Original Article

Chinese patent herbal medicine (Shufeng Jiedu capsule) for acute upper respiratory tract infections: A systematic review and meta-analysis

Ying-ying Zhang [a,1], Ru-yu Xia [a,1], Shi-bing Liang [a], Xiao-yang Hu [b], Meng-yuan Dai [c], Yi-lin Li [d], Le-yi Zhao [d], Michael Moore [b], Yu-tong Fei [a], Jian-ping Liu [a,*]

[a] Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China
[b] School of Primary Care, Population Sciences, and Medical Education, University of Southampton, Southampton, United Kingdom
[c] Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Anhui Medical University, Hefei, China
[d] Beijing University of Chinese Medicine, Beijing, China

ARTICLE INFO

ABSTRACT

Background: Shufeng Jiedu capsule has been widely used in China for acute upper respiratory tract infections (AURTIs). The aim of this study was to evaluate its effectiveness and safety for AURTIs.

Methods: Randomized controlled trials comparing SFJD with conventional drug for patients with AURTIs were included. Eight databases were searched from their inceptions to February 2021. Data was synthesized using risk ration (RR) or mean difference (MD) with their 95% confidence interval (CI). The primary outcome was resolution time of typical symptoms.

Results: Twenty-five RCTs involving 3410 patients were included. SFJD in combination with conventional drug was associated with; in common cold shortening the duration of fever (MD −1.54 days, 95% CI [−2.15,−0.92], I^2 = 80%, n = 385, 3 trials) and cough (MD −1.22 days, 95% CI [−1.52, −0.93]); in herpangina, shortening the duration of fever (MD -0.68 days, 95% CI [−1.15, −0.21], I^2 = 68%, n = 140, 2 trials) and blistering (MD −0.99 days, 95% CI [−1.23, −0.76], n = 386, 3 trials); in acute tonsillitis and acute pharyngitis shortening the duration of fever (MD −1.13 days, 95% CI [−1.36, −0.90], I^2 = 33%, n = 688, 7 trials) and sore throat (MD −1.13 days, 95% CI [−1.40, −0.86], I^2 = 84.1%, n = 1194, 10 trials). SFJD also improving their cure rate with a range (1–5 days). No serious adverse events were reported.

Conclusion: Low certainty evidence suggests that SFJD appears to shorten the duration of symptoms in AURTIs, improve cure rate and seems safe for application. However, high quality placebo controlled trials are warranted to confirm its benefit.

1. Introduction

Upper respiratory tract infections (URTIs) are one of the most commonly occurring diseases. In 2017, the global incidence of URTIs was 17.1 billion worldwide [1], which posed substantial socioeconomic burden to public health. The global 6090,503 disability-adjusted life years due to URTIs were lost in 2016[2]. Acute upper respiratory tract infections (AURTIs) are the most common type of URTIs. According to the International Statistical Classification of Diseases (ICD-10), AURTIs include common cold, acute sinusitis, acute pharyngitis, acute tonsillitis, acute laryngitis and tracheitis, acute epiglottitis, and acute upper respiratory infections of multiple and unspecified sites [3]. AURTIs are predominantly viral, and most AURTIs are mild and self-limited within 7 days [4]. Antibiotics are recommended only for specific URTIs and validated clinical indications (such as acute pharyngitis and acute tonsillitis caused by streptococcus) in existing guidelines, for other AURTIs, symptomatic treatment were recommended [5,6]. It was reported that the majority of antibiotic prescriptions for AURTIs were unnecessary and ineffective[7–9]. Additionally, inappropriate use of antibiotics may lead to bacterial resistance, and as many as 35,000 people die each year as a result in US [10].

* Corresponding author.
E-mail address: liujp@bucm.edu.cn (J.-p. Liu).
[1] Ying-Ying Zhang and Ru-Yu Xia are co-first authors.

Shufeng Jiedu (SFJD) capsule as an oral Chinese patent herbal medicine has been widely used in China for the treatment of AURTIs for 30 years [11]. The ingredients of SFJD were presented in (Supplementary material). SFJD has been recommended in several Chinese national guidelines for the treatment of AURTIs [12–14]. There are many clinical trials comparing the effect of SFJD with conventional drug for the treatment of AURTIs. Additionally, an in vitro study of antibacterial testing suggested that SFJD capsule had a broad-spectrum antibacterial effect [15], moreover, SFJD combined with oseltamivir had synergistic antiviral effects on respiratory infection [16]. However, there is no systematic review to evaluate the effectiveness of SFJD on AURTIs. Therefore, this systematic review aims to collect all relevant randomized controlled trials (RCTs) on SFJD capsule for patients with AURTIs and to evaluate its therapeutic effect and safety.

2. Methods

This systematic review was reported following PRISMA [17] statement, and the protocol has been registered on INPLASY (INPLASY202050083)[18].

2.1. Inclusion and exclusion criteria

2.1.1. Inclusion criteria
Parallel group RCTs regardless of blinding were included. The study population (P) was patients diagnosed with AURTIs or one of the classification of AURTIs regardless of gender, age or ethnicity from primary care or outpatient department of hospitals. AURTIs might include common cold, acute rhinitis, herpangina, acute pharyngitis or acute tonsillitis. The interventions (I) were SFJD capsule used alone or in combination with conventional drug. Conventional drug referred to symptomatic treatment (e.g., antipyretic and decongestant, etc.), symptomatic treatment plus antivirals or antibiotics. The controls (C) were placebo or conventional drug. The primary outcome (O) was the duration of typical symptoms in AURTIs (time to fever, cough, blisters or sore throat resolution). The secondary outcomes were cure rate and adverse events. Follow up of outcome measurements were all limited to within 5 days of treatment.

2.1.2. Exclusion criteria
Studies with a course of treatment over 7 days, and studies with other Chinese patent medicine controlled or studies failed to report the minimal required outcomes were excluded.

2.2. Search strategy

PubMed, the Cochrane Library, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), SinoMed and Wanfang databases were searched from their inceptions to February 2021. A systematic search was also conducted in Clinical Trials.gov (www.clinicaltrials.gov) and Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx). Search strategy for PubMed: Shufengjiedu[Title/Abstract] OR Shu Feng Jie Du [Title/Abstract] OR Shu-Feng-Jie-Du [Title/Abstract] OR Shufeng Jiedu [Title/Abstract] OR Shufeng-Jiedu [Title/Abstract]. There was no limitation of language.

2.3. Study selection and data extraction

After removing duplicates, two authors (YY Zhang and RY Xia) independently screened studies by titles and abstracts. In the full text screening process, uncertainty and insufficient information was determined for eligibility through obtaining full texts, and discrepancies were resolved by discussion or determined by a third-party adjudication. Reasons for excluding studies were recorded at

this stage. A predefined data extraction form was used by paired reviewers (YY Zhang and SB Liang; YL Li and LY Zhao) to extract data independently, including study ID, population, interventions, comparisons, outcomes, and design characteristics (sample size, setting and funding).

2.4. Quality assessments

The quality assessment of individual trial was performed using Cochrane Risk of Bias tool 2.0[19]. This revised tool includes five items as following: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. The included trials were assessed as low risk of bias, some concerns or high risk of bias in each domain[19,20]. The method of GRADE [21] (Grading of Recommendations Assessment, Development and Evaluation) was employed to rate the certainty of evidence in five domains (risk of bias, directness, precision, consistency, and the possibility of publication bias).

2.5. Data synthesis

For dichotomous data, we calculated risk ratio (RR) with 95% confidence interval (CI); for continuous data, we calculated mean difference (MD) with 95% CI. Cochrane Review Manager 5.4 software was employed for data analyses. In meta-analysis, Cochrane Q test and I^2 statistic were employed to assess statistical heterogeneity [20]. A fixed-effects model was considered when $I^2 < 30\%$, otherwise, a random-effects model was used. According to the classification of AURTIs in ICD-10[3], there is no substantial pathophysiologic difference between common cold and acute rhinitis, and therefore we combined them together. Additionally, conventional drug refers to symptomatic treatment used alone or in combination with antibiotics or antivirals, they were considered as a whole. We lumped them together to demonstrate the overall differences of therapeutic effect between SFJD and conventional drug, as well as to make the results more clearly. Funnel plots were performed through Review Manager 5.4 software to detect the possibility of publication bias, if ten or more studies were included in a meta-analysis. To explain heterogeneity, we predefined subgroup analysis in terms of the severity of AURTIs and different ages of patients (adults, children aged between 2 and 14 years old). When the primary outcomes showed clinically meaningful differences between groups, sensitivity analysis was employed to test the robustness of the results in following methodological domains: comparison between clear and unclear randomization concealment; comparison between placebo used and not used; comparison between reported loss- to-follow-up and not reported.

3. Results

3.1. Screening

Initially 1524 records were retrieved. Among which 908 duplicates were removed. 550 records were excluded after title and abstract screening, remaining 66 records. Full-text screening identified 25 RCTs involving 3410 participants, of which 1069 were children. One placebo controlled trial on common cold [29] was narratively described and hence could not be included in the quantitative synthesis (Fig. 1).

3.2. Study characteristics

There were ten trials [22–31] focused on common cold, three [33–35] on herpangina, four [36–39] on acute pharyngitis, seven [40–46] on

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┌─────────────────────────────────────┐
│  Records identified through databases │
│  searching (n=1524). PubMed-34, the   │
│  Cochrane library-10, Embase-54, Web  │
│  of science-96; CNKI-369, Wan         │
│  Fang-359, VIP-317, Sino-Med-283, and │
│  ongoing trials 2.                    │
└─────────────────────────────────────┘
                 │
                 ▼
┌─────────────────────────────────────┐
│  Records after duplicates removed     │
│  (n=908)                              │
└─────────────────────────────────────┘
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┌──────────────────────────┐        ┌──────────────────────────┐
│  Records screened (n=616) │───────▶│  Records excluded (n=550) │
└──────────────────────────┘        └──────────────────────────┘
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                 ▼
┌──────────────────────────┐        ┌─────────────────────────────────┐
│  Full text studies        │───────▶│  Full text studies excluded      │
│  assessed for eligibility │        │  （n=41）                         │
│  (n=66)                   │        │  Not RCTs (n= 13)                │
└──────────────────────────┘        │  Chronic URTIs (n= 7)            │
                 │                    │  Ineligible controls (n=13)      │
                 ▼                    │  Studies with a course of        │
┌──────────────────────────┐        │  treatment over 7 days (n=5)     │
│  Studies included in      │        │  Ineligible outcomes (n=3)       │
│  qualitative synthesis    │        └─────────────────────────────────┘
│  (n=25)                   │
└──────────────────────────┘
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│  Studies included in      │
│  quantitative synthesis   │
│  (meta-analysis)          │
│  RCTs (n=24)              │
└──────────────────────────┘
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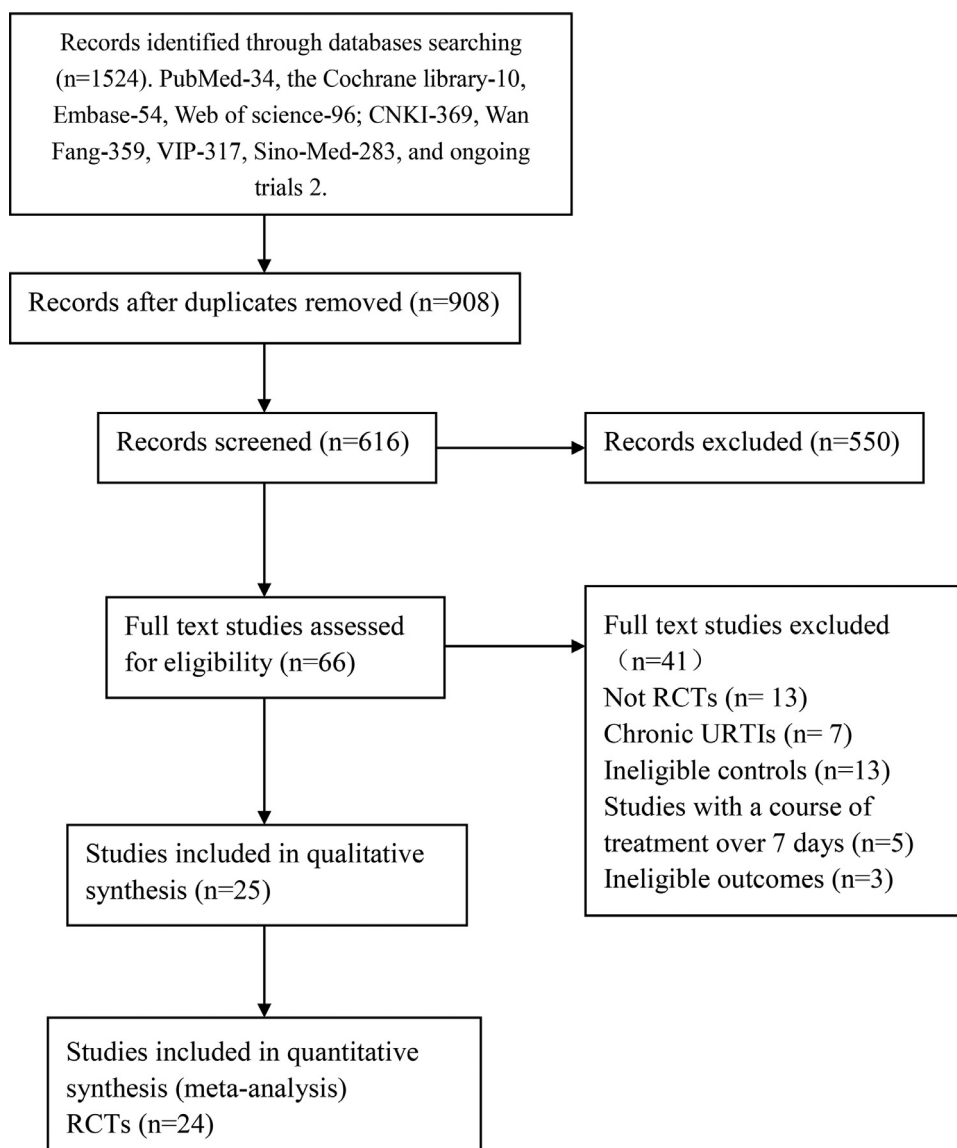
Fig. 1. Flow chart of study selection. RCT: randomized controlled trials; URTIs: upper respiratory tract infections.

acute tonsillitis and one [32] on acute rhinitis. All trials were conducted in China and there was only one [29] multi-center trial, the rest were single center trials. None of the trials reported the funding or conflicts of interest. Sample size varied from 60 to 246 and the mean age varied from 2.4 to 70.9 years. Baseline major symptoms reported were fever, cough and stuffy nose in common cold; fever and blisters in herpangina; fever and sore throat in acute pharyngitis and acute tonsillitis. The duration of treatment varied from 3 to 7 days, and the outcomes were all measured within 5 days from starting treatment. The baseline body temperature in trials were presented in (Table 1). The criteria details of cure rate in individual studies were presented in (Supplementary material). The dose reported in these trials was three times daily administration of SFJD, for adults and children over 10 years old was 4 capsules per time, 3 capsules for 6 to 10 years old, 2 capsules for 3 to 6 years old, and 1 capsule for 2 to 3 years old. Conventional drug referred to symptomatic treatment used alone or in combination with antibiotics or antivirals. Symptomatic treatment included antipyretic [22,24,33,45], decongestant [26,36], antitussive [22–24], expectorants [25, 28] and saline nasal spray [32]; antiviral drugs included ribavirin [22–23,34–35] and interferon [33]; antibiotics included amoxi-

cillin [41,45], cefaclor [40,46] and cefuroxime [42,44]. Only one included trial was placebo controlled [29]. The characteristics of included trials were shown in Table 1.

3.3. Risk of bias assessment

In terms of randomization process, the baseline data were comparable in all the included trials.

Clear random allocation sequence and allocation concealment were reported in only one trial[29], and which was assessed as low risk of bias. Besides, the remaining 24 trials [22–28,30–46] only mentioned random without describing detailed randomization methods. In terms of deviations from intended interventions, participants and personnel were blinded in only two trials[28–29]. Apart from that, deviations from interventions were not mentioned in other 23 trials [22–27,30–46], and therefore the majority of the included trials were assessed as some concerns in this domain. All trials were considered as low risk of bias in missing outcome data domain due to complete outcome data or there was evidence that the result was not biased by the missing data. In terms of measurement of outcomes, nineteen trials [22–24, 26,32–46] were assessed as

Table 1
Characteristics of included randomized trials on SFJD capsules for AURTIs.

Study ID	Population	Sample size	Average age (year)	Male (%)	Time from symptom onset when included (Hours)	TCM syndrome differentiation	Baseline major symptoms	Intervention	Comparison	Treatment duration (days)	Measurement time of outcomes (days)	Outcomes reported[a]
Common cold							**Fever, cough**					
Chen H 2016 [22]	Children	78/78	6.3/6.5	44.9/52.6	NR	NR	>37.3°C	SFJD+ST +ribavirin	ST +ribavirin	7d	5d	2,3,6
Zhou XF 2016[23]	Children	70/70	5.1/4.8	48.6/44.348	48hr	Wind-heat syndrome	37.3–41.6°C	SFJD +ST+ ribavirin	ST+ ribavirin	5d	5d	2,3,6
Wang Q 2018[24]	Children	45/44	7.15/7.2	53.3/52.27	NR	NR	>37.3°C	SFJD +ST+ antivirals	ST+ antivirals	5d	5d	2,3,6
Zhang YP 2014[25]	Adults	110/110	40.2/39.81	54.5/59.0	NR	NR	>37.3°C	SFJD+ST	ST	7d	1d	1
Ye XQ 2013[26]	Adults	100/100	38.55/37.85	52/49	48hr	Wind-heat syndrome	37.3–39.0°C	SFJD+ST	ST	3d	3d	1,2,6
Zhao JL 2018[27]	Adults	61/62	45.69/45.21	49.1/53.2	NR	NR	>37.3°C	SFJD+ST	ST	3d	3d	1,6
Zhang B 2020[28]	Adults	119/118	31.94/35.94	56.8/54.6	NR	NR	37.3–39.0°C	SFJD+ST	ST	3d	3d	1,6
Xu YL 2015[29]	Adults	120/120	49.24/47.77	60/57.9	36hr	Wind-heat syndrome	37.3–39.0°C	SFJD	placebo	7d	3d	1,2,6
Wu XJ 2015[30]	Adults	112/119	70.9/70.8	59.8/59.8	NR	NR	>37.3°C	SFJD+ST+ antibiotics	ST+ antibiotics	7d	3d	1
Zhao LB 2020 [31]	Adults	78/78	37.3/36.8	52.3/51.3	36h	Wind-heat syndrome	37.1–39.1°C	SFJD +ST+ antivirals	ST+ antivirals	5d	5d	6
Acute rhinitis							**Fever, stuffy nose**					
Li Y 2015[32]	Adults	30/30	49.2/50.3	43.3/46.7	72hr	Wind-heat syndrome	>37.3°C	SFJD+ST	ST	7d	5d	6
Herpangina							**Fever, blisters**					
Yang Y 2019[33]	Children	35/35	4.55/4.2	51.4/42.9	48hr	NR	>37.3°C	SFJD +ST+ interferon	ST+ interferon	5d	5d	2,5,6
Yang ML 2016[34]	Children	123/123	4.2/4.1	49.6/47.9	48hr	NR	>37.3°C	SFJD+ST+ ribavirin	ST+ ribavirin	5d	5d	2,5,6
Liu CX 2015[35]	Children	37/33	2.4/2.5	NR	48hr	NR	37.3–41.0°C	SFJD +ST+ ribavirin	ST+ ribavirin	5d	5d	2,5,6
Acute pharyngitis							**Fever, sore throat**					
Zhu SM 2019[36]	Adults	38/38	41.34/41.25	57.9/52.6	48hr	Wind-heat syndrome	37.3–38.5°C	SFJD+ ST	ST	5d	5d	4,6
Jiang JQ 2018[37]	Adults	48/48	37/39.81	47.9/43.8	48hr	NR	>37.3°C	SFJD+ST	ST	7d	5d	4,6
Dong W 2020[38]	Adults	45/45	30.1/32.1	48.89/53.33	36h	NR	>37.3°C	SFJD+ST	ST	6s	5d	2,4
Zhou QQ 2020[39]	Adults	106/106	32.75/30.63	69.8/74.53	48h	NR	NR	SFJD+ST	ST	7d	5d	4

Table 1 (continued)

Study ID	Population	Sample size	Average age (year)	Male (%)	Time from symptom onset when included (Hours)	TCM syndrome differentiation	Baseline major symptoms	Intervention	Comparison	Treatment duration (days)	Measurement time of outcomes (days)	Outcomes reported[a]
Acute tonsillitis							**Fever, sore throat**					
Zhang JY 2015[40]	Adults	45/45	22.94/24.17	68.9/60	48hr	NR	37.3–39.1°C	SFJD +ST+ cefaclor	ST+ cefaclor	7d	5d	2,4,6
Wang ZB 2018[41]	Adults	55/55	16.39/20.73	56.4/49.1	72hr	NR	>37.3°C	SFJD +ST+ amoxicillin	ST+ amoxicillin	7d	5d	2,4,6
Li G 2017[42]	Adults	50/50	27.1/27.3	56/52	NR	NR	≥38.0 °C	SFJD +ST+ cefuroxime	ST+ cefuroxime	5d	5d	2,4,6
Li BR 2020[43]	Adults	50/50	22/21	52/42	NR	NR	>37.3°C	SFJD+ST+ penicillin	ST+ penicillin	7d	5d	2,4,6
Zhao ZY 2015[44]	Children	58/50	5.9/6.1	53.4/54	72hr	NR	≥38.0 °C	SFJD +ST+ cefuroxime	ST+ cefuroxime	5d	5d	2,4,6
Yang X2017 [45]	Children	35/35	3.52/3.53	48.6/51.4	48hr	NR	38.4–39.8 °C	SFJD +ST+ amoxicillin	ST+ amoxicillin	5d	5d	2,4,6
Huang PL 2016[46]	Children	60/60	7.12/6.74	51.7/53.3	72h	Wind-heat syndrome	>37.3°C	SFJD +ST+ cefaclor	ST+ cefaclor	6d	5d	2,4,6

Notes: AURTIs, acute upper respiratory tract infections; d, days; hr, hours; NR, not reported; SFJD, Shufeng Jiedu; ST, symptomatic treatment.
Outcomes: 1, Resolution rate of fever at day 3 of treatment; 2, Time to fever resolution; 3, Time to cough resolution; 4, Time to sore throat resolution; 5, Time to blister resolution; 6, Cure rate.
[a] 1–5 were primary outcomes, 6 was secondary outcome.

high risk of bias due to the outcomes were patients self-reported and likely influenced, other 6 trials [25,27–31] were of low risk of bias since the outcomes were objective or outcome assessors were not aware of the interventions received by participants. In terms of selection of the reported result, twenty-one trials [22–24,29–46] were assessed as some concerns due to lack of pre-specified analysis plan, four trials [25–28] were assessed as high risk of bias due to lack of pre-specified analysis plan and multiple time points outcome measurements. The overall bias was assessed as low for only one trial [29] and high for the remaining 24 trials [22–28,30–46]. The methodological quality of the included trials were shown in Fig. 2.

3.4. Effect estimates

3.4.1. Common cold/acute rhinitis

There were 10 trials [22–31] focused on common cold, of these, three trials [22–24] reported the time to fever and cough resolution, as well as the cure rate, the other 7 trials [25–31] reported the cure rate. Only one trial [32] on acute rhinitis and reported the cure rate.

3.4.1.1. Time to fever and cough resolution. Three trials [22–24] compared SFJD plus conventional drug (symptomatic treatment and antivirals) with conventional drug for common cold in children, and reported the time to fever and cough resolution. The pooled results showed that SFJD was superior to control group in shortening the time to fever resolution (MD −1.54 days, 95% CI [−2.15, −0.92], I^2 = 80%, n = 385, 3 trials, very low certainty) and cough resolution (MD −1.22 days, 95% CI [−1.52, −0.93], n = 385, 3 trials, low certainty) (Table 2, Supplementary material).

3.4.1.2. Clinical cure. SFJD combined with conventional drug (symptomatic treatment alone [25–28,32], symptomatic treatment plus antivirals [22–24,31] or symptomatic treatment plus antibiotics [30]) were also found more effective than conventional drug in improving the cure rate in common cold with a range (1–5 days) of treatment (RR 1.26, 95% CI [1.17, 1.35], n = 1593, 10 trials [22–28,30–32], low certainty) (Fig. 3, Table 2). Subgroup analysis by age suggested that SFJD in combination with conventional drug was still superior to conventional drug in improving the cure rate in adults (RR 1.27, 95%CI [1.18, 1.36], n = 1208, 7 trials [25–28, 30–32], moderate certainty). But this effect was not significant in children (RR 1.22, 95%CI [0.97, 1.54], n = 385, 3 trials [22–24] low certainty) (Fig. 3, Table 2). There was only one double blinded, placebo-controlled trial [29] which comparing the effect of SFJD with placebo on common cold, the result was narratively described. The cure rate was 44.2% in SFJD group and 9.3% in placebo group (RR 4.74, 95%CI [2.61, 8.61], n = 238, 1 trial, moderate certainty) (Supplementary material).

3.4.2. Herpangina
3.4.2.1. Time to fever and blisters resolution. Three trials [33–35] compared SFJD in combination with conventional drug (symptomatic treatment plus antivirals) with conventional drug on herpangina. Which showed that SFJD plus conventional drug was superior to conventional drug in shortening the duration of fever (MD −0.68 days, 95% CI [−1.15, −0.21], I^2 = 68%, n = 140, 2 trials, very low certainty) and blisters (MD −0.99 days, 95% CI [−1.23, −0.76], n = 386, 3 trials, low certainty) (Supplementary material).

3.4.2.2. Clinical cure. The cure rate was defined as resolution of fever and blisters with a range (1–5 days) of treatment. SFJD plus conventional drug was superior to conventional drug for cure rate (RR 1.30, 95% CI [1.12, 1.51], n = 386, 3 trials, low certainty) (Supplementary material).

3.4.3. Acute tonsillitis and acute pharyngitis
3.4.3.1. Time to fever and sore throat resolution. SFJD plus conventional drug (symptomatic treatment and antibiotics) compared with conventional drug for acute tonsillitis and acute pharyngitis. Seven trials [40–46] indicated that the duration of fever was shorter in SFJD group than conventional drug group (MD −1.13 days, 95% CI [−1.36, −0.90], I^2 = 33%, n = 688, 7 trials, moderate certainty) (Fig. 4, Table 3). This effect was still observed regardless of adults (MD −1.24 days, 95% CI [−1.46, −1.01], n = 390, 4 trials, low certainty) or children (MD −0.93 days, 95% CI [−1.30, −0.55], n = 298, 3 trials, low certainty).

SFJD was also more effective than conventional drug (symptomatic treatment alone or symptomatic treatment plus antibiotics) in shortening the time to sore throat resolution in acute tonsillitis and acute pharyngitis (MD −1.13 days, 95% CI [−1.40, −0.86], I^2 = 84.1%, n = 1194, 10 trials, low certainty). This effect was still observed regardless of adults (MD −1.29 days, 95% CI [−1.60, −0.97], I^2 = 70%, n = 896, 7 trials, low certainty) or children (MD −0.73 days, 95% CI [−1.03, −0.43], n = 298, 3 trials, low certainty) (Table 3, Supplementary material).

3.4.3.2. Clinical cure. The criteria for cure rate was resolution of sore throat and fever with a range (1–5 days). SFJD was superior to conventional drug (symptomatic treatment alone or symptomatic treatment plus antibiotics) for cure rate (RR 1.26, 95% CI [1.13, 1.41], I^2 = 29.4%, n = 1082, 10 trials, low certainty) (Table 3, Supplementary material). This effect was still observed regardless of the age of patients.

3.4.4. Adverse events
There were 7 trials [25–26,31,36,38,40,46] reported transient and minor gastrointestinal adverse events both in SFJD group (nausea in 6 cases, diarrhea in 4 cases) and in conventional drug group (nausea in 9 cases, diarrhea in 3 cases). SFJD was not judged as directly related to nausea and diarrhea in these trials, and no serious adverse events were reported in the included trials.

3.4.5. Publication bias
Funnel plots of cure rate in common cold seems to be symmetrical (Supplementary materials: Fig. 8), and funnel plots of time to sore throat resolution in acute tonsillitis and acute pharyngitis seems to be asymmetrical (Supplementary materials: Fig. 9). Suggesting that we cannot rule out the possibility of publication bias.

3.4.6. Additional analysis
We were unable to conduct sensitivity analysis for placebo or allocation concealment in any meaningful primary outcomes, since the allocation concealment was clearly described in only one placebo-controlled trial [29] and the trial was narratively described. Two trials [25,29] reported drop outs but under different outcomes. Predefined subgroup analysis via the age of patients (adults and children) was conducted for 3 outcomes under common cold, acute tonsillitis and acute pharyngitis, we were unable to conduct other meaningful subgroup analysis due to limited trials.

3.4.7. Certainty of evidence
GRADE approaches were employed to rate the certainty of evidence from all available outcomes. The quality of the evidence was downgraded to low or very low certainty due to lack of the blinding, imprecision (small number of events of less than 300 or number of patients included was less than 400), inconsistency (I square value was large) or indirectness of age (adults and children). The detailed evidence summary of outcomes were presented in (Table. 2,3, Supplementary material).
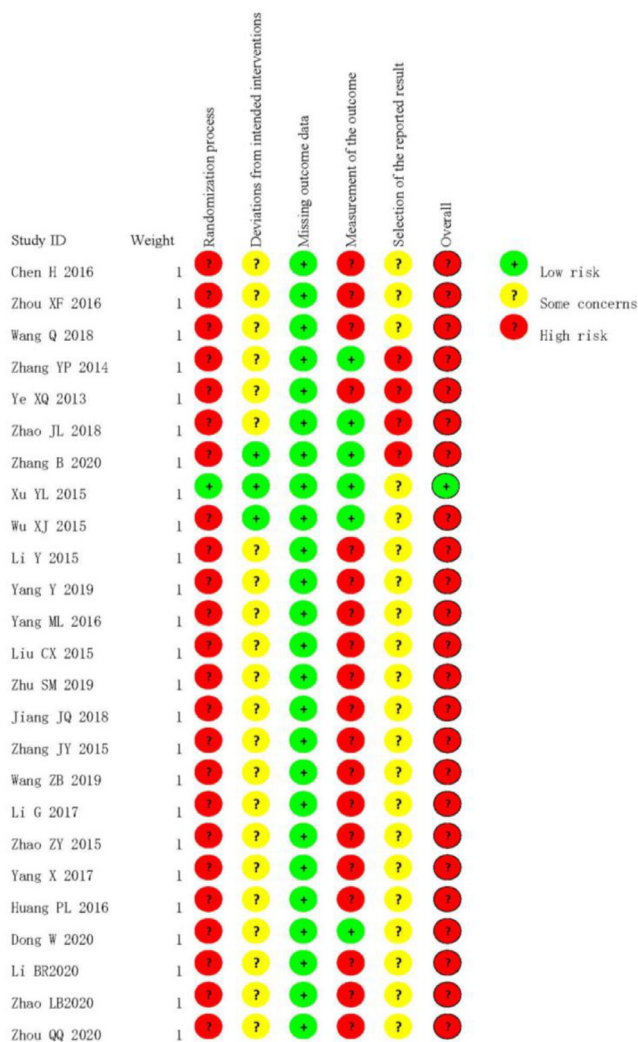
（a）Risk of bias summary
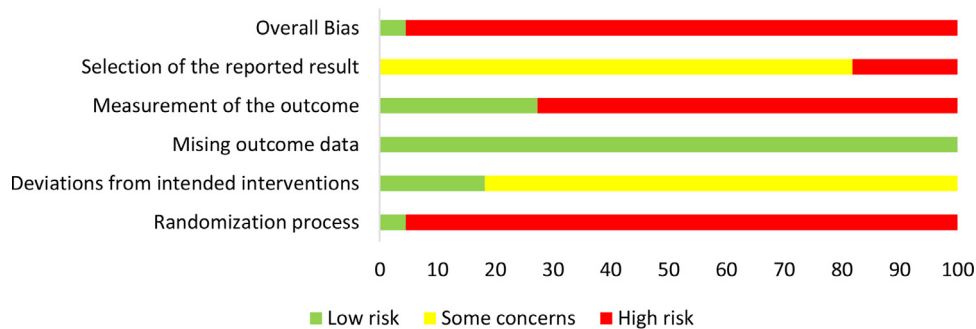
(b) Risk of bias graph

Fig. 2. (a) Risk of bias summary.
Fig. 2(b) Risk of bias graph.

Table 2
Evidence summary of common cold/ acute rhinitis: SFJD +conventional drug versus conventional drug.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SFJD+ conventional drug	conventional drug	Relative (95% CI)	Absolute (95% CI)		
Time to fever resolution												
3	randomized trials	serious[a]	serious [b]	not serious	serious [c]	undetected	193	192	-	MD **1.54 lower** (2.15 lower to 0.92 lower)	⊕○○○ VERY LOW	CRITICAL
Time to cough resolution												
3	randomized trials	serious a	not serious	not serious	serious [c]	undetected	193	192	-	MD **1.22 lower** (1.52 lower to 0.93 lower)	⊕⊕○○ LOW	CRITICAL
Cure rate												
10	randomized trials	serious [a]	not serious	serious [d]	not serious	undetected	554/792 (69.9%)	446/801 (57.7%)	**RR 1.26** (1.17 to 1.35)	**145 more per 1000** (from 95 more to 195 more)	⊕⊕○○ LOW	IMPORTANT
Cure rate in adults												
7	randomized trials	serious [a]	not serious	not serious	not serious	undetected	463/599 (77.3%)	372/609 (61.1%)	**RR 1.27** (1.18 to 1.36)	**165 more per 1000** (from 110 more to 2more)	⊕⊕⊕○ MODERATE	IMPORTANT
Cure rate in children												
3	randomized trials	serious [a]	not serious	not serious	serious[e]	undetected	91/193 (47.2%)	74/192 (38.5%)	**RR 1.22** (0.97 to 1.54)	**85 more per 1000** (from 12 fewer to 208 more)	⊕⊕○○ LOW	IMPORTANT

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
GRADE Working Group grades of evidence.
Moderate certainty (⊕⊕⊕○): We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty (⊕⊕○○): Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low certainty (⊕○○○): We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
Notes: CI, confidence interval; RR, risk ratio; SFJD, ShuFeng JieDu.
[a] The blinding method was not used.
[b] I square value was large.
[c] Number of patients included was less than 400.
[d] Indirectness of age (adults and children).
[e] A small number of events of less than 300.

Table 3

Evidence summary of acute tonsillitis and acute pharyngitis: SFJD + conventional drug versus conventional drug.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	SFJD +conventional drug	conventional drug	Relative (95% CI)	Absolute (95% CI)		
Time to fever resolution												
7	RCTs	serious [a]	not serious	serious [b]	not serious	undetected	348	340	-	MD **1.13 d lower** (1.36 lower to 0.90 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Time to fever resolution- adults												
4	RCTs	serious [a]	not serious	not serious	serious [c]	undetected	195	195	-	MD **1.24 d lower** (1.46 lower to 1.01 lower)	⊕⊕◯◯ LOW	CRITICAL
Time to fever resolution - children												
3	RCTs	serious [a]	not serious	not serious	serious [c]	undetected	153	145	-	MD **0.93 d lower** (1.30 lower to 0.55 lower)	⊕⊕◯◯ LOW	CRITICAL
Time to sore throat resolution												
10	RCTs	serious [a]	not serious	serious [b]	not serious	undetected	601	593	-	MD **1.13 d lower** (1.40 lower to 0.86 lower)	⊕⊕◯◯ LOW	CRITICAL
Time to sore throat resolution - adults												
7	RCTs	serious [a]	serious [d]	not serious	not serious	undetected	448	448	-	MD **1.29 d lower** (1.60 lower to 0.97 lower)	⊕⊕◯◯ LOW	CRITICAL
Time to sore throat resolution – children												
3	RCTs	serious [a]	not serious	not serious	serious [c]	undetected	153	145	-	MD **0.73 d lower** (1.03 lower to 0.43 lower)	⊕⊕◯◯ LOW	CRITICAL

Table 3 (*continued*)

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	SFJD +conventional drug	conventional drug	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Certainty assessment							**№ of patients**		**Effect**		**Certainty**	**Importance**
Cure rate												
10	RCTs	serious [a]	not serious	serious [b]	serious	undetected	289/545 (53.0%)	228/537 (42.5%)	RR 1.26 (1.13 to 1.41)	110more per 1000 (from 55 more to 174 more)	⊕⊕◯◯ LOW	IMPORTANT
cure rate - adults												
7	RCTs	serious [a]	not serious	not serious	serious	undetected	239/392 (61.0%)	197/392 (50.3%)	RR 1.21 (1.09 to 1.35)	106 more per 1000 (from 45 fewer to 176 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
cure rate - children												
3	RCTs	serious [a]	not serious	not serious	serious [e]	undetected	50/153 (32.7%)	31/145 (21.4%)	RR 1.54 (1.05 to 2.26)	115 more per 1000 (from 11 more to 269 more)	⊕⊕◯◯ LOW	IMPORTANT

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence.

Low certainty (⊕⊕◯◯): Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect;

Very low certainty (⊕◯◯◯): We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect;

Notes: CI, Confidence interval; MD, Mean difference; RCTs, Randomized controlled trial; RR, Risk ratio; SFJD, ShuFeng JieDu.

[a] The blinding method was not used.

[b] Indirectness of age (adults and children).

[c] Number of patients included was less than 400.

[d] *I* square value was large.

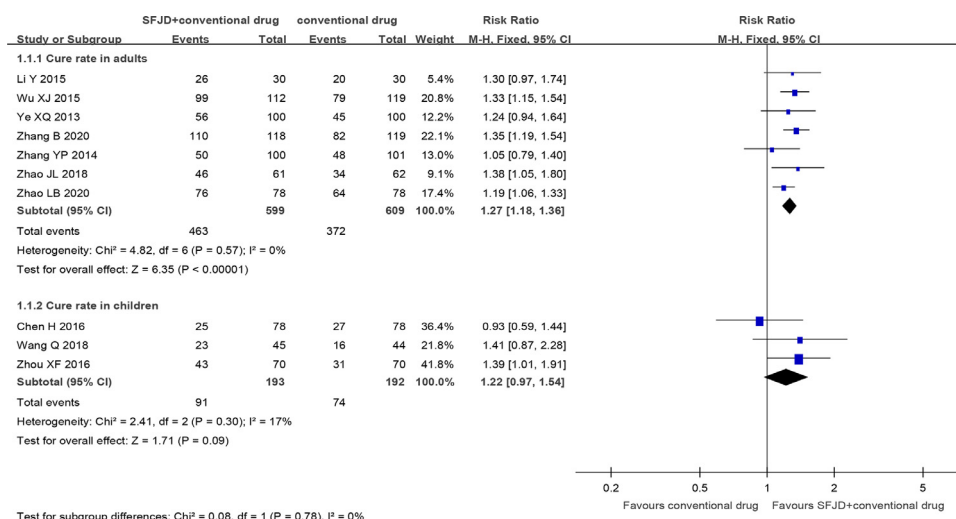[e] A small number of events of less than 300.

Fig. 3. Cure rate with a range (1–5days) of treatment in common cold. SFJD, Shufeng Jiedu.
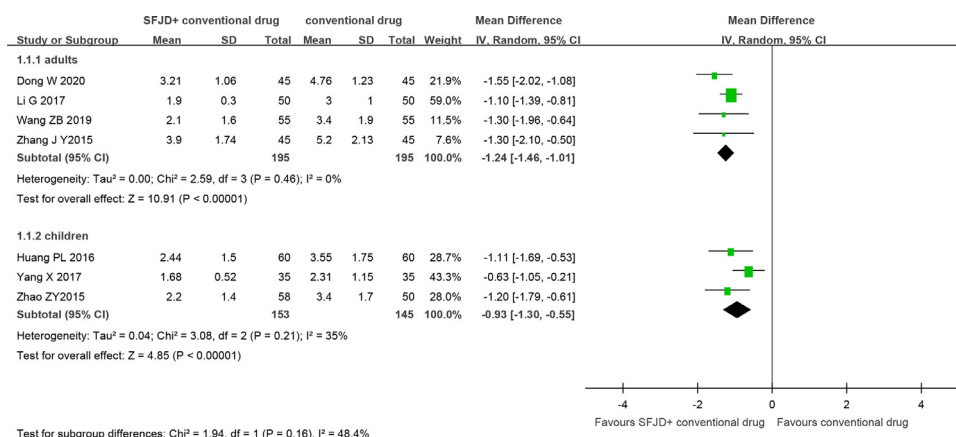

Fig. 4. Time to fever resolution (d) in acute tonsillitis and acute pharyngitis. SFJD, Shufeng Jiedu.

4. Discussion

4.1. Main findings

Low certainty evidence suggested that SFJD capsule as an adjunctive treatment to conventional drug was more beneficial than conventional drug alone to shorten the duration of symptoms in AURTIs, as well as improve cure rate with a range (1–5 days) of treatment. In common cold we found that SFJD was superior to conventional drug alone in shortening the duration of cough (−1.22 days) and fever (−1.54 days), as well as improving cure rate by 14.1%. In herpangina, SFJD plus conventional drug was more effective in shortening the duration of fever (−0.68 days), blisters (−0.99 days) and improving the cure rate by 15.8%. In acute tonsillitis and acute pharyngitis, SFJD combined with conventional drug was superior to conventional drug in shortening the duration of fever (−1.13 days), sore throat (−1.13 days) and increasing cure rate by 11%. These effects were still observed regardless of age. However, due to high risk of bias and small sample size, we downgraded these outcomes from high to low or very low certainty. In addition, there was no serious adverse events reported in the included trials.

4.2. Relation to previous research

Currently, there was one systematic review[47] on SFJD for chronic obstructive pulmonary disease (COPD) suggested that SFJD

may be beneficial to shorten the length of hospitalization and improve symptoms related to COPD. Another prior systematic review[11] narratively reviewed the clinical and experimental findings of Chinese herbal medicine for the treatment of AURTIs. Suggesting that SFJD capsule was effective in improving symptoms of AURTIs, such as fever and cough. Which was consistent with our study. However, only one RCT on SFJD for AURTIs was identified and meta-analysis was not performed in this previous review. We conducted a more comprehensive search and meta-analysis was performed for more available outcomes. In addition, the protocol of this systematic review was registered prospectively and GRADE approaches were employed to assess the certainty of evidence.

4.3. Strengths and limitations

This is the first systematic review and meta-analysis based on RCTs to assess therapeutic effect and safety of Chinese patent herbal medicine SFJD capsule for AURTIs. We comprehensively searched the Chinese and English databases and identified all available RCTs. The outcomes were all assessed within 5 days of treatment, since many types of AURTIs were self-limited in 7 days[4]. The protocol of this systematic review was registered on INPLASY, and subgroup analysis via the age of patients was conducted. The methodological quality of RCTs were evaluated comprehensively by the latest Cochrane Risk of Bias tool 2.0, and GRADE criteria was also employed to determine the certainty of evidence.

However, there are several limitations. Firstly, antibiotics are not recommended for most AURTIs in guidelines, but they were used in the included trials. Secondly, predefined outcomes of symptom improvement rate and the severity of AURTIs were not reported in included trials. Additionally, only one double-blinded, placebo-controlled trial was assessed as having low risk of bias, the remaining included trials were of high risk of bias.

4.4. Implications for clinical practice

The diagnosis and treatment of AURTIs should strictly following guidelines. Antibiotics are recommended only for specific AURTIs (such as acute pharyngitis and acute tonsillitis caused by streptococcus) in existing guidelines, for other AURTIs, symptomatic treatment were recommended[5,6]. Standard care following guidelines are recommended, considering the potential effect of SFJD capsule, it might be a safe symptomatic treatment for AURTIs.

4.5. Implications for research

SFJD may have a role to play for the relief of symptoms from common AURTIs, but there is uncertainty due to the high risk of bias in the current studies. High quality placebo controlled RCTs with SFJD used alone or in combination with standard care are needed. Outcome reporting needs to be improved, the time from symptoms onset when included and the time point for every outcome measured should be clearly reported, since most AURTIs resolve from 3 to 7 days [4]. In addition, cure rate was widely used in these trials as composite outcomes[48] (usually included a set of symptoms and signs), but the detailed measurement of individual symptoms or signs could not be determined.

4.6. Conclusion

Currently, low certainty evidence suggests that SFJD may be effective in shortening the duration of typical symptoms in AURTIs, and improve cure rate with a range (1–5 days) of treatment. No serious adverse event was reported. However, high quality placebo-controlled trials are needed to confirm its benefits.

4.7. Author contributions

Conceptualization: YY Zhang, JP Liu and RY Xia. Methodology: RY Xia and S B Liang. Software: YY Zhang and S B Liang; YL Li and LY Zhao. Formal Analysis: YY Zhang and RY Xia. Data Curation: YY Zhang and RY Xia. Writing – Original Draft: YY Zhang. Writing – Review & Editing: RY Xia, SB Liang, XY Hu, MY Dai, YL Li, LY Zhao, M Moore, YT Fei and JP Liu. Funding Acquisition: JP Liu. YY Zhang and RY Xia are co-first authors. All authors approved the final manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

Ethical statement

This work did not require an ethical approval as it does not involve any human or animal experiment.

Data availability

The data will be made available upon request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2021.100726.

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