**Review Article**

**Meta-Analysis of Xihuang Pill Efficacy When Combined with Chemotherapy for Treatment of Breast Cancer**

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**Objective.** To systematically evaluate the efficacy of Xihuang pill (XHP) in breast cancer patients receiving chemotherapy. **Methods.** Three English and four Chinese databases were searched. Literature was screened using EndNote X7 and data were analyzed by Review Manager. **Results.** This review included 13 randomized clinical studies of 1272 patients. The results showed that XHP increased the tumor response [risk ratio (RR) = 2.91; 95% confidence interval (CI): 1.98-4.26] and improved Karnofsky performance score (KPS) for breast cancer patients receiving chemotherapy [RR = 4.96; 95% CI = 2.07-11.86]. In addition, XHP treatment significantly reduced chemotherapy-induced adverse events, including nausea and vomiting [RR = 0.50; 95% CI = 0.33-0.74], WBC reduction [RR = 0.71; 95% CI = 0.47-1.06], platelet reduction [RR = 0.53; 95% CI = 0.19-1.44], hemoglobin reduction [RR = 0.31; 95% CI = 0.19-0.52], and hepatic function damage [RR = 0.63; 95% CI = 0.35-1.11]. **Conclusion.** XHP combined with chemotherapy in comparison with chemotherapy alone could significantly enhance the tumor response, improve KPS, and alleviate toxicity induced by chemotherapy in breast cancer patients.

1. **Introduction**

Breast cancer is one of the most common types of malignant tumors among women worldwide and is also the leading cause of cancer death among women in the world [1]. Approximately 252,710 new cases of invasive breast cancer and 40,610 breast cancer deaths are expected to occur among US women in 2017 [2]. In the developing world, the incidence rate of breast cancer has been increasing due to extended life expectancies, developing urbanization, and the adoption of stressful modern lifestyles [3]. Surgery [4], chemotherapy [5], endocrinotherapy [6], molecular targeted therapy [7], and immunotherapy [8] are the primary anticancer treatments currently being utilized. However more and more studies have shown that these therapies are also associated with numerous postoperative complications, toxicities, and side effects, such as deep vein thrombosis (DVT) [9], upper limb edema [10], myelosuppression [11], liver and renal function, gastrointestinal tract reaction [12], cardiac damage [13], peripheral neurotoxicity, menopause like syndrome [14], or local radiation damage [15]. In addition, breast cancer has an ability to develop resistance to this conventional therapeutics over time [16], and some cancers are insensitive to chemotherapy or radiotherapy [17]. These factors restrict the use of these treatment modalities and impact the prognosis of breast cancer patients. Therefore, it is essential to discover an effective and adjuvant therapeutic agent with low toxicity and fewer adverse side effects for breast cancer treatment.

Traditional Chinese medicine (TCM), an important component of complementary and alternative medicine, evolved almost 3,000 years ago in China with its own unique system of medical theories about pathogenesis, diagnostics, therapeutic principles, and prescriptions [18, 19]. Chinese herbal medicine (CHM) is a mainstay of TCM that mainly consists of medicinal herbs, acupuncture, moxibustion, massage, food therapy, and therapeutic exercise for both treatment and prevention.
2. Methods

2.1. Database and Search Strategy. We searched for relevant studies published in the following electronic publication databases: Embase, PubMed, Cochrane, Web of Knowledge, the Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), China Journal Full-Text Database, and Wanfang Data (for unpublished graduate theses in China) from their inception to August 2018. We executed a comprehensive literature review of randomized controlled trials (RCTs) that combined treatments (Xihuang pill or Xihuang capsule with chemotherapy) for breast cancer patients. The following search terms were used: (Breast Neoplasm OR Neoplasm, Breast OR Breast Tumors OR Breast Tumor OR Tumor, Breast OR Tumors, Breast OR Neoplasms, Breast OR Breast Carcinoma OR Breast Carcinomas OR Carcinoma, Breast OR Carcinomas, Breast OR Mammary Neoplasms, Human OR Human Mammary Neoplasm OR Human Mammary Neoplasms OR Neoplasm, Human Mammary OR Neoplasms, Human Mammary OR Mammary Neoplasm, Human OR Breast Cancer OR Cancer, Breast OR Mammary Cancer OR Cancer, Mammary OR Cancers, Mammary OR Mammary Cancers OR Malignant Neoplasm of Breast OR Breast Malignant Neoplasm OR Breast Malignant Neoplasms OR Malignant Tumor of Breast OR Breast Malignant Tumor OR Breast Malignant Tumors OR Cancer of Breast OR Cancer of the Breast AND (Xihuang pill OR Xihuang capsule). Studies were restricted to those of human subjects without restriction on language, and the above terms in Chinese were searched in Chinese databases.

2.2. Inclusion Criteria. All the studies selected for meta-analysis met the following inclusion criteria: (1) patients in each trials were cytologically or pathologically confirmed as breast cancer; (2) patients received chemotherapy combined with XHP in the treatment group compared to the administration of chemotherapy alone in the control group; (3) RCTs; (4) outcomes included immediate tumor response, quality of life (QoL) using Karnofsky performance score (KPS), immune system response, reduction in adverse reaction of chemotherapy such as myelosuppression, gastrointestinal reaction, and hepatic function damage.

2.3. Exclusion Criteria. Studies were excluded due based the following criteria: (1) studies did not meet the above inclusion criteria; (2) use of compounds other than XHP, other traditional Chinese medicine intervention in the treatment group; (3) nonoriginal research or duplicate publication; (4) trials with missing data or documentation of data errors; (5) laboratory studies or review literature.

2.4. Data Extraction and Quality Assessment. Two authors (Dan Mao and Lei Feng) independently examined all the titles and abstracts identified as potentially eligible trials, culled obviously unqualified literatures, and then reviewed full texts that might have satisfied the inclusion criteria. Data was extracted from the selected trials into a standard data extract form. The extracted data included first author and year of publication, study size, detail of randomization, age of participants, details of methodology, specifics of the control interventions, durations of treatment, outcome measures, and adverse reactions.

We assessed the methodological quality of each RCT using risk of bias tool in accordance with the Cochrane Hand-book for Systematic Reviews of Interventions. Risk
of bias judgment includes six criteria: random sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data addressed, free of selective reporting, and other bias based on imbalance of the baseline information. The quality of all included trials was categorized as three potential bias judgments: low, unclear, or high risk of bias. Trials which met all criteria were categorized to low risk of bias, trials which showed that entries met none of the criteria were categorized to high risk of bias, and other trials were categorized to unclear risk of bias if insufficient information was available to make a judgment. All risks for biased data are presented in Figures 2 and 3. Disagreements between the two authors were resolved through consensus or arbitrated by a third author (Siqi Huang).

2.5. Statistical Analysis. The articles were managed with EndNote X7, and statistical analyses were carried out using Review Manager 5.3 software from the Cochrane Collaboration. Data were summarized using risk ratio (RR) with 95% confidence intervals (CI) for discontinuous variables or mean difference (MD) with 95% CI calculated for continuous data. Dichotomous data were expressed as relative risk (RR) or odds ratio (OR) with 95% CI. Heterogeneity across trials was tested with the $I^2$ test. If $I^2 \leq 50\%$ or $P \geq 0.1$, a fixed model was applied. On the other hand, $I^2 > 50\%$ or $P < 0.1$ indicated that a possibility of statistical heterogeneity and so a random-effects model was adopted. The differences between the treatment groups and control groups were considered to be statistically significant when $P < 0.5$.

3. Results

3.1. Search Results and Study Characteristics. We identified 344 studies through screening of electronic databases. There were 57 studies rejected due to duplication in EndNote X7. After reading titles and abstracts, 147 potentially relevant articles were retrieved. There were 23 literature reviews, 4 case reports, 10 studies were expert experience, 47 were basic/mechanistic studies, and 32 studies were protocols. After further screening, each of these remaining articles was assessed in detail. Eighteen full-text articles did not meet inclusion criteria: 2 studies were not RCTs; 2 studies included participants without only cancer; 12 studies combined other therapies; and 2 studies not investigate targeted outcomes. Finally, a total of 13 studies were included in our analysis (Figure 1) [43–55]. The 13 trials were published between 2010 and 2018 (Table 1). A total of 1272 patients were enrolled in these studies, of which 636 patients participated in chemotherapy combined with XHP and 636 received chemotherapy alone.

3.2. Risk of Bias. All patients recruited in the included studies were women with breast cancer, and basically all of the included studies could be evaluated as unclear or high risk in that available data was limited. All trials were described as randomized, with ten trials [43–46, 48–50, 52–54] mentioning a detailed description of the randomization method. Those were considered as low risk as patients were randomly divided into groups. Allocation concealment was not reported in any studies. Attempts to contact the authors by phone or e-mail were unsuccessful. None of the studies gave details about blinding of participants or personnel.
# Table 1: Characteristics of 13 included trails.

| Study             | Sample size (T/C) | Control group intervention | Treatment group intervention | Duration (week) | Assessment of outcome |
|-------------------|-------------------|----------------------------|------------------------------|-----------------|-----------------------|
| Chen, 2016 [43]   | 100(50/50)        | CAF                        | XHC+CAF                      | 6               | Tumor response, survival time, chemotoxicity |
| Hong, et al., 2014 [44] | 84(42/42)        | TAC                        | XHP+TAC                      | 18              | Tumor response, KPS, chemotoxicity, OS, PFS |
| Jin, et al., 2010 [45] | 60(30/30)        | CAF                        | XHP+CAF                      | 6               | Symptom curative effect of TCM, CD4+, CD8+ |
| Mao, et al., 2014 [46] | 68(34/34)        | NR                         | XHC+Chemotherapy             | 8               | Tumor response, three-year survival rate, KPS, recurrence and metastasis rate |
| Wang, 2018 [47]   | 123(64/59)        | TP                         | XHP+TP                       | 12              | Tumor response, KPS, tumor marker, chemotoxicity, one-year/two-year survival rate |
| Wang, 2015 [48]   | 80(40/40)         | CA                         | XHC+CA                       | 6               | Tumor response, MST, PFS, chemotoxicity |
| Wang, et al. 2017 [49] | 98(49/49)        | CAF                        | XHP+CAF                      | 8               | Tumor response, tumor marker, CD3+, CD4+, CD4+/CD8+, coagulation function, chemotoxicity |
| Wang, 2017 [50]   | 60(26/34)         | AC-T                       | XHC+AC-T                     | 24              | KPS, CD4+, CD8+, CD4+/CD8+, tumor marker, indicators of inflammatory response, CD3+, CD4+ |
| Wu, 2016 [51]     | 90(45/45)         | TEC                        | XHP+TEC                      | 18              | Tumor response, tumor marker, KPS, chemotoxicity |
| Xu, et al., [52]  | 253(128/125)      | TP                         | XHP+TP                       | 3               | Tumor response, tumor marker, KPS, chemotoxicity |
| Yue, et al., [53] | 78(39/39)         | TAC                        | XHP+TAC                      | 18              | Tumor response, P53, HER2, TOP II |
| Zhang, et al., [54] | 90(45/45)        | AC+4-T+4                   | XHC+AC+4-T+4                 | 12              | KPS, quality of life, chemotoxicity |
| Zhou, et al., [55] | 88(44/44)        | GP                         | XHC+GP                       | 6               | Tumor response, chemotoxicity, TNF-α, VEGF, MMP-2, MMP-9 |

*Notes:* XHC: Xihuang capsule, XHP: Xihuang pill, TG: treatment group, CG: control group, KPS: Karnofsky performance score, OS: overall survival, PFS: progression-free-survival, and MST: median survival time.
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias

Low risk of bias
Unclear risk of bias
High risk of bias

Figure 2: Risk of bias graph.

Figure 3: Risk of bias summary.
or blinding of outcome assessment. Six studies described the follow-up process [43, 44, 46–48, 50]; we considered these studies to be low risk. It was not possible to evaluate whether all expected outcomes were reported. And we could not conclude if there were no other biases in each study. Our quality assessment of each methodological parameter is shown in Figures 2 and 3.

### 3.3. Effects of the Intervention

#### 3.3.1. Tumor Response

Results from nine studies stated the tumor response [43–45, 47–49, 52, 53, 55]; 490 patients using chemotherapy combined with XHP were reported to have complete response (CR) or partial response (PR), while 482 patients using chemotherapy only were reported as CR or PR, indicating that the treatment of breast cancer was significantly more effective when chemotherapy was combined with XHP (risk ratio (RR) = 1.49, 95% CI = 1.33-1.68, and p < 0.00001, 972 patients). There was no significant heterogeneity among these studies (χ² = 6.08; p = 0.67; I² = 0%) (Figure 4) and a funnel plot was created to indicate publication bias (Figure 5).

#### 3.3.2. Performance Status

Changes in Karnofsky performance score (KPS) were analyzed as two types of data in the included studies. The first type reflected the improvement or stabilization of the KPS (ten-point cutoff); the second type was the mean ± SD of KPS data before and after treatment. Only two [46, 54] of the 13 studies, evaluating 158 patients, reported an improvement in KPS. Results from these two studies showed that the combined use of chemotherapy and XHP was significantly related to improved KPS (RR = 4.94; 95% CI = 2.06-11.87; P = 0.0004, 158 patients). There was no significant heterogeneity observed among these studies (χ² = 0.01; p = 0.93; I² = 0%) (Figure 6).

Four studies [44, 47, 50, 52] reported pre- and post-treatment KPS. Pretreatment KPS data were not significantly different between the two treatment arms (RR = 0.59; 95% CI: −0.81–1.99; P = 0.41; I² = 0%, 520 patients; Figure 7). However, the pooled results of posttreatment KPS were significantly higher in the XHP combined with chemotherapy group than in the chemotherapy group (RR = 19.02; 95% CI: 7.14–30.90; P = 0.002; 520 patients). Heterogeneity among the four studies was low (χ² = 147.98; P < 0.00001; I² = 98%) (Figure 8).
3.3.3. Reduction in Chemotherapeutic Toxicity. Nausea and vomiting are one of the most distressing adverse events that can occur with chemotherapy [56]. Remarkably, the frequency of nausea and vomiting was reduced significantly in patients treated by XHP combined with chemotherapy (RR = 0.51; 95% CI = 0.39-0.67; \( P = 0.008 \); eight studies; 916 patients) [43, 44, 47–49, 52, 54, 55]. Heterogeneity testing showed \( \chi^2 = 12.65; \quad \text{df} = 3; \quad P < 0.00001; \quad I^2 = 45\% \) (Figure 9). The reduction of grade I-IV WBC inhibition was not significantly different between the two groups (RR = 0.76; 95% CI = 0.54-1.05; \( P = 0.09 \); six studies; 736 patients) [44, 47-49, 52, 54, 55]. Heterogeneity testing resulted in \( \chi^2 = 12.98; \quad \text{df} = 5; \quad P < 0.01; \quad I^2 = 25\% \) (Figure 10(a)). In a sensitivity analysis, by eliminating one study [52], the reduction of WBC inhibition at grades I-IV was significantly less frequent in the XHP combined with chemotherapy group (RR = 0.56; 95% CI = 0.36-0.88; \( P = 0.01 \); five studies; 483 patients) (Figure 10(b)). The reduction of platelet inhibition at the toxicity grade of I-IV in patients was not significantly different between the two arms (RR = 0.53; 95% CI = 0.19-1.44; \( P = 0.21 \); three studies; 272 patients) [44, 49, 54]; heterogeneity test results were \( \chi^2 = 5.08; \quad P = 0.08; \quad I^2 = 61\% \) (Figure 11(a)). In sensitivity analysis, by eliminating one study [44], statistical heterogeneity disappeared (\( I^2 = 0\% \)). Therefore, fixed-effects model was selected for meta-analysis; the reduction of platelet inhibition at toxicity grades I-IV was statistically less frequent in the XHP combined with chemotherapy group (RR = 0.31; 95% CI = 0.14-0.71; \( P = 0.02 \); two studies; 188 patients) (Figure 11(b)). Grade I-IV chemotherapy-induced reductions in hemoglobin counts were significantly less frequent in the XHP combined with chemotherapy group (RR = 0.31; 95% CI = 0.19-0.52; \( P < 0.0001 \); three studies; 262 patients) [44, 54, 55]. The heterogeneity test showed \( \chi^2 = 8.09; \quad P < 0.0001; \quad I^2 = 75\% \) (Figure 12).
we detected no significant between-study heterogeneity ($\chi^2 = 5.06; P = 0.05; I^2 = 21\%$) (Figure 13).

### 3.3.4. Immunoregulation.

Pretreatment levels with CD3+, CD4+, CD8+, and CD4+/CD8+ cells did not have significant difference between the XHP combined with chemotherapy group and the chemotherapy group (CD3+, RR = 0.06, 95% CI = 0.93-1.14, $P = 0.68$, $I^2 = 0\%$; CD4+, RR = 0.08, 95% CI = 0.68-1.34, $P = 0.12$, $I^2 = 0\%$; CD8+, RR = 0.85, 95% CI = -0.85-0.10, $P = 0.35$, $I^2 = 0\%$; CD4+/CD8+, RR = 0.02, 95% CI = 0.98-1.02, $P = 0.82$, $I^2 = 0\%$) (Figures 14–17).

After the treatment of XHP combined with chemotherapy, there was a significant rise in CD3+ cells levels (RR = 8.98, 95% CI = 5.01-12.95, $P < 0.0001$; two studies; 188 patients) [49, 51]. The heterogeneity testing for this result was $\chi^2 = 4.90$, $P < 0.0001$; $I^2 = 80\%$ (Figure 18). Combined therapy also showed a significant advantage in CD4+ cells after treatment (RR = 4.00, 95% CI = -2.59-8.99, $P = 0.43$; CD4+/CD8+, RR = 0.02, 95% CI = -0.08-0.02, $P = 0.47$; $I^2 = 0\%$) (Figures 19–21).
CI = 1.14-6.87; \( P = 0.006 \); four studies; 308 patients) [45, 49–51]. Heterogeneity testing showed \( \chi^2 = 25.78; \ P < 0.00001; \ I^2 = 88\% \) (Figure 19). In addition, there was a significant improvement in CD8+ cell levels in combined therapy group (RR = -4.04; 95% CI = -6.19-1.89; \( P = 0.0002 \); three studies; 218 patients) [45, 49, 50]; heterogeneity testing was \( \chi^2 = 4.34; \ P = 0.11; \ I^2 = 54\% \) (Figure 20). However, posttreatment CD4+/CD8+ levels were not significantly different between the two treatment arms (RR = 0.12; 95% CI = -0.10-0.35; \( P = 0.28; \ I^2 = 57\% \); two studies; 158 patients) [49, 50]; heterogeneity testing \( \chi^2 = 2.32; \ P = 0.13; \ I^2 = 57\% \) (Figure 21).
4. Discussion

This meta-analysis of 13 RCTs, including 1272 patients, shows that, compared with chemotherapy alone, combination treatment with XHP and chemotherapy had better outcomes, which is evidenced by the significant improvement in the tumor response and performance status among breast cancer patients. Furthermore, combined therapy offers a significant reduction in chemotherapy-induced adverse events, including nausea and vomiting, WBC reduction, platelet reduction, and hemoglobin reduction. These results were strongly encouraging and suggested that the combination
of XHP and chemotherapy might be a beneficial clinically therapeutic method superior to chemotherapy alone. These unique advantages could, to some extent, support the use of an integrated TCM and Western approach to medicine in the treatment of breast cancer.

Chemotherapy plays a key role in the systemic treatment of postoperative breast cancer patients, which is a widely used strategy for improving breast cancer survival [57]. Bone marrow suppression, gastrointestinal reactions, hepatic function damage, and immune system destruction are the most obvious chemotherapy-induced side effects [58]. Many patients are unable to tolerate such effects, which can limit its clinical application and impact prognosis. Cancer treatment with chemical agents is destructive to malignant cells and tissues, as well as nontumor tissues. TCM theory holds that the toxicity of chemotherapy may lead to an imbalance of Qi and blood, dysfunction of the viscera, and increased accumulation of pathogenic factors such as toxic heat blood stasis in the body [59].

XHP has many beneficial effects such as heat-clearance and detoxification, activating blood circulation to dissipate blood stasis, and disintegrating scleroma, which was recorded to have effects on treating furunculosis, scrofula, and neoplasms in ancient China [39]. In recent studies, many Chinese medicine experts suggest that XHP could adjust imbalances in the internal body for processes like anti-inflammatory action, reducing temperature, promoting blood circulation, removing toxins, and remarkable antineoplastic properties when complementing chemotherapy against breast cancer [29]. However, most studies on the clinical efficacy of XHP are based on either case reports or expert experience, and it is difficult to reach evidence-based conclusions. This meta-analysis was performed to provide evidence on the usage and justify the clinical application of XHP in breast cancer chemotherapy.

Based on the existing data, we analyzed the mean values of CD3+, CD4+, CD8+, and CD4+/CD8+ ratios in both the XHP combined with chemotherapy group and chemotherapy alone group. Due to mixed quality and the small sample sizes of the included studies, we were unable to clarify whether XHP was part immunoregulation. Although results of these measurements showed that there was a significant enhancement in CD3+ and CD4+ cells levels, as well as obvious suppression of CD8+ cells levels in patients treated with XHP combined with chemotherapy, the change in CD4/CD8 ratio had no statistical significance. Hence, the above evidence is too limited to make a conclusion with confidence. Although the molecular mechanism of action is not fully understood, the improvements in the efficiency of chemotherapy and reductions in chemotherapy-induced adverse events are major advantages for using XHP as an adjunctive therapy in the treatment of breast cancer. The
finding that XHP has potential benefits for breast cancer therapy is similar to other reviews [60–63].

There are several strengths and limitations to this study that should be noted. First, we strictly followed the principle of evidence-based medicine to conduct this search, overcame the inconsistency of the included results to provide reliable evidence for the clinical application of XHP. And all reviewers received high-quality training in meta-analyses. One limitation was language bias which was unavoidable because all of the included studies were conducted and published in China. Next, none of the included trials clearly described allocation concealment or blinding processes, which may contribute to high selection risk and performance bias. Third, the lack of multicenter and large size RCTs trials makes it difficult to ignore the low quality of several included studies. Fourth, there was significant heterogeneity in the reduction of WBC inhibition and platelets inhibition; however, sensitivity analysis eliminated the heterogeneity. Differences in sample size, patient age, tumor stage and grade, chemotherapy regimens, and other factors among the studies might also be responsible for the heterogeneity. Additionally, most of the included trials reported positive results. Some negative or nonsensical outcomes selectively unreported may lead to publication bias, which limited integrated analysis. Lastly, only three publications provided information about follow-up. It is therefore impossible to judge long-term efficacy; this flaw may lead to potential biases and influence the final outcomes.

Nevertheless, our findings clearly support the use of XHP in combination with chemotherapy in the clinical management of patients with breast cancer. With the modern extensive application of TCM theories and remarkable therapeutic effects, these methodologies have attracted more public attention and the widespread usage of TCM continues [64]. Accordingly, efforts should be made to conduct more high-level clinical researches such as on medication safety and long-time follow-up to further legitimize TCM worldwide for routine care in the treatment of breast cancer.

5. Conclusion

In summary, this meta-analysis demonstrates that XHP could be considered an effective and safe adjunctive treatment to chemotherapy in comparison with chemotherapy alone among breast cancer patients. In addition, XHP was found to have multitarget effects in cancer treatment due to the complex mixture of compound. However, the lack of sufficient molecular evidence still limits the acceptance and application of XHP outside of China. Therefore, further investigation is required to determine the potential mechanisms for antitumor therapeutic effects of XHP. Due to uncertain methodological rules used in many trials, in further studies strict adherence to modern assessment rules will be implemented.

Conflicts of Interest

The authors declare no conflicts of interest with respect to this research, authorship, and/or its publication.

Authors’ Contributions

Dan Mao and Lei Feng contributed equally to this work. Dan Mao, Lei Feng, and Siqi Huang retrieved data. Dan Mao and Lei Feng analyzed data, wrote and revised this paper, and retrieved data. Shaofan Zhang and Weijun Peng conceived and supervised the study. Sifang Zhang interpreted data and edited the paper.

References

[1] F. Bray, J. Ferlay, and I. Soerjomataram, “Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries,” CA: A Cancer Journal for Clinicians, vol. 68, no. 6, pp. 394–424, 2018.
[2] C. E. DeSantis, J. M. A. Goding Sauer, L. A. Newman, and A. Jemal, “Breast cancer statistics, 2017, racial disparity in mortality by state,” CA: A Cancer Journal for Clinicians, vol. 67, no. 6, pp. 439–448, 2017.
[3] B.-N. Zhang, W.-Q. Chen, and X. Zhang, “China faces a challenge of breast cancer prevention and control,” Zhong Hua Zhong Liu Za Zhi, vol. 38, no. 10, pp. 798–800, 2016.
[4] G. M. Rauch, “ASO author reflections: elimination of breast cancer surgery in complete responders after neoadjuvant chemotherapy: imaging perspective,” Annals of Surgical Oncology, vol. 25, no. S3, pp. 628–629, 2018.
[5] F. Barbosa C Rocha, A. B. Falcone, A. C. Buzaid, J. M. Pimenta, G. Schvartsman, and A. L. Frasson, “Neoadjuvant therapy for breast cancer treatment: an expert panel recommendation from the Brazilian Society of Breast Surgeons 2018,” Breast Cancer Research and Treatment, vol. 172, no. 2, pp. 265–272, 2018.
[6] X. Wan, Y. Zhang, J. Ma, C. Tan, X. Zeng, and L. Peng, “Ribociclib in hormone-receptor-positive advanced breast cancer: Establishing a value-based cost in China,” The Breast Journal, vol. 43, pp. 1–6, 2019.
[7] Y.-H. Li, Y. Zhou, Y.-W. Wang et al., “Comparison of apatinib and capecitabine (Xeloda) with capecitabine (Xeloda) in advanced triple-negative breast cancer as third-line therapy: A retrospective study,” Medicine, vol. 97, no. 36, p. e12222, 2018.
[8] L.-Y. Yu, J. Tang, C.-M. Zhang et al.,”New immunotherapy strategies in breast cancer,” International Journal of Environmental Research and Public Health, vol. 14, no. 1, pp. 68–98, 2017.
[9] Z. Wang, C. Deng, K. Zhu et al., “Cyclophosphamide, epirubicin and fluorouracil chemotherapy-induced alteration of haemostasis markers in breast cancer patients,” Molecular and Clinical Oncology, vol. 3, no. 5, pp. 1088–1092, 2015.
[10] L. Angooti Oshnari, S. A. Hosseini, S. Haghhighat et al., “The effect of complete decongestive therapy on edema volume reduction and pain in women with post breast surgery lymph edema,” Iranian Journal of Cancer Prevention, vol. 9, no. 2, p. e4209, 2016.
[11] J. Hong, X. Chen, J. Huang et al., “Danggui Buxue decoction, a classical formula of traditional Chinese medicine, fails to prevent myelosuppression in breast cancer patients treated with adjuvant chemotherapy: a prospective study,” Integrative Cancer Therapies, vol. 16, no. 3, pp. 406–413, 2017.
[12] M. Tang, P. Horsley, and C. R. Lewis, “Emergency department presentations in early stage breast cancer patients receiving adjuvant and neoadjuvant chemotherapy,” Internal Medicine Journal, vol. 48, no. 5, pp. 583–587, 2018.
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[13] M. A. Nicolazzi, A. Carnicelli, M. Fuorlo et al., “Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer,” European Review for Medical and Pharmacological Sciences, vol. 22, no. 7, pp. 2175–2185, 2018.

[14] S. D. Baxter, W. A. Teft, Y.-H. Choi, E. Winquist, and R. B. Kim, “Tamoxifen-associated hot flash severity is inversely correlated with endoxifen concentration and CYP3A4,” Breast Cancer Research and Treatment, vol. 145, no. 2, pp. 419–428, 2014.

[15] Z. Brownlee, R. Garg, M. LISTO, P. Zavitsanos, D. E. Wazer, and K. E. Huber, “Late complications of radiation therapy for breast cancer: Evolution in techniques and risk over time,” Gland Surgery, vol. 7, no. 4, pp. 371–378, 2018.

[16] R. Doddapaneni, K. Patel, N. Chowdhury, and M. Singh, “Reversal of drug-resistance by nocaspine chemo-sensitization in docetaxel resistant triple negative breast cancer,” Scientific Reports, vol. 7, no. 1, p. 15824, 2017.

[17] G. Rubovszky and Z. Horváth, “Recent advances in the neoadjuvant treatment of breast cancer,” Journal of Breast Cancer, vol. 20, no. 2, pp. 119–131, 2017.

[18] W. Peng, S. Zhang, Z. Zhang et al., “Jianpi Jiedu decoction, a traditional Chinese medicine formula, inhibits tumorigenesis, metastasis, and angiogenesis through the mTOR/HIF-1α/VEGF pathway,” Journal of Ethnopharmacology, vol. 224, pp. 140–148, 2018.

[19] F. Qi, L. Zhao, A. Zhou et al., “The advantages of using traditional Chinese medicine as an adjunctive therapy in the whole course of cancer treatment instead of only terminal stage of cancer,” Bioscience Trends, vol. 9, no. 1, pp. 16–34, 2015.

[20] C.-X. Sheng, Z.-Q. Chen, H.-J. Cui et al., “Is the Chinese medicinal formula Guipi Decoction effective as an adjunctive treatment for depression? A meta-analysis of randomized controlled trials,” Chinese Journal of Integrative Medicine, vol. 23, no. 5, pp. 386-95, 2017.

[21] H. Meng, N. Peng, M. Yu et al., “Treatment of triple-negative breast cancer with Chinese herbal medicine: A prospective cohort study protocol,” Medicine, vol. 96, no. 44, p. e8408, 2017.

[22] C. Huang, H. Chang, S. Su et al., “Traditional Chinese medicine is associated with a decreased risk of heart failure in breast cancer patients receiving doxorubicin treatment,” Journal of Ethnopharmacology, vol. 229, pp. 15–21, 2019.

[23] Y. Zhou, B. Zhao, W. Wu et al., “Shenmai injection for the treatment of cancer-related fatigue in advanced non-small cell lung cancer patients undergoing chemotherapy: study protocol for a randomized controlled trial,” Trials, vol. 19, no. 1, p. 474, 2018.

[24] S. B. Park, D. Goldstein, A. V. Krishnan et al., “Chemotherapy-induced peripheral neurotoxicity: a critical analysis,” CA: A Cancer Journal for Clinicians, vol. 63, no. 6, pp. 419–437, 2013.

[25] Y. Tsai, J. Lai, P. Lo, C. Chen, and J. Lin, “Prescription of Chinese herbal products is associated with a decreased risk of invasive breast cancer,” Medicine, vol. 96, no. 35, p. e7918, 2017.

[26] W. Liang, DT. Yew, KL. Hon et al., “Indispensable value of clinical trials in the modernization of traditional Chinese medicine: 12 years’ experience at CUHK and future perspectives,” The American Journal of Chinese Medicine, vol. 42, no. 3, pp. 587–604, 2014.

[27] Z. Lu, J. Moody, B. L. Marx, and T. Hammerstrom, "Treatment of chemotherapy-induced peripheral neuropathy in integrative oncology: a survey of acupuncture and oriental medicine practitioners," The Journal of Alternative and Complementary Medicine, vol. 23, no. 12, pp. 964–970, 2017.

[28] F.-X. Lin, L.-F. Tian, C.-Y. Lei, C.-C. Ding, L. Shi, and S.-F. Zhang, “Chinese medicine for outcomes in colorectal cancer patients: A retrospective clinical study,” Chinese Journal of Integrative Medicine, vol. 23, no. 9, pp. 648–653, 2017.

[29] Q.-J. Guo, J. Lin, R. Liu et al., “Review on the applications and molecular mechanisms of Xihuang Pill in tumor treatment,” Evident Based Complement Alternative Med, Article ID 854307, pp. 1–10, 2015.

[30] Y. Shen, “A randomized parallel control study of Xihuang pill combined with western medicine in the treatment of breast cancer,” Journal of Practical Traditional Chinese Internal Medicine, vol. 28, no. 3, pp. 127-128, 2014.

[31] X.-Q. Wu, “Effect of Xihuang pill combined with hepatic artery chemoembolization on survival and prognosis of patients with advanced hepatic cancer,” Jiangxi Medical Journal, vol. 51, no. 8, pp. 774–775, 2016.

[32] H. Zhang, “Short-term effect of Xihuang capsule supplemented to intensity-modulated radiotherapy for re-irradiation of recurrent esophageal cancer,” Journal of Practical Oncology, vol. 33, no. 1, pp. 61–65, 2018.

[33] Q. Yang, “Chemotherapy with oxaliplatin and tegafur gimeracil oteracil potassium capsule versus oxaliplatin-assisted Xihuang capsules in the treatment of patients with advanced gastric cancer and its effects on T cell subsets, survival rate and adverse reactions,” Journal of Clinical Medicine in Practice, vol. 21, no. 17, pp. 51–54, 2017.

[34] D. Yu and G. Y. An, “Clinical effects of Xihuang Pill combined with chemotherapy in patients with advanced colorectal cancer,” Evidence-Based Complementary and Alternative Medicine, vol. 2017, Article ID 5936086, 5 pages, 2017.

[35] X.-H. Dong, “Clinical effect of Xihuang Pill combined with CHOP chemotherapy in treating B-cell non-Hodgkin lymphoma,” Clinical Journal of Traditional Chinese Medicine, vol. 30, no. 8, pp. 1492–1494, 2018.

[36] G.-M. Chen, B. Peng, J. Zhu et al., “Clinical observation on treating bone metastases cancer pain with Xihuang Pills plus 3-dimensional conformal radiation,” Clinical Journal of Chinese Medicine, vol. 9, no. 32, pp. 120-121, 2017.

[37] L. Su, Y. Jiang, Y. Xu et al., “Xihuang pill promotes apoptosis of Treg cells in the tumor microenvironment in 4T1 mouse breast cancer by upregulating MEK1/SEK1/JNK1/AP-1 pathway,” Biomedicine & Pharmacotherapy, vol. 102, pp. 1111–1119, 2018.

[38] W. Zheng, S. Han, S. Jiang et al., “Multiple effects of Xihuang pill aqueous extract on the Hs578T triple-negative breast cancer cell line,” Biomedical Reports, vol. 5, no. 5, pp. 559–566, 2016.

[39] G. Pan, W. Wang, L. Wang et al., “Anti-breast cancer effects and mechanisms of Xihuang pill on human breast cancer cell lines,” Journal of Traditional Chinese Medicine, vol. 33, no. 6, pp. 770–778, 2013.

[40] X.-Y. Li, L. Su, Y.-M. Jiang et al., “The antitumor effect of Xihuang Pill on treg cells decreased in tumor microenvironment of 4T1 breast tumor-bearing mice by P38/AKT–AP-1 signaling pathway,” Evidence-Based Complementary and Alternative Medicine, vol. 2018, Article ID 6714829, 13 pages, 2018.

[41] J. Zhang, F.-H. Zhang, and S.-J. Yang, “Anticancer effects of Xi Huang Capsule on breast cancer in vivo,” Traditional Medicine Research, vol. 2, no. 1, pp. 33–40, 2017.

[42] J. Hao, Z. Jin, H. Zhu et al., “Antiestrogenic activity of the Xi-Huang formula for breast cancer by targeting the estrogen
receptor α," *Cellular Physiology and Biochemistry*, vol. 47, no. 6, pp. 2199–2215, 2018.

[43] L. Chen, "The effect of Xihuang Capsule combined with chemotherapy in the treatment of middle and advanced breast cancer," *China health standard management*, vol. 7, no. 13, pp. 151–152, 2016.

[44] R. Hong, Y.-Q. Wu, and Y. Wu, "Effects of Xihuang pill in assistant treatment of patients with advanced breast cancer," *China Journal of Chinese Materia Medica*, vol. 39, no. 06, pp. 1120–1123, 2014.

[45] J. Jin, "Intergrated Xihuang pills and chemotherapy in treating 30 patients with breast cancer," *Chinese Journal of Traditional Chinese Medicine*, vol. 25, no. 5, pp. 715–716, 2010.

[46] D. Mao, L.-Z. Huang, C.-H. Zhou et al., "Efficacy of Xihuang Capsule in patients of triple-negative breast cancer receiving adjuvant chemotherapy postoperative," *Journal of New Chinese Medicine*, vol. 46, no. 4, pp. 155–157, 2014.

[47] B. Wang, "Clinical study on Xihuang Pills combined with TP regimen in treatment of middle and advanced breast cancer," *Drugs & Clinic*, vol. 33, no. 7, pp. 1746–1750, 2018.

[48] L. Wang, "Therapeutic effect of Xihuang Capsule combined with chemotherapy on advanced breast cancer," *Journal of Traditional Chinese Medicine*, vol. 43, no. 6, pp. 82–84, 2015.

[49] P. Wang and C.-X. Liu, "Effect of Xihuang pills combined with CAF treating patients with advanced breast cancer," *Pharmacology and Clinic of Traditional Chinese Medicine*, vol. 33, no. 5, pp. 186–189, 2017.

[50] Q.-D. Wang, *The Application of Adjuvant Therapy of Breast Cancer with Xihuang Capsule*, Shanxi medical university, 2017.

[51] G.-Y. Wu, "Anti-breast cancer effects of Xihuang pills as adjuvant and the effect on immune functions in patients with breast cancer," *Shanxi Medical Journal*, vol. 45, no. 21, pp. 2477–2479, 2016.

[52] G.-S. Xu, X.-L. Xie, and D.-X. Sun, "Effect of Xihuang Pill Combined with TG regimen for advanced breast cancer patients and the influence on quality of life," *Journal of Traditional Chinese Medicine*, vol. 36, no. 1, pp. 232–234, 2018.

[53] Y.-H. Yue, Y. Zeng, and H.-F. Zhen, "Effect of TAC and Xihuang Pill on Levels of P53, Human Epidermal Growth Factor Receptor 2 and TopoisomeraseII in Patients Breast Cancer at StageIII," *Progress in Modern Biomedicine*, vol. 17, no. 8, pp. 1505–1508, 2017.

[54] J. Zhang, Y. Zhang, H.-Y. Meng et al., "Clinical study of Xihuang Capsules as an adjuvant therapy for breast-cancer patients undergoing chemotherapy," *Global Traditional Chinese Medicine*, vol. 8, no. 1, pp. 9–12, 2015.

[55] X. Zhou, P.-L. Liao, W.-Y. Wu et al., "Effect of Xihuang Capsule combined with GP regimen on Serum Levels of TNF-α, VEGF, MMP-2 and MMP-9 of patients with advanced breast cancer," *Progress in Modern Biomedicine*, vol. 17, no. 23, pp. 4525–4528, 2017.

[56] M. Nawa-Nishigaki, R. Kobayashi, A. Suzuki et al., "Control of nausea and vomiting in patients receiving anthracycline/cyclophosphamide chemotherapy for breast cancer," *Anticancer Reseach*, vol. 38, no. 2, pp. 877–884, 2018.

[57] A. Rasic, A. Sofic, S. Beslija et al., "Effects of adding taxane to anthracycline-based neoadjuvant chemotherapy in locally advanced breast cancer," *Med Glas (Zenica)*, vol. 16, no. 1, pp. 1–6, 2019.

[58] E. Tahover, A. Segal, R. Isacson et al., "Dexrazoxane added to doxorubicin-based adjuvant chemotherapy of breast cancer: A retrospective cohort study with a comparative analysis of toxicity and survival," *Anti-Cancer Drugs*, vol. 28, no. 7, pp. 787–794, 2017.

[59] S. Zhang, L. Shi, D. Mao et al., "Use of Jianpi Jiedu herbs in patients with advanced colorectal cancer: a systematic review and meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2018, Article ID 6180810, 13 pages, 2018.

[60] X. Sun, X. Zhang, J.-Y. Nian et al., "Chinese herbal medicine as adjunctive therapy to chemotherapy for breast cancer: a systematic review and meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2016, Article ID 3281968, 19 pages, 2016.

[61] L. Zhu, L. Li, Y. Li, J. Wang, and Q. Wang, "Chinese herbal medicine as an adjunctive therapy for breast cancer: a systematic review and meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2016, Article ID 9469276, 17 pages, 2016.

[62] Y. Li, X. Zhu, A. Bensusan et al., "Herbal medicine for hot flushes induced by endocrine therapy in women with breast cancer: a systematic review and meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2016, Article ID 1327251, II pages, 2016.

[63] W. Wang, L. Xu, and C. Shen, "Effects of traditional chinese medicine in treatment of breast cancer patients after mastectomy: a meta-analysis," *Cell Biochemistry and Biophysics*, vol. 71, no. 3, pp. 1299–1306, 2015.

[64] S. Wang, S. Long, and W. Wu, "Application of traditional chinese medicines as personalized therapy in human cancers," *American Journal of Chinese Medicine*, vol. 46, no. 05, pp. 953–970, 2018.