Systematic Review and Meta-Analysis

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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

Editor: Bingrong Zhou.

Ethical implication statements were not necessary, because this study was a meta-analysis and only associated with the related literature research.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Choi J, Chang S, Kim E, Min SY. Integrative treatment of herbal medicine with western medicine on coronary artery lesions in children with Kawasaki disease. Medicine 2022;101:7(e28802).

Received: 26 October 2021 / Received in final form: 21 January 2022 / Accepted: 24 January 2022

http://dx.doi.org/10.1097/MD.0000000000028802

American Heart Association published the most recent guidelines in 2017.[3] 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.[6] 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 $\geq$ 10, or absolute dimension $\geq$ 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 2 g/kg infusion over 12 hours for the first 10 days. Aspirin is taken at a moderate-dose (30–50 mg/kg/day) or high-dose (80–100 mg/kg/day) in the acute phase, and a low dose (3–5 mg/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 $\geq$ 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 "remed*"[Title/Abstract] OR "Chinese medic*"[Title/Abstract] OR "Korean medic*"[Title/Abstract] OR "Kampo"[Title/Abstract] OR "formul*"[Title/Abstract] OR "herbal drug*"[Title/Abstract] OR "herbal medicine*"[Title/Abstract] OR "plant*"[Title/Abstract] OR "Chinese drug*"[Title/Abstract] OR "Chinese prescrip*"[Title/Abstract] OR "Chinese materica*"[Title/Abstract] OR "traditional medic*"[Title/Abstract] OR "traditional Chinese medic*"[Title/Abstract] OR "east Asian traditional medic*"[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 limitations of the number of herbs, formulations, and doses. 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 (f/u 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 6 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,[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,[32] 1 study of glucocorticoid,[24] 1 study of methylprednisolone,[25] and 1 study of ceftezole[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 f/u 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.[25,28,33] 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.[24,28,31] 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

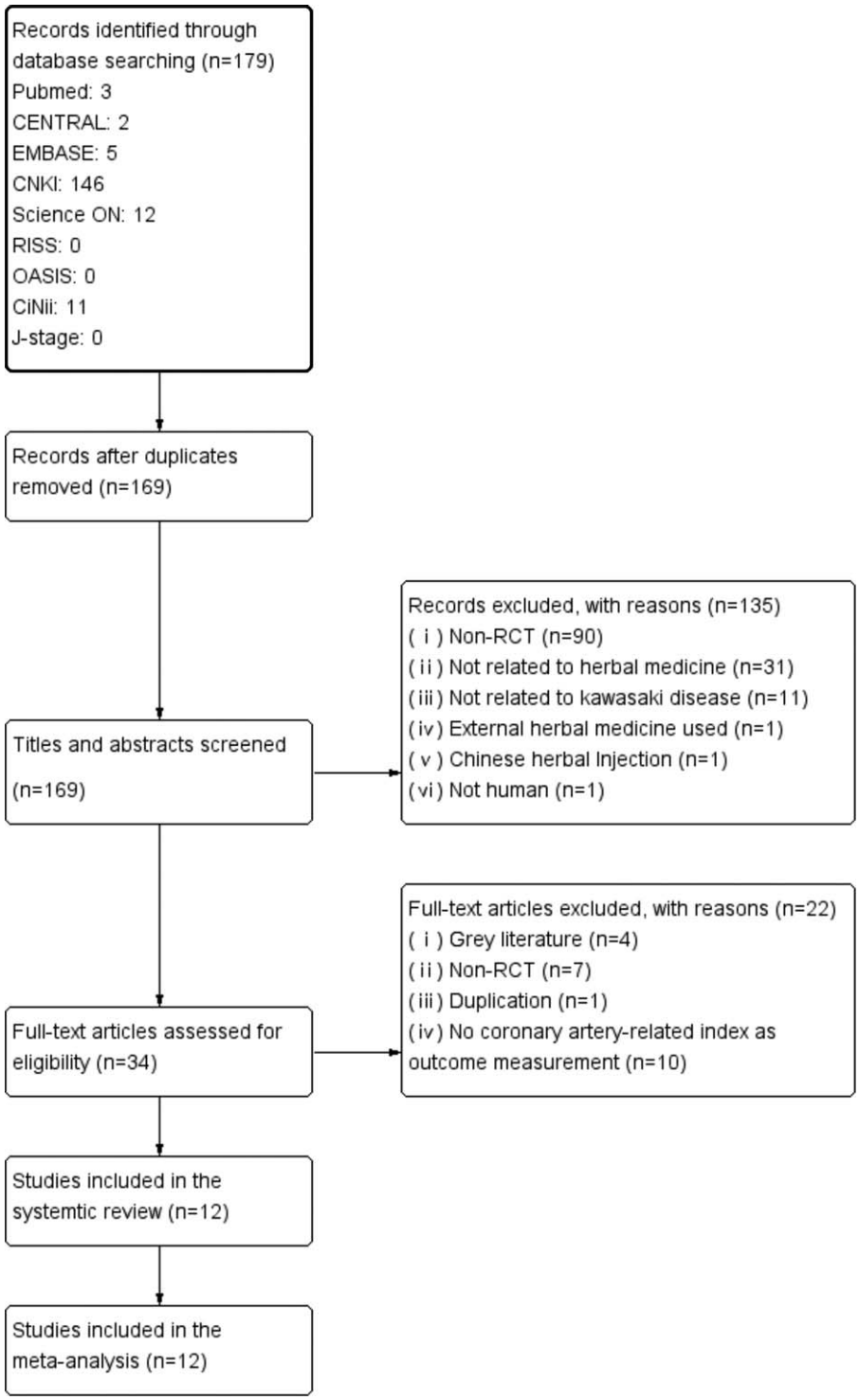

Figure 1. PRISMA flow diagram of the study screening and selection process. CENTRAL = The Cochrane Central Register of Controlled Trials, CiNii = Citation Information by National Institute of Informatics, CNKI = Chinese National Knowledge Infrastructure, OASIS = Oriental Medicine Advanced Searching Integrated System, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized controlled trial.

evaluated as "unclear risk".[25–27,29,30,32–34] 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.[28] Only the study of Liu[29] 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

Table 1

Basic characteristics of the included studies.

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
An (2017)[23]	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) IVIG 2 g/(kg.d) q.d. (2) Oral aspirin 100 mg/(kg.d) t.i.d. (→ 30 mg/[kg.d] b.i.d.)	1 mo
Chen (2014)[24]	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) RCMHJ, ACA, AAP (2) Phase of burnt of both Qi and Yin	HM + (C)	(1) IVIG 2 g/(kg.d) q.d. (2) Oral aspirin 30–50 mg/(kg.d) t.i.d. (→ 3–5 mg/[kg.d] q.d.) (3) Oral persentine 3–5 mg/(kg.d) t.i.d.: if patients have CALs or aspirin-resistant (4) Oral glucocorticoid 2 mg/(kg.d) q.d.: if curative effect is poor	3 mo
Da (2013)[25]	86 (46/40)	Single-center RCT	NR	8 mo–6 yr	55/29	Zhufutang practical pediatrics (7th edition)	HM + (C)	(1) Oral aspirin 30–50 mg/(kg.d) t.i.d.–q.i.d. for 14 d (→ 5 mg/[kg.d] q.d.) (2) IVIG 1 g/(kg.d) for 2 d (3) Oral persentine 3–5 mg/(kg.d): if platelets are elevated (4) Methylprednisolone 2 mg/(kg.d) for 3 d: if patients have CALs	3 mo
Geng (2005)[26]	45 (23/22)	Single-center RCT	NR	E: 11 mo–5 yr (2.8) yr C: 1–4.5 (2.6) yr	E: 12/11 C: 12/10	RCMHJ	HM + (C)	(1) Gamma globulin 400 mg/(kg.d) for 4 d (2) Oral aspirin 50 mg/(kg.d) t.i.d. for 2 w (→ 3–5 mg/[kg.d] q.d.) (3) Antibiotics + energy mixture + electrolyte supplement IV	1 mo
Li (2009)[27]	68 (34/34)	Single-center RCT	NR	7 mo–14 yr	NR	NR	HM + (C)	(1) Oral aspirin (2) IVIG (3) High-dose vitamin C injection, antibiotics, cardiomyocyte nutrients, rest, etc	NR
Liao (2008)[28]	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: 19/6 C: 16/7	RCMHJ	HM + (C)	(1) IVIG 1 g/(kg.d) for 2 d (2) Oral aspirin 30–50 mg/(kg.d) (→ 3–5 mg/[kg.d])	4 wk
Liu (2017)[29]	60 (30/30)	Single-center RCT	NR	E: (3.29 ± 1.17) yr C: (3.56 ± 1.25) yr	E: 16/14 C: 15/15	RCMHJ	HM + (C) + IVIG 350 mg/kg q.d. for 5 d	(1) Oral aspirin 50–80 mg/(kg.d) (→ 5–10 mg/[kg.d]) (2) symptomatic and energy mixture + water and electrolyte balance treatment	4 wk
Ren (2016)[30]	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: 45/35 C: 47/33	Japanese MCLS Research Society (2002)	HM + (C)	(1) IVIG 2 g/(kg.d) for 10–12 h (2) Oral aspirin 30–50 mg/(kg.d) t.i.d. (→3–5 mg/[kg.d])	4 wk

(*continued*)

Table 1
(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: (3.39±0.68) yr C: (3.35±0.65) yr	E: 27/14 C: 28/13	(1) AHA (2) Phase of burnt of both Qi 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	E: 12/8 C: 11/10	Pediatrics of TCM	HM + (C)	(1) IMG 1 g/(kg.d) q.d. for 2 d (2) Oral prednisone 3 mg/(kg d) for 2 wk (3) Oral persentine 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: (2.52±1.41) yr C: (2.14±1.12) yr	E: 44/26 C: 50/22	NR	HM + (C)	(1) Ceftezole 100 mg/(kg.d) IV for acute phase (2) IMG 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.

Table 2

Results of the included studies.

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 E: 3 cases recovered completely C: 5 cases recovered, 3 cases improved significantly
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) (ii), (1) (iii), (1) (iv), (1) (v), (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*)

Table 2

(continued).

First author (yr)	Outcome measurements	Intergroup differences	Adverse events & complication	Follow-up
	proBNP (ii) PCT (iii) CRP (4) CAL prevalence rate: (i) CAD (ii) CAA (iii) CAT (5) Adverse effect			
Tian (2007)[32]	(1) SDT – fever (2) Laboratory indicators: (i) WBC (ii) ESR (iii) CRP (3) CAL recovery rate: CAD	(1), (2) (i), (2) (ii) $P < .01$ & (2) (iii), (3) $P < .05$ in favor of the experimental group	NR	NR
Wang (2018)[33]	(1) TER (2) SDT: (i) fever (ii) rash (iii) mucosal hyperemia (iv) lymph node enlargement (3) Laboratory indicators: (i) PLT (ii) WBC (iii) Hb (iv) PCT (4) CAL prevalence rate	(1), (2), (4) $P < .05$, in favor of the experimental group	NR	NR
Wei (2006)[34]	(1) TER (2) SDT: (i) fever (ii) rash (iii) conjunctival hyperemia (iv) sclerosis of limbs and feet (v) peeling (vi) lymphadenopathy (vii) perianal flushing and peeling (3) ECG abnormality: (i) T wave changes (ii) Arrhythmia (4) CAL prevalence rate: CAD	(1), (4) $P < .05$, in favor of the experimental group	NR	(1) ECG: per 1–2 wk, if CAL completely normal once 1–3 mo (2) ECHO: per 1–3 mo, if CAL completely normal once 3–6 mo and then once 6 mo–6 yr

C = control group, CAA = coronary artery aneurysm, CAD = coronary artery dilatation, CAL = coronary artery lesion, CAT = coronary artery thrombosis, CRP = C-reactive protein, E = experimental group, ECG = electrocardiogram, ECO = echocardiography, ESR = erythrocyte sedimentation rate, HB = hemoglobin, IL = interleukin, m = month, MPV = mean platelet volume, NR = not reported, NT-proBNP = N-terminal pro-brain natriuretic peptide, PCT = plateletcrit, PDW = platelet distribution width, PLT = platelet, SDT = symptom disappearance time, TCM = traditional Chinese medicine, TER = total effective rate, TNF-α = tumor necrosis factor-α, w = week, WBC = white blood cell, y = year.

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.[25] 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.[29,33,34] One study added not only herbal medicine but also IVIG to the control intervention in the integrative treatment group.[29] The other 2 studies had differences in treatment periods in 2 groups.[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 ($P = .54$, $I^2 = 0$), 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 accessed 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 ($P = .49$, $I^2 = 0$) 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 ($P = .47$, $I^2 = 0\%$), 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, Glycyrrhizae Radix 3 g, Gypsum fibrosum 2 g, Liriopis 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 3 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 burnt of 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, Bombycis Corpus 8 g if palms and soles flushing, plus Radix Rehmanniae 6 g, Moutan Radicis Cortex 6 g (2) 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 Liriopis tuber 6 g, Dendrobii Herba 6 g if enlarged lymph nodes in the neck, plus Prunellae Herba 6 g, Taraxaci Herba 6 g (3) Carthami Flos 3 g, Adenophorae Radix 6 g, Liriopis Tuber 6 g, Schizandrae Fructus 6 g, Astragali Radix 6 g, Persicae Semen 6 g If loss of appetite, plus Crataegi Fructus 6 g, Hoelen 6 g If low fever ongoing, plus Lycii Cortex Radicis 6 g, Gypsophilae Radix 6 g
Geng (2005)[26]	Qingrehuayu decoction	OA	NR	NR	Bubali Cornu 10 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, Cnidium officinale Makino 8 g
Li (2009)[27]	Modified Baihu decoction	OA or retention enema	NR	200 mL	Gypsum fibrosum 30 g, Anemarrhenae Rhizoma 6 g, Boiled Glycyrrhizae Radix 6 g, Oryzae Semen 10 g, Gardeniae Fructus 6 g, Scutellariae Radix 10 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 Galli Stomachichum Corium 10 g, Hordei Fructus Germinatus 10 g, Massa Medicata Fermentata 10 g, Crataegi Fructus 10 g If bloating, plus Saussureae Radix 10 g, Amomi Semen 8 g
Liao (2008)[28]	(1) Modified Qingying 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, Glycyrrhizae Radix 4 g (2) Lophatheri Herba 5 g, Gypsum fibrosum 15 g, Liriopis Tuber 8 g, Pseudostellariae Radix 8 g, Dendrobii Herba 6 g, Phragmitis Rhizoma 8 g, Scrophulariae Radix 8 g, Paeoniae Radix rubra 8 g, Radix Salviae Miltiorrhizae 8 g, Glycyrrhizae Radix 4 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, Lumbricus 10 g, Radix Rehmanniae 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 Rehmanniae 3–10 g, Paeoniae Radix rubra 5–10 g, Lithospermi Radix 5–10 g, Bubali Cornu 5–10 g, Radix Salviae Miltiorrhizae 5–20 g

(*continued*)

Table 3

(continued).

First author (yr)	Intervention	Administration	Frequency	Dosages	Composition
Sha (2021)[31]	Modified Huanglianjiedu decoction plus Baihu decoction	OA	6 mo–3 yr: t.i.d.–q.i.d. 4–6 yr: t.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 Suspensae 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]	Jieduhuayu decoction	OA	b.i.d.	200 mL	Flos Lonicerae 10 g, Fructus Forsythiae Suspensae 10 g, Bubali Cornu 10 g, Radix Rehmanniae 10 g, Lumbricus 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 Suspensae 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 Suspensae 8 g, Lophatheri Herba 5 g, Glycyrrhizae Radix 4 g (3) Adenophorae Radix 15 g, Liriopis Tuber 15 g, Trichosanthis 15 g, Polygonati Rhizoma 10 g, Dolichoris Semen 6 g, Glycyrrhizae Radix 6 g
Wei (2006)[34]	Qingrejieduhuoxue prescription	OA	b.i.d.–q.i.d.	NR	Radix Rehmanniae, Radix Salviae Miltiorrhizae, Bubali Cornu, Moutan Radicis Cortex, Flos Lonicerae, Fructus Forsythiae Suspensae, 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 pharyngeal, 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.

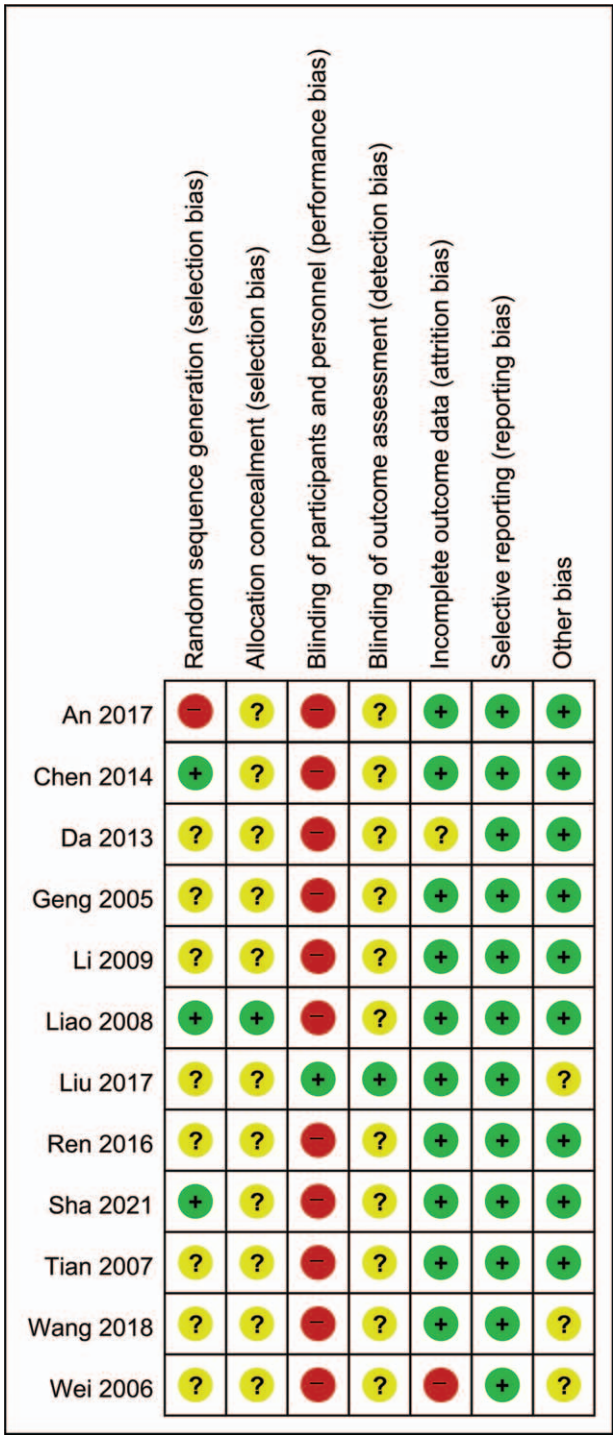

Figure 2. Risk of bias graph.

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 $\geq$ 10, diameter $\geq$ 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 mm^3, 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

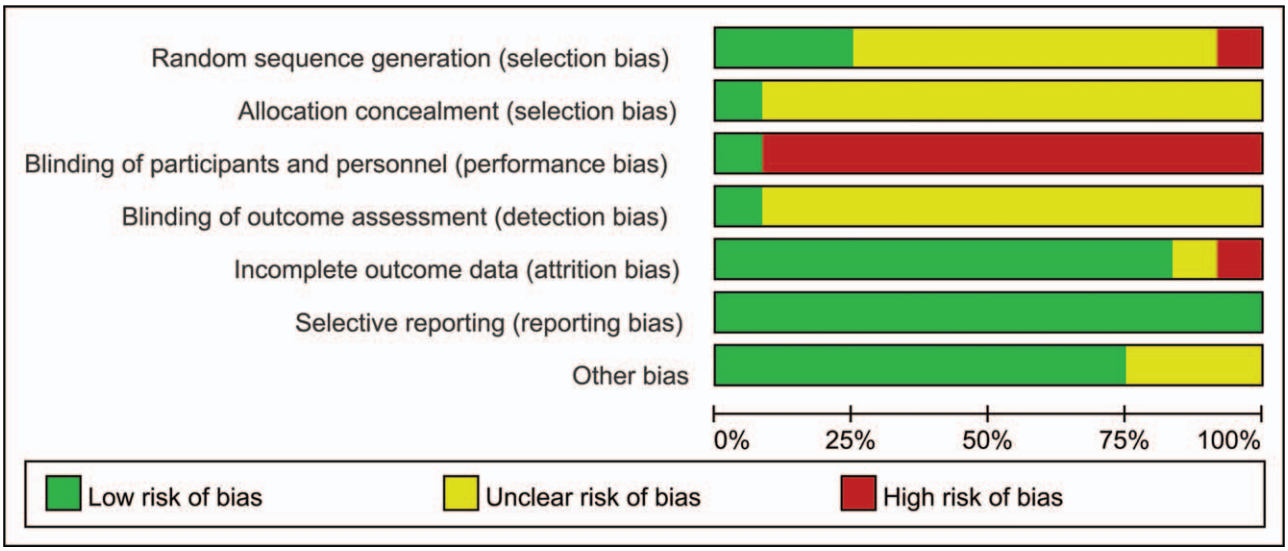

Figure 3. Risk of bias summary.

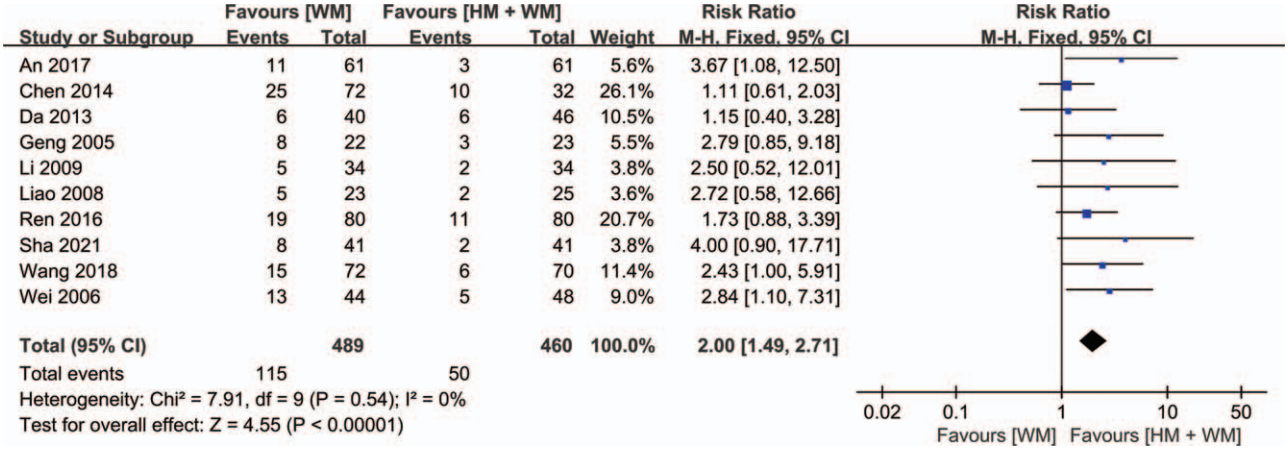

Figure 4. Forest plot of the CAL prevalence rate of integrative treatment compared with conventional western treatment. CAL = coronary artery lesion, CI = confidence interval, HM = herbal medicine, WM = western medicine.

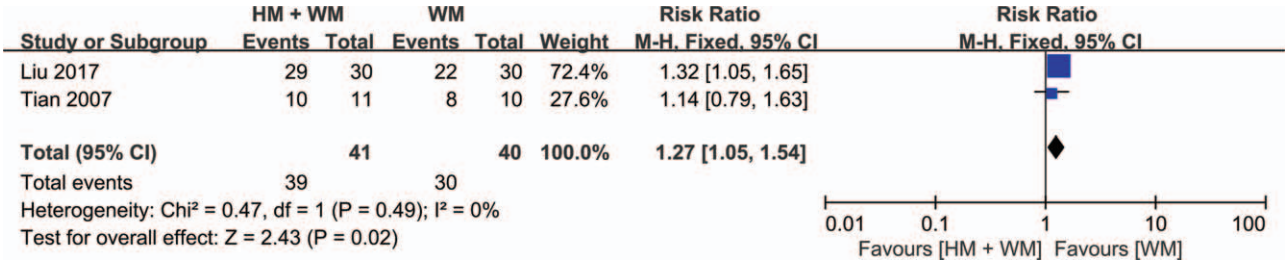

Figure 5. Forest plot of the CAL recovery rate of integrative treatment compared with conventional western treatment. CAL = coronary artery lesion, CI = confidence interval, HM = herbal medicine, WM = western medicine.

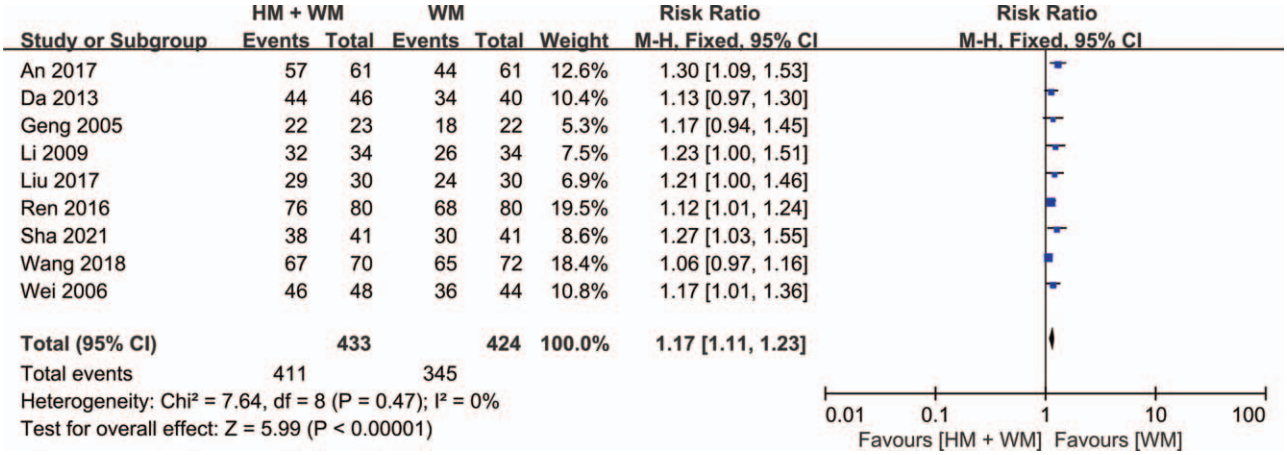

Figure 6. Forest plot of the TER of integrative treatment compared with conventional western treatment. CI = confidence interval, HM = herbal medicine, TER = total effective rate, WM = western medicine.

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 Jieduhuayu 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 fibrosum 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

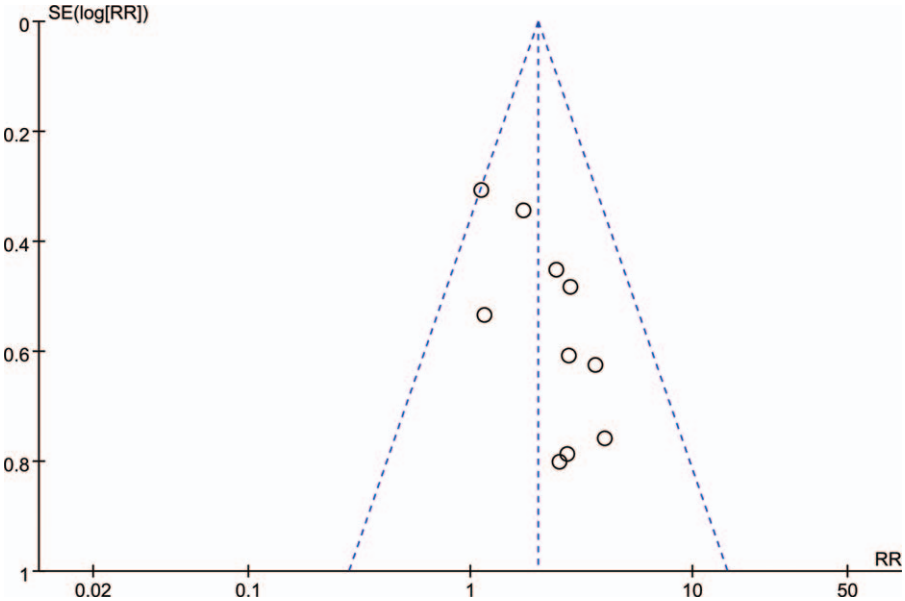

Figure 7. Funnel plot of the CAL prevalence rate. CAL = coronary artery lesion, RR = risk ratio.

protective effects.[46] Gypsum fibrosum has antipyretic activity[47] and removes heat to cool the blood.

The multicompound 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.[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[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.[29] Another study reported no side effects in each of the 2. Therefore, no firm conclusions about safety could be drawn.[31]

4.2. Comparison to previous reviews

One systematic review[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[29,31] that reported adverse events and 2 studies[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 blinding 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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Formal analysis: Jungyoon Choi, Seokjoo Chang.
Investigation: Jungyoon Choi, Seokjoo Chang.
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Supervision: Eunjin Kim, Sang Yeon Min.
Validation: Eunjin Kim, Sang Yeon Min.
Visualization: Jungyoon Choi, Seokjoo Chang.
Writing – original draft: Jungyoon Choi.
Writing – review & editing: Jungyoon Choi, Eunjin Kim, Sang Yeon Min.

References

[1] Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Arerugi 1967;16:178–222.
[2] Agarwal S, Agrawal DK. Kawasaki disease: etiopathogenesis and novel treatment strategies. Expert Rev Clin Immunol 2017;13:247–58.
[3] Singh S, Jindal AK, Pilania RK. Diagnosis of Kawasaki disease. Int J Rheum Dis 2018;21:36–44.
[4] McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927–99.
[5] Saguil A, Fargo M, Grogan S. Diagnosis and management of Kawasaki disease. Am Fam Physician 2015;91:365–71.
[6] Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004;114:1708–33.
[7] Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 1996;94:1379–85.
[8] Hayasaka S, Nakamura Y, Yashiro M, et al. Analysis of fatal cases of Kawasaki disease in Japan using vital statistical data over 27 years. J Epidemiol 2003;13:246–50.
[9] Fukushige J, Takahashi N, Ueda Y, Ueda K. Incidence and clinical features of incomplete Kawasaki disease. Acta Paediatr 1994;83:1057–60.
[10] Witt MT, Minich LL, Bohnsack JF, Young PC. Kawasaki disease: more patients are being diagnosed who do not meet American Heart Association criteria. Pediatrics 1999;104:e10.
[11] Rife E, Gedalia A. Kawasaki disease: an update. Curr Rheumatol Rep 2020;22:75.

[12] Bayers S, Shulman ST, Paller AS. Kawasaki disease: part II. Complications and treatment. J Am Acad Dermatol 2013;69:513.e1–8.e1. quiz 521–2.
[13] Akagi T, Ogawa S, Ino T, et al. Catheter interventional treatment in Kawasaki disease: a report from the Japanese Pediatric Interventional Cardiology Investigation group. J Pediatr 2000;137:181–6.
[14] Kitamura S. The role of coronary bypass operation on children with Kawasaki disease. Coron Artery Dis 2002;13:437–47.
[15] Kemmotsu Y, Nakayama T, Matsuura H, Saji T. Clinical characteristics of aseptic meningitis induced by intravenous immunoglobulin in patients with Kawasaki disease. Pediatr Rheumatol Online J 2011;9:28.
[16] Hamada H, Suzuki H, Abe J, et al. Inflammatory cytokine profiles during cyclosporin treatment for immunoglobulin-resistant Kawasaki disease. Cytokine 2012;60:681–5.
[17] Lee JH, Hung HY, Huang FY. Kawasaki disease with Reye syndrome: report of one case. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1992;33:67–71.
[18] Chen JY, Yin JM, Du ZD, Hao J, Yan HM. Qing Re Liang Xue decoction alleviates hypercoagulability in Kawasaki disease. Evid Based Complement Altern Med 2015;2015:864597.
[19] Qi SH, Wei B. Advances in the application of Chinese and western medicines for coronary artery thrombosis caused by Kawasaki disease. Chin Pediatr Integr Tradit West Med 2021;13:311–6.
[20] Yang XN, Deng J, Ye QN. Meta-analysis of the treatment for Kawasaki disease with Weiqi and Yingxue differentiation. Chin Pediatr Integr Tradit West Med 2021;13:185–90.
[21] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[22] Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142.
[23] An N, Li C, Duan BX, et al. Effect evaluation on traditional Chinese medicine combined with western medicine treatment of Kawasaki. Chin Arch Tradit Chin Med 2017;35:1310–2.
[24] Chen JY, Du ZD, Yan HM. Clinical efficacy observation of the heat-clearing and blood-cooling method in acute stage of Kawasaki disease. Beijing J Tradit Chin Med 2014;33:650–3.
[25] Da ZH. Experience in diagnosis and treatment of 86 cases of Kawasaki disease in children with integrated traditional Chinese and western medicine. Chin Prim Health Care 2013;27:110–1.
[26] Geng SY, Zhang J, Zhao YN. Observation on the clinical efficacy of 23 cases of Kawasaki disease with Qingre Huayu decoction. J Hebei Tradit Chin Med Pharmacol 2005;20:8–9.
[27] Li YJ, Li Y. Clinical observation on 68 cases of Kawasaki disease in children treated with integrated traditional Chinese and western medicine. Chin Community Dr 2009;1:148.
[28] Liao RS, Du SJ. Effect of heat-clearing and blood-activating herbs on platelet parameters in children with Kawasaki disease. J Guangzhou Univ Tradit Chin Med 2008;25:492–4.
[29] Liu J. Clinical observation of Jiedu Huayu dDecoction combined with gamma globulin in the treatment of Kawasaki disease. Shaanxi J Tradit Chin Med 2017;38:180–1.
[30] Ren LL, Wang CX, Li J, Liu SZ. Observation on the efficacy of Chinese medicine combined with gamma globulin and aspirin in the treatment of Kawasaki disease. Mod J Integr Tradit Chin West Med 2016; 25:1890–2.
[31] Sha BW, Zhao DM. Observation on the curative effect of Huanglian Jiedu decoction plus Baihu decoction in the treatment of children's Kawasaki disease (Qiying and burnt syndrome) and their effects on the levels of NT-proBNP, PCT and CRP in the peripheral blood of children. J Emerg Tradit Chin Med 2021;30:524–6.
[32] Tian ZW. Treatment of 20 cases of Kawasaki disease with Jieduhuayu decoction. Henan Tradit Chin Med 2007;27:37–8.
[33] Wang XH, He F, Zhang DL. Clinical observation on treatment of coronary artery lesion of Kawasaki disease by stages of TCM. Chin J Clin Ration Drug Use 2018;11:100–2.
[34] Wei JH, Wu LX, Xiao PX. Clinical observation for the combined traditional Chinese and western medicine in treating infantile Kawasaki disease of 48 cases. J Hebei N Univ 2006;23:34–6.
[35] Orenstein JM, Shulman ST, Fox LM, et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study. PLoS One 2012;7:e38998.
[36] McCrindle BW. Kawasaki disease: a childhood disease with important consequences into adulthood. Circulation 2009;120:6–8.
[37] McCrindle BW, Harris KC. Coronary artery aneurysms after Kawasaki disease: understanding the pathology. Can J Cardiol 2018;34:1094–7.
[38] Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation 2006;114:2710–38.
[39] Wang BY, Wang Y. Progress in treatment of Kawasaki disease with infliximab. Chin J Mod Med 2019;29:46–50.
[40] Soriano-Ramos M, Martínez-Del Val E, Negreira Cepeda S, et al. Risk of coronary artery involvement in Kawasaki disease. Arch Argent Pediatr 2016;114:107–13.
[41] Hu HZ. Treating Kawasaki disease from "heart". Shanghai J Tradit Chin Med 1997;26–7. doi: 10.16305/j.1007-1334.1997.01.017.
[42] Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. Eur Heart J 2014;35:1782–91.
[43] Zhao L, Xiang KL, Liu RX, Xie ZP, Zhang SM, Dai SJ. Anti-inflammatory and antiviral labdane diterpenoids from the fruits of *Forsythia suspensa*. Bioorg Chem 2020;96:103651.
[44] Li Y, Cai W, Weng X, et al. Lonicerae Japonicae Flos and Lonicerae Flos: a systematic pharmacology review. Evid Based Complement Altern Med 2015;2015:905063.
[45] Liu C, Ma R, Wang L, et al. Rehmanniae Radix in osteoporosis: a review of traditional Chinese medicinal uses, phytochemistry, pharmacokinetics and pharmacology. J Ethnopharmacol 2017;198:351–62.
[46] Guo R, Li L, Su J, et al. Pharmacological activity and mechanism of tanshinone IIA in related diseases. Drug Des Devel Ther 2020;14: 4735–48.
[47] Wang H, Wang M, Li X. Evaluation of the antipyretic activity of Gypsum Fibrosum and its constituents. Asian J Tradit Med 2009;4:82–4.
[48] Kim HU, Ryu JY, Lee JO, Lee SY. A systems approach to traditional oriental medicine. Nat Biotechnol 2015;33:264–8.