical efficacy of the native curcumin is weak due to its low bioavailability and high metabolism in the gastrointestinal tract. During the last decade, researchers have come up with different formulations with a focus on improving the bioavailability of curcumin. As a result, a significant number of bioavailable curcumin-based formulations were introduced with the varying range of enhanced bioavailability. The purpose of this review is to collate the published clinical studies of curcumin products with improved bioavailability over conventional (unformulated) curcumin. Based on the literature search, 11 curcumin formulations with available human bioavailability and pharmacokinetics data were included in this review. Further, the data on clinical study design, analytical method, pharmacokinetic parameters and other relevant details of each formulation were extracted. Based on a review of these studies, it is evident that better bioavailability of formulated curcumin products is mostly attributed to improved solubility, stability, and possibly low first-pass metabolism. The review hopes to provide a quick reference guide for anyone looking information on these bioavailable curcumin formulations. Based on the published reports, NovaSol® (185), CurcuWin® (136) and LongVida® (100) exhibited over 100-fold higher bioavailability relative to reference unformulated curcumin. Suggested mechanisms accounting for improved bioavailability of the formulations and details on the bioanalysis methods are also discussed.

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1. Introduction

Curcuma longa Linn. (Zingiberaceae), also known as turmeric, is a perennial plant native to tropical regions of South Asia. Since ages, the rhizomes of the plant have been used in Indian (Ayurveda) and Chinese medicine system as a remedy for a variety of ailments. Traditionally, curcumin is widely used as a spice, food preservative, and a coloring agent. Many curcumin-based products which includes capsules, ointments, tablets, cosmetics are currently marketed worldwide. Curcumin (diferuloylmethane; 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a primary, orange hydrophobic polyphenol pigment obtained from *C. longa* rhizome [1]. Other reported constituents of curcumin include demethoxycurcumin, bisdemethoxycurcumin and volatile oils [1]. Commercially available curcumin contains a mixture of 75% curcumin, 15% demethoxycurcumin, and 5% bisdemethoxycurcumin (about 5%) [2]. However, the focus of this review is limited to highly abundant curcumin.

Extensive research on curcumin over the past decade has demonstrated the ability of this compound to modulate multiple cellular targets, and hence potential as a preventive and therapeutic against a broad range of diseases. The compound possesses a broad range of biological activities (Fig. 1) that include antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities [3]. A large number of *in vitro* studies on curcumin have highlighted its antioxidant [4], anti-inflammatory [5], anticancer [1], antiproliferative [6], nephroprotective [7], neuroprotective [8], hepatoprotective [9], immunomodulatory [10], and chemopreventive effects [11]. Also, *in vitro* studies have reported that curcumin modulates multiple cell signaling pathways, downregulates cell survival gene products, upregulates p53, p21 and p27 and induce apoptosis [12–14]. An in-depth review of the therapeutic roles of curcumin has been previously published elsewhere [15]. Curcumin is currently marketed as a dietary supplement in many countries worldwide and also carries a generally recognized safe status. However, despite the proven preclinical efficacy, poor solubility, low absorption from the gut, rapid metabolism, and rapid systemic elimination contribute to an overall low oral bioavailability [16]. Curcumin is a hydrophobic molecule with a logP of 3.2, which makes it practically insoluble in water [17]. Further, curcumin has a reported half-life of 10 min in phosphate buffer at physiological pH (7.4) because of its high instability in alkaline pH [18]. This further limits the therapeutic potential of curcumin and continues to be a primary concern in its clinical use. Even after taking gram doses of curcumin, very low plasma curcumin levels were detected for conventional curcumin [19].

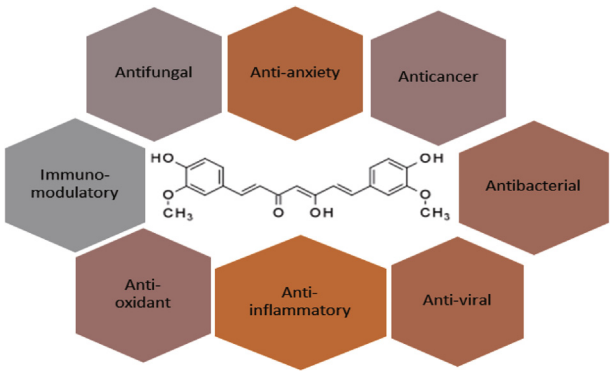

Fig. 1. Some of the reported biological activities associated with curcumin.

Over the past few years, enormous emphases have been laid on improving the bioavailability of plant extracts of human benefit using various pharmaceutical means. Maximizing oral bioavailability directly influences plasma concentration as well as the therapeutic effects of a compound. Basic thumb rule of all the approaches is to improve the solubility and hence the bioavailability of curcumin. An increase in oral bioavailability is expected to directly influence plasma concentration as well as therapeutic effects of curcumin. This will result in lowering of the curcumin doses and the dose frequency. A large number of approaches have been utilized to increase the solubility and subsequently the bioavailability of curcumin [20]. Few of the strategies adopted for improving the bioavailability of curcumin include curcumin–piperine complex, curcumin nanoparticles, cyclodextrin inclusions, curcumin liposomes, and curcumin phospholipids' complex [3]. The last study reviewing the clinical research on curcumin focused on the preclinical and clinical pharmacological reports was published in 2009 [21]. Since then, a variety of curcumin formulations have been developed, and subsequent clinical studies with improved bioavailability have been published. While a large number of such formulations are developed in academia and as garage projects, only a few of them are available in the market in one form or another. Significant differences in study design, volunteer ethnicity, methods of sample analysis, sampling time and product administration were noted.

2. Methods

A literature search was conducted on PubMed/MEDLINE, Embase, Google Scholar, Cochrane Library and EBSCO between January 2017 and November 2017. There was no restriction placed during searches regarding the language, region, or time of publication. Search terms used to collect the references from electronic search were "bioavailable curcumin," "curcumin bioavailability," and "curcumin clinical study." The abstracts of relevant reviews were inspected, and only pharmacokinetic investigations in healthy human volunteers were retrieved for the final data extraction. All the *in vitro* and animal studies were excluded. Clinical studies with formulations which are commercially available in one form or other were selected for this review. Eleven curcumin formulations were finally selected for the review and data were extracted from published clinical bioavailability studies in human.

3. Discussion

3.1. Overview of bioavailable curcumin formulations

A detailed table with the curcumin formulations, their major ingredients, manufacturer and the reported relative bioavailability (RB) in human is given in Table 1. A significant variation in the choice of ingredients was observed among the formulations included in this review. Similarly, it was observed that the strategies used by manufacturers to enhance the bioavailability of curcumin were entirely different too. Increased solubility and protection from acidic pH (stability) in the gastrointestinal tract were mainly reported to enhance the bioavailability of curcumin.

3.1.1. Meriva®

Meriva® is a curcumin-phosphatidylcholine phytosome complex of soy lecithin, microcrystalline cellulose and 18%–20% curcuminoids [22]. Curcumin has two phenolic hydroxyls and one enolic hydroxyl group which can form hydrogen bonds with complementary polar groups of phospholipids. Once curcumin is complexed with phosphatidylcholine, the hydrophobic core of the phytosome protects it from degradation while increasing the cellular uptake through facilitated diffusion across lipophilic cell membranes [22,32]. A randomized, double-blind, crossover study in human found that curcumin absorption was about 29-fold higher for Meriva® compared to unformulated curcuminoid mixture [22]. Interestingly, the plasma demethoxycurcumin was found as a major plasma curcuminoid despite the curcumin content being four times higher in the formulation. This suggests that lecithin favors the higher bioavailability of demethoxycurcumin from Meriva®.

3.1.2. LongVida®

LongVida® is a solid lipid curcumin particle (SLCP)-based formulation with improved bioavailability compared to unformulated curcumin [23]. The curcumin content of LongVida® is between 20% and 30%. The SLCP complex protects the curcumin from rapid degradation and excretion thereby improving the systemic curcumin concentration and half-life [23]. Other formulation parameters such as curcumin/lipid/antioxidant ratio and globule-size distribution are suggested to extend the absorption of curcumin from the formulation [23]. LongVida® is formulated of turmeric powder with soy lecithin containing purified phospholipids, docosahexaenoic acid, vegetable stearic acid, ascorbyl (vitamin C) esters and other insert ingredients [23]. A single-dose, crossover, double-blind, comparative pharmacokinetic study in healthy volunteers found its human RB was approximately 100 [23].

3.1.3. CurQfen™

CurQfen™ is a novel formulation of turmeric powder and soluble dietary fibers derived from fenugreek (*Trigonella foenum-graecum*) [24]. Soluble fibers, composed of galactose and mannose units form a nondigestible gel hydrocolloid. The hydrocolloid is suggested to undergoes fermentation in the colon by the action of β-mannanase and protect against curcumin degradation in the gastrointestinal tract [33]. The concentration of curcumin in the formulation is about 40%, and the amorphous formulation delivers a slow release of stable colloidal curcumin for improved absorption. In a study in human, oral absorption of curcumin from CurQfen™ at a dose of 1500 mg (equivalent to 600 mg curcumin) was 15.8 times more bioavailable compared to unformulated curcumin [24]. Prolonged release from nondigestible soluble fibers, leading to protection from enzymatic degradation gastrointestinal tract was proposed as a possible mechanism for increased bioavailability of curcumin [24].

3.1.4. MicroActive curcumin

MicroActive curcumin is a micronized formulation of 25% curcuminoids in a proprietary sustained-release matrix consisted of polyglycerol esters of fatty acids, medium-chain triglycerides, hydroxypropyl methylcellulose, sodium alginate, and microcrystalline cellulose [25]. The surfactants, oil, and polymers in the formulation were suggested to improve the absorption mainly through a sustained release and stabilization of curcumin in the intestine [25]. The bioavailability of MicroActive curcumin was 9.7 times as compared to unformulated 95% pure curcumin in a single-dose bioavailability study in healthy human volunteers [25].

3.1.5. Micronized curcumin

Micronized curcumin is prepared using "concentrated powder form" technology and comprises 25% curcumin power, 58% triacetin and 16.7% panodan and further spray drying on porous silicon dioxide [26]. The concentration of curcumin in the finished micronized curcumin powder is 14.1% [26]. The micronized curcumin was 9-fold better bioavailable than unformulated curcumin in a comparative single-blind crossover study in healthy adult men and women [26]. Micronization of curcumin was suggested to improve the absorption. The process reduces the average diameter

Table 1
Composition, manufacturer and reported relative human bioavailability of different formulations.

Formulation	Manufacturer	Formulation details	References
Meriva®	Indena SpA., Italy	Phytosome technology (curcumin, soy lecithin, microcrystalline cellulose, and 18%–20% curcuminoids)	[22]
LongVida®	Verdure Sciences, USA	SLCP™ technology (solid lipid curcumin particle lipids, phosphatidylcholine, and 20% curcumin)	[23]
CurQfen™	Spiceuticals, India (Akay Group)	Fenugreek soluble fiber blend, and 40% curcumin	[24]
MicroActive curcumin	BioActives LLC, USA	25% curcuminoids, a proprietary mixture of polyglycerol esters of fatty acids, medium-chain triglycerides, hydroxypropyl methylcellulose, sodium alginate, and microcrystalline cellulose	[25]
Micronized curcumin	Raps GmbH & Co., KG, Germany	Micronized powder (58.3% triacetin, 16.7% panodan, and 25% curcumin powder)	[26]
NovaSol®	Frutarom, Israel	Liquid micelles (93% Tween 80, and 7% curcumin powder)	[26]
CurcuWin®	OmniActive Health Technologies, India	63%–75% polyvinyl pyrrolidine, 10%–40% cellulosic derivatives, 1%–3% natural antioxidants, and 20%–28% turmeric extract	[27]
Biocurcumax™ (BCM-95®)	Arjuna Natural Extracts Ltd. India (Dolcas Biotech)	Curcuminoid, essential oil of turmeric (45% ar-turmerone), and curcuminoids	[28]
Curcumin C3 Complex® + Bioperine	Sabinsa, USA	Bioperine, and curcuminoids	[29]
Cavacurmin®	Wacker Chemie AG, Germany	γ-Cyclodextrin, and ~15% (w/w) total curcuminoids	[30]
Theracurmin™	Theravalues Corp., Japan	Colloidal-nanoparticles (12% curcuminoids, 46% glycerin, 4% gum ghatti, 38% water, and 10% curcumin)	[31]

of drug particles which improves the rate of dissolution by increasing the surface area to drug ratio [34]. Subsequently, slow diffusion of drug particle protects it from degradation and improves the absorption.

3.1.6. NovaSol® (micellar curcumin)

Micellization is a common technique to improve the solubility of hydrophilic drugs. NovaSol® curcumin micelles were formulated of 7% curcumin powder (6% curcumin) and 93% Tween-80 [26]. In a single-blind crossover study in healthy adult men and women, the bioavailability of curcumin from NovaSol® was 185 folds higher than that of the same dose of unformulated curcumin [26]. Curcumin incorporated with a nonionic surfactant Tween 80 (polysorbate 80) leads to the formation of liquid micelles which improves dissolution and absorption.

3.1.7. CurcuWin®

CurcuWin® is a novel water-soluble curcumin formulation containing 20%–28% turmeric powder, 63%–75% polyvinyl pyrrolidine (a hydrophilic carrier), 10%–40% cellulosic derivatives and 1%–3% natural antioxidants [27]. In a randomized, double-blind, crossover study, the RB of CurcuWin® was 136 times compared to unformulated curcumin [27]. The increase in oral absorption of the curcumin was attributed to increased solubility similar to other formulations included in the study. Additionally, tocopherol and ascorbyl palmitate were suggested to prevent degradation of curcumin [27].

3.1.8. Biocurcumax™

Biocurcumax™ (BCM-95®) is a formulation of turmeric powder and essential oils of turmeric (45% ar-turmerone) [28]. The relative human bioavailability of the complex in a crossover study was about 6.9-fold compared to unformulated curcumin [28]. The improved absorption of curcumin from the formulation was indicated to noncurcuminoid components of turmeric.

3.1.9. Curcumin C3 Complex® + Bioperine

Bioperine is one of the first bioavailability enhancers used to improve the oral absorption of curcumin in humans. Piperine, the main active constituent of bioperine, is a P-glycoprotein inhibitor and hence improves the absorption by decreasing the efflux of absorbed curcumin in the intestine [35]. Bioperine also inhibits uridine diphosphate-glucuronosyltransferase (UGT) and hence improves the freely available curcumin in the systemic circulation. When curcumin was given with piperine (20 mg/kg body weight), the RB of curcumin was 20-fold compared to curcumin alone [29].

3.1.10. Cavacurmin®

Cavacurmin® is a γ-cyclodextrin-based formulation of curcumin developed by Wacker Chemie AG, Germany [30]. Cyclodextrins consist of nonreducing chiral glucose-building blocks arranged in a ring structure with hydrophilic glucose-building blocks facing outwards which results in a lipophilic cavity on the inside [36]. Curcumin fits in this lipophilic cavity by weak van der Waals forces, resulting in an inclusion complex with cyclodextrin. The resulting inclusion complexes improve curcumin's aqueous solubility, and hence the absorption. Cavacurmin® showed an 85-fold increase in bioavailability in comparison to unformulated curcumin administered in a crossover study in human [30]. It was suggested that Cavacurmin® is transported unchanged through the stomach into the upper intestinal tract where curcumin is absorbed while cyclodextrin molecules are hydrolyzed by human amylases [30].

3.1.11. Theracurmin™

Theracurmin™ is a colloidal nanoparticle-based formulation of curcumin. The formulation consists of 10% (w/w) curcumin, 2% other curcuminoids such as demethoxycurcumin and bisdemethoxycurcumin, 46% glycerin, 4% gum ghatti, and 38% water [31]. The colloidal nanoparticle dispersion of curcumin improves the solubility and its oral bioavailability as found in a human pharmacokinetic study [31]. The RB of curcumin from Theracurmin™ in healthy volunteers was almost 16 time as compared to unformulated curcumin. The authors reported that gum ghatti was responsible for improving the solubility and stability of curcumin formulation. Subsequently, wet-grinding of this mixture yields nanoparticles which are 100 times smaller than the unformulated curcumin powder. The combination of improved solubility and reduced particle size enhances the clinical bioavailability of Theracurmin™ [31].

3.2. Comparison of different study parameters

3.2.1. Clinical study design

Most studies were conducted with a blinded, randomized crossover design (see Table 2 for complete details). Participants in randomized, double-blind studies are randomly assigned to the treatment group, and neither researchers nor volunteers are aware of the treatment. It removes bias in the study and is therefore considered "gold standard" of clinical trials [37]. A crossover design is a within-subject design where each participant serves as his/her control and receives all treatments, where each is separated by "washout" period in which no treatment is given [38].

Five formulations included in this review were studied in the Asians and six in Caucasians. Most of the studies had poor gender balance except for Theracurmin™, NovaSol® and micronized curcumin. No information on the gender was available for BCM-95® (Biocurcumax™) study. Three studies (LongVida®, CurQfen™ and Curcumin C3 Complex® + Bioperine) recruited only males whereas other studies included volunteers from both sexes. The maximum number of volunteers in a study was 23 (micronized curcumin and NovaSol®) and a minimum of six volunteers were recruited for

Table 2
Clinical study design parameters of the different curcumin-based formulations.

Formulation	Clinical study design	Number of subjects	Subject ethnicity	References
Meriva®	Randomized, double-blind, crossover	9 (8 males, 1 female)	Caucasian	[22]
LongVida®	Randomized, crossover, double-blind	6 (all males)	Asian (Indian)	[23]
CurQfen™	Crossover	8 (all males)	Asian (Indian)	[24]
MicroActive curcumin	Crossover	12 (11 males, 1 female)	11 Caucasian, 1 African-American	[25]
Micronized curcumin	Randomized, double-blind, crossover	23 (10 males, 13 females)	Caucasian	[26]
NovaSol®	Randomized, double-blind, crossover	23 (10 males, 13 females)	Caucasian	[26]
CurcuWin®	Randomized, double-blind, crossover	12 (11 males, 1 female)	11 Caucasian, 1 African-American	[27]
Biocurcumax™ (BCM-95®)	Crossover	11 (gender not reported)	Asian (Indian)	[28]
Curcumin C3 Complex® + Bioperine	Randomized, crossover	10 (all males)	Asian (Indian)	[29]
Cavacurmin®	Randomized, double-blind, crossover	12 (11 males, 1 female)	11 Caucasian, 1 African-American	[30]
Theracurmin™	Randomized, crossover	14 (8 males, 6 females)	Asian (Japan)	[31]

LongVida® pharmacokinetic study. Schiborr et al. [26] found that systemic concentration of curcumin was higher in women than men dosed with Novasol® and micronized curcumin. The details on the ethnicity, gender, and the number of subjects for these studies are given in Table 2.

3.2.2. Curcumin administration

Conventional (unformulated) or formulated curcumin was administered orally in all the studies. The composition and content of food given to volunteers after administration of curcumin dose differed significantly. Except for Theracurmin™, volunteers were fasted overnight before getting the drug, and the curcumin-free food was provided after drug administration. No information on fasting status and meals provided to subjects was reported by authors in the Theracurmin™ study [31]. CurcuWin® and Cavacurmin® were given to overnight fasted individuals who were fed first meal 4 h after administration of curcumin [27,30]. In contrast, Cuomo et al. [22] gave a high-fat meal immediately after curcumin (Meriva®) administration. MicroActive curcumin and NovaSol® were administered after subjects were given breakfast (30% fat) [26]. It is worth reiterating here that high-fat meal diet is known to increase the mean transit time in the intestine and may thereby enhance the exposure of the drug for absorption [39].

3.2.3. Analysis method and quantification of curcumin

A significant variation in the analysis of curcumin in human plasma was seen in the trials (Table 3). While some studies used high-performance liquid chromatography for quantification, others utilized liquid chromatography–mass spectrometer (LC–MS). Separation of curcumin was achieved by reverse-phase liquid chromatography in all the studies. Plasma was used for quantification of curcumin in all the studies except the one with piperine where serum was utilized [29]. Despite the fact that curcumin is extensively conjugated by UGT after absorption [40], studies with CurQfen™, LongVida®, Curcumin C3 Complex® + Bioperine and Biocurcumax™ measured free curcumin in the plasma. It is interesting to note here that quantification of free curcumin in these studies is mainly at odd with the previous pharmacokinetic studies in rat and human. It appears that in those formulations where free curcumin was measured, the formulation per se hindered the direct access of curcumin (to UGT) and protected from conjugation. Conversely, in all other studies, plasma was hydrolyzed before quantification of curcumin. The hydrolysis of conjugated curcumin in plasma was achieved using β-glucuronidase/sulfatase from *Helix pomatia* which has been historically used for quantification of glucuronide-bound compounds [41]. Glucuronidase liberates the hydrophilic aglycone moiety attached to curcumin by UGT and allows for quantification of curcumin. None of the studies which hydrolyzed the plasma samples quantified the free curcumin in plasma without hydrolysis. Initial aglycone curcumin should have been subtracted from deconjugated curcumin as that would have allowed more meaningful data to the researchers.

Liquid–liquid extraction of curcumin from plasma was adopted by all the studies in the review. Methanol, chloroform, ethyl acetate and a mixture of ethyl acetate with methanol were among the solvents used for extraction of curcumin. The choice of solvent for extraction of curcumin and its conjugates is debatable. As curcumin is a lipophilic compound, use of ethyl acetate is an ideal solvent for the extraction of free curcumin from plasma. However, the conjugation of glucuronic acid to curcumin by UGT makes it hydrophilic and would lead to suboptimal extraction with ethyl acetate. Alternatively, a 1:1 (v/v) mixture of ethyl acetate/diethyl ether can be used for extraction of free and conjugated curcumin from plasma [41]. Acetonitrile and methanol also extract a significant number of phospholipids from plasma. Methyl tert-butyl ether and *n*-butyl chloride remove the negligible amount of plasma

Table 3
Analytical methods and related parameters of the different curcumin-based formulations.

Formulation	Analysis technique	Internal standard	Sample hydrolysis	Extraction solvent	Analyte measured	References
Meriva®	HPLC–MS/MS	Not used	Hydrolysis, β-glucuronidase/sulfatase	Ethyl acetate	Free curcumin after hydrolysis	[22]
LongVida®	HPLC-PDA	Not used	No hydrolysis	Methanol	Free curcumin	[23]
CurQfen™	HPLC-UV	Not used	No hydrolysis	Ethyl acetate	Free curcumin	[24]
MicroActive curcumin	HPLC-UV	Not used	Hydrolysis, β-glucuronidase/sulfatase	95% Ethyl acetate + 5% methanol	Free curcumin after hydrolysis	[25]
Micronized curcumin	HPLC-fluorescence	Not used	Hydrolysis, β-glucuronidase/sulfatase	95% Ethyl acetate + 5% methanol	Free curcumin after hydrolysis	[26]
NovaSol®	HPLC-fluorescence	Not used	Hydrolysis, β-glucuronidase/sulfatase	95% Ethyl acetate + 5% methanol	Free curcumin after hydrolysis	[26]
CurcuWin®	HPLC–MS/MS	Salbutamol	Hydrolysis, β-glucuronidase/sulfatase	Ethyl acetate	Free curcumin after hydrolysis	[27]
Biocurcumax™ (BCM-95®)	HPLC-UV	Not used	No hydrolysis	Ethyl acetate	Free curcumin	[28]
Curcumin C3 Complex® + Bioperine	HPLC-UV	Not used	No hydrolysis	Methanol*	Free curcumin	[29]
Cavacurmin®	HPLC–MS/MS	Salbutamol	Hydrolysis, β-glucuronidase/sulfatase	Ethyl acetate	Free curcumin after hydrolysis	[30]
Theracurmin™	HPLC–MS/MS	Mepronil	Hydrolysis, β-glucuronidase/sulfatase	Chloroform	Free curcumin after hydrolysis	[31]

* Used the serum for quantification of curcumin. HPLC: high-performance liquid chromatography; MS: mass spectrometer; PDA: photodiode array; UV: ultraviolet.

phospholipids and should be considered by researchers in future studies [42]. We and others have previously described in detail the methodology to study matrix effects including common phospholipid transitions to be monitored [42,43]. Elution of curcumin at the same retention time of phospholipids should be avoided, and chromatographic conditions should be modified accordingly to separate the compound of interest and co-eluting phospholipids. Nowadays, hydrolysis can be avoided altogether, and free curcumin and conjugated curcumin can be simultaneously quantified on selective and sensitive LC–MS/MS instruments. Pure standards of curcumin's conjugates are commercially available. This offers a quick and simple sample preparation without the need of hydrolysis step which can introduce variability due to incomplete hydrolysis of the curcumin conjugates among samples. Also, curcumin conjugates are bound significantly to plasma proteins and can add to the variability in hydrolysis efficiency.

It is worth mentioning that most studies did not use an internal standard during the analysis of the plasma or serum samples from the bioavailability studies. This is a significant shortcoming in these studies as an internal standard improves the accuracy, precision, and robustness of the quantitative assay [44]. Interestingly, salbutamol was used as internal standard in CurcuWin® and Cavacurmin® clinical studies, and mepronil was used in Theracurmin™ study [27,31].

3.2.4. Pharmacokinetic parameters

Absorption, distribution, metabolism, and excretion determine the fate of a drug after administration. The oral bioavailability of a drug is the fraction of administered drug that reaches systemic circulation escaping the first-pass metabolism in the intestine and liver. Besides hepatic and intestinal metabolism, oral bioavailability is also dependent on several other factors. Such important factors include physicochemical properties of the drug, degradation in the lumen, lipophilicity of the drug, gastric emptying time and dose. The information on pharmacokinetic parameters of different formulations is tabulated in Table 4.

The maximum observed systemic concentration of a drug is termed as C_{max} (maximum drug concentration) whereas the time to reach this level is called T_{max}, time to reach maximum drug concentration; C_{max} represents the rate at which a compound is absorbed; the area under the drug concentration–time curve (AUC) denotes the extent of absorption of the drug. AUC is often used to compare the RB of a new formulation with a reference product. A direct comparison of AUC, T_{max}, and C_{max} among the formulations is not possible due to variability in the dose of curcumin administered. However, it is evident from the Table 4 that all the curcumin formulations significantly increased the AUC and C_{max} when compared to unformulated curcumin. As AUC is dependent on the rate of elimination and administered dose of a drug, it is evident that formulating curcumin prolongs the systemic exposure. It is important to note that while some formulations increased the T_{max}, others had an opposite effect. The T_{max} for unformulated curcumin (control) among the different studies ranged from 0.5 to 12 h showing almost a 15-fold difference. In contrast, for bioavailable formulations, T_{max} ranged from 0.69 to 8.8 h among formulations with an approximately 12-fold range.

3.2.5. RB

AUC presents a more reliable measure of bioavailability compared to C_{max} as it takes into account the systemic exposure of drug

Table 4
Pharmacokinetic parameters of curcumin from the different curcumin-based formulations and reference (unformulated curcumin).

Formulation	Intervention	Dose	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng · h/mL)	$t_{1/2}$ (h)	RB curcumin	References
Meriva®	Formulation[a]	297 mg curcumin	50.3 ± 12.7	3.8 ± 0.6	538.0 ± 130.7[1]	NR	48	[22]
	Control[a]	1295 mg curcumin	9.0 ± 2.8	6.9 ± 2.2	122.5 ± 29.3[1]	NR		
LongVida®	Formulation[a]	650 mg curcuminoids	22.4 ± 1.9	2.4 ± 0.4	95.3 ± 4.6[1]	7.5 ± 2.4	100	[23]
	Control[a]	650 mg curcuminoids	< 1	ND	ND	ND		
CurQfen™	Formulation[b]	600 mg curcumin	0.4 ± 0.2 (μg/g)	1	8100 ± 287[2] (μg · h/g)	NR	15.8	[24]
	Control[b]	1000 mg curcumin	0.02 ± 0.01 (μg/g)	0.5	510 ± 123[2] (μg · h/g)	NR		
MicroActive curcumin	Formulation[c]	500 mg curcumin	NR	4[d]	887.5 ± 549.9[3]	NR	9.7	[25]
	Control[c]	500 mg curcumin	NR	NR	91.8 ± 50.0[3]	NR		
Micronized curcumin	Formulation[b]	410 mg curcumin	15.3 ± 8.9	8.8 ± 6.4	214.6 ± 106.4[3]	NR	9	[26]
	Control[b]	410 mg curcumin	2.6 ± 4.9	7.5 ± 8.2	24.1 ± 42.6[3]	NR		
NovaSol®	Formulation[b]	410 mg curcumin	1189.1 ± 518.7	1.1 ± 0.4	4474.7 ± 1675.2[3]	NR	185	[26]
	Control[b]	410 mg curcumin	2.6 ± 4.9	7.5 ± 8.2	24.1 ± 42.6[3]	NR		
CurcuWin®	Formulation[a]	376 mg curcuminoids	27.3 ± 6.4	1.4 ± 0.5	307.6 ± 44.6[3]	NR	136.3	[27]
	Control[a]	1800 mg total curcuminoids	2.3 ± 0.3	7.4 ± 1.0	10.8 ± 1.7[3]	NR		
Biocurcumax™ (BCM-95®)	Formulation[c]	2000 mg curcuminoids	456.9[d] (μg/g)	3.44[d]	3201.3[d4] (μg · h/g)	4.96[d]	27	[28]
	Control[c]	2000 mg curcuminoids	149.8[d] (μg/g)	2[d]	461.9[d4] (μg · h/g)	2.63[d]		
Curcumin C3 Complex® + Bioperine	Formulation[a]	2000 mg curcumin with bioperine	180 ± 30	0.69 ± 0.07	80 ± 10[5]	0.11 ± 0.02	20	[29]
	Control[a]	2000 mg curcumin	6 ± 5	1[d]	4[d5]	NR		
Cavacurmin®	Formulation[a]	376 mg curcuminoids	73.2 ± 17.5	1[d]	327.7 ± 58.1[3]	NR	85	[30]
	Control[a]	1800 mg total curcuminoids	ND	12[d]	3.9 ± 0.5[3]	NR		
Theracurmin™	Formulation[b]	30 mg curcumin	29.5 ± 12.9	1[d]	113 ± 61[2]	NR	15.9	[31]
	Control[b]	30 mg curcumin	1.8 ± 2.0	6[d]	4.1 ± 7.0[2]	NR		

Control: unformulated curcumin.
NR: not reported; ND: not detected; AUC: area under the drug concentration–time curve; C_{max}: maximum drug concentration; RB: relative bioavailability; T_{max}: time at maximum drug concentration.
[a] Mean ± standard error of mean.
[b] Mean ± standard deviation.
[c] Mean.
[d] No reported standard deviation or error.
[1] AUC_{0-t}.
[2] AUC_{0-24}.
[3] AUC_{0-12}.
[4] AUC_{0-inf}.
[5] AUC_{0-6}.

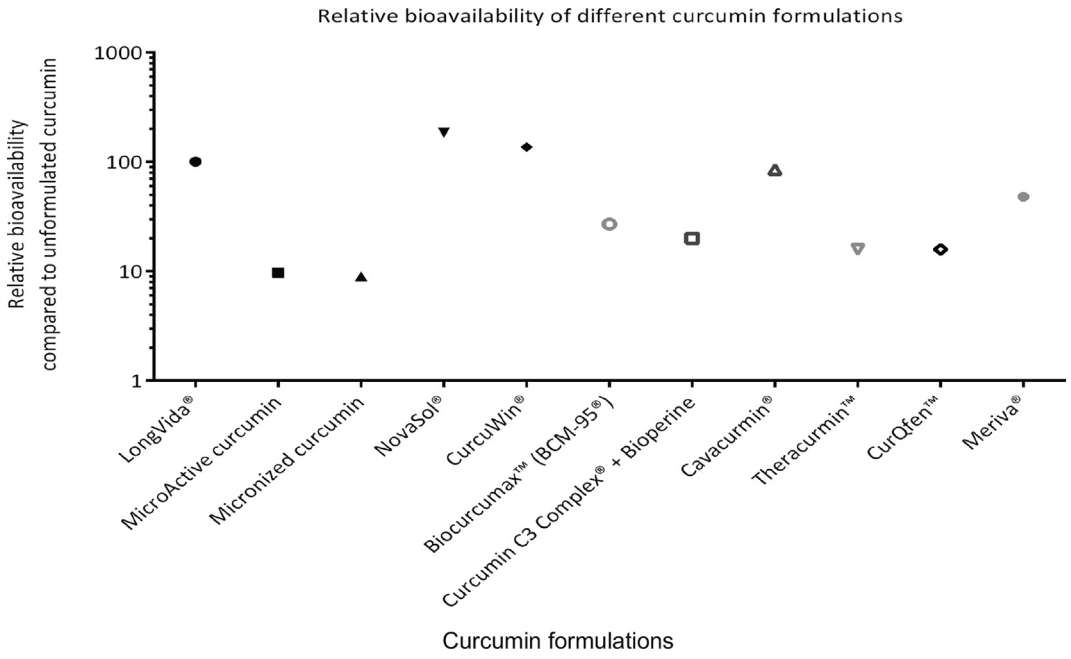

Fig. 2. Relative bioavailability of different curcumin formulations.

over time. In contrast, C_{max} measures only one-time point and is less robust to gauge the extent of total absorption. Therefore, RB of formulated curcumin compared to unformulated curcumin was used to determine the improvement in the absorption. The RB was calculated using the equation given below:

$$RB = \frac{(AUC_{0-t}FC) \times (\text{Dose UC})}{(AUC_{0-t}UC) \times (\text{Dose FC})}$$

where Dose UC is the dose of unformulated curcumin, Dose FC represents dose of formulated curcumin and AUC_{0-t} represents the area under the curve over time (0–t) for formulated curcumin (FC) and unformulated curcumin (UC), respectively.

RB ranged from 9 to 185 among the eleven bioavailable curcumin formulations (Fig. 2). NovaSol® (185-fold) was reported with highest RB compared to unformulated curcumin, and Micronized curcumin (9-fold) with the least (Table 4). Micelle-based curcumin formulation NovaSol® was reported to escape phase separation in gastrointestinal tract, delivering most of the curcumin to the intestinal wall for absorption. CurcuWin® and LongVida® were also reported to have $\geq$100-fold bioavailability relative to conventional unformulated curcumin, suggesting that approaches which increase the total surface area significantly, improve the bioavailability.

3.3. Limitations

Interestingly, a substantial difference in the pharmacokinetic parameters of curcumin from different formulations could be attributed to dissimilarities in dose, formulation, clinical design, analysis methods and populations in which the formulations were studied. Significant differences in the sampling time after oral administration in these studies may impact the AUC, C_{max} and T_{max}. The different gastric emptying time contributes significantly to the interindividual and interpopulation variability in drug absorption from the intestine. Therefore, the choice of food and time after which the meal was provided to volunteer may also impact the bioavailability and is another constraint when comparing these studies. An accurate comparison of different formulations can only be achieved by a large crossover study, comparing different formulations, using the same analytical method (free or conjugated curcumin) and a same method of administration (fasted or nonfasted, ethnicity). Such studies have been attempted in the past but only a handful of formulations were studied, and results were often different than the one reported by original articles due to the reasons listed above [27,30].

4. Conclusion

Curcumin's health benefits are limited due to poor solubility and pharmacokinetics. Efforts are currently made by different research groups to improve the bioavailability of curcumin to harness the proven *in vitro* efficacy and therapeutic promise. The recent decade has seen a rise in curcumin-based formulations addressing its solubility and stability. However, extensive variability in the studies makes it difficult to directly compare and conclude which formulation is better than the other. The absolute values of these studies are difficult to compare due to variances in study design, population, analytical methods, and administration of the product. Harmonized large clinical studies in human are needed to investigate how these curcumin formulations compare to each other but remain a constraint due to monetary and commercial reasons.

Conflict of interest

The review provides author's perspective of these curcumin formulations and has no conflict of interest to declare.

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