



## Original Article

## Quantitative determination of multi-class bioactive constituents for quality control of Yiqi Jiangzhi Granules

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## ARTICLE INFO

## Article history:

Received 1 June 2021

Revised 30 September 2021

Accepted 11 October 2021

Available online 12 March 2022

## Keywords:

multiple reaction monitoring

quality control

traditional Chinese medicine

UPLC-ESI-MS/MS

Yiqi Jiangzhi Granules

## ABSTRACT

**Objective:** To establish a reliable and sensitive method for evaluating quality of Yiqi Jiangzhi Granules (YQJZG).

**Methods:** Ultra performance liquid chromatography electrospray ionization tandem mass spectrometry (UPLC-ESI-MS/MS) was employed for simultaneous determination of eight marker components. Separation was performed on an AQUITY UPLC® HSS T3 column, the mobile phase consisted of acetonitrile as the organic phase and 0.1% (volume percentage) formic acid as the aqueous. Eight marker components, ginsenoside Rg1 (GRg1), ginsenoside Re (GRe), ginsenoside Rb1 (GRb1), typhaneoside (TEO), isorhamnetin-3-O-neohesperidoside (IN), hesperidin (HPD), aurantio-obtusin-6-O-β-D-glucoside (AG) and curcumin (CCM), were detected by multiple reaction monitoring (MRM) mode. The Chinese Pharmacopoeia (2020 edition) was regarded as the guidance document for this method validation.

**Results:** The method showed good linearity ( $R^2 \geq 0.9990$ ). The relative standard deviation (RSD) values for the instrument precision, intermediate precision and repeatability were less than 2.91%, 2.88%, and 3.54%, respectively. The average recovery varied from 91.08% to 103.89%, with RSD below 3.81%. Sample solutions were found to be stable within 24 h at 4 °C (RSD < 2.85%). Eight marker components were successfully determined from three batches of YQJZG.

**Conclusion:** The proposed UPLC-ESI-MS/MS method was found to be simple, fast and sensitive, and can be used for the routine quality assessment of YQJZG. Simultaneously, this method may provide a new and powerful tool of quality control for other traditional Chinese medicine analogous formulae.

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## 1. Introduction

Yiqi Jiangzhi Granules (YQJZG), a traditional Chinese medicine formula, is composed of 10 traditional Chinese medicine (TCM) slices including *Ginseng Radix et Rhizoma*, *Curcumae Longae Rhizoma*, *Citri Reticulatae Pericarpium*, *Typhae Pollen*, *Cassiae Semen*, *Nelumbinis Folium*, *Crataegi Fructus*, *Atractylodis Macrocephalae Rhizoma*, *Alismatis Rhizoma*, and *Laminariae Thallus Eckloniae Thallus*. It is believed that YQJZG has the effect of replenishing *qi* and invigorating spleen, activating blood circulation and removing blood stasis. Our previous study revealed that YQJZG could lower the blood lipid levels, and effectively reduce the total cholesterol and triglyceride content in hyperlipidemic rats. The research results have been applied for patent (Patent No.: CN201810595093.5.) (Liu, Wang, Jiang & Cai, 2018).

In our previous work, a preliminarily study on the chemical composition of YQJZG was conducted. Using ultra-high

performance liquid chromatography-linear ion trap/electrostatic orbitrap combined high resolution mass spectrometry (UPLC-LTQ/Orbitrap MS) technology, a total of 97 compounds were identified, including flavonoids, alkaloids, phenolic acids, anthraquinones, triterpenoids, sesquiterpenoids, and etc (Zhang et al., 2020). In order to control the quality of YQJZG effectively, it was necessary to establish a method for the content determination of multi-class bioactive marker components of YQJZG.

Modern pharmacological studies have shown that flavonoids, anthraquinones and terpenoids from the YQJZG exhibited therapeutic effects on cardiovascular diseases (Chang, Zhang, Zhang, Zhao & Sun, 2020; Xiong et al., 2019). Curcumin (CCM) in *Curcumae Longae Rhizoma*, typhaneoside (TEO) in *Typhae Pollen* and hesperidin (HPD) in *Citri Reticulatae Pericarpium* and can effectively lower the levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), while increase the level of high-density lipoprotein cholesterol (HDL-C) and vascular endothelial growth factor (VEGF) in the plasma of hyperlipidemic rats (Manzoni et al., 2019; Saadati et al., 2019; Liu et al., 2018; Jung et al., 2006). Ginsenosides, especially GRg1, GRb1 and GRe,

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can regulate blood lipid, blood pressure and improve cardiac function from different ways (Kim, 2018). They fully embody that TCMs have the characteristics of multiple components, multiple targets and multiple pathways in the treatment of hyperlipidemia. So, we selected representative active ingredients containing GRg1, GRe, GRb1, CCM, aurantio-obtusin-6-O- $\beta$ -D-glucoside (AG), isorhamnetin-3-O-neohesperidoside (IN), TEO and HPD of YQJZG as the marker components for the content determination. This provides a methodological basis for the quality control of YQJZG.

However, the application of the ultraviolet detector in the determination of saponins is extremely restricted because of a lack of long conjugated systems in their structures. Besides, ginsenosides are low in content and are susceptible to interference by other components in this formula. Although we purified and enriched it using different ways, the requirements of content determination using the HPLC-PDA cannot be met. In recent years, UPLC-MS/MS has developed rapidly and has been widely used in the research field of TCMs. It has the advantages of efficient separation ability, high sensitivity and specificity for quantitation, which is especially suitable for the determination of multi-components in Chinese medicine formulae (Wang et al., 2014; Wang et al., 2012; Yi et al., 2019).

Based on the above information, a fully validated UPLC-MS/MS method was developed for the determination of multi components in YQJZG. Then, this new method was successfully utilized for the content determination of three batches of YQJZG produced in the

laboratory. This method greatly simplified the previous enrichment and impurities removal steps. What's more, this developed method provides certain reference significance for the determination of components with weak ultraviolet absorption, low content and easily interfered by other impurities in other TCM formulae.

## 2. Materials and methods

### 2.1. Reagents and materials

Both acetonitrile and methanol (HPLC grade) were purchased from Fisher Scientific (Fair Lawn, NJ, USA). Other chemical reagents were analytical grade and were purchased from Beihua Fine Chemicals Co., Ltd. (Beijing, China). CCM, HPD, GRg1, GRe, GRb1, AG, IN and TEO (Fig. 1) were purchased from National Institutes for Food and Drug Control (NFDC) (Beijing, China). The purity for each reference compound was >98%. The following control TCM slices were also bought from National Institutes for Food and Drug Control (NFDC) (Beijing, China), including *Ginseng Radix et Rhizoma*, *Curcumae Longae Rhizoma*, *Citri Reticulatae Pericarpium*, *Cassiae Semen*, *Typhae Pollen*. All TCMs (*Ginseng Radix et Rhizoma*, *Curcumae Longae Rhizoma*, *Citri Reticulatae Pericarpium*, *Typhae Pollen*, *Cassiae Semen*, *Nelumbinis Folium*, *Crataegi Fructus*, *Atractylodis Macrocephalae Rhizoma*, *Alismatis Rhizoma* and *Laminariae Thallus Eckloniae Thallus*) applied in this experiment were bought from Hancaotang

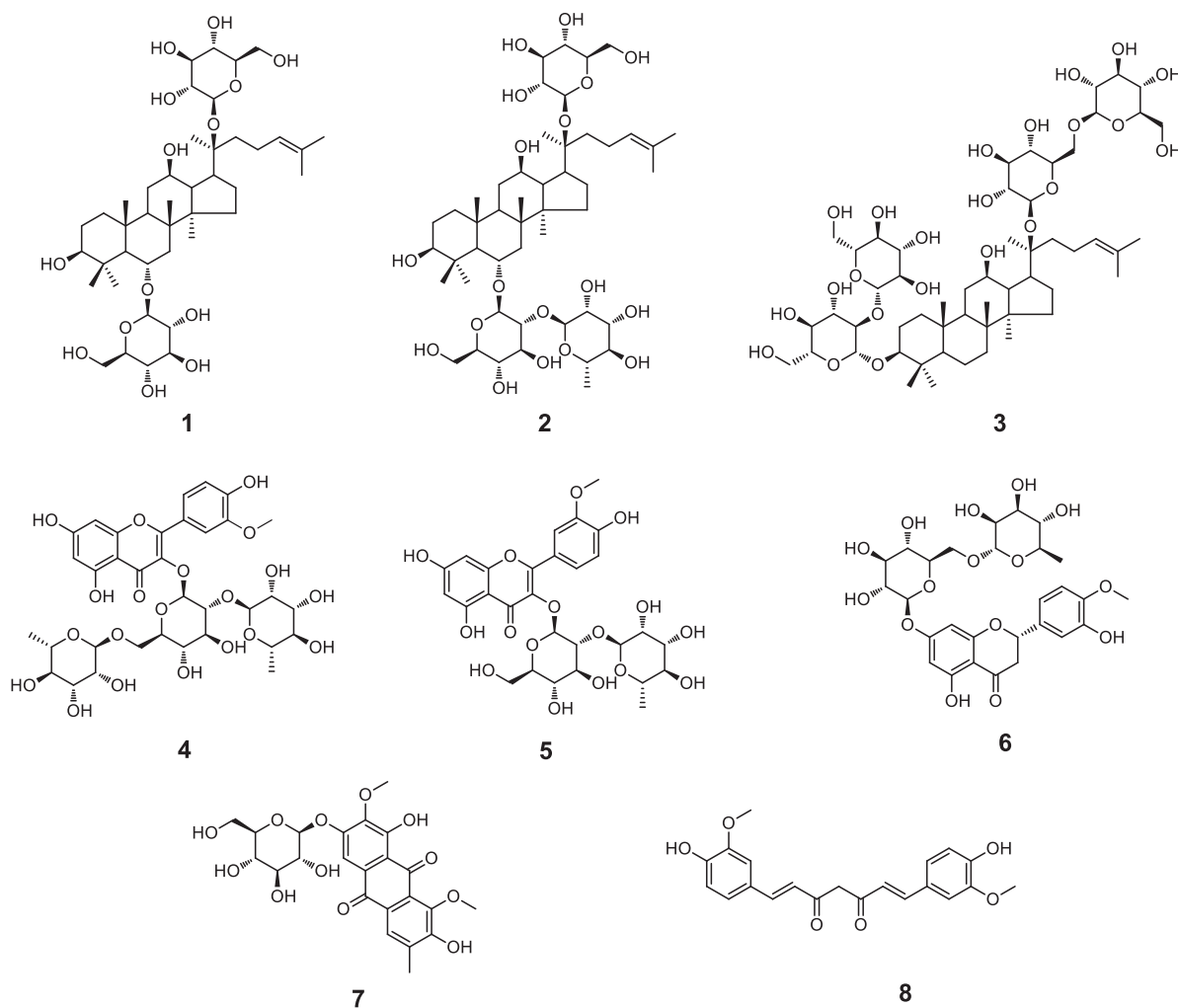


Fig. 1. Chemical structures of eight marker components in Yiqi Jiangzhi Granules: 1 GRg1; 2 GRe; 3 GRb1; 4 TEO; 5 IN; 6 HPD; 7 AG; 8 CCM.

Pharmaceutical Co., Ltd. (Hebei, China). Three batches of YQJZG were produced in the laboratory. Synergy UV water purification system (Millipore, Bedford, MA, USA) and SARTORIUS-BS124S electronic analytical balance (Sartorius, Goettingen, Lower Saxony, Germany) were made to provide ultrapure water and weigh materials, respectively.

## 2.2. Preparation of standard solutions

Reference substances of GRg1, GRe, GRb1, AG, IN, CCM, TEO and HPD were weighed precisely and dissolved into methanol to prepare the mixed stock solutions of reference standards with the concentrations of 109.0 µg/mL, 198.0 µg/mL, 196.0 µg/mL, 398.0 µg/mL, 244.0 µg/mL, 10.1 µg/mL, 160.0 µg/mL, and 308.0 µg/mL, respectively. Then, a series of concentrations of calibration standard solutions were produced by diluting the mixed stock solution with the methanol. The working solutions were all stored at 4 °C in a refrigerator until analysis and filtered through a 0.22 µm membrane before injection.

## 2.3. Preparation of sample solutions

YQJZG (100 mg) was accurately weighed and sonicated (Ultrasonic machine, KO-100DE, Kunshan, China) in methanol (25 mL) for 30 min (100 W, 40 kHz). And then, sample solutions were naturally cooled to room temperature and 0.5 mL of filtered solutions were transferred to a 5 mL volumetric flask, diluted with methanol to scale. Finally, the solution was filtered through a 0.22 µm filter membrane before analysis.

## 2.4. Preparation of negative samples

According to the proportion of the prescription, traditional Chinese medicinal herbs without *Ginseng Radix et Rhizoma* were weighed to make the negative samples based on the preparation method of YQJZG. Then, the negative samples were prepared in accordance with the method elaborated in “preparation of sample solution”. The negative samples of other TCM slices such as *Curcumae Longae Rhizoma*, *Citri Reticulatae Pericarpium*, *Cassiae Semen* and *Typhae Pollen* were made by the same way.

## 2.5. Conditions of UPLC–ESI–MS/MS analysis

Chromatographic analysis was performed on an ACQUITY UPLC system equipped with a XEVO TQ-S triple quadrupole mass spectrometer and an ESI source (Waters, Milford, MA, USA). All target components were separated on an ACQUITY UPLC® HSS T3 (2.1 × 100 mm, 1.8 µm) column maintained at 30 °C. The mobile phase was made up of 0.1% aqueous solution of formic acid (A)-acetonitrile (B). The optimized gradient elution program was used 5%–25% B at 0–1 min, then kept constant within 1–2 min, 25%–33% B at 2–3 min, 33%–35% B at 3–6 min, 35%–95% B at

6–9 min, and maintained with acetonitrile 95% at 9–10 min. The flow rate was 0.3 mL/min, and the injection volume was 2 µL.

The optimized parameters for the MRM method were performed in negative ionization mode with the settings as follows: The ionization voltage of the capillary was set at 3000 V, ion source temperature was set at 150 °C, sheath gas temperature 400 °C, sheath gas flow 800 L/h. Furthermore, other parameters, such as collision energy (CID) and cone-hole voltage for all tested compounds were given Table 1.

## 2.6. Method validation

In this paper, the Chinese Pharmacopoeia (2020 edition) was regarded as the guidance document for this method validation (Chinese Pharmacopoeia Committee, 2020). The specificity, linearity, limit of detection and quantification, stability, accuracy and precision (intra-day precision and inter-day precision) were evaluated during the validation of this analytic method. The specificity of this method was validated by analyzing the sample solutions, mixed standard solutions, and every negative sample solution.

### 2.6.1. Specificity

The sample solution, standard mixed solution and negative sample solutions were separately injected into UPLC–MS/MS under the optimized conditions, and the total ion chromatograms and multi-channel MRM chromatograms of each sample were recorded respectively.

### 2.6.2. Limit of quantification and linearity

To prepare standard solutions, the eight reference compounds were accurately weighed, dissolved, and diluted to appropriate concentrations to establish calibration curves. Linearity was evaluated through the correlation coefficient ( $R^2$ ) value of the calibration curves constructed between peak area ( $y$ ) and the concentration of the component ( $x$ ). Limit of detection (LOD) and limit of quantification (LOQ) were calculated by performing a serial dilution of standard solutions when the signal-to-noise ratios ( $S/N$ ) of analytes were about 3 and 10, respectively.

### 2.6.3. Stability

Stability studies were carried out as a part of the method validation. The same tested solutions, which were prepared and placed at 4 °C, were injected into UPLC–MS/MS at different time points (0, 1, 2, 4, 8, 12, and 24 h).

### 2.6.4. Repeatability and precision

The repeatability was assayed by the analysis of the six parallel sample solutions with the same batch under the same analytical conditions. The investigation of instrument precision was carried out by analyzing the mixed standard solution in six replicate injections under the optimal conditions. The intermediate precision was carried out by different operators on different dates by analyzing

**Table 1**  
Optimized fragment voltage and collision energy for marker components under negative MRM mode.

Analytes	$t_R$ (min)	Precursorion ( $m/z$ )	Product ion ( $m/z$ )	Time of detention (s)	Cone-hole voltage (V)	Collision energy (eV)
GRg1	3.95	847.50	801.50	0.003	80	22
GRe	3.97	945.54	637.31	0.003	80	34
GRb1	7.06	1107.60	179.03	0.003	80	50
TEO	2.64	769.26	314.13	0.025	98	38
IN	2.68	623.20	314.13	0.025	90	30
HPD	3.47	609.16	301.12	0.025	22	18
AG	4.00	491.16	476.15	0.025	12	22
CCM	8.82	367.29	217.15	0.025	50	8

six replications prepared from the same batch. The peak areas of every analytical compound and RSD values were calculated.

### 2.6.5. Accuracy

To investigate the accuracy of this analytical method, six portions of YQJZG from the same batch were weighed, each of which was about 50 mg. Then, a certain amount of control standard solution was added into the samples. Then, the six portions of sample solutions were prepared by referring to the method as described in "Preparation of sample solutions". The RSD was used to measure its accuracy which was also evaluated by a recovery test.

### 2.7. Application to samples

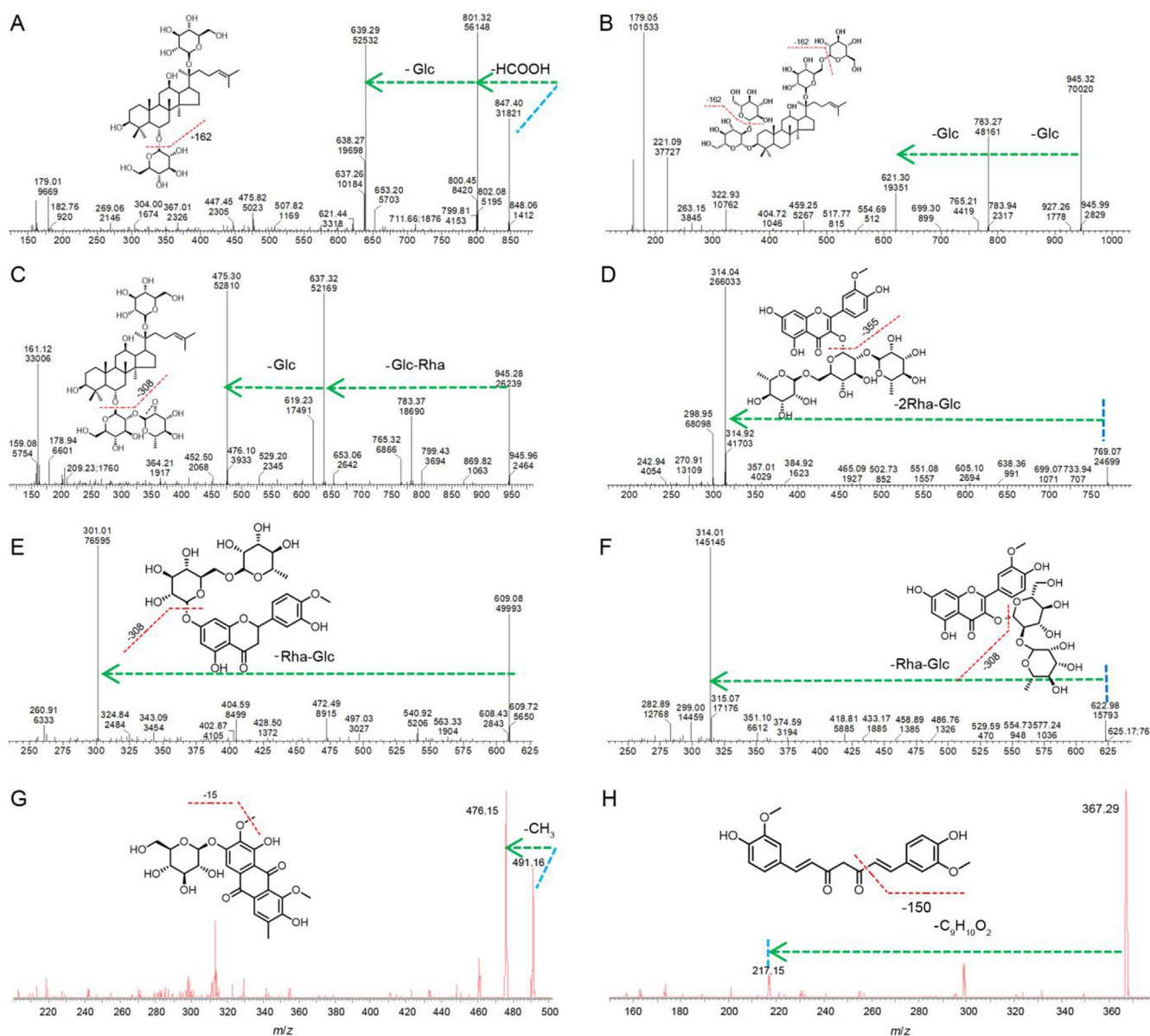
In order to evaluate the applicability of this developed method, three batches of YQJZG manufactured in the laboratory were prepared as the sample solutions in accordance with the method as described in "Preparation of sample solution". They were injected into UPLC-MS/MS under the optimized conditions, respectively.

## 3. Results and discussion

### 3.1. Method development

These compounds contained many phenolic hydroxyl groups. They can easily lose hydrogen protons or bind to negative ions and have better corresponding values in the negative ion mode. Thus, the negative ion mode was selected for MRM detection in this work. All the tested compounds were detected with the formation of  $[M-H]^-$  deprotonated molecule ion and  $[M+HCOOH-H]^-$  adduct ion in negative ESI mode. Among them, seven compounds were detected with  $[M-H]^-$  ions at  $m/z$  945.54 (GRe), 623.20 (IN), 1107.60 (GRb1), 609.16 (HPD), 367.29 (CCM), 769.26 (TEO) and 491.16 (AG). In addition, GRg1 was identified with  $[M+HCOOH-H]^-$  ion at  $m/z$  847.50.

In the  $MS^2$  spectra (Fig. 2), a fragment at  $m/z$  801.50 for GRg1 was confirmed as the most intense fragment ion peak and may have been obtained from  $[M-H]^-$  by losing a molecule of formic acid. Fragments at  $m/z$  637.31, 314.13 and 301.12 were observed



**Fig. 2.**  $MS^2$  spectra of eight marker components (A: GRg1; B: GRb1; C: GRe; D: TEO; E: HPD; F: IN; G: AG; H: CCM) in YQJZG. A–F: manual tuning mode; G–H: automatic tuning mode.

in GRe, IN and HPD as the most intense peaks, which may have been due to  $[M\text{-rhamnose-glucose-H}]^-$ . GRb1 was displayed with a fragment at  $m/z$  179.03 as the most intense peak, which may be attributed to  $[\text{Glucose-H}]^-$ . TEO showed its most powerful product ion peak at  $m/z$  314.13, potentially derived from  $[M\text{-glucose-2rhamnose-H}]^-$ . AG produced its most intense product ion peak at  $m/z$  476.15, possibly owing to  $[M\text{-CH}_3\text{-H}]^-$ . CCM showed its most prominent fragment ions peak at  $m/z$  217.15, potentially derived from  $[M\text{-C}_9\text{H}_{10}\text{O}_2\text{-H}]^-$ . Therefore, the quantification and identification of each compound were employed using the following MRM conditions:  $m/z$  847.50  $\rightarrow$  801.50 for GRg1,  $m/z$  945.54  $\rightarrow$  637.31 for GRe,  $m/z$  1107.60  $\rightarrow$  179.03 for GRb1,  $m/z$  769.26  $\rightarrow$  314.13 for TEO,  $m/z$  623.20  $\rightarrow$  314.13 for IN,  $m/z$  609.16  $\rightarrow$  301.12 for HPD,  $m/z$  491.16  $\rightarrow$  476.15 for AG and  $m/z$  367.29  $\rightarrow$  217.15 for CCM.

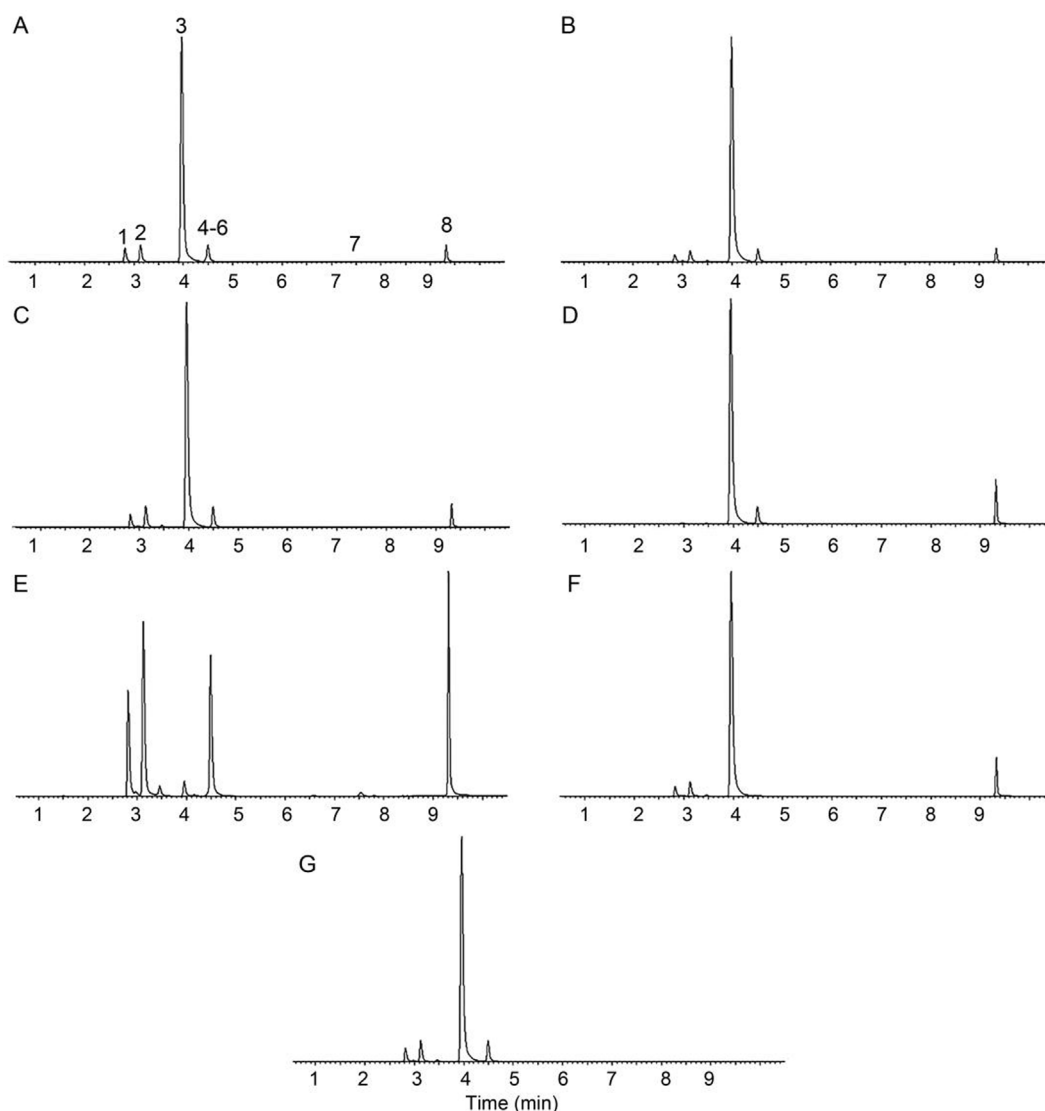
During the development of this method, we used two tuning modes to optimize the chromatographic parameters and look for ion peaks for quantification. As we marked in Fig. 2, manual tuning mode was used for Fig. 2A–F, and automatic tuning mode was used for Fig. 2G and H. We initially wanted to optimize the chromatographic parameters of the eight compounds by using manual tuning mode. In the end, the ion peaks of six compounds (GRg1, GRe, GRb1, TEO, HPD, IN) used for quantification were found through this mode, while AG and CCM were not founded the ion peaks used for quantification through this mode. We tried to optimize the chromatographic conditions of them by using automatic tuning mode and successfully found their ion peaks for quantification.

### 3.2. Method validation

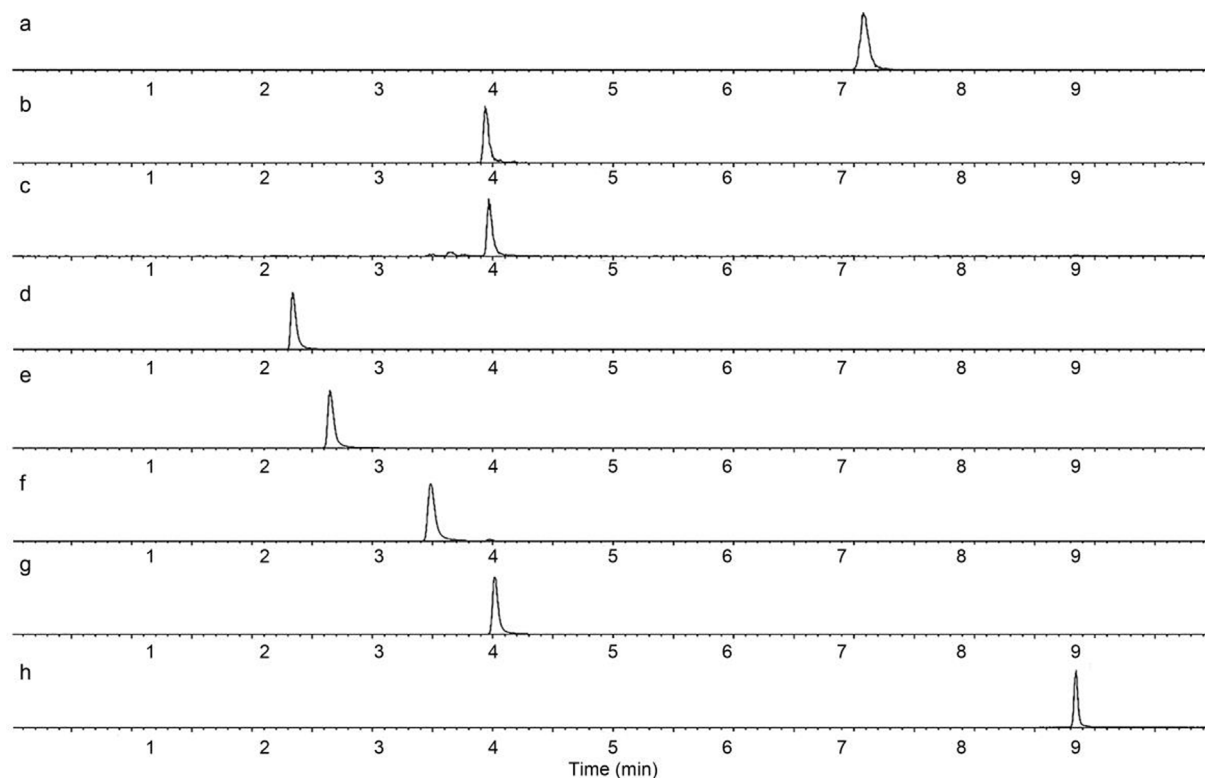
#### 3.2.1. Specificity

Total ion chromatograms of each sample and multi-channel MRM chromatograms of mixed standards solution were recorded, and the results were shown in Fig. 3 and Fig. 4. The experimental results showed that the tested components were not interfered by other impurities in the samples, indicating that the method has good specificity.

Three ginsenosides were difficult to be observed in this total ion chromatogram (Fig. 3). But it did not affect the content determination. Due to the high sensitivity of mass spectrometry, a small



**Fig. 3.** Total ion chromatograms for mixed standard solution, sample solution, and negative sample solutions. (A): mixed standard solution; (B): sample solution; (C): negative sample solution without *Ginseng Radix et Rhizoma*; (D): negative sample solution without *Typhae Pollen*; (E): negative sample solution without *Citri Reticulatae Pericarpium*; (F): negative sample solution without *Cassiae Semen*; (g): negative sample solution without *Curcumae Longae Rhizoma*; 1. TEO; 2. IN; 3. HPD; 4. AG; 5. GRg1; 6. GRe; 7. GRb1; 8. CCM.



**Fig. 4.** Multi-channel MRM chromatography for the mixed standard solution. (a) GRb1 channel; (b) GRe channel; (c) GRg1 channel; (d) TEO channel; (e) IN Channel; (f) HPD channel; (g) AG channel; (h) CCM channel.

number of sample residues often exist in experimental applications. All negative samples' multi-channel MRM chromatograms (Figs. S1–S5) were observed. They were found that the target compounds had some interference, which was caused by the sample residue of the instrument itself, rather than poor specificity. The residual contents are usually three orders of magnitude lower than the normal content determination from the corresponding intensities. When the residual is not very serious, it does not affect the sample determination.

### 3.2.2. Limit of detection, limit of quantification and linearity

The results of the regression analysis for each marker component, along with the LOD and LOQ values, were shown in Table 2. The calibration curves were determined based on the relative content of each compound in YQJZG. All calibration curves showed good linearity with correlation coefficients ( $R^2$ ) within the range from 0.9990 to 0.9998.

### 3.2.3. Stability, precision and accuracy

The sample solutions were stable within 24 h at 4 °C (RSD < 2.86%). These data indicated that this developed method

was reliable and stable for the quantification of marker components in YQJZG (Table 3). Six independent mixed standard solutions were prepared and analyzed for evaluating the instrument precision (RSD < 2.91%). The results of the precision determination were shown in Table 3. The RSD values for the repeatability and intermediate precision were less than 3.54% and 2.88% respectively. According to the results, this quantitative method has good precision and has access to satisfy the requirements of the experiment. As shown in Table 3, the average recovery rates and RSD values of each target component were up to the standards of the Chinese Pharmacopoeia (2020 edition). This analytical method was manifested to be reliable.

### 3.3. Determination of samples

The proposed UPLC-MS/MS method was used to analyze the eight compounds in three batches of YQJZG. Multi-channel MRM chromatograms of sample solutions were recorded (Fig. 5). The contents of marker components in YQJZG were calculated using the regression equations for the peak area versus concentrations. Table 4 showed the contents of marker components in YQJZG.

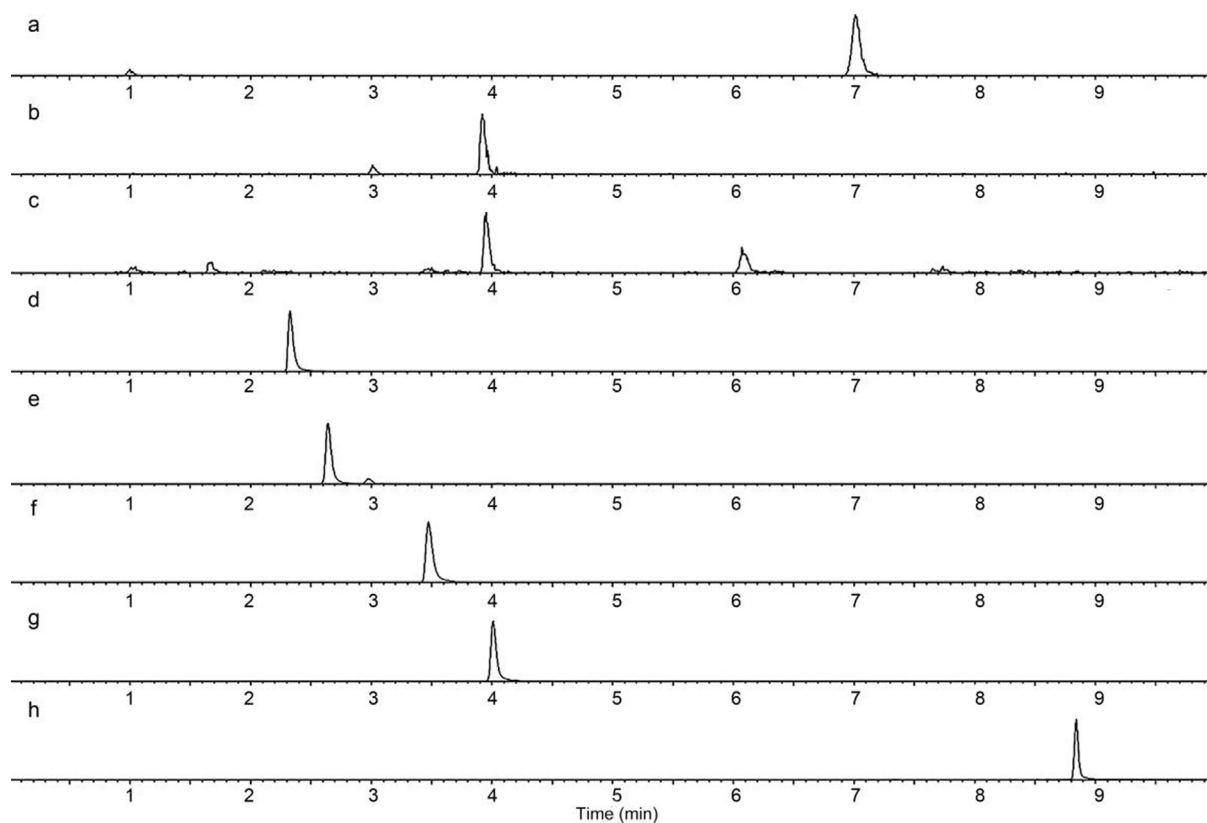
**Table 2**  
Calibration curves and limit of detection for eight marker components in YQJZG.

Analytes	Calibration curve*	$R^2$	Linear range (ng/mL)	LOD (ng/mL)	LOQ (ng/mL)
GRg1	$y = 35.5467x - 41.0527$	0.9998	13.08–104.64	0.18	0.43
GRe	$y = 21.2182x - 83.5767$	0.9996	11.88–118.80	0.15	0.57
GRb1	$y = 58.6352x - 130.663$	0.9996	14.74–132.65	0.11	0.39
TEO	$y = 1027.01x + 956.703$	0.9993	47.47–414.72	0.02	0.08
IN	$y = 1695.25x + 5538.88$	0.9990	35.14–351.36	0.02	0.11
HPD	$y = 1392.21x + 45380.2$	0.9990	492.80–4928.00	0.04	0.22
AG	$y = 3947.57x - 9292.51$	0.9999	15.92–159.20	0.04	0.11
CCM	$y = 446.023x + 17976.6$	0.9991	161.60–1454.40	0.14	0.40

Note: \*In the regression equation  $y = a + b$ , where  $y$  refers to the peak area and  $x$  refers to the concentration of the analytes (ng/mL).

**Table 3**  
Repeatability, precision, accuracy and stability of eight marker components in YQJZG ( $n = 6$ ).

Analytes	Repeatability RSD (%)	Instrument precision RSD (%)	Intermediate precision RSD (%)	Stability RSD (%)	Accuracy	
					Average recovery (%)	RSD (%)
GRg1	3.53	2.14	2.25	2.85	95.69	3.26
GRe	1.97	2.90	1.08	2.67	94.49	3.15
GRb1	2.91	1.91	1.35	1.05	91.08	3.72
TEO	2.15	0.33	2.79	2.43	94.45	3.81
IN	1.75	1.48	2.87	2.53	96.89	3.17
HPD	1.36	0.91	1.46	2.20	93.91	2.01
AG	1.30	1.03	0.17	2.74	92.51	2.15
CCM	1.11	1.34	0.16	2.40	103.89	1.97

**Fig. 5.** Multi-channel MRM chromatography for sample solutions. (a) GRb1 channel; (b) GRe channel; (c) GRg1 channel; (d) TEO channel; (e) IN Channel; (f) HPD channel; (g) AG channel; (h) CCM channel.**Table 4**  
Determination results of three batches of samples.

Analytes	Batch 1 (%)	Batch 2 (%)	Batch 3 (%)	Mean (%)	RSD (%)
GRg1	0.0182	0.0183	0.0179	0.0181	1.43
GRe	0.0125	0.0120	0.0124	0.0123	1.93
GRb1	0.0238	0.0236	0.0233	0.0236	1.19
TEO	0.0344	0.0354	0.0348	0.0349	1.54
IN	0.0369	0.0380	0.0376	0.0375	1.49
HPD	1.0888	1.0776	1.0811	1.0825	0.53
AG	0.0180	0.0191	0.0183	0.0185	3.11
CCM	0.1236	0.1105	0.1055	0.1132	8.27

#### 4. Conclusion

In this study, an accurate and feasible UPLC-ESI-MS/MS method was developed for the determination of eight marker components

in YQJZG, including three triterpenoid saponins without a conjugate system in their structures. This established method was validated in terms of specificity, linearity, stability, repeatability, precision and accuracy. Using this novel method, the run time

for the separation of eight compounds were only 10 min in a single chromatographic run and successfully applied to the content determination of three batches of YQJZG. This novel method can be applied to systematic quality evaluation of YQJZG and can provide certain reference significance for the content determination of multiple types and different polar components in other TCM analogous formulae, especially those with weak ultraviolet absorption, low content and easily interfered by other impurities.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Acknowledgements

This work was supported by the Natural Science Foundation of Beijing Municipality (No. 7192117).

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.chmed.2022.03.001>.

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