European Review for Medical and Pharmacological Sciences 2023; 27: 3053-3062

Oral Chinese Medicine for the treatment of targeted therapy-induced diarrhea: a systematic review and meta-analysis

H. LIU, Q.-Y. LI, X. WANG, J. SHI

Yueyang Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China

Hui Liu and Quan-Yao Li share first authorship

Abstract. – OBJECTIVE: The treatment of targeted therapy-induced diarrhea, a common adverse reaction of targeted therapy, with traditional Chinese Medicine (TCM) has unique advantages; however, a unified TCM prescription is currently missing in clinical practice, and objective outcome indicators are lacking. Here, we aimed to provide medical evidence for the use of oral TCM in the treatment of targeted therapy-induced diarrhea. To this end, we systematically reviewed the literature evaluating the clinical efficacy of oral TCM for the treatment of targeted therapy-induced diarrhea.

MATERIALS AND METHODS: The Chinese National Knowledge Infrastructure, China Biology Medicine disc, Technology Journal Database, Wanfang Medical Network, PubMed, Cochrane Library, EMBASE, MEDLINE, and OVID databases were used for a literature search of clinical randomized controlled trials examining the use of oral TCM in the treatment of targeted therapy-induced diarrhea until February 2022. A meta-analysis was performed using RevMan 5.3 software.

RESULTS: In total, 490 relevant studies were screened, 480 were excluded based on the inclusion and exclusion criteria, and 10 clinical studies were finally included. The 10 studies included a total of 555 patients: 279 in the treatment group and 276 in the control group. The improvements in total clinical efficiency, TCM syndrome score, and graded efficacy of diarrhea in the treatment group were better than those in the control group ($p<0.01$); however, there was no difference in the Karnofsky Performance Scale score between the groups. The funnel plot for total clinical efficiency was symmetrical, and the publication bias was found to be low.

CONCLUSIONS: Oral TCM is an effective treatment for targeted therapy-induced diarrhea and can significantly improve the clinical symptoms and quality of life of patients.

Key Words:
Traditional Chinese medicine, Targeted therapy, Diarrhea, Clinical efficiency, Quality of life.

Introduction

In recent years, molecular-targeted therapy has become a major part of cancer therapy because of its excellent clinical effects. Targeted therapy consists of designing therapeutic drugs that can specifically bind to identified carcinogenic sites and trigger tumor cell death without affecting the surrounding normal tissue cells[1]. Compared with those of traditional chemotherapy, targeted therapy can effectively prolong the survival time of patients and improve their quality of life[2,3]. In addition, it has fewer toxic side effects and higher safety; however, a series of adverse effects, including diarrhea, cannot be avoided during treatment[4-7]. Targeted therapy-induced diarrhea mainly manifests as increased stool frequency, changes in stool characteristics, such as watery and loose stools, mild fatigue, and malnutrition. Severe cases can lead to electrolyte imbalance, hypovolemia, shock, and even death. Patients often reduce the dose owing to intolerance and may even be forced to discontinue treatment. At present, there are few related research, and there is a lack of guidance and norms for clinical treatment. Commonly used antidiarrheal drugs in clinical practice have good antidiarrheal effect, but there are problems, such as short duration of action and high recurrence rate, which are inconvenient for long-term clinical application. TCM has a long history of use in the treatment of diarrhea, and its curative effect is remarkable. It can relieve the symptoms of diarrhea, improve

Corresponding Author: Jun Shi, MD; e-mail: shijundoctor@163.com

the quality of life of patients, and effectively prevent tumor recurrence and metastasis[8]. In this study, we systematically reviewed the literature evaluating the clinical efficacy of oral TCM for the treatment of targeted therapy-induced diarrhea. Our aim was to provide high-quality clinical evidence for the use of TCM in the treatment of targeted therapy-induced diarrhea to guide clinical treatment.

Materials and Methods

Literature Search Strategy

The database search strategy was developed as required by the Cochrane Handbook for Systematic Reviews (i.e., Chinese National Knowledge Infrastructure), China Biology Medicine disc, VIP, and Wanfang Medical Network. The PubMed (MEDLINE, OLDMEDLINE, Record in process, Record supplied by publisher), Cochrane Library, EMBASE, MEDLINE, and OVID (All Ovid Journals and Full Text Journals of Shanghai University of Traditional Chinese Medical) databases were searched in English. The keywords searched were "targeted drugs", "targeted therapy", "diarrhea", "herbal medicine", and "traditional Chinese medicine". Foreign language database is subject words combined with free words. In addition, we manually retrieved related articles to obtain as much information as possible.

Inclusion Criteria

1) Study type: clinical randomized controlled trials assessing the treatment of targeted therapy-induced diarrhea using oral TCM.
2) Type of participant: patients with a pathological or cytological diagnosis of malignancy who developed diarrhea after targeted therapy. Participants were not restricted by sex, age, or nationality.
3) Intervention measures: the control group was treated with conventional Western medicine and the treatment group was treated with oral TCM and other treatment.
4) Included literature: no limited language and publisher restrictions.
5) Outcome indicators:
   1) Main outcome measures: TCM syndrome integral, grade efficacy of diarrhea[9,10] and total clinical efficiency[11]. The latter was divided into the following: clinical cure (clinical symptoms and signs disappeared and the syndrome score was reduced by ≥90%); significant effect (clinical symptoms and signs were significantly reduced and the syndrome score was reduced by ≥70%); effective (clinical symptoms and signs were improved and the score was reduced by ≥30%); ineffective (clinical symptoms and signs without significant improvement or even aggravated and the score was reduced by less than 30%). The formula used was: (score before treatment − score after treatment) ÷ score before treatment × 100%.
   2) Secondary outcome measures: diarrhea recurrence and Karnofsky Performance Scale (KPS)[12].

Exclusion Criteria

1) Non-randomized controlled trials.
2) Self-cross-control studies.
3) Studies that did not meet the outcome indicators or could not provide valid data.
4) Duplicate articles.
5) Patients with diarrhea caused by other causes, such as irritable bowel syndrome, allergic enteritis, infectious diarrhea, ulcerative colitis, malabsorption, parasitic infection, poisoning, bacillary dysentery, cholera, typhoid and paratyphoid fever, radiation enteritis, hyperthyroidism, hypothyroidism, food and drug allergies, radiation enteritis, and metabolic diseases.
6) Patients with persistent or chronic diarrhea before the use of targeted drugs.
7) Intervention measures excluding oral TCM treatment.

Literature Screening and Data Extraction

Two researchers independently screened the literature according to the inclusion and exclusion criteria, performed preliminary screening by reading the titles, abstracts, and keywords of the articles, read the full text for rescreening, and cross-checked the screening results. Any disagreement was resolved through negotiations with a third party. Main extraction contents: author name, publication year, number, grouping method, intervention measures, and outcome measures.

Literature Quality Evaluation

According to the recommendations of the Cochrane Collaboration, a new "risk of bias assessment" tool jointly developed by methodological experts, editors, and systematic reviewers was used to evaluate the quality of the included liter-

ature[13], addressing six aspects: (1) random allocation scheme; (2) allocation scheme concealment; (3) blind method for study subjects, investigators, and testers; (4) integrity of data; (5) selective reporting of study results; and (6) other sources of bias. For each study result, "yes" (low bias), "no" (high bias), and "unclear" (lack of relevant information or uncertain bias) judgments were made for the above six items.

Statistical Analysis

RevMan 5.3 (Review Manager Web, The Cochrane collaboration, Copenhagen, Denmark) was used for meta-analysis of the results of the included articles. A heterogeneity test was performed on the results of each study. When no statistical significance was found ($p>0.05$, $I^2<50\%$), indicating that there was no heterogeneity between the included studies, the fixed-effects model was used for analysis. When statistical significance was found ($p<0.05$, $I^2>50\%$), indicating that there was heterogeneity between the included studies, it was necessary to further analyze the source of heterogeneity and determine whether the random-effects model could be used for analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were used for the efficacy analysis of dichotomous variables, and the standardized mean difference (SMD) and its 95% CI were used for the efficacy analysis of continuous variables.

Results

Results of the Literature Search

Using this search strategy, 490 relevant articles were retrieved. The Express software was used to screen 100 duplicate articles. The articles were further screened by reading their titles and abstracts. The remaining 57 articles were screened by reading their full text. Finally, 10 articles were included in the review, based on the inclusion and exclusion criteria (Figure 1).

Basic Characteristics and Quality Evaluation of the Included Articles

In total, 10 randomized controlled trials were included in this review. The 10 studies included 555 cases, 279 in the treatment group and 276 in the control group. Table I presents basic information on the studies included in this review.

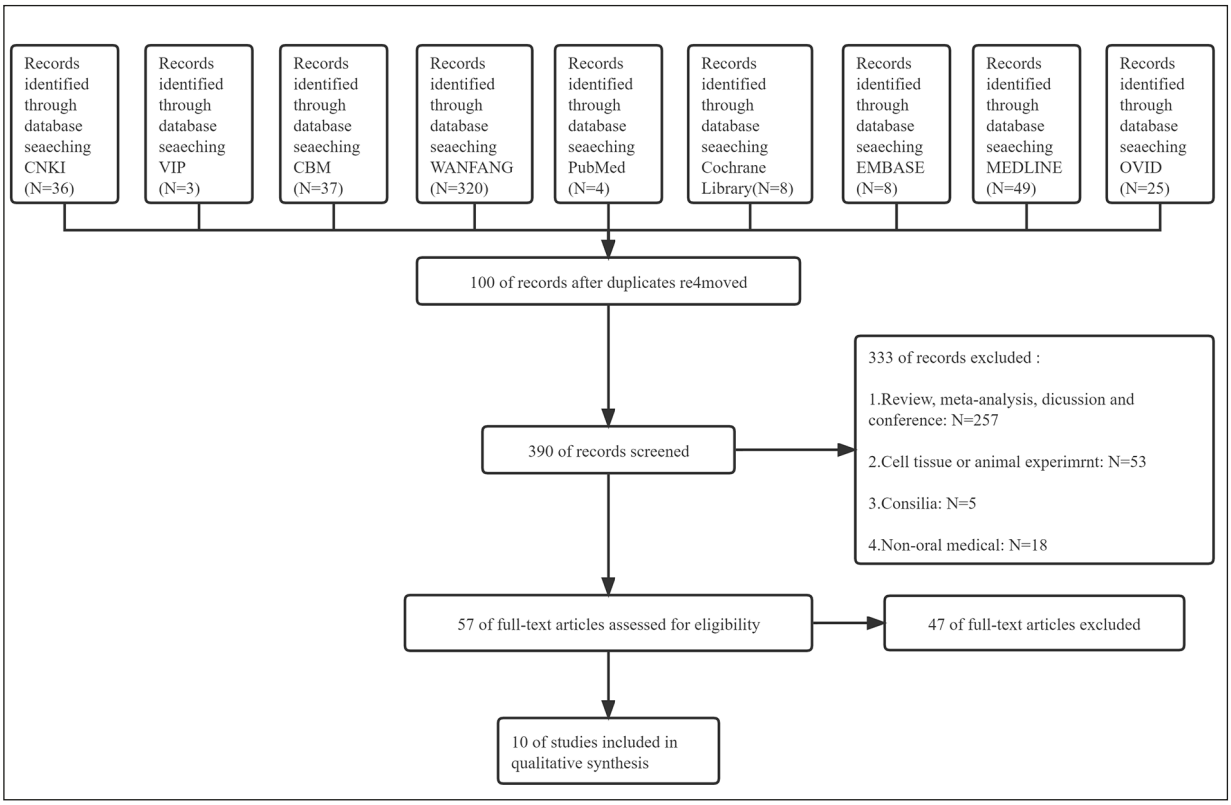

Figure 1. Flow diagram of the literature search.

Table I. Basic characteristics of the included articles.

Author	Year of publication	Country	Sample capacity		Grouping method	Baseline (age, sex, and other factors)	Intervention study		Outcome indicator
			Control group	Treatment group			Control group	Treatment group	
Shi[9]	2106	China	33	33	Table of random number	Unanimous	Loperamide	Oral TCM	1, 4, 5
Chen et al[22]	2017	China	33	34	Table of random number	Unanimous	Monteonite+ Bifidobacterium	Oral TCM	1, 2
Wang[21]	2019	China	27	27	Not described	Unanimous	Monteonite	Oral TCM+ acupoint application	1, 3, 5
Wang[21]	2019	China	25	26	Random	Unanimous	Monteonite	Oral TCM	1, 5
Zhang et al[19]	2019	China	15	15	Table of random number	Unanimous	Monteonite+ Bacillus licheniformis	Oral TCM	1, 2
Lu et al[18]	2020	China	23	24	Random	Unanimous	Monteonite	Monteonite+ Oral TCM	3, 5
Liu et al[17]	2020	China	30	30	Random	Unanimous	Monteonite+ *Bifidobacterium*	Monteonite+ *Bifidobacterium*+ Oral TCM	1, 3, 5
Chen16	2021	China	30	30	Random	Unanimous	Monteonite	Monteonite+ Oral TCM	1, 2, 3, 4, 5
Li and Cao[14]	2021	China	20	20	Table of random number	Unanimous	Monteonite+ *Bifidobacterium*	Oral TCM	1, 2
Zhang15	2021	China	40	40	Random	Unanimous	Loperamide	Loperamide+ Oral TCM	1, 2, 3, 4, 5

1. Total clinical efficiency, 2. TCM syndrome integral, 3. Efficacy of the Diarrhea Classification 4. The diarrhea recurrence rate was 5. KPS, oral traditional Chinese medicine.

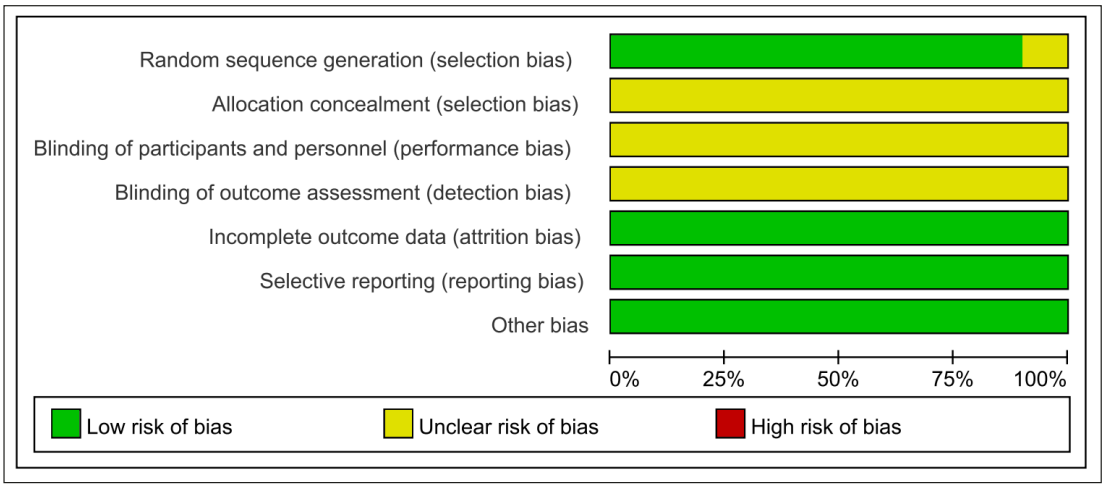

Figure 2. Risk of bias.

Among the 10 studies[9,14-22], four[9,14,16,19] used random number tables, five[15,17,18,21,22] only mentioned random assignment, and one[20] did not mention randomization. None of the studies mentioned allocation concealment, blinding, selective reporting, or other types of bias (Figures 2 and 3).

Meta-Analysis Results

Main outcome indicators

Nine studies[9,14-17,19-22] included 507 patients, 254 in the treatment group and 253 in the control group. The heterogeneity test showed homogeneity among the nine studies ($p>0.05$, $I^2=43\%$); therefore, a fixed-effects model was used. The meta-analysis showed significant differences between the treatment and control groups in improving the total clinical efficiency [RR=1.37, 95% CI (1.24, 1.52), $p<0.0$] (Figure 4).

TCM syndrome integral

Five studies[14-16,19,22] included 277 patients, 139 in the treatment group and 138 in the control group. The heterogeneity test indicated heterogeneity among the five studies ($p<0.05$, $I^2=90\%$); therefore, a random-effects model was used. The meta-analysis showed significant differences between the groups in improving the TCM syndrome integral [SMD = -2.00, 95% CI (-2.95, -1.06), $p<0.01$] (Figure 5).

Grade efficacy of diarrhea

Five studies[15,17,18,20,22] included 301 patients, 151 in the treatment group and 150 in the control group. The heterogeneity test indicated homogeneity among the five studies ($p>0.05$, $I^2=0\%$); thus, a fixed-effects model was used. The meta-analysis showed significant differences be-

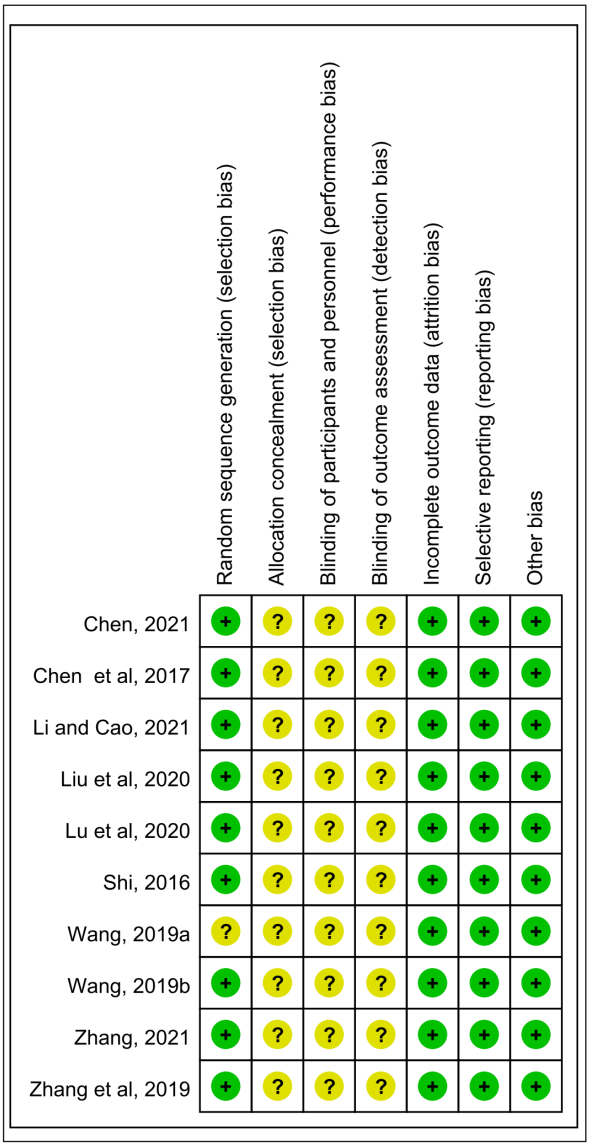

Figure 3. Summary of the risk of bias.

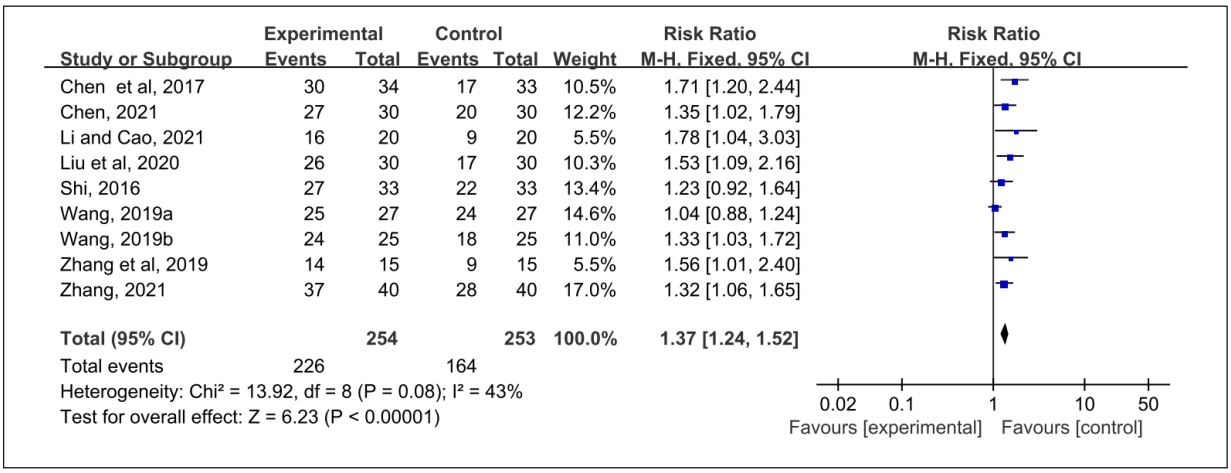

Figure 4. Total clinical efficiency.

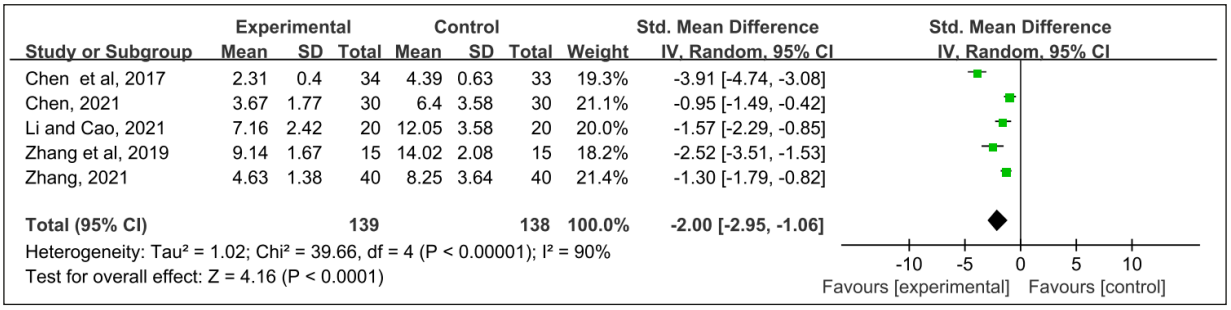

Figure 5. TCM syndrome integral.

tween the groups in improving the diarrhea classification [RR=1.24, 95% CI (1.12, 1.38), $p<0.01$] (Figure 6).

Secondary Outcome Indicators

Diarrhea recurrence

Three studies[9,15,16] included 148 patients, 81 in the treatment group and 67 in the control group. The heterogeneity test showed homogeneity among the three studies ($p>0.05$, $I^2=66\%$). Therefore, a fixed-effects model was used. The meta-analysis showed significant differences between the groups in the reduction of diarrhea recurrence [RR=0.44, 95% CI (0.27, 0,72), $p<0.01$] (Figure 7).

KPS

Seven studies[9,15,16,17,18,20,21] included 417 patients, 209 in the treatment group and 208 in the control

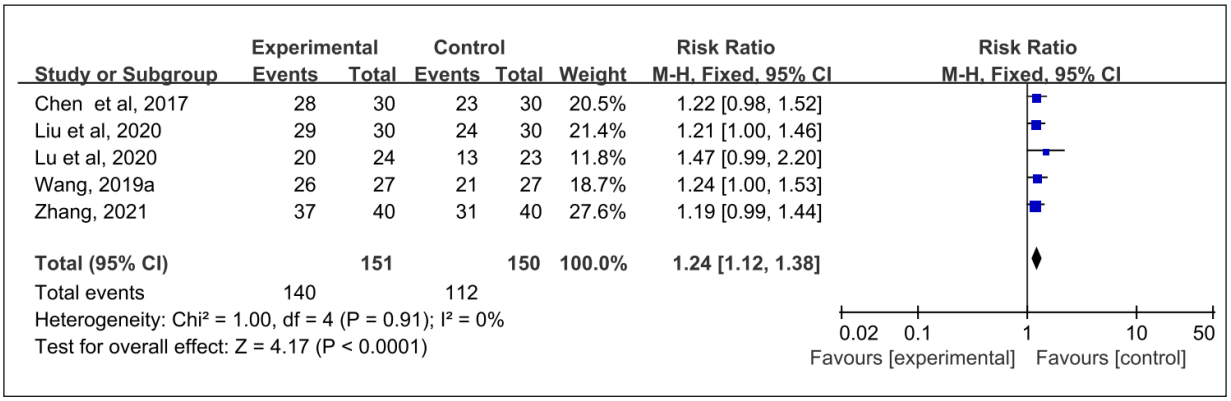

Figure 6. Grade efficacy of diarrhea.

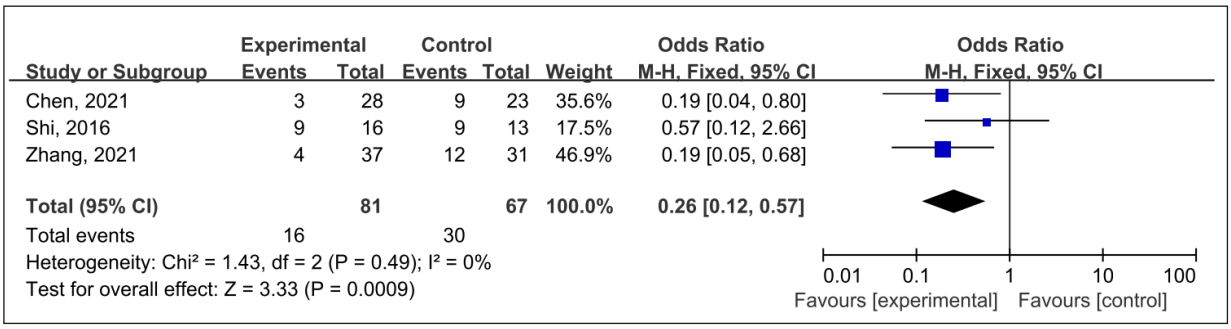

Figure 7. Diarrhea recurrence.

group. The heterogeneity test showed heterogeneity among the seven studies (p<0.05, I^2=89%). Thus, a random-effects model was used. The meta-analysis showed no significant differences between the treatment and control groups in terms of improving KPS (RR=1.14, 95% CI (0.99, 1.31), p>0.05] (Figure 8).

Sensitivity Analysis

To test the effect of each KPS study on this meta-analysis, a sensitivity analysis was performed. When changing from the random-effects model to a fixed-effects model for sensitivity analysis, the results changed, and the difference was significant (Figure 9). According to the forest map

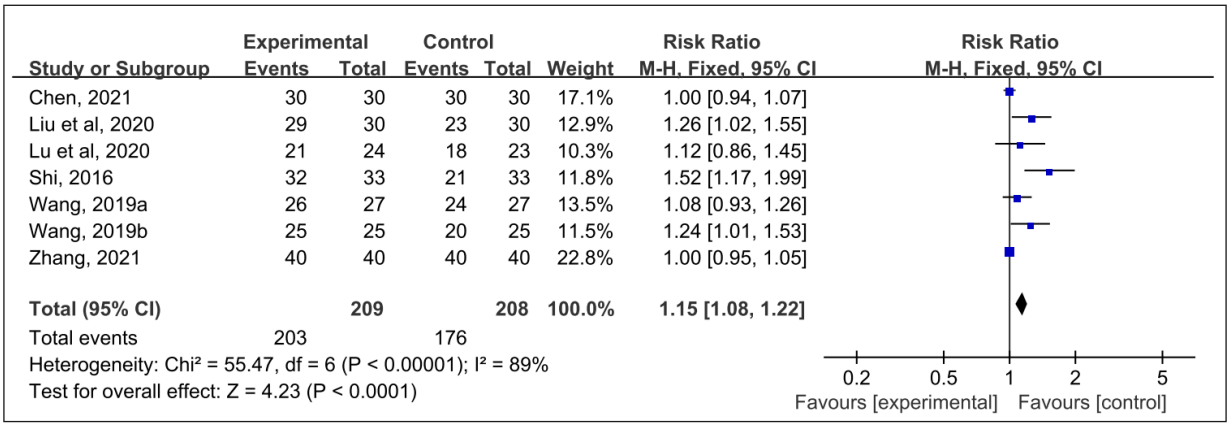

Figure 8. Karnofsky Performance Scale (KPS).

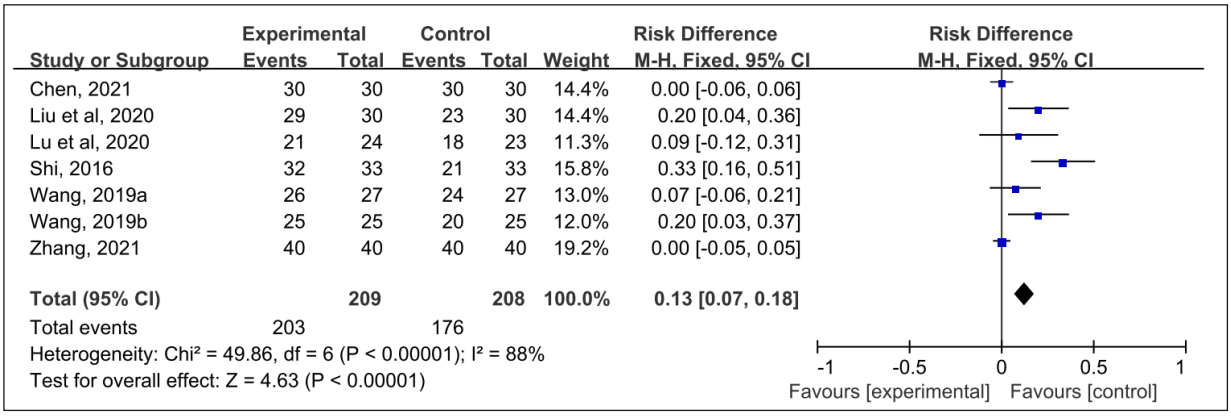

Figure 9. KPS (Fixed-effects model).

results, the heterogeneity derived from Chen et al[16] and Zhang[15].

Detection of Publication Bias

A funnel plot was created by mapping the total clinical efficiency of the outcome index (Figure 10). Basic symmetry was found on the left and right sides, indicating low publication bias. These findings demonstrate that oral TCM can improve the total clinical efficacy of targeted drugs by treating targeted therapy-induced diarrhea and improving the quality of life of patients with reliable results.

Discussion

Targeted therapy-induced diarrhea is mainly characterized by repeated episodes of diarrhea and belongs to the category of "diarrhea" in TCM. Modern Chinese medicine believes that targeted drugs belong to the "drug poison" category[23], which can easily damage the spleen and stomach, causing diarrhea[24]. After targeted drug treatment, toxicity leads to yin deficiency[25]. In addition, patients with cancer have several deficiencies which lead to diarrhea that, in turn, aggravates the patients' condition. Therefore, targeted therapy-induced diarrhea is a syndrome of the deficiency-excess complex, in which deficiency is the main factor. Treatment should focus on treating the deficiency by tonification.

TCM has unique advantages in the treatment of targeted therapy-induced diarrhea. One study has shown that oral TCM treatment can significantly improve the TCM syndrome, clinical efficacy, and quality of life of patients[16]. Wang[20] found that TCM treatment can significantly relieve diarrheal symptoms and improve the quality of life of patients. Wang[26] found that oral TCM treatment can significantly improve the total clinical efficiency, reduce diarrhea recurrence, and improve the quality of life of patients, and confirmed the effectiveness and safety of oral TCM for targeted therapy-induced diarrhea.

Ten related studies[9,14-22] were included in the present study. The results showed that the total clinical efficiency and efficacy of the diarrhea classification were significantly higher in the treatment group than in the control group ($p<0.01$). Furthermore, the TCM syndrome integral and diarrhea recurrence were significantly better in the treatment group than in the control group ($p<0.01$). However, there were no significant differences in the KPS improvement. When the fixed-effects model was used, the difference was significant, and the heterogeneity results were shown to result from Chen et al[16] and Zhang[15], the reason is that the quality of the literature included in this study was poor, which leads to high heterogeneity.

Thus, oral TCM has certain advantages in the treatment of targeted therapy-induced diarrhea. It can significantly improve the total clinical efficacy, reduce the TCM syndrome integral and diarrhea recurrence, and improve the clinical

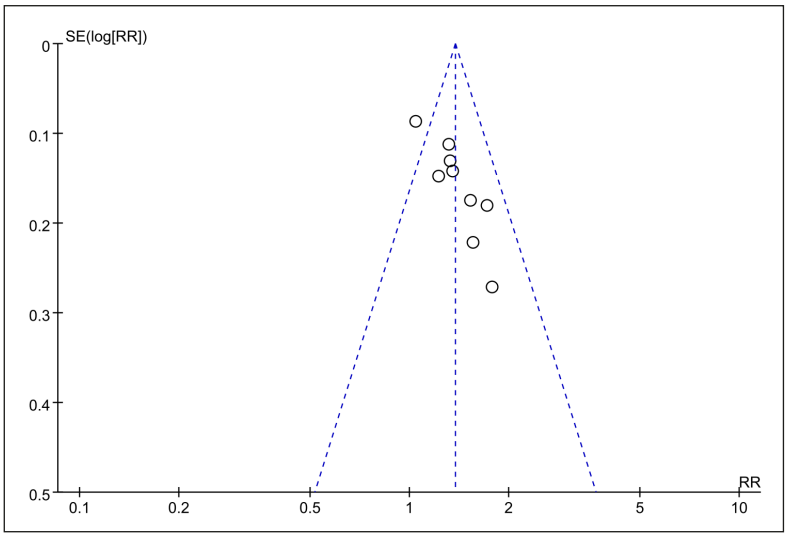

Figure 10. Funnel plot of total clinical efficiency.

symptoms. However, it did not result in significant improvements in the KPS. The KPS scale is a quantitative assessment tool used to determine a patient's health status. However, it is subjective to a certain extent; therefore, evaluating the treatment of targeted therapy-induced diarrhea may be subjective. Based on the results of this study, the drug should be targeted according to the clinical symptoms of patients.

Limitations

This study had certain limitations. First, different TCM prescriptions, treatment frequency and duration, and other factors may have caused heterogeneity among various studies. Second, the clinical efficacy evaluation criteria of the studies included in this review were mainly based on scales that have certain subjectivity. Finally, the quality of the literature included in this study was poor with some risk of bias. In addition, the sample size of the included studies was small, and there was no basis for reporting the estimated sample size, which would lead to poor test effectiveness.

Conclusions

The results of this study show that, compared with other therapies, oral TCM has advantages in treating targeted therapy-induced diarrhea. It can significantly improve the total clinical efficacy and symptoms, reduce the TCM syndrome integral and diarrhea recurrence, and provide guidance for clinical practice. Owing to the limitations of this study, higher-quality randomized controlled trials are needed to evaluate the clinical efficacy of oral TCM for targeted therapy-induced diarrhea. The results of meta-analyses can be further refined to guide clinical practice by standardizing clinical studies.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflict of interests.

Acknowledgements

The authors would like to thank all the researchers in our working group.

Informed Consent

Not applicable.

Funding

The study was funded Shanghai Charity Cancer Research Center Fund Project (2017-2020). Outstanding undergraduates track the integration of undergraduate, master's, and doctoral programs (2021.7-2024.7).

Authors' Contribution

J. Shi obtained funding for the study. J. Shi, H. Liu, Q.-Y. Li, and X. Wang designed the trial. H. Liu and Q.-Y. Li wrote the first draft of the manuscript and X. Wang participated in the revision of the subsequent draft. All the authors approved the final version of the manuscript.

References

1) Dobbelstein M, Moll, U. Targeting tumour-supportive cellular machineries in anticancer drug development. Nat Rev Drug Discov 2014; 13: 179-196.
2) Qu T, Zhou XM, Liu HC, Zhao S, Zhang Y, Zhang QY. Progress in the application of immune checkpoint inhibitors in malignant lymphomas. Clin Oncol China 2016; 43: 922-926.
3) Lan F, Li RM, Yang LY, Hu JH. Progress in anti-tumor immunotherapy with programmed cell death protein 1 and its ligand inhibitors. Int J Pharm Res 2016; 43: 813-817.
4) Nishimura T, Tada H, Nakagawa M, Teramukai S, Matsui S, Fukushima M. Lessons from gefitinib-induced interstitial lung disease in Japan: problems in approval, pharmacovigilance, and regulatory decision-making procedures. Pharm Pract 2006; 4: 168-178.
5) Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Xu CR, Massey D, Kim M, Shi Y, Geater SL. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15: 213-222.
6) Qi WX, Sun Y J, Shen Z, Yao Y. Risk of interstitial lung disease associated with EGFR-TKIs in advanced non-small-cell lung cancer: a meta-analysis of 24 phase III clinical trials. J Chemother 2015; 27: 40-51.
7) Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, Ahn MJ, Kim SW, Su WC, Horn L, Haggstrom D, Felip E, Kim JH, Frewer P, Cantarini M, Brown KH, Dickinson PA, Ghiorghiu S, Ranson M. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 2015; 372: 1689-1699.

8) Tian SD, Chen XY. Characteristics and advantages of TCM in the treatment of malignant tumors. Mod Chin Med Clin 2019; 26: 8-17.
9) Shi H. Clinical Study on TCM Intervention for Related Diarrhea in Non-Small Cell Lung Cancer. Beijing Univ Trad Chin Med 2016. Available at: https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD201602&filename=1016069120.nh.
10) Zhang SF. Observation of the efficacy of probiotics in treating chemotherapy-associated diarrhea in digestive tract tumors. Chin Pract Med 2014; 9: 138-139.
11) Zheng XY. Guidelines for Clinical Research of New Chinese Medicine Drugs (Trial). China Medical Science and Technology Publishing House, 2002.
12) Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma-with Particular Reference to Bronchogenic Carcinoma. Cancer 1948; 1: 634-56.
13) Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz K, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
14) Li G, Cao QX. Observation of clinical efficacy of spleen in the treatment of gefitinib-related diarrhoea. Chin Trad Chin Med Technol 2021; 28: 654-655.
15) Zhang XL. Clinical observation of flavored Pinellia diarrhea soup combined with loperamide for afatinib-associated diarrhoea. Anhui Univ Trad Chin Med 2021. Available at: https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD202201&filename=1022408976.nh.
16) Chen GW. Observation of Clinical Efficacy of Chinese Pill in NSCLC Targeted Therapy With Related Diarrhea. Fujian Univ Trad Chin Med 2021. Available at: https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD202201&filename=1021610800.nh.
17) Liu JL, Yan L, Wu YC, Zhang J, Li WQ, Liu LG, Xing Y, Guo YH, Fu XY. Clinical observation of diarrhoea caused by oral EGFR-TKI in non-small cell lung cancer. Inner Mongolian Trad Chin Med 2020; 39: 5-8.
18) Lu S, Wang X, Zhou XK. Clinical study of warm kidney and spleen method in the treatment of sorafenib. Chin J Integr Trad Chin West Med 2020; 28: 177-179.
19) Zhang F, Chen B, Wu YN, Peng JP, Jing J, Sun KW. Clinical study on sorafenib-related diarrhoea. Hunan Univ Trad Chin Med 2019; 39: 1148-1152.
20) Wang Y. Clinical Observation of Self-Nourishing Yin Antidiarrhea Prescription Combined with Umbilical Cord Therapy for EGFR-TKIs-Related Diarrhea. Beijing Univ Trad Chin Med 2019. Available at: https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD201902&filename=1019141266.nh.
21) Wang Y. Clinical Observation of Related Diarrhea (Yang Deficiency Syndrome of Spleen and Kidney). Chengdu Univ Trad Chin Med 2019. Available at: https://kns.cnki.net/KCMS/detail/detail.aspx?dbname=CMFD202001&filename=1019632426.nh
22) Chen BY, Li YJ, Chen ZS. The treatment of 34 cases of sorafenib-related diarrhea. Fujian Trad Chin Med 2017; 48: 57-58.
23) Chinese Society of Lung Cancer, Chinese Anti-Cancer Association. [EGFR-TKI ADR Management Chinese Expert Consensus]. Zhongguo Fei Ai Za Zhi 2019; 22: 57-81.
24) Yang XD, Wang XM. Wang Xiaomin syndrome differentiation and treatment with targeted drugs for lung cancer test case 2. Beijing Trad Chin Med 2009; 11: 889-890.
25) Sun JL, Liu JX. Analysis of the clinical efficacy of TCM syndrome differentiation combined with gefitinib in late non-small cell lung cancer. Sichuan Trad Chin Med 2009; 27: 64-66.
26) Wang JL. Clinical treatment and effect evaluation of spleen and kidney Yang deficiency diarrhea. Prescr Drugs China 2020; 18: 124-126.