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Evidence-Based Integrative Medicine

Shenqi Fuzheng Injection Combined with Chemotherapy for Acute Leukemia: A Meta-Analysis*

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ABSTRACT **Objective**: To evaluate to the efficacy and safety of Shenqi Fuzheng Injection (SFI) combined with chemotherapy in the treatment of acute leukemia (AL) by meta-analysis. **Methods**: PubMed, Cochrane library, Embase, SinoMed, China National Knowledge Infrastructure (CNKI), VIP Journal Integration Platform, Wanfang Database were searched from establishment to November 1, 2018. The randomized controlled trials (RCTs) of SFI combined with chemotherapy in the treatment of AL were included. The Cochrane risk assessment form (RevMan 5.1) was used to evaluate the quality of included studies. **Results**: A total of 14 RCTs and 1,088 patients was included. The quality evaluation was mostly low risk or unclear. Meta-analysis showed that compared with chemotherapy alone, SFI combined with chemotherapy can improve the total clinical effective rate in patients with AL (*RR*=1.15, 95% CI: 1.056–1.177; *P*=0.0001), and relieve adverse reactions caused by chemotherapy drugs, including infection (*RR*=0.561, 95% CI: 0.397–0.792; *P*=0.001), nausea and vomiting (*RR*=0.662, 95% CI: 0.524–0.835; *P*=0.001), bleeding (*RR*=0.548, 95% CI: 0.39–0.768; *P*=0.0001), cardiotoxicity (*RR*=0.230, 95% CI: 0.080–0.660; *P*=0.006) and hyperhidrosis (*RR*=0.348, 95% CI: 0.208–0.581; *P*=0.0001). The incidence rates of adverse reactions in SFI combined with chemotherapy group were significantly lower than that of the chemotherapy alone group (*P*<0.01). **Conclusions**: Shenqi Fuzheng Injection combined with chemotherapy has good efficacy and safety for AL, and it can alleviate the adverse reactions caused by chemotherapy. However, subject to the limitations of the methodological quality of the literature, the conclusions of this study need to be further verified by large-scale and multi-center RCTs.

KEYWORDS Shenqi Fuzheng Injection, chemotherapy, meta-analysis, acute leukemia, chemotherapy, Chinese medicine

Acute leukemia (AL) is a disease caused by malignant cloning of hematopoietic stem cells. During the onset of AL, immature cells and blast cells proliferate abnormally and accumulate in the bone marrow, resulting in the suppression on the normal hematopoietic function, and further infiltrates extramedullary organs, such as lymph nodes, spleen and liver,[1] leading to symptoms such as infiltration, infection, bleeding and anemia in clinic.[2] At present, chemotherapy is mainly used for the treatment of AL. However, most chemotherapeutic drugs have cytotoxicity. While suppressing and killing leukemia cells, they also kill normal cells and inhibit the body's immunity and bone marrow hematopoietic function.[3] As an adjuvant treatment of AL, complementary therapies have become increasingly common.[4] Chinese medicine (CM), as one of most popular of complementary therapies, has the characteristics of multiple targets and low toxicity, and is often used in clinical treatment of tumors along with chemotherapy drugs to reduce the side effects of chemotherapy.

The main ingredients of Shenqi Fuzheng Injection (参芪扶正注射液, SFI) consists of *Codonopsis Radix* and *Hedysarum Multijugum* Maxim. *Codonopsis Radix* can enhance the body's immunity, increase the content of white blood cells, red blood cells and hemoglobin, inhibit the production of inflammatory factors and regulate gastrointestinal motility.[5,6] *Hedysarum Multijugum* Maxim has the function of enhancing immune function and exerts complete immune recovery effect on lymphocyte function in

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cancer patients. The main medicinal ingredients of SFI are basically clear, and have been used clinically for many years. They are often used in the adjuvant treatment of qi deficiency syndrome of lung cancer,[7] breast cancer,[8] and are also commonly used in the treatment of cardiovascular, cerebrovascular[9] and hematological diseases.[10] It has been confirmed that the combined application of SFI and chemotherapy has obvious synergistic, sensitizing, and attenuating effects, and is mild in adverse reactions.[11] *In vitro* study has reported that SFI can act on dendritic cells (DCs) that completely relieve the syndrome of leukemia patients after chemotherapy and enhance the function of DCs by increasing its secretion of interleukin (IL)-12 and reducing the expression of indoleamine 2,3-dioxygenase (IDO). It also enhances the immune function of patients and has the auxiliary effect of anti-tumor.[12] Many recent researchs have shown that it can effectively reduce the side effects of chemotherapy, however, there is no systematic and comprehensive evidence-based research in the treatment of AL.[13,14] This study comprehensively and systematically collected RCTs on SFI combined with chemotherapy in the treatment of AL. Meta-analysis was used to comprehensively evaluate the efficacy and safety of SFI in the treatment of AL, so as to provide a reference for the clinical treatment.

METHODS

Inclusion Criteria

Research Type

All randomized contraled trials (RCTs) regarding SFI combined with chemotherapeutic drugs in treatment of AL were included, regardless of the use of blind method and published in all languages.

Research Objects

All patients were diagnosed with AL and met the criteria for Diagnosis and Efficacy of Hematological Diseases.[13] All patients were diagnosed by peripheral blood and bone marrow, morphology, cell histochemical staining, immunohistochemistry and other examinations. Gender, age, race, region and disease severity are not limited.

Intervention Measures

All the patients in the control and experimental groups were treated with chemotherapy drugs, and patients in the experimental group was treated with SFI on the basis of chemotherapy drugs. There was no limit on the dosage and course of treatment. Corresponding treatment should be given to patients with infection and other conditions. The patients in the control group simply used chemotherapy drugs, which include HD (cytarabine plus daunorubicin/adriamycin), VDLP (vincristine plus daunorubicin plus aspartase plus prednisone), FLAG (fradabin plus high-dose cytarabine plus granulocyte colony stimulating factor), DA (daunorubicin plus cytarabine), VDCP (vincristine plus daunorubicin plus cyclophosphamide plus prednisone), HOAP (harringtonine plus vincristine plus cytarabine plus prednisone), MA (mitoxantrone plus cytarabine) and HA (cephalotaxine plus cytarabine plus thioguanine) chemotherapy regimens.

Outcome Measurement

The total clinical effective rate was reported as the primary outcome. According to the "Acute leukemia diagnosis and treatment routine" formulated by the Chinese Society of Integrated Traditional and Western Medicine Hematology Committee in 2007:[14] complete remission (CR) is defined as: (1) symptoms and signs caused by leukemia cell infiltration disappear and life become normal or almost normal; (2) Hb ⩾100 g/L (male adult), or ⩾90 g/L (female and child), N absolute value ⩾11.5×10^9/L, platelet (PLT) ⩾100×10^9/L, no leukemia cells in the peripheral blood leukocytes; (3) bone marrow: myeloblast type Ⅰ plus type Ⅱ or primary mononuclear plus naive monocytes or primitive lymphoid plus naive lymphocytes <5%, erythroid and megakaryocytes are normal, and the M7 type, the original megakaryocyte plus naive megakaryocyte basically disappears. Partial remission refers to: myeloblasts type Ⅰ plus type Ⅱ (proto-mononuclear plus macrophage mononuclear cells or proto-lymphoid plus naive lymphocytes) >5% and ⩽20%, or one of the clinical hemogram fails to reach the CR criteria. Unresolved: bone marrow, blood, and improvement of clinical symptoms fail to reach the above mentioned criteria. Adverse reactions and their improvement were secondary outcome measures.

Exclusion Criteria

The following studies were excluded: (1) non-randomized controlled experimental literature including animal experiment, cell experiment, review and case report; (2) poor routine medication record, that is, drug name, dose and medication course were not clearly

recorded; (3) RCTs with efficacy evaluation criteria were inconsistent with the conventional diagnosis and treatment of AL, incorrect experimental data or irrelevant outcome indicators; (4) study which combined with other drugs; and (5) articles that are repeatedly published.

Data Source and Search Strategy

PubMed, Embase, Cochrane library, China Knowledge Network (CNKI), China Biomedical Literature Database (SinoMed), VIP Journal Integration Platform and Wanfang Database were searched from the inception to November 1, 2018. The subject terms "acute leukemia" and "Shenqi Fuzheng Injection" were adopted.

Data Extraction

Two researchers independently reviewed literature topics and abstracts, and screened out irrelevant literature and reviews. For RCTs, the full texts were read to determine whether they met the inclusion criteria. If there was disagreement on the information extracted from the included study, it should be determined through discussion or consultation with a third party. The extracted information included: (1) the basic information including the first author and year of publication; (2) basic characteristics of the subjects, including the number of experimental group and control group, gender composition, average age, and specific details of the intervention measures; (3) outcome indicators and measurement data; and (4) study design types and key factors of risk assessment of bias.

Quality Evaluation of RCTs

The quality evaluation was independently conducted by 2 investigators (Meng FX and Yang X) and cross-checked. If there has disagreement, it was resolved by the discussion or the third researcher (Li ML). The risk of bias in the included studies was assessed using the Cochrane evaluation system.

Statistical Analysis

Statistical data were collected using the Stata11.0 software. Relative risk (*RR*) was used for the dichotomy variables, and 95% confidence interval (95% CI) was calculated. The heterogeneity between studies was tested by Cochrane Q, and evaluated by I^2. When $P>0.1$, I^2 takes less than 50%, the fixed effect model was adopted for meta-analysis; Otherwise, the random effect model was adopted on the premise of excluding clinical heterogeneity. If clinical or methodological heterogeneity exists, subgroup analysis was used. Sensitivity analysis was performed to determine the stability of the results. Funnel plots were drawn to analyze whether publication bias existed.

RESULTS

Basic Features of Included Studies

A total of 118 studies were firstly retrieved from 7 databases. A total of 74 literature including 65 duplicate references, 3 reviews, 2 cell experimental studies and 4 other drugs studies were removed. A total of 44 clinical articles were further read for full text. Totally 30 articles (1 non-randomized study, 5 studies with incompatible interventions, 20 studies without relevant outcome indicators, and 4 studies without complete efficacy evaluation) were excluded. Finally, 14 studies[15-28] containing 1,088 cases, with 541 in the control groups and 547 in the experimental groups were included for meta-analysis, respectively. The literature screening flow chart is shown in Figure 1, and the general characteristics of included studies is presented in Appendix 1.

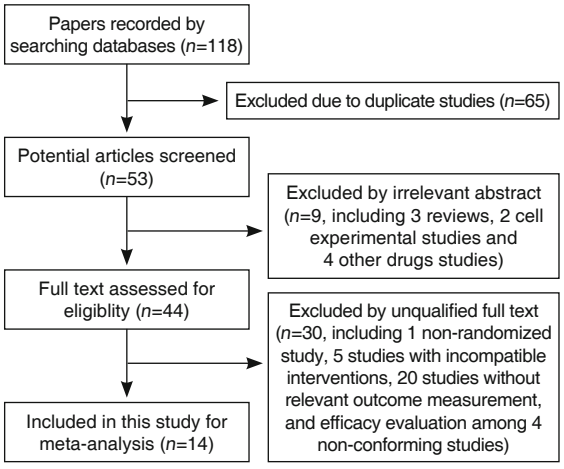

Figure 1. Searching Flow Chart of Meta-analysis on SFI Combined with Chemotherapy for AL

Heterogeneity Evaluation

The result of heterogeneity evaluation indicated that there was no significant heterogeneity between literature that included in this study (I^2=0.00%, P=0.98, Figure 2A).

Sensitivity Analysis

As shown in Figure 2B, there was no qualitative change in the combined effect size, indicating that the results of this study were stable.

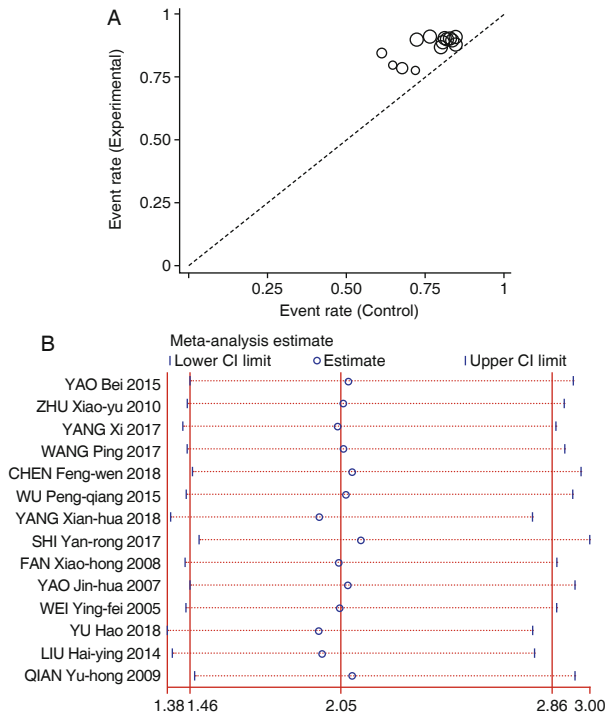

Figure 2. Heterogeneity Evaluation (A) and Sensitivity Analysis (B)

Evaluation of Methodological Quality

Regarding the random allocation method, 1 study[23] used the double-blind method, 3 studies[10,25,28] were grouped according to the random number table, 1 study[20] was randomly grouped according to the sampling method. These studies were rated as "low risk". Additionally, 1 study[16] was randomly grouped according to the order of admission, which was rated as "high risk". The other 8 studies were rated as "unclear" due to lackness of the grouping methods. There was no selective reported outcome among the 14 studies, and all cases were not withdrawn or dropped, and the data was complete. Therefore, the selective report and data integrity were rated as "low risk". Other risks were not available or not reported, rating as "unclear" (Appendix 2).

Meta-Analysis of Included Studies

Clinical Total Effective Rate

A total of 14 studies[15-28] included basically consistent definitions for total effective rate. Meta-analysis results showed that total effective rate of combined use of SFI and chemotherapy was superior to that of chemotherapy alone in patients with AL (*RR*=1.11, 95% CI: 1.06–1.18, *P*=0.0001), as shown in Figure 3.

Adverse Reactions and Improvement

The adverse reactions in this study mainly include infection, nausea and vomiting, bleeding, cardiotoxicity and hyperhidrosis.

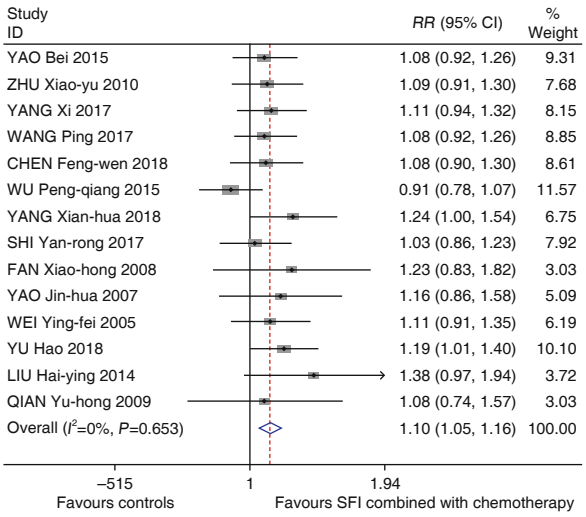

Figure 3. Clinical Total Effective Rate

Infections

Five studies[17,20-23] reported infection. Compared with chemotherapy alone, SFI combined with chemotherapy treatment could improve the infection condition of patients with AL (*RR*=0.561, 95% CI=0.397–0.792, *P*=0.001; Figure 4A).

Nausea and Vomiting

Six studies[17,18,20-22,24] investigated nausea and vomiting. SFI combined with chemotherapy could reduce the incidence of nausea and vomiting compared with chemotherapy alone (*RR*=0.662, 95% CI: 0.524–0.835, *P*=0.001; Figure 4B).

Bleeding

Five studies[17,20-23] compared the bleeding condition. Bleeding of patients in the experimental group was alleviated compared with the control group (*RR*=0.548, 95% CI: 0.39–0.768, *P*=0.0001; Figure 4C).

Cardiotoxicity

Three studies[17-19] reported cardiotoxicity. SFI combined with chemotherapy can alleviate cardiotoxicity in patients compared with the control group (*RR*=0.230, 95% CI: 0.080–0.660, *P*=0.006; Figure 4D).

Sweating

Three studies[17,21,23] compared sweating. Compared with chemotherapy alone, SFI combined with chemotherapy can alleviate the patient's hyperhidrosis (*RR*=0.348, 95% CI: 0.208–0.581, *P*=0.0001; Figure 4E).

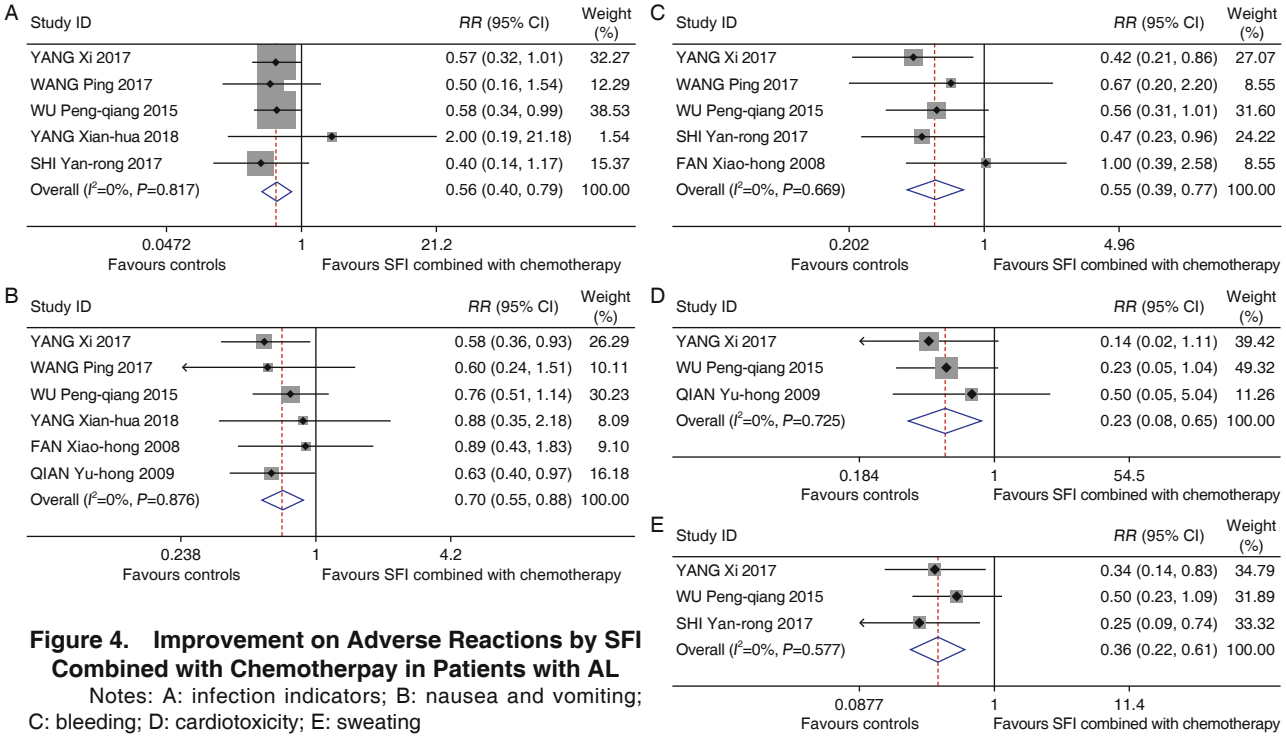

Figure 4. Improvement on Adverse Reactions by SFI Combined with Chemotherpay in Patients with AL

Notes: A: infection indicators; B: nausea and vomiting; C: bleeding; D: cardiotoxicity; E: sweating

Evaluation of Publication Bias

The inverted funnel plot was drawn for the clinical total effective rate indicators, as shown in Appendix 2, indicating the existence of a small amount of publication bias.

DISCUSSION

AL is a kind of hematopoietic system malignant tumor, chemotherapy is still the main treatment for most patients with AL. The main reason of unsatisfied treatment effect is drug resistance and toxicity. With the continuous development of CM, CM combined with chemotherapy has been widely used in clinical practice. There have been many reports on the treatment of AL by SFI combined with different chemotherapy schemes, however, no systematic evidence-based medical studies have been reported so far.

In this study, the efficacy and safety of SFI in the treatment of AL were comprehensively evaluated by meta-analysis. The results showed that compared with the chemotherapy alone, SFI combined with chemotherpay could improve the clinical total effective rate of patients with AL and reduce the incidence of adverse reactions including infection, nausea and vomiting, bleeding, etc. after chemotherapy. However, our study also has some limitations. For example, this study did not define the classification of patients with AL, and the severity of the disease, which may lead to bias. In addition, only 1[23] of the 14 included studies was blinded design, 3 trials[12,25,28] were randomized according to a table of random numbers, 1 trial[20] was randomized according to random sampling, and 1 study[16] was randomized according to the order of admission, the specific random methods of the remaining studies were unknown. This may have a big impact on the final result. It is worth noting that although this study conducted a systematic and comprehensive search of commonly used databases in both Chinese and English, the studies included in this study were all in Chinese, lacking relevant research support from foreign literature, and the representative population was very limited, which may be related to the use of SFI in China.

In summary, based on the current research results, SFI combined with chemotherapeutic drugs in the treatment of AL has a certain effect, and can reduce adverse reactions related to chemotherapeutic drugs. Compared with chemotherapy alone, SFI combined with chemotherapy has a higher overall clinical effectiveness in treating AL. It can significantly alleviate adverse reactions caused by chemotherapy drugs, such as infections, nausea and vomiting, bleeding, cardiotoxicity and hyperhidrosis. This study suggests that the combination of Chinese and Western methods can be formed in the clinical treatment of AL.

Conflict of Interest

The authors have no conflicts of interests.

Author Contributions

Meng FX designed this study and prepared the manuscript; Yang X and Meng FX researched literature and performed the data analysis, Li ML evaluated the quality of the included study.

Electronic Supplementary Material: Supplementary material (Appendixes 1 and 2) are available in the online version of this article at DOI: https://doi.org/10.1007/s11655-020-3264-7.

REFERENCES

1. Xia YZ, Chen Y, Wang Z. Effect of Shenqi Fuzheng Injection combined with thalidomide on the proportion of peripheral blood regulatory T cells in acute myeloid leukemia. Chin J Tradit Chin Med (Chin) 2016;34:1215-1217.
2. Li H, He M, Li LG, et al. Effects of Shenqi Fuzheng Injection combined with decitabine on serum HGF, VEGF and LDH levels in patients with acute myeloid leukemia. Prog Modern Biomed 2018;18:3400-3403.
3. Chen SZ, Qi XM, Qian DY, et al. Clinical observation of Shenqi Fuzheng Injection in preventing cardiotoxicity of anthracyclines. J Pract Clin Med 2017;21:163-164.
4. Chen KH, Yeh MH, Livneh H, et al. Association of traditional Chinese medicine therapy and the risk of dementia in patients with hypertension: a nationwide population-based cohort study. BMC Complement Altern Med 2017;17:178-183.
5. Zhou WD, Xiang L, Lu HQ. Experimental study on the improvement of 5-fluorouracil-induced small intestinal mucositis by *Codonopsis pilosula* polysaccharides. Liaoning J Tradit Chin Med (Chin) 2016;43:1495-1497.
6. Zeng D, Huang ZY, Su DY. Effects of *Codonopsis pilosula* extract on reproductive performance and blood parameters of sows. Feed Res 2016;13:31-34.
7. Wang WJ. Feasibility study of Shenqi Fuzheng Injection combined with chemotherapy for lung cancer treatment. J Mathematical Med 2019;32:102-103.
8. Hu BY, Yang XY, Sun YC. Clinical observation of Shenqi Fuzheng Injection combined with CAF chemotherapy in the treatment of breast cancer. Chin J Tradit Chin Med (Chin) 2018;36:2778-2780.
9. Xiao D, Zhang HZ, Zuo XH. Effect of Shenqi Fuzheng Injection on heart failure after acute myocardial infarction in the elderly. J Integr Tradit West Med Card Cerebr Dis (Chin) 2016;14:106-110.
10. Chai HY. Effect of Shenqi Fuzheng Injection on bone marrow hematopoietic function and immune function in patients with acute lymphocytic leukemia. Bengbu Med Coll (Chin) 2017;42:1356-1362.
11. Jia JW, Liu YQ. Treatment of advanced gastric cancer with Shenqi Fuzheng Injection combined with FOLFOX4 regimen observation of the curative effect of cancer. J Pract Cancer (Chin) 2009;24:275-281.
12. Chen ZC, Wang HX, Swimming S, et, al. Effect of Shenqi Fuzheng Injection on dendritic cells in patients with acute myeloid leukemia *in vitro*. J Clin Intern Med (Chin) 2007;24:455-459.
13. Zhang H, Chen T, Shang L. ShenQi FuZheng Injection as an adjunctive treatment to chemotherapy in breast cancer patients: a meta-analysis. Pharmaceutical Biol 2019;57:612-624.
14. Wu JH, Xie BC, Wang QH, Zhou CH, Xu DH. Systematic review of Shenqi Fuzheng Injection combined with chemotherapy for treatment of breast cancer. Chin J Chin Mater Med (Chin) 2019;44:589-596.
15. Zhang WQ, Zhang JH, Wu ZL, et al. Meta-analysis of Shenqi Fuzheng Injection combined with chemotherapy in treatment of colorectal cancer. Med Plant 2018;9:83-88.
16. Zhang ZN, ed. Blood disease diagnosis and efficacy criteria. 2nd version. Beijing: Science Press;1998:168.
17. Chinese Society of Integrated Traditional and Western Medicine Hematology Committee. Acute leukemia diagnosis and treatment routine. Wuhan: The 8th National Symposium on Integrated Traditional Chinese and Western Medicine Hematology Symposium; 2007:8.
18. Yao B, Zhang YL, Chen WL. Shenqi Fuzheng Injection for hematopoiesis and immunity in patients with acute lymphoblastic leukemia. Modern Biomed Prog (Chin) 2015;15:808-811.
19. Zhu XY, Zhang XZ, Zhong XY. Effects of Shenqi Fuzheng Injection on hematopoietic function and immune function in patients with hematologic malignancies. Chin J Integr Tradit West Med (Chin) 2010;30:205-207.
20. Yang X, Xu ZL. The efficacy of Shenqi Fuzheng Injection combined with FLAG regimen in the treatment of refractory acute lymphoblastic leukemia and its effect on serum IFN-γ and IL-10. Modern J Integr Tradit Chin West Med (Chin) 2017;26:826-829.
21. Qian YH. Effect of Shenmao Fuzheng Injection combined with chemotherapy on telomerase activity of bone marrow cells in patients with acute leukemia [Dissertation]. Guangzhou: Guangzhou University of Traditional Chinese Medicine; 2009.
22. Chen FW, He HM. Effect of Shenqi Fuzheng Injection combined with chemotherapy on cellular immune function in patients with acute lymphocytic leukemia. Jilin Med J (Chin) 2018;39:1255-1257.
23. Wang P. Effect of Shenqi Fuzheng Injection combined with chemotherapy on cellular immune function in patients with acute lymphocytic leukemia. Med J Chin People's Health

(Chin) 2017;29:89-90.
24. Wu PQ, Yuan KF, Jing L. Effect of Shenqi Fuzheng Injection combined with chemotherapy on the efficacy and immune function of patients with acute myeloid leukemia. Chin Tradit Herb Drugs (Chin) 2015;46:401-404.
25. Yang XH, Chen J, Zhao HF. Effect of Shenqi Fuzheng Injection combined with chemotherapy on acute leukemia and its effects on T lymphocyte subsets, serum interferon-γ and interleukin. Eval Anal Drug-Use Hosp Chin (Chin) 2018;18:1200-1202.
26. Shi YR. Clinical effect of Shenqi Fuzheng Injection combined with chemotherapy on acute leukemia and its effect on the immune function of patients. Chin J Pract Med (Chin) 2017;44:114-117.
27. Fan XH. Clinical observation of Shenqi Fuzheng Injection combined with chemotherapy in the treatment of refractory relapse acute leukemia [Dissertation]. Hanzhou: Zhejiang University of Traditional Chinese Medicine; 2008.
28. Yu H, Yong F, Cao F. The efficacy of Shenqi Fuzheng Injection combined with chemotherapy in the treatment of hematological malignancies and its effects on hematopoiesis and immunity. World Chin Med (Chin) 2018;13:2136-2139.
29. Yao JH, Xia XJ. Therapeutic effect of Shenqi Fuzheng Injection combined with chemotherapy in the treatment of 38 cases of acute leukemia. J New Chin Med (Chin) 2007;39:77-78.
30. Wei YF, Wang SY, Ren LL. Effect of Shenqi Fuzheng Injection combined with chemotherapy on acute leukemia and T lymphocyte subsets and serum IFN-γ, IL-10, IL-2 level of influence. Chin J Integr Tradit West Med (Chin) 2005;25:303-306.
31. Liu HY. Fuzheng Peiben method exerts the detoxicating and tonifying effect on patients with acute leukemia undergoing chemotherapy. China Health Indust 2014;24:38-39.
32. Dong BY, Wang C, Tan L. Inhibitory effect of Shenqi Fuzheng Injection combined with docetaxel on lung cancer cells. J Zhejiang Univer (Chin) 2017;18:76-78.
33. Liao Q, Xing R. Progress in pharmacological action and clinical application of Shenqi Fuzheng Injection. Chin Pharm (Chin) 2016;24:3455-3456.
34. Xia YZ, Chen Y, Wang Z. Effect of Shenqi Fuzheng Injection combined with thalidomide on the proportion of peripheral blood regulatory T cells in acute myeloid leukemia. Chin J Tradit Chin Med (Chin) 2016;34:1215-1217.

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