Review Article

The Method of Activating Blood and Dredging Collaterals for Reducing Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta-Analysis

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Background. Chemotherapy-induced peripheral neuropathy (CIPN) remains as a big unsolved challenge for cancer patients and oncologists. However, there is no effective treatment to prevent and cure it. This systematic review and meta-analysis chiefly aimed to assess the effectiveness and safety on the method of activating blood and dredging collaterals in traditional Chinese medicine (TCM) for reducing CIPN.

Methods. Two authors comprehensively searched all the randomized controlled trials (RCTs) via PubMed, Cochrane, China National Knowledge Infrastructure (CNKI), and Wanfang Database of China Science Periodical Database (CSPD). The Review Manager (RevMan) 5.0 was used to conduct the meta-analysis. Results. 20 trials including 1481 participants were analyzed. 15 trials tested the incidence of all-grade CIPN which was significantly lower in intervention arm and 16 trails presented that the result of high-grade CIPN was the same. The total effective rate of the use of Chinese herbs was 77.19% versus 45.79% in the comparator group. Besides, the use of Chinese herbs statistically promoted the sensory nerve conduction velocity (SNCV) and the motor nerve conduction velocity (MNCV). Besides, the quality of life (QoL) in the intervention group was better than the comparator one. Herbs-related adverse events were skin allergy, skin chap, and scald, which could be managed well.

Conclusions. The work involving studies of the effectiveness and safety on TCM for reducing CIPN prove to be encouraging. Herbs with the function of activating blood and dredging collaterals were found to potentially promote the curative effects as well as making improvements of SNCV and MNCV. However, in the future, more double-blind, multicenter, large-scale RCTs and more comprehensive researches are still required.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is an inevitable dose-limiting side effect and approximately 30–40% of patients treated with neurotoxic chemotherapy agents, such as platinum, vinca alkaloids, and taxanes, will suffer from it [1]. Pain CIPN can be extremely disabling, with a marked impact on quality of life, functional ability, and risks of noncompliance with cancer treatment. Those side effects can result in a dose reduction of chemotherapy regime, even terminating the course of treatment, thus limiting therapeutic efficacy. Shi Q et al. [2] found that high-grade CIPN (grades 3-4) was more likely to occur in 3-month treatment vs. 6-month treatment of CapeOX or FOLFOX (3% vs. 9% for CapeOX; 3% vs. 16% for FOLFOX.) Besides, CIPN apparently increases the financial burden on patients as well as the annual costs of healthcare [3].

Research reports that paclitaxel-induced mechanical allodynia is due to the transcriptional increase in matrix metalloproteinases (MMP) 2 and 9 and decrease of metallopeptidase inhibitor 1 (TIMP1) [4]. And the route of drug administration is considered as an important factor in the development of
CIPN [5, 6]. A study indicates that older age, cardiovascular drugs, and preexisting nerve compression syndromes are likely to increase neuropathy risk [7]. Conventional therapy options for CIPN include antidepressants, anticonvulsants, neuromodulation, and physical therapy [8]. A recent RCT proved that sensorimotor training and whole-body vibration training were promising to reduce symptoms [9]. Clinical reports show dorsal root ganglion (DRG) stimulation may be useful for alleviating the neuropathic pain [8]. There are 15 CIPN-directed clinical trials sponsored by the National Cancer Institute, and it is concluded that alpha-lipoic acid, intravenous calcium/magnesium, vitamin E, or glutathione acts as the prevention, and nortriptyline, gabapentin, lamotrigine, amifostine, or duluoxetine acts as symptomatic treatment [10]. Although CIPN can cause dose reduction or even chemotherapy termination in cancer patients, there is still no FDA-approved validated treatment for preventing or reversing the condition of CIPN.

In recent years, Chinese herbal medicine (CHM) has been common and eligible in cancer-related symptom management. Meta-analysis showed that the combination of CHM and conventional treatment can significantly reduce the neuropathy pain [11]. Many TCM oncologists insist that one of the pathogeneses of CIPN is believed to be qi stagnation and blood stasis in collaterals, so promoting blood circulation and dredging collaterals to remove meridian obstruction contribute to the prevention and relief of CIPN. A study proved that specific Chinese herbs and their components of activating xue (blood), such as Angelica, tetramethylpyrazine, astragaloside, and safflower, can function as antithrombolyis and improve microcirculation in nervous system [12]. Dangshen and its active constituents, tanshinone IIA (TIIA) and cryptotanshinone (CRY), were investigated to be effective in reverting chemotherapy-induced neuropathic pain [13]. Safflower extract and acetylglutamide injection is investigated to be efficient in reducing the nerve injury and promoting recovery of peripheral innervations in animal test [14]. There has been some systematic review or meta-analysis about the therapeutic effect of herbal medicine such as Guilong Tongluo decoction, Yiqi Huoxue decoction, Radix Atragali- Based Chinese Herbal Medicine, or Goshajinkigan CIPN [15–17]. However, no systematic review to date has reported the method of activating blood and dredging collaterals in reducing chemotherapy-induced peripheral neuropathy. In this meta-analysis, we aim to investigate the effectiveness and safety of this traditional Chinese medicine treatment when used in prevention and treatment of CIPN. We want to discover whether using Chinese herbs will be better than other alternatives, such as placebo, no intervention, or some western medicines.

2. Materials and Methods

2.1. Database and Search Strategies. We comprehensively searched the following electronic databases using keywords of “Chemotherapy-induced peripheral neuropathy” or “CIPN”, “activating blood and dredging collaterals” or “dispersing blood stasis” or “Chinese medicine ABDC therapy” or “Danggui” or “rhizome of chuanxiong” or “safflower” or “Guizhi” or “Astragali radix” or “Chi Shao” or “Salvia” or “NiuXi” or “Maidenhair Tree” or “Ginkgophyta” etc., “Randomized Controlled Trials as Topic” or “controlled clinical trial∗” or “randomized∗” or “placebo” or “clinical trial∗” or “controlled trial∗” etc. without language or publication date limitations: PubMed, Cochrane, China National Knowledge Infrastructure (CNKI), and Wanfang Database of China Science Periodical Database (CSPD). Applying to each database, we modified the search strategies, respectively. All of those searches were completed before December 2018.

This systematic review has been registered in PROSPERO, and the registration ID is CRD42018116749.

2.2. Inclusion Criteria. We included all high quality randomized controlled trials (RCTs) investigating the effects of herbal medicine which had the function of activating blood and dredging collaterals for preventing and treating CIPN in cancer patients without restriction time or language. Among those trials, the number of patients in each arm was more than 15 and the Jadad score was 4-7 points.

2.2.1. Participants Types. The participants were included to meet the following criteria:

(1) Age of 18 years or older
(2) Patients who were diagnosed with cancer and received chemotherapy regardless of type of cancer, sex, race and location
(3) CIPN diagnosed by clinical assessment or additional investigation such as nerve conduction velocity

2.2.2. Types of Interventions. All types of herbal medicines which could activate blood and dredge collaterals were included. There were no limitations on the composition of prescription, the origin, the mode of delivery (e.g., oral, intravenous, or per cutaneous), dosage, and duration of treatment.

Control intervention would include no TCM treatment; or placebo; or conventional therapeutic agents, such as vitamin E or Ca/Mg infusions. Trials of herbal medicine meeting the standard plus conventional medicine versus the same conventional medicine alone were also included.

2.3. Outcome Measures

2.3.1. Main Outcomes. (1) Clinical effectiveness was assessed by objective methods such as World Health Organization (WHO) grade [38], National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) CIPN grade [39], or Levi’s grade [40].

(2) Complete remission (CR) meant the grade of CIPN reduced to 0 grade and all symptoms disappeared. Partial remission (PR) meant the grade of CIPN reduced more than 1 grade and the symptoms abated. The effective rate was the sum of CR and PR. Nonperceptible (NP) meant symptoms had not abated after therapy, and the grade of CIPN did not reduce.

(3) Incidence rate of CIPN was assessed by the above methods.
(4) Nerve Conduction Velocity (sensory nerve conduction velocity (SNCV) and motor sensory nerve conduction velocity (MNCV)) was evaluated after 1 week of TCM treatment or more.

2.3.2. Additional Outcomes. (1) High frequency herbs (2) The characteristics of the formulas (3) Quality of life assessed with Karnofsky (KPS) scale or Eastern Cooperative Oncology Group (ECOG) scale (4) Extracted incidence rates of adverse events relative to chemotherapy or herbal medicine

2.4. Exclusion Criteria. We excluded those trials that used the herbal medicine with other functions; whose number of patients in any arm was less than 15; that were assessed to be of low quality with the Jadad score being 1-3; that had not used the same baseline therapy; or that employed the methods of acupuncture or moxibustion.

2.5. Risk of Bias Analysis. Two authors independently assessed the risk of bias which was described in the Cochrane handbook for systematic reviews of interventions [18]. We classified the potential bias as high, low, or unclear. The following items were assessed:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other bias

2.6. Research Selection and Statistic Collection. Two review authors screened articles based on titles and abstracts firstly after eliminating the duplicate publications. Then the full-text versions of the papers that met the inclusion criteria were retained and data on patient characteristics, treatment details, and clinical outcomes were extracted independently. Differences in opinion would be resolved by a third reviewer. Reference lists of the included studies were checked by hand.

2.7. Quality Assessment. Improved Jadad scale was applied to assess the quality of RCTs, and the items included randomization, blinding of participants, personnel, outcome assessors, incomplete outcome data, and other threats to validity [18]. 4–7 points represent high quality, while 1–3 points represent low quality.

2.8. Statistical Analysis and Data Synthesis. RevMan 5.3 software provided by Cochrane Collaboration was performed for the data analysis. We used mean difference (MD) analysis with 95% confidence intervals (CI) for continuous outcomes and risk ratios (RR) or odds ratio (OR) with 95% CI for binary outcomes. In case that different measurement scales were used, standardized mean difference (SMD) analysis with 95% CI was conducted. We tested the heterogeneity through I², and it would present as significant when I² was over 50% or P < 0.05. We would perform random effect model if there was significant heterogeneity, while fixed effect model would be used when the heterogeneity was moderate [18]. If the included studies were ≥10, funnel plots would be employed to assess reporting bias. Subgroup analyses were done based on the types of the interventions and comparators.

3. Results

3.1. Description of Studies. The flow diagram was depicted as in Figure 1. We primarily identified 330 studies searched by strategy and hand from the above 4 electronic databases (Figure 1). After reviewing the titles and abstracts, we excluded 220 studies, including 97 duplicate articles, 7 non-RCTs, 26 basic experiments, 30 clinical experiences, 39 reviews, and 21 irrelevant studies. We retrieved the full texts of 110 articles for further evaluations, of which 90 studies were excluded for the reasons of inappropriate comparator, non-RCTs, incomplete outcomes, low quality, and patients number ≤15. In the end, a total of 20 trials were included for this review [19–37, 41].

3.2. Characteristics of Included Studies. Table 1 shows the characteristics of included studies. In summary, a total of 1481 patients were included in 20 trials with 30 patients being dropped from the study. The mean size of the participants was 74.05 people, ranging from 36 to 128 per trial. The baseline characteristics in the included trials were comparable between the intervention groups and the comparator groups. As for the types of cancer, ten trials referred to the colorectal cancer, seven studied gastric cancer, nine tested with various types of cancer, and one studied ovarian cancer. The chemotherapy regimens in participants included oxaliplatin based chemotherapy (n= 9 trials), FOLFOX 4 (n= 4 trials), XELOX (n= 1 trial), cisplatin based chemotherapy (n= 1 trial), mFOLFOX6 (n= 1 trial), TP (paclitaxel and cisplatin) (n= 2 trials), and no specific common regimen (n= 2 trials).

Regarding the regimens of comparators, Cobamamide was used in one trial, Mecobalamin was used in three, a placebo was used in three, Tropisetron and dexamethasone were used in one, and hand and foot baths of warm water were used in two. The other 10 trials compared interventions with no additional treatment. The range of the treatment duration was from 7 days to 32 weeks.

Additionally, it provides information of the outcomes indexes. For the assessment of the incidence rate or the clinical improvement, 8 trials used Levi's grade, 7 used NCIC-CTC grade, 4 used WHO criteria, 2 used the researcher's own criteria, and 1 used the Nimodipine Trichotomy. Besides, 8 studies reported the NCV (nerve conduction velocity) involving the MNCV (motor nerve conduction velocity) and the SNCV (sensory nerve conduction velocity). Five trials tested the QoL and 9 studies reported the adverse events.

3.3. Intervention Comparisons. As shown in Table 1, 10 trials compared herbs with no intervention or with placebo.
Five trials tested herbs against western medications, such as Cobamamide, Thymopentin, Mecobalamin, Glutathione, Methycobal, calcium gluconate, and magnesium sulfate. Furthermore, another 5 trials tested herbs in combined regimens compared to the same western medications. In view of the administration method, three forms of dosage were employed, respectively: oral dosage form including decoction or granules (n=7 trials), topical administration involving hand and foot baths or fumigation or compress or gel (n=10 trials), and intravenous infusion (n=3 trials).

Table 2 demonstrates the characteristics of the 17 different formulas researched in the total 20 trials. The most frequent prescription was modified Huangqi Guizhi Wuwu Decoction (n=5 trials). Some prescriptions constituted by the researchers themselves were combined or transformed from it (n=6 trials). Others are made up of other herbs with the function of activating blood and dredging collaterals (n=6 trials). The high frequency Chinese herbs are shown in Table 3. The top five herbs are Guizhi (n=14, 10.53%), Huangqi (n=9, 6.77%), Baishao (n=9, 6.77%), Danggui (n=7, 5.26%), and Chuanxiong (n=7, 5.26%).

3.4. Risk of Bias Analysis Outcomes. All the results are shown in Figures 7(a) and 7(b).

3.4.1. Random Sequence Generation. Eight studies were judged to be at low risk of bias for using a computer random number generator or random number table method, ten were judged to be at unclear risk of bias for not mentioning random sequence generation, and the remaining two studies were judged to be at high risk of bias for using the wrong way.
| First author | Year | Sample size (dropout) | Mean age (year) (median/range) | Cancer Types | Common treatment (regimen) | Interventions (regimen, participants) | Comparators (regimen, participants) | Main Outcomes |
|--------------|------|-----------------------|-------------------------------|--------------|---------------------------|----------------------------------------|--------------------------------------|---------------|
| Chen, Mou [18] | 2015 | 79 (0) | 50.12±10.21 | Gastric and colorectal cancer | Hand and foot bath of Huoxue Tongluo decoction(30 min, tid for 2wks, n=42) | No additional Tx. (n=37) | (1) Incidence rate (NCI-CTC; sensory neuropathy) (2) QoL (KPS) (3) Adverse events |
| Li, Cai [19] | 2017 | 65 (0) | I:53 C:56 | colorectal cancer | Hand and foot bath, fumigation of Wenjing Huoxue formula(15 min, qd for 6 wk, n=34) | No additional Tx. (n=31) | (1) Incidence rate (Levi's grade) (2) QoL (KPS) (3) Adverse events |
| Lou [20] | 2014 | 102(1) | I:59.84±9.30 C:57.94±10.55 | Various types of cancer | Oxaliplatin based CTx. (1) Oxaliplatin/paclitaxel based CTx. (2) AD pro injection (80ml qd) (3) Thymopentin(1 mg qd) (for 14 days) | Hand and foot bath of Network Vessel-freeing Formula(30 min, qd for 14 days, n=34) | Cobamamide for intramuscular injection(1mg qd for 14 days, n=34) | (1) Clinical effectiveness (Nimodipine trichotomy) (2) Incidence rate (researcher's own criteria) (3) Adverse events |
| Qin [21] | 2012 | 68 (0) | I:57.2±8.6 C:59.5±7.9 | Various types of cancer | (1) Oxaliplatin based CTx. (2) Mecobalamin for intramuscular injection (0.5 mg tiw) (3) AD pro injection (50ml qd) (4) Thymopentin for subcutaneous injection(1.6 mg biw) (for 14 days) | Hand and foot bath of modified Huangqi-Guizhi Wuwu decoction(30 min, qd for 14 days, n=30) | No additional Tx. (n=30) | (1) Clinical improvement (NCI-CTC; sensory neuropathy,) (2) Clinical symptom (GPCR-NCM) (3) Adverse events |
| Shen [22] | 2015 | 60 (0) | I:59.67±12.72 C:56.57±11.32 | Various types of cancer | Hand and foot bath of modified Tongluo decoction (during CTx, 20 min, bid, n=54) | No additional Tx. (n=51) | (1) Incidence rate (WHO grade) (2) Clinical symptom (TCSS) (3) Adverse events |
| Tang [23] | 2014 | 128(23) | I:59.46±11.51 C:61.16±9.47 | Gastric and colorectal cancer | Oxaliplatin based CTx (for 6-8 cycles) | Hand and foot bath of Yangxue Wenjing Tongluo decoction (during CTx, 20 min, bid, n=54) | No additional Tx. (n=51) | (1) Incidence rate (WHO grade) (2) Clinical symptom (TCSS) (3) Adverse events |
| Yi, Li [24] | 2017 | 100 (0) | Not mentioned colorectal cancer | Oxaliplatin based CTx.(21 d/cycle for 6 cycles) | Hand and foot bath of Tongluo Zhibi decoction during CTx, 30 min, qd for 6 cycles, n=50) | Warm water for Hand and foot bath (during CTx, 30 min, qd for 6 cycles, n=50) | (1) Incidence rate (Levi's grade) (2) QoL (KPS) (3) Adverse events |
| First author | Year | Sample size | Mean age (year) | Cancer Types | Common treatment | Interventions (regimen, participants) | Comparators (regimen, participants) | Main Outcomes |
|--------------|------|-------------|----------------|--------------|----------------|---------------------------------------|--------------------------------------|---------------|
| Zhang [25]   | 2015 | 64 (0)     | Not mentioned  | Gastric and colorectal cancer | FOLFOX 4 | Hand and foot bath of Tongjing, Huoxue formula (during CTx, 1000ml, 30 min, qd for 7 d, n=32) | Warm water for Hand and foot bath (during CTx, 1000ml, 30 min, qd for 7 d, n=32) | (1)Clinical improvement (Levi’s grade, NCI-CTC) (2)QoL (KPS) |
| Feng [26]    | 2014 | 120 (0)    | 53.18±13.61 I:51.95±11.37 | Various types of cancer | (1)Cisplatin based CTx. (2)Glutathione | Herbal Compress (for 7 d, n=60) | No additional Tx. (n=60) | (1)Incidence rate (WHO grade) (2)Duration time (3)Herbal related adverse events |
| Xu, Zhang [27] | 2018 | 67 (0)     | 57.89±11.54 I:54.71±12.24 | Various types of cancer | Not mentioned. | (1)Xiaotan Tongluo Gel for external use (1 mL/cm², 14 d/cycle for 2 cycles, n=36) (2)Mecobalamin tablets (0.5 mg tid) | (1)Placebo Gel for external use (1 mL/cm², 14 d/cycle for 2 cycles, n=31) (2)Mecobalamin tablets (0.5 mg tid) | (1)Clinical improvement (NCI-CTC; sensory neuropathy) (2)Clinical symptom (GPCR-NCM) (3)NCV (1)SNCV: median nerve/fibular nerve (2)MNCV: median nerve/ fibular nerve |
| Chen, Huang [28] | 2018 | 58 (0)     | 42-78 I:43 C:43-78 | Gastric and colorectal cancer | (1)FOLFOX4(2wks/cycle for 4 cycles) (2)Methycobal Injection for Intramuscular injection (0.5 mg qd during CTx) | Astragalus injection for intravenous infusion (30ml qd during CTx, n=29) | No additional Tx. (n=29) | (1)Incidence rate (WHO grade) (2)QoL (KPS) (3)NCV (1)SNCV: median nerve/peroneus communis nerve (2)MNCV: median nerve/ Peroneus communis nerve |
| Cheng [29]   | 2014 | 36 (0)     | 46 I:49 C:49 | Various types of cancer | Oxaliplatin based CTx. (130mg/m²,d1,2,d/4 cycle for 4 cycles) | Tanshinone IIA Sodium Sulfonate Injection for intravenous infusion (80mg qd for d1-3, n=18) | | (1)Tropisetron (5mg/d) (2)dxm (5mg/d) During CTx (n=18) | (1)Incidence rate (Levi’s grade) (2)SNCV/MNCV (3)SOD/MDA |
| Cui [30]     | 2009 | 40 (0)     | 60 I:63 C:63 | Gastric and colorectal cancer | Oxaliplatin based CTx. (130mg/m²,d1,2,d for 1 cycle) | Astragalus injection for intravenous infusion (30ml qd for d1-7, n=20) | No additional Tx. (n=20) | | (1)Incidence rate (Levi’s grade) (2)NGF |
### Table 1: Continued.

| First author Year | Sample size (dropout) | Mean age (year) | Cancer Types | Common treatment (regimen) | Interventions (regimen, participants) | Comparators (regimen, participants) | Main Outcomes |
|-------------------|-----------------------|-----------------|--------------|-----------------------------|---------------------------------------|--------------------------------------|---------------|
| Li, Sun [31] 2017 | 56 (0)                | I: 58.89 ± 8.75C: 57.71 ± 9.31 | Various types of cancer | n.c. | Herbal medicine for oral dosage form | Granulas of Chinese Medicine of modified Huangqi-Guizhi Wuwu and Shentong Zhuyu (10g, bid for 1 month, n=28) | Placebo (10g, bid for 1 month, n=28) | (1) Clinical improvement (NCI-CTC, sensory neuropathy) (2) NRS (numbness) (3) ECOG PS (EORTC QLQ-C30) (4) Adverse events |
| Liu, Zhou [32] 2011 | 90 (5)                | I: 61.47 ± 9.05C: 60.43 ± 9.48 | Various types of cancer | Oxaliplatin based CTx (130mg/m².d, every 21 days/cycle, for 2 cycles) | Wangqi Guizhi Wuwu decotion (100ml, bid for 42 days, during CTx, n=28) | Mecobalamin (0.5 mg tid for 42 days, n=29) | (1) Clinical improvement (Levi’s grade) (2) NCV (1) SNCV: median nerve/fibular nerve (2) MNCV: median nerve/fibular nerve (3) Effective rate |
| Peng [33] 2015    | 96 (0)                | I: 57.2 C: 55.7 | Gastric and colorectal cancer | (1)mFOLFOX6 (2 wks/cycle for 4 cycles) (2)Calcium gluconate, magnesium sulfate for injection (before CTx, for 2 days) | Danggui Sini Decoction combined with Yanghe Decotion (150ml, bid for 8 wks, during CTx, n=48) | No additional Tx. (n=48) | (1) Incidence rate (Levi’s grade) (2) NCV (1) SNCV: median nerve/fibular nerve (2) MNCV: median nerve/fibular nerve (3) Hemodynamic parameters |
| Chen, Yi [34] 2016 | 70 (0)                | I: 63.9 ± 7.9C: 64.0 ± 8.1 | Colorectal cancer | Oxaliplatin based CTx (21 d/cycle for 4 cycles) | Tongluo Zhibi decoction (1wk before CTx-the end, n=35) | No additional Tx. (n=35) | (1) Incidence rate (researcher’s own criteria) (2) NCV (3) SNCV/SNAPA |
| Shi [35] 2010     | 56 (0)                | I: 62.8 C: 62.1 | Gastric and colorectal cancer | FOLFOX 4 (for 4 cycles) | Wenjing Decoction (bid for 2 months, during CTx, n=30) | No additional Tx. (n=26) | Incidence rate (Levi’s grade) |
| Xu [36] 2016      | 76 (0)                | I: 45.3 ± 5.8C: 44.9 ± 5.5 | Ovarian cancer | TP (21 d/cycle for 6 cycles) | Modified Wangqi Guizhi Wuwu decotion (150ml, qd for 2 wks, during CTx, n=38) | Mecobalamin tablets (0.5 mg tid for 2 wks, n=38) | (1) Incidence rate (NCI-CTC, sensory neuropathy) (2) NCV (1) SNCV: median nerve/fibular nerve (2) MNCV: median nerve/fibular nerve |
3.4.2. Allocation Concealment. Eight studies were judged to be at low risk of bias for reporting allocation concealment or the allocation method having no influence on the results. Nine studies did not mention allocation concealment being judged to be at unclear risk of bias.

3.4.3. Blinding of Participants and Personnel. Five trials set up placebo arm and reported blinding of patients and study personnel being judged to be at low risk of bias. Thirteen studies did not blind the study participants or personnel to be regarded as high risk of bias. Two studies were judged to be at unclear risk of bias for not mentioning it.

3.4.4. Blinding of Outcome Assessors. Five studies were judged to be at low risk of bias for setting up placebo arm or blinding the data collectors or being analyzed to have little possibility to break the blinding. While the remaining fifteen studies did not mention the outcome assessors blinding, they were judged to be at unclear risk of bias.

3.4.5. Incomplete Outcome Data. Patients in sixteen trials were reported to complete the whole course of treatment. Another four studies reported the reasons of the drop-out participants which were assessed to have no clinical effect on the outcome data. As a result, all the 20 studies were judged to be at low risk of bias.

3.4.6. Selective Reporting. All trials were not registered anywhere and provided no information of the selective report, to be judged to be at unclear risk of bias.

3.4.7. Other Bias. All the studies were judged to be at unclear risk of bias for being tested to be free of other apparent bias.

3.5. Therapeutic Effects

3.5.1. Incidence of All-Grade CIPN (Figure 2(a)). A total of fifteen trials tested the incidence of all-grade (grades 1-4) CIPN. Among those trials, based on the types of the interventions and comparators, we did subgroup analyses. Eight trials compared herbs based intervention to no intervention or placebo after we excluded one [32] in which there was no difference in the event between intervention and comparator. Chinese herbs intervention might have promising beneficial effects in preventing or reducing CIPN occurrence (n = 617 patients; OR, 0.36, 95% CI, 0.22 to 0.54, P = 0.00001). Three trials compared Chinese herbs to western medications, including Tropisetron, dxm, and Mecobalamin. It was discovered that herbs showed beneficial influences on preventing or reducing CIPN occurrence (n = 142 patients; OR, 0.22, 95% CI, 0.09 to 0.54, P = 0.0008). In addition, four trials compared Chinese herbs plus Methycobal Injection, calcium gluconate, magnesium sulfate for injection, Glutathione, AD pro injection, and Thymopentin for subcutaneous injection with the same western medications. It was demonstrated that herbs in combined remedies significantly prevented or reduced CIPN occurrence (n = 334 patients; OR, 0.36, 95% CI, 0.22 to 0.59, P < 0.0001).

3.5.2. Incidence of High-Grade CIPN (Figure 2(b)). Sixteen trials reported the incidence of high-grade (grades 3-4) CIPN. Nine trials compared herbs to no intervention or placebo. It was assessed that Chinese herbs had promising potential in preventing or reducing CIPN occurrence (n = 673 patients; OR, 0.34, 95% CI, 0.20 to 0.61, P = 0.0002). Three trials compared Chinese herbs to western medications, including Tropisetron, dxm, and Mecobalamin. Four trials compared Chinese herbs plus Methycobal Injection, calcium gluconate, magnesium sulfate for injection, Glutathione, AD pro injection, and Thymopentin for subcutaneous injection with the same western medications. It was demonstrated that herbs in combined remedies significantly prevented or reduced CIPN occurrence (n = 334 patients; OR, 0.36, 95% CI, 0.22 to 0.59, P < 0.0001).

| Interventions (regimen, participants) | Comparators (regimen, participants) | Main Outcomes |
|---------------------------------------|--------------------------------------|---------------|
| (1)TP(21 d/cycle for 6 cycles)         | Mecobalamin tablets (0.5 mg, tid for 14 d/cycle) during CTx, for 6 cycles (n=25) | (1)Incidence rate (WHO grade) |
| (2)MHT3 inhibitor                      |                                                     | (2)NCV       |
|                                       |                                                     | (1)NVC: median nerve/funcular nerve |
|                                       |                                                     | (2)MNCV: median nerve/funcular nerve |

Table 1: Continued.

FOLFOX: folinic acid, fluorouracil, and oxaliplatin, XELOX: capecitabine and oxaliplatin, TP: paclitaxel and cisplatin, n.c.: no common treatment, Tx.: treatment, CTx.: chemotherapy, d: day, min: minute, qd: twice a day, tid: three times a day, biw: twice a week, tiw: three times a week, GPCR-NCM: Guiding Principles for Clinical Research of New Chinese Medicines, TCSS: Toronto Clinical Scoring System, NCI-CTC: National Cancer Institute Common Toxicity Criteria for Adverse Events, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30, ECOG PS: Eastern Cooperative Oncology Group performance status, NCCN: National Comprehensive Cancer Network Guidelines for Adult Cancer, WHO: World Health Organization, QoL: quality of life, KPS: Karnofsky Performance Scale, PNCV: peripheral nerve conduction velocity, NCV: nerve conduction velocity, MNCV: motor nerve conduction velocity, NVC: sensory nerve conduction velocity, SNAPA: sensory nerve action potential amplitude, NGF: nerve growth factor, SOD: superoxide dismutase, MDA: malondialdehyde, NRS: Numerical Rating Scale.
Table 2: The characteristics of the formulas.

| First author | Year | Name of the formula | Composition (daily dosage)                                                                 | Jadad score |
|--------------|------|---------------------|--------------------------------------------------------------------------------------------|-------------|
| Chen, Mou    | 2015 | Huoxue Tongluo decoction | Cassia Twig (10), Astragalus (25), Salvia (10), Peach Kernel (10), Safflower (5), Angelica Sinensis (10), Rhizoma ligustici chuanxiong (10), Millettia Reticulata (5), White Peony Root (30), Herba Lycopodi (30), Clematis Root (30) | 4           |
| Chen, Yi     | 2016 | Tongluo Zhibi decoction | Angelica Sinensis (20), Rhizoma ligustici chuanxiong (15), Notopterygium (20), Trogopteroum feces (20), Prepared Monkshood (5), Radix Aconiti Kunzezooffi Preparata (5), Achyranthes Bidentata (20), Lanceolata (20), Loranthus Parasiticus (15), Glycyrrhiza (3) | 4           |
| Chen, Huang  | 2018 | Astragalus injection  | Tanshinone IIA                                                                                           | 4           |
| Cui          | 2009 | Astragalus injection  | Mountain Spicy Tree Root and Rhizome (60), Millettia Reticulata (40), Altingia chinii (60), large diamond (40), Caulis Tinosporae Sinensis (60), Bauhinia Championii Benthi (60) | 4           |
| Feng         | 2014 | Herbal Compress      | Caulis Tinosporae Sinensis (30), Cassia Twig (30), Chinese Angelica Root (15), Chinese Mugwort Leaf (30), Mint (15), Biota Orientalis (30), Lu Lu Tong (30), Rhizoma ligustici chuanxiong (10) | 4           |
| Li, Cai      | 2017 | Wenjing Huoxue formula Granulas of Chinese Medicine of modified Huangqi-Guizhi Wuwu and Shentong Zhuyu Wangqi Guizhi Wuwu decoction | Astragalus, Cassia Twig, White Peony Root, Ginger, Safflower, etc. (dosage not available) | 6           |
| Li, Sun      | 2017 | Wenjing tongluo formula: Danggui Sini Decoction combined with Yanghe Decoction Network Vessel-freeing Formula Modified Huangqi-Guizhi Wuwu Decoction | Atractylodes (30), Cassia Twig (12), White Peony Root (15), Ginger (12), Jujube (15) | 5           |
| Liu, Zhou    | 2011 | Wenjing tongluo formula: Danggui Sini Decoction | Geranium Herba, Aconiti Tuber, Cinnamomi Ramulus, Carthami Flos (the proportions are 4: 2: 3: 2) | 7           |
| Lou          | 2014 | Wenjing tongluo formula: Danggui Sini Decoction | Cassia Twig (15), White Peony Root (15), Glycyrrhiza (3), Ginger (15), Jujube (15), Angelica Sinensis (10), Asarum (10), Dried Ginger (10), Antler Glue (10), Cinnamon (10), Seeds of Brassica Alba (10), Ephedra (10), Prepared Radix Rehmanniae (10) | 4           |
| Peng         | 2015 | Wenjing tongluo formula: Danggui Sini Decoction | Atractylodes (30), Cassia Twig (12), White Peony Root (15), Ginger (12), Jujube (15), Angelica Sinensis (10), Asarum (10), Dried Ginger (10), Antler Glue (10), Cinnamon (10), Seeds of Brassica Alba (10), Ephedra (10), Prepared Radix Rehmanniae (10) | 4           |
| Qin          | 2012 | Wenjing Decoction    | Cassia Twig (12), Astragalus (20), Salvia (15), Peach Kernel (12), Safflower (10), Angelica Sinensis (12), Rhizoma ligustici chuanxiong (15), Millettia Reticulata (30), White Peony Root (12), Zedoary Tumeric (10) | 4           |
| Shen         | 2015 | Wenjing Decoction    | Atractylodes (50), White Peony Root (15), Cassia Twig (12), Dried Ginger (10), Jujube (10), Angelica Sinensis (12), Safflower (10), Millettia Reticulata (30), Clematis Root (10) | 4           |
| Shi          | 2010 | Wenjing Decoction    | Evodia Rutaecarpa (6-10), Angelica Sinensis (12), Rhizoma ligustici chuanxiong (10), White Peony Root (10), Lanceolata (30), Cassia Twig (6), Donkey Hide Gelatin (15), Ginger (2 slices), Cortex Moutan (10), Glycyrrhiza (6), Pinellia Ternate (10), Tuber of Dwarf Lilyturf (10), Astragalus (30) | 4           |
### Table 2: Continued.

| First author | Year | Name of the formula | Composition (daily dosage) | Jadad score |
|--------------|------|----------------------|----------------------------|-------------|
| Tang         | 2014 | Yangxue Tongluo Decoction | Astragalus (30), Angelica Sinensis (10), Aconite (10), Millettia Reticulata (30), Chinese mugwort leaf (10), Lu Lu Tong (10), Safflower (10) | 4           |
| Xu, Zhang    | 2018 | Xiaotan Tongluo Gel Modified Wangqi Guizhi Wuwu Decoction | Arisaema Consanguineum, Pinelliae Tuber, Scorpion, Pleione Rhizome, Clematis Root, Cassia Twig, Safflower, Baked Licorice (the proportions are 5:5:2:5:5:2:3:2) | 5           |
| Xu           | 2016 | White Peony Root (12), Cassia Twig (12), Astragalus (25), Jujube (6), Ginger (15) |                        | 4           |
| Yi, Li       | 2017 | Tongluo Zhibi Decoction Jiawei Wangqi Guizhi Wuwu decoction | Cassia Twig (15), Salvia (30), Red Peony Root (20), Rhizoma ligustici chuanxiong (20), Cynanchum Paniculatum (30), Clematis Root (30), Borneol (10), Asarum (10), North Papaya (20) | 4           |
| Yu, Su       | 2014 | Epimedium (30), Geranium wilfordii Maxim (30), Cassia Twig (18), Rhizoma ligustici chuanxiong (18) |                        | 4           |

### Table 3: The high frequency Chinese herbs.

| English name                      | Chinese name | Counts | Frequency(%) |
|----------------------------------|--------------|--------|--------------|
| Cassia twig                      | Guizhi       | 14     | 10.53%       |
| Astragalus                       | Huangqi      | 9      | 6.77%        |
| White Peony Root                 | Baishao      | 9      | 6.77%        |
| Angelica Sinensis                | Danggui      | 7      | 5.26%        |
| Rhizoma ligustici chuanxiong     | Chuanxiong   | 7      | 5.26%        |
| Safflower                        | Honghua      | 7      | 5.26%        |
| Ginger                           | Shengjiang   | 6      | 4.51%        |
| Millettia Reticulata             | Jixueteng    | 5      | 3.76%        |
| Jujube                           | Dazao        | 5      | 3.76%        |
| Clematis root                    | Weilingxian  | 4      | 3.00%        |
| Glycyrrhiza                      | Gancao       | 4      | 3.00%        |
| Salvia                           | Danshen      | 3      | 2.26%        |

gluconate, magnesium sulfate for injection, Glutathione, AD pro injection, and Thymopentin for subcutaneous injection with the same western medications. Although there was no significant difference between groups in the above seven trials, in the total sixteen trials, it was in favour of the intervention (n = 1149 patients; OR, 0.35, 95% CI, 0.22 to 0.57, P < 0.0001).

3.5.3. Curative Effects of the Method of Activating Blood and Dredging Collaterals for Reducing CIPN (Figure 3). To sum up, six trials including 418 participants reported curative effects of the method of activating blood and dredging collaterals for reducing CIPN. The total effective rate of the use of Chinese herbs was 77.19% versus 45.79% in the comparator group. Three studies compared curative effects of Chinese herbs to no additional treatment or placebo. Chinese herbs were proved to be more efficient in relieving CIPN (n = 233 patients; OR, 4.57, 95% CI, 2.48 to 8.40, P < 0.00001). Two trials making comparison of Chinese herbs and western medications such as Cobamamide and Mecobalamin and herbs were suggested to be effective in CIPN relief (n = 125 patients; OR, 4.91, 95% CI, 1.10 to 21.81, P = 0.04). One trial compared Chinese herbs plus Mecobalamin, AD pro injection, and Thymopentin, and applying herbs was also
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| Study or Subgroup | Intervention | Comparator | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|------------------|-------------|------------|--------------------------------|--------------------------------|
|                  | Events      | Total      | Weight                         |                                |
|                  |             |            |                                |                                |
| 1.1.1 herbs versus no intervention/placebo |
| Chen, Mou 2015   | 23          | 42         | 30                              | 37.9%                          |
|                  | 0.28 [0.10, 0.79] |            |                                |                                |
| Chen, Yi 2016   | 11          | 35         | 25                              | 35.7%                          |
|                  | 0.18 [0.07, 0.51] |            |                                |                                |
| Cui 2009         | 6           | 20         | 18                              | 2.7%                           |
|                  | 0.05 [0.01, 0.27] |            |                                |                                |
| Li, Cal 2017     | 8           | 34         | 17                              | 31.7%                          |
|                  | 0.23 [0.09, 0.73] |            |                                |                                |
| Li, Cal 2014     | 44          | 68         | 32                              | 34.9%                          |
|                  | 0.11 [0.03, 0.32] |            |                                |                                |
| Shi 2010         | 8           | 30         | 21                              | 5.1%                           |
|                  | 0.09 [0.02, 0.31] |            |                                |                                |
| Tang 2014        | 32          | 54         | 40                              | 51.1%                          |
|                  | 0.46 [0.17, 0.95] |            |                                |                                |
| Yi, Li 2017      | 29          | 50         | 40                              | 50.1%                          |
|                  | 0.35 [0.14, 0.84] |            |                                |                                |
| Subtotal (95% CI)|             | 333        | 284                            | 55.9%                          |
|                  | 0.22 [0.14, 0.34] |            |                                |                                |
| Total events     | 161         | 223        |                                |                                |
| Heterogeneity:   | Tau^2 = 0.09; ChI^2 = 9.61, df = 7 (P = 0.25); P^2 = 22% |
| Test for overall effect: Z = 6.79 (P < 0.00001) |

1.1.2 herbs versus western medications

| Study or Subgroup | Intervention | Comparator | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|------------------|-------------|------------|--------------------------------|--------------------------------|
|                  | Events      | Total      | Weight                         |                                |
|                  |             |            |                                |                                |
| (a) Figure 2: (a) Forest plot of comparison: incidence of all-grade chemotherapy-induced peripheral neuropathy. (b) Forest plot of comparison: incidence of high-grade chemotherapy-induced peripheral neuropathy.

(b)
more effective in relieving CIPN (n = 60 patients; OR, 4.13, 95% CI, 1.39 to 12.27, \( P = 0.01 \)).

3.5.4. Sensory Nerve Conduction Velocity (SNCV). As shown in Figure 4(a), eight trials analyzed the sensory nerve conduction velocity of the fibula nerve. It was attested that the Chinese herbs had beneficial influences on improving the SNCV of the fibula nerve (MD 4.59 m/s, 95% CI 3.23 to 5.96, \( P < 0.0001 \)). Besides, Figure 4(b) indicated that six trials assessed the sensory nerve conduction velocity of the median nerve. It was discovered that the use of Chinese herbs statistically promoted the SNCV of the median nerve (MD 4.00 m/s, 95% CI 2.01 to 5.99, \( P < 0.0001 \)).

3.5.5. Motor Nerve Conduction Velocity. Figure 5(a) showed seven trials tested the motor nerve conduction velocity of the fibula nerve, which proved that the Chinese herbs were more effective in improving the MNCV of the fibula nerve (MD 4.53 m/s, 95% CI 2.23 to 6.83, \( P = 0.0001 \)). In addition, Figure 5(b) revealed that six trials detected the MNCV of the median nerve, where Chinese herbs were proved to be valid in enhancing the MNCV of the median nerve (MD 3.25 m/s, 95% CI 1.07 to 5.42, \( P < 0.0001 \)).

3.6. Quality of Life (QoL) and Adverse Events. Five trials reported QoL (KPS score > 60 or ECOG score ≤ 2). Two trials [19, 26] reported the comparison of the percentage of patients with QoL improvement. Three trials [20, 25, 29] indicated differences of KPS scores or levels between two groups. One trial [32] investigated the ECOG PS based on the EORTC QLQ-C30. Thus, QoL could not be combined and analyzed in the meta-analysis. On the whole, the quality of life in the intervention group was better than the comparator one.

Among the total 20 studies, three trials [21, 24, 27] reported the herbs-related adverse events, such as skin allergy, skin chap, and scald, while three trials [20, 24, 25] showed the chemotherapy-induced adverse events, including myelosuppression, hematological toxicity, and gastrointestinal side effect.

3.7. Publication Bias. In Figures 6(a) and 6(b), the funnel plots of the incidence comparison of all-grade CIPN and high-grade CIPN demonstrated near-symmetry. Therefore, we found no significant publication bias.

4. Discussions

4.1. Advantages. We have attempted to analyze four main outcomes to evaluate the effectiveness on CIPN of herbal medicines alone or combined with western therapies in comparison with different comparators. The words of "activating blood" mean removing blood stasis, antiplatelet aggregation, and ameliorating the blood circulation of body, etc.; "dredging collaterals" refers to improving the microcirculation in
nervous system, protecting the neurons, anti-ischemic, and neurotransmitter modulatory effects, etc.

Chinese herbs selected and combined based on the method of activating blood and dredging collaterals were suggested to have a preventive and therapeutic role in reducing CIPN, not only for all-grade CIPN, but also for high-grade CIPN, as well as promoting curative effectiveness. Numerous prior works have focused on verifying it. Chen D et al.'s review [42] reported that Niuche Shenqi Wan were found to display potential therapeutic effects for preventing the genesis and development of CIPN via restoring the slowed blood flow, inhibiting oxidative stress and activating the C fiber. Liu et al.'s

Figure 4: (a) Forest plot of comparison: sensory nerve conduction velocity of the fibula nerve. (b) Forest plot of comparison: sensory nerve conduction velocity of the median nerve.
RCT [43] indicated that Guilong Tongluo decoction could delay the onset time of grades 1–4 neurotoxicity (9.4 vs. 6.5 weeks, \( P < 0.05 \)). Interestingly, we discovered that, among the high frequency herbs, Guizhi, Huangqi, and Baisha were the main compounds of the formula Wangqi Guizhi Wuwu decoction. Huangqi Guizhi Wuwu decoction is an herbal formula recorded in “Synopsis of the Golden Chamber” for improving limb numbness and pain. And its extract AC591 was clarified to prevent oxaliplatin-induced neuropathy, such as cold hyperalgesia and mechanical allodynia as well as morphological damage of dorsal root ganglion, and might be a promising adjuvant to alleviate sensory symptoms in

### Figure 5

(a) Forest plot of comparison: motor nerve conduction velocity of the fibula nerve. (b) Forest plot of comparison: motor nerve conduction velocity of the median nerve.

| Study or Subgroup | intervention Mean | SD | Total | Comparator Mean | SD | Total | Weight | Mean Difference | Mean Difference |
|------------------|------------------|----|-------|-----------------|----|-------|--------|----------------|----------------|
|                   |                  |    |       |                 |    |       |        |                |                |
| **4.2.1 herbs versus no intervention/placbo** |                 |    |       |                 |    |       |        |                |                |
| Xu, Zhang 2018   | 62.78            | 6.5| 36    | 49.42           | 3.58| 31    | 14.9%  | 3.36 [1.41, 5.31] |                |
| Subtotal (95% CI)| 36               |    | 14.9% |                 |    |        |        | 3.36 [1.41, 5.31] |                |
| Heterogeneity: Not applicable |          |    |       |                 |    |       |        |                |                |
| Test for overall effect: Z = 3.37 (\( P = 0.0007 \)) |          |    |       |                 |    |       |        |                |                |

| **4.2.2 herbs versus western medications** |                 |    |       |                 |    |       |        |                |                |
| Cheng 2014       | 43.5             | 3.6| 18    | 38.5            | 3.9| 18    | 16.0%  | 5.00 [3.86, 6.15] |                |
| Liu, Zhou 2011  | 47.01            | 4.02| 22    | 48.19           | 4.565| 24 | 13.9%  | -1.18 [-3.66, 1.30] |                |
| Xu 2016         | 47.8             | 3.2| 38    | 39.4            | 2.9| 38    | 15.7%  | 8.40 [7.03, 9.77] |                |
| Yu, Su 2014     | 47.1             | 4.25| 25    | 39.1            | 3.6| 24    | 14.6%  | 8.00 [5.87, 10.13] |                |
| Subtotal (95% CI)| 103              |    | 14.9% |                 |    |        |        | 5.15 [1.78, 8.53] |                |
| Heterogeneity: \( \tau^2 = 11.00 \); \( \chi^2 = 50.10 \), df = 3 (\( P < 0.00001 \)); \( I^2 = 94\% \) |          |    |       |                 |    |       |        |                |                |
| Test for overall effect: Z = 2.99 (\( P = 0.003 \)) |          |    |       |                 |    |       |        |                |                |

| **4.2.3 herbs in combined remedies versus the same western medications** |                 |    |       |                 |    |       |        |                |                |
| Chen, Huang 2018| 42.9             | 7.5| 29    | 38.6            | 6.8| 29    | 11.7%  | 4.30 [0.62, 7.98] |                |
| Peng 2015       | 41.7             | 7.3| 38    | 38.6            | 7| 48    | 13.2%  | 3.10 [0.24, 5.96] |                |
| Subtotal (95% CI)| 77               |    | 24.9% |                 |    |        |        | 3.55 [1.29, 5.81] |                |
| Heterogeneity: \( \tau^2 = 0.00 \); \( \chi^2 = 0.25 \), df = 1 (\( P = 0.61 \)); \( I^2 = 0\% \) |          |    |       |                 |    |       |        |                |                |
| Test for overall effect: Z = 3.08 (\( P = 0.002 \)) |          |    |       |                 |    |       |        |                |                |
| Total (95% CI)  | 216              |    | 100.0%|                 |    |        |        | 4.53 [2.23, 6.83] |                |
| Heterogeneity: \( \tau^2 = 6.28 \); \( \chi^2 = 58.54 \), df = 6 (\( P < 0.00001 \)); \( I^2 = 90\% \) |          |    |       |                 |    |       |        |                |                |
| Test for overall effect: Z = 3.86 (\( P = 0.0001 \)) |          |    |       |                 |    |       |        |                |                |
| Test for subgroup differences: \( \chi^2 = 0.84 \), df = 2 (\( P = 0.66 \)); \( I^2 = 0\% \) |          |    |       |                 |    |       |        |                |                |

(b)
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5. Conclusions

In general, this systematic review and meta-analysis results will hopefully serve as useful feedback information for preventing and relieving chemotherapy-induced peripheral neuropathy. Herbs with the function of activating blood and dredging collaterals were found to potentially promote the curative effects as well as making improvements of SNCV and MNCV.

But the evidence is not sufficient to draw a definite conclusion for the small participant sizes, the low methodological quality, the uncomprehensive subgroup analysis, and so on. In the future, more double-blind, multicenter, large-scale RCTs and more overall researches are still required before final goal of achieving effective improvement of CIPN by using traditional Chinese medicine can be completed.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Figure 7: (a) Risk of bias graph. (b) Risk of bias summary: review of authors’ assessment about each risk of bias item for each included study. “+”: low risk of bias; “?”: unclear risk of bias; “−”: high risk of bias.
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