

Dose escalation and pharmacokinetic study of nanoparticle curcumin, a potential anti-cancer agent with improved bioavailability, in healthy human volunteers

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Abstract

Background: More and more preclinical studies support the idea that curcumin, a plant-derived natural polyphenol, could be a promising anti-cancer drug. However poor bioavailability has limited its efficacy in clinical trials, and plasma curcumin levels remain low despite patients taking gram doses of curcumin.

Methods: This study aimed to evaluate the safety and pharmacokinetics of newly developed nanoparticle curcumin with increased water solubility (named THERACURMIN). Six healthy human volunteers were recruited and received THERACURMIN at a single oral dose of 150 mg. After an interval of two weeks, the same subjects then received THERACURMIN at a single dose of 210 mg. Plasma curcumin levels were measured at 0, 1, 2, 4, 6, and 24 h after THERACURMIN intake using high performance liquid chromatography (HPLC).

Results: One subject reported grade 1 diarrhea after intake of 150 mg THERACURMIN. No other toxicities were observed in this study. C_{max} for THERACURMIN at 150 mg and 210 mg was 189 ± 48 and 275 ± 67 ng/ml (mean \pm S.E.M.), respectively and the area under the curve for 24 h was estimated to be 2649 ± 350 and 3649 ± 430 ng/ml \times h (mean \pm S.E.M.),

respectively. The $t_{1/2}$ was estimated to be 9.7 ± 2.1 h for 150 mg and 13.0 ± 3.3 h for 210 mg.

Conclusion: THERACURMIN can safely increase plasma curcumin levels in a dose dependent manner at least up to 210 mg without saturating the absorption system. To the best of our knowledge, THERACURMIN is the first nanoparticle formulation of curcumin which demonstrates improved bioavailability in human subjects. We believe this compound could be a promising tool when testing the potential anti-cancer effects of curcumin in clinical trials.

Keywords: curcumin, nanotechnology, bioavailability, THERACURMIN

1. Introduction

Curcumin is derived from turmeric (*Curcuma longa*) and is a natural polyphenol. Curcumin has long been used as a food, coloring agent and traditional medicine. More and more data support the idea that this chemical could be a promising anti-cancer drug [1, 8, 31]. Several investigators, including ourselves, have tested plasma curcumin levels in clinical trials and reported that plasma levels remained low in spite of taking gram doses of curcumin [7, 10, 14, 27]. Furthermore, more than 8 g of curcumin intake did not increase blood curcumin levels in healthy volunteers [34]. Thus, poor bioavailability is the major weak point of curcumin and has been the main hurdle for physicians seeking to verify the therapeutic efficacy of this promising agent in clinical trials. Therefore, many researchers are now focusing on improving its bioavailability through several approaches including innovative drug delivery systems (liposomes, nanoparticles and phospholipids) [2, 4, 6, 9, 11, 15, 17-19, 22, 24, 26, 29, 30, 32], the use of adjuvants [28] or the development of new curcumin analogues [13, 20, 23]. One of these approaches, a nanoparticle-based drug delivery system, has now been widely used to improve water solubility of hydrophobic agents [3, 5, 12, 21]. By applying this nanoparticle-based drug delivery system to curcumin, a new form of curcumin (THERACURMIN) has been developed. THERACURMIN has improved water

solubility with its mean particle size of 0.19 μm , and oral administration of THERACURMIN demonstrated more than 30-fold higher bioavailability compared to that of conventional curcumin in rat models [25]. Furthermore, C_{max} for THERACURMIN at 30 mg was 30 ng/ml, while it was lower than 2 ng/ml after 30 mg of conventional curcumin intake in healthy human subjects [25]. However, it was not determined whether higher doses of THERACURMIN could safely increase plasma curcumin levels in a dose dependent manner.

Therefore, in this study we aimed to determine the safety and improved bioavailability of THERACURMIN at dose levels higher than 30 mg.

2. Materials and Methods

2.1. Preparation of THERACURMIN

THERACURMIN was provided by the Theravalues Corporation (Tokyo, Japan).

THERACURMIN was prepared as follows. Firstly, gum ghatti, which mainly consists of polysaccharides obtained from the exudation of ghatti trees, was dissolved in water to make gum ghatti solution. Curcumin powder was mixed into this solution, and water and glycerin were added to adjust the weight. The mixture was ground using a wet grinding mill (DYNO-MILL[®]KDL, Willy A Bachofen AG), and then dispersed by a high-pressure homogenizer (Homogenizer 15MR-8TA, APV Gaulin). Stable THERACURMIN was obtained from this procedure. The particle size of THERACURMIN was measured by a laser diffraction scattering method using Microtrac MT-30000II (Microtrac Inc., Montgomeryville, USA). THERACURMIN consisted of 10% curcumin, 2% other curcuminoids such as demethoxycurcumin and bisdemethoxycurcumin, 46% glycerin, 4% gum ghatti, and 38% water. THERACURMIN was provided in capsule form and each capsule contained 30 mg of THERACURMIN.

2.2. Clinical Trial Design

Six healthy human volunteers with normal organ function were recruited. None of the subjects were taking daily medications. They were asked to avoid all foods containing high concentrations of curcumin within one day before and one day after THERACURMIN intake. Initially, the six subjects received THERACURMIN at a single dose of 150 mg (level 0). Adverse events were graded based on the National Cancer Institute Common Toxicity Criteria version 3.0 [33]. Any grade 3 or higher adverse events were pre-defined as dose limiting toxicities (DLT). If the incidence of DLT was two or lower out of six subjects, then we planned to evaluate the safety of THERACURMIN at a single dose of 210 mg (level 1) in the same subjects without DLT at level 0 after an interval of two weeks. Blood samples (2 ml) were collected in tubes containing EDTA just before THERACURMIN intake (0 h) and at 1, 2, 4, 6, and 24 h after THERACURMIN intake. The protocol was approved by the institutional review board at Kyoto University Hospital and registered in the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (ID 000003488). All protocol procedures were carried out at Kyoto University Hospital.

2.3. Sample preparation and measurement of plasma curcumin levels using an

HPLC-MS/MS system

Plasma curcumin levels were measured as previously reported [14]. A 0.1 ml aliquot of each plasma sample was transferred to a 10 ml glass tube and then 0.11 ml of 0.1M sodium acetate buffer (pH 5.0) containing 1000 U β -glucuronidase was added. The resulting solutions were incubated to hydrolyze the curcumin conjugates at 37°C for 1 h. Following the addition of 10 μ l of Internal Standard (IS) working solution (500 ng/ml), a 0.5 ml volume of chloroform was added as an extraction solvent. The sample was vortexed for 1 min followed by ultrasonic vibration for 15 min and then centrifugation at 1610g for 5 min. The organic layer was transferred to a 1 ml glass tube and evaporated to dryness using a centrifuge concentrator. The dried extract was reconstituted in 100 μ l of 50% acetonitrile (MeCN) containing 0.05% formic acid (FA) and then centrifuged at 7700g for 10 min. A 10 μ l aliquot of the supernatant from the reconstituted sample solution was injected into the chromatographic system.

The high performance liquid chromatography – tandem mass spectrometry (HPLC-MS/MS) system consisted of Prominence micro-LC system (Shimadzu, Kyoto, Japan) and an API 3200 tandem mass spectrometer (Applied Biosystems, CA, USA) with electrospray ionization (ESI). Samples were subjected to Atlantis T3 (2.1 x 150 mm, 3 μ m) (Waters, Milford, USA) as a separation C-18 column using a gradient of binding solvent (0.05% FA/H₂O) and elution solvent (0.05% FA/MeCN) at a flow rate of 0.2 ml/min and a column

temperature of 40°C. Separation of samples was conducted by a 35-min linear gradient (5-95% elution solvent). The mass spectrometer was operated under multiple reaction monitoring (MRM) mode with a collision energy of 23 eV for curcumin and 33 eV for mepronil. The transitions (precursor to product) monitored were m/z 369→285 for curcumin, 270→119 for mepronil. Chromatograms were integrated using the ANALYST version 1.5 software.

Stock solutions of curcumin and mepronil were prepared at a concentration of 1000 ng/ml in methanol (MeOH). The stock solution of mepronil was further diluted with 55% MeOH to prepare a calibration standard at a concentration of 100 ng/ml. The stock solution of curcumin was further diluted with 62% MeOH to prepare a calibration standard at a concentration of 200 ng/ml. Curcumin solution (200 ng/ml) was diluted with 50% MeOH to prepare the following standard solutions: 0.4, 0.8, 1.6, 3.1, 6.3, 12.5, 25.0, 50.0, and 100.0 ng/ml. These solutions were mixed with IS solution (100 ng/ml) at a ratio of 1:1 to prepare IS-containing calibration samples of 0.2-100.0 ng/ml (curcumin) and 50 ng/ml (mepronil). Stock solution (1000 ng/ml) of mepronil was further diluted with MeOH to prepare the IS working solution at a concentration of 500 ng/ml.

2.4. Pharmacokinetic analysis

Area under the curve (AUC) is calculated using the trapezoidal method. Maximum concentrations (C_{\max}) and T_{\max} are the observed values. The $t_{1/2}$ value was calculated by dividing 0.693 by the terminal rate constant, which was derived from the slope of the natural log-transformed concentrations and times on the terminal elimination phase of the decay curve.

3. Results

3.1. Subjects and Adverse Events

Six healthy Japanese volunteers consisted of five males and one female (mean age, 44 years; range, 38-51 years; mean body mass index, 24.4; range 20.2-27.8). Only one subject (case 1, Table 1) reported Grade 1 diarrhea lasting from day 1 through day 4 after 150 mg of THERACURMIN intake. However diarrhea did not recur after the second, 210 mg dose of THERACURMIN in this subject. No other adverse events were observed in this study.

3.2. Plasma concentration of total curcumin

Figure 1 shows the size characterization of THERACURMIN using a laser diffraction scattering method and Figure 2 shows representative HPLC chromatograms of plasma after enzymatic hydrolysis. Peak plasma curcumin levels after 150 mg THERACURMIN intake ranged from 152 to 285 ng/ml and C_{max} was 189 ± 48 ng/ml (mean \pm S.E.M.), while peak plasma curcumin levels after 210 mg THERACURMIN intake ranged from 221 to 594 ng/ml and C_{max} was 275 ± 67 ng/ml (mean \pm S.E.M.) (Figure 3). The area under the curve for 24 h was estimated to be 2649 ± 350 and 3649 ± 430 ng/ml \times h (mean \pm S.E.M.), respectively. The $t_{1/2}$ were estimated to be 9.7 ± 2.1 h for 150 mg and 13.0 ± 3.3 h for 210 mg. Total curcumin was still detectable in plasma at the 24-h time point.

4. Discussion

A number of preclinical studies have demonstrated that curcumin could be a promising anti-cancer drug [1, 8, 31]. However, poor bioavailability is the major weak point in its clinical application: plasma curcumin levels remain low in spite of taking gram doses of curcumin [7, 10, 14, 16, 27, 28] (Table 2). Lao et al. conducted a dose escalation study of curcumin in twenty-four healthy volunteers and could detect plasma curcumin in only two subjects who took 10 g or 12 g of oral curcumin [16]. In another study by Garcea et al., only trace amounts of curcumin were detected after intake of 3.6 g oral curcumin [10]. Furthermore, intake of more than 8g curcumin per day was not acceptable to patients [7] and could not increase the blood curcumin levels, probably due to saturation of the absorption system [34]. Therefore, improving bioavailability is essential in order to see the potential benefits of curcumin in clinical studies.

Nanoparticle-based drug delivery systems are suitable for improving water solubility of hydrophobic agents like curcumin, and various forms of nanoparticle curcumin have recently been synthesized [2, 6, 9, 11, 15, 22, 24, 26, 29, 30]. Bisht et al. have synthesized polymeric nanoparticle encapsulated curcumin composed of N-isopropylacrylamide, N-vinyl-2-pyrrolidone and poly-ethyleneglycol-monoacrylate and reported that the efficacy of this nanoparticle encapsulated curcumin was similar to that of conventional curcumin *in vitro*

and *in vivo* [6]. Shaikh et al. have also reported the improved bioavailability of curcumin with nanoparticle encapsulation in rat models [26]. Similarly, THERACURMIN has improved water solubility with its mean particle size of 0.19 μm (Figure 1), and oral administration of THERACURMIN demonstrated more than 30-fold higher bioavailability compared to that of conventional curcumin in rat models. C_{max} for THERACURMIN at 30 mg was 30 ng/ml, while it was lower than 2 ng/ml after 30 mg of conventional curcumin intake in healthy human subjects [25]. However, it was not determined whether higher doses of THERACURMIN could safely increase plasma curcumin levels in a dose dependent manner. Therefore, we proceeded to determine the safety and improved bioavailability of THERACURMIN at dose levels higher than 30 mg.

With a dose of 150 mg of THERACURMIN, we observed a plasma curcumin level (189 ± 48 ng/ml, mean \pm S.E.M.), which compared well with the level observed after intake of 8g of conventional curcumin in our previous study in pancreatic cancer patients (134 ± 70 ng/ml) [14], or in other previous studies using gram doses of curcumin (Table 2). Only one subject reported grade 1 diarrhea lasting for 4 days after 150mg of THERACURMIN intake and no DLT was observed. Therefore, we proceeded to evaluate a dose of 210 mg of THERACURMIN in the same subjects after an interval of 2 weeks. As expected, plasma curcumin levels increased in a dose dependent manner (275 ± 67 ng/ml, mean \pm S.E.M.)

without saturating the absorption system. No adverse events including diarrhea, which was observed at a dose of 150 mg, were reported.

Our current results demonstrate that THERACURMIN can safely increase the plasma curcumin level in a dose dependent manner at least up to 210 mg. In rat models, THERACURMIN was able to increase plasma curcumin levels in a dose dependent manner up to at least 80 mg/kg without increasing toxicity (unpublished data). This suggests that an intake of more than 210 mg THERACURMIN may be able to increase plasma curcumin levels higher without saturating the absorption system in human subjects and further studies are now underway to test this hypothesis.

To the best of our knowledge, THERACURMIN is the first nanoparticle formulation which demonstrates improved bioavailability in human subjects. We believe this compound could be a promising tool when testing the potential anti-cancer effects of curcumin in clinical trials.

Several clinical trials are now underway to evaluate the therapeutic efficacy of THERACURMIN in cancer patients.

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Conflict of interest: none.

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Figure 1. Size characterization of THERACURMIN using laser diffraction scattering method

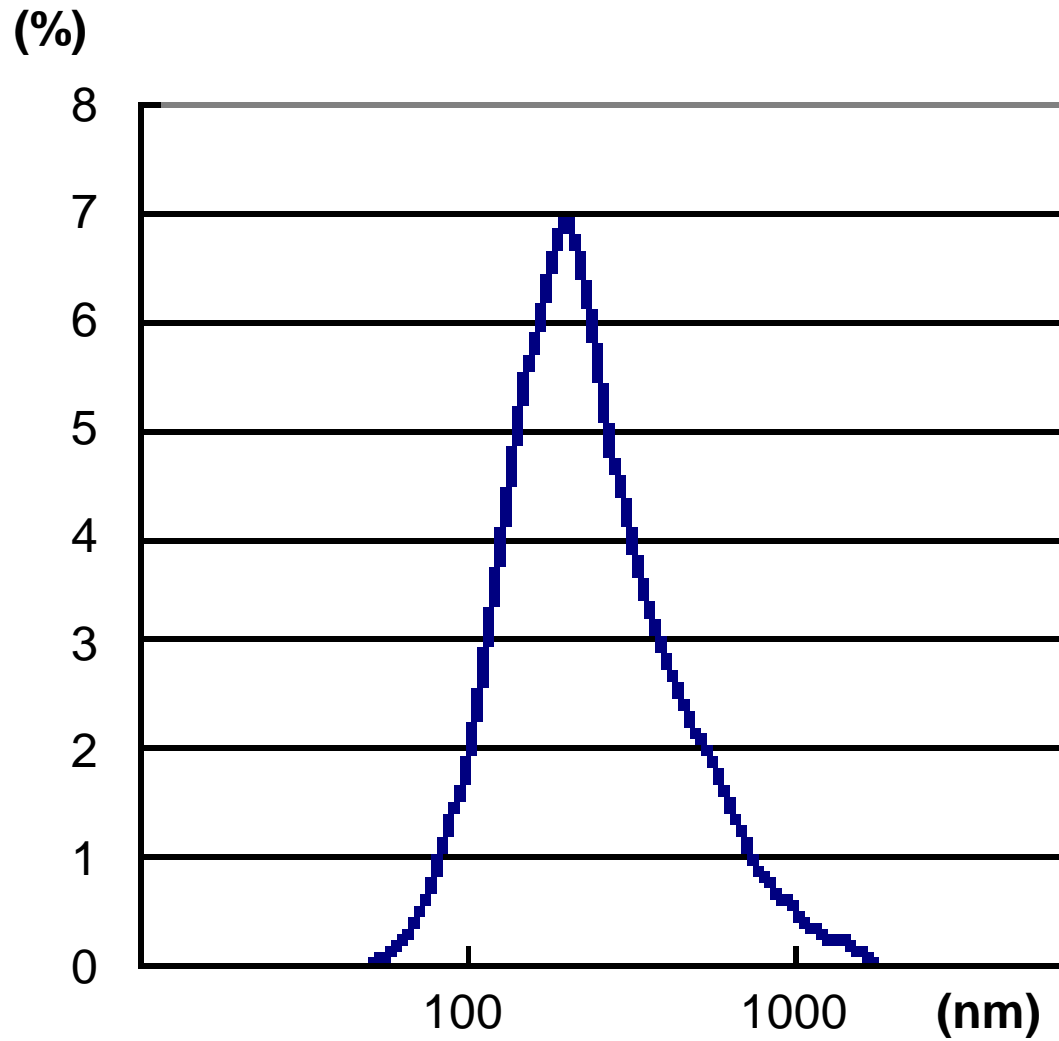


Figure 2. Representative examples of HPLC chromatograms (case 5 after oral intake of 210 mg of THERACURMIN)

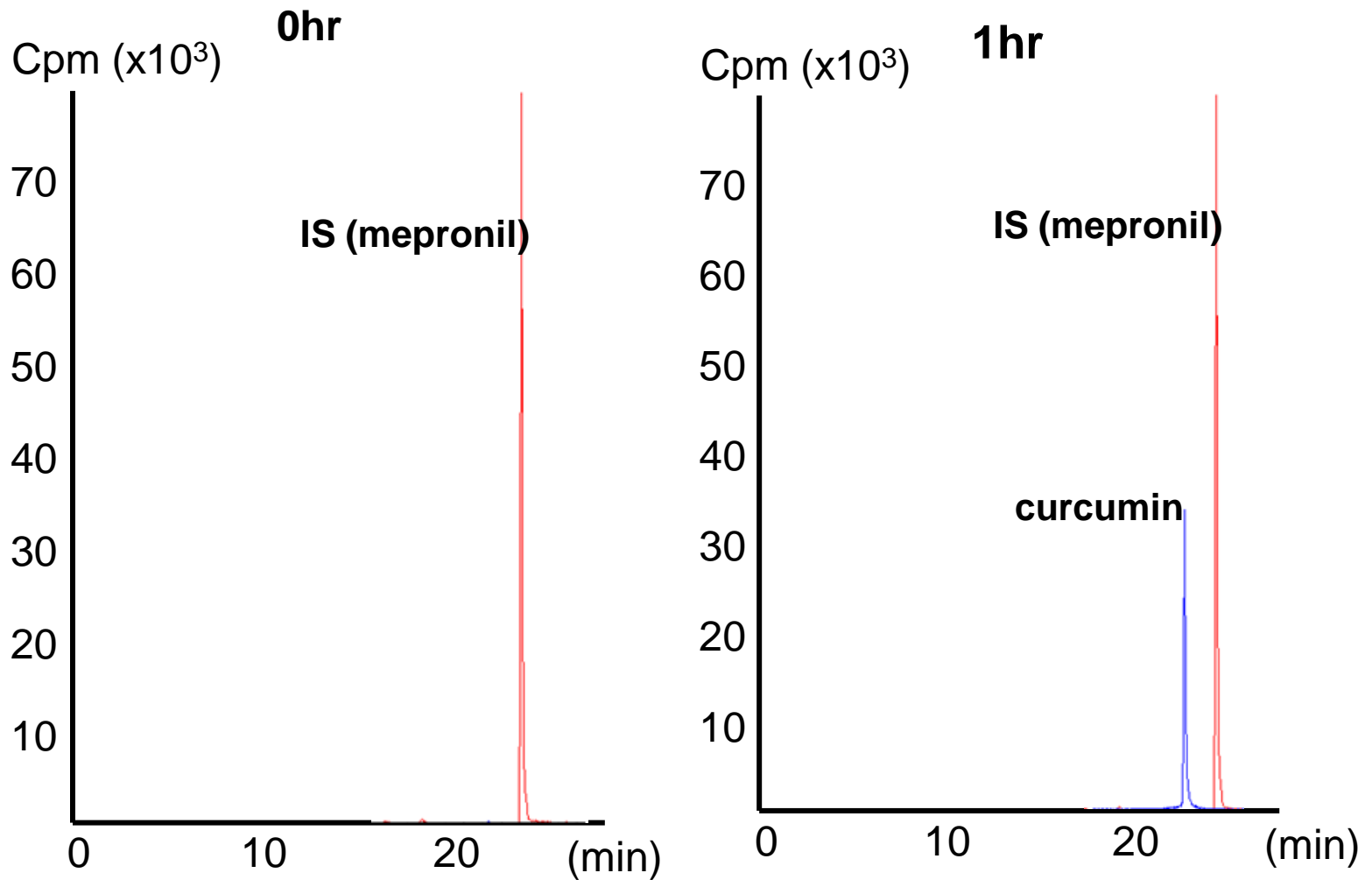


Figure 3. Time course of plasma curcumin levels after intake of 150 mg (solid line) and 210 mg (dashed line) THERACURMIN (n=6). Error bar represents S.E.M.

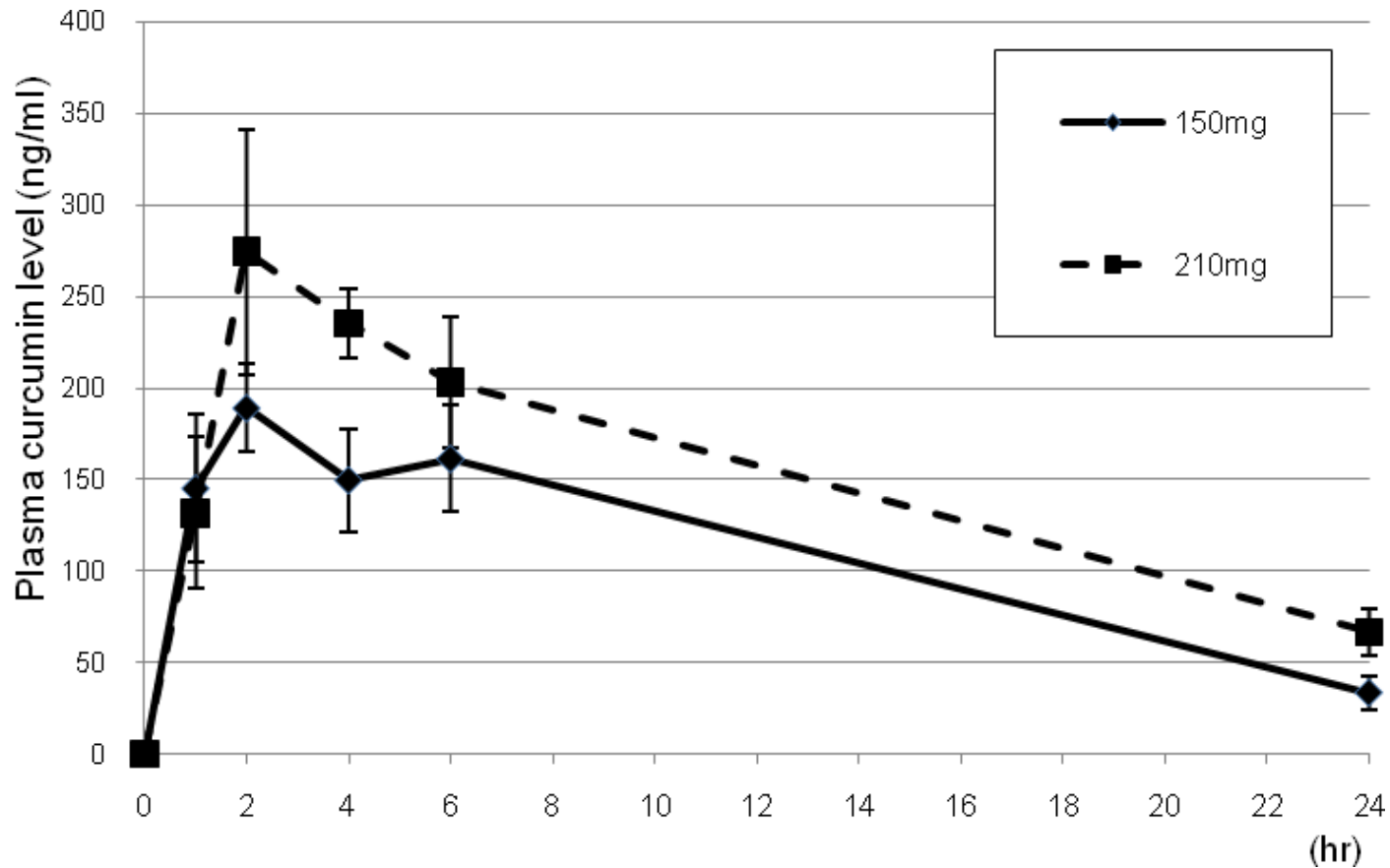


Table 1. Characteristics and pharmacokinetic parameters of study subjects

				150mg				210mg			
	gender	age	BMI	Cmax	T1/2 (h)	Tmax (h)	AUC	Cmax	T1/2 (h)	Tmax (h)	AUC
case1	male	44	24.2	270	6.4	1.0	1791	594	9.3	2.0	3763
case2	male	40	20.2	247	13.3	2.0	3221	284	17.3	6.0	4455
case3	female	51	27.8	220	12.0	2.0	2048	290	6.8	2.0	2324
case4	male	47	25.7	152	5.4	6.0	2102	221	9.0	4.0	2503
case5	male	38	23.9	285	5.0	4.0	4048	324	9.4	6.0	4980
case6	male	44	24.7	171	15.8	6.0	2679	254	26.1	4.0	3863

Units for Cmax and area under the curve (AUC_{0-24hr}) were ng/ml and ng/ml × h, respectively.

Table 2. Comparison of the published studies reporting plasma curcumin levels in human subjects after oral intake of curcumin.

	Subjects	Dose of curcumin	Sample size	Reported plasma curcumin level (mean \pm SE)
Shoba et al.	healthy volunteers	2 g/day	8	6 \pm 5 ng/ml
Chen et al.	patients with precancerous lesions	8 g/day	2	651 \pm 688 ng/ml
Sharma et al.	colorectal cancer patients	3.6 g/day	3	4 \pm 0.2 ng/ml
Lao et al.	healthy volunteers	12 g/day	3 (1)	57 ng/ml* ¹
Garcia et al.	colorectal cancer patients	3.6 g/day	3	below 1 ng/ml
Vareed et al.	healthy volunteers	8 g/day	6	2300 \pm 260 ng/ml
Kanai et al.	pancreatic cancer patients	8 g/day	5	134 \pm 70 ng/ml
Sasaki et al.	healthy volunteers	0.03 g/day* ²	7	29.5 \pm 13 ng/ml
Current study	healthy volunteers	0.21 g/day* ²	6	275 \pm 67 ng/ml

*¹Plasma curcumin was detected in only one subject.

*²THERACURMIN was used in these studies