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Does the traditional Chinese medicine theory of five circuits and six qi improve treatment effectiveness? A systematic review of randomized controlled trials

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KEYWORDS

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Effectiveness;
Evaluation

Abstract *Objective:* To evaluate whether the traditional Chinese medicine (TCM) theory of five circuits and six qi (FCSQ) is beneficial in terms of improving clinical effectiveness.

Methods: Randomized controlled trials (RCTs) evaluating the clinical value of FCSQ theory were reviewed. Multiple databases (China Network Knowledge Infrastructure, Chinese Scientific Journals Database, Wanfang Data, SinoMed, Cochrane Library, PubMed, and Embase) were systematically searched from inception to June 12, 2018. Two authors independently extracted the data and performed a methodological quality assessment of the RCTs. RevMan 5.3 software was used for the data analysis. The effect sizes for the primary outcome measures were expressed as relative risks or mean differences with 95% confidence intervals.

Results: A total of 13 RCTs were selected, involving 12 types of diseases and 4695 patients. The methodological quality of the RCTs was generally low. Five studies compared the effectiveness of TCM treatments guided by FCSQ theory with conventional TCM therapies, and the remaining eight studies compared the effectiveness of TCM treatments guided by FCSQ theory with biomedical treatments. All of the RCTs reported that the effectiveness of the treatment intervention was better than that of the intervention in the control group.

Conclusion: Because of many methodological problems in existing clinical studies, it remains impossible to definitively conclude that FCSQ theory can improve clinical effectiveness. It is difficult to unify the clinical application of FCSQ theory. The feasibility and repeatability of FCSQ as an intervention should be given more attention in future clinical research. Future work should also follow international norms for clinical research implementation and reporting to provide high-quality evidence for evaluating the clinical value of FCSQ theory.

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Introduction

The theory of five circuits and six qi (FCSQ; five circuits refers to wood, fire, earth, metal, and water; six qi indicate wind, cold, summer heat, dampness, dryness, fire) is an essential part of traditional Chinese medicine (TCM). The theory represents a holistic view held by early doctors based on the correspondence between heaven and humankind. It is a doctrine for understanding the laws of nature and climate change, as well as their impact on human diseases. FCSQ theory, which is based on the theory of yin and yang and uses symbols such as “heaven” and “earth” as deductive tools, has been passed down from the era of *Yellow Emperor’s Canon of Medicine*. Using current meteorological data and data on the incidence of diseases, scholars have conducted a series of studies to evaluate the correlations between FCSQ and climate change, occurrence of diseases, and TCM patterns.^{1–4} These studies have found varying levels of correlation between the complete meteorological data, based on continuous modern meteorological observations, and the climate mode deduced from FCSQ. Furthermore, a relationship between FCSQ and common diseases has been found in some internal medicine and TCM patterns. All of this previous work has objectively proven that FCSQ exerts an influence on human life activities and provided a basis for using FCSQ theory to treat diseases in TCM clinical practice. Unique effects were observed for TCM treatments guided by FCSQ theory for epidemic cerebrospinal meningitis in North China in the 1950s and severe acute respiratory syndrome in China in 2003.⁵ In recent years, a number of studies on FCSQ have been published.

Nevertheless, the clinical value of FCSQ theory is very controversial in the field of TCM, and doubts have existed since the theory’s emergence. Some medical doctors have explicitly opposed FCSQ theory. For example, in the Ming Dynasty, Xiyong Miu wrote a chapter entitled “On the falseness of FCSQ” in his book, *Commentary on Shen Nong’s Classic of the Materia Medica*. He believed that what was called FCSQ theory by later generations was not beneficial for treatment, because there was no mention of FCSQ recorded in the books written by Zhongjing Zhang, Tuo Hua, Shuhe Wang, and others. Xiyong Miu therefore denied the significance of FCSQ theory in TCM. During the Republic of China era (1911–1949), two important controversies regarding FCSQ occurred in the field of TCM, and stances denying or proposing the abolishment of FCSQ theory were predominant. Yuanlei Lu, one of the representatives of this view, published an article entitled “Overthrowing FCSQ fundamentally” in 1934 to express the idea that there is no reason for FCSQ theory to exist.⁶ Currently, the body of work on FCSQ is increasing, but applications of the theory have not been given much importance in mainstream TCM clinical practice. Is FCSQ theory beneficial for improving

the effectiveness of treatments? To answer this question, it is insufficient to rely on traditional literature reviews, theoretical derivations, or medical reports. Therefore, to provide evidence-based medical evidence on this controversial issue in the field of TCM, we systematically collected and evaluated randomized controlled trials (RCTs) that examined FCSQ theory in the treatment of diseases.

Materials and methods

Searching strategy

The databases searched included China Network Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database, Wanfang Data, SinoMed, Cochrane Library, PubMed, and Embase, which were queried from their inception to June 12, 2018. The search terms were “yunqi” (circuit and qi), “wuyun” (five circuits), “liuqi” (six qi), “keqi” (guest qi), “zhuqi” (dominant qi), “sitian” (celestial control), “zaiquan” (terrestrial effect), “suiyun” (circuit of year, that’s the characteristics of one circuit in the whole year), “suiji” (random), and “zhongyi” (TCM). These terms were selected as MeSH terms, free words, or keywords in combinations for comprehensive retrieval based on different characteristics of the selected databases. For example, in CNKI, a Chinese-language database, we retrieved records with “yunqi,” “wuyun,” “liuqi,” “zhuqi,” “keqi,” “sitian,” “zaiquan,” or “suiyun” in the title field in addition to “suiji” and “zhongyi” in the full text. In the PubMed database, the search string was “(((((((five yun and six qi [Title]) OR yunqi [Title]) OR sitian [Title]) OR zaiquan [Title]) OR zhuqi [Title]) OR keqi [Title]) AND random) AND traditional Chinese medicine.” No publication format or language limitations were defined.

Inclusion/exclusion criteria

The inclusion criteria were as follows: (i) study design type: randomized controlled trials aimed at evaluating the clinical effectiveness of FCSQ; (ii) study subject: any disease type; (iii) intervention: experimental group receiving TCM treatments guided by FCSQ theory, including traditional Chinese herbal medicine, acupuncture and moxibustion, and tuina massage and control group receiving conventional TCM treatments without FCSQ, biomedicine, or placebo; and (iv) outcomes: because of the varying disease types covered, we selected primary outcomes such as effectiveness rate for evaluating the improvement of symptoms, signs, and laboratory tests, as well as mentions of adverse reactions.

Exclusion criteria included the following aspects: (i) duplicate publications (only the original publication was included); (ii) publications including only “yunqi” (circuit

and qi) in intervention measures (e.g., the *Wenzhen Yunqi* Formula), without including or reflecting on FCSQ thought; and (iii) publications of abstracts only that did not provide the details of the research design or access to the full-text report of the study.

Methodological quality evaluation

For the methodological quality evaluation, we adopted the Cochrane Collaboration's tool for assessing risk of bias.⁷ The items included random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment, as well as incomplete outcome data, selective reporting, and other biases. The possible evaluations for each item were applicable, non-applicable, and unclear, corresponding to low, high, and unclear risks of bias, respectively. Two investigators (YH and JS) assessed the quality of each study independently and cross-checked their assessments. In case of disagreement, the evaluation was determined through discussion or submission to a third researcher (JH).

Data extraction and analysis

After discussion, we designed the data extraction form. The data were extracted independently by two authors. The extracted contents included titles, characteristics of the research methods, basic information on the subjects, interventions applied in the treatment and control groups, courses of treatment, consideration of FCSQ in the intervention for the treatment group, outcomes, and adverse events.

The data analysis included an analysis of the consideration of FCSQ in the treatment and a statistical analysis of outcomes. For the analysis of FCSQ being considered in the treatment, descriptive methods were used. For the statistical analysis of outcomes, RevMan 5.3.5 analysis software, provided by the Cochrane Collaboration, was adopted to quantify the primary outcomes. For measurement data, weighted mean differences are expressed. For enumeration data, relative risks and their 95% confidence intervals are presented. When two or more studies had good clinical homogeneity in terms of researched diseases, intervention measures, and outcomes, we planned to conduct a pooled meta-analysis, applying the corresponding model based on the results of the heterogeneity test. Where possible, subgroup analyses were performed according to the different modes of FCSQ application and the type of control measures. If not, only the effect sizes (expressed as relative risks or mean differences with 95% confidence intervals) of the individual studies are described.

Results

Results of the search

After searching the above-mentioned databases, 143 articles were obtained. Of these articles, 130 were removed because of duplication, irrelevance, or failure to meet the inclusion criteria. The remaining articles included 13 RCTs,

which were included for further analysis. All studies were conducted in China and published in Chinese (Fig. 1).

Characteristics of included studies

A total of 13 RCTs^{8–20} involving 4695 patients were included in the analysis. In these studies, 12 categories of diseases/patterns were mentioned, including cough,⁸ rheumatoid arthritis,⁹ post-menstruation deficiency,¹⁰ psoriasis,^{11,12} peptic ulcer,¹³ hypertension,¹⁴ hand-foot-and-mouth disease,¹⁵ menopausal insomnia,¹⁶ dizziness,¹⁷ externally contracted cough,¹⁸ insomnia after stroke,¹⁹ and chronic fatigue syndrome.²⁰ The average sample size in these studies was 361, with a maximum of 3666 and a minimum of 60 subjects. The longest course of treatment was 1 year, and the shortest was 5 days. Outcomes reported in these studies included symptom scores, laboratory test indicators, morbidity, and recurrence rate. Symptom scores were the primary outcome of 11 studies. Seven articles reported the occurrence of adverse reactions.^{8,9,12,14,16–18} With regard to interventions in the treatment group, 10 studies used oral administration of traditional Chinese herbal medicine^{8–12,14–18} (combined with the regular biomedicine or external treatment in four for these studies), and the other three studies used acupuncture therapy,¹⁹ tuina massage,²⁰ or acupoint application therapy.¹³

The interventions using FCSQ theory can be divided into three categories: TCM prescriptions or external therapy devised by the researchers based on the theory of FCSQ,^{8–13,19,20} the use of an FCSQ formula taken directly from the work of early medical doctors,^{14,15} and formulas conforming to the "heavenly stems and earthly branches" from *Sanyin Sitian Fang*, an FCSQ monograph written by Wuze Chen in the Northern Song Dynasty (960–1127 AD).^{16–18} As for the control group, in six studies, control subjects were treated with conventional biomedicine,^{9,10,12,14,16,18} and three studies^{13,19,20} used traditional

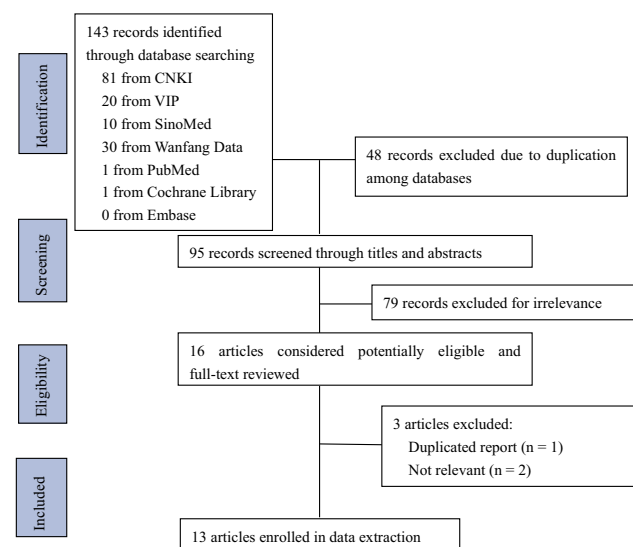


Figure 1 Selection of randomized controlled trial studies on the five circuits and six qi.

Table 1 Basic characteristics of the included randomized controlled trials.

Research ID	Disease	Sample size	Intervention	Control measures	Treatment group		Control group		Treatment course	Outcomes	Adverse reactions		Funding
					N	Age (yrs; mean (SD))	N	Age (yrs; mean (SD))			Treatment group (n)	Control group (n)	
Zhang WH 2012	Insomnia/liver-kidney deficiency	67	<i>Wuwei Shenping</i> Decoction	Estazolam tablet	35	48.26 (1.13)	32	49.17 (0.90)	4 weeks	PSQJ score	1	13	+
Wang JX 2012	Cough/Yangming dryness metal	72	<i>Chaiqin Daozhi</i> Powder	Oral solution for relieving cough for children	36	25–36 months	36	25–36 months	5 days	Cough grading score	0	0	–
Li XY 2014	Rheumatoid arthritis	90	Modified <i>Yishen Jianpi Tongluo</i> formula	Methotrexate + salazosulfapyridine	45	39 (5.00)	45	41 (7.00)	3 weeks	VAS score, HAQ score, and DAS-28 score	0	2	+
Bian XF 2015	Hypertension	60	Nifedipine + modified <i>Wumei</i> Pill	Nifedipine controlled release tablet	30	59.4 (9.88)	30	59.6 (9.16)	4 weeks	Pattern scoring	0	0	–
Liu MJ 2015	Chronic fatigue syndrome	60	Tuina massage based on FCSQ theory	Traditional Tuina therapy	30	17–60	30	17–60	4 weeks	Symptom scoring	NP	NP	+
Li WH 2015	Poststroke insomnia	60	Conventional acupunctural therapy based on point selection + moxibustion on SP 9	Conventional acupoint therapy	30	Unspecified	30	Unspecified	2 weeks	PSQJ score	NP	NP	+
Li L 2016	Hand-foot-and-mouth disease	3666	<i>Sandou</i> Decoction + regular diet	Regular diet	1886	2–6.7	1780	2–6.7	2 months	Hand-foot-and-mouth disease morbidity	NP	NP	+
Yan Y 2016	Menopathy/liver depression and kidney deficiency pattern	60	<i>Shugan Yishen</i> Decoction under FCSQ theory guidance	Sequential therapy of progynova and dydrogesterone tablet	30	30.367 (4.09)	30	30.433 (5.31)	3 months	Symptom integral comparison	NP	NP	–
Li W 2017	Psoriasis/damp-heat pattern	282	Regulate qi, regulate body, and govern disease	Conventional TCM pattern identification and treatment	215	33	67	Unspecified	6 months	PASI score, VAS score, and DLQI score	NP	NP	–
An X 2017	Dizziness/liver-fire flaming pattern	62	Canalith repositioning + <i>Zichai</i> Decoction	Canalith repositioning combined with <i>Qiangli Dingxuan</i> Tablet	31	52.12 (6.49)	31	51.92 (6.62)	2 weeks	Symptom score	0	0	+
Yuan B 2017	Exogenous cough/exterior cold and interior heat pattern	90	<i>Ziyuan</i> Decoction	Robitussin oral solution	60	46.17 (16.56)	30	44.28 (13.65)	7 months	Symptom score	0	0	–

(continued on next page)

Table 1 (continued)

Research ID	Disease	Sample size	Intervention	Control measures		Treatment group		Control group		Treatment course	Outcomes	Adverse reactions		Funding
				N	Age (yrs; mean (SD))	N	Age (yrs; mean (SD))	Treatment group (n)	Control group (n)			Treatment group (n)	Control group (n)	
Zhou SR 2016	Psoriasis vulgaris	62	TCM formula under the guidance of FCSQ theory + acitretin	30	Unspecified	32	Unspecified	4 weeks	Symptom improvement		5	15	–	
Zhou XL 2015	Peptic ulcer	60	External application of back-shu acupoint based on six qi theory application	30	41.1 (12.50)	30	44.2 (9.10)	1 year	Symptom score, recurrence rate		NP	NP	+	

Abbreviations: NP: not reported; SP 9: Yinlingquan point; PSQI: Pittsburgh Sleep Quality Index; VAS: Visual Analogue Scale; HAQ: health assessment questionnaire; DAS-28: disease activity score-28; FCSQ: five circuits and six qi; TCM: traditional Chinese medicine; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index.

external treatments to compare the effectiveness between external treatments under the guidance of FCSQ with external treatments that were not guided by FCSQ. Chinese patent medicine,⁸ prescription based on conventional pattern identification and treatment,¹¹ and diet therapy¹⁵ were each applied as the control treatment in one study, and an external treatment combined with Chinese patent medicine was the control treatment in one study.¹⁷ The basic characteristics of each study are shown in Table 1. The FCSQ thought included and the basis for FCSQ as an intervention in the treatment group are displayed in Table 2.

Methodological quality of the included studies

Five RCTs^{8,14,16,17,19} used a random-number table for random assignment; the other studies mentioned only “*suiji fenzu*” (random grouping), without specifying the randomization technique. One study¹⁹ mentioned using the random-number table generated by the SPSS, Version 17.0 software package; sequential encoding; and opaque, sealed envelopes containing subjects’ randomized groupings. None of the studies mentioned blinding. Two RCTs^{8,18} reported the study dropout rate, but they did not analyze these subjects’ data. We cannot judge whether there was selective reporting bias because there was no clinical protocol registration in the examined studies. With regard to other research biases, seven studies^{9,13,15–17,19,20} reported receiving funding for related projects. All of the included studies reported consistent baseline data for the treatment and control groups. None of the studies reported the method of sample size calculation. The methodological quality of the included RCTs is displayed in Fig. 2.

Effectiveness evaluation

Of the 13 included studies, the disease types, intervention measures, and outcomes of 10 varied. Although the disease type (i.e., insomnia) was the same in two RCTs, the interventions were different, and there was significant heterogeneity. Pooling the studies into a meta-analysis was therefore not possible, and only estimates of effects from single study are described. Our results showed that all of the included studies reported that the effectiveness of the FCSQ treatment was superior to the control treatment (Table 3).

Adverse reactions

Four RCTs^{8,9,12,16} reported specific adverse reactions. Loose stools occurred among children receiving an FCSQ-formula treatment for cough⁸; nausea and loss of appetite occurred among those treated with methotrexate for rheumatoid arthritis⁹; and skin or mucous dryness, desquamation, and itching occurred among those treated with traditional Chinese herbal medicine for psoriasis vulgaris.¹² Mild diarrhea occurred in the menopausal insomnia treatment group, whereas drowsiness, dizziness, headache, and diarrhea occurred in the control group.¹⁶ Three RCTs reported that there were no adverse reactions,^{14,17,18} and

Table 2 Therapeutic basis for FCSQ in the 13 included randomized controlled trials.

Research ID	Disease	Year	Features of stems and branches in selected year	Application mode of FCSQ	Therapeutic thought of FCSQ	Evidence for FCSQ treatment
Zhang WH 2012	Insomnia/liver-kidney deficiency	Xin Mao year	Celestial control is <i>Yangming</i> dryness metal, dryness exuberance in the first half year; terrestrial effect is <i>Shaoyin</i> sovereign fire, fire excess in the next half year	Joining of guest qi with dominant qi among six qi	1. <i>Wuweizi</i> Decoction for diseases in Xin year by five circuits 2. <i>Shenping</i> Decoction for diseases in Mao You years characterized by <i>Yangming</i> celestial control and <i>Shaoyin</i> terrestrial effect	<i>Celestial Control Formula Based on the Three Etiologies</i>
Wang JX 2012	Cough/ <i>Yangming</i> dryness metal	Xin Mao year	Celestial control is <i>Yangming</i> dryness metal, combination of fire heat and dryness heat	Joining of guest qi with dominant qi	Focus on joining of guest qi with dominant qi, the formula exerts on unblocking intestinal <i>fu</i> -organs and clear metal and moistening dryness in order to clear accumulated heat in <i>Yangming</i> , descending counterflow of fire, and recovering dryness metal injury	
Li XY 2014	Rheumatoid arthritis	Gui Si year	Celestial control is <i>Jueyin</i> wind wood, and terrestrial effect is <i>Shaoyang</i> ministerial fire; wind qi is dominant in the first half year; fire qi is dominant in the next half year	Circuit of year + guest qi of celestial control and terrestrial effect	According to the characteristics of stems and branches, herbs modified on the basis of empirical formulae	Herbal prescription based on the characteristics of stems and branches
Bian XF 2015	Hypertension/ <i>Jueyin</i> pattern	Jia Wu year	Dominant circuit is <i>Jueyin</i> wind wood, excess earth circuit. Dominant qi is <i>Jueyin</i> wind wood in <i>Chuzhiqi</i> (referring to solar terms of <i>Dahan</i> , <i>Lichun</i> , <i>Yushui</i> , and <i>Jingzhe</i>), and guest qi is also <i>Jueyin</i> wind wood	Circuit of year + joining of guest qi with dominant qi	According to the characteristics of stems and branches, herbal prescription is based on pattern identification. <i>Wumei</i> Pill is used to regulate yin-yang balance of the human body	Herbal prescription based on the characteristics of stems and branches
Liu MJ 2015	Chronic fatigue syndrome	/	/	Unspecified	According to the characteristics of stems and branches, tuina manipulation is drafted based on different channels	Self-devised manipulations based on the characteristics of stems and branches
Li WH 2015	Poststroke insomnia	Jia Wu year	Excess earth circuit, severe damp qi	Circuit of year mode alone	Due to excess earth circuit, the spleen channel encumbered easily by damp qi, SP 9 is selected to rectify the spleen and dissolve dampness	Point selected based on the characteristics of stems and branches
Li L 2016	Hand-foot-and-mouth disease	Yi Wei year	Dominant and guest qi are both <i>Shaoyin</i> sovereign fire	Circuit of year + joining of guest qi with dominant qi	Based on the characteristics of stems and branches, the formula is used to tonify the kidney and enrich yin, clear and descend sovereign fire	Herbal prescription based on the characteristics of stems and branches (continued on next page)

Table 2 (continued)

Research ID	Disease	Year	Features of stems and branches in selected year	Application mode of FCSQ	Therapeutic thought of FCSQ	Evidence for FCSQ treatment
Yan Y 2016	Menopathy/liver depression and kidney deficiency pattern	Yi Wei year	Circuit of year is insufficiency of metal, celestial control is <i>Taiyin</i> damp earth, and terrestrial effect is <i>Taiyang</i> cold water.	Circuit of year + guest qi in celestial control and terrestrial effect	Based on the characteristics of stems and branches, medication is selected following the principle of wood and fire being exuberant, excess damp-heat in the first half year, and excess cold qi in the next half year.	Herbal prescription based on the characteristics of stems and branches
Li W 2017	Psoriasis/damp-heat	/	The characteristics of stems and branches are deduced by the date of birth.	Circuit of year + guest qi in celestial control and terrestrial effect	Medication with the effect of regulating qi is determined based on the characteristics of stems and branches in patient's date of birth.	Herbal prescription based on the characteristics of stems and branches
An X 2017	Dizziness/liver-fire flaming	Yi Wei year	Circuit of year is insufficiency of metal, celestial control is <i>Taiyin</i> damp earth, and terrestrial effect is <i>Taiyang</i> cold water.	Circuit of year + guest qi in celestial control and terrestrial effect	Based on the characteristics of stems and branches, method of assisting metal to calm wood are used for liver fire upflaming, and <i>Ziwan</i> Decoction and <i>Xiaochaihu</i> Decoction are appropriate.	<i>Celestial Control Formula Based on the Three Etiologies</i>
Yuan B 2017	Exogenous cough/ exterior cold and interior heat	/	/	FCSQ formula and formula selection based on pattern identification	Cold contraction due to lung deficiency combined with heat constraint.	<i>Celestial Control Formula Based on the Three Etiologies</i>
Zhou SR 2016	Psoriasis vulgaris	Bing Shen year	Excessive water, celestial control is <i>Shaoyang</i> ministerial fire and terrestrial effect is <i>Jueyin</i> wind wood	Circuit of year + guest qi in celestial control and terrestrial effect	According to the characteristics of stems and branches, modified <i>Xiaochaihu</i> Decoction combined with <i>Chuanlian Fuling</i> Decoction is appropriate.	Herbal prescription based on the characteristics of stems and branches
Zhou XL 2015	Peptic ulcer	/	/	Dominant qi	According to the relationship between dominant qi and <i>zang-fu</i> organs, medications and acupoints for external application are adjusted following the six qi.	Herbal prescription based on the characteristics of stems and branches

Abbreviation: FCSQ: five circuits and six qi.

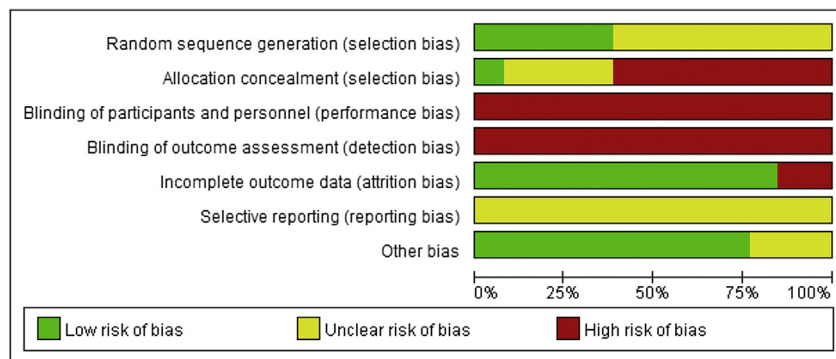


Figure 2 Risk of bias in the 13 included randomized controlled trials.

the remaining six RCTs^{10,11,13,15,19,20} did not report on adverse events.

Discussion

In this study, 13 RCTs evaluating the safety and effectiveness of applying FCSQ theory to treat diseases were systematically reviewed. The effectiveness of TCM treatments in the FCSQ treatment groups was higher, compared with the effectiveness of either conventional TCM treatments without guidance from FCSQ theory or Western medicine treatments, and these differences were significant. However, because of the low methodological quality of the included studies and inability to rule out publication bias, we cannot definitively conclude that FCSQ theory improves the effectiveness of TCM. The results in our study are similar to those of a 2014 narrative review by Liu et al,²¹ which evaluated four RCTs and two case reports that used FCSQ theory. This previous review pointed out that there have been few evaluations of the effectiveness of applications of FCSQ theory in clinical trials, that the research quality has been low, that there has been obvious publication bias in case reports, and that the demonstration of causal relationships has been weak; therefore, a precise conclusion on FCSQ treatment could not be drawn. In contrast to this previous article, we adopted the Cochrane Collaboration's tool for assessing risk of bias and included all published RCTs on the evaluation of the clinical effectiveness of FCSQ, thus avoiding selection bias in our literature search. Additionally, we summarized the ways in which FCSQ theory has been applied in existing clinical research. We found that the methodological quality of relevant studies published in recent years had not significantly improved, compared with earlier work.

Two types of methodological problems were common in the included RCTs. The first type includes common problems in TCM clinical research.^{22–24} For example, the examined studies do not design, perform, or report on research in accordance with international standards on clinical research; the details of the random allocation are inappropriately concealed (or may even not be reported at all); there is a lack of information on the sample size calculation; the studies do not report on study dropouts or provide intention-to-treat analyses of their data; evaluations of subjective outcomes are performed without

blinding; and there is no clinical trial registration, resulting in an inability to judge publication bias, selective reporting bias, and other biases. The other type of problem is specific to the formulation of control treatments and FCSQ-informed interventions. First, the main FCSQ-specific problem is the unreasonable design of control treatments. Western medicine alone has been used in the control group in many studies, without including a group receiving conventional TCM treatment without FCSQ as a control. In this case, even if the effectiveness of the FCSQ treatment is higher than that of the treatment in the control group, we can only reach the conclusion that the effectiveness of TCM is better than that of Western medicine; with this study design, it is impossible to prove whether or not the observed effectiveness is the result of guidance by FCSQ theory. Second, no reliable evidence is provided on the formulation of interventions for FCSQ treatment groups, leading to problematic performance and poor repeatability. In most studies, the FCSQ treatment interventions were based on the researchers' own experience or prescriptions devised by the researchers with consideration of the features of FCSQ. These studies have usually not reported the rules applied for herbal prescription or even defined whether their interventions were related to FCSQ theory. For instance, in a clinical trial for treating hypertension based on FCSQ theory,¹⁴ the *Wumei* Pill from *Treatise on Cold Damage* was used in the FCSQ treatment group. The authors analyzed the FCSQ characteristics only in the year of the study and stated that the *Wumei* Pill was effective for hypertension occurring in that year; they did not clarify the evidence for formulating prescriptions based on aspects of FCSQ theory. In terms of how FCSQ theory is applied, we can conclude that applications considering the characteristics of the "heavenly stems and earthly branches" are the most common in clinical practice. The various problems that occurred in designing interventions for FCSQ treatment groups suggest that the feasibility and repeatability of FCSQ interventions should be given more attention in future clinical research to provide high-quality evidence for assessing the clinical value of FCSQ theory.

For future clinical practice and research, it remains meaningful to explore how to apply FCSQ theory to guide disease diagnosis and treatment. There is a need for high-quality trials to evaluate the clinical value of FCSQ theory and answer whether TCM diagnoses and treatments based on FCSQ theory are beneficial for improving effectiveness.

Table 3 Effectiveness evaluation of FCSQ-guided treatments in the 13 included randomized controlled trials.

Study ID	Disease/pattern	Intervention	Control measure	Primary outcomes	Effect size (MD/RR, 95%CI)	P
Zhang WH 2012	Insomnia/liver-kidney deficiency	<i>Wuwei Shenping</i> Decoction	Estazolam tablet	PSQI score	MD: 4.06 [2.90, 5.22]	<.05
Wang JX 2012	Cough/ <i>Yangming</i> dryness metal	<i>Chaiqin Daozhi</i> Powder	Oral solution for relieving cough for children	Syndrome aggregate score	MD: -6.49 [-8.83, -4.15]	.001
Li XY 2014	Rheumatoid arthritis	Modified <i>Yishen Jianpi Tongluo</i> formula	Methotrexate + salazosulfapyridine	VAS score	MD: -11.00 [-15.76, -6.24]	<.01
Bian XF 2015	Hypertension	Nifedipine + modified <i>Wumei</i> Pill	Nifedipine controlled release tablet	Systolic blood pressure	MD: -6.13 [-11.02, -1.24]	.01
Liu MJ 2015	Chronic fatigue syndrome	Tuina massage based on FCSQ theory	Traditional Tuina therapy	Symptoms integral score before and after treatment	MD: -2.56 [-4.91, -0.21]	.03
Li WH 2015	Poststroke insomnia	Conventional acupunctural therapy based on point selection + moxibustion on SP 9	Conventional acupoint therapy	Cure and marked effectiveness rate	RR: 1.39 [1.00, 1.94]	.048
Li L 2016	Hand-foot-and-mouth disease	<i>Sandou</i> Decoction + regular diet	Regular diet	Hand-foot-and-mouth disease morbidity	RR: 0.47 [0.26, 0.84]	<.001
Yan Y 2016	Menopathy/liver depression and kidney deficiency pattern	<i>Shugan Yishen</i> Decoction under FCSQ theory guidance	Sequential therapy of estrogen and progesterone	Symptoms integral score	MD: -3.65 [-6.26, -1.05]	.008
Li W 2017	Psoriasis/damp-heat pattern	Regulating qi, regulating body, and dominating disease	Conventional TCM pattern identification and treatment	PASI score	MD: -2.18 [-2.97, -1.39]	0.00
An X 2017	Dizziness/liver-fire flaming pattern	Canalith repositioning + <i>Zichai</i> Decoction	Canalith repositioning combined with <i>Qiangli Dingxuan</i> Tablet	Cure rate	RR: 0.03 [-0.00, 0.47]	<.05
Yuan B 2017	Exogenous cough/ exterior cold and interior heat pattern	<i>Ziyuan</i> Decoction	Robitussin oral solution	LCQ score before and after treatment	MD: 3.84 [2.35, 5.33]	.032
Zhou SR 2016	Psoriasis vulgaris	TCM formula under the guidance of FCSQ theory + acitretin	Acitretin	Cure rate	RR: 2.49 [1.10, 5.63]	.01
Zhou XL 2015	Peptic ulcer	External application of back- <i>shu</i> acupoint based on six qi theory	Conventional acupoint application	Symptoms integral score	MD: -12.70 [-16.99, -8.41]	<.01

Abbreviations: FCSQ: five circuits and six qi; MD: mean difference; RR: relative risk; CI: confidence interval; PSQI: Pittsburgh Sleep Quality Index; VAS: Visual Analogue Scale; TCM: traditional Chinese medicine; PASI: Psoriasis Area and Severity Index; SP 9: Yinlingquan point; LCQ: Leicester Cough Questionnaire.

We strongly recommend that future research follow the relevant international guidelines for clinical research design and reporting (e.g., the Consolidated Standards of Reporting Trials [CONSORT] statement²⁵ or CONSORT for TCM²⁶), to avoid various biases and to obtain reliable outcomes. Furthermore, the particularity of FCSQ clinical research should be fully considered. First, future work should select diseases that are strongly correlated with FCSQ. Second, it is important to design a reasonable control treatment—A conventional TCM treatment without FCSQ is usually needed as a control intervention, and, if possible, a Western medicine treatment or placebo control is desirable. Third, the determination of FCSQ interventions should have sufficient justification, good operability, and repeatability. We recommend referring to well-recognized FCSQ formulae recorded in the early FCSQ literature, such as the therapeutic principles in the “seven great chapters” on FCSQ in *Yellow Emperor’s Canon of Medicine* and the monograph on FCSQ theory, *Sanyin Sitian Fang*, produced during the Northern Song Dynasty. Corresponding intervention measures should then be determined in accordance with the specific characteristics of the “heavenly stems and earthly branches” during that month and year.

Conclusion

In this study, we systematically evaluated the clinical value of FCSQ theory based on 13 selected RCTs, finding that positive results were reported in all of the studies. Although there are many methodological shortcomings in the current literature and the value of FCSQ theory cannot be fully affirmed, its application value in clinical practice is undeniable. The present study provides a reference for the clinical application of FCSQ theory in TCM in the future. Only by combining the characteristics of FCSQ theory in TCM, adopting appropriate clinical research methods, designing reasonable study protocols, and following international guidelines for designing and reporting clinical research can we provide more substantial evidence for the clinical application of FCSQ theory.

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Conflicts of interest

None declared.

CRedit authorship contribution statement

Qiaoling Tang: Writing - original draft, conceptualization, formal analysis, funding acquisition. **Yu Hao:** Data curation, investigation. **Jia Song:** Data curation, investigation. **Lingzhi Sun:** Methodology. **Juan He:** Writing - review & editing, conceptualization, supervision.

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