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Therapeutic and immunomodulatory effects of Bojungikki-tang on cancer: a scoping review

Eunbyul Cho[1†], Se Won Na[2†] and Mi-Kyung Jeong[2*]

Abstract

Background Cancer remains a major global health concern, with conventional treatments often limited by side effects and resistance. Bojungikki-tang (BJIKT), a traditional herbal formula, has shown promise in alleviating cancer-related symptoms and enhancing anti-cancer effects when combined with conventional treatments. As immune checkpoint inhibitors (ICIs) have become the standard for cancer treatment, a combination of BJIKT and ICIs may exhibit immune-mediated anti-cancer effects. This review aims to summarize the recent evidence on BJIKT use in cancer treatment, investigate its immunomodulatory effects, and identify research gaps.

Methods This review was conducted and reported following the Arksey and O'Malley framework and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Scoping Review. A comprehensive search of six electronic databases was conducted, and studies published between 2013 and 2022 were identified. Reports on oral administration of BJIKT to patients with cancer were included and analyzed by two reviewers. The extracted data were synthesized using descriptive reporting and meta-analysis.

Results Overall, 56 studies met the inclusion criteria: 36 human studies, 14 experimental studies, and 6 reviews on clinical and preclinical investigations. The use of BJIKT in restoring immune function and improving fatigue, cancer-related fever, and quality of life after chemotherapy has been reported in clinical studies. The different medication forms of BJIKT included decoction, extract granules, pills, and water extract. The meta-analysis revealed a significantly higher Karnofsky Performance Scale score in the BJIKT plus chemotherapy group than in the chemotherapy alone group. Preclinical studies have demonstrated that BJIKT has anti-cancer effects, enhances gastrointestinal function and immunomodulatory effects, and supports favorable chemotherapy outcomes.

Conclusion In recent clinical research on BJIKT, its impact on fatigue, quality of life, and alleviating cancer-related fever has mostly been examined. The direct anti-cancer activities and immunomodulatory mechanisms of BJIKT have been reported in preclinical studies; however, clinical research on BJIKT-induced enhancement of immune function is lacking. Further research on the efficacy and safety of ICI combined with BJIKT and the association of immunomarker changes with clinical outcomes is required to precisely identify the effect of BJIKT on immune system modulation.

Keywords Bojungikki-tang, Bu-Zhong-Yi-Qi-Tang, Cancer, Immune system, Hochu-ekki-to

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Background

Cancer is a major public health concern worldwide. The mortality rates of cancers with a high incidence are decreasing in high-income countries but increasing in low- and middle-income countries. Approximately 24.5 million new cancer cases and 9.6 million cancer-related deaths were recorded in 2017 [1]. Cancer treatment has evolved over the last quarter-century, with cytotoxic chemotherapy regimens and targeted anticancer drugs becoming the standard of care [2]. However, the side effects of these drugs have necessitated the use of additional treatments. Herbal medicine, a typical treatment modality in East Asian medicine, has been explored as a potential adjuvant approach during conventional cancer treatments such as chemotherapy, radiotherapy, or targeted therapy to enhance efficacy and improve complications and post-operative symptoms [3–6].

In recent decades, immune checkpoint inhibitors (ICIs) have emerged as a new paradigm in cancer therapy to treat solid tumors by activating the immune response against tumor cells that have evaded the patient's immune system [7]. However, low response rates owing to resistance and treatment-related toxicity have limited the clinical use of ICIs [8]. Currently, other treatment modalities are being explored to enhance the therapeutic benefits of ICIs and overcome these limitations [9]. Considering the adverse effects of conventional drugs in combination with ICIs [9, 10], the potential of using herbal medicines adjunctively in cancer treatment needs to be explored.

Bojungikki-tang (BJIKT) is one of the most commonly used herbal medicines for patients with cancer [11]. It alleviates cachexia, cancer-related anorexia [12], and fatigue and improves quality of life [13]. It is also known for its anti-cancer and immunomodulatory activities, inhibiting cancer cell growth and enhancing immunity, as supported by preclinical findings [3, 14–17]. In a recent study, BJIKT enhanced the effects of programmed death 1 (PD-1) blockade [18]. Furthermore, in a previous meta-analysis of randomized controlled trials (RCTs), BJIKT combined with conventional treatment resulted in higher objective response and disease control than conventional treatment alone [19]. However, a comprehensive analysis of the evidence supporting BJIKT use in cancer treatment, including experimental and clinical studies, particularly those focusing on its immunomodulatory effects, has not been reported. Therefore, in this study, we aimed to comprehensively review the evidence supporting the use of BJIKT for treating cancer and its specific mechanisms of action in the immune system.

Materials and methods

Study design

This scoping review was conducted to collect various data and analyze the types of evidence, data sources, and research gaps. This review adhered to the methodology of Arksey and O'Malley [20] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist (see Additional file 1, 2) [21]. We also referred to the Joanna Briggs Institute methodology for scoping reviews [22]. The review protocol was registered with the Open Science Framework (https://osf.io/9j2sn) on December 5, 2022. This review was completed without amendments to the protocol. The review steps are as follows:

Step 1: Identifying the research question

The researchers (EC, SWN, and MKJ) agreed to focus on the immune-related actions of BJIKT and its therapeutic effects on cancer. The research questions were: "What is the reported efficacy of BJIKT against cancer?" and "How does BJIKT affect the immune system"?

Step 2: Identifying relevant studies

We searched MEDLINE using PubMed, the Cochrane Central Register of Controlled Trials, the Oriental Medicine Advanced Searching Integrated System, the Korean Studies Information Service System, the Research Information Sharing Service, and the China National Knowledge Infrastructure. The search, which was conducted on December 5, 2022, covered terms such as "cancer*," "carcinoma*," "neoplasm*," "tumor*," "Bojungikki*," "Bu-Zhong-Yi-Qi*," "Buzhongyiqi*," "Hochu-ekki-to," and "TJ-41" (see Additional file 3). The search period was set to the last decade (January 2013 to December 2022) to capture recent research trends.

Step 3: Study selection

We established the literature selection criteria through discussions among the researchers. The inclusion criteria for this scoping review were defined based on the P-I-C-O-S structure: (1) Participants: patients with cancer; (2) Intervention: oral administration of BJIKT, regardless of formulations such as decoctions and extracts; (3) Comparison: Not limited; (4) Outcome: Not limited; and (5) Study design: Not limited. We included preclinical studies, clinical studies, and reviews and analyses of secondary data sources. The search was limited to articles written in English, Chinese, or Korean. We excluded studies in which BJIKT was used in combination with interventions other than conventional care, such as acupuncture and other herbal medicines. Reviews of classic texts or experts' personal experiences were also excluded.

After removing duplicate articles, the titles and abstracts of identified studies were screened for relevance. The full texts of the relevant articles were carefully reviewed for inclusion and exclusion criteria. Two authors (EC and SWN) independently selected the studies, and disagreements were resolved through group discussions with a third reviewer (MKJ).

Step 4: Charting the data

We developed a predefined data extraction form using Microsoft Excel. Two authors (EC and SWN) independently conducted pilot charts of three included articles and reviewed the data extraction form. The form included publication year, first author, article title, literature type (including journal article, dissertation, and textbook), country where the study was conducted, language, study design, types of cancer, treatment modalities for cancer, comparison, outcome measures, primary outcomes, and reported immune-related effects. The two authors (EC and SWN) charted the data, and MKJ checked the extraction.

Step 5: Collating, summarizing, and reporting the results

Tables were used to summarize the overall research trends of the included studies. A meta-analysis was conducted by extracting studies with identical outcomes between the intervention and control groups by tabulating study characteristics. The clinical efficacy of BJIKT was assessed using meta-analysis and presented as plots using Reviewer Manager (version 5.4). The mean differences (MD) of continuous data and their 95% confidence intervals (CI) were calculated. Heterogeneity was assessed using I^2 statistics. A fixed-effects model was used when I^2 was < 50%; otherwise, a random-effects model was used. The risk of bias was independently assessed by two researchers (EC and MKJ) and categorized as 'low,' 'unclear,' or 'high' risk of bias using the Cochrane Collaboration Risk of Bias Assessment tool [23]. Due to the small number of studies included in the meta-analysis, subgroup and sensitivity analyses and publication bias and small study effect assessments were not conducted. The immunomodulatory effects of BJIKT in preclinical and clinical studies were categorized and presented as a figure. Finally, we discussed the research questions and implications of our findings for future studies.

Results

Study selection

The initial search yielded 121 records after excluding duplicates. During the first screening, 24 records that did not meet our criteria and one that was not retrieved were excluded. During the second screening, 96 potentially relevant records were reviewed for full text. Finally, 56 studies were included in this review (Fig. 1).

Among the 56 included studies, 36 were human studies, including reviews of clinical studies and secondary data analyses, 14 included experimental data, and 6 were reviews of preclinical and clinical studies (3 from China [4, 5, 24], 2 from Japan [11, 25], and 1 from Germany [12]). Of the 56 reports, 29 were published in English, 22 in Chinese, and 5 in Korean. Thirty studies were conducted in China, 14 in Japan, 9 in the Republic of Korea, 2 in Taiwan, and 1 in Germany (see Additional file 4).

Findings from preclinical studies

The literature included 20 preclinical studies (11 experimental studies, 8 literature reviews, and 1 study on network pharmacology). The experimental studies included 5 in vivo studies [26–30], 5 in vitro studies [31–35], and 1 study that included both types of experiments [36]. Among these experimental studies, 6 were conducted in China [26, 28, 29, 33, 35, 36], 3 in the Republic of Korea [27, 30, 31], and 2 in Japan [32, 34].

Therapeutic actions of BJIKT in cancer treatment

BJIKT has demonstrated anti-cancer effects, primarily through the modulation of immune responses and direct anti-cancer activities. Its ability to inhibit proliferation and induce apoptosis in various cancer cell lines, such as hepatocellular carcinoma (Hep3B, HepG2, and HA22T), while exhibiting minimal effects on normal cells, has been reported in studies. This finding suggests its potential for selective cancer targeting [11, 31].

In addition to its anti-cancer properties, BJIKT enhances gastrointestinal function by improving motility and nutrient absorption, as evidenced in a CT-26 colon cancer cell-injected mouse model. It also exhibits significant immunomodulatory effects, as evidenced by its ability to prevent neutrophil count reduction and increase red blood cell count and hemoglobin levels [27]. In another study, BJIKT decreased tumor weight, increased median survival time, and increased body weight in a 4T1 breast cancer cell mouse model [28]. Furthermore, BJIKT increased the immune index to normal levels in splenectomized mice [37].

The role of BJIKT in supporting chemotherapeutic outcomes, such as cisplatin resistance, by promoting intrinsic apoptotic pathways and autophagy in combination with cisplatin in A549/DDP human lung carcinoma cells has been reported in another study [38]. Table 1 summarizes the effects of BJIKT in preclinical experiments.

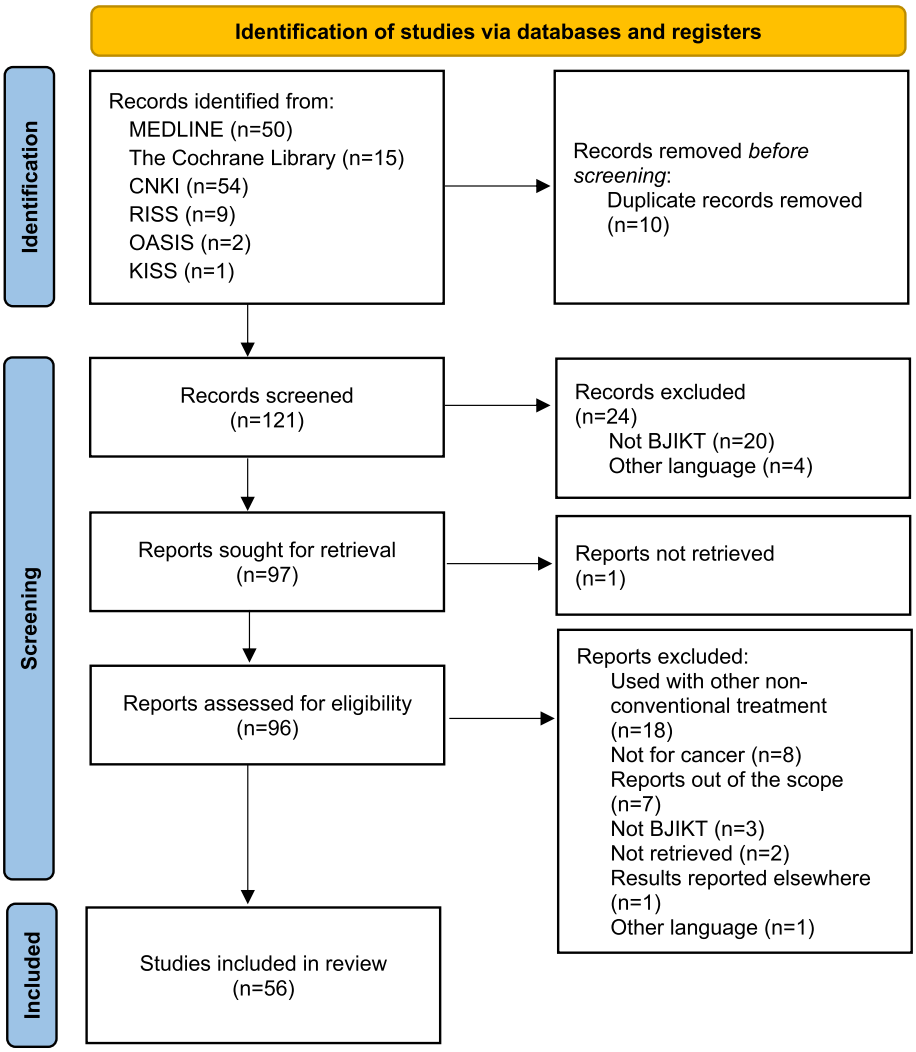

Fig. 1 PRISMA flow chart for the study selection

Additional file 5 presents the composition of BJIKT used in the experimental studies.

Findings from clinical studies

Clinical studies, excluding reviews, secondary data analyses, and protocols, included 19 RCTs, 2 case reports [39, 40], 1 prospective cohort study [41], and 1 case series [42]. Table 2 summarizes the details of the included RCTs. In the cohort study [41], the efficacy and safety of BJIKT were compared with those of high- and low-dose Astragali Radix. Four trials have been registered: 2 in Japan [43, 44], 1 in China [45], and 1 in Korea [46]. Two secondary data analyses have been reported in Taiwan, indicating that BJIKT is a commonly used Chinese herbal medicine for treating lung and colon cancers [47, 48]. Li et al. revealed that individuals using herbal medicine for lung cancer exhibited a lower mortality hazard ratio (0.48, $p < 0.001$) and higher cumulative survival probability ($p < 0.0001$) than non-users [48]. Seven reviews [6, 19, 49–53] of clinical studies exist, one of which supplemented case presentations [52].

Use of BJIKT in clinical studies

We analyzed 27 clinical studies, including RCTs, case reports, prospective cohort studies, case series, and registered trials. The purposes of using BJIKT were to restore immune function [55, 70], improve fatigue [38, 39, 41, 44, 56, 57, 59, 61, 62, 68, 70], alleviate adverse reactions and enhance quality of life after chemotherapy [39, 60, 69], alleviate cancer-related fever [54, 63–66], improve dyspnea and general weakness [40], support physical strength [42], reduce adverse reactions and increase compliance with chemotherapy [67], improve clinical efficacy

Table 1 Preclinical evidence of the anti-cancer activity of BJIKT reported in experimental studies ($N = 11$)

Study (Country)	Study design	Type of cancer	Treatment intervention	Control intervention	Key findings of the study
2013 Lee (Korea) [31]	Research article (in vitro)	Hep3B, HepG2, HASST- liver cancer	BJIKT	None	1. Inhibited the proliferation of liver cancer cells 2. Induced liver cancer cell apoptosis
2013 Yang (China) [26]	Research article (in vivo)	Colon cancer lung metastasis model	BJIKT	None	1. Upregulated NKG2D expression in NK cells 2. Upregulated Treg cell levels
2014 Hong (Korea) [27]	Research article (in vivo)	CT-26 cancer cell—colon cancer	BJIKT + Magace (with or without)	None	1. Prevented loss of appetite 2. Prevented weight loss 3. Decreased muscle mass loss 4. Prevented neutrophil count reduction 5. Increased red blood cell count and hemoglobin levels 6. Increased red blood cell volume (hematocrit)
2014 Ouyang (China) [28]	Research article (in vivo)	4 T1 cancer cell—breast cancer	BJIKT + Paclitaxel (with or without)	None	1. Tendency of decreased tumor weight, longer median survival times, and increased body weight
2015 Sato (Japan) [32]	Research article (in vitro)	HeLa cell—human cervical cancer	BJIKT	Cisplatin	1. Decreased cell survival and increased apoptosis in HeLa cells 2. Increased protein expression of p53 and active caspase-3 3. Decreased protein expression of p-Akt and the Bcl-2/Bax ratio
2016 Gou (China) [29]	Research article (in vivo)	Gastrointestinal toxicity (cancer-related fatigue)	BJIKT	5-fluorouracil (Chemotherapy)	1. Suppressed weight loss and diarrhea 2. Reduced neutrophil infiltration, nitrite levels, and levels of inflammatory factors (tumor necrosis factor α and interleukin 1) 3. Reduced intestinal damage, including shortened villi height, crypt destruction, apoptosis, and necrosis, in intestinal mucosal epithelia
2017 Yu (China) [33]	Research article (in vitro)	A549/DDP cells -human lung carcinoma (cisplatin-resistant cells)	BJIKT	Cisplatin	1. Induced intrinsic apoptotic pathways 2. Activated autophagy

Table 1 (continued)

Study (Country)	Study design	Type of cancer	Treatment intervention	Control intervention	Key findings of the study
2020 Xu (China) [36]	Research article (in vivo/in vitro)	MFC cells-gastric cancer	BJIKT + 5-fluorouracil (with or without)	None	1. Increased survival times 2. Increased CD4(+) and CD8(+) counts and proportions of CD8(+) PD-1(+) T cells 3. Decreased PD-1(+) Treg cells 4. Inhibited PD-L1 expression by the PI3K/AKT pathway 5. Promoted proliferation, activation, and cytotoxicity of T lymphocytes
2021 Kiyomi (Japan) [34]	Research article (in vitro)	Human PBMC	BJIKT	None	1. Decreased PBMC proliferation 2. Increased the percentage of CD8(+) T cells 3. Suppressed Treg cells 4. Induced IL-6 and IL-17A secretion 5. Increased IFN-γ and TNF-α secretion 6. Decreased TGF-β secretion
2022 Li (China) [35]	Research article (in vitro)	FADU cells—human laryngeal squamous carcinoma cells	BJIKT	None	1. Inhibited the proliferation of laryngeal squamous cell carcinoma cells
2022 Chun (Korea) [30]	Research article (in vivo)	MC38 cells -colorectal cancer	BJIKT + anti-PD-L1 (with or without)	None	1. Suppressed tumor growth 2. Induced antitumor immune responses 3. Increased the proportion of cytotoxic T lymphocytes and NK cells in tumor tissues

BJIKT Bojung-ikki-tang, *NK* Natural killer, *IFN* Interferon, *TNF* Tumor necrosis factor, *TGF* Tumor growth factor, *PD-L1* Programmed death-ligand-1

Table 2 Characteristics of included randomized controlled trials ($N=19$)

Study (country)	Number of patients (T,C)	Mean age	Sex (Male, Female)	Type of cancer	Treatment group	Control group	Duration of treatment	Purpose of using BJIKT	Outcome measures
2013 Xu (China) [54]	30,30	(T)57.967 ± 10.077, (C)56.500 ± 10.318	41,19	Lung, liver, intestine, gastric	BJIKT	Indomethacin	3 weeks	Cancerous fever	1. Clinical situations 2. Body temperature changes 3. Syndrome integral 4. Karnofsky performance status 5. Adverse reactions
2014 Lee (Korea) [55]	7,6	(T)66 ± 6, (C)64 ± 6	7,6	NS	BJIKT	Placebo (vitamin)	4 weeks	Restore immune function	1. Absolute counts and percentages of lymphocyte and lymphocyte subsets
2016 Zhu (China) [56]	34,26	NS	NS	Gastric	BJIKT + Chemotherapy	Chemotherapy	56 days (28 days*2 cycle)	Cancer-related fatigue	1. FACIT-F 2. CFS 3. BFI 4. Gastric cancer symptom rating scale 5. Physicochemical indicators
2016 Liu (China) [57]	41,41	NS	45,37	Mammary, rectal, lung, colon	BJIKT + Chemotherapy	Chemotherapy	21 days	Cancer-related fatigue	1. FSI 2. Peripheral blood count changes (incidence of hemoglobin, platelet, WBC decrease) 3. Incidence of nausea and vomiting 4. Liver and kidney function
2017 Zhang (China) [58]	35,35	38.5	30,40	Thyroid	BJIKT + Levothyroxine	Levothyroxine	3 months	Improve clinical efficacy and depression	1. HAMD-17 2. Clinical efficacy categorized into 3 groups
2017 Chen (China) [59]	30,30	(T)58.03 ± 5.22, (C)57.64 ± 5.18	34,26	B cell lymphoma, gastric, colorectal	BJIKT + Chemotherapy	Chemotherapy	3 weeks	Cancer-related fatigue	1. Quality of life 2. Relief of fatigue 3. Incidence of adverse reactions
2018 Li (China) [60]	40,40	NS	47,33	NS	BJIKT + Chemotherapy	Chemotherapy	42 days	Adverse reactions after chemotherapy	1. Conditions of bone marrow suppression and digestive tract reaction 2. KPS score

Table 2 (continued)

Study (country)	Number of patients (T,C)	Mean age	Sex (Male, Female)	Type of cancer	Treatment group	Control group	Duration of treatment	Purpose of using BJIKT	Outcome measures
2018 Lin (China) [61]	32,32	(T)64.8, (C)64.5	37,27	NSCLC	BJIKT + Conventional therapy	Conventional therapy	14 days	Carcinogenic fatigue	1. PFS 2. KPS score 3. TCM syndrome integral
2018 Yang (China) [62]	40,40	(T)74.89 ± 10.18, (C)75.01 ± 10.61	49,31	Lung, gastric, esophagus, rectal, nasopharyngeal	BJIKT + Western medicine	Western medicine	4 weeks	Cancer-related fatigue and quality of life	1. PFS 2. EORTC-QLQ-C30
2018 Zheng (China) [63]	37,37	(T)53.09 ± 4.46, (C)53.15 ± 4.28	42,32	NS	BJIKT	Indomethacin	1 week	Cancer-related fever	1. Average fever reduction time 2. Total effective rate of fever reduction (categorized as normal/stable/ineffective) 3. KPS score 4. Adverse reactions
2018 Chen (China) [64]	50,50	(T)57.8 ± 10.4, (C)57.0 ± 11.0	72,28	Lung, liver, intestine, gastric, others	BJIKT + Indomethacin	Indomethacin	3 weeks	Cancer-related fever	1. TCM syndrome (total efficacy categorized scores: 0–3) 2. Body temperature 3. KPS score 4. Overall treatment effect 5. Incidence of adverse reaction
2019 Wang (China) [65]	40,40	(T)57.85 ± 2.14, (C)57.64 ± 2.16	47,33	NS	BJIKT	Indomethacin	3 weeks	Cancer-related fever	1. Body temperature (efficacy categorized into 3 groups) 2. SF-36
2019 Yu (China) [38]	30,30	58.07 ± 6.36	36,24	B cell lymphoma, colorectal, gastric	BJIKT + Western medicine	Western medicine	4 weeks	Cancer-related fatigue	1. PFS 2. Adverse reactions 3. Improvement in daily life
2019 Zhang (China) [66]	25,25	NS	35,15	Hepatocellular, malignant lymphoma, breast, colorectal, gastric, multiple myeloma, renal	BJIKT	Indomethacin	10 days	Cancer-related fever	1. Body temperature (efficacy categorized into 3 groups) 2. Symptomatic relief (fatigue, nausea, palpitations, and somnolence)

Table 2 (continued)

Study (country)	Number of patients (T,C)	Mean age	Sex (Male, Female)	Type of cancer	Treatment group	Control group	Duration of treatment	Purpose of using BJIKT	Outcome measures
2019 Okabe (Japan) [67]	55,55	NS	74,36	Gastric	BJIKT (TJ-41) + S-1	S-1	1 year	Reduce adverse reactions and increase compliance with S-1 adjuvant therapy	1. The completion rate of S-1 2. Adverse events 3. Relative dose intensity 4. Relapse-free survival (RFS) 5. Overall survival (OS)
2020 Ning (China) [68]	38,36	(T)61.0 ± 12.5, (C)61.2 ± 9.0	33,41	Colorectal	BJIKT + Conventional therapy	Conventional therapy	12 weeks (4 weeks*3 cycle)	Cancer-related fatigue	1. PFS 2. KPS score 3. TCM syndrome score
2021 Luo (China) [69]	48,48	(T)NS, (C)60.41 ± 5.93	54,42	NSCLC	modified BJIKT + Western medicine	Western medicine	6 weeks (2 weeks*3 cycle)	Reduce side effects of chemotherapy, promote tumor shrinkage, and improve quality of life	1. Serum CEA and CYFRA21-1 2. IGF-1, VEGF, and TGF-β1 3. Serum CD4(+) CD8(+), CD4(+), and IgG 4. Pulmonary function index 5. Adverse reactions
2022 Liu (China) [70]	52,51	(T)41.11 ± 3.69, (C)40.66 ± 3.66	61,42	Gastric	BJIKT + Chemotherapy	Chemotherapy	6 weeks (3 weeks*2 cycle)	Cancer-related fatigue and immune function	1. PFS score 2. Levels of CD3(+), CD4(+), CD8(+), and CD4(+) CD8(+) 3. Levels of CEA, CA19-9, and CA72-4 4. Adverse reactions
2022 Edahiro (China) [71]	21,21	(IQR)(T)46–67, (C)52–62	17,25	Myeloproliferative neoplasm	BJIKT	None	8 weeks	Reduction in myeloproliferative neoplasm-related symptoms	1. MPN-SAF TSS 2. EORTC QLQ-C30

BJIKT Bojung-ikki-tang, *T* Treatment group, *C* Control group, *NS* Not specified, *TJ-41* Bojung-ikki-tang, *S-1* S-1 adjuvant chemotherapy, *NSCLC* Non-small cell lung cancer, *CFS* Cancer fatigue scale, *BFI* Brief fatigue inventory, *FSI* Fatigue symptom inventory, *WBC* White blood cell, *SF-36* Short form 36 health survey, *HAMD* Hamilton depression rating scale, *PFS* Piper fatigue scale, *KPS* Karnofsky performance status, *TCM* Traditional Chinese medicine, *EORTC-QLQ* European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, *CEA* Carcinoembryonic antigen, *CA* Carbohydrate antigen, *MPN-SAF TSS* Myeloproliferative neoplasm symptom assessment form total symptom score, *IQR* Interquartile range

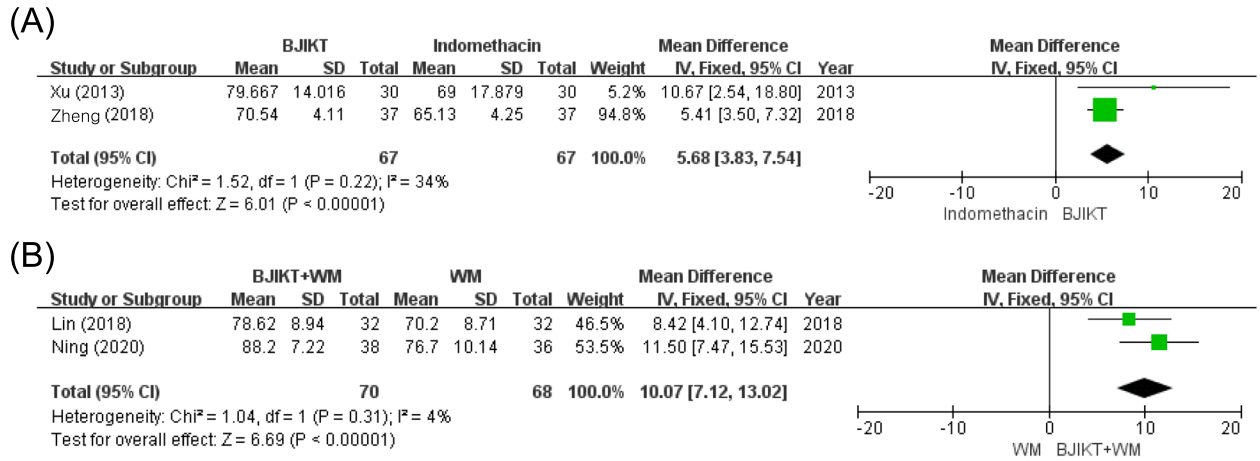

Fig. 2 Forest plot for meta-analysis. **A** Forest plot of KPS between BJIKT and Indomethacin groups for cancer treatment. **B** Forest plot of KPS between BJIKT plus WM and WM alone groups for cancer treatment. The position of the rectangle indicates the effect size and direction of the individual study, and the size of the rectangle indicates the weight. The black diamond represents the effect size

and depression [58], and alleviate myeloproliferative neoplasm-related symptoms [71]. The treatment duration ranged from 1 to 12 weeks. The medication forms of BJIKT were decoction ($n=17$), extract granules ($n=3$), pills ($n=1$), and water extract ($n=1$), which were not reported in five studies (see Additional file 6).

Clinical efficacy and safety of BJIKT

In the 19 RCTs, the most common cancer type was gastric cancer ($n=9$), followed by lung cancer ($n=6$) and colorectal cancer ($n=4$). In 12 RCTs, BJIKT was administered in combination with Western medical therapy in the intervention group. Among the 12 RCTs, 6 [56, 57, 59, 60, 67, 70] involved the use of BJIKT plus chemotherapy in the intervention arm and chemotherapy alone in the control arm. In five RCTs, only BJIKT was used in the intervention group, with three RCTs involving the use of indomethacin in the control group to assess the effect on cancer-related fever [54, 63, 65], one involving the use of a placebo (vitamin) in the control group [55], and one in which no treatment was assigned to the control group [71] (Table 2).

Meta-analyses conducted using identical treatment and control groups and outcome measures yielded the following results. In two studies ($n=134$; intervention group = 67; control group = 67) [54, 63], results on the Karnofsky Performance Scale (KPS) were reported. The meta-analysis revealed a significantly higher KPS score in the BJIKT group than in the indomethacin group (MD = 5.68, 95% CI [3.83–7.54]; $p<0.00001$, $I^2=34\%$) (Fig. 2A). Four studies reported using BJIKT in combination with Western medicine (WM) or unspecified conventional therapy [38, 61, 62, 68]. In two studies (n = 138, experimental group = 70, control group = 68) [61, 68], the KPS results were compared between the BJIKT plus WM and WM alone groups. The pooled analysis showed a significantly higher KPS score in the BJIKT plus WM group than in the WM alone group (MD = 10.07, 95% CI [7.12–13.02]; $p<0.00001$, $I^2=4\%$) (Fig. 2B). Notably, most RCTs included in the meta-analyses had unclear risk of bias domains, including unclear missing results (see Additional file 7).

Safety analysis revealed diarrhea ($n=1$) [54] and nausea and vomiting ($n=1$) [63] as adverse reactions to BJIKT alone.

Immunomodulatory effects of BJIKT reported in preclinical and clinical studies

Lymphocyte modulation and enhancement

In a 2014 study from Korea, Lee et al. [55] reported a significant elevation in CD19(+) B cell counts in the peripheral blood of patients, indicating an enhancement of the humoral immune response, which is crucial for adaptive immunity. With further expansion of lymphocyte activity, Yamaguchi et al. [25] reported significant increases in CD3(+) and CD3(+) CD4(+) cell counts in the peripheral blood of patients, contributing to improved immune functionality and quality of life. In the same year, Kuchta et al. [12] reported that BJIKT increased CD3(+) and CD3(+) CD4(+) T cell counts in the peripheral blood of patients and inhibited the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-10, tumor growth factor (TGF)-β 1, and interferon (IFN). Finally, Liu et al. [57] reported a decrease in the percentage of CD3(+), CD4(+), and CD8(+) cells and an increase in the CD4(+)/CD8(+)

ratio in the peripheral blood of patients with gastric cancer. Notably, Xu et al. [36] reported that BJIKT increased the survival times and the percentage of CD4(+) and CD8(+) T cells in a mouse forestomach carcinoma (MFC) gastric cancer cell model.

Regulation of immune suppression and enhancement

Chao et al. [47] reported that BJIKT effectively prevented surgical stress-induced immune suppression by maintaining natural killer (NK) cell activity in the peripheral blood of patients with gastrointestinal malignancies. In an in vitro study, Kiyomi et al. [34] reported complex immune regulation through decreased human peripheral blood mononuclear cell proliferation, increased CD8(+) T cell counts, suppression of regulatory T (Treg) cells, and modulation of cytokines, including elevated levels of IL-6, IL-17A, IFN-γ, and TNF-α and decreased levels of TGF-β. Shimizu et al. [42] reported that BJIKT restored antitumor T-cell responses, maintained NK cell activity, and inhibited the production of proinflammatory cytokines, particularly IL-6, in the peripheral blood of patients. In mice with colon adenocarcinoma-induced cachexia, BJIKT significantly reduced serum IL-6 levels and IL-6 expression in macrophages in surrounding tissues [12]. In addition, Lee et al. [7] reported that BJIKT improves systemic inflammation and enhances overall immunological capacity. These effects appear to result from BJIKT enhancing the anti-cancer effect of gefitinib in patients with advanced non-small cell lung cancer (NSCLC) harboring an epidermal growth factor receptor mutation, potentially delaying the acquired resistance that limits gefitinib efficacy.

Tumor microenvironment and cancer therapy response

In a preclinical study by Wang et al. [24], BJIKT reversed cisplatin resistance in lung cancer cells by inducing apoptosis and autophagy and mitigated 5-fluorouracil-induced intestinal mucositis in mice by suppressing the upregulation of inflammatory cytokines, potentially reducing the gastrointestinal side effects of chemotherapy. In the clinical segment of the same study, BJIKT was reported to protect organs against radiation damage, ameliorate localized radiotherapy-induced immune deterioration, and effectively manage the side effects associated with cancer treatment. Further emphasizing tumor microenvironment management, Zhang et al. [4] reported that BJIKT modulates peripheral immunity, suppresses immune escape mechanisms in tumors, and alleviates neuroinflammation and oxidative stress in the hippocampus of a mouse model of chronic fatigue syndrome, underscoring its impact on peripheral and central immune responses. In an in vitro study, BJIKT inhibited proliferation and induced apoptosis in various cancer cell lines, such as hepatocellular carcinoma (Hep3B, HepG2, and HA22T), while exhibiting minimal effects on normal cells [31]. In another in vitro study, BJIKT induced intrinsic apoptosis pathways and activated autophagy in A549/DDP human lung carcinoma cells [33]. In another RCT, Luo et al. [69] reported that BJIKT decreased levels of vascular endothelial growth factor and cytokines, such as insulin-like growth factor-1 and TGF-β, frequently implicated in cancer progression and immune suppression in postoperative patients with NSCLC after chemotherapy. Furthermore, BJIKT increased the proportion of CD8(+) PD-1(+) T cells, decreased the number of PD-1(+) Tregs, and inhibited programmed death-ligand-1 (PD-L1) expression through the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway in an MFC gastric cancer cell model [36]. In another preclinical study, Chun et al. [30] reported that BJIKT suppressed tumor growth and improved antitumor immune responses to PD-L1 immunotherapies, such as ICIs, by increasing the proportion of cytotoxic T lymphocytes and NK cells in the tumor tissues of an MC38 colorectal cancer cell mouse model (Table 3). Figure 3 illustrates the immunomodulatory effects of BJIKT, suggested in preclinical and clinical studies.

Discussion

In the present review, we explored BJIKT use in cancer treatment and gained a better understanding of its immune-related effects and potential for future combinations with ICIs. We also identified a research gap regarding BJIKT use in combination with ICIs, which are currently emerging as a new paradigm in cancer treatment.

Main findings and interpretation

Question 1. What is the reported efficacy of BJIKT in treating cancer?

In clinical studies, BJIKT has been used to treat various types of cancer, such as NSCLC, gastric cancer, and liver cancer, for durations ranging from 1 to 12 weeks. The interventions have shown favorable outcomes, with BJIKT improving clinical symptoms of cancer, enhancing quality of life, relieving fatigue, and reducing fever. Owing to the heterogeneity of the intervention and control groups and the outcomes of the RCTs, the meta-analysis was only feasible for KPS. A higher KPS indicates better functional status and ability to perform daily activities [72]. Our meta-analysis revealed that BJIKT plus chemotherapy enhances patients' quality of life, suggesting that BJIKT in combination with chemotherapy can be considered in clinical practice. Compared with indomethacin, BJIKT significantly improved functional status. Notably,

Table 3 Preclinical and clinical evidence of the immunomodulatory effects of BJIKT in included studies ($N=12$)

Study (country)	Study design	Type of cancer	Key findings of the study
2014 Lee (Korea) [55]	RCT	Lung, Rectum, Common bile duct, Gastrointestinal, Esophagus, Pyriform sinus, Breast, Liver, Ovary, and Uterus	1. Increased CD19(+) B cells
2014 Chao (Taiwan) [47]	Secondary data analysis	NS	1. Prevented surgical stress-induced immune suppression by maintaining NK cell activity
2015 Yamaguchi (Japan) [25]	Literature review	Oral cancer	1. Increased lymphocyte cell-surface antigens 2. Increased CD3(+) cells 3. Increased CD3(+) CD4(+) cells 4. Increased immune function 5. Increased QOL
2018 Wang (China) [24]	Literature review (in vivo)	NS	Preclinical: 1. Reversed cisplatin resistance through induction of apoptosis and autophagy in lung cancer cells 2. Inhibited 5-FU-induced intestinal mucositis through the suppression of inflammatory cytokine up-regulation Clinical: 1. Protected intestine and hematopoietic organs against radiation damage 2. Improved localized radiotherapy-induced immune deterioration 3. Improved cancer-related fatigue and QOL 4. Reduced radiation or chemotherapy-induced side effects
2020 Kim (Korea) [19]	Literature review	Gastric cancer, NSCLC, and Lung cancer	1. Increased the percentage of CD4(+) and CD4(+) CD8(+) cells 2. Decreased the percentage of CD8(+) cells
2020 Kuchta (Germany) [12]	Literature review (in vivo, in vitro)	NS	1. Increased lymphocyte cell-surface antigens (CD3(+) and CD3(+) CD4(+) cells) 2. Inhibited TNF-α, IL-6, IL-10, TGF- β1, and INF-γ production
2021 Kiyomi (Japan) [34]	Experimental study (in vitro)	NS	1. Decreased PBMC proliferation 2. Increased the percentage of CD8(+) T cells 3. Suppressed Treg cells 4. Induced IL-6 and IL-17A secretion 5. Increased IFN-γ and TNF-α secretion 6. Decreased TGF-β secretion
2021 Shimizu (Japan) [42]	Case series	Pancreatic cancer, Gastric cancer, and Thyroid cancer	1. Restored antitumor T cell responses by normalizing serum corticosterone, IL-12, and costimulatory molecule expression 2. Maintained NK cell activity and suppression of stress mediators 3. Inhibited proinflammatory cytokine production, particularly IL-6 4. Enhanced cisplatin-induced apoptosis 5. Inhibited cytokine-mediated apoptosis or necrosis, thus reducing the gastrointestinal side effects of cancer chemotherapy 6. Replenished B cell after radiotherapy
2021 Lee (Korea) [40]	Case report	NSCLC	1. Ameliorated systemic inflammation and improved immunological capacity

Table 3 (continued)

Study (country)	Study design	Type of cancer	Key findings of the study
2021 Zhang (China) [4]	Literature review (in vivo)	NS	1. Modulated peripheral immunity and suppressed the immune escape of tumors by increasing the infiltration of tumor lymphocytes, decreasing the expression of PD-1 in peripheral blood, and reducing the infiltration of PD-1 and PD-L1 in tumors 2. Alleviated neuroinflammation and oxidative stress by reducing the expression of IL-1β, IL-6, and IFN-γ in the hippocampus
2021 Luo (China) [69]	RCT	NSCLC	1. Decreased IGF-1, TGF- β, and VEGF levels
2022 Liu (China) [70]	RCT	Gastric cancer	1. Decreased the percentage of CD3(+), CD4(+), CD8(+) cells 2. Increased CD4(+)/CD8(+) ratio

NS Not specific, *BJIKT* Bojung-ikki-tang, *NK* Natural killer, *QOL* Quality of life, *NSCLC* Non-small cell lung cancer, *TNF* Tumor necrosis factor, *IL* Interleukin, *PD-L1* Programmed death-ligand-1, *IFN* Interferon, *TGF* Tumor growth factor, *IGF* Insulin-like growth factor, *VEGF* Vascular endothelial growth factor

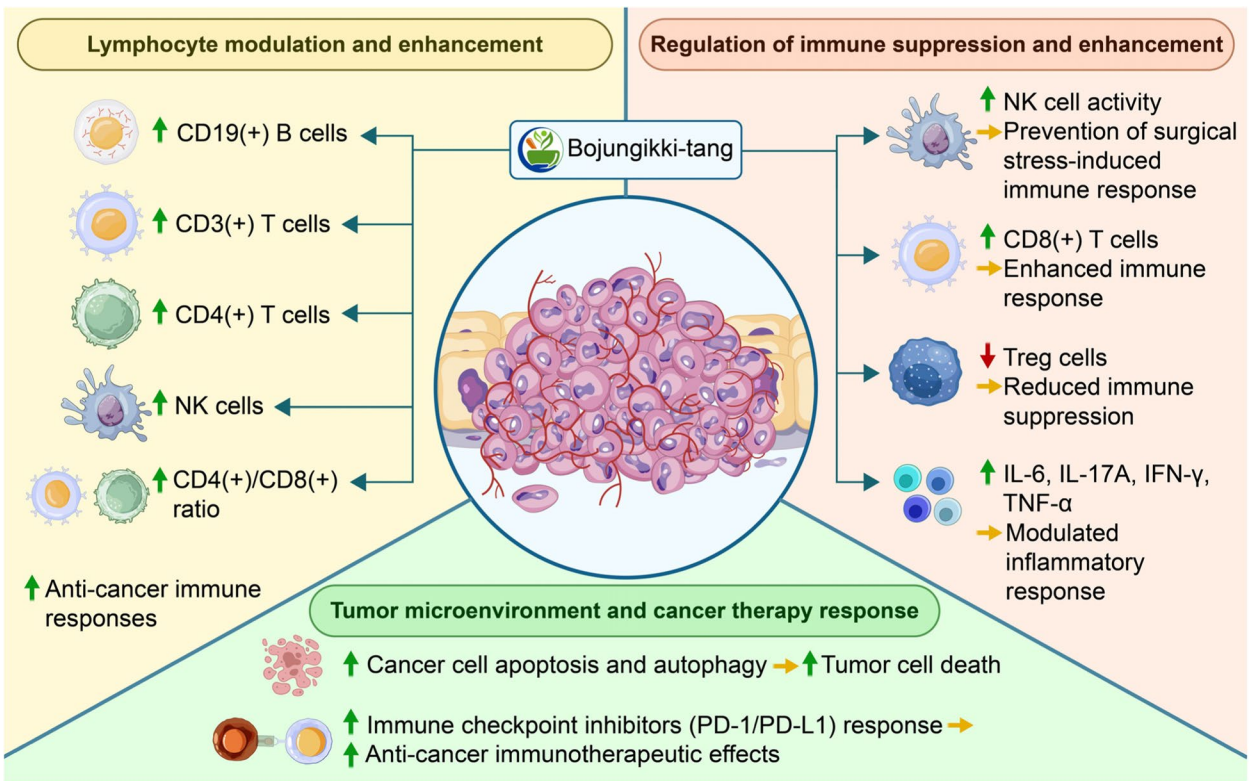

Fig. 3 Graphical abstract illustrating Bojungikki-tang's immunomodulatory effects on anti-cancer immune system. This figure shows how Bojungikki-tang impacts lymphocyte function, regulates immune suppression and activation, and influences the tumor microenvironment to enhance anti-cancer responses

in most studies in which BJIKT was compared with indomethacin, BJIKT was more effective in relieving fever, although not statistically validated.

BJIKT has been traditionally used to alleviate symptoms of fatigue. In several studies using different fatigue scales, positive outcomes for BJIKT have been reported. In a recent network pharmacology study, BJIKT was reported to be effective against chronic fatigue syndrome by interacting with multiple components, targets, and pathways [73]. Considering that fatigue is a highly

prevalent symptom of cancer, alleviating it can improve patients' quality of life [74]. Because the outcome measures for fatigue were diverse, no quantitative synthesis could be conducted in this study. Therefore, further clinical trials on BJIKT, including fatigue scales, are required for objective evaluation.

Clinical studies on BJIKT included in the present review mainly focused on alleviating symptoms such as fatigue and cancer-related fever and improving quality of life. Meanwhile, in East Asian medicine, BJIKT has been used primarily for gastrointestinal symptoms, such as appetite loss or indigestion [75]; however, only a few clinical studies on cancer in the present review included gastrointestinal symptoms as outcomes. Notably, in some clinical studies [38, 56] in the present review, nausea and vomiting occurred less frequently or improved better in the treatment group than in the control group. Quality of life scales, such as the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30), assess symptoms such as nausea, vomiting, and appetite loss. Yang et al. [62] reported higher EORTC-QLQ-C30 scores in the treatment group (BJIKT plus Western medicine) than in the control group (Western medicine alone). However, clinical research involving symptom indicators other than fatigue and fever is lacking; therefore, future studies are required to examine the effect of BJIKT on nausea, vomiting, and appetite loss in patients with cancer using quality-of-life symptom scores.

Furthermore, it has been suggested in existing studies that BJIKT can contribute to improving survival rates in patients with cancer. In a real-world data study in Taiwan, a 4.9% higher 5-year survival rate was observed when Chinese herbal medicine was integrated with conventional treatment for NSCLC. In this study, BJIKT was the third most common herbal medicine prescribed to patients, suggesting that BJIKT may improve survival rates in patients with NSCLC [76]. This finding is consistent with other real-world findings included in the present review, indicating a higher survival probability in individuals using herbal medicine, including BJIKT, than in non-users [48].

However, there are very few clinical trials in which cancer size control, survival rate, and biomarkers have been compared between BJIKT plus ICI, and ICI alone [77]. Therefore, we conducted a clinical trial to examine the safety and efficacy of BJIKT in patients with advanced NSCLC receiving ICI therapy [78]. Further clinical studies are required to determine how BJIKT, in combination with ICIs, affects survival, prognosis, and adverse events in patients with cancer, and identify biomarkers associated with treatment response and survival.

Question 2. How does BJIKT affect the immune system?

BJIKT exhibits comprehensive immunomodulatory effects, significantly enhancing innate and adaptive immune responses while demonstrating pronounced anti-cancer properties. T lymphocytes play crucial roles in tumor-adaptive immune responses and immunosuppression [79]. CD4(+) T cells activate CD8(+) T cells, which directly target and destroy cancer cells, as well as innate immune cells (NK and dendritic cells) by producing IL-2 and IL-15. Notably, some CD4(+) T cells directly kill tumor cells [80]. Treg cells suppress immune responses by secreting IL-10 and TGF-β, consuming IL-2, and inhibiting dendritic cell activity, contributing to tumor immune suppression [81]. Therefore, enhancing the antitumor activity of T cells and regulating immune suppression is crucial to improving the tumor immune microenvironment. Yang et al. [26] reported the upregulation of NK group 2D expression in NK cells and increased Treg cell levels, indicating significant modulation of the immune response in a mouse colon cancer lung metastasis model. The balance between T helper (Th) 17 and Treg cells plays an essential role in autoimmune diseases, inflammation, and tumor immune responses. The authors reported that Th17 and Treg cells exhibit opposite differentiation and inhibit each other's functions while maintaining the balance of the local microenvironment. In addition, reversing inflammatory immune evasion during tumor metastasis by transforming Treg cells into Th17 cells rather than eliminating them is important. Kuchta et al. [12] reported that BJIKT increases the proportion of CD3(+) and CD3(+) CD4(+) cells while inhibiting pro-inflammatory cytokines, such as TNF-α, IL-6, IL-10, TGF-β1, and IFN-γ, in the peripheral blood of patients. However, Liu et al. [70] reported that BJIKT decreased the percentage of CD3(+), CD4(+), and CD8(+) cells and increased the CD4(+)/CD8(+) ratio, indicating a more regulated adaptive immune response in the peripheral blood of patients with gastric cancer.

PD-1 and PD-L1 play crucial roles in the immune evasion of cancer cells. These interactions play a significant role in cancer immunotherapy [82]. BJIKT enhanced the proportion of CD4(+), CD8(+), and CD8(+) PD-1(+) T cells, decreased the proportion of PD-1(+) Treg cells, inhibited PD-L1 expression through the PI3K/AKT pathway, and promoted T lymphocyte proliferation, activation, and cytotoxicity in an MFC gastric cancer cell model [36]. Chun et al. [30] reported that BJIKT improves antitumor immune responses by increasing the number of cytotoxic T lymphocytes and NK cells in tumor tissues treated with an anti-PD-L1 antibody combination in a mouse model of colorectal cancer.

The CD4(+)/CD8(+) ratio plays a crucial role in the immune response to cancer. Its significance in predicting the outcomes of patients undergoing ICI therapy has been reported in several studies. Based on the results of clinical studies, patients with a higher baseline CD4(+)/CD8(+) ratio tend to have better responses to immunotherapy and longer survival [83, 84]. These findings underscore the value of CD4(+)/CD8(+) ratio as a biomarker for predicting and monitoring responses to ICI therapy. In some clinical studies included in the present review, an increase in the CD4(+)/CD8(+) ratio was reported as a common outcome associated with the modulation of circulating T lymphocytes after BJIKT treatment. Overall, BJIKT may enhance the immune response of patients with cancer, as evidenced by the increased CD4(+)/CD8(+) ratio after BJIKT treatment.

Furthermore, although direct evidence is lacking, BJIKT may also influence other immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 and T cell immunoglobulin and mucin-domain containing-3. Considering the broader immunomodulatory effects of BJIKT, including its ability to enhance cytotoxic T cell function and reduce Treg cell activity, it is plausible that BJIKT could also impact these additional checkpoints. Collectively, these findings highlight the potential of BJIKT to enhance immune function, regulate immune responses, and exert anti-cancer immunotherapeutic effects, making it a promising candidate for integrative cancer therapy and immunomodulation.

Study limitations

This study has provided evidence of the therapeutic and immunomodulatory effects of BJIKT in cancer treatment; however, some limitations should be acknowledged. In studies in which herbal decoctions were used, BJIKT was often combined with other herbs, making it difficult to determine the effectiveness of BJIKT alone. In East Asian Medicine, herbal extracts are generally manufactured by pharmaceutical companies in quantities based on the original prescription; however, the constituents and doses of the herbal decoctions can be adjusted at the physician's discretion. Herbal decoctions enable personalized treatment based on a patient's condition; however, their exact efficacy and safety cannot be predicted using individual prescriptions. In addition, meta-analyses are limited because of the lack of common outcome measures and differences between the intervention and control groups. The risk of bias summary showed that most of the items were unclear. Notably, in some RCTs published in China, arbitrary categorizations or definitions of outcomes, such as body temperature, were used to assess efficacy. Because we limited the published languages to English, Korean, and Chinese, some studies published in other languages might not have been included in this review.

Implications for future research

This review presents the results of experimental and clinical studies on BJIKT conducted over the last decade. BJIKT has been investigated as a potential adjunctive therapy in cancer treatment, with most RCTs focusing on its use in combination with chemotherapy. The combination of BJIKT with targeted therapy was documented in only one case report, and none of the included studies included the results of combination therapy with an ICI. Experimental findings regarding the immune-related effects of BJIKT suggest the possibility of enhanced immune function. However, the effects of BJIKT on the immune system have been investigated in only a few clinical studies. The levels of CD3(+), CD4(+), and CD8(+) T cells and the CD4(+)/CD8(+) ratio have been used in clinical studies to evaluate immunoregulation. Previous meta-analyses have revealed that compared with chemotherapy alone, herbal medicines combined with chemotherapy significantly increase CD3(+) and CD4(+) levels and the CD4(+)/CD8(+) ratio while decreasing CD8(+) levels. These results indicate improvements in immune function; however, the significance of the CD4(+)/CD8(+) ratio remains unclear [85]. Therefore, clinical trials are required to evaluate the combination of BJIKT with ICIs, investigate improvements in survival, response rate, and adverse events, and explore the immune-related mechanisms of BJIKT through in-depth immune profiling and its correlation with clinical outcomes. Furthermore, rigorously designed RCTs using outcome measures with established validity and reliability, such as the Piper Fatigue Scale and KPS, are required to evaluate efficacy. An integrative approach to cancer treatment that combines herbal medicine with conventional therapies can further enhance the effectiveness of conventional therapies, improve patient's quality of life, and mitigate adverse reactions.

Conclusion

Over the past decade, the effects of BJIKT on cancer have been reported in various studies, primarily in East Asia. Preclinical studies on BJIKT use in treating cancer have mainly focused on the immune response and immunomodulatory effects of BJIKT. RCTs, which accounted for > 50% of the clinical studies on BJIKT, primarily focused on assessing the improvement in quality of life induced by chemotherapy plus BJIKT compared with chemotherapy alone and the

effectiveness of BJIKT in relieving cancer-related fever compared with non-steroidal anti-inflammatory drugs. With ICIs becoming a new paradigm in cancer treatment, investigating the clinical efficacy and safety of combination therapy with BJIKT and the association of immunomarker changes with clinical outcomes is crucial to further elucidate the effect of BJIKT on immune system modulation.

Abbreviations

PBMC	Peripheral blood mononuclear cells
BJIKT	Bojungikki-tang
ICIs	Immune checkpoint inhibitors
NK	Natural killer
TNF	Tumor necrosis factor
IL	Interleukin
TGF	Tumor growth factor
INF	Interferon
PD-1	Programmed death 1
PD-L1	Programmed death-ligand-1
RCT	Randomized controlled trial
Treg	Regulatory T
NSCLC	Non-small cell lung cancer
PI3K/AKT	Phosphatidylinositol 3-kinase/protein kinase B
EORTC-QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
Th17	T helper 17

Supplementary Information

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Additional file 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. PRISMA-ScR checklist items and page numbers reported in this paper.

Additional file 2. PRISMA 2020 checklist items and location where each item is reported in this paper.

Additional file 3. Search terms used in each database. A full search strategies in this scoping review.

Additional file 4. Summary of general characterics included in this review ($N=56$). General characteristics of 56 studies included in this review.

Additional file 5. Composition of BJIKT in experimental studies. Constitutients of BJIKT in experimental studies included in this review.

Additional file 6. Purpose of using BJIKT and its constituent herbs and dosages. Purpose and composition of BJIKT in clinical studies.

Additional file 7. Risk of bias graph and summary. Risk of bias graph and risk of bias summary for meta-analysis.

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Authors' contributions
EC: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. SWN: Data curation, Formal analysis, Investigation, Writing – original draft. MKJ: Conceptualization, Project administration, Supervision, Writing – review & editing.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncol. 2019;5:1749–68.
2. Zugazagoitia J, Guedes C, Ponce S, Ferrer I, Molina-Pinelo S, Paz-Ares L. Current challenges in cancer treatment. Clin ther. 2016;38:1551–66.
3. Qi F, Li A, Inagaki Y, Gao J, Li J, Kokudo N, Li X-K, Tang W. Chinese herbal medicines as adjuvant treatment during chemo- or radio-therapy for cancer. BioSci Trends. 2010;4:297–307.
4. Zhang X, Qiu H, Li C, Cai P, Qi F. The positive role of traditional Chinese medicine as an adjunctive therapy for cancer. Biosci Trends. 2021;15:283–98.
5. Qi F, Zhao L, Zhou A, Zhang B, Li A, Wang Z, Han J. 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. BioSci Trends. 2015;9:16–34.
6. Okumi H, Koyama A. Kampo medicine for palliative care in Japan. Biopsychosocial Med. 2014;8:6.
7. Lee MA. Current status of cancer immunotherapy with immune checkpoint inhibitors. J Korean Med Assoc. 2021;64:326–31.
8. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell. 2017;168:707–23.
9. Vafaei S, Zekiy AO, Khanamir RA, Zaman BA, Ghayourvahdat A, Azimizonuzi H, Zamani M. Combination therapy with immune checkpoint inhibitors (ICIs); a new frontier. Cancer Cell Int. 2022;22:2.
10. Park R, Lopes L, Cristancho CR, Riano IM, Saeed A. Treatment-related adverse events of combination immune checkpoint inhibitors: systematic review and meta-analysis. Front Oncol. 2020;10: 258.
11. Amitani M, Amitani H, Sloan RA, Suzuki H, Sameshima N, Asakawa A, Nerome Y, Owaki T, Inui A, Hoshino E. The translational aspect of complementary and alternative medicine for cancer with particular emphasis on Kampo. Front Pharmacol. 2015;6:150.
12. Kuchta K, Cameron S. Phytotherapy for cachexia: Where do we stand? Front Pharmacol. 2020;11:917.
13. Jeong JS, Ryu BH, Kim JS, Park JW, Choi WC, Yoon SW. Bojungikki-tang for cancer-related fatigue: a pilot randomized clinical trial. Integr Cancer Ther. 2010;9:331–8.
14. Yang A-K, He S-M, Liu L, Liu J-P, Qian Wei M, Zhou S-F. Herbal interactions with anticancer drugs: mechanistic and clinical considerations. Curr Med Chem. 2010;17:1635–78.
15. Zhu K, Fukasawa I, Furuno M, Inaba F, Yamazaki T, Kamemori T, Kousaka N, Ota Y, Hayashi M, Maehama T, et al. Inhibitory effects of herbal drugs on

the growth of human ovarian cancer cell lines through the induction of apoptosis. Gynecol Oncol. 2005;97:405–9.
16. Kao S-T, Yeh C-C, Hsieh C-C, Yang M-D, Lee M-R, Liu H-S, Lin J-G. The Chinese medicine Bu-Zhong-Yi-Qi-Tang inhibited proliferation of hepatoma cell lines by inducing apoptosis via G0/G1 arrest. Life Sci. 2001;69:1485–96.
17. Li T, Tamada K, Abe K, Tada H, Onoe Y, Tatsugami K, Harada M, Kubo C, Nomoto K. The restoration of the antitumor T cell response from stress-induced suppression using a traditional Chinese herbal medicine Hochu-ekki-to (TJ-41:Bu-Zhong-Yi-Qi-Tang). Immunopharmacology. 1999;43:11–21.
18. Chun J, Kang HN, Yi J-M, Hong SH, Park S-M, Jeong M-K. Bojungikki-tang enhances the effect of PD-1 blockade in a syngeneic murine model of lung carcinoma. Processes. 2022;10: 1683.
19. Kim J. The efficacy of Bojungikki-tang as an adjunctive therapy for cancer: a systematic review and meta-analysis. Doctor of Philosophy. Seoul: Kyung Hee University; 2020.
20. Arksey H, O'malley L. Scoping studies: towards a methodological framework. International journal of social research methodology. 2005;8:19–32.
21. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MD, Horsley T, Weeks L. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169:467–73.
22. Peters MD, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H. Chapter 11: scoping reviews. JBI manual for evidence synthesis. 2020;169:467–473.
23. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:343.
24. Wang Z, Qi F, Cui Y, Zhao L, Sun X, Tang W, Cai P. An update on Chinese herbal medicines as adjuvant treatment of anticancer therapeutics. Biosci Trends. 2018;12:220–39.
25. Yamaguchi K. Traditional Japanese herbal medicines for treatment of odontopathy. Front Pharmacol. 2015;6:176.
26. Yang XJ. Study on the mechanism of different meridian-returning and tonic formulas in the treatment of lung metastatic cancer. Master's degree: Beijing University of Chinese Medicine; 2013.
27. Hong E-H. The effects of Bojungikgi-tang(BJ-T) for hematopoietic function and weight loss in colon cancer induced mouse model. Graduate school of Kyung Hee University; 2014.
28. Ouyang M, Liu Y, Tan W, Xiao Y, Yu K, Sun X, Huang Y, Cheng J, RLuo R, Zhao X. Bu-zhong-yi-qi pill alleviate the chemotherapy-related fatigue in 4 T1 murine breast cancer model. BMC Complement Altern Med. 2014;14:497.
29. Gou H, Gu L, Shang B, Xiong Y, Wang C. Protective effect of Bu-Zhong-Yi-Qi decoction, the water extract of Chinese traditional herbal medicine, on 5-fluorouracil-induced intestinal mucositis in mice. Hum Exp Toxicol. 2016;35:1243–51.
30. Chun J, Park S-M, Yi J-M, Ha IJ, Kang HN, Jeong M-K. Bojungikki-Tang improves response to PD-L1 immunotherapy by regulating the tumor microenvironment in MC38 tumor-bearing mice. Front Pharmacol. 2022;13: 901563.
31. Lee SD, Park YC. Toxicology for herbal medicine. Paju: Korean Studies Information; 2013.
32. Sato T, Kita K, Sato C, Kaneda A. Hochu-ekki-to (Bu-zhong-yi-qi-tang), a herbal medicine, enhances cisplatin-induced apoptosis in HeLa cells. Mol Med Rep. 2015;12:6215–20.
33. Yu N, Xiong Y, Wang C. Bu-Zhong-Yi-Qi Decoction, the Water Extract of Chinese Traditional Herbal Medicine, Enhances Cisplatin Cytotoxicity in A549/DDP Cells through Induction of Apoptosis and Autophagy. Biomed Res Int. 2017;2017:3692797.
34. Kiyomi A, Matsuda A, Nara M, Yamazaki K, Imai S, Sugiura M. Immunological differences in human peripheral blood mononuclear cells treated with traditional Japanese herbal medicines Hochuekkito, Juzentaihoto, and Ninjin'yoeito from different pharmaceutical companies. Evid Based Complement Alternat Med. 2021;2021:7605057.
35. Li F. Mechanism study on inhibition of laryngeal squamous cell carcinoma model based on LncRNA UCA1/miRNA-185-5P pathway Fuzheng Exorcism. Master's degree: Luzhou: Southwest Medical University; 2022.
36. Xu R, Wu J, Zhang X, Zou X, Li C, Wang H, Yuan M, Chen M, Sun Q, Liu S. Modified Bu-zhong-yi-qi decoction synergies with 5 fluorouracile to inhibits gastric cancer progress via PD-1/PD- L1-dependent T cell immunization. Pharmacol Res. 2020;152: 104623.
37. Zang LM. Main pharmacological effects and research progress of Bu-zhong-yi-qi decoction. Zhejiang Journal Animal Science and Veterinary Medicine. 2014;3:18–9.
38. Yu JH, Jiang Z, Long WN, Jun PL, Wang WL. Improvement of cancer-caused fatigue by Bu-zhong-yi-qi decoction. Jilin Journal of Traditional Chinese Medicine. 2019;39:886–9.
39. Lee E, Choi Y, Kwak M. Effects of Bojungikki-tang extracts on improvement of fatigue and quality of life in patient with cervical cancer after concurrent chemoradiation therapy : a case. The Journal of East-West Medicine. 2015;40:25–34.
40. Lee B-J, Kim K-I, Choi C-W, Kim JY, Lee J-H. Long-term progression-free survival in a patient with advanced non-small-cell lung cancer treated with low-dose gefitinib and traditional herbal medicine: a case report. Medicine (Baltimore). 2021;100: e24292.
41. Ning B, Li B, Hao S, Wang X. Clinical study on the treatment of cancer-related fatigue of spleen qi deficiency after surgery for non-small cell lung cancer by adding Bu-zhong-yi-qi decoction. Lishizhen Medicine and Materia Medica Research. 2020;31:2685–8.
42. Shimizu M, Takayama S, Kikuchi A, Arita R, Ono R, Ishizawa K, Ishii T. Kampo medicine treatment for advanced pancreatic cancer: A case series. Front Nutr. 2021;8: 702812.
43. A study on the efficacy and safety of Hochuekkito for anorexia of elderly gastric cancer patients. https://doi.org/10.1002/central/CN-01880734/full.
44. Clinical evaluation of the efficacy and safety of Hochuekkito for fatigue in patients with myeloproliferative neoplasms. https://doi.org/10.1002/central/CN-01902636/full.
45. Effects of Buzhongyiqi pills on appetite in patients with gastrointestinal cancer : a randomized controlled clinical research. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02184914/full.
46. Safety and efficacy of Bojungikki-tang in advanced NSCLC patients being treated with immune checkpoint inhibitor: a pilot multicenter, randomized, placebo-controlled study. https://doi.org/10.1002/central/CN-02351983/full.
47. Chao T-H, Fu P-K, Chang C-H, Chang S-N, Mao FC, Lin C-H, Evidence-based Chinese Medicine Research Group. Prescription patterns of Chinese herbal products for post-surgery colon cancer patients in Taiwan. J Ethnopharmacol. 2014;155:702–708.
48. Li T-M, Yu Y-H, Tsai F-J, Cheng C-F, Wu Y-C, Ho T-J, Liu X, Tsang H, Lin T-H, Liao C-C, et al. Characteristics of Chinese herbal medicine usage and its effect on survival of lung cancer patients in Taiwan. J Ethnopharmacol. 2018;213:92–100.
49. Niimi N. Systemic kampo learning method: modern kampo for beginners. Seoul: Cheonghong; 2015.
50. Hu XW, Li HJ, Qi YF. Exploring the treatment ideas of cancer fever based on Dongguan yin-fire theory. J Sichuan Tradit Chin Med. 2019;37:34–6.
51. Motoo Y. Evidence-based cancer supportive cancer with herbal medicine. Seoul: Cheonghong; 2020.
52. Motoo Y. Role of Kampo medicine in modern cancer therapy: towards completion of standard treatment. J Nippon Med Sch. 2022;89:139–44.
53. Motoo Y, Cameron S. Kampo medicines for supportive care of patients with cancer: A brief review. Integr Med Res. 2022;11: 100839.
54. Xu D. The clinical research of the effect of Buzhong Yiqi decoction in the treatment of Qi-blood deficiency type of cancerous fever. Guangzhou: Guangzhou University of Chinese Medicine; 2013.
55. Lee AJ, Lee HJ, Kim JD, Jung HJ, Bae SH, Ryoo HM, Kim SG. Changes of Peripheral Blood Lymphocyte Subtypes in Patients with End Stage Cancer Administered Localized Radiotherapy and Bojungikki-Tang. Evidence-Based Complement Alternative Med. 2014;2014(1):207613.
56. Zhu GD, Liu F, Zhu ZG, Sun QX, Xu X, Chen GP, Zhu Y. Clinical observation on the treatment of cancer-related fatigue in the interphase of chemotherapy for gastric cancer by Bu-zhong-yi-qi-tang. Mod Hosp. 2016;16:1169–71.
57. Liu YY, Han T, Zhang SH, Chen WC, Zhang GZ, Zheng ZD, Xie XD. Clinical observation on the treatment of cancer-related fatigue in patients with advanced tumors by Bu-zhong-yi-qi-tang. Clin Misdiagnosis Mistherapy. 2016;29:88–91.
58. Zhang H, Zhou YZ. An intervention study of Bu-zhong-yi-qi-tang plus reduction on thyroid cancer after surgery. Inner Mongol Journal of Traditional Chinese Medicine. 2017;36:59–60.

59. Chen ZC, Cai HB, Liang J. Effects of Buzhong Yiqi Decoction on cancer-related fatigue. Journal of Youjiang Medical University for Nationalities. 2017;39:217–9.
60. Li GL. Effect of Buzhong Yiqi decoction on the adverse reactions after chemotherapy of middle–late stage malignant tumor. J Shanxi Coll Tradit Chin Med. 2018;19:32–4.
61. Lin ZR, Pan P. Clinical observation on the treatment of cancer-related fatigue by Bu-Zhong-Yi-Qi Decoction. Guangming Journal of Chinese Medicine. 2018;33:2039–41.
62. Yang CW, Zhu Z, Chen YQ, Chen ZJ, Huang QG, Peng SZ. Clinical investigation on the improvement of cancer-related fatigue in patients with advanced malignant tumors by Bu-Zhong-Yi-Qi Decoction. Clinical Journal of Chinese Medicine. 2018;10:74–6.
63. Zheng YH, Zhang HG. Clinical study on the treatment of cancerous fever with qi and blood deficiency by Bu-Zhong-Yi-Qi Decoction. Chinese Journal of Geriatric Care. 2018;16:40–2.
64. Chen J, Hu L, Guo T. Clinical analysis of using Buzhong Yiqi Decoction in the treatment of cancerous fever with Qi deficiency and blood. Journal of Sichuan of Traditional Chinese Medicine. 2018;36:72–4.
65. Wang C, Ma Y. Observations on the efficacy of Bu-zhong-yi-qi decoction in the treatment of cancerous fever. Journal of Clinical Medicine Literature. 2019;6:155.
66. Zhang Q, Zhang A. Clinical observation of Buzhong Yiqi tang in treating cancerous fever. China's Naturopathy. 2019;27:41–2.
67. Okabe H, Kinjo Y, Obama K, Hosogi H, Hata H, Asao Y, Harada H, Manaka D, Itami A, Teramukai S, et al. A randomized phase II study of S-1 adjuvant chemotherapy with or without Hochu-ekki-to, a Japanese herbal medicine, for stage II/III gastric cancer: the KUGC07 (SHOT) trial. Front Oncol. 2019;9:294.
68. Ning B. Clinical study on Jiawei Buzhong Yiqi decoction in the treatment of cancer-related fatigue after colorectal cancer. Master's degree. Taiyuan: Shanxi Provincial Institute of TCM; 2020.
69. Luo W, Wang T, Xiong G-j, Li Z-w, Qian C, Yang C-y, Fan G-y, Ruan Z-l, Yu X-w, Wang R. Effect and safety of modified Buzhong Yiqitang on VEGF, IGF-1, TGF-β1, and immune function in postoperative patients with non-small cell lung cancer after chemotherapy. Chinese Journal of Experimental Traditional Medical Formulae. 2021;27:90–95.
70. Liu HY. Exploring the effect of Bu-Zhong-Yi-Qi Decoction on cancer-related fatigue and immune function in patients with gastric cancer in the interphase of chemotherapy. J Med Theor & Prac. 2022;35:3663–5.
71. Edahiro Y, Koike M, Nojiri S, Harada Y, Gotoh A, Fujibayashi K, Nishizaki Y, Yanagisawa N, Takaku T, Nitta H, et al. A pilot study examining the efficacy of hochuekkito for improving quality of life in patients with myeloproliferative neoplasms. Jpn J Clin Oncol. 2022;52:872–8.
72. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky performance status scale: an examination of its reliability and validity in a research setting. Cancer. 1984;53:2002–7.
73. Zhang J, Liu X, Li X, Ying Z, Liu W. Mechanism of action of Bu Zhong Yi Qi Decoction in the treatment of chronic fatigue syndrome based on network pharmacology and molecular docking. Pharmacological Research-Modern Chinese Medicine. 2022;4: 100139.
74. Ryan JL, Carroll JK, Ryan EP, Mustian KM, Fiscella K, Morrow GR. Mechanisms of cancer-related fatigue. Oncologist. 2007;12:22–34.
75. Kuroiwa A, Yan H, Eshita A, Naitoh S, Nagayama A. Effect of a traditional Japanese herbal medicine, Hochu-ekki-to (Bu-Zhong-Yi-Qi Tang), on immunity in elderly persons. Int Immunopharmacol. 2004;4:317–24.
76. Wang CY, Huang HS, Su YC, Tu CY, Hsia TC, Huang ST. Conventional treatment integrated with Chinese herbal medicine improves the survival rate of patients with advanced non-small cell lung cancer. Complement Ther Med. 2018;40:29–36.
77. Yu YX, Wang S, Liu ZN, Zhang X, Hu ZX, Dong HJ, Lu XY, Zheng JB, Cui HJ. Traditional Chinese medicine in the era of immune checkpoint inhibitor: theory, development, and future directions. Chin Med. 2023;18:59.
78. Ko MM, Jeong MK, Choi CM, Lee SH, Chun J, Yi JM, Jang H, Lee SY. Safety and efficacy of Bojungikki-Tang in advanced NSCLC patients receiving treatment with immune checkpoint inhibitors: protocol for a multicenter, double-blind, randomized, placebo-controlled pilot trial. Int J Environ Res Public Health. 2023;20:4507.
79. Rivoltini L, Carrabba M, Huber V, Castelli C, Novellino L, Dalerba P, Mortarini R, Arancia G, Anichini A, Fais S. Immunity to cancer: attack and escape in T lymphocyte–tumor cell interaction. Immunol Rev. 2002;188:97–113.
80. Hiraoka K, Miyamoto M, Cho Y, Suzuoki M, Oshikiri T, Nakakubo Y, Itoh T, Ohbuchi T, Kondo S, Katoh H. Concurrent infiltration by CD8+ T cells and CD4+ T cells is a favourable prognostic factor in non-small-cell lung carcinoma. Br J Cancer. 2006;94:275–80.
81. Jarnicki AG, Lysaght J, Todryk S, Mills KH. Suppression of antitumor immunity by IL-10 and TGF-β-producing T cells infiltrating the growing tumor: influence of tumor environment on the induction of CD4+ and CD8+ regulatory T cells. J Immunol. 2006;177:896–904.
82. Diskin B, Adam S, Cassini MF, Sanchez G, Liria M, Aykut B, Buttar C, Li E, Sundberg B, Salas RD. PD-L1 engagement on T cells promotes self-tolerance and suppression of neighboring macrophages and effector T cells in cancer. Nat Immunol. 2020;21:442–54.
83. Gorgulho J, Roderburg C, Beier F, Bokemeyer C, Brümmendorf TH, Loosen SH, Luedde T. Soluble lymphocyte activation gene-3 (sLAG3) and CD4/CD8 ratio dynamics as predictive biomarkers in patients undergoing immune checkpoint blockade for solid malignancies. Br J Cancer. 2024;130:1013–22.
84. Lee P-H, Yang T-Y, Chen K-C, Huang Y-H, Tseng J-S, Hsu K-H, Wu Y-C, Liu K-J, Chang G-C. Higher CD4/CD8 ratio of pleural effusion predicts better survival for lung cancer patients receiving immune checkpoint inhibitors. Sci Rep. 2021;11:9381.
85. Zhu L, Li L, Li Y, Wang J, Wang Q. Chinese herbal medicine as an adjunctive therapy for breast cancer: A systematic review and meta-analysis. Evidence-Based Complementary and Alternative Medicine. 2016;2016:9469276.

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