PharmaNutrition 4 (2016) 1–8

Contents lists available at ScienceDirect

PharmaNutrition

journal homepage: www.elsevier.com/locate/phanu

Highly bioavailable curcumin (Theracurmin): Its development and clinical application

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ARTICLE INFO

Article history:
Received 28 April 2015
Received in revised form 4 November 2015
Accepted 4 November 2015
Available online 10 November 2015

Keywords:
Highly bioavailable curcumin
Antioxidant
Anti-inflammatory
Theracurmin

ABSTRACT

Curcumin is a polyphenol with antioxidant and anti-inflammatory properties. It is highly lipophilic and sparingly soluble in water and very little is absorbed when it is ingested; therefore, improving its absorbability is a major priority. We developed a highly bioavailable curcumin called Theracurmin using submicron particle formation and surface controlled technology. In human study, the area under the blood concentration–time curve (AUC) after oral administration of Theracurmin was 27-fold higher than that of commercially available curcumin. Preclinical safety tests were conducted and no adverse effects were confirmed. The effects of Theracurmin on cancer (lung, pancreatic, and prostate), cardiovascular disease (heart disease), vascular function (arterial stiffness and central blood pressure), and bone and cartilage (knee osteoarthritis) were evaluated by collaborating with universities and medical institutions. In this paper, we present the development of Theracurmin and its effects in an animal model as well as in human clinical studies.

1. Development of highly bioavailable curcumin (Theracurmin)

Low oral bioavailability is one of the major reasons why curcumin has been unsuccessful in achieving therapeutic outcomes, despite its pleiotropic pharmacological properties [1]. To increase its absorption through the intestinal membrane, a higher concentration at the membrane surface is essential. Many curcumin delivery methods with increased solubility and stability or accessibility, in or to the GI tract, have been reported [2].

A number of attempts have been made to improve the absorption of curcumin using technologies such as submicron suspensions [3], phosphatidylcholine complexes [4], and solid lipid nanoparticles [5].

A submicron crystal solid dispersion of curcumin, Theracurmin, was prepared as follows; first, gum ghatti, 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 was added to adjust the weight. This mixture was ground by a wet grinding mill (DYNO-MILL® KDL, Willy A Bachofen AG), and then, dispersed by a high-pressure homogenizer. After this procedure, stable THERACURMIN was obtained. THERACURMIN consisted of 10 w/w% of curcumin, 2% of other curcuminoids such as demethoxycurcumin and isdemethoxycurcumin, 4% of gum ghatti, and 84% of water. When curcumin in Theracurmin was orally administered to rats at doses of 5 mg/kg and 30 mg/kg, C_{max} was 764 ng/ml (T_{max} = 1 h) and 1697 ng/ml (T_{max} = 2 h), respectively. A 30-mg dose of curcumin in Theracurmin or conventional curcumin was administered to healthy human volunteers. The area under the blood concentration–time curve (AUC) for Theracurmin was 27-fold higher than that for curcumin for food additive as pigment offered commercially, and C_{max} was 30 ng/ml (T_{max} = 1 h). Curcumin in Theracurmin at higher doses of 150 mg and 210 mg were also tested, and the C_{max} values were 189 ng/ml (T_{max} = 4 h) and 275 ng/ml (T_{max} = 2 h), respectively. In these studies, plasma curcumin was assayed after hydrolysis with glucuronidase [3].

Recently, many curcumin products with increased bioavailability have been introduced in the market [4,5]. However, it is difficult to compare the literature in terms of the absorption efficiency because of the different conditions of experiments, dosages, and analytical methods. Table 1 and Fig. 1 show the comparison of the products BCM-95, Meriva, and Theracurmin (Curcuminoids 83–88%, Curcumin 79–84%) in a double-blinded, three-way crossover study [6]. Among several attempts that have been made

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http://dx.doi.org/10.1016/j.phanu.2015.11.001
2213-4344/

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,*Curcuma longa*extract (Curcuminoids 83–88%, Curcumin 79–84%), 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	*Curcuma longa* 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	*Curcuma longa* extract (root)/Phosphatidylcholine complex), Hypromellose (capsule), Leucine, Calcium citratelaurate, Silicon dioxide, Microcrystalline cellulose	75 mg/ capsule	150 mg (2 capsules)	152.5 ± 20.3

to improve absorption of curcumin, Theracurmin has been shown to be one of the most promising.

2. Effect of curcumin on cancer

Resistance to erlotinib in lung cancer may be related to the activation of nuclear factor kappa B (NFkappaB)-related pathways in association with a decrease in ikappaB levels. Therefore, the effects of coadministration of erlotinib and curcumin on lung cancer cells (PC9) were evaluated [7]. Expression of ikappaB was elevated in PC9 cells by curcumin administration, and pretreatment with siRNAs for ikappaB significantly attenuated the decrease in cell viability after coadministration of erlotinib and curcumin (Fig. 2). Coadministration of erlotinib and/or Theracurmin on the growth of PC9 tumors in mice was then investigated. The body weight of the animals did not significantly differ between any of the treatment groups during the experiment ($n = 5$ in each group). The general behavior of the animals also appeared to be similar in all groups. Coadministration of erlotinib and/or Theracurmin decreased the growth of PC9 tumors in mice, and statistically significant reduction was achieved only by coadministration of erlotinib and Theracurmin (Fig. 3). Histological studies of these tumors showed that the region of necrosis was significantly increased in the coadministered group in comparison with the control group. Based on the results of these findings, safety evaluation of the coadministration of erlotinib and Theracurmin in non-small cell lung cancer patients is now underway (University Hospital Medical Information Network in Japan (UMIN) 000013424).

In 2014, Masashi Kanai published a review in the World Journal of Gastroenterology [8] titled "Therapeutic applications of curcumin for patients with pancreatic cancer." He mentioned that many papers have reported the anticancer effects of curcumin against pancreatic cancer in vitro and in vivo as well as in clinical trials in patients with pancreatic cancer. However, because of poor bioavailability, curcumin doses of >8 g/day do not lead to further increases in plasma curcumin levels, and even in multigram doses, curcumin plasma levels remained low (ng/ml) [9–11]. Kanai highlighted Theracurmin as a curcumin product with improved bioavailability. To verify the improved bioavailability of Theracurmin in human subjects, dose-escalation and pharmacokinetics studies were conducted. Six healthy human volunteers were recruited and given Theracurmin via a single oral dose of curcumin 150 mg. Following an interval of 2 weeks, the same subjects were given Theracurmin via a single oral dose of curcumin 210 mg. The C_{max} values for curcumin in Theracurmin for 150 and 210 mg doses were 189 and 275 ng/ml, respectively. No toxicity associated with Theracurmin intake was observed in this study [12]. These results

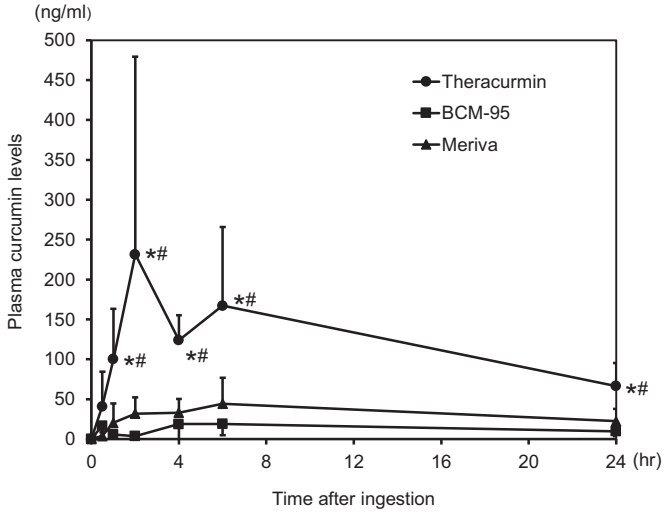

Fig. 1. Change in plasma concentration of curcumin in healthy volunteers. ●, Theracurmin; ◆, BCM-95; ▲, Meriva. Each point and bar represents the mean ± SD ($n = 9$). $^{*}P < 0.05$ vs. BCM-95. # $P < 0.05$ vs. Meriva. Sample preparation and measurement of plasma curcumin levels: Each plasma sample was incubated with beta-glucuronidase to hydrolyze the curcumin conjugates. After extraction with chloroform, the dried extracts were reconstituted in 50% MeOH and injected into a chromatographic system. Plasma concentrations of curcumin were measured using the HPLC-MS/MS system.
Adapted from Sunagawa et al. [6]. Colloidal submicron-particle curcumin exhibits high absorption efficiency: A double-blind, 3-way crossover study. J Nutr Sci Vitaminol 2015;61:37–44.