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Short communication

A high performance liquid chromatography method for the simultaneous determination of arctiin, chlorogenic acid and glycyrrhizin in a Chinese proprietary medicine

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Abstract

A high performance liquid chromatography (HPLC) method was developed for the simultaneous determination of arctiin, chlorogenic acid and glycyrrhizin in the tablets of a Chinese proprietary medicine named, "Yin Qiao Jie Du Pian". The analysis was performed by a reverse phase gradient elution, using an aqueous mobile phase (containing 0.4% acetic acid and 4.5% tetrahydrofuran) modified by acetonitrile and detection made simultaneously at three wavelengths. The method was validated for specificity, accuracy, precision and limits of detection and quantification. Tablets of seven commercial brands were analyzed and found to contain different amounts of the three bioactive markers. This raised the question of the quality and the efficacy of the products. The method developed can be used for the quality control of "Yin Qiao Jie Du" tablets.

Keywords: Chinese proprietary medicine; Chinese patent formula; Yin Qiao Jie Du tablet; Arctiin; Chlorogenic acid; Glycyrrhizin; High performance liquid chromatography; HPLC

1. Introduction

The fundamental philosophy of traditional Chinese medicine (TCM) is to maintain good health through the restoration of a balance in internal energy or the 'qi' of the body. One way to achieve this balance is through the administration of herbs. In the practice of TCM, the Chinese physician may prescribe an individualized mixture of herbs for a patient, or a Chinese patent formula may be recommended for use. Chinese patent formulae are complex mixtures of herbs that have been used for hundreds of years, and each formula is carefully concocted to provide desirable therapeutic outcomes.

Today, Chinese patent formulae are made readily available to consumers because many of them are manufactured into dosage forms that are easy to administer. Such finished herbal products are also known as Chinese proprietary medicines (CPM). To use the name of a certain Chinese patent formula, manufacturers are obliged to adhere to the specifications on the proportions of herbs indicated in the formula. This is important, as the right proportion of the various herbs in the formula confers its desired therapeutic action. Deviation from the formula may result in a less efficacious product. In some cases, manufacturers may enhance the efficacy of their products by adding additional herbs or even synthetic drugs; this is an acceptable practice as long as clinical trials conducted are able to prove higher efficacy and patient safety, as well. Therefore, the quality and effectiveness of the CPM will depend on the compliance to the specifications and the quality of the raw herbs used. Quality of CPM can be assured through analysis of the constitutive herbs of the CPM. Since Chinese patent formulae are composed of several herbs and there are many constituents in each herb, the analysis of such

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a complex mixture certainly presents a great challenge to the pharmaceutical analysts.

This article focuses on the pharmaceutical analysis of "Yin Qiao Jie Du" (YQJD) tablets. This CPM is commonly used to manage the symptoms of influenza, acute tonsillitis and fever caused by excessive "exogenous heat". The use of YQJD has escalated especially during the recent threat of SARS and avian flu. The tablets are produced from a traditional Chinese patent formula called "Yin Qiao San", which has been used for hundreds of years in China. The formula of "Yin Qiao San" [1] includes the following nine herbs, namely: *Lonicera japonica* Thunb. (flower, 17.86%); *Forsythia suspensa* Vahl (fruit, 17.86%); *Arctium lappa* L. (fruit, 10.71%); *Platycodon grandiflorum* (root, 10.71%); *Mentha arvensis* L. (herb, 10.71%); *Glycine max*. Merill (seed, 8.93%); *Glycyrrhiza uralensis* Fish (root, 8.93%); *Lohphatherum gracile* Brongniart (leaf, 7.14%) and *Schizonepeta tenuifolia* Briq. (herb, 7.14%). However, in Chinese Pharmacopoeia, there are no quality control measures for active ingredients in these formulae and no limits imposed on them either. In this study, the approach to the analysis of the formula is to select major active constituents in the formulation and use them as the bioactive markers. To this end, the three natural product constituents are identified as arctiin, chlorogenic acid and glycyrrhizin (Fig. 1). Arctiin, which comes from the fruit of *Arctium lappa* L., is found to have both anti-inflammatory and free radical scavenging effects [2,3]. Chlorogenic acid, which is the main component in the flower of *Lonicera japonica* Thunb., is also known to possess anti-inflammatory and free radical scavenging properties [4–6]. While glycyrrhizin, which is derived from the root of *Glycyrrhiza uralensis* fish, is reported to exhibit anti-viral and hepatoprotective properties [7,8].

Currently, there are several analytical methods available for the determination of the active ingredients in YQJD tablets [9–15]. However, these reported methods are only able to determine one active ingredient, even though there are several biomarkers in YQJD tablets. Therefore, this study aims at developing a new HPLC method that is able to quantify the three bioactive markers simultaneously in different brands of YQJD tablets. The outcome of the study will provide a validated HPLC method for the analysis of YQJD tablets. The results of the analysis will give an indication of the quality of the products manufactured by the various pharmaceutical companies.

2. Experimental

2.1. Materials and chemicals

Seven different brands of "Yin Qiao Jie Du" tablets (brand A–G; where G1 and G2 are two different batches of brand G) were purchased from Chinese pharmacy stores in Singapore. Chlorogenic acid was purchased from Sigma (St. Louis, MO, USA) while glycyrrhizin was purchased from TCI (Tokyo, Japan). Arctiin was extracted and purified from the crude fruit of *Arctium lappa* L. (purchased from a local Chinese

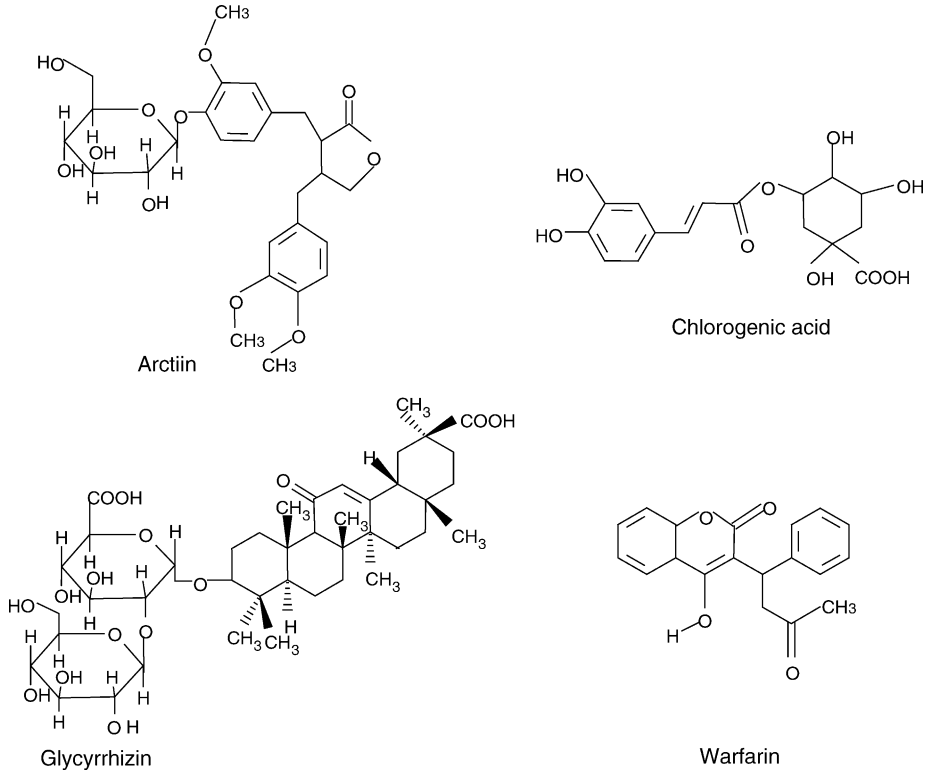

Fig. 1. Structures of bioactive markers and the internal standard warfarin.

pharmacy store) in our own lab. The authenticity of arctiin was confirmed by using UV, IR, NMR and HPLC with a photodiode array detector and comparing the data and melting point with those reported in literature [16]. The internal standard warfarin was also obtained from Sigma. Acetonitrile and tetrahydrofuran (THF, HPLC grade) were supplied by BDH (Poole, UK), and AR grade glacial acetic acid was obtained from Mallinckrodt (Paris, KY, USA). Ultrapure water with a resistivity greater than 18 mΩ was collected from a certified Millipore Milli-Q system (Bedford, MA, USA).

2.2. Liquid chromatographic conditions

HPLC analysis was carried out on a HP-1050 system (Irvine, CA, USA) equipped with a HP-1050 quaternary pump, a degasser, a photodiode array detector and a HP-1100 autosampler. The system was controlled by an AST Bravo MS5200m personal computer (Irvine, CA, USA) using HP ChemStation for LC 3D software (Rev. A.05.04.). Deionized water, containing 0.4% acetic acid and 4.5% THF, modified with acetonitrile was used as the mobile phase. The analysis was carried out on a Phenomenex column (Lichrosorb 10 RP-18, 250 × 4.0 mm, 10 μm, Torrance, CA, USA) by gradient elution beginning with a mobile phase composition of 5:95 (aqueous phase:acetonitrile) and gradually changed to 25:75 in the first 15 min. For the next 35 min, the composition of the mobile phase was changed from 25:75 to 60:40. The injection volume was 10 μL. Then the column was re-equilibrated for another 10 min, using a mobile phase composition of 5:95 (aqueous phase: acetonitrile) before the next injection. The elution was carried out at ambient temperature (25 °C) and the flow rate was maintained at 1.0 mL/min throughout the elution. Detection was made simultaneously at three different wavelengths, viz. 254, 280 and 326 nm, according to the wavelength at maximum absorbance (λ_{max} values) of the bioactive markers.

2.3. Preparation of standard solutions

One hundred milligrams each of arctiin, chlorogenic acid and glycyrrhizin were accurately weighed and placed in a 100 mL volumetric flask. Aqueous ethanol (50% (v/v)) was used as the solvent to give a 1 mg/mL mixed standard solution. Ten milligrams of warfarin were accurately weighed and transferred into a 25 mL volumetric flask to obtain a 0.4 mg/mL internal standard solution using 50% (v/v) aqueous ethanol. An appropriate quantity of the standard solution were mixed with 0.5 mL internal standard solution in separate 10 mL volumetric flasks and made up to volume with aqueous ethanol to give a series of standard solutions (0.01, 0.05, 0.10, 0.25, 0.50 and 0.95 mg/mL) for plotting the calibration curve.

2.4. Preparation of sample solutions

Ten tablets of each brand A–G of YQJD tablets (the equivalent of one daily dosage) were powdered by an electrical blender and sieved through a #8 mesh sieve. The powder was transferred into a 100 mL volumetric flask and 50 mL of 50% (v/v) ethanol was added. The mixture was sonicated in a water bath (maintained at room temperature) for 50 min. The mixture was filtered under vacuum where the residue was extracted again by sonification using 40 mL 50% (v/v) ethanol for another 30 min. The resulting mixture was filtered again, and the residue was washed with 10 mL 50% (v/v) ethanol. The filtrate from the second extract was combined with that of the first extract and aqueous ethanol was added to give 100 mL as stock solution in a 100 mL volumetric flask. Internal standard solution (0.05 mL) was added into a 10 mL volumetric flask before adding the sample solution, which was filtered through a 4.5 μm Millipore filter membrane (Bedford, MA, USA). The resultant filtrate was used as the sample solution for HPLC analysis. Eight sample solutions were prepared following the above procedures.

2.5. Preparation of solutions for recovery test

Ten YQJD tablets from brand C were powdered by electric blender and sieved through a #8 mesh sieve. The powder was transferred into a 100 mL volumetric flask together with 0.5 mL of the mixed standard solution and 49.5 mL of 50% (v/v) aqueous ethanol. The resultant mixture was sonicated in a water bath (maintained at room temperature) for 50 min and filtered under vacuum. The residue was extracted again using 40 mL of 50% (v/v) ethanol for another 30 min. The extract was filtered, and the residue was washed with 10 mL of aqueous ethanol. The filtrate from the second extract was combined with that of the first extract and aqueous ethanol was added to give 100 mL as stock solution in a 100 mL volumetric flask. The internal standard solution (0.5 mL) was added to a 10 mL volumetric flask before adding the sample solution, which was filtered through a 4.5 μm Millipore filter membrane. The resultant filtrate was used as the sample solution for HPLC analysis to calculate the recovery. This procedure was repeated using 2.5, 5.0 and 10.0 mL of the mixed standard solution and the control was performed without the addition of the mixed standard solution. The recovery of the bioactive markers was determined as the difference between samples without addition of the compounds and samples in which the different amounts of marker compounds (0.5, 2.5, 5.0, 10.0 mg) were added. The original drug concentrations present in the control were subtracted from the total concentration, thus only the added drug was determined and compared with the known added amounts of marker compounds to calculate the recovery.

3. Results and discussion

3.1. Method development for the HPLC analysis

A common limitation of multiple component analysis is the low sensitivity of detection for some of the analytes under

a selected single monitoring wavelength. Very often, not all the components are detectable to the same extent at a given wavelength due to the different chromophoric characteristics of the analytes. However, with a photodiode array detector, detection at more than one wavelength at the same time is possible. In this study, a HPLC method was successfully developed to analyze multiple components in the YQJD tablets.

The λ_{max} value of each of the bioactive markers was determined and used as the wavelength of detection. Hence, the three wavelengths chosen for maximum detection were 254 nm for glycyrrhizin, 280 nm for arctiin and 326 nm for chlorogenic acid. Warfarin was selected to be used as the internal standard in the HPLC analysis to avoid overlapping with the peaks from the various constituents of YQJD tablets.

The initial separation of the extracts from YQJD tablets was carried out on a Lichrosorb 10 RP-18 column using a mixture of methanol and water as the mobile phase. Good separation was not achieved although a gradient elution method was employed. Acidification of the mobile phase using acetic acid was found to be able to improve the separation. This could be attributed to the lesser extent of ionization of chlorogenic acid, glycyrrhizin and warfarin at the acidic pH, thus increasing their retention on the column. However, under this condition, chlorogenic acid was still not separated from the other components. Changing the modifier of the mobile phase from methanol to acetonitrile was only able to improve the separation marginally, but there was still some overlapping between the peak of chlorogenic acid and its adjacent peaks. In order to increase the eluting power, 4.5% (v/v) tetrahydrofuran (THF) was added into the acidified mobile phase. A gradient elution was subsequently carried out beginning from the aqueous phase to modifier ratio of 5:95 (aqueous phase:acetonitrile) and gradually switching to a ratio of 25:75 during the first 15 min. Chlorogenic acid was found

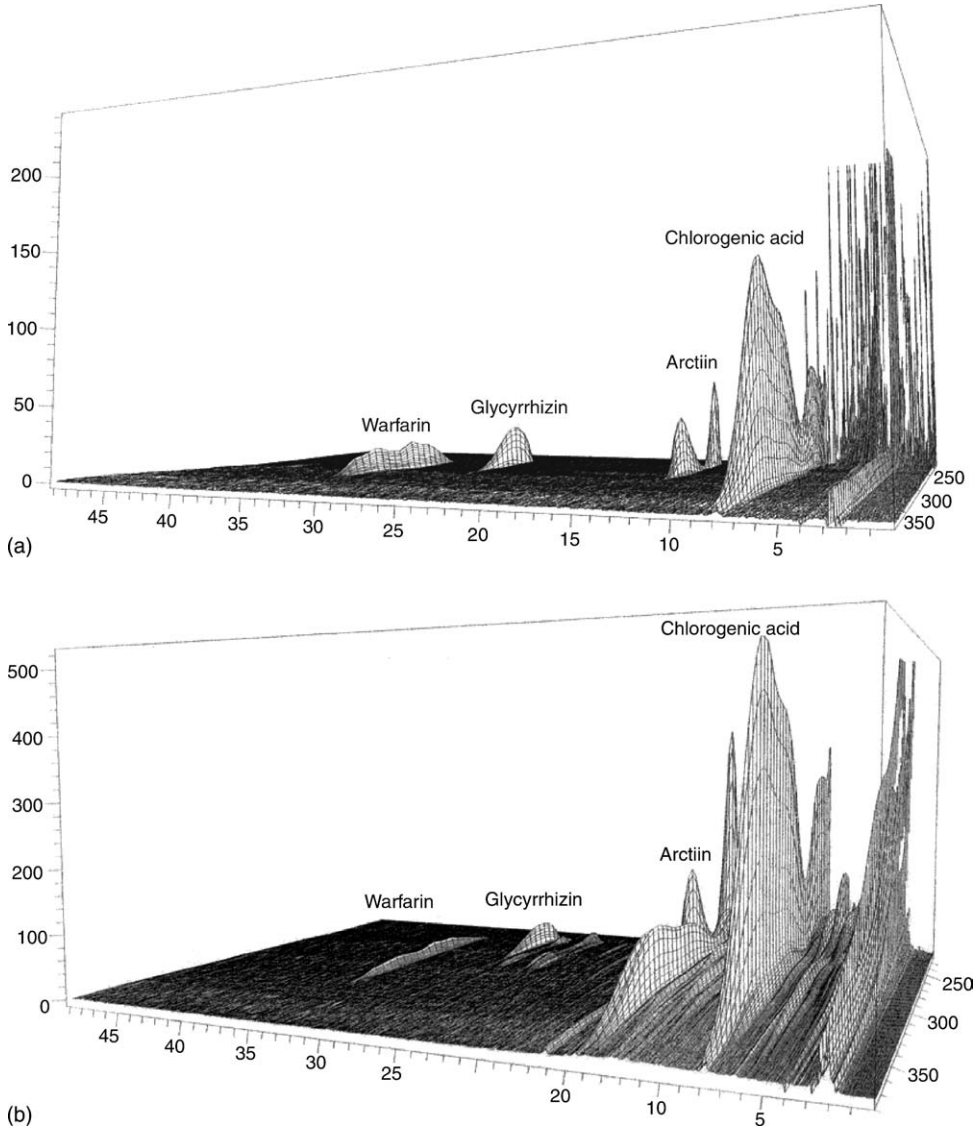

Fig. 2. (a) HPLC chromatogram and UV 3D spectra of the bioactive markers and internal standard (X, 0–50 min; Y, −3.3 to 242.9 mAU; Z, 210–380 nm); (b) HPLC chromatogram and UV 3D spectra of a brand of YQJD tablet containing the internal standard (X, 0–50 min; Y, −9.6 to 535.8 mAU; Z, 210–380 nm).

Table 1
Table showing the data of system suitability testing

Analytes	Capacity factor (K')	Theoretical plates[a] (N)	Tailing factor (T)	Resolution (R_s)	Selectivity (α)
Chlorogenic acid	2.0	8802	0.9	43.9	2.4
Arctiin	4.8	34008	1.1	69.3	2.0
Glycyrrhizin	9.7	68871	1.1	23.4	1.2
Warfarin	12.0	53961	1.0		

[a] Calculated as $N = 5.54\,(t_r/t_w)^2$.

to separate from the other components under this gradient elution profile. Subsequently, gradient elution was continued from the ratio of 25:75 to 60:40 in the following 35 min to ensure that all the components with different polarities were eluted out. The use of a buffer system of sodium dihydrogen phosphate was attempted but did not give better separation, and hence was not adopted in the final method. Under the optimized chromatographic conditions, good separation of the bioactive markers and the internal standard was achieved, with the retention times of chlorogenic acid, arctiin, glycyrrhizin and warfarin determined as 8.5 ± 0.1 min, 16.2 ± 0.1 min, 31.6 ± 0.1 min and 38.1 ± 0.1 min, respectively. The chromatogram of a product together with the 3D spectra of the constituents is shown in Fig. 2b. With the optimized chromatographic conditions, chlorogenic acid, arctiin, glycyrrhizin and the internal standard warfarin were found to be sufficiently well resolved for quantification. The system was tested for suitability prior to the analysis (Table 1). The resolution is calculated as $R_s = 1.18(t_2 - t_1)/(W_{0.5,1} + W_{0.5,2})$, where t_1 and t_2 are the retention times for two peaks, respectively. $W_{0.5,1}$ and $W_{0.5,2}$ are their bandwidths at half height of peaks.

3.2. Method validation

The analytical method described above was used to analyze the YQJD tablets. This method was validated for its specificity, linearity, precision, accuracy, limit of detection and limit of quantification with the following results.

The retention times and ultraviolet (UV) absorption spectra of the eluted peaks from the samples were compared with those obtained from the standards. The retention times and the UV spectra of the eluted bioactive markers from the samples agreed well with those of the standards (Fig. 3), indicating the identity and purity of the peaks eluted from the samples. Therefore, the specificity of the method was validated.

For quantification of the bioactive markers, a calibration curve for each marker was constructed and tested for linearity. The peak ratios between bioactive markers at different concentrations and internal standard are determined and shown in Table 2. The plot of peak ratio (Y) against the concentration (X, mg/mL) for each of the bioactive markers was evaluated using linear regression analysis. The regression equations and correlation coefficients (R^2) of arctiin, glycyrrhizin and chlorogenic acid were derived as $Y = 18.521X + 0.0967$ ($R^2 = 0.9993$), $Y = 15.287X + 0.001$ ($R^2 = 1.0000$) and $Y = 84.214X + 0.001$ ($R^2 = 0.9992$), respectively. All the calibration graphs were constructed in the concentration range of 0.01–0.95 mg/mL.

The intra-day and inter-day analyses of arctiin, chlorogenic acid and glycyrrhizin were demonstrated to show excel-

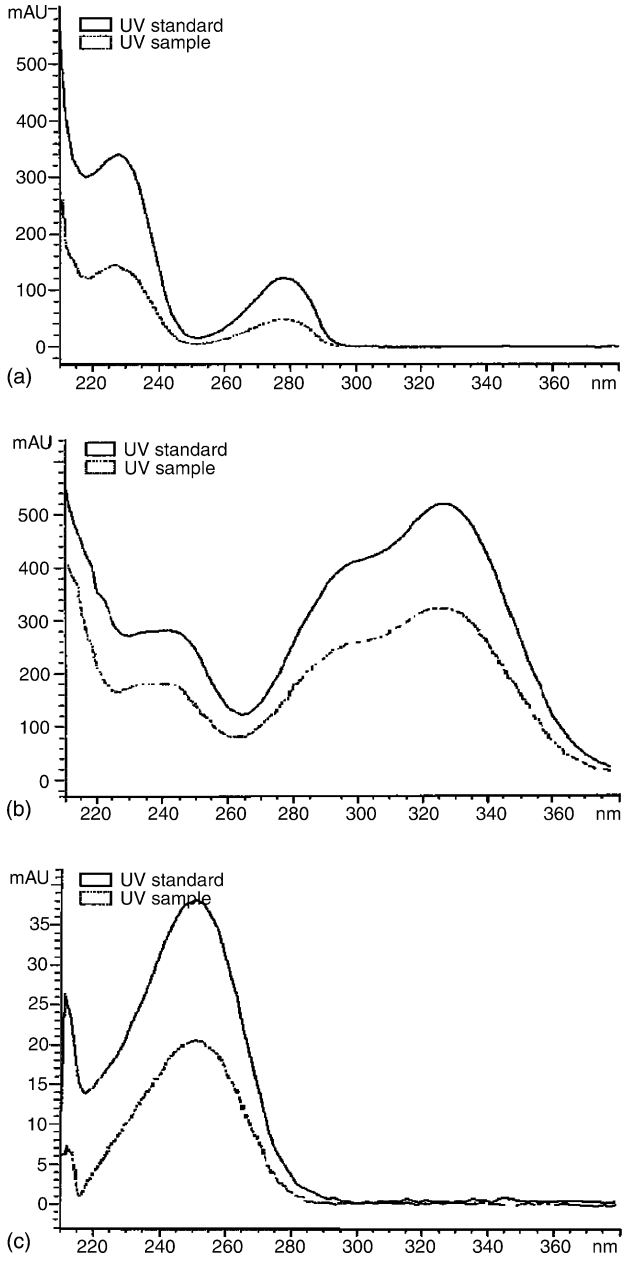

Fig. 3. Overlay of UV spectra of the bioactive markers in the samples and standards at the same retention time: (a) Arctiin; (b) Chlorogenic acid; (c) Glycyrrhizin.

Table 2
The peak ratio between the bioactive markers and the internal standard

Bioactive markers	Concentration (mg/mL)	Peak ratio
Arctiin	0.01	0.164
	0.05	0.945
	0.1	2.051
	0.25	5.007
	0.5	9.129
	0.95	17.732
Chlorogenic acid	0.01	0.793
	0.05	3.456
	0.1	8.053
	0.25	22.698
	0.5	41.861
	0.95	79.781
Glycyrrhizin	0.01	0.161
	0.05	0.735
	0.1	1.555
	0.25	3.862
	0.5	7.583
	0.95	14.544

lent method precision. The precision of the analyses were expressed as relative standard deviations (R.S.D.), which ranged between 0.01 and 0.53% for intra-day analysis; and between 0.12 and 0.80% for inter-day analysis (Table 3). The standard deviation of the retention times of arctiin, chlorogenic acid and glycyrrhizin were found to be 0.13, 0.05 and 0.12 min, respectively ($n = 5$).

The sample preparation procedure was evaluated by the percentage of recovery of the bioactive markers added to the sample of YQJD tablets before extraction. Recoveries were calculated as the percentages of amount found in the sample solution, which were spiked with the known amount of the markers (Table 4). The recovery of all three bioactive markers was excellent with more than 95% of the compounds being recovered in all cases.

The limit of detection (LOD) and the limit of quantification (LOQ) were calculated based on the standard deviation of the response (σ) and the slope of the calibration curve (S) at levels approaching the lower limits using the following equations: $\mathrm{LOD} = 3.3(\sigma/S)$ and $\mathrm{LOQ} = 10(\sigma/S)$. The standard deviation of the response was determined based on the standard deviation of the measurement of spectroscopic blank signal of 10 blank injections, which contained internal standard only. The LOD results for each of the standard compounds were found to be 1.22 ng for arctiin, 0.27 ng for chlorogenic acid and 1.48 ng for glycyrrhizin. The LOQ results were determined to be 3.69 ng for arctiin, 0.81 ng for chlorogenic acid and 4.47 ng for glycyrrhizin. Among the three bioactive markers, chlorogenic acid appeared to be the most sensitive, in terms of UV detection. This is attributed to the conjugation between the catechol and the enone group within its chemical structure. This conjugation gave rise to increase in absorptivity, and hence, better detection at low concentrations. Glycyrrhizin, on the other hand, does not have a strong chromophore, hence its UV absorbance was generally reduced and detection weakened. However, this was compensated by the abundance of glycyrrhizin present in the preparations making its detection discernible in the chromatograms.

Table 3
Intra-day ($n = 5$) and inter-day ($n = 4$) precision of HPLC analysis of arctiin, chlorogenic acid and glycyrrhizin

Bioactive markers	Concentration (mg/mL)	R.S.D. (%)	
		Intra-day	Inter-day
Arctiin	0.05	0.33	0.43
	0.10	0.01	0.51
	0.25	0.01	0.17
Chlorogenic acid	0.05	0.32	0.80
	0.10	0.20	0.50
	0.25	0.07	0.49
Glycyrrhizin	0.05	0.53	0.64
	0.10	0.09	0.12
	0.25	0.06	0.20

Table 4
Recovery tests for arctiin, chlorogenic acid and glycyrrhizin ($n = 5$)

Bioactive markers	Amount added (mg)	Amount found (mg)	Recovery (%)
Arctiin	0.50	0.48	96.0
	2.50	2.49	99.6
	5.00	4.87	97.4
	10.00	9.91	99.1
Chlorogenic acid	0.50	0.48	96.0
	2.50	2.45	98.0
	5.00	4.94	98.8
	10.00	9.96	99.6
Glycyrrhizin	0.50	0.48	95.6
	2.50	2.45	98.0
	5.00	5.01	100.2
	10.00	9.85	98.5

3.3. Determination of the bioactive markers in the seven brands of YQJD tablets

The optimized chromatographic method was used to determine the concentration (mg/mL) of the three bioactive markers in the seven brands of YQJD tablets, and the results are presented in Table 5. All the seven products were accompanied by product inserts that reflected the same patent formula, the "Ying Qiao San" as described in the Chinese Pharmacopoeia [1]. In a few of the products, additional ingredients (eg. antelope) were included to the standard Chinese patent formula. As such, it is not unreasonable to expect that all the products should display the same content profile for the three bioactive markers. However, the results of the analyses showed that there was a wide variation in the content of the three bioactive markers in each brand of the tablets as demonstrated in Fig. 4. Product A was found to contain the highest amount of arctiin and chlorogenic acid, while product E contained the most glycyrrhizin. Arctiin and gly-

Table 5
Concentrations of arctiin, chlorogenic acid and glycyrrhizin in YQJD sample solution (mean ± S.D., $n = 5$)

Sample	Arctiin (mg/mL)	R.S.D. (%)	Chlorogenic acid (mg/mL)	R.S.D. (%)	Glycyrrhizin (mg/mL)	R.S.D. (%)
A	0.439 ± 0.003	0.78	0.308 ± 0.002	0.49	0.121 ± 0.002	1.57
B	0.232 ± 0.003	1.12	0.048 ± 0.002	3.55	0.077 ± 0.001	1.17
C	0.066 ± 0.000	0.45	0.025 ± 0.000	1.19	0.036 ± 0.000	1.12
D	0.000 ± 0.000	0.00	0.075 ± 0.001	1.59	0.000 ± 0.000	0.00
E	0.313 ± 0.007	2.30	0.264 ± 0.003	0.95	0.204 ± 0.002	0.74
F	0.216 ± 0.001	0.28	0.051 ± 0.001	0.98	0.074 ± 0.000	0.41
G1	0.056 ± 0.001	1.07	0.041 ± 0.000	0.98	0.056 ± 0.001	1.07
G2	0.366 ± 0.002	0.55	0.157 ± 0.002	1.15	0.149 ± 0.001	0.81

cyrrhizin were not detected at all in product D. This suggested that the manufacturer might not have added the fruit of *Arctium lappa* L. and the root of *Glycyrrhiza uralensis* fish in the manufacturing of product D. It was interesting to note that G1 and G2, which were two batches of the same YQJD product manufactured from the same factory, also showed considerable variation in the content of the markers between them.

It is obvious from the above results that there is a great disparity in terms of the quantity of the three bioactive markers found among the seven different brands of YQJD tablets being analyzed. In addition, the two batches of the same preparation (sample G1 and G2), produced by the same manufacturer, also showed inconsistent amount of the three markers. It is, therefore, questionable as to whether all the eight herbal products will give rise to the same efficacy.

The disparity in the amount of the markers present in the tablets may be attributed to several factors. The quality of the individual crude herbs used may not be the same and, as a result, the content of the bioactive markers will differ appreciably. This is in turn reflected in the finished product. In addition, some of the manufacturers may not have adopted sufficiently good manufacturing practice (GMP) and, as a result, there is inconsistency in the content of the bioactive markers present in different brands of the same CPM, as well as variation from batch to batch. Currently, there are no limits imposed on arctiin, chlorogenic acid, glycyrrhizin or other active ingredients in Chinese Pharmacopoeia or other regulatory documents. However, this should be implemented in the future to ensure the quality and safety of herbal medicines.

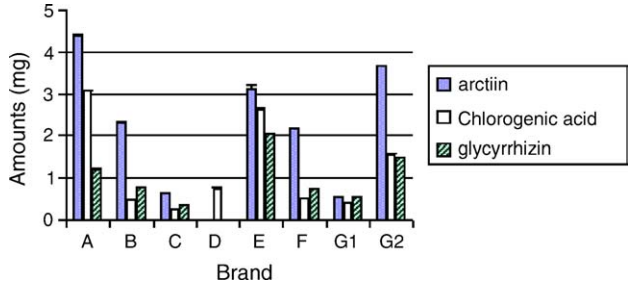

Fig. 4. The amounts in milligrams (mean ± S.D.) of arctiin, chlorogenic acid and glycyrrhizin in one YQJD tablet.

4. Conclusion

It is demonstrated that the sample preparation and HPLC method that are developed in this study are applicable to the simultaneous analysis of arctiin, chlorogenic acid and glycyrrhizin in YQJD tablets. The method has been validated and can be used, with reasonable confidence, for both identification and quantification of the three bioactive markers found in YQJD tablets. The results of the analysis on the seven brands of the CPM have shown that the amount of each of the three bioactive markers varies considerably among the products from the different manufacturers. This raised the question of whether the various YQJD tablets would exhibit equivalent efficacy. The analytical method developed can be used for the quality control of "Yin Qiao Jie Du" tablets. Nevertheless, the onus must be placed on the manufacturers to ensure that their products are processed according to good manufacturing practice. This will help to assure access to good quality products with minimal inter-product variation. As the use of CPM is gaining popularity across different cultures through easy accessibility, it is important that good quality products are available to maximize therapeutic outcomes and consumers' safety.

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