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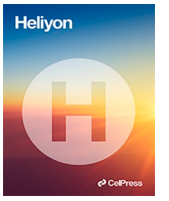

Research article

Efficacy and safety of compound kushen injection for treating advanced colorectal cancer: A protocol for a systematic review and meta-analysis

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A B S T R A C T

Introduction: Compound Kushen Injection (CKI) is a traditional Chinese medicine extracted from *Sophora flavescens* Aiton and *Heterosmilax japonica* Kunth. Widely utilized in China for the comprehensive treatment of colorectal cancer (CRC), this study aims to systematically assess the efficacy and safety of CKI when combined with chemotherapy for the treatment of advanced CRC, based on available data.

Methods: Randomized controlled trials investigating the efficacy and safety of CKI combined with chemotherapy in the treatment of advanced CRC will be comprehensively searched from databases, including PubMed, Web of Science, Cochrane Library, EMBASE, China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang, Chinese Biomedicine Database Searches, Chinese Clinical Trial Registry, and ClinicalTrials.gov until November 2022. Two independent reviewers will screen the studies, assess the risk of bias, and extract data in duplicate. The ROB2 tool will be employed to assess the quality of included studies. Stata 16 will be used for data analysis, and publication bias will be assessed using funnel plots and Egger's test. The quality of evidence will be evaluated according to GRADE, and trial sequence analysis (TSA) will be utilized to calculate the final total sample size required for the meta-analysis. The results of this systematic review will be published in a peer-reviewed journal. The proposed review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022380106).

Discussion: This systematic review will integrate current evidence on CKI in advanced CRC and analyze the clinical efficacy and safety of CKI combined with different chemotherapy regimens, providing valuable guidance on the use of CKI in CRC patients.

1. Introduction

According to the latest global burden of cancer data for 2020 released by the International Agency for Research on Cancer (IARC), China ranks first in new cancer cases and deaths worldwide, and colorectal cancer (CRC) ranks third in incidence and second in mortality among malignant tumors [1]. The cancer incidence and mortality statistics in China, released in 2022, indicate that the incidence and mortality of CRC will be 29.51/100,000 and 14.14/100,000, respectively [2]. The occurrence of CRC is closely related to changes in dietary structure and lifestyle. In recent years, the incidence and mortality rates of CRC have steadily decreased in Western countries due to the availability of early diagnosis and treatment [3]. However, due to the aging population, industrialization, and changes in dietary structure, the number of CRC cases continues to increase in China, where it is now the second most common cancer behind gastric cancer [4]. The high incidence of CRC not only causes heavy medical and economic burdens but also leads to a

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considerable loss of social productivity. Therefore, screening for effective drugs and improving the therapeutic effects of CRC treatments are of great clinical significance.

Traditional Chinese medicine (TCM) is a distinctive element in cancer treatment in China [5]. A survey revealed that over 80% of cancer patients in China have undergone TCM treatment, attributing its popularity to its cost-effectiveness, minimal side effects, and significant improvement in quality of life [6–8]. Anti-cancer Chinese patent medicines within TCM contribute to comprehensive cancer treatment protocols, serving as a reference for clinical applications [9,10]. Compound Kushen Injection (CKI), derived from *Sophora flavescens* Aiton and *Heterosmilax japonica* Kunth, received approval from the China Food and Drug Administration in 1995 [11] and has since been extensively utilized in the clinical management of various malignant tumors, including CRC, demonstrating notable therapeutic effects [12]. The primary constituents of CKI, matrine, and oxymatrine, activate pro-apoptotic genes, regulate the cell cycle, impede DNA synthesis, inhibit cancer metastasis and invasion, reverse multidrug resistance, and prevent or alleviate chemotherapeutic toxicity [11,13–15]. Notably, Yang et al. [16] observed that CKI boasts the highest number of randomized controlled trials (RCTs) among Chinese herbal injections used for cancer treatment.

Despite recent systematic reviews assessing the clinical efficacy of CKI in CRC, certain shortcomings persist. Firstly, no review has systematically evaluated the overall quality of evidence. Secondly, it has been approximately five years since the last similar review published by Yu et al. [17] in 2017, with a search deadline of January 31, 2017. Given the increasing use of CKI in CRC treatment, a growing number of RCTs have emerged in recent years [18–20]. Furthermore, cumulative meta-analyses, when updated with new trials, undergo repeated significance tests, potentially leading to false-positive results and type-I errors [21]. Consequently, this study aims to update the evidence, employing trial sequence analysis (TSA) to account for the risk of random errors and ensure data reliability. In summary, our objective is to conduct a systematic review to impartially assess the efficacy and safety of CKI in CRC treatment, evaluate the overall quality of evidence, and ascertain the stability of current conclusions.

2. Materials and methods

The proposed review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022380106). The study will be conducted in full accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P), as detailed in Supplementary Material 1.

2.1. Eligibility criteria

2.1.1. Type of studies

The study design will be an RCT, irrespective of the use of a blinding method. All included studies will be required to provide detailed descriptions of the randomization process, utilizing methods such as random number tables and stratified randomization. The study will exclusively consider publications in English and Chinese, representing a limitation. Gray literature, encompassing conference papers, theses, dissertations, and unpublished studies, will be eligible for inclusion as long as sufficient information on methods and results is available. Exclusions will comprise abstracts, observational studies, study protocols, letters, comments, case reports, and animal studies.

2.1.2. Types of participants

We will include trials in which the study population comprises individuals with advanced (stage III or IV) CRC regardless of the pathological types. Patients with secondary CRC or other malignant tumors will not be considered.

2.1.3. Types of interventions

The treatment group will comprise participants who underwent treatment with CKI in conjunction with chemotherapy, administered either orally or intravenously. Patients who received neoadjuvant or arterial infusion chemotherapy will be excluded.

2.1.4. Types of comparators

The control group will include participants with chemotherapy only.

2.1.5. Types of outcomes

This study aims to assess primary efficacy outcomes focusing on short-term survival indicators, specifically the objective response rate (ORR) and disease control rate (DCR). Secondary efficacy outcomes will encompass long-term survival, performance status (measured by KPS score or the rate of KPS improvement), immune indicators, and the incidence of adverse reactions (such as leukopenia, liver, and kidney function, and gastrointestinal reactions).

The assessment of ORR and DCR aligns with response evaluations in anti-cancer treatment, conducted according to the criteria outlined by the World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST). Tumor disease changes, including complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD), will be utilized for evaluation. ORR is defined as CR + PR, while DCR is defined as CR + PR + SD.

2.2. Search strategy

Relevant RCTs will be systematically searched across multiple databases, including PubMed, Web of Science, Cochrane Library,

EMBASE, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP database), Wanfang, and Chinese Biomedicine Database (CBM), from inception to November 2022. The search will be updated before manuscript submission. Only studies published in Chinese and English will be included. The Chinese Clinical Trial Registry (ChiCTR, https://www.chictr.org.cn/) and ClinicalTrials.gov (https://clinicaltrials.gov/) will also be searched for ongoing and completed trials.

The search strategy will utilize a combination of controlled vocabulary (Medical Subject Headings and Emtree terms) and free-text terms. Terms such as "Colorectal Neoplasms," "Colonic Neoplasms," "Rectal Neoplasms," "Advanced," "Recurrence," "Metastasis," "Stage III," "Stage IV," "compound kushen Injection," and "randomized controlled trial" will be used to inform the PubMed search strategy (Supplementary Material 2). Adaptations to this strategy will be made for other databases. Retrieved studies, references in reviews, clinical studies, and additional Chinese language journals will be potential sources, reviewed manually by one author (JW).

2.3. Study selection

Screening and selection were summarized using a PRISMA flow diagram in Fig. 1. The search results will be imported into EndNote 20. Two review authors (JW and XM) will independently access the titles and summaries of the database search results after removing duplicates. The full text will then be reviewed and assessed according to the eligibility criteria. RCTs that meet the eligibility criteria will be included. Any disagreements will be resolved through discussion or interposition with another review member (XW).

2.4. Data extraction

Microsoft Excel will be employed for data extraction. The included trials yield the following data: (1) identification information (publication year and first author); (2) general information (randomization process and sample size); (3) participant details (clinical stage, average age, and sex); (4) intervention specifics (dosage and duration of CKI); (5) comparison details (chemotherapy regimen, dose, frequency, and treatment duration); and (6) outcome particulars.

2.5. Risk of bias assessment

We will utilize ROB2 (version 2 of the Cochrane tool for assessing the risk of bias in randomized trials), as provided by the Cochrane

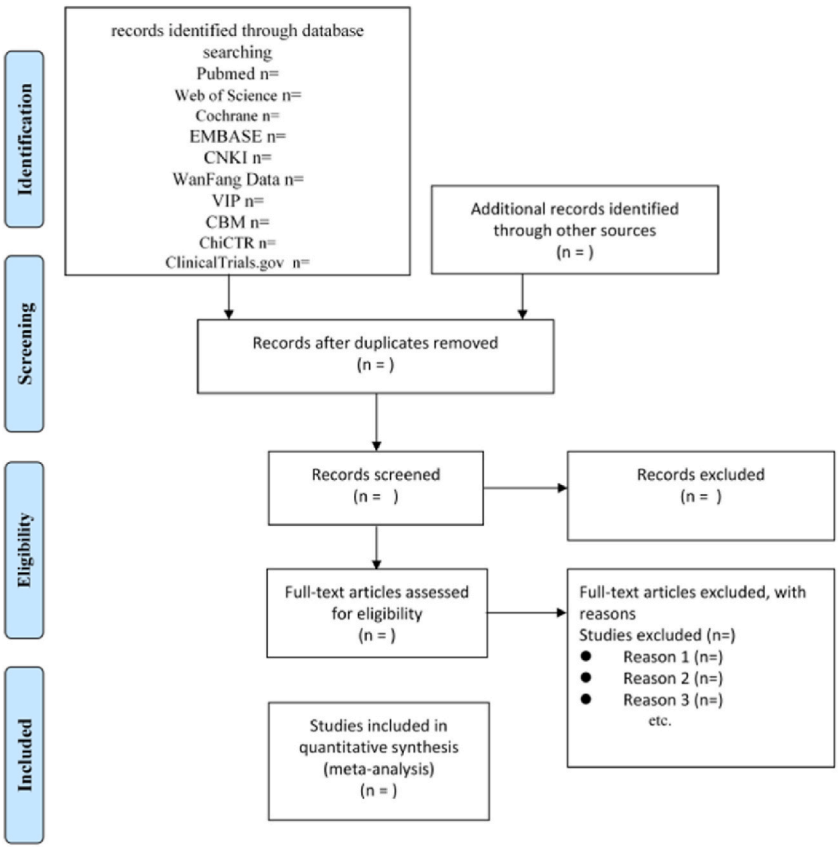

Fig. 1. Flow diagram of the literature search.

Methodology Group, to evaluate the quality of the included trials [22]. ROB2 encompasses the following five areas of assessment: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The investigators (JW and XM) will work independently, categorizing the risk of bias in each field into three levels: 'low,' 'some concerns,' and 'high' risk of bias. This classification is based on responses to multiple signal questions in each field, including Yes (Y), Probably Yes (PY), Probably No (PN), No (N), and No Information (NI).

2.6. Data synthesis

The meta-analysis will be conducted using Stata 16 software when adequate data on primary or secondary outcomes are obtained, the results among the studies are homogeneous, and forest plots will be presented. Binary variables will be analyzed using relative risk (RR), and continuous variables will be assessed using mean difference (MD). The random-effects model will be employed when clinical or statistical heterogeneity exists; otherwise, the fixed-effects model will be used for data synthesis. Statistical inconsistencies will be quantified using the I^2 statistic. An I^2 value of >50% will be considered indicative of substantial heterogeneity, while an $I^2 > 75\%$ is considered indicative of significant heterogeneity [23]. Studies will be quantitatively synthesized when there are three or more RCT reports within a single grouping. In some cases, such as different effect measures, limited comparative evidence, or considerable heterogeneity, meta-analyses might be excluded, and narrative synthesis will be utilized. Given the strong correlation between the two antitumor treatment response evaluation criteria, WHO and RECIST are considered homogeneous [24].

2.7. Subgroup analysis

Possible sources of heterogeneity and confounding factors will be explored through subgroup analysis and meta-regression, if warranted. We plan to conduct prespecified subgroup analyses based on the location of the tumor, different chemotherapy regimens, doses, and duration of CKI if sufficient data are available.

2.8. Sensitivity analysis

A sensitivity analysis will be conducted to assess the robustness and stability of critical outcomes. Trials will be excluded from the analysis if they meet any of the following criteria: (1) high risk of bias, which could potentially influence the effect size; (2) considerable heterogeneity ($I^2 \geq 75\%$); and (3) insufficient data availability or other features recognized by at least two reviewers.

2.9. Publication bias

Funnel plots and Egger's test [25] will be employed for a visual inspection when there are at least ten studies with the same outcome. It aims to evaluate the potential existence of publication bias.

2.10. Quality of evidence

The GRADE method will be utilized to evaluate and grade the quality of evidence for each outcome measure, considering five aspects: risk of bias, inconsistency, indirectness, imprecision, and publication bias [26]. GRADE Pro GDT software procedures and guidelines [27] will be followed. The GRADE evaluation will be conducted by JW and XM, who will use footnotes to justify decisions on downgrading or upgrading ratings. Any disagreements will be resolved through consultation with a third review author (XW) until a consensus was reached.

2.11. Trial sequential analysis

In a meta-analysis, the risk of reaching a false-positive or false-negative conclusion should be minimized. Therefore, we will use the TSA Software (Copenhagen Trial Unit, Copenhagen, Denmark) to control the risk of random errors and assess whether the results are conclusive. TSA allows the estimation of the required sample size to detect or reject a prespecified realistic intervention effect, and the TSA can adjust the CIs. If the accrued information size is too small compared with the required information size, the TSA-adjusted CI becomes wider than the traditional 95% CI, and the threshold for statistical significance is restricted. However, when the required amount of information is reached, they become identical.

3. Discussion

Natural compounds with anti-cancer activities show promising prospects for application in cancer therapy. Multicomponent pharmaceutical agents can achieve a synergistic effect, boosting cytotoxicity in cancer cells and exerting additional effects on the tumor environment and immune response to tumors [28–31]. CKI is a crucial representative complementary and alternative drug for CRC in China, exerting anti-tumor effects through various biological processes or multi-target pathways [32–34]. Network pharmacology, experimental studies, and clinical trials have substantiated the beneficial role of CKI in CRC treatment [32,35]. The components of CKI are effective in blocking cancer migration and invasion, potentially by reducing lamellipodial abundance, length of extension, and the area of F-actin polymerization [36]. Therefore, the pharmacological complexity of CKI may make it more effective

in blocking cell migration than single agents. revealed that CKI synergistically enhances the ability of cisplatin to mediate antitumor activity in p53-R273H/P309S mutant CRC cells via induction of the extrinsic apoptotic pathway by specifically increasing the expression of DR5 [37–39]. This study will provide evidence for the potential application of CKI combined with cisplatin in the treatment of p53-mutated CRC. Another study demonstrated that CKI effectively induces cell cycle arrest in CRC cells in vitro and suppresses CRC development in *vivo* by downregulating the expression of p53 and CHEK1 [40]. An RCT involving 78 patients with advanced CRC showed that CKI combined with FOLFOX4 increased the overall response rate by 12.8% and prolonged the 1-year progression-free survival rate by 15.39% compared to chemotherapy alone [16]. Chemotherapy with CKIs has been extensively adopted in clinical practice to synergize therapeutic effects, attenuate side effects, relieve cancer pain, and treat cancer ascites, suggesting that CKI possesses a broad spectrum of anti-cancer properties [41,42].

This study aims to consolidate current evidence on CKI in advanced CRC and analyze the clinical efficacy and safety of CKI when combined with various chemotherapy regimens. The primary strength of this study lies in the selection of trials that employed a clear randomization method, eliminating any instances of ambiguous random expressions. This meticulous approach results in a higher level of evidence. Simultaneously, the introduction of TSA facilitates the timely summarization of meta-analyses. This process allows for the termination of ineffective trials and the early promotion of effective ones. Consequently, establishing termination criteria for clinical trials at the earliest opportunity is crucial. In clinical trials, a comprehensive assessment of results from various studies is essential for understanding their authenticity and reliability. However, potential biases may exist in some studies. To address and rectify the impact of these biases, funnel plots, and Egger's test will be employed for a meticulous evaluation of the study results and interpretation of conclusions. Owing to limited resources, we are compelled to exclude unpublished studies and those not published in English or Chinese languages, potentially introducing a selection bias into our research. The ROB2 will be employed to assess the quality of each study across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. While this research is a protocol, there is no detailed information on the risk of specific bias domains, which may impact the comprehensive evaluation of study validity. Relevant details will be expounded upon in a forthcoming publication. Notably, we will include patients with advanced CRC and do not distinguish specific pathological types. Subgroup analysis will be used to analyze the classification of CRC in the future text. Despite the established role of CKI in alleviating cancer and mitigating side effects, there exists a critical gap in long-term safety data, particularly in combination with chemotherapy. Consequently, we advocate for additional long-term safety clinical trials focusing on the combined use of CKI and chemotherapy for CRC treatment in the future.

This study primarily centers on the Chinese population, prompting concerns regarding the generalizability of the findings to diverse global populations. To gain a more comprehensive understanding of the CRC problem and to develop more effective public health policies, there is a need to extend the generalization of our findings to a broader global population. We recommend conducting global multicenter trials in the future. The study will offer valuable guidance on the use of CKI in patients with CRC. We aspire to update the available evidence with data obtained from upcoming trials, contributing to the refinement of clinical practices and the advancement of global health initiatives.

Data availability statement

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding authors.

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Ethics declarations

An ethics statement was not required for this study type, because no human or animal subjects or materials were used.

CRediT authorship contribution statement

Jingyuan Wu: Writing – original draft, Software, Resources, Methodology, Formal analysis, Data curation. **Xinyi Ma:** Writing – original draft, Methodology, Formal analysis, Data curation. **Xinmiao Wang:** Writing – original draft, Software, Methodology, Investigation, Data curation. **Guanghui Zhu:** Writing – review & editing. **Heping Wang:** Writing – review & editing. **Jie Li:** Writing – review & editing, Visualization, Validation, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26981.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 71 (2021) 209–249, https://doi.org/10.3322/caac.21660.

[2] R. Zheng, S. Zhang, H. Zeng, S. Wang, K. Sun, R. Chen, L. Li, W. Wei, J. He, Cancer incidence and mortality in China, Journal of the National Cancer Center 2 (2022) 1–9, https://doi.org/10.1016/j.jncc.2022.02.002, 2016.

[3] R.L. Siegel, K.D. Miller, A. Goding Sauer, S.A. Fedewa, L.F. Butterly, J.C. Anderson, A. Cercek, R.A. Smith, A. Jemal, Colorectal cancer statistics, 2020, CA Cancer J Clin 70 (2020) 145–164, https://doi.org/10.3322/caac.21601.

[4] W. Cao, H.-D. Chen, Y.-W. Yu, N. Li, W.-Q. Chen, Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020, Chin Med J (Engl) 134 (2021) 783–791, https://doi.org/10.1097/CM9.0000000000001474.

[5] L. Jiao, L. Bi, Y. Lu, Q. Wang, Y. Gong, J. Shi, L. Xu, Cancer chemoprevention and therapy using Chinese herbal medicine, Biol. Proced. Online 20 (2018) 1, https://doi.org/10.1186/s12575-017-0066-1.

[6] J.L. McQuade, Z. Meng, Z. Chen, Q. Wei, Y. Zhang, W. Bei, J.L. Palmer, L. Cohen, Utilization of and attitudes towards traditional Chinese medicine therapies in a Chinese cancer hospital: a survey of patients and physicians, Evid Based Complement Alternat Med (2012) 504507, https://doi.org/10.1155/2012/504507, 2012.

[7] N.R. Rarokar, S.D. Saoji, N.V. Deole, M. Gaikwad, A. Pandey, C. Kamaraj, S.V. Chinni, V. Subramaniyan, G. Ramachawolran, S. Dharashivkar, Preparation and formula optimization of cephalexin loaded transferosomal gel by QbD to enhance the transdermal delivery: in vitro, ex vivo and in vivo study, J. Drug Deliv. Sci. Technol. 89 (2023) 104968, https://doi.org/10.1016/j.jddst.2023.104968.

[8] N. Mujafarkani, F.M.M. Ahamed, K.S. Babu, S. Debnath, A.A. Sayed, G.M. Albadrani, M.Q. Al-Ghadi, V. Kumarasamy, V. Subramaniyan, C. Kamaraj, M. M. Abdel-Daim, Unveiling a novel terpolymer-metal complex: a detailed exploration of synthesis, characterization, and its potential as an antimicrobial and antioxidant agent, Heliyon 9 (2023) e20459, https://doi.org/10.1016/j.heliyon.2023.e20459.

[9] S. Wang, S. Long, Z. Deng, W. Wu, Positive role of Chinese herbal medicine in cancer immune regulation, Am. J. Chin. Med. 48 (2020) 1577–1592, https://doi.org/10.1142/S0192415X20500780.

[10] G. Ke, J. Zhang, W. Gao, J. Chen, L. Liu, S. Wang, H. Zhang, G. Yan, Application of advanced technology in traditional Chinese medicine for cancer therapy, Front. Pharmacol. 13 (2022) 1038063, https://doi.org/10.3389/fphar.2022.1038063.

[11] W. Wang, R. You, W. Qin, L. Hai, M. Fang, G. Huang, R. Kang, M. Li, Y. Qiao, J. Li, A. Li, Anti-tumor activities of active ingredients in compound kushen injection, Acta Pharmacol. Sin. 36 (2015) 676–679, https://doi.org/10.1038/aps.2015.24.

[12] T.N. Aung, Z. Qu, R.D. Kortschak, D.L. Adelson, Understanding the effectiveness of natural compound mixtures in cancer through their molecular mode of action, Int. J. Mol. Sci. 18 (2017) 656, https://doi.org/10.3390/ijms18030656.

[13] C. Chang, S.-P. Liu, C.-H. Fang, R.-S. He, Z. Wang, Y.-Q. Zhu, S.-W. Jiang, Effects of matrine on the proliferation of HT29 human colon cancer cells and its antitumor mechanism, Oncol. Lett. 6 (2013) 699–704, https://doi.org/10.3892/ol.2013.1449.

[14] R. Thapa, O. Afzal, G. Gupta, A.A. Bhat, W.H. Almalki, S.I. Alzarea, I. Kazmi, A.S.A. Altamimi, V. Subramaniyan, L. Thangavelu, S.K. Singh, K. Dua, Unveiling the connection: long-chain non-coding RNAs and critical signaling pathways in breast cancer, Pathol. Res. Pract. 249 (2023) 154736, https://doi.org/10.1016/j.prp.2023.154736.

[15] P. Bhatt, V. Kumar, V. Subramaniyan, K. Nagarajan, M. Sekar, S.V. Chinni, G. Ramachawolran, Plasma modification techniques for natural polymer-based drug delivery systems, Pharmaceutics 15 (2023) 2066, https://doi.org/10.3390/pharmaceutics15082066.

[16] M. Yang, S.-J. Zhu, C. Shen, R. Zhai, D.-D. Li, M. Fang, J.-N. Xu, Y.-N. Gan, L. Yang, Z.-Y. Ren, R.-X. Zheng, N. Robinson, J.-P. Liu, Clinical application of Chinese herbal injection for cancer care: evidence-mapping of the systematic reviews, meta-analyses, and randomized controlled trials, Front. Pharmacol. 12 (2021) 666368, https://doi.org/10.3389/fphar.2021.666368.

[17] L. Yu, Y. Zhou, Y. Yang, F. Lu, Y. Fan, Efficacy and safety of compound kushen injection on patients with advanced colon cancer: a meta-analysis of randomized controlled trials, Evid Based Complement Alternat Med (2017) 7102514, https://doi.org/10.1155/2017/7102514, 2017.

[18] W. Song, Clinical study of compound kushen injection combined with chemotherapy in treatment of advanced colon cancer, Liaoning J. Tradit. Chin. Med 48 (2021) 159–160.

[19] X. Gao, H. Sun, Y. Guo, L. Wang, X. Ma, Clinical study of compound kushen injection combined with chemotherapy in treatment of advanced colon cancer, Liaoning J. Tradit. Chin. Med 48 (2021) 128–130.

[20] W. Liu, X. Liu, Clinical efficacy and survival analysis of compound Kushen injection combined with FOLFOX4 in the treatment of 78 patients with advanced colorectal cancer, Anti-Tumor Pharm. 12 (2022) 391–395.

[21] Z. Mao, L. Gao, G. Wang, C. Liu, Y. Zhao, W. Gu, H. Kang, F. Zhou, Subglottic secretion suction for preventing ventilator-associated pneumonia: an updated meta-analysis and trial sequential analysis, Crit. Care 20 (2016) 353, https://doi.org/10.1186/s13054-016-1527-7.

[22] J.A.C. Sterne, J. Savović, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, C.J. Cates, H.-Y. Cheng, M.S. Corbett, S.M. Eldridge, J.R. Emberson, M.A. Hernán, S. Hopewell, A. Hróbjartsson, D.R. Junqueira, P. Jüni, J.J. Kirkham, T. Lasserson, T. Li, A. McAleenan, B.C. Reeves, S. Shepperd, I. Shrier, L.A. Stewart, K. Tilling, I.R. White, P.F. Whiting, J.P.T. Higgins, RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ 366 (2019) l4898, https://doi.org/10.1136/bmj.l4898.

[23] M. Cumpston, T. Li, M.J. Page, J. Chandler, V.A. Welch, J.P. Higgins, J. Thomas, Updated Guidance for Trusted Systematic Reviews: a New Edition of the Cochrane Handbook for Systematic Reviews of Interventions, Cochrane Database of Systematic Reviews, 2019, https://doi.org/10.1002/14651858.ED000142.

[24] M. Aras, T.Y. Erdil, F. Dane, S. Gungor, T. Ones, F. Dede, S. Inanir, H.T. Turoglu, Comparison of WHO, RECIST 1.1, EORTC, and PERCIST criteria in the evaluation of treatment response in malignant solid tumors, Nucl. Med. Commun. 37 (2016) 9–15, https://doi.org/10.1097/MNM.0000000000000401.

[25] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (1997) 629–634, https://doi.org/10.1136/bmj.315.7109.629.

[26] G.H. Guyatt, A.D. Oxman, G.E. Vist, R. Kunz, Y. Falck-Ytter, P. Alonso-Coello, H.J. Schünemann, GRADE Working Group, GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, BMJ 336 (2008) 924–926, https://doi.org/10.1136/bmj.39489.470347.AD.

[27] E.K. Arnesen, J.J. Christensen, R. Andersen, H. Eneroth, M. Erkkola, A. Høyer, E.W. Lemming, H.M. Meltzer, Þ.I. Halldórsson, I. Þórsdóttir, U. Schwab, E. Trolle, R. Blomhoff, The Nordic Nutrition Recommendations 2022 - handbook for qualified systematic reviews, Food Nutr. Res. 64 (2020), https://doi.org/10.29219/fnr.v64.4404.

[28] L. Gao, K.-X. Wang, Y.-Z. Zhou, J.-S. Fang, X.-M. Qin, G.-H. Du, Uncovering the anticancer mechanism of Compound Kushen Injection against HCC by integrating quantitative analysis, network analysis and experimental validation, Sci. Rep. 8 (2018) 624, https://doi.org/10.1038/s41598-017-18325-7.

[29] X. Zhou, S.W. Seto, D. Chang, H. Kiat, V. Razmovski-Naumovski, K. Chan, A. Bensoussan, Synergistic effects of Chinese herbal medicine: a comprehensive review of methodology and current research, Front. Pharmacol. 7 (2016) 201, https://doi.org/10.3389/fphar.2016.00201.

[30] A.A. Bhat, R. Thapa, A. Goyal, V. Subramaniyan, D. Kumar, S. Gupta, S.K. Singh, K. Dua, G. Gupta, Curcumin-based nanoformulations as an emerging therapeutic strategy for inflammatory lung diseases, Future Med. Chem. 15 (2023) 583–586, https://doi.org/10.4155/fmc-2023-0048.

[31] S. Mukherjee, S. Nag, N. Mukerjee, S. Maitra, R. Muthusamy, N.K. Fuloria, S. Fuloria, M.D. Adhikari, K. Anand, N. Thorat, V. Subramaniyan, S. Gorai, Unlocking exosome-based theragnostic signatures: deciphering secrets of ovarian cancer metastasis, ACS Omega 8 (2023) 36614–36627, https://doi.org/10.1021/acsomega.3c02837.

[32] R. He, S. Ou, S. Chen, S. Ding, Network pharmacology-based study on the molecular biological mechanism of action for compound kushen injection in anti-cancer effect, Med Sci Monit 26 (2020) e918520, https://doi.org/10.12659/MSM.918520.

[33] N. Rajan, S. Debnath, K. Perveen, F. Khan, B. Pandey, A. Srivastava, M.N. Khanam, V. Subramaniyan, V. Kumarasamy, P.J. Paul, M. Lal, Optimizing hybrid vigor: a comprehensive analysis of genetic distance and heterosis in eggplant landraces, Front. Plant Sci. 14 (2023) 1238870, https://doi.org/10.3389/fpls.2023.1238870.

[34] S. Akash, J. Baeza, S. Mahmood, N. Mukerjee, V. Subramaniyan, M.R. Islam, G. Gupta, V. Rajakumari, S.V. Chinni, G. Ramachawolran, F.M. Saleh, G. M. Albadrani, A.A. Sayed, M.M. Abdel-Daim, Development of a new drug candidate for the inhibition of Lassa virus glycoprotein and nucleoprotein by modification of evodiamine as promising therapeutic agents, Front. Microbiol. 14 (2023) 1206872, https://doi.org/10.3389/fmicb.2023.1206872.

[35] Z. Ye, X. Yao, Z. Chen, Q. Jin, Q. You, Exploring the nucleotide molecular mechanism of compound kushen injection for lung adenocarcinoma based on network pharmacology and molecular docking, Front. Oncol. 12 (2022) 1013052, https://doi.org/10.3389/fonc.2022.1013052.

[36] S. Nourmohammadi, T.N. Aung, J. Cui, J.V. Pei, M.L. De Ieso, Y. Harata-Lee, Z. Qu, D.L. Adelson, A.J. Yool, Effect of compound kushen injection, a natural compound mixture, and its identified chemical components on migration and invasion of colon, brain, and breast cancer cell lines, Front. Oncol. 9 (2019) 314, https://doi.org/10.3389/fonc.2019.00314.

[37] X. Wu, Y. Lu, X. Qin, Combination of Compound Kushen Injection and cisplatin shows synergistic antitumor activity in p53-R273H/P309S mutant colorectal cancer cells through inducing apoptosis, J. Ethnopharmacol. 283 (2022) 114690, https://doi.org/10.1016/j.jep.2021.114690.

[38] S.K. Gothwal, K. Goyal, H.C. Barjatya, B.L. Bhakar, R. Dahiya, Y. Singh, T.K. Saini, M. Agrawal, V. Subramaniyan, G. Gupta, Estimating the correlation between TYG and CIMT in non-diabetic adult patients, Obesity Medicine 35 (2022) 100460, https://doi.org/10.1016/j.obmed.2022.100460.

[39] S. Singh, null Hema, N. Sharma, M. Sachdeva, T. Behl, I. Zahoor, N.K. Fuloria, M. Sekar, S. Fuloria, V. Subramaniyan, A.M. Alsubayiel, H.G. Dailah, T. Naved, S. Bhatia, A. Al-Harrasi, L. Aleya, Focusing the pivotal role of nanotechnology in Huntington's disease: an insight into the recent advancements, Environ. Sci. Pollut. Res. Int. 29 (2022) 73809–73827, https://doi.org/10.1007/s11356-022-22830-2.

[40] J. Sun, M. Li, T. Lin, D. Wang, J. Chen, Y. Zhang, Q. Mu, H. Su, N. Wu, A. Liu, Y. Yu, Y. Liu, S. Wang, X. Yu, J. Guo, W. Yu, Cell cycle arrest is an important mechanism of action of compound Kushen injection in the prevention of colorectal cancer, Sci. Rep. 12 (2022) 4384, https://doi.org/10.1038/s41598-022-08336-4.

[41] Y.-M. Guo, Y.-X. Huang, H.-H. Shen, X.-X. Sang, X. Ma, Y.-L. Zhao, X.-H. Xiao, Efficacy of compound kushen injection in relieving cancer-related pain: a systematic review and meta-analysis, Evid Based Complement Alternat Med (2015) 840742, https://doi.org/10.1155/2015/840742, 2015.

[42] S.Z. Safi, L. Saeed, H. Shah, Z. Latif, A. Ali, M. Imran, N. Muhammad, T.B. Emran, V. Subramaniyan, I.S.B. Ismail, Mechanisms of β-adrenergic receptors agonists in mediating pro and anti-apoptotic pathways in hyperglycemic Müller cells, Mol. Biol. Rep. 49 (2022) 9473–9480, https://doi.org/10.1007/s11033-022-07816-0.