

## Evaluation of an Oral Carrier System in Rats: Bioavailability and Antioxidant Properties of Liposome-Encapsulated Curcumin

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To enhance the curcumin absorption by oral administration, liposome-encapsulated curcumin (LEC) was prepared from commercially available lecithins (SLP-WHITE and SLP-PC70) and examined for its interfacial and biochemical properties. A LEC prepared from 5 wt % of SLP-PC70 and 2.5 wt % of curcumin gave a good dispersibility with 68.0% encapsulation efficiency for curcumin, while those from SLP-WHITE did not. Moreover, the resulting LEC using SLP-PC70 was confirmed to be composed of small unilamellar vesicles with a diameter of approximately 263 nm. The resulting LEC was then examined for its effect on bioavailability in Sprague–Dawley (SD) rats. Three forms of curcumin [curcumin, a mixture of curcumin and SLP-PC70 (lecithin), and LEC] were then administered orally to SD rats at a dose of 100 mg curcumin/kg body weight. The pharmacokinetic parameters following curcumin administration were determined in each form. Pharmacokinetic parameters after oral administration of LEC were compared to those of curcumin and a mixture of curcumin and lecithin. High bioavailability of curcumin was evident in the case of oral LEC; a faster rate and better absorption of curcumin were observed as compared to the other forms. Oral LEC gave higher  $C_{max}$  and shorter  $T_{max}$  values, as well as a higher value for the area under the blood concentration–time curve, at all time points. These results indicated that curcumin enhanced the gastrointestinal absorption by liposomes encapsulation. Interestingly, the plasma antioxidant activity following oral LEC was significantly higher than that of the other treatments. In addition, the plasma curcumin concentration was significantly correlated to plasma antioxidant activities, and enhanced curcumin plasma concentrations might exert a stronger influence on food functionality of curcumin. The available information strongly suggests that liposome encapsulation of ingredients such as curcumin may be used as a novel nutrient delivery system.

**KEYWORDS:** Liposome; curcumin; oral administration; pharmacokinetics; antioxidant activity

### INTRODUCTION

*Curcuma longa* L. (Ukon) rhizomes have been widely used for centuries as an indigenous medicine in India and other Asian countries (1). The medicinal properties have been attributed to the main component present in the rhizome, curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], which exhibits anti-HIV (2), antitumor (3, 4), antioxidant (5, 6), and anti-inflammatory activities (7–9). To date, a number of studies have tried to elucidate the pharmacokinetics of curcumin, as it is poorly absorbed from the gastrointestinal (GI) tract after oral administration due to its low water solubility (10) and low stability against GI fluids and/or alkali/higher pH conditions (11). These characteristics lead to an unacceptably low oral bioavailability.

To enhance the bioavailability and food functionality of curcumin, we focused our attention on the feasibility of using liposomes as an efficient carrier of functional food materials. Liposomes are nanoparticles prepared from phospholipids (12). There have been several reports on the employment of liposomes to protect pharmaceuticals such as insulin (13), peptides (14), calcitonin (15), and cyclosporin (16) from enzymatic degradation and to efficiently deliver them into the bloodstream.

Liposome-encapsulated Ukon extract (LUE), which contains curcumin, has previously been developed, and its biochemical characteristics have been evaluated in our laboratory (17). It was confirmed to be composed of small unilamellar vesicles (SUVs) with a diameter of approximately 100 nm. On treatment with simulated gastric and intestinal fluids, the LUE showed a 2-fold higher residual rate of curcumin as compared to the unencapsulated extract. The bioactivity of the LUE was further examined for its suppressive effect on carbon tetrachloride (CCl<sub>4</sub>)-induced

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**Table 1.** Composition of Edible Lecithins Used in This Study

type of lecithin	wt %				total
	PC	PE	PI	PA	
SLP-WHITE (soybean, unhydrogenated)	35.5	29.5	19.0	16.0	100.0
SLP-PC70 (soybean, unhydrogenated)	80.1	15.4	2.5	2.0	100.0

liver injury in mice. Interestingly, oral administration of LUE at a dose of 10 mg Ukon extract/kg body weight showed a much higher suppressive effect on serum aspartate aminotransferase and alanine aminotransferase levels as compared to the unencapsulated extract at a dose of 33 mg/kg. To demonstrate the high functionality of LUE in more detail, the increased curcumin absorption due to encapsulation required investigation.

Thus, the purpose of this study was to provide evidence of liposomal enhancement of the oral delivery of curcumin. We prepared liposome-encapsulated curcumin (LEC) from two kinds of lecithins and curcumin using the mechanochemical method with a microfluidizer (18, 19) and investigated particle size by dynamic light scattering (DLS) measurements and electron microscopy. We also evaluated the plasma pharmacokinetics of curcumin concentrations from the most stable LEC formulation after oral administration in rats. The plasma antioxidant activity of rats orally administered with LEC was also examined using the trolox equivalent antioxidant capacity (TEAC) assay (20). To our knowledge, this is the first report on the pharmacokinetics and biochemical characterization of LEC.

## MATERIALS AND METHODS

**Materials.** Curcumin (purity, >98%) was purchased from Wako Pure Chemical Co. (Osaka, Japan). Two kinds of soybean lecithins, SLP-WHITE and SLP-PC70, were purchased from Tsuji Oil Mill Co. Ltd. (Mie, Japan) and were the only sources of lecithin used. The average compositions of phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), and phosphatidic acid (PA), as provided by the supplier, are summarized in Table 1. Sulfatase type H-5 ( $\beta$ -glucuronidase/sulfatase) and 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) were purchased from Sigma Ltd. (Tokyo, Japan). Manganese dioxide and trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) were purchased from Kanto Chemical Co. Inc. (Tokyo, Japan). All other chemicals and reagents were purchased from Wako Pure Chemical Co.

**Preparation of LEC.** Two types of LEC were prepared from SLP-WHITE and SLP-PC70 as follows. Curcumin (2.5 g) was added into deionized water (0.5 L) and then force dispersed by a homogenizer (TK Homo Mixer Mark II, Primix Co. Ltd., Osaka, Japan) at 35 °C with 4000 rpm for 1 min. Thereafter, lecithin aqueous solution (0.5 L, 10 wt %) was added into the dispersed curcumin solution with dispersion for another 15 min. The obtained liposomal suspensions (1.0 L) were then processed with a microfluidizer (M110-E/H, Mizuho Industrial Co. Ltd., Osaka, Japan). The operation was carried out with an inlet pressure of 100 MPa and at 1 pass for 5 min, unless otherwise indicated.

**Purification of LEC.** Free and liposomal curcumin (using SLP-WHITE and SLP-PC70) were separated by gel permeation chromatography (GPC, Toyopearl HW-50, 2.0 cm  $\times$  40 cm) and were washed with water. A flow adaptor was adjusted to the column, and fractions of 5.0 mL were collected at a flow rate of 0.5 mL/min. A LEC prepared from SLP-PC70 gave a good dispersibility, while those from SLP-WHITE did not. Accordingly, the purified LEC solution (SLP-PC70 LEC) was then used in the subsequent experiments, unless otherwise indicated.

**Determination of Encapsulation Efficiency.** Purified LEC (using SLP-WHITE and SLP-PC70), as described above, was evaporated to dryness in vacuo, and the residue was dissolved in methanol. The curcumin content in this solution was determined by high-performance liquid chromatography (HPLC). In brief, this solution was injected onto a HPLC column (Puresil 5  $\mu$ m, 4.6 mm  $\times$  150 mm) kept at 40 °C. The mobile phase was a mixture of acetonitrile/water (48:52, v/v) with 10 mM trifluoroacetic acid, and the flow rate was 1 mL/min. The eluent was

monitored with a photodiode array detector (SPD-M20A, Shimadzu Corp., Kyoto, Japan), which recorded the absorption spectra of curcumin at 420 nm. Quantification of curcumin was performed by calculating the peak area of the HPLC absorbance profile (at 420 nm) of purified curcumin and comparing it to the peak area of the samples. The encapsulation efficiency was calculated from the following equation:

$$\text{encapsulation efficiency (\%)} = \frac{[\text{concentration of curcumin (after gel permeation)}/\text{concentration of curcumin (before gel permeation)}] \times 100$$

**Measurement of Purified LEC Particle Size.** The particle size of purified LEC was estimated by DLS detector at 24 °C using a FPAR-1000 (Otsuka Electronics Co. Ltd., Osaka, Japan). The light source was a diode-pumped solid-state laser with a wavelength of 658 nm and a scattering angle of 90°. The diffusivity of the liposomal suspension ( $D$ ) was obtained with the above measurement, and the average LEC diameter ( $d_{\text{hy}}$ ) was calculated as follows:

$$d_{\text{hy}} = kT/3\pi\eta D$$

where  $k$  is the Boltzmann constant,  $T$  is the absolute temperature,  $\pi$  is the circular constant, and  $\eta$  is the viscosity.

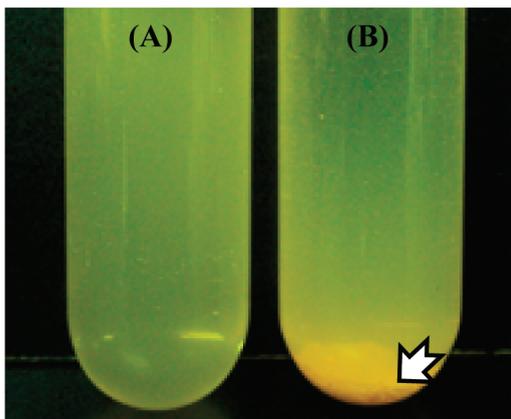
**Observation of Purified LEC by Freeze-Fracture Electron Microscopy (FFEM).** FFEM was used to determine the structure of purified LEC. The sample was frozen with liquid nitrogen at -189 °C. The fracture process was performed with a JFD-9010 (JEOL, Tokyo, Japan) at -130 °C, and the fractured surface was then replicated by evaporating platinum at an angle of 60°, followed by carbon at an angle of 90° to strengthen the replica. The replicate was placed on a 400 mesh copper grid after being washed with water, methanol, and chloroform. It was then examined and photographed using a JEM-1011 (JEOL) transmission electron microscope.

**Experimental Design for Oral Administration.** Male Sprague-Dawley rats (age, 7 weeks; Japan SLC Inc., Shizuoka, Japan), weighing 230–260 g, were housed in a temperature- (23  $\pm$  1 °C) and light- (12 h light/dark cycle) controlled room. They were allowed ad libitum access to distilled water and commercial feed (Oriental Yeast Co. Ltd., Tokyo, Japan) for 7 days. Rats were randomly divided into three groups. The first group comprised the control and was given curcumin only (curcumin group). The second and third groups were given a curcumin and lecithin mixture (mixture group) and LEC (LEC group), respectively. The curcumin dose in all samples was fixed at 100 mg curcumin/kg body weight. The mixture group received a lecithin (SLP-PC70) dose that was roughly equivalent to the lecithin component of LEC. The samples were orally administered by direct stomach intubation. Prior to and 30, 60, and 120 min after administration, blood was harvested from the abdominal great vein of rats under light anesthesia (diethyl ether) and placed into heparinized tubes. Plasma was immediately prepared by centrifugation at 1000g for 15 min at 4 °C and stored at -80 °C until use. This study was conducted in accordance with the Guidelines for Animal Experimentation of Kanehide Bio Co. Ltd.

Plasma (200  $\mu$ L) was mixed with 200  $\mu$ L of 0.1 M sodium phosphate buffer (pH 6.8) containing 0.1% EDTA, 200  $\mu$ L of distilled water, and 600  $\mu$ L of methanol. The mixture was vortexed for 3 min, and 4 mL of hexane was added. The mixture was shaken vigorously and centrifuged at 1000g for 10 min at 4 °C. After the hexane layer was discarded, 1.2 mL of distilled water and 3 mL of ethyl acetate were added to the mixture (aqueous-methanol layer). This was shaken vigorously and centrifuged at 1000g for 15 min at 4 °C, and the ethyl acetate layer was collected. This ethyl acetate extraction was repeated three times. The combined extractions were evaporated to dryness in vacuo, and the residue was dissolved in 100  $\mu$ L of methanol. An aliquot of this solution was analyzed for the content of curcumin by HPLC as mentioned above.

**LC-MS Analysis.** LC-MS analysis was performed by a Mariner mass spectrometer (JNM-400, Jasco, Tokyo, Japan) using a puresil 5  $\mu$ m ODS column (150 mm  $\times$  4.6 mm) kept at 40 °C. The mobile phase was a mixture of acetonitrile/water (48:52, v/v) with 10 mM trifluoroacetic acid, and the flow rate was 1 mL/min. The electrospray ionization mode (positive) was used for detection.

**Enzymatic Hydrolysis of Conjugated Curcumin.** Enzymatic hydrolysis was performed prior to HPLC analysis to detect the conjugated



**Figure 1.** Visual observation of LEC solutions prepared from two different lecithins by the mechanochemical method. (A) SLP-PC70 and (B) SLP-WHITE. Liposomal solutions, composed of 5 wt % of either lecithin A or B and 2.5 wt % of curcumin, were subjected to microfluidization treatment (100 MPa, 1 pass) after a homogenization treatment. The arrow indicates precipitation.

curcumin. For conjugates with both glucuronide and sulfate, plasma (200  $\mu$ L) was mixed with 200  $\mu$ L of sulfatase type H-5 (glucuronidase/sulfatase) solution in 0.1 M sodium acetate buffer (pH 5.0) and incubated at 37  $^{\circ}$ C for 60 min. This sulfatase type H-5 preparation was found to have substantial  $\beta$ -glucuronidase activity, being equivalent to 100 U of sulfatase and 2000 U of  $\beta$ -glucuronidase.

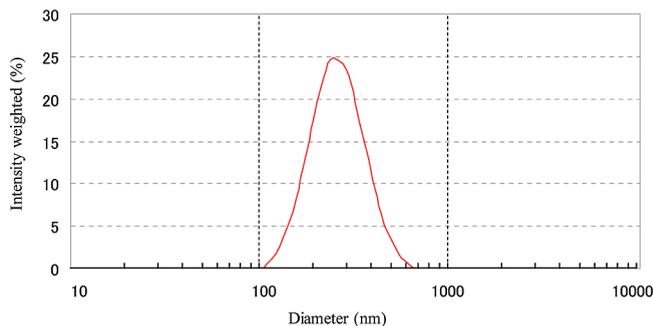
**Plasma TEAC Assay.** The TEAC assay was performed according to Miller et al. (20). ABTS radical cations were prepared by adding solid manganese dioxide to a 5 mM aqueous stock solution of ABTS. The ABTS radical cations were passed through a Whatman #1 filter paper and a PVDF syringe filter. The concentration was adjusted with 75 mM Na/K phosphate buffer (pH 7.0) to an absorbance of 0.7 at 734 nm and preincubated at 30  $^{\circ}$ C prior to use as an antioxidant standard. Plasma samples were diluted 1:30 in Na/K phosphate buffer (75 mM, pH 7.0). A total of 200  $\mu$ L of ABTS radical cation solution was mixed with 20  $\mu$ L of diluted plasma in 96-well plates, and the absorbance was read after 75 min. Samples were analyzed in triplicate. A fresh trolox was used as an antioxidant standard; a trolox standard curve was prepared for each batch of plasma analyses, and micromolar trolox equivalents (TEs) were calculated.

**Statistical Analysis.** Results are expressed as means  $\pm$  standard errors (SEs). Data were analyzed by one-way analysis of variance, and differences among the means of groups were analyzed by the Bonferroni procedure as a post hoc test. Differences were considered significant at  $P < 0.05$ .

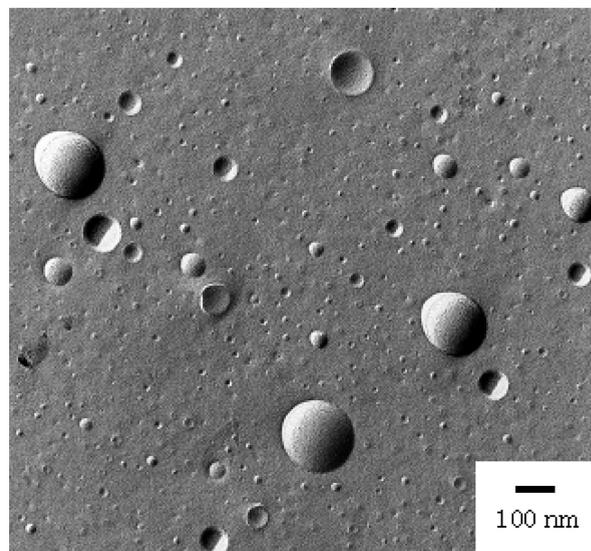
## RESULTS AND DISCUSSION

**Preparation of LEC.** We have previously developed a new mechanochemical method for the large-scale preparation of liposomes from commercially available soybean lecithins (17, 21). LEC was obtained by this method using homogenization and microfluidization under optimal conditions.

**Figure 1** shows LEC solutions prepared from a combination of 2.5 wt % of curcumin and 5 wt % of either the lecithin SLP-PC70 (A) or SLP-WHITE (B), respectively. One day after preparation, the SLP-PC70 LEC solution remained well dispersed, whereas the SLP-WHITE LEC solution developed phase separation and precipitated, probably due to the aggregation and/or fusion of liposomes. Interestingly, SLP-PC70 LEC also showed a higher encapsulation efficiency for curcumin (68.0 wt %) as compared to SLP-WHITE LEC (less than 10.0 wt %). Curcumin has low solubility in water and is thus likely to be incorporated into the phospholipid bilayer. Began et al. (22) reported that curcumin shows high binding affinity toward PC. SLP-PC70 has a higher



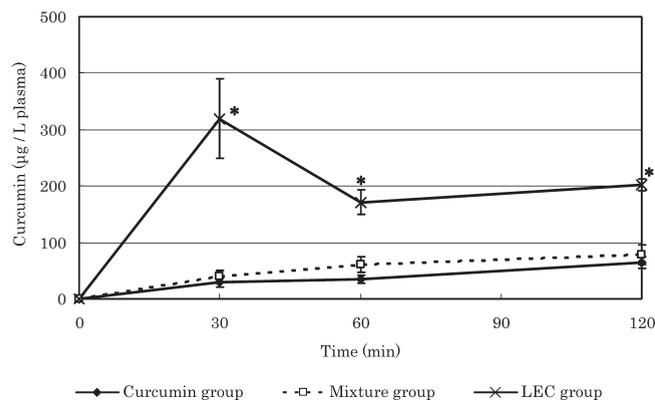
**Figure 2.** Particle size distribution of purified LEC prepared by the mechanochemical method. The hydrodynamic diameter was determined to be  $263 \pm 86.0$  nm (mean  $\pm$  SD).



**Figure 3.** Freeze fracture electron micrograph of purified LEC prepared by the mechanochemical method. The liposome solution was composed of 5 wt % SLP-PC70 and 2.5 wt % curcumin treated by ultrahigh pressure homogenization (100 MPa, 1 pass) after homogenization. The scale is 100 nm. The particle size of LEC was approximately 220 nm.

content of PC (80 wt %) as compared to the SLP-WHITE used in this study (**Table 1**). It thus seems reasonable that SLP-PC70 should provide stable LEC with good dispersion and is likely to be the most appropriate candidate for curcumin encapsulation. To determine the direct structure of the obtained SLP-PC70 LEC, DLS and FFEM were performed. **Figure 2** shows the LEC size distribution; the mean hydrodynamic diameter was determined to be 263 nm (SD, 86.0 nm). **Figure 3** shows a typical FFEM image of LEC, confirming that they form SUVs. The particle size of LEC was approximately 220 nm, which corresponds well to the mean diameter obtained from the above DLS measurement. We then evaluated the pharmacokinetics and biochemical properties of the resulting LEC in subsequent experiments.

**Plasma Pharmacokinetics of Curcumin Preparations.** On the basis of the previous studies, LEC prepared from SLP-PC70 and curcumin was chosen for the pharmacokinetics studies. **Figure 4** shows the mean plasma curcumin concentration versus time profiles before and after oral administration of curcumin, a mixture of curcumin and lecithin, and LEC, at a dose of 100 mg of curcumin/kg body weight for each treatment group. The peak concentration ( $C_{\max}$ ) and time of peak concentration ( $T_{\max}$ ) were obtained directly from the individual plasma curcumin concentration versus time profiles. The area under the concentration–time



**Figure 4.** Concentration of curcumin in rat plasma after a single oral administration of: curcumin, a mixture of curcumin and lecithin, and LEC (100 mg curcumin/kg body weight). Curcumin group (●), mixture group (□), and LEC group (×). The asterisks represent a significant difference at  $P < 0.01$  (vs curcumin group). Values are represented as means  $\pm$  SEMs ( $n = 7$ ).

**Table 2.** Pharmacokinetic Parameters Derived from Rat Plasma Curcumin Levels vs Time Profiles<sup>a</sup>

sample	AUC <sub>0–120min</sub> ( $\mu\text{g min/L}$ )	$C_{\text{max}}$ ( $\mu\text{g/L plasma}$ )	$T_{\text{max}}$ (min)
curcumin group	5342.6	64.6 $\pm$ 10.7	120
mixture group	7132.6	78.3 $\pm$ 17.9	120
LEC group	26502.8	319.2 $\pm$ 70.4	30

<sup>a</sup> AUC, area under the blood concentration vs time curve;  $C_{\text{max}}$ , maximum concentration; and  $T_{\text{max}}$ , time to reach  $C_{\text{max}}$ .

curve from 0 to 120 min (AUC<sub>0–120</sub>) was calculated using the trapezoidal method (23). The AUC determines the bioavailability of the drug for a given dose of the formulation. These oral pharmacokinetic parameters are listed in **Table 2**. As shown in **Figure 4**, plasma curcumin concentrations were significantly higher in rats administrated LEC than in those administrated curcumin only, at all time points. The  $C_{\text{max}}$  value of curcumin in the LEC group (319.2  $\pm$  70.4  $\mu\text{g/L}$ ) was higher than that obtained with curcumin only (64.6  $\pm$  10.7  $\mu\text{g/L}$ ) (**Table 2**). The AUC<sub>0–120</sub> value of curcumin after oral administration of LEC was 26502.8  $\mu\text{g min/L}$ , which was 4.96-fold greater than that after curcumin-only administration. Several lines of studies have demonstrated that coadministration of lecithin may enhance curcumin absorption and systemic bioavailability (24). It could thus be possible that liposome lecithin itself may exert an activation effect on curcumin absorption in the GI tract. However, our experiment revealed that a mixture of curcumin and lecithin had little effect on enhanced curcumin absorption by oral administration (**Figure 4**). Accordingly, it seems that the encapsulation of curcumin leads to a substantial improvement in curcumin absorption. We considered three possible explanations of the above results: (1) Enhanced bioavailability of LEC might be attributed to the direct uptake of nanoparticles through the GI tract, (2) increased permeability by surfactants, and (3) decreased degradation and clearance. First, the uptake of curcumin in a liposome-encapsulated form could be accomplished through the GI tract, where particle size plays a dominant role in absorption rate (25). The mechanisms involved in such uptake include the diffusion of particles through mucus and accessibility to an enterocyte surface, epithelial interaction and cellular trafficking, and exocytosis and systemic dissemination. A liposome size of approximately 200 nm allows for efficient uptake in the intestine, particularly in the lymphoid sections of this tissue (26), and therefore bypass of the first-pass metabolism in the liver (27). Second, GI absorption of drugs with low water

**Table 3.** ABTS Radical Cation Scavenging Activity of Rat Plasma before and after Oral Administration of Curcumin, a Mixture of Curcumin and Lecithin, and LEC<sup>a</sup>

sample plasma	ABTS radical cation scavenging activity ( $\mu\text{mol TE}/20 \mu\text{L plasma}$ )			
	0 min	30 min	60 min	120 min
curcumin group	1.99 $\pm$ 0.91	8.58 $\pm$ 2.86	7.42 $\pm$ 1.22	5.77 $\pm$ 1.56
mixture group	1.99 $\pm$ 0.91	7.24 $\pm$ 1.22	9.21 $\pm$ 2.11	9.12 $\pm$ 0.54
LEC group	1.99 $\pm$ 0.91	21.99 $\pm$ 2.06*	13.72 $\pm$ 2.28*	15.46 $\pm$ 0.51*

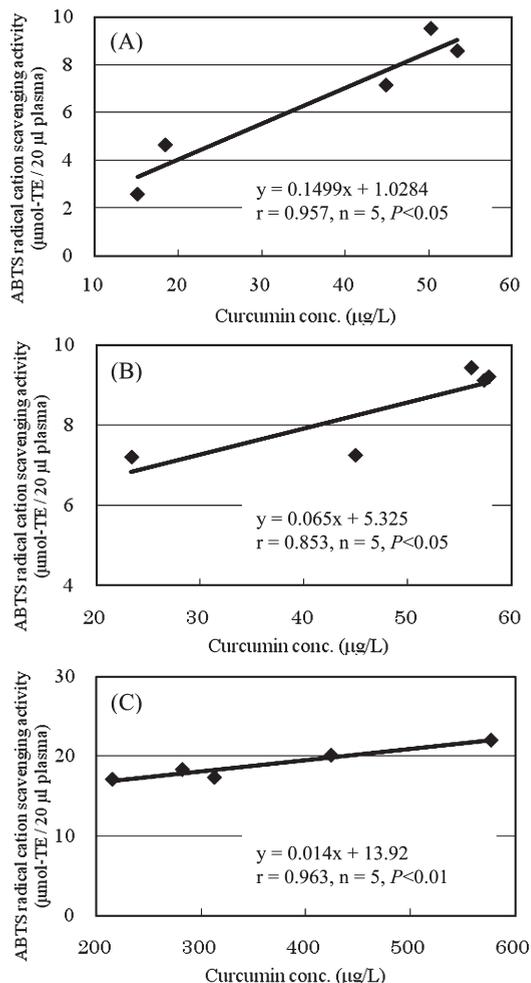
<sup>a</sup> The asterisks represent significant differences at  $P < 0.05$  (vs curcumin group). Values are represented as means  $\pm$  SDs ( $n = 5$ ).

solubility is enhanced when they are emulsified to increase surface area (28). Thus, the surfactants involved in the formulations could affect the permeability and solubility of drugs across the membrane of the GI tract. Third, by incorporation into liposomes, curcumin can be embedded into the phospholipid bilayer. This reduces its exposure to bacteria as well as enzymatic degradation during the absorption process. Encapsulation also allows for prolonged contact with the intestinal wall due to the adhesive property that liposomes exhibit toward the epithelial mucosal surface of the small intestine (29). Accordingly, it seems that encapsulation of curcumin is highly advantageous for optimizing food functionality. Recent studies have found that curcumin has an antioxidant activity in vitro (30). We evaluated the antioxidant activity of the resulting curcumin-containing plasma in the subsequent experiments.

**Plasma Antioxidant Activity after LEC Administration.** We investigated whether plasma antioxidant activity is affected by the enhanced bioavailability of curcumin after LEC administration. The TEAC assay was used to measure plasma antioxidant activity. **Table 3** shows ABTS radical cation scavenging activity of plasma before and after oral administration of curcumin, a mixture of curcumin and lecithin, and LEC. Plasma antioxidant activities increased in all treatment groups after oral administration. There was no significant difference in plasma antioxidant activity between the curcumin and the mixture groups, whereas the plasma antioxidant activity of the LEC group was significantly higher than either of the other treatment groups at all time points. In addition, the plasma antioxidant activity and plasma curcumin concentration at 30 min after oral administration were significantly correlated in all groups (**Figure 5**). It appears that the plasma antioxidant activity was positively correlated to plasma curcumin concentrations. Therefore, it is thought that the curcumin absorption has direct influence on the blood antioxidation.

The goal of our study was to provide evidence of the relationship between the results of our previous study (17), which revealed a substantial improvement in hepatoprotective activity by LUE, and the increased curcumin absorption due to liposome encapsulation. One of the mechanisms involved in mouse liver damage, induced by the  $\text{CCl}_4$  model, is considered to be the biotransformation of  $\text{CCl}_4$  to the toxic trichloromethyl radical by the cytochrome P450 enzyme system, resulting in lipid peroxidation and liver injury (31–33). In the present study, plasma scavenged the ABTS radical cations in a curcumin concentration-dependent manner. Thus, the curcumin-associated radical scavenging action of plasma may contribute to its hepatoprotective action in  $\text{CCl}_4$ -induced liver injury. The trichloromethyl radicals or lipid peroxides generated by  $\text{CCl}_4$  treatment may have been scavenged by plasma curcumin in the Ukon extract. Accordingly, the encapsulation of curcumin in the Ukon extract might effect a great improvement in hepatoprotective activity.

Future study should attempt to reveal the mechanisms involved in liposome-associated curcumin absorption and subsequent transcytosis and to correlate in vitro observations to this in



**Figure 5.** Correlation between concentration of curcumin and ABTS radical cation scavenging activity in rat plasma 30 min after oral administration of (A) curcumin, (B) a mixture of curcumin and lecithin, and (C) LEC. Statistical analysis was done with linear regression analysis.

vivo performance. These liposomal formulations can enable enhanced curcumin food functionalization.

#### ABBREVIATIONS USED

ABTS, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; AUC, area under the concentration–time curve; DLS, dynamic light scattering detector; FFEM, freeze-fracture electron microscopy; GI, gastrointestinal; LEC, liposome-encapsulated curcumin; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; SUVs, small unilamellar vesicles; TEAC, trolox equivalent antioxidant capacity.

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