Dispersive Micro Solid-Phase Extraction with Graphene Oxide for the Determination of Phenolic Compounds in Dietary Supplements by Ultra High Performance Liquid Chromatography Coupled with Quadrupole Time-of-Flight Tandem Mass Spectrometry

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Abstract This report described the use of graphite oxide (GO) as sorbent in dispersive micro solid-phase extraction (DMSPE), together with ultra high performance liquid chromatography coupled with quadrupole time-of-flight tandem mass spectrometry (UHPLC-Q-TOF/MS), for the determination of phenolic compounds (protocatechuic aldehyde, caffeic acid, and rosmarinic acid) in dietary supplements. The extraction conditions such as sample agitation, agitation time, sorbent amount, and type and volume of the eluent were optimized. The results showed that GO-assisted DMSPE exhibited higher enrichment factors for tested solutes as compared to the normal extraction. Under the most favorable conditions, good limits of detection (0.07–0.21 ng/mL) and repeatability of extraction (RSDs below 5.6 %, $n=5$) were obtained. The developed method was applied to determine phenolic analytes with satisfactory recoveries, which were 90.1–96.4 % for Danshen and 85.5–97.6 % for Danshen injection, respectively.

Shuai-Shuai Hu, Wan Cao, Jian-Hua Da, and Han-Bin Dai contributed equally to this work.

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Introduction

Nanomaterials are those particles that present at least one external dimension in the size range from approximately 1–100 nm. Over the past decade, they have attracted much attention taking into account their special features like high surface-to-volume ratio, biocompatibility, and unique thermal, mechanical, or electronic properties (Valcárcel et al. 2008; Nilsson et al. 2007). These materials, including carbon nanotubes, graphene, carbon nanofibers, fullerenes, metal nanoparticles, quantum dots, carbon nanocones-disks, and nanohorns, as well as their functionalized forms, were coming into use in electronics, textiles, healthcare, environmental protection, and other areas (Moliner-Martínez et al. 2009; Cao et al. 2013). More recently, graphene, a new type of carbon-based nanomaterial with one single atomic layer thick sheet of graphite, has sparked great excitement in the field of research and development due to its ultra-high specific surface areas, and is likely to continue to be for a long time. Nowadays, the distinctive properties of graphene and graphene-based materials have been used to develop innovative applications in analytical chemistry such as spectrophotometric analysis (Sun et al. 2014), sensors (Yoo et al. 2013), and mass spectrometry analysis (Kawasaki et al. 2012). Meanwhile, the application of graphene in sample preparation has attracted a great deal of attention in recent years, and it also gotten

satisfactory results in solid-phase extraction (SPE). For example, Guan et al. (2013, 2014) demonstrated the use of graphene as a novel sorbent for analysis of pesticide multiresidue in crops. Zawisza et al. (2013) established a graphene oxide (GO) approach for the determination of trace amounts of metal ions. However, these technologies offered the disadvantages of time-consuming, relatively large quantities of solvents, and multistep extraction procedures, which greatly limited their applications.

Sample treatment is a vital part of the whole process of analysis, and it is essential when target analytes are separated from the interfering matrix components or direct analysis is impossible due to the lack of selectivity and sensitivity. Recent trends in this field are clearly towards simplification, miniaturization, automation, high-throughput performance, and low solvent consumption. The most common and widespread sample preparation method is solid-phase microextraction (SPME), which is based on the adsorption of target analytes from the headspace or the aqueous phase of a matrix and subsequent elution in the appropriate solvent (Zhang et al. 2012; Ge and Lee 2013; Kataoka et al. 2013; Wen and Zhu 2014). Among them, dispersive micro solid-phase extraction (DMSPE) has been recently applied to separation and enrichment of trace analytes in water samples because of its simplicity, rapidity, high enrichment factor, good recovery, low consumption of organic solvents, and ability to combine with different detection techniques (Jiménez-Soto et al. 2012a, b; Galán-Cano et al. 2013; Tsai et al. 2009; Galán-Cano et al. 2011; Chung et al. 2013; Kocot et al. 2013; Fu et al. 2012; Giannoulis et al. 2012). The sorbent materials used, which were the core of DMSPE, determined the selectivity and enrichment efficiency of analytes. Up to now, several materials have been investigated as absorbents in previous studies, including single-walled carbon nanohorns (Jiménez-Soto et al. 2012a, b), methylimidazolium-hexafluorophosphate functionalized silica (Galán-Cano et al. 2013), silica-based PSA (Tsai et al. 2009), RP-C_{18} (Galán-Cano et al. 2011; Chung et al. 2013), multiwalled carbon nanotubes (Kocot et al. 2013), Carboxen™ 1003 (Fu et al. 2012), and ferromagnetic nanoparticles (Giannoulis et al. 2012). As far as DMSPE is concerned, the utilization of graphene has not been reported in the literature. Additionally, DMSPE should be expected to have better performance for plant samples.

Salvia miltiorrhiza, also known as Danshen (DS), is a perennial plant in the genus *Salvia*, highly valued for its roots in China and, to a lesser extent, in Japan, the USA, and European countries (Cao et al. 2008a, b). Nowadays, it is widely used for the treatment of cardiovascular disorders, also for food auxiliary agent. Danshen injection (DSI) is made from the aqueous extract of *S. miltiorrhiza* and widely used in clinics as a treatment for a diversity of ailments, particularly cardiovascular and cerebrovascular diseases. Pharmacological and chemical investigations on DSI found that phenolic

compounds were the major active constituents responsible for the therapeutic efficacy (Chang et al. 2008). Therefore, it is important to determine and quantify phenolic compounds in dietary supplements. In our current work, the use of GO was evaluated for the first time under a DMSPE mode for the separation and preconcentration of phenolic analytes which were finally determined by ultra high performance liquid chromatography coupled with quadrupole time-of-flight tandem mass spectrometry (UHPLC-Q-TOF/MS). The effects of DMSPE (i.e., sample agitation, agitation time, sorbent amount, type, and volume of the eluent) on the microextraction were systematically investigated in order to select the optimal values for analytes determination at trace levels. Finally, the developed procedure has been applied for the determination of target analytes in DS and DSI.

Experimental

Reagents and Materials

GO was purchased from Nanjing XFNano Material Tech Co., Ltd. (Nanjing, China). Chromatographic grade methanol and acetonitrile were obtained from Sigma-Aldrich Shanghai Trading Co. Ltd. (Shanghai, China). Analytically pure ethanol and acetone were supplied by Hangzhou Chemical Reagent Co., Ltd. (Hangzhou, China). Ultrapure water was produced using a Milli-Q water purification system (Millipore, Billerica, MA, USA). All other chemicals were of analytical grade. The syringes (20 mL) were purchased from Hangzhou chemical reagent Co., Ltd. (Hangzhou, China).

The tested standards including protocatechuic aldehyde (PA), caffeic acid (CA), and rosmarinic acid (RA) were purchased from Shanghai Winherb Medical Technology Co., Ltd. (Shanghai, China). The chemical structures of three compounds are depicted in Fig. 1. DS and DSI were purchased from Hangzhou local drugstore (Hangzhou, China).

Protocatechuic aldehyde   Caffeic acid

Rosmarinic acid
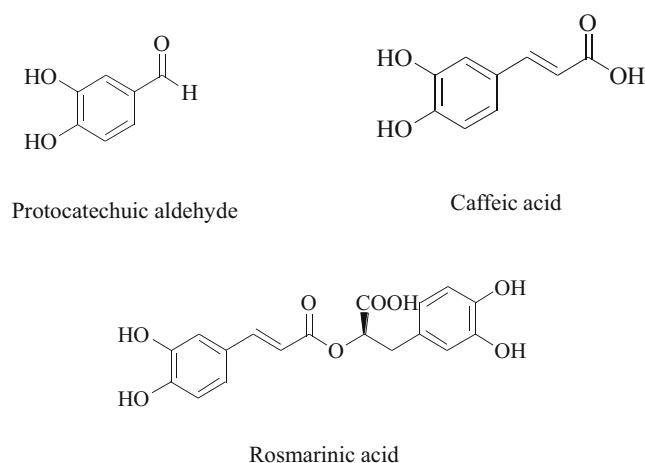
Fig. 1 Chemical structures of three analytes

UHPLC-Q-TOF/MS Analysis

Chromatographic analyses of phenolic components were carried out on an Agilent UHPLC system (consisting of a binary pump, vacuum degasser, thermostated column compartment, and autosampler) (Agilent 1290 Infinity LC, Agilent Technologies, Santa Clara, CA, USA) using Agilent Zorbax StableBond-C$_{18}$ column (2.1 mm× 50 mm, 1.8 μm) maintained at 35 °C. The mobile phase was gradient elution which was mixed with solvents A (0.01 % formic acid, v/v) and B (acetonitrile). The gradient program was as follows: 0–5 min, 10–25 % B; 5–6 min, 25–30 % B; 6–7 min, 30–100 % B. During the separation, the flow rate was maintained at 0.4 mL/min and the injection volume was 1 μL.

The MS analysis of target compounds was carried out on a 6530 Q-TOF/MS (Agilent Technologies, Santa Clara, CA, USA). The instrument was equipped with an ESI source operated in the negative ion mode, and the mass rang was recorded across the range 100–2,000 m/z. The source operation parameters were set as follows: capillary voltage 3,500 V, gas temperature 350 °C, drying gas 12 L/min, nebulizer pressure 45 psig, skimmer voltage 65 V, octopole RF 750 V, and fragmentor voltage 175 V. All the acquisition and analysis of data were controlled by Mass Hunter software (version B 05.00 Qualitative Analysis).

Preparation of Samples

DS was comminuted a homogeneous size by a mill, sieved through a no. 60 mesh. The powder sample accurately weighed (0.3 g) was added to a round-bottomed flask containing 70 % methanol and the mixture was ultrasonicated for 1 h. DSI was diluted directly to 10 ml with deionized water. The resultant solutions were filtered through a membrane (0.45 μm) and extracted by DMSPE.

Preparation of Functionalized Graphene

The GO was prepared from natural graphite flakes using a chemical exfoliation method, which was provided by Nanjing XFNano Material Tech Co., Ltd. Then, the functionalized graphite was dispersed by 30-min ultrasonication in water to form stable 0.2 wt% GO dispersion, which was used for the DMSPE.

GO-DMSPE Procedure

For the extraction of phenolic compounds, an aliquot of 10 mL of sample or an aqueous standard containing target analytes was placed in a 25-mL glass vial, and 1 mL of a 0.2 mg mL^{-1} GO suspension was added. Subsequently, the mixture was agitated using an orbital shaker for 2 min,

favoring the extraction of the phenolic components. Then, the sorbent was isolated from the sample by a 0.45 μm nylon filter previously conditioned passing 2 mL of methanol and 2 mL of ultrapure water. The sorbent enriched with the analytes was washed with 100 μL of methanol. The eluate was collected in a glass vial for the further UHPLC-Q-TOF/MS analysis. Schematic demonstration of GO-DMSPE is shown in Fig. 2.

Results and Discussion

Optimization of UHPLC-Q-TOF/MS Conditions

In the present study, three selective LC columns with different fillers, i.e., (1) Agilent StableBond-C$_{18}$ column (2.1 mm× 50 mm, 1.8 μm), (2) Agilent Extend-C$_{18}$ column (2.1 mm× 50 mm, 1.8 μm), and (3) Agilent Eclipse XDB column (2.1 mm×50 mm, 1.8 μm), were compared for their separation efficiencies. The results showed that the separation efficiency of column 1 was obviously better than that of other two columns. As the mobile-phase modifier, the addition of 0.01 % formic acid could enhance the ionization and improve peak shape. Because most of the analytes had carboxyl group in their structure, the negative ion mode and ESI source were adopted for the assay of PA, CA, and RA. The [M-H]$^-$ ions were selected as the precursor ions to produce MS/MS spectra. In addition, the main Q-TOF/MS parameters (capillary voltage, gas temperature, drying gas flow rate, nebulizer gas pressure, skimmer voltage, fragmentor voltage, and the collision energy) were optimized to provide the best possible sensitivity. The optimized MS parameters were summarized in the "Experimental" section.

Optimization of Extraction Conditions

In order to achieve the best extraction efficiency of the DMSPE for target analytes, several parameters including sample agitation, extraction time, GO concentration, eluent type, and eluent volume were investigated in depth.

Effect of Sample Agitation

The agitation of the sample is an essential step in analysis, greatly influencing the extraction efficiency. For this reason, three forms of sample agitation including magnetic stirring, ultrasound, and orbital shaker were examined in detail, using phenolic acids as model analytes taking into account their phenolic and acidic characteristics. Magnetic stirrer has been vastly used as a benchmark technique in chemistry and biology that employed a rotating magnetic field to cause a stir bar immersed in a liquid to spin very quickly. From Fig. 3, it can

Fig. 2 Schematic demonstrating
GO-DMSPE. For detail, see text
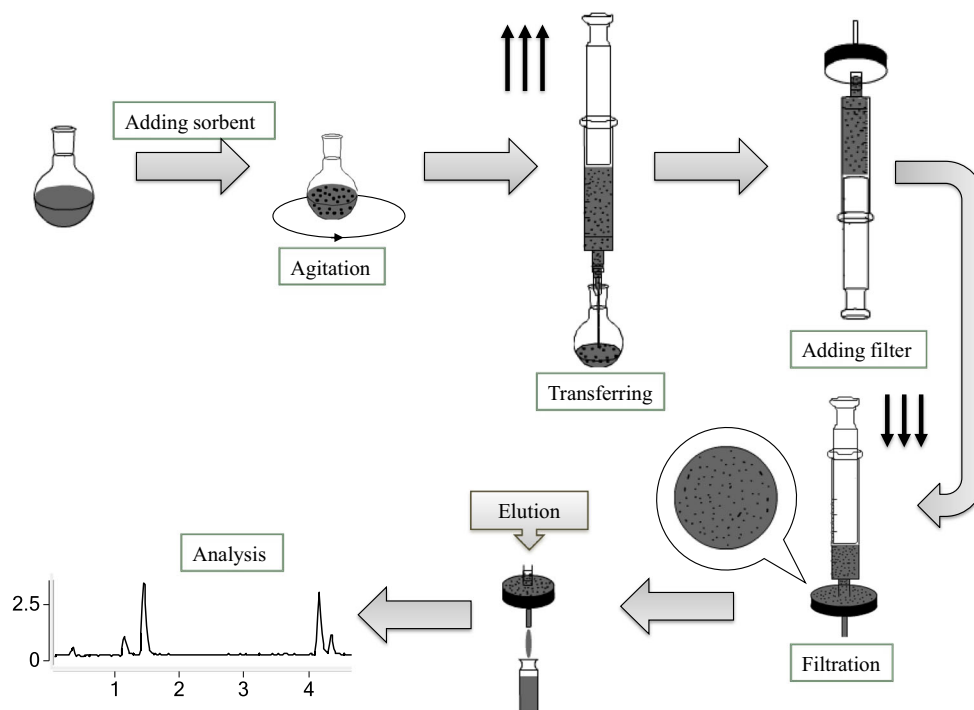
be clearly seen that for all analytes, the magnetic stirrer showed lower peak areas among these methods. It might result from the competitive adsorption of analytes to stir bars. The ultrasonic agitation, also known as sonication, is the act of applying cavitation bubbles induced by high-frequency pressure waves to agitate particles in a sample, for various purposes. The results, which were presented in Fig. 3, showed that extraction efficiencies of sonication were higher than that of magnetic stirring, and yet lower than that of orbital shaker. Compared to orbital shaker, the use of sonication probably reduced the mass transfer rate of concentrated analytes into the dispersion phase of GO. Orbital shaker is known for its simplicity and rotary

swirling action used extensively in the sample preparation. An obvious increase in the efficiency of extraction (Fig. 3) presented as peak areas was observed for three analytes when the orbital shaker was employed to assist the extraction. The mechanism for this may be related to the enhancement of the interaction between the sample and the extractant, which was also commonly found in the extraction process, leading to the increase of the extraction efficiency. As a result, the method of agitation with orbital shaker was selected for the subsequent experiments.

Agitation Time

It is well-known that agitation time is one of the prime factors that affect the amount of the analytes extracted because mass transfer between the sample solution and the GO is a time-dependent process (Kataoka and Saito 2011). So it was investigated by changing the extraction time from 1 to 16 min, as shown in Fig. 4. It demonstrated that, as the extraction time was increased from 1 to 2 min, the peak areas for three analytes greatly increased as expected; after 2 min, the extraction efficiency decreased. Compared to PA and CA, RA showed a sharp decrease in extraction efficiency when the extraction was varied from 2 to 8 min. This could be due to the relative low diffusion coefficient of RA, which has the highest molecular weight among these analytes. It was made clear that an extraction plateau was reached in 4 min for PA and CA, and 8 min for RA. Based on this observation, 2 min was sufficient to achieve high extraction efficiency for the extraction of
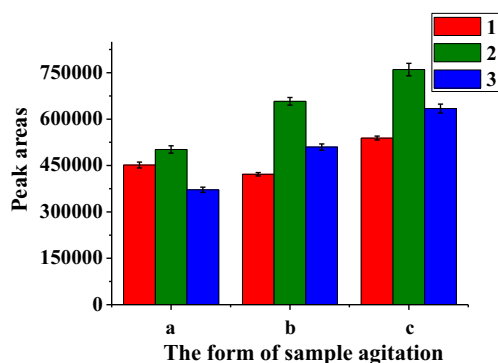
Fig. 3 Effect of the form of sample agitation in the extraction of the target analytes (analytes concentrations of 80 ng/mL). **a** Magnetic stirring, **b** ultrasound, and **c** orbital shaker. Analytes: (*1*) protocatechuic aldehyde, (*2*) caffeic acid, (*3*) rosmarinic acid
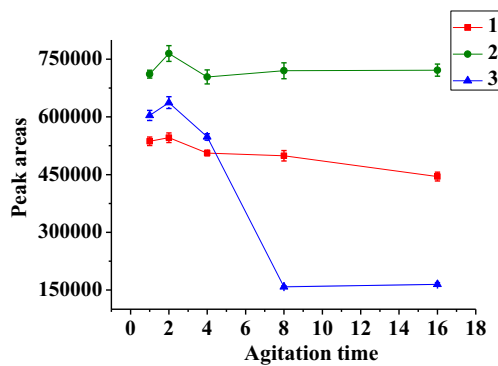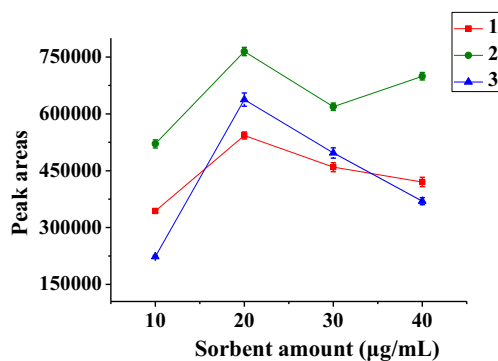
Fig. 4 Effect of agitation time (1, 2, 4, 8, and 16 min) in the extraction of target analytes (analytes concentrations of 80 ng/mL). Analytes: (*1*) protocatechuic aldehyde, (*2*) caffeic acid, (*3*) rosmarinic acid

Fig. 6 Effect of eluent type in the extraction of the target analytes (analytes concentrations of 80 ng/mL). **a** Ethanol, **b** acetonitrile, **c** water, **d** acetone, and **e** methanol. Analytes: (*1*) protocatechuic aldehyde, (*2*) caffeic acid, (*3*) rosmarinic acid
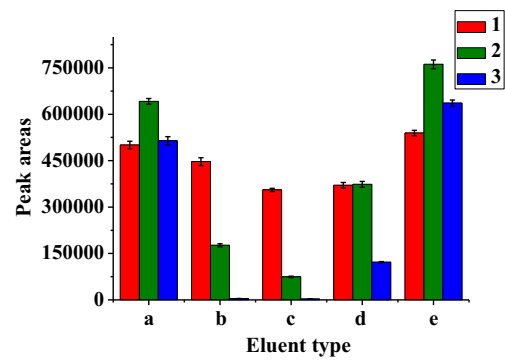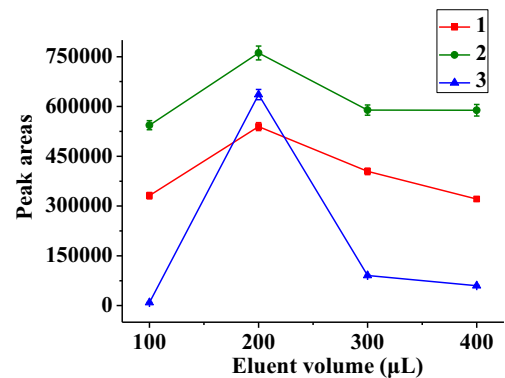
target compounds. Therefore, in this study, 2 min was selected as the agitation time for the DMSPE step.

Sorbent Amount

In this DMSPE, GO was employed as the sorbent for the extraction of the phenolic compounds. An appropriate sorbent concentration should be used to ensure an effective extraction of target analytes in the aqueous solution. The effect of sorbent amount on sample extraction was studied in the range of 10 to 40 μg/mL with ultrapure water as the dispersion solvent. As shown in Fig. 5, the peak areas of analytes increased as the amount of GO was varied between 10 and 20 μg/mL. Evidently, increasing GO concentration could significantly increase the enrichment factors. However, a significant reduction in the extraction capacity was observed upon increasing the amount from 20 to 40 μg/mL (Fig. 5). This aspect could be ascribed to the fact that the available surface area was inadequate to interact with the analytes at higher GO concentrations due to the aggregation of the nanomaterials. On the basis of the observations mentioned above, further experiments were carried out adding 20 μg/mL of the dispersed GO in 10 mL of the aqueous sample.

Type and Volume of the Eluent

Once target analytes were extracted, they should be eluted from the DMSPE device into a suitable organic solvent. In this work, the five eluents including ethanol, acetonitrile, water, acetone, and methanol were tested with 200 μL of solvent in a 10-mL vial containing three analytes at 80 ng/mL. The extraction efficiency for five solvents was compared, as shown in Fig. 6. It is seen that the largest peak areas for all analytes were obtained with methanol, followed by ethanol, acetone, acetonitrile, and water. It revealed that methanol had strong adsorption affinity to the phenolic analytes. Moreover, it was observed that methanol and ethanol gave better results in terms of chromatographic peak shapes of analytes in comparison with those obtained with the other solvents, since they were more compatible with UHPLC-Q-TOF/MS. Therefore, methanol was chosen as the eluent.

The elution volume was one of the critical parameters that affected the efficiency of extraction for the analytes. The methanol volume was studied between 100 and 400 μL, the results being summarized in Fig. 7. As it can be seen, the peak areas reached the maximum at 200 μL for all the studied analytes, indicating that elution volume had obvious effect

Fig. 5 Effect of sorbent amount in the extraction of the target analytes (analytes concentrations of 80 ng/mL). Analytes: (*1*) protocatechuic aldehyde, (*2*) caffeic acid, (*3*) rosmarinic acid

Fig. 7 Effect of eluent volume (100-400 μL) in the extraction of the target analytes (analytes concentrations of 80 ng/mL). Analytes: (*1*) protocatechuic aldehyde, (*2*) caffeic acid, (*3*) rosmarinic acid

Table 1 The performance characteristics of the proposed method

Analytes	Regression equation	Linear range (ng/mL)	r^2	Precision				LOD (ng/mL)	
				Intraday ($n=6$)		Interday ($n=3$)		Conventional method[a]	Proposed method
				Retention time	Peak areas	Retention time	Peak areas		
PA	y=3,999x+1,520	2.72–272.00	0.9980	0.64	2.39	0.81	4.23	18	0.21
CA	y=12,529x−5673	2.00–200.00	0.9990	0.52	2.83	0.62	6.23	8	0.07
RA	y=12,155x−3750	2.30–230.00	0.9990	0.22	3.03	0.51	5.56	10	0.10

[a] The accurately weighed Danshen sample (0.3 g) was suspended in 50 mL 70 % methanol and extracted in an ultrasonic bath at room temperature for 1 h. Then, the solution was filtered through a membrane filter (0.45 μm), and an aliquot of 1 μL of the filtrate was injected into UHPLC-Q-TOF/MS for analysis

on the extraction efficiency. Subsequently, as elution volume was increased from 200 to 400 μL, the peak areas for all the analytes decreased, as expected, due to the dilution effect. There, the elution volume of 200 μL was chosen for the following experiments.

Method Evaluation

To assess the performance of DMSPE with the GO sorbent, validation parameters including the linearity, precision, repeatability, and limits of detection (LODs) of the method were investigated under the optimized working conditions. The results obtained are summarized in Table 1. The calibration curves were constructed by plotting the mean peak area versus sample concentration. The linearity of calibration plots were obtained over the range of 2.72–272.00 ng/mL for PA, 2.00–200.00 ng/mL for CA, and 2.30–232.00 ng/mL for RA, with good squared regression coefficients (r^2) greater than 0.9900 for all analytes. The intraday precision of the method, expressed as the relative standard deviation (RSD) of six measurements, was lower than 0.64 % for retention time, and 3.03 % for peak areas, respectively. Interday precision of retention time and peak areas across 3 days of analysis was lower than 0.81 and 6.23 %, respectively, which was deemed as satisfactory. The repeatability of the method was achieved by five repeated extractions of DS samples, which varied in the range from 3.3 to 5.6 %. LODs, calculated as the

concentration of the analytes at signal-to-noise ratios of 3, were in the interval between 0.07 and 0.21 ng/mL. Compared with normal extraction (Table 1), 86–114-fold sensitivity enhancement in terms of LODs was achieved using DMSPE.

Sample Analysis

The optimized GO-based DMSPE coupled with UHPLC-Q-TOF/MS method was applied to the enrichment of phenolic compounds in DS samples collected from a local drugstore. The results are given in Table 2. For identification of phenolic analytes contained in the dietary supplements, mass fragmentation with high-resolution MS data provided valuable information (Table 2). All analytes produced abundant [M-H]$^-$ ions as the base peak in negative ESI-MS spectra. Three analytes were unambiguously identified via comparing their retention times, exact molecular masses, and MS/MS spectral data with the references. The phenolic compounds were detected in DS and DSI, ranging from 0.07 to 2.89 mg/g and 25.26 to 989.36 μg/mL, respectively. Figure 8 shows a typical chromatogram of the standard solution and DSI with DMSPE. The sample solution was spiked with 40.0 ng/L phenolic analytes to evaluate the accuracy of the proposed method. It was found that the overall recoveries of DS and DSI were 90.1–96.4 and 85.5–97.6 % for target analytes, respectively (Table 2). Additionally, as it can be observed from Table 3, our proposal based on the use of DMSPE with UHPLC-Q-TOF/MS

Table 2 The MS data, content, and recovery of target analytes

Analytes	Formula	t_R (min)	[M-H]$^-$	Collision Energy (N)	MS/MS	Content[a]		Recovery[a] ($n=3$)	
						DS (mg/g)	DSI (μg/mL)	DS (%)	DSI (%)
PA	$C_7H_6O_3$	1.133	137.0348	15	108.0116,111.5078,129.2485	0.07	989.36	90.1	85.5
CA	$C_9H_8O_4$	1.433	179.0467	15	112.9822,134.9887,137.0367	0.01	25.26	96.4	97.6
RA	$C_{18}H_{16}O_8$	4.151	359.0935	15	105.1833,170.5222,292.9423	2.89	121.12	93.7	90.8

[a] *DS* Danshen, *DSI* Danshen injection
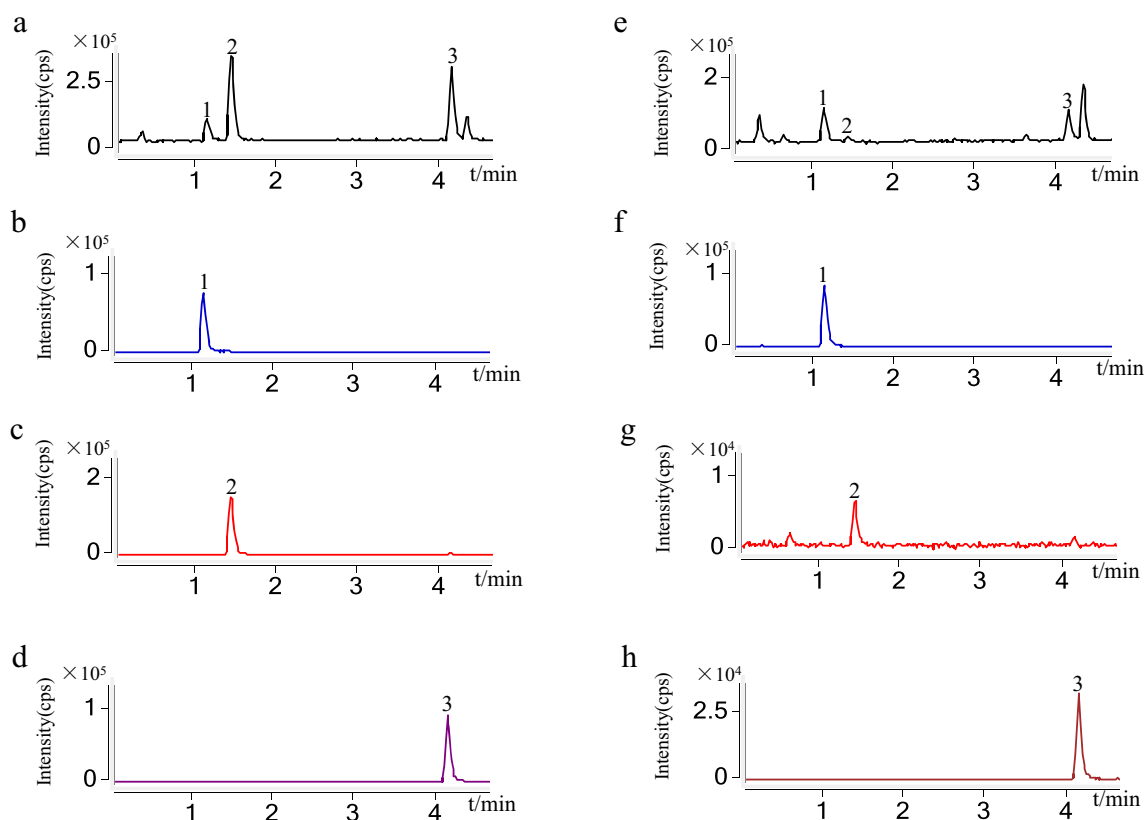
Fig. 8 The total ion chromatograms (TICs) of standard solution (analytes concentrations of 80 ng/mL) (**a**) and sample solution (**e**). Extracted ion chromatograms (EICs) of protocatechuic aldehyde (**b**), caffeic acid (**c**), rosmarinic acid (**d**) in standard solution; EICs of protocatechuic aldehyde (**f**), caffeic acid (**g**), rosmarinic acid (**h**) in sample solution. Analytes: (*1*) protocatechuic aldehyde, (*2*) caffeic acid, (*3*) rosmarinic acid

presented the lowest limits of detection and competitive sensitivity compared with other methods such as ultrasonic extraction, hollow fiber solvent bar microextraction, liquid-liquid extraction, and so on (Cao et al. 2008a, b; Ma et al 2014; Cao et al. 2008a, b; Gong et al 2009; Duan et al 2012; Liu et al 2006; Zhao et al 2011; Cao et al 2010). Moreover, it

Table 3 Comparison of the proposed method with reported approaches for the determination of phenolic analytes in plant samples

Extraction technique[a]	Instrumental technique[b]	Sample volume (mL)	LOD[c] (ng/mL)	Reference
UE, DS	HPLC	50	30–70	Cao et al. 2008a, b
HF-SBME, DS	HPLC	50	0.76	Ma et al 2014
UE, DS	MEEKC	10	410–430	Cao et al. 2008a, b
UE, DS	RRLC-TOF/MS	25	40	Gong et al 2009
UE, DS	CE-MS	10	15	Duan et al 2012
DM, DSI	HPLC	6	40–150	Liu et al 2006
LLE, DSI	LC-ESI/MS	10	20	Zhao et al 2011
DM, DSI	MEEKC	15	2,800	Cao et al 2010
DMSPE, DS, DSI	UHPLC-Q-TOF/MS	10	0.07–0.21	This Method

[a] Extraction techniques: UE, ultrasonic extraction; HF-SBME, hollow fiber solvent bar microextraction; DM, dilution method; LLE, liquid-liquid extraction; DMSPE, dispersive micro solid-phase extraction; DS, Danshen; DSI, Danshen injection

[b] Instrumental techniques: HPLC, high performance liquid chromatography; MEEKC, microemulsion electrokinetic chromatography; RRLC-TOF/MS, rapid resolution liquid chromatography and electrospray ionization time-of-flight mass spectrometry; CE-MS, capillary electrophoresis-mass spectrometry; LC-ESI/MS, liquid chromatography electrospray ionization-mass spectrometry; UHPLC-Q-TOF/MS, ultra high performance liquid chromatography coupled with quadrupole time-of-flight tandem mass spectrometry

[c] LOD, limit of detection

required less organic solvent, simpler extraction procedure, and shorter extraction time than its counterparts. Based on the discussion above, this developed method appeared to be an appropriate technique for analyzing phenolic components in complex samples.

Conclusions

In the present study, a new DMSPE method in combination with UHPLC-Q-TOF/MS was developed for the preconcentration of the phenolic components in dietary supplements. The method provided a wide linear range, good precision, low LODs, and good recoveries for the analysis of such samples. Compared with conventional extraction techniques, the proposed method exhibited high sensitivity and selectivity for the studied analytes under the optimal experimental conditions. Overall, the DMSPE method appeared to be a good alternative extraction method for the determination of water-soluble compounds in complex plant matrices.

Conflict of Interest   Shuai-Shuai Hu declares that he has no conflict of interest. Wan Cao declares that he has no conflict of interest. Jian-Hua Da declares that he has no conflict of interest. Han-Bin Dai declares that he has no conflict of interest. Jun Cao declares that he has no conflict of interest. Li-Hong Ye declares that he has no conflict of interest. Xing-Ying Li declares that he has no conflict of interest. Chu Chu declares that he has no conflict of interest. This article does not contain any studies with human or animal subjects.

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