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High-performance liquid chromatographic analysis of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol in ginger-containing dietary supplements, spices, teas, and beverages☆

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Abstract

Ginger root powder is widely used as a dietary supplement as well as a spice and flavoring agent in foods and beverages. In this study, we developed a high-performance liquid chromatographic (HPLC) method that is suitable for the analysis of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol in a wide variety of ginger-containing dietary supplements, spices, teas, mints, and beverages. 6-Gingerol, 6-shogaol, 8-gingerol, and 10-gingerol were extracted from various ginger-containing products with ethyl acetate and analyzed by HPLC on a C-8 reversed phase column at 282 nm. The recoveries of 6-, 8-, and 10-gingerol, and 6-shogaol from the ginger dietary supplements and ginger-containing products were 94.7 ± 4.1, 93.6 ± 3.4, 94.9 ± 4.0, 97.1 ± 3.8%, respectively. The within-day coefficients of variation for 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol standards at 50.0 μg/mL were 2.54, 2.38, 2.55, and 2.31%, respectively. The lower limit of quantitation was 25 ng injected. The standard curves for 6-, 8-, and 10-gingerol and 6-shogaol were linear from 10.0 to 1000 μg/mL. The variation (CV's) in the 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol concentrations of nine different ginger root dietary supplements were 115.2, 45.7, 72.3, and 141.7%, respectively. The gingerol composition of various ginger-containing spices, teas, and beverages also were found to vary widely. The proposed method can be used for the analysis and standardization of 6-, 8-, and 10-gingerol in ginger-containing dietary supplements, spices, food products and beverages and as a method for determining the amounts of 6-shogaol as a marker for 6-gingerol stability.
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Keywords: HPLC analysis; Ginger dietary supplements; 6-Gingerol; 6-Shogaol; 8-Gingerol; 10-Gingerol; Ginger spices; Ginger beverages

1. Introduction

Ginger (*Zingiber officinale* Roscoe) is widely used as a spice, but also as a dietary supplement for treating nausea [1], pregnancy-related nausea [2–7] and motion sickness [8]. A recent comprehensive review of six double-blind, randomized controlled trials has shown that ginger may be effective in treating pregnancy-related nausea and vomiting [7], however, other studies have shown that ginger is not effective in the treating postoperative nausea, motion sickness, or nausea of other etiology [8]. The factors contributing to the variability in clinical response to ginger are not known, but could be due to differences in the quality of the ginger products used or to differences in the composition of the ginger powders and ginger extracts used in the studies.

If ginger is to be used successfully as a dietary supplement, the composition of its major components will have to be determined and standardized. None of the ginger powders or extracts used in previous clinical studies was analyzed prior to use [2–8] and this represents a major limitation of the studies. 6-Gingerol, 6-shogaol, 8-gingerol, and 10-gingerol have been identified as the principal pungent components of ginger powder [9–13]. They have been shown to have analgesic, antipyretic, and cardiotonic properties [14] and to inhibit spontaneous motor activities and prostaglandin biosynthesis [15]. In addition, 6-gingerol has been shown to have antioxidant and anti-inflammatory properties [15,16], to suppress cytokine formation [15,16], and to promote angiogenesis [17]. 6-Shogaol, a dehy-

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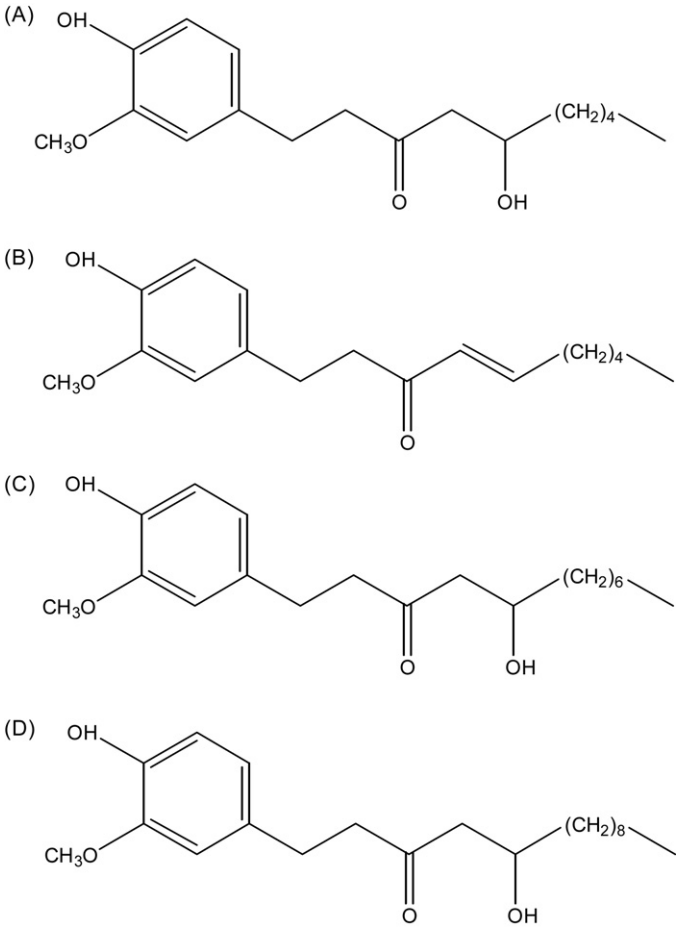

Fig. 1. Chemical structures of 6-gingerol (A), 6-shogaol (B), 8-gingerol (C), and 10-gingerol (D).

dration product of 6-gingerol, is also found in ginger powder, but not in fresh ginger powder [12]. 6-Shogaol appears to be formed from 6-gingerol during thermal processing and long-term storage [12,13]. The chemical structures of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol are shown in Fig. 1.

Several high-performance liquid chromatographic (HPLC) [9,11,13] and gas-chromatographic–mass-spectrometric (GC/MS) methods [10,12] have been developed for the analysis of 6-gingerol and 6-shogaol. The analytical methods were primarily used for identification of the mass spectra of the gingerol standards [10] and for the identification of the pungent compounds in ginger [9,10,12,13]. The methods though were not used for the quantitative analysis of the gingerol metabolites in ginger rhizomes, ginger dietary supplements or in ginger-containing foods and beverages. There are several disadvantages associated with GC and GC/MS methods for analyzing 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol. For example, the gas-chromatographic column temperatures used for the analyses of the gingerols have been shown to result in significant conversion of 6-gingerol to 6-shogaol [10,12].

In this study, we developed a simple procedure for extracting 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol from ginger-containing dietary supplements, spices, teas, and beverages. We also developed a HPLC method for the quantitative analysis of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol in ginger root dietary supplements and in the ginger-containing food products and beverages. In this study, we provide information on the gingerol and shogaol composition of a USP reference standard powdered ginger as well as ginger root dietary supplements, spices, teas, mints, and beverages.

2. Materials and methods

2.1. Chemicals

6-Gingerol, 6-shogaol, 8-gingerol, and 10-gingerol were obtained from ChromaDex Inc. (Santa Ana, CA). USP Reference Standard Powdered Ginger (Cat. No. 29150-4) was obtained from U.S. Pharmacopeia (USP, Rockville, MD). HPLC-grade methanol and ethyl acetate were obtained from Fisher Scientific (Fair Lawn, NJ). Ginger root dietary supplements, ginger spices, beverages, teas, and mints were obtained randomly from San Antonio area pharmacies, health food stores, or grocery stores.

2.2. Extraction procedure

The 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol composition was determined in nine ginger root dietary supplements, three ginger spices, six ginger beverages, and in a ginger root extract dietary supplement, a USP powdered ginger reference standard, a ginger tea, and a ginger mint. For the analysis of ginger root dietary supplements, 10 capsules containing ginger powder were opened, placed in a beaker, and mixed to insure that a homogenous sample was obtained. The ginger spices and teas were also placed in a beaker; however, the ginger mints were ground up with a mortar and pestle prior to extraction. The capsule of ginger root extract dietary supplement was cut open and then extracted with ethyl acetate. Two hundred and fifty milligrams of the ginger-containing dietary supplements, spices, teas, and mints were weighed out in duplicate and placed in separate 16 mm × 125 mm round-bottom glass centrifuge tubes. Ten milliliters of ethyl acetate were then added with a Repipet to each of the tubes. The tubes were capped, mixed briefly, and then extracted on an Eberbach shaker at slow speed for about 30 min. The samples were centrifuged at 2500 ± 100 rpm (rotor 216, IEC CentraGP8R, Needham Heights, MA, USA) for 20 min at 25 ± 4 °C. The ethyl acetate was transferred with a Pasteur pipette to separate 16 mm × 125 mm glass conical centrifuge tubes and the extracts were evaporated under nitrogen at 45 ± 2 °C in a Zymark Turbovap (Caliper Life Sciences, Hopkinton, MA). The ginger dietary supplements, spices, teas, and mints were then re-extracted with 10.0 mL of ethyl acetate and the extracts were transferred to the tubes containing the first extract. After evaporating the ethyl acetate, each extract was reconstituted in 2.0 mL of the mobile phase (methanol–water 65:35, v/v). The extracts were vortex mixed for about 25 s and centrifuged at 2500 ± 100 rpm for 20 min to further remove any particulate material. The extracts were then transferred with a Pasteur pipette to 700-μL injection vials and capped.

The ginger-containing beverages were extracted by adding 10 mL of each ginger beverage, 20 mL of deionized water, and 100 mL of ethyl acetate to 250 mL separatory funnels. The samples were mixed in a horizontal position on an Eberbach shaker for 30 min. After phase separation, the bottom aqueous layer was collected in a volumetric flask. The ethyl acetate phase was then collected in a 250 mL beaker and allowed to air dry in the hood. Each aqueous layer was then re-extracted with 100 mL of ethyl acetate and the first and second ethyl acetate extracts were combined. After evaporation, the extracts were resuspended in 5.0 mL of mobile phase (methanol–water, 65:35, v/v). To ensure complete transfer, a second 5.0 mL aliquot of the mobile phase was added to each beaker. The samples were then centrifuged at 2500 ± 100 rpm for 20 min to remove any insoluble material in the samples.

2.3. Preparation of 6-gingerol, 6-shogaol, 8-gingerol and 10-gingerol standards

6-Gingerol, 6-shogaol, 8-gingerol, and 10-gingerol used for preparing the standards were dried over silica gel for at least 3 h under vacuum. Approximately, 10.0 mg of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol were weighed and transferred to separate 16 mm × 125 mm screw-capped glass centrifuge tubes. Sufficient HPLC-grade methanol was added to each standard to produce a stock standard of 1.0 mg/mL. Standards containing 1000.0 μg/mL of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol were prepared by transferring 5.0 mL (5000 μg) of each of the stock standards to a 16 mm × 125 mm conical centrifuge tube, evaporating the methanol at 45 ± 2 °C, and reconstituting in 10.0 mL of methanol–water (65:35, v/v). Serial dilutions of the 500.0 μg/mL standard were made to produce the 250.0, 100.0, 50.0, 25.0 and 10.0 μg/mL working standards. All ginger standards were capped and stored at 4 ± 4 °C until used.

2.4. HPLC chromatographic analysis

The ginger extracts were analyzed on a HPLC system consisting of a Waters 600E Controller, 717 Autosampler, 996 Photodiode Array Detector (PDA), and a Millennium 2010 Chromatography Manager (Waters, Milford, MA). Chromatographic analysis was performed on a 3.9 mm × 150 mm Waters Symmetry C-8 reversed phase column (Cat. No. WATO 54235) with methanol–water (65:35, v/v) as the mobile phase. The HPLC operating parameters were as follows: injection volume, 25 μL; column flow rate, 1.0 mL/min; chromatographic run time, 48.0 min; PDA spectra recording, 282 nm. The 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol peak identifications were based on the retention times of the standards and further confirmed by comparing their photodiode array spectra to those of the individual standards.

3. Results

In this study, we evaluated both ethyl acetate and ethanol as solvents for extracting 6-gingerol, 6-shogaol, 8-gingerol and 10-gingerol from the ginger powders and ginger dietary supplements, spices, teas, and mints. Recoveries were calculated by combining the amounts of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol obtained with a single extraction with the amounts obtained with a second extraction. This total amount was considered to represent a 100% recovery since a third extraction did not yield any appreciable amount of 6-gingerol, 6-shogaol, 8-gingerol, or 10-gingerol. The recovery of the first extract was determined by dividing the amount of each component obtained in the first extraction by the total amount obtained in the first and second extraction. With a single extraction, the recoveries of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol from the ginger dietary supplements and ginger-containing products with ethyl acetate were 94.7 ± 4.1, 93.6 ± 3.4, 94.9 ± 4.0, and 97.1 ± 3.8, respectively, ($n = 5$). Ethanol also was evaluated as an extraction solvent. With ethanol, the recoveries of 6-gingerol and 6-shogaol were greater than 98% with a single extraction. Even though the amounts of 6-gingerol and 6-shogaol obtained with ethyl acetate were similar to those obtained with ethanol, ethyl acetate was selected as the extraction solvent since it is immiscible with water and could be used to extract ginger-containing beverages. Ethyl acetate was also selected since it is less polar than ethanol and would likely result in fewer problems with co-extractable interferences

6-Gingerol, 6-shogaol, 8-gingerol, 10-gingerol were quantitated by HPLC using external standards. Both C-8 and C-18 reversed phase columns were evaluated. With methanol–water (65:35, v/v) mobile phase, the C-8 columns resulted in better resolution of the ginger metabolites from co-extractable interferences than the C-18 column. HPLC chromatograms of extracts of a ginger dietary supplement, USP ginger powder reference standard, ginger spice, ginger tea, and a ginger beverage are shown in Fig. 2. We did not notice any substance that might interfere with the analysis of 6-gingerol, 6-shogaol, 8-gingerol, or 10-gingerol in any of the ginger powders or in any of the ginger-containing products.

The standard curves for 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol were linear from 10.0 to 1000.0 μg/mL (correlation coefficient ≥0.996). The within-day CV's for 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol standards at 50 μg/mL ($n = 5$) were 2.54, 2.38, 2.55, and 2.31%, respectively; at 100 μg/mL ($n = 5$), they were 1.92, 1.81, 1.87, and 1.74%, respectively. We also determined the within-day CV's of ginger dietary supplements, spices, teas, and beverages to determine the variability of the results associated with the different matrices. The CV's for duplicate analyses of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol ranged from 0.4 to 10.1; the average CV for 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol were 2.8, 4.4, 4.0, and 5.7%, respectively. The lower limit of quantitation for 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol was at least 25 ng injected onto the column (25 μL injection of 1.0 μg/mL) and was more than adequate for the analyses performed in this study.

The ginger dietary supplements that were analyzed are listed in Table 1. Of the 10 ginger dietary supplements analyzed, 7 contained either 530 or 550 mg of ginger root powder per capsule, one contained 250 mg of ginger root powder, one was obtained

in bulk form from a self-serve herbs bin (Sun Harvest Farms), and one contained a ginger root extract (Enzymatic Therapy) (Table 1).

The 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol concentrations of the ginger dietary supplements were analyzed in duplicate and represent mean values (Table 1). The 6-gingerol concentration in the different ginger dietary supplements was found to be higher than that of the 8- or 10-gingerol concentration, but not always higher than that of 6-shogaol. Across brands, the 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol concentrations varied widely. For example, Nature's Plus ginger dietary supplement did not contain any measurable amount of 6-, 8-, or 10-gingerol, whereas the Sun Harvest ginger root powder contained 9.43 mg/g of 6-gingerol. On average, 1 g of ginger powder contained 2.56 ± 2.95, 1.27 ± 0.58, 0.47 ± 0.34, and 0.36 ± 0.51 mg (mean $\pm$ SD) of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol, respectively (Table 1). On a weight basis, 6-gingerol made up about 0.256% of the ginger powder, whereas the 6-shogaol, 8-gingerol, and 10-gingerol made up 0.127, 0.047, and 0.036%, respectively.

The 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol concentrations of three ginger spices, a ginger tea, and a ginger mint are given in Table 2. The Whole Foods ginger spice contained the

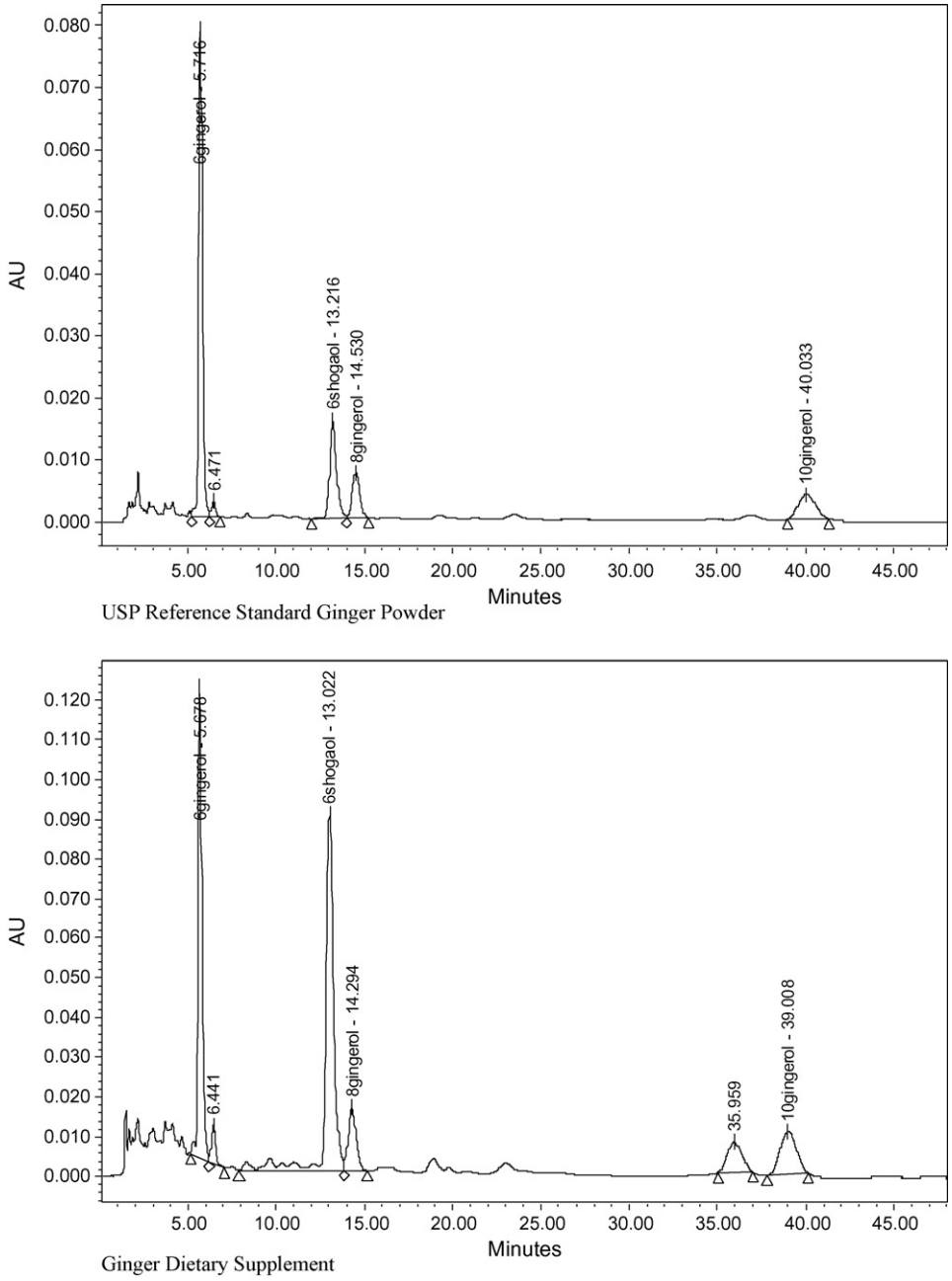

Fig. 2. HPLC chromatograms of 6-gingerol, 6-shogaol, 8-gingerol, 10-gingerol in extracts of USP powdered ginger, ginger dietary supplement, ginger spice, ginger tea, and ginger root beer.

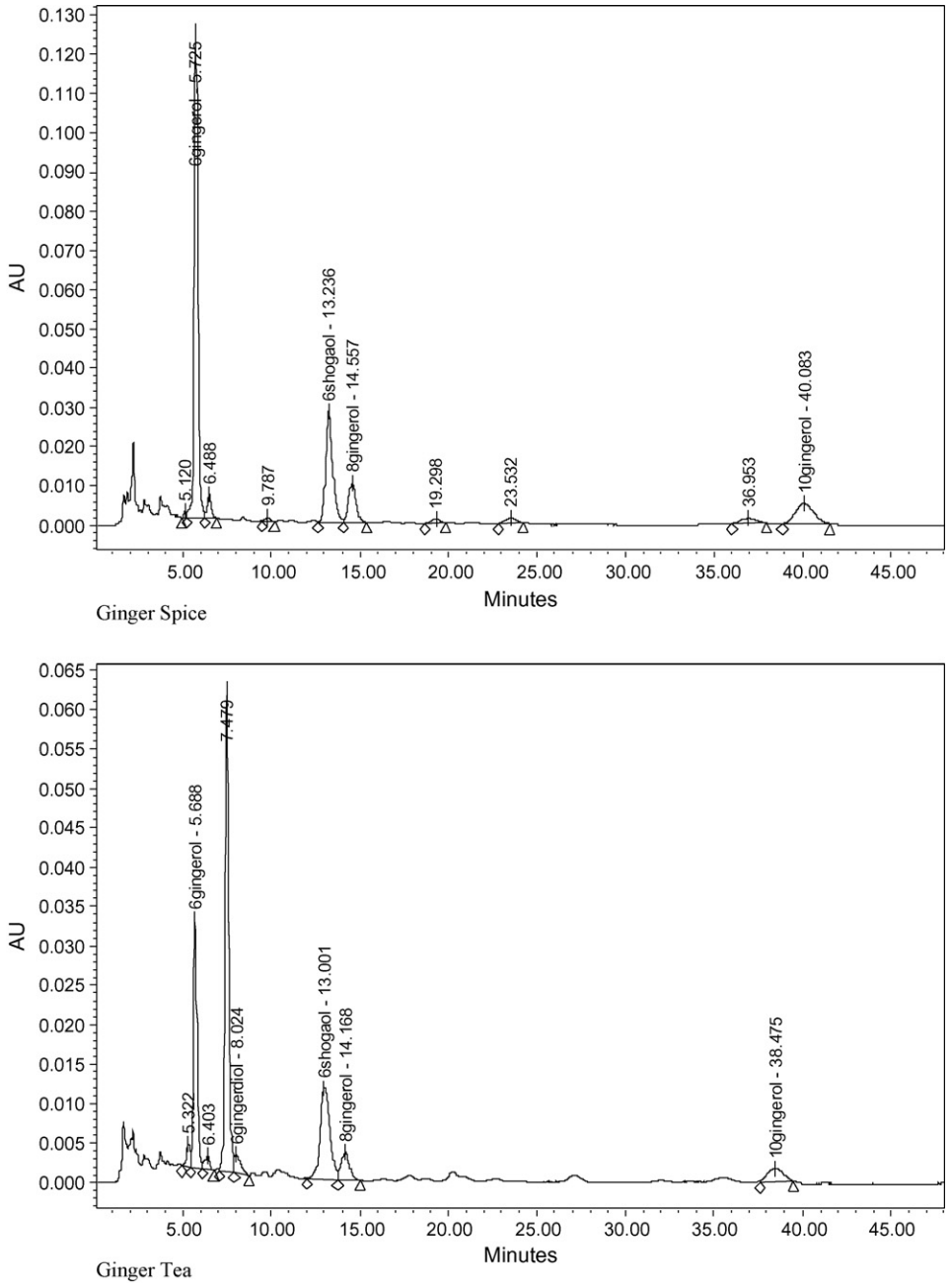

Fig. 2. (*Continued*)

highest concentration of 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol and the Altoids ginger mints contained the lowest concentration. The gingerol concentrations found in the ginger spices and in the ginger tea are much like those found in the ginger powder dietary supplements.

Table 3 shows the 6-gingerol, 6-shogaol, 8-gingerol, and 10-gingerol concentrations of various ginger-containing beverages. The 6-gingerol concentration in 4 of the 6 beverages ranged from 0.42 to 1.65 μg/mL of 6-gingerol, whereas in 2 of the beverages the 6-gingerol levels were 3.83 and 5.61 μg/mL. The 6-shogaol concentration also varied considerably from beverage to beverage and in two cases were as high as or higher than the 6-gingerol concentration.

4. Discussion

The HPLC method for quantitating 6-, 8-, 10-gingerol, and 6-shogaol is simple, reproducible, and accurate and is applicable to the analysis of a wide variety of ginger-containing products. The method has a relatively low coefficient of variation and there were no noticeable co-extractable substances found in any of the ginger-containing products that might interfere with the analysis of 6-, 8-, 10-gingerol, or 6-shogaol. The HPLC method has advantages over GC/MS methods in that the high temperatures associated with GC/MS analysis has been shown to result in conversion of 6-gingerol to 6-shogaol [10,12]. We have also noticed that 6-gingeol is converted to 6-shogaol during GC/MS analysis

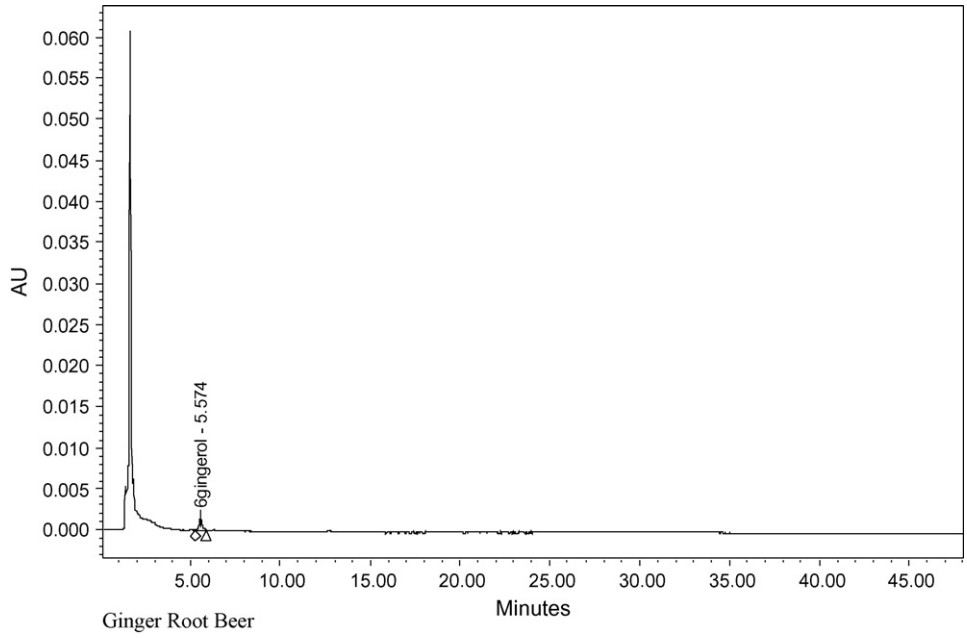

Fig. 2. (*Continued*).

as well as with halogenated acid anhydride derivatizing reagents (unpublished data). With this HPLC method, we did not notice any degradation of the gingerol metabolites or any loss of the gingerol and 6-shogaol standards kept for 2 years at $4 \pm 4\,^{\circ}C$.

Our results indicate that there is considerable variation in the gingerol and shogaol content of the over-the-counter ginger root dietary supplements as well as in the ginger spices and beverages. In this study, we analyzed only one product from

Table 1
6-Gingerol, 6-shogaol, 8-gingerol and 10-gingerol composition of ginger dietary supplements and USP ginger powder

Ginger root powder dietary supplements	6-Gingerol (mg/g)	6-Shogaol (mg/g)	8-Gingerol (mg/g)	10-Gingerol (mg/g)
Nature's Plus	0	0.16	0	0
Nature's Way	1.17	1.18	0.51	0
Nature's Herbs	1.17	1.66	0.52	0
Solaray	1.24	1.17	0.51	0
Now	1.25	1.57	0.74	0.36
Rexall	1.63	1.11	0.39	0
Nature's Resource	1.88	0.77	0.49	0.83
GNC	5.24	1.64	1.1	1.4
Sun Harvest Farms	9.43	2.18	0	0
Mean	2.56	1.27	0.47	0.36
Standard deviation	2.95	0.58	0.34	0.51
% CV	115.2	45.7	72.3	141.7
Ginger root extract dietary supplements				
Enzymatic Therapy[a]	4.78[a]	10.23[a]	2.43[a]	1.62[a]
USP reference standard				
USP Powdered Ginger	3.25	1.27	1.51	1.34

[a] 6-Gingerol, 6-shogaol, 8-gingerol, and 10-gingerol concentrations of Enzymatic Therapy capsules are expressed on a mg/capsule basis.

Table 2
6-Gingerol, 6-shogaol, 8-gingerol, and 10-gingerol composition of various ginger spices as well as a ginger tea and ginger mint

Ginger spice, tea, or mint	6-Gingerol (mg/g)	6-Shogaol (mg/g)	8-Gingerol (mg/g)	10-Gingerol (mg/g)
Frontier Herbs Spice	4.5	2.5	0	0
Whole Foods Spice	5.40	2.39	2.14	1.68
Tones Ground Spice	1.24	1.64	0.78	0.78
Yogi Ginger Tea	1.42	1.37	0.78	0.22
Altoids Ginger Mints	0.18	0.08	0.11	0

Table 3
6-Gingerol, 6-shogaol, 8-gingerol, and 10-gingerol composition of various ginger-containing beverages[a]

Ginger beverage	6-Gingerol (μg/mL)	6-Shogaol (μg/mL)	8-Gingerol (μg/mL)	10-Gingerol (μg/mL)
Hill Country Fare Ginger Ale	0.42	0	0	0
Cock-n-Bull Ginger Beer	0.52	5.55	0.19	0
Reed Beer	1.65	0	0	0
Mystic Seaport Ginger Beer	0.92	0.26	0	0
Fiery Ginger Beer	3.83	0.87	0.23	0
Jamaican Ginger Beer	5.61	5.51	0.34	0

[a] Gingerol concentrations of the ginger-containing beverages are expressed in μg/mL.

each manufacturer. Therefore, the quantitative results may not be representative of the product or the manufacturer. Information on the composition and quality of the dietary supplements are critical to the safe and effective use of ginger dietary supplements as the ginger dietary supplements are widely used to treat pregnancy-related nausea and vomiting [2–7]. The variability in composition of ginger dietary supplements might account for some of the variability in the efficacy found in clinical trials of pregnancy-related nausea [2–7] as well as other forms of nausea and motion sickness [8]. Ginger mints also have been used to relieve nausea associated with pregnancy, but, as we have shown, the gingerol concentrations are low compared to those of the average ginger dietary supplement. Additional information on the variation in the gingerol composition of the dietary supplements and in the variation in labeling has been recently reported [18].

Chemical and chromatographic analyses of the ginger root powders and extracts used in clinical trials have not been performed [2–8]. This represents a major limitation of those studies. The wide variability of the gingerol and 6-shogaol in the dietary supplements indicates that the gingerol and shogaol composition of the ginger powders and extracts will need to be performed prior to performing additional clinical studies. Such information is needed if one study is to be referable to another study and if the efficacy found with one dose is to be related to the efficacy obtained with a higher or lower dose. HPLC analyses will provide useful information on the safest and most effective dose range and, hopefully, such analyses will become standard practice in future clinical trials of dietary supplements. Additionally, the chromatographic profiles might be useful in providing information on adulteration, quality of ginger rhizome, efficiency of extraction, and the effects of processing. Fresh ginger, for example, contains very little 6-shogaol, but with heat and processing, 6-gingerol loses water and is converted to 6-shogaol [12,13]. In this regard, the ratio of 6-gingerol to 6-shogaol may serve as a marker of 6-gingerol stability and ginger quality. In summary, the HPLC method described here is accurate, reproducible, and easy to perform, and unlike GC/MS methods, it does not lead to degradation of any of the gingerols.

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