REVIEW ARTICLE

Efficacy and Safety of Huangqi Guizhi Wuwu Decoction for Oxaliplatin-Induced Peripheral Neurotoxicity: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective • Oxaliplatin is a first-line chemotherapy drug for the treatment of colorectal cancer, but its induced oxaliplatin-induced peripheral neurotoxicity (OIPN) affect the chemotherapy process and quality of life of tumor patients. OIPN is a serious and potentially permanent side effect of cancer treatment. Currently, no unified standard has been established for preventing and treating OIPN in Western medicine. Therefore, it is very important to seek effective prevention and treatment measures. Many clinical trials have reported that Huangqi Guizhi Wuwu decoction can effectively prevent OIPN, but substantial evidence base to support this treatment is lacking. We collected existing literature and evaluated the clinical efficacy and safety of Huangqi Guizhi Wuwu decoction for OIPN by performing a meta-analysis.

Methods • We systematically searched China National Knowledge Internet (CNKI), VIP, Wan Fang Database, Pubmed, EMBASE, and Cochrane Library from inception through to Oct 2022 to identify only randomized controlled trials examining the prevention of OIPN using Huangqi Guizhi Wuwu decoction. This search was supplemented by manual retrieval, including dissertations and conference papers. All data were analyzed using RevMan 5.3 software.

Results • A total of 18 papers involving 564 patients in the treatment group and 523 patients in the control group were included. A total of 17 articles reported the overall incidence of peripheral neurotoxicity (I^2 = 0%), and the overall incidence of peripheral neurotoxicity in the treatment group was 0.27 times higher than in the control group (95% CI: 0.20-0.36). A total of 16 articles reported the incidence of level III–IV severe peripheral neurotoxicity (I^2 = 0%), which was 0.16 times higher in the treatment group than in the control group (95% CI: 0.09-0.32). In the Huangqi Guizhi Wuwu VS no-interference subgroup, it showed that the incidence of severe peripheral neurotoxicity in the treat group was significantly lower than in the control group (OR:0.13, 95% CI:0.06-0.28). But in the Huangqi Guizhi Wuwu VS west medicine therapy subgroup, no significant difference between Huangqi Quizhi Wuwu and conventional Western medicine was observed for the prevention and treatment of severe OIPN (OR:0.37, 95% CI:0.09-1.53). A total of 2 articles were reported median nerve conduction velocity (I^2 = 51.2%); and no significant difference was found between the treatment and control groups (SMD: 1.43; 95% CI: 0.80-2.08); 4 studies showed Huangqi Guizhi Wuwu decoction did not increase the incidence of chemotherapy-related adverse reactions and was safe.

Conclusions • Our current findings support the application of Huangqi Guizhi Wuwu decoction for the clinical prevention and treatment of patients with OIPN. However, high-quality RCT research is still needed to further exploration. The potential impact of Huangqi Guizhi Wuwu decoction on the quality of life or treatment compliance of cancer patients needs further research. (*Altern Ther Health Med.* 2024;30(1):446-453).

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INTRODUCTION

Oxaliplatin (L-OHP) is a new generation of platinum-based chemotherapy that is primarily used as a first- or second-line treatment and postoperative adjuvant therapy for advanced gastrointestinal cancer. Recent data show that L-OHP is also effective for ovarian cancer, breast cancer, pancreatic cancer, non-small-cell lung cancer, melanoma, testicular tumors, and lymphoma.[1] However, the clinical application of L-OHP is limited due to peripheral neurotoxic side effects. The incidence of oxaliplatin-induced peripheral neurotoxicity (OIPN) has been reported as high as 79%.[2] The primary manifestation of OIPN is paresthesia of the lower limbs. Based on the timing of symptom onset, peripheral neurotoxicity can be divided into acute peripheral neurotoxicity and chronic peripheral neurotoxicity. Hand

and foot numbness and paresthesia typically appear within 24 hours after chemotherapy in acute peripheral neurotoxicity case. In contrast, symptoms may not appear for several days or weeks in cases of chronic peripheral neurotoxicity.[3] Severe peripheral neurotoxicity can lead to patients reducing chemotherapy drug doses or ceasing treatment completely, which can affect tumor treatment and control, leading to physiological and psychological effects and reducing the quality of life for patients.The symptoms of numbness and sensory abnormalities in the hands and feet caused by peripheral neurotoxicity have an impact on the patient's physiology, psychology, and quality of life. Severe peripheral neurotoxicity requires patients to reduce the dosage or even discontinue chemotherapy drugs, which will inevitably affect the effective treatment and control of tumors.

Currently, no unified standard has been established for preventing and treating OIPN in Western medicine. The clinical response is typically the shift to the intermittent administration of L-OHP,[4] adjusting the dose, or changing to a different chemotherapy regimen altogether.[5] The commonly used drugs for treating OIPN in clinical practice include: neurotrophic drugs (B vitamins), glutathione, glutamine, free radical scavengers amphotericin, lipoic acid, calcium magnesium mixture, etc.[6] Although many drugs have been suggested, the clinical efficacy of these drugs has yet to be unanimously recognized.

Chronic OIPN can be categorized as "Bizheng" in traditional Chinese medicine.[7] After chemotherapy, deficiency of both qi and blood, imbalance of camp and health, loss of nourishment in muscles and meridians, and obstruction of collaterals and collaterals can lead to Bizheng.Our team's preliminary basic research found that Huangqi Guizhi Wuwu decoction can improve nerve damage in rats after chemotherapy, and there is a statistically significant difference compared to mecobalamine treatment. Its mechanism may be mediated by downregulating the expression of NR2B in the L4-6 spinal cord of rats and upregulating the level of pNF-H protein in DRG.Clinical evidence suggests that Huangqi Guizhi Wuwu decoction can prevent chronic OIPN.[8] Huangqi Guizhi Wuwu decoction was first described in the Synopsis of the Golden Chamber. Huangqi Guizhi Wuwu decoction is based on Guizhi decoction, without fried licorice, and with twice as much ginger. Huangqi, Guizhi Wuwu decoction can relieve muscle pain and harmonize Ying and Wei. Fried licorice was removed to avoid moderation and enhance the power of eliminating pathogenic factors. Ginger is pungent and sweet, which can disperse into Yang. Using twice as much ginger can warm the Yang and unblock the pulse, whereas the addition of Huangqi was performed to warm and replenish qi. Therefore, Huangqi Guizhi Wuwu is designed to replenish qi, warm the Yang, and harmonize Ying and Xingbi, and is commonly used clinically to prevent OIPN. Given the limited options in Western medicine, we sought to explore the potential of Huangqi Guizhi Wuwu decoction, a traditional Chinese medicine, in preventing and treating OIPN.

METHODS

Registration information

This systematic review and meta-analysis were registered on the Prospero platform with registration number CRD42021239877.Detailed information can be logged in https://www.crd.york.ac.uk/PROSPERO.

Inclusion criteria

Type of study: All randomized controlled trials (RCTs) on the use of Huangqi Guizhi Wuwu decoction to prevent and treat OIPN were selected, regardless of the blinding method and allocation concealment strategies applied.

Object of study: Patients diagnosed with malignant tumors by histopathology, cytology, or imaging and those who were confirmed to have used L-OHP during their chemotherapy regimens were included, regardless of sex, age, or disease type.

Interventions: The treatment group was treated with Huangqi Guizhi Wuwu decoction or Huangqi Guizhi Wuwu decoction combined with conventional Western medicine. The control group was treated with a placebo or conventional Western medicine. The treatment and control groups were treated with the same chemotherapy regimen containing L-OHP. Chinese traditional medicine therapy was performed in the form of oral medication, fumigation, and washing in the form of decoctum or granules. The control group was treated with Western medicine, regardless of the type of medicines used.

Exclusion criteria

Research results or patent reports with only abstracts and without full-text availability; repeatedly reported literature; literature with incomplete data; failure to indicate the final outcome after the full-text data was reviewed; study subjects who experienced peripheral neurotoxicity after L-OHP use combined with other drugs; subjects who experienced peripheral neurotoxicity before the start of the original study; and studies that applied any other Chinese medical methods, such as fumigation and washing, cupping, massage, and acupuncture, to the experimental group.

Document retrieval strategy

A full search was performed on the China National Knowledge Internet (CNKI), Wanfang Database, VIP Chinese Science and Technology Journal Database (VIP), National Library of Medicine (PubMed), and Embase. These databases were searched for any literature describing randomized controlled trials (RCTs) using Huangqi Guizhi Wuwu decoction to prevent and treat OIPN published from database inception to Oct 2022. The database search was supplemented by a manual search, which included academic dissertations and conference papers. The publication languages were limited to Chinese and English. The search words were "Huangqi Guizhi Wuwu," "Chinese herb medicine," "Oxaliplatin," "peripheral neurotoxicity," and others.

Literature screening and data extraction

Two researchers (Jialin Yu, Shanshan Chen) searched for literature independently. EndnoteX7 was used to establish a database for the initially retrieved documents, and the automatic duplicate search function was used to delete duplicate retrieved documents. After reading the titles and abstracts of identified studies, those studies that did not meet the inclusion criteria were removed. The full texts of the remaining publications were obtained, and the two researchers read the full text strictly following the inclusion and exclusion criteria to select included studies. Develop a data extraction table based on the relevant content of the "Cochrane Intervention System Evaluation Manual" and the research content of this project. The extracted content includes basic information, research object characteristics, research methods, outcome indicators, intervention measures, and outcome indicators.Among them,the outcome indicators included the overall incidence of peripheral neurotoxicity,the incidence of level III–IV severe peripheral neurotoxicity (level III–IV response, according to the World Health Organization (WHO) or the National Cancer Institute (NCI)'s toxic side effect grading standard) and median nerve conduction velocity. Safety indicators included the incidence of myelosuppression, the incidence of liver and kidney functional lesions, the incidence of gastrointestinal reactions, and the incidence of other adverse events.The two researchers decided whether or not to include the documents with different opinions after checking them through discussion or a third party judgment.

Literature quality assessment

The latest version of the bias risk assessment tool (version 5.1.0), developed by the Cochrane Collaboration Network, was used to evaluate the methodological quality of the included studies. The following aspects were evaluated, including how random assignments were generated and randomized, whether patients and physicians were blinded, whether outcome measures were blinded, whether there were missing data and reports of exit and loss of follow-up, and whether there were selective outcome reports..

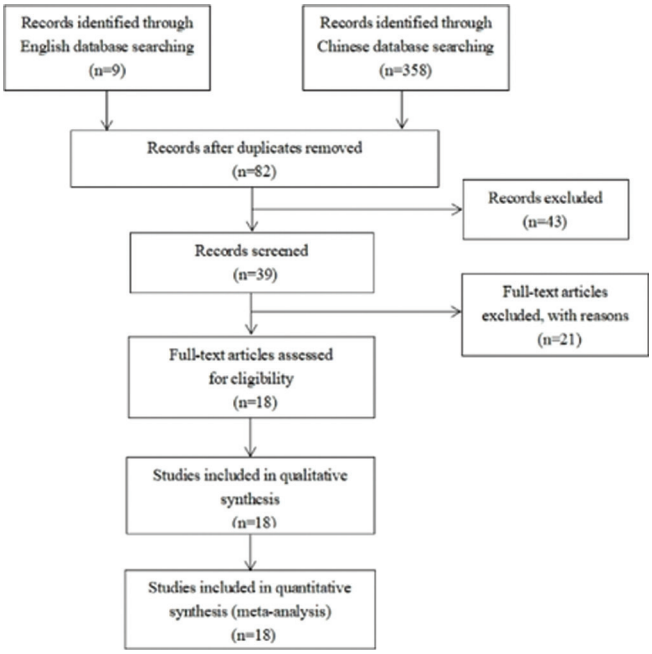
Outcome Indicators

The observed outcome indicators include the following points.Firstly,efficacy indicators included: the overall incidence of peripheral neurotoxicity,the incidence of level III-IV severe peripheral neurotoxicity,median nerve conduction velocity.Secondly. safety indicators included: occurrence of blood toxicity, liver and kidney function injury and gastrointestinal reactions.

Statistical analysis

We used Stata (version 15.0) for all statistical analyses. If two or more homogeneous statistical magnitudes were identified, these statistical magnitudes were merged for a meta-analysis. The overall incidence of peripheral neurotoxicity and the incidence of level III–IV severe peripheral neurotoxicity were counted data, represented by relative risk (OR) and its 95% confidence interval (CI), and median nerve conduction velocity was a quantitative data, represented by the mean difference (MD) and its 95%CI. Funnel plot is one of the commonly used methods for identifying publication bias, and publication bias was discussed and explored through funnel plot analysis.Egger's test is also a common method for quantitatively evaluating publication bias in meta-analysis.We assessed funnel plot asymmetry using Egger tests and defined significant publication bias as a $P < .05$. The trim-and-fill computation was used to estimate the effects of publication bias on the interpretation of the results.[9] In addition,we used the Cochran Q test to assess heterogeneity between studies.[10] We also did I^2 testing to assess the magnitude of heterogeneity between studies, with values greater than 50% regarded as being indicative of moderate-to-high heterogeneity.[11] We performed the sensitivity analysis after removing the articles one by one and drew the Metaninf graph with Stata (version 15.0). If the point estimate after deleting a study falls outside the 95%CI of the total effect size, the study is considered to have a large impact on the combined effect size and is highly sensitive, requiring further review of the study. Otherwise, it means that the sensitivity is low, and the results of the original Meta-analysis or system evaluation are stable.

Figure 1. Flow chart of the studies included in this systematic review.



RESULTS

Results of literature screening (Figure 1): The databases were thoroughly searched using the formulated search words, resulting in a total of 367 related studies identified. EndNote's automatic duplicate identification function automatically deleted duplicate literature from the primary search results. Two researchers read the titles and abstracts of the remaining

Table 1. Basic characteristics of the included studies

Author Year	Sample size		Sex		Mean age (year) (median/range)		Disease type	Chemotherapy	Intervention		Outcome index	Adverse effects
	Experimental	Control	Experimental	Control	Experimental	Control			Experimental	Control		
Liu Hui 2011	30	28	Men 18 Women 12	Men 21 Women 9	61.47	61.47	Gastroenteric tumor, Lung cancer	Containing oxaliplatin	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	ABC	Unpainted
Zou Shansi 2015	21	21	Men 11 Women 10	Men 11 Women 10	32–70		Gastric cancer, Colorectal cancer	FOLFOX	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	AB	Unpainted
Wu Guannan 2015	44	45	Men 32 Women 12	Men 31 Women 14	49.2	51.5	Gastric cancer	PTX + L-OHP	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	AB	Unpainted
Mu Dacheng 2016	57	57	Men 25 Women 32	Men 23 Women 34	48.72	47.92	Gastric cancer	PTX + L-OHP	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	AB	Unpainted
Hu Guangyin 2010	23	19	Men 28 Women 14	Unknown	21–68	Unknown	Gastric cancer, Colorectal cancer	FOLFOX4	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy + Mecobalamin, Vitamin B	AB	Unpainted
Cao Shunjin 2013	25	24	Men 15 Women 10	Men 11 Women 13	55	54	Colorectal cancer	FOLFOX4	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy + Mecobalamin	AB	Unpainted
Wang Yian 2011	31	30	Men 37 Women 24	Unknown	32–71	Unknown	Gastric cancer, Colorectal cancer	FOLFOX	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	AB	Unpainted
He Yingyue 2012	20	20	Men 22 Women 18	Unknown	34–72	Unknown	Gastric cancer, Colorectal cancer	FOLFOX4	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	AB	Unpainted
Xu Haijun 2011	33	23	Men 24 Women 22	Unknown	30–75	Unknown	Gastroenteric tumor	FOLFOX4	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy+ Mecobalamin	AB	Unpainted
Li Daoming 2014	24	24	Men 28 Women 20	Unknown	Average 52	Unknown	Colorectal cancer	FOLFOX6	Chemotherapy+Huangqi Guizhi Wuwu	Chemotherapy	AB	Unpainted
Yang Yang 2017	33	33	Men 18 Women 12	Men 16 Women 14	18–75	Unknown	Colorectal cancer	FOLFOX6	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	ABCDF	Evaluated
Wang Fei 2012	40	40	Men 25 Women 15	Men 23 Women 17	29–70	Unknown	Gastric cancer, Colorectal cancer	FOLFOX	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	AB	Unpainted
Xu Chengxing 2017	34	34	Men 19 Women 15	Men 20 Women 14	52.4	51.8	Gastric cancer, Colorectal cancer	mFOLFOX	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherap y+ Mecobalamin	AB	Unpainted
Wang Yong 2018	30	31	Men 18 Women 12	Men 20 Women 11	54.167	54.097	Gastric cancer or Colorectal cancer	mFOLFOX	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	ADEF	Evaluated
Li Yuan 2006	31	31	Men 21 Women 10	Men 21 Women 10	34–75		Gastric cancer, Colorectal cancer	FOLFOX	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy	AB	Unpainted
He Liu 2010	32	31	Men 18 Women 14	Men 18 Women 13	38–74	40–72	Gastric cancer	FOLFOX	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy +GSH	ABDEF	Evaluated
Cheng Songhai 2013	28	26	Men 13 Women 15	Men 12 Women 14	43–59	41–60	Colorectal cancer	Containing oxaliplatin	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy + Mecobalamin	AB	Evaluated
Ma Jun 2019	28	28	Men 19 Women 9	Men 16 Women 12	60.07 ± 8.16	62.79 ± 8.43	Colorectal cancer	mFOLFOX6, XELOX	Chemotherapy + Huangqi Guizhi Wuwu	Chemotherapy + Placebo	CD	Evaluated

Notes: FOLFOX: oxaliplatin + 5-fluorouracil + calcium folinate: XELOX: oxaliplatin + capecitabine; GSH: glutathione; PTX: paclitaxel. A: The overall incidence of peripheral neurotoxicity; B: The incidence of level III–IV severe peripheral neurotoxicity; C: Median nerve conduction velocity; D: The incidence of hepatotoxicity; E: The incidence of gastrointestinal reactions; F: The incidence of liver and kidney damage; G: The occurrence of other adverse events.

Figure 2. Risk of bias graph

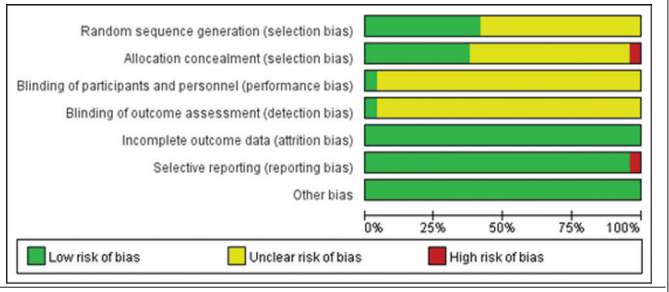
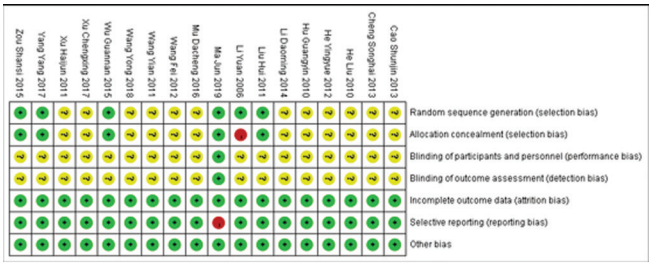


Figure 3. Risk of bias summary



82 studies independently. They removed documents that did not meet the inclusion criteria, such as case reports, experiences, animal experiments, reviews, and research progress reports, and culled repeatedly reported studies. After the abstract and title review, 39 studies remained. The full texts for the remaining 39 studies were obtained, and the two researchers reviewed the full texts independently to select studies strictly following pre-defined inclusion and exclusion criteria. Finally, 18 studies that met the criteria were included.[12-29]

Inclusion study characteristics

General characteristics: A total of 18 studies were included, among which 17 were published in Chinese and one was published in English. The original clinical trials were performed on patients who were primarily diagnosed with digestive system tumors, and the chemotherapy regimen was typically based on folinic acid, fluorouracil (5-FU), and oxaliplatin (FOLFOX) regimen. The Western medicine included in the control group was most commonly mecobalamin. The basic characteristics of the included studies are detailed in Table 1.

The Traditional Chinese medicine characteristics included in the study: The decoctions in the treatment group used in the included studies were all based on the prescription of Huangqi Guizhi Wuwu decoction, and the primary intervention method was oral decoction delivery.

Literature quality assessment: The percentage of risk of bias for each of the included studies is detailed in Figure 2, and the contributors to the risk of bias for each study are specified in Figure 3. The 18 included studies[12-29] all described the use of random allocation, among which 5 studies[12,15,16,27,29] used the "random number table method," one study[28] used the "SAS software code allocation number," and the remaining

12 studies[13,14,17–26] did not describe the randomization method in detail. One study[28] indicated the use of allocation concealment and blinding (both the implementer and the subject were blinded), while the remaining studies were not described. One study[28] has reporting bias and did not report the expected main outcome.Furthermore, incomplete result data and other biases are evaluated as low risk.

Meta-analysis of the overall incidence of peripheral neurotoxicity

The 17 included studies reported the overall incidence of peripheral neurotoxicity (I^2 = 0%). We conducted a meta-analysis of the total incidence of peripheral neurotoxicity in these 17 studies. However, due to the different interventions between the experimental and control groups, we also conducted a subgroup analysis to examine Huangqi Guizhi Wuwu decoction VS no intervention and Huangqi Guizhi Wuwu decoction VS Western medicine. The OR was estimated using a fixed effects model to calculate the overall incidence of peripheral neurotoxicity, which was 0.27 times higher in the treatment group than in the control group (95% CI: 0.20-0.36) (Figure 4).This indicates that Huangqi Guizhi Wuwu decoction has a lower overall incidence of OIPN and better therapeutic effect compared to chemotherapy or conventional Western medicine.

Meta-analysis of the incidence of level III–IV severe peripheral neurotoxicity

A total of 16 studies were included, which reported the incidence of level III–IV severe peripheral neurotoxicity (I^2 = 0%). The studies were divided into groups according to different intervention measures applied to the treatment group and the control group to observe the effective rate of Huangqi Guizhi Wuwu decoction in preventing and treating severe OIPN. The OR was estimated using a fixed effects model to calculate the incidence of level III–IV severe peripheral neurotoxicity, which was 0.16 times higher in the treatment group than in the control group (95% CI: 0.09 -0.32) (Figure 5).In the Huangqi Guizhi Wuwu VS no-interference subgroup,it showed that the incidence of severe peripheral neurotoxicity in the treat group was significantly lower than in the control group.But in the Huangqi Guizhi Wuwu VS west medicine therapy subgroup,no significant difference between Huangqi Quizhi Wuwu and conventional Western medicine was observed for the prevention and treatment of severe OIPN.

Meta-analysis of median nerve conduction velocity

A total of 3 literature studies were included. However, Ma Jun's[28] study only measured the conduction velocity of the finger 1–median wrist nerve and the finger 3–median wrist nerve separately. The conduction velocity of the median nerve was not described; therefore, this study was excluded. Two studies, by Liu Hui[27] and Yang Yang[12], were included (n = 114). The results (Figure 6) showed moderate heterogeneity (I^2 = 51.2%, P = .152), and a random-effects model was used for the combined analysis. No significant difference was found between the treatment and control groups (SMD: 1.43; 95% CI: 0.80-2.08; Figure 6).

Figure 4. The overall incidence of peripheral neurotoxicity.

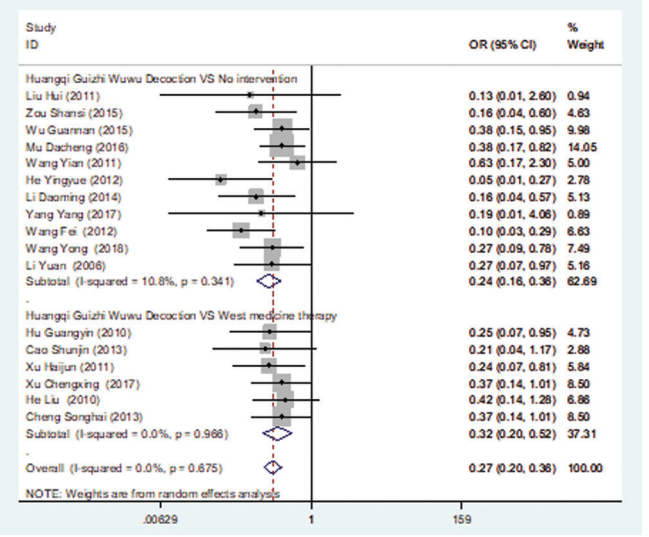


Figure 5. The incidence of level III–IV severe peripheral neurotoxicity.

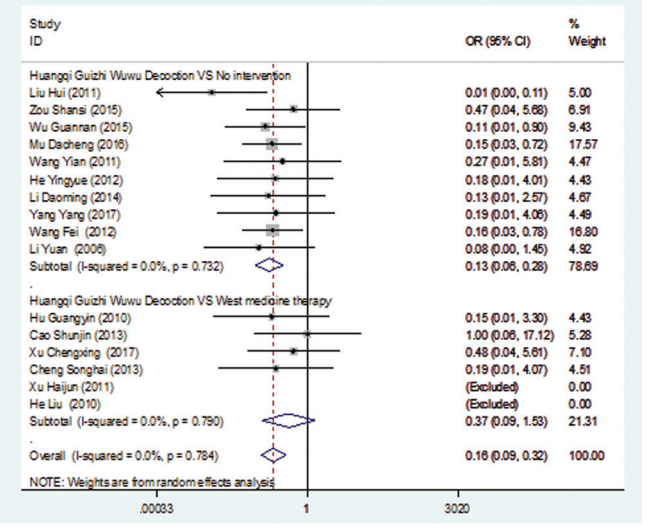


Figure 6. Median nerve conduction velocity

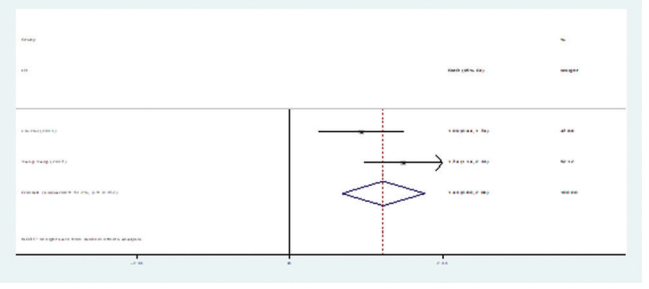


Table 2. Safety evaluation

Author Year	Sample size	The incidence of myelosuppression	The incidence of liver and kidney functional damage	The incidence of gastrointestinal reactions	Electrocardiogram changes
Wang Yong 2018	Experimental (n = 30)	43.33%	13.33%	53.33%	Not evaluated
	Control (n = 31)	53.84%	16.13%	67.74%	
Yang Yang 2017	Experimental (n = 30)	40.00%	6.67%	Not evaluated	Not evaluated
	Control (n = 30)	46.67%	10.00%		
He Liu 2010	Experimental (n = 32)	25.00%	The difference was not statistically significant		
	Control (n = 31)	50.00%			
Ma Jun 2019	Experimental (n = 28)	21.43%	3.57%	Not evaluated	3.57%
	Control (n = 28)	25.00%	7.41%		3.57%

Figure 7. Egger's test (A. The incidence of peripheral neurotoxicity B. The incidence of level III–IV severe peripheral neurotoxicity).

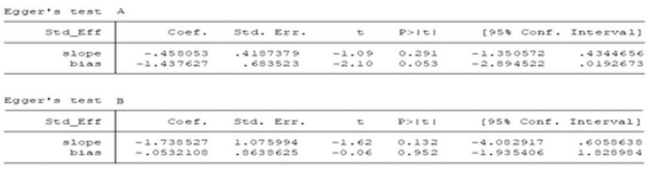
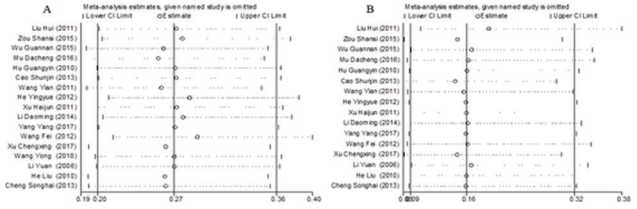


Figure 8. Metaninf graph (A. The incidence of peripheral neurotoxicity B. The incidence of severe peripheral neurotoxicity).



Safety evaluation

Of the 18 includes studies, only 4 mentioned adverse reactions (Table 2). Because the adverse reactions mentioned described differed, they could not be merged in a meta-analysis and are only qualitatively described. Wang Yong et al.[13] mentioned the incidence of reduced white blood cells, platelets, and hemoglobin, the incidence of liver and kidney functional damage, and the incidence of gastrointestinal reactions. The results showed no increase in the main adverse reactions of chemotherapy among patients using Huangqi Guizhi Wuwu decoction. The study by Yang Yang et al.[12] reported the incidence of myelosuppression and liver damage in the treatment and control groups after chemotherapy. All adverse effects were tested by Chi-square test ($P > .05$), and the difference was not significant, indicating that Huangqi Guizhi Wuwu decoction was safe when used to prevent OIPN. He Liu[23] mentioned that the incidence of degree III–IV leukopenia was 25% in the treatment group, significantly lower than 50% in the control group ($P < .05$). No significant difference in hemoglobin, platelets, liver and kidney function, or electrocardiogram changes were noted between the two groups of patients ($P > .05$). The Huangqi Guizhi Wuwu decoction did not affect the patient's hemogram, liver and kidney function, or electrocardiogram changes. In the study by Ma Jun[28] study, the occurrence of bone marrow suppression, liver and kidney toxicity, and arrhythmia were evaluated, and no significant differences were reported between the test group and the control group.

Publication Bias and sensitivity analysis

Due to the number of included studies, only the incidence of peripheral neurotoxicity and the incidence of severe peripheral neurotoxicity (Figure 7) were tested for publication bias. Using Stata15.0 software for analysis, the results showed that Huangqi Guizhi Wuwu decoction has no publication bias in preventing and treating total OIPN or the incidence of severe OIPN. Sensitivity analysis is to evaluate the stability of meta-analysis models, and its position in the meta-analysis process should not be underestimated.As shown in the figure, the point after deleting each study falls within 95% CI of the total effect, indicating that a single study has a small impact on the combined effect and the robustness of the study is good (Figure 8).

DISCUSSION

OIPN is a serious and potentially permanent side effect of cancer treatment.[30] Patients treated with L-OHP typically experience the onset of acute OIPN symptoms. Still, some patients develop chronic sensory loss that has been hypothesized to be caused by neuronal damage in the dorsal root ganglia.[31] The pathogenesis of OIPN has been hypothesized to be associated with oxalate, an L-OHP metabolite that can affect the sodium channel.[32] Other scholars believe that the dorsal root ganglion is targeted by platinum agents toxicity, and the aggregation of L-OHP in the dorsal nerve root can reduce superoxide dismutase synthesis, increasing free radicals concentrations, which results in peripheral nerve toxicity. The degree of pathological nerve damage is associated with the cumulative dose of drug toxicity.[33] Basso et al.[34] found that gene polymorphisms and the reduced conductance of the calcium-activated potassium channel SK3 were also closely related to the pathogenesis of acute neurotoxicity. Chronic neurotoxicity was dose-limited, and the symptoms were aggravated with the increase in the cumulative dose.

Despite intense investigations at both preclinical and clinical levels, no treatment has been developed to prevent OIPN, and only limited evidence to support the efficacy of duloxetine under treatment settings has been provided.[35] Huangqi Guizhi Wuwu decoction, recorded in Synopsis of the Golden Chamber, is a classic prescription for treating "XueBi" in clinic. Huangqi Guizhi Wuwu decoction can be used for all patients with qi deficiency, blood stagnation, and disharmony between Ying and Wei. A mechanistic study showed that Huangqi Guizhi Wuwu decoction can reduce oxaliplatin-induced peripheral neuropathic pain by down-

regulating the expression of sodium channel Nav l.7 subtype protein and its genes in the dorsal root ganglia.[36] Other researchers have demonstrated that Huangqi, Gui Zhi, and Wu Wu Tang can reduce platinum accumulation and downstream cellular damage such as nucleus shrinkage and mitochondrial swelling.[37] It can improve oxaliplatin-induced peripheral neuropathy in rats by up-regulating the activity of superoxide dismutase (SD), and lowering the amount of MDA in the serum and spinal cord, as well as ameliorating the pain sensitivity and the oxygenation stress in the dorsal root ganglia.Moreover,it can also reduce the death rate of neuronal cell during chemotherapy. The destruction of cells triggers the apoptotic program, which in turn leads to the dysfunction of the entire nervous system.[38]

Our results showed that in patients receiving L-OHP chemotherapy, adding Huangqi Guizhi Wuwu decoction effectively reduced the overall incidence of OIPN and the incidence of severe OIPN compared with chemotherapy alone. Compared with Western medicine treatment, Huangqi Guizhi Wuwu decoction reduced the overall incidence of OIPN, but no significant difference between Huangqi Quizhi Wuwu and conventional Western medicine was observed for the prevention and treatment of severe OIPN. Due to the small number of studies, the meta-analysis examining nerve conduction had moderate heterogeneity, and insufficient evidence was identified to support the use of Huangqi Guizhi Wuwu decoction to improve the effects of L-OHP on nerve conduction. In terms of safety, 4 studies showed Huangqi Guizhi Wuwu decoction did not increase the incidence of chemotherapy-related adverse reactions and was safe. These data show that when oxaliplatin chemotherapy is used in the clinic, choosing Huangqi Guizhi Wuwu decoction can reduce the incidence of neurotoxicity, the effect is better than that of western drugs, and the safety is good. When severe OIPN occurs, its efficacy is comparable to that of western drugs. Oxaliplatin is a highly toxic product, which can injure the body's yang qi, so Huangqi Guizhi Wuwu decoction is that in addition to alleviating the neurotoxicity, it also benefits the qi and warmth of the meridians, and improves the patient's overall physical condition.

The limitations of this analysis include the quality of the literature, which was generally poor based on the assessment of the research methodology of the studies included in this analysis. The 18 included studies mentioned random allocations, but most did not describe the random method in detail or specify whether allocation concealment schemes were applied. Only one study used a blinding method, and none of the other studies stated whether blinding was applied. The failure to implement a blinding method can easily lead to measurement bias. The sample size of the included studies was small, and only one article explains the rationale for sample size estimations, which leads to a decrease in the power of the test. Regarding the observation indicators, whether OIPN was improved by the combination of Huangqi Guizhi Wuwu decoction and Western medicine compared with Western medicine alone was not explored. Few studies reported on nerve conduction velocity or drug safety, which could not be quantitatively analyzed.Poor design of included studies reduces the credibility of Meta-analytic evidence. In the future, researchers can improve the quality of clinical studies by conducting multicenter, large-sample clinical randomized controlled studies and standardizing the operations related to study design, such as the implementation of allocation concealment and blinding, the implementation of blinding of outcome testers, and the analysis of shedding cases.Randomized controlled studies of Huangqi Guizhi Wuwu decoction with western drugs such as Duloxetine for neurotoxicity can also be conducted to further explore their efficacy and safety.

The results of this meta-analysis may provide medical practitioners with some reference value for adding Huangqi Guizhi Wuwu decoction to prevent and treat neurotoxicity while using oxaliplatin chemotherapy.

CONCLUSIONS

In conclusion, our meta-analysis suggests that Huangqi Guizhi Wuwu decoction holds promise as an intervention for the prevention and treatment of oxaliplatin-induced peripheral neurotoxicity (OIPN). These findings, although encouraging, are based on studies with certain limitations, including small sample sizes and variations in methodology. Therefore, while our results support the potential efficacy and safety of Huangqi Guizhi Wuwu decoction, further research in the form of well-designed multicenter, large-sample clinical randomized controlled trials is needed to confirm and refine these findings. Nonetheless, this traditional Chinese medicine offers a valuable avenue for exploration in the management of OIPN, a distressing side effect of cancer treatment with limited existing therapeutic options.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

JY and JH designed the study and performed the experiments, SC and GW collected the data, JG, RD and LL analyzed the data, JY and JH prepared the manuscript. All authors read and approved the final manuscript.

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FOOTNOTE

Reporting Checklist: The authors have completed the PRISMA reporting checklist.

ETHICAL COMPLIANCE

Not applicable.

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