Rapid Profiling of Chemical Constituents in Qingfei Paidu Granules Using High Performance Liquid Chromatography Coupled with Q Exactive Mass Spectrometry

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Abstract
Qingfei Paidu (QFPD) granules have played a critical role during the Coronavirus Disease 2019 (COVID-19) in China. However, worldwide acceptance has been a problem because of the complex ingredients and unique theory of treatment. In this study, high-performance liquid chromatography (HPLC)-Q Exactive Orbitrap-mass spectrometry (MS) and the Orbitrap traditional Chinese medicine library (OTCML) were used to investigate the chemical constituents of QFPD granules. By comparing retention times, masses, isotope ion patterns, and MS² profiles, 108 compounds were putatively identified using the OTCML combined with manual verification, including 12 alkaloids, 49 flavonoids, 13 terpenoids, 14 phenylpropanoids, 4 phenolic acids, 5 phenols, and 11 other phytochemicals. Of these compounds, 17 were confirmed using reference standards. In addition, representative compounds of these different chemical types were used as examples to analyze the fragmentation pathways and characteristic product ions. Moreover, 20 herbs within the QFPD granules were also identified to establish the sources of these chemical components. This is the first rapid profiling of the chemical constituents of QFPD granules using HPLC-Q Exactive Orbitrap-MS and yields valuable information for further quality control and mechanistic studies of QFPD granules.

Keywords Chemical constituent identification · Qingfei Paidu granules · HPLC-Q Exactive Orbitrap-MS · Orbitrap traditional Chinese medicine library

Introduction
Qingfei Paidu (QFPD) granules and decoctions are effective traditional Chinese medicines (TCMs) that are included in the Guidelines for Diagnosis and Treatment of COVID-19 Pneumonia, issued by the National Heath Commission of the People’s Republic of China [1]. QFPD granules and decoctions are based on the following four formulae: Maxing-Shigan-Tang, Wuling-San, Xiaocaihu-Tang, and Shegan-Mahuang-Tang [2], which are different forms of prescription QFPD. QFPD granules contain 20 herbs: Ephedrae Herba, Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle, Armeniacae Semen Amarum, Cinnamomi Ramulus, Pogoste- monis Herba, Alismatis Rhizoma, Polyporus, Atractylodis Macrocephalae Rhizoma, Poria, Bupleuri Radix, Scutellariae Radix, Pinelliae Rhizoma Praeparatum Cum Zingibere Et Alumine, Zingiberis Rhizoma Recens, Asteris Radix Et Rhizoma, Farfarae Flos, Belamcandae Rhizoma, Asari Radix Et Rhizoma, Dioscoreae Rhizoma, Aurantii Fructus Immaturus, and Citri Reticulatae Pericarpium. In addition, QFPD contains the mineral Gypsum Fibrosum.

In China, QFPD granules and decoctions have been widely used to treat patients infected with SARS-CoV-2 owing to positive treatment results. Early treatment with prescription QFPD was associated with favorable patient outcomes and may be an effective strategy for epidemic control...
Functional network pharmacology analysis units showed that QFPD protected against COVID-19 through anti-viral and anti-inflammatory activities [2]. A systematic pharmacological study illustrated that QFPD exhibited immune regulation, anti-infection and anti-inflammatory properties, and multi-organ protection [3]. QFPD granules were, therefore, approved for market use by the National Medical Products Administration in China [4]. However, worldwide acceptance of QFPD granules is challenging because of the TCM complexity, and unique theory of treatment, in addition to quality and safety issues [5, 6]. Thus, comprehensive identification of the chemical components of QFPD granules is extremely critical for quality control, in addition to identification of the active ingredients and investigation of the mechanism-of-action.

Few analytical strategies have been applied to study the chemical constituents of QFPD decoctions, and no detailed analysis of the chemical composition of QFPD granules has been reported [7–9]. Hybrid quadrupole-Orbitrap mass spectrometry (MS) is a powerful tool for structure elucidation of TCMs due to its high resolution and high-quality MS² fragmentation patterns. In this study, high-performance liquid chromatography (HPLC)-Q Exactive Orbitrap-MS was used to analyze the chemical constituents of QFPD granules, with 108 compounds putatively identified, including 12 alkaloids, 49 flavonoids, 13 terpenoids, 14 phenylpropanoids, 4 phenolic acids, 5 phenols, and 11 other phytochemicals. The individual herbs within the QFPD granules were also analyzed. The aim of this study is to develop an analytical method for elucidating the chemical constituents of QFPD granules and provide valuable quality control and mechanism-of-action data.

Material and Methods

Reagents and Materials

QFPD granules were a gift from Renmin Hospital of Wuhan University. The 21 raw materials were purchased from Yifeng Pharmacy Chain Co., Ltd. (Changde, China). Acetonitrile (HPLC grade) and methanol (HPLC grade) were purchased from Merck (Darmstadt, Germany). Formic acid was purchased from Thermo Fisher Scientific (Waltham, MA, USA). Watsons distilled water was obtained from Jinrong Mall (Beijing, China).

Authentic standards of cytokine, sucrose, citric acid, uridine, adenosine, 2-pyridinelinecarboxylic acid, and guanosine were purchased from Sigma-Aldrich (St. Louis, MO, USA). Nicotinic acid was obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Nicotinamide and tangeterin were purchased from Shanghai Aladdin Bio-Chem Technology Co., Ltd. (Shanghai, China). Salicylic acid was acquired from Ascender Chemical Co., Ltd. (Shanghai, China). Glycyrrhizin acid, 18-β-glycyrrhetinic acid, isoliquiritigenin, baicalin, and narirutin were purchased from Shanghai Macklin Biochemical Co., Ltd. (Shanghai, China). Chlorogenic acid was a gift from Thermo Fisher Scientific.

Standard Solutions and Sample Preparations

The QFPD granules were ground, and the resultant powder (0.4 g) was accurately weighed, dissolved in 60% methanol (v/v; 20 mL), and sonicated for 30 min, resulting in partial precipitation of the QFPD granules. The solution was centrifuged, and the supernatant was filtered through a 0.22 μm membrane prior to HPLC-Q Exactive Orbitrap-MS.

The individual raw materials were treated using the same procedure.

The authentic standards were dissolved in 50% methanol and stored at – 80 °C. Prior to qualitative analysis, they were mixed appropriate concentrations and filtered using a 0.22 μm membrane.

HPLC-Q Exactive Hybrid Quadrupole-Orbitrap MS

LC–MS was performed using an UltiMate 3000 UPLC system (Thermo Fisher Scientific), autosampler, a vacuum degasser, binary pump, and column compartment. A Hypersil Gold aQ C18 column (2.1 × 150 mm, 3 μm) was used at 40 °C for chromatography. The mobile phase consisted of acetonitrile/0.1% formic acid (A) and water/0.1% formic acid (B) at a flow rate of 0.2 mL/min. The following gradient elution program was used: 0–2 min, 0–5% (A); 2–42 min, 5–95% (A); 42–46.9 min, 95% (A); 46.9–47 min, 95–5% (A); 47–50 min, 5% (A). The total run time was 50 min, and the sample injection volume was 5 μL.

A Q Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thermo Fisher Scientific) with heated electrospray ionization (ESI) was used. Source parameters were optimized with a spray voltage of 3.5 kV (+)/3.2 kV (−). The other parameters were set as follows: capillary temperature, 320 °C; auxiliary gas temperature, 350 °C; sheath gas, 40 Arb; auxiliary gas, 15 Arb; sweep gas, 0 Arb; S-lens RF level, 50.

The Orbitrap mass detector was operated in full scan plus data-dependent MS² mode. The MS resolution was set at 70,000 for the full scan and 17,500 for the MS² scan. The automatic gain control target and maximum injection time were 1 × 10⁶ ions capacity and 100 ms, respectively. The top N (N: the number of most abundant ions for fragmentation) was five, while the scan range was m/z 100–1500. The normalized collision energies were 20%.
Data Analysis Using the Orbitrap Traditional Chinese Medicine Library (OTCML) and Manual Verification

The raw data were imported into the Compound Discoverer (CD) software, which is integrated into the OTCML. The molecular masses, retention times, fragments, and peak areas from both the positive and negative ESI modes were compared to the mzVault library, which was integrated into CD. The mzVault spectral library (Thermo Fisher Scientific) contained the retention times, precise mass ions, and MS² fragments of 1200 commercial reference standards, which were analyzed using Q Exactive Orbitrap-MS. The software identified peaks with high mass accuracy (< 10 ppm) and an isotope pattern variation within 85%. The molecular compositions adhered to the H/C ratio rules and were matched to potential compounds using ring and double-bond equivalents. The MS² profiles were compared with the reference spectra from the mzVault library. Compounds were identified only when the match score was > 85. In addition, compound identification accuracy was improved by comparing the obtained data and possible fragmentation patterns with those in the literature, and the corresponding individual herb pieces components were analyzed to determine the source of each compound and elucidate chemical compositions.

Results and discussion

Positive and negative ion modes were used to detect the chemical compounds within the QFPD granules. The base peak chromatograms (BPCs) of the QFPD granules are shown in Fig. 1. In total, 108 compounds are putatively identified (Table 1). The BPCs of the individual herb pieces are shown in Figs. S1 and S2. Compound identification is summarized below.

Alkaloids

Twelve alkaloids were detected. Compounds 19, 20, 21, 15, and 16 are observed in the positive BPC of QFPD, with no matching identification results after data processing using the OTCML. The mass spectra of compounds 15, 19, and 21 display the same fragment ions at m/z 117.0701 (Fig. S3). The mass spectra of compounds 19 and 20 exhibit the same [M+H]+ ions at m/z 166.1226 (C10H15NO), with the same fragment ions also observed at m/z 148.1120 [M+H]

![Fig. 1 Base peak chromatograms of QFPD granules obtained using high performance liquid chromatography-Q Exactive hybrid quadrupole-Orbitrap mass spectrometry. A Electrospray ionization in the positive mode (ESI(+)), B electrospray ionization in the negative mode (ESI(−))](image-url)
Table 1 Identification of the chemical components of QFPD granules using high performance liquid chromatography-Q Exactive hybrid quadrupole-Orbitrap mass spectrometry combined with the Orbitrap traditional Chinese medicine library

| No. | RT (min) | Formula | Potential compound | Detected m/z | Characterized MS² | Compound class | Herb | Refs |
|-----|----------|---------|--------------------|--------------|-------------------|----------------|------|------|
| 1   | 2.11     | C₁₂H₂₂O₁₁ | Sucrose            | 341.1069 [M – H]⁻ | 89.0235          | Miscellaneous | PR   | [10] |
| 2   | 2.12     | C₄H₆NO₂  | 2-Pyrrolidinocarboxylic acid | 116.0709 [M + H]⁺ | 116.0708          | Miscellaneous | DR   | [11] |
| 3   | 2.12     | C₅H₇NO₂  | Cytosine           | 112.0508 [M + H]⁺ | 112.0508b         | Alkaloids      | AR   |      |
| 4   | 2.13     | C₅H₁₁NO₂ | Betaine            | 118.0865 [M + H]⁺ | 118.0864b         | Alkaloids      | AE   |      |
| 5   | 2.14     | C₆H₈O₇   | Trigonelline       | 138.0550 [M + H]⁺ | 138.0550b         | Alkaloids      | PC   | [12] |
| 6   | 2.2      | C₆H₈O₇   | Citric acid        | 191.0185 [M – H]⁻ | 111.0078b         | Miscellaneous | GR   |      |
| 7   | 2.66     | C₆H₇NO₂  | Nicotinic acid     | 124.0395 [M + H]⁺ | 124.0394b         | Alkaloids      |      |      |
| 8   | 2.69     | C₉H₁₂N₂O₅ | Uridine           | 243.0608 [M – H]⁻ | 200.0554          | Miscellaneous | PR   | [13] |
| 9   | 2.69     | C₉H₁₂N₂Oₐ | Nicotinamide      | 123.0555 [M + H]⁺ | 123.0554b         | Alkaloids      | FF   |      |
| 10  | 2.73     | C₁₀H₁₃N₂O₅ | Adenosine         | 268.1041 [M + H]⁺ | 136.0618b         | Miscellaneous | PC   | [14] |
| 11  | 2.87     | C₁₀H₁₅N₂Oₐ | Guanosine         | 284.0989 [M + H]⁺ | 152.0567b         | Miscellaneous | PC   | [14] |
| 12  | 3.41     | C₁₀H₁₃O₇ | Gallic acid        | 169.013 [M – H]⁻ | 125.0233b         | Phenolic acids |      |      |
| 13  | 3.9      | C₉H₁₅N₂O | l-Phenylalanine   | 166.0863 [M + H]⁺ | 120.0809b         | Miscellaneous |      |      |
| 14  | 4.22     | C₆H₈O₇   | 5-Hydroxymethylfurfural | 127.0392 [M + H]⁺ | 109.0288b         | Miscellaneous | PC   | [15] |
| 15  | 4.68     | C₆H₆NO   | l-norephedrine    | 152.1069 [M + H]⁺ | 134.0965b         | Alkaloids      | EH   | [16] |
| 16  | 5.12     | C₆H₆NO   | d-norpseudoephedrine | 152.1069 [M + H]⁺ | 134.0965b         | Alkaloids      | EH   | [16] |
| 17  | 5.24     | C₁₅H₁₄O₇ | (−)-Gallocatechin | 305.0651 [M – H]⁻ | 219.0654          | Phenols        |      |      |
| 18  | 5.32     | C₇H₆O₄   | Protocatechuic acid | 153.0181 [M – H]⁻ | 109.0284b         | Phenolic acids | GR   | [15] |
| 19  | 6.09     | C₉H₁₃NO  | l-ephedrine       | 166.1226 [M + H]⁺ | 148.1120b         | Alkaloids      | EH   | [16] |
| 20  | 6.47     | C₁₀H₁₃NO | d-pseudoephedrine | 166.1226 [M + H]⁺ | 148.1120b         | Alkaloids      | EH   | [16] |
| 21  | 6.99     | C₁₁H₁₂NO | Methylephedrine   | 180.1382 [M + H]⁺ | 162.1276b         | Alkaloids      | EH   | [16] |
| 22  | 7.26     | C₆H₆O₃   | Protocatechualdehyde | 137.0233 [M – H]⁻ | 137.0233b         | Phenols        | CR   | [15] |
Table 1 (continued)

| No. | RT (min) | Formula       | Potential compound                                | Detected m/z          | Characterized MS<sup>2</sup> | Compound class       | Herb | Refs  |
|-----|----------|---------------|--------------------------------------------------|-----------------------|-----------------------------|----------------------|------|-------|
| 23c | 9.16     | C<sub>20</sub>H<sub>27</sub>NO<sub>11</sub> | Amygdalin                             | 456.1492 [M – H]<sup>−</sup> | 323.0963, 221.0653, 161.0443, 59.0132<sup>b</sup> | Miscellaneous       | AS   | [17]  |
| 24<sup>ad</sup> | 9.43     | C<sub>16</sub>H<sub>18</sub>O<sub>9</sub> | Chlorogenic acid                       | 353.0862 [M – H]<sup>−</sup> | 191.0548<sup>b</sup>, 135.0441, 179.0337 | Phenylpropanoids    | FF   | [18]  |
| 25  | 9.46     | C<sub>9</sub>H<sub>10</sub>O<sub>4</sub> | Esculetin                              | 177.0181 [M – H]<sup>−</sup> | 177.0180<sup>b</sup>, 149.0236, 133.0284, 105.0336 | Phenylpropanoids    |      |       |
| 26  | 9.48     | C<sub>10</sub>H<sub>16</sub>O<sub>5</sub> | p-Hydroxybenzaldehyde                   | 212.0285 [M – H]<sup>−</sup> | 121.0284<sup>b</sup>, 93.0336 | Phenols             |      |       |
| 27  | 9.78     | C<sub>8</sub>H<sub>10</sub>O<sub>4</sub> | Caffeic acid                           | 179.0337 [M – H]<sup>−</sup> | 135.0441<sup>b</sup> | Phenolic acids       |      |       |
| 28<sup>a</sup> | 10.49   | C<sub>13</sub>H<sub>14</sub>O<sub>6</sub> | Catechin hydrate                       | 289.0703 [M – H]<sup>−</sup> | 245.0805, 123.044, 109.0284<sup>b</sup> | Flavonoids          |      |       |
| 29<sup>a</sup> | 10.63   | C<sub>15</sub>H<sub>20</sub>O<sub>7</sub> | Taxifolin                              | 303.0494 [M – H]<sup>−</sup> | 177.018, 125.0233<sup>b</sup> | Flavonoids          | SR   | [19]  |
| 30<sup>c</sup> | 10.98   | C<sub>22</sub>H<sub>26</sub>O<sub>15</sub> | Vicenin II                             | 593.1482 [M – H]<sup>−</sup> | 353.0648<sup>b</sup>, 383.0753, 473.1062, 297.075 | Flavonoids          | GR   | [8]   |
| 31  | 11.12    | C<sub>23</sub>H<sub>25</sub>O<sub>12</sub> | 1,3-Dicaffeoylquinic acid              | 515.1168 [M – H]<sup>−</sup> | 353.0859, 191.0547<sup>b</sup>, 179.0336, 135.0444 | Phenylpropanoids    |      |       |
| 32  | 11.87    | C<sub>9</sub>H<sub>10</sub>O<sub>4</sub> | p-Coumaric acid                        | 163.0400 [M – H]<sup>−</sup> | 119.0496<sup>b</sup>, 163.0394 | Phenylpropanoids    |      |       |
| 33<sup>ae</sup> | 11.95   | C<sub>26</sub>H<sub>28</sub>O<sub>14</sub> | Isoschaftoside                         | 563.1376 [M – H]<sup>−</sup> | 353.0648<sup>b</sup>, 383.0754, 473.1073 | Flavonoids          | GR   | [20]  |
| 34  | 11.96    | C<sub>10</sub>H<sub>14</sub>O<sub>4</sub> | 3,5-Dimethoxy-4-hydroxybenzaldehyde     | 183.0652 [M + H]<sup>+</sup> | 140.0469, 123.0443, 95.0497<sup>b</sup> | Phenols             | CR   | [15]  |
| 35  | 12.18    | C<sub>21</sub>H<sub>20</sub>O<sub>11</sub> | Orientin                               | 447.0913 [M – H]<sup>−</sup> | 357.06, 327.0496<sup>b</sup>, 299.0541, 133.028 | Alkaloids           | CP   | [21]  |
| 36  | 12.6     | C<sub>10</sub>H<sub>14</sub>O<sub>4</sub> | Scopoletin                             | 193.0497 [M + H]<sup>+</sup> | 193.0496<sup>b</sup>, 178.026, 133.0285 | Phenylpropanoids    | AF   | [22]  |
| 37<sup>ae</sup> | 12.7    | C<sub>20</sub>H<sub>21</sub>O<sub>13</sub> | Naringenin 7-O-(2-β-D-apiofuranosyl)-β-D-glucopyranoside | 549.1588 [M – H]<sup>−</sup> | 255.0649, 135.0077, 119.0492<sup>b</sup> | Flavonoids          | GR   | [20]  |
| 38  | 12.84    | C<sub>10</sub>H<sub>14</sub>O<sub>4</sub> | Ferulic acid                           | 193.0492 [M – H]<sup>−</sup> | 178.0258, 134.0362<sup>b</sup> | Phenylpropanoids    |      |       |
| 39  | 13.03    | C<sub>11</sub>H<sub>10</sub>O<sub>5</sub> | Isofraxidin                            | 223.0601 [M + H]<sup>+</sup> | 223.0601<sup>b</sup>, 190.0261, 162.0311 | Phenylpropanoids    |      |       |
| 40<sup>f</sup> | 13.04   | C<sub>25</sub>H<sub>30</sub>O<sub>15</sub> | Eriocitrin                             | 595.1638 [M – H]<sup>−</sup> | 459.1152, 151.0025<sup>b</sup>, 135.0441 | Flavonoids          | CP   | [21]  |
| 41<sup>c</sup> | 13.04   | C<sub>28</sub>H<sub>30</sub>O<sub>13</sub> | Liquiritin apioside                    | 549.1586 [M – H]<sup>−</sup> | 119.0491<sup>b</sup>, 135.0077, 255.0649 | Flavonoids          | GR   | [20]  |
| No. | RT (min) | Formula | Potential compound | Detected m/z | Characterized MS<sup>2</sup> | Compound class | Herb | Refs |
|-----|----------|---------|--------------------|--------------|-----------------------------|----------------|------|------|
| 42<sup>c</sup> | 13.18    | C<sub>27</sub>H<sub>30</sub>O<sub>16</sub> | Rutin | 609.1431[m – H]<sup>−</sup> | 300.0258<sup>b</sup> 271.0234 255.0284 | Flavonoids |      |      |
| 43  | 13.39    | C<sub>9</sub>H<sub>6</sub>O<sub>4</sub> | 5,7-Dihydroxychromone | 177.0180[m – H]<sup>−</sup> | 177.0180<sup>b</sup> 135.0076 | Flavonoids |      |      |
| 44<sup>d</sup> | 13.75    | C<sub>9</sub>H<sub>6</sub>O<sub>3</sub> | Salicylic acid | 137.0233[m – H]<sup>−</sup> | 137.0233<sup>b</sup> 93.0337<sup>b</sup> | Phenolic acids | AE [15] |      |
| 45  | 13.8     | C<sub>14</sub>H<sub>12</sub>O<sub>4</sub> | Piceatannol | 243.0648[m – H]<sup>−</sup> | 243.0648<sup>b</sup> 201.0544 159.0439 | Phenols |      |      |
| 46  | 13.84    | C<sub>25</sub>H<sub>26</sub>O<sub>12</sub> | Isochlorogenic acid B | 515.1165[m – H]<sup>−</sup> | 353.0856 191.0547 179.0336 135.0440<sup>b</sup> | Phenylpropanoids | FF [18] |      |
| 47<sup>cd</sup> | 13.89    | C<sub>25</sub>H<sub>26</sub>O<sub>14</sub> | Narirutin | 581.1863 [M+H]<sup>+</sup> | 273.0755<sup>b</sup> 153.0181 85.0289 71.0498 | Flavonoids | CP [21] |      |
| 48<sup>a</sup> | 14.02    | C<sub>29</sub>H<sub>36</sub>O<sub>15</sub> | Verbascoside | 623.1945[m – H]<sup>−</sup> | 461.1639 161.0231<sup>b</sup> 133.0283 | Phenylpropanoids | PH [15] |      |
| 49  | 14.13    | C<sub>25</sub>H<sub>26</sub>O<sub>12</sub> | 3,5-Dicaffeoylquinic acid | 515.1165[m – H]<sup>−</sup> | 353.0878 191.0558<sup>b</sup> 179.0346 135.0448<sup>b</sup> | Phenylpropanoids | FF [18] |      |
| 50  | 14.14    | C<sub>22</sub>H<sub>22</sub>O<sub>4</sub> | Tectoridin | 463.1234[M+H]<sup>+</sup> | 301.0705<sup>b</sup> 286.047 | Flavonoids | BH [24] [25] |      |
| 51<sup>ad</sup> | 14.27    | C<sub>27</sub>H<sub>26</sub>O<sub>14</sub> | Naringin | 579.1688[m – H]<sup>−</sup> | 271.0597 151.0025<sup>b</sup> 119.0491 107.0129 | Flavonoids | AF [23] CP [21] |      |
| 52  | 14.57    | C<sub>9</sub>H<sub>6</sub>O<sub>4</sub> | Azelaic acid | 187.0962[m – H]<sup>−</sup> | 125.0960<sup>b</sup> 97.0649 | Miscellaneous |      |      |
| 53  | 14.62    | C<sub>24</sub>H<sub>24</sub>O<sub>15</sub> | Neohesperidin | 609.1796[m – H]<sup>−</sup> | 609.1791 301.0700<sup>b</sup> 286.0466 | Flavonoids | CP |      |
| 54  | 14.95    | C<sub>25</sub>H<sub>26</sub>O<sub>12</sub> | Isochlorogenic acid C | 515.1166[m – H]<sup>−</sup> | 353.0888 191.0558 173.0452 135.0448<sup>b</sup> | Phenylpropanoids | FF [18] |      |
| 55<sup>c</sup> | 15       | C<sub>26</sub>H<sub>26</sub>O<sub>15</sub> | Hesperidin | 609.1796[m – H]<sup>−</sup> | 609.1791 301.0699<sup>b</sup> 286.0466 | Flavonoids | CP [26] |      |
| 56  | 15.06    | C<sub>26</sub>H<sub>26</sub>O<sub>13</sub> | Iridin | 523.1445[M+H]<sup>+</sup> | 361.0915<sup>b</sup> 346.0679 331.0445 | Flavonoids | BH [25] |      |
| 57  | 15.06    | C<sub>9</sub>H<sub>6</sub>O<sub>2</sub> | Coumarin | 147.0440[M+H]<sup>+</sup> | 147.0440<sup>b</sup> 103.0546 91.0547 | Phenylpropanoids | CR [15] EH |      |
| 58<sup>a</sup> | 15.63    | C<sub>14</sub>H<sub>12</sub>O<sub>6</sub> | Eriodictyol | 287.0547[m – H]<sup>−</sup> | 287.0547 161.0231 125.0233<sup>b</sup> | Flavonoids | AF [23] |      |
| 59<sup>c</sup> | 15.86    | C<sub>26</sub>H<sub>30</sub>O<sub>13</sub> | Isoliquiritin apioside | 549.1589[m – H]<sup>−</sup> | 255.0649 153.0181 135.0077 119.0491<sup>b</sup> | Flavonoids | GR [20] |      |
Table 1 (continued)

| No. | RT (min) | Formula | Potential compound | Detected \( m/z \) | Characterized MS\(^2\) | Compound class | Herb | Refs |
|-----|----------|---------|--------------------|---------------------|------------------------|----------------|------|------|
| 60  | 16.06    | C\(_{22}\)H\(_{22}\)O\(_9\) | Ononin            | 431.1336 [M + H]\(^+\) | 269.0807\(^b\)          | Flavonoids     | GR   | [27] |
| 61\(^{ed}\) | 16.08    | C\(_{21}\)H\(_{18}\)O\(_{11}\) | Baicalin          | 445.0753 [M – H]\(^-\) | 269.0439\(^b\)          | Flavonoids     | SR   | [19] |
| 62  | 16.15    | C\(_{21}\)H\(_{20}\)O\(_{10}\) | Oroxin A         | 433.1129 [M + H]\(^+\) | 271.0599\(^b\)          | Flavonoids     | SR   | [19] |
| 63\(^{e}\) | 16.23    | C\(_{21}\)H\(_{22}\)O\(_9\) | Isoliquiritin     | 419.1334 [M + H]\(^+\) | 257.0806\(^b\)          | Flavonoids     | GR   | [20] |
| 64\(^{e}\) | 16.51    | C\(_{15}\)H\(_{12}\)O\(_4\) | Liquiritigenin   | 255.0651 [M – H]\(^-\) | 135.0078\(^b\)          | Flavonoids     | GR   | [20] |
| 65  | 16.87    | C\(_{11}\)H\(_{4}\)O\(_4\) | Bergaptol         | 201.0180 [M – H]\(^-\) | 201.0192\(^b\)          | Phenylpropanoids |      |      |
| 66\(^{e}\) | 16.92    | C\(_{21}\)H\(_{18}\)O\(_{11}\) | Norwogonin-8-gluconide | 445.0753 [M – H]\(^-\) | 269.0441\(^b\)          | Flavonoids     | SR   | [19] |
| 67  | 17.2     | C\(_{24}\)H\(_{34}\)O\(_{14}\) | Poncirin          | 593.1842 [M – H]\(^-\) | 593.184              | Flavonoids     | AF   | [23] |
| 68  | 17.24    | C\(_{21}\)H\(_{18}\)O\(_{11}\) | Norwogonin-7-gluconide | 445.0752 [M – H]\(^-\) | 269.0439\(^b\)          | Flavonoids     | SR   | [19] |
| 69\(^{e}\) | 17.51    | C\(_{22}\)H\(_{20}\)O\(_{11}\) | Oroxylin A-7-O-β-d-gluconide | 459.0910 [M – H]\(^-\) | 283.0595              | Flavonoids     | SR   | [19] |
| 70\(^{e}\) | 18.11    | C\(_{21}\)H\(_{18}\)O\(_{11}\) | Baicalein-6-gluconide | 445.0754 [M – H]\(^-\) | 269.0441\(^b\)          | Flavonoids     | SR   | [19] |
| 71\(^{e}\) | 18.14    | C\(_{22}\)H\(_{20}\)O\(_{11}\) | Wogonoside        | 459.0909 [M – H]\(^-\) | 283.0595              | Flavonoids     | SR   | [19] |
| 72  | 18.58    | C\(_{13}\)H\(_{12}\)O\(_3\) | Naringenin chalcone | 273.0756 [M + H]\(^+\) | 273.0757              | Flavonoids     | GR   | [20] |
| 73\(^{e}\) | 19.32    | C\(_{16}\)H\(_{14}\)O\(_6\) | Hesperetin        | 301.0702 [M – H]\(^-\) | 301.0702\(^b\)          | Flavonoids     | CP   | [26] |
| 74  | 19.38    | C\(_{16}\)H\(_{12}\)O\(_6\) | Tectorigenin      | 299.0546 [M – H]\(^-\) | 284.0301\(^b\)          | Flavonoids     |      |      |
| 75\(^{ec}\) | 20.01    | C\(_{18}\)H\(_{16}\)O\(_8\) | Irigenin          | 359.0756 [M – H]\(^-\) | 344.0519\(^b\)          | Flavonoids     | BH   | [24] |
| 76  | 20.03    | C\(_{16}\)H\(_{12}\)O\(_7\) | Isorhamnetin      | 315.0496 [M – H]\(^-\) | 315.0496\(^b\)          | Flavonoids     | AE   | [28] |
| 77\(^{e}\) | 20.15    | C\(_{13}\)H\(_{14}\)O\(_7\) | Iristectorigenin B | 329.0652 [M – H]\(^-\) | 314.0417\(^b\)          | Flavonoids     | BH   | [24] |
| 78  | 20.39    | C\(_{15}\)H\(_{10}\)O\(_5\) | Baicalein         | 269.0443 [M – H]\(^-\) | 269.0457\(^b\)          | Flavonoids     | SR   | [19] |
| 79\(^{ed}\) | 20.97    | C\(_{15}\)H\(_{12}\)O\(_4\) | Isoliquiritigenin | 255.0650 [M – H]\(^-\) | 135.0076\(^b\)          | Flavonoids     | GR   | [20] |
| 80  | 21.08    | C\(_{16}\)H\(_{12}\)O\(_4\) | Formononetin      | 269.0807 [M + H]\(^+\) | 269.0807\(^b\)          | Flavonoids     | GR   | [20] |
| No.  | RT (min) | Formula       | Potential compound          | Detected m/z (ESI) | Characterized MS² | Compound class | Herb | Refs |
|------|---------|---------------|-----------------------------|-------------------|-------------------|----------------|------|------|
| 81a  | 21.35   | C_{15}H_{16}O_{4} | Isomeranzin                | 261.1119 [M + H]⁺ | 189.0546b, 159.0439, 131.0492 | Phenylpropanoids |      |      |
| 82a  | 21.65   | C_{42}H_{62}O_{17} | Licorice-saponin G2         | 837.3869 [M – H]⁻ | 837.386, 351.0552, 193.0341, 113.0235b | Terpenoids    | GR  | [20] |
| 83c  | 21.83   | C_{26}H_{30}O_{8} | Limonin                     | 469.1846 [M – H]⁻ | 469.1831b, 249.0909, 229.1214 | Terpenoids    | AF  | [22] |
| 84   | 21.83   | C_{15}H_{22}O_{2} | Curcumenol                 | 235.1693 [M + H]⁺ | 235.169, 217.1558, 199.1482b | Terpenoids    |      |      |
| 85   | 22.15   | C_{20}H_{20}O_{7} | Isosinensetin              | 373.1283 [M + H]⁺ | 373.1281b, 343.0812 | Flavonoids    | CP  | [26] |
| 86c  | 22.64   | C_{30}H_{46}O_{4} | 18 β-Glycyrrhetinic acid    | 471.3469 [M + H]⁺ | 417.3471b, 453.3362 | Terpenoids    | GR  | [29] |
| 87c  | 22.65   | C_{42}H_{62}O_{16} | Glycyrrhizic acid          | 821.3926 [M – H]⁻ | 821.3915b, 351.056, 113.0234 | Terpenoids    | GR  | [20] |
| 88   | 22.72   | C_{20}H_{16}O_{6} | Irisflorentin              | 387.1073 [M + H]⁺ | 387.1073b, 372.0843, 357.0603, 329.0654 | Flavonoids    | BH  | [25] |
| 89   | 22.84   | C_{20}H_{20}O_{7} | Senisetin                  | 373.1282 [M + H]⁺ | 373.1281b, 343.0809 | Flavonoids    | CP  | [26] |
| 90   | 22.98   | C_{14}H_{14}O_{6} | Dichotomitin               | 359.0762 [M + H]⁺ | 359.0761b, 344.0526, 326.0421, 299.0549 | Flavonoids    | BH  | [24] |
| 91a  | 23.16   | C_{16}H_{12}O_{5} | Wogonin                    | 285.0757 [M + H]⁺ | 285.0756, 270.0521b | Flavonoids    | SR  | [19] |
| 92   | 23.34   | C_{42}H_{62}O_{16} | isomer of Glycyrrhizic acid | 821.3922 [M – H]⁻ | 821.3919b, 351.0551, 113.0235 | Terpenoids    | GR  |      |
| 93c  | 23.57   | C_{42}H_{68}O_{13} | Saikosaponin A             | 825.4599 [M + COOH]⁻ | 779.4534b, 617.4010, 59.0132 | Terpenoids    | BR  | [26] |
| 94   | 23.91   | C_{17}H_{14}O_{6} | Pectolinarigenin           | 313.0703 [M – H]⁻ | 313.0701, 283.0233b, 255.0286 | Flavonoids    | SR  | [19] |
| 95   | 23.99   | C_{21}H_{22}O_{6} | Nobiletin                  | 403.1388 [M + H]⁺ | 403.1388, 373.0917b, 211.0238, 183.0288 | Flavonoids    | CP  | [26] |
| 96a  | 24.04   | C_{19}H_{14}O_{6} | 6-Demethoxytangeretin      | 343.1174 [M + H]⁺ | 343.1173, 313.0705b, 285.0756 | Flavonoids    | CP  | [26] |
| 97c  | 24.09   | C_{42}H_{68}O_{13} | Saikosaponin B1            | 825.4599 [M + COOH]⁻ | 779.4542b, 617.4028, 59.0132 | Terpenoids    | BR  |      |
| 98c  | 24.13   | C_{16}H_{12}O_{5} | Oroxylin A                 | 285.0758 [M + H]⁺ | 285.0757, 270.0523b, 168.0054 | Flavonoids    | SR  | [19] |

GR: Glycyrrhiza uralensis; CP: C. pachypodi; BH: B. hirsutum; SR: S. root; Refs: [19]–[26].
– H2O]+ and 133.0887 [M + H – H2O – CH3]+. According to the literature [16], they are identified as L-ephedrine (19) and D-pseudoephedrine (20). The mass spectrum of compound 21 (methylephedrine) reveals a peak representing the protonated molecule [M + H]+, at m/z 180.1382, and fragment ion peaks at m/z 162.1276 [M + H – H2O]+ and 147.1041 [M + H – H2O – CH3]+. The mass spectra of compounds 15 (α-norephedrine) and 16 (D-norpseudoephedrine) reveal the same peak at m/z 152.1069, and MS2 peaks at m/z 134.0965 [M + H – H2O]+ and 117.0701 [M + H – H2O – NH3]+. However, they exhibit different retention times. These compounds are phytochemicals present in Ephedrae Herba.

Table 1 (continued)

| No. | RT (min) | Formula | Potential compound | Detected m/z | Characterized MS2 | Compound class | Herb | Refs |
|-----|---------|---------|-------------------|--------------|------------------|---------------|------|------|
| 99  | 24.21   | C15H20O3 | Atractylenolide III | 249.1486 [M + H]+ | 231.1379b | Terpenoids | AM | [30] |
|     |         |         |                   | 249.1481 | 213.1276 |         |      |      |
|     |         |         |                   | 163.0752 |         |         |      |      |
| 100 | 24.49   | C22H25O9 | Heptamethoxyflavone | 433.1493 [M + H]+ | 403.1021 | Flavonoids | GR | [26] |
|     |         |         |                   | 433.1492 | 165.0546 |         |      |      |
| 101 | 24.7    | C42H68O13 | Saikosaponin D | 825.4594 [M + COOH]− | 779.4537b | Terpenoids | BR |      |
|     |         |         |                   | 617.4034 | 59.0132 |         |      |      |
| 102 | 25.67   | C20H20O7 | Tangeretin | 373.1280 [M + H]+ | 373.1278 | Flavonoids | CP | [26] |
|     |         |         |                   | 358.1043 | 343.0808b |         |      |      |
|     |         |         |                   | 328.0573 |         |         |      |      |
| 103 | 26.41   | C20H20O8 | 5-O-Demethylnobiletin | 389.1230 [M + H]+ | 389.1227b | Flavonoids | CP | [21] |
|     |         |         |                   | 359.076 | 341.0652 |         |      |      |
| 104 | 26.68   | C32H48O6 | Alisol C 23-acetate | 529.3526 [M + H]+ | 529.3521b | Terpenoids | AR | [31] |
|     |         |         |                   | 469.3314 | 451.3204 |         |      |      |
|     |         |         |                   | 415.2842 |         |         |      |      |
| 105 | 27.85   | C15H20O2 | Atractylenolide II | 233.1536 [M + H]+ | 233.1536b | Terpenoids | AM | [30] |
|     |         |         |                   | 215.1432 | 187.1482 |         |      |      |
|     |         |         |                   | 151.0753 |         |         |      |      |
| 106 | 27.94   | C12H16O4 | Pogostone | 225.1122 [M + H]+ | 207.1015 | Miscellaneous | PH | [32] |
|     |         |         |                   | 139.039 | 81.0705b |         |      |      |
| 107 | 34.7    | C32H50O5 | Alisol B 23-acetate | 515.3733 [M + H]+ | 437.3412 | Terpenoids | AR | [31] |
|     |         |         |                   | 339.2679 | 419.3305 |         |      |      |
|     |         |         |                   | 97.0653b |         |         |      |      |
| 108 | 35.79   | C18H30O2 | α-Linolenic acid | 279.2318 [M + H]+ | 95.086 | Alkaloids |      |      |
|     |         |         |                   | 81.0705 | 67.055b |         |      |      |

**RT** retention time

a Representative retention time, as more than one peak was identified for this compound

b Base fragment ion

c Compounds detected using both the positive and negative electrospray ionization modes. m/z: mass-to-charge ratio

d Compounds identified by comparison with reference standards. Herb: Compound detected within herb experimentally and also the reference reported the source of the compound. Ref.: The references that reported the sources of the compounds. EH (Ephedrae Herba), GR (Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle), AS (Armeniacae semen Amarum), CR (Cinnamomi Ramulus), PH (Pogostemonis Herba), AR (Alismatis Rhizoma), PP (Polytropus), AM (Atractylodis Macrocephalae Rhizoma), PR (Poria), BR (Bupleuri Radix), SR (Scutellariae Radix); PC (Pinelliae Rhizoma Praeparatum Cum Zingibere Et Alumine), ZR (Zingiberis Rhizoma Recens), AE (Asteris Radix Et Rhizoma), FF (Farfarae Flos), BH (Belamcandae Rhizoma), RE (Asari Radix Et Rhizoma), DR (Dioscoreae Rhizoma), AF (Aurantii Fructus Immaturus); CP (Citri Reticulatae Pericarpium)
standards. Nicotinic acid and nicotinamide exhibit the same structural skeleton, and fragment ion peaks at \( m/z \) 96.0448 \([\text{M} + \text{H} – \text{CO}]^+\) are observed in the MS\(^2\) profiles. Their possible fragmentation pathways and library match results are shown in Fig. S4. The MS\(^2\) profile of compound 5 reveals a peak representing a protonated molecule, \([\text{M} + \text{H}]^+\), at \( m/z \) 138.0550 and peaks at \( m/z \) 110.0603 \([\text{M} + \text{H} – \text{CO}]^+\) and 94.0656 \([\text{M} + \text{H} – \text{CO} – \text{O}]^+\). Therefore, compound 5 is deduced to be trigonelline.

Flavonoids

Forty-nine compounds were identified as flavonoids. Compounds 47 and 51 were identified as narirutin and naringin, respectively, by comparison with the OTCML. Furthermore, compound 47 was confirmed using a reference standard. They were detected in both the positive and negative ESI modes, displaying similar MS and MS\(^2\) profiles and library match results are shown in Fig. S5. As examples, the mass spectra of compounds 85 and 89 reveal peaks representing \([\text{M} + \text{H}]^+\) ions at \( m/z \) 373.1283 and characterized fragment ions at \( m/z \) 343.08 \([\text{M} + \text{H} – 2\text{CH}_3]^+\). The spectra are very similar, and the compounds were identified using the OTCML by the different retention times and slight differences in the spectra. Compound 102 (tangeretin) was further confirmed using a reference standard. Compounds 30 and 33 showed similar MS\(^2\) patterns, but the molecular ions were different, indicating the same basic structure. These compounds were assigned as vicenin II [8] and isoschaftoside [20, 33], respectively. For example, the mass spectrum of compound 30 revealed peaks representing the \([\text{M} – \text{H}]^-\) ion at \( m/z \) 593.1482 and fragment ions at \( m/z \) 297.0750 \([\text{M} – \text{H} – \text{Glc} – \text{Glc}]^-\), \( m/z \) 473.1062 \([\text{M} – \text{H} – 120]^-\), \( m/z \) 383.0753 \([\text{M} – \text{H} – 210]^-\), and \( m/z \) 353.0648 \([\text{M} – \text{H} – 240]^-\). These are characterized fragment ions of the hexose ring-opening reaction [33]. The similarities of the MS and MS\(^2\) profiles of compounds 37, 41, and 59 indicated isomers. By comparing the data in the OTCML combined with literature data [20], they were deduced as naringenin 7-O-(2-β-D-apiofuranosyl)-β-D-glucopyranoside (37), liquiritin apioside (41), and isoliquiritin apioside (59). The mass spectra of compounds 61, 68, 66, and 70 revealed peaks representing \([\text{M} – \text{H}]^-\) ions at \( m/z \) 445.07 and dominant fragment ions at \( m/z \) 269.04, along with \([\text{M} + \text{H}]^+\) ions at \( m/z \) 447.09 and dominant fragment ions at \( m/z \) 271.05. Individual herb pieces component mass spectra showed that these compounds, baicalin (61), norwogonin-7-glucuronide (68), norwogonin-8-glucuronide (66) and baicalein-6-glucuronide (70), were chemical components of Scutellariae Radix [19], and baicalin (61) was identified using a reference standard. Based on the literature [26], compounds 73 and 100 were assigned as hesperetin and heptamethoxyflavone, respectively. Compound 79 (isoliquiritigenin) was identified using a reference standard.

Phenylpropanoids

Fourteen compounds were identified as phenylpropanoids. Compounds 31 (1,3-dicaffeoylquinic acid), 46 (isochlorogenic acid B), 49 (3,5-dicaffeoylquinic acid) and 53 (isochlorogenic acid C) were identified using the OTCML. Compound 24 (chlorogenic acid) was identified using a reference standard. Compounds 31, 46, 49 and 53 were isomers with skeletons similar to those of quinic and caffeic acid, generating similar MS and MS\(^2\) profiles and distinguished by their retention times. For example, the MS\(^2\) profile of compound 46 revealed peaks representing fragment ions at \( m/z \) 191.0547 \([\text{quinic acid} – \text{H}]^-\), 179.0336 \([\text{caffeic acid} – \text{H}]^-\) and 135.0440 \([\text{caffeic acid} – \text{CO}_2 – \text{H}]^-\). The mass spectrum of compound 38 (ferulic acid) showed peaks representing a \([\text{M} – \text{H}]^-\) ion at \( m/z \) 193.0492 and the main fragment ions at \( m/z \) 134.0362 \([\text{M} – \text{H} – \text{CH}_3 – \text{CO}_2]^+\) and 178.0258 \([\text{M} – \text{H} – \text{CH}_3]^+\). Compounds 32 (p-coumaric acid), 57 (coumarin), 65 (bergaptole) and 25 (esculetin) were assigned using the OTCML.

Phenolic Acids and Phenols

Four phenolic acids were identified, and they exhibited the same fragmentation pattern. The MS\(^2\) profile of compound 12 (gallic acid) revealed peaks representing \([\text{M} – \text{H}]^-\) at
and dominant fragment ions at m/z 529.3521 [M + H]+, 97.0285 [M – H – CO2 – CO]− and 69.0337 [M – H – CO2 – CO – CO]−. The mass spectrum of compound 18 (protocatechuic acid) revealed a peak representing a base fragment ion at m/z 109.0284 [M – H – CO2]−. Compound 44 (salicylic acid) was identified by comparison with a reference standard. All of these compounds exhibited successive losses of H2O, CO and CO2 during fragmentation [34, 35].

Five phenols were identified. Compound 26 (p-hydroxybenzaldehyde) produced several clear fragment ions at high collision energies. Compound 22 (protocatechualdehyde) was identified using the OTCML. The phenols also showed neutral losses of CO, CH3 and H2O in the MS2 profiles.

**Terpenoids**

Thirteen terpenoids are identified. The mass spectra of compounds 82 and 87 reveal peaks representing [M + H]+ ions at m/z 839.4061 and 823.4108, respectively. The mass spectrum of compound 82 (licorice-saponin G2) reveals peaks representing fragment ions at m/z 469.3314 [Aglycone + H – H2O]+, 487.3412 [Aglycone + H]+ and 451.3212 [Aglycone + H – 2H2O]− [36]. Compound 87 displays a similar fragmentation pattern, yet is 16 Da smaller than compound 82. Compound 87 was then confirmed as glycyrrhetic acid through a comparison between the negative ESI mode data, a reference standard, and literature data [20]. These spectra are shown in Fig. S6. The mass spectrum of compound 86, 18 β-glycyrrhetinic acid, reveals a peak representing [M + H]+ at m/z 471.3469. These are triterpenic acids. Compound 86 (18 β-glycyrrhetinic acid) was also identified using a reference standard.

The MS2 profile of compound 104 showed peaks representing a protonated molecule, [M + H]+, at m/z 529.3526 and dominant fragment ions at m/z 529.3521 [M + H]+, 469.3314 [M + H – HAc]−, 451.3204 [M + H – HAc – H2O]− and 415.2842 [M + H – C4H8O – H2O]−. This compound was identified as alisol C 23-acetate using the OTCML. The mass spectrum of compound 107, alisol B 23-acetate, revealed a peak representing [M + H]+ at m/z 515.3733.

The mass spectrum of compound 93 revealed peaks representing a [M + H]+ ion at m/z 781.4732 and fragment ions at m/z 455.3518 [M + H – H2O – Fuc (fucose) Glc]− and 437.3412 [M + H – 2H2O – FucGlc]−. This compound was identified as saikosaponin A by comparison with data obtained from the OTCML. The mass spectrum of compound 83 exhibited peaks representing [M + H]+ at m/z 471.2016 and fragment ions at m/z 425.1957 [M + H – 46]− and 161.0597. According to the literature [23] and the data in the OTCML, it was limonin.

The mass spectra of compounds 99 and 105 revealed peaks representing [M + H]+ ions at m/z 249.1486 and 233.1536, respectively. They were identified as atractylenolide III and atractylenolide II, respectively, using the OTCML. The MS2 profile of atractylenolide III revealed peaks representing fragment ions at m/z 249.1481 [M + H]+, 231.1379 [M + H – H2O]+, 213.1276 [M + H – 2H2O] and 203.1140 [M + H – H2O – CO]− [30].

**Other Phytochemicals**

Eleven compounds were identified by comparing the obtained data to the information in the OTCML, including the hydrophilic compounds 1 (sucrose), 2 (2-pyrollidine-carboxylic acid), 6 (citric acid), 8 (uridine), 10 (adenosine) and 11 (guanosine). These compounds were also confirmed using reference standards.

**Quantification Analysis**

The extracted ion chromatograms (EICs) of 17 authentic standards compared with those of their corresponding detected compounds within QFPD granules are shown in Fig. 2. The HPLC-Q Exactive hybrid quadrupole-Orbitrap MS method was also used for quantification analysis of these 17 constituents within QFPD granules. The concentration of each constituent was obtained using the respective calibration curve and their contents within the QFPD granules are listed in Table 2.

**Compounds from Individual Herbs Within QFPD Granules**

In total, 265 compounds were putatively identified using the OTCML combined with manual verification from 20 herbs that are components of QFPD granules (Table S1), including 33 alkaloids, 106 flavonoids, 28 terpenoids, 41 phenylpropanoids, 10 phenolic acids, 18 phenols and 29 other phytochemicals. Of these, 172 compounds were from only one herb, and 104 compounds were from more than two herbs. Within the QFPD granules, 59 compounds were from only one herb and 49 compounds were from more than two herbs.

**Conclusions**

In this study, HPLC-Q Exactive hybrid quadrupole-Orbitrap MS coupled with the OTCML which is an automatic data analysis platform, was used to study the chemical profile of QFPD granules, an effective TCM prescribed to treat the symptoms of SARS-CoV-2 infections. Furthermore, manual
verification ensured compound identification. A total of 108 compounds were putatively identified from QFPD granules, including alkaloids, flavonoids, phenylpropanoids, phenolic acids, phenols, terpenoids and other phytochemicals. This allowed rapid chemical composition screening of QFPD granules, providing potentially valuable information for quality control and further clinical application.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10337-021-04085-0.

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Table 2 Contents of the constituents within QFPD granules

| No | Compound                  | Conc. (mg/g) |
|----|---------------------------|-------------|
| 1  | Sucrose                   | 0.683 ± 0.185 |
| 2  | 2-Pyrrolidinocarboxylic acid | 0.803 ± 0.017 |
| 3  | Cytosine                  | 0.009 ± 0.0008 |
| 4  | Citric acid               | 4.309 ± 0.352 |
| 5  | Nicotinic acid            | 0.011 ± 0.0007 |
| 6  | Uridine                   | 0.029 ± 0.005 |
| 7  | Nicotinamide              | 0.006 ± 0.0003 |
| 8  | Guanosine                 | 0.135 ± 0.004 |
| 9  | Chlorogenic acid          | 0.854 ± 0.015 |
| 10 | Salicylic acid            | 0.016 ± 0.002 |
| 11 | Narirutin                 | 0.699 ± 0.119 |
| 12 | Baicalin                  | 4.383 ± 1.107 |
| 13 | Isoliquiritigenin         | 0.007 ± 0.00005 |
| 14 | 18 β-Glycyrrhetinic Acid  | 0.0005 ± 0.000007 |
| 15 | Glycyrrhizic acid         | 2.199 ± 0.127 |
| 16 | Tangeretin                | 0.003 ± 0.0003 |

Data present the (average ± standard deviation) of three replicates. Conc. (mg/g): mg of the constituent/g of QFPD granules

Declarations

Conflict of Interest The authors declare that there are no conflicts of interest.

Ethical Statement We certify that this manuscript is original, has not been previously published and will not be submitted elsewhere for publication while under consideration by *Chromatographia*. This study is not split into several parts and submitted to various journals. Results are presented clearly, honestly and without fabrication. No data, text, or theories by others are presented as our own.

Human and Animal Rights Explicit permission to submit has been received from all co-authors. All the authors whose name appear on the submission have contributed sufficiently to this study. This manuscript does not contain any studies involving humans or animals.

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