Curcumin has various biological activities including antioxidant and antiinflammatory actions, and alcohol detoxification. However, because of its poor absorption efficiency, it is difficult for orally administered curcumin to reach blood levels sufficient to realize its bioactivities. We have generated capsules and tablets containing Theracurmin, a highly absorptive curcumin. In addition, we recently created a drinkable preparation of Theracurmin. To evaluate the absorption efficiency of this type of curcumin, we performed a single-dose, double-blind, 4-way crossover study. We compared plasma curcumin levels after the administration of Theracurmin beverage and 3 other drinkable types of curcumin sold in Japan. Twenty-four healthy subjects (male/female = 13/11, age: 23–32) were administered with these 4 drinkable preparations of curcumin. The area under the blood concentration–time curve at 0–8 h was found to be 1.5 to 4.0-fold higher with Theracurmin than with the other 3 kinds of curcumin beverage. Moreover, maximal plasma curcumin concentrations (0–8 h) of Theracurmin were 1.8 to 3.8 times higher than those of the other 3 curcumin beverages. These data indicate that our newly prepared Theracurmin beverage exhibits a much better absorption efficiency than other kinds of curcumin beverage sold in Japan.

Key words curcumin; drinkable preparation; Theracurmin; human; plasma level

Curcumin is a yellow-colored substance widely known as turmeric, which is prepared from the root of the Curcuma longa plant, a member of the ginger family (Zingiberaceae) and native to India and Southeast Asia. Curcumin is well-known to have a broad spectrum of biological and pharmacological activities, such as antioxidant, antiinflammatory, antibacterial, antifungal, and antitumor activities, as described in many reports. Moreover, curcumin also possesses cardio- and neuroprotective effects. Curcumin has been used to treat a broad range of common ailments in Indian Ayurvedic medicine for at least 4000 years, as well as in Chinese, Arabic, and other traditional medicines. Curcumin is in modern use worldwide as a cooking spice, flavouring agent, and colorant. One of the reasons why curcumin has a long and long history of use is its safety. No studies in either animals or humans have demonstrated significant toxicity associated with the use of curcumin, even at high doses. However, a problem with the use of curcumin is its poor water solubility and short biological half-life.

Several approaches have been tested to increase the oral bioavailability of curcumin, including adjuvant, nanoparticles, micelles, phospholipid delivery systems, and liposomes. However, no suitable delivery options, such as a soluble formulation of curcumin, have been found so far. Here, we have generated Theracurmin, a highly absorptive form of curcumin, using a technique of a micro-particle and surface-controlled colloidal dispersion. Theracurmin consisted of 10 w/w% of curcumin, 2% of other curcuminoids such as demethoxycurcumin and isodemethoxycurcumin, 46% glycerin, 4% gum ghatti, and 38% water. Theracurmin demonstrated oral bioavailability nearly 30-times higher than that of curcumin powder in both rats and humans. A minimal dose of Theracurmin was sufficient to improve the left ventricular systolic function in post-myocardial infarction rats, suggesting the clinical usefulness of Theracurmin for heart failure treatment.

Several curcumin beverages are sold as health foods in many countries including Japan. However, it has yet to be determined whether plasma curcumin levels sufficient to demonstrate bioactivities can be obtained by taking these beverages. Without improving the absorption efficiency of these beverages containing curcumin, their bioactivities might not be significant. We created the drinkable preparation of Theracurmin and performed a clinical study in humans using Theracurmin beverage and other curcumin beverages sold in Japan to compare the plasma levels of curcumin.

MATERIALS AND METHODS

Drinkable Preparations Theracurmin was obtained from Theravals Corporation (Tokyo, Japan). A drinkable preparation containing Theracurmin was prepared. There other 3 commercial drinkable preparations containing curcumin were obtained from a store. These 4 drinkable preparations were re-bottled in new, unified bottles and labeled A to D, respectively. The contents of these health beverages are indicated in

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Table 1. Composition of Each Drink Containing Curcumin

<table>
<thead>
<tr>
<th>Sample</th>
<th>Curcumin content (display value)</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drink A</td>
<td>30 mg/100 mL</td>
<td>Water, sugar group (high-fructose corn syrup, sugar), cinnamon extract, ginger, alanine, acidulant, turmeric colorant (Theracurmin), vitamin C, flavor, niacinamide, sweetener (licorice, sucralose), calcium pantothenate, vitamin B₆, vitamin B₉, vitamin B₁₂, vitamin B₂, vitamin B₃, vitamin B₁</td>
</tr>
<tr>
<td>Drink B</td>
<td>30 mg/100 mL</td>
<td>Water, sugar, turmeric extract, Korean ginseng extract, alanine, trehalose, citric acid, arginine, flavor, turmeric colorant, vitamin C, sweetener (sucralose), niacin, vitamin B₂, vitamin B₉, vitamin B₁₂, vitamin B₁, vitamin P, phenylalanine, isoleucine, threonine, monosodium glutamate</td>
</tr>
<tr>
<td>Drink C</td>
<td>40 mg/120 mL</td>
<td>Water, high-fructose corn syrup, dextrin, Curcuma longa extract, Curcuma zedoaria extract, acidulant, vitamin C, polysaccharide thickener, turmeric colorant, inositol, flavor, cyclic oligosaccharide, sweetener (sucralose, acesulfame potassium, thaumatin), niacin, vitamin B₂, vitamin E, emulsifier, vitamin B₁</td>
</tr>
<tr>
<td>Drink D</td>
<td>30 mg/100 mL</td>
<td>Water, high-fructose corn syrup, dextrin, Curcuma longa extract, salt, acidulant, vitamin C, polysaccharide thickener, inositol, turmeric colorant, flavor, cyclic oligosaccharide, niacin, sweetener (sucralose, acesulfame potassium, thaumatin), vitamin E, vitamin B₁, antioxidant (catechin)</td>
</tr>
</tbody>
</table>

Table 2. Assignment of Volunteers in Cross-over Study

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=6)</th>
<th>Group 2 (n=6)</th>
<th>Group 3 (n=6)</th>
<th>Group 4 (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st week</td>
<td>Drink A</td>
<td>Drink A</td>
<td>Drink C</td>
<td>Drink C</td>
</tr>
<tr>
<td>2nd week</td>
<td>Drink B</td>
<td>Drink B</td>
<td>Drink D</td>
<td>Drink D</td>
</tr>
<tr>
<td>3rd week</td>
<td>Drink C</td>
<td>Drink C</td>
<td>Drink A</td>
<td>Drink B</td>
</tr>
<tr>
<td>4th week</td>
<td>Drink D</td>
<td>Drink D</td>
<td>Drink B</td>
<td>Drink C</td>
</tr>
</tbody>
</table>
As shown in Table 3, the AUC \(_{0–8\,h}\) values of A became about 1.5 to 4.0-fold higher than those of the other 3 kinds of curcumin beverage. Plasma C\(_{\text{max}}\) (0–8 h) of Theracurmin were 1.8 to 3.8 times higher than those of the other 3 curcumin beverages (Table 3). No significant differences were observed between genders. The results of this study indicate that the bioavailability as measured by the AUC is significantly higher with Theracurmin beverage than the other 3 curcumin beverages.

To compare the absorption rates, we evaluated AUC \(_{0–2\,h}\), AUC \(_{0–4\,h}\), and AUC \(_{0–8\,h}\). The AUC \(_{0–2\,h}\) of A was 1.3-, 2.4-, and 2.4-fold higher than that of B, C, and D, respectively, the AUC \(_{0–4\,h}\) was 1.4-, 2.7-, and 3.3-fold higher, and the AUC \(_{0–8\,h}\) was 1.5-, 3.0-, and 4.0-fold higher in A than B, C, and D. The
The differences of AUC among volunteers were marked. To determine whether low or high absorption efficiency in each individual is shared by all 4 types of curcumin beverage, we examined AUC correlations among these beverages in each individual. As shown in Fig. 2, significant good correlations were observed between any 2 types of curcumin beverage. These findings suggest that individual differences in the pharmacokinetics of curcumin are shared by all 4 types of curcumin beverage.

DISCUSSION

We have newly created a drinkable preparation of Theracurmin, a highly absorptive curcumin. The present double-blind, 4-way crossover study in healthy volunteers demonstrated that the Theracurmin beverage yielded higher Cmax and AUC than the other curcumin beverages sold in Japan. This indicates that Theracurmin beverage possesses a higher absorption efficiency compared with other curcumin beverages.

The problem of curcumin after oral administration is its poor systemic bioavailability, due to its low solubility in water as many other natural polyphenols, and its rapid metabolism. Recently, drug delivery systems accompanied by nanoparticle technology have emerged as prominent solutions to the bioavailability as therapeutic agents. Although nanoparticle-based delivery systems might be suitable for highly hydrophobic agents like curcumin to circumvent the pitfalls of poor aqueous solubility, very few studies have been reported regarding curcumin nanoparticles. A polymer-based nanoparticle of curcumin, “nanocurcumin,” with a particle size of less than 100nm size was synthesized. While nanocurcumin works well as curcumin in vitro, no efficacy of nanocurcumin over free curcumin in vivo has been reported. Curcuminoid-loaded solid lipid nanoparticles were developed for long-term stability at room temperature and reduced light and oxygen sensitivity. To increase the bioavailability of curcumin, nanoparticles encapsulating curcumin have been prepared by the emulsion technique. These include an optimized poly(lactide-co-glycolide acid) nano-formulation, dextran sulfate-chitosan nanoparticles with curcumin, polymeric nanoparticle-encapsulated curcumin, and water-dispersible hybrid nanogels. However, these nanoparticle-based systems for curcumin delivery are still in their infancy, and much progress is warranted in this area. Here, we have generated highly absorptive curcumin, Theracurmin, using a micro-particle and surface-controlled colloidal dispersion method, which markedly improves oral bioavailability.

We reported that the plasma curcumin level reaches a maximum at 1 h after the oral administration of 30mg of Theracurmin in healthy volunteers. Many reports indicate that oral administration of curcumin in humans and rodents results in peak plasma levels at around 1 h after the intake. However, in this study, drinkable types of curcumin including the Theracurmin beverage yielded maximum plasma curcumin levels more than 8h after drinking. In all experiments of pharmacokinetics, subjects were in completely fasting states before and after taking samples. Thus, the influence of meals could be discounted. A number of clinical studies demonstrated that concomitant food and drug intake reduces Cmax but increases AUC. These findings suggest that food intake increases the overall bioavailability but reduces the peak systemic exposure.
relative to fasting conditions. Therefore, one of the reasons for the delayed peak is that drinkable types of curcumin contain many components other than curcumin, which may affect its absorption speed. In normal life, it is expected that curcumin beverages are taken before and after meals, and their absorption speeds should be slower than those indicated by pharmacokinetic experiments. Another reason for this delay in the curcumin peak is enterohepatic circulation. When curcumin was given orally to rats, most of it was excreted in the feces and negligible amounts were found in the urine.

Intravenous and intraperitoneal administrations of curcumin resulted in biliary excretion in rats. These data indicate that curcumin is re-absorbed from feces and that the plasma concentration of curcumin is maintained at high levels for a long time. This may be useful to exert and sustain the physiological effects of the drinkable types of curcumin, especially Theracurmin beverage.

In this study, we compared plasma levels of curcumin in Theracurmin beverage and those of other curcumin beverages sold in Japan. We reported that the plasma level of curcumin is significantly higher after the oral administration of Theracurmin than that of curcumin powder in humans. Since the compositions differ between Theracurmin beverage and other curcumin beverages (Table 1), such differences may affect curcumin levels. However, as the precise composition, origin, extraction method, and curcumin modification of each beverage are unclear, the substitution of curcumin beverages with Theracurmin was impossible. Further pharmacokinetic studies are needed to clarify possible effects of the beverage components on blood curcumin levels.

Curcumin is the active ingredient of the dietary spice turmeric and has been consumed for medicinal purposes for thousands of years. Modern science has shown that curcumin modulates various signaling molecules, including inflammatory molecules, transcription factors, enzymes, protein kinases, and protein reductases. Moreover, curcumin has been reported to possess bioactivity, such as anti-inflammatory, anti-oxidant, pro-apoptotic, chemopreventive, chemotherapeutic, anti-proliferative, wound healing, anti-nociceptive, anti-parasitic, and anti-malarial properties. Animal studies have suggested that curcumin may be active against a wide range of human diseases, including diabetes, obesity, neurologic and psychiatric disorders, and cancer, as well as chronic illnesses affecting the eyes, lungs, liver, kidneys, and gastrointestinal and cardiovascular systems. Curcumin has been shown to have the potential to improve many diseases in human research as well as experimental studies including cultured cells and animal models. In addition, more than 90 clinical trials using supplemental curcumin are on-going in many countries. Furthermore, curcumin is used as a supplement in several countries, including India, Japan, the United States, Thailand, China, Korea, Turkey, South Africa, Nepal, and Pakistan.

However, this inexpensive, apparently well-tolerated, and potentially active curcumin has yet been approved for the treatment of any human disease. Many clinical trials evaluating curcumin’s safety and efficacy against human ailments have already been completed. In the near future, curcumin may be used not only in health foods, but also medical agents.

We have shown that curcumin exhibits biological activity to prevent the deterioration of systolic functions in rat heart failure models at $C_{\text{max}}$ with $10.7 \pm 1.7$ and $5.0 \pm 2.4$ ng/mL. In this study, $C_{\text{max}}$ of Theracurmin beverage was $25.5 \pm 12.2$ ng/mL, which is higher than those with protective effects on the heart. We previously examined whether Theracurmin exerts effects on alcohol metabolism after drinking ethanol in healthy volunteers. We demonstrated that Theracurmin could reduce plasma levels of acetaldehyde, a product of ethanol. These data indicate that Theracurmin directly affects the metabolism of acetaldehyde and accelerates the detoxification of ethanol. The $AUC_{0-\infty}$ value which reduces the plasma concentration of acetaldehyde after ethanol consumption in human is $113 \pm 61$ ng/mL·h and almost comparable to $AUC_{0-\infty}$, $(121.2 \pm 65.6$ ng/mL·h) after taking Theracurmin beverage in this study.

Therefore, Theracurmin beverage may be useful to obtain plasma curcumin levels sufficient to exert beneficial effects such as alcohol detoxication. Moreover, many studies indicate that curcumin shows powerful hepatoprotective effects against oxidative damage caused by several hepatotoxins including ethanol. In those studies, curcumin, not only attenuated lipid peroxidation but also recovered the activity of endogenous antioxidant defense system. Therefore, Theracurmin might provide protection against alcoholic liver damage.

These findings demonstrate that Theracurmin beverage shows the highest bioavailability among currently available preparations of curcumin. Thus, it may be useful to exert its physiological benefits in humans at lower dosages.

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Conflict of Interest Contributing authors Y. Otsuka, T. Hamada and A. Imaizumi are full-time employees of Theravales Corporation. Y. Nonaka, T. Fuwa and T. Teramoto are full-time employees of Suntory Beverage and Food Limited. The other authors declare that no competing interests exist.

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