Review Article

A Systematic Review of Herbal Medicine in the Treatment of Cirrhotic Ascites

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Objectives: The purpose of this study was to investigate the trend in the research on cirrhotic ascites using t herbal medicine.

Methods: This review was conducted using six electronic databases(NDSL, KMBASE, Koreantk, KISS, KISTI, KoreaMed) with no restriction in year. The search term was ‘liver cirrhosis’, ‘ascites’, or ‘cirrhotic ascites’, ‘herbal medicine’, ‘traditional Chinese medicine’, and ‘randomized clinical trial’, and there was no restriction in year. The searched studies were analyzed according to the type of research.

Results: After scanning the titles and abstracts, 13 articles were ultimately included. Of the outcome measures of 13 studies, effective rate, liver function test, and ascites regression time were included in the meta-analysis, which showed that the effective rate of herbal medicine-supportive treatment combination therapy was 1.27 times higher than that of supportive treatment alone, and the difference was statistically significant.

Conclusions: We analyzed the trends of cirrhotic ascites treatment in herbal medicine through this review. It is necessary to conduct further studies, such as well-designed clinical trials based on the results from experimental research.

Key Words : cirrhotic ascites, herbal medicine, systematic review, meta analysis

Introduction

According to the Statistics Korea’s 2017 Causes of Death Statistics, mortality rate for liver disease was 13.3 deaths per 100,000 population, making it the eighth leading cause of death¹⁾. Along with liver cancer, liver cirrhosis is one of the major causes of death in patients with chronic liver disease and the end-stage of all chronic liver diseases. Pathological characteristics of liver cirrhosis are the formation of regenerative nodules and

extensive fibrosis, resulting in reduction in liver parenchyma and altered liver function and blood flow, which in turn can lead to ascites, variceal bleeding, jaundice, coagulopathy, and hepatic encephalopathy²⁾. Of these complications, ascites causes abdominal bloating and systemic discomfort due to increased weight and abdominal circumference and accompanying peripheral edema. In addition, patients complain of reduced meal size and dyspnea from abdominal organ compression, decreasing patients’ quality of life, which can

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lead to mental pain and depression²⁻⁴). To treat ascites in liver cirrhosis, nutritional therapy, restricted sodium intake, pharmacological treatment, such as diuretics, and abdominal paracentesis are used in modern medicine.⁵) However, prognosis for patients with decompensated cirrhosis and ascites is poor, with one- and two-year survival rate of only 60% and 45%, respectively⁶).

In Korean medicine, jaundice, distention and fullness, aggregation-accumulation, and hypochondriac pain are considered to be part of liver diseases, and ascites, in particular, fall under distention and fullness⁷). Study results related to the therapeutic effect of Korean medicine on liver cirrhosis have been continuously reported through clinical trials⁸⁻¹¹). However, in the past 10 years in Korea, there have been no reports of clinical trials related to use of herbal medicine in the treatment of ascites in liver cirrhosis. Therefore, the authors conducted a systematic review of Korean and international clinical trials that provided herbal medicine treatment in patients with cirrhotic ascites in order to contribute to the vitalization of herbal medicine use in the treatment of cirrhotic ascites. Here, we report the objective evidence drawn from the review.

Participants and methods

1. Participants

Herbal medicine articles that investigated the therapeutic effect of herbal medicine in patients with liver cirrhosis and ascites were included. The PICO-SD (participants, intervention, comparison, outcome, study design) format was followed for the systematic review.

- 1) Participants: Patients with cirrhotic ascites
- 2) Intervention: Herbal medicine treatment (oral herbal preparation prescribed by a doctor)
- 3) Comparison: no restriction on control group
- 4) Outcome: no restriction on outcomes
- 5) Study design: randomized controlled trials (RCT)

2. Methods

1) Database selection and literature search

The Korean literature databases of National Digital Science Library (<http://www.ndsl.kr>), Korean Medical Database (<http://kmbase.medric.or.kr>), Korean studies Information Service System (<http://kiss.kstudy.com>), Society KISTI (<http://society.kisti.re.kr>), KoreaMed (<http://www.koreamed.org>), Korean Traditional Knowledge Portal (<http://www.koreantk.com>), and Korea Institute of Oriental Medicine (<http://oasis.kiom.re.kr>) were searched to identify Korean articles. The keywords used in the Korean search engines were 'liver cirrhosis', 'ascites', or 'cirrhotic ascites', 'herbal medicine', and 'randomized controlled trial'.

The databases of PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), EMBASE (<http://www.embase.com>), Cochrane CENTRAL (<http://www.thecochranelibrary.com>), and CNKI (<http://www.cnki.net>) were searched to identify international articles, and the keywords used in the search engines were 'liver cirrhosis' or 'ascites', 'herbal medicine' or 'traditional Chinese medicine', and 'randomized controlled trial'.

2) Study selection

Two investigators (LYR and CNK) independently searched and selected the studies. The identified

Fig. 1. Flow diagram of the selection process

studies were combined, and duplicates were removed. The titles and abstracts of studies were initially screened based on the inclusion and exclusion criteria, and only RCTs that used herbal medicine treatment for the purpose of treating cirrhotic ascites were selected through full-text review. Any disagreements between the two investigators were resolved by majority vote after review by a third investigator (KKS).

The search was conducted between March 14 and 16, 2019 for studies published up to February 2019 without language restriction. Of the identified articles, RCTs that provided oral herbal medicine prescription in patients with cirrhotic ascites were selected, and studies were excluded if they were non-clinical in vivo or in vitro studies, not an original publication, reported as abstracts only, or provided herbal medicine treatment as an enema or a patch were excluded (Fig. 1).

3) Data analysis

Following a full-text review of the selected

studies, data on publication year, number of participants, treatment method and length of intervention and control groups, assessment tools, therapeutic effect, and incidence of adverse events of each study were extracted. Any disagreements on data extraction were resolved by consultation with a third investigator.

4) Risk of bias assessment

The Cochrane's Risk of Bias (RoB) tool was used as this systematic review only included RCTs. This tool assesses bias across seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, handling of incomplete outcome data, selective outcome reporting, and other sources of bias that compromise the validity. For detailed criteria of each domain, NECA's systematic review manual¹²⁾ was used.

5) Publication bias

Publication bias is a type of reporting bias that

occurs when the likelihood of a study being published is associated with statistical significance of study's outcome. It is commonly assessed using a funnel plot, and Egger's regression test was performed as a statistical test.

6) Meta-analysis

Statistical analysis of the studies included in the systematic review was performed using the Cochrane Collaboration's RevMan (Review Manager) version 5.3. To measure effect size, risk ratio (RR) with two-sided 95% confidence interval (CI) was calculated for dichotomous outcome variables mean difference (MD) with 95% CI was calculated for continuous outcome variables. After assessing heterogeneity using Higgins I^2 test, the summary statistics from each study were combined for meta-analysis using both fixed-effects and random-effects models.

Results

1. Data extraction

After removing duplicates, a total of 262 studies were identified by the literature search of a total of 11 databases conducted between March 14 to 16, 2019. After scanning the titles and abstracts, we excluded 230 articles that were not RCTs and not relevant to cirrhotic ascites and oral herbal medicine treatment. Following full-text review of the 32 articles initially identified, 13 articles¹³⁻²⁵⁾ that met inclusion criteria were ultimately included.

2. Data analysis

1) Study design

The thirteen studies ultimately selected were RCTs conducted in China and Iran between 2005 and 2018. These articles investigated the effects of oral herbal medicine on cirrhotic ascites when used as a stand-alone therapy or in combination with acupuncture and western medicine (Table 1).

2) Intervention and control groups

(1) Duration of treatment

Duration of medicine administration varied by studies, ranging from 21 days to 6 months, with a mean duration of 99.7 days. Duration of medicine administration was 3 months in five studies^{14,16,18,22,24)}, 6 months in two studies^{13,15)}, 5 months in two studies²⁰⁻²¹⁾, and 2 months in two studies^{17,25)} (Table 1).

(2) Intervention group design

Of the selected studies, 10 studies^{13-16,18-20,22,24-25)} provided herbal medicine treatment in combination with supportive treatment of western medicine and compared its effect with that of supportive treatment alone. One study²¹⁾ compared herbal medicine stand-alone therapy with supportive treatment. Two studies^{17,23)} provided additional herbal medicine; one study provided herbal medicine, acupuncture, and supportive treatment and compared it with supportive treatment¹⁷⁾, and one study provided herbal medicine in combination with moxibustion and supportive treatment and compared it with supportive treatment²³⁾. The herbal preparations used for intervention were as follows (Table 2).

(3) Control group design

Control groups in all studies received supportive

Table 1. Summary of randomized controlled trials

Author (Year)	Sample size		Intervention	Control	Adverse events	Outcome measures	Duration
	Intervention group (male/ female)	Control group (male/ female)					
Huseini ¹³ (2005)	18(16/2)	18(16/2)	Liv-25 1 tablet/time 3 times/day + supportive treatment(diuretics, vitamins, lactulose) herbal medicine 1/2 decoction /day 2 times/day + supportive treatment(lamivudine 0.1g/day, conventional liver-protecting enzymes, restrict water and sodium intake, reduce portal hypertension, correct electrolyte imbalance, protein, diuretics, antibiotics, high calorie high protein low salt low fat diet, multivitamins)	placebo tablet 1 tablet/time 3 times/day + supportive treatment(diuretics, vitamins, lactulose) supportive treatment(lamivudine 0.1g/day, conventional liver-protecting enzymes, restrict water and sodium intake, reduce portal hypertension, correct electrolyte imbalance, protein, diuretics, antibiotics, high calorie high protein low salt low fat diet, multivitamins)	not reported	①②③	6months
Liao ¹⁴ (2012)	20(18/2)	20(19/1)	herbal medicine 1/2 decoction /day 2 times/day + supportive treatment(lamivudine 0.1g/day, conventional liver-protecting enzymes, restrict water and sodium intake, reduce portal hypertension, correct electrolyte imbalance, protein, diuretics, antibiotics, high calorie high protein low salt low fat diet, multivitamins)	supportive treatment(lamivudine 0.1g/day, conventional liver-protecting enzymes, restrict water and sodium intake, reduce portal hypertension, correct electrolyte imbalance, protein, diuretics, antibiotics, high calorie high protein low salt low fat diet, multivitamins)	not reported	③④⑤⑥⑦	3months
Liao ¹⁵ (2015)	40	40	herbal medicine 1/2 decoction/day 2 times/day 1 pill/time 3 times/day + supportive treatment(lamivudine 0.1g/day, adefovir dipivoxil 10mg/day, antiviral therapy, bed rest during treatment, moderate drinking water, strict control of liquid input, low-salt, low-fat, high-protein, high-calorie, high-vitamin diet, diuretics, glutathione needle, propranolol, serum albumin)	supportive treatment(lamivudine 0.1g/day, adefovir dipivoxil 10mg/day, antiviral therapy, bed rest during treatment, moderate drinking water, strict control of liquid input, low-salt, low-fat, high-protein, high-calorie, high-vitamin diet, diuretics, glutathione needle, propranolol, serum albumin)	not reported	②③⑦⑧	6months
Liu ¹⁶ (2012)	33	34	herbal medicine 2 times/day + supportive treatment(limit water and salt intake, liver protection drugs, diuretics, ammonium glycyrrhizinate, vitamin C, vitamin K, potassium magnesium aspartate injection, albumin)	supportive treatment(limit water and salt intake, liver protection drugs, diuretics, ammonium glycyrrhizinate, vitamin C, vitamin K, potassium magnesium aspartate injection, albumin)	not reported	⑧	3months

Table 1. Summary of randomized controlled trials

Author (Year)	Sample size		Intervention	Control	Duration	Outcome measures	Adverse events
	Intervention group (male/ female)	Control group (male/ female)					
Liu ¹⁷ (2017)	41(27/14)	39(27/13)	herbal medicine 1 decoction/day + acupuncture 30minutes/time 1time/day	supportive treatment(albumin, diuretic, reduced glutathione, vitamin B, liver protection, maintain water, electrolytes, acid-base balance)	2months	⑧⑨⑩⑪	not reported
			supportive treatment(albumin, diuretic, reduced glutathione, vitamin B, liver protection, maintain water, electrolytes, acid-base balance)				
Qi ¹⁸ (2017)	48(35/13)	48(37/11)	herbal medicine 2times/day + supportive treatment(restricted water and salt intake, diuretic, vitamin C, multivitamin B2)	supportive treatment(restricted water and salt intake, diuretic, vitamin C, multivitamin B2)	3months	⑧	not reported
			herbal medicine 2times/day + supportive treatment(multivitamin B, glucrolactone tablets, spironolactone tablets, hydrochlorothiazide tablets, restricted the intake of water and salt, albumin)				
Shen ¹⁹ (2011)	32(24/8)	32(25/8)	herbal medicine 2times/day 1 decoction/day + supportive treatment(multivitamin B, glucrolactone tablets, spironolactone tablets, hydrochlorothiazide tablets, restricted the intake of water and salt, albumin)	supportive treatment(multivitamin B, glucrolactone tablets, spironolactone tablets, hydrochlorothiazide tablets, restricted the intake of water and salt, albumin)	45days	⑥⑧⑨⑪	not reported
			herbal medicine 2times/day 1 decoction/day + supportive treatment(bed rest, low-protein and high-calorie diet, restricted intake of water and sodium, diuretic)				
Miao ²⁰ (2018)	30(17/13)	30(18/12)	herbal medicine 2times/day 1 decoction/day + supportive treatment(bed rest, low-protein and high-calorie diet, restricted intake of water and sodium, diuretic)	supportive treatment(bed rest, low-protein and high-calorie diet, restricted intake of water and sodium, diuretic)	5months	⑥	1. treatment group : 1 case of hyponatremia and 1 case of renal dysfunction. 2. control group : 3 cases of hyponatremia, 3 cases of renal dysfunction and 2 cases of hepatic encephalopathy(p<0.05).

Table 1. Summary of randomized controlled trials (Continued)

Author (Year)	Sample size		Intervention	Control	Duration	Outcome measures	Adverse events
	Intervention group (male/ female)	Control group (male/ female)					
Yao ²¹ (2009)	36(36/0)	22(22/0)	herbal medicine 2times/day 1 decoction/day	supportive treatment (spironolactone, vitamin C, vitamin B6 and other cirrhosis supportive treatment)	5months	⑧	not reported
Yao ²² (2017)	36(27/9)	36(25/11)	herbal medicine 2times/day 1 decoction/day + supportive treatment (furosemide tablets 20 mg, glutathione injection, serum albumin)	supportive treatment (furosemide tablets 20 mg, glutathione injection, serum albumin)	3months	③⑧⑪⑫	1. treatment group : 1 case of headache and 1 case of nausea. 2. control group : 1 case of dizziness and 2 cases of nausea(p>0.05).
Yu ²³ (2014)	32(21/11)	30(20/10)	herbal medicine 2times/day 1 decoction/day + moxibustion treatment 1time/day + supportive treatment (liver protection, diuresis, albumin)	supportive treatment (liver protection, diuresis, albumin)	21days	③⑧	not reported
Zhang ²⁴ (2008)	30(22/8)	24(19/5)	herbal medicine + supportive treatment (bed rest, restricted water and salt intake, liver protection, antiviral therapy, albumin, diuretics)	supportive treatment (bed rest, restricted water and salt intake, liver protection, antiviral therapy, albumin, diuretics)	3months	③④⑤⑥⑧	not reported
Zhao ²⁵ (2016)	41(27/14)	41(28/13)	herbal medicine 2times/day 1 decoction/day + supportive treatment (vitamin, albumin, diuretics, restricted intake of water and salt)	supportive treatment (vitamin, albumin, diuretics, restricted intake of water and salt)	2months	⑥⑧	1. treatment group : 4 case of hyponatremia and 1 case of hepatic encephalopathy. 2. control group : 14 cases of hyponatremia, 8 cases of renal dysfunction and 7 cases of hepatic encephalopathy(p<0.05).

① : Degree of ascites. ② : Child pugh score. ③ : Liver function test. ④ : Comparison of liver fibrosis indicators. ⑤ : Comparison of B-ultrasound examination. ⑥ : Ascites regression time. ⑦ : Comparison of HBV-DNA and E antigen negative conversion rate. ⑧ : Effective rate. ⑨ : Body weight. ⑩ : Abdominal circumference. ⑪ : 24 hour urine volume. ⑫ : Comparison of portal hemodynamics.

Fig.2. Results of Meta-analysis for the Effective Rate(HM+ST vs ST)

Abbreviations: HM, herbal medicine; ST, supportive treatment

treatment of western medicine, and, with the exception of one study²¹⁾, intervention groups also received the same supportive treatment. Studies included various supportive treatments, including bed rest, restricted water and salt intake, albumin, and diuretics, and detailed description is presented in table 1.

3) Outcome measures

Outcome measures used in the selected studies were effective rate, ascites regression time, liver function test, 24 hour urine volume, and Child-Pugh score. Of these, effective rate was used in 10 studies^{15-19,21-25)}, liver function test was used in six studies^{13-15,22-24)}, and ascites regression time was used in five studies^{14,19-20,24-25)} as outcome measures. Of the outcome measures, effective rate, liver function test, and ascites regression time were included in the meta-analysis.

4) Therapeutic effect

Of the selected studies, 10 studies that compared herbal medicine-supportive treatment combination therapy with supportive treatment stand-alone therapy^{13-16,18-20,22,24-25)} were included in the meta-analysis.

(1) Effective rate

Effective rate of herbal medicine-supportive treatment combination therapy was 1.27 times higher than that of the supportive treatment stand-alone therapy, indicating herbal medicine-supportive treatment combination therapy is significantly more effective in treating cirrhotic ascites. A low degree of heterogeneity was observed across the studies (Risk Ratio=1.27, 95% CI: 1.17 to 1.38, $p < 0.001$, $I^2 = 0\%$, Fig. 2)

(2) Liver function test

A subgroup analysis was performed to compare liver function test of herbal medicine-supportive treatment combination therapy and supportive treatment stand-alone therapy. The intervention group showed significant effect than the control group and a high degree of heterogeneity of 98% was observed across the studies (Mean Difference = -11.39, 95% CI: -15.08 to -7.69, $p < 0.001$, $I^2 = 98\%$, Fig. 3).

(3) Ascites regression time

Although not statistically significant, ascites regression time of the herbal medicine-supportive treatment combination therapy was 30.76 days

Fig. 3. Results of Meta-analysis for the Liver Function Test(HM+ST vs ST)

Abbreviations: HM, herbal medicine; ST, supportive treatment; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ALB, albumin

Table 2. Composition of the herbal preparations used in treatment

Study	Preparation name	Composition
Huseini ¹³ (2005)	Liv-52	Capparis spinosa, Cichorium Intybus 65mg respectively, Solanum nigrum, T.arjuna 32mg, Cassia occidentalis, Achillea millefolium, Tamarix gallica 16mg respectively
Liao ¹⁴ (2012)	herbal medicine	Astragali Radix(黄芪), Alismatis Rhizoma(泽泻), Atractylodis Rhizoma Alba(白朮), Artemisiae Capillaris Herba(茵陈蒿), Poria Sclerotium(茯苓), Salviae Miltiorrhizae Radix(丹参), Bupleuri Radix(柴胡), Aurantii Fructus Immaturus(枳实), Leonuri Herba(益母草), Pelodiscis Carapax(鳖甲)
Liao ¹⁵ (2015)	herbal medicine	compound formula
Liu ¹⁶ (2012)	herbal medicine	Salviae Miltiorrhizae Radix(丹参), Paeoniae Radix(芍药(白)), Persicae Semen(桃仁), Manitis Squama(穿山甲), Astragali Radix(黄芪), Polyporus(猪苓) 30g respectively, Atractylodis Rhizoma Alba(白朮), Poria Sclerotium(茯苓), Aurantii Fructus Immaturus(枳实), Arecae Pericarpium(大腹皮) 15g respectively, Alismatis Rhizoma(泽泻), Angelicae Gigantis Radix(当归) 12g respectively, Glycyrrhizae Radix et Rhizoma(甘草) 6g, Zizyphi Fructus(大枣) 5g
Liu ¹⁷ (2017)	herbal medicine	Poria Sclerotium(茯苓) 30g, Alismatis Rhizoma(泽泻), Polyporus(猪苓), Atractylodis Rhizoma Alba(白朮) 15g respectively, Cinnamomi Ramulus(桂枝) 10g
Qi ¹⁸ (2017)	herbal medicine	Salviae Miltiorrhizae Radix(丹参) 20g, Cnidii Rhizoma(川芎), Bupleuri Radix(柴胡), Leonuri Herba(益母草), Poria Sclerotium(茯苓), Citri Unshius Pericarpium Immaturus(青皮), Galli Gigeriae Endothelium Corneum(鸡内金), Cyperi Rhizoma(香附子), Alismatis Rhizoma(泽泻), Imperata cylindrica(白茅根) 15g respectively
Shen ¹⁹ (2011)	herbal medicine	Astragali Radix(黄芪), Codonopsis Pilosulae Radix(党参), Polyporus(猪苓), Salviae Miltiorrhizae Radix(丹参) 30g respectively, Atractylodis Rhizoma Alba(白朮), Poria Sclerotium(茯苓), Polygoni Cuspidati Rhizoma et Radix(虎杖根) 15g respectively, Sparganii Rhizoma(三棱), Curcumae Rhizoma(莪朮), Cnidii Rhizoma(川芎), Paeoniae Radix(芍药(白)), Citri Unshius Pericarpium Immaturus(青皮), Bupleuri Radix(柴胡), Cyperi Rhizoma(香附子), Curcumae Radix(鬱金), Schisandrae Fructus(五味子) 10g respectively, Glycyrrhizae Radix et Rhizoma(甘草) 6g compound formula

less than that of the supportive treatment stand-alone therapy. A high degree of heterogeneity of 100% was observed across the studies (Mean Difference=-30.76, 95% CI:-62.37 to 0.84, $p=0.06$, $I^2=100\%$, Fig. 4).

5) Bias assessment

Assessment of risk of bias was performed for the 13 articles included in this review using Cochrane risk of bias tool. With respect to random sequence generation domain, three articles^{13,21,23)} that used a table of random

Table 2. Composition of the herbal preparations used in treatment (Continued)

Study	Preparation name	Composition
Miao ²⁰ (2018)	herbal medicine	Pseudostellaria angustifolia(太子参), Astragali Radix(黄芪), Plantaginis Semen(車前子) 12g respectively, Atractylodis Rhizoma Alba(白朮), Arecae Pericarpium(大腹皮), Alismatis Rhizoma(澤瀉), Curcumae Radix(鬱金), Salviae Miltiorrhizae Radix(丹参) 10g respectively, Cinnamomi Ramulus(桂枝), Citri Unshius Pericarpium Immaturus(青皮) 6g respectively compound formula
Yao ²¹ (2009)	herbal medicine	Poria Sclerotium(茯苓), Achyranthis Radix(牛膝), Aucklandiae Radix(木香), Bupleuri Radix(柴胡), Amomi Fructus(砂仁) 30g respectively, Atractylodis Rhizoma Alba(白朮), Polyporus(猪苓), Alismatis Rhizoma(澤瀉), Salviae Miltiorrhizae Radix(丹参) 15g respectively, Clematidis Radix(威靈仙), Angelicae Gigantis Radix(當歸) 10g respectively, Curcumae Longae Rhizoma(薑黃), Scorpio(全蝎) 6g respectively, Glycyrrhizae Radix et Rhizoma(甘草) 10g compound formula
Yao ²² (2017)	herbal medicine	Astragali Radix(黄芪) 30g, Atractylodis Rhizoma Alba(白朮), Salviae Miltiorrhizae Radix(丹参), Imperata cylindrica(白茅根), Pelodiscis Carapax(鳖甲) 20g respectively, Polyporus(猪苓), Alismatis Rhizoma(澤瀉), Poria Sclerotium(茯苓), Angelicae Gigantis Radix(當歸), Codonopsis Pilosulae Radix(黨参), Arecae Pericarpium(大腹皮), Bupleuri Radix(柴胡) 15g respectively, Plantaginis Semen(車前子) 12g, Curcumae Rhizoma(莪朮), Glycyrrhizae Radix et Rhizoma(甘草) 10g respectively, Schisandrae Fructus(五味子), Cinnamomi Ramulus(桂枝) 6g respectively compound formula
Yu ²³ (2014)	herbal medicine	Cistanchis Herba(肉苁蓉), Salviae Miltiorrhizae Radix(丹参) 20g respectively, Aconiti Lateralis Radix Preparata(附子), Lycopi Herba(澤蘭), Angelicae Gigantis Radix(當歸) 10g respectively, Cinnamomi Ramulus(桂枝), Persicae Semen(桃仁) 6g respectively, Zingiberis Rhizoma(乾薑) 5g, Glycyrrhizae Radix et Rhizoma(甘草) 4g compound formula
Zhang ²⁴ (2008)	herbal medicine	① Artemisiae Capillaris Herba(茵陳蒿), Coicis Semen(薏苡仁), Isatidis Radix(板藍根), Smilacis Rhizoma(土茯苓), Arecae Pericarpium(大腹皮) 30g respectively, Paeoniae Radix(芍藥(白)) 25g, Salviae Miltiorrhizae Radix(丹参) 20g, Lycopi Herba(澤蘭), Gardeniae Fructus(梔子), Curcumae Rhizoma(莪朮), Curcumae Radix(鬱金), Pharbitidis Semen(牽牛子) 15g respectively, Rhei Radix et Rhizoma(大黃), Glycyrrhizae Radix et Rhizoma(甘草) 6g respectively, Notoginseng Radix Et Rhizoma(三七粉(冲服)) 3g ② Atractylodis Rhizoma Alba(白朮) 60g, Imperata cylindrica(白茅根) 45g, Astragali Radix(黄芪), Poria Sclerotium(茯苓), Coicis Semen(薏苡仁), Arecae Pericarpium(大腹皮) 30g respectively, Codonopsis Pilosulae Radix(黨参), Oryzae Fructus Germinatus(炒谷芽), Hordei Fructus Germinatus(炒麦芽) 20g respectively, Eucommiae Cortex(杜仲), Morindae Radix(巴戟天), Amomi Fructus(砂仁) 15g respectively, Glycyrrhizae Radix et Rhizoma(甘草), Zingiberis Rhizoma(乾薑), Cinnamomi Ramulus(桂枝) 6g respectively ③ Atractylodis Rhizoma Alba(白朮) 30g, Rehmanniae Radix Recens(生地黃), Oryzae Fructus Germinatus(炒谷芽), Hordei Fructus Germinatus(炒麦芽), Artemisiae Capillaris Herba(茵陳蒿), Isatidis Radix(板藍根), Lycopi Herba(澤蘭), Bubalus bubalis L.(水牛角) 15g respectively, Melandrii Herba(王不留行) 12g
Zhao ²⁵ (2016)	herbal medicine	Salviae Miltiorrhizae Radix(丹参), Artemisiae Capillaris Herba(茵陳蒿), Poria Sclerotium(茯苓), Astragali Radix(黄芪) 20g respectively, Leonuri Herba(益母草), Pelodiscis Carapax(鳖甲), Ginseng Radix(白参), Paeoniae Radix(芍藥(白)), Arecae Pericarpium(大腹皮) 15g respectively, Citri Unshius Pericarpium(陳皮), Alismatis Rhizoma(澤瀉) 10g, Atractylodis Rhizoma Alba(白朮) respectively

Fig. 4. Results of Meta-analysis for the Ascites Regression Time(HM+ST vs ST)
 Abbreviations: HM, herbal medicine; ST, supportive treatment;

Fig 5. Risk of bias graph

numbers were assessed as having low risk, while the rest of the articles provided no details and were assessed as having unclear risk. All articles provided no details on allocation concealment, and therefore were assessed as having unclear risk. With respect to blinding of participants and personnel domain, one article¹³⁾ that used placebo was assessed as having low risk, while the rest of the articles were assessed as having high risk because blinding was deemed not possible due to the nature of intervention method that included herbal decoction. With respect to blinding of outcome assessor domain, one article¹³⁾ that reported using blinding was assessed as having low risk, while the rest of the articles provided no details and were assessed as having unclear risk. With respect to incomplete outcome data domain, 10 articles^{13,16-17,19-25)} that reported missing values

and confirmed no errors were assessed as having low risk, while the rest of the articles did not provide details and were assessed as having unclear risk. With respect to selective reporting domain, 10 articles^{13-17,19-22,25)} that did not have study protocol but reported all pre-specified outcomes and all expected outcomes were assessed as having low risk, while the rest of the articles provided no details and were assessed as having unclear risk. With respect to other sources of bias domain, most articles did not provide sufficient information or evidence, and therefore all articles were assessed as having unclear risk (Fig. 5, Fig. 6).

6) Publication bias

Inspection of the funnel plot showed low risk of publication bias (Fig. 7)

Fig. 6. Risk of bias summary

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Huseini 2005	+	?	+	+	+	+	?
Liao 2012	?	?	+	?	?	+	?
Liao 2015	?	?	+	?	?	+	?
Liu 2012	?	?	+	?	+	+	?
Liu 2017	?	?	+	?	+	+	?
Qi 2017	?	?	+	?	?	?	?
Shen 2011	?	?	+	?	+	+	?
Yan 2018	?	?	+	?	+	+	?
Yao 2009	+	?	+	?	+	+	?
Yao 2017	?	?	+	?	+	+	?
Yu 2014	+	?	+	?	+	?	?
Zhang 2008	?	?	+	?	+	?	?
Zhao 2016	?	?	+	?	+	+	?

Fig. 7. Funnel plot for the outcome of effective rate (HM+ST vs ST)

Abbreviations: HM, herbal medicine; ST, supportive treatment;

7) Safety

Of the 13 studies included in this review, a total of three studies^{20,22,25)} reported adverse events. One study²⁰⁾ one case of hyponatremia and one case of renal function occurred in the intervention group, whereas three cases of hyponatremia, three cases of renal dysfunction, and two cases of hepatic encephalopathy occurred in the control group, indicating that the safety of the intervention group was significantly higher than that of the control group ($p<0.05$). In another study²²⁾, symptoms of headache and nausea occurred, but there was no significant difference between the intervention and control groups. In the third study²⁵⁾, four cases of hyponatremia and one case of hepatic encephalopathy occurred in the intervention group, whereas 14 cases of hyponatremia, eight cases of renal dysfunction, and seven cases of hepatic encephalopathy occurred in the control group, indicating the safety of the intervention groups was significantly higher than that of the control group ($p<0.05$).

Discussion and conclusions

The present study performed a systematic review of RCT articles that provided oral herbal medicine treatment in patients with cirrhotic ascites. Through this review, we aimed to provide objective assessment of the effectiveness and applicability of oral herbal medicine treatment in patients with cirrhotic ascites. A total of 11 Korean and international databases were searched and 13 studies¹³⁻²⁵⁾ were ultimately selected for analysis.

Thirteen studies¹³⁻²⁵⁾ included in the present study investigated the effect of herbal medicine -supportive treatment combination therapy on ascites in liver cirrhosis. These studies have been continuously published since 2005, with 12 studies¹⁴⁻²⁵⁾ conducted in China and one study¹³⁾ published in Iran. From this, it can be speculated that there has been a continued interest in herbal medicine in the treatment of cirrhotic ascites, centering on China.

Of the outcome measures of 13 studies, effective rate, liver function test, and ascites regression time were included in the meta-analysis, which showed that the effective rate of herbal medicine-supportive treatment combination therapy was 1.27 times higher than that of supportive treatment alone, and the difference was statistically significant. The herbal medicine-supportive treatment combination therapy also had a significant effect on liver function test. Although ascites regression time of the herbal medicine -supportive treatment combination therapy was 30.76 days less than that of supportive treatment alone, the difference was not statistically significant. Despite the fact

that the difference in ascites regression time was not significant, we believe that use of herbal medicine-supportive treatment combination therapy will be of value in the treatment of cirrhotic ascites.

Risk of bias assessment of the 13 articles included in the systematic review revealed high performance bias. We believe that this was due to the fact that blinding was not possible because of the nature of intervention method that included herbal decoction. Most studies did not have detailed report on bias assessment, which made it difficult to assess bias except for performance bias. We believe that future studies that address this issue will provide stronger evidence.

There is a limitation in that the majority of the studies included in the present study did not categorize or take into consideration the degree of ascites and syndrome differentiation despite the fact that treatment method and course of disease may vary depending on those factors. Only one study¹³⁾ classified the degree of ascites as without, mild, moderate, or severe and assessed the proportion after 6 months of administration of herbal medicine intervention. Two studies^{14,15)} reported the degree of ascites in subjects participating in the experiment by classifying it as mild, moderate, severe, or moderate volume and large volume, but these were not reflected when reporting the study results. The other ten studies¹⁶⁻²⁵⁾ did not report the degree of ascites of the participants. Furthermore, despite the various causes of ascites, only two studies^{15,24)} provided prescription according to syndrome differentiation. Three studies^{13,16-17)} used one prescription, without taking into account syndrome differentiation, and

seven studies^{14,18-23,25)} added or subtracted herbs from the basic formula according to the accompanying symptoms. As such, most studies provided the same prescription without taking into account syndrome differentiation. In addition, it is disappointing that even the study¹³⁾ that reported the degree of ascites and performed comparative evaluation used a general prescription without providing different treatment methods according to the degree of ascites. In the future, more significant conclusions may be drawn if appropriate prescriptions are given according to the degree of ascites and syndrome differentiation.

The present study performed a systematic review and meta-analysis of published RCTs in order to investigate the effect of oral herbal medicine treatment in patients with cirrhotic ascites. The results showed that oral herbal medicine-supportive treatment combination therapy was significantly more effective in effective rate and liver function test than supportive treatment alone, while no significant difference was found in ascites regression time. Through this study, we demonstrated that oral herbal medicine-supportive treatment combination therapy is significantly more effective than supportive treatment alone in treating patients with cirrhotic ascites. We believe that there is a need to establish stronger evidence through future clinical trials on herbal medicine in the treatment of cirrhotic ascites that addresses the above limitations.

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