Research Article

Investigation of the Chemical Changes from Crude and Processed Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma Herbal Pair Extracts by Using Q Exactive High-Performance Benchtop Quadrupole-Orbitrap LC-MS/MS

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Received 20 January 2014; Revised 7 March 2014; Accepted 20 March 2014; Published 4 May 2014

1. Introduction

Traditional Chinese medicine (TCM) processing is regarded as a pharmaceutical technology based on TCM theory, the requirements of different syndrome treatment, the quality nature of medicine, and different demands of clinical dispensing and preparations [1]. It is one of the characteristics in application of TCM. The compatible components of prescription are composed of prepared Chinese crude drugs after TCM processing.

The prescription compatibility and TCM processing are not only two major features of clinical medication in TCM, but are also critical to distinguish TCM from natural medicine. The research on structural features, compatible effect, and material basis of the herbal pair is the important support in the study of the prescription compatibility since the herbal pair is the minimum unit in prescription of TCM [2, 3]. They play a guidance and significant role in reveal of the compatibility rule and the scientific connotation. The herbal pair compatibility theory can explain the relationship of the prescription compatibility to some extent. The research on the relationship between the herbal pair compatibility and the prescription compatibility contributes to the elucidation of the prescription compatibility mechanism and the action mechanism of treatment. There are many herbal pairs commonly used in the clinical practice of TCM, such as the herbal pairs of Paeonia Lactiflora-Liquorice, Ginseng-Aconite, and Aconite-Rhizome Zingiberis [4, 5] besides the
| No. | $t_R$ (min) | Compound name | Formula | Paeoniae Radix Alba | Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair |
|-----|-------------|---------------|---------|---------------------|-------------------------|
|     |             |               |         | Crude (Measured area) | Processed (Measured area) | Crude (Measured area) | Processed (Measured area) |
| 1   | 0.84        | 6-O-galloylsucrose | C$_{19}$H$_{26}$O$_{15}$ | 1.8570E+08 | 1.9012E+08 | 4.2870E+07 | 4.4158E+07 |
| 2   | 0.84        | Glucogallin | C$_{13}$H$_{16}$O$_{10}$ | 2.9739E+08 | 2.5698E+08 | 1.0931E+08 | — |
| 3   | 1.05        | Desbenzoylpaeoniflorin | C$_{18}$H$_{23}$O$_{10}$ | 1.6682E+08 | 1.6263E+08 | 9.8300E+07 | — |
| 4   | 1.06        | 1’-O-galloylsucrose | C$_{9}$H$_{32}$O$_{16}$ | 3.2574E+08 | 2.9123E+08 | — | — |
| 5   | 1.07        | 1-O-glucopyranosyl paeonisulfone | C$_{16}$H$_{24}$O$_{10}$ | 2.8667E+08 | 2.3654E+08 | 1.1532E+08 | — |
| 6   | 1.13        | Gallic acid | C$_{6}$H$_{6}$O$_{5}$ | 4.1152E+09 | 4.0736E+09 | 2.7186E+09 | 3.1711E+09 |
| 7   | 1.18        | Oxypaeoniflorin sulfonate | C$_{23}$H$_{28}$O$_{14}$S | 4.9527E+08 | 3.5407E+08 | 6.1568E+09 | 8.5010E+07 |
| 8   | 1.22        | Ethyl gallate | C$_{9}$H$_{10}$O$_{5}$ | 5.1351E+07 | 6.7200E+07 | 1.5592E+07 | 4.8337E+07 |
| 9   | 1.22        | 6-O-galloylsu | C$_{23}$H$_{28}$O$_{14}$ | 9.9020E+07 | 9.5040E+07 | 5.3798E+07 | — |
| 10  | 1.26        | 6-O-galloyl desbenzoylpaeoniflorin | C$_{16}$H$_{24}$O$_{8}$ | 1.0875E+08 | 1.1180E+08 | — | 3.7130E+07 |
| 11  | 1.30        | Paeoniflorin sulfonate I | C$_{23}$H$_{28}$O$_{13}$S | 5.3777E+07 | 3.6391E+07 | 7.3077E+06 | 7.7185E+07 |
| 12  | 1.30        | Mudanpioside E sulfonate | C$_{24}$H$_{30}$O$_{15}$S | 5.3777E+07 | 3.6391E+07 | 7.3077E+06 | 7.7185E+07 |
| 13  | 1.43        | 6-O-galloyl lactinolide | C$_{16}$H$_{26}$O$_{9}$ | 7.4342E+08 | 6.5904E+08 | 4.0712E+08 | 3.1407E+08 |
| 14  | 1.59        | Paeoniflorinsulfonate I | C$_{23}$H$_{28}$O$_{13}$S | 3.1881E+10 | 2.3387E+10 | 6.6200E+09 | 5.5241E+10 |
| 15  | 1.64        | Paeoniflorinsulfonate II | C$_{23}$H$_{28}$O$_{13}$S | 5.3777E+07 | 3.6391E+07 | 7.3077E+06 | 7.7185E+07 |
| 16  | 1.97        | Oxypaeoniflorin | C$_{23}$H$_{28}$O$_{12}$ | 2.3173E+09 | 2.4115E+09 | 1.6734E+09 | 1.4513E+09 |
| 17  | 2.36        | Galloantin | C$_{27}$H$_{24}$O$_{18}$ | 2.2850E+08 | 2.2458E+08 | 1.6284E+08 | 1.6703E+08 |
| 18  | 2.37        | 1-O-benzoylsucrose | C$_{19}$H$_{26}$O$_{12}$ | 1.3761E+08 | 1.3161E+08 | 1.1673E+08 | 8.2986E+07 |
| 19  | 2.41        | d-catechin | C$_{15}$H$_{14}$O$_{6}$ | 3.7822E+09 | 4.2278E+09 | 2.6339E+09 | 2.5982E+09 |
| 20  | 2.63        | Methyl gallate | C$_{8}$H$_{6}$O$_{5}$ | 2.3823E+10 | 2.4116E+10 | 2.3388E+10 | — |
| 21  | 2.63        | Salicylic acid | C$_{9}$H$_{8}$O$_{5}$ | 2.3823E+10 | 2.4116E+10 | 2.3388E+10 | 1.7399E+10 |
| 22  | 2.72        | Albiflorin R1 | C$_{23}$H$_{28}$O$_{11}$ | 5.2469E+08 | 5.6725E+08 | 5.6329E+08 | 4.5647E+08 |
| 23  | 2.82        | Kaempferol-3,7-di-O-glucoside | C$_{27}$H$_{30}$O$_{16}$ | 3.8065E+07 | 2.1896E+07 | 3.5719E+07 | 1.5513E+07 |
| 24  | 2.82        | Paenoside | C$_{27}$H$_{30}$O$_{16}$ | 3.8065E+07 | 2.1896E+07 | 3.5719E+07 | 1.5513E+07 |
| 25  | 3.06        | Galloylpaeoniflorin | C$_{30}$H$_{32}$O$_{15}$ | 1.3912E+08 | 1.5200E+08 | 1.1501E+08 | 1.0863E+08 |
| 26  | 3.46        | Paeonilactone B | C$_{10}$H$_{12}$O$_{4}$ | 9.0325E+07 | 9.3539E+07 | 5.1257E+07 | 8.9597E+07 |
| 27  | 3.93        | Isomaltopaeoniflorin | C$_{29}$H$_{38}$O$_{16}$ | 3.0588E+08 | 3.1627E+08 | 3.0588E+08 | 3.1627E+08 |
| 28  | 4.07        | Albiflorin | C$_{25}$H$_{30}$O$_{12}$ | 7.943E+08 | 5.6793E+08 | 1.5501E+08 | 1.4886E+09 |
| No. | $t_R$ (min) | Compound name | Formula | Paeoniae Radix Alba | Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair |
|-----|-------------|---------------|---------|---------------------|---------------------------------------------------------------|
|     |             |               |         | Crude (Measured area) | Processed (Measured area) Crude (Measured area) Processed (Measured area) |
| 37  | 4.34        | Galloylpaeoniflorin isomer | C$_{30}$H$_{32}$O$_{15}$ | 6.7592E+08 | 7.4322E+08 | 6.0470E+08 | 5.4051E+08 |
| 38  | 4.38        | 1,2,3,6-tetra-O-galloylglucose | C$_{34}$H$_{32}$O$_{22}$ | 4.6602E+08 | 3.4977E+08 | 4.0697E+08 | 3.6901E+08 |
| 39  | 4.38        | Tetragalloyl glucose A | C$_{34}$H$_{32}$O$_{22}$ | 4.6602E+08 | 3.4977E+08 | 4.0697E+08 | 3.6901E+08 |
| 40  | 4.56        | Mudanpioside F | C$_{26}$H$_{26}$O$_{8}$ | 8.4156E+07 | 8.2734E+07 | 7.2666E+07 | 7.9227E+07 |
| 41  | 4.60        | Oxypaeoniflorin isomer | C$_{21}$H$_{26}$O$_{12}$ | 9.6610E+08 | 9.8706E+08 | 9.2464E+08 | 8.7359E+08 |
| 42  | 4.65        | Gallotannin | C$_{27}$H$_{26}$O$_{18}$ | 6.7737E+07 | — | — | — |
| 43  | 4.77        | Paeoniflorin | C$_{25}$H$_{32}$O$_{11}$ | 5.9556E+10 | 6.1356E+10 | 5.9929E+10 | 5.8832E+10 |
| 44  | 4.89        | Paeoniflorin sulfonate II | C$_{23}$H$_{28}$O$_{13}$S | 1.1095E+08 | 1.4567E+08 | 5.5052E+07 | 2.7813E+08 |
| 45  | 4.98        | Isogalloylpaeoniflorin sulfonate | C$_{30}$H$_{32}$O$_{17}$S | 3.6742E+07 | — | — | — |
| 46  | 5.05        | Ethyl gallate | C$_{6}$H$_{8}$O$_{5}$ | 6.0669E+07 | 5.4850E+07 | 1.6618E+07 | 2.6790E+07 |
| 47  | 5.05        | Methyl salicylate | C$_{6}$H$_{8}$O$_{5}$ | 6.0669E+07 | 5.4850E+07 | 1.6618E+07 | 2.6790E+07 |
| 48  | 5.15        | Benzoic acid | C$_{6}$H$_{4}$O$_{2}$ | 4.0163E+07 | 4.5493E+07 | 2.9695E+07 | 2.9727E+07 |
| 49  | 5.25        | Paconol | C$_{6}$H$_{12}$O$_{4}$ | 6.8567E+07 | 7.4129E+07 | 9.9992E+07 | 6.5619E+07 |
| 50  | 5.25        | 4-hydroxy-3-methoxy acetonaphone | C$_{9}$H$_{10}$O$_{3}$ | 6.8567E+07 | 7.4129E+07 | 9.9992E+07 | 6.5619E+07 |
| 51  | 5.31        | ortho-oxypaeoniflorin | C$_{23}$H$_{16}$O$_{12}$ | 1.9080E+09 | 1.9263E+09 | 1.8732E+09 | 1.6842E+09 |
| 52  | 5.63        | Ethyl gallate | C$_{9}$H$_{10}$O$_{3}$ | 1.4627E+08 | 1.2812E+08 | 1.0365E+08 | 8.8155E+07 |
| 53  | 5.63        | Methyl salicylate | C$_{9}$H$_{10}$O$_{3}$ | 1.4627E+08 | 1.2812E+08 | 1.0365E+08 | 8.8155E+07 |
| 54  | 5.66        | Kaempferol-3-O-glucoside | C$_{21}$H$_{20}$O$_{11}$ | 1.6012E+07 | 1.7385E+07 | — | — |
| 55  | 5.66        | Astragalin | C$_{21}$H$_{20}$O$_{11}$ | 1.6012E+07 | 1.7385E+07 | — | — |
| 56  | 6.01        | Eugeniin | C$_{41}$H$_{30}$O$_{26}$ | 2.7483E+08 | 3.0279E+08 | 2.8080E+08 | 3.0479E+08 |
| 57  | 6.01        | Dihydroxymethyl benzoyl tetragalloyl glucose | C$_{41}$H$_{30}$O$_{26}$ | 2.7483E+08 | 3.0279E+08 | 2.8080E+08 | 3.0479E+08 |
| 58  | 6.03        | 1,2,3,6-tetra-O-galloylglucose isomer A | C$_{34}$H$_{32}$O$_{22}$ | 1.3555E+09 | — | 1.1980E+09 | 1.1039E+09 |
| 59  | 6.03        | Tetragalloyl glucose B | C$_{34}$H$_{32}$O$_{22}$ | 1.3555E+09 | — | — | — |
| 60  | 6.08        | Astragalin | C$_{25}$H$_{26}$O$_{21}$ | 1.5009E+07 | 1.8552E+07 | 1.5922E+07 | 1.4002E+07 |
| 61  | 6.09        | Isomaltopaeoniflorin isomer | C$_{29}$H$_{38}$O$_{16}$ | 7.5172E+07 | — | — | — |
| 62  | 6.47        | 1,2,3,6-tetra-O-galloylglucose isomer B | C$_{34}$H$_{32}$O$_{22}$ | 1.5882E+09 | — | — | 1.2570E+09 |
| 63  | 6.47        | Tetragalloyl glucose C | C$_{34}$H$_{32}$O$_{22}$ | 1.5882E+09 | — | — | 1.2570E+09 |
| 64  | 6.85        | 3,6-di-O-galloyl paoniorin | C$_{37}$H$_{40}$O$_{19}$ | 7.6512E+07 | — | — | — |
| 65  | 6.96        | 1,2,3,6-tetra-O-galloylglucose | C$_{34}$H$_{32}$O$_{22}$ | 4.4729E+08 | 4.5825E+08 | 4.0642E+08 | 4.2393E+08 |
| 66  | 6.96        | Tetragalloyl glucose D | C$_{34}$H$_{32}$O$_{22}$ | 4.4729E+08 | 4.5825E+08 | 4.0642E+08 | 4.2393E+08 |
| 67  | 7.35        | Galloylpaeoniflorin isomer I | C$_{30}$H$_{32}$O$_{15}$ | 1.2156E+10 | 1.2451E+10 | 1.1484E+10 | 1.0962E+10 |
| 68  | 7.60        | 1-O-glucopyranosyl-8-O-benzoyl paonisuffrone | C$_{33}$H$_{32}$O$_{22}$ | 4.3983E+07 | 4.5347E+07 | 4.4927E+07 | 3.9869E+07 |
| 69  | 7.71        | Glucopyranosylalbiorin isomer I | C$_{29}$H$_{38}$O$_{16}$ | 7.2982E+07 | 7.9341E+07 | — | 1.8872E+07 |
| No. | $t_R$ (min) | Compound name                        | Formula                  | Paeoniae Radix Alba Crude | Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair Measured area (Crude) | Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair Measured area (Processed) |
|-----|-------------|--------------------------------------|--------------------------|---------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| 70  | 8.18        | 1-O-glucopyranosyl-8-O-benzoyl paeonisuffrone | C_{23}H_{28}O_{10}        | 7.464E+07                 | 6.5957E+07                                                             | 5.9832E+07                                                             |
| 71  | 8.31        | Ortho-oxypaeoniflorin                 | C_{23}H_{26}O_{12}        | 2.4469E+07                | 2.3932E+07                                                         | 2.2796E+07                                                         |
| 72  | 8.45        | 1,2,3,4,6-Penta-O-galloyl-D-glucopyranose | C_{41}H_{32}O_{16}        | 1.1843E+10                | 1.0905E+10                                                          | 1.0518E+10                                                          |
| 73  | 8.45        | Pentagalloyl glucose                  | C_{23}H_{23}O_{10}        | 1.0818E+08                | 1.3689E+08                                                          | ——                                                                     |
| 74  | 8.64        | Lactiflorin                           | C_{30}H_{32}O_{15}        | 3.2696E+09                | ——                                                                     | ——                                                                     |
| 75  | 8.80        | Galloylalbiroin                       | C_{29}H_{38}O_{16}        | 2.3457E+08                | ——                                                                     | ——                                                                     |
| 76  | 9.17        | Astragalin                            | C_{20}H_{24}O_{12}        | 6.3346E+09                | ——                                                                     | ——                                                                     |
| 77  | 9.25        | Lactinolide                           | C_{20}H_{24}O_{12}        | 6.3346E+09                | ——                                                                     | ——                                                                     |
| 78  | 9.29        | Galloylpaeoniflorin isomer II         | C_{20}H_{24}O_{12}        | 6.3346E+09                | ——                                                                     | ——                                                                     |
| 79  | 9.68        | Glucopyranosylalbiorin isomer II      | C_{20}H_{24}O_{12}        | 6.3346E+09                | ——                                                                     | ——                                                                     |
| 80  | 9.84        | Hexagalloyl glucose                   | C_{48}H_{36}O_{18}        | 4.9153E+07                | ——                                                                     | 5.7793E+08                                                         |
| 81  | 9.95        | Oxybenzoyloxypongeaoniflorin          | C_{30}H_{32}O_{15}        | 1.4385E+07                | 1.1051E+07                                                          | 1.1345E+07                                                          |
| 82  | 10.07       | 1-O-glucopyranosyl-8-O-benzoyl paeonisuffrone | C_{23}H_{28}O_{10}        | 3.6916E+09                | 3.5634E+09                                                          | 3.1333E+09                                                          |
| 83  | 10.29       | Albiflorin RI isomer I                | C_{23}H_{26}O_{12}        | 6.3346E+09                | 6.6205E+09                                                          | 5.9528E+09                                                          |
| 84  | 10.74       | Hexagalloyl glucose                   | C_{48}H_{36}O_{18}        | 4.9225E+08                | 2.5582E+08                                                          | 1.9395E+09                                                          |
| 85  | 10.76       | Lactiflorin                           | C_{23}H_{26}O_{12}        | 1.2785E+09                | 3.5174E+09                                                          | 9.9713E+08                                                          |
| 86  | 10.84       | Benzoylpaeoniflorin Sulfonate         | C_{30}H_{32}O_{15}        | 9.0616E+08                | 6.4075E+08                                                          | 1.5946E+09                                                          |
| 87  | 10.88       | 3,6-di-O-galloyl paeniorin            | C_{37}H_{30}O_{19}        | 1.6123E+08                | ——                                                                     | ——                                                                     |
| 88  | 10.95       | Ortho-oxypaeoniflorin isomer          | C_{23}H_{26}O_{12}        | 5.5563E+07                | 5.8774E+07                                                          | 5.6640E+07                                                          |
| 89  | 11.52       | 3,6-di-O-galloyl paeniorin            | C_{37}H_{30}O_{19}        | 3.6509E+08                | 3.9290E+08                                                          | 5.2162E+08                                                          |
| 90  | 11.72       | 3,6-di-O-galloyl paeniorin isomer     | C_{37}H_{30}O_{19}        | 9.7356E+08                | ——                                                                     | 9.5929E+08                                                          |
| 91  | 11.75       | Galloylalbiroin isomer I              | C_{29}H_{38}O_{16}        | 3.1333E+09                | ——                                                                     | ——                                                                     |
| 92  | 11.84       | Oxyapaeoniflorin sulphonate isomer    | C_{23}H_{28}O_{16}S       | 2.1063E+08                | 1.9747E+07                                                          | 1.3875E+07                                                          |
| 93  | 12.15       | 1-O-glucopyranosyl-8-O-benzoyl paeonisuffrone | C_{23}H_{28}O_{10}        | 7.2104E+07                | 6.7309E+07                                                          | 6.5917E+07                                                          |
| 94  | 12.15       | Oxybenzoyloxypongeaoniflorin          | C_{30}H_{32}O_{15}        | 1.9982E+08                | ——                                                                     | 1.8628E+08                                                          |
| 95  | 12.18       | Benzoyloxypongeaoniflorin             | C_{30}H_{32}O_{15}        | 2.0822E+08                | 2.0163E+08                                                          | 1.9074E+08                                                          |
| 96  | 13.42       | Benzoyloxypongeaoniflorin isomer      | C_{30}H_{32}O_{15}        | 8.6458E+07                | 7.6048E+07                                                          | 7.2791E+07                                                          |
| 97  | 13.44       | Benzoyloxypongeaoniflorin isomer I    | C_{30}H_{32}O_{15}        | 1.4728E+07                | 1.7389E+07                                                          | 1.5360E+07                                                          |
| 98  | 13.85       | Galloylalbiroin isomer II             | C_{30}H_{32}O_{15}        | 9.6403E+07                | 1.2196E+08                                                          | 1.0506E+08                                                          |
| 99  | 14.05       | Oxybenzoyloxypongeaoniflorin isomer II | C_{30}H_{32}O_{15}        | 2.5323E+07                | 2.9603E+07                                                          | 2.3556E+07                                                          |
| 100 | 14.13       | Benzoxypongeaoniflorin                | C_{30}H_{32}O_{15}        | 3.8096E+07                | 3.8557E+07                                                          | 3.7499E+07                                                          |
| No. | $t_R$ (min) | Compound name | Formula | Paeoniae Radix Alba (Measured area) | Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair (Measured area) |
|-----|-------------|---------------|---------|-------------------------------------|--------------------------------------------------------------------------------|
|     |             |               |         | Crude | Processed                           | Crude | Processed                           |
| 101 | 15.07       | Benzoyloxyzaeniflorin isomer I | C$_{30}$H$_{32}$O$_{13}$ | 1.9827E+07 | 2.3616E+07                          | —     | —                                   |
| 102 | 15.38       | Benzoyloxyzaeniflorin isomer II | C$_{30}$H$_{32}$O$_{13}$ | 1.1841E+07 | 1.3730E+07                          | —     | —                                   |
| 103 | 16.01       | Oxybenzoyl-zaeniflorin | C$_{30}$H$_{32}$O$_{12}$ | 1.8152E+07 | 1.9835E+07                          | 1.8391E+07 | 1.2391E+10              |
| 104 | 16.95       | Isobenzoyl-zaeniflorin | C$_{30}$H$_{32}$O$_{12}$ | 1.2225E+10 | 1.3228E+10                          | 1.2158E+10 | 1.2391E+10              |
| 105 | 16.95       | Oxybenzoyl-zaeniflorin isomer I | C$_{30}$H$_{32}$O$_{12}$ | 1.2225E+10 | 1.3228E+10                          | 1.2158E+10 | 1.2391E+10              |
| 106 | 17.23       | Benzoylzaeniflorin Sulfonate | C$_{30}$H$_{32}$O$_{14}$S | 1.5680E+07 | 1.2235E+07                          | 5.6573E+06 | 3.5831E+07             |
| 107 | 17.48       | Isobenzoyl-zaeniflorin isomer I | C$_{30}$H$_{32}$O$_{12}$ | 5.4138E+09 | 5.4432E+09                          | 5.2522E+09 | 5.3238E+09             |
| 108 | 17.48       | Oxybenzoyl-zaeniflorin isomer II | C$_{30}$H$_{32}$O$_{12}$ | 5.4138E+09 | 5.4432E+09                          | 5.2522E+09 | 5.3238E+09             |
| 109 | 17.86       | Benzoylzaeniflorin | C$_{30}$H$_{32}$O$_{13}$ | 3.4347E+07 | 3.4852E+07                          | 3.5980E+07 | 3.8814E+07             |
| 110 | 18.55       | Benzoylzaeniflorin isomer | C$_{30}$H$_{32}$O$_{13}$ | 1.5397E+07 | 1.7656E+07                          | 1.7246E+07 | 1.8012E+07             |
| 111 | 18.69       | Albiflorin R1 isomer II | C$_{23}$H$_{28}$O$_{11}$ | 2.0046E+07 | 1.9851E+07                          | 2.3462E+07 | 5.6105E+06             |
| 112 | 19.30       | Albiflorin R1 isomer III | C$_{23}$H$_{28}$O$_{11}$ | 2.9827E+06 |                               | —     |                                   |
| 113 | 21.79       | Palbinone | C$_{22}$H$_{30}$O$_{4}$ | 8.9687E+07 | 1.3174E+08                          | 1.2834E+08 | 5.7610E+07             |
| 114 | 21.93       | Isobenzoyl-zaeniflorin isomer II | C$_{30}$H$_{32}$O$_{12}$ | 4.5356E+08 | 4.2874E+07                          | 3.4016E+08 | 2.7347E+08             |
| 115 | 21.93       | Oxysbenzoyl-zaeniflorin isomer III | C$_{30}$H$_{32}$O$_{12}$ | 4.5356E+08 | 4.2874E+07                          | 3.4016E+08 | 2.7347E+08             |
| 116 | 22.15       | Paonilactinone | C$_{30}$H$_{30}$O$_{2}$ | 7.0423E+06 | 3.7108E+06                          | 8.0036E+06 | 6.6886E+06             |
| 117 | 36.46       | Hederagenin | C$_{30}$H$_{30}$O$_{4}$ | 7.6725E+07 | 8.1456E+07                          | 9.7498E+07 | 4.7332E+07             |
| 118 | 37.31       | 23-hydroxybetulinic acid | C$_{30}$H$_{32}$O$_{4}$ | 3.9836E+07 | 4.0995E+07                          | 3.9906E+07 | 2.2611E+07             |
| 119 | 38.14       | Astrantiagenin D | C$_{30}$H$_{46}$O$_{4}$ | 7.8714E+06 | 7.9560E+06                          | 1.1904E+07 | 3.8958E+06             |
| 120 | 43.00       | Astrantiagenin D isomer | C$_{30}$H$_{46}$O$_{4}$ | 4.0450E+06 |                               | 3.1583E+06 | 6.6886E+06             |
| 121 | 45.65       | Oleanolic acid | C$_{30}$H$_{46}$O$_{3}$ | 1.1266E+08 | 9.4258E+07                          | 7.6434E+07 | 4.3295E+07             |
| 122 | 46.10       | Betulinic acid | C$_{30}$H$_{46}$O$_{3}$ | 6.2494E+06 | 2.3289E+07                          | 4.0534E+07 | 2.3912E+07             |
| 123 | 52.48       | Daucosterol | C$_{30}$H$_{50}$O$_{6}$ | 1.4060E+07 | 1.9624E+07                          | 8.5440E+06 | 6.3156E+06             |

Paoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair frequently used in all China dynasties [6, 7]. Paoniae Radix Alba nourishes blood and liver, and Atractylodis Macrocephalae Rhizoma helps invigorate spleen and eliminate dampness [8–12]. Thus, the compatibility of these two medicines could help achieve the goal of purging wood from the earth, regulating the functions of liver and spleen, benefiting qi, and nourishing blood [13–15]. Although the compositions of these two medicines have been extensively studied, the appropriate processing method of them, such as frying, which is believed by the practitioners of traditional medicine to have the effects for enhancing the efficacy of the medicine, and their underlying compatibility mechanism are still under investigation.

The objective of this study is to investigate the qualitative, preprocessing, and postprocessing changes in the composition and compatibility of Paoniae Radix Alba and Atractylodis Macrocephalae Rhizoma by using Q Exactive hybrid quadrupole-Orbitrap mass spectrometer combined with high-performance quadrupole precursor selection with high-resolution and accurate-mass Orbitrap detection. The work could serve as a theoretical basis for the development of medicines from Paoniae Radix Alba and Atractylodis Macrcephalae Rhizoma, and the reasonable clinical medication. Furthermore, it provides new insights into the investigation of the herbal pair and for the study of the appropriate processing method for Chinese herbal medicines and their underlying compatibility mechanism.
### Table 2: Major chemical constituents identified in crude and processed Atractylodis Macrocephalae Rhizoma and in crude and processed Paeoniae Radix Alba–Atractylodis Macrocephalae Rhizoma herbal pair.

| No. | $t_R$ (min) | Compound name | Formula | Atractylodis Macrocephalae Rhizoma | Paeoniae Radix Alba–Atractylodis Macrocephalae Rhizoma herbal pair |
|-----|-------------|---------------|---------|----------------------------------|---------------------------------------------------------------|
|     |             |               |         | Crude | Processed | Crude | Processed |
| 1   | 1.72        | Protocatechuic acid | C$_7$H$_6$O$_4$ | 2.0389E+07 | 1.4454E+07 | 2.0881E+07 | 2.4383E+07 |
| 2   | 2.67        | Protocatechuic acid isomer I | C$_7$H$_6$O$_4$ | 9.6661E+07 | — | — | — |
| 3   | 3.24        | Caffeic acid | C$_9$H$_8$O$_4$ | 3.6818E+08 | 1.7393E+08 | 2.8796E+08 | 1.2882E+08 |
| 4   | 3.73        | Protocatechuic acid isomer II | C$_7$H$_6$O$_4$ | 2.0846E+07 | — | — | 1.2022E+07 |
| 5   | 4.21        | Dictamnoside A isomer I | C$_{21}$H$_{36}$O$_9$ | 1.8843E+07 | 2.4981E+07 | 1.0636E+07 | 1.3140E+07 |
| 6   | 4.70        | Dictamnoside A isomer II | C$_{21}$H$_{36}$O$_9$ | 2.8770E+07 | 3.4768E+07 | 1.0395E+07 | 1.4208E+07 |
| 7   | 5.63        | Scopoletin | C$_{13}$H$_{10}$O | 9.6615E+09 | 1.1991E+09 | 7.5446E+09 | 9.4190E+09 |
| 8   | 5.82        | Dictamnoside A | C$_{15}$H$_{18}$O$_2$ | 6.4158E+07 | 4.1494E+07 | 6.1562E+07 | 5.3342E+07 |
| 9   | 8.77        | Atractylentriol | C$_{41}$H$_{52}$O$_3$ | 1.2538E+07 | 5.4052E+06 | — | — |
| 10  | 9.33        | Ferulic acid | C$_{15}$H$_{20}$O$_2$ | 1.3953E+08 | 9.1214E+06 | 1.1912E+07 | 9.6849E+06 |
| 11  | 25.81       | Atractylenolide I isomer | C$_{21}$H$_{26}$O$_5$ | 4.5226E+08 | 4.2401E+09 | 5.9401E+09 | 6.5277E+09 |
| 12  | 25.83       | Atractylenolide III | C$_{21}$H$_{26}$O$_5$ | 2.5549E+09 | 1.8023E+09 | 2.8280E+09 | 3.1632E+09 |
| 13  | 25.90       | 12-methylbutyryl-14-acetyl-2E,8EZ,10E-atractylentriol | C$_{21}$H$_{26}$O$_5$ | 7.5991E+07 | — | — | 9.6849E+06 |
| 14  | 26.95       | 12-methylbutyryl-14-acetyl-2E,8EZ,10E-atractylentriol isomer | C$_{21}$H$_{26}$O$_5$ | 4.5226E+09 | 4.2401E+09 | 5.9401E+09 | 6.5277E+09 |
| 15  | 26.95       | Atractylenolide II isomer | C$_{21}$H$_{26}$O$_5$ | 2.5549E+09 | 1.8023E+09 | 2.8280E+09 | 3.1632E+09 |
| 16  | 31.00       | Atractylenolide II | C$_{21}$H$_{26}$O$_5$ | 2.5549E+09 | 1.8023E+09 | 2.8280E+09 | 3.1632E+09 |
| 17  | 33.44       | Atractylodin | C$_{16}$H$_{30}$O$_4$ | 6.4158E+09 | 4.1494E+07 | 6.1562E+07 | 5.3342E+07 |
| 18  | 35.07       | Atractylenolide I isomer | C$_{13}$H$_{10}$O$_2$ | 8.2226E+08 | 1.4781E+09 | 1.0831E+09 | 3.2083E+09 |
| 19  | 35.94       | Atractylenolide I | C$_{13}$H$_{10}$O$_2$ | 8.8877E+09 | 7.2520E+09 | 8.3857E+09 | 1.2742E+10 |
| 20  | 39.03       | 12-methylbutyryl-14-acetyl-2E,8EZ,10E-atractylentriol isomer | C$_{21}$H$_{26}$O$_5$ | 7.5991E+07 | — | — | 9.6849E+06 |
| 21  | 39.81       | Dibutyl phthalate | C$_{16}$H$_{22}$O$_4$ | 1.1372E+08 | 9.8325E+07 | 1.2659E+08 | 1.4865E+08 |
| 22  | 40.00       | 12-methylbutyl-14-acetyl-2E,8EZ,10E-atractylentriol isomer II | C$_{21}$H$_{26}$O$_5$ | 3.8810E+07 | 7.7498E+07 | 3.3885E+07 | 7.0522E+07 |
| 23  | 40.26       | Dibutyl phthalate isomer | C$_{16}$H$_{22}$O$_4$ | 1.0631E+08 | 5.4902E+07 | 6.1958E+07 | 4.6227E+07 |
| 24  | 41.50       | 14-methylbutyryl-2E,8EZ,10E-atractylentriol | C$_{16}$H$_{22}$O$_4$ | 4.9587E+07 | 2.8423E+07 | 5.1146E+07 | 4.7855E+07 |
| 25  | 46.43       | Spinasteryl | C$_{29}$H$_{48}$O | 8.6778E+08 | 7.9096E+06 | 1.0609E+07 | 7.7832E+06 |
| 26  | 47.32       | Atractylon | C$_{15}$H$_{20}$O | 7.4433E+07 | 5.4063E+06 | 6.6146E+07 | — |
| 27  | 47.37       | Biatractylolide | C$_{30}$H$_{38}$O$_4$ | 1.0949E+09 | 9.5656E+08 | 1.2797E+09 | — |
| 28  | 47.96       | Linoleic acid | C$_{15}$H$_{20}$O$_2$ | 1.8499E+08 | 1.5042E+08 | 1.8777E+08 | 2.3743E+08 |
| 29  | 48.25       | Linoleic acid isomer | C$_{15}$H$_{20}$O$_2$ | 2.1059E+07 | — | — | — |
| 30  | 48.59       | Biepiasterolid isomer | C$_{30}$H$_{38}$O$_4$ | 9.0255E+08 | 7.0863E+08 | 7.4011E+08 | — |
| 31  | 48.90       | Atractylon isomer | C$_{15}$H$_{20}$O | 9.5308E+07 | 8.7683E+07 | 8.2967E+07 | 1.0132E+08 |
| 32  | 49.42       | Palmitic acid | C$_{16}$H$_{32}$O$_2$ | 2.2356E+07 | 2.2942E+07 | 2.5949E+07 | 2.0153E+07 |
2. Experimental

2.1. Chemicals, Solvents, and Herbal Materials. Paeoniae Radix Alba and Atractylodis Macrocephalae Rhizoma samples were acquired from Zhejiang suppliers. All of these herbal samples were authenticated by Professor Jianwei Chen (College of Pharmacy, Nanjing University of Chinese Medicine). HPLC-grade acetonitrile and formic acid were obtained from Merck (Darmstadt, Germany). Deionized water was purified using the Milli-Q system (Millipore, Bedford, MA, USA). All other reagents and chemicals were analytical grade.

2.2. Preparation of the Sample Solutions. The dried and powdered samples of crude and processed Paeoniae Radix Alba, crude and processed Atractylodis Macrocephalae Rhizoma, and their crude and processed herbal pair extracts (1:1, g/g)
Figure 2: Continued.
were prepared. A total of 2.0 g of each sample powder was accurately weighed and transferred into a 50 mL round bottom flask with 20 mL of 70% methanol aqueous solution (v/v) and refluxed in a 80°C water bath for 1 h. The filtrate was collected after filtration and the residue was then refluxed with 20 mL of 70% methanol aqueous solution in a 80°C water bath for 1 h, the filtrate was collected again after filtration and the residue was removed. Finally, the combined filtrates were treated by rotary evaporation concentration and the resultant residue was dissolved and transferred into a 25 mL volumetric flask with 70% methanol aqueous solution to make it up to a final concentration of 0.08 g mL⁻¹. All solutions were stored at 4°C and filtered through a 0.22 μm filter membrane before injection into the HPLC system.

2.3. Liquid Chromatography and Mass Spectrometry. Analyses were performed by using Dionex UltiMate 3000 HPLC system (Dionex, Sunnyvale, CA, USA) with a diode array detector. Detection wavelengths were set at 255 nm. A Thermo Scientific Hypersil Gold C₁₈ column (100 mm × 2.1 mm, 1.9 μm) was used with a flow rate of 0.35 mL min⁻¹. The injection volume was 5 μL, and the column temperature was maintained at 30°C. The sample separation was performed according to the previous reports with minor modification [16–18]. The mobile phase was composed of (a) aqueous formic acid (0.1%, v/v) and (b) acetonitrile under following gradient elution: 10–55% B from 0 to 40 min, 55–90% B from 40 to 51 min, 90% B from 51 to 56 min, 90–10% B from 56 to 56.1 min, and 10% B from 56.1 to 60 min. Mass spectrometry was performed on a Q Exactive high-resolution benchtop quadrupole Orbitrap mass spectrometer (Thermo Fisher Scientific, San Jose, USA) using a heated electrospray ionization (HESI-II) source for ionization of the target compounds in positive and negative ion modes. The key parameters were as follows: ionization voltage, +3.0 kV/−2.8 kV; sheath gas pressure, 35 arbitrary units; auxiliary gas, 10 arbitrary units; heat temperature, 300°C; and capillary temperature, 300°C. For
Figure 3: Total ion chromatograms of crude (a) and processed (b) Atractylodis Macrocephalae Rhizoma obtained from both positive and negative ion modes.

3. Results and Discussion

3.1. Identification of the Main Components in Crude and Processed Paeoniae Radix Alba. Tentative identification of the main compounds in crude and processed Paeoniae Radix Alba samples was generated based on elemental composition data determined from accurate mass measurements and comparison with the literature data. The total ion chromatograms of crude and processed Paeoniae Radix Alba samples obtained from both positive and negative ion modes were shown in Figure 1. In the preliminary study, the Q Exactive mass spectrometer was confirmed to be highly selective and sensitive. Under the present chromatographic and MS
Figure 4: Mass spectra of atractylenolide I (a), atractylenolide II (b), and atractylenolide III (c).
conditions, 123 and 101 compounds were identified in crude and processed Paeoniae Radix Alba samples, respectively. Compounds 16, 30, 31, 42, 45, 58, 59, 61, 62, 63, 64, 75, 78, 80, 87, 90, 91, 94, 95, 103, 112, and 120 were not detected in processed Paeoniae Radix Alba sample. Meanwhile, the ESI-MS data of crude and processed samples demonstrated that the peak areas of components 8, 113, and 122 varied significantly, and their amounts were dramatically increased in processed sample. The results were shown in Table 1.

From ESI-MS information, it was found that the sensitivities for all kinds of components in Paeoniae Radix Alba were high in both positive and negative ion modes.
In present study, we chose peaks 1, 2, and 3 to explain the identification process using Q Exactive high-performance benchtop quadrupole-Orbitrap LC-MS/MS. Peaks 1, 2, and 3 were eluted at retention times of 4.08, 4.79, and 8.47 min, respectively. Peak 1 showed the [M+H]⁺ at m/z 481.16986, [2M+NH₄]⁺ at m/z 978.35950, [M–H]⁻ at m/z 479.15591, [M–H+HCOOH]⁻ at m/z 525.16101, and [2M–H+HCOOH]⁻ at m/z 1005.32404. The corresponding elemental compositions were C₂₃H₃₅O₁₁, C₄₆H₆₀O₁₂N, C₂₃H₃₂O₁₁, C₂₃H₂₅O₁₃, and C₄₇H₄₃O₂₆ respectively. On the basis of above data we deduced that the elemental composition of peak 1 was C₂₃H₂₆O₁₁. The molecular ion of peak 1 could be assigned as albidiflorin. Peaks 2 and 3 were therefore identified as paeoniflorin, and 1, 2, 3, 4, 6-penta-O-galloyl-beta-D-glucopyranose with above mentioned method. The mass spectra and proposed fragmentations of albidiflorin, paeoniflorin, and 1, 2, 3, 4, 6-penta-O-galloyl-beta-D-glucopyranose were shown in Figure 2.

3.2. Identification of the Main Components in Crude and Processed Atractylodis Macrocephalae Rhizoma. Figure 3 showed the total ion chromatograms of crude and processed Atractylodis Macrocephalae Rhizoma samples obtained from both positive and negative ion modes. 32 and 26 compounds were identified in crude and processed Atractylodis Macrocephalae Rhizoma samples, respectively. Compounds 2, 4, 13, 14, 17, and 29 were not detected in processed Atractylodis Macrocephalae Rhizoma sample. Moreover, the amounts of compounds 14, 17, and 29 were not detected in processed Atractylodis Macrocephalae Rhizoma samples, respectively. Compounds 2, 4, 13, and 27 were significantly decreased while those of compounds 15, 19, and 21 were increased after compatibility with crude Atractylodis Macrocephalae Rhizoma. For processed Atractylodis Macrocephalae Rhizoma, compounds 9, 20, 26, 27, and 30 were not found except the relative contents of compounds 5, 6, and 8 were decreased while those of compounds 15, 19, 21, and 31 were increased after its compatibility with processed Atractylodis Macrocephalae Rhizoma. The results were presented in Figure 5 and Table 1.

3.4. Analysis of the Chemical Changes of Atractylodis Macrocephalae Rhizoma after Compatibility with Paeoniae Radix Alba. For crude Atractylodis Macrocephalae Rhizoma, the relative contents of compounds 17, 18, and 25 were increased clearly except those of compounds 6, 23, and 30 decreased considerably and six compounds including protocatechuic acid isomer I, protocatechuic acid isomer II, atracylenoltriol, 12-methylbutyryl-14-acetyl-2E, 8EZ, 10E-atracylenoltriol, 12-methylbutyryl-14-acetyl-2E, 8EZ, 10E-atracylenoltriol isomer, and linoleic acid isomer were lost after its compatibility with crude Paeoniae Radix Alba. For processed Atractylodis Macrocephalae Rhizoma, compounds 9, 20, 26, 27, and 30 were not found except the relative contents of compounds 5, 6, and 8 were decreased while those of compounds 15, 19, 21, and 31 were increased after its compatibility with processed Paeoniae Radix Alba. Furthermore, compound 4 (protocatechuic acid isomer II) was not found in processed Atractylodis Macrocephalae Rhizoma but could be detected in processed Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair by using Exact Finder and MassFrontier softwares. The above results illustrated that Paeoniae Radix Alba significantly changed the components of Atractylodis Macrocephalae Rhizoma in solution when they decocted together. The corresponding results were presented in Figure 5 and Table 2.

4. Conclusions

Q Exactive high-performance benchtop quadrupole-Orbitrap LC-MS/MS is a powerful tool for discriminating the chemical changes between single herbal and co-decoting medicines. In our present study, the Q Exactive high-performance benchtop quadrupole-Orbitrap LC-MS/MS based on chemical profiling approach was used to evaluate chemical constitution between co-decotion and single decoction of Paeoniae Radix Alba and Atractylodis Macrocephalae Rhizoma. For crude Paeoniae Radix Alba, the relative contents of most compounds were dramatically decreased except those of compounds 80, 90, 98, 113, 119, and 122 were significantly increased and 19 compounds were not detected after its compatibility with crude Atractylodis Macrocephalae Rhizoma. For processed Paeoniae Radix Alba, the relative contents of compounds 12, 36, 84, and 86 were remarkably increased except 12 compounds including pedunculagin, oxyzaenol, 6-O-glucopyranosyl-lactonide, 1, 2, 3, 6-tetra-O-galloylglucose isomer A, 1, 2, 3, 6-tetra-O-galloylglucose isomer B, tetragalloylglucose C, galloyloxypaeoniflorin isomer II, hexagalloylglucose, 3, 6-di-O-galloyl paeoniorin isomer, oxybenzoyl-oxypaeoniflorin, benzoyloxypaeoniflorin, and albidiflorin RI isomer III were newly generated. Atractylodis Macrocephalae Rhizoma herbal pair extracts was proposed. The results showed that processing and compatibility of TCM could significantly change the chemical composition of Paeoniae Radix Alba and Atractylodis Macrocephalae Rhizoma. The developed
method is considered to provide a scientific foundation for deeply elucidating the processing and compatibility mechanism of Paeonieae Radix Alba and Atractylodis Macrocephalae Rhizoma.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution

Gang Cao, Qinglin Li, Hao Cai, and Sicong Tu contributed equally to this work.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (nos. 81202918, 81173546, and 30940093), the Natural Science Foundation of Jiangsu Province, China (no. BK2009495), the International Science and Technology Cooperation Project of Jiangsu Province, China (no. B2011053), the Open Project of National First-Class Key Discipline for Science of Chinese Materia Medica, Nanjing University of Chinese Medicine (no. 2011ZYX2-006), the Project of Science and Technology for Chinese Medicine of Zhejiang Province, China (no. 2013KYB183), the Science and Technology Project of Hangzhou, China (nos. 20130533B68, 2013813A23), the Chinese Medicine Research Program of Zhejiang Province, China (nos. 2014ZQ008, 2008ZA002), the Project of Science Technology Department of Zhejiang Province, China (no. 2013C33SAJC0003), and the Science Foundation of Zhejiang Chinese Medical University (nos. 2011ZY25, 2013ZZ12).

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