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The effectiveness of Kanggan granules in treating hand, foot and mouth disease in children: a meta-analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 July 2026 and was last updated on 29 July 2026.

INTRODUCTION

Review question / Objective This systematic review and meta-analysis aimed to evaluate the efficacy and safety of Kanggan granules for the treatment of children with hand, foot, and mouth disease (HFMD).

The review question was formulated according to the PICOS framework:

Population (P): Children diagnosed with hand, foot, and mouth disease (HFMD), regardless of disease severity, age, or sex.

Intervention (I): Kanggan granules administered alone or in combination with conventional therapies.

Comparator (C): Conventional treatment alone or other standard medical treatments without Kanggan granules.

Outcomes (O): The primary outcome was the clinical effectiveness rate. Secondary outcomes included herpes regression time, oral ulcer healing time, fever reduction time, hospitalization duration, and reported adverse events.

Study design (S): Randomized controlled trials (RCTs) evaluating Kanggan granules for HFMD treatment were eligible for inclusion.

The objective of this review was to systematically synthesize available evidence from randomized controlled trials to determine whether Kanggan granules provide additional clinical benefits compared with conventional treatment alone and to assess the certainty and safety of the available evidence.

Condition being studied Hand, foot, and mouth disease (HFMD) is a common acute infectious disease primarily affecting infants and young children, particularly those under 5 years of age. It is mainly caused by enteroviruses, including enterovirus A71 (EV-A71), coxsackievirus A16, and

other enterovirus serotypes. HFMD is characterized by fever, oral ulcers, and vesicular eruptions on the hands, feet, and mouth. Although most cases are self-limiting and resolve within approximately one week, a subset of children may develop severe complications, including neurological involvement, myocarditis, pulmonary edema, and systemic inflammatory responses, especially in EV-A71-associated infections.

Currently, management of HFMD mainly relies on supportive and symptomatic treatments, as effective specific antiviral therapies remain limited. Conventional treatments may include antipyretics, fluid management, nutritional support, and, in selected cases, antiviral or immunomodulatory agents. However, concerns regarding limited therapeutic options and potential adverse effects have encouraged the exploration of complementary therapies.

Kanggan granules, a traditional Chinese medicine formulation containing herbal components such as Lonicera japonica Flos, Paeonia lactiflora Radix, and Corydalis yanhusuo Rhizoma, have been widely used in clinical practice for children with HFMD. Previous clinical studies have suggested that Kanggan granules may improve symptom resolution, including fever reduction, regression of herpes lesions, and healing of oral ulcers. Experimental studies have also indicated potential antiviral, anti-inflammatory, and immunomodulatory properties; however, these mechanisms have not been directly validated in clinical trials.

Despite increasing clinical use, the efficacy and safety of Kanggan granules for HFMD remain uncertain due to variations in study quality, treatment protocols, outcome definitions, and limited safety reporting. Therefore, this systematic review and meta-analysis was conducted to comprehensively evaluate the clinical effectiveness and safety of Kanggan granules in children with HFMD.

METHODS

Participant or population The population of interest includes children diagnosed with hand, foot, and mouth disease (HFMD). Participants of any sex, ethnicity, or geographic region will be considered eligible. Studies involving pediatric patients who met recognized diagnostic criteria for HFMD, including national or clinical diagnostic guidelines, will be included.

Eligible participants are children with confirmed HFMD who received treatment in clinical settings. The review will include patients with different disease severities, provided that the diagnosis of HFMD was clearly established. No restrictions will be applied regarding age range, disease duration, or baseline clinical characteristics.

Studies involving mixed populations will only be included if pediatric HFMD patients can be separately identified and relevant outcome data can be extracted. Studies involving adults, non-human subjects, patients without a confirmed HFMD diagnosis, or populations with insufficient clinical information will be excluded.

The target population therefore represents children with HFMD for whom the effectiveness and safety of Kanggan granules-based therapy are evaluated.

Intervention The intervention of interest is Kanggan granules used for the treatment of children with hand, foot, and mouth disease (HFMD).

Studies evaluating Kanggan granules administered as monotherapy or as an adjunctive therapy combined with conventional treatments will be considered eligible. The dosage, administration frequency, and treatment duration will be recorded according to the descriptions provided in the original studies.

Kanggan granules are a traditional Chinese medicine formulation mainly composed of herbal ingredients including Lonicera japonica Flos, Paeonia lactiflora Radix, and Corydalis yanhusuo Rhizoma. Previous clinical applications have suggested potential benefits in improving HFMD-related symptoms, such as fever, oral ulcers, and vesicular eruptions.

The intervention group may receive Kanggan granules alone or Kanggan granules combined with conventional therapies, including antiviral agents, immunomodulatory drugs, or symptomatic supportive treatments. The effects of these interventions will be evaluated compared with eligible control groups receiving conventional treatment without Kanggan granules.

Studies using other Chinese herbal medicines or formulations without Kanggan granules as the primary intervention will be excluded.

Comparator The comparator of interest is conventional treatment without Kanggan granules

for children with hand, foot, and mouth disease (HFMD).

Eligible control groups will include children receiving standard medical management, including symptomatic supportive treatment, antiviral therapy, immunomodulatory agents, or other conventional pharmacological treatments according to local clinical practice. The control intervention may include agents such as ribavirin, recombinant human interferon α-1b, Yanhuning, Shuanghuanglian, or supportive care, provided that Kanggan granules are not administered.

Studies comparing Kanggan granules alone or combined with conventional treatment against conventional treatment alone will be included. The specific types, dosage, and duration of comparator interventions will be extracted and analyzed based on the original study reports.

Studies without an appropriate comparator group, studies comparing different formulations or dosages of Kanggan granules only, or studies lacking sufficient comparative outcome data will be excluded.

Study designs to be included Randomized controlled trials (RCTs) will be included in this systematic review and meta-analysis. Studies must compare Kanggan granules alone or in combination with conventional treatment against conventional treatment without Kanggan granules in children with hand, foot, and mouth disease (HFMD). Both blinded and non-blinded RCTs will be considered eligible. Non-randomized studies, observational studies, case reports, case series, reviews, meta-analyses, animal studies, and laboratory studies will be excluded.

Eligibility criteria Additional eligibility criteria will include the following:

Studies will be eligible if they meet all predefined criteria: (1) participants are children diagnosed with hand, foot, and mouth disease (HFMD) according to recognized diagnostic criteria or clinical guidelines; (2) the intervention is Kanggan granules administered alone or combined with conventional therapy; (3) the comparator group receives conventional treatment without Kanggan granules; (4) the study reports at least one relevant clinical outcome, including total effectiveness rate, herpes regression time, oral ulcer healing time, fever reduction time, hospitalization duration, or adverse events; and (5) sufficient data are available for extraction and quantitative analysis.

Studies will be excluded if they are duplicate publications, report overlapping patient populations, lack sufficient clinical outcome data, involve non-human subjects, or are reviews, case reports, conference abstracts, letters, or basic experimental studies. Studies with unclear randomized allocation or incomplete outcome reporting will be assessed carefully according to risk of bias criteria.

Information sources A comprehensive literature search will be conducted in multiple electronic databases, including PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP database, from database inception to June 30, 2024.

The search strategy will combine controlled vocabulary terms and free-text keywords related to "Kanggan granules" and "hand, foot, and mouth disease (HFMD)". No language restrictions will be applied. Reference lists of all included studies and relevant systematic reviews will also be manually screened to identify additional eligible studies.

Published randomized controlled trials will be the primary information source. Grey literature, conference proceedings, dissertations, and clinical trial registries will not be included because this review focuses on published clinical trials. Study authors will not be routinely contacted unless clarification of unclear or missing information is required.

Main outcome(s) The primary outcome of this review is the clinical effectiveness rate of Kanggan granules for children with hand, foot, and mouth disease (HFMD). The effectiveness rate will be expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Secondary outcomes include:
(1) herpes regression time;
(2) oral ulcer healing time;
(3) fever reduction time;
(4) duration of hospitalization; and
(5) adverse events or safety outcomes.

For dichotomous outcomes, pooled effects will be calculated using ORs with 95% CIs. For continuous outcomes, mean differences (MDs) with 95% CIs will be used. Outcomes will be analyzed according to the follow-up or treatment duration reported in the original studies.

The safety profile of Kanggan granules will be assessed based on the incidence and type of reported adverse events.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included randomized controlled trials (RCTs) will be independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool.

The following domains will be evaluated: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result.

Each domain will be categorized as "low risk of bias", "some concerns", or "high risk of bias" according to the RoB 2 guidance. Any disagreements between reviewers will be resolved through discussion or consultation with a third reviewer.

The overall risk of bias for each study will be summarized and presented using appropriate graphical tools. The certainty of evidence for major outcomes will also be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Strategy of data synthesis Data from eligible studies will be extracted and synthesized using Review Manager (RevMan) and Stata software. A quantitative meta-analysis will be performed when studies are sufficiently homogeneous in terms of participants, interventions, comparators, and outcomes.

For dichotomous outcomes, pooled effect estimates will be presented as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes, mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs will be calculated. Statistical heterogeneity among studies will be assessed using the Chi-square test and I^2 statistic. An I^2 value of >50% will indicate substantial heterogeneity.

A fixed-effects model will be applied when heterogeneity is low (I^2 ≤50%). When substantial heterogeneity exists (I^2 >50%), a random-effects model will be used, and potential sources of heterogeneity will be explored through subgroup analyses based on treatment regimen, disease severity, study characteristics, or risk of bias when sufficient data are available.

Sensitivity analyses will be conducted by excluding studies with high risk of bias or using alternative statistical models to assess the robustness of the pooled results.

Publication bias will be evaluated using funnel plots and statistical tests (such as Egger's test) when the number of included studies for an outcome is sufficient (generally ≥10 studies).

The certainty of evidence for major outcomes will be assessed using the GRADE framework.

Subgroup analysis Subgroup analyses will be performed when sufficient data are available to explore potential sources of heterogeneity and assess whether treatment effects vary across different study characteristics.

Planned subgroup analyses include:

(1) Treatment regimen: Kanggan granules used alone versus Kanggan granules combined with conventional therapy.

(2) Comparator regimen: Different types of conventional treatments used in the control group (e.g., antiviral agents, immunomodulatory therapies, or supportive treatment).

(3) Disease severity: Different clinical severity categories of HFMD, when reported.

(4) Risk of bias: Studies will be stratified according to overall methodological quality (low risk of bias versus some concerns/high risk of bias).

(5) Study characteristics: Differences in sample size, treatment duration, and publication characteristics may also be explored if adequate information is available.

Subgroup analyses will be interpreted cautiously because the number of available randomized controlled trials may be limited. Results will be considered exploratory and used primarily to identify potential explanations for observed heterogeneity.

Sensitivity analysis Sensitivity analyses will be conducted to evaluate the robustness and stability of the pooled results. The primary approach will involve repeating meta-analyses after sequentially excluding individual studies using a leave-one-out method to determine whether any single study has

a disproportionate influence on the overall effect estimate.

Additional sensitivity analyses will be performed by excluding studies with a high risk of bias or significant methodological limitations. The pooled effects will also be reanalyzed using alternative statistical models (e.g., fixed-effects model versus random-effects model) to assess whether the conclusions are affected by model selection.

For outcomes with substantial heterogeneity, sensitivity analyses will be used together with subgroup analyses to explore potential sources of variability, including differences in intervention protocols, comparator treatments, treatment duration, and study characteristics.

If sensitivity analyses produce results consistent with the primary analysis, the findings will be considered robust. Conversely, substantial changes in effect estimates will be reported and interpreted cautiously, considering the methodological quality and clinical heterogeneity of the included studies.

Country(ies) involved China (all authors and affiliations are based in China).

Keywords Hand, foot, and mouth disease; Children; Kanggan granules; Traditional Chinese medicine; Randomized controlled trial; Meta-analysis; Systematic review.

Contributions of each author

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