Meta-analysis of the Regulatory Effects of Ginseng and Ginseng-like Drugs on the Quality of Life and Immune Function of Cancer Patients

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Abstract: Objective To evaluate the regulatory effects of ginseng and ginseng-like drugs in improving the quality of life and immune function of cancer patients by meta-analysis. Methods Using "Ginseng", "Ginseng Decoction", "Ginsenosides", "Ginseng Polysaccharides", "Korean Ginseng", "Shanshen", "Shenqi Fuzheng Injection", "Kangai Injection", "Aidi Injection", "Ginseng Yangrong Soup" and "Buzhong Yiqi Soup" as Chinese keywords, "Ginseng", "Ginseng Soup", "Ginsenosides", "Ginseng Polysaccharides" as English keywords, the Chinese knowledge was retrieved. Online database (CNKI, VIP Chinese sci-tech periodicals database (VIP), Wanfang full-text database and other Chinese databases and Cochrane Library, EMBASE, PubMed and other English databases, the deadline for searching literature is May 2022. According to the inclusion criteria, the literatures related to this study were screened out, read the full text to obtain the relevant data, and then used the Review Manager5.3 software for meta-analysis. According to the purpose of this study, ginseng and ginseng-like drug monotherapy or combined with other drug intervention methods were used as the experimental group; other intervention methods including placebo were used as the control group. Observation indicators were: CD+4 T cell ratio, CD+4/CD+8 ratio, TNF-α level, TCM symptom score and KPS score. Results A total of 16 articles were involved in this study, including 1506 patients. All participants are mainly from China and the United States. Six studies reported an increase in the proportion of CD+4 T cells in patients treated with ginseng and ginseng-like drugs (OR=0.14; 95% CI=0.18-0.25; P<0.0001), and five studies reported CD+4/CD+8 The expression of T cells was increased (OR=0.18; 95% CI=0.09-0.35; P<0.0001). Four studies reported a decrease in TNF-α levels after treatment with ginseng-like drugs (OR=0.16; 95%CI=0.08-0.31; P<0.00001). There was no statistically significant difference between ginseng drug treatment and TCM symptom scores, but ginseng drug treatment was associated with a decrease in the KPS score of patients. Conclusion The treatment of ginseng and ginseng-like drugs can improve the quality of life of cancer patients and regulate the immune function of patients, which is worthy of clinical promotion.

Keywords: Ginseng; Ginsenosides; Meta-analysis; CD+4 T Cells; KPS Score.

1. Introduction

In recent years, traditional Chinese medicine has gradually played an important role in the treatment of malignant tumors. Studies have found that ginseng and ginseng-like drugs have been used in a variety of tumor diseases, such as lung cancer, colon cancer, cervical cancer, etc., and have the effect of improving the fatigue of chemotherapy patients.[1]. And studies have shown that ginseng preparations can improve immune function and quality of life in patients with digestive tract malignant tumors. [2].

The main components of ginseng are ginsenosides and ginseng polysaccharides, which are a relatively important class of drugs in traditional Chinese medicine.[3]. Ginseng and ginseng-like drugs can be clinically used as adjuvant drugs for chemotherapy in cancer patients [4]. However, the efficacy evaluation of ginseng, ginsenosides and polysaccharides in various cancer treatments is not stable, and it is difficult to objectively draw a reliable and effective conclusion. The study by Kim et al [5] found that the immune parameters of cholangiocarcinoma treated with ginseng adjuvant chemotherapy did not significantly improve during treatment. However, Chun et al [6] found that the immune status and quality of life were significantly improved in gynecological cancer patients treated with ginseng. The current research has not reached a unified conclusion on the efficacy of ginseng and ginseng-like drugs, so it is of great significance to objectively study and compare the efficacy of ginseng and its components as adjuvant drugs for chemotherapy on cancer.

Meta-analysis is a statistical method that combines the results of different studies with different sample sizes, by identifying a common outcome measure, weighting data from individual trials to arrive at the results of the analysis [7]. Meta-analysis can more objectively estimate the clinical effect of drugs, and by comparing the therapeutic effects of different regimens, it can clearly reveal the advantages and disadvantages of different regimens in treatment [8]. Therefore, this study used Meta-analysis to evaluate the efficacy of ginseng and its components as adjuvant drugs for chemotherapy in cancer patients, and used subgroup analysis to further compare the beneficial effects of ginseng, ginsenosides and polysaccharides on quality of life and immune function regulation.

2. Data and Methods

2.1. Literature Search Strategy

According to the retrieval strategy recommended by the Cochrane Collaboration, use Chinese search terms to search CNKI, Chinese Science and Technology Periodicals Database (VIP), Wanfang Database and other Chinese databases; use English search terms to search for published literature in Pubmed, Web of science before May 2022, Medline and the
Cochrane Library Foreign Language Database. The following Chinese and English terms were randomly combined as the retrieval strategy: "ginseng", "ginseng soup", "ginsenosides", "ginseng polysaccharides", "Korean ginseng", "Shanshen", "Shenqi Fuzheng Injection", "Kangai Injection", "Aidi Injection", "Ginseng Yangrong Decoction" and "Buzhong Yiqi Decoction" are Chinese keywords, "Ginseng", "Ginseng Soup", "Ginsenosides", "Ginseng Polysaccharides" are English keywords words, and manually screened out potentially relevant studies.

2.2. Inclusion and Exclusion Criteria
The criteria are as follows: (1) All cases were pathologically diagnosed as malignant tumors; (2) The ratio of CD+4 T cells, the ratio of CD+4/CD+8, the level of TNF-α, and the level of IL-6 were determined by immunohistochemistry and IHC, or quantitative reverse transcriptase PCR (QRT-PCR) for evaluation; (3) The full text is published in Chinese or English, which can be directly extracted or calculated from the original literature; (4) For duplicate published items or overlapping data, only recent or overlapping data are selected. More comprehensive articles, the exclusion criteria were as follows: (1) duplicate literature studies; (2) lack of sufficient data; (3) case reports, animal studies, reviews. Article eligibility was independently assessed by 2 researchers. Inconsistent literature should be fully discussed or third-party judgment should be introduced.

2.3. Data Extraction
For the included studies, we extracted the following information: first author, year of publication, country, tumor type, sample size, grade, stage. Multivariate data were used if univariate and multivariate HR or OR were reported. In this study, patients treated with ginseng and ginseng-like drugs were set as the experimental group, and other programs were set as the control group.

2.4. Quality Evaluation
The quality of included articles was independently assessed by 2 reviewers using the Newcastle-Ottawa Scale (NOS). Articles with a NOS score ≥ 6 were defined as high-quality articles. Any disagreements were resolved by discussion between the two evaluators.

2.5. Statistical Analysis
Meta-analysis was performed using RevMan5.2 software provided by Cochrane Collaboration. The strength of the association between the expression of the observations and malignancy was assessed with the 95% CI for OR. Pooled OR was tested using a Z-test with a test level of α = 0.1. Subgroup analyses were performed according to possible heterogeneity factors, and the I2 test was used to verify between-study heterogeneity. Heterogeneity among the included studies was assessed using the I2 test. If there was no statistical heterogeneity (p >0.1, I2<50%), a fixed-effects model was used; if there was statistical heterogeneity (p ≤0.1, I2 ≥50%), a random-effects model was used. And through subgroup analysis, looking for the source of heterogeneity. Sensitivity analysis was done by removing each study one by one, looking for sources of heterogeneity, and checking the stability of the results of this study by looking at heterogeneity, effect scales. p < 0.05 indicates statistical significance.

3. Results
3.1. Literature Search
A total of 106 databases were searched, including CNK 13, VIP 21,18 in Wanfang, PubMed 6, and 48 in other databases. They were screened strictly according to the inclusion and exclusion criteria, and 16 articles were finally included in the study. As shown in Figure 1.
Table 1. Basic characteristics of the studies included

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Experimental design</th>
<th>Country</th>
<th>Baseline balance</th>
<th>Cancer type</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao Xu/2022[9]</td>
<td>Case-control</td>
<td>China</td>
<td>Yes</td>
<td>—</td>
<td>68</td>
</tr>
<tr>
<td>Zhang Qinfen/2017[10]</td>
<td>Case-control</td>
<td>China</td>
<td>Yes</td>
<td>Ovarian cancer</td>
<td>52</td>
</tr>
<tr>
<td>Gu Chengzhen/2021[12]</td>
<td>Case-control</td>
<td>China</td>
<td>Yes</td>
<td>Lung, liver, bone marrow cancer</td>
<td>20</td>
</tr>
<tr>
<td>He Bin/2017[14]</td>
<td>Retrospective study</td>
<td>China</td>
<td>Yes</td>
<td>Nasopharyngeal carcinoma</td>
<td>50</td>
</tr>
<tr>
<td>Xie Fangyun[15]</td>
<td>Retrospective study</td>
<td>China</td>
<td>Yes</td>
<td>Nasopharyngeal carcinoma</td>
<td>128</td>
</tr>
<tr>
<td>Hanada/2021[16]</td>
<td>Prospective study</td>
<td>American</td>
<td>Yes</td>
<td>Colon cancer</td>
<td>34</td>
</tr>
<tr>
<td>Kim/2021[17]</td>
<td>Case-control</td>
<td>American</td>
<td>Yes</td>
<td>Cholangiocarcinoma, pancreatic cancer</td>
<td>88</td>
</tr>
<tr>
<td>Chung/2021[18]</td>
<td>RCT</td>
<td>American</td>
<td>Yes</td>
<td>Gynecologic Oncology</td>
<td>55</td>
</tr>
<tr>
<td>Guglielmo/2020[19]</td>
<td>RCT</td>
<td>American</td>
<td>Yes</td>
<td>Head and neck cancer</td>
<td>76</td>
</tr>
<tr>
<td>Yennurajalingam/2017[21]</td>
<td>RCT</td>
<td>American</td>
<td>Yes</td>
<td>—</td>
<td>188</td>
</tr>
<tr>
<td>Kim/2017[22]</td>
<td>RCT</td>
<td>American</td>
<td>Yes</td>
<td>Ovarian cancer</td>
<td>30</td>
</tr>
<tr>
<td>Yang Shenshen/2021[23]</td>
<td>EAST multicenter study</td>
<td>American</td>
<td>Yes</td>
<td>—</td>
<td>145</td>
</tr>
</tbody>
</table>

3.3. Assessment of Methods and Risk of Bias

This study included literature quality for BSHS-A scoring, including various dimensions such as cheap selection, performance bias, and reporting bias. Risk of bias assessment of included studies was performed using assessment tools and methods recommended by the Cochrane Handbook, as shown in picture 2.

![Figure 2. Scale scale of methodological quality evaluation](image)

3.4. Results Index and Heterogeneity Analysis

3.4.1. Changes in the Proportion of CD+4 T Cells After Treatment with Ginseng and Ginseng-like Drugs

Six studies reported increased expression of CD+4 T cells in cancer patients treated with ginseng and ginseng-like drugs. There was heterogeneity in the changes of CD+4 T cells between malignant tumors and controls (Tau2=0.25; Chi²=14.95; P=0.04; I²=53%). Using a random effect model, the results of Meta analysis showed that the proportion of CD+4T cells after treatment with ginseng and ginseng-like drugs was higher than that in the control group (OR=0.14; 95% CI=0.18-0.25; P<0.0001). As shown in Figure 3.
3.4.2. Changes in the Ratio of CD+4/CD+8 T Cells after Ginseng and Ginseng-like Drug Treatment

Five studies reported changes in the expression of CD+4/CD+8 T cells in cancer patients treated with ginseng and ginseng-like drugs. Four of the studies showed increased expression of CD+4/CD+8 T cells and one study showed decreased expression of CD+4/CD+8 T cells. Heterogeneity was significant (I²=82%, P<0.00001). Sensitivity analyses did not reveal sources of heterogeneity. Subgroup analysis excluded 2 breast cancer studies, and there was still significant heterogeneity between the two groups (I²=71%, P<0.0001). Differences in disease type were not the main cause of heterogeneity, so no source of heterogeneity was identified. Choose a random effects model to combine the data. Obtained from statistical software as shown in Figure 4.

![Figure 4. Forest plot of changes in the proportion of CD+4 T cells after treatment with ginseng and ginseng-like drugs](image)

3.4.3. Changes of TNF-α Levels after Treatment with Ginseng and Ginseng-like Drugs

Changes in TNF-α levels after drug treatment were reported in 5 studies, which showed that TNF-α levels were reduced after treatment with ginseng-like drugs. Heterogeneity was significant (I²=67%, P<0.00001). Sensitivity analyses did not reveal sources of heterogeneity and therefore no sources of heterogeneity were identified, and a random-effects model was chosen to combine the data. The deep forest map was obtained through statistical software analysis, as shown in Figure 5.

![Figure 5. Forest plot of changes in TNF-α levels after treatment with ginseng and ginseng-like drugs](image)

3.4.4. Correlation of Ginseng and Ginseng-like Drug Treatment with TCM Symptom Score and KPS Score

Seven studies reported changes in TCM symptom scores and KPS scores after drug treatment. There was heterogeneity in the changes of TCM symptom score and KPS score between the control group and the experimental group (Tau²=0.30; Chi²=2.48; P=0.32; I²=65%). Using a random effect model, the results showed that there was no significant difference between ginseng drug treatment and TCM symptom scores (OR=1.25; 95%CI=0.71-3.32; P=0.72). However, ginseng-like drug treatment was associated with KPS score. There was no heterogeneity in the KPS score of ginseng drug treatment in different tumor patients (Chi²=0.73; df=1; P=0.39; I²=0%). Using a fixed effect model, the results showed that there was a statistically significant difference in
the expression of KPS scores between patients after treatment (OR=2.1; 95%CI=1.37-3.01; P<0.01).

4. Discussion

Regarding cancer, a recent study showed that oral administration of ginseng polysaccharide combined with anti-PD-1-mAb could improve the therapeutic sensitivity of anti-PD-1-mAb in tumor patients [25]. This effect may be related to ginseng polysaccharide-induced remodeling of the gut microbiota in non-responders to chemotherapy, resulting in increased amounts of metabolites such as short-chain fatty acids (SCFAs) and down-regulated IDO activity. Therefore, we speculate that the regulatory effects of ginseng active components in the antitumor immunity and tumor immunosuppressive microenvironment may be partially related to the gut microbiota. However, the interrelationship between the effects of ginseng active components on the tumor immune microenvironment and tumor immunotherapy remains unclear. In this study, the meta-analysis method was used to provide strong evidence on the regulation of immune function and quality of life of ginseng and ginseng-like drugs in tumor patients.

A total of 16 articles were included in this study, and Meta-analysis was used to evaluate the regulatory effects of ginseng and ginseng-like drugs in improving the quality of life and immune function of cancer patients. The results showed that after treatment with ginseng and ginseng-like drugs, the proportion of CD+4T cells and the ratio of CD+4/CD+8 T cells in tumor patients were significantly increased; the use of ginseng and ginseng-like drugs decreased the level of TNF-α and KPS score. However, there was no significant difference in the correlation between ginseng and ginseng-like drug treatment and TCM symptom score.

There is heterogeneity in the therapeutic effects of ginseng and ginseng-like drugs in many literatures, which may be related to various reasons such as tumor type, detection method, disease stage, and degree of disease differentiation. In addition, the included studies did not include studies in languages other than Chinese and English, which may have publication bias. In addition, the sample size and data of the included studies were too small to allow a comprehensive analysis. Not all literature was analyzed for clinical stage and data. Not all literature was analyzed for clinical stage and data.

Ginseng is a versatile natural herb that has been shown to have good anti-inflammatory, antioxidant and anti-aging therapeutic properties [26]. In fact, ginsenosides, which are mainly found in ginseng roots, are considered to be the most important bioactive components in ginseng preparations. So far, more than 180 ginsenosides have been isolated from ginseng [27]. In addition, another active component of ginseng, polysaccharides, also has beneficial activity in improving the quality of life of ginseng and ginseng-like drugs in tumor patients.

During tumor therapy, the immunosuppressive microenvironment limits tumor therapy [29]. Determination of lymphocyte subsets in peripheral blood is a valid assessment method. Immune function CD4+ is an important indicator of the activity of T lymphocytes, and T lymphocytes are immune cell subtypes that reflect the immunity of the body [30]. In this study, both polysaccharides and ginsenosides can significantly enhance the reduction of CD4+ induced by chemotherapy, indicating that both polysaccharides and ginsenosides can improve the body's immunity. Furthermore, a reduction in the CD4+ to CD8+ ratio is often associated with tumor progression. The treatment of ginseng and its preparations significantly benefited CD4+/CD8+ levels in tumor patients during chemotherapy (P<0.0001), indicating that ginsenosides have a good effect on enhancing anti-tumor cell immunity during chemotherapy.

To sum up, this paper studies the therapeutic intervention of ginseng and ginseng-like drugs on tumor patients, and observes the changes of CD+4T cell ratio, CD+4/CD+8 ratio, TNF-α level, TCM symptom score and KPS score. Previous studies have not been stable in evaluating the efficacy of ginseng and its preparations in tumors, and it is difficult to objectively draw a reliable and effective conclusion. Therefore, we used Meta-analysis fever method to evaluate the effect of ginseng and ginseng-like drugs on the quality of life of cancer patients, and regulation of immune function. This study found that the proportion of CD+4 T cells and the expression of CD+4/CD+8 T cells increased in patients treated with ginseng and ginseng-like drugs. The expression level of TNF-α decreased after treatment with ginseng drugs. There was no statistically significant difference between ginseng drug treatment and TCM symptom scores, but ginseng drug treatment was associated with a decrease in the KPS score of patients. The studies included in this paper are still small, which may bias the conclusions of the studies to a certain extent, and more research literature is needed in the future for further evaluation.

References


[8] Hiroko Keichi, Takarada Shinya, Miyao Nariaki et al. Thromboembolic events in left ventricular non-compaction:
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