Review

Research Progress on Quality Control Methods for Xiaochaihu Preparations

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Abstract: Xiaochaihu (XCH) is a classic Chinese medicine formula. XCH tablet, XCH granule, XCH capsule, and XCH effervescent tablet are included in the Chinese Pharmacopoeia. In this review, the formula and quality standards of XCH preparations at home and abroad were compared. The differences in manufacturing process of XCH preparations are discussed. The progress of research on the qualitative identification, quantitative detection and fingerprint chromatogram/specific chromatogram of XCH preparations was reviewed. The characteristic components of Pinelliae Rhizoma Praeparatum Cum Zingibere Et Alumine and Jujubae Fructus was rarely analyzed for XCH preparations. It is suggested that the specificity of drug quality detection methods should be improved. Considering drug safety and drug efficacy, it is suggested to set the upper and lower limits of the content of saikosaponins. The standards for heavy metals and other limited items for XCH preparations are also suggested to be set.

Keywords: Xiaochaihu (XCH) formula; preparations; quality control; standard

1. Introduction to XCH Formula

Xiaochaihu (XCH) formula, which was created by Zhang Zhongjing in the East Han Dynasty, is capable of inducing sweat to dispel heat, channeling the liver, regulating the spleen, soothing the stomach [1], etc. Traditionally, the recipe is composed of Bupleuri Radix, Scutellariae Radix, Ginseng Radix Et Rhizoma, Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle, Zingiberis Rhizoma Recens, Jujubae Fructus, and Pinelliae Rhizoma [2]. According to the principle of JUN-CHEN-ZUO-SHI (emperor-minister-assistant-courier in English), in this formula, Bupleuri Radix is JUN, Scutellariae Radix is CHEN, Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle is SHI, and the others are ZUO. Modern research has verified that XCH has anti-inflammatory [3] and antitumor [4] functions and regulates the endocrine system [5]. Clinically, the formula is applied to treat various diseases of the respiratory system [6], digestive system [7], urogenital system [8], immune system [9], circulatory system [10], etc. The mechanism of XCH acting on the human body can be preliminarily explored by means of liquid chromatography-mass spectrometry, network pharmacology, and animal experiments. For fever, the widest application of XCH, potential antipyretic mechanism includes the reduction of inflammation level, inhibition of endogenous pyrogen and COX-2 [11]. Some active ingredients of XCH including quercetin, baicalein, and hanbaicalein can significantly inhibit the growth of hepatocellular carcinoma and induce apoptosis of hepatocellular carcinoma cells [12]. In recent years, many novel applications have been reported, including the prevention and treatment of meticillin-resistant Staphylococcus aureus [13], syncytial virus, and adenovirus [14], as well as the inhibition of influenza A virus [15], etc. For the period from 2000 to 2020, an overall trend of a steady rise in the numbers of publications in the field of XCH could be found. In the
database of www.cnki.net, the number has grown annually and ranged from about 150 to nearly 400 works [16].

2. Formula Differences of Existing XCH Preparations

Capsules, granules, pills, tablets, and other XCH preparations are all on the Chinese domestic market. Among those, XCH tablets, XCH effervescent tablets, XCH capsules, and XCH granules were included in the 2020 edition of the Chinese Pharmacopoeia [17]. The Pharmaceuticals and Medical Devices Agency in Japan [18] has published more than 10 kinds of XCH preparations, which are mainly granules or tablets. The Japanese Pharmacopoeia includes two different specifications of the Shosaikoto extract [19]. In Korea, Soshiho-Tang is widely used as a classic recommendation, which is mainly sold in granules [20].

The raw materials of the Japanese XCH preparations are Pinelliae Rhizoma, Ginseng Radix, Bupleuri Radix, Scutellariae Radix, Glycyrrhizae Radix, Zingiberis Rhizoma Recens, and Jujubae Fructus. However, the main XCH preparations on the Chinese market use Pinelliae Rhizoma Praeparatum Cum Zingibere Et Alumine (Jiangbanxia), Codonopsis Radix, Bupleuri Radix, Scutellariae Radix, Glycyrrhizae Radix, Zingiberis Rhizoma Recens, and Jujubae Fructus as raw materials. Table 1 shows four XCH preparations that are listed in the Chinese Pharmacopoeia. The JUN material Bupleuri Radix is the highest in mass ratio among the four dosage forms included in Chinese Pharmacopoeia, accounting for approximately 30%. The raw material mass ratio of XCH tablets and XCH capsules is exactly the same, and the mass ratio of Jiangbanxia is higher than those of XCH effervescent tablets and XCH granules. Regarding the materials of Japanese XCH preparations, the mass ratio of Pinelliae Rhizoma is lower than that of Bupleuri Radix but higher than that of any other herb. The mass ratio values of Glycyrrhizae Radix and Zingiberis Rhizoma Recens are both lower than 10%.

*Pinelliae Rhizoma* can cause adverse reactions, such as mucosal irritation [21], hepatorenal toxicity [22], and pregnancy toxicity [23,24]. It has been reported that the needle crystals of calcium oxalate and its lectin protein contained in *Pinelliae Rhizoma* are the main irritant toxic substances [25,26]. In China, there is a long history to use *Zingiberis Rhizoma Recens* to alleviate the toxicity of *Pinellia ternata*. The processing standards for preparing Jiangbanxia have been established [27]. Therefore, the use of Jiangbanxia in XCH preparations in China is conducive to improving drug safety [28].

In Table 1, we compared the amount and mass ratio of raw materials in different XCH preparations which were included in the Chinese and Japanese Pharmacopoeia [17,19]. By having materials divided by the total weight, the mass ratios are calculated and listed.
Table 1. Formula amount of raw materials, their mass ratio and preparation amount in different XCH preparations in pharmacopoeias.

| Raw Materials               | XCH Tablets & XCH Capsules | XCH Effervescent Tablets | XCH Granules | Shosaikoto Extract (Japanese) |
|-----------------------------|-----------------------------|---------------------------|--------------|--------------------------------|
|                             | Amount (g) | Mass Ratio (%) | Amount (g) | Mass Ratio (%) | Amount (g) | Mass Ratio (%) | Amount (g) | Mass Ratio (%) | Amount (g) | Mass Ratio (%) |
| Bupleuri Radix              | 445        | 29.6          | 1550       | 31.0          | 150       | 31.0          | 7          | 29.2          | 6          | 26.1          |
| Jiangbanxia                 | 222        | 14.8          | 575        | 11.5          | 56        | 11.5          | -          | -             | -          | -             |
| Pinelliae Rhizoma           | -          | -             | -          | -             | -          | -             | 5          | 20.8          | 5          | 21.7          |
| Scutellariae Radix          | 167        | 11.1          | 575        | 11.5          | 56        | 11.5          | 3          | 12.5          | 3          | 13.0          |
| Codonopsis Radix            | 167        | 11.1          | 575        | 11.5          | 56        | 11.5          | -          | -             | -          | -             |
| Ginseng Radix               | -          | -             | -          | -             | -          | -             | 3          | 12.5          | 3          | 13.0          |
| Glycyrrhizae Radix          | 167        | 11.1          | 575        | 11.5          | 56        | 11.5          | 2          | 8.33          | 2          | 8.70          |
| Zingiberis Rhizoma Recens   | 167        | 11.1          | 575        | 11.5          | 56        | 11.5          | 1          | 4.17          | 1          | 4.35          |
| Jujubae Fructus             | 167        | 11.1          | 575        | 11.5          | 56        | 11.5          | 3          | 12.5          | 3          | 13.0          |
| Preparation amount          | XCH tablets: 1000 tablets, 0.4 g each; XCH capsules: 1000 capsules, 0.4 g each; | XCH effervescent tablets: 1000 tablets, 2.5 g each | XCH granules: 1000 g (combined with sucrose); 400 g (combined with mannitol); 250 g (combined with lactose) | Not specified |
3. Differences in XCH Preparation Methods

There are different manufacturing processes for preparing XCH [29–32] preparations. Manufacturing processes included in the Chinese Pharmacopoeia [17] are shown in Figures 1–4. For Codonopsis Radix, Glycyrrhizae Radix, Bupleuri Radix, Scutellariae Radix, and Jujubae Fructus, the plants are extracted with water decoction. Jiangbanxia and Zingiberis Rhizoma Recens are extracted with ethanol solution with percolation. Compared with water decoction process, the percolation process is time consuming and solvent consuming. However, the volatilization or degradation of active components can be effectively decreased with the percolation process because it is operated at a low temperature. It has been reported that gingerols are easily degraded at a high temperature [33]. Therefore, it is reasonable to extract active components from Jiangbanxia and Zingiberis Rhizoma Recens with a percolation process [34]. Gingerol and other components in Zingiberis Rhizoma Recens have low solubility in water [35]. Therefore, ethanol solution is generally used as the percolation solvent [36].

In the production process for XCH capsules and XCH tablets, part of Codonopsis Radix and Glycyrrhizae Radix are directly crushed and added, which is significantly different from the process of XCH effervescent tablets and XCH granules. Codonopsis Radix and Glycyrrhizae Radix powder can play a role similar as excipients [37]. The excipients in XCH preparations vary depending on the formulation forms.

Apart from the manufacturing processes included in the Chinese Pharmacopoeia mentioned above, there are several other manufacturing processes for different XCH preparations, such as XCH sustained release tablets [38], nano XCH preparations [39], and others [40,41].

Figure 1. XCH tablets Production Process.
Figure 2. XCH effervescent tablets Production Process.

Figure 3. XCH granules Production Process.
There are two kinds of qualitative methods for the preparations of XCH in production: microscopic identification and thin-layer chromatography (TLC) identification. The identification methods and reference materials from the Chinese Pharmacopoeia and the Japanese Pharmacopoeia are summarized in Table 2.

The method involving the microscopic identification of medicinal materials is suitable for fragmentary medicinal materials or powdered medicinal materials. Raw powdered medicinal materials of *Glycyrrhizae Radix* and *Codonopsis Radix* are used in the manufacturing of XCH tablets and XCH capsules, which is suitable to be analyzed with microscopic identification. Both Chinese and Japanese XCH preparations adopt thin-layer identification, but there are obvious differences. First, in Chinese Pharmacopoeia, thin-layer identification uses only reference substances in Japanese Pharmacopoeia, thin-layer identification uses reference medicinal materials, including *Glycyrrhizae Radix*, *Bupleuri Radix*, and *Codonopsis Radix*. However, thin-layer identification uses only reference substances in Japanese Pharmacopoeia. Second, Japanese thin-layer identification uses more reference substances, including the index components from *Bupleuri Radix*, *Zingiberis Rhizoma Recens*, *Scutellariae Radix*, *Glycyrrhizae Radix* and *Ginseng Radix*. In contrast, the use of reference medicinal materials in thin-layer identification can provide more information than using reference substances, which is conducive to assessing the authenticity of the medicinal materials used. Both Chinese and Japanese XCH preparations quantitatively analyze baicalin contents. Therefore, it seems unnecessary to use baicalin as the reference substance in thin-layer identification.

Silica gel G thin layer plate is mostly widely used in TLC identification. A mixed solvent of ethyl acetate-butanol-formic acid-water is usually used for baicalin identification. A mixed solvent of chloroform-methanol-water is usually used for the identification of *Glycyrrhizae Radix*.
Table 2. Qualitative identification method and comparison of XCH preparations in the Chinese and Japanese Pharmacopoeias.

| Preparations               | Identification Method                        | TLC Reference Substance | TLC Control Crude Drug               |
|----------------------------|---------------------------------------------|-------------------------|-------------------------------------|
| XCH tablets                | Microscopic Identification, Thin-Layer Chromatography Identification | Baicalin                | Glycyrrhizae Radix                  |
| XCH effervescent tablets   | Thin-Layer Chromatography Identification    | Baicalin                | Glycyrrhizae Radix, Bupleuri Radix  |
| XCH capsules               | Microscopic Identification, Thin-Layer Chromatography Identification | -                       | Glycyrrhizae Radix, Bupleuri Radix  |
| XCH granules               | Thin-Layer Chromatography Identification    | Baicalin                | Glycyrrhizae Radix, Bupleuri Radix  |
| Shosaikoto Extract (Japanese) | Thin-Layer Chromatography Identification | Saikosaponin B2, 6-Gingerol, Wogonin, Ginsenoside Rb1, Liquiritin | -                                   |

4.2. Quantitative Determination

Table 3 lists the quantitative detection methods for XCH preparations in Chinese Pharmacopoeia and Japan Pharmacopoeia. According to the Chinese Pharmacopoeia, the XCH tablets weight 0.4 g per tablet, the XCH capsules weight 0.4 g per capsule, and the XCH effervescent tablets weight 2.5 g per tablet. The XCH granules have three specifications (10 g/4 g/2.5 g per bag) due to the various preparation methods. The only quantitative determined index component for XCH preparations mentioned in the 2020 edition of the Chinese Pharmacopoeia is baicalin, while the determination of baicalin, saikosaponin B2, and glycyrrhizic acid are required in Japan Pharmacopoeia. Considering that there are seven medicinal materials in the formula for XCH preparations, more index components should be determined to control drug quality. The Chinese Pharmacopoeia specifies a lower limit for baicalin, while the Japanese Pharmacopoeia specifies both the upper and lower limits for the contents of saikosaponin B2, baicalin, and glycyrrhizic acid. Herbal materials of XCH preparations were often decocted before quantitative analysis. Methanol is a common solvent for sample preparation.

Table 3. Comparison of quantitative detection methods for XCH preparations in the Chinese and Japanese Pharmacopoeias.

| Preparations               | Detection Component | Prescribed Limit                        |
|----------------------------|---------------------|----------------------------------------|
| XCH tablets                | Baicalin            | Not lower than 2.0 mg per tablet/capsule |
| XCH capsules               | Baicalin            | Not lower than 20.0 mg per tablet/package|
| XCH effervescent tablets   | Saikosaponin B2, baicalin and glycyrrhizic acid | Saikosaponin B2: 2–8 mg               |
| XCH granules               | Saikosaponin B2, baicalin and glycyrrhizic acid | Saikosaponin B2: 2--8 mg               |

Table 4 lists the published works on the quantitative detection of XCH preparations. In such work, the raw materials often went under decoction treatment before they were put into use. In addition, methanol is a common solvent in the procedure. HPLC technology is used to separate the components of XCH preparations. The detectors stated in the literature are mostly ultraviolet detectors, and a few are diode array detectors (DAD) and mass spectrometer detectors. Since the content of a saikosaponin is low, mass spectrometer detectors are used more often to analyze it. In some papers, the method of quantitative analysis of multiple components by a single marker (QAMS) was used, which can reduce
the cost of testing. There are more reports on the detection of index components of *Bupleuri Radix* and *Scutellariae Radix*, which reflects the emphasis on JUN and CHEN drugs. Some literature has detected gingerol, liquiritin, glycyrrhizic acid, lobetyolin, and other substances, which can help control the contents of chemical components in *Zingiberis Rhizoma Recens*, *Glycyrrhizae Radix*, and *Codonopsis Radix*. However, there are still few detections of index components in *Jujubae Fructus* and Jiangbanxia.

Table 4. Quantitative detection methods for the XCH formula.

| Year | Apparatus | Quantified Components | Other Instructions | Reference |
|------|-----------|-----------------------|--------------------|-----------|
| 1    | 2020 HPLC| Baicalin, Wogonoside, Baicalein, Wogonin, Ammonium Glycyrrhizinate, Saikosaponin B2, Saikosaponin B1 | QAMS              | [42]      |
| 2    | 2018 HPLC| 6-Gingerol            |                    | [43]      |
| 3    | 2018 HPLC| Ginsenoside Rg1, Ginsenoside Re, Ginsenoside Rb1, Saikosaponin A, Saikosaponin D | QAMS              | [44]      |
| 4    | 2018 HPLC| Baicalin, Baicalein, Wogonin |                    | [45]      |
| 5    | 2017 HPLC| Saikosaponin A, Saikosaponin D, Saikosaponin B1, Baicalin, Ginsenoside Rb1, Ginsenoside Re, 6-Gingerol, Liquiritin, Ammonium Glycyrrhizinate | -                | [29]      |
| 6    | 2017 HPLC| Lobeteylin, Liquiritin, Baicalin, Baicalein | Detection wavelength switched | [46]      |
| 7    | 2016 HPLC| Baicalin              | -                  | [47]      |
| 8    | 2016 UPLC| Baicalin              | -                  | [48]      |
| 9    | 2015 HPLC-MSMS| Saikosaponin A, Saikosaponin D | -            | [49]      |
| 10   | 2015 HPLC| Liquiritin, Baicalin, Wogonoside, Baicalein, Wogonin | -            | [50]      |
| 11   | 2015 HPLC| Baicalin              | -                  | [51]      |
| 12   | 2015 HPLC| Saikosaponin, Baicalin, Ginsenoside Rg1, Liquiritin, Ephedrine, 6-Gingerol | -            | [52]      |
| 13   | 2014 HPLC| Saikosaponin A, Baicalin | -                  | [53]      |
| 14   | 2014 HPLC| Liquiritin, Baicalin, Wogonoside, Baicalein, Ammonium Glycyrrhizinate, Saikosaponin A, Wogonin | -            | [54]      |
| 15   | 2014 HPLC| Saikosaponin B2       | -                  | [55]      |
| 16   | 2013 HPLC| Saikosaponin, Baicalin, Glycyrrhizic acid | -            | [56]      |
| 17   | 2012 Capillary electrophoresis| Saikosaponin A, Saikosaponin D | -            | [57]      |
| 18   | 2012 HPLC| Baicalin              | -                  | [58]      |
| 19   | 2012 HPLC| Baicalin              | -                  | [59]      |
| 20   | 2010 HPLC| Baicalin, Wogonoside  | -                  | [60]      |
| 21   | 2010 HPLC| Baicalin, Baicalein, Wogonoside, Wogonin, Glycyrrhizic acid | -            | [61]      |
| 22   | 2010 HPLC| Saikosaponin A        | -                  | [62]      |
| 23   | 2007 HPLC-DAD-MS| Saikosaponin A, Baicalin, Glycyrrhizic acid | -            | [63]      |
| 24   | 2007 HPLC| Baicalin              | -                  | [64]      |
| 25   | 2006 HPLC/DAD| Baicalin, Glycyrrhizic acid | -            | [65]      |
| 26   | 2006 HPLC-MSMS| Cytidine, Tyrosine, Uridine, Adenine, Guanosine, Phenylalanine, Adenosine, Tryptophan | -            | [66]      |
| 27   | 2004 HPLC-MSMS| Saikosaponin A, B1, B2, C, D, G, H, I | -            | [67]      |

"-" means there is no special instruction that is necessary to be presented.
4.3. Fingerprint and Specific Chromatogram

Fingerprint and specific chromatogram detection methods can reflect the overall characteristics of Chinese medicines and are widely used in drug quality analysis. At present, the application of these two methods represents a significant research progress. Both qualitative identification and quantitative detection can be carried out on the basis of fingerprint and specific chromatograms. A summary of the fingerprint and specific chromatogram detection methods for XCH preparations is shown in Table 5. Compared with the quantitative methods listed in Table 4, fingerprint and specific chromatogram detection can identify more components in chromatographic peaks, therefore providing more information. At present, the most identified components are the saponins in *Bupleuri Radix*, flavonoids of *Scutellariae Radix*, gingerol in *Zingiberis Rhizoma Recens*, liquiritin, and glycyrrhizic acid in *Glycyrrhizae Radix*, etc. However, the characteristic components of *Jujubae Fructus* and Jiangbanxia have not been identified.

In some of the research works, a quantitative fingerprint or specific chromatogram of the XCH preparation was obtained. The quantitatively determined components are mainly from *Scutellariae Radix*, *Glycyrrhizae Radix*, *Bupleuri Radix*, and *Codonopsis Radix*. Wang et al. [68] compared the HPLC spectra of XCH granules at different wavelengths and concluded that spectral analysis at a single ultraviolet absorption wavelength is not suitable for quality detection. Liu et al. used charged aerosol detector (CAD) to analyze saikosaponins [69]. Compared with using evaporative light scattering detector (ELSD), lower detection limit and wider detection range can be realized with CAD.

In some studies, the active substances in *Bupleuri Radix* such as saikosaponin A and saikosaponin D were not detected in XCH granules, which may be due to the hydrolysis of saikosaponin during decoction [70]. There are also reports that the existing detection methods often add an acid to the mobile phase, and saikosaponin A and saikosaponin D are prone to degrade under acidic conditions, which makes them difficult to detect [71].

| Year | Apparatus         | Quantitative Determined Components                  | Qualitatively Identified Components | Detection Method                      | Reference |
|------|-------------------|-----------------------------------------------------|-------------------------------------|---------------------------------------|-----------|
| 1    | 2021 HPLC-CAD     | Saikosaponin A, B1, B2, C, G, H, I                 | Saikosaponin A, B1, B2, C, G, H, I  | Fingerprint chromatogram              | [69]      |
| 2    | 2021 UHPLC        | Liquiritin, Baicalin, Wogonin, Baicalein, Glycyrrhizin G2, Glycyrrhizic acid, Saikosaponin B2, Saikosaponin B1 | -                                   | Fingerprint chromatogram              | [71]      |
| 3    | 2018 UPLC         | Liquiritin, Baicalin, Berberine, Wogonoside, Baicalein, Ammonium Glycyrrhizinate | Liquiritin, Baicalin, Berberine, Wogonoside, Baicalein, Ammonium Glycyrrhizinate | Specific chromatogram                  | [72]      |
| 4    | 2017 HPLC         | -                                                   | -                                   | Fingerprint chromatogram              | [73]      |
| 5    | 2017 HPLC         | -                                                   | -                                   | Fingerprint chromatogram              | [74]      |
| 6    | 2016 HPLC         | Lobetyolin, Saikosaponin A                          | Lobetyolin, Saikosaponin A          | Specific chromatogram                  | [75]      |
| 7    | 2016 HPLC         | Baicalin, Ammonium Glycyrrhizinate                  | Baicalin, Ammonium Glycyrrhizinate  | Specific chromatogram                  | [68]      |
| 8    | 2015 HPLC-ELSD    | -                                                   | Liquiritin, Ginsenoside Re, Baicalin, Wogonoside, Baicalein, Ginsenoside Rb1 | Fingerprint chromatogram              | [76]      |
### Table 5. Cont.

| Year | Apparatus                  | Quantitative Determined Components                                                                 | Qualitatively Identified Components                                                                 | Detection Method                          | Reference |
|------|----------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------|-----------|
| 9    | HPLC                       | Liquiritin, Baicalin, Wogonoside, Baicalein, Ammonium Glycyrrhizinate, Saikosaponin A, Wogonin       | Liquiritin, Baicalin, Wogonoside, Baicalein, Ammonium Glycyrrhizinate, Saikosaponin A, Wogonin       | Specific chromatogram                     | [54]      |
| 10   | HPLC                       | -                                                                                                    | Liquiritin, Baicalin, Wogonoside, Baicalein, Ammonium Glycyrrhizinate, Saikosaponin A, Wogonin       | Fingerprint chromatogram                  | [77]      |
| 11   | HPLC                       | Baicalin, Glycyrrhizic acid                                                                       | Baicalin, Glycyrrhizic acid                                                                       | Fingerprint chromatogram                  | [78]      |
| 12   | HPLC                       | -                                                                                                    | Liquiritin, Baicalin, Ononin, Wogonoside, Saikosaponin A, Skullcapflavone II, etc.                  | Fingerprint chromatogram                  | [79]      |
| 13   | HPLC-DAD-ESI-MS            | Homogenstic acid, Baicalin, Glycyrrhizic acid, Saikosaponin A, 6-Gingerol, Ginsenoside Rg3          | -                                                                                                    | Fingerprint chromatogram                  | [80]      |
| 14   | HPLC                       | Baicalin, Wogonoside, Baicalein, Wogonin, Glycyrrhetinic acid                                      | Baicalin, Wogonoside, Baicalein, Wogonin, Glycyrrhetic acid                                      | Specific chromatogram                     | [81]      |
| 15   | UPLC                       | -                                                                                                    | Glycyrrhizin, Ginsenoside Rg1, Baicalin, Isowogonoin, Baicalein, Saikosaponin A                   | Fingerprint chromatogram                  | [82]      |
| 16   | HPLC                       | Baicalin, Wogonoside, Baicalein, Wogonin                                                          | Baicalin, Wogonoside, Baicalein, Wogonin                                                         | Specific chromatogram                     | [83]      |
| 17   | HPLC-DAD                   | -                                                                                                    | -                                                                                                    | Fingerprint chromatogram                  | [84]      |
| 18   | HPLC-TOF/MS                | -                                                                                                    | Liquiritin, Baicalin, Wogonoside, Ginsenoside Rg1, Glycyrrhizic acid                              | Fingerprint chromatogram                  | [85]      |
| 19   | HPLC                       | -                                                                                                    | -                                                                                                    | Fingerprint chromatogram                  | [86]      |

"-" means there is no quantitative determined or qualitatively identified component.

In conclusion, a fingerprint/specific chromatogram can be used to characterize multiple chemical component information of XCH preparations. However, fingerprint/specific chromatogram is not included in Chinese Pharmacopoeia. Further development of quality control technology with use of the fingerprint/specific chromatogram is required for XCH preparations.

### 5. Prospect on the Development Direction of Quality Control of XCH Preparations

#### 5.1. Improvement in the Specificity of Quality Testing

According to Chinese Pharmacopoeia, Glycyrrhizae Radix, Bupleuri Radix and Codonopsis Radix are used as TLC reference materials, and baicalin is used as a TLC reference substance in qualitative identification. However, less attention has been given to Zingiberis Rhizoma Recens, Jujubae Fructus, and Jiangbanxia. The specific components of Jiangbanxia and Jujubae Fructus are not quantitatively analyzed in literature. Recently, guanosine, uridine, hypoxanthine and several other components were analyzed [87], which do not especially belong to Jiangbanxia, but it still suggests a way to improve the specificity of HPLC detection by detecting these compositions with strong polarity.
It is essential to distinguish the authenticity of *Bupleuri Radix*. There are 36 species, 17 varieties, and seven forms distributed all over China [88]. Among them, *Bupleurum marginatum var. stenophyllum* and even poisonous *Bupleurum longiradiatum* are common varieties that are all easy to mix up [89]. To confirm whether or not *Bupleurum marginatum var. stenophyllum* had been added, Liu et al. using the retention time and peak area of the specific ion detected in the mass spectrum as standards [90]. Liang et al. tried to establish near-infrared spectrum models to distinguish products of different factories, which provided a practical technology for low-cost and rapid detection [91]. Lai et al. used a polymerase chain reaction (PCR) method based on the site specificity of the Internal Transcribed Spacer (ITS) sequence to identify *Bupleurum marginatum var. stenophyllum* from *Bupleurum chinense* DC [92]. These new technologies provide ideas for improving the specificity of analytical methods. *Bupleurum scorzonerifolium* Willd and *Bupleurum chinense* DC are both included in the Chinese Pharmacopoeia, but National Institutes for Food and Drug Control can provide only the reference material of *Bupleurum chinense* DC. Hence, the lack of reference material of *Bupleurum scorzonerifolium* Willd is a problem for quality control of *Bupleuri Radix*.

5.2. Setting Reasonable Content Range of Index Components from Bupleuri Radix

*Bupleuri Radix* is the JUN of XCH formula. Thus far, qualitative identification using the reference material of *Bupleuri Radix* was adopted in Chinese Pharmacopoeia. However, considering drug safety and efficacy, the contents of saikosaponins should be controlled in specific ranges. Studies have indicated that saikosaponins are important active ingredients of *Bupleuri Radix*, which has antipyretic, anti-inflammatory and antitumor activities. Therefore, it is necessary to set up lower limits for their contents [93,94]. Moreover, some reference materials have reported that *Bupleuri Radix* has a certain degree of toxicity when taken in a large dose for a long period of time, and its toxic side effects are often caused by its saponins and volatile substances, which mainly affect the liver [95]. Therefore, from the perspective of drug safety, it is necessary to set up upper limits for saikosaponins. At present, the upper and lower limits of the saikosaponin B2 content are set up in the Japanese Pharmacopoeia, which is worth referencing. When setting up the lower limit, companies can consider collecting big data from clinical practice. Accordingly, the needs of drug quality control indicators can be taken into consideration, such as drug interactions and medications for special populations.

5.3. Strengthening the Standard of Limited Detected Items

In recent years, great progress in the control of heavy metals, pesticides, and biological toxins in Chinese medicines and extracts was achieved. The Chinese Pharmacopoeia has specially listed items General Principle for Inspection of Crude Drugs and Decoction Pieces and Guidelines for Establishment of Limit for Harmful Residue of Traditional Chinese Medicine, which have provided guidance for controlling heavy metals, pesticides and biological toxins for medicinal materials. The Chinese Pharmacopoeia stipulates that *Jujubae Fructus* needs to be tested for aflatoxin, *Glycyrrhizae Radix* needs to be tested for heavy metals, harmful elements and pesticide residues, and *Codonopsis Radix* needs to be tested for sulfur dioxide residues, all of which help to guarantee the safety of XCH preparations. However, the current guidelines for XCH preparations still require more relevant limiting items for heavy metals, pesticides and biological toxins, and other toxic ingredients. The Japanese Pharmacopoeia stipulates the limits of heavy metals and arsenic in XCH preparations. It takes the increase in heavy metals during the production process into account, which is more rigorous and improves the level of quality control.

Therefore, from the perspective of drug safety, XCH preparations require an upper limit for the amounts of certain active ingredients, heavy metals, pesticides, biotoxins, and other toxic components. Similar quality control problems exist for many other Chinese medicines. Therefore, the development direction of quality control presented in this work can also be referenced for that of other Chinese medicines.
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