

## Colloidal Submicron-Particle Curcumin Exhibits High Absorption Efficiency —A Double-Blind, 3-Way Crossover Study—

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**Summary** Curcumin is a major constituent of the spice turmeric and has various biological activities, including anticancer, antioxidant, and anti-inflammatory properties, as well as alcohol detoxification. However, because of its poor absorption efficiency, it is difficult for orally administered curcumin to reach blood levels sufficient to exert its bioactivities. To overcome this problem, several curcumin preparations with a drug-delivery system (DDS) have been developed to increase the bioavailability of curcumin after oral administration, and tested as functional foods and potential medical agents in humans. We have also produced capsules containing Theracurmin, curcumin dispersed with colloidal submicron-particles. To evaluate the absorption efficiency of three types of DDS curcumin, we performed a double-blind, 3-way crossover study. We compared plasma curcumin levels after the administration of Theracurmin and 2 other capsule types of curcumin with DDS, BCM-95 (micronized curcumin with turmeric essential oils) and Meriva (curcumin-phospholipid). Nine healthy subjects (male/female=5/4, age: 24–32 y old) were administered these 3 preparations of DDS curcumin, at commonly used dosages. Six capsules of Theracurmin, 1 capsule of BCM-95, and 2 capsules of Meriva contain  $182.4 \pm 1.0$ ,  $279.3 \pm 10.7$ , and  $152.5 \pm 20.3$  mg of curcumin, respectively. The maximal plasma curcumin concentration (0–24 h) of Theracurmin was 10.7 to 5.6 times higher than those of BCM-95 and Meriva, respectively. Moreover, the area under the blood concentration-time curve at 0–24 h was found to be 11.0- and 4.6-fold higher with Theracurmin than BCM-95 and Meriva, respectively. These data indicate that Theracurmin exhibits a much higher absorption efficiency than other curcumin DDS preparations.

**Key Words** curcumin, colloidal submicron particles, human, plasma levels, drug-delivery system

Curcumin is the major yellow-orange pigment of turmeric, a common spice and coloring agent derived from *Curcuma longa*, and known for thousands of years as an Ayurvedic medicine. Now, curcumin is not only a health food, such as a food additive and dietary supplement, but also a drug candidate with prospective multipotent therapeutic applications (1, 2). The use of curcumin in Ayurveda, Chinese, Arabic, and other traditional medicines is well documented for a wide variety of ailments, including gastric problems, inflammatory conditions,

hepatic disorders, gynecological problems, infectious diseases, sprains, boils, cough, cold, asthma, and dental problems (3). The use of curcumin in traditional and modern medicine has been extensively reviewed in several previous reports (4, 5). Many studies revealed that curcumin has a broad spectrum of biological and pharmacological activities (6), such as antioxidant, anti-inflammatory (7), antibacterial (8), and anticarcinogenic activities (9), as well as cardio- and neuroprotective effects (10–12). Curcumin is a highly pleiotropic molecule with an excellent safety profile (13, 14). However, curcumin cannot achieve its optimum therapeutic effectiveness in vivo due to its low solubility and poor

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Table 1. Composition of each curcumin capsule.

| Sample      | Manufacturing method                                         | Ingredients                                                                                                                                                                   | Curcumin content | Dosage used in this study (number of capsules) | Measured value (mg) |
|-------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|------------------------------------------------|---------------------|
| Theracurmin | Curcumin dispersed with colloidal submicron-particles        | Theracurmin (dextrin, maltose, <i>Curcuma longa</i> extract, gum ghatti, citric acid), cornstarch, silicon dioxide, calcium stearate, hydroxypropyl methylcellulose (capsule) | 30 mg/capsule    | 180 mg (6 capsules)                            | 182.4±6.0           |
| BCM-95      | Curcumin complex with essential oils of the turmeric rhizome | <i>Curcuma longa</i> extract with essential oils of turmeric rhizome, rice flour, vegetable cellulose (capsule), vegetable stearate, silica                                   | 260 mg/capsule   | 260 mg (1 capsule)                             | 279.3±10.7          |
| Meriva      | Curcumin complex with phosphatidylcholine from soy lecithin  | <i>Curcuma longa</i> extract (root)/phosphatidylcholine complex, hypromellose (capsule), leucine, calcium citratelaurate, silicon dioxide, microcrystalline cellulose         | 75 mg/capsule    | 150 mg (2 capsules)                            | 152.5±20.3          |

gastrointestinal absorption and systemic bioavailability (15–17).

In order to increase its solubility, stability, and pharmacological activities, studies on chemically modified curcumin derivatives as well as improved formulations and delivery systems have been performed to achieve optimum therapeutic effects. Adjuvants, nanoparticles, micelles, phospholipid delivery systems, and liposomes have been tested to overcome this problem (2, 16, 18, 19). There are several curcumin formulations that can improve the bioavailability of curcumin in human. One of these curcumin formulations is BCM-95, generated by micronizing curcumin and adding turmeric essential oils to enhance absorption naturally. The relative bioavailability of BCM-95 was found to be about 6.9-fold higher than that of normal curcumin in humans (20). Another lecithinized formulation of curcumin, Meriva, was tested in healthy volunteers, and found to improve absorption to about a 29-fold higher level than corresponding normal curcumin (21). Theracurmin, curcumin dispersed with colloidal submicron-particles, demonstrated oral bioavailability nearly 30 times higher than that of curcumin powder in both rats and humans (22, 23).

These 3 preparations of drug-delivery system (DDS) curcumin are commonly sold as health foods and used in clinical studies in many countries because several reports have indicated that plasma curcumin levels sufficient to demonstrate bioactivities can be obtained and some beneficial effects are observed by taking these preparations. However, no study measuring plasma curcumin levels in the same volunteers taking these curcumin preparations has been reported. Here, we performed a clinical study in humans to compare the plasma levels of curcumin using these preparations sold.

## MATERIALS AND METHODS

*Curcumin preparations.* Theracurmin was supplied

Table 2. Assignment of volunteers in cross-over study.

|             | Group 1 (n=3) | Group 2 (n=3) | Group 3 (n=3) |
|-------------|---------------|---------------|---------------|
| First week  | Theracurmin   | Meriva        | BCM-95        |
| Second week | BCM-95        | Theracurmin   | Meriva        |
| Third week  | Meriva        | BCM-95        | Theracurmin   |

by the Theravalues Corporation (Tokyo, Japan) (22). The 2 other commercial preparations containing curcumin were obtained from stores: BCM-95 was from Life Extension Foundation and Meriva was from Thorne Research Inc. It is standard to administer the same doses of curcumin in this kind of crossover study. Although the amount of curcumin in each preparation was different, we could not unify the amounts in all preparations. This is because there is a possibility of the degradation of curcumin itself and disintegration of its micelles due to instability caused by destroying preparations in an attempt to standardize the amount. The dosage of each curcumin preparation was determined based on recommended amounts for commercial use and clinical studies (17, 21, 24–29). The clinical benefits were obtained at these doses. Capsules of these 3 preparations were placed in brown envelopes and labeled A to C, respectively. The contents of these health foods are indicated in Table 1.

*Subjects.* The Institutional Review Board of Shizuoka General Hospital approved this study. All subjects provided written informed consent prior to participation in compliance with the Declaration of Helsinki. Nine healthy subjects consented to the study. Screening procedures included the medical history, physical exam, hematologic profile, and blood chemistries. Subjects were not taking any medications nor were they taking

any dietary or herbal supplements. Women could not be pregnant or breast-feeding.

**Study design and procedures.** Subjects participated in a single-dose, double-blind, 3-way crossover study. They were divided into three groups as shown in Table 2. In each group, the three types of curcumin capsule of curcumin were administered every 7 d. Subjects did not take curcumin-containing food for more than 7 d before this study and fasted overnight except for water. In the morning, blood specimens were obtained immediately prior to taking the curcumin preparations and at 0.5, 1, 2, 4, 6, and 24 h after taking them. Curcumin capsules were taken with a sip of mineral water. Subjects fasted except for water until blood sampling 6 h after taking the preparations. All blood specimens were drawn in 5-mL blood-collecting vessels containing heparin. They were immediately placed in an ice bath and protected from light. Vessels were centrifuged at  $1,500 \times g$  for 20 min at  $4^\circ\text{C}$  to separate the plasma. The plasma samples were then frozen at  $-70^\circ\text{C}$ .

**Sample preparation and measurement of plasma curcumin levels.** Blood sample preparation and the measurement of plasma curcumin levels were previously reported (22, 30). Briefly, each plasma sample was incubated with 0.1 M sodium acetate buffer (pH 5.0) containing 1,000 U  $\beta$ -glucuronidase (Wako Pure Chemical Industries, Ltd., Japan) at  $37^\circ\text{C}$  for 1 h to hydrolyze the curcumin conjugates. After extraction with chloroform, the dried extracts were reconstituted in 100  $\mu\text{L}$  of 50% methanol and injected into a chromatographic system. Plasma concentrations of curcumin were measured using the HPLC-MS/MS system comprising the Prominence micro-LC system (Shimadzu, Kyoto, Japan) and an API 3200 tandem mass spectrometer (Applied Biosystems, Foster City, CA) with (+) ESI, as described previously (23).

**Pharmacokinetics.** The area under the curve (AUC) was calculated using the trapezoidal method (30). Maximum concentrations ( $C_{\text{max}}$ ) were the observed values.

**Statistical analysis.** Data are expressed as the mean  $\pm$  standard deviation (SD). For evaluation of the curcumin absorption, the non-parametric Kruskal-Wallis test followed by the Steel-Dwass test was used.

$p < 0.05$  was considered statistically significant.

## RESULTS

### Actual amount of curcumin in each preparation

First, we analyzed the actual amounts of curcumin in each of the 3 preparations of DDS curcumin using the HPLC-MS/MS system. Results are presented in Table 1. The reported and actually measured values in 6 capsules of Theracurmin were 180 and  $182.4 \pm 6.0$  mg, respectively. Those in 1 capsule of BCM-95 were 260 and  $279.3 \pm 10.7$  mg and those in 2 capsules of Meriva were 150 and  $152.5 \pm 20.3$  mg, respectively.

### Subject demographic characteristics and disposition

Nine subjects were enrolled in this study; the cohort included 5 males (56%), the cohort included 5 males and 4 females, with a mean age of 25 (24–32). The mean body weight was 62 (49–92) kg, mean height was 1.70 (1.53–1.84) m, and mean BMI was 21.6 (18.0–28.7)  $\text{kg}/\text{m}^2$ . No subjects were withdrawn from the study. No adverse effects were observed.

### Pharmacokinetics

The time course of mean plasma curcumin concentration in healthy volunteers ( $n=9$ ) administered a single oral dose of each curcumin capsule are shown in

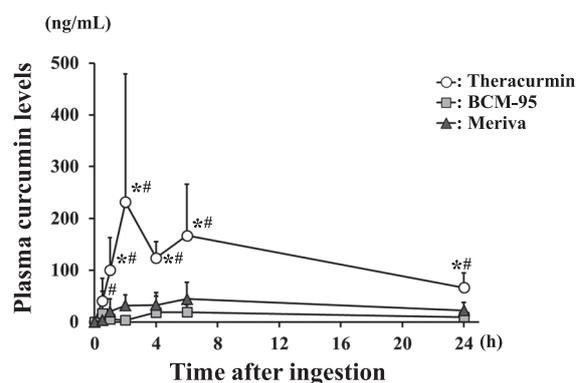


Fig. 1. Change in plasma concentration of curcumin in healthy volunteers. ●, Theracurmin. ◆, BCM-95, ▲, Meriva. Each point and bar represents the mean  $\pm$  SD ( $n=9$ ). \*  $p < 0.05$  versus BCM-95. #  $p < 0.05$  versus Meriva.

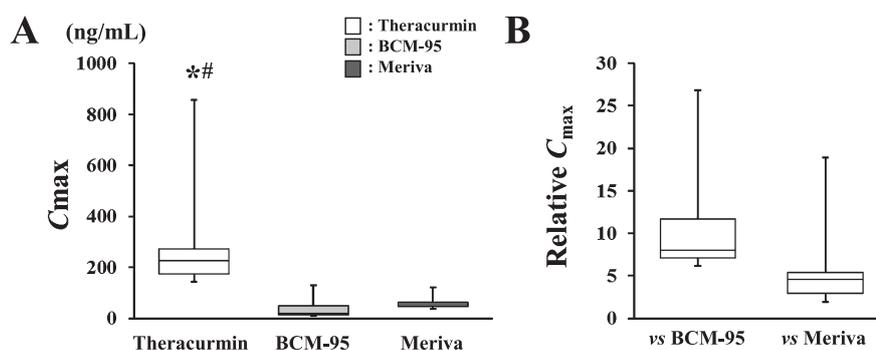


Fig. 2. Maximum concentration of curcumin in healthy volunteers. A: Box plots of  $C_{\text{max}}$  are represented as graphically depicting groups of numerical data through their five-number summaries (minimum, 25%, median, 75%, and maximum). B: Box plot of  $C_{\text{max}}$  values with Theracurmin normalized by those with BCM-95 and Meriva and expressed as relative values in individual volunteers, respectively. \*  $p < 0.05$  versus BCM-95. #  $p < 0.05$  versus Meriva.

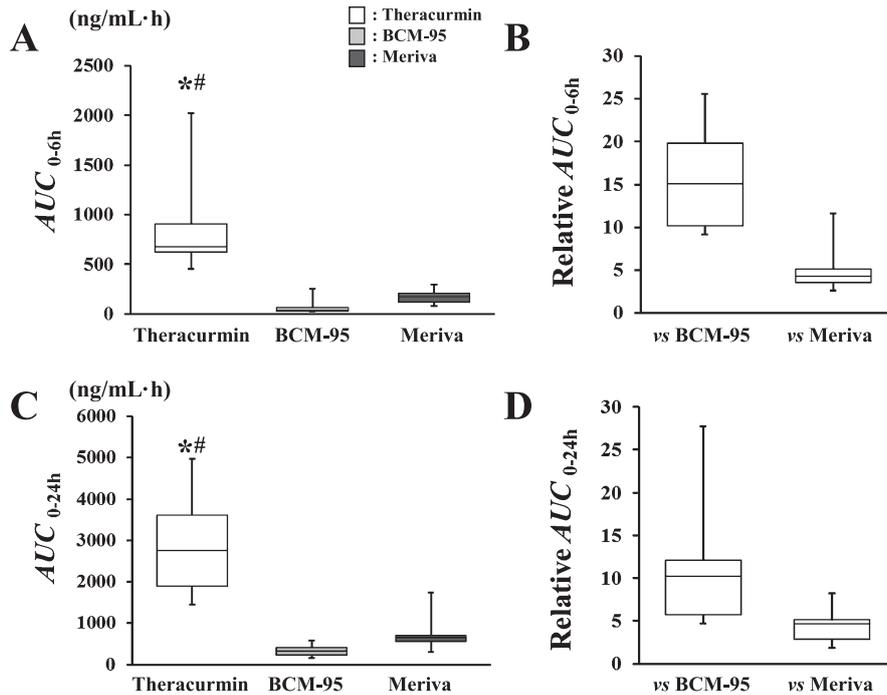


Fig. 3. Bioavailability of curcumin in healthy volunteers. A, C: Box plots of  $AUC_{0-6h}$  (A) and  $AUC_{0-24h}$  (C) are represented as graphically depicting groups of numerical volunteers through their five-number summaries. B, D: Box plots of  $AUC_{0-6h}$  (B) and  $AUC_{0-24h}$  (D) with Theracurmin normalized by those with BCM-95 and Meriva and expressed as relative values in individual volunteers, respectively. \*  $p < 0.05$  versus BCM-95. #  $p < 0.05$  versus Meriva.

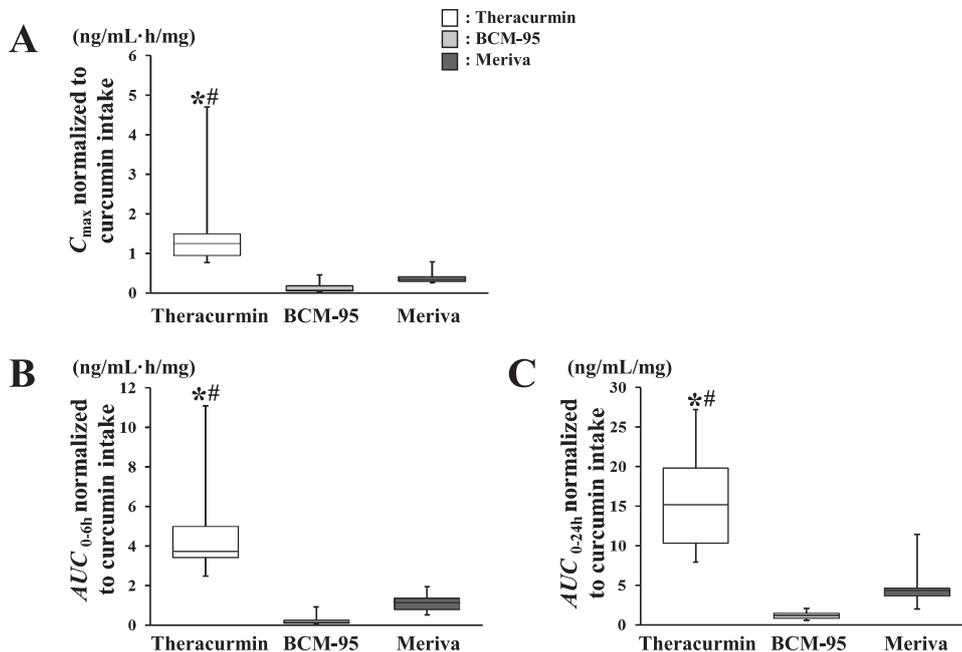


Fig. 4. Normalized bioavailability of curcumin in healthy volunteers. A–C:  $C_{max}$  (A),  $AUC_{0-6h}$  (B) and  $AUC_{0-24h}$  (C) of each curcumin capsule normalized by measured curcumin contents respectively, and exhibited as box plots. \*  $p < 0.05$  versus BCM-95. #  $p < 0.05$  versus Meriva.

Fig. 1. For all treatments, plasma curcumin levels were quantifiable 30 min after administration. At all points, plasma levels of curcumin were higher with Theracurmin than BCM-95 or Meriva. Two peak plasma concentrations were observed with Theracurmin and BCM-95. Those were 2 and 6 h and 0.5 and 6 h after taking

capsules of Theracurmin and BCM-95, respectively. In Meriva, 6 h after the administration was determined as a peak plasma concentration. As evident from Fig. 1, the absorption of curcumin from Theracurmin peaked in the first peak at 2 h (mean: 231.5 ng/mL). This value decreased during the succeeding hour to 124.0 ng/mL

and then reached the second peak at 6 h (167.1 ng/mL). Thereafter, the values gradually decreased. However, even at 24 h, some residual curcumin remained in the blood (mean: 66.4 ng/mL), which was higher than C<sub>max</sub> of BCM-95 (mean: 45.0 ng/mL) and Meriva (mean: 58.8 ng/mL)

C<sub>max</sub> values with each curcumin capsule were described as box plots (Fig. 2A). The distribution of C<sub>max</sub> with Theracurmin displayed a high level compared with those of BCM-95 and Meriva. The mean value of maximum curcumin concentration with Theracurmin reached 287.2 ng/mL and was significantly higher than those with BCM-95 and Meriva. Relative mean values of C<sub>max</sub> with Theracurmin were also 10.7- and 5.6-fold higher than those with BCM-95 and Meriva in individual volunteers, respectively (Fig. 2B).

The AUC was calculated using the trapezoidal method from 0 to 6 h (AUC<sub>0-6h</sub>) and 0 to 24 h (AUC<sub>0-24h</sub>). As shown in Fig. 3A and C, the box plots of AUC<sub>0-6h</sub> and AUC<sub>0-24h</sub> with Theracurmin likewise showed a higher level distribution compared with BCM-95 and Meriva. AUC<sub>0-6h</sub> was 16.1- and 5.6-fold higher on the average with Theracurmin than with BCM-95 and Meriva, respectively, and AUC<sub>0-24h</sub> was 11.0- and 4.6-fold higher with Theracurmin than with BCM-95 and Meriva in individual volunteers, respectively (Fig. 3B and D). In case of the values of C<sub>max</sub> and AUC normalized to curcumin intake by dividing the measured C<sub>max</sub> and AUC by the corresponding measured curcumin dosage of each administration, similar results were observed (Fig. 4A-C).

The results of this study indicate that the bioavailability as measured by the C<sub>max</sub> and AUC is significantly higher with Theracurmin than with the other 2 curcumin DDS preparations.

## DISCUSSION

The present double-blind, 3-way crossover study in healthy volunteers demonstrated that Theracurmin yielded a higher C<sub>max</sub> and AUC than the other curcumin DDS preparations. This indicates that Theracurmin possesses a higher absorption efficiency compared with other curcumin preparations, suggesting the usefulness of an oral curcumin preparation using this system.

Natural curcumin in its original form has a low bioavailability. After oral ingestion, very little may actually reach the systemic circulation, and even less may reach organs and tissues (17). Many attempts have been made to improve the formulation of curcumin and/or its delivery system (31). Theracurmin showed the highest C<sub>max</sub> and AUC among the 3 curcumin preparations in this study. Theracurmin was developed using a sub-micron-particle and surface-controlled drug-delivery system (22). Theracurmin has a high dispersibility, low aggregability, and high solubility in water and exhibits an over 30-fold higher bioavailability than conventional curcumin in rats and humans. BCM-95 is prepared by micronizing curcumin and adding turmeric essential oils (32). Although dissolution in oil induces no modi-

fication of its structure, it can then be directly absorbed into chylomicrons and subsequently into the lymphatic system, bypassing the liver and “the first pass phenomenon” (16). Although BCM-95 and Theracurmin are micronized, the main differences are their solvents (BCM-95: turmeric essential oil, Theracurmin: gum ghatti and glycerin). Moreover, the micronizing approach might be different. These differences may affect the absorption efficacy of curcumin through the intestine.

Meriva is a mixture of natural curcuminoids and a phospholipid formulation, produced with a lecithinized formation method. Curcumin is covered by phospholipid particles at its surface and has been shown to strongly bind to phospholipid micelles, positioning the water-labile  $\beta$ -diketone moiety in the lipid bilayer and protecting it from hydrolytic fragmentation, the major mechanism of degradation in water (33). As a result, Meriva has been shown to improve absorption compared to the natural form (30-fold improvement on a molecular basis) (21). The differences between Meriva and Theracurmin are phospholipid micelles and colloidal particles, respectively. Micelles are structurally larger than colloidal particles, and this difference in size is very important for absorption efficacy. Moreover, Theracurmin is micronized but Meriva is not. This also affects their dispersibility in water. However, Theracurmin's degradation efficacy in water has not been reported so far, although Meriva possesses a structure protecting it from degradation. Not only the size of the formulation and its absorption efficacy but also its degradation should be considered to understand the clinical efficiency of curcumin. Although the precise methods to manufacture each preparation are unclear, they might be different from each other. So, if these methods are combined and a new DDS curcumin preparation is generated, there is a possibility that it will show a higher bioavailability than existing ones.

Only a few clinical studies have been reported using these DDS curcumin preparations. The clinical efficacy of Meriva was tested in patients with several diseases. Meriva improved curcumin bioavailability and joint pain and function in osteoarthritis (OA) patients (30), could alleviate side effects associated with chemo- and radiotherapy in patients under treatment for solid tumors (24), had pain-relieving properties (34), was effective for patients with benign prostatic hyperplasia (BPH) (35), and was effective in the management of central serous chorioretinopathy (36, 37), diabetic microangiopathy and retinopathy (38), and chronic anterior uveitis (39). Some clinical studies showed that BCM-95 had beneficial effects on patients with rheumatoid arthritis (RA) (40) and oral submucous fibrosis (OSMF) (41). Theracurmin was reported to be able to potentially improve the age-related decline in endothelial function (26) and systolic blood pressure (27) in postmenopausal women. These studies showed not only the efficacy but also the long-term safety of these DDS curcumin formulations in humans.

In this study, we used amounts of the curcumin preparation according to the common doses reported in

papers or used in ongoing clinical trials. The total curcumin content in each preparation was considered to be approximately equal without breaking the capsules. Theracurmin was reported to be used at 100–400 mg in patients with cancer or healthy elderly volunteers for chronic treatment in clinical studies, indicating that at least 400 mg of Theracurmin was safe (24–27). Moreover, more than 10 phase 2 clinical trials are now ongoing using 180 mg of Theracurmin, and no significant adverse effect has been reported so far. So, in this study, volunteers were administered with 180 mg of Theracurmin. From 1 to 8 capsules (approximately 260–2,080 mg of curcumin) BCM-95 were used for clinical trials (20, 28, 32, 41). Since even 1 capsule had beneficial effects on patients with RA, we used 1 capsule (260 mg of curcumin) in this study to adjust the curcumin level in all groups. Meriva was used at doses from 500 mg to 2 g (100 to 400 mg of curcuminoid) (21, 29, 30, 34, 36, 37). As 2 capsules of Meriva (150 mg of curcumin) were commonly used as health food and were reported to be safe and efficacious in patients with OA (21), we chose 2 capsules of Meriva. Despite these considerations, we found that the actually measured values of Theracurmin, BCM-95, and Meriva were slightly different (Table 1). Moreover, since the oral amounts of these curcumin preparations in this study were different, we normalized the data by dividing the observed AUC by the corresponding actually measured value following each administration (Fig. 4A–C). After normalization, AUC<sub>0–24h</sub> and C<sub>max</sub> were significantly higher with Theracurmin than with BCM-95 and Meriva. Although the plasma curcumin levels increased dependently with the intake dose, the correlation between plasma curcumin levels and intake doses of these forms of DDS curcumin was not linear in some clinical studies (21, 25). Therefore, further pharmacokinetic studies are needed to clarify the possible effects of the oral doses on blood curcumin levels by adjusting the same intake doses of DDS curcumin or examining the effects of multiple doses.

Diphasic peaks of the plasma curcumin concentration were observed in this study. The first peak was at 2 h after Theracurmin intake; 2 h later the curcumin levels decreased, and the second peak was at 6 h after administration. The same re-rise phenomenon of curcumin levels after Theracurmin was observed in our previous report and in another study (25, 30). Moreover, since not only Theracurmin but also Meriva and BCM-95 led to a biphasic blood concentration of curcumin (Fig. 1), there might be some common mechanisms regarding the pharmacokinetics of curcumin itself in vivo. After orally administration of curcumin, 75% of the dose was excreted in feces and its glucuronide and sulphate conjugates were detected in the urine (42, 43). After intravenous and intraperitoneal administrations of curcumin to rats, a large amount and its metabolites were excreted in the bile, mainly as glucuronides (44). These findings suggested that curcumin undergoes glucuronate conjugation during absorption via the enteron, and that it is likely to undergo enterohepatic recirculation (45). Thus, the re-absorption of curcumin from the feces is one of

the reasons for the diphasic peaks of plasma curcumin levels. More precise studies, such as one using RI-labeled curcumin, are awaited to clarify the details.

The bioavailability was significantly improved by taking Theracurmin. Theracurmin may exert clinical benefits in humans at lower dosages because curcumin possesses dose-dependent effects. Although the oral administration of 10 or 12 g of natural curcumin was safe in a previous clinical study (14), there is a possibility of unexpected side effects due to high plasma curcumin levels as a result of improvement of the absorption efficiency. Long-term administration of Theracurmin at a dose of 150 mg is safe and well-tolerated (24). Moreover, a 6-mo, ongoing clinical study using 180 mg of Theracurmin has so far indicated that Theracurmin at this dose is safe (Morimoto, unpublished data). Thus, Theracurmin may be safely used as a health food and medicine.

Due to the increased bioavailability with the new formulation of curcumin, Theracurmin, we consequently expect the clinical efficacy to be enhanced. Further clinical studies are needed to investigate this.

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