Chinese Herbal Medicine for Chemotherapy-Induced Leukopenia: A Systematic Review and Meta-Analysis of High-Quality Randomized Controlled Trials

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Aim: We conducted a systematic review of high-quality randomized controlled trials (RCTs) to assess the efficacy and safety of Chinese herbal medicine (CHM) for the treatment of chemotherapy-induced leukopenia (CIL).

Methods: Eight electronic databases were searched from the date of inception to November 4, 2020 for high-quality RCTs that met the requirements of at least four key domains of the Cochrane risk of bias (RoB) tool. RevMan 5.3 was applied for the meta-analysis.

Results: Fourteen RCTs involving 1,053 patients were included. The pooled results showed that CHM + chemotherapy exerted greater beneficial effects on white blood cell (WBC), neutrophil (NEU), hemoglobin (Hb), and platelet (PLT) counts in addition to the Karnofsky performance scale (KPS) score, but showed no significant difference on granulocyte colony-stimulating factor (G-CSF) dosage compared with chemotherapy alone. Placebo (PBO) + chemotherapy and CHM + chemotherapy groups showed no significant differences in terms of reduction of the incidence of neutropenia. CHM + chemotherapy was superior to Western medicine (WM) + chemotherapy in improving the WBC count, KPS, infection amount, G-CSF use rate, and incidence of leukopenia. In addition, no severe adverse events were observed in the 14 RCTs.

Conclusion: CHM in combination with chemotherapy could effectively improve the clinical symptoms of CIL when compared with chemotherapy alone or Western medicine + chemotherapy, except when comparing with PBO + chemotherapy. While CHMs were generally safe for clinical use and exerted no severe side effects in the 14 RCTs, high-quality RCTs with larger sample sizes are essential to reduce study heterogeneity.

Keywords: traditional Chinese medicine, systematic review, meta-analysis, Chinese herbal medicine, chemotherapy-induced leukopenia
**INTRODUCTION**

Chemotherapy is widely applied for treatment of multiple cancer types, with one or more anticancer drugs generally used as part of a standardized chemotherapy regimen in the clinic (Johnstone et al., 2002). However, chemotherapy drugs often have poor targeting problems, and combined application of several drugs inevitably results in a series of adverse events (Sarah, 2013), such as bone marrow dysfunction, peripheral neuropathy, chronic pain, sleep disorders, nausea and vomiting, fatigue, and flushes, which not only negatively affect curative effects but also lead to severe patients’ discomfort and poor quality of life (QOL) posttreatment (Torre et al., 2015; Kato et al., 2019; Makary et al., 2019). Bone marrow suppression remains a major toxic effect (Yeshurun et al., 2014), which is characterized by a decrease in three critical cell types: leukocytes, erythrocytes, and platelets. Leukopenia is one of the most prominent effects of bone marrow suppression (Park et al., 2015) and often accompanied by severe infection and bleeding. Long-term usage of cytotoxic drugs is clearly associated with chemotherapy-induced leukopenia (CIL) (Merryman et al., 2012). To increase the white blood cell (WBC) counts within a short time frame for the maintenance of therapeutic efficacy and continue subsequent courses of treatment, granulocyte colony-stimulating factor (G-CSF) is commonly used to treat CIL (Winkler et al., 2016). However, while the effects of G-CSF are rapid, side effects, such as myalgia and fever, are also commonly reported (Yamauchi et al., 2014), making its usage less acceptable in the clinic. Moreover, for patients with severe myelosuppression, repeated treatment is required to maintain the curative effects of chemotherapy. Once medication is stopped, patients are prone to recurrent episodes of illness (Yang et al., 2015). Therefore, treatments that can facilitate effective and stable relief of CIL and promote patients’ QOL by consolidating the clinical value of previous chemotherapeutic regimens and ensuring continuation of therapy are currently a hot topic of research.

Recent studies have shown that traditional Chinese medicine (TCM) aiming to provide personalized treatment plans with multi-targeted and long-lasting effects together with fewer side effects (Zhang et al., 2015) can alleviate the adverse events of...

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**FIGURE 1 | Flowchart of screening process.**

- **Identification**
  - Records identified through database searching (n = 6197)
  - Additional records identified through other sources (n = 0)
- **Screening**
  - Records after duplicates removed (n = 4703)
  - Records excluded based on title and abstract (n = 4274)
    - Irrelevant literature: 3264
    - Reviews: 201
    - Animal experiments: 372
    - Other TCM methods: 437
- **Eligibility**
  - Full-text articles assessed for eligibility (n = 429)
  - Full-text articles excluded, with reasons (n = 415)
    - Not meet inclusion criteria: 257
    - No available data: 2
    - Not high quality: 156
- **Included**
  - Studies included in qualitative synthesis (n = 14)
  - Studies included in quantitative synthesis (meta-analysis) (n = 14)
conventional chemotherapy (Li et al., 2019). Based on the key treatment concept of syndrome differentiation, TCM has been popularized and widely applied for patients on chemotherapy, including Chinese herbal medicine (CHM), Chinese patent drug, acupuncture, cupping, and other treatments (Li et al., 2018).

Accumulating reports have confirmed beneficial effects of TCM on adverse conditions resulting from bone marrow suppression after chemotherapy. In earlier pharmacological studies, administration of CHM as an adjuvant treatment significantly improved WBC counts in patients with CIL (Liu and Bi, 2015),

| First author and publication year | Publication language | Sample size and characteristics (M/F, age (years)) | Course of disease | Intervention and dose | Course of treatment (days) | Main outcomes |
|----------------------------------|----------------------|--------------------------------------------------|------------------|----------------------|---------------------------|---------------|
| Liu (2013)                       | Chinese              | 28 (20/8) 53.8 ± 3.6 28 (21/7) 54.2 ± 5.8 | 0.1–7.8 years    | Fuzheng Guben decoction, 1 dose, bid + chemotherapy | 60 | WBC count, G-CSF dosage, adverse events |
| Qian and Li (2013)               | Chinese              | 62 (32/30) 60.20 ± 7.79 58 (31/27) 60.40 ± 8.86 NA | Hua Liao Jian du decoction + chemotherapy | Chemotherapy | 21 | WBC count, Hb count, PLT count, KPS, adverse events |
| Liu and Yao (2014)               | Chinese              | 38 (20/18) 34–64 38 (22/16) 28–67 | NA | Husui decoction 1 dose, tid + chemotherapy | 14 | WBC count, NEU count, G-CSF dosage, adverse events |
| Zhao and Lu (2016)               | Chinese              | 15 (6/15) 53.07 ± 7.72 15 (0/15) 48.00 ± 9.80 NA | Fuzheng Shengbai decoction, 1 dose, bid + chemotherapy | Chemotherapy | 21 | WBC count, NEU count, Hb count, PLT count, KPS, adverse events |
| Li and Liu (2019)                | Chinese              | 26 (12/14) 53.78 ± 5.95 26 (11/15) 54.13 ± 6.37 | NA | Jianpi Shengsui gel, 15–20 g, tid + chemotherapy | 42 | WBC count, NEU count, Hb count, PLT count, KPS, adverse events |
| Huang and Zhang (2020)           | Chinese              | 29 (18/11) 62.00 ± 6.35 28 (16/12) 63.97 ± 6.33 | NA | Yisui Shengxue capsules 1.8 g, tid + chemotherapy | 21 | WBC count, NEU count, Hb count, PLT count, KPS, adverse events |
| Mok et al. (2007)                | English              | 55 (5/50) 32–75 56 (6/50) 39–72 | NA | CHM granules, 3–10 g, qd + chemotherapy | 28 | Incidence of neutropenia, adverse events |
| Yuan and Zhang (2016)            | Chinese              | 27 (15/12) 59.37 ± 5.869 26 (13/13) 59.67 ± 6.449 1-21 month | Qing Shengbai granules, 12 g, bid + chemotherapy | Placebo, 3–10 g, qd + chemotherapy | 42 ± 7 | Incidence of neutropenia, adverse events |
| Ren and Wu (2015)                | Chinese              | 20 (12/8) 58.19 ± 8.67 20 (13/7) 55.5 ± 5.6 10–24 months | Fuzheng Shengbai decoction, 1 dose, bid + chemotherapy | Leukogen tablets 20 mg, tid + chemotherapy | 21 | WBC count, adverse events |
| Wang and Li (2017)               | Chinese              | 45 (23/22) 54.87 ± 8.137 45 (24/21) 54.73 ± 7.347 | NA | Modified Liu Wei Di Huo decoction 1 dose, tid + chemotherapy | 21 | WBC count, KPS improvement, G-CSF use rate, adverse events |
| Wang (2011)                      | Chinese              | 45 (24/21) 35–74 44 (23/21) 34–75 | NA | Leucogen 20 mg and Batyl alcohol 100 mg, tid + chemotherapy | 14 | WBC count, KPS improvement, infection amount |
| Zou (2015)                       | Chinese              | 47 (20/27) 55.7 ± 16.3 48 (21/27) 55.5 ± 16.7 | NA | Sanhuang Sanxian decoction, 1 dose, bid + chemotherapy | 30 | Incidence of leukopenia, infection amount, adverse events |
| Wang et al. (2016)               | Chinese              | 60 (38/22) 66.17 ± 5.23 58 (36/22) 66.82 ± 4.96 | NA | Shuanghuan Shengbai granules, 30 g, bid + chemotherapy | 14 | Incidence of leukopenia, G-CSF use rate, adverse events |
| Li et al. (2020)                 | Chinese              | 33 (12/21) 58.41 ± 8.12 33 (13/20) 58.35 ± 8.13 7.64 weeks | NA | Bazhen decoction 400 ml/d + chemotherapy | 28 | WBC count, adverse events |

M/F, male/female; NA, not available; WBC, white blood cell; NEU, neutrophil; Hb, hemoglobin; PLT, platelet; KPS, Karnofsky performance scale; G-CSF, granulocyte colony-stimulating factor.
| First author and publication year | Chinese herbal medicine | Ingredients of herb prescription | Latin name | English name | Chinese name |
|----------------------------------|-------------------------|---------------------------------|------------|-------------|-------------|
| Liu (2013)                       | Fuzheng Guben decoction | Processed product of Glycyrrhiza uralensis Fisch. | Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle | Zhirgancao |
| Liu (2013)                       |                         | Horn processed product of Cervus nippon Temminck | Cervi Cornus Colla | Lujiaqiao |
| Liu (2013)                       |                         | Rehmannia glutinosa Libosch | Rehmanniae Radix Praeparata | Shudihuang |
| Liu (2013)                       |                         | Psoralea corylifolia L. | Psoraleae Fructus | Buguzhi |
| Liu (2013)                       |                         | Dipsacus asper Wall. ex Henry | Dipsaci Radix | Xufuian |
| Liu (2013)                       |                         | Polia cocos (Schw.) Wolf | Polia | Fuling |
| Liu (2013)                       |                         | Atractylodes macrocephala Koidz | Atractylodis Macrocephalae Rhizoma | Baizhu |
| Liu (2013)                       |                         | Pseudostellaria heterophylla (Miq.) Pax ex pax et Hoffm | Pseudostellariae Radix | Taizisheng |
| Qian and Li (2013)               | Hua Liao Jian du decoction | Panax ginseng C. A. Mey | Ginseng Radix et Rhizoma Rubra | Hongshen |
| Qian and Li (2013)               |                         | Astragalus membranaceus (Fisch.) Bge. | Astragal Radix | Huangqi |
| Qian and Li (2013)               |                         | Atractylodes macrocephala Koidz. | Atractylodis Macrocephalae Rhizoma | Baizhu |
| Qian and Li (2013)               |                         | Angelica sinensis (Oliv.) Dels | Angelicae Sinensis Radix | Danggui |
| Qian and Li (2013)               |                         | Equus asinus L. | Asini Corii Colla | Ejiao |
| Qian and Li (2013)               |                         | Horn processed product of Cervus nippon Temminck | Cervi Cornus Colla | Lujiaqiao |
| Qian and Li (2013)               |                         | Processed product of Carapax et Plastrum Testudinis | Testudinis Carapacis et Plastri Colla | Guibanjiao |
| Liu and Yao (2014)               | Husui decoction         | Citrus reticulata Blanco | Citri Reticulatae Pericarpium | Chenpi |
| Liu and Yao (2014)               |                         | Glycyrrhiza uralensis Fisch. | Glycyrrhizae Radix et Rhizoma | Gancao |
| Liu and Yao (2014)               |                         | Panax ginseng C. A. Mey | Ginseng Radix et Rhizoma | Renshen |
| Liu and Yao (2014)               |                         | Astragalus membranaceus (Fisch.) Bge. | Astragal Radix | Huangqi |
| Liu and Yao (2014)               |                         | Lycium barbarum L. | Lycii Fructus | Goouzi |
| Liu and Yao (2014)               |                         | Atractylodes macrocephala Koidz. | Atractylodis Macrocephalae Rhizoma | Baizhu |
| Liu and Yao (2014)               |                         | Rehmannia glutinosa Libosch | Rehmanniae Radix Praeparata | Shudihuang |
| Liu and Yao (2014)               |                         | Angelica sinensis (Oliv.) Dels | Angelicae Sinensis Radix | Danggui |
| Liu and Yao (2014)               |                         | Spatholobus suberectus Dunn | Spatholobi Caulis | Jixueteng |
| Liu and Yao (2014)               |                         | Equus asinus L. | Asini Corii Colla | Ejiao |
| Liu and Yao (2014)               |                         | Horn processed product of Cervus nippon Temminck | Cervi Cornus Colla | Lujiaqiao |
| Zhao and Lu (2016)               | Fuzheng Shengbai decoction | Cuscuta australis R. Br. | Cuscutae Semen | Tusizi |
| Zhao and Lu (2016)               |                         | Oryza sativa L. | Oryzae Fructus Germinatus | Daoya |
| Zhao and Lu (2016)               |                         | Hordeum vulgare L. | Hordei Fructus Germinatus | Chaomaiya |
| Zhao and Lu (2016)               |                         | Aucklandia lappa Decne | Aucklandiae Radix | Muxiang |
| Zhao and Lu (2016)               |                         | Glycyrrhiza uralensis Fisch. | Glycyrrhizae Radix et Rhizoma | Gancao |
| Zhao and Lu (2016)               |                         | Curculigo orchoides Gaertn | Curculiginis Rhizoma | Xianmao |
| Zhao and Lu (2016)               |                         | Morinda officinalis How | Morindae Officinalis Radix | Baijitan |
| Zhao and Lu (2016)               |                         | Ligustrum lucidum At. | Ligustri Lucidi Fructus | Nizhenzi |
| Zhao and Lu (2016)               |                         | Eclipta prostrata L. | Ecliptae Herba | Mohanian |
| Zhao and Lu (2016)               |                         | Sanguisorba officinalis L. | Sanguisorbae Radix | Diju |
| Zhao and Lu (2016)               |                         | Pyrrosia lingua (Bak.) Ching | Pyrrosiae Foli | Shiwei |
| Zhao and Lu (2016)               |                         | Codonopsis pilosula (Franch.) Nanf. | Codonopsis Radix | Dangshen |
| Zhao and Lu (2016)               |                         | Atractylodes macrocephala Koidz | Atractylodis Macrocephalae Rhizoma | Baizhu |
| Zhao and Lu (2016)               |                         | (Continued on following page) | (Continued on following page) | (Continued on following page) | (Continued on following page) |
| First author and publication year | Chinese herbal medicine | Ingredients of herb prescription | Latin name | English name | Chinese name |
|------------------------------------|--------------------------|----------------------------------|------------|--------------|--------------|
| Li and Liu (2019)                  | Jianpi Shengui plaster   | Codonopsis pilosula (Franch.) Nanrf. | Codonopsis Radix | Dangshen   |
|                                   |                          | Lycium barbarum L.               | Lycii Fructus | Gouqi       |
|                                   |                          | Polygonatum kingianum Coll. et Hemsl. | Polygonati Rhizoma | Huangqi     |
|                                   |                          | Ligusticum L.                    | Ligustri Lucidi Fructus | Nuizheng |
|                                   |                          | Eclipta prostrata L.             | Ecliptae Herba | Mohranian   |
|                                   |                          | Stomach of Gallus domesticus Brisson | Galli Gigeri endothelium corneum | Jinejin |
|                                   |                          | Hordeum vulgare L.               | Hordei Fructus Germinatus | Maya       |
|                                   |                          | Crataegus pinnatifida Bge        | Crataei Fructus | Shanzhao    |
|                                   |                          | Cyperus rotundus L.              | Cyperi Rhizoma | Xiangfu     |
|                                   |                          | Glucidtemmens                    | Yuanzhensheng | Yuanzhentang |
|                                   |                          | Equus asinus L.                  | Asini cori colla | Ejiao       |
|                                   |                          | Polygonatum odoratum (Mil.) Druce | Polygonati Odorati Rhizoma | Yuzhu    |
|                                   |                          | Ophiopogon japonicus (L.) Ker-Gawl | Ophiopogonis Radix | Maxdang    |
|                                   |                          | Cervus nippon Temminck           | Cervi Cornus Pantotrichum | Luron |
| Huang and Zhang (2020)             | Yisui Shengxue capsule   | Epimedium brevicomum Maxim       | Epimedi Foliun | Yin yanghao |
|                                   |                          | Zingiber officinalis Rosc        | Zingiberis Rhizoma | Ganjjang  |
|                                   |                          | Panax ginseng C. A. Mey          | Ginseng Radix et Rhizoma | Ren shen |
|                                   |                          | Atractylodes macrocephala Koidz  | Atractylodis Macrocephalae Rhizoma | Baizhu |
|                                   |                          | Astragalus membranaceus (Fisch.) Bge | Astragali Radix | Huangqi |
|                                   |                          | Amomum volatum Lour              | Amomi Fructus | Sharen      |
|                                   |                          | Magneto Magnetite                | Magnettum | Cishi       |
|                                   |                          | Comus officinales Sieb. et Zucc  | Comi Fructus | Jiuyrou     |
|                                   |                          | Processed product of polygonum multiflorum Thunb | Polygoni Multiflori Radix Praeparata | Zhi shou hwou |
|                                   |                          | Equus asinus L                   | Asini cori colla | Ejiao |
|                                   |                          | Rheum palmatum L                 | Rheei Radix et Rhizoma | Dahuang |
|                                   |                          | Processed product of Glycyrrhiza uralensis Fisch | Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle | Zhigancao |
| Mok et al. (2007)                 | CHM granules             | A combination of single-itemized herbs from the stocking 225 different types of commonly used herbs (see Appendix for details) | | | |
| Yuan and Zhang (2016)             | QijingShengbai granules  | Panax quinquefolium L            | Panacis Quinquefoli Radix | Xiyangshen |
|                                   |                          | Astragalus membranaceus (Fisch.) Bge | Astragali Radix | Huangqi |
|                                   |                          | Angelica sinensis (Oliv.) Delis   | Angelicae Sinensis Radix | Danggui |
|                                   |                          | Eclipta prostrata L              | Ecliptae Herba | Mohranian |
|                                   |                          | Polygonatum kingianum Coll. et Hemsl. | Polygonati Rhizoma | Huangqi |
|                                   |                          | Lycium barbarum L               | Lycii Fructus | Gouqi       |
|                                   |                          | Hor processed product of Cervus nippon Temminck | Cervi Cornus Colla | Lujiaqiao |
| Ren and Wu (2015)                 | Fuzhengshengbai decoction | Epimedium brevicomum Maxim       | Epimedi Foliun | Yin yang hao |
|                                   |                          | Psoraleae corylifolia L          | Psoraleae Fructus | Buguzhi |
|                                   |                          | Spatholobus suberectus Dunn      | Spathohboli Caulis | Jia xie feng |
|                                   |                          | Codonopsis pilosula (Franch.) Nanrf. | Codonopsis Radix | Dang shen |
|                                   |                          | Astragalus membranaceus (Fisch.) Bge | Astragali Radix | Huangqi |
|                                   |                          | Gastrodia elata Bl               | Gastrodiae Rhizoma | Tianma |
|                                   |                          | Angelica sinensis (Oliv.) Delis   | Angelicae Sinensis Radix | Danggui |
|                                   |                          | Rehmannia glutinosa Libosch      | Rehmanniae Radix Praeparata | Shuidhuang |
|                                   |                          | Alisma orientate (Sam.) Juizep   | Alismatis Rhizoma | Zexie |
|                                   |                          | Cassia obtusifolia L             | Cassiae Semen | Juemingzi |
|                                   |                          | Cuscuta australis R. Br          | Cuscutae Semen | Tuszi |
|                                   |                          | Lycium barbarum L                | Lycii Fructus | Gouqi |
|                                   |                          | Eucommia ulmoides Oliv           | Eucommiae Cortex | Duzhong |
|                                   |                          | Atractylodes macrocephala Koidz  | Atractylodis Macrocephalae Rhizoma | Baizhu |
|                                   |                          | Paeonia lactiflora Pall          | Paeoniae Radix Alba | Baishao |
|                                   |                          | Glycyrrhiza uralensis Fisch      | Glycyrrhizae Radix et Rhizoma | Gancao |

(Continued on following page)
relieved tumor-related fatigue and dizziness (Han and Jiang, 2018), elevated patients’ QOL (Li et al., 2019), and reduced toxic side effects (Jia et al., 2014). Data from previous meta-analyses clearly suggested that CHM is more effective than conventional oral Western medicine (WM) for the treatment of CIL induced by specific tumors (Li et al., 2015; Zhang et al., 2016).

### TABLE 2 | (Continued) Components of Chinese herbal medicine used in the included trials.

| First author and publication year | Chinese herbal medicine | Ingredients of herb prescription |
|-----------------------------------|-------------------------|---------------------------------|
| Wang and Li (2017)               | Modified Liu wei di Huang decoction | Rehmannia glutinosa Libosch, Comus officinalis Sieb. et Zucc, Dioscorea opposita Thunb, Epimedium brevicomu Maxim, Achyranthes bidentata Bl, Eucommia ulmoides Oliv, Poria cocos (Schw.) Wolf, Alisma orientate (Sam.) Juzep, Paeonia suffrutcosa Andr, Panax ginseng C. A. Mey, Atractylodes macrocephala Koidz, Astragalus membranaceus (Fisch.) Bge, Cretaegus pinnatifida Bge, Aucklandia lappa Decne, Massa Medicata Fermentata |
| Wang (2011)                      | Modified Sancai Fengsui decoction | Panax ginseng C. A. Mey, Asparagus cochinchinensis (Lour.) Merr, Rehmannia glutinosa Libosch, Phellodendron chinense Schneid, Amomum villosum Lour, Astragalus membranaceus (Fisch.) Bge, Glehnia litoralis Fr. Schmidt, Cistanche deserticola Y. C. Ma, Angelica sinensis (Oliv.) Delits, Spaltholobus suberectus Dunn, Schisandra chinensis (Turch.) Baill, Gastrodia elata Bl, Atractylodes macrocephala Koidz |
| Zou (2015)                       | Sanhuang Sanxian decoction | Astragalus membranaceus (Fisch.) Bge, Polygonatum kingianum Coll. et Hemsl, Scutellaria baicalensis Georgi, Agrimonia pilosa Ledeb, Epimedium brevicomu Maxim, Cistanches deserticola Y. C. Ma, Angelica sinensis (Oliv.) Delits, Paeonia lactiflora Pall, Lycium barbarum L. |
| Wang et al. (2016)               | Shuanghuang Shengbai granules | Astragalus membranaceus (Fisch.) Bge, Astragalus membranaceus (Fisch.) Bge, Drynaria fortune (Kunze) J. Sm, Epimedium brevicomu Maxim, Trichosanthes kirilowii Maxim |
| Li et al. (2020)                 | Bazhen decoction | Codonopsis pilosula (Franch.) Nannf, Astragalus membranaceus (Fisch.) Bge, Rehmannia glutinosa Libosch, Paeonia lactiflora pall, Ligusticum chuanxiong Hort, Poria cocos (Schw.) Wolf, Atractylodes macrocephala Koidz, Angelica sinensis (Oliv.) Delits, Dioscorea opposita Thunb, Spaltholobus suberectus Dunn, Lycium barbarum L. |

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2019), which we find enlightening, but limiting due to different CHM methods and tumor types. Two other systematic reviews and meta-analyses were not limited by the CHM method or tumor type (Li et al., 2016; Niu et al., 2018), but their clinical application and conclusive reliability were unfortunately affected by the low methodological quality of the included literature. Accordingly, we conducted a comprehensive advanced systematic review and meta-analysis of the effects of CHM on CIL, focusing on high-quality RCTs.

MATERIALS AND METHODS

Our study was conducted according to the guidelines provided by the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) and Cochrane Handbook (Higgins et al., 2011).

Search Strategy

We performed a comprehensive search of 4 English electronic databases (PubMed, Web of Science, Cochrane Library, and Elsevier) from the date of inception to November 4, 2020 and 4 Chinese electronic databases (China National Knowledge Infrastructure, Chinese Biomedical Database, Chinese VIP Information Database, and Wanfang Med Database). The following medical subject heading (MeSH) terms and free text words were used for the search: “Chinese Medicine,” “Chinese Herbal Medicine,” “Chinese patent medicine,” “leukopenia,” “hypoleucocytosis,” “hypoleucocytosis,” “neutropenia,” and “bone marrow suppression.” In the Chinese electronic databases, keywords were searched in Chinese characters and Pinyin. There was no limitation on language used.

Inclusion and Exclusion Criteria

Inclusion Criteria

Inclusion criteria were based on the following:

(1) Type of participant: diagnosis of cancer with chemotherapy-induced leukopenia.

(2) Type of study: only high-quality randomized controlled trials (RCTs) related to Chinese herbal medicine in the treatment of CIL, which met the requirements of at least four key domains of the Cochrane risk of bias (RoB) tool, along with trials published in the form of dissertations were selected as eligible studies.

(3) Type of intervention: participants in the intervention groups were treated with CHM in combination with chemotherapeutic drugs. There was no limitation with regard to the form of CHM used (e.g., decoction, capsule, and granule), dosage, or treatment duration. The control groups used chemotherapy alone, chemotherapeutic drugs plus placebo, or chemotherapeutic drugs plus Western medicine, which used to raise leukocytes. All participants were treated via oral administration.

(4) Type of outcome measure: primary outcome measures were white blood cell (WBC), neutrophil (NEU), hemoglobin (Hb), and platelet (PLT) counts in addition to the incidence of leukopenia and neutropenia. Secondary outcome measures were the Karnofsky performance scale (KPS) score and improvement, infection amount, granulocyte colony-stimulating factor (G-CSF) dosage and use rate, and adverse events.

Exclusion Criteria

Exclusion criteria were as follows:

(1) Patients with leukopenia not caused by chemotherapy.

(2) Duplicate studies, review, animal experiments, and conference abstracts.

(3) Nonoral TCM methods, such as acupuncture, moxibustion, massage, and acupoint injection, in the intervention group or use of CHM drugs in the control group.

Data Extraction

Two reviewers (QW and HY) independently extracted the relevant data according to the predetermined inclusion and exclusion criteria. The following information was obtained using a standard data extraction form: 1) general information: publication year, language, and first author; 2) characteristics of participants: sample size, age, and gender; 3) intervention information: intervention method, medication dose, and course of treatment; and 4) outcome measures. To resolve any disagreements, the two reviewers discussed the issue or consulted the corresponding author (G-HX).

Risk of Bias Assessment

The RoB tool was used to assess the methodological quality of included studies (Higgins et al., 2011). Seven aspects were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. RCTs that met the requirements of at least 4 of the above parameters were selected for the final analysis.
RevMan 5.3 was used for statistical analysis. Chi-square test and $I^2$ statistic were employed to assess the heterogeneity between intervention and control results. In cases where $I^2$ was < 50% or chi-square $p$ value was > 0.1, a fixed-effects model was used. Otherwise, a random-effects model was applied. $p$ values < 0.05 were considered statistically significant.

### WBC counts

| Study or Subgroup | Mean (SD) | Weight | Mean (SD) | Weight |
|-------------------|-----------|--------|-----------|--------|
| Experimental      | Control   |         |           |         |
| Huang and Zhang, 2020 | 3.18 (0.96) | 28 | 2.59 (0.91) | 28 |
| Li and Liu, 2019  | 1.83 (0.54) | 26 | 1.27 (0.68) | 26 |
| Liu and Yao, 2014 | 4.14 (0.44) | 38 | 3.84 (0.36) | 38 |
| Zhao and Lu, 2016 | 4.42 (0.81) | 15 | 3.81 (0.37) | 15 |

Total (95% CI) = 108, $I^2 = 3.54$, df = 3 ($p = 0.32$), $p = 15\%$.

Test for overall effect: $Z = 2.33 (p = 0.02)$

### NEU counts

| Study or Subgroup | Mean (SD) | Weight | Mean (SD) | Weight |
|-------------------|-----------|--------|-----------|--------|
| Experimental      | Control   |         |           |         |
| Huang and Zhang, 2020 | 122.05 (8.9) | 28 | 122.32 (8.36) | 28 |
| Li and Liu, 2019  | 179 (5.43) | 26 | 177 (3.29) | 26 |
| Qian and Li, 2013 | 138.8 (61.66) | 62 | 119.9 (45.25) | 68 |
| Zhao and Lu, 2016 | 196.67 (57.06) | 15 | 190.67 (47.76) | 15 |

Total (95% CI) = 132, $I^2 = 0.08$, df = 3 ($p = 0.09$), $p = 54\%$.

Test for overall effect: $Z = 3.23 (p = 0.007)$

### Hb counts

| Study or Subgroup | Mean (SD) | Weight | Mean (SD) | Weight |
|-------------------|-----------|--------|-----------|--------|
| Experimental      | Control   |         |           |         |
| Huang and Zhang, 2020 | 155.01 (13.83) | 29 | 146.03 (10.8) | 28 |
| Li and Liu, 2019  | 179 (5.43) | 26 | 177 (3.29) | 26 |
| Zhao and Lu, 2016 | 196.67 (57.06) | 15 | 190.67 (47.76) | 15 |

Total (95% CI) = 132, $I^2 = 0.08$, df = 3 ($p = 0.09$), $p = 54\%$.

Test for overall effect: $Z = 3.23 (p = 0.007)$

### PLT counts

| Study or Subgroup | Mean (SD) | Weight | Mean (SD) | Weight |
|-------------------|-----------|--------|-----------|--------|
| Experimental      | Control   |         |           |         |
| Huang and Zhang, 2020 | 75.9 (5.83) | 29 | 70.57 (7.63) | 28 |
| Li and Liu, 2019  | 78.46 (6.75) | 26 | 73.65 (6.97) | 26 |
| Qian and Li, 2013 | 79.33 (2.47) | 62 | 66.67 (4.63) | 58 |
| Zhao and Lu, 2016 | 76.66 (6.4) | 15 | 73.33 (8.16) | 15 |

Total (95% CI) = 132, $I^2 = 0.08$, df = 3 ($p = 0.09$), $p = 54\%$.

Test for overall effect: $Z = 3.23 (p = 0.007)$

### KPS

| Study or Subgroup | Mean (SD) | Weight | Mean (SD) | Weight |
|-------------------|-----------|--------|-----------|--------|
| Experimental      | Control   |         |           |         |
| Liu, 2013         | 2.38 (0.46) | 28 | 4.83 (0.63) | 28 |
| Liu and Yao, 2014 | 7.89 (33.94) | 38 | 27.8 (70.76) | 36 |

Total (95% CI) = 66, $I^2 = 0.08$, df = 3 ($p = 0.09$), $p = 54\%$.

Test for overall effect: $Z = 3.37 (p = 0.001)$

### G-CSF dosage

**FIGURE 2 | Forest plots of CM + chemotherapy vs. chemotherapy.**
were considered statistically significant. The risk ratio (RR) with 95% confidence interval (CI) was used to calculate the dichotomous data, while the mean difference (MD) or standardized mean difference (SMD) was used to express the continuous data.

Assessment of Evidence Quality
The overall quality of the evidence for each outcome was assessed by two reviewers (QW and HY) in accordance with the methodology recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria (Schunemann et al., 2008). In the system, quality of the evidence varies in four levels: very low quality, low quality, moderate quality, and high quality. Risk of bias, inconsistency, indirectness, imprecision, and other factors (e.g., publication bias) are factors relating to lowering the level of evidence. According to specific criteria such as large $I^2$ indicating inconsistency, the level of evidence from RCTs can be downgraded by one or two levels. Summary of findings table for outcomes was performed using GRADEpro GDT.

RESULTS

Study Selection
A total of 6,197 studies were identified after searching eight databases, from which 1,494 duplicates were removed. Among the remaining 4,703 records, 4,274 were excluded for various reasons after screening according to titles and abstracts. Specifically, 3,264 studies were irrelevant, 437 used other TCM methods, 372 were animal experiments, and 201 were reviews. Comprehensive reading of the full text of the remaining 429 articles resulted in exclusion of 415 studies due to the following reasons: 257 articles did not meet the inclusion criteria, two had no available data, and 156 had low methodological quality. Finally, 14 RCTs with RoB scores ≥4 were included (Mok et al., 2007; Wang, 2011; Liu, 2013; Qian and Li, 2013; Liu and Yao, 2014; Ren and Wu, 2015; Zhou, 2015; Wang et al., 2016; Yuan and Zhang, 2016; Zhao and Lu, 2016; Wang and Li, 2017; Li and Liu, 2019; Huang and Zhang, 2020; Li et al., 2020). Sample sizes of studies published from 2007 to 2020 ranged from 30 to 120, which included a total of 530 patients in the treatment and 523 in the control groups. Six studies compared CHM + chemotherapy with chemotherapy alone ($n = 391$) (Liu, 2013; Qian and Li, 2013; Liu and Yao, 2014; Zhao and Lu, 2016; Li and Liu, 2019; Huang and Zhang, 2020), and two compared CHM + chemotherapy with placebo (PBO)+ chemotherapy ($n = 164$) (Mok et al., 2007; Yuan and Zhang, 2016). Six studies compared CHM + chemotherapy with WM + chemotherapy ($n = 498$) (Wang, 2011; Ren and Wu, 2015; Zhou, 2015; Wang et al., 2016; Wang and Li, 2017; Li et al., 2020). The treatment courses lasted from 14 to 60 days. The preparations used for treatment in the intervention groups of the 14 RCTs were administered orally in the form of decoction (nine comparative analyses), granules (three comparative analyses), capsules, and gel (one comparative analysis separately). The characteristics of the 14 trials are presented in Table 1, and the components are described in Table 2.

Risk of Bias Assessment
Risk of bias (ROB) data are shown in Table 3. All 14 RCTs specified the methods of random sequence generation. Only one study reported the allocation concealment method (Wang and Li, 2017). Two studies blinded both participants and personnel (Mok et al., 2007; Yuan and Zhang, 2016), and one blinded outcome assessment (Mok et al., 2007). As shown in the table, one article scored six points (Mok et al., 2007), two scored five points (Yuan and Zhang, 2016; Wang and Li, 2017), and eleven scored four points (Wang, 2011; Liu, 2013; Qian and Li, 2013; Liu and Yao, 2014; Ren and Wu, 2015; Zhou, 2015; Wang et al., 2016; Zhao and Lu, 2016; Li and Liu, 2019; Huang and Zhang, 2020; Li et al., 2020). A flowchart of the screening process is presented in Figure 1.

Assessment of Efficacy
Chinese Herbal Medicine Plus Chemotherapy Versus Chemotherapy Alone
Six comparative studies (Liu, 2013; Qian and Li, 2013; Liu and Yao, 2014; Zhao and Lu, 2016; Li and Liu, 2019; Huang and Zhang, 2020) were included for analysis. The results of the meta-analysis disclosed a significant increase in WBC counts with CHM +
chemotherapy, compared with chemotherapy alone (n = 391, MD = 0.52, 95% CI: 0.37 to 0.66, $I^2 = 64\%$, $p < 0.00001$). Data from pooled studies additionally showed that combined treatment with CHM and chemotherapy induced a significant increase in NEU, Hb, and PLT counts and KPS ($p < 0.00001$; $p = 0.02$; $p = 0.0007$; $p = 0.006$), aside from G-CSF dosage ($p = 0.17$; Figure 2).

### WBC counts

| Study or Subgroup | Experimental Events | Control Events | Total | Risk Ratio M-H Fixed, 95% CI |
|-------------------|---------------------|----------------|-------|-----------------------------|
| Wang, 2011        | 33                  | 45             | 68    | 1.70 [1.16, 2.49]           |
| Wang and Li, 2017 | 22                  | 43             | 65    | 1.79 [1.02, 3.14]           |
| **Total (95% CI)**| **88**              | **86**         | **174**| **1.73 [1.26, 2.39]**       |
| **Total events**  | 55                  | 31             |       |                             |

### KPS improvement

| Study or Subgroup | Experimental Events | Control Events | Total | Risk Ratio M-H Fixed, 95% CI |
|-------------------|---------------------|----------------|-------|-----------------------------|
| Wang, 2011        | 0                   | 45             | 44    | 0.08 [0.00, 1.30]           |
| Zou, 2015         | 7                   | 48             | 55    | 0.30 [0.14, 0.63]           |
| **Total (95% CI)**| **93**              | **91**         | **184**| **0.25 [0.12, 0.51]**       |
| **Total events**  | 7                   | 29             |       |                             |

### Infection amount

| Study or Subgroup | Experimental Events | Control Events | Total | Risk Ratio M-H Fixed, 95% CI |
|-------------------|---------------------|----------------|-------|-----------------------------|
| Wang and Li, 2017 | 2                   | 43             | 45    | 0.65 [0.11, 3.70]           |
| Wang et al., 2018 | 3                   | 60             | 63    | 0.26 [0.08, 0.90]           |
| **Total (95% CI)**| **103**             | **100**        | **203**| **0.35 [0.13, 0.92]**       |
| **Total events**  | 5                   | 14             |       |                             |

### G-CSF use rate

| Study or Subgroup | Experimental Events | Control Events | Total | Risk Ratio M-H Fixed, 95% CI |
|-------------------|---------------------|----------------|-------|-----------------------------|
| Wang et al., 2016 | 3                   | 60             | 63    | 0.29 [0.08, 1.00]           |
| Zou, 2015         | 0                   | 47             | 47    | 0.15 [0.01, 2.75]           |
| **Total (95% CI)**| **107**             | **106**        | **213**| **0.25 [0.08, 0.79]**       |
| **Total events**  | 3                   | 13             |       |                             |

### Incidence of Leukopenia

Figure 4 | Forest plots of CHM + chemotherapy vs. WM + chemotherapy.
Chinese Herbal Medicine Plus Chemotherapy Versus Placebo Plus Chemotherapy

Two studies (Mok et al., 2007; Yuan and Zhang, 2016) were included for analysis. The pooled results showed no significant differences in reducing the incidence of neutropenia ($n = 164$, RR 0.95, 95% CI: 0.69 to 1.33, $I^2 = 74\%$, $p = 0.78$; Figure 3).

Chinese Herbal Medicine Plus Chemotherapy Versus Western medicine Plus Chemotherapy

Six studies compared CHM + chemotherapy with WM + chemotherapy (Wang, 2011; Ren and Wu, 2015; Zou, 2015; Wang et al., 2016; Wang and Li, 2017; Li et al., 2020). The pooled results revealed significant differences in WBC counts, KPS improvement, infection amount, G-CSF use rate, and incidence of leukopenia ($p < 0.05$) between the groups (Figure 4).

### Table 4: Assessment of evidence quality.

| Outcomes | Anticipated absolute effects | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) |
|----------|-----------------------------|--------------------------|------------------------------|-------------------------------|
| CHM+ chemotherapy vs. chemotherapy | | | | |
| WBC counts | 0.52 MD higher (0.37 to 0.66 higher) | RR 0.95 (0.69 to 1.33) | 391 (6 RCTs) | OOO Moderate due to risk of bias |
| NEU counts | 0.41 MD higher (0.26 to 0.55 higher) | RR 0.35 (0.13 to 0.92) | 259 (4 RCTs) | OOO Moderate due to risk of bias |
| Hb counts | 0.46 SMD higher (0.07 to 0.86 higher) | RR 0.25 (0.08 to 0.79) | 259 (4 RCTs) | OOO Moderate due to risk of bias |
| PLT counts | 10.15 MD higher (4.3 to 16.0 higher) | RR 0.25 (0.08 to 0.79) | 132 (2 RCTs) | OOO Moderate due to risk of bias |
| G-CSF dosage | 2.5 MD higher (6.07 lower to 1.07 higher) | RR 0.95 (0.69 to 1.33) | 391 (6 RCTs) | OOO Moderate due to risk of bias |
| CHM+ chemotherapy vs. PBO+ chemotherapy | | | | |
| Incidence of neutropenia | | | 160 (2 RCTs) | OOO Low due to inconsistency, imprecision |
| CHM+ Chemotherapy vs. WM+ Chemotherapy | | | | |
| WBC counts | 0.80 MD higher (0.20 to 1.40 higher) | RR 1.73 (1.26 to 2.39) | 174 (2 RCTs) | OOO Moderate due to risk of bias |
| KPS improvement | | | 184 (2 RCTs) | OOO Moderate due to risk of bias |
| Infection amount | | | 203 (2 RCTs) | OOO Moderate due to risk of bias |
| G-CSF use rate | | | 213 (2 RCTs) | OOO Moderate due to risk of bias |
| Incidence of leukopenia | | | | |

### Adverse Events

One study (Liu, 2013) reported vomiting and nausea in one case from the experimental group and nine cases from the control group. Both symptoms disappeared after reduction of the treatment dose. Another study (Mok et al., 2007) described occurrence of nausea, vomiting, and anorexia in both the experimental and control groups. In particular, CHM had a significant impact on control of nausea. Two studies (Wang and Li, 2017; Huang and Zhang, 2020) also reported nausea and vomiting in both experimental and control groups, with no significant differences in the two groups. Zou (2015) reported adverse events, such as slight muscle aches, fatigue, low-grade fever, nausea, and vomiting, which were relieved after symptomatic treatment, while Wang et al. (2016) noted one case of mild diarrhea in the intervention group and remission after dosage reduction. No severe adverse events were reported in three studies (Wang, 2011; Ren and Wu, 2015; Yuan and Zhang, 2016). Li et al. (2020) reported rash, dizziness, nausea, and vomiting in the experimental group, which indicated no significant difference compared with the control group. Five other studies (Qian and Li, 2013; Liu and Yao, 2014; Zhao and Lu, 2016; Li and Liu, 2019; Huang and Zhang, 2020) showed no significant differences in liver and kidney functions of patients from both experimental and control groups. The collective results from the 14 RCTs indicate that CHM exerts no severe side effects and is generally safe for human use.

### Assessment of Evidence Quality

Comparing CHM + chemotherapy with chemotherapy alone or PBO + chemotherapy or WM + chemotherapy, the overall quality of evidence according to each outcome measures was moderate or low. The results of GRADE assessments are presented in Table 4.

### Discussion

Cancer remains a severe public health problem with rapidly increasing incidence and mortality rates and is the leading cause of death worldwide (Bray et al., 2018; Siegel et al., 2020). Chemotherapy is currently the main treatment modality for cancer. However, CIL is the most common adverse effect of chemotherapy, which is directly associated with survival rates.
G-CSF is commonly used to relieve side effects and improve the QOL of patients with CIL (Disis, 2005; Ohnaka et al., 2013; Cornes et al., 2018). However, despite rapid effects, the drug is not suitable for long-term use in all patients owing to its high cost and secondary malignancy risk (Lyman et al., 2013; Lyman, et al., 2018). Thus, increasing number of patients have turned to complementary and alternative medicines to control symptoms and improve the QOL (Kuo et al., 2018; Knecht et al., 2020). CHM has received considerable research attention over the past few years and is widely applied following chemotherapy for various cancer types. Compared with G-CSF, the long-lasting effects and affordability of CHM have made it the preferred treatment of choice for many patients in China. Based on continued evaluation of clinical efficacy from meta-analyses together with accumulating experimental and pharmacological insights into their mechanisms of action, CHM drugs could increasingly benefit patients with chemotherapy-induced leukopenia (CIL) worldwide (Jia et al., 2015; Yang et al., 2017; Chen et al., 2018).

Trials included in previous meta-analyses (Li et al., 2016; Niu et al., 2018) had low methodological quality, with no information on blinding and allocation concealment. This updated systematic review included 14 high-quality studies that were divided into three subgroups to reduce heterogeneity, with a total of 1,053 selected patients. Earlier studies by Li et al. (2016) and Niu et al. (2018) had few evaluation indicators, and both showed superiority of CHM in improving the clinical efficacy rate. Niu and coworkers (2018) additionally demonstrated that CHM could enhance the KPS score.

In the current meta-analysis, the methodological quality was adjusted, the latest literature was included, and more specific indicators were evaluated, with the aim of providing a comprehensive and reliable reference for subsequent research. Pooled data on comparative analyses of CHM + chemotherapy and chemotherapy alone revealed that CHM had greater beneficial effects on several indicators, including WBC, NEU, Hb, and PLT counts, as well as KPS, but not G-CSF dosage. The CHM + chemotherapy group was non-inferior to the PBO + chemotherapy group for the incidence of neutropenia, supporting the findings of Liew et al. (2019) and Mok et al. (2007); CHM did not reduce hematologic toxicity associated with chemotherapy. The CHM + chemotherapy group was superior to the WM + chemotherapy group in terms of improvement of the WBC counts, KPS score, infection amount, G-CSF use rate, and incidence of leukopenia. In addition, CHM drugs were generally safe and induced no severe adverse events.

Our study has several limitations that should be taken into consideration. First, the methodological quality of the included studies was generally low. Although we searched both English and Chinese databases, potential selection bias may have been introduced since most of the included records retrieved were Chinese. Second, although all the trials met the requirements of at least four parameters of the Cochrane RoB tool, some methodological restrictions existed in primary studies. Only one study reported the method of allocation concealment that could lead to selection bias. Only two described blinding of participants and personnel, and one described blinding of outcome assessment. Missing blinding may cause detection bias. It is difficult to conduct adequate blinding in CHM RCTs due to different smells and tastes of CHM decoctions. Third, different components, doses, and duration of CHM interventions may have caused potential heterogeneity. Fourth, some indicators appeared less frequently, only in two studies. Finally, the small sample of subgroup and the quality of the evidence lead the conclusion to be more objective and explicit, giving us inspiration to design related clinical intervention.

CONCLUSION

CHM in combination with chemotherapy could improve clinical symptoms of CIL when compared with chemotherapy alone or Western medicine + chemotherapy, except when comparing with PBO + chemotherapy. While CHMs were generally safe and exerted no severe side effects in all 14 RCTs, larger sample sizes and high-quality RCTs are required to reduce study heterogeneity.

AUTHOR CONTRIBUTIONS

QW designed the study and wrote the article. HY and QW performed the literature database search, data collection, extraction, and assessment of evidence quality. Q-qW and W-tL performed data analysis and rationalization of the results. B-by helped with improving the writing of the manuscript. Y-mB and G-hX supervised all aspects of the study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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APPENDIX

Radix Scrophulariae, Polyporus, Coix Lacrymabojii, Semen Plantaginis, Herba Lysimachiae, Spora Lygodii, Herba Artemisiae Scopariae, Fructus Kochiae, Herba Dianthi, Herba Plantaginis, Pericarpium Arecae, Rhizoma Smilacis Glabrae, processed Radix Aconiti, Rhizoma Zingiberis, Cinnamomum Cassia, Herba Asari, Fructus Evodiae, Radix Aconiti Kusnezoffii, Citrus Reticulata, Fructus Auranti Immaturus, Citrus medica, Cypereus Rotundus, Wuyao, Fructus Toosendan, Caulis Perillae, Massa Medicata Fermentata, Fructus Hordei Germinatus, Fructus Crataegi, Semen Raphani, Herba seu Radix Cirsii Japonici, Herba Cephalanoploris, Radix Sanguisorbae, Sophora Japonica, Thuja orientalis, Herba, Agrimonieae, Radizoma Bletillae, Pollen Typhae, Radix Notoginseng, Radix Pangrifoliae, Rhizoma Chuanxiong, Olibanum, Myrrha, Rhizoma Corydelis, Radix Curcumae, Rhizoma Curcumae, Rhizoma Sparganii, Radix Salviae Miltiorrhizae, Herba Leonuri, Semen Persicae, Flos Carthami, Faeces Trogopterori, Achyranthes Bidentata Blume, Cyathula Oficialis Kuan, Squama Manitia, Lignum Dalbergiae Odoriferae, Fructus Liquidambaris, processed Rhizoma Pinelliae, Rhizoma Pinelliae, Rhizoma Arisaematis, Rhizoma Typhonii, Radix Aconiti Coreani, Radix Platycodi, Flos Inulae, Bulbus Fritillariae Thunbergii, Rhizoma Cynanchi Stauntonii, Fructus Trichosanthis, Bulbus Fritillariae Cirrhosae, Caulis Bambusae in Taeniam, Bitter Apricot Kernel, Sargassium Fusiforme, Radix Stemona, Radix Stemona, Loquat leaf, Radix Scutellariae, Sangbaipi, Semen Lepidii, Stir-baked Flos Farfarae, Radix Peucedani, Ferrosoferric Oxide, Os DracoNiss Fossilia, Semen Ziziphi Spinosae, Semen Biotae, Radix Polygalae, Cortex Albiziae, Radix Codonopsis, Radix Pseudostellariae, Radix Astragali, Rhizoma Atractylodis Macrocephalae, Rhizoma Dioscoreae, Glycyrrhiza Uralensis, Radix Panacis Quinquefolii, Ziziphus Jujuba, Radix Morindae Oficialis, Herba Cistanches, Rhizoma Curculiginis, Herba Epimedi, Cortex Eucommiae, Radix Dipsaci, Rhizoma Cibotti, Rhizoma Drynariae, Fructus Psoraleae, Fructus Alpiniae Oxyphyllae, Cuscuia Japonica, Herba Cynomorii, Radix Angelicae Sinensis, Rehmannia glutinosa, Radix Polygoni Multiflori, Radix Paeoniae Alba, Radix Ophiopogonis, Herba Dendrobii, Bulbus lili, Fructus Lycii, Herba Ecliptae, Ligustrum Lucidum, Radix Glehniae, Rhizoma Atractylodis Macrocephalae, Fructus Schisandrae, Fructus Trifoli Levis, Radix Oryzae Glutinosae, Radix Ephedrae, Fructus Corni, Fructus Rosae Laevigatae, Fructus Rubi, Concha Arcaee, Folium Ginseng, Radix Adenophorae.