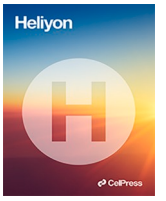
Heliyon 10 (2024) e37830

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Traditional herbal medicine Oryeongsan for heart failure: A systematic review and meta-analysis

Da Hae Jung [a,1], Han-Gyul Lee [b,1], Seungwon Kwon [b,*], Won Jung Ha [a], Seung-Yeon Cho [c], Woo-Sang Jung [b], Seong-Uk Park [c], Sang-Kwan Moon [b], Jung-Mi Park [c], Chang-Nam Ko [c]

[a] *Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, Seoul, Republic of Korea*
[b] *Department of Cardiology and Neurology, Kyung Hee University College of Korean Medicine, Kyung Hee University Medical Center, Seoul, Republic of Korea*
[c] *Stroke and Neurological Disorders Center, Kyung Hee University College of Korean Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea*

A R T I C L E I N F O

Keywords:
Heart failure
Oryeongsan
Diuretics
Left ventricular ejection fraction
Systematic review
Meta-analysis

A B S T R A C T

Background and objective: Heart failure (HF) is associated with high mortality and hospitalization rates, and its prevalence increases with age. As congestion is the most common cause of hospitalization for HF, diuretics are the most prescribed drugs. However, these agents have side effects due to electrolyte imbalance. In Asian countries, Oryeongsan (ORS) and its variants are used to manage fluid imbalances, including HF congestion. Therefore, ORS is considered a complementary treatment to overcome the limitations of diuretics. This review aimed to elucidate the safety and effectiveness of ORS combined with conventional Western medicine (CWM) for HF.

Materials and methods: A literature search was conducted using the PubMed, Embase, CENTRAL, Scopus, CiNii, CNKI, and ScienceON databases to retrieve relevant studies published up to July 2024. Two independent investigators were involved in the data collection and analysis. Randomized controlled trials (RCTs) that evaluated the effects of ORS and its variants in combination with CWM as treatments for HF were selected. The outcome measures included left ventricular ejection fraction (LVEF), total effective rate (TER), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), 6-min Walk Test (6MWT), Minnesota Living with Heart Failure Questionnaire (MLHF-Q), serum brain natriuretic peptide (BNP) level, serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level, 24-h urine volume, Lee's score, and New York Heart Association (NYHA) grade I ratio for effectiveness; and incidence of adverse events (AEs) for safety. The methodological quality of the included RCTs was assessed using the Cochrane's Risk of Bias tool.

Results: Fifty-nine RCTs that comprised 5069 participants and compared CWM combined with ORS and its variants (treatment group) to CWM alone or CWM plus placebo (control group) were included. Based on the meta-analysis, LVEF was found to significantly improve (mean difference: 6.36, 95 % confidence interval: 5.11 to 7.61, $P < 0.00001$) in the treatment group. TER, LVEDD, LVESD, 6MWT, MLHF-Q, serum BNP and NT-proBNP levels, 24-h urine volume, Lee's score, and

* Corresponding author. Department of Cardiology and Neurology, Kyung Hee University College of Korean Medicine, Kyung Hee University Medical Center, Seoul, 02447, Republic of Korea.
E-mail address: kkokkottung@hanmail.net (S. Kwon).
[1] These authors are contributed equally as first authors.

https://doi.org/10.1016/j.heliyon.2024.e37830
Received 10 May 2024; Received in revised form 17 August 2024; Accepted 10 September 2024
Available online 11 September 2024

NYHA grade I ratio were also significantly improved in the treatment group compared with the control group with CWM alone. LVEF and TER were improved without significance in the treatment group compared with the control group with CWM plus placebo. The incidence of AEs did not significantly differ between the two groups.

Conclusions: Combining CWM with ORS or its variants was more effective than CWM alone in managing HF and could serve as a relatively safe treatment for HF. Further studies are required to validate the findings of the present study.

1. Introduction

Heart failure (HF) is a condition in which the heart cannot pump sufficient blood to meet the needs of the body. HF may result from an increased oxygen demand by the tissues caused by myocardial infarction, hypertension, cardiomyopathy, increased peripheral vascular resistance, or anemia [1]. The number of patients living with HF has been increasing owing to rapid population aging and improved survival after diagnosis [2,3]. Based on a 2019 meta-analysis, the estimated 1-, 2-,5-, and 10-year survival rates of HF were 86.5 %, 72.6 %, 56.7 %, and 34.9 %, respectively [4].

HF is associated with a significant healthcare burden. In 2018, the total expenses per drug, hospitalization, and outpatient clinic visit were ₩11.19 trillion, ₩630,757,729,150, and ₩78,172,589,880, respectively. Further, the medical expenses per hospitalization and outpatient clinic visit for individual patients were ₩8,306,657 and ₩35,110, respectively [5].

Congestion is the most common cause of hospitalization for HF. Congestion often develops gradually prior to hospitalization, and loop-, thiazide-, and potassium-sparing diuretics are the most prescribed drugs to treat this condition [6]. The most common side effects of loop diuretics include electrolyte imbalances, such as hypokalemia and hyponatremia. Thiazide diuretics block the $Na^+/2Cl^-/K^+$ co transporter (NIKCC2) at the distal convoluted tubule to increase water and salt excretion, causing sodium influx into the collecting ducts, which enhances the exchange of Na with K, leading to K depletion [6]. The use of non-potassium-sparing diuretics in patients with left ventricular dysfunction can cause electrolyte imbalances, resulting in arrhythmias. These diuretics are also associated with an increased risk of arrhythmia-induced death [7]. Digoxin is one of the oldest heart failure medications in use to date. Digoxin competes with potassium on sodium–potassium pump (Na^+/K^+-ATPase). Individuals with hypokalemia become more sensitive to digoxin and are at a high risk of developing digoxin toxicity [8], which increases automaticity. Digoxin is highly likely to cause ventricular arrhythmia [9]. Therefore, alternative treatments are required owing to the therapeutic limitations of these drugs.

Oryeongsan (ORS, Goreisan in Japanese and Wulingsan in Chinese) is a formulation comprising five herbal medicines, *Poria sclerotium*, *Polyporus*, *Alismatis rhizoma*, *Atractylodis rhizoma alba*, and *Cinnamomi ramulus*, and has long been used to treat various abnormalities in fluid balance. According to a previous study, ORS decreases water excretion to maintain homeostasis in individuals with excessive loss of body fluid owing to its bidirectional diuretic effects [10]. Furthermore, ORS is less likely to cause adverse events owing to electrolyte imbalances, including hypokalemia due to its diuretic properties [11,12]. Therefore, ORS is considered a complementary treatment to overcome the limitations of thiazide diuretics. The effects of ORS on HF have been actively investigated in Japan and China; In Japan, ORS is widely used safely in elderly HF patients with fluid retention because it does not cause dehydration, renal dysfunction, and electrolyte abnormalities [13]. There has also been a case report of successful treatment with ORS for patients with congestive heart failure who have failed to manage congestion with diuretics [14]. Based on these, a multicenter randomized controlled trial of ORS on HF (GOREISAN-HF) is currently underway to advance the efficacy and safety evidence for ORS in HF (NCT04691700) [13]. In China, a previous meta-analysis revealed the combination of conventional western medicine and ORS has better effectiveness for HF treatment [15]. Based on a 2022 systemic literature review and meta-analysis on ORS and chronic HF, which included 19 randomized controlled trials (RCTs), the combination of ORS and regular treatment was more effective in improving heart failure than regular treatment alone, with no difference in adverse events [16]. However, the study had some limitations: only patients with chronic HF were included and the clinical heterogeneity of ORS variants were not considered, despite the use of different ORS variants by most RCTs included in the analysis. Moreover, the small sample size resulted in methodological limitations.

Several clinical studies have been published on ORS; however, the few systematic literature reviews and meta-analyses published to date have certain limitations. Therefore, this systematic review and meta-analysis aimed to evaluate the safety and efficacy of ORS and its variants in patients with different types of HF by examining RCTs that compared ORS and its variants alone and in combination with conventional therapies, defined as conventional Western medicine (CWM), or placebos.

2. Methods

2.1. Protocol registration

This systematic literature review and meta-analysis was registered in the Research Registry on September 27, 2022 (registration number 1458). This study was conducted according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17].

2.2. Database and literature search

Literature published up to July 31st, 2024 was retrieved from seven databases (PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Citation Information by Nii (CiNii), China National Knowledge Infrastructure Database (CNKI), and ScienceON). The following search terms were used without limitations: "Wuling (Chinese)," "Gorei (Japanese)," and "Oryeong (Korean)" for ORS; "Heart failure," "Cardiac failure," "heart decompensation," and "myocardial failure" for HF; and "randomized controlled trial" and "randomized controlled trial" for RCT. The specific search terms according to each database are presented in Supplement 1.

2.3. Inclusion and exclusion criteria

2.3.1. Study design

Only RCTs were included, with no restrictions on the year or language of publication. Quasi-RCTs, non-RCTs, case reports, case series, uncontrolled trials, animal studies, and in vitro studies were excluded. Studies that did not provide detailed outcomes or crossover trials were excluded to preclude the possibility of carryover effects.

2.3.2. Study participants

Studies that recruited patients diagnosed with HF based on examination findings and various tests (echocardiography, radiography, and blood tests) were included. The type of HF, sex, age, race, symptom severity, illness duration, and clinical environment were not limited.

2.3.3. Intervention methods

Studies involving treatment groups that received ORS or ORS variants combined with CWM were included. Interventions comprising the oral administration of ORS and ORS variants were included. Dosage, frequency, duration, and formulation (decoction, extract, pill, capsule, and powder) were not limited. Studies that used intravenous or acupoint injections, or ORS and its variants without CWM were excluded.

2.3.4. Control group

Studies with control groups that received CWM alone or combined with placebo were included. Studies comparing therapeutic methods in traditional East Asian medicine (herbal medicines, acupuncture, or moxibustion) or the effects of these methods on ORS and its variants were excluded.

2.3.5. Outcome measures

Studies that evaluated the therapeutic effects and safety in patients with HF using the following outcome measures were included: therapeutic effects-primary outcome for left ventricular ejection fraction (LVEF) and secondary outcomes for total effective rate (TER), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), 6-min Walk Test (6 MWT), Minnesota Living with Heart Failure Questionnaire (MLHF-Q), serum brain natriuretic peptide (BNP) level, serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level, 24-h urine volume, Lee's score, and the New York Heart Association (NYHA) grade I; and safety-incidences of adverse events (AEs). If a study mentioned various TERs, such as the effective rate of the NYHA grade or the Chinese medicine sign score, only studies that mentioned the NYHA grade and TER were included.

2.4. Data collection and analysis

Two independent investigators (SK and DHJ) were involved in the data collection and analysis. All bibliographic data from the selected studies were summarized in Endnote X9 (Clarivate Analytics). In the first screening, the titles and abstracts were reviewed after removing duplicates. During the second screening, full-text reviews of the remaining studies were conducted. A PRISMA flowchart was generated to illustrate the selection process. Data, including the first author, year of publication, language, study design, intervention, duration of treatment, outcome measures, and methods of statistical analysis, were independently extracted from the included studies using standardized data extraction methods and then organized. Disagreements were resolved by consensus.

2.5. Quality assessment

Two investigators (SK and DHJ) independently assessed the quality of the included studies according to Cochrane's Risk of Bias tool RoB) [18]. Each article was evaluated using the following seven items: selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and other biases. Each item was rated as "low-risk," "high-risk," or "unclear." Each item was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [19]. Any disagreements between the two investigators were resolved by consensus.

2.6. Statistical analysis

Data generation and statistical analyses were performed using RevMan 5.4.1 software. Based on the type and control intervention

used, the studies were divided into two groups for data generation:

Group I: ORS and its variants + CWM vs. CWM alone.

Group II: ORS and its variants + CWM vs. placebo + CWM.

The 95 % confidence interval (CI) of the risk ratio (RR) was calculated for binary data, while the 95 % CI and mean difference (MD) were calculated for continuous data. All meta-analyses were connected using a random effects model. A P value < 0.05 was considered to indicate statistical significance. Methodological heterogeneity was assessed using the study design or risk of bias. Any study with a large heterogeneity compared to other studies was excluded from the analysis. Regarding clinical heterogeneity, studies with clinically and significantly different methods of administration or interventions were excluded from the analysis. As the composition and dosage of ORS and its variants were not standardized, a sub-group analysis was planned to determine whether clinical heterogeneity occurred due to modified doses, as needed. Statistical heterogeneity among the included studies was evaluated using the Higgins I^2 test. Regarding studies with high heterogeneity, those with sufficient information to determine the causes of heterogeneity, if any, were used to perform subgroup analysis. Finally, a funnel plot was generated to detect potential publication bias.

3. Results

3.1. Study selection

A total of 114 studies were obtained via a search of electronic databases. Following the removal of duplicates, 109 studies were selected and reviewed for eligibility. During the initial screening, 29 studies were excluded based on their titles and abstracts. In the second screening, four non-RCTs, 14 studies lacking treatment groups, two studies lacking control groups, and one study that did not mention outcome measures were excluded. Finally, 59 studies were included in the analysis (Fig. 1).

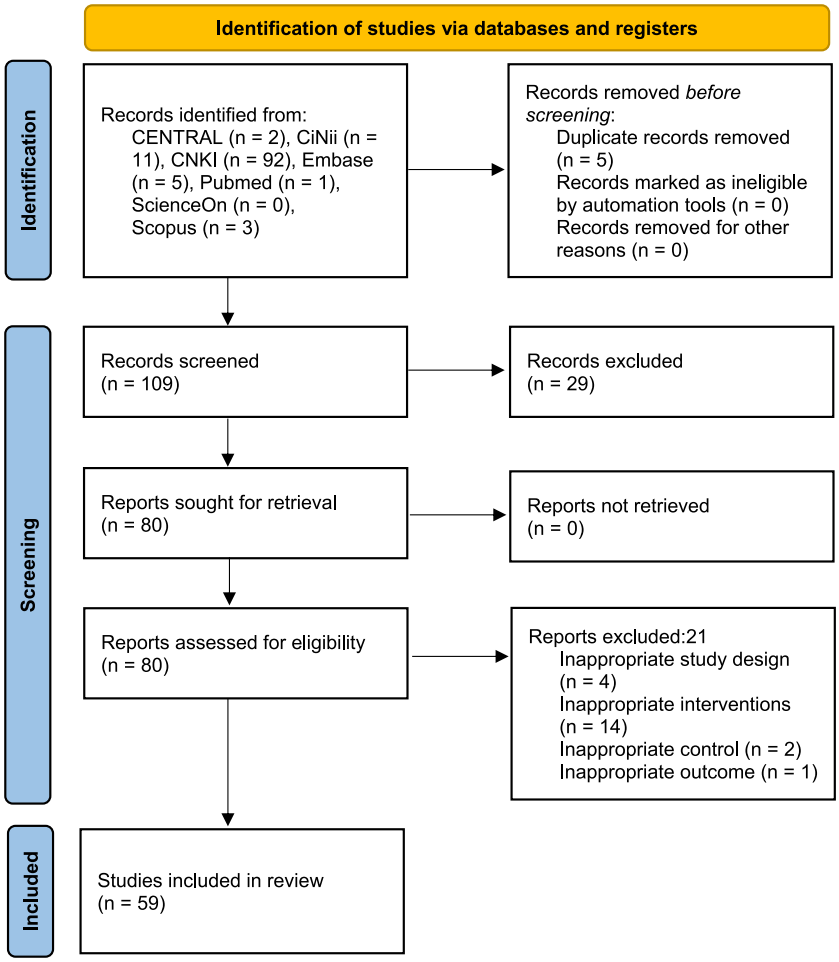


Fig. 1. PRISMA flow chart of the selection process.

3.2. Characteristics of the included studies

All 59 included studies were Chinese studies published between 2005 and 2023. A total of 5069 participants (2552 and 2517 in the treatment and control groups, respectively) were included in the studies. CWMs were administered to treat HF in all studies (Table 1). In nine studies [20–28], ORS was administered as a monotherapy; however, in the remaining studies, ORS was added, reduced, or co-administered with other drugs. In 27 studies [20,21,23,25–48], a predetermined drug was co-administered with a modified dose of herbal medicine based on the symptoms (Supplement 2).

3.3. Efficacy outcomes of ORS

Thirty-six studies [21–23,26,29,30,32–36,38,41,43,45,46,48–67] demonstrated better LVEF in the treatment group than in the control group or before treatment. Thirteen studies [23,27,32,33,35,45,48,52,55,59,60,64,67] and eleven studies [31,34,48,49,53,61,63–65,68,69] revealed better LVEDD and MLHF-Q scores than before therapy in the treatment or control groups, respectively. BNP levels were significantly higher in the treatment group than in the control group and pre-therapy in nine studies [20,26,31,38,44,55,57,70,71]. Lee's score was significantly improved in the treatment group in five studies [48,49,53,64,72]. Significant improvements in LVESD, 6 MWT, and NT-proBNP levels were observed post-therapy in the treatment group compared to those pre-therapy and in the control group in six [23,45,48,52,60,64], seventeen [22,26,30,31,33,48,49,51–54,64–66,70–72], and twenty [22,24,26,29,30,36,38,40,49–54,63–68], studies, respectively. All studies with TER except two studies [25,58] presented significant improvement in TER in the treatment group compared to that in the control group (Table 1).

3.4. Safety outcomes of ORS

Nine [34,39,53,62,65,67,69,72,73] studies reported no AEs in either group. Typical AEs included electrolyte imbalance and gastrointestinal symptoms; electrolyte imbalance was the most reported AEs, which occurred in 42 participants (21 in each group). No serious AEs leading to dropouts were reported in eight studies [29–31,36,37,52,64,68]. The incidences of serious AEs were similar between the treatment and control groups. Compared to the treatment group, four-fold more participants in the control group experienced AEs (Table 1).

3.5. Risk of bias evaluation

Figs. 2 and 3 illustrate the risk of bias of the included studies. Sixteen studies [22,31,37,38,41,49,50,52,65–68,70,72,73,76] that used appropriate random sequences were determined to have a low risk of bias. In the allocation concealment domain, three studies [31,68,73] that used opaque envelopes with serial numbers for allocation concealment were determined to have a low risk of bias. In terms of performance bias, two studies [25,28] that used a placebo were found to have a low risk of bias. Regarding detection bias, one study [68] that did not blind the outcome assessment was determined to have a high risk of bias. In terms of attrition bias, two studies [69,74] with dropout data were determined to have a high risk of bias. In terms of reporting bias, one study [68], which reported the protocol, was considered to have a low risk of bias. No other bias was noted in any study.

3.6. Meta-analysis

3.6.1. LVEF

In group I, LVEF was used as an outcome measure in 36 studies [21–23,26,29,30,32–36,38,41,43,45,46,48–67]. The LVEF in the treatment group was significantly higher than that in the control group, with statistical heterogeneity found among the studies (MD: 6.36, 95 % CI: 5.11 to 7.61, $P < 0.00001$, $I^2 = 94$ %). The funnel plot was symmetrical and no publication bias was observed (Fig. 4). In Group II, LVEF was used as an outcome measure in one study [53]. The LVEF in the treatment group was lower than that in the control group; however, the difference was not statistically significant.

3.6.2. TER

In group I, TER was used as an outcome measure in 50 studies [20,21,23–27,29,30,32–48,50–53,55–63,65,66,68,70–72,74–78]. The TER in the treatment group was significantly higher than that in the control group, with no heterogeneity found among the studies (RR: 1.20, 95 % CI: 1.17 to 1.23, $P < 0.00001$, $I^2 = 1$ %). Asymmetry in the funnel plots indicated possible publication bias (Supplement 3). In Group II, TER was used as an outcome measure in two studies [25,28]. The TER in the treatment group was higher than that in the control group; however, no significant difference was found (RR: 1.02, 95 % CI: 0.93 to 1.13, $P = 0.64$) (Supplement 4).

3.6.3. LVEDD

In Group I, LVEDD was used as an outcome measure in thirteen studies [23,27,31–33,35,45,48,52,55,60,64,67]. The LVEDD in the treatment group was significantly lower than that in the control group, with statistical heterogeneity found among the studies (MD: 5.21, 95 % CI: 7.21 to −3.22, $P < 0.0001$, $I^2 = 96$ %). The funnel plot was symmetrical and no publication bias was observed (Supplement 5). In group II, LVEDD was not used as an outcome measure.

Table 1
Characteristics of the included studies and the efficacy and safety outcomes of ORS.

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
An 2022 [63]	CHF	37/37	(I) 17/20 (C)15/22	(I) 60.16 ± 17.31 (C) 63.22 ± 16.53	Oryeongseunghamtang + CWM	CWM	4	① TER ② NT-proBNP ③ LVEF ④ MLHF-Q	① (I) 34/37 (91.89 %) (C) 26/37 (70.27 %) ② (I) 462.16 ± 121.47 (C) 726.38 ± 224.03 ③ (I) 45.51 ± 6.09 (C) 42.05 ± 4.62 ④ (I) 23.19 ± 3.05 (C) 35.24 ± 3.91	NR
Cao 2016 [44]	CHF	26/26	(I) 15/11 (C) 16/10	(I) 66.87 ± 9.89 (C) 67.98 ± 10.32	ORS variant 4 + Control group intervention	CWM + Captopril 12.5 mg tid po, if heart function Grade III–IV, metoprolol tartrate 12.5 mg bid po	8	① TER ② BNP	① (I) 25/26 (96.15 %) (C) 22/26 (84.62 %) ② (I) 223.18 ± 169.21 (C) 316.21 ± 260.97	NR
Chen 2013 [28]	CCHF	40/30	(I) 22/18 (C) 14/16	(I) 68.2 ± 9.6 (C) 66.6 ± 9.9	ORS + CWM	Placebo + CWM	2	① TER	① (I) 38/40 (95 %) (C) 28/30 (93 %)	NR
Chen 2019 [55]	AHF	74/71	(I) 40/34 (C) 36/35	(I) 63.17 ± 6.59 (C) 62.97 ± 7.22	ORS + Jinmutang + Sambutang + Control group intervention	CWM + Urapidil hydrochloride 50 mg IV (100–400 μg/min) for 3–10 days. if heart function improved, dose reduced for 2 days.	1.43	① TER ② LVEF ③ LVEDD ④ BNP	① (I) 70/74 (94.59 %) (C) 60/71 (84.51 %) ② (I) 48.94 ± 2.05 (C) 46.73 ± 2.14 ③ (I) 48.92 ± 2.27 (C) 51.84 ± 2.31 ④ (I) 827.56 ± 179.06	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
									(C) 935.38 ± 164.52	
Chen 2022 [69]	CHF	30/29	(I) 12/18 (C) 13/16	(I) 73.41 ± 5.8 (C) 74.56 ± 10.43	ORS + Gyejibokryunghwan + Control group intervention	Furosemide 20 mg qd po, Spironolactone 20 mg qd po, Perindopril 4 mg qd po, Valsartan sodium 80 mg qd po, Metoprolol succinate 47.5 mg qd po, Ivabradine 5 mg qd po, Digoxin 0.125 mg qd po, according to clinical indications	4	① TER ② MLHF-Q	① (I) 27/30 (90.00 %) (C) 18/29 (62.01 %) ② (I) 35.60 ± 16.55 (C) 49.10 ± 19.08	0/30, 0/29
Chi 2013 [24]	CHF	80/80	(I) 45/35 (C) 48/32	(I) 54.89 ± 6.26 (C) 55.11 ± 6.29	(Furosemide 5 days → ORS 5 days) * 2 + CWM	Furosemide 20 mg bid po 20 days + CWM	2.86	① TER ② NT-proBNP ③ Urine 24-h volume	① (I) 73/80 (91.25 %) (C) 63/80 (78.75 %) ② (I) 456.48 ± 65.77 (C) 649.82 ± 78.46 ③ (I) 2245.78 ± 118.75 (C) 1546.67 ± 94.68	NR
Deng 2020 [54]	CHF	53/47	(I) 30/23 (C) 25/22	(I) 56.93 ± 10.21 (C) 56.16 ± 10.87	ORS + Bojungikgitang + CWM	CWM	2	① LVEF ② 6MWT ③ NT-proBNP	① (I) 52.89 ± 3.74 (C) 48.51 ± 3.93 ② (I) 392.88 ± 61.87 (C) 337.73 ± 58.52 ③ (I) 48.92 ± 2.27 (C) 51.84 ± 2.31	NR
Ding 2019 [21]	CHF	40/40	(I) 22/18 (C) 24/16	(I) 58.60 ± 5.90 (C) 59.20 ± 5.70	ORS + CWM	CWM	2	① TER ② LVEF ③ Urine 24-h volume	① (I) 38/40 (95.0 %) (C) 33/40 (82.5 %) ② (I) 48.1 ± 11.7 (C) 42.2 ± 11.6 ③ (I) 1636.8 ± 391.7 (C) 1311.7 ± 338.5	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
Du 2011 [73]	HF due to CAD	30/30	(I) 14/16 (C) 15/15	(I) 61.32 ± 4.89 (C) 59.78 ± 5.26	ORS + Sambutang + Control group intervention	Furosemide 20 mg qd po, spironolactone 20 mg qd po, perindopril 20 mg or valsartan 80 mg qd po, aspirin 0.1 g qd po, metoprolol tartrate 6.25 mg bid po + CWM	4	① TER ② BNP	① (I) 26/30 (C) 27/30 ② (I) 273.53 ± 71.66 (C) 222.44 ± 64.76	0/30, 0/30
Duan 2021 [50]	CHF	43/43	(I) 26/17 (C) 27/16	(I) 3.46 ± 1.25 (C) 3.62 ± 1.31	Saengmaekikgi ORS + Control group intervention	CWM + Spironolactone 20 mg qd po, furosemide 20 mg qd po; if LVEF<50 %, digoxin 0.125 mg qd po	2	① TER ② LVEF ③ NT-proBNP	① (I) 40/43 (93.02 %) (C) 35/43 (81.40 %) ② (I) 52.92 ± 3.56 (C) 48.58 ± 3.88 ③ (I) 381.69 ± 41.27 (C) 437.75 ± 52.63	NR
Gao 2017 [49]	–	60/60	(I) 26/34 (C) 28/32	(I) 58.52 ± 10.65 (C) 57.96 ± 10.52	ORS + Bojungikgitang + CWM	CWM	2	① LVEF ② 6MWT ③ MLHF-Q ④ NT-proBNP ⑤ Lee's score ⑥ NYHA grade I	① (I) 52.88 ± 3.75 (C) 48.52 ± 3.92 ② (I) 392.87 ± 61.86 (C) 337.72 ± 58.51 ③ (I) 28.62 ± 10.86 (C) 41.57 ± 11.26 ④ (I) 452.64 ± 96.54 (C) 932.76 ± 105.62 ⑤ (I) 2.81 ± 1.14 (C) 3.97 ± 1.08 ⑥ (I) 34/60 (C) 26/60	NR
Gao 2023 [64]	CHF	40/40	(I) 26/14 (C) 25/15	(I) 61.69 ± 13.11 (C) 62.45 ± 11.78	ORS variant 6 + CWM	CWM	4	① LVEF ② LVEDD ③ LVESD ④ NT-proBNP ⑤ 6MWT ⑥ MLHF-Q ⑦ Lee's score	① (I) 52.05 ± 3.60 (C) 47.30 ± 3.51 ② (I) 41.74 ± 2.90 (C) 46.45 ± 3.29	4/40(GI issues 1, Dz 1, N/V 2), 3/40 (Dz 2, N/V 1)

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
								⑧ NYHA grade I	③ (I) 43.20 ± 3.19 (C) 48.05 ± 3.86 ④ (I) 893.65 ± 147.03 (C) 1140.15 ± 214.06 ⑤ (I) 366.25 ± 21.80 (C) 332.70 ± 42.31 ⑥ (I) 30.50 ± 3.75 (C) 34.15 ± 3.82 ⑦ (I) 3.26 ± 0.34 (C) 4.15 ± 0.45 ⑧ (I) 13/40 (C) 9/40	
Hong 2018 [38]	Left sided HF	41/41	(I) 20/21 (C) 18/23	(I) 68.2 ± 6.6 (C) 68.1 ± 7.0	ORS + Yijunghwan + Control group intervention	CWM + Metoprolol tartrate 25 mg bid po, candesartan 4 mg qd po, furosemide 20 mg qd po	1.43	① TER ② LVEF ③ BNP ④ NT-proBNP	① (I) 40/41 (97.6 %) (C) 27/41 (65.9 %) ② (I) 58.22 ± 12.16 (C) 64.02 ± 11.44 ③ (I) 115.1 ± 22.5 (C) 256.4 ± 22.9 ④ (I) 637.2 ± 13.5 (C) 854.5 ± 27.6	NR
Hu 2005 [25]	CCHF	30/20	NR	(I) 68.23 ± 9.58 (C) 66.60 ± 9.90	ORS + CWM	Placebo + CWM	2	① TER ② LVEF	① (I) 28/30 (93.3 %) (C) 18/20 (80 %) ② (I) 49.03 ± 14.77 (C) 51.10 ± 13.21	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
Hu 2021 [45]	HF	28/28	(I) 16/12 (C)17/11	(I) 72.3 ± 1.4 (C) 72.4 ± 1.7	ORS + Jinmutang + Control group intervention	CWM + Carvedilol IV, furosemide 10–20 mg, spironolactone 20 mg qd–bid po, captopril 12.5 mg bid po, nitroglycerin 5 mg IV q24hr for 5 days	2	① TER ② LVEF ③ LVEDD ④ LVESD	① (I) 27/28 (96.43 %) (C) 22/28 (78.57 %) ② (I) 47.78 ± 4.8 (C) 36.76 ± 4.11 ③ (I) 43.27 ± 3.1 (C) 58.52 ± 4.74 ④ (I) 31.48 ± 2.65 (C) 45.23 ± 3.62	NR
Huang 2013 [62]	CHF	48/48	(I) 25/23 (C) 24/24	(I) 63.51 ± 6.21 (C) 62.83 ± 6.52	Dangal ORS + Control group intervention	CWM + if edema present, spironolactone, hydrochlorothiazide. If high HR, isosorbide dinitrate, nitroglycerin, cedilanid or digoxin.	4	① TER ② LVEF	① (I) 42/48 (91.66 %) (C) 33/48 (70.83 %) ② (I) 48.2 ± 3.2 (C) 41.7 ± 3.0	0/48, 0/48
Jiang 2017 [29]	–	34/34	(I) 20/14 (C) 21/13	(I) 41.98 ± 7.96 (C) 42.35 ± 8.12	ORS + Dohongsamultang + Control group intervention	CWM + Furosemide 40 mg–1 g IV (80 mg/h), spironolactone 40–120 mg/day bid–qid po	2	① TER ② LVEF ③ Urine 24-h volume ④ NT-proBNP	① (I) 32/34 (94.1 %) (C) 26/34 (76.5 %) ② (I) 49.36 ± 3.65 (C) 43.17 ± 3.02 ③ (I) 1368.41 ± 364.39 (C) 903.65 ± 312.47 ④ (I) 358.32 ± 29.67 (C) 413.26 ± 41.65	3/34(GI issues 1, HA 2), 4/34(GI issues 2, HA 1, hypoK^+ 1)
Jing 2006 [61]	CHF	30/30	36/24	52	Hwanggisammaek ORS + CWM	CWM	48	① TER ② LVEF ③ MLHF-Q ④ NYHA grade I	① (I) 25/30 (83.33 %) (C) 17/30 (56.67 %) ② (I) 63.24 ± 7.12 (C) 46.63 ± 6.61	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
									③ (I) 51.23 ± 3.71 (C) 46.63 ± 3.62 ④ (I)16/30 (C) 8/30	
Li 2014 [23]	Intractable HF	35/35	41/29	60.6 ± 0.9	ORS + CWM	CWM	2	① TER ② LVEF ③ LVEDD ④ LVESD	① (I) 32/35 (91.4 %) (C) 21/35 (60.0 %) ② (I) 40 ± 12 (C) 32 ± 8 ③ (I) 70 ± 21 (C) 82 ± 25 ④ (I) 45 ± 19 (C) 59 ± 23	NR
Li 2016 [40]	Acute aggravation of CHF	44/44	(I) 31/13 (C) 29/15	(I) 69 ± 3 (C) 68 ± 1.5	ORS variant 1 + Control group intervention	CWM + Digoxin 0.125 mg, benazepril 5–10 mg qd, spironolactone 25 mg, furosemide 25 mg, metoprolol 12.5 mg, trimetazidine 25 mg qd(bid) po	1.43	① TER ② NT-proBNP	① (I) 43/44 (97.73 %) (C) 39/44 (88.64 %) ② (I) 1032 ± 17.26 (C) 1257 ± 12.74	NR
Li 2017 [33]	HF w. CAD	30/30	(I) 17/13 (C)19/11	(I) 65.23 ± 9.62 (C) 65.46 ± 9.30	ORS + Dohongsamultang + Control group intervention	CWM + Furosemide 20 mg qd, benazepril 10 mg qd, metoprolol 25 mg qd, digoxin 0.125 mg qd, aspirin 100 mg qd, isosorbide mononitrate 20 mg bid po	NR	① TER ② LVEF ③ LVEDD ④ 6MWT ⑤ Urine 24-h volume	① (I) 27/30 (90.0 %) (C) 23/30 (76.67 %) ② (I) 47.56 ± 12.31 (C) 41.03 ± 11.30 ③ (I) 53.79 ± 5.76 (C) 59.91 ± 6.03 ④ (I) 410.30 ± 114.31 (C) 385.67 ± 13.39 ⑤ (I) 1621.22 ± 387.56 (C) 1283.14 ± 341.20	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
Li 2018 [32]	HF w. edema	99/99	(I) 61/38 (C) 59/40	(I) 65.0 ± 11.2 (C) 63.7 ± 12.4	ORS + Dohongsamultang + CWM	CWM	4	① TER ② LVEF ③ LVEDD ④ Urine 24-h volume	① (I) 93/99 (93.94 %) (C) 83/99 (83.84 %) ② (I) 47.1 ± 12.3 (C) 41.2 ± 11.4 ③ (I) 53.6 ± 5.5 (C) 59.7 ± 5.9 ④ (I) 1635.00 ± 377.00 (C) 1279.00 ± 362.00	NR
Li 2019 [68]	PAA w. HF	44/44	(I) 27/17 (C) 26/18	(I) 70 (C) 69	ORS + Samryeongbaekchulsan + CWM	CWM	2	① TER ② MLHF-Q ③ NT-proBNP	① (I) 40/44 (C) 36/44 ② (I) 24.31 ± 9.34 (C) 29.15 ± 11.25 ③ (I) 780 ± 564 (C) 994 ± 339	3/44, 2/44 (All GI issues)
Li 2022 [74]	HF	37/35	(I) 19/18 (C) 18/17	(I) 66.2 ± 5.9 (C) 65.9 ± 4.2	ORS variant 7 + Control group intervention	Isosorbide mononitrate 40 mg qd po, Furosemide 20 mg qd po, Spironolactone 20 mg qd po, digoxin 0.125 mg qd po	1	① TER	① (I) 32/37 (86.49 %) (C) 23/35 (65.71 %)	NR
Liang 2005 [56]	HF w. CMP	30/30	NR	15–80	Hwangisammaek ORS + CWM	CWM	48	① TER ② LVEF	① (I) 25/30 (83.3 %) (C) 17/30 (56.7 %) ② (I) 61.5 ± 7.2 (C) 47.2 ± 6.6	NR
Lin 2016 [57]	CHF	40/40	(I) 17/23 (C) 19/21	(I) 64.5 ± 11.5 (C) 65.5 ± 10.5	Gigap ORS + CWM	CWM	4	① TER ② LVEF ③ BNP	① (I) 37/40 (92.5 %) (C) 24/40 (57.5 %) ② (I) 50 ± 11 (C) 41 ± 15 ③ (I) 453 ± 120.6	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
									(C) 656.5 ± 215.8	
Liu 2010 [75]	CPHD w. HF	30/30	(I) 18/12 (C) 16/14	(I) 64.5 (C) 63.7	ORS + Jinmutang + CWM	CWM	2	① TER	① (I) 28/30 (93.3 %) (C) 23/30 (76.67 %)	NR
Liu 2013 [46]	PHD w. HF	38/38	(I) 28/10 (C) 26/12	(I) 65.8 (C) 65.1	ORS + Jinmutang + Junglyeokdaejosapetang + Control group intervention	Ambroxol 30 mg tid po, aminophylline 0.25 mg IV q24hr, carvedilol 0.2–0.4 mg IV q24hr, hydrochlorothiazide 25 mg tid po, dexamethasone IV bolus + CWM	NR	① TER	① (I) 35/38 (92.11 %) (C) 27/38 (71.05 %)	NR
Liu 2015 [72]	CHF	22/22	(I) 12/10 (C) 11/11	(I) 63.36 ± 6.973 (C) 62.36 ± 6.441	ORS + Samgisamultang + CWM	CWM	2	① TER ② 6MWT ③ NT-proBNP ④ Lee's score	① (I) 19/22 (86.36 %) (C) 18/22 (81.82 %) ② (I) 478.91 ± 91.105 (C) 445.50 ± 88.031 ③ (I) 970.820 ± 960.845 (C) 1699.77 ± 1741.903 ④ (I) 4.18 ± 4.148 (C) 4.59 ± 4.136	0/22, 0/22
Liu 2017 [26]	CHF	60/60	(I) 33/27 (C) 31/29	(I) 69.2 (C) 66.2	ORS + Control group intervention	Valsartan/Hydrochlorothiazide 80/12.5 mg qd po + CWM	4	① TER ② LVEF ③ BNP	① (I) 57/60 (78.3 %) (C) 47/60 (95.0 %) ② (I) 48.4 ± 3.4 (C) 41.9 ± 3.2 ③ (I) 112.48 ± 54.63 (C) 182.24 ± 65.55	NR
Lu 2011 [47]	CHF	30/30	32/28	40–78	ORS + Hwanggijinmutang + Control group intervention	CWM + Furosemide 20 mg IV for 5 days, cedilanid 0.2–0.4 mg IV for 5 days; after cedilanid, digoxin 0.125 mg qd po. Dexamethasone 10 mg IV. Nitroglycerin 5–10 mg 5 drops /min IV drip. If low BP, dopamine 20 mg IV, if PHD, phentolamine 10 mg IV q24hr.	1.43	① TER	① (I) 28/30 (93.3 %) (C) 20/30 (66.7 %)	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
Lu 2023 [66]	CHF	43/43	(I) 23/20 (C) 25/18	(I) 63.53 ± 10.48 (C) 63.78 ± 10.25	ORS variant 5 + Control group intervention	Benazepril hydrochloride 10 mg qd po, Metoprolol succinate 47.5 mg qd po, Spironolactone 20 mg bid po, Furosemide 20 mg qd po, Digoxin 0.25 mg qd po	4	① TER ② NT-proBNP ③ 6MWT ④ LVEF	① (I) 41/43 (95.35 %) (C) 35/43 (81.40 %) ② (I) 742.18 ± 70.56 (C) 879.15 ± 73.471 ③ (I) 569.24 ± 64.301 (C) 434.81 ± 55.22 ④ (I) 55.76 ± 4.81 (C) 52.56 ± 4.45	NR
Mu 2006 [41]	CHF	118/115	(I) 67/51 (C) 65/50	(I) 60.5 ± 13.5 (C) 58.3 ± 12.7	ORS + Sambutang + Control group intervention	Captopril 25–50 mg tid, hydrochlorothiazide 25 mg bid, isosorbide dinitrate 10 mg bid, digoxin po + CWM	2	① TER ② LVEF	① (I) 115/118 (97.46 %) (C) 92/115 (80.0 %) ② (I) 58.92 ± 10.18 (C) 41.92 ± 9.79	NR
Nie 2022 [48]	CHF	61/61	(I) 35/26 (C) 33/28	(I) 57.63 ± 2.12 (C) 57.81 ± 2.09	ORS + Xinbao Hwan + Control group intervention	Perindopril tert-butylamine 2 mg qd po, Furosemide 20 mg qd po, Metoprolol tartrate 6.25 mg bid po, Aspirin, 20 mg qd po	3	① TER ② LVEF ③ LVEDD ④ LVESD ⑤ 6MWT ⑥ MLHF-Q ⑦ Lee's score	① (I) 55/61 (90.16 %) (C) 46/61 (75.41 %) ② (I) 55.81 ± 3.66 (C) 48.55 ± 2.82 ③ (I) 43.52 ± 1.33 (C) 48.77 ± 1.62 ④ (I) 32.27 ± 2.71 (C) 41.32 ± 3.02 ⑤ (I) 590.04 ± 42.33 (C) 512.36 ± 33.57 ⑥ (I) 39.44 ± 7.33 (C) 49.57 ± 8.36	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
									⑦ (I) 5.37 ± 1.16 (C) 9.12 ± 1.55	
Ning 2012 [43]	CHF	70/70	(I) 36/34 (C) 43/27	(I) 61.36 ± 11.65 (C) 63.33 ± 7.16	Gigap ORS + Control group intervention	Isosorbide dinitrate 20 mg tid, spironolactone 20 mg qd, digoxin 0.25 mg qd po + CWM	12	① TER ② LVEF	① (I) 67/70 (95.71 %) (C) 53/70 (75.71 %) ② (I) 46.64 ± 3.79 (C) 35.58 ± 3.42	NR
Pan 2018 [76]	CHF	35/35	41/29	64.4 ± 5.8	ORS + Bojungikgitang + CWM	CWM	4	① TER	① (I) 32/35 (91.43 %) (C) 26/35 (72.29 %)	NR
Peng 2019 [22]	HF	90/90	(I) 49/41 (C) 47/43	(I) 62.1 ± 5.8 (C) 62.7 ± 6.1	ORS + Control group intervention	CWM + Furosemide 20 mg bid po	4	① LVEF ② 6MWT ③ NT-proBNP	① (I) 40.76 ± 7.60 (C) 35.39 ± 9.26 ② (I) 555.4 ± 40.4 (C) 497.9 ± 29.7 ③ (I) 3756.48 ± 225.77 (C) 3945.39 ± 129.26	NR
Ren 2020 [37]	HF w. Edema	25/25	(I) 19/6 (C) 20/5	(I) 63.28 ± 8.72 (C) 62.25 ± 9.75	ORS + Dohongsamultang + CWM	Furosemide 20–40 mg qd po (Maximum, 100 mg/day) + CWM	8	① TER	① (I) 24/25 (96.00 %) (C) 19/25 (76.00 %)	3(N/V 2, Arr. 1), 10(N/V 5, Arr. 5)
Su 2017 [39]	PHD w. HF	30/30	30/30	65.3 ± 6.9	ORS + Dohongeum + CWM	CWM	1	① TER	① (I) 24/25 (83.3 %) (C) 19/25 (73.3 %)	0/30, 0/30
Sun 2020 [53]	CHF	36/38	(I) 19/17 (C) 20/18	(I) 46–55: 13 56–65: 6 66–75: 19 (C) 46–55: 9 56–65: 11 66–75: 16	ORS + Boyanghwanotang + CWM	CWM	4	① TER ② LVEF ③ 6MWT ④ NT-proBNP ⑤ MLHF-Q ⑥ Lee's score ⑦ NYHA grade I	① (I) 33/36 (91.66 %) (C) 32/38 (76.32 %) ② (I) 47.67 ± 2.70 (C) 46.03 ± 3.77 ③ (I) 550.380 ± 22.734 (C) 466.183 ± 19.780	0/36, 0/38

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
									④ (I) 1308.00 ± 218.00 (C) 1517.58 ± 115.37 ⑤ (I) 19.47 ± 4.53 (C) 27.82 ± 4.25 ⑥ (I) 3.56 ± 1.76 (C) 4.17 ± 1.25 ⑦ (I) 23/36 (C) 20/38	
Tang 2020 (A) [30]	CHF	51/51	(I) 27/24 (C) 35/16	(I) 71.5 (C) 70.3	ORS + Bojungikgitang + Control group intervention	CWM + Sacubitril/Valsartan 50 mg bid po.	4	① TER ② LVEF ③ 6MWT ④ NT-proBNP	① (I) 49/51 (96.07 %) (C) 43/51 (84.31 %) ② (I) 58.28 ± 6.62 (C) 41.78 ± 5.33 ③ (I) 348.14 ± 49.89 (C) 268.76 ± 41.35 ④ (I) 1340.62 ± 282.41 (C) 2235.43 ± 317.32	HA, Dz, HR decrease, HTN, low BP
Tang 2020 (B) [31]	CHF or ADHF	45/44	(I) 25/20 (C) 26/18	(I) 60.96 ± 9.31 (C) 61.34 ± 8.66	ORS + Jinmutang + Control group intervention	CWM + Furosemide 20–40 mg IV; subsequently, furosemide 20 mg po thrice/day for 5 days, or hydrochlorothiazide, torsemide, tolvaptan, etc. If oliguria is present, low-dose dopamine. If SBP ≥110 mmHg, nitroglycerin 30 mg IV. If SBP ≥90 mmHg, perindopril 4 mg or valsartan 80 mg qd po. Metoprolol succinate 11.875 mg– maximum dosage po. Spironolactone 20 mg po. If ICM, aspirin 0.1 g qd, atorvastatin 20 mg or rosuvastatin 10 mg qd, trimetazidine 35 mg bid po.	1	① LVEF ② LVEDD ③ 6MWT ④ BNP ⑤ MLHF-Q	① (I) 36.08 ± 6.37 (C) 35.86 ± 4.45 ② (I) 53.69 ± 4.08 (C) 54.02 ± 3.77 ③ (I) 296.69 ± 73.12 (C) 254.49 ± 83.27 ④ (I) 226.73 ± 72.39 (C) 517.27 ± 98.14 ⑤ (I) 46.43 ± 8.45	37/45(EI 20, LFT issues 2, RFT worsens 4, GI issues 10, others 1), 33/44(EI 18, LFT issues 3, RFT worsens 3, GI issues 7, others 2)

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
									(C) 47.31 ± 7.95	
Tu 2023 [65]	Diastolic HF	30/29	(I) 13/17 (C) 10/19	(I) 79.67 ± 5.93 (C) 78.03 ± 4.96	ORS + Gyejibokryunghwan + Control group intervention	Furosemide 20 mg qd po, Spironolactone 20 mg qd po, Enalapril 2.5 mg qd po or cannot tolerate ACEI, vasilate Tan 80 mg qd po, metoprolol succinate ER 23.75–47.50 mg qd po	4	① TER ② 6MWT ③ MLHF-Q ④ LVEF ⑤ E/A ⑥ NT-proBNP	① (I) 27/30 (90.00 %) (C) 19/29 (65.52 %) ② (I) 491.20 ± 15.93 (C) 459.97 ± 35.16 ③ (I) 32.40 ± 4.57 (C) 41.66 ± 5.53 ④ (I) 61.77 ± 2.45 (C) 59.72 ± 2.71 ⑤ (I) 1.24 ± 0.21 (C) 1.19 ± 0.36 ⑥ (I) 889.61 ± 104.26 (C) 1403.66 ± 489.63	0/30, 0/29
Wang 2007 [58]	DCM w. HF	30/30	32/28	52 ± 13.6	Hwangisammaekoryeongtang + CWM	CWM	48	① TER ② LVEF ③ NYHA grade I	① (I) 25/30 (83 %) (C) 17/30 (57 %) ② (I) 61.5 ± 7.2 (C) 47.2 ± 6.6 ③ (I) 16/30 (C) 10/30	NR
Wang 2010 [42]	CHF	35/35	(I) 22/13 (C) 23/12	(I) 62.3 ± 12.58 (C) 63.6 ± 11.37	ORS + Paljintang + Control group intervention	CWM + Grade II: Captopril 12.5 mg bid, furosemide 20 mg qod, metoprolol 25 mg bid po. Grade III: Captopril 12.5–25 mg bid, furosemide 20 mg qd 1–3 d, h/d 2–4 d, metoprolol 12.5–25 mg bid po. Grade IV: Captopril 12.5–25 mg bid, furosemide 20 mg bid, digoxin 0.125 mg qd, spironolactone 20 mg bid po	1.43	① TER	① (I) 33/35 (94.29 %) (C) 25/35 (71.43 %)	NR
Wang 2017 (A) [51]	HF	30/30	(I) 17/13 (C) 20/10	(I) 63.134 ± 6.107 (C)	ORS variant 3+ Control group intervention	Benazepril 5–10 mg qd, metoprolol 6.25–25 mg qd, spironolactone 10–20 mg qd, furosemide 20 mg qd, digoxin 0.125 mg qd po + CWM	4	① TER ② LVEF ③ 6MWT ④ LVEF	① (I) 27/30 (90.00 %) (C) 23/30 (76.67 %)	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
				63.954 ± 6.956					② (I) 45.917 ± 2.967 (C) 45.753 ± 2.935 ③ (I) 553.413 ± 37.831 (C) 462.791 ± 35.619 ④ (I)1218.212 ± 266.274 (C)1435.684 ± 355.043	
Wang 2017 (B) [52]	CHF	34/34	(I) 18/16 (C) 20/14	(I) 68.76 ± 7.12 (C) 68.24 ± 6.79	ORS + Bojungikgitang + Control group intervention	Digoxin 0.125–0.25 mg qd, furosemide 20–40 mg qd, captopril 12.5–25 mg qd po + CWM	12	① TER ② LVEF ③ LVEDD ④ LVESD ⑤ 6MWT ⑥ NT-proBNP	① (I) 31/34 (91.66 %) (C) 24/34 (76.32 %) ② (I) 49.9 ± 6.5 (C) 43.2 ± 6.9 ③ (I) 46.6 ± 4.6 (C) 56.4 ± 4.4 ④ (I) 37.4 ± 4.7 (C) 44.7 ± 4.9 ⑤ (I) 484.7 ± 62.6 (C) 416.9 ± 72.4 ⑥ (I) 412.2 ± 42.8 (C) 792.7 ± 56.8	1/34(N/V 1), 1/34 (Abd. pain 1)
Wang 2018 (A) [35]	CHF	48/48	(I) 26/22 (C) 28/20	(I) 62.28 ± 4.42 (C) 62.24 ± 4.46	ORS + Dohongsamultang + Control group intervention	Furosemide 20 mg qd, benazepril 10 mg qd, metoprolol 25 mg qd, aspirin 100 mg qd, isosorbide mononitrate 20 mg bid, digoxin 0.125 mg PRN po + CWM	NR	① TER ② LVEF ③ LVEDD ④ Urine 24-h volume	① (I) 44/48 (93.75 %) (C) 39/48 (81.25 %) ② (I) 48.71 ± 3.16 (C) 41.13 ± 3.03 ③ (I) 51.35 ± 3.78 (C) 58.89 ± 3.92 ④ (I) 1623.65 ± 16.56	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
									(C) 1285.41 ± 13.48	
Wang 2018 (B) [71]	HF	43/43	(I) 24/19 (C) 26/17	(I) 53.5 ± 7.3 (C) 52.7 ± 6.9	ORS + Bojungikgitang + Control group intervention	Digoxin 0.125 mg, hydrochlorothiazide 25 mg, spironolactone 10 mg, isosorbide mononitrate 40 mg, metoprolol tartrate 47.5 mg, acertil 4 mg qd, potassium magnesium Aspartate tid + CWM	2	① TER ② 6MWT ③ BNP	① (I) 40/43 (93.75 %) (C) 33/43 (81.25 %) ② (I) 384.5 ± 57.6 (C) 301.8 ± 40.5 ③ (I) 549.6 ± 67.3 (C) 872.6 ± 105.7	NR
Wang 2019 [36]	HF w. pulmonary Edema	35/35	34/36	NR	ORS + Dohongsamultang + Control group intervention	Furosemide 40–80 mg IV, spironolactone 40–120 mg bid–qid po + CWM	2	① TER ② LVEF ③ NT-proBNP ④ Urine 24-h volume	① (I) 34/35 (97.14 %) (C) 26/35 (74.86 %) ② (I) 49.45 ± 3.06 (C) 42.43 ± 3.46 ③ (I) 381 ± 48.63 (C) 411 ± 42.51 ④ (I) 1348 ± 368.32 (C) 948 ± 324.62	4/35(GI issues 2, HA 1, hypoKa$^+$ 1), 5/35(GI issues 1, HA 2, hypoKa$^+$ 2)
Weng 2020 [70]	HFpEF	40/40	(I) 22/18 (C) 24/16	(I) 57.64 ± 4.26 (C) 56.56 ± 5.09	ORS variant 2 + CWM	CWM	8	① TER ② 6MWT ③ BNP	① (I) 38/40 (95 %) (C) 34/40 (85 %) ② (I) 482.10 ± 9.97 (C) 420.06 ± 22.07 ③ (I) 69.77 ± 4.82 (C) 87.67 ± 8.04	NR
Xue 2018 [20]	CHF	30/30	(I) 16/14 (C) 18/12	(I) 64.35 ± 4.19 (C) 65.31 ± 5.47	ORS + Control group intervention	Valsartan/Hydrochlorothiazide 80/12.5 mg qd po + CWM	4	① TER ② LVEF ③ BNP	① (I) 29/30 (96.67 %) (C) 23/30 (76.67 %) ② (I) 48.5 ± 4.3 (C) 40.5 ± 2.3	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
									③ (I) 112.84 ± 53.64 (C) 181.02 ± 65.14	
Yang 2014 [77]	CHF	35/35	(I) 19/16 (C) 19/16	(I) 63.1 ± 9.9 (C) 63.7 ± 8.1	ORS Jinmutang + CWM	CWM	4	① TER	① (I) 28/35 (97.14 %) (C) 20/35 (60.00 %)	NR
Yang 2018 [78]	DCM+ HF	51/51	(I) 32/19 (C) 31/20	(I) 51.58 ± 0.98 (C) 51.68 ± 1.02	Hwanggisammaekoryeongtang + Control group intervention	Metoprolol tartrate 3.125–25 mg bid, Coenzyme Q10 10 mg tid, ketamine 0.2 g tid po	12	① TER ② 6MWT	① (I) 48/51 (94.12 %) (C) 41/51 (80.39 %) ② (I) 460.25 ± 6.52 (C) 235.54 ± 4.20	NR
Yi 2017 [34]	CHF	46/46	(I) 25/21 (C) 27/19	(I) 79.2 ± 7.9 (C) 75.8 ± 8.5	ORS + Jinmutang + CWM	CWM	4	① TER ② MLHF-Q	① (I) 41/46 (89.1 %) (C) 33/46 (71.7 %) ② (I) 30.36 ± 8.34 (C) 45.34 ± 10.28	0/46, 0/46
Zhang 2006 [27]	CCHF	28/28	(I) 14/14 (C) 16/12	(I) 62 (C) 60	ORS + Control group intervention	CWM + Furosemide 10–20 mg q12–24hr infusion or hydrochlorothiazide 25 mg + spironolactone 20 mg qd–bid, Captopril 12.5–25 mg qd–bid po or nitroglycerin 10–80 μg/min or sodium nitroprusside 6.25–50 μg/min IV infusion; if no improvement in 2 weeks, cedilanid 0.2–0.4 mg q12–24hr infusion, if improved, digoxin 0.1225–0.25 mg qd po	2	① TER	① (I) 26/28 (92.9 %) (C) 22/28 (78.6 %)	NR
Zhang 2021 [60]	CAD w. HF	45/45	(I) 22/23 (C) 24/21	(I) 61.33 ± 3.51 (C) 59.12 ± 2.24	ORS + Bojungikgitang + Control group intervention	Metoprolol tartrate 6.25–50 mg bid–tid po + CWM	2	① TER ② LVEF ③ LVEDD ④ LVESD	① (I) 44/45 (97.78 %) (C) 38/45 (84.44 %) ② (I) 48.01 ± 8.12 (C) 42.22 ± 6.41 ③ (I) 36.47 ± 3.33 (C) 41.21 ± 4.52	NR

(*continued on next page*)

Table 1 (*continued*)

Author Year	Type of HF	Sample Size (I/C)	Male/Female	Mean age (Year)	Intervention		Duration	Outcome measurement	Result	Adverse events
					Treatment	Control				
									④ (I) 56.50 ± 5.78 (C) 61.16 ± 6.89	
Zhou 2023 [67]	CHF	35/35	(I) 19/16 (C) 15/20	(I) 63.50 ± 9.45 (C) 63.84 ± 7.87	ORS + Shaengmaeksan + Control group intervention	Tolvaptan 7.5 mg qd po + CWM	2	① LVEF ② LVEDD ③ NT-proBNP ④ NYHA grade I ⑤ Urine 24-h volume	① (I) 49.31 ± 4.92 (C) 45.80 ± 4.99 ② (I) 53.31 ± 4.31 (C) 58.11 ± 4.42 ③ (I) 2464.00 ± 890.29 (C) 4345.14 ± 625.69 ④ (I) 21/35 (C) 16/35 ⑤ (I) 1697.14 ± 179.03 (C) 499.43 ± 177.08	0/35, 0/35
Zhu 2015 [59]	HF	50/50	(I) 28/22 (C) 29/21	(I) 45.97 ± 4.87 (C) 46.18 ± 3.27	ORS + Jinmutang + CWM	CWM	4	① TER ② LVEF ③ LVEDD	① (I) 49/50 (98.00 %) (C) 30/50 (60.00 %) ② (I) 67.36 ± 8.41 (C) 62.72 ± 2.98 ③ (I) 58.42 ± 6.68 (C) 51.75 ± 2.95	NR

The duration unit is week.

ADHF, Acute decompensated heart failure; AHF, Acute Heart failure; Arr., Arrhythmia; bid, bis in die (twice a day); BP, Blood pressure; C, Control group; CAD, Coronary artery disease; CCHF, Chronic congestive heart failure; CHF, Chronic heart failure; CMP, Cardiomyopathy; CPHD, Chronic pulmonary heart disease; CWM, Conventional western medicine; DCM, Dilated cardiomyopathy; Dz, Dizziness; E/A, Peak value of early diastolic blood flow velocity/Peak value of late diastolic blood flow velocity ratio; EI, Electrolyte imbalance; GI, Gastrointestinal; HA, Headache; HF, Heart failure; HFpEF, Heart failure with preserved ejection fraction; HR, Heart rate; HTN, Hypertension; hypoK^{+},hypokalemia; I, Intervention group; ICM, Ischemic cardiomyopathy; IV, Intravenous injection; LFT, Liver function test; NR, not reported; N/V, Nausea and vomiting; ORS, Oryeongsan; po, per os (by mouth); PAA, Pulmonary Arterial Aneurysm; PHD, Pulmonary Heart Disease; q, Every; q24 h, every 24 h; PRN, pro re nata (when necessary); qd, quaque die (once per day); qid, quarter in die (4 times per day); qod, Quaque altera die (every other day); RFT, Renal function test; tid, Ter in die (thrice a day); w., with.

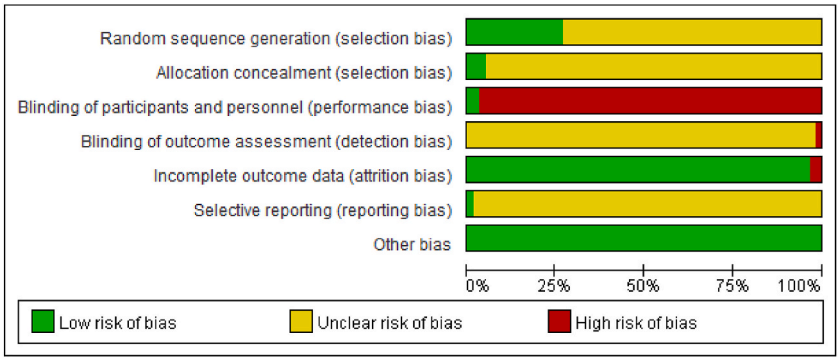


Fig. 2. Risk of bias graph depicting percentage across all included studies.

3.6.4. LVESD

In group I, LVESD was used as an outcome measure in six studies [23,45,48,52,60,64]. The LVESD in the treatment group was significantly lower than that in the control group, with statistical heterogeneity found among the studies (MD: 8.37, 95 % CI: 11.38 to −5.35, P < 0.00001, I^2 = 93 %) (Supplement 6A). In group II, LVESD was not used as an outcome measure.

3.6.5. 6MWT

In group I, 6MWT was used as an outcome measure in seventeen studies [22,26,30,31,33,48,49,51–54,64–66,70–72]. The 6MWT in the treatment group was significantly higher than that in the control group, with statistical heterogeneity found among the studies (MD: 73.00, 95 % CI: 21.89 to 124.11, P < 0.00001, I^2 = 100 %). Asymmetry in the funnel plots indicated possible publication bias (Supplement 7). In Group II, the 6MWT was not used as an outcome measure.

3.6.6. Serum BNP level

In group I, serum BNP level was used as an outcome measure in ten studies [20,26,31,38,44,55,57,70,71,73]. The serum BNP level in the treatment group was significantly lower than that in the control group, with statistical heterogeneity found among the studies (MD: 125.84, 95 % CI: 187.10 to −64.58, P < 0.0001, I^2 = 99 %). The funnel plot was symmetrical and no publication bias was noted (Supplement 8). In group II, the serum BNP level was not used as an outcome measure.

3.6.7. Serum NT-proBNP level

In Group I, the serum NT-proBNP level was used as an outcome measure in twenty studies [22,24,29,30,36,38,40,49–54,63–68,72]. The serum NT-proBNP level in the treatment group was significantly lower than that in the control group, with statistical heterogeneity found among the studies (MD: 294.50, 95 % CI: 347.37 to −241.62, P < 0.00001, I^2 = 99 %). Asymmetry in the funnel plots indicated possible publication bias (Supplement 9). In group II, the serum NT-proBNP level was not used as an outcome measure.

3.6.8. 24-h urine volume

In Group I, 24-h urine volume was used as an outcome measure in eight studies [21,24,29,32,33,35,36,67]. The 24-h urine volume in the treatment group was significantly higher than that in the control group, with statistical heterogeneity found among the studies (MD: 519.13, 95 % CI: 310.22 to 728.03, P < 0.00001, I^2 = 99 %) (Supplement 6 B). In Group II, the 24-h urine volume was not used as an outcome measure.

3.6.9. MLHF-Q

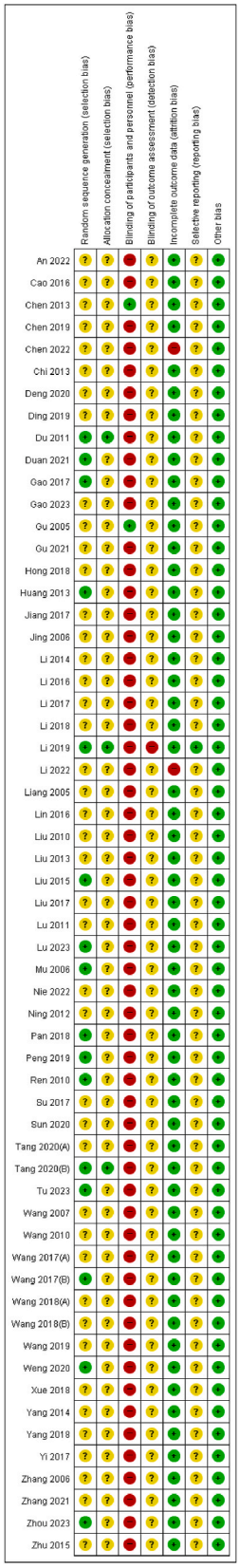
In Group I, MLHF-Q was used as an outcome measure in eleven studies [31,34,48,49,53,61,63–65,68,69]. The MLHF-Q in the treatment group was significantly lower than that in the control group, with statistical heterogeneity found among the studies (MD: 7.60, 95 % CI: 11.47 to −3.72, P < 0.00001, I^2 = 96 %) (Supplement 6C). In Group II, the MLHF-Q was not used as an outcome measure.

3.6.10. Lee's score

In group I, Lee's score was used as an outcome measure in five studies [48,49,53,64,72]. The Lee's score in the treatment group was significantly lower than that in the control group, with statistical heterogeneity found among the studies (MD: 1.47, 95 % CI: 2.62 to −0.33, P < 0.00001, I^2 = 97 %) (Supplement 6D). In group II, Lee's score was not used as an outcome measure.

3.6.11. NYHA grade I ratio

In group I, NYHA grade I ratio was used as an outcome measure in six studies [49,53,58,61,64,67]. The NYHA grade I ratio in the treatment group was significantly higher than that in the control group, with no statistical heterogeneity found among the studies (RR: 1.37, 95 % CI: 1.12 to 1.67, P = 0.002, I^2 = 0 %) (Supplement 6E). In Group II, the NYHA grade I ratio was not used as an outcome measure.



(caption on next page)

Fig. 3. Risk of bias summary of the included studies
"+" = low risk of bias, "−" = high risk of bias, "?" = unclear risk of bias.

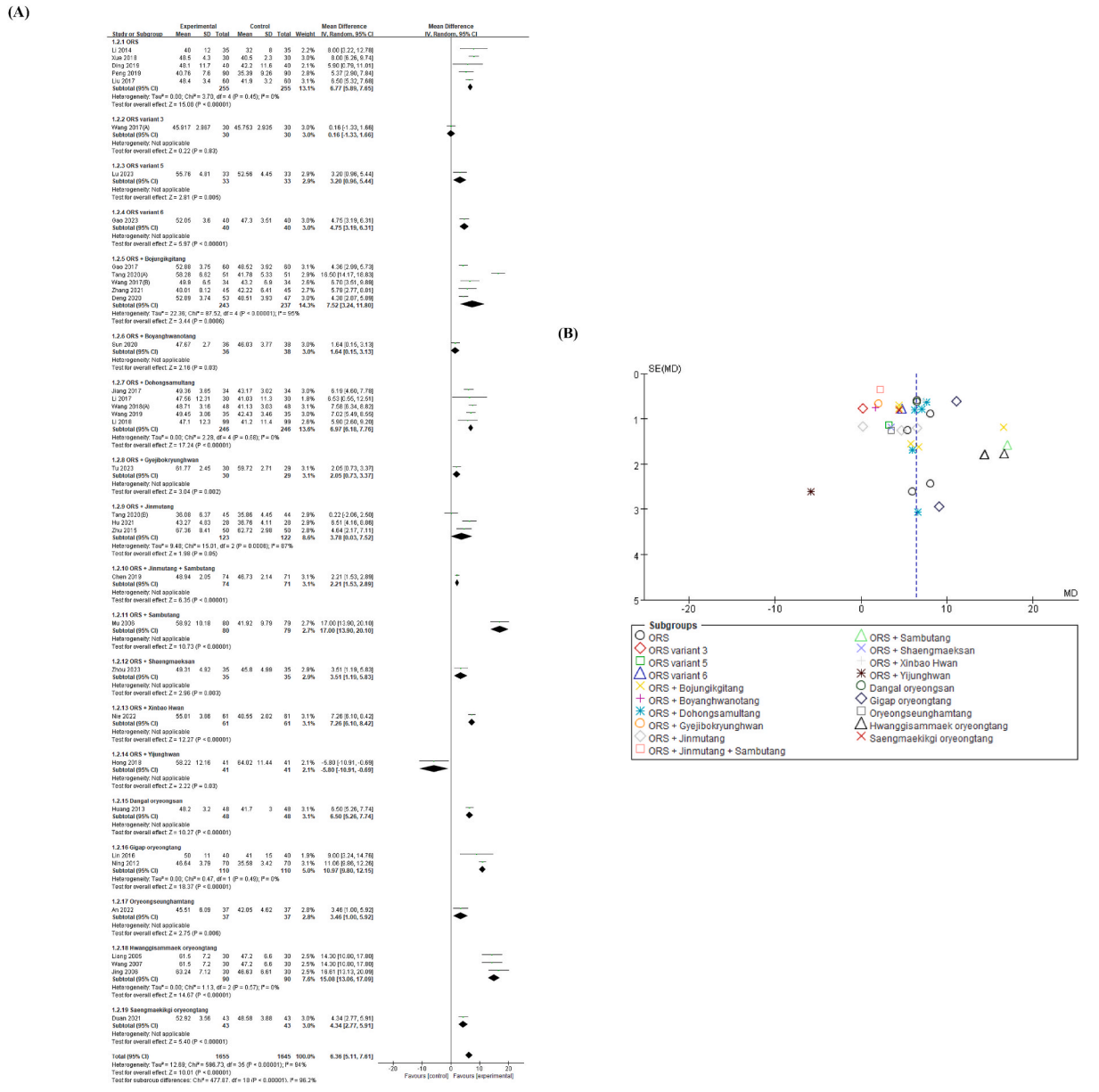


Fig. 4. LVEF forest plot and funnel plot of ORS + CWM vs CWM (A), LVEF forest plot of ORS + CWM vs CWM; (B), LVEF funnel plot of ORS + CWM vs CWM; LVEF, Left ventricular ejection fraction; ORS, Oryeongsan; CWM, conventional Western medicine; SD, Standard deviation.

3.6.12. AEs

The incidence of AEs was reported in sixteen studies [29,31,34,36,37,39,52,53,62,64,65,67–69,72,73]. The incidence of AEs in the treatment group was lower than that in the control group; however, this result was not considered significant (RR: 0.99, 95 % CI: 0.74–1.34, P = 0.38) (Supplement 10).

4. Discussion

Improvement in congestion can significantly improve the quality of life of patients with HF and reduce the incidence of cardiovascular events [79]. Diuretics are the conventional treatment for managing congestion [8]; however, these drugs are associated with

side effects, such as arrhythmia, electrolyte imbalance, or severe dehydration. In particular, loop diuretics reportedly activate the renin-angiotensin-aldosterone and sympathetic nervous systems, which play important roles in HF progression [80]. Traditional Asian medicine may help overcome this limitation.

In traditional East Asian medicine, ORS has been used for "water retention patterns." Since its introduction in "Treatise on Cold Damage Diseases," ORS has been prescribed for "diuresis and warm yang" to relieve various symptoms, such as headache, diarrhea, and dysuria. Accordingly, ORS has been used to treat various disorders involving water metabolism, such as edema, hypertension, hydrocele, urologic diseases, primary insomnia, menstrual cramps, and chronic subdural hematoma [81]. Despite its unknown mechanism of action, ORS may inhibit aquaporins (AQPs) that are distributed in different cell types in the kidneys and central nervous system, thereby modulating abnormal water metabolism in the body. Furthermore, ORS has a bidirectional diuretic effect and induces diuresis in patients with edema or anti-diuresis in patients with dehydration [82]. Based on an animal model study [83], ORS inhibited the expression of aquaporin-2 (AQP2). A previous case report [84] presented decreased AQP2 and cyclic adenosine monophosphate (cAMP) in the urine of patients with chronic HF who received ORS. We presumed that, similar to tolvaptan, ORS improved congestive HF by inhibiting cAMP-AQP2 by interfering with water reabsorption and inducing diuresis. Moreover, in addition to its diuretic effect, ORS has been demonstrated to exert an anti-inflammatory effect by inhibiting AQP3, AQP4, and AQP5, which overexpress chemokines [85].

In this systematic review and meta-analysis, 51 RCTs were examined to elucidate the safety and efficacy of ORS and its variants, alone or in combination with CWM, in patients with HF. According to the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for HF management [86], repeated evaluation of LVEF is appropriate for patients receiving treatments that may significantly affect the structure and function of the heart. Accordingly, LVEF was set as the primary outcome to objectively assess improvement in HF.

The meta-analysis in this study revealed that ORS and its variants significantly improved LVEF in the treatment group. Notably, the improvement in LVEF was statistically significant in 27 of the 30 studies. In addition to LVEF, the improvements in 24-h urine volume, serum BNP and NT-proBNP levels, 6MWT, and Lee's score were found to be statistically significant. These results indicate that ORS improves both subjective symptoms, such as TER, and objective therapeutic indicators. The LVEF was 6.87-fold higher in the treatment group than in the control group. Therefore, ORS is highly likely to positively affect the survival rate of patients with HF.

The MLHF-Q score and incidence of AEs were lower in the treatment group than in the control group; however, the difference was not statistically significant. As the difference in the incidence of AEs was not significant between the control and treatment groups, we assumed that the reported AEs (such as electrolyte imbalance) were caused by CWM rather than ORS. Thus, we concluded that ORS is safe for the treatment of HF. However, in studies that co-administered a placebo with CWM to the control group, improvements in both LVEF and TER were not statistically significant in the treatment group compared to the control group. As only two studies used a placebo, and their sample size (120 participants) was smaller than that of other studies, further RCTs using placebo with more participants are required.

This study had several limitations. First, the homogeneity between participants was low as the included studies had different diagnostic criteria for participants and evaluation criteria for improvement in HF. Some studies did not describe the diagnostic or evaluation criteria in detail, while some did not mention these criteria. Second, as most studies had a high or unclear overall risk of bias and the quality was low, reliability was unclear. Third, despite studies in Korean, English, Japanese, and Chinese being included in the search, a high likelihood of regional and linguistic publication bias is expected as the included studies were all written in Chinese. Fourth, ORS used in each study was mostly decoction, which is one of the main formulations of herbal medicine and is characterized by flexibility in composition and dosage, led to the details of the ORS varied in each study. This prevented us from conducting a dose-dependent effect analysis because we could not analyze standardized ORS. Fifth, few of the included studies classified heart failure according to LVEF, which made it difficult to analyze by type of heart failure. Sixth, since included studies reporting AEs had a maximum observation period of 12 weeks, with the majority of studies having shorter observation periods of 2–4 weeks, the long-term safety of ORS could not be validated. Finally, many of the findings in this study were heterogeneous. In the subgroup analysis by all ORS variant types, we found that the I^2 values were often less than 50 % across items, but in some cases were greater than 50 %. We speculate that ORS variation may have contributed to some of the heterogeneity, but it was not enough to explain all of the findings, which remains a limitation of this study. Therefore, to complement the limitations of this study and increase the level of evidence of ORS in HF, a large-scale, long-term, multicenter randomized controlled study with diagnostic criteria, detailed subtype of HF and standardized ORS should be conducted in the future.

In conclusion, based on this review, co-administering ORS or its variants with CWM improved LVEF, LVEDD, LVESD, 24-h urine volume, and serum BNP and NT-proBNP levels in patients with HF. Therefore, ORS combined with CWM should be considered for patients with HF. In addition, studies using higher levels of evidence for the treatment of HF and highly reliable outcome measures should be conducted in the future.

5. Conclusion

In patients with HF, combining ORS or its variants with CWM significantly improved LVEF, LVEDD, LVESD, 24-h urine output, serum BNP, and NT-proBNP compared with CWM alone, with no significant difference in AEs. ORS and its variants are suggested to be effective and safe alternative treatments for patients with HF. More rigorously designed, high-quality, larger scale global RCTs on ORS for HF should be conducted in the future to solidify the findings of this study.

Ethical approval

None.

Funding

This work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea [grant number RS-2023-KH142002].

Data availability

Data will be available on request.

CRediT authorship contribution statement

Da Hae Jung: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Han-Gyul Lee:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Seungwon Kwon:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Won Jung Ha:** Writing – review & editing. **Seung-Yeon Cho:** Writing – review & editing. **Woo-Sang Jung:** Writing – review & editing. **Seong-Uk Park:** Writing – review & editing. **Sang-Kwan Moon:** Writing – review & editing. **Jung-Mi Park:** Writing – review & editing. **Chang-Nam Ko:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Seungwon Kwon reports financial support was provided by Korea Health Industry Development Institute. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This manuscript was written based on the thesis of Da Hae Jung for a master's degree at Kyung Hee University in 2023.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37830.

PRISMA, 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses; CENTRAL, Cochrane Central Register of Controlled Trials; CiNii, Citation Information by Nii; CNKI, China National Knowledge Infrastructure Database.

References

[1] A.A. Inamdar, A.C. Inamdar, Heart failure: diagnosis, management and utilization, J. Clin. Med. 5 (2016).
[2] A. Groenewegen, F.H. Rutten, A. Mosterd, A.W. Hoes, Epidemiology of heart failure, Eur. J. Heart Fail. 22 (2020) 1342–1356.
[3] P. Ponikowski, S.D. Anker, K.F. AlHabib, M.R. Cowie, T.L. Force, S. Hu, T. Jaarsma, H. Krum, V. Rastogi, L.E. Rohde, U.C. Samal, H. Shimokawa, B. Budi Siswanto, K. Sliwa, G. Filippatos, Heart failure: preventing disease and death worldwide, ESC Heart Fail 1 (2014) 4–25.
[4] N.R. Jones, A.K. Roalfe, I. Adoki, F.D.R. Hobbs, C.J. Taylor, Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis, Eur. J. Heart Fail. 21 (2019) 1306–1325.
[5] J.J. Park, C.J. Lee, S.J. Park, J.O. Choi, S. Choi, S.M. Park, E.Y. Choi, E.J. Kim, B.S. Yoo, S.M. Kang, M.H. Park, J. Lee, D.J. Choi, Heart failure statistics in Korea, 2020: a report from the Korean society of heart failure, Int J Heart Fail 3 (2021) 224–236.
[6] G. Casu, P. Merella, Diuretic therapy in heart failure - current approaches, Eur. Cardiol. 10 (2015) 42–47.
[7] H.A. Cooper, D.L. Dries, C.E. Davis, Y.L. Shen, M.J. Domanski, Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction, Circulation 100 (1999) 1311–1315.
[8] O.J. Ziff, D. Kotecha, Digoxin: the good and the bad, Trends Cardiovasc. Med. 26 (2016) 585–595.
[9] A. Bielecka-Dabrowa, D.P. Mikhailidis, L. Jones, J. Rysz, W.S. Aronow, M. Banach, The meaning of hypokalemia in heart failure, Int. J. Cardiol. 158 (2012) 12–17.
[10] Y.M. Ahn, H.Y. Kim, D.G. Kang, K.W. Cho, H.S. Lee, Herbal medicine (Oryeongsan) for fluid and sodium balance in renal cortex of spontaneously hypertensive rats, Integr Med Res 13 (2024) 101007.
[11] S.K. Kim, S. Lee, M.K. Lee, S. Lee, A systems pharmacology approach to investigate the mechanism of Oryeong-san formula for the treatment of hypertension, J. Ethnopharmacol. 244 (2019) 112129.
[12] N. Ohnishi, K. Nagasawa, T. Yokoyama, The verification of regulatory effects of Kampo formulations on body fluid using model mice, J. Tradit. Med. 17 (2000).
[13] H. Yaku, K. Kaneda, J. Kitamura, T. Kato, T. Kimura, Kampo medicine for the holistic approach to older adults with heart failure, J. Cardiol. 80 (2022) 306–312.
[14] M. Tamano, S. Kato, A. Okamura, T. Hoshino, S. Takahashi, Two cases of severe heart failure in the elderly successfully treated with Goreisan, Kampo Medicine (2018) 275–280.
[15] F. Gao, S. Yi, X. Xu, A meta-analysis of clinical efficacy on Wuling San treatment for chronic heart failure, Int. J. Translat. Community Med. (2018) 1160–1164.

[16] Z. Li, L. Ren, R. Gu, C. Zhou, X. Tong, J. Hu, The efficacy and safety of Wulingsan modified formulas for chronic heart failure patients: a systematic review and meta-analysis, J. Thorac. Dis. 14 (2022) 1232–1242.
[17] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Bmj 372 (2021) n71.
[18] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, P. Jüni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A. Sterne, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, Bmj 343 (2011) d5928.
[19] M. Cumpston, T. Li, M.J. Page, J. Chandler, V.A. Welch, J.P. Higgins, J. Thomas, Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions, Cochrane Database Syst. Rev. 10 (2019). Ed000142.
[20] Y. Xue, Study on the application effect of Wuling Powder in the treatment of chronic heart failure, Cardiovascular Disease J Integrated Traditional Chinese and Western Medicine 6 (91) (2018) +93.
[21] Min Ding, Lu Chao, Clinical study on modified wuling powder combined with routine western medicine for chronic heart failure, J New Chinese Medicine 51 (2019) 63–65.
[22] Xiaoping Peng, Siliang Wu, Deng Limin, Zhao Bin, Ding Jianguang, Zhou Yongzhi, Wang Ling, Clinical effect of Wuling powder combined with furosemide in treatment of chronic heart failure with edema syndrome due to Yang deficiency, Hunan J Traditional Chinese Medicine 35 (2019) 1–3, 15.
[23] Z. Li, Y. Wang, Observation on the clinical effect of Wuling Powder in the treatment of refractory heart failure, China J of Clinical Rational Drug Use 7 (2014) 121–122.
[24] M. Chi, Y. Yan, Clinical observation on the interval use of wuling powder and furosemide in the treatment of chronic heart failure, Strait Pharmaceutical Journal 25 (2013) 99–100.
[25] H. Wenqing, Clinical Observation of Chronic CHF Treated by Warming Yang and Diuretic Guangzhou University of Traditional Chinese Medicine, 2005, p. 36. Guangzhou.
[26] Minghui Liu, Zhao Shuhua, Wuling San in treating 60 cases of chronic heart failure, Western J Traditional Chinese Medicine 30 (2017) 74–75.
[27] L. Zhang, Observation on the efficacy of modified Wuling Powder in the treatment of 28 cases of congestive heart failure, China Medical Herald 3 (2006) 107.
[28] J. Chen, P. Jiang, T. Fan, Application of traditional Chinese medicine method of warming yang and diluting water in the treatment of heart failure, Modern J Integrated Traditional Chinese and Western Medicine 22 (2013) 1751–1752.
[29] T. Jiang, Clinical Observation on 34 Cases of Heart Failure and Edema Treated with Integrated Traditional Chinese and Western Medicine, Chinese J Ethnomedicine and Ethnopharmacy, vol. 26, 2017, pp. 86–87.
[30] T. Qun, Clinical observation on buzhong yiqi decoction and wuling powder combined with sacubitril valsartan in the treatment of chronic heart failure, Chinese Medicine Modern Distance Education of China 18 (2020) 140–142.
[31] P. Tang, Clinical Observation on the Modification of Zhenwu Decoction and Wuling Powder in the Treatment of Acute Decompensated Heart Failure with Yang Deficiency and Water Excessive Syndrome, Hunan University of Chinese Medicine, Changsha, 2020.
[32] W. Li, Clinical observation on treatment of heart failure edema with integrated traditional Chinese and western medicine, J Practical Traditional Chinese Medicine 34 (2018) 945.
[33] L. Yan, Efficacy of the Taohong Siwu decoction plus Wuling San on heart failure and edema, CJCM 9 (2017) 36–37.
[34] X. Yi, M. Liu, Clinical observation on 46 cases of chronic heart failure treated by zhenwu decoction and wuling powder, Yunnan J Traditional Chinese Medicine and Materia Medica 38 (2017) 54–55.
[35] B. Wang, Analysis of the effect of Taohong Siwu Decoction combined with Wuling Powder in the treatment of heart failure and edema, Chin Med J Metall Indus 35 (2018) 687.
[36] L. Wang, Evaluation of the effectiveness of integrated traditional Chinese and Western medicine in the treatment of heart failure complicated with pulmonary edema, Contemporary Medical Symposium 17 (2019) 204–205.
[37] Q. Ren, Analysis on the recovery effect of modified Taohong Siwu Decoction and Wuling Powder in the treatment of heart failure and edema, Cardiovascular Disease J Integrated Traditional Chinese and Western Medicine 8 (2020) 159–160.
[38] J. Hong, X. Hou, H. Chen, Observation on efficacy of Wuling powder and Lizhong pill in the treatment of 41 cases of chronic left ventricular dysfunction, China Prac Med 13 (2018) 93–95.
[39] X. Su, Z. He, S. Luo, W. Sun, Clinical observation on 30 cases of cor pulmonale and heart failure treated with modified Wuling San and Taohong Yin, Hunan J Traditional Chinese Medicine 33 (2017) 42–44.
[40] F. Li, Clinical observation on integrated traditional Chinese and western medicine in the treatment of acute episodes of chronic heart failure, J Practical Traditional Chinese Medicine 32 (2016) 991.
[41] M. Xiao-jing, Clinical observation on treatment of chronic congestive heart failure with combined TCM and WM, Shanxi J of TCM 22 (2006) 24–25.
[42] C. Wang, Y. Zhou, Thirty five cases of chronic congestive heart failure treated with Bazhen Decoction and Wuling Powder, Henan Traditional Chinese Medicine 30 (2010) 989.
[43] Ning Ruihua, Zhi Liqin, Revised Wuling Powder Treat Chronic Heart Failure, vol. 36, J Zhejiang Chinese Medical University, 2012, pp. 143–144.
[44] J. Cao, Observation on the efficacy of integrated traditional Chinese and Western medicine in the treatment of chronic heart failure, J Practical Traditional Chinese Medicine 32 (2016) 148–149.
[45] W. Hu, Observation on the efficacy of Zhenwu Decoction combined with Wuling Powder in the treatment of yang deficiency and water-generated heart failure and its impact on cardiac function, Prevention and Treatment of Cardiovascular Disease 11 (2021) 26–28.
[46] Q. Liu, J. Zhang, Observation on the therapeutic effect of warming yang and diuresis, purging the lungs and relieving asthma in the treatment of pulmonary heart disease and heart failure, Chinese Community Doctors 15 (2013) 188–189.
[47] Y. Lu, Observation on the Efficacy of Huangqi Zhenwu Decoction Combined with Wuling Powder in the Treatment of Chronic Heart Failure, Chinese Community Doctors, vol. 13, 2011, p. 244.
[48] Yingying Nie, Yelin Song, Yinghong Lu, Jingxiang Zhou, Effect of xinbao pill(心宝丸) and wuling powder(五苓散) on serum AngII and gal-3 protein levels in patients with chronic heart failure of edema due to yang deficiency type, Chinese Archives of Traditional Chinese Medicine 40 (2022) 222–225.
[49] Weikeng Gao, Fu Yan, Effect of Buzhong Yiqi Wuling decoction on heart function and plasma levels of NT-proBNP and CysC in patients with chronic heart failure, J. Guangxi Med. Univ. 34 (2017) 1141–1144.
[50] C. Duan, Clinical observation on the treatment of chronic heart failure with shengmai yiqi wuling decoction, CJGMCM 36 (2021) 2935–2937.
[51] Y. Wang, Clinical Study on the Treatment of Chronic Heart Failure with Yang Deficiency and Water Overflow Syndrome with Modified Wuling Powder, Hunan University of Chinese Medicine, 2017, p. 43. Chansha.
[52] W. Zhuanzhuan, Clinical effects of Buzhong Yiqi Wuling decoction combined carvedilol in the patients with chronic heart failure, Contemporary Medical Symposium 17 (2017) 1792–1795.
[53] S. Zongle, Clinical Observation on the Treatment of Chronic Heart Failure of Qi Deficiency and Blood Stasis Type with Buyang Huanwu Decoction and Wuling Powder Changchun University of Chinese Medicine, Changchun, 2020, p. 44.
[54] P. Deng, Clinical efficacy and safety of Buzhong Yiqi Wuling Decoction combined with Western medicine in the treatment of chronic heart failure (CHF), Guide of Chinese Medicine 18 (2020) 179–180.
[55] L. Chen, L. Shu, Seventy four cases of acute left heart failure treated with modified Zhenwu Decoction and Shenfu Decoction Wuling Powder combined with urapidil, Zhejiang J Traditional Chinese Medicine 54 (2019) 427.
[56] L. Bi-wei, Study of Huangqi-Shenmai-Wuling decoction on the treatment of dilated cardiomyopathy complicated with heart failure, J. Guangdong Coll. Pharm. 21 (2005) 345–346.
[57] Lin Lin, Zhi Liqin, Effect of Qijiawuling decoction on serum brain natriuretic peptide and Cardiac function for patients with chronic heart failure, Modern Traditional Chinese Medicine 36 (2016) 14–16.

[58] J. Wang, W. Song, Y. Qu, Modified Astragalus Shenmai Wuling Decoction in the treatment of dilated cardiomyopathy combined with heart failure, Guangdong Medical Journal 28 (2007) 825–826.
[59] L. Zhu, Analysis of the efficacy of Zhenwu Decoction combined with Wuling Powder in the treatment of yang deficiency and water-generated heart failure, Cardiovascular Disease J Integrated Traditional Chinese and Western Medicine 3 (2015) 31–33.
[60] S. Zhang, Observation on the efficacy of Buzhong Yiqi Wuling Decoction combined with metoprolol in the treatment of coronary heart disease complicated with chronic heart failure, Aero. Med. 32 (2021) 198–199.
[61] Jing Xiaoli, Dongping Wang, Jianbo Liu, The clinical observation on Huangqishenmaiwuling decoction for CHF, JETCM 15 (2006) 8–10.
[62] X. Huang, J. Huang, Y. Niu, Y. Liu, J. Gao, D. Meng, Effects of Dange Wuling Powder on cardiac function and left ventricular ejection fraction in patients with chronic heart failure, Yunnan J Traditional Chinese Medicine and Materia Medica 34 (2013) 10–12.
[63] An Tongzhi, Xing Jin, Guimin Zhang, Li Li, Zhang Xin, Clinical observation on wuling shengxian decoction in the treatment of chronic left heart failure, Chinese Medicine Modern Distance Education of China 20 (2022) 66–68.
[64] Cong Gao, Le Zhang, Hong Lin, Jing Zhang, Chan Chen, Clinical effect of modified wuling powder combined with conventional western medicine on patients with chronic heart failure(qi deficiency and blood stasis type), Chinese Archives of Traditional Chinese Medicine 41 (2023) 177–180.
[65] Tu Yadan, Hr Deying, Ren Yi, Clinical observation of wuling powder combined with Guizhi fuling pill on patients with diastolic heart failure(yang deficiency blood stasis and water retention syndrome), Hubei Journal of Traditional Chinese Medicine 45 (2023) 3–7.
[66] Wentao Lu, Bin Yuan, Huichao Zhang, Effect of wuling powder on NT-proBNP, CysC and cTnI levels in patients with chronic heart failure of yang deficiency and water generalization, Information on Traditional Chinese Medicine 40 (2023) 60–65.
[67] Zhou Li-Ji, Yang Shuai, Jiang Guang-Jun, Wei Guo-Ya, Feng Xue-Gong, Clinical study of shengmai powder plus modified wuling powder combined with tolvaptan for the treatment of chronic heart failure accompanied by diuretic resistance, Journal of Guangzhou University of Traditional Chinese Medicine 40 (2023) 316–321.
[68] L. Hui, The Clinical Research of the Treatment of the Acute Attack Stage of Chronic Pulmonary Heart Disease Accompanied Heart Failure by the Method of Invigorating Spleen and Infiltrating Dampness, Chengdu University of Traditional Chinese Medicine, Chengdu, 2019, p. 210.
[69] Chen Yong, Wang Jie, Yang Tong, Du Lei, Cao Jin, Hr De-ying, Ren Yi, Clinical study on five substances powder with Poria combined with cinnamon twig and Poria pill in the treatment of chronic heart failure, Henan Traditional Chinese Medicine 42 (2022) 1143–1146.
[70] Weng Hui-Zhen, Zhao Hua-Yun, Peng Yi, Luo Zhi-Min, Huang Jia-Wen, Effect of modified wuling powder on heart failure with preserved ejection fraction differentiated as yang deficiency and blood stasis syndrome, J Guangzhou University of Traditional Chinese Medicine 37 (2020) 1207–1211.
[71] S. Wang, Clinical efficacy and safety of Buzhong Yiqi Wuling Decoction combined with Western medicine in the treatment of chronic heart failure (CHF), J North Pharmacy 15 (2018) 172–173.
[72] L. Ying, Evaluation of Shenqisiwutang Combined with Wulingsan Clinical Efficacy of Heart and Lung Qi Deficiency and Blood Stasis Type of Chronic Heart Failure with Serum NT-proBNP, Chengdu University of Traditional Chinese Medicine, Chengdu, 2015, p. 57.
[73] S. Du, Clinical Study of SFWLS in the Treatment of Heart Failure Which Is Induced by Coronary Heart Disease (Syndrome of Qi Deficiency and Blood Stagnation), Guangzhou University of Chinese Medicine, Guangzhou, 2011, p. 53.
[74] L. Singming, Effect of guizhi qu shaoyao decoction combined with wuling powder in the treatment of edema due to heart failure, inner Mongolia, J. Tradit. Chin. Med. 41 (2022) 44–45.
[75] Junfeng Liu, Feng Chunhua, Efficacy observation on integrating Chinese and Western medicine on 60 cases of chronic pulmonary heart disease with heart failure, Mod Diagn Treat 21 (2010) 86–87.
[76] M. Pan, Clinical observation on Buzhong Yiqi Wuling Decoction combined with Western medicine in the treatment of chronic heart failure, China Higher Medical Education 7 (142) (2018) 144.
[77] D. Yang, Zhenwu Decoction combined with Wuling Powder to treat 35 cases of yang deficiency and water-generated heart failure, Chinese Medicine Modern Distance Education of China 12 (2014) 35–36.
[78] Z. Yang, Clinical observation on the treatment of dilated cardiomyopathy and heart failure with modified Astragalus shenmai wuling decoction, J Practical Traditional Chinese Medicine 34 (2018) 445.
[79] S. Selvaraj, B. Claggett, A. Pozzi, J.J.V. McMurray, P.S. Jhund, M. Packer, A.S. Desai, E.F. Lewis, M. Vaduganathan, M.P. Lefkowitz, J.L. Rouleau, V.C. Shi, M. R. Zile, K. Swedberg, S.D. Solomon, Prognostic implications of congestion on physical examination among contemporary patients with heart failure and reduced ejection fraction: paradigm-hf, Circulation 140 (2019) 1369–1379.
[80] G.M. Felker, C.M. O'Connor, E. Braunwald, Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil?, Circulation, Heart Fail. 2 (2009) 56–62.
[81] E.-J. Seok, S.-Y. Jeon, W.-B. Kim, D.-H. Kim, S.-I. Lee, An analysis of clinical studies on Oryeong-San, Herbal Formula Science 26 (2018) 341–362.
[82] K.-w.K. Min-jeong Jeong, Ja-yeon Kang, Jee-hyun Yoon, Yoo-min Choi, Hong-jun Kim, Seung-ho Sun, In-soo jang, an overview of the applicability of oryung-san as an antihypertensive agent, The Journal of Internal Korean Medicine 38 (2017) 443–454.
[83] T. Kurita, K. Nakamura, M. Tabuchi, M. Orita, K. Ooshima, H. Higashino, Effects of Gorei-san: a traditional Japanese Kampo medicine, on aquaporin 1, 2, 3, 4 and V2R mRNA expression in rat kidney and forebrain, J. Med. Sci. 11 (2011) 30–38.
[84] K. Kakeshita, T. Imamura, H. Onoda, K. Kinugawa, Impact of Goreisan upon aquaporin-2-incorporated aquaresis system in patients with congestive heart failure, CEN Case Rep 12 (2023) 73–77.
[85] R. Inada, K. Miyamoto, N. Tanaka, K. Moriguchi, S. Kusunoki, Oryeongsan (goreisan) ameliorates experimental autoimmune encephalomyelitis, Intern Med 59 (2020) 55–60.
[86] P.A. Heidenreich, B. Bozkurt, D. Aguilar, L.A. Allen, J.J. Byun, M.M. Colvin, A. Deswal, M.H. Drazner, S.M. Dunlay, L.R. Evers, J.C. Fang, S.E. Fedson, G. C. Fonarow, S.S. Hayek, A.F. Hernandez, P. Khazanie, M.M. Kittleson, C.S. Lee, M.S. Link, C.A. Milano, L.C. Nnacheta, A.T. Sandhu, L.W. Stevenson, O. Vardeny, A.R. Vest, C.W. Yancy, AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/ American heart association joint committee on clinical practice guidelines, Circulation 145 (2022) (2022) e876–e894.