Efficacy and safety of compound Kushen injection combined with chemotherapy on postoperative patients with breast cancer

A meta-analysis of randomized controlled trials

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Abstract

Background: This meta-analysis aimed to assess efficacy and safety of combination of Kushen and chemotherapy or chemotherapy alone among postoperative patients with breast cancer receiving.

Methods: A systematic literature search was conducted for relevant randomized controlled trials from 2000 to July 2017. Primary outcomes were clinical response rate (CRR) and performance status improvement by Karnofsky performance scale score (KPSS); secondary outcomes were adverse drug reactions (ADRs) rate and tumor marker decrease rate. Quality assessment and data analysis were performed with Review Manager 5.3.

Results: A total of 16 studies with 1315 participants were included in the analysis. Compared with chemotherapy alone, compound Kushen injection (CKI or K) combined with chemotherapy did not significant increase CRR. However, performance status improvement rate was significantly higher among patients given Kushen injection combined with chemotherapy (relative risk 1.25, 95% confidence interval 1.09–1.42, P = .001). In the analysis of ADRs, combination of Kushen and chemotherapy was indicated to significantly reduce the rate liver dysfunction, kidney dysfunction, nausea and vomiting, diarrhea, hair loss, platelet decrease, and oral mucositis.

Conclusion: Using CKI on the basis of chemotherapy might improve performance status and reduce ADRs among postoperative patients with breast cancer.

Abbreviations: ADRs = adverse drug reactions, CI = confidential interval, CKI = compound Kushen injection, CRR = clinical response rate, IARC = International Agency for Research on Cancer, KPSS = Karnofsky performance scale score, RCTs = randomized controlled trials, RR = relative risk, SD = stable disease, TCM = traditional Chinese medicine.

Keywords: breast cancer, chemotherapy, compound Kushen injection, meta-analysis

1. Introduction

Breast cancer is the most common malignancy among the women worldwide. According to data released by International Agency for Research on Cancer (IARC), in the year of 2008, the number of new cases of female breast cancer has been up to 1,380,000, accounting for 22.9% that of overall cases of female malignant tumor; 460,000 women died at breast cancer, accounting for 1.37% of overall death for malignant tumor among women, and 1.7% of overall death among women. In China, the number of new cases of female breast cancer annually is about 169,000. Breast cancer is the 2nd most common malignant tumor among the Chinese women. It causes 45,000 deaths annually and is ranked the 6th as the most common causes of death among various malignant tumors. In comparison with other countries in the world, incidence and mortality of breast cancer among Chinese women is low. According to estimation of IARC, standardized incidence of breast cancer in Chinese women in 2008 was 21.6/100,000, ranked 99th among 184 countries with statistics globally; the standardized mortality is 5.7/100,000, ranked 145th. Both rates were significantly lower than the world average. However, due to the large population base of China, the annual new cases of breast cancer in China, which was 169,000 cases, accounting for 12.25% that of overall new cases, ranked 2nd in the world. Furthermore, incidence and mortality of breast cancer in China are rising rapidly, that the standardized incidence grew 4.0 to 7.3 times higher, from the year of 1988 to 2007. The standardized mortality had increased from 3.74/100,000 to 5.09/100,000 during the period from 1970 to 2004 or 2005. Therefore, breast cancer has been a serious burden for societies of China and the whole world. Seeking for effective and safe treatment strategies for breast cancer is an urgent task for medical researchers.
Integrated traditional Chinese and western medicine therapy have been the distinctive methods of Chinese people in malignant tumors treatment. Traditional Chinese medicine (TCM) in combination with chemotherapy can enhance the efficacy and reduce chemotherapy-induced toxicity in treatment of various kinds of carcinoma. The common TCMs widely applied for breast cancer treatment include compound Kushen injection (CKI). The CKI is extracted from 2 medical herbs, Radix Sophorae Flavescentis and Rhizoma Smilacis Glabrae. It is a detailed-recorded in Shen Nong Ben Cao Jing, a famous ancient Chinese medicine book, indicated for cancerous pain and blooding. It has a long history of use for the treatment of solid tumors, inflammation, and other disease. In modern clinical practice, it has also been widely used as adjuvant therapy to treat breast cancer and other various carcinoma such as nonsmall-cell lung cancer, primary liver cancer, digestion cancer, etc. and indicated various pharmacologic actions including pain relief, ensuring hemostasis, anti-inflammatory activity, and anti-fibrosis.

A large number of clinical trials evaluating the clinical benefit of combination of Kushen and chemotherapy or radiotherapy among patients with breast cancer or other tumors had been carried out in China. However, for many reasons, most of those randomized controlled trials (RCTs) have not been registered with relatively low quality and the results were generally published in Chinese journals. This situation was not good for application and further study of Kushen injection in anti-tumor treatment. In recent years, accompanying more and more attention paid to Kushen adjuvant effect on cancer patients, a few registered RCTs with high quality have been carried out in recent years. In addition, a few meta-analysis upon efficacy and safety of Kushen injection as adjuvant therapy in cancer patients have been published in international journals. These provided more reliable and systematic evidence for clinical benefit of Kushen on tumor treatment. However, there is no meta-analysis upon use of CKI for breast cancer published in international journals; therefore, we conducted systematic analysis on relative studies, aiming to provide guidance for clinical application and future research of Kushen combined with chemotherapy in breast cancer treatment.

2. Methods

2.1. Inclusion and exclusion criteria

The studies included in the present meta-analysis must meet the following criteria:

1. Types of studies: RCT.
2. Types of participants: breast cancer patients who had received radical or modified radical mastectomy or breast-conserving surgery in 3 months before receiving intervention drugs. Diagnosis for all patients conforms to “guidelines and standard for diagnosis and treatment of breast cancer of Chinese Anti-cancer Association”; patients who have serious liver and kidney dysfunction, or concurrent infection, or Karnofsky scores <70, or are intolerable to experimental drugs are excluded.
3. Types of interventions: after surgery, patients in the controlled group were given the regular chemotherapy treatment; patients in the experimental group were given the same type of chemotherapy plus CKI.
4. Types of outcome measures: primary outcomes were response rate and performance status improvement rate; secondary outcomes were adverse drug reaction (ADR) rate and tumor marker decreasing rate. Response rate (%) = number of complete response rate patients / total patients number × 100%. Efficacy assessment follows RECIST standard. Complete response: complete disappearance of the tumor in response to treatment. Partial response: The shrinkage of tumor size ≥50%. Stable disease (SD): Tumor sizes do not appear to change. Progressive disease: tumor size increase and the disease is progressing or worsening. Performance status was assessed by the Karnofsky performance score. KPSS increase ≥10 points was considered improvement of performance status. KPSS decrease ≥10 points was considered lower performance status. KPSS increase or decrease <10 points was considered stable performance status. The ADR assessment met the common toxicity criteria of chemotherapy drugs drafted by WHO (1991). Assessed ADRs include liver function impairment, kidney function impairment, leukocyte level decrease, diarrhea, nausea and vomiting, hair loss, platelet decrease, and oral mucositis.

Tumor marker level increasing from normal range to abnormal range, or increasing 25% was considered tumor marker increasing. Tumor marker level decreasing from abnormal range to normal range, or decreasing 25% was considered tumor marker decreasing. Tumor marker level increasing or decreasing <50%, and staying in 1 range without crossing over, was considered stable. Tumor marker decrease rate = number of patients with decreased tumor marker / total patients number.

2.2. Literature search

The following databases were searched for relevant RCTs dated from the year of 2000 to July 2017: PubMed, Cochrane library, Embase, and 4 Chinese medical databases: CNKI, CBM, VIP, and Wan-Fang Database. Retrieval terms include “Matrine Injection,” “Breast Cancer,” “Kushen injection,” “Yan Shu Injection,” and “chemotherapy.” References of important articles retrieved were manually searched.

2.3. Data extraction and quality assessment

Two researchers screened the articles of RCTs respectively and extracted the data with uniform standardized table. They independently examined the title and abstract of the articles to make the preliminary screening to exclude the studies that do not meet criteria. They continued to review the main text. When there existed disagreement, they discussed with a 3rd independent medical expert to resolve it.

The researchers referred to the Cochrane handbook for systematic reviews of interventions, and made bias risk assessment for the included RCTs with Cochrane risk of bias tool. The following measurements were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting. Each measurement was categorized into 3 grades, low bias risk, unclear bias risk, and high bias risk.

2.4. Statistical analysis

Relative risk (RR) for response rate, performance status improvement rate, different types of ADRs, and tumor markers decreasing rate were calculated and compared between the 2
that the random-effects model is a better choice than the statistical estimates of effect, because some researchers suggested that the random-effects model is a better choice than the fixed-effect model when making medical decisions. All confidence intervals (CI) had 2-sided probability coverage of 95%. Publication bias estimation was conducted using the funnel plot. All calculation was conducted using the Review Manager 5.3 software downloaded from the website of Cochrane community (http://community.cochrane.org/tools/review-production-tools/revman-5/revman-5-download).

3. Results

3.1. Literature search and characteristics of included RCTs

A total of 136 articles were identified in retrieval. Reviewers excluded 104 articles in preliminary screening. The remaining 32 articles were reviewed by main text. Afterward, 16 articles were excluded, for the following reasons: in 5 studies, intervention after surgery include other intervention, such as radiotherapy and transarterial chemoembolization; in 4 studies, the interval between surgery and experimental drug intervention was unclear; 2 studies have not included the measurements we analyze; the measurements of 5 studies were not suitable for calculation of overall effect. Finally, 16 studies in total were included in the analysis (Fig. 1). The total number of patients included was 1315, in which experimental group included 660 patients and control group included 655 patients.

All included RCTs were carried out in China between the year 2009 and 2017, performed in single center and published in Chinese journals. Details of the individual studies are as described in Table 1. The chemotherapy varied among the studies, but all were regular regimen. The doses of administered Kushen injection ranged from 12 to 30 mL. Six studies had reported clinical response rate (CRR, short term). Eight studies reported performance status improvement by KPSS in which 4 studies adopted measurement of performance status improvement rate. Three studies compared the tumor marker CEA and CA15-3 decrease rate between the 2 intervention groups. All studies were RCTs and it was reported that there was no significant difference between 2 intervention groups in respect to the age, diagnosis, stage, performance status, etc, in all studies. However, the randomization generation methods were not well described. Blindness had not been adopted in all studies. Most of the studies did not include follow-up period. Only two studies had mentioned follow-up. One study reported 3 death due to primary breast cancer during follow-up and 1 study reported 1 drop-out due to drug allergy. Based on Cochrane risk of bias tool, all the included studies were rated as studies with high bias risk (Table 2).

4. Outcomes

4.1. The clinical response

In this analysis, we had pooled the data of 6 studies and made heterogeneity test. In the test of statistical heterogeneity, the 4 studies compared average KPSS cannot be included as well. In heterogeneity test, $P = .02$ (>.01) indicated no significant difference between the included studies. The result of pooled RR calculation indicated that there was no significant difference in respect to CRR between the 2 intervention groups (RR 1.07, 95% CI 0.78–1.47, $P = .66$) (Fig. 2).

4.2. Performance status improvement

Four studies reported performance status improvement rate had been included in the analysis. Due to statistical calculation limitation, the 4 studies compared average KPSS cannot be included as well. In heterogeneity test, $P = .31$, $I^2 = 17%$, which indicated small heterogeneity between the studies. Random-effects model was still adopted due to the reasons mentioned in former part. The pooled RR calculation indicated that the Kushen injection combined with chemotherapy can significantly increase performance status improvement rate compared with chemotherapy alone (RR 1.25, 95% CI 1.09–1.42, $P < .0001$) (Fig. 3).

4.3. Adverse reactions

We calculated pooled RR for liver dysfunction, kidney dysfunction, leukocyte decrease, nausea and vomiting, diarrhea, hair loss, platelet decrease, and oral mucositis. The results are summarized in Table 3. Except for the analysis of leukocyte decreased ($P = .008$, $I^2 = 68%$), the rest of the analysis all demonstrated small heterogeneity. $P$-values obtained in these analyses all demonstrated statistical significance between the 2 intervention groups. These results suggested Kushen injection combined with chemotherapy might significantly decrease the ADRs of liver dysfunction, kidney dysfunction, nausea and vomiting, diarrhea, hair loss, platelet decrease, and oral mucositis.

4.4. Tumor marker decrease

The forest plot information for meta-analysis of tumor marker decrease is summarized in Table 4. The pooled estimates demonstrated that there was no significant difference in 2 tumor marker decrease rates between the 2 interventions (CEA: RR 1.45, 95% CI 0.99–2.12, $P = .06$; CA15-3: RR 1.68, 95% CI 1.00–2.83, $P = .08$). However, significant heterogeneity exists between included studies (CEA: $P = .01$, $I^2 = 76%$; CA15-3: $P = .99$, $I^2 = 0%$).
A funnel plot was adopted to analyze the publication bias. The 6 studies included only four studies, therefore its funnel plot had not been performed.

5. Discussion
According to analysis result, Kushen injection combined with chemotherapy is not superior to chemotherapy alone among postoperative patients with breast cancer in respect to response rate. The response rate analysis had included 6 studies. In the forest plot, the 95% CI horizontal line of risk ratio of only 1 study dropped to be living with the invalid upright string right side completely, which indicated this study support the superiority of combination of Kushen injection and chemotherapy over chemotherapy alone in respect to response rate. However, the rest 5 studies and the result of overall effect demonstrated that Kushen injection combined with chemotherapy did not improve response rate significantly compared with chemotherapy alone.

In the analysis of performance status improvement, Kushen injection combined with chemotherapy seems to be superior to chemotherapy alone. Among the 4 studies included, 95% CI
The horizontal lines of risk ratio of 3 studies are completely living on the right side of the invalid upright string, so does that of the overall effect, which indicated the superiority of combination therapy. This analysis included only 4 studies, which had reported performance status improvement rate. Other 4 studies had also reported effect of experimental drug on performance status, but the measurements are average KPSS before and after treatment, which cannot be included for analysis for overall effect; otherwise more studies could be included in the analysis and analysis conclusion could be more convincing and reliable.

As to the analysis of tumor marker decrease rate, it was indicated Kushen combined with chemotherapy did not significantly change the tumor marker decrease rate. According to the analysis result of ADRs, Kushen injection combined with chemotherapy had significantly decreased the rate of liver dysfunction, kidney dysfunction, nausea and vomiting, diarrhea, hair loss, platelet decrease, and oral mucositis, which suggested that Kushen injection might ease the toxic reaction induced by chemotherapy.

It was widely accepted that in solid tumor treatment, therapy for 1 target is not adequate to suppress the progression of tumor. Clinical studies had shown that multi-target suppression is superior on anti-tumor effect to that of single-target therapy. Multi-target therapy might decrease toxicity and prevent drug resistance induced by single target therapy. Multi-target suppression has been the future direction of tumor treatment.132

Traditional herbal medicine is usually from natural origin, containing multiple components. These features make them natural and good candidate for cancer treatment. In clinical practice, TCM combined with chemotherapy or radiotherapy has shown to protect patients from impairment induced by chemotherapy or radiotherapy, decreased the ADRs, and even improve anti-tumor efficacy.133 Inclusion of TCM in research upon anti-tumor would be promising and beneficial.

Kushen had been applied in tumor treatment for a long time in China. In Chinese traditional medicine, it is recorded that Kushen had the effects of heat clearing and damp inhibiting, blood cooling and toxin relieving, stagnation eliminating, and pain relieving.

| ADRs                  | Number of studies | Number of patients | Heterogeneity (P/I) | RR (95% CI)       | P     |
|-----------------------|-------------------|--------------------|---------------------|-------------------|-------|
| Liver dysfunction     | 8                 | 1371               | 0.03/54%            | (RR 0.42, 95% CI 0.27 to 0.66) | .0001 |
| Kidney dysfunction    | 4                 | 355                | 0.94/0%             | (RR 0.53, 95% CI 0.31 to 0.90) | .02   |
| Leukocyte decrease    | 6                 | 1050               | 0.008/68%           | (RR 0.75, 95% CI 0.62 to 0.92) | .005  |
| Nausea and vomiting   | 9                 | 739                | 0.96/0%             | (RR 0.62, 95% CI 0.52 to 0.72) | <.00001 |
| Diarrhea              | 3                 | 234                | 0.70/0%             | (RR 0.49, 95% CI 0.31 to 0.77) | .002  |
| Hair loss             | 3                 | 202                | 0.74/0%             | (RR 0.52, 95% CI 0.38 to 0.72) | <.0001 |
| Platelet decrease     | 3                 | 240                | 0.86/0%             | (RR 0.44, 95% CI 0.29 to 0.67) | <.0003 |
| Oral mucositis        | 4                 | 399                | 0.89/0%             | (RR 0.19, 95% CI 0.07 to 0.47) | .0004 |

ADR = adverse drug reactions, CI = confidential interval, RR = relative risk.
releasing,[134] Modern scientific studies had explored the mechanism of anti-tumor activity of Kushen. In vitro, CKI suppressed tumor cell growth by inducing apoptosis[135] and inhibits the migration, invasion and adhesion capacity by downregulating the expression of CD44v6 protein.[136] As one of the major alkaloids of CKI, Kushen has been well documented to have anti-tumor effects in different cancer cells, including breast cancer cell lines (MCF-7), gastric cancer cells (SGC-7901 and MKN45), gallbladder carcinoma cells (GBCS), osteosarcoma tumor cells (UMR-108), and liver cancer cells (HepG2).[137,138] Specifically, Kushen effect on breast cancer has also been explored. In mice, Kushen injection can suppress human breast cancer stem-like cells by downregulating the canonical Wnt/β-catenin pathway.[139] In vitro, Kushen injection inhibited proliferation of MCF-7 human breast cancer cell line by breaking the cell cycle, and induced apoptosis in a dose-dependent fashion.[140] Moreover, its effect of analgesic, haemostatic, anti-stress, anti-inflammation, and immune function improvement had been proven in vitro.[8] In the clinical trials for Kushen combined with chemotherapy upon breast cancer, almost all evidenced Kushen as adjuvant therapy can improve life quality, decrease ADRs and improve immune function (not analyzed in the present meta-analysis). In the present meta-analysis, overall effect demonstrated that Kushen injection can improve life quality and decrease ADRs. These positive results encouraged us to make further exploration and investigation toward Kushen injection in tumor treatment, such that it can be more widely recognized and applied.

This meta-analysis is the 1st one of CKI combined with chemotherapy on breast cancer patients published in international journals. There are 2 meta-analysis in the same topics were published in Chinese journals[141,142] in the year of 2012. The present meta-analysis had updated the trials and reviewers had strictly followed the inclusion and exclusion criteria.

| Tumor marker | Number of studies | Number of patients | Heterogeneity (I²) | RR (95% CI) | P |
|--------------|------------------|--------------------|-------------------|-------------|---|
| CA15-3       | 3                | 980                | .01/7%            | RR 1.68, 95% CI 0.99–2.12 | .06 |
| CEA          | 3                | 980                | .0006/87%         | RR 1.68, 95% CI 1.00–2.83 | .05 |

CA=carcino antigen, CEA=carcinoembryonic antigen, CI= confidential interval, RR=relative risk.

The limitations of the study are as follows: Up to date, none of the trials investigating Kushen combined chemotherapy on breast cancer patients had registered. All of the trials have not been rigorously designed and are methodologically inadequate. Randomization and allocation was only mentioned, but details have not been described. Blinding was carried out in none of the trials. In the quality assessment, the trials included are all rated as studies with high bias risk and low quality. Those disadvantages will decrease the reliability of the collected data and even the conclusion. However, the consistency of the published results is fairly good, so the conclusion of the present meta-analysis shall be still reliable. All the studies were carried out in China, and published in Chinese journals, which might lead to limited generalization of analysis conclusion, and on the contrary, publication bias. However, according to funnel plot, the publication bias in the analysis of clinical response was not obvious. There is lack of uniform standard for measurements. Some measurements in trials are not suitable for meta-analysis, therefore a few trials or some certain measurements in trials cannot be included in the analysis. For example, many studies had reported the positive effect of Kushen combined with chemotherapy on immune function, which was measured with average immunoglobulin level or T-cell subset level. Due to limitation of measurements physicians will take into account.

In conclusion, the present meta-analysis supported that CKI combined with chemotherapy might improve performance status and decrease rate of ADRs compared with chemotherapy alone, but might not improve CRR. However, we still need more RCTs with good designing, rigorous execution, multi-centers, large sample, and long-enough follow-up period to further validate the clinical effect of Kushen as adjuvant therapy among patients with breast cancer.

Author contributions

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References

[1] Yuping W. Prevalence of breast cancer in China. Med Hyg 2016;2016:00128.
[2] Zhang M, Huang ZZ, Zheng Y. Estimates and prediction on incidence, mortality and prevalence of breast cancer in China, 2008 [in Chinese]. Chin J Epidemiol 2012;33:1049–51.

[3] Dong J, Su SY, Wang MY, et al. Shenqi fuzheng, an injection concocted from Chinese medicinal herbs, combined with platinum-based chemotherapy for advanced non-small cell lung cancer: a systematic review. J Exp Clin Cancer Res 2010;29:137.

[4] Liu X, Yang Q, Xi Y, et al. Kanglai injection combined with chemotherapy versus chemotherapy alone in the treatment of advanced non-small cell lung carcinoma. J Cancer Res Ther 2014;1:46–51.

[5] Ma X, Li RS, Wang J. The therapeutic efficacy and safety of compound Kushen injection combined with transarterial chemobrolization in unresectable hepatocellular carcinoma: an update systematic review and meta-analysis. Front Pharmacol 2016;7:70.

[6] Sun FG, Sun XY. Sophora flavescens. In: Shen Nong Ben Cao Jing. Scientific and Technical Documents Publishing House 1999;59.

[7] Zhou SK, Zhang RL, Xu YF, et al. Antioxidant and immunity activities of Fufang Kushen injection liquid. Molecules 2012;17:6481–90.

[8] Ma Yue, Zhang Qwei, Wang Zhimin, et al. Advance in study on compound Kushen injection. Chin J Exp Trad Med Form 2012;18:342–4.

[9] Tu H, Lei B, Meng S, et al. Efficacy of compound Kushen injection in combination with induction chemotherapy for treating adult patients newly diagnosed with acute leukemia. Evid Based Complement Alternat Med 2016;2016:3121402.

[10] Wang XQ, Liu J, Lin HS, et al. A multicenter randomized controlled open-label trial to assay the efficacy of compound kusheninjection in combination with single-agent chemotherapy in treatment of elderly patients with advanced non-small cell lung cancer: study protocol for a randomized controlled trial. Trials 2016;17:124.

[11] Zhang D, Wu J, Liu S. Network meta-analysis of Chinese herbal injections combined with the chemotherapy for the treatment of pancreatic cancer. Medicine (Baltimore) 2017;96:e7005.

[12] Yanju B, Yang L, Hua B, et al. A systematic review and meta-analysis on the use of traditional Chinese medicine compoundkushen injection for bone cancer pain. Support Care Cancer 2014;22:825–36.

[13] DerSimonian R, Laird N. Meta-analysis: in decision models. Med Decis Making 2005;25:646–54.

[14] A Da Lai Ti, Ai Xiaoye, Zhang Jiazhennan, et al. Toxic and side effects of compound kusheninjection in post operative patients with breast cancer. J Cancer Res Clinic 2011;23:629.

[15] Dai ZJ, Gao J, Wu WY, et al. Effect ofmatrine injections on invasion and metastasis of gastric carcinoma SGC-7901 cells in vitro [in Chinese]. Zhong. Yao Cai 2007;30:815–9.

[16] Xue W, You RL, Qin WJ, et al. Antitumomr. activities of Kushen in breast cancer adjuvant chemotherapy. Acta Pharm Sinica 2009;44:219–25.

[17] Zhao Xin, Bui Wei, Fang Tao. Progress of anti-tumore mechanism of Chinese herbal medicine. Guangdong Med J 2014;35:466–9.

[18] Li CM. Clinical application of compound matrine injection. J Dis Monit Control 2010;14:330.

[19] Dai ZJ, Gao J, Wu WY, et al. Effect ofmatrine injections on invasion and metastasis of gastric carcinoma SGC-7901 cells in vitro [in Chinese]. Zhong. Yao Cai 2007;30:815–9.

[20] Shao SG. Small interfering RNA mediated multi-target therapy of cancer. Acta Pharm Sinica 2009;44:219–25.

[21] Sun M, Cao H, Sun L, et al. Antitumor and metastasis of gastric carcinoma cells induced by matrine injection [in Chinese]. Zhonghua Wei Chang Wai Ke Za Zhi 2008;13:261–3.

[22] Wang S, Cui J, Harata-Lee Y, et al. Identification of candidate anti-cancer molecular mechanisms of compound Kushen injection using functional genomics. Oncotarget 2016;7:6603–19.

[23] Liu Lei, Wu Wenjue, Zhou Zhonghao. Meta-analysis of short-term efficacy and survival quality of compound kusheninjection combined with chemotherapy among breast cancer patients. Zhejiang J Trad Chin Med 2012;47:297–9.

[24] Cheng Kai, Jiang Gang. Meta-analysis of compound sophora flavescens injection as adjunctive treatment for breast cancer. XXXX 2012;23:1128–30.