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ORIGINAL ARTICLE

Jinhua Qinggan Granule UHPLC-Q-extractive-Orbitrap-MS assay: Putative identification of 45 potential *anti*-Covid-19 constituents, confidential addition, and pharmacopoeia quality-markers recommendation

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Abstract

The study combined UHPLC-Q-Orbitrap-MS analysis with authentic standards, to create a novel strategy for isomers recognition and putative identification. Through the strategy, *anti*-Covid-19 *Jinhua Qinggan* Granule was found to comprise 28 isomers and 45 potential *anti*-Covid-19 constituents. The detection of three constituents (Danshensu, cryptotanshin, and tanshinone IIA) suggests Danshen as confidential additive. Based on this, 6 constituents are recommended as quality-marker candidates, including chlorogenic acid, acteoside, peimisine, baicalein, licoricesaponin H2, and tanshinone IIA. Obviously, the study can not only help the public to really understand the Granule's formula and chemistry, but also facilitate its Pharmacopoeia collection in future.

Keywords: Isomer recognition, Pharmacopoeia collection, Q-marker, Quality-control, Three Chinese medicines and three Chinese recipes

1. Introduction

Nowadays, Covid-19 has not come to the end around the world. Traditional Chinese medicines (TCM), however, has been proven to play more and more important role in personal protection, especially "three Chinese medicines and three Chinese recipes". The so-called "three Chinese medicines" refer to *Jinhua Qinggan* Granule (金花清感顆粒, Fig. 1), *Lianhua Qingwen* Capsule (連花清瘟膠囊), and *Xuebijing* Injection (血必净註射液); while three Chinese recipes include *Qingfei Paidu* Decoction (清肺排毒湯), *Huashi Baidu* Recipe (化濕敗毒方), and *Xuanfei Baidu* Recipe (宣肺敗毒方). All of these are approved by National Health Commission (NHC) of China for Covid-19 prevention and treatment in 2020 [1,2]. Of these, *Jinhua Qinggan* Granule was reported to attenuate acute lung injury; thus it could prevent the deterioration, to benefit mild and moderate Covid-19 patients [3,4]. At present, it is playing a key role for Covid-19 prevention for Chinese (especially elder Chinese).

However, *Jinhua Qinggan* Granule lacks a specific and systematic study concerning its constituents until now. The ignorance of constituents has hindered the clinical application, to great extent. By comparison, *Lianhua Qingwen* Capsule and *Qingfei Paidu* Decoction have been extensively studied for their constituents [5,6]. These chemical studies apparently have benefited their clinical applications. Therefore, it now has become urgent to identify the constituents of *Jinhua Qinggan* Granule.

On the other hand, *Jinhua Qinggan* Granule is a highly complicated mixture. According to the declaration of NHC official, the Granule is made up with 12 Chinese medicine materials, including

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Fig. 1. The photo of Jinhua Qinggan Granule (The below indicates package information).

Lonicera japonica Thunb. (Jinyinhua, 金銀花), Gypsum Fibrosum (Shigao, 石膏), *Ephedra sinica* Stapf (Mahuang, 麻黃), *Prunus armeniaca* L. (Kuxingren, 苦杏仁), *Scutellaria baicalensis* Georgi (Huangqin, 黃芩), *Forsythia suspensa* (Thunb.) Vahl (Lianqiao, 連翹), *Fritillaria thunbergii* Miq. (Zhebeimu, 浙貝母), *Anemarrhena asphodeloides* Bunge (Zhimu, 知母), *Arctium lappa* L. (Niubangzi, 牛蒡子), *Artemisia annua* L. (Qinghao, 青蒿), *Mentha canadensis* L. (Bohe, 薄荷), and Glycyrrhiza inflate Batalin (Gancao, 甘草). Of these Chinese medicine materials, Jinyinhua and mineral Shigao are regarded as the "Monarch" (君藥), according to the *Monarch-Minister-Assistant-Guide* theory in TCM; Gancao however acts as the role of "Guide" (使藥).

In a word, *Jinhua Qinggan* Granule contains various Chinese medicine materials. Thus, its chemical identification would be a highly challenging work. The conventional HPLC-UV method (including HPLC-DAD) may be incompetent for this. A typical instance is the previous work which identified only 6 constituents [7].

The study thereby used ultra-high performance liquid chromatography-quadrupole-Orbitrap mass spectrometry (UHPLC-Q-Orbitrap MS/MS) analysis, an emerging technology, to identify the constituents. Compared with the HPLC-UV technology, the UHPLC-Q-Orbitrap MS/MS is undoubtedly much more effective, for its high MS spectra resolution.

Before analysis, the present study has already built a library of authentic standards (including isomers). Through comparison with authentic standards in retention time (R.T.) value, molecular ion peak, and MS fragmenting elucidation, the study was able to putatively identify the constituents and recognize isomers. Thus, it can provide highly reliable information.

It is worth mentioning that, *Jinhua Qinggan* Granule was developed as an emergency *anti*-viral medicine, to treat H1N1 influenza pandemic in 2009 [3,8]. Therefore, it has not been collected in Chinese Pharmacopoeia until now. Because of this, it real formula may be confidential. In other words, the Granule may comprise other Chinese medicine materials, besides the twelve mentioned above. The mystery however will be ultimately uncovered in the study.

Finally, the present study tried to recommend quality-marker (Q-marker) candidates for Pharmacopoeia Committee. It would promote a possibility, that is, *Jinhua Qinggan* Granule will be listed as a medicine against infectious viruses (e.g., Covid-19) in Chinese Pharmacopoeia in the future.

2. Materials and methods

2.1. Medicine materials

Jinhua Qinggan Granule was manufactured by Changxieju Pharmaceutical Co., LTD (Beijing, China). The lot number was 20211206, the expiring date was 13th, Nov. 2024 (Fig. 1 below).

2.2. Chemicals

Astragalin (kaempferol 3-*O*-glucoside, Cas. 480-10-4, $C_{21}H_{20}O_{11}$, 448.38, 97%), oroxin A (baicalein 7-*O*-glucoside, Cas. 57396-78-8, $C_{21}H_{20}O_{10}$, 432.38, 97%), mangiferin (Cas. 4773-96-0, $C_{19}H_{18}O_{11}$, 422.34, 97%), luteolin 7-*O*-glucuronide (29741-10-4, $C_{21}H_{18}O_{12}$, 462.36, 97%), ethyl caffeate (Cas. 102-37-4, $C_{11}H_{12}O_4$, 208.12, 97%), scutellarin (Cas. 27740-01-8, $C_{21}H_{18}O_{12}$, 462.37, 97%), 6-gingerol (Cas. 23513-14-6, $C_{17}H_{26}O_3$, 293.39, 97%), methyl benzoate (Cas. 93-58-3, $C_8H_8O_2$, 136.148, 97%), rutin (Cas. 153-18-4, $C_{27}H_{30}O_{16}$, M.W. 610.518, 98%), baicalein (Cas. 491-67-8, $C_{15}H_{10}O_5$, 270.24, 97%), wogonin (Cas. 632-85-9, $C_{16}H_{12}O_5$, 284.26, 97%), chlorogenic acid (Cas. 327-97-9, $C_{16}H_{18}O_9$, M.W. 354.31, 98%), isoquercitrin (Cas. 482-35-9, $C_{21}H_{20}O_{12}$, M.W. 464.38, 98%), isochlorogenic acid C (4,5-*O*-dicaffeoylquinic acid, Cas. 57378-72-0, $C_{25}H_{24}O_{12}$, M.W. 516.45, 98%), vanillic acid (Cas. 121-34-6, $C_8H_8O_4$, M.W. 168.15, 98%), luteoloside (Cas. 5373-11-5, $C_{21}H_{20}O_{11}$, M.W. 448.38, 98%), and salidroside (Cas. 10338-51-9, $C_{14}H_{20}O_7$, 300.304, 97%) were obtained from Chengdu Alfa Biotechnology Co., Ltd (Chengdu, China).

18β-Glycyrrhetinic acid (Cas. 471-53-4, $C_{30}H_{46}O_4$, M.W. 4470.7, 98%), cosmosiin (apigenin 7-*O*-glucoside, Cas. 578-74-5, $C_{21}H_{20}O_{10}$, 432.4, 98%), licoricesaponin H2 (Cas. 135815-61-1, $C_{42}H_{62}O_{16}$, 822.9, 98%), liquiritin (Cas. 551-15-5, $C_{21}H_{22}O_9$, 418.4, 98%), quinic acid (Cas. 77-95-2, $C_7H_{12}O_6$, M.W. 192.2, 98%), rhein (Cas. 478-43-3, $C_{15}H_8O_6$, 284.2, 98%), cryptotanshinone (35825-57-1, $C_{19}H_{20}O_3$, 296.4, 98%), scoparone (Cas. 120-08-1, $C_{11}H_{10}O_4$, 206.2, 98%), and tanshinone IIA (Cas. 568-72-9, $C_{19}H_{18}O_3$, 294.4, 98%) were from Shaanxi Herbest Co. Ltd. (Boji, China).

Acteoside (verbascoside, Cas. 61276-17-3, $C_{29}H_{36}O_{15}$, M.W. 624.59, 98%), isoviolanthin (Cas. 40788-84-9, $C_{27}H_{30}O_{14}$, M.W. 578.519, 98%), isoliquiritigenin (Cas. 961-29-5, $C_{15}H_{12}O_4$, M.W. 256.253, 98%), formononetin (Cas. 485-72-3, $C_{16}H_{12}O_4$, M.W. 268.264, 98%), 1,3-*O*-dicaffeoylquinic acid (Cas. 19870-46-3, $C_{25}H_{24}O_{12}$, 516.455, 97%), 3,4-dicaffeoylquinic acid (3,4-*O*-dicaffeoylquinic acid, Cas. 14534-61-3, $C_{25}H_{24}O_{12}$, 516.455, 97%), pectolinarigenin (Cas. 520-12-7, $C_{17}H_{14}O_6$, 314.29, 97%), neomangiferin (Cas. 64809-67-2, $C_{25}H_{28}O_{16}$, 584.48, 97%), diosmin (Cas. 520-27-4, $C_{28}H_{32}O_{15}$, 608.54, 97%), peimisine (ebeiensine, Cas. 19773-24-1, $C_{27}H_{41}NO_3$, 427.629, 98%), solancarpidine (Cas. 126-17-0, $C_{27}H_{43}NO_2$, 413.62, 98%), sophocarpine (13,14-Didehydromatridin-15-one, Cas. 145572-44-7, $C_{15}H_{22}N_2O$, 246.35, 98%), daidzein (Cas. 486-66-8, $C_{15}H_{10}O_4$, 254.24, 97%); calycosin (Cas. 20575-57-9, $C_{16}H_{12}O_5$, 284.27, 97%), scutellarein (Cas. 529-53-3, $C_{15}H_{10}O_6$, 286.24, 97%), 5-*O*-caffeoylquinic acid (neochlorogenic acid, Cas. 906-33-2, $C_{16}H_{18}O_9$, 354.311, 97%), 4-*O*-caffeoylquinic acid (cryptochlorogenic acid, Cas. 905-99-7, $C_{16}H_{18}O_9$, 354.311, 97%), and irigenin (548-76-5, $C_{18}H_{16}O_8$, 360.31, 97%) were obtained from Chengdu Biopurify Phytochemicals Ltd. (Chengdu, China).

Chrysin (Cas. 480-40-0, $C_{15}H_{10}O_4$, M.W. 254.24, 98%), viscidulin I (Cas. 92519-95-4, $C_{15}H_{10}O_7$, M.W. 302.24, 98%), 2′,6′-dihydroxypinobanksin (Cas. 80366-15-0, $C_{15}H_{12}O_7$, 304.24, 98%), sophoricoside (Cas. 152-95-4, $C_{21}H_{20}O_{10}$, 432.38, 98%), isorhamnetin-3-*O*-β-D-glucoside (Cas. 5041-82-7, $C_{22}H_{22}O_{12}$, 478.4, 98%), 6-prenylapigenin (Cas. 68097-13-2, $C_{20}H_{18}O_5$, 338.36, 98%), forsythoside B (Cas. 81525-13-5, $C_{34}H_{44}O_{19}$, 756.7, 98%), dalbergioidin (Cas. 30368-42-4, $C_{15}H_{12}O_6$, 288.65, 98%), (−)-epipinoresinol (Cas. 10061-38-8, $C_{20}H_{22}O_6$, 358.39, 96%), and (+)-epipinoresinol (Cas. 24404-50-0, $C_{20}H_{22}O_6$, 358.39, 96%) were purchased from BioBioPha Co., Ltd. (Kunming, China).

Esculetin (Cas. 305-01-1, $C_9H_6O_4$, M.W. 178. 41, 98%), scopoletin (Cas. 92-61-5, $C_{10}H_8O_4$, M.W. 192.17, 98%), vitexin (Cas. 3681-93-4, $C_{21}H_{20}O_{10}$, M.W. 432.10, 98%), and isoschaftoside (apigenin-6-arabinoside-8-glucoside, Cas. 52012-29-0, $C_{26}H_{28}O_{14}$, M.W. 564.49, 98%), quercetin (Cas. 117-39-5, $C_{15}H_{10}O_7$, M.W. 302.23, 98%), *S*-naringenin (Cas. 480-41-1, $C_{15}H_{12}O_5$, M.W. 272.25, 98%), vicenin-2 (Cas. 23666-13-9, $C_{27}H_{30}O_{15}$, M.W. 594.518, 98%), and schaftoside (apigenin-6-glucoside-8-arabinoside, Cas. 51938-32-0, $C_{26}H_{28}O_{14}$, M.W. 564.49, 98%) were purchased from Sichuan Weikeqi Biological Technology Co., Ltd. (Chengdu, China).

Chloesteryl acetate (Cas. 604-35-3, $C_{29}H_{48}O_2$, 428.69, 97%) and protocatechuic acid (Cas. 99-50-3, $C_7H_6O_4$, 154.12, 97%) were form Sigma–Aldrich (Shanghai, China); Caffeic acid (Cas. 331-39-5, $C_9H_8O_4$, 97%) and emodin (Cas. 518-82-1, $C_{15}H_{10}O_5$, M.W. 270.24, 97%) were obtained from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). D-Gluconic acid (Cas. 526-95-4, $C_6H_{11}O_7$, M.W. 195.15, 98%) was from TCI Chemical Co. (Shanghai, China). *R*-rosmarinic acid (Cas. 20283-92-5, $C_{18}H_{16}O_8$, M.W. 360.3, 98%) and ferulic acid (Cas. 1135-24-6, $C_{10}H_{10}O_4$, M.W. 194.19, 98%) were purchased from Aladdin Chemistry Co. (Shanghai, China). L-Tryptophan (Cas. 73-22-3, $C_{11}H_{12}N_2O_2$, M.W. 204.23, 98%) was from J&K Scientific Co., Ltd. (Beijing, China). Danshensu (Cas. 76822-21-4, $C_9H_{10}O_5$, M.W. 198.17, 97%) was from Shanghai Acmec Biochemical Co., Ltd (Shanghai, China). Caffeine (Cas. 58-08-2, $C_8H_{10}N_4O_2$, M.W. 194.191, 98%) was prepared using sublimation method from Green tea [9]. Methanol and water were of mass spectra purity grade.

2.3. The preparations of standard solution and sample solution

The standard solution was prepared using methanol, according to previous method [10]. However, herein the concentration was approximately 100 μg/mL for short-term storage at 4 °C. The sample solution of *Jinhua Qinggan* Granule was prepared through the following experimental procedure (Fig. 2) [9]. The prepared sample solution (30 mg/mL) was stocked in a refrigerator at 4 °C for the following analysis.

2.4. Establishment of standards library using ultra-high-performance liquid chromatography coupled with quadrupole Exactive-Orbitrap MS (UHPLC-Q-Orbitrap-MS) analysis

The study selected a series of authentic standards (including isomers with specific structure or configuration) to establish a basic library. All these

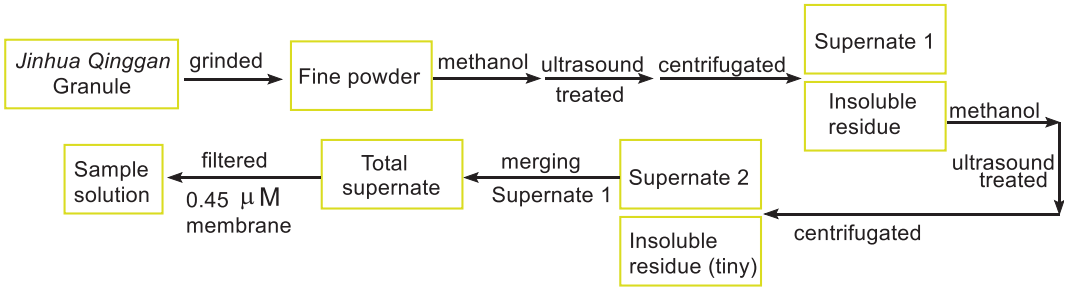

Fig. 2. The preparation of sample solution of Jinhua Qinggan Granule.

authentic standards were analyzed using UHPLC-Q-Orbitrap-MS apparatus (Thermo Fisher Scientific, Waltham, MA, USA). The chromatography condition was detailed described as the followings: 0–5 min, 10% phase B; 5–14.5 min, 10–100% phase B; 14.5–16 min, 100% phase B; 16.1 min, switched to 10% phase B. The switched state was then kept up for 4 min to equilibrate system. Herein phase A referred to 0.1% HCOOH aqueous solution; while phase B was 100% CH_3OH. The flow rate was 0.4 mL/min. The column temperature was set at 40 °C. The chromatographic column was Accucore RP-MS LC C_{18} column (100 mm × 2.1 mm, 2.6 μm, Thermo Fisher).

The Q-Orbitrap mass spectrometer however was connected with heat electrospray ionization (HEST) and operated under the following conditions: *m/z* 100–1200 for MS full scan range; the gas with 10, 40, and 0 (arbitrary units) for auxiliary gas, sheath gas, and sweep gas respectively; negative ion for analysis mode with 4.5 kV spray voltage. The full MS resolution was 70000 and dd-MS^2 was 17500, while their AGC target were set as 2×10^5. The stepped NCE (normalized collision energy) for MS/MS acquisition was set to −20, 50, and 90 V. Both the auxiliary gas heater and capillary were at 450 °C. Nitrogen (N_2) was used for spray stabilization and the damping gas in the C-trap.

The prepared standard solution was diluted using methanol at 10 μg/mL. The diluted solution was automatically injected by means of batch processing software. The injection volume was set at 3 μL.

2.5. Jinhua Qinggan Granule analysis using UHPLC-Q-Orbitrap-MS

The prepared sample solution of *Jinhua Qinggan* Granule was automatically injected by means of batch processing software. The injection volume was 3 μL. It was analyzed using UHPLC-Q-Orbitrap-MS apparatus, under the same condition as the standard solution.

2.6. Isomer recognition and constituent putative identification using software package and manual MS spectra elucidation

The raw data acquisition and data process of both standard solution and sample solution were accomplished using Xcalibur 4.1 and TraceFinder General Quan software package (Thermo Fisher Scientific Inc., Waltham, MA, USA) [11]. The data acquisition condition was set as follows: 100–1200 Da mass range; 5 ppm mass tolerance; 5 S/N threshold; 10 min RT window override; 90% isotopic pattern fit threshold. The software-acquired raw data included R.T. value, molecular peak ([M−H]), MS/MS profile, MS/MS fragment. The raw MS/MS fragment data, characteristic MS/MS fragments, however were further verified by manual operation.

The spectra comparison between standards library with sample was also fulfilled via the software package and manual operation. The comparison included R.T. value, MS molecular peak, MS/MS fragment, and MS/MS profile. On the basis of comparison, the possible isomer structure or constituent were further identified by manual MS elucidation, to fulfill isomer recognition and constituent putative identification.

3. Results

3.1. UHPLC-Q-Orbitrap-MS identification

In the present study, the UHPLC-Q-Exactive-Orbitrap MS/MS analysis was applied to identify constituents from sample solution. Through the analysis, two total-ion-current (TIC) chromatographic diagrams were obtained (Fig. 3); Correspondingly, the chromatography and mass spectra (MS) information was illustrated in Table 1, including R.T. values, molecular ion peak, and MS fragments. All these chromatography and MS information were compared with those of authentic standards in the library, to achieve putative

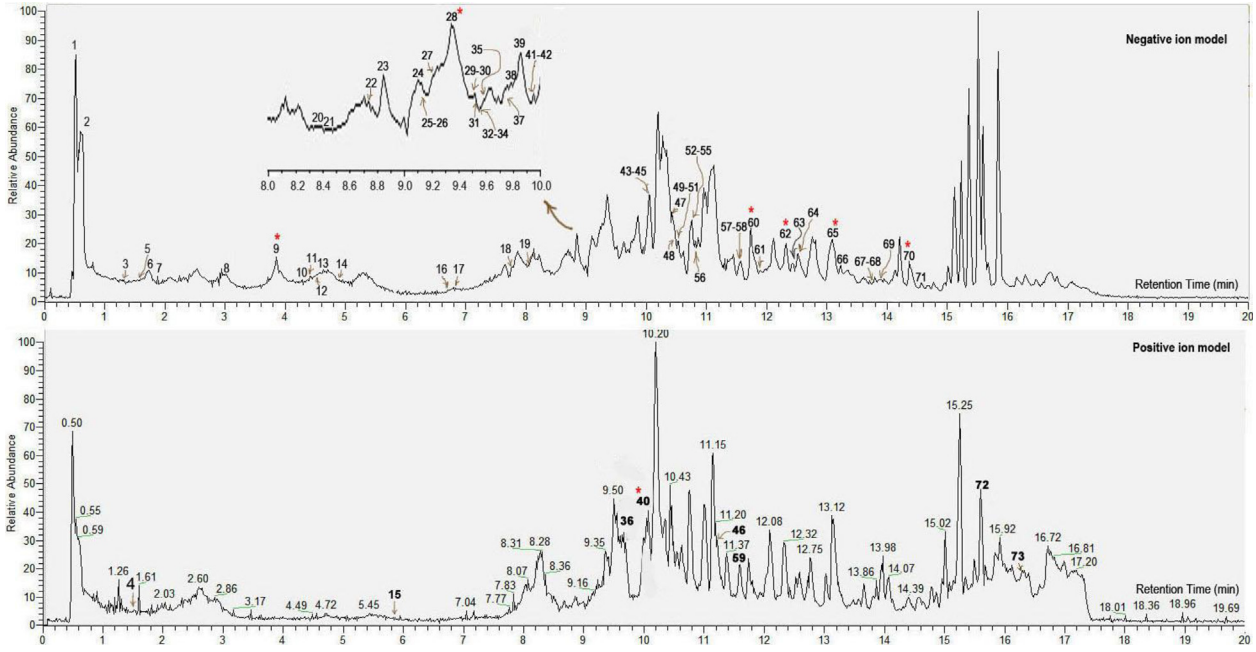

Fig. 3. The total-ion-current (TIC) of Jinhua Qinggan Granule in the UHPLC-Q-Orbitrap-MS analysis (negative ion mode and positive ion model).

identification. As seen in Fig. 4 and Table 1, there were at least 73 constituents (**1**–**73**) in *Jinhuajingang* Granule. Meanwhile, the fragments of all identified constituents were elucidated in Supplements. In particular, the MS elucidation diagrams of 6 constituents were also shown in Figs. 5–10, including chlorogenic acid, acteoside, peimisine, baicalein, licoricesaponin H2, and tanshinone IIA.

4. Discussion

The study however, has established a library using a set of authentic standards, especially isomers with definite configuration. Through comparison under the same experimental conditions, 73 constituents have been putatively identified and listed in Table 1 and Fig. 4. It can be seen that, three caffeoylquinic acid isomers (**6**, **9**, and **14**) and two schaftoside isomer (**23** and **26**) have been successfully recognized in the study. Other 23 isomers have also been recognized, including astragalin isomers (**32** and **44**), baicalein isomers (**60** and **67**), calycosin isomers (**55** and **62**), chrysin isomers (**49** and **63**), cosmosiin-A isomers (**25**, **41**, **42**, and **48**), dicaffeoylquinic acid isomers (**17**, **35**, and **39**), epipinoresinol isomers (**50** and **52**), irigenin isomers (**37** and **57**), luteolin 7-*O*-glucuronide isomers (**36** and **51**), and quercetin isomers (**18** and **53**). As seen in Fig. 4, the 28 isomers have covered all types of isomers, including positional isomers (e.g., **17**, **35**, and **39**), skeleton isomers (**49** and **63**), functional group isomers (**60** and **67**), and stereo-isomers (**50** and **52**). The successful recognition of all 28 isomers has suggested our strategy as an effective tool to recognize all types isomers. Compared with the previous method [12], this can be considered as an innovation in analysis chemistry.

The innovative approach has clearly suggested the addition of Danshen (*Salviae miltiorrhizae* radix et rhizome, 丹参) into the Granule. This is because that three Danshen-derived constituents, i.e., Danshensu (**3**), cryptotanshinone (**68**), and tanshinone IIA (**70**), have been simultaneously detected out in the study. The addition can help to enhance its therapeutic effects, and thus can be considered as a fine-tune under the guide of Monarch-Minister-Assistant-Guide theory.

Interestingly, the so-called "fine-tune" is exactly confidential in TCM. Similar instances could also be observed in *Yunnan Baiyao* and *Pien-Tze-Huang*, two famous TCM patent medicines. The confidential addition of *Yunnan Baiyao* is known to cause a public crisis in Hong Kong (2013). The present study however, has partly uncovered the confidential addition, by means of modern chemical analysis. Now it is clear that, *Jinhua Qinggan* Granule comprises at least 13 Chinese medicine materials, that is, Jinyinhua, Shigao, Mahuang, Kuxingren, Huangqin, Lianqiao, Zhebeimu, Zhimu, Niubangzi, Qinghao, Bohe, Gancao, and Danshen. Other Chinese medicine material (e.g., Ganjiang) may also be included in the Granule.

Table 1. The main experimental results of 45 potential anti-Covid-19 constituents and 28 other constituents from Jinhuajingang Granule.

No.	R.T. min	Classification	Name	Formula	M.W.	Molecular ion peak and fragment (*m/z*)	Resource	*Anti*-Covid-19 potential
1	0.49	Sugar	D-Gluconic acid	$C_6H_{12}O_7$		**195.0503, 177.0395, 159.0290, 129.0183**, 99.0076, 87.0076, 75.0076		
2	0.52	Aliphatic acid	quinic acid	$C_7H_{12}O_6$	192.17	**191.0552, 173.0446, 155.0340, 127.0390**, 109.0284, 99.0440, 93.0334, 85.0283, 81.0334, 71.0127, 67.0177	Lianqiao [33]	
3	1.33	Phenolic acid ester	Danshensu	$C_9H_{10}O_5$	198.17	**197.0453, 179.0343, 135.0442, 123.0442**, 109.0284, 99.9244, 95.0488, 89.0383, 72.9919	Danshen (confidential addition) [13]	[34]
4	1.47	Alkaloid	sophocarpine	$C_{15}H_{22}N_2O$	246.35	**247.1802, 245.1647**, 229.1693, 186.1151, **179.1541**, 174.0914, 150.1279, 138.1277, 136.1120, 134.0959, 122.0965, 110.0969, 108.0811, 98.0967		[35]
5	1.6	Phenolic acid	protocatechuic acid	$C_7H_6O_4$	154.12	154.0220, **153.0185**, 110.0317, **109.0285, 108.0207, 91.0178**, 81.0334, 65.0021	Jinyinhua [36], Mahuang [37,38] Lianqiao [39]	
6	1.76	Caffeoylquinic acid	neochlorogenic acid (5-*O*-caffeoylquinic acid)	$C_{16}H_{18}O_9$	354.311	**353.0876, 191.0555, 179.0341, 173.0447**, 161.0240, **135.0443**, 127.0390, 107.0491, 93.0335, 85.0284, 81.0333	Kuxingren [40], Jinyinhua [36] Niubangzi [41,42],	[43]
7	1.84	Amino acid	L-tryptophan	$C_{11}H_{12}N_2O_2$	204	**203.0822, 159.0916, 142.0653**, 130.0649, **116.0496**, 74.0236, 72.0078	Mahuang [37,38]	
8	3	Glycoside	salidroside	$C_{14}H_{20}O_7$	300.304	**299.1126, 179.0560, 137.0235, 119.0492**, 113.0231, 101.0231, 89.0233, 85.0281, 71.0127	Huangqin [44–46], Lianqiao [33,39],	[47]
9	3.85	Caffeoylquinic acid	chlorogenic acid*	$C_{16}H_{18}O_9$	354.31	**353.0873, 191.0554, 173.0446, 161.0236, 109.0285**, 93.0335, 85.0283, 81.0333	Jinyinhua [36] Mahuang [37,38] Niubangzi [41,42], Kuxingren [40]′ Lianqiao [33,39] [33,39], Huangqin [44–46],	[23]
10	4.29	Coumarin	esculetin	$C_9H_6O_4$	178.41	**177.0185, 149.0235**, 139.0386, **133.0285, 121.0283**, 107.0127, **105.0335**, 93.0335, 89.0385, 81.0333, 77.0384	Lianqiao [39]	[16]
11	4.43	Phenolic acid	vanillic acid	$C_8H_8O_4$	168.15	**167.0388, 152.0108, 123.0439, 108.0206**	Mahuang [37,38] Lianqiao [39]	[48]
12	4.47	Flavonoid	2′, 6′-dihydroxypino banksin (2′,3,5,6′, 7-pentahydroxy flavanone)	$C_{15}H_{12}O_7$	304.24	**303.0509**, 285.0403, **275.0563**, 259.0606, 217.0506, 193.0499, 177.0185, 175.0391, **151.0028, 149.0236**, 147.0439, 133.0286, **125.0234**, 121.0283, 119.0490, 107.0127, 83.0127, 65.0022	Huangqin [49]	
13	4.65	Phenolic acid	caffeic acid	$C_9H_8O_4$	180.16	**179.0342**, 136.0473, **135.0442**, 133.0289, **117.0335**, 107.0492, 93.0334, 89.0385, 65.0387	Jinyinhua [36], Mahuang [37,38], Kuxingren [40], Lianqiao [33,39], Niubangzi [41,42], Qinghao [50]	[51]

(*continued on next page*)

Table 1. (continued)

No.	R.T. min	Classification	Name	Formula	M.W.	Molecular ion peak and fragment (*m/z*)	Resource	*Anti*-Covid-19 potential
14	4.86	Caffeoylquinic acid	4-*O*-caffeoylquinic acid (cryptochlorogenic acid)	$C_{16}H_{18}O_9$	354.311	**353.0877**, **191.0554**, 179.0341, **173.0447**, **161.0230**, **135.0442**, 132.0212, 111.0440, 99.0448, 93.0334, 85.0283, 67.0178	Jinyinhua [36] Niubangzi [41,42], Kuxingren [40],	
15	5.82	Alkaloid	caffeine	$C_8H_{10}N_4O_2$	194.191	**195.0874**, **138.0661**, **123.0430**, 83.0609, 69.0455	Niubangzi [42]	[52]
16	6.73	Xanthone	neomangiferin	$C_{25}H_{28}O_{16}$	584.48	**583.1304**, 565.1211, 493.0981, **463.0881**, 421.0778, 343.0475, 331.0457, 313.0351, **301.0353**, 285.0407, 271.0248, **259.0246**, 229.0139, 215.0345, 187.0394, 171.0443, 109.0284	Zhimu [53,54]	
17	6.81	Caffeoylquinic acid	1,3-*O*-dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	516.455	**515.1191**, **353.0878**, 335.0776, **191.0555**, **179.0343**, **161.0238**, **135.0443**, 127.0397, 107.0493, 85.0284, 81.0331	Jinyinhua [36] Niubangzi [41,42]	[55]
18	7.83	Flavonoid	viscidulin I	$C_{15}H_{10}O_7$	302.24	**301.0353**, 283.0247, 273.0411, 239.0343, 227.0347, 215.035, 201.0549, 193.0135, 187.0394, 171.0443, 159.0443, **151.0029**, 148.0157, 145.0285, 133.0285, 125.0234, **121.0283**, 119.0129, **107.0128**, 93.0333, 91.0178	Huangqin [44–46],	
19	8.05	Xanthone	mangiferin	$C_{19}H_{18}O_{11}$	422.34	**421.0777**, 403.0670, **331.0457**, 313.0351, **301.0353**, 298.0105, 285.0400, **271.0248**, 259.0246, **243.0296**, 227.0345, 215.0344, 199.0396, 187.0394, 171.0443, 159.0442, 143.0495, 109.0283, 95.0129, 79.0177	Zhimu [53,54]	[16,56,57]
20	8.39	Flavonoid	vicenin-2	$C_{27}H_{30}O_{15}$	594.52	**593.1510**, 503.1222, **473.1085**, 395.0803, 383.0769, 365.0660, 353.0663, 337.0723, **325.0716**, **297.0768**, **283.0607**, 203.0341, 161.0236, 135.0444, 117.0336, 93.0335, 79.0178	Mahuang [37,38]	[58]
21	8.43	Coumarin	scopoletin	$C_{10}H_8O_4$	192.17	**191.0344**, **176.0107**, **148.0157**, 138.0315, 123.0080, **120.0207**, **104.0257**, 92.0255	Mahuang [37,38], Qinghao [50],	[59]
22	8.72	Phenolic acid	ferulic acid	$C_{10}H_{10}O_4$	194.19	**193.0500**, 179.0297, **178.0264**, **149.0598**, **134.0364**, 132.0208, 121.0286, 106.0414	Mahuang [37,38], Huangqin [44–46], Kuxingren [40], Lianqiao [33,39],	[60]
23	8.86	Flavonoid	schaftoside (apigenin-6-glucoside-8-arabinoside)	$C_{26}H_{28}O_{14}$	564.5	**563.1395**, **473.1084**, 443.0972, 413.0854, 395.0784, **383.0769**, 353.0663, 337.0716, 325.0717, 311.0563, **297.0768**, 283.0610, 267.0664, 239.0714, 203.0342, 177.0183, 161.0235, 135.0442, **117.0335**, 93.0334, 79.0177	Huangqin [44–46],	[61]
24	9.11	Saponin	liquiritin	$C_{21}H_{22}O_9$	418.4	**255.0660**, 211.0394, 183.0451, 153.0185, **135.0078**, **119.0492**, 108.0204, 93.0334, 91.0178, 89.0232, 65.0021	Gancao [62–64]	[65]
25	9.19	Flavonoid	vitexin	$C_{21}H_{20}O_{10}$	432	**431.0985**, **341.0663**, 323.0568, **311.0560**, 293.0464, **283.0612**, 268.0374, 239.0713, 211.0393, 161.0240, 149.0234, **135.0446**, 121.0286, 117.0336	Mahuang [37,38] Zhimu [53,54]	[66]

26	9.2	Flavonoid	isoschaftoside (apigenin-6-arabinoside -8-glucoside)	$C_{26}H_{28}O_{14}$	564.49	**563.1398**, **473.1071**, 443.0971, **383.0746**, **365.0654**, 353.0656, 337.0714, 325.0715, **297.0769**, 283.0605, 251.0714, 225.0562, 203.0346, 161.0237, 135.0444, 117.0333, 117.0186, 93.0334, 79.0175	Huangqin [44–46],	[58]
27	9.23	Phenylpropanoid	forsythoside B	$C_{34}H_{44}O_{19}$	756.7	**755.2389**, 623.1978, **593.2012**, 179.0348, **161.0236**, **133.0286**, 89.0236	Lianqiao [39]	
28	9.34	Phenylpropanoid	acteoside (verbascoside) *	$C_{29}H_{36}O_{15}$	624.59	**623.1979**, **461.1674**, 179.0340, **161.0236**, **133.0285**	Lianqiao [33,39], Huangqin [44–46]	[22]
29	9.43	Anthraquinone	rhein	$C_{15}H_8O_6$		**284.0327**, **255.0299**, **240.0430**, 227.0349, 211.0399, **183.0444**, **155.0494**, 141.0334, 132.0210, 117.0338, 82.0045, 65.0020	Mahuang [37,38]	[67]
30	9.47	Coumarin	scoparone	$C_{11}H_{10}O_4$	206.19	**207.0652**, **191.0338**, 189.0910, 179.0701, 174.0309, 174.0309, **163.0389**, 161.0599, 151.0754, **146.0362**, 139.0753, 135.0441, 109.0650, 107.0495, 95.0496, 91.0548, 90.0470, 78.0471, 65.0394		
31	9.5	Flavonoid	rutin	$C_{27}H_{30}O_{16}$	610.52	**609.1456**, **300.0273**, 283.0254, **271.0248**, **255.0297**, **243.0296**, 227.0346, 199.0395, 171.0443, 151.0027, 143.0492, 108.0206, 65.0021	Jinyinhua [36], Mahuang [37,38] Qinghao [50], Huangqin [44–46], Lianqiao [33,39],	[58]
32	9.52	Flavonoid	luteoloside (cynaroside)	$C_{21}H_{20}O_{11}$	448.38	**447.0934**, **284.0327**, 255.0294, **227.0348**, 199.0394, 183.0443, 151.0029, 133.0285, 121.0283, 107.0128, 83.0127, 63.0229	Huangqin [68]	
33	9.52	Flavonoid	isoquercitrin	$C_{21}H_{20}O_{12}$	464.38	**463.0879**, **300.0275**, 283.0255, **271.0248**, **255.0297**, **243.0296**, 227.0346, 199.0395, 151.0027, 108.0205, 65.0022	Jinyinhua [36]	[69]
34	9.53	Flavonoid	isoviolanthin	$C_{27}H_{30}O_{14}$	578.52	**577.1559**, 503.1109, 457.1143, 413.0853, **383.0771**, **353.0663**, 325.0713, **297.0767**, **267.0661**, 203.0345, 177.0184, 161.0235, 135.0441, 117.0336, 109.0282, 93.0334, 79.0178		
35	9.59	Caffeoylquinic acid	3,4-*O*-dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	516.455	**515.1182**, **353.0878**, 335.0783, **191.0555**, **173.0448**, 161.0236, **135.0443**, 127.0392, 111.0440, 93.0335, 85.0284, 67.0178	Jinyinhua [36] Lianqiao [33,39], Niubangzi [41,42]	[70]
36	9.72	Flavonoid	scutellarin	$C_{21}H_{18}O_{12}$	462.37	**463.0861**, **287.0547**, **269.0435**, **241.0481**, 169.0131, 119.0493, 95.0133, 85.0290	Huangqin [44–46]	[71]
37	9.73	Phenolic acid	*R*-rosmarinic acid	$C_{18}H_{16}O_8$	360.31	**197.0450**, **179.0343**, **161.0236**, 135.0442, **133.0286**, **123.0442**, 115.0179		[19]
38	9.79	Flavonoid	dalbergioidin	$C_{15}H_{12}O_6$	288.65	177.0182, 165.0191, **161.0235**, 159.0448, **135.0442**, **125.0234**, 83.0126		
39	9.84	Caffeoylquinic acid	4,5-*O*-dicaffeoylquinic acid (isochlorogenic acid C)	$C_{25}H_{24}O_{12}$	516.45	**353.0876**, 203.0345, **191.0554**, **179.0342**, **173.0447**, 161.0238, **135.0442**, 127.0391, 111.0442, 93.0335, 85.0283, 67.0178	Jinyinhua [36] Lianqiao [33,39], Niubangzi [41,42]	
40	9.92	Alkaloid	peimisine (ebeiensine) *	$C_{27}H_{41}NO_3$	427.629	**410.3040**, 393.2769, **337.2153**, 303.1956, 213.1639, **197.1322**, 142.0777, 119.0857, **114.0917**, 84.0814, 67.0550	Zhebeimu [72]	[21]
41	9.93	Flavonoid	cosmosiin (apigenin 7-*O*-glucoside)	$C_{21}H_{20}O_{10}$	432.4	**268.0378**, **239.0345**, 223.1337, 211.0397, 195.0446, 183.0444, **151.0029**, 117.0335, 83.0128, 63.0229	Huangqin [44–46],	

(*continued on next page*)

Table 1. (continued)

No.	R.T. min	Classification	Name	Formula	M.W.	Molecular ion peak and fragment (*m/z*)	Resource	*Anti*-Covid-19 potential
42	9.94	Flavonoid	sophoricoside	$C_{21}H_{20}O_{10}$	432.381	**268.0379**, **239.0348**, 223.0399, **211.0397**, 195.0447, 183.0446, 63.0229		
43	10.04	Flavonoid	diosmin	$C_{28}H_{32}O_{15}$	608.54	**299.0561**, **284.0327**, 255.0297, 227.0346, **151.0028**, **133.0285**, 107.0128		[73]
44	10.06	Flavonoid	astragalin	$C_{21}H_{20}O_{11}$	448.38	**284.0327**, **255.0298**, 239.0347, **227.0346**, **211.0395**, **199.0397**, 183.0444, 171.0446, 167.0493, 155.0495, 139.0545, 65.0019	Jinyinhua [36] Huangqin [44–46] Lianqiao [33,39]	[74]
45	10.09	Flavonoid	isorhamnetin-3-*O*-*β*-D-glucoside	$C_{22}H_{22}O_{12}$	478.41	**314.0433**, **285.0404**, **271.0251**, 257.0453, **243.0296**, 215.0346, 199.0397, 171.0445, 143.0493, 109.0286, 65.0019	Qinghao [50]	[75]
46	10.26	Ester	methyl benzoate	$C_8H_8O_2$	136.148	**122.0364**, 107.0495, 95.0498, **94.0418**, 91.0548, 81.0704, **77.0393**, 66.0472		
47	10.46	Flavonoid	scutellarein	$C_{15}H_{10}O_6$	286.239	267.0299, **257.0458**, **239.0351**, **211.0390**, 195.0441, 185.0598, **139.0028**, 137.0232, 119.0490, **117.0336**, 111.0078, 65.0021	Huangqin [44–46],	[71]
48	10.5	Flavonoid	oroxin A (baicalein 7-*O*-glucoside)	$C_{21}H_{20}O_{10}$	432.38	**269.0456**, **241.0504**, **223.0396**, 136.9871, **111.0077**, 65.0021	Huangqin [44–46]	
49	10.56	Flavonoid	daidzein	$C_{15}H_{10}O_4$	254.24	**223.0396**, **208.0524**, 195.0442, 180.0574, **135.0077**, 132.0207, **117.0337**		
50	10.57	Lignin	(−)-epipinoresinol	$C_{20}H_{22}O_6$	358.39	342.1107, **313.1458**, **221.081524**, 209.0816, 161.0600, 147.0443, 137.0599, **122.0364**, 11539.0493, 93.0335, 83.0127	Lianqiao [33,39]	
51	10.58	Flavonoid	luteolin 7-*O*-glucuronide	$C_{21}H_{18}O_{12}$	462.36	380.2826, **285.0405**, **241.540502**, 199.0397, **133.0284**, 65.0022	Jinyinhua [36], Mahuang [37,38]	[76]
52	10.67	Lignin	(+)-epipinoresinol	$C_{20}H_{22}O_6$	358.39	**342.1105**, **221.0815**, 161.0595, 55147.0444, **122.0364**, 93.0335, 83.0127	Lianqiao [33,39]	
53	10.69	Flavonoid	quercetin	$C_{15}H_{10}O_7$	302.23	**245.0448**, **211.0403**, 178.9980, 164.0104, **151.0028**, 149.0232, 139.0393, 121.0286, 117.0335, 109.0285, 107.0127, **93.0334**, 83.0127, 65.0021, 63.0228	Jinyinhua [36] Mahuang [37,38] Huangqin [44–46], Kuxingren [40], Lianqiao [33,39], Zhebeimu [72], Niubangzi [41,42], Qinghao [50],	[77,78]
54	10.72	Phenolic ester	ethyl caffeate	$C_{11}H_{12}O_4$	208.12	**179.0342**, **161.0237**, 137.0238, 135.0442, **133.0286**, 115.0179, 105.0336		
55	10.78	Flavonoid	calycosin	$C_{16}H_{12}O_5$	284.27	**268.0378**, 251.0350, **239.0345**, **211.0397**, 195.0448, **183.0444**, 167.0495, 155.0494, 148.0155, 135.0079, 119.0127, 91.0177, 65.0020		
56	10.93	Flavonoid	*S*-naringenin	$C_{15}H_{12}O_5$	272.25	187.0391, **177.0188**, 165.0185, **151.0028**, **119.0492**, 117.0336, **107.0128**, 93.0334, 83.0126, 65.0021, 63.0228	Mahuang [37,38]	[79,80]
57	11.52	Flavonoid	irigenin	$C_{18}H_{16}O_8$	360.31	**344.0535**, 329.0302, **314.0068**, 311.0193, 301.0354, **286.0118**, **270.0168**, 258.0168, 230.0216, 202.0266, **185.0237**, 174.0313, **65.0021**		[19]

58	11.54	Chalcone	isoliquiritigenin	$C_{15}H_{12}O_4$	256.257	169.0646, 153.0185, **135.0078**, **119.0493**, 117.0338, **93.0335**, 91.0178	Gancao [63,64,81]	[82]
59	11.58	Alkaloid	solancarpidine	$C_{27}H_{43}NO_2$	413.62	**396.3246**, **253.1938**, 105.0702, 91.0548, **79.0549**, 67.0550		
60	11.77	Flavonoid	baicalein*	$C_{15}H_{10}O_5$	270.24	**251.0349**, 241.0504, 225.0548, **223.0397**, 213.0556, 185.0601, 169.0650, 151.0543, 141.0703, **136.9871**, 123.0078, 111.0078, **101.0387**, 95.0126	Huangqin [13]	[19]
61	11.84	Flavonoid	formononetin	$C_{16}H_{12}O_4$	268.26	**252.0426**, **223.0395**, 208.0530, **195.0446**, 180.0577, **167.0493**, 153.0188, 135.0078, **132.0207**, 116.0261, 104.0257, 91.0178		[83]
62	12.37	Flavonoid	wogonin	$C_{16}H_{12}O_5$	284.26	**268.0379**, **239.0340**, **224.0481**, 211.0393, 198.0314, 184.0525, **165.9898**, 163.0028, 143.0492, 139.0545, 109.9999, 95.0127, **82.0048**, 65.0021	Huangqin [44–46], Lianqiao [33,39],	[84]
63	12.48	Flavonoid	chrysin	$C_{15}H_{10}O_4$	254.24	225.0542, **209.0602**, 197.0598, 187.0393, 181.0649, **151.0027**, **143.0493**, 139.0541, 121.0282, 119.0492, **101.0384**, 89.0021, 63.0228	Jinyinhua [36] Huangqin [44–46],	[85]
64	12.55	Flavonoid	pectolinarigenin	$C_{17}H_{14}O_6$	314.29	**298.0484**, **283.0247**, 269.0444, **255.2970**, 239.0348, **227.0349**, 211.0394, 185.0235, 164.9821, 136.9870, **117.0336**, 65.0015	Jinyinhua [36],	[86]
65	13.1	Saponin	licoricesaponin H2 *	$C_{42}H_{62}O_{16}$	822.9	**193.0349**, **113.0234**, **85.0283**	Gancao [62]	[20]
66	13.23	Flavonoid	6-prenylapigenin	$C_{20}H_{18}O_5$	338.36346	**321.0769**, **293.0461**, 281.0455, 253.0505, **237.0557**, **209.0605**, **133.0285**, **117.0337**, 65.0018		
67	13.78	Anthraquinone	emodin	$C_{15}H_{10}O_5$	270.24	**241.0503**, **227.0350**, 225.0553, 223.0393, **210.0319**, 195.0446, **182.0367**, 171.0444, 157.0650, **115.0543**, 105.0336, 92.1612		[87]
68	13.78	Phenanthra quinone	cryptotanshinone	$C_{19}H_{20}O_3$	296.4	**268.1107**, 249.0916, 235.0760, 221.0952, 207.0811, 193.1016, 183.0801, 178.0778, 165.0699, **153.0699**, 141.0698, **128.0621**, 115.0544, 91.0545	Danshen (confi dential addition) [13]	[15]
69	13.86	Steroid	diosgenin	$C_{27}H_{42}O_3$	414.6	283.2414, **271.2053**, **253.1948**, 211.1481, 197.1326, 171.1167, 119.0858, 105.0702, **91.0548**, 79.0549, 69.0706		
70	14.26	Phenanthra quinone	tanshinone IIA*	$C_{19}H_{18}O_3$	294.3	**280.1089**, 277.2162, 262.0979, 249.1270, 234.1039, 219.0802, **195.0795**, 191.0855, 189.0703, **178.0776**, 165.0696, **152.0617**	Danshen (confi dential addition) [13]	[15–19]
71	14.57	Saponin	18β-glycyrrhetinic acid	$C_{30}H_{46}O_4$	470.68	**425.3437**, **355.2644**		
72	15.63	Phytophenol	6-gingerol	$C_{17}H_{26}O_4$	294.39	277.1618, 179.0527, 167.0525, 165.0368, **151.0754**, 137.042, 135.0804, **133.0648**, 107.0861, **105.0702**, 103.0546, 95.0496, 91.0548, 87.0269	Ganjiang (confi dential addition ?) [13]	[88]
73	16.25	Steroid	chloesteryl acetate	$C_{29}H_{48}O_2$	428.69	401.3393, 303.2321, **233.1535**, **205.1221**, 177.0907, **165.0909**, 161.0596, 149.0961, 122.0727, **105.0702**, 91.0546, 67.0550		

Note: The original MS spectra and identification process were detailed in Suppl. 1–73. The *m/z* value in bold means the characteristic fragments. The *m/z* values below 50 were also found by the Xcalibur 4.1 Software package, despite that the scan mode rang was set at *m/z* 100–1200 in the mass spectra.

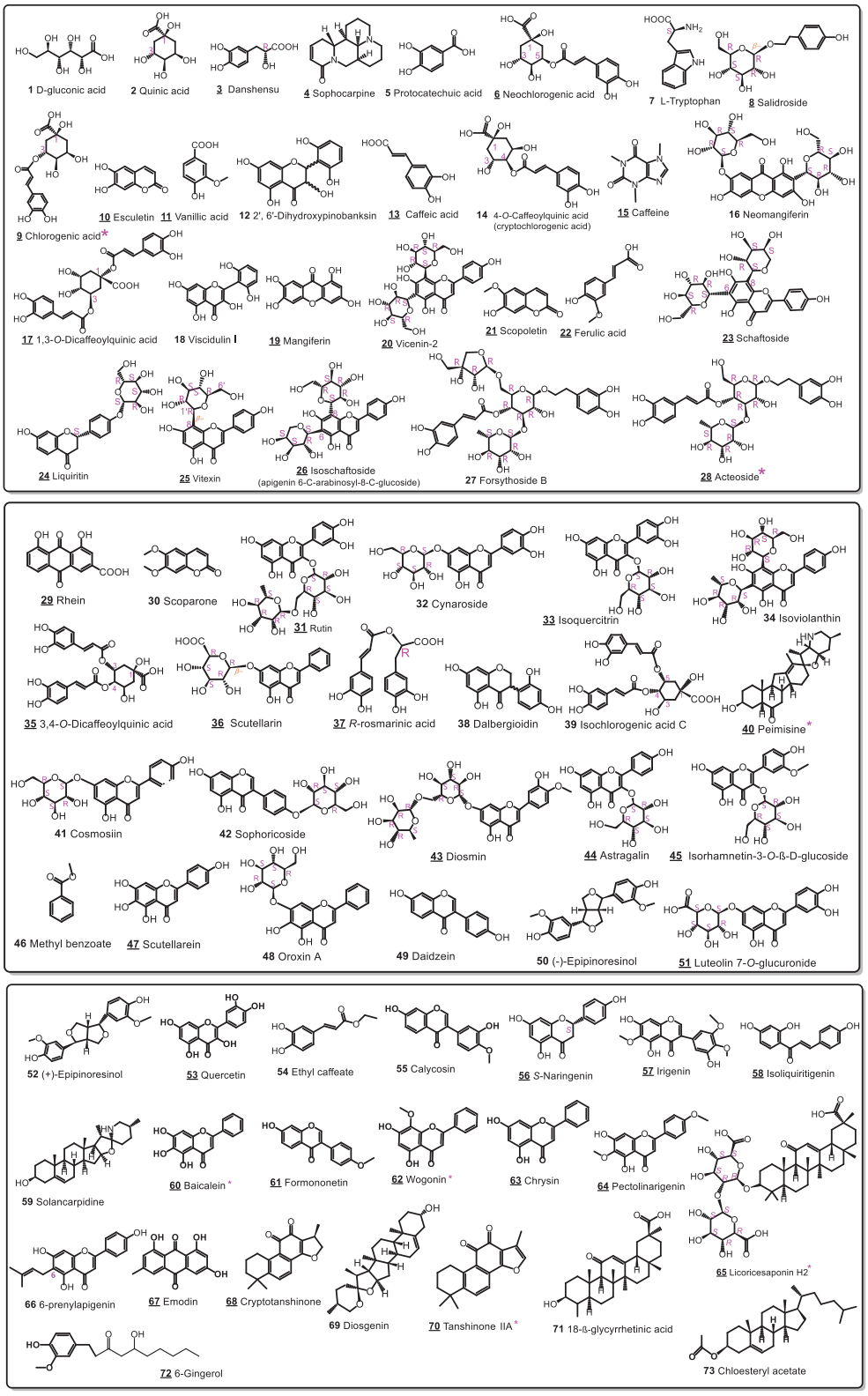

Fig. 4. The structures of 73 identified constituents from Jinhua Qinggan Granule. The red "" indicates the Q-marker candidate for pharmacopoeia. The wave line in **12** and **38** means the uncertain stereo-configuration. The chiral atoms in sugar residue are marked using R/S absolute configuration to avoid the possible confusion. The number underlined means the constituent with anti-Covid-19 potential.*

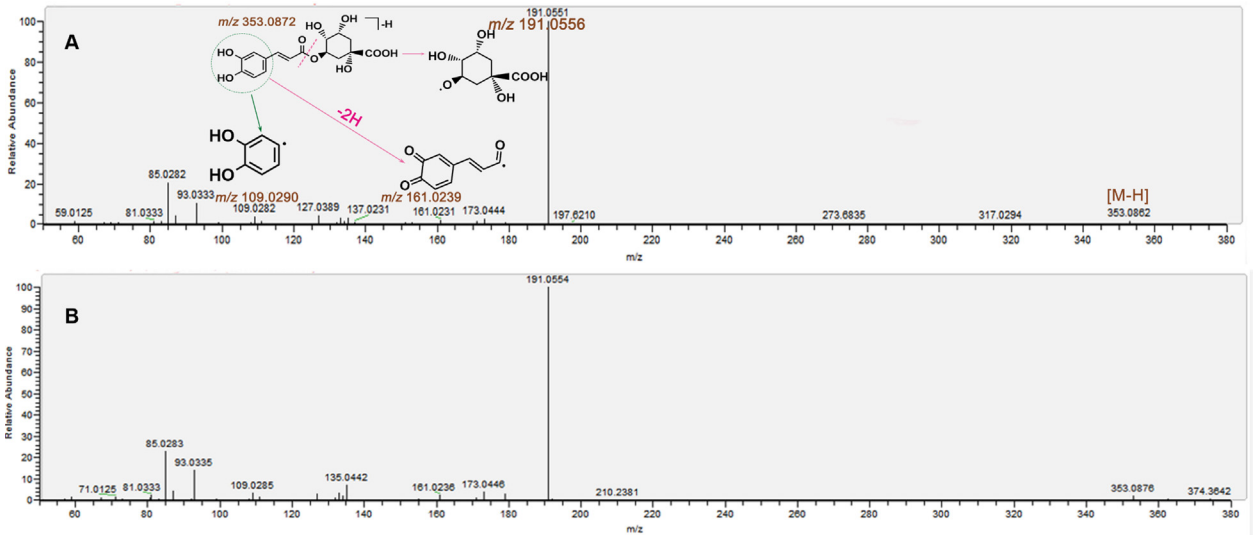

Fig. 5. The MS fragments of standard chlorogenic acid (upper) and peak at R.T. 3.85 (below). The m/z values in brown were calculated ones. The m/z calculation was based on the relative atomic masses of C (12.0000), H (1.007825), O (15.994915), and N (14.003074). It can be recognized from its two isomers neochlorogenic acid and cryptochlorogenic acid MS/MS profile and R.T. values (Suppl. 6, 9, and 14).

As one patent TCM medicine, *Jinhua Qinggan* Granule will possibly be collected in the Chinese Pharmacopoeia in future. As such, it is necessary to select one or more Q-markers for Pharmacopoeia. Strictly, each of 13 Chinese medicine materials (including Danshen) should be characterized using at least one Q-marker, to avoid possible adulterant. However, the current pharmacopoeia seems to allow 1–2 Q-markers, to characterize a complicated recipe consisting of several or even dozens of Chinese medicine materials [13]. Accordingly, the study tried to initially recommend 6 Q-markers, for consideration by Chinese pharmacopoeia-committee. As seen in Table 2, the six were chlorogenic acid **(9)**, acteoside **(28)**, peimisine **(40)**, baicalein **(60)**, licoricesaponin H2 **(65)**, and tanshinone IIA **(70)**.

The initial recommendation was based on the "five principles", including specificity, testability,

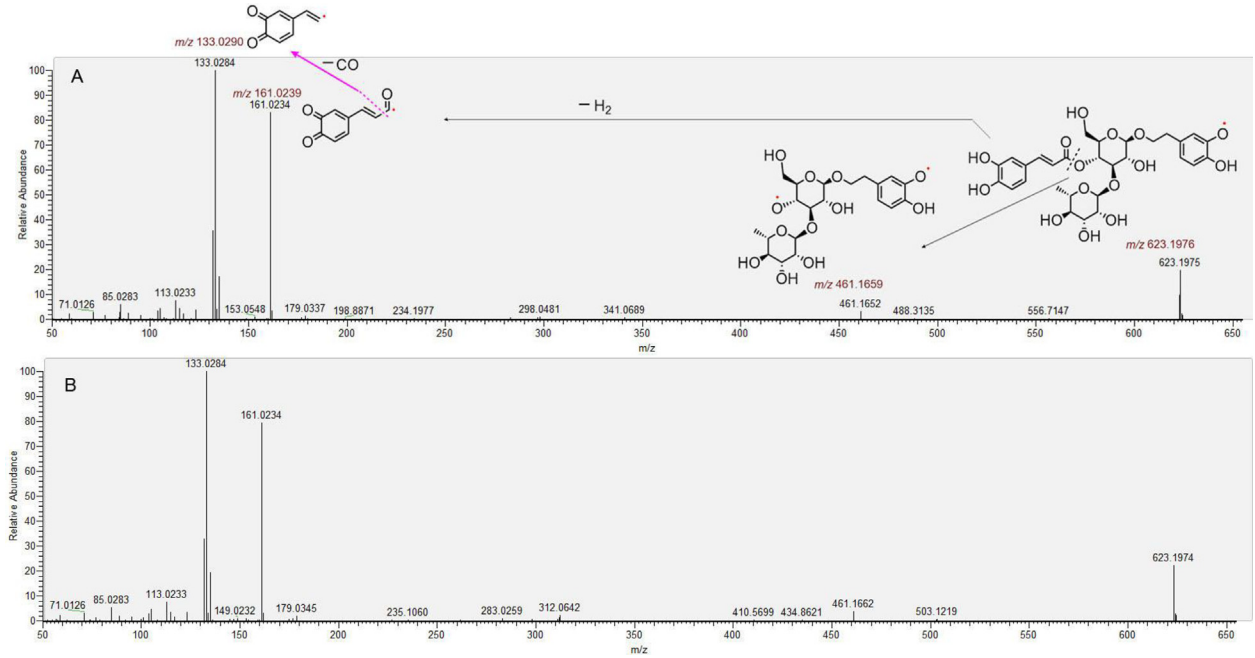

Fig. 6. The MS fragments of standard acteoside (upper) and peak at R.T. 9.34 (below). The m/z values in brown were calculated ones. The m/z calculation was based on the relative atomic masses of C (12.0000), H (1.007825), O (15.994915), and N (14.003074).

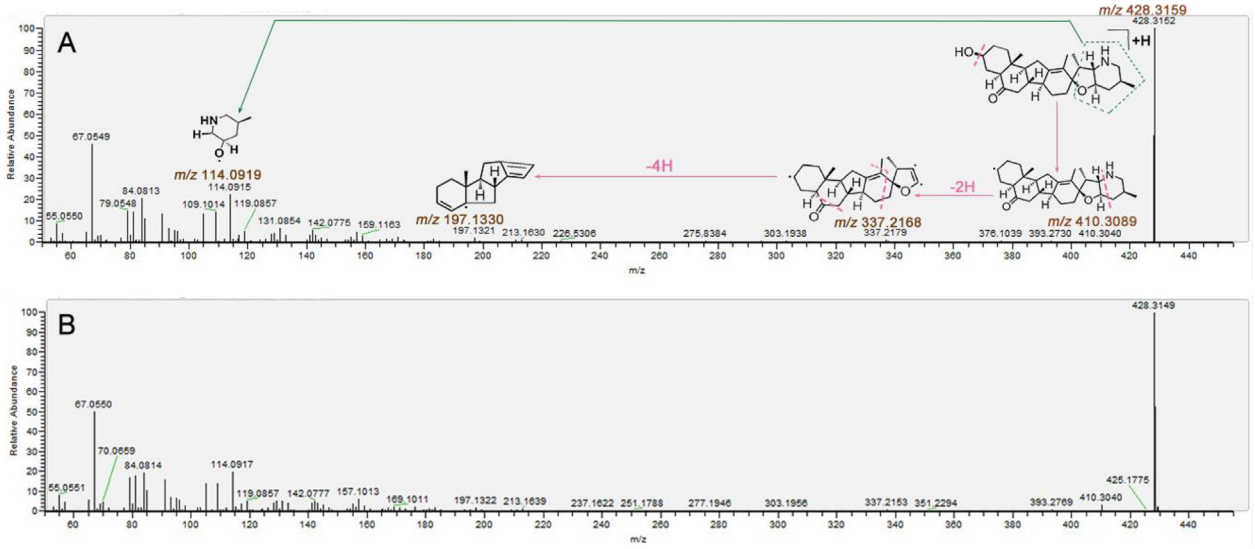

Fig. 7. The MS fragments of standard peimisine (upper) and peak at R.T. 9.92 (below). The m/z values in brown were calculated ones. The m/z calculation was based on the relative atomic masses of C (12.0000), H (1.007825), O (15.994915), and N (14.003074).

traceability, efficiency-relevance, and TCM theory-relevance. These principles were recently proposed by Liu Changxiao, a Chinese Academician [14]. As seen in Table 2, these recommended Q-markers can characterize different plants (i.e., Chinese medicine materials), respectively. Especially, four Q-markers (**40, 60, 65,** and **70**) can respectively characterize Zhebeimu, Huangqin, Gancao, and Danshen in the Granule. For example, if the Q-marker **40** is not found, this means Zhebeimu is absent in the Granule and thus there is adulterant. Thus, the recommendation Q-markers have high specificity and effectiveness.

As seen in Table 2, all these Q-markers can also simultaneously characterize nine Chinese medicine materials (i.e., Jinyinhua, Mahuang, Niubangzi, Kuxingren, Lianqiao, Huangqin, Zhebeimu, Gancao, and Danshen). On the other hand, all these characterized Chinese medicine materials play a key role in the whole recipe, according to the *Monarch-Minister-Assistant-Guide* theory. The proportion of total characterization was calculated as 69% (6 ÷ 13); while the proportion of specific characterization was calculated as 31% (4 ÷ 13). The two proportion values are much higher than those of current Q-marker in Pharmacopoeia. For

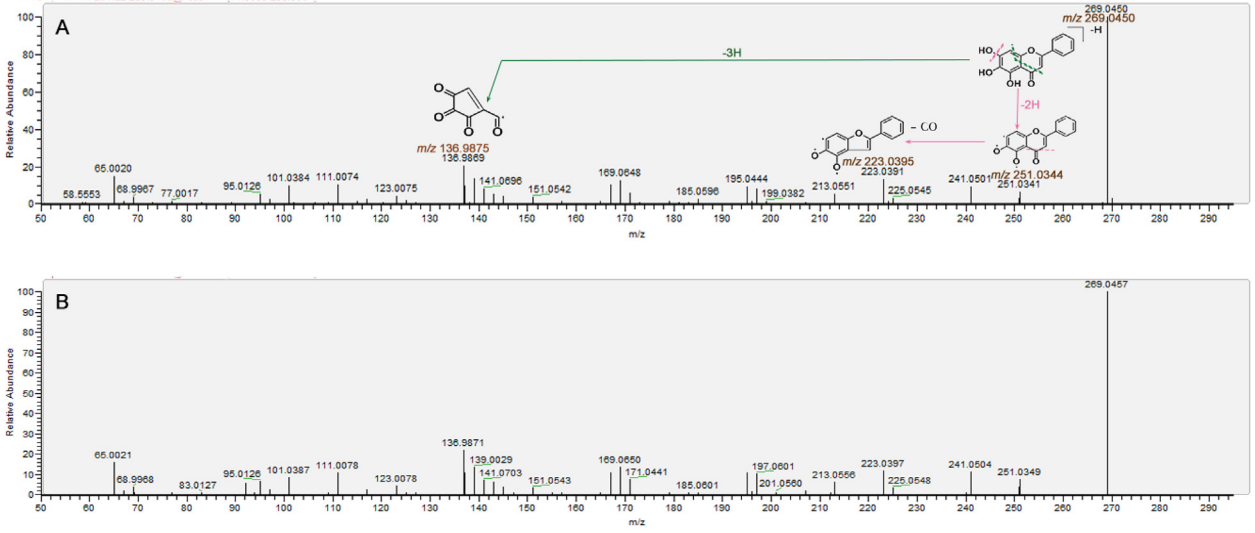

Fig. 8. The MS fragments of standard baicalein (upper) and peak at R.T. 11.77 (below). The m/z values in brown were calculated ones. The m/z calculation was based on the relative atomic masses of C (12.0000), H (1.007825), O (15.994915), and N (14.003074).

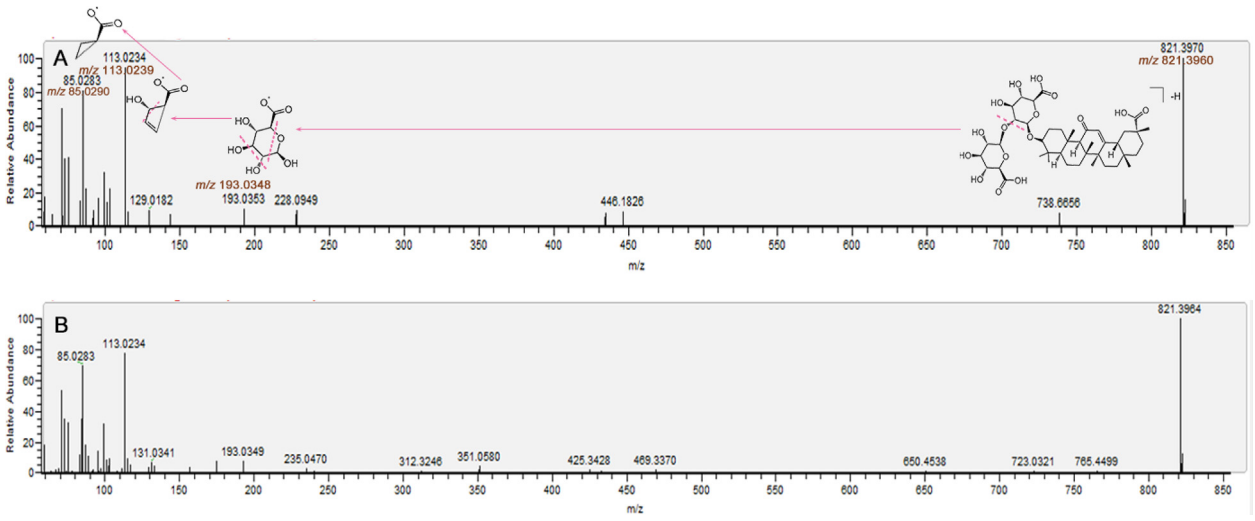

Fig. 9. The MS fragments of standard licoricesaponin H2 (upper) and peak at R.T. 13.10 (below). The m/z values in brown were calculated ones. The m/z calculation was based on the relative atomic masses of C (12.0000), H (1.007825), O (15.994915), and N (14.003074).

example, a famous TCM recipe *Xiaochaihu* Granule was advised to be used for *anti*-Covid-19. Its total proportion and specific proportion are 28.5% (2 ÷ 7) and 28.5%, respectively [13]. Undoubtedly, the recommended Q-markers possess high specificity, TCM theory relevance, and wide applicability.

In addition to TCM theory relevance, the efficiency-relevance was also an important character of these recommended Q-markers. As seen in Table 1, all of them have been reported to have similar *anti*-Covid-19 potential, to *Jinhua Qinggan* Granule [15–23]. Besides efficiency-relevance, they also showed good testability, because all of them exhibited strong peak sign and high separation-degree (Fig. 3). In particular, their R.T. values were respectively 3.85, 9.34, 9.92, 11.77, 13.1, and 14.26 min, meaning that they would be effectively separated by means of other analytic approaches as well.

Previous studies suggested that, all Q-markers could be detected out after body metabolism [24–30]. Among them, two Q-markers (**9** and **60**) could also withstand heating or illumination process, to be successfully detected out [31,32]; while three Q-markers (**9**, **60**, and **70**) have already been used in the current pharmacopoeia [13]. These apparently highlight the traceability of the recommended Q-markers system. In short, the recommend Q-markers have adhered to Liu's five principles, and thus they can be fully considered by Pharmacopoeia committee.

Finally, it should be emphasized that, (1) despite that these discussions are of sufficient evidence and

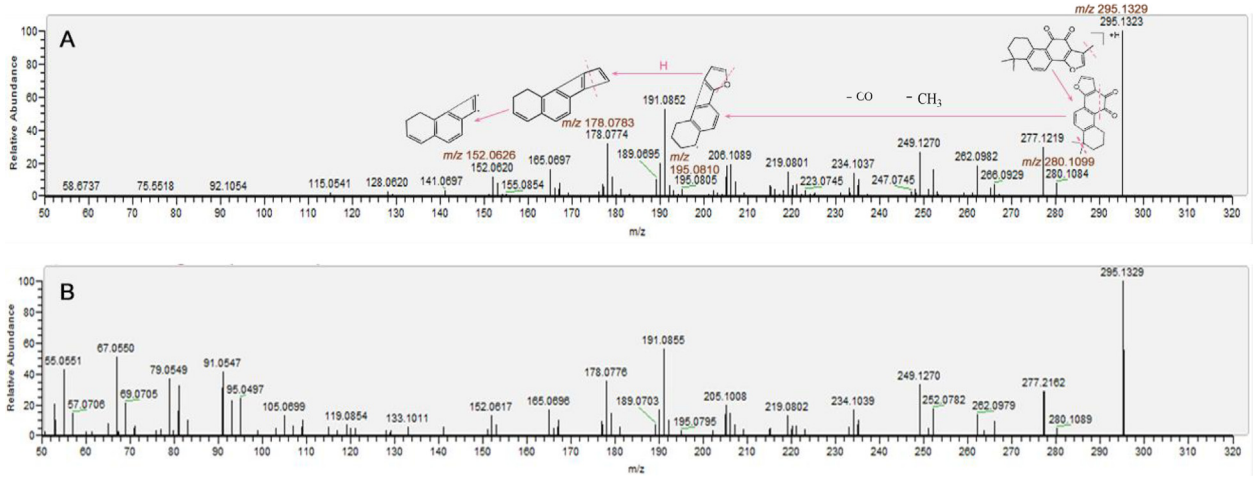

Fig. 10. The MS fragments of standard tanshinone IIA (upper) and peak at R.T. 14.26 (below). The m/z values in brown were calculated ones. The m/z calculation was based on the relative atomic masses of C (12.0000), H (1.007825), O (15.994915), and N (14.003074).

Table 2. The characters and relevant information of 6 recommended Q-markers.

Q-marker	characterized plants [13,33,36–40,44–46,62,72]	specificity	traceability	TCM theory-relevance	efficiency-relevance	testability
chlorogenic acid **(9)**	Jinyinhua; Mahuang; Niubangzi; Kuxingren; Lianqiao	×	√ [13,24]	√	√	√
acteoside **(28)**	Lianqiao, Huangqin	✓	√ [25]	√	√	√
peimisine **(40)**	Zhebeimu	√	√ [26]	√	√	√
baicalein **(60)**	Huangqin	√ [13]	√ [13,27,28]	√	√	√
licoricesaponin H2 **(65)**	Gancao	√ [62,89]	√ [29]	√	√	√
tanshinone IIA **(70)**	Danshen	√ [13]	√ [13,30]	√	√	√

logical deduction, however the official adoption of Q-marker candidates relies on the consideration of Pharmacopoeia Committee. Nevertheless, without these evidence, Pharmacopoeia committee cannot find a new and applicable Q-marker. In other words, the current study at least provides important and fundamental evidence for Pharmacopoeia Committee. (2) *Jinhua Qinggan* Granule as an emergency medicine is produced by only one factory nowadays. Thus, there was no accumulated evidence for further study (especially quantification comparison). If more pharmaceutical factories are approved for *Jinhua Qinggan* Granule manufacture in future, the Q-marker recommendation can be further validated for its Pharmacopoeia collection. Further validation can be achieved by the data from different manufacturers and corresponding threshold values of these Q-markers. (3) Nevertheless, the present study, as an academic activity, has not any administrative compulsion or legal authority.

5. Conclusions

By means of putative identification, *Jinhua Qinggan* Granule is evidenced to comprise 45 potential *anti*-Covid-19 constituents, including 20 flavonoids (vicenin-2, rutin, pectolinarigenin, isorhamnetin-3-*O*-*β*-D-Glucoside, *S*-naringenin, diosmin, luteolin 7-*O*-glucuronide, scutellarin, chrysin, formononetin, baicalein, wogonin, scutellarein, quercetin, vitexin, astragalin, luteoloside, isoquercitrin, schaftoside, and isoschaftoside), four caffeoylquinic acids (chlorogenic acid, neochlorogenic acid, 3,4-*O*-dicaffeoylquinic acid, and 1,3-*O*-dicaffeoylquinic acid), three phenolic acids (caffeic acid, danshensu ferulic acid, and *R*-rosmarinic acid), three alkaloids (caffeine, peimisine, and sophocarpine), three saponins (licoricesaponin H2, 18*β*-glycyrrhetinic acid, and liquiritin), two coumarins (esculetin and scopoletin), two anthraquinones (emodin and rhein), two phenanthraquinones (cryptotanshinone and tanshinone IIA), as well as one xanthone (mangiferin), one chalcone (isoliquiritigenin), one phenylpropanoid (acteoside), and one glycoside (salidroside).

In addition, there are other 28 "non-bioactive" constituents. Of all identified constituents, 28 isomers have been successfully recognized using our novel strategy. The detection of Danshensu, cryptotanshinone, and tanshinone IIA further indicates a confidential addition of Danshen into the Granule. Six potential *anti*-viral constituents are recommended as the Q-markers of *Jinhua Qinggan* Granule for the possible Pharmacopoeia collection, including chlorogenic acid, acteoside, peimisine, baicalein, licoricesaponin H2, and tanshinone IIA.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

None.

Authors' contributions

XL contributed to the project design and paper writing. JZ contributed to literature review and constituent identification. RC and CL contributed to data analyses and software. SC contributed to paper revision. All authors read and approved the final manuscript.

Availability of data and material

All the data used to support the findings of this study are available from the corresponding author upon reasonable request.

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Not applicable.

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