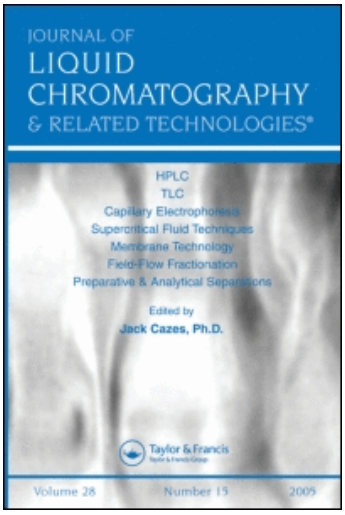

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ABSTRACT

A total of 21 ginseng products, including Asian ginseng (*Panax ginseng*) and North American ginseng (*Panax quinquefolius*) in the form of powdered roots, capsules, liquid extracts, caplets, tablets, and softgels, etc., were analyzed for ginsenoside content by using high performance liquid chromatography (HPLC) with ultraviolet detection at 203 nm. The present method was validated for linearity, sensitivity, reproducibility, and recovery. Two methods of extraction for powdered ginseng root samples were compared by employing (1) sonication with methanol (3×30 min) and (2) extraction with 30% methanol (50°C, 30 min), with the former yielding a higher efficiency for the

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extraction of ginsenosides from powdered ginseng roots. Analysis of 21 ginseng products revealed that the ginsenoside content in Asian ginseng (*P. ginseng*) is generally lower than that in North American ginseng (*P. quinquefolius*). The comparability of ginsenosides profiles might help to identify the origin of the ginseng.

INTRODUCTION

Ginseng, *Panax ginseng* C. A. Meyer, and *Panax quinquefolius* L. (Araliaceae) have long been used as tonic,[1] and currently are components of a number of herbal dietary supplements in the United States. Many studies have suggested that the pharmacological effects of ginseng are due to the presence of a class of characteristic constituents, i.e., ginsenosides, and these studies have been well reviewed.[1–4] More than 30 ginsenosides have been isolated and identified from ginseng[1,5,6] and six of them, ginsenosides Rg_1, Re, Rb_1, Rc, Rb_2, and Rd, were reported to account for up to 90% of the total ginsenosides content in ginseng.[7]

Ginseng and its products are commercially available as dried roots, dried root powders, liquid extracts, teas, and formulated into tablets, capsules, caplets, and softgels, etc., and are marketed as dietary supplements in the USA under the Dietary Supplement Health and Education Act (DSHEA) of 1994. According to DSHEA, the FDA no longer regulates the dietary supplement industry the way it watches over prescription and over-the-counter drugs. Dietary supplements do not get the same pre-market safety and efficacy evaluation that drugs get, nor does the FDA set standards to ensure that labels accurately reflect content.[8] Ginseng products are normally labeled with the content of milligram of ginseng root or milliliter of ginseng root extract, and have not been subjected to mandated quality assurance (QA) standards. Therefore, it is not surprising that the ginseng product quality might differ from brand to brand, and even from lot to lot.

A number of methods for the determination of ginsenosides are available in the literature. However, methods such as colorimetry might overestimate results and cannot give information on individual ginsenosides; thin layer chromatography has a challenge in reproducibility, gas chromatography (GC) and gas chromatography coupled with mass detection (GC-MS) have difficulties in sample preparation.[9,10] High performance liquid chromatography (HPLC) methods have been the most successful and are now widely accepted.[11–15] There have been several publications regarding the HPLC analysis of ginsenosides in ginseng products in Asia,[11] Europe,[15] and North America.[14,16] A recent publication revealed that the content of ginsenosides in the North American market ranged from 0.036% to 4.27%, with the concentrations of

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ginsenosides found ranging from 10.8% to 327.7% of that claimed on the label.[16] However, the reported sample preparation procedure employed a step of solid-phase extraction with 30% methanol eluting non-ginsenoside compounds, as well as matrix, and leaving the ginsenosides on the SPE column before methanol was used to finally elute the ginsenosides, which might introduce a loss of polar ginsenosides, such as ginsenoside Rg_1 and Re. Another concern is that the extraction of ginsenosides with 30% methanol at 50°C for 30 min might not recover 100% of ginsenosides from the samples. This prompted us to make a comparison for the extraction efficacy of the method with what we have been using for ginseng analysis since the establishment of Functional Food for Health (FFH) Core Analytical Laboratory at the University of Illinois at Chicago.[17,18]

On the other hand, ginseng products are also in the form of liquid extracts, tablets, caplets, and softgels; there should be a specific way for sample preparation to maximize ginsenoside recovery prior to HPLC analysis. In the present paper, a validated method is presented to evaluate the quality of 21 ginseng products produced from *P. ginseng* and *P. quinquefolius* by analyzing six major ginsenosides, e.g., ginsenoside Rg_1, Re, Rb_1, Rc, Rb_2, and Rd.

EXPERIMENTAL

Chemicals and Materials

High performance liquid chromatography grade acetonitrile, hexane, and methanol were obtained from Fisher Scientific Co. (Fair Lawn, NJ, USA). Deionized (DI) water was obtained with an in-house Nano-pure® water system (Barnstead, Newton, MA, USA). Reference ginsenoside standards (Rg_1, Re, Rb_1, Rc, Rb_2, and Rd) were isolated, purified, and identified in the Program for Collaborative Research in the Pharmaceutical Sciences (PCRPS), College of Pharmacy, University of Illinois at Chicago. Ginseng products were obtained from different sources and labeled 1–21.

Apparatus

A Waters 2690 Alliance HPLC system (Milford, MA, USA), equipped with a 996 photodiode array UV detector, an in-line degasser, and an autosampler was used for solvent delivery and detection. The separations were carried out on a Waters Spherisorb ODS-2 RP-18 column (250 × 4.6 mm, 5 μm particle size, serial # 0123391941L-011, Milford, MA, USA), protected by a Waters Delta-Pak RP-18 guard column (Waters Technology Ireland, Ltd, Wexford, Ireland), and set at room temperature. The solvents used for separation were water, solvent A, and

acetonitrile, solvent B. Solvent gradient conditions are summarized in Table 1. All injections were 10 μL in volume.

Prior to each run, the HPLC–UV system was allowed to warm up for 20–30 min and the pumps were primed using the protocol suggested by the manufacturer. Using freshly prepared mobile phase, the baseline was monitored until stable before the samples were run.

Sample Preparation

Powdered Roots and Capsules

Method I: A portion of powdered root sample (0.5 g) or the content of a capsule was accurately weighed into a 20 mL PTFE-capped sample vial. Methanol, 15 mL was added and the resulting mixture was sonicated at 25–30°C for 30 min. After cooling, the mixture was filtered through a filter paper (Whatman # 40) into a 250 mL round-bottom flask. The residue was washed with methanol (3 × 15 mL) while on the filter and then returned to the vial. A second 15 mL of methanol was added and the mixture was sonicated at 25–30°C for 30 min. The extract was filtered into the same round-bottom flask, and the residue was washed with methanol (3 × 15 mL) while on the filter. The above procedure was repeated one more time. The combined methanol extracts were evaporated to dryness, under vacuum, at 45–50°C. The residue was re-dissolved with methanol (4 × 2 mL) and transferred to a 10 mL volumetric flask, and made up to the volume with methanol. The sample solution was filtered through a 0.2 μm nylon cartridge just prior to HPLC analysis.

Method II: This method was modified from that of Harkey et al.[16] Ten milliliters of 30% methanol in water was added to 250 mg of powdered ginseng

Table 1. Solvent Gradient

Final Time (min)	Flow Rate (mL/min)	Solvent A (Water, %)	Solvent B (Acetonitrile, %)
0	1.6	80	20
20	1.6	80	20
60	1.6	58	42
61	1.6	10	90
65	1.6	10	90
66	1.6	80	20
70	1.6	80	20

roots. The mixture was mixed with vortex for 10 s, heated at 50°C for 30 min, and mixed again with vortex for 10 s, consecutively, and then centrifuged (15 min, room temperature). Supernatant fluid, 10 μL, was injected into a HPLC–UV system.

Softgels

The ginseng softgel was cut with a razor blade and the content was accurately weighted into a 50 mL flask. Ten milliliters of solvent I (hexane : methanol : water, 4 : 3 : 2, upper phase) was added and the mixture was sonicated for 3–5 min at 25–30°C. The solution was transferred to a 125 mL separatory funnel. To the residue, 10 mL of solvent II (hexane : methanol : water, 4 : 3 : 2, lower phase) was added and the mixture was sonicated for 3–5 min at 25–30°C. The solution was transferred to the same separatory funnel. The above extraction procedure was repeated twice. The resulting extract (~60 mL) was shaken and left standing until the upper and lower phases were totally separated. The lower phase was collected into a 250 mL round-bottom flask. To the separatory funnel, 10 mL of solvent II was added and the funnel was thoroughly shaken and left standing. The resulting lower phase was collected into the same flask. This procedure was repeated one more time. The combined lower phase (~50 mL) was evaporated under reduced pressure at 45–50°C, and the resulting residue was dissolved and transferred with about 5 mL of methanol and about 5 mL of methanol/water (1 : 1), consecutively, to a 10 mL volumetric flask and made up to the volume with methanol. The sample solution was filtered through a 0.2 μm nylon cartridge just prior to HPLC analysis.

Fluid Extract

Fluid extract (5.0 mL) was transferred to a 10 mL PTFE capped tube and centrifuged for 15 min, and 1 mL of the supernatant was transferred to HPLC sample vial just prior to HPLC analysis.

Tablets and Caplets

These products usually contain ginseng root powders or extracts and accessory agents. To facilitate extraction, 80% methanol was employed to replace methanol for the extraction. One dose of product sample was accurately weighed into a 20 mL PTFE capped sample vial and extracted with 80% methanol (3×15 mL), as described for the extraction of powdered roots and capsules. The combined methanolic extracts were evaporated to dryness, under vacuum, at

45–50°C. The residue was re-dissolved with methanol (4 × 2 mL) and transferred to a 10 mL volumetric flask, and made up to the volume with methanol. The sample solution was filtered through a 0.2 μm nylon cartridge just prior to HPLC analysis.

Quantification

For quantification, an external standard method was used. The calibration curves were established with ginsenosides Rg_1, Re, Rc, Rb_2, Rb_1, and Rd in the concentrations of 25–300 μg/mL in methanol. The peak area was used for generation of calibration curves of ginsenosides.

RESULTS AND DISCUSSION

High Performance Liquid Chromatography Analysis

A number of HPLC solvent systems have been described in the literature for the analysis of ginsenosides. However, most of these methods employed a non-organic solvent, or long HPLC separation procedure (>60 min);[11,13,19,20] some of these methods even failed to get baseline separation of two characteristic ginsenosides, ginsenoside Rg_1 and Re.[14] The current solvent system was selected because not only could the ginsenosides be simultaneously determined, but also the different ginsenosides in each group were well separated. A typical HPLC–UV chromatogram of reference ginsenoside standards is shown in Fig. 1. Ginsenosides Rg_1, Re, Rb_1, Rc, Rb_2, and Rd were observed at the retention times of 26.58, 27.89, 45.52, 46.84, 48.01, and 50.65 min, respectively.

Comparison of Extraction Efficiency

Several methods have been proposed for the extraction of ginsenosides from ginseng samples, including Soxhlet-extracting 1.5 g of ground sample with 30 mL of methanol,[19] refluxing 2.0 g of ground sample with 50% ethanol (3 × 7 mL),[11] extracting 0.5–3.0 g of ground sample with 70% methanol (5 × 20∼30 mL) at room temperature,[20,21] sonicating 300 mg of ground sample with 70% methanol (3 × 10 mL),[19] and sonicating 500 mg of ground sample with 25 mL of methanol.[14] In the current study, two modified extraction methods (method I and method II) were compared by replicate analyses of the same powdered Asian ginseng root sample for the extraction efficiency. As shown in Table 2, there was a significant difference between method I and method II with regard to extraction efficiency. The method with higher extraction efficiency

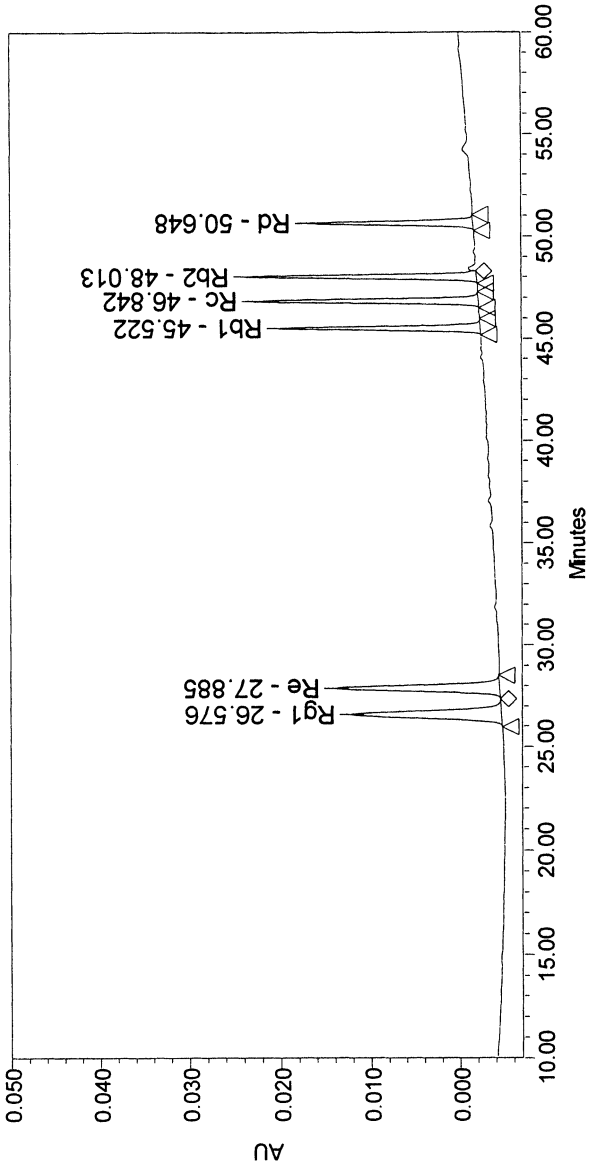

Figure 1. Typical HPLC chromatogram of ginsenoside reference standards Rg_1, Re, Rb_1, Rc, Rb_2 and Rd, with retention times of 26.58, 27.89, 45.52, 46.84, 48.01 and 50.65 min, respectively.

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Table 2. Comparison of Extraction Efficiency of Method I and Method II

	Ginsenosides Content (% ± SD)					
Method	Rg_1	Re	Rb_1	Rc	Rb_2	Rd
I[a]	0.267 ± 0.008	2.135 ± 0.018	3.839 ± 0.050	1.457 ± 0.013	0.366 ± 0.005	1.876 ± 0.012
II[b]	0.247 ± 0.018	1.953 ± 0.073	3.370 ± 0.086	1.253 ± 0.029	0.323 ± 0.008	1.578 ± 0.033

[a] $n = 3$, [b] $n = 5$.

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(method I) was chosen for the analysis of powdered ginseng roots, capsules, caplets, and tablets tested herein.

Method Validation

Linearity

Linearity of reference standards was studied for ginsenosides Rg_1, Re, Rb_1, Rc, Rb_2, and Rd, respectively, and expressed in terms of correlation coefficient (r^2). The correlation coefficient (r^2) was found to be better than 0.998 for all of the reference ginsenoside standards in the range of 25 to 300 μg/mL.

Detection Limits

The limits of detection (LOD), determined according to signal/noise >3, was 10 ng on the column for ginsenosides Rg_1, Re, Rb_1, Rc, Rb_2, and Rd, respectively.

Intra-Day and Inter-Day Accuracy and Precision

The intra-day and inter-day accuracy and precision were assessed by injecting a set of three controls for ginsenosides Rg_1, Re, and Rb_1 prepared at 75, 125, and 250 μg/mL, respectively, on three consecutive days ($n = 3$) and calculating the concentrations of each control based on the calibration curves. In the intra-day assay, it was observed that controls were quantified to be 99.73, 98.40, and 100% of the actual values for ginsenosides Rg_1, Re, and Rb_1, respectively. The variation (RSD %) within the controls was found to be 1.17, 0.59, and 1.11% for ginsenosides Rg_1, Re, and Rb_1, respectively. The inter-day RSD (%) and relative error (RE, %) were observed at 0.35, 1.20, and 1.48%, and 0.93, 1.60, and 2.00%, for ginsenosides Rg_1, Re, and Rb_1, respectively.

Recovery

Powdered roots and capsules: Ginseng powder (5.0 g) was extracted in a 50 mL flask with 25 mL of methanol by means of sonication for 30 min. After filtration, the residue was put back to the same flask and 25 mL of fresh methanol was added to the flask and sonicated for another 30 min before the filtration. The above extraction procedure was repeated until no ginsenoside peak was detected

in the filtrate by HPLC–UV described as above. The residue was thoroughly dried and a portion of the dried residue (0.5 g) was accurately weighed into a 20 mL PTFE capped sample vial. To the vial, 1 mL of standard recovery working solution (containing 0.3, 0.5 and 1.0 mg/mL of ginsenosides Rg_1, Re, and Rb_1, respectively) and 15 mL of methanol were added. Triplicate recovery samples were prepared following the method described in sample preparation. Also, a blank recovery sample (without adding ginsenosides Rg_1, Re, and Rb_1) was prepared and analyzed for the comparison. The observed recovery (%) (RSD, %) were 103 (3.31), 99.4 (0.52), and 99.7% (1.02%) for ginsenosides Rg_1, Re, and Rb_1, respectively.

Softgels: Reference ginsenosides Rg_1, Re, and Rb_1 were accurately weighed into a 10 mL volumetric flask to make the concentrations of 2.75, 1.641, and 1.274 mg/mL, respectively. An aliquot (1 mL) of reference standard solution was added to a 125 mL separation funnel. Hexane (1.8 mL), methanol (0.35 mL), and water (0.9 mL) were added to the funnel according to the ratio of hexane : methanol : water (4 : 3 : 2) and the recovery sample was prepared according to the procedure as described above. Triplicate samples were prepared and analyzed. The average recovery for ginsenosides Rg_1, Re, and Rb_1 [% (RSD, %)] were found to be 96.87 (5.53), 102.91 (3.49), and 105.46% (3.5%), respectively. For further confirmation, ginseng softgel was cut with a razor blade and the content was accurately weighed into 50 mL flask. One milliliter of reference ginsenoside standard mixture (Rg_1, Re, Rb_1) in methanol (2.75, 1.641, and 1.274 mg/mL, respectively) and corresponding volume of hexane (1.8 mL), methanol (0.35 mL), and water (0.9 mL), according to the ratio of hexane : methanol : water (4 : 3 : 2), were added and the resulting mixture was shaken for a while before liquid–liquid extraction, as described in sample preparation. Triplicate recovery samples and samples without adding reference standards were prepared and analyzed, respectively. Ginsenosides Rg_1, Re, and Rb_1 were quantitated according to the equation. The speculated concentrations of ginsenosides Rg_1, Re, and Rb_1 were calculated based on the results of sample analysis. The calculated concentrations of ginsenosides Rg_1, Re and Rb_1 were obtained by subtracting the speculated concentrations from that detected in the spiked samples. By comparing calculated concentrations with spiked concentrations of ginsenosides Rg_1, Re, and Rb_1. The recovery [% (RSD, %)] was found to be 99.64 (12.46), 95.49 (0.47), and 111.60% (10.27%) for ginsenosides Rg_1, Re, and Rb_1, respectively.

Sample Analysis

The present method was applied to the analysis of ginsenosides content in a series of ginseng products. Typical HPLC chromatographic profiles, showing baseline resolution, of the methanolic extracts of Asian and North American ginseng products are presented in Figs. 2 and 3, respectively. The ginsenosides in

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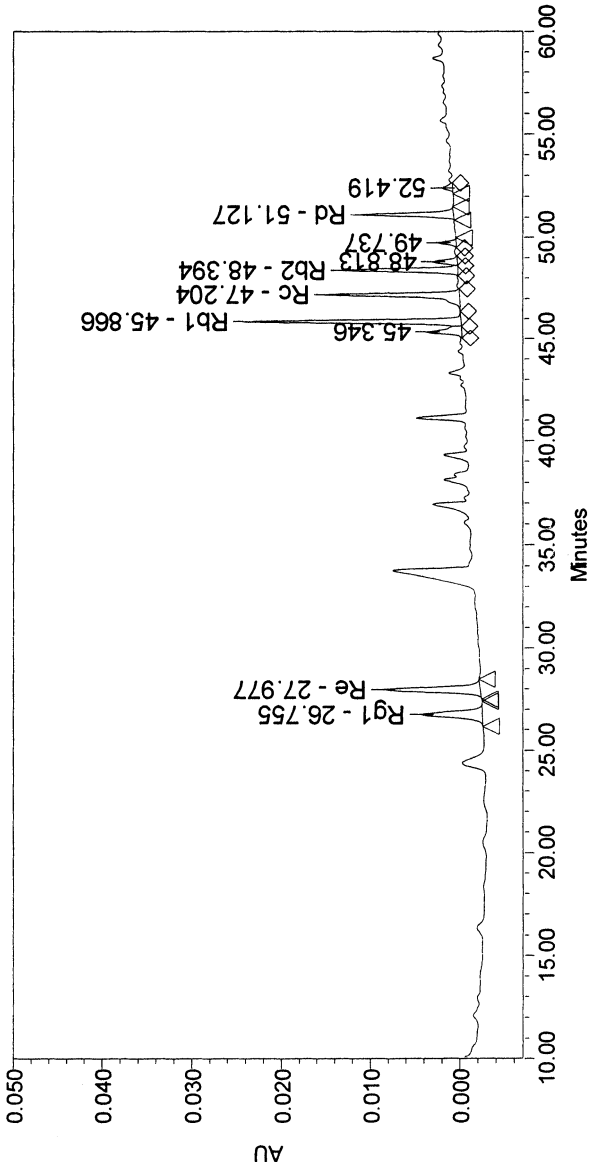

Figure 2. Typical HPLC chromatogram of Asian ginseng methanolic extract.

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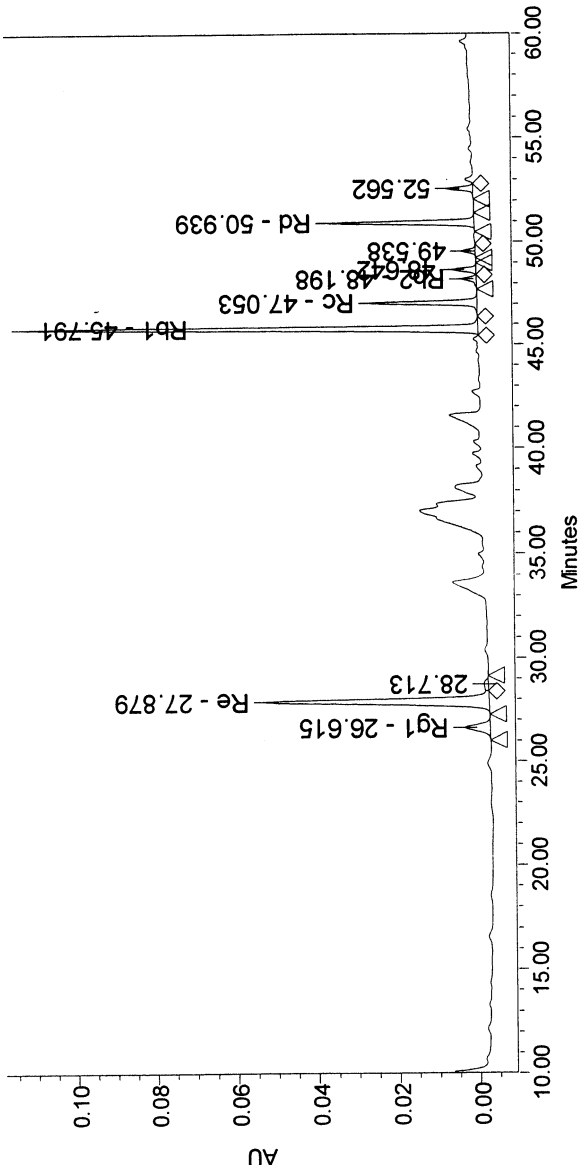

Figure 3. Typical HPLC chromatogram of North American ginseng methanolic extract.

Table 3. Content of Ginsenosides in Ginseng Products

Sample	Sources	Rg_1	Re	Rb_1	Rc	Rb_2	Rd	Content (%, w/w)	Rg_1/Rb_1
Powdered roots and capsules									
1	Asian	0.30	0.34	0.77	0.51	0.37	0.33	2.62	0.39
2	North American	0.17	1.23	3.09	0.32	0.05	0.67	5.53	0.06
3	Asian	0.29	1.94	3.3	1.29	0.21	1.69	8.72	0.09
4	Asian	0.32	0.34	0.77	0.52	0.37	0.33	2.65	0.4
5	Asian	0.34	0.92	1.16	0.98	0.65	0.75	4.8	0.29
6	North American	0.17	1.24	3.18	0.34	0.05	0.65	5.63	0.05
7	North American	0.27	1.26	1.75	0.45	0.18	1.17	5.08	0.15
8	North American	0.17	1.17	2.9	0.7	0.11	1.09	6.14	0.06
9	Asian	0.15	0.23	0.43	0.29	0.2	0.23	1.53	0.35
10	North American	0.18	1.19	2.92	0.71	0.11	1.13	6.24	0.06
11	North American	0.18	1.39	2.49	0.51	0.08	0.89	5.54	0.07
12	North American	0.39	2.04	4.47	0.67	0.11	1.21	8.89	0.09
13	North American	0.31	1.97	6.37	0.64	0.03	1.61	10.93	0.05
14	Asian	0.46	1.25	2.86	2.35	1.39	1.65	9.96	0.16
15	Asian	0.34	0.45	0.76	0.55	0.37	0.35	2.82	0.45
16	Asian	0.13	0.99	2.28	0.65	0.09	1.01	5.15	0.06
Softgel									
17	Asian	0.17	0.46	0.91	0.88	0.51	0.66	3.59	0.19
18	Asian	0.18	0.49	0.98	0.92	0.56	0.69	3.82	0.18
Caplet									
19	Asian	0.39	0.94	0.31	0.23	0.21	0.67	2.75	1.25
Tablet									
20	Asian	0.34	0.79	0.50	0.29	0.12	0.33	2.37	0.68
Liquid (mg/mL)									
21	North American	0.10	0.77	1.96	0.36	0.04	0.71	3.94	0.05

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the samples were identified by comparing the retention times of reference standards with those obtained in the sample chromatograms. Due to the lack of availability of all ginsenoside reference standards in sufficient quantity, only ginsenosides Rg_1, Re, Rb_1, Rc, Rb_2, and Rd were employed in the current research. All of these products were found to contain ginsenosides Rg_1, Re, Rb_1, Rb_2, Rc, and Rd, etc., and the content of each ginsenoside is presented in Table 3. As can be deduced from the table, the amount of ginsenosides in all ginseng products tested varied between 1.53–10.93% ($n = 21$), showing a significant product-to-product variability. North American ginseng (*P. quinquefolius*) yielded the relatively higher ginsenosides content, ranging from 5.08 to 10.93%, than that of Asian ginseng (*P. ginseng*), ranging from 1.53 to 9.96%. Of the 21 ginseng products tested, six were labeled as containing a specific concentration of ginsenosides. Of these six, five were found to contain more than the labeled concentration of ginsenosides. However, since there is no publication comparing the efficacy of different ginseng products and since no dose-response studies have been reported, it is difficult to relate possible beneficial effects of ginseng products to the composition of ginsenosides. Also, it is well known that ginseng contains several groups of natural products other than ginsenosides that might have biological activity.[22,23] The biological activity of ginseng might be due to the presence of the whole mixture of its constituents, rather than a single compound or a group of compounds.

On the other hand, it might be interesting to observe that North American ginseng samples generally possess a lower Rg_1/Rb_1 ratio than that of Asian ginseng samples. Taking into consideration, reports that ginsenoside Rb_1 acts as a weak CNS depressant and, in contrast, ginsenoside Rg_1 stimulates the CNS, the lower ratio of Rg_1/Rb_1 might be a reflection of the so-called "cool" characteristic of North American ginseng, and the higher ratio of Rg_1/Rb_1 in Asian ginseng could be one of the reasons of its so-called "warm" property described in ethnopharmacology.[5]

CONCLUSION

A HPLC method has been proposed using ultraviolet detection for the determination of ginsenosides in ginseng products with detection limits of 10 ng of ginsenoside on the column. Different extraction approaches have been presented for the extraction of ginsenosides from powdered dried ginseng roots, capsules, caplets, tablets, softgels, and liquid formulae, etc. The current method was reliable and reproducible. In view of the variability of the ginsenoside content in ginseng products, a better regulation and effective control (Good Manufacturing Practice, GMP) is highly desirable.

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REFERENCES

1. Liu, C.X.; Xiao, P.G. J. Ethnopharmacol. **1992**, *36*, 27–38.
2. Attele, A.S.; Wu, J.A.; Yuan, C.S. Biochem. Pharmacol. **1999**, *58*, 1685–1693.
3. Gillis, C.N. Biochem. Pharmacol. **1997**, *54*, 1–8.
4. Mahady, G.B.; Gyllenhaal, C.; Fong, H.H.S.; Farnsworth, N.R. Nutr. Clin. Care **2000**, *3*, 90–101.
5. Shibata, S.; Tanaka, O.; Shoji, J.; Saito, H.C. Chemistry and Pharmacology of *Panax.* In *Economic and Medicinal Plant Research*; Wagner, H., Hikino, H., Farnsworth, N.R., Eds.; Academic Press: Orlando, 1985; Vol. I, 218–284.
6. Sticher, O. CHEMTECH **1998**, *28*, 26–32.
7. Sollorz, G. Deutsch. Apoth. Ztg. **1985**, *125*, 2052–2055.
8. Smith, I.K. Time **2000**, July 31, 68 pp.
9. Cui, J.F. Eur. J. Pharm. Sci. **1995**, *3*, 77–85.
10. Cui, J.F.; Garle, M.; Bjorkhem, I.; Eneroth, P. Scand. J. Clin. Lab. Invest. **1996**, *56*, 151–160.
11. Chuang, W.C.; Wu, H.K.; Sheu, S.J.; Chiou, S.H.; Chang, H.C.; Chen, Y.P. Planta Med. **1995**, *61*, 459–465.
12. Fitzloff, J.F.; Yat, P.; Lu, Z.Z.; Awang, D.V.C.; van Breemen, R.B.; Hall, T.; Blumenthal, M.; Fong, H.H.S. Perspectives on the Quality Assurance of Ginseng Products in North America. In *Proceedings of the 7th International Symposium on Ginseng*, Seoul, Korea, 1998, 138–145.
13. Lang, W.S.; Lou, Z.C.; But, P.P.H. J. Chin. Pharm. Sci. **1993**, *2*, 133–143.
14. Ma, Y.C.; Zhu, J.; Benkrima, L.; Luo, M.; Sun, L.H.; Sain, S.; Kont, K.; Plaut-Carcasson, Y.Y. J. Herbs Spices Med. Plants **1995**, *3*, 41–50.
15. Soldati, F.; Sticher, O. Planta Med. **1980**, *38*, 348–357.
16. Harkey, M.R.; Henderson, G.L.; Gershwin, M.R.; Stern, J.S.; Hackman, R.M. Am J. Clin. Nutr. **2001**, *73*, 1101–1106.
17. Li, W.K.; Gu, C.G.; Zhang, H.J.; Awang, D.V.C; Fitzloff, J.F.; Fong, H.H.S.; van Breemen, R.B. Anal. Chem. **2000**, *72*, 5417–5422.
18. Li, W.K.; Fitzloff, J.F. J. Pharm. Biomed. Anal. **2001**, *25*, 257–265.

19. Court, W.A.; Hendel, J.G.; Elmi, J. J. Chromatogr. **1996**, *755*, 11–17.
20. Yamaguchi, H.; Matsuura, H.; Kasai, R.; Tanaka, O.; Satake, M.; Kohda, H.; Izumi, H.; Nuno, M.; Katsuki, S.; Isoda, S.; Shoji, J.; Goto, K. Chem. Pharm. Bull. **1988**, *36*, 4177–4181.
21. Samukawa, K.I.; Yamashita, H.; Matsuda, H.; Kubo, M. Chem. Pharm. Bull. **1995**, *43*, 137–141.
22. Okuda, H.; Zheng, Y.; Matsuura, Y.; Takaku, T.; Kameda, K. Studies on Biologically Active Substances in Non-saponin Fraction of Korean Red Ginseng. In *Proceedings of the 6th International Ginseng Symposium*, Seoul, Korea, 1993, 110–112.
23. Matsunaga, H.; Katano, M.; Yamamoto, H.; Fujito, H.; Mori, M.; Tanaka, K. Chem. Pharm. Bull. **1990**, *38*, 3480–3482.

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