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A synthesis of the evidence regarding safety of a Chinese herbal formula Shufeng Jiedu: A pharmacological review

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ABSTRACT

Shufeng Jiedu capsule (SFJDC) is a Chinese herbal medicine formula for treating acute respiratory tract infections. This review aims to assess its potential safety for clinical setting.

Systematic literature searches were conducted across multiple databases to: investigate the phytochemistry and safety data on SFJD and its constituents; and to produce a meta-analysis of RCTs reporting safety concerns (all ages) receiving SFJDC capsule (any condition). The primary outcome was the incidence of adverse events (AEs) or complications associated with taking SFJDC with/without usual care compared with placebo or usual care.

Pharmacovigilance data reporting AEs to the Chinese National Adverse Drug Reaction Monitoring System in 2017/2018 was analysed.

Safety information was insufficient regarding pregnancy/lactation (all herbs). Laboratory studies raised theoretical concerns regarding saikosaponins A and D elevating blood glucose; glycyrrhizin inducing hypertension and hypokalaemia; and saikosaponins/resveratrol/lignans reducing platelet activity. However, these occurred at much higher doses than used clinically.

Sixty-four RCTs (7612 participants) met the meta-analysis criteria. Fourteen additional trials and two case studies were also considered. Minor AEs included nausea/vomiting, diarrhoea, unspecified gastrointestinal discomfort, dizziness and rash; these were not significantly different (statistically) to control groups.

Across 2017 and 2018 sales of SFJDC packs (content 36 capsules) totalled 23.2 million. AEs recorded were 169 (2017) and 198 (2018). The majority were gastrointestinal, and improved on stopping SFJDC. None included the potential phytochemical concerns (regarding platelets, hypertension, hypokalaemia, blood glucose).

No serious AEs were identified from the included trials or pharmacovigilance data.

No substantive safety concerns were identified for SFJD for clinical use; excluding pregnant/lactating women.

1. Introduction

Treatment of respiratory tract infections with antibiotics comprised the majority of all antibiotic prescribing in primary care in England in 2015. This totalled 46% of all prescriptions administered, with 10.4% prescribed for coughs and 8.8% for lower respiratory tract infections [1]. Moreover, prescribing for chronic respiratory conditions by UK primary care such as chronic obstructive pulmonary disease (COPD) now accounts for three times more antibiotic prescriptions than for the general population due to acute exacerbations of this condition [2].

Shufeng Jiedu capsule (SFJDC) is a patented traditional Chinese herbal medicine (TCM) formula that is widely used in China for treating acute respiratory tract infections with fever, such as tonsillitis and influenza [3]. Preliminary research in China has shown that when administered alongside usual care, SFJDC can reduce the duration of hospitalisation in patients suffering from acute exacerbations of chronic obstructive pulmonary disease (AECOPD) [4]. SFJDC is going to be tested in a Phase 3 feasibility study in the UK with a further clinical trial in China. The purpose of the trials is to investigate whether administration of SFJDC combined with standard care may aid the recovery of patients with AECOPD and reduce the necessity for antibiotics.

SFJDC comprises eight Chinese herbs: *Bupleurum chinense* DC (root), *Fallopia japonica* Houtt (rhizome/root), *Forsythia suspensa* (Thunb) Vahl. (fruit), *Glycyrrhiza uralensis* Fisch (rhizome/root), *Isatis indigotica* L. (root), *Patrinia scabiosaefolia* Fisch (aerial parts), *Phragmites communis* Trin. (rhizome) and *Verbena officinalis* L. (aerial parts): English, Pin Yin, Latin synonyms and pharmaceutical names are in Appendix A. The capsules have been approved by the China Food and Drug Administration

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for treating patients with influenza and pneumonia [5]. The capsule preparation is registered in the Chinese Pharmacopoeia for "dispersing heat and cleansing toxins" [6].

The individual herbs contained in SFJDC have a variety of traditional uses, and reported therapeutic actions range from anti-inflammatory activity to elimination of toxins [5]. As a TCM it is believed in China that the herbs work synergistically with each other [7]. The main mechanism of action and therapeutics for the formula are not fully established, although in a clinical setting (n = 120) SFJDC has demonstrated antipyretic activity [8], as well as anti-inflammatory and immunomodulatory effects in rats [8]. In another clinical multi-centre study, 130 patients with an acute viral upper respiratory tract infection, a third of whom had the H1N1 virus, showed a reduction in fever after taking SFJD. The fever abated within 4 hours in 30% of patients and by 72 hours in 90% [9].

Anti-infective properties of the formula have been demonstrated in a mouse model: SFJDC (0.55 g/kg) was shown to reduce mortality caused by *Staphylococcus aureus* infection by 26% and increase survival time by 3 days compared with amoxicillin (89% and 6 days respectively). For *Streptococcus sp*. SFJD reduced mortality by 71% (compared with amoxicillin 100%) and increased survival time by 6 days [3].

SFJDC has demonstrated antimicrobial action *in vitro* against several bacterial organisms, both gram positive and negative, including *Staphylococcus aureus, Streptococcus pneumonia* and *Pseudomonas aeruginosa* although the minimum inhibitory concentrations (MIC) were high at 1.5 mg/mL, 3.1 mg/mL and 12.5 mg/mL respectively [3].

With limited clinical data available on SFJDC this review has been undertaken to investigate the evidence on the safety of the herbal preparation. It includes a narrative review on the phytochemistry and pharmacology of the 8 individual herbs and SFJDC formula, as well as a systematic review and meta-analysis of adverse events reported in clinical studies and an examination of available pharmacovigilance data.

2. Methods

2.1. Databases

A literature search was conducted up to October 2019 across PubMed, Web of Science, Science Direct, EMBASE and the Cochrane databases. The narrative review into the pharmacology of the individual herbs and SFJDC formula also encompassed Ovid, herbal texts, pharmacological safety books and the Chinese Pharmacopoeia [10], whilst for the meta-analysis a systematic search was conducted across the aforementioned databases; the Chinese Science and Technology Journal Database (VIP), China National Knowledge Infrastructure (CNKI), Wan Fang, and the Sino-Med Database (in Chinese). All databases were searched from their inception to October 2019. Full search criteria and terms are included in Appendix B.

2.2. Pharmacovigilance data

AEs reported by the UK public on taking individual herbs contained in SFJDC were searched on the Medicines and Healthcare Products Regulatory Agency (MHRA) Yellow Card System from inception to the end of 2020. Patient data on AEs reported to the National Adverse Drug Reaction Monitoring System in China (NADRMS) in 2018/2019 was supplied by Jiren, the manufacturer of SFJDC. In the event of an unexpected AE, a patient informs their physician, the drug manufacturer, or the local adverse drug reaction monitoring agency, who completes a form for submission to NADRMS.

2.3. Inclusion and exclusion criteria

Search criteria on the pharmacology/phytochemistry of the individual herbs included their names in English/Latin/Chinese and the terms: safety; toxicity; activity; therapeutics; efficacy; *in vitro; in vivo*; drug interactions; clinical studies; case studies; phytochemical constituent and pharmacokinetics. Publications on TCM formulas in combination with other herbs, or which analysed extraction methods, genetics, phylogeny, botany, and cultivation were excluded.

Clinical research reporting any safety concerns in all age groups receiving SFJDC for any condition (all languages) was included. Placebo and usual care (such as antipyretics, antivirals, antibiotics, anti-inflammatories, steroids or corticosteroids) were comparators. Information regarding SFJDC in combination with other remedies, or potential interactions with other medications was collected.

2.4. Primary outcome

The primary outcome for the meta-analysis was the incidence of any AEs/side effects, anaphylactic, allergic, hypersensitivity reactions, or complications due to taking SFJDC on its own or in combination with usual care compared with placebo or usual care. Serious safety events were defined according to the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines as any event that: leads to death, is life-threatening, requires or prolongs hospitalisation, leads to persistent or significant disability; or altered biochemistry results such as liver and kidney function tests (alanine aminotransferase and creatinine) (ICH, 1999).

2.5. Data selection, collection and extraction

Literature searching (JT, ZJW) was followed by independent screening by 3 reviewers (JT, ZJW, YZ). Disagreements were resolved through discussion with a fourth reviewer (XYH) to meet final consensus. Researchers were not blinded to the authors' affiliations, journal of publication, or study results. After downloading from databases or entering manually into Endnote for de-duplicating, three review authors (ZJW, YZ, JT) independently extracted data from the included trials.

2.6. Data analysis

Findings on the safety of the individual herbs were summarised and reported narratively.

For the RCTs between-study heterogeneity was assessed using the I^2-statistic whereby $I^2 > 30\%$ represented moderate heterogeneity, $I^2 > 50\%$ significant heterogeneity and $I^2 > 75\%$ considerable heterogeneity [11]. Where I^2 values were above 50%, potential sources of heterogeneity were further investigated in a sensitivity analysis and taken into account when interpreting the findings. As high levels of heterogeneity were expected due to different ailments, a random effects model was utilized to pool the overall effects [11]. Funnel plot tests for asymmetry were conducted to investigate potential reporting bias where there were sufficient studies (n>10) under a single meta-analysis [12].

Where standard deviation was not reported with means, it was calculated from the information reported such as confidence intervals (CIs), p-values, or F-values. Intention to treat (ITT) analysis was utilized for all outcomes as far as possible. The number of participants whose data was available at baseline and at the last follow-up, and the rate of loss to follow-up were recorded.

The subgroup analysis was performed on the primary outcome on the same interventions used for different conditions and resultant different AEs, and on secondary outcomes on different interventions with different conditions.

A sensitivity analysis was performed to confirm the robustness of reported data. AEs in RCTs which included 'safety' as an outcome in the aim, title or outcome were compared to the results of all the included studies.

Table 1
Constituents of possible concern compared to quantity present in SFJD and recommended TCM dose.

Theoretical Safety Concern/ Phytochemical Constituent	Quantity used in *in vitro/vivo* study	Maximum Concentration of Constituent in Plant	Total Plant Quantity to Produce Daily SFJD Dose Versus Daily TCM Dose [10]
Antiplatelet			
Saikosaponin A *B. chinense* [15]	Platelet aggregation similar to aspirin *in vitro* stimulated by ADP at a concentration of 10^{-5}M	Saikosaponin A 3.9 mg/g	SFJD = 4.32 g TCM dose = 3-10 g
Resveratrol *F. japonica* [17]	Platelet aggregation inhibited by 4mg/kg in rabbits	Resveratrol 4.3 mg/g	SFJD = 5.40 g TCM dose = 9-15 g
Lignans (phillyrin) *F. suspensa* [19]	PAF inhibited 89% by 100 μg/mL aqueous solution	Lignans 1.3 mg/g	SFJD = 4.32 g TCM dose = 6-15 g
May elevate glucose			
Saikosaponin A, D *B. chinense* [16]	2.5 and 5 mg/kg in rats	Saikosaponin A 3.9 mg/g Saikosaponin D 4.6 mg/g	SFJD = 4.32 g TCM dose = 3-10 g
Hypertensive			
Glycyrrhizin *G. uralensis*	*N/A - see clinical data in results*	Glycyrrhizin 81.3 mg/g	SFJD = 2.16 g TCM dose = 2-10 g
Hypokalaemic			
Glycyrrhizin *G. uralensis*	*N/A - see clinical data in results*	Glycyrrhizin 81.3 mg/g	SFJD = 2.16 g TCM dose = 2-10 g

Table 2
LD50 of each herb.

Herb	LD_{50}
Bupleurum chinense	>2g/kg oral administration of aqueous extract, mice [24]
Fallopia japonica	Not determined
Forsythia suspensa	172.2g/kg oral administration, mice (extract type unspecified) [20]
Glycyrrhiza glabra	>7.5 g /kg oral administration extract with approx. 53% glycyrrhizin, mice [13]
Isatis indigotica	Not determined
Patrinia scabiosaefolia	Not determined
Phragmites communis	Not determined
Verbena officinalis	>2g/kg oral administration 80% methanol extract, mice [25]

3. Results relating to individual herbs contained in SFJDC – potential safety issues

A full exposition of these results is included Table 1, which includes dosing data on SFJDC for reference. Table 2 contains LD_{50} data on the herbs where available.

3.1. *Glycyrrhiza uralensis*

The European Medicine Association (EMA) has concluded that short-term use (4-6 weeks) of liquorice preparations is considered safe (based on clinical data) [13]. Nevertheless, serious side effects of hypertension and hypokalaemia have been reported when using *Glycyrrhiza*. In susceptible individuals continual daily consumption of low doses of liquorice, equal to 80-100 mg of glycyrryzic acid, have reportedly induced hypertension [13]. Based on a study with 30 volunteers consuming 100 g liquorice daily containing 270 mg glycyrrhizin for 4 weeks, below normal levels of serum potassium and aldosterone were induced, with potassium falling 0.24 mmol/l on average [14].

3.2. *Bupleurum chinense*

Saikosaponin A in *Bupleurum chinense* has been shown to inhibit human platelet aggregation *in vitro* stimulated by adenosine diphosphate (ADP) with efficacy similar to aspirin at a concentration of 10^{-5} M. It also inhibits platelet thromboxane formation from exogenous and endogenous arachidonic acid in a dose dependent manner [15].

There were also findings relating to *Bupleurum chinense* affecting blood glucose. Intraperitoneal administration of the constituents saikosaponins A and D in rats at levels of 5 mg/kg and 2.5 mg/kg respectively were found to increase blood glucose [16].

3.3. *Fallopia japonica*

Resveratrol in *Fallopia japonica* has demonstrated antiplatelet activity in pre-clinical studies [17]. Platelet aggregation has been inhibited *in vivo* at a dose of 4mg/kg/day in rabbits. *In vitro* studies have shown that doses of 0.1, 1.0 and 10.0μM trans-Resveratrol can inhibit store-operated Ca2+ channels in human platelets [18]. Caution is advised when used in pregnancy due to insufficient information [10].

3.4. *Forsythia suspensa*

Anti-platelet activity has been observed *in vitro* with *Forsythia suspensa*, possibly due to lignans. The binding of platelet activating factor (PAF) was significantly inhibited 89% by 100 μg/mL hot aqueous extract of the fruit [19]. *Forsythia suspensa* is traditionally considered to be an emmenagogue so should be avoided in pregnancy [20].

3.5. *Verbena officinalis*

A case report indicated that consumption of *Verbena off.* (quantity unknown) during the early stages of pregnancy induced an abortifacient effect [21]. A subsequent study with rats induced foetal abnormalities at a dose of 2g/kg [22].

3.6. *Patrinia scabiosaefolia*

Patrinia scabiosaefolia is used in TCM to clear toxins from the body but it is not recommended to take it when the appetite is poor or diarrhoea is present [23]. No safety data exists for pregnancy.

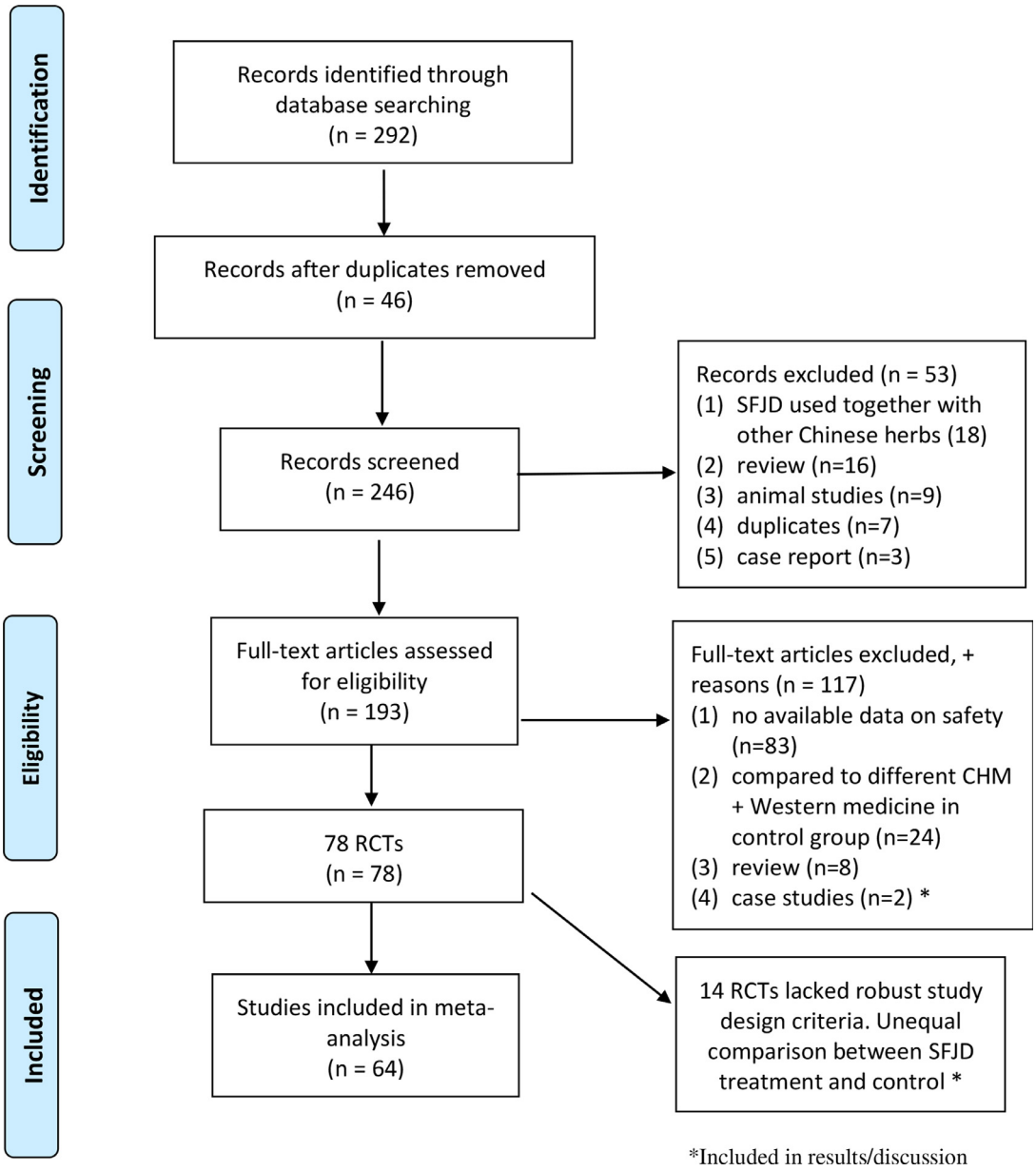


Fig. 1. Flowchart of inclusions and exclusions.

3.7. Phragmites communis

No precautions exist. There is a lack of data regarding use in pregnancy/lactation.

3.8. Isatis indigotica

No side effects reported, and no safety data exists for pregnancy/lactation.

4. Results of systematic search/meta-analysis of AEs in SFJD clinical studies

4.1. Studies identified

Initially 292 potential studies were identified, with 46 excluded due to duplication. After screening titles and abstracts, 193 papers were read in full. Of these, 64 studies met the inclusion criteria for the meta-analysis (Fig. 1). They comprised randomised controlled trials (RCTs) involving 7612 participants in total (individual studies ranged from 30 to 502 patients). Fourteen trials did not qualify for the meta-analysis: an equal comparison could not be made between the study and the control arm. For example, SFJD versus another TCM formula. There were also 2 case studies. All were Chinese studies (see Appendix C for study characteristics).

Forty-four (69%) of the included RCTs focused on patients with respiratory conditions including unspecified respiratory tract infections [24], upper respiratory tract infections [25–30], flu [31–33], pharyngitis [34,35] pharyngoconjunctival fever [36], cough [37], acute exacerbation of chronic obstructive pulmonary disease (AECOPD) [38–49], sinusitis [50–52], laryngitis [53], tonsillitis [54–59], pneumonia [60–65], and bronchitis [66]. Twenty (31%) RCTs reported other conditions including hand-foot-and-mouth disease (HFMD) [67–69], thyroiditis [70], herpes zoster [71,72], chicken pox [73], otitis media [74–79], gastric

ulcer [80], psoriasis [81], pityriasis rosea [82,83] and mouth ulcers [84–86]. The results of the included trials were divided into two groups: one focused on respiratory conditions (44 trials), and the second focused on other conditions (20 trials).

All comparators were usual care except one which was placebo [27].

Just over two-thirds (69%) recruited adults, whilst twenty included trials (31%) focussed on conditions in children (under 16 years) [24–26,28–30,36,37,54,57,58,66–69,75,79,84–86].

4.2. Main findings on adverse events

4.2.1. RCTs in meta-analysis (studies = 64, total participants = 7612; SFJDC group = 3834)

Twenty included trials reported no AEs in either the active or control [27,31,37,38,41,42,45,50,53,55,56,58,61,65,71,73,76,84,85,86]. No serious safety events were reported, whilst 44 included trials reported minor AEs with specific symptoms. Nausea/vomiting was reported by 1% of those who received SFJDC (42/3834) across 29 trials; 0.6% (25/3834) experienced diarrhoea across 22 trials; 0.3% (11/3834) experienced gastrointestinal discomfort across 11 trials; 0.2% (6/3834) had a rash (6 trials); and 0.1% (4/3834) reported dizziness (5 trials).

Some rare AEs were recorded after using SFJDC. One trial reported tiredness (2 participants) [33]; one trial reported phlebitis (1 participant) [64]; one trial reported elevation of transaminase (2 participants) [52]; one trial recorded pneumonia (2 participants) [32]. There were three trials which reported dry mouth/bitter taste (5 participants) [46,47,52].

4.2.1.1. SFJD versus Placebo (study = 1, total participants = 240). One trial evaluated safety comparing SFJDC to placebo; it reported no adverse events in either group [27].

4.2.1.2. SFJD + Usual care versus usual care (studies = 63, participants = 7372). Meta-analysis suggested that SFJDC combined with usual care showed no significant difference in the number of adverse events versus usual care for respiratory conditions or other conditions.

In the respiratory conditions group, there was no difference between SFJDC combined with usual care versus usual care for nausea/vomiting (RR 1.16, 95% CI [0.71, 1.89]; P=0.96, I^2=0%, studies=23, participants=2542), and the findings were similar for diarrhoea (RR 0.96, 95% CI [0.51, 1.79]; P=0.91, I^2=0%, studies=16, participants=1899), gastrointestinal discomfort (RR 0.89, 95% CI [0.37, 2.14]; P=0.85, I^2=0%, studies=8, participants=902), rash (RR 0.49, 95% CI [0.16, 1.48]; P=0.89, I^2=0%, studies=7, participants=908), and dizziness (RR 0.43, 95% CI [0.06, 2.89]; P=0.84, I^2=0%, studies=2, participants=4) (Fig. 2).

In the group related to other conditions, there was no difference between SFJDC combined with usual care versus usual care for nausea/vomiting (RR 0.82, 95% CI [0.31, 2.18]; P=0.89, I^2=0%, studies=6, participants=682), and the findings were similar for diarrhoea (RR 1.03, 95% CI [0.34, 3.08]; P=0.83, I^2=0%, studies=6, participants=664], rash (RR 0.55, 95% CI [0.15, 2.04]; P=0.72, I^2=0%, studies=4, participants=438), dizziness (RR 0.42, 95% CI [0.12, 1.45]; P=0.74, I^2=0%, studies=3, participants=380), and gastrointestinal discomfort (RR 3.04, 95% CI [0.33, 28.30]; P=0.99, I^2=0%, studies=2, participants=166) (Fig. 3).

4.2.2. RCTs not qualifying for meta-analysis (studies = 14; total participants = 2171; SFJDC group = 1181)

The AEs reported in the SFJDC arm of the 14 studies excluded from the meta-analysis coincided with those reported in the 64 included studies. Out of a total of 1181 participants across the 14 studies there were 8 (0.7%) reports of nausea in 4 studies [87–90], 5 (0.4%) of diarrhoea in 4 studies [91–94], 4 (0.3%) of abdominal discomfort in 2 studies [88,95], 2 (0.2%) of dizziness in one study [88] and 1 (0.1%) of a reported rash [96].

Table 3
Reported pharmacovigilance data (NADRMS).

No. of Products Sold/Reaction reported	2017	2018
No. of Packets SFJD sold	**10.3 million**	**12.9 million**
Total number of cases reported	**169**	**198**
Digestive System (eg: nausea)	131	154
Skin condition (eg: pruritus)	28	23
Dizziness	5	3
Unspecified anaphylactic reaction	3	2
Respiratory symptoms	2	1
Circulatory symptoms	-	2

4.2.3. Sensitivity analysis

The sensitivity analysis indicated that there was no suggestion of different outcome when including studies which explicitly included 'safety' in their aim/title/outcome (see Appendix D).

4.2.4. Case studies (studies = 2)

Two case studies reported single incidents of AEs: one patient experienced a rash and facial oedema three days post SFJDC [97], the other reported dizziness, a headache and an increase in blood pressure approximately 30 minutes after taking SFJDC [98]. Both cases resolved 3 to 4 hours after stopping SFJDC.

4.3. Pharmacovigilance

4.3.1. MHRA yellow card system

Two of the component herbs (*Glycyrrhiza* and *Verbena*) have been reported to the MHRA Yellow Card system. Since 1969 there have been 134 reports for *Glycyrrhiza* as a monotherapy; the highest for an individual system (n=22) were gastrointestinal [99]. These related to the species as a whole. The most common reported side effects for *Verbena off.* were also gastrointestinal. Since 1988 they totalled 8 out of 24 total incidents for its use as a single herb [100].

4.3.2. Pharmacovigilance data supplied to NADRMS (Table 3)

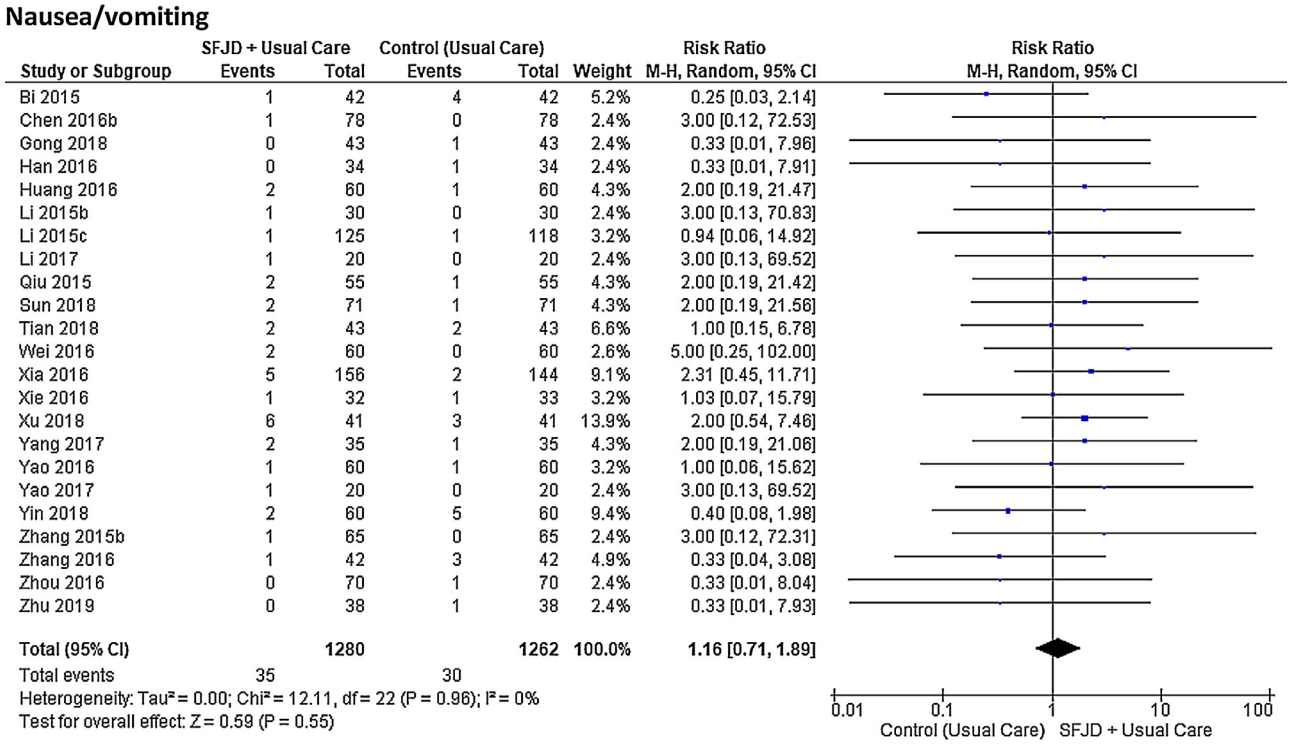
Out of over 23 million packets of SFJDC sold in 2017 and 2018 there were 169 and 198 minor AEs reported respectively. The majority were gastrointestinal, which improved on stopping the medication (Table 3).

5. Discussion

5.1. Main findings

SFJDC has been an approved TCM medicine by the Chinese Food and Drug Administration since 2009 [5], and is prescribed by medical practitioners as well as used in clinical settings for respiratory tract infections [7]. It is not available to purchase by the general public. This study provides an overview of the evidence of the safety of SFJDC based on investigations into the pharmacology of the individual herbs and overall formula, a systematic search with meta-analysis of randomized controlled clinical trials as well as pharmacovigilance data reporting AEs. It is the first time an independent safety review on the widely used SFJDC formula has been produced. It is based on a literature search on the phytochemicals, pharmacology, clinical studies as well as MHRA Yellow Card reporting on the individual plants and SFJDC formula; 78 RCTs involving 8793 participants including 64 in a meta-analysis (n=7612); two case studies; and two years reported data supplied to the Chinese pharmacovigilance system relating to sales of over 20 million boxes of SFJDC.

No serious AEs were recorded in the RCTs or pharmacovigilance data. Minor AEs reported in the latter were mainly gastrointestinal (over 70%). In fact, minor gastrointestinal AEs were reported across all 3 data sources, although in the meta-analysis of RCTs there was no significant difference between the number of AEs amongst those taking SFJDC compared with usual care. The AEs in the 14 studies not qualifying for meta-analysis, whereby SFJDC could not be compared directly to the control



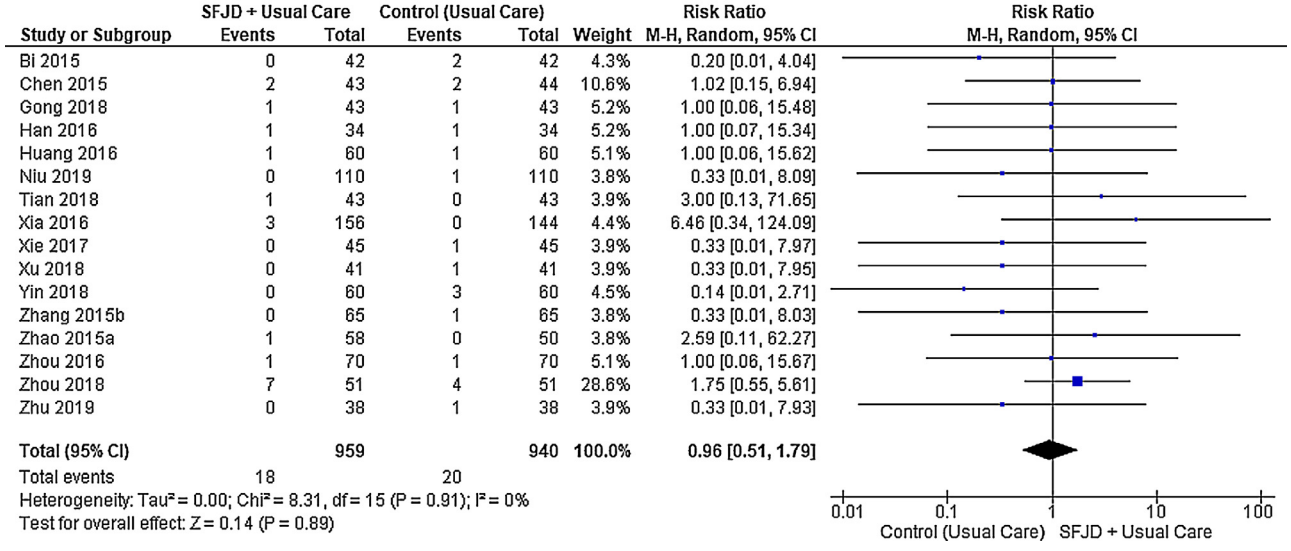
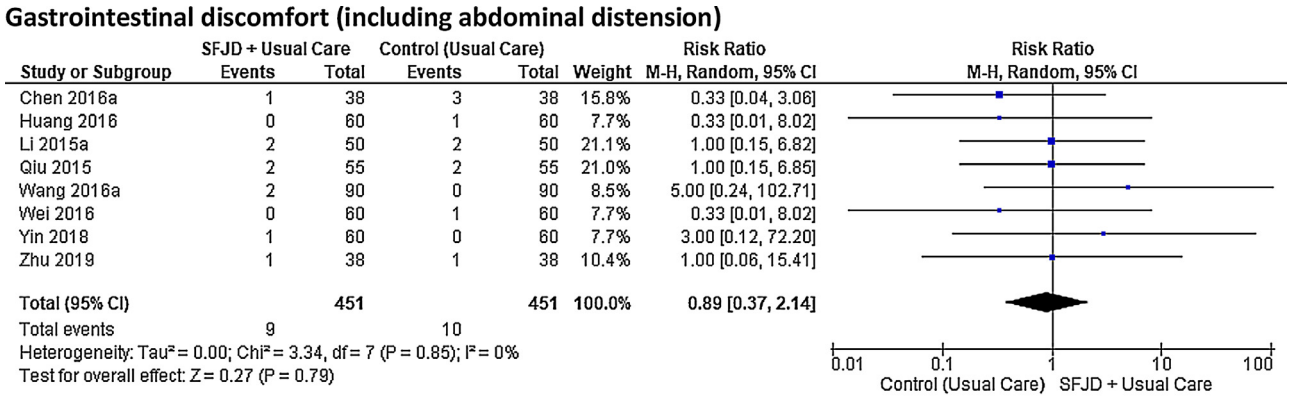
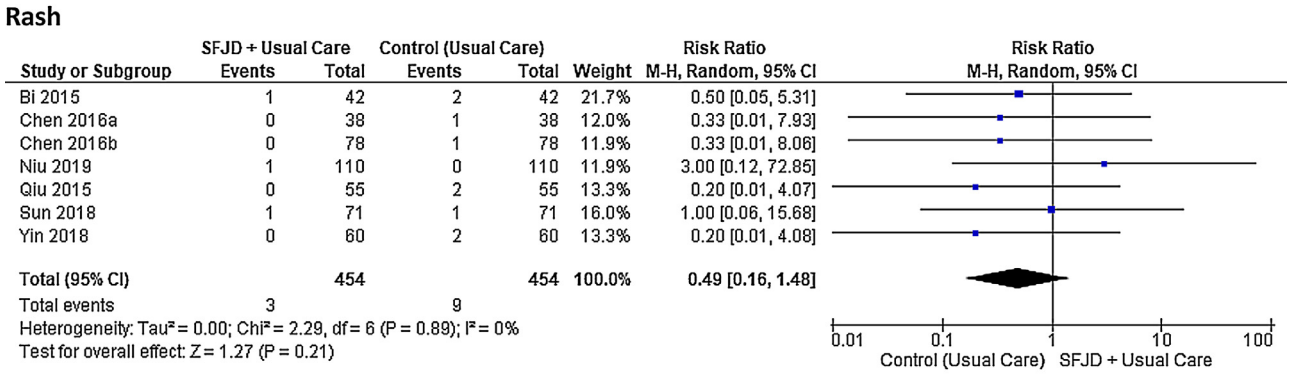


Fig. 2. Meta-analysis of AEs reported in respiratory conditions.

arm(s), coincided with those reported in the RCTs; the majority also comprised gastrointestinal effects.

Whilst no specific herb-drug interactions were reported in any of the studies examined, based on the phytochemistry there may be theoretical concerns about patients taking anticoagulants, hypotensive, diuretic or antidiabetic medication alongside SFJDC. Nevertheless, the potential effects on platelets, blood pressure, potassium and blood glucose produced by 4 constituents (saikosaponins, lignans, resveratrol and glycyrrhizin) were not evident in either the RCTs or the pharmacovigilance data. The investigations into platelets and blood glucose were based on *in vitro* and *in vivo* studies where quantities used in the experiments were significantly higher than the traditional doses (Table 1). For example, the maximum possible quantity of saikosaponin A in a daily dose of SFJD is 16.85 mg. This is almost certainly too low to produce harmful levels of platelet inhibition even if the compound is as bioavailable as aspirin, 30 mg of which taken daily can suppress platelet thromboxane synthesis [101]. Additionally, regarding *Glycyrrhiza*, where findings included several case studies reporting hypertension and hypokalemia, in all cases the herb had either been consumed in a single high dose, greater than the recommended maximum daily dose [102], or a small quantity had been taken daily over a long period: at least a year [103]. Moreover, not only does glycyrrhizin have poor bioavailability [13], the maximum





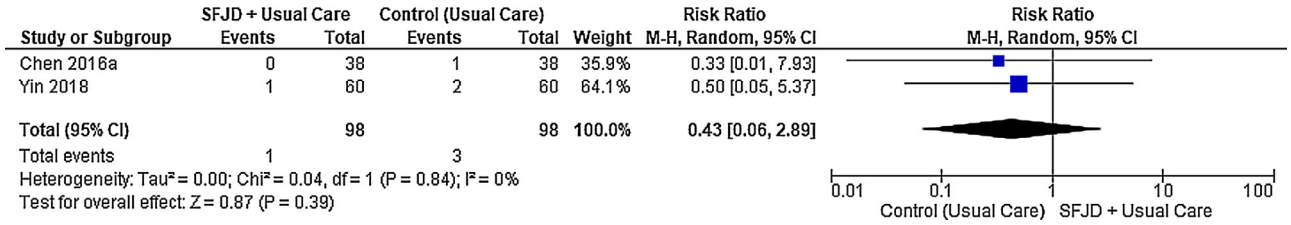


Fig. 2. Continued

quantity of the herb present in the daily dose of SFJDC (2.16 g) is only 21.6% of the maximum recommended TCM dose of 10 g according to the Chinese Pharmacopoeia [6], which equates to 2.16 grams daily.

The maximum duration of treatment for SFJDC in the RCTs for lower RTIs such as pneumonia and AECOPD is 14 days, thus limiting the exposure to all constituents [4]. Furthermore, in trials for chronic sinusitis SFJDC was administered for over 160 days and incurred no major AEs: 168 days with 41 participants [52] and 180 days with 50 participants [50].

There was insufficient safety information on all the herbs for pregnancy and lactation. Moreover, according to traditional use *Fallopia japonica, Forsythia suspensa* and *Verbena off.* were considered potential uterine stimulants [20,21,104].

5.2. Strengths and limitations

This review benefited from a range of data sources, comprehensive literature searches and retrieval of all relevant RCTs to enable subgroup analyses. The findings of the meta-analysis were limited by a lack of high-quality methodology in the RCTs. Only one of the trials was double-blinded, and only one included a placebo as the intervention. Most did not have a protocol registration, there were unclear conflicts of interest and some lacked baseline data for comparison between groups. Despite these limitations there is no clear signal to suggest significant harms associated with use of SFJDC.

5.3. Conclusion

Based on the findings of this review SFJDC is safe to prescribe to adults (excluding pregnant or lactating women) as well children in a clinical setting. Clinicians should be aware of the hypothetical interactions based on individual ingredients but we have no evidence that these are translated into harm in the formulation of SFJDC.

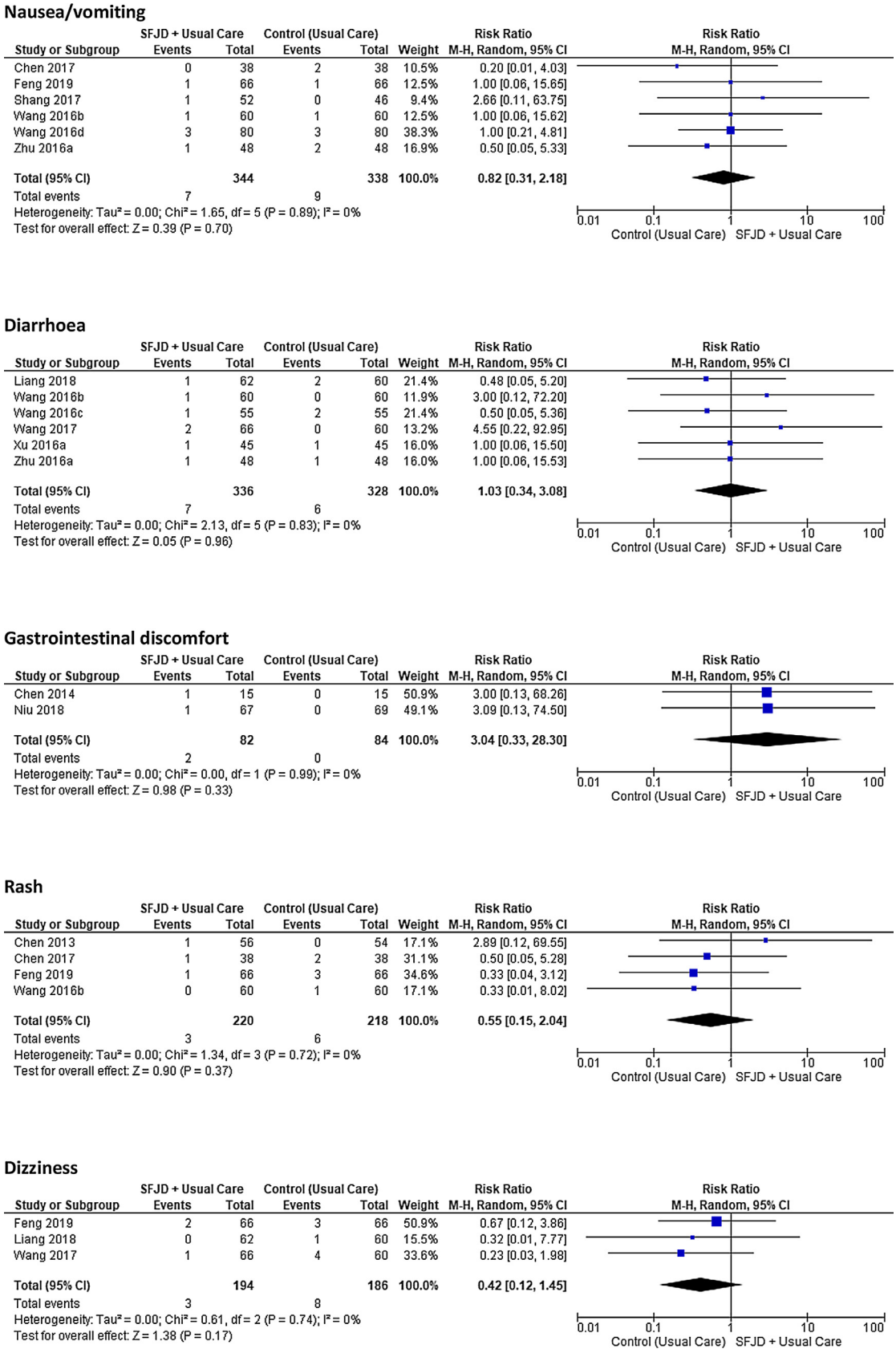


Fig. 3. Meta-analysis of AEs reported in non-respiratory conditions.

Authors contributions

JT and ZJW performed the searches. ZJW, YZ and JT did the screening and data extraction. JT, ZJW and XYH analysed the data. XYH, JT, ZJW, MW and MM contributed to the design of the study. JT drafted the text. XYH and MM are corresponding authors.

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Declaration of Competing Interest

All authors in this study claimed no conflict of interest. SFJDC is produced by Jiren in China who are partners in the proposed research, but Jiren had no direct involvement in the review.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.prmcm.2021.100017.

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