Integrative treatment of herbal medicine with western medicine on coronary artery lesions in children with Kawasaki disease

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Abstract

Background: Kawasaki disease (KD) is a major cause of coronary artery lesions (CALs) in children. Approximately 10% to 20% of children treated with intravenous immunoglobulin are intravenous immunoglobulin-resistant. This study evaluated the efficacy and safety of adding herbal medicine to conventional western medicines versus conventional western medicines alone for CALs in children with KD.

Methods: This study searched 9 electronic databases until August 31, 2021. The inclusion criteria were the randomized controlled trials (RCTs) that assessed the CALs in children with KD and compared integrative treatment with conventional western treatments. Two authors searched independently for RCTs, including eligible articles that fulfilled the inclusion criteria, extracted data, and assessed the methodological quality using the Cochrane risk of bias tool. Meta-analysis was conducted using Cochrane Collaboration’s Review Manager 5.4 software. The effect size was presented as the risk ratio (RR), and the fixed-effect models were used to pool the results.

Results: The finally selected 12 studies included a total of 1030 KD patients. According to a meta-analysis, the integrative treatment showed better results than the conventional treatment in the CAL prevalence rate (RR = 2.00; 95% confidence interval [CI], 1.49–2.71; P < .00001), CAL recovery rate (RR = 1.27; 95% CI, 1.05–1.54; P = .02), and total effective rate (RR = 1.17; 95% CI, 1.11–1.23; P < .00001). Only 2 studies referred to the safety of the treatment. The asymmetrical funnel plot of the CAL prevalence rate indicated the possibility of potential publication bias.

Conclusions: This review found the integrative treatment to be more effective in reducing the CAL prevalence rate and increasing the CAL recovery rate and total effective rate in KD patients than conventional western treatment. However, additional well-designed RCTs will be needed further to compensate restrictions of insufficient trials on safety, methodological quality, and publication bias.

Abbreviations: CAA = coronary artery aneurysm, CAD = coronary artery dilatation, CAL = coronary artery lesion, CI = confidence interval, IL = interleukin, IVIG = intravenous immunoglobulin, KD = Kawasaki disease, RCT = randomized controlled trial, RR = risk ratio, TER = total effective rate, TNF = tumor necrosis factor.

Keywords: coronary artery lesions, herbal medicine, integrative treatment, Kawasaki disease, meta-analysis

1. Introduction

Kawasaki disease (KD) is an acute febrile vasculitis that occurs in children under the age of 5 years. KD was first reported in 1961 by Tomisaku Kawasaki,[1] but the etiopathogenesis is still unknown.[2] KD is presumed to be a complex interaction of genetic factors, infections, and immunity.[2] A diagnosis of KD is made from the clinical symptoms. After several revisions, the
American Heart Association published the most recent guidelines in 2017.[13] Typical KD is diagnosed when a fever is present for at least 5 or more days with at least 4 of the 5 following principal clinical features: extremity changes (acute: edema and erythema, and subacute: periungual peeling of the skin), irregular rash, bilateral conjunctival hyperemia without purulent, erythema of the lips and oral cavity with lip cracking, and cervical lymphadenopathy.[3–5]

The most severe complication of KD is coronary artery lesions (CAL), such as coronary artery dilatation (CAD), coronary artery aneurysm (CAA), coronary artery thrombus, and angina pectoris.[10] In the acute phase, CAD and CAA can be found in 30% and 20% to 25% of children without intravenous immunoglobulin (IVIG) treatment, respectively.[6,7] Although KD has a good prognosis with a mortality of 0.2%, most causes of death are myocardial infarction.[8] Therefore cardiovascular sequelae are important in terms of life prognosis. Approximately 10% to 20% of KD patients do not fulfill the criteria for typical KD and are referred to as atypical KD. The clinical, laboratory, and echocardiography findings can support the diagnosis of atypical KD.[9] Witt et al[10] reported that atypical KD has a high risk of CAA at 20% compared to 7% for typical KD.

The treatment and management guidelines of CALs are divided into 5 risk categories utilizing the Z scores and absolute luminal dimensions.[4,11] The Z-scores are the coronary dimensions that reflect the changes in the coronary artery size according to the child’s age.[11] The highest prognosis risk group was the risk level 5 (Z score ≥ 10, or absolute dimension ≥ 8 mm).[4] The American Heart Association and the American Academy of Pediatrics recommend a combination of IVIG and aspirin to acute KD patients to prevent cardiovascular diseases.[12] As the main treatment, high-dose IVIG is administered as a single dose of 2g/kg infusion over 12 hours for the first 10days. Aspirin is taken at a moderate-dose (30–50mg/kg/day) or high-dose (80–100mg/kg/day) in the acute phase, and a low dose (3–5mg/kg/day) after fever for antithrombotic action.[9] Corticosteroids, tumor necrosis factor (TNF) inhibition, interleukin (IL) 1 inhibition, and calcineurin inhibition are used as adjuvant therapies.[9] Surgery, such as coronary artery stenting[13] or bypass grafting,[14] may be recommended for children with giant aneurysms (diameter ≥ 8 mm).

IVIG generally does not have severe side effects, but there are differences in the adverse events for each biological IVIG product. Studies of the development of aseptic meningitis[15] or coombs benign hemolytic anemia[16] after IVIG have been published. Taking high-dose aspirin after KD has resulted in Reye syndrome.[17] In traditional Chinese medicine, herbal medicine plus conventional western medicine is typically used for CALs in KD patients.[18–20] This study examined the clinical efficacy and safety of integrative therapy (herbal medicine combined with western medicine) through a systematic literature review and meta-analysis.

2. Methods

This systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[21] The protocol of this review was registered in PROSPERO (an International Prospective Register of Systematic Reviews), with the registration number: CRD42020175677 (Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020175677)

The review is ongoing because there are amendments to the inclusion criteria for additional outcome measures for the indicators related to CALs.

2.1. Data sources and search strategy

The following 9 electronic databases were searched: 3 English electronic databases (PubMed, The Cochrane Central Register of Controlled Trials, and EMBASE), 1 Chinese electronic database (Chinese National Knowledge Infrastructure), 3 Korean electronic databases (Science ON, Research Information Sharing Service, and Oriental Medicine Advanced Searching Integrated System), and 2 Japanese electronic databases (J-stage and citation information by National Institute of Informatics). The data was searched until August 31, 2021, and there were no language and year restrictions.

The following search term was used in Pubmed: (“Kawasaki disease”[Title/Abstract] OR “Kawasaki syndrome”[Title/Abstract] OR “mucocutaneous lymph node syndrome”[Title/Abstract]) AND (“herb”[Title/Abstract] OR “decoction”[Title/Abstract] OR “remedy”[Title/Abstract] OR “Chinese medicine”[Title/Abstract] OR “Korean medicine”[Title/Abstract] OR “Kampo”[Title/Abstract] OR “formula”[Title/Abstract] OR “herbal drug”[Title/Abstract] OR “herbal medicine”[Title/Abstract] OR “plant”[Title/Abstract] OR “Chinese drug”[Title/Abstract] OR “Chinese herb”[Title/Abstract] OR “Chinese prescription”[Title/Abstract]) OR “Chinese materia medica”[Title/Abstract] OR “traditional medicine”[Title/Abstract] OR “traditional Chinese medicine”[Title/Abstract] OR “east Asian traditional medicine”[Title/Abstract]).

Slight modification of combinations of key words and free words were performed as a search strategy in other databases using each country’s language. A detailed search strategy for each database is attached separately (see File 1, Supplemental Digital Content, which illustrates the search strategy for each database used in this review, http://links.lww.com/MD2/A884).

2.2. Inclusion and exclusion criteria

Only randomized controlled trials (RCTs) that assessed the CALs in children with KD were included; non-RCTs and gray literature were excluded. Children (<18 years) who fulfilled the criteria for typical KD were included. Only integrative treatment groups were selected for the interventions: oral administration with no restrictions on the type of western medicine. The types of comparators were conventional western drug treatments, and there were no restrictions on the type of western medicine. Selected studies assessed the indicators relative to CALs as the main outcomes; no further limitations were placed on additional outcomes.

2.3. Study selection and data extraction

Two review authors (JYC and SJC) independently searched the electro-database to identify studies. The title and abstracts of the studies were retrieved first, and the full text of the article was viewed in the final stage. Disagreements between 2 reviewers were solved by discussion, but if there was still a lack of consensus, it was resolved through a discussion among all the authors.

Two review authors (JYC and SJC) independently extracted data from the included details of the study: study design (type of RCT, sample size), patient characteristics (duration of illness, range of age, average age, sex, diagnostic criteria), intervention
(herbal medicine combined with western medicine – formulation, frequency, dosages, composition, treatment period), comparators (western medicine), outcome measurement (prevalence rate of CAL, recovery rate of CAL, diameter of the coronary artery, and electrocardiogram abnormality), adverse events and complications (fatigue, nausea, and dizziness), and timing of outcome measurements (ifu period). Tables 1–3 list the main data.

2.4. Quality assessment

Two review authors (JYC and SJC) independently assessed the methodological quality using the Cochrane risk of bias tool\(^{[22]}\) in the included RCTs. The types of bias evaluated were as follows: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of the outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The above list was checked and assessed using the “high”, “low”, and “unclear” risk of bias.

2.5. Statistical analysis

The Review Manager software version 5.4 (The Cochrane Collaboration, London, UK) was utilized for meta-analysis to evaluate the heterogeneity because all the included studies used the same types of populations, interventions, and comparators. For dichotomous variables, the results were calculated as the risk ratios (RR) with a 95% confidence interval (CI). The prevalence rate of CAL, recovery rate of CAL, and total effective rate (TER) are presented as RR by a forest plot to estimate the overall effect. Heterogeneity was assessed using the Higgins $I^2$ index. $I^2 \geq 50\%$ was considered to be indicative of potential heterogeneity, and $I^2 \geq 75\%$ was indicative of considerable heterogeneity. Meta-analysis results showed no heterogeneity ($I^2 = 0\%, P > .1$). Therefore, a fixed-effects model was used for pooling, and additional analyses, such as sensitivity analysis, subgroup analysis, and meta-regression analysis, were not performed. Potential publication bias was estimated using a funnel plot if more than 10 trials were included. Descriptive analysis was conducted when the number of reported studies was only one or when the heterogeneity was too high to be synthesized.

3. Results

3.1. Study selection

One hundred seventy-nine records were identified in the 9 databases searched: 3 studies in Pubmed; 2 studies in the Cochrane Central Register of Controlled Trials; 5 studies in EMBASE; 146 studies in the Chinese national knowledge infrastructure; 12 studies in Science ON; 11 studies in citation information by National Institute of Informatics; no studies in Research Information Sharing Service, Oriental Medicine Advanced Searching Integrated System, and J-stage. After removing the duplicates, 169 records were screened for eligibility. After retrieving the title and abstracts of the studies, 135 articles were excluded for the following reasons: non-RCT, not related to herbal medicine, not related to KD, nonhuman studies, and not using oral herbal medicines. After reviewing the full text of the remaining 34 studies, 22 studies were excluded for the following reasons: gray literature, non-RCT, duplication, and no CAL-related index as the outcome measurement. This study finally included 12 articles\(^{[23–34]}\) in a systematic review and meta-analysis (Fig. 1).

3.2. Characteristics of the studies

Table 1 lists the basic characteristics of the included studies. All trials were conducted in China and were composed of 1 multicenter RCT study\(^{[33]}\) and 11 single-center RCTs\(^{[23–32,34]}\). One thousand thirty patients were included, and the sample sizes varied from 41 to 160. The disease duration was presented in 5 studies\(^{[23,24,28,30,31,33]}\). The patients’ ages ranged from 6 months to 14 years, and their gender was recorded in 11 studies\(^{[23–26,28–34]}\). All were patients diagnosed with KD, and 3 studies\(^{[23,27,33]}\) did not provide clear diagnostic criteria. The most used diagnostic criterion was from the Research Committee of the Ministry of Health of Japan.\(^{[24,26,28,29]}\)

All reviewed studies evaluated the effectiveness of integrative therapy. Only 2 studies\(^{[27,30]}\) took herbal medicine orally or as an enema, and the remaining 10 studies took it orally. Most of the studies added herbal medicine to the western medicine used in the control group. In 1 study,\(^{[29]}\) however, the experimental group was composed of herbal medicine plus the control intervention as well as adding IVIG 350 mg.

All control groups were treated with oral aspirin in common. Eleven studies of gamma globulin,\(^{[21–23,28,30–34]}\) 4 studies of persentine,\(^{[24,25,32,34]}\) 3 studies of adjuvant therapy (antibiotics + energy mixture + electrolyte supplement + Vit C),\(^{[26,27,29]}\) 1 study of prednisone,\(^{[22]}\) 1 study of glucocorticoid,\(^{[31]}\) 1 study of methylprednisolone,\(^{[25]}\) and 1 study of ceftizole\(^{[33]}\) were used. Eleven studies\(^{[23–26,28–34]}\) described the treatment duration from 2 weeks to 3 months (Table 1).

Table 2 lists the results, adverse events, and ifu duration of the studies. All trials evaluated the CAL-related outcome measurements, for example, 10 studies of the CAL prevalence rate,\(^{[24–28,30,31,33,34]}\) 2 studies of CAL recovery rate,\(^{[29,32]}\) and 1 case of electrocardiogram abnormality.\(^{[34]}\) One study used the diameter of the left ventricle, left atrium, coronary artery,\(^{[24]}\) On the other hand, electrocardiogram abnormality\(^{[34]}\) and cardiovascular diameter\(^{[24]}\) had no statistical significance between the experimental group and the control group.

The evaluation indicators related to clinical symptoms were as follows: 9 studies of the clinical symptom disappearance time,\(^{[23,24,26,27,29,30,32–34]}\) 9 studies of the TER,\(^{[24,26,28,30,32–34]}\) 1 study of the number of patients with clinical symptoms,\(^{[24]}\) and 1 study of the clinical symptom scores.\(^{[31]}\)

Laboratory indicators, such as inflammatory factor levels or platelet index, were used in 8 studies.\(^{[23,24,28–33]}\) Adverse effects were reported in only 2 studies.\(^{[29,31]}\) The patients with CAL were followed up in 2 studies.\(^{[26,34]}\) One study\(^{[26]}\) checked the electrocardiogram and echocardiogram for 6 months after discharge, and another study\(^{[34]}\) checked them until 6 years after the CAL had returned to normal (Table 2).

Table 3 lists the ingredients of the herbal medicines. All the herbal medicines used in the included RCTs were decoction, and prescriptions were classified according to the stage in 3 studies.\(^{[23,28,31]}\) The most used frequency was twice a day (b.i.d.) in 7 studies,\(^{[24,28,29,31–34]}\) and the doses also varied from 20 mL to 300 mL with 7 studies (Table 3).\(^{[23–25,27,29,31,32]}\)

3.3. Assessment of methodological quality

Of the 12 included studies, 3 studies were assessed as having a “low risk” of bias for random sequence generation by using the random number table method.\(^{[24,28,33]}\) In contrast, 1 study was rated as a “high risk” of bias because they used the even and odd order of treatment sequence.\(^{[23]}\) The remaining 8 studies were
evaluated as “unclear risk.” Only 1 study was measured to have a “low risk” of bias for allocation concealment by using the Statistical Package for the Social Sciences version 12.0 (IBM SPSS Statistics, Armonk, New York, USA), and the rest of the studies were evaluated to have an “unclear risk” of bias. Only the study of Liu divided the subjects into the experiment and control group using a random double-blind method. Thus, there was a “low risk” of bias for the blinding of participants, personnel, and outcome assessment. The remaining 11 trials were rated as a “high risk” of bias for the blinding of participants, personnel, and outcome assessment.

Figure 1. PRISMA flow diagram of the study screening and selection process. CENTRAL = The Cochrane Central Register of Controlled Trials, CiNii = Citation Information by National Institute of Informatics, CNKI = Chinese National Knowledge Infrastructure, OASIS = Oriental Medicine Advanced Searching Integrated System, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized controlled trial.
| First author | Sample size (E/C) | Study design | Duration of illness (mean) | Age (mean) | Gender (M/F) | Diagnostic criteria | Experimental intervention (E) | Control intervention (C) | Periods |
|--------------|------------------|--------------|----------------------------|------------|--------------|--------------------|-----------------------|---------------------------|---------|
| An (2017)    | 122 (61/61)      | Single-center RCT | E: 1–7 (3.31 ± 1.39) d C: 2–6 (3.15 ± 1.24) d | E: 1–6 (3.39 ± 0.67) yr C: 1–7 (3.78 ± 0.75) yr | E: 36/25 C: 35/26 | NR | HM + (C) | 1 mo |
| Chen (2014)  | 104 (32/72)      | Single-center RCT | E: (8.7 ± 2.2) d C: (9.4 ± 3.1) d | E: (2.1 ± 1.3) yr C: (2.2 ± 2.4) yr | E: 22/10 C: 48/24 | (1) RCMU, ACA, AAP | HM + (C) | 3 mo |
| Da (2013)    | 86 (46/40)       | Single-center RCT | | 8 mo–6 yr | 55/29 | Zhufutang practical pediatrics (7th edition) | HM + (C) | 3 mo |
| Geng (2005)  | 45 (23/22)       | Single-center RCT | | | | | | |
| Li (2009)    | 68 (34/34)       | Single-center RCT | | 7 mo–14 yr | NR NR | | HM + (C) | NR |
| Liao (2008)  | 48 (25/23)       | Single-center RCT | E: (5.21 ± 3.4) d C: (5.45 ± 2.9) d | E: (3.1 ± 4.2) yr C: (2.6 ± 5.4) yr | E: 19/66 C: 16/7 | RCMU | HM + (C) | 4 wk |
| Liu (2017)   | 60 (30/30)       | Single-center RCT | E: (3.29±1.17) yr C: (3.56±1.25) yr | E: 16/14 C: 15/15 | RCMU | HM + (C) + IVIG 350 mg/kg q.d. for 5 d | 4 wk |
| Ren (2016)   | 160 (80/80)      | Single-center RCT | E: 3–6 (4.2 ± 2.1) d C: 2–7 (4.5 ± 2.3) d | E: 1–7 (3.3 ± 1.2) yr C: 1–6 (3.1 ± 1.3) yr | E: 45/25 C: 47/33 | Japanese MCLS Research Society (2002) | HM + (C) | 4 wk |

(continued)
| First author (yr)   | Sample size (E/C) | Study design | Duration of illness (mean) | Age (mean) | Gender (M/F) | Diagnostic criteria | Experimental intervention (E) | Control intervention (C) | Periods |
|---------------------|------------------|--------------|----------------------------|------------|--------------|---------------------|-------------------------------|---------------------------|---------|
| Sha (2021)[31]      | 82 (41/41)       | Single-center RCT | E: (3.41 ± 1.01) d   | C: (3.36 ± 1.02) d | E: 27/14     | (1) AHA (2) Phase of burnt of both Q and Yin | HM + (C)                      | (1) IGIV 2 g/(kg.d) q.d. for 10–12 h (2) Oral aspirin 50 mg/(kg.d) t.i.d. (→5 mg/[kg.d] q.d.) | 2 wk    |
| Tian (2007)[32]     | 41 (20/21)       | Single-center RCT | NR                        | E: 2–7 yr   | C: 2–6 yr | Pediatrics of TCM | HM + (C)                      | (1) IVIG 1 g/(kg.d) q.d. for 2 d (2) Oral prednisone 3 mg/(kg.d) for 2 wk (3) Oral persetine 5 mg/(kg.d) for 4 wk (4) Oral aspirin 50 mg/(kg.d) (→5 mg/[kg.d] for 4 wk when ESR return to normal) | 4 wk    |
| Wang (2018)[33]     | 142 (70/72)      | Multicenter RCT | E: 1–10 (5.18 ± 1.46) d | C: 1–10 (5.08 ± 1.40) d | E: 44/26     | NR | HM + (C)                      | (1) Ceftriaxone 100 mg/(kg.d) IV for acute phase (2) IVIG 1 g/(kg.d) for 2 d (3) Oral aspirin 30–50 mg/(kg.d) (→3–5 mg/[kg.d]) | (1) E: 21 d (2) C: 6–12 wk |
| Wei (2006)[34]      | 92 (48/44)       | Single-center RCT | NR                        | 6 mo–9 yr   | 54/38        | 3rd International Conference on KD | HM + (C)                      | (1) Oral aspirin 30–50 mg/(kg.d) (→3–5 mg/[kg.d]) q.d. (2) Gamma globulin 1 g/(kg.d) for 2 d (3) Oral persentine 3–5 mg/[kg.d] t.i.d. for 2 d | (1) E: 1 mo (2) C: 3 mo |

→ = means to change to the following after fever, AAP = American Academy of Pediatrics, ACA = American Cardiovascular Association, AHA = American Heart Association, b.i.d. = twice a day, C = control intervention, CAL = coronary artery lesion, d = day, E = experimental intervention, ESR = erythrocyte sedimentation rate, F = female, h = hour, HM = herbal medicine, IGIV = Immune globulin intravenous, IV = intravenous, KD = Kawasaki disease, M = male, m = month, MCLS = mucocutaneous lymph node syndrome, NR = not reported, q.d. = once a day, q.i.d. = 4 times a day, RCMHJ = Research Committee of the Ministry of Health of Japan, t.i.d. = 3 times a day, TCM = traditional Chinese medicine, w = week, y = year.
| First author (yr) | Outcome measurements                                                                 | Intergroup differences                  | Adverse events & complication | Follow-up       |
|-------------------|---------------------------------------------------------------------------------------|----------------------------------------|------------------------------|-----------------|
| An (2017)[23]    | (1) TER (2) SDT: (i) fever (ii) lymph node enlargement (iii) rash (3) CAL prevalence rate: (i) CAA (ii) CAD (4) Laboratory indicators - Inflammatory factor levels: (i) IL-6 (ii) IL-8 (iii) TNF-α | (1), (2), (3), (4) *P* < .05, in favor of the experimental group | NR              | NR              |
| Chen (2014)[24]  | (1) the number of patients with clinical symptoms: (i) red in the throat (ii) rash (iii) bright red and chapped lips (iv) lymph node enlargement (v) sclerosis of limbs and feet (2) SDT: fever (3) Laboratory indicators: (i) WBC (ii) PLT (iii) CRP (iv) ESR (4) CAL prevalence rate (5) Cardiovascular diameter: (i) left atrium anteroposterior (ii) left ventricular anteroposterior diameter (iii) left coronary artery diameter (iv) right coronary artery diameter | (1), (2), (3) (i), (3) (iii), (3) (iv), (4) No statistical difference. (3) (ii) *P* < .05, in favor of the experimental group | NR              | NR              |
| Da (2013)[25]    | (1) TER (2) CAL prevalence rate                                                      | (1), (2) *P* < .05, in favor of the experimental group | NR              | NR              |
| Geng (2005)[26]  | (1) TER (2) SDT: fever (3) CAL prevalence rate: CAD                                  | (1), (2), (3) *P* < .01, in favor of the experimental group | NR              | 6 mo            |
| Li (2009)[27]    | (1) SDT: (i) fever (ii) lymph node enlargement (iii) rash (iv) platelet recovery (v) mucosal hyperemia recovery (vi) hospital visit period (2) TER (3) CAL prevalence rate: CAD (1) (i), (3) (iii), (1) (iv), (1) (vi), (2), (3) *P* < .05, in favor of the experimental group | NR              | NR              |
| Liao (2008)[28]  | (1) Laboratory indicators - platelet index: (i) PLT (ii) MPV (iii) PDW (iv) PCT (2) CAL prevalence rate | 2, 3, 4 wk of (1) (i), 2, 3 wk of (1) (ii) & (1) (iii), (2) *P* < .05, in favor of the experimental group | NR              | NR              |
| Liu (2017)[29]   | (1) TER (2) SDT (3) Laboratory indicators: (i) CRP (ii) WBC (iii) ESR (iv) PLT (4) CAL recovery rate: CAD (5) Adverse effect | (1), (2), (3) (i), (3) (iii), (4) *P* < .05, in favor of the experimental group | Fatigue, nausea, dizziness No statistically significant | NR              |
| Ren (2016)[30]   | (1) TER (2) SDT: (i) fever (ii) rash (iii) mucosal hyperemia (iv) lymph node enlargement (3) CAL prevalence rate: (i) CAD (ii) CAA (4) Laboratory indicators - inflammatory factor levels: (i) IL-6 (ii) IL-8 (iii) TNF-α | (1), (2), (3) (ii), (4) *P* < .05, in favor of the experimental group | NR              | NR              |
| Sha (2021)[31]   | (1) TER (2) Clinical symptom scores: (i) fever (ii) conjunctival hyperemia (iii) oral mucosal changes (iv) rash (v) limb changes (vi) lymphadenopathy (3) Laboratory indicators: (i) NT- | (1), (4) *P* < .05 & (2), (3) *P* < .01 in favor of the experimental group | None            | NR              |

(continued)
participants and personnel category, and “unclear” bias for blinding of the outcome assessment category. One study was judged as having an “unclear risk” of bias for incomplete outcome data because the number of men and women and the CAL prevalence rate differed from those described in the text, abstract, and table. Another study was ranked as having a “high risk” of bias because the follow-up electrocardiogram and echocardiogram results of patients with coronary artery complications were missing, but the remaining had a “low risk” of bias.[34] All 12 studies were judged to have a “low risk” of bias for selective reporting. Three studies rated the “unclear risk” of the other bias with possible baseline imbalances in the experimental and control groups.[29,32,33,34] One study added not only herbal medicine but also IVIG to the control intervention in the integrative treatment group. The other 2 studies had only herbal medicine but also IVIG to the control intervention in the integrative treatment group.[29,32,33,34] The remaining 9 studies had a “low risk” of bias (Figs. 2 and 3).

3.4. Meta-analysis results

3.4.1. CAL prevalence rate. Ten studies evaluated the CAL prevalence rate (CAD, CAA, and CAT) and included a total of 949 patients.[23–28,30,31,33,34] The intergroup differences were reported as P < .05 in 8 studies,[23,25,27,28,30,31,33,34] and P < .01 in 1 study.[26] Hence, the results were statistically significant in favor of integrative treatment group. On the other hand, 1 study reported there was no statistically significant difference between the 2 groups.[24] Meta-analysis revealed no heterogeneity (P = .54, I² = 0), and a fixed model was used for data pooling. The western medicine treatment group had a significantly higher prevalence of CAL than the integrative treatment group (RR = 2.00; 95% CI, 1.49–2.71; P < .00001) (Fig. 4).

3.4.2. CAL recovery rate. Two studies assessed the CAL recovery rate after 4 weeks of treatment, and a total of 81 patients were included.[29,32] In the study by Liu,[29] 30 each in the experimental and control groups had CAL and the CAL recovery rate was evaluated. On the other hand, the study by Tian[32] showed that 11 out of 20 experimental groups and 10 out of 21 control groups had CAL. In both studies, the recovery rate was significantly higher than that of the control group (P < .05). There was no heterogeneity (P = .49, I² = 0) due to the meta-analysis, and the number of trials included was minimal, so a fixed model was used. The integrative treatment group had a higher CAL recovery rate of 27% than the western treatment group (RR = 1.27; 95% CI, 1.05–1.54; P = .02) (Fig. 5).

3.4.3. Total effective rate. All 9 studies reporting the TER were included in the meta-analysis, and a total of 956 patients were included.[23,25–30,33,34] The intergroup differences were reported as P < .05 in 8 studies[23,25,27–30,33,34] and P < .01 in 1 study,[26] so they were statistically significant in favor of the integrative treatment group. According to the meta-analysis, there is no heterogeneity (P = .47, I² = 0%), and a fixed model was used for the estimation. The integrative treatment group showed a significantly higher TER score of 17% than the western medicine treatment group (RR = 1.17; 95% CI, 1.11–1.23; P < .00001) (Fig. 6).
### Table 3
Composition of herbal medicines in the included studies.

| First author (yr) | Intervention | Administration | Frequency | Dosages | Composition |
|-------------------|--------------|----------------|-----------|---------|-------------|
| An (2017) [23]    | Self-made prescription | OA | NR | 200–300 mL | Flos Lonicerae 2 g, Codonopsis lanceolata 3 g, Fructus Forsythiae Suspensae 2 g, Menthae Herba 5 g, Glycyrrhizeae Radix 3 g, Gypsum fibrosum 2 g, Linopis tuber 3 g, Lophatheri Herba 5 g |
| Chen (2014) [24]  | Qingreliangxue prescription | OA | b.i.d. | <1 yr: 20 mL, 1–3 yr: 50 mL, >3 yr: 100 mL | Gypsum fibrosum 15 g, Anemarrhenae Rhizoma 9 g, Flos Lonicerae 6 g, Fructus Forsythiae Suspensae 6 g, Scutellariae Radix 9 g, Radix Salviae Miltiorrhizae 9 g, Lophatheri Herba 5 g, Moutan Radicis Cortex 9 g, Radix Rehmanniae 8 g, Gardeniae Fructus 6 g, Antelopis Cornu 0.15 g |
| Da (2013) [25]    | (1) Yinqiao-san hwajae: Syndrome of disease of both Wei and Qi (2) Modified Qingwenbaidu decoction: Syndrome of burntof both Qi and Yin (3) Huangqishengmai decoction hwajae: Syndrome of deficiency of both Qi and Yin | OA | NR | <1 yr: 40–60 mL, 1–3 yr: 60–120 mL, >3 yr: 120–200 mL | (1) Flos Lonicerae 6 g, Fructus Forsythiae Suspensae 6 g, Menthae Herba 6 g, Arctii Fructus 6 g, Tamaricis Ramulus 6 g, Scrophulariae Radix 6 g, Phragmitis Rhizoma 6 g If high fever and irritability, plus Gypsum fibrosum 12 g, Anemarrhenae Rhizoma 6 g If lymph node enlargement, plus Fritillariae Bulbus 8 g, Bupleuri Radix 6 g, Paeoniae Radix rubra 6 g, Gypsum fibrosum 12 g, Bubali Cornu 6 g, Moutan Radicis Cortex 6 g, Anemarrhenae Rhizoma 6 g, Gardeniae Fructus 6 g, Scrophulariae Radix 6 g, Radix Rehmanniae 6 g, Carthami Flos 6 g, Radix Salviae Miltiorrhizae 6 g If severe hot injury to Yin, plus Litopis tuber 6 g, Dendrobii Herba 6 g If enlarged lymph nodes in the neck, plus Primulae Herba 6 g, Taraxaci Herba 6 g If loss of appetite, plus Crataegi Fructus 6 g, Hoelen 6 g If low fever ongoing, plus Lycii Cortex Radicis 6 g, Gypsotheca Radix 6 g If severe fever, plus Trichosanthis 10 g, Bupleuri Radix 10 g, Imperatae Rhizoma 20 g If severe sweating & metal loss, plus Astragali Radix 15 g If loss of appetite, plus Galls Stomachichum Corium 10 g, Hordei Fructus Germinatus 10 g, Massa Medicata Fermentata 10 g, Cnidium of cinale Makino 8 g If if bloating, plus Saussureae Radix 10 g, Angelicae Gigantis Radix 6 g, Radix rubra 6 g, Cicadae Periostacum 6 g |
| Geng (2005) [26]  | Qingrehuayu decoction | OA | NR | NR | Gypsum fibrosum 30 g, Anemarrhenae Rhizoma 6 g, Bubali Cornu 15 g, Flos Lonicerae 10 g, Fructus Forsythiae Suspensae 10 g, Scutellariae Radix 10 g, Moutan Radicis Cortex 10 g, Paeoniae Radix rubra 10 g, Radix Salviae Miltiorrhizae 10 g, Gypsum fibrosum 18 g, Radix Rehmanniae 8 g, Oryzae Semen 6 g, Phellodendri Cortex Radicis 6 g, Glycyrrhizeae Radix 6 g If severe fever, plus Trichosanthis 10 g, Bupleuri Radix 10 g, Imperatae Rhizoma 20 g If severe sweating & metal loss, plus Astragali Radix 15 g If loss of appetite, plus Galls Stomachichum Corium 10 g, Hordei Fructus Germinatus 10 g, Masala Medicata Fermentata 10 g, Cnidium of cinale Makino 8 g |
| Li (2009) [27]    | Modified Baihu decoction | OA or retention enema | NR | 200 mL | Gypsum fibrosum 30 g, Anemarrhenae Rhizoma 6 g, Bubali Cornu 15 g, Flos Lonicerae 10 g, Fructus Forsythiae Suspensae 10 g, Scutellariae Radix 10 g, Moutan Radicis Cortex 10 g, Paeoniae Radix rubra 10 g, Radix Salviae Miltiorrhizae 10 g, Gypsum fibrosum 18 g, Radix Rehmanniae 8 g, Oryzae Semen 6 g, Phellodendri Cortex Radicis 6 g, Glycyrrhizeae Radix 6 g If severe fever, plus Trichosanthis 10 g, Bupleuri Radix 10 g, Imperatae Rhizoma 20 g If severe sweating & metal loss, plus Astragali Radix 15 g If loss of appetite, plus Galls Stomachichum Corium 10 g, Hordei Fructus Germinatus 10 g, Massa Medicata Fermentata 10 g, Cnidium of cinale Makino 8 g |
| Liao (2008) [28]  | (1) Modified Qingwen decoction for fever (2) Modified Zhuyeshigao decoction after fever | OA | b.i.d.–t.i.d. | NR | (1) Bubali Cornu 15 g, Radix Rehmanniae 8 g, Scrophulariae Radix 8 g, Lophatheri Herba 5 g, Radix Salviae Miltiorrhizae 8 g, Flos Lonicerae 8 g, Fructus Forsythiae Suspensae 8 g, Moutan Radicis Cortex 8 g, Paeoniae Radix rubra 8 g, Glycyrrhizeae Radix 8 g If severe fever, plus Trichosanthis 10 g, Bupleuri Radix 10 g, Imperatae Rhizoma 20 g If severe sweating & metal loss, plus Astragali Radix 15 g If loss of appetite, plus Galls Stomachichum Corium 10 g, Hordei Fructus Germinatus 10 g, Massa Medicata Fermentata 10 g, Cnidium of cinale Makino 8 g |
| Liu (2017) [29]   | Jieduhuayu decoction | OA | b.i.d. | 200 mL | Bubali Cornu 10 g, Flos Lonicerae 10 g, Fructus Forsythiae Suspensae 10 g, Lumbini 10 g, Radix Salviae Miltiorrhizae 6 g, Angelicae Gigantis Radix 6 g, Radix rubra 6 g, Cicadae Periostacum 6 g |
| Ren (2016) [30]   | Self-made prescription | OA or retention enema | NR | NR | Flos Lonicerae 3–12 g, Fructus Forsythiae Suspensae 3–10 g, Gypsum fibrosum 5–20 g, Lophatheri Herba 5–10 g, Radix Salviae Miltiorrhizae 5–20 g |

(continued)
| First author (yr) | Intervention | Administration | Frequency | Dosages | Composition |
|-------------------|--------------|----------------|-----------|---------|-------------|
| Sha (2021)[31] | Modified Huanglianjiued decoction plus Baihu decoction | OA | 6 mo–3 yr: t.i.d.; 4–6 yr: q.i.d. | 6 mo–3 yr: 50–100 mL; 4–6 yr: 150 mL | Gypsum fibrosum 25 g, Scrophulariae Radix 10 g, Paeoniae Radix rubra 10 g, Gardeniae Fructus 10 g, Anemarrhenae Rhizoma 10 g, Fructus Forsythiae Suspensa 10 g, Lophatheri Herba 10 g, Radix Rehmanniae 6 g, Moutan Radicis Cortex 6 g, Glycyrrhizae Radix 6 g, Platycodi Radix 6 g, Bubali Cornu 3 g, Scutellariae Radix 3 g, Coptidis Rhizoma 2 g, | |
| Tian (2007)[32] | Jiexihuayu decoction | OA | b.i.d. | 200 mL | Flos Lonicerae 10 g, Fructus Forsythiae Suspensa 10 g, Bubali Cornu 10 g, Radix Rehmanniae 10 g, Lumbinicus 10 g, Angelicae Gigantis Radix 6 g, Paeoniae Radix rubra 6 g, Radix Salviae Miltiorrhizae 6 g, Cicadae Periostacum 6 g, | |
| Wang (2018)[33] | (1) Yinqiao-san: Phase of disease of both Wei and Qi (< 5 d) (2) Qingying decoction: Phase of burnt of both Qi and Yin (6–10 d) (3) Shashenmaidong decoction: Phase of deficiency of both Qi and Yin (11–21 d) | OA | b.i.d. | NR | (1) Phragmitis Rhizoma 15 g, Flos Lonicerae 10 g, Lophatheri Herba 10 g, Fructus Forsythiae Suspensa 10 g, Schizonepetae Spica 6 g, Menthae Herba 6 g, Cicadae Periostacum 3 g, (2) Bubali Cornu 15 g, Radix Rehmanniae 8 g, Radix Salviae Miltiorrhizae 8 g, Flos Lonicerae 8 g, Fructus Forsythiae Suspensa 8 g, Lophatheri Herba 5 g, Glycyrrhizae Radix 4 g, (3) Adenophorae Radix 15 g, Lithospermi Tuber 15 g, Trichosanthis 15 g, Polygonati Rhizoma 10 g, Dolichoris Semen 6 g, Glycyrrhizae Radix 6 g, | |
| Wei (2006)[34] | Qingreibiumdihuo prescription | OA | b.i.d.–q.i.d. | NR | Radix Rehmanniae, Radix Salviae Miltiorrhizae, Bubali Cornu, Moutan Radicis Cortex, Flos Lonicerae, Fructus Forsythiae Suspensa, Cnidium officinale Makino, Carthami Flos, Curcumae Tuber, Gypsum fibrosum, Paeoniae Radix rubra If lymph nodes enlargement, plus Prunellae Herba If dry lips, plus Dendrobii Herba, Trichosanthis If red pharynx, plus Folium isatidis, Sophorae Subprostratae Radix If fever subsides, reduce Gypsum fibrosum, Bubali Cornu | |

b.i.d. = twice a day, d = day, m = month, NR = not reported, OA = oral administration, q.i.d. = 4 times a day, t.i.d. = 3 times a day, y = year.
3.5. Adverse events

Two studies referred to the safety of treatment. [29,31] Liu [29] reported 1 case of fatigue and 1 case of dizziness were reported in the experimental group and 1 case of nausea was reported in the control group, but there was no statistical significance between the 2 groups. In the study by Sha and Zhao, [31] there were no side effects, such as allergies, vomiting, and diarrhea, in both groups during the safety comparison treatment period. There were no abnormalities in liver function and kidney function tests before and after patient treatment.

3.6. Assessment of publication bias

The asymmetrical funnel plot of the CAL prevalence rate indicated the possibility of potential publication bias. The remaining outcome measurements did not estimate the publication bias because less than 10 trials were included (Fig. 7).

4. Discussion

KD can induce inflammation in the coronary artery, pericardium, myocardial, and valve, and can be accompanied by changes in the electrocardiogram, such as arrhythmia, extended PR intervals, nonspecific ST waves, and T wave changes. [4] In the acute phase, necrotizing arteritis that forms CAA and destroys arterial structures is characteristic, [35] and arterial invasion extends from the proximal region to the distal region. [4] The long-term sequelae of CAA include subacute or chronic inflammation and lumen myofibroblast proliferation, often lasting into adulthood. [35] Moreover, giant aneurysms (Z score ≥ 10, diameter ≥ 8 mm) contribute to early morbidity and mortality. [36]

CAL evaluations are observed mainly with an echocardiogram that can reflect the luminal dimensions of coronary arteries and changes in arterial function. Magnetic resonance imaging, computed tomography, and angiography can be used when necessary. [37] The high-risk factors of CALs were male sex, age < 12 months or > 8 years, fever duration > 10 days, leukocytosis > 15,000 per mm³, low hemoglobin (< 10 g/dL), thrombocytopenia, and hypoalbuminemia. [38]

Although the vascular complications tended to decrease significantly, the prevalence of intractable KD is increasing every year. [39] One study reported that 10% to 20% of children treated with IVIG are IVIG-resistant. [40] New KD treatments, such as infliximab, are being developed, but their effectiveness and safety are unclear. [39] Integrative therapies, including herbal medicines, are also being used as an alternative.

Among the herbal medicines, oral therapy was chosen as an intervention because it is inexpensive and convenient, easy to access, and relatively safe because it is absorbed through the digestive system. Other dosage methods were excluded because the heterogeneity due to the absorption rate or methodological differences would increase.

4.1. Summary of evidence

Meta-analysis revealed a good therapeutic effect on the CAL prevalence rate, CAL recovery rate, and TER (P < .05). This suggests that integrative therapy effectively eliminates the symptoms of KD and has potential for the prevention and treatment of CAL.

According to the Weiqi and Yingxue differentiation in traditional oriental medicine, the treatment methods of CALs can be distinguished into “three stages of treatment focusing on removing blood stasis”. Herbal medicines concentrate on clearing heat and detoxification in the acute phase, supplementing Qi and nourishing Yin in the subacute phase, as well as promoting blood circulation and removing blood stasis in the recovery phase. [19] According to Hu, [41] “eliminating blood stasis by activating blood circulation” aims to control the increase in
Figure 3. Risk of bias summary.

Figure 4. Forest plot of the CAL prevalence rate of integrative treatment compared with conventional western treatment. CAL = coronary artery lesion, CI = confidence interval, HM = herbal medicine, WM = western medicine.

Figure 5. Forest plot of the CAL recovery rate of integrative treatment compared with conventional western treatment. CAL = coronary artery lesion, CI = confidence interval, HM = herbal medicine, WM = western medicine.
platelets and lower the blood viscosity, which has positive implications for the prevention and treatment of CAA and CAT. Chen et al.[18] reported that the integrative medicine group using Qing Re Liang Xue decoction had a shorter fever duration and lower IL-33 and TNF-α levels than those in the western medicine group. Inflammatory factors, such as IL-6, TNF-α, C-reactive protein, and adhesion molecules, participate in the formation of blood stasis directly or indirectly,[42] so integrative treatment can improve the hypercoagulable state of KD patients.

Seventeen prescriptions were included in 12 studies. Modified Yinqiao-san,[25,33] modified Baihu decoction, [27,31] modified Qingying decoction, [28,33] and modified Jiedu Huayu decoction, [29,32] were overlapped in 2 different studies. The Yinqiao-san has the function of sending toxins out of the surface with spicy and cool medicinal properties, clearing heat, and detoxification.[33] The Baihu decoction has the function of clearing away heat and forming fluid.[31] The Qingying decoction has the function of cooling Ying, detoxification, diathermy, and nourishing yin.[33] The Jiedu Huayu decoction can clear heat, detoxify, promote blood circulation, and remove blood stasis.[32]

For the 5 most used ingredient herbs, Fructus Forsythiae Suspensae had the most with 12, Flos Lonicerae and Radix Rehmanniae with 11, Radix Salviae Miltiorrhizae, and Gypsum followed by 10. Pharmacologically, Fructus Forsythiae Suspensae and Lonicerae Flos showed antibacterial, antiviral, antipyretic, and anti-inflammatory activities.[43,44] Radix Rehmanniae regulates the functions of the kidney and liver and improves blood circulation.[45] Radix Salviae Miltiorrhizae can also act as an antiarrhythmic, anticoagulant, and antithrombotic, and have a neuroprotective role, so it has myocardial

![Figure 6. Forest plot of the TER of integrative treatment compared with conventional western treatment. CI = confidence interval, HM = herbal medicine, TER = total effective rate, WM = western medicine.](image1)

![Figure 7. Funnel plot of the CAL prevalence rate. CAL = coronary artery lesion, RR = risk ratio.](image2)
protective effects.\textsuperscript{[46]} Gypsum fibrosum has antipyretic activity\textsuperscript{[47]} and removes heat to cool the blood.

The multipound of traditional oriental medicine has a drug effect on multitargets through synergistic effects. The degree of structural similarity between traditional oriental medicine compounds and human metabolites is much higher than that of human metabolites and conventional small-molecule drugs.\textsuperscript{[48]}

Therefore, when using herbal medicines as a multipound rather than using each individual ingredient as a single pound, there are potential positive effects in improving the efficacy, reducing side effects, and controlling symptoms compared to western medicine.

Only 2 RCTs\textsuperscript{[29,31]} referred to adverse events and complications. One study reported 1 adverse event group in the experimental and control group, but there was no significant difference between the 2 groups.\textsuperscript{[29]} Another study reported no side effects in each of the 2. Therefore, no firm conclusions about safety could be drawn.\textsuperscript{[31]}

4.2. Comparison to previous reviews

One systematic review\textsuperscript{[20]} included intervention measurements as Weiqi and Yingxue differentiation treatments plus conventional western medicine treatments for KD patients. The study performed a meta-analysis for significantly effective rate and TER. On the other hand, all RCTs using herbal medicines taken in the oral form were included, even if they did not use Weiqi and Yingxue differentiation treatment. In addition, the meta-analysis included the CAL prevalence rate, CAL recovery rate, and TER. The findings of this review suggested that integrative therapy was competent at the coronary artery abnormality and clinical effectiveness compared to conventional western medicines ($P < .05$). This study provides evidence for future studies.

4.3. Limitation

This study has several limitations. First, all RCTs included were conducted in China, which could cause location bias. Second, there were only 2 studies\textsuperscript{[29,31]} that reported adverse events and 2 studies\textsuperscript{[26,34]} that conducted a follow-up. Third, the ages and symptoms of patients, the composition of each herbal medicine prescription, frequency and doses of each herbal medicine, and the duration of treatment were different. An evaluation of the overall effects of herbal medicines may be limited because of the diversity of these herbal medicines. Fourth, the incorrect methodological design of individual studies is a problem. Blinding the participants and therapists to decoction formulations is difficult. All trials used decoction, and 11 trials were rated as “high-risk” bias for binding of the participants and personnel. Fifth, an asymmetrical funnel plot of the CAL prevalence rate indicated a potential possibility that the meta-analysis results might be overestimated.

4.4. Suggestion for future research

At the time of the literature search, this study was the first systematic review and meta-analysis of integrative therapy for CALs in KD. Although inhibiting acute inflammation is important for reducing the CAL risk, the long-term follow-up of CALs is required to improve the prognosis and prevent chronic complications. Additional studies are needed regarding safety and adverse effects information is necessary. There is an urgent need for novel high-quality RCT studies of herbal medicines using a unified pill or powder formulations instead of decoctions to compensate for the diversity and low methodological quality of herbal medicines. Studies focusing on frequently used ingredient herbs and the advantages of herbal medicine as a multipound will be needed for KD patients.

5. Conclusion

This systematic review suggested that herbal medicines combined with conventional western treatment were more effective on coronary artery abnormalities and showed higher clinical effectiveness than conventional western medicines. On the other hand, there were the restrictions of insufficient trials on safety, methodological quality of the included studies, diversity of herbal medicines, and potential of location bias and publication bias. Additional well-designed and large-scale RCT studies will be needed to supplement these results.

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