A Systematic Review and Meta-Analysis of Randomized Controlled Trials on Treating Ulcerative Colitis by the Integration Method of Heat-Clearing, Damp-Excreting, Spleen-Strengthening, and Stasis-Removing of Traditional Chinese Medicine with Western Medicine

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Objective: The objective of this study was to systematically evaluate the clinical efficacy of the integration method of heat-clearing, dampness-excreting, spleen-strengthening, and stasis-removing from traditional Chinese medicine (TCM) combined with Western medicine for the treatment of ulcerative colitis (UC). Materials and Methods: The databases China National Knowledge Infrastructure, China Biology Medicine disc (CBMdisc), WANFANG, VIP, and PubMed were searched for randomized controlled trials investigating the integration of the TCM methods of clearing heat, draining dampness, invigorating the spleen, and removing stasis, combined with Western medicine to treat UC from January 2009 to March 2019. Two reviewers independently conducted literature searches, screenings, data extractions, and literature bias evaluations. A meta-analysis was conducted using RevMan 5.3 and Stata 13.0 software. Results: In total, 15 studies involving 1289 patients were included. The results of the meta-analysis showed that the total effective rate of treatment in the experimental groups was higher than that of the control groups (relative risk [RR] = 1.27, 95% confidence interval [CI]: 1.21, 1.35, Z = 8.74, P < 0.00001). The total effective rate of oral TCM combined with Western medicine was higher than that of the control groups (RR = 1.24, 95% CI: 1.15, 1.33, Z = 5.88, P < 0.00001). The total effective rate of oral TCM with enemas combined with Western medicine was higher than that of the control group (RR = 1.30, 95% CI: 1.12, 1.50, Z = 3.52, P = 0.0004). The comparison between Western medicine alone and oral TCM combined with enteroscopy and Western medicine showed that the effective rate of enteroscopy (RR = 1.18, 95% CI: 1.05, 1.33, Z = 2.86, P = 0.004) and the symptom scores before and after treatment all improved more in the combined treatment groups than in those of the Western medicine group alone, with statistically significant differences (RR = −4.23, 95% CI: −4.93, −3.53, Z = 11.84, P < 0.00001). Conclusion: The integration of the TCM methods of heat clearing, dampness excreting, spleen strengthening, and stasis removing combined with Western medicine can significantly improve the cure rate of UC, and is an effective method to treat UC.

Keywords: Clearing heat, draining dampness, invigorating spleen, meta-analysis, removing stasis, ulcerative colitis
to China's statistics, its peak age of occurrence is 20–49 years, with little gender difference, and the male–female ratio of UC patients is 1–1.3:1. It is estimated that the prevalence of UC in China is 11.6/100,000. At present, there is no epidemiological data on large sample populations. The clinical manifestations of UC are persistent or recurrent diarrhea with mucopurulent bloody stool accompanied by abdominal pain, tenesmus, and various degrees of systemic symptoms. The course of the disease is often 4–6 weeks or more, and may additionally affect the skin, mucous membrane, joints, eyes, or liver. Mucopurulent bloody stool is the most common symptom of UC. Diarrhea with a course <6 weeks is often distinguished from some infectious enteritis.

Adverse reactions such as gastrointestinal discomfort, dizziness, headache, rash, and even severe adverse reactions such as anemia, bone marrow suppression, and respiratory tract infections often occur with commonly used treatments such as sulfasalazine, azathioprine, budesonide, and infliximab. Therefore, there is a search for more effective treatments of UC with fewer adverse reactions. Although there is no clear name of UC in ancient books of traditional Chinese medicine (TCM), according to the clinical symptoms such as mucopurulent bloody stool and the characteristics of recurrence, it can be summarized as “Liji” and “Jiuli.” By looking, listening, asking, and feeling the pulse, one could determine “Liji” as the excess of heat and dampness, blood stasis, and spleen deficiency. Therefore, when preparing treatments, it is important to clear heat and remove dampness, strengthen the spleen, and improve blood stasis, which are conducive to increasing the therapeutic effect of UC.

At present, TCM is known to be very effective for treating UC. In order to provide evidence for the integration of the TCM methods of heat clearing, dampness excreting, spleen strengthening, and stasis removing combined with Western medicine in UC treatment, we performed a systematic review and meta-analysis of the current literature.

### MATERIALS AND METHODS

#### Literature selection

To search the literature for relevant studies, key Chinese words used were “Qingre Lishi” (clearing heat and draining dampness), “Jianpi” (invigorating the spleen), “Yiqi” (tonifying qi), “Huoxue” (promoting blood circulation), “Huayu” (removing stasis), “Kuiyangxing Jiechangyan” (ulcerative colitis), “Zhongyao” (traditional Chinese medicine/Chinese herbs), “Suiji” (random), “Duizhao” (controlled), “Linchuang Shiyan” (clinical trials), and the English words: “heat-clearing,” “damp-excreting,” “spleen-strengthening,” “stasis-removing,” “ulcerative colitis,” and “UC.” The selected databases were China National Knowledge Infrastructure, China Biology Medicine (CBM), Wanfang database, VIP database, and PubMed. The literature was searched for publications between January 2009 and March 2019.

### Inclusion criteria

The inclusion criteria for this review were randomized controlled trials (RCTs); patients with UC diagnosis; publication between January and March 2019; and the integration of TCM through oral administration alone or combined with enteroclysis for heat clearing, dampness excreting, spleen strengthening, and stasis removing along with Western medicine in the experimental group against a control group treated with Western medicine alone. Specifically, Western medicine treatment had to be included in both groups, with identical types of medicine and course of treatment. In addition, primary outcome indicators included comprehensive treatment effectiveness, rate of reduction in clinical symptoms, and efficacy shown by endoscope, and secondary outcome indicators included TCM syndrome scores and the comparison of treatment effectiveness of different TCM syndromes.

### Exclusion criteria

The exclusion criteria were any study that was not an RCT; treatment of UC with TCM herbs alone and Western medicine alone; RCTs with the integration of enteroclysis with TCM herbs with Western medicine and treatment with Western medicine alone; RCTs without the number of people in each group specified; and studies that did not treat UC with the TCM herbs for heat-clearing, dampness-excreting, spleen-strengthening, and stasis-removing functions.

### Evaluation standard

The Cochrane Collaboration’s tool for assessing the risk of bias was used to evaluate the quality of the literature, including selection bias due to the inadequate generation of a randomized sequence or inadequate concealment of allocations before assignment; performance or detection bias due to lack of blinding; attrition bias due to the amount, nature, or handling of incomplete outcome data; reporting bias due to selective outcomes; and bias due to problems not covered elsewhere. For each study, “low-risk,” “unclear,” and “high-risk bias” were evaluated based on the Cochrane criteria.

### Literature screening and data extraction

Two researchers screened the literature and extracted data according to the inclusion criteria independently. If there was disagreement, the two researchers would discuss it together or a third researcher would assist in making a decision. The main data extracted were general information such as the first author, the date of publication, and the source and title of the study; basic features of the studies such as the method of randomized grouping of the participants, male–female ratio, interventional methods used in each group, and follow-ups; and outcomes measured such as the effective rate and adverse reactions.

### Statistical analysis

A meta-analysis was performed using RevMan 5.3.
A meta-analysis of randomized controlled trials on treating ulcerative colitis (Haymarket, London, SW1Y 4QX, UK) and Stata 13.0 (Texas, USA) software. The heterogeneity test was conducted using the Chi-square test on all the included study results with the standard level set at $\alpha = 0.1$. When $P \geq 0.1$ and $P \leq 50\%$, which indicates homogeneity of the results, the meta-analysis can be conducted using the fixed-effects model. When $P < 0.1$ and $P > 50\%$, which indicates certain heterogeneity of the results, the heterogeneity is within the acceptable range, and the meta-analysis can be conducted using the fixed-effects model. When $P < 0.1$ and $P > 50\%$, which indicates relatively significant heterogeneity among the results, further analysis of the source of the heterogeneity should be undertaken. When there is an absence of obvious clinical experimental indicators such as categorical variables, the relative risk (RR) should be taken as the effect size. When there is an absence of obvious clinical experimental indicators such as numerical variables, the weighted mean difference and the standard mean difference should be taken instead. The interval estimations were all set at a 95% confidence interval (CI). The existence of publication bias was analyzed using Begg’s test and Egger’s test.

**RESULTS**

**Retrieval and screening process**

After searching the Chinese databases for the keywords described previously, 2897 studies were retrieved. A primary screening of the titles and abstracts resulted in 279 studies meeting the inclusion criteria. After an extensive reading of the articles for secondary screening, the following articles were excluded: 74 were not RCTs; 62 did not involve the treatment of UC with the TCM herbs for functions of heat clearing, dampness excreting, spleen strengthening, and stasis removing; 31 involved the treatment of UC with enteroclysis of the TCM decoction; 92 compared the effects of TCM herbs alone to Western medicine; 1 had the total effectiveness rate as the only outcome; 1 used electro-acupuncture therapy; 1 did not specify the treatment course; and 2 did not specify the number of participants or the male–female ratio in each group. The final number of included studies was 15. Our screening process is shown in Figure 1.

**Basic features of the included studies**

After screening, 15 RCTs from Chinese databases were included in this study. Within those 15 studies, 1289 UC patients were included. All the experimental groups were treated with the integration of the TCM methods of heat clearing, dampness excreting, spleen strengthening, and stasis removing combined with Western medicine. Of these, 645 patients were in experimental groups and 644 patients were in control groups. The age range and average age were described in all the included studies, with a minimum age of 18 years and a maximum age of 72 years. In terms of the number of male and female patients, apart from the two studies without this information, a total of 636 male patients and 522 female patients were included in the other 13 studies. In terms of the disease course, three studies did not mention any information, two studies only described the average disease course among all the included patients, and the other ten studies provided details of the longest and shortest disease courses in the study. Of those 11 studies, the shortest disease course was 3 days and the longest disease course was 20 years. The statistical analysis of the experimental group’s baseline information was clearly described in all the 15 studies and the baselines between the two groups were similar and comparable.

All RCTs were published in medical journals. Experimental groups in all the studies were treated with the integration of the TCM methods for heat clearing, dampness excreting, spleen strengthening, and stasis removing combined with Western medicine, and control groups were treated with Western medicine alone. The treatments used in the experimental groups included eight studies$^{[5,6,7,8,9,10,11,12]}$ with oral administration of TCM herbs and seven studies$^{[13,14,15,16,17,18,19]}$ with enteroclysis of TCM herbs. The overview of the studies is shown in Table 1.

**Quality evaluation of literature methodologies**

For randomized sequence generation, four studies$^{[7,9,10,11]}$ used a random number table, with a relatively low risk of bias. The other 11 studies$^{[5,6,8,12–19]}$ did not describe the specific method for randomization and only used the term “random,” so the risk of bias could not be judged. None of the studies used a blind method nor described the concealment of allocations, so the risk of bias could not be judged. All the studies were low-quality studies. Figures 2 depict the results of the quality evaluation and analysis conducted on all the included RCTs according to the quality evaluation criteria.
Statistical analysis results

Analysis of total clinical effective rate

The experimental groups were treated with TCM herbs based on previous Western medicine treatments. The success of treatment was divided into the following three levels: cured, improved, and ineffective. The number of effective cases was determined by adding the cured and improved cases together. The meta-analysis on the summarized data of the included studies demonstrated that of the 645 patients in the experimental groups, 586 were treated effectively, and of the 644 patients in the control groups, 459 were treated successfully. All studies described the total clinical effective rate, and there was no statistically significant heterogeneity between different studies ($P = 0.07, I^2 = 0\% < 50\%$). Considering that these studies were homogeneous, the meta-analysis was conducted using the fixed-effect model, and the difference was statistically significant ($RR = 4.11, 95\% CI: 2.98, 5.67, Z = 8.62, P < 0.00001$), indicating that the effective rate of
the experimental group was higher than that of the control group [Figure 3].

Subgroup analysis of total clinical effective rate
Seven studies used oral TCM and enemas combined with Western medicine to treat UC and compared that to Western medicine alone. Eight studies only used oral TCM combined with Western medicine. Therefore, a subgroup analysis was performed. All the studies were divided into an oral medicine group and an oral–enema group. Research statistics showed that the oral group and the control group had no obvious heterogeneity ($P = 0.50$, $I^2 = 0% < 50%$). Considering that these studies were homogeneous, the meta-analysis was conducted using the fixed-effect model, and the result showed an RR = 1.24, a 95% CI of 1.15, 1.33, a $Z = 5.88$, and a $P < 0.00001$. The oral–enema group and control group had no obvious heterogeneity between the groups ($P = 0.0001$, $I^2 = 73% > 50%$). Considering that these studies had homogeneity, the meta-analysis was conducted using the random effects model, and the result showed a statistically significant difference (RR = 1.30, 95% CI: 1.12, 1.50, $Z = 3.52$, $P = 0.0004$). The results showed that the comprehensive curative effect of the subgroup was better than that of the control group [Figures 4 and 5].

Analysis on publication bias
The researchers conducted a Begg’s test and an Egger’s test using Stata software to determine if there was publication bias. The Begg’s and Egger’s test revealed $P < 0.05$, suggesting publication bias. After removing four studies [7, 15, 8, 18] with a relatively low total effective rate, the researchers conducted a Begg’s and Egger’s test again, with $P > 0.05$, suggesting that there was no publication bias [Figure 6].

Analysis of the enteroscope effective rate
Of the 15 included studies, four studies [7, 15, 8, 9] recorded the enteroscope effective rate. There was no significant heterogeneity between the different studies ($P = 0.93$, $I^2 = 0% < 50%$). Considering these studies were homogeneous, the meta-analysis was conducted using the fixed effect model, the result of which was an RR = 1.18, a 95% CI (1.05, 1.33), a $Z = 2.86$, and a $P = 0.004$, showing a statistically significant difference. This suggested that the enteroscope effective rate of treating UC by the integration of an enteroscope with the oral TCM treatment methods for heat-clearing, dampness-excreting, spleen-strengthening, and stasis-removing along with western medicine was higher than western medicine treatment alone [Figure 7].

Comparison of symptom scores before and after treatment
Of the 15 included studies, two studies [6, 12] applied the same evaluation standard of symptom scores, the grading and scoring of the severity of TCM symptoms according to “The Guiding Principles for Clinical Study of New Chinese Medicine in Treating Diarrhea.” [20] Specifically, a score of 0 meant no symptoms, and score of 1, 2, and 3 meant slight, medium, and severe symptoms, respectively. There was no significant heterogeneity between the different studies ($P = 0.65$, $I^2 = 0% < 50%$). Considering these studies were homogeneous, the meta-analysis was conducted using the fixed effect model. The result showed a statistically significant difference (RR = −4.23, 95% CI [−4.93, −3.53], $Z = 11.84$, $P < 0.00001$). The symptom score after treating the experimental group was lower than that of the control group, indicating there was higher treatment success in the experimental group [Figure 8].

Of the 15 included studies, six studies [6, 14, 15, 16, 11, 18] used a basic treatment of oral sulfasalazine, so a subgroup analysis could be performed. There was no significant heterogeneity between the

Figure 2: Quality evaluation and analysis

Figure 3: Total effective rate
different studies ($P = 0.88, F = 0\% <50\%)$. Considering these studies were homogeneous, the meta-analysis was conducted using the fixed effect model, the result of which showed a statistically significant difference (RR = 1.21, 95% CI [1.12, 1.32], $Z = 4.67, P < 0.00001$), which indicated that the total effective rate in the experimental group was better than that of the control group (oral sulfasalazine group) [Figure 9].

**Evaluation of adverse reactions**

Of the 15 included studies, five studies\textsuperscript{6,8-10,17} described adverse reactions, among which two\textsuperscript{10,17} showed no significant adverse reactions in the control group or the treatment group. In the other three studies,\textsuperscript{9,10,17} the 116 patients in the control group experienced nausea and vomiting in two cases, fatigue in four cases, and fever in one case. Of the 116 patients in the
treatment group, three experienced nausea and vomiting, two experienced dizziness, and one patient had abdominal pain and diarrhea. However, all the adverse reaction symptoms were mild, and all the patients were able to complete the medication therapies. Due to the insufficient observation of adverse reactions in the other included studies, the safety of this regimen cannot be conclusively determined based on the existing evidence.

**Discussion**

In Western medicine, 5-aminosalicylic acid (5-ASA) is commonly used to treat mild or moderate UC, and steroid pulse therapy is used to induce, relieve, and control the symptoms of severe active UC. After the symptoms are relieved, the dose of oral steroids is gradually reduced, and 5-ASA is administered simultaneously to maintain the effect. If the patient is steroid resistant or steroid dependent, immunosuppressants or biological agents can also be used. UC can also be treated with the integration of TCM and Western medicine, using methods to clear the intestines, resolve dampness, cool the blood, and remove toxins combined with glucocorticoids. Glucocorticoid-resistant/dependent UC should be treated by integrating TCM syndrome differentiation and Western medicine. In terms of Western medicine, thiopurine drugs such as azathioprine and biological agents (anti-tumor necrosis factor monoclonal antibody or vedolizumab) can be used.

At present, the etiology and pathogenesis of UC remain unclear. It is widely believed that UC is caused by many factors involving genetics; the environment; psychology; and diet. These lead to intestinal mucosal barrier damage, neuroendocrine dysfunction, and immune imbalance, causing local ulceration of the intestinal mucosa. According to traditional medicine, the pathogenesis of UC is mainly related to six exogenous pathogens, namely improper diet; affect-mind dissatisfaction, and congenital deficiency of endowment, which leads to abnormal spleen and stomach movement; endogenous dampness and heat; block qi and blood; qi stagnation and blood stasis; and intestinal conduction loss. At present, most studies show that the most active UC is associated with dampness heat of the large intestine according to the TCM syndrome differentiation, which is an excessive syndrome, and its main pathogenesis is heat dampness accumulating in the large intestine and the imbalance of qi and the blood. Many studies have shown that TCM plays a therapeutic role in UC by inhibiting inflammatory signaling pathways such as KF-κB, TLR4-MyD88-NF-κB, mitogen-activated protein kinase, JAK/STAT, and PI3K-AKT-mTOR, among others. Therefore, TCM used to clear away heat and dampness, invigorate the spleen, and remove blood stasis can act on the gastrointestinal tract and heal ulcers, greatly improving patients’ confidence in treatment and their quality of life.

Herein, a meta-analysis was conducted on 15 studies. Although

**Figure 7: Analysis on enteroscope effective rate of five studies**

| Study or Subgroup | Control | Experimental | Control | Experimental | Total | Total | Weight | Risk Ratio | Risk Ratio |
|-------------------|---------|--------------|---------|--------------|-------|-------|--------|------------|------------|
|                   | Events  | Total        | Events  | Total        |       |       |        | M-H, Fixed | CI         |
|                   |         |              |         |              |       |       |        | 95% CI     | 95% CI     |
| LI ZW 2012        | 19      | 20           | 15      | 15           | 44    | 29    | 1.27   | 0.96, 1.66 | 2012       |
| Jiang KS 2014     | 24      | 30           | 26      | 26           | 50    | 38    | 1.16   | 0.85, 1.60 | 2014       |
| Wang HL 2017      | 28      | 32           | 28      | 28           | 56    | 43    | 1.10   | 0.85, 1.47 | 2017       |
| Sheng RD 2017     | 39      | 48           | 38      | 38           | 77    | 66    | 1.14   | 0.92, 1.42 | 2017       |
| Total (95% CI)    | 140     | 140          | 100.00  | 100.00       | 1.18  | 1.05, 1.33 |         |            |            |
| Total events      | 123     | 104          |         |              |       |       |        |            |            |
| Heterogeneity: Ch² | 0.43    | df = 3       |         |              | 0.93  | 0.00  | 0.04   |            |            |
| Test for overall effect: Z = 2.86 (p = 0.004) | | | | | | | | | |

**Figure 8: Comparison of symptom scores before and after treatment from two studies**

| Study or Subgroup | Control | Experimental | Mean Difference | IV, Fixed, 95% CI |
|-------------------|---------|--------------|----------------|-------------------|
|                   | Mean    | SD       | Total | Mean | SD | Mean | 95% CI      | Mean | 95% CI      |
|                   |         |         | Total | Mean | SD |      |             |      |             |
| Han I 2012        | 3.51    | 2.23     | 36    | 35.8 | 6.43 | -4.45 | -6.32, -3.28 | -4.53 | -6.32, -3.28 |
| Wang G 2019       | 4.56    | 1.23     | 43    | 43.6 | 6.42 | -4.11 | -6.38, -1.84 | -4.11 | -6.38, -1.84 |
| Total (95% CI)    | 79      |          | 100.00|      |    |      |             |      |             |
| Heterogeneity: Ch² | 0.21    | df = 1   |         | 0.65 | 0.00 | 0.04 | -0.00001   | 0.00 | -0.00001   |
| Test for overall effect: Z = 11.84 (p = 0.00001) | | | | | | | | | |
these studies used different modified prescriptions based on TCM syndrome differentiation, all these modifications were based on the TCM method of heat clearing, dampness excreting, spleen strengthening, and stasis removing, and all studies showed that the curative effect of treating UC by the integration of these with Western medicine is better than using Western medicine alone. All studies were randomized, with clear interventions and comparable baselines. However, there was limited description of the study designs, randomization methods, and allocation concealments, so it is difficult to judge if they were scientific and reasonable, if there was publication bias, or if there was sufficient quality of methodology. In addition, only five studies\cite{6,8-10,17} mentioned adverse events. The lack of a specific description of adverse events makes security analysis difficult to conduct. The number of studies included and the cases in this analysis were also relatively small, and the basic conditions such as the stage of the disease and the disease course, the age of the patients, and result indicators were not uniform. In addition, there was difference in the duration of treatment in the studies, and most studies did not mention the specific randomization methods, leading to low quality and credibility overall. The above deficiencies, therefore, affect the meta-analysis results and the strength of the argument. Further scientific studies with prospective, multicentric, large-scale, randomized, and double-blind controlled trials should be conducted to draw conclusions that are more convincing. Future researchers should pay attention to different methods of treatment and prescriptions at different stages of the disease. Randomized Controlled Trial (RCT) should be double blinded with allocation concealment, and follow-ups should be recorded to ensure the credibility of the results. Selecting only high-quality studies would enhance the evidence that TCM is therapeutic through the theory of evidence-based medicine.

**Conclusion**

Treating UC with Western medicine combined with TCM based on UC’s features of internal retention of dampness and heat, blocked vessels, and meridians by blood stasis and qi stagnation caused by the accumulation of stasis could better address both symptoms and root causes with a relatively higher success rate compared to treatment with Western medicine alone. This review provides evidence for treating UC with both TCM methods and Western medicine combined.

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**Conflicts of interest**

There are no conflicts of interest.

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Study on Medication Rules of Modern Chinese Herbal Medicine in the Treatment of Non-small Cell Lung Cancer Based on Data Mining

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Abstract

Objective: Based on data mining technology, we attempted to explore the medication rules of modern traditional Chinese medicine (TCM) compounds in non-small cell lung cancer (NSCLC) treatment, to provide a reference for clinical drug use. Methods: From 2010 to 2017, TCM compounds used for NSCLC treatment were collected from the Beijing 301 Hospital. The modern TCM compounds utilized in the treatment of NSCLC were established in the prescription database. Excel, SPSS 22, and SPSS Modeler 14.2 software were utilized for the frequency analysis, factor analysis, cluster analysis, and association analysis. Then, the quantitative and qualitative analyses of the regularity of TCM compound medications were performed, and the possible mechanism was discussed. Results: The treatment of NSCLC using Chinese herbal compounds involved 231 prescriptions, 389 types of Chinese herbs, and 135 types of high-frequency Chinese herbs. Of these, Fritillaria cirrhosa, stir-baked fried Scutellariae, raw Os Draconis, Poria cocos (Schw.) Wolf, and Scutellaria barbata were the top five frequently prescribed Chinese herbs. Among the 39 types of drugs, heat-clearing and detoxifying drugs and qi-tonifying drugs were the leading. Cold, warm, flat, slightly cold, sweet, bitter, and pungent of four properties and five tastes and the meridians of lung, spleen, and stomach were most commonly selected. Factor analysis extracted 12 common factors, and the cumulative contribution rate was 65.595%, which mainly contained tonifying qi and blood; tonifying yin, clearing away heat, and eliminating stagnation; tonifying the spleen, regulating qi, and eliminating phlegm. Forty drug groups were obtained by cluster analysis; a total of 63 association rules were obtained by association analysis. The pairs of Poria cocos → dried tangerine peel and fried Atractylodes macrocephala → dried tangerine peel were commonly used in NSCLC, while the three most frequent herb groups were raw Astragulus → fried A. macrocephala and Portia cocos; raw-medicated leaven → fried A. macrocephala and Portia cocos; and dried tangerine peel → fried A. macrocephala and Portia cocos. Conclusion: Lung cancer is mainly caused by qi stagnation, phlegm obstruction, phlegm, and blood stasis. Based on the principle of strengthening the body and dispelling pathogens, clinical treatment of NSCLC involves clearing heat and detoxifying, tonifying the spleen, regulating qi, eliminating phlegm to dispel pathogens, and tonifying qi and blood to strengthen the body.

Keywords: Data mining, modern Chinese medicine compounds, non-small cell lung cancer

Introduction

Lung cancer is a malignant tumor that occurs in the bronchial mucosa, glands, and alveolar epithelium. Studies have demonstrated that lung cancer has the highest incidence and mortality rate in China. Furthermore, non-small cell lung cancer (NSCLC) accounts for 75%–80% of all lung cancers, which is a serious threat to human health. Early symptoms of lung cancer are mainly cough or dry cough, which are extremely common for patients to notice. Hence, lung cancer is usually discovered in the middle and later stages when the possibility of surgery, radiotherapy, or chemotherapy is no longer available. A large number of clinical studies have shown that Chinese compounds used for NSCLC, to provide a reference for clinical drug use. From 2010 to 2017, TCM compounds used for NSCLC treatment were collected from the Beijing 301 Hospital. The modern TCM compounds utilized in the treatment of NSCLC were established in the prescription database. Excel, SPSS 22, and SPSS Modeler 14.2 software were utilized for the frequency analysis, factor analysis, cluster analysis, and association analysis. Then, the quantitative and qualitative analyses of the regularity of TCM compound medications were performed, and the possible mechanism was discussed. Results: The treatment of NSCLC using Chinese herbal compounds involved 231 prescriptions, 389 types of Chinese herbs, and 135 types of high-frequency Chinese herbs. Of these, Fritillaria cirrhosa, stir-baked fried Scutellariae, raw Os Draconis, Poria cocos (Schw.) Wolf, and Scutellaria barbata were the top five frequently prescribed Chinese herbs. Among the 39 types of drugs, heat-clearing and detoxifying drugs and qi-tonifying drugs were the leading. Cold, warm, flat, slightly cold, sweet, bitter, and pungent of four properties and five tastes and the meridians of lung, spleen, and stomach were most commonly selected. Factor analysis extracted 12 common factors, and the cumulative contribution rate was 65.595%, which mainly contained tonifying qi and blood; tonifying yin, clearing away heat, and eliminating stagnation; tonifying the spleen, regulating qi, and eliminating phlegm. Forty drug groups were obtained by cluster analysis; a total of 63 association rules were obtained by association analysis. The pairs of Poria cocos → dried tangerine peel and fried Atractylodes macrocephala → dried tangerine peel were commonly used in NSCLC, while the three most frequent herb groups were raw Astragulus → fried A. macrocephala and Portia cocos; raw-medicated leaven → fried A. macrocephala and Portia cocos; and dried tangerine peel → fried A. macrocephala and Portia cocos. Conclusion: Lung cancer is mainly caused by qi stagnation, phlegm obstruction, phlegm, and blood stasis. Based on the principle of strengthening the body and dispelling pathogens, clinical treatment of NSCLC involves clearing heat and detoxifying, tonifying the spleen, regulating qi, eliminating phlegm to dispel pathogens, and tonifying qi and blood to strengthen the body.

Keywords: Data mining, modern Chinese medicine compounds, non-small cell lung cancer

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medicine has unique advantages in inhibiting malignant tumor growth, regulating immunity, increasing the efficiency, and reducing side effects of radiotherapy or chemotherapy.

In ancient books of traditional Chinese medicine (TCM), there is no mention of “lung cancer,” but similar records of lung cancer symptoms have been documented. For example, “Suwen Qibinglun” (one ancient book of Chinese medicine) said, “the disease is called Xiji, which has the symptoms of fulness under the ribs and adverse rising of qi, etc.” “Shengji Zonglu” (another ancient book) recorded, “pulmonary retention, also called Xiben, expresses cough and hemoptysis.” The pathogenesis of lung cancer[6,7] is extremely complicated, in which the deficiency of healthy qi is considered primary while the spread of pathogen toxins to the whole body is considered secondary.

In this article, we attempted to analyze the data of Chinese medicine compounds utilized for NSCLC treatment (in the chemotherapy stage) from the Beijing 301 Hospital, during 2010–2017. We performed frequency analysis,[8] cluster analysis,[9] association rule analysis,[10] and factor analysis, to calculate the frequency of TCM and its four natures, five flavors, meridian tropism, and efficacy variables. We assessed drug groups for treating lung cancer, analyzed the combination rules of various Chinese medicines in compounds quantitatively and qualitatively, analyzed the law of drug utilization, and discussed various consensus and rules for the use of TCM in NSCLC treatment.

All these outcomes could provide objective data for the clinical treatment of NSCLC, improving the efficacy of TCM in the treatment of lung cancer and providing reference for future clinical treatment and novel drug research and development.

**SEARCH METHODS**

**Prescription source**

From 2010 to 2017, TCM compounds used for NSCLC treatment (with chemotherapy treatment) were collected from the Beijing 301 Hospital, obtained from the National Scientific Data Sharing Platform for Population and Health.

**CHINESE MEDICINE COMPOUND SCREENING AND ENTRY**

**Inclusion criteria**

All TCM compounds for NSCLC treatment were included.

**Data specification**

We referred to the “Twelfth Five-Year Plan” textbook of “Chinese Pharmacy” and the 2015 edition of the “Chinese Pharmacopoeia” of the National Higher Hospital of TCM and regulated the names of TCMs, such as Epimedium and Xianlingpi, termed Epimedium in this research. Furthermore, efficacy was classified. For example, *Codonopsis pilosula*, processed licorice, and fried *Atractylodes macrocephala* were classified as qi-tonifying drugs. Cooked rehmannia, peony, and *Angelica* were classified as blood-tonifying drugs.

**Data processing and analysis**

The TCM compounds utilized for the treatment of NSCLC were established in the prescription database using the Excel software. Excel (Microsoft Corporation, Redmond, Washington, USA) was used for frequency analysis, SPSS 22.0 (SPSS 21 Inc., Chicago, IL, USA) was used for factor and cluster analysis, and the SPSS Modeler 14.2 (Inc., Chicago, IL, USA) software for employed for association rule analysis.

**RESULTS AND ANALYSIS**

Based on the search and screening, 231 Chinese medicinal compounds were finally determined, and the Chinese herbal compounds were sorted to establish a database of Chinese herbal medicines for treating NSCLC as shown in Table 1.

**Analysis of absolute frequency and percentage frequency**

**Analysis of absolute frequency and percentage frequency of high-frequency traditional Chinese medicine**

The database listed a total of 389 types of Chinese herbal medicines. The Chinese herbal medicines whose frequency was below the average absolute frequency were excluded. A total of 135 types of Chinese herbal medicines remained, and the absolute frequency and percentage frequency analysis results are shown in Table 2, with the arrangement of the Chinese herbal medicines in order of absolute frequency from high to low.

**Efficacy analysis of high-frequency traditional Chinese medicine**

Table 3 and Figure 1 present the heat-clearing and toxin-resolving drugs, especially *Hedyotis diffusa* and *Cremastra appendiculata* (D.Don) Makino, which are most commonly used in modern Chinese medicine for NSCLC treatment, with a percentage frequency of 7.98%. The second was the qi-tonifying drugs (7.75%), demonstrating no significant difference compared to the first. The percentage frequency of each of the top five categories of TCM was over 5.5%. Furthermore, the heat-clearing, toxin-resolving, and qi-tonifying drugs were at the forefront of these data mining results, indicating the importance to strengthen the body and dispel pathogens during NSCLC treatment.

**Analysis of meridian tropism of high-frequency traditional Chinese medicine**

The meridian tropism of high-frequency Chinese medicine was 12. Arranged in the order of frequency from high to low, the frequency analysis results are shown in Table 4 and Figure 2. The top six meridian tropisms were as follows: lung meridian (39.36%), spleen meridian (34.46%), liver meridian (55.80%), stomach meridian (34.15%), heart meridian (29.35%), and kidney meridian (29.35%), while each absolute frequency was over 1200. Furthermore, in lung cancer treatment, replenishing the spleen and stomach and regulating the heart, liver, and kidney were crucial.

**Analysis of the four natures of high-frequency traditional Chinese medicine**

Based on the analysis results in Table 5 and Figure 3, the first
In Table 6 and Figure 4, in high-frequency Chinese medicines, the top three of the five flavors presented were sweet (66.26%), bitter (48.88%), and pungent (42.06%), with each absolute frequency exceeding 2400. Chinese medicines with the three flavors, i.e., sweet, bitter, and pungent were more commonly used for the treatment of NSCLC.

Factor analysis
In Table 7, factor analysis was performed on every single Chinese medicine with an absolute frequency of over 41, and the results are presented in Table 7 and Figure 5. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was 0.850, which was over 0.5 ($P < 0.05$). Hence, factor analysis could be applied. In Table 8, twelve common factors were finally extracted based on a featured root greater than one, and the cumulative contribution rate was 65.595%. In Table 9, according to the principle that the load factor was greater than 0.5, ten groups of several drug-combination factors affecting NSCLC treatment were finally extracted. The extraction results and the specific treatment methods reflected by each group of drugs are shown in Table 10.

Cluster analysis
The cluster analysis was performed on Chinese medicines with a frequency of 20 times or greater. The results of the analysis and the results of the combined extraction are shown in Table 11 and Figure 6.

Analysis results of association rules
According to the association rules, the parameter support degree was over ten, and the confidence level was over 50 (the support degree reflected the frequency of the drug groups; the confidence level reflected the reliability degree and...
Table 2: Frequency analysis of high-frequency traditional Chinese medicine

| Serial number | Chinese medicine                  | Absolute frequency | Percentage (%) |
|---------------|----------------------------------|--------------------|---------------|
| 1             | Scopolamum nigrum                 | 126                | 86.82         |
| 2             | Radix paeoniae                    | 68                 | 46.32         |
| 3             | Pinelliae taimanae                | 62                 | 41.13         |
| 4             | Nelumbinis plumula                | 55                 | 38.53         |
| 5             | Tangerine peel                    | 40                 | 27.41         |
| 6             | Radix salviae                     | 35                 | 23.68         |
| 7             | Phellodendri cortex              | 30                 | 20.51         |
| 8             | Fructus percom Fructus           | 28                 | 18.84         |
| 9             | Angelicae sinensis               | 25                 | 16.88         |
| 10            | Gentianae rhizomae               | 24                 | 16.28         |
| 11            | Rhizoma phragmitis               | 21                 | 14.29         |
| 12            | Atractylodis rhizomae            | 20                 | 13.79         |
| 13            | Angelicae soulie                   | 18                 | 12.12         |
| 14            | Alismatis rhizomae               | 17                 | 11.57         |
| 15            | Cimicifugae rhizomae             | 16                 | 10.91         |
| 16            | Angelicae archangelica           | 14                 | 9.52          |
| 17            | Cimicifugae archangelica         | 13                 | 8.66          |
| 18            | Angelicae gigas                   | 12                 | 8.04          |
| 19            | Angelicae gigas                   | 11                 | 7.37          |
| 20            | Angelicae gigas                   | 10                 | 6.67          |
| 21            | Angelicae gigas                   | 9                  | 5.96          |
| 22            | Angelicae gigas                   | 8                  | 5.36          |
| 23            | Angelicae gigas                   | 7                  | 4.76          |
| 24            | Angelicae gigas                   | 6                  | 3.93          |
| 25            | Angelicae gigas                   | 5                  | 3.33          |
| 26            | Angelicae gigas                   | 4                  | 2.64          |
| 27            | Angelicae gigas                   | 3                  | 1.95          |
| 28            | Angelicae gigas                   | 2                  | 1.28          |
| 29            | Angelicae gigas                   | 1                  | 0.64          |

Contd...
Using a priori for correlation analysis, the degree of association among TCM compounds was evaluated in the sNSCLC treatment, and the results are presented in Table 12. There were 63 association rules for the drug groups. Among these, there were 36 association rules for the 36 drug pairs and 27 association rules for the 27 drug groups of the three Chinese medicines. As shown in Table 12, the two TCM association rules, two drug pairs, Poria cocos (Schw.) Wolf → tangerine peel and processed Atractylodes → tangerine peel, ranked first with 73.20% support. In addition, in the three TCM association rules, the three-drug groups, which were raw Scutellariae → processed Atractylodes and Poria cocos, raw-mediated leaven → processed Atractylodes and Poria cocos, tangerine peel → processed Atractylodes and Poria cocos, ranked first with 58.82% support.

**Discussion**

Lung cancer is a common malignant tumor that has a high disease incidence in clinics. In TCM, it is termed “Fei Ji” and “Xi Ben.”
### Table 3: Efficacy analysis of high-frequency traditional Chinese medicine

| Efficacy                                             | Absolute frequency (%) | Chinese medicine                                                                 |
|------------------------------------------------------|------------------------|----------------------------------------------------------------------------------|
| Heat-clearing and toxin-resolving drugs              | 440 (7.98)             | *Hedysos diffusa*, *Crestula appendiculata* (D.Don) *Makino, Solanum nigrum, Scutellaria barbata, Hypericum erectum* thorn, Golden lotus flower, Herba patriniae, *Oroxylum indicum, Polygonum bistorta* L., *Houttuynia cordata* thorn |
| Qi-tonifying drugs                                   | 427 (7.75)             | Processed *Astragalus membranaceus*, Fried *Atractylodes*, Raw *Scutellariae*, Processed licorice, Raw licorice, *Codonopsis pilosula, Raw Atractylodes, Pseudostellaria heterophylla* |
| Yin-nourishing drugs                                 | 336 (6.09)             | *Glehia littoralis, Asparagus, Ophiopogon japonicas, Dendrobium, Ligusticum isticum, processed Trionyx carapax, Lily, Radix adenophora, Polygonati rhizome |
| Drugs of clearing away heat to resolve phlegm       | 310 (5.62)             | *Fritillaria cibrosa, Fritillaria thunbergii* miq, the Root of balloon flower, Bobbostenma panicul, atum, Semen benincasae, Arcae concha |
| Heat-purging-fire drugs                              | 303 (5.5)              | Raw gypsum; Raw *genenia jasminoides, Prunella vulgaris* L., Rhizoma phragmitis, *Lophatherum gracile, Fried cassia tora* |
| Rectifying-Qi drugs                                  | 285 (5.17)             | Raw *Cyperus rotundus* L., Tangerine peel, Toosendan fructus, Aurantii fructus, Processed *Cyperus rotundus* L, *Fructus aurantii* immaturus |
| Heart-nourishing, spirit-quieting drugs              | 253 (4.59)             | Processed spinozae Ziziphí semen, Spinozae Ziziphi semen, *Polysalia tenuifolia, Sempatycladí, Poría cocos* (Schw.) wolf, Nelumbinis pluuma |
| Phlegm cough and asthma drugs                        | 244 (4.43)             | Processed loquat leaves, Processed radix stemonae, Raw farfarae flos, Armeniaceae semen, *Perilla frutescens* seed, Raw loquat leaves radix stemonae |
| Heat-clearing, damp-drying drugs                     | 238 (4.32)             | Fried *Scutellariae*, Coptidis rhizome |
| Digestant drugs                                      | 217 (3.94)             | Raw malt, endothelium corneum gigeriage galli, Coked crataegi fructus, Raw massa medica, Ferramentata, Processed crataegus pinnatifida Bunge, Raw crataegus pinnatifida bunge |
| Drugs for inducing diuresis to alleviate edema       | 182 (3.3)              | *Poría cocos, Raw coicis semen, Poría cocos, Waxgourd peel, Processed coicis semen |
| Drugs of warming and resolving cold-phlegm           | 157 (2.85)             | Inula japonica thumb, Pinelliae rhizome |
| Drugs for inducing diuresis for treating stranguria  | 155 (2.81)             | Juncus effuses, Talc, Rhizoma diosectoeae sectemloabe |
| Dispersing wind-heat drugs                           | 142 (2.58)             | *Chrysanthemum*, Mulberry leaves, Bupleuri radix, Vinegar-processed bupleuri radix |
| Blood-activating menstruation-regulating drugs       | 142 (2.58)             | Salvia miltiorrhiza Bge, Polygony orientalis fructus, Peach kernel, Salvia chinensis herba, *Crocus sativus* L. |
| Blood-enriching drugs                                | 141 (2.56)             | Processed radix polygoni multiflora, Raw angelia, Raw peony, Angelica |
| Drugs for cooling blood to arrest bleeding           | 136 (2.47)             | Raw *sanguisorba officinalis* L, Rhizoma imperatae, *Platycladus orientalis* leaf |
| Yang-nourishing drugs                                | 122 (2.21)             | Epimedium, *Cistanche deserticola*, Paris polyphilla smith |
| Heavy settling spirit-quieting drugs                 | 113 (2.05)             | *Raw Os Draconis* |
| Heat-clearing blood-cooling drugs                    | 112 (2.03)             | *Scrophularia ningpoensis* hemsl, Lithospermum, Radix paconiac rubra, Rehmanniae radix |
| Dispersing wind-cold drugs                           | 104 (1.89)             | *Asari radix et rhizome, Windproof, Cinnamomí ramulus* |
| Astringing blood-stanching drugs                     | 89 (1.61)              | Raw lotus roots |
| Drugs of relieving rheumatism and qi and strengthening muscles and bones | 75 (1.36)              | *Taxillus chinensis* (DC.) danser, *Cibotium barometz* |
| Anthelmintic drugs                                   | 74 (1.34)              | Raw areca catechu L, Scorched areca seed |
| Qi-disinhibiting phlegm-sweeping drugs               | 71 (1.29)              | Mustard seed |
| Drugs for blood circulation and painkiller           | 69 (1.25)              | Turmeric, *Ligusticum, Chuanxiong Hort* |
| Wind-extinguishing tetany-checking drugs             | 69 (1.25)              | Pearl powder, *Gastrodiae* rhizome |
| Damp dispersing drugs                                | 65 (1.18)              | *Magnolia officinalis, Amomum villosum* Lour, *Alpinia katsumadai* Hayata |
| Smoothing liver yang medicine drugs                  | 65 (1.18)              | *Conhea margaritifera, Raw oyster* |
| Drugs of securing essence, reducing urination and checking discharge | 64 (1.16)              | *Fructus corni, Rosae laevigatae fructus* |
| Wind-damp-dispelling heat-clearing drugs             | 62 (1.12)              | *Stephaniea tetrandrae* radix |
| Removing necrotic tissue and promoting tissue regeneration drugs | 58 (1.05)              | *Borax* |
| Lung-intestine astringent drugs                      | 38 (0.69)              | *Schisandra* |
| Drugs of breaking blood stasis to resolve lumps      | 34 (0.62)              | *Sputum* |
| Drugs of clearing away heat to resolve phlegm        | 31 (0.56)              | *Trichosanthes pericarpium* |
| Stasis-transforming blood-stanching drugs            | 28 (0.51)              | Radix notoginseng |
| Interior-warming drugs                               | 24 (0.44)              | Dried ginger |
| Drugs for detoxicating insecticide and anti-itch     | 19 (0.34)              | *Cnidium monnieri* (L.) cuss |
| Moist precipitating drugs                            | 19 (0.34)              | *Cannabis fructus* |
Table 4: Analysis of meridian tropism of high-frequency traditional Chinese medicine

| Meridian tropism       | Absolute frequency (%) |
|------------------------|------------------------|
| Lung meridian          | 3216 (58.33)           |
| Spleen meridian        | 2189 (39.71)           |
| Liver meridian         | 2170 (39.36)           |
| Stomach meridian       | 1982 (35.95)           |
| Heart meridian         | 1593 (28.9)            |
| Kidney meridian        | 1282 (23.25)           |
| Large intestine meridian| 808 (14.66)            |
| Gallbladder meridian   | 511 (9.27)             |
| Small intestine meridian| 471 (8.54)             |
| Bladder meridian       | 289 (5.24)             |
| Triple Energizer meridian| 191 (3.46)            |
| Pericardium meridian   | 94 (1.71)              |

Table 5: Frequency analysis of the four natures of high-frequency traditional Chinese medicine

| Four natures   | Absolute frequency (%) |
|----------------|------------------------|
| Cold           | 1232 (22.35)           |
| Warm           | 1186 (21.51)           |
| Gentle         | 1186 (21.51)           |
| Slight cold    | 1016 (18.43)           |
| Slight warm    | 395 (7.16)             |
| Cool           | 330 (5.99)             |
| Great cold     | 120 (2.18)             |
| Hot            | 46 (0.83)              |

Table 6: Analysis of five flavors of high frequency traditional Chinese medicine

| Five flavors        | Absolute frequency (%) |
|---------------------|------------------------|
| Sweet               | 3085 (55.95864)        |
| Bitter              | 2314 (41.97352)        |
| Pungent             | 1552 (28.15164)        |
| Salty               | 464 (8.416470)         |
| Slight bitter       | 443 (8.035552)         |
| Astringency         | 443 (8.035552)         |
| Mild-natured        | 420 (7.618357)         |
| Sour                | 341 (6.18538)          |
| Slight pungent      | 128 (2.321785)         |
| Slight sweet        | 119 (2.158534)         |

Table 7: Kaiser-Meyer-Olkin and Bartlett’s test

| Statistical terms           | Value  |
|-----------------------------|--------|
| KMO measure of sampling adequacy | 0.850  |
| Bartlett’s test of sphericity |        |
| Approximately $\chi^2$      | 5473.291 |
| df                          | 1081   |
| Significant                 | 0.000  |

Significant is the $P$ value of Bartlett’s spherical test ($P<0.05$ has statistical significance). KMO: Kaiser-Meyer-Olkin

Figure 6: Dendrogram using average linkage (between groups)