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Original Article

Efficacy and safety of herbal medicine (Binafuxi granules) for the common cold with fever: A multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial

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ABSTRACT

Background: Binafuxi granules are a traditional Uighur medicine (TUM) for treating the common cold with fever. However, high-quality clinical studies supporting its efficacy and safety are lacking.
Methods: In this multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial, patients with common cold and fever were randomly assigned to a high-dose group, low-dose group, and placebo group in a 1:1:1 ratio. Outcomes were time to fever relief, time to fever clearance, proportion of afebrile patients, time to symptom disappearance, rate of symptom disappearance, effective rate, emergency drug usage and safety assessment.
Results: A total of 235 patients were recruited. Of these, 234 were included in the full analysis set (FAS), and 217 were included in the per-protocol set (PPS). In the FAS analysis, the median time to fever relief was 6.00 h, 5.54 h and 10.65 h ($P = 0.31$) in the high-dose group, low-dose group and placebo group, respectively. The median time to fever clearance was 18.29 h, 20.08 h and 25.00 h ($P = 0.0018$), respectively, and the proportion of afebrile patients was 92.4%, 89.7% and 71.4% ($P = 0.0002$), respectively. There was a significant difference in the disappearance time and disappearance rate of all symptoms and of individual symptoms. No serious adverse events were found.
Conclusions: Binafuxi granules can dose-dependently shorten the fever course and improve clinical symptoms in patients suffering from the common cold with fever.
Trial Registration: This trial was registered at Chinese Clinical Trial Registry (ChiCTR-IIR-17013379).

1. Introduction

The common cold is a spontaneously remitting infection of the acute upper respiratory tract, mostly caused by viral infections.[1,2] It occurs in all seasons, especially in winter and spring. The hallmark clinical manifestations include nasal congestion and discharge, sneezing, sore throat, chills, fever, and cough,[3] while fever is a common cause for seeking treatment. Although the common cold with fever is always self-limiting, it still causes a considerable societal burden associated with absence from school or work and frequent doctor visits.[4] Currently, treatment for the common cold is supportive and symptomatic. However, side effects such as drowsiness and stomach pain are common, leading to the wide use of alternative medicines.

Traditional Uighur medicine (TUM), with a history of more than 2500 years, has been a vital part of traditional ethnic medicine globally, mainly applied over Central Asia, North Africa, and South Europe.[5] Its magnificent theoretical system is rooted in the wis-

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Table 1
The herbal composition of Binafuxi granules.

Chinese name	English name	Latin name	Possible compounds	Possible pharmacological activities
Tian Shan Jin Cai	Whole part of *Viola kunawarensis* Royle	Viola kunawarensis Royle	Hrysin, heptadactone, umbellifera lactone, kaempferol and quercetin, et al.[6]	Inhibit the release of TNF-α, IL-6, IL-1β, suppress protein expression of p-IκBa and nuclear translocation of NF-κB, p65, et al.[7,8]
He Guo Teng Gen	Root of operculina turpethus	*Operculina turpethum* (L.) Silva Manso	Coumarins, α-and β-turpethein, turpethinic acids (A, B, C, D, and E), cycloartenol, et al.[9]	Antibacterial, anti-inflammatory, analgesic, hepatoprotective, anti-arthritic, antidiarrheal, antidiabetic, and cytotoxic properties, et al.[9,10]
Gan Cao Qinq Gao	Licorice extract	*Glycyrrhiza uralensis* Fisch.	Glycyrrhetinic acid, isoangustone A, licochalcone A,B,C,D,E, licorisoflavan A, et al.[11]	Antitumor, antimicrobial, antiviral, anti-inflammatory, immunoregulatory, et al.[10, 11]
Mei Gui Hua	Flower of rose	*Rosa rugosa* Thunb	Flavonoids, citronellol, geraniol, phenylethanol, terpenoids, et al.[12]	Antibacterial, antioxidative, regulating blood lipid, antithrombotic, et al.[12,13]
Si Ka Mo Ni Ya Zhi	Scammonia resin	*Convovulus scammonia* L.	Scammonin, gum, starch.[14]	Eliminate body dampness evil and swelling.[14]
A Li Hong	Sporogenous body of *Fomes officinalis*	*Fomes officinalis* Ames	Fomitopsin C, 3-keto-dehydrosulfurenic, dehydrosulphurenic acid, et al.[15]	Inhibit the lactate dehydrogenase release, malondialdehyde level and the over accumulation of reactive oxygen species, et al.[16,17]

dom and experience of ancient medical practitioners in Xinjiang Province (China) and the integration of essence from other ethnic medicines, such as traditional Chinese medicine, ancient Greek medicine, Egyptian medicine, Arabian medicine, Unani medicine, and Indian medicine. Based on TUM theory, the common cold with fever is related to abnormal conditions of heat and body fluid, and the treatment principle is to restore the balance through ample clearance of heat and excessive body fluid.

The prescription of Binafuxi is composed of six herbs (Table 1), with a history of treating the common cold with fever for more than 300 years. It derives from ancient Uygur Medical Classics *Mahzinul Murakkibat* and *Karabadin Azam* and has the function of removing abnormal body fluid and dispelling heat. Binafuxi granules have been approved by the State Food and Drug Administration of China (SFDA) for clinical trials in patients with common cold and fever (2014 L01342).

Therefore, a multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial was designed to investigate the efficacy and safety of Binafuxi granules in patients with the common cold and fever.

2. Methods

2.1. Trial design

2.1.1. Inclusion criteria of participants

The detailed study design has been reported.[18] Briefly, this study was a multi-arm, double-blind, placebo-controlled, phase II clinical trial. Patients were recruited from the outpatient centers of five hospitals across China during December 2017 and December 2020. Patients who were 18–65 years old, had been clinically diagnosed with a common cold caused by acute upper respiratory tract infection,[19] fulfilled the TUM symptoms and signs diagnostic criteria based on the clinical research guidelines for the treatment of the common cold with the new Uyghur medicine (2017),[20] and had exhibited fever (37.5 °C $\leq$ axillary body temperature $\leq$ 39.0 °C) within the past 24 h were included in the trial. Patients who had concomitant influenza, pneumonia, tuberculosis, primary ciliary dyskinesia syndrome, acute nasal diseases (rhinitis, sinusitis, *etc.*), nasal mucosa dysfunctions, chronic lung diseases (asthma, COPD, bronchiectasis, *etc.*); had taken drugs for the common cold two weeks before inclusion; or had serious primary dysfunction in the cardiovascular, pulmonary, kidney, liver, neurological or hematological system were excluded from the trial. The detailed inclusion and exclusion criteria are provided in the published protocol.[18] All patients voluntarily participated and provided signed informed consent.

2.1.2. Medicinal preparation

The main components of Binafuxi are shown in Table 1. The herb names have been checked in http://mpns.kew.org/mpns-portal/ except for *Fomes officinalis* Ames, which is a local herb of Xinjiang Uygur Autonomous Region of China not familiar to the public. However, *Fomes officinalis* Ames has been used in many studies recently.[15,16,17] *Viola kunawarensis* Royle is the local herb of Xinjiang Uygur Autonomous region of China; *Operculina turpethum* (L.) Silva Manso grows in the southern region of China; *Glycyrrhiza uralensis* Fisch. grows in the northern region of China; *Rosa rugosa* Thunb grows in the eastern region of China; *Convovulus scammonia* L. is harvested in Pakistan.[14] The origin of each herb was authenticated according to the Pharmacopoeia of the People's Republic of China.[21]

The component of Binafuxi granules is consistent with the original prescription. Eleven grams of Binafuxi granules equals the daily dosage of raw drugs, and 5.5 g of Binafuxi granules, twice daily were determined as the treatment dose, which was set as the high-dose group, while the low-dose group was given Binafuxi granules (2.75 g) and placebo granule (2.75 g), and the placebo group was given placebo granules (5.50 g) twice a day. Considering the characteristics of Chinese herbal medicine, a placebo was prepared by a 20-fold dilution of 2.75 g Binafuxi granules and maltodextrin with the addition of artificial pigment and flavoring agents.[22] The Binafuxi granules (batch Y170521) and placebos (batch Y170520) were identical in appearance, color, and taste. All drugs were concealed in uniform packages with the same labels except drug numbers. The production and packaging of Binafuxi granules as well as placebo granules were provided by Xinjiang Yinduolan Pharmaceutical Co., Ltd.

2.1.3. Intervention

Participants received two bags of Binafuxi granules each time (2.75 g per bag) in the high-dose group, one bag of Binafuxi granules (2.75 g per bag) and one bag of placebo granules each time (2.75 g per bag) in the low-dose group, and two bags of placebo granules each time (2.75 g per bag) in the placebo group. The test drugs were taken orally and twice daily for three consecutive days.

During the study period, if the patients' body temperature was higher than 39.0 °C or dropped by lower than 0.5 °C within 48 h after medication, they were treated with ibuprofen as an emergency drug according to the doctor's advice. The detailed drug usage was carefully recorded. Ibuprofen was distributed to the patients together with the test drugs but were ordered not be taken without the doctor's advice.

Medications for concomitant diseases, such as hypertension, were allowed. The medications' dosage, duration, and names were

recorded in the case report forms (CRFs). Any other medications or physical therapies, such as cupping, massage, and acupuncture for the common cold, were not allowed during the whole study.

2.1.4. Outcome measurements

The outcome measurements were evaluated at the time of enrollment (Day 0) and on the fourth day after medication (Day 4). In this study, a mercury thermometer was used to record the axillary body temperature. An axillary body temperature of 37.2 °C or less was considered normal. The body temperature was measured and recorded every one hour in the first 6 h after medication and then every three hours until it returned to normal. The temperature measurement was stopped if the body temperature remained normal for more than 24 h. Recording was not required during the sleeping period (from 9 p.m. to 6 a.m.).

Outcomes were as follows: Main outcome: Time to fever relief, defined as the time from first use of medication to the first drop of body temperature by 0.5 °C. Secondary outcomes: (1) Time to fever clearance**,** defined as the time from first use of medication to the first drop of body temperature to normal, without relapse for at least 24 h. (2) Proportion of afebrile patients, defined as the proportion of patients with a normal body temperature after three days of medication. (3) The time to common cold symptom (all symptoms and individual symptoms) disappearance and the rate of common cold symptom (all symptoms and individual symptoms) disappearance were calculated by a four-graded Likert-type symptom and sign severity scale (Supplementary Table 1). The time to symptom disappearance was defined as the time from first use of medication to the disappearance of all symptoms or specific individual symptoms, when the score was graded as 0 without recurrence within 24 h according to the medical history and diary card. The rate of symptom disappearance was defined as the percentage of patients whose symptoms or specific individual symptoms disappeared. For patients whose symptoms did not disappear or disappeared for less than 24 h after three days of treatment, telephone follow-up was conducted until all symptoms disappeared. (4) The effective rate was evaluated according to the percentage of cumulative symptom score reduction (PSSR) recorded on the fourth day. A PSSR $\geq$ 70% was considered effective, and a PSSR $<$ 70% was considered ineffective. The formula was as follows:

$$\text{PSSR} = \left(\frac{\text{symptom scores at baseline} - \text{symptom scores after intervention}}{\text{symptom scores at baseline}}\right) \times 100\%.$$

(5) After the intervention, emergency drug (chewable ibuprofen tablets) was recovered and calculated. Emergency drug usage was defined as the percentage of tablets consumed. (6) Compliance was assessed by patient diaries and returned units of the test drug.

2.1.5. Sample size calculation

The sample size was determined by one-way analysis of variance F tests using Effect Size in PASS (version 15.0.5), with 90% power and a significance level of 0.05. Taking $\eta 2$ as an alternative measure of effect size, the sample size was calculated by $\sigma \mathrm{m}2/(\sigma \mathrm{m}^2 + \sigma^2)$, with $\eta^2 = 0.0099 \approx 0.01$ as a small effect, $\eta^2 = 0.0588 \approx 0.06$ as a medium effect, and $\eta^2 = 0.1379 \approx 0.14$ as a large effect.[23] Therefore, the sample size of each group was estimated to be 68 cases. Considering a drop-out rate of 15%, 78 subjects were recruited in each group. Ultimately, a total of 235 patients were needed for this trial.

2.1.6. Randomization and blinding

Participants were randomly assigned to one of three treatment groups with stratified block randomization method by SAS 9.4 software (SAS, Cary, NC, USA), enabling randomization and stratification for each center. The randomization schedule was jointly created by the Clinical Trials Unit of West China Hospital of Sichuan University and Xinjiang Yinduolan Pharmaceutical Co., Ltd. The random number list was then generated by a statistician who was not involved in the data collection or analysis. The random code table was established and sealed by the statistical analysis unit . A total of three copies were submitted to the Clinical Trials Unit of West China Hospital of Sichuan University, the organizing institution (Xinjiang Yinduolan Pharmaceutical Co., Ltd.), and an independent statistical analysis group for proper storage. Emergency letters in which the random code and group assignment were included were prepared by a statistician.

Staffs unrelated to the clinical observation, supervision and statistical analysis of this clinical trial pasted the corresponding drug number on the uniform position of the drug outer package according to the formed processing code. Participants, investigators, and statisticians were blinded to the treatment allocation throughout the study. Subjects were isolated from each other after enrollment and were advised to take the medications at home to avoid any discussions about the drugs.

2.1.7. Safety assessment

A safety assessment was conducted at baseline and the fourth day after medication, including vital signs, routine blood tests, urine and sediment analysis, routine stool tests, electrolyte (K^+, Na^+, Cl^-) measurements, liver and renal function tests, chest X-ray imaging and electrocardiograms. The detailed safety assessments are provided in the published protocol.[18]

Adverse events (AEs) referred to all adverse medical events, including new diseases, abnormal symptoms, and abnormal laboratory examinations that occurred after taking the test drugs. Significant AEs referred to those that led to drug reduction, drug withdrawal, or a need for treatment. Serious AEs referred to those that led to death or to life-threatening, permanent or severe disability or dysfunction. Drug-related AEs were evaluated by authorized clinicians under blinded conditions according to the following considerations: (1) was there a reasonable time sequence between the test drug administration and the adverse event; (2) was it a commonly reported adverse event related to the test drug; (3) was the adverse event relieved or disappeared after test drug reduction or withdrawal; (4) did the adverse event reoccur after reuse of the test drug; and (5) was the adverse event caused by combined drugs used for patient comorbidities.

All AEs that occurred during the trial were graded into three levels by authorized clinicians: (1) mild: without symptoms or with mild symptoms, not needing therapy; (2) moderate: with symptoms, requiring treatment; and (3) severe: with serious symptoms, leading to hospitalization or prolonged hospitalization, disability, or limited self-care daily activities, necessitating immediate medication discontinuation.

During the trial, participants with AEs received appropriate drugs for treatment by doctor, then the researcher would evaluate whether the drugs used have an impact on the efficacy or safety evaluation of the test drug and determine whether the participant need to withdraw from the trial after AEs treatment. In this study, we obtained AEs by asking patients and checking medical examination recordings. All patients with AEs were followed until they were properly treated and recovered. The treatments and outcomes of AEs were recorded entirely in the study medical records and CRFs, with relevant examination reports being attached.

2.2. Statistical analysis

The statistical analysis was performed by using SAS 9.4 software (SAS, Cary, NC, USA). The detailed statistical analysis plan has been published.[18] Baseline demographics of gender (male%), combined diseases (%), allergic history (%), concomitant medication use, concomitant medication use and compliance assessment were compared by Chi-square test, while age (year), body temperature (°C), average course of fever (hour) and total symptom score

were compared using analysis of variance (ANOVA). The primary outcome of time to fever relief was analyzed using the log-rank test and Kaplan-Meier curves were constructed. Similarly, the secondary outcomes of time to fever clearance and time to common cold symptom (all symptoms and individual symptoms) disappearance were analyzed using the log-rank method. The secondary outcomes of proportion of afebrile subjects, the rate of common cold symptom (all symptoms and individual symptoms) disappearance, clinical effective and emergency drug used were compared by Cochran-Mantel-Haenszel Chi-square test among groups and the 95% confidence interval (95%CI) of the inter-group difference were calculated. The secondary outcome of TUM symptom score was compared by analysis of variance and the Bonferroni method. A two-sided P value <0.05 was considered statistically significant.

3. Results

In this study, 276 subjects were screened from five clinical trial centers from September 2018 to September 2019, with 235 cases ultimately recruited (79 cases in the high-dose group, 78 cases in the low-dose group and 78 cases in the placebo group) (Fig. 1). Among them, one patient in the low-dose group failed to complete the study, and the dropout rate was 0.43%; one patient in the placebo control group was excluded for lacking effective indicator evaluation. There were 234 patients included in the FAS population, 217 patients included in the PPS population, and 235 patients included in the SS population. The main reasons for exclusion from the PPS population were inclusion criteria violation, poor compliance, unexpected drug usage, and improper body temperature recording. Patients who took the rescue drug (ibuprofen) when their body temperature raised above 39.0 °C or did not drop significantly at 48 h post administration according to the physician's advice, were included in the PPS analysis. Patients who took ibuprofen in violation of the requirements were excluded from the PPS data set.

3.1. Baseline demographics, clinical characteristics, and compliance assessment

The baseline demographics and clinical characteristics were comparable among the groups ($P > 0.05$) (Table 2). There was no significant difference in drug exposure or drug compliance among the groups ($P > 0.05$).

3.2. Outcomes

3.2.1. Main outcome: Time to fever relief

There was no significant difference among the three groups after the log-rank test in either the FAS or PPS analysis population ($P = 0.3058$ in the FAS analysis and $P = 0.4994$ in the PPS analysis) (Supplementary Table 2). Six hours after Binafuxi granule administration, the rates of fever relief were 54.1%, 52.6%, 38.3% in the FAS population ($P = 0.2227$) and 52.7%, 52.0%, 40.3% ($P = 0.2394$) in the PPS population in the high-dose group, low-dose group, and placebo control group, respectively. According to the Kaplan–Meier curves, high-dose Binafuxi granules showed a better effect in relieving fever than low-dose Binafuxi granules and placebo (Fig. 2A).

3.2.2. Secondary outcomes

3.2.2.1. Time to fever clearance. In the FAS analysis, the median times to fever clearance in the high-dose group, low-dose group and placebo control group were 18.29 h, 20.08 h, and 25.00 h, respectively. In the PPS analysis, the median time to fever clearance was 16.83 h, 20.33 h, and 23.25 h, respectively (Supplementary Table 3 and Fig. 2B). A significant difference was found in both the FAS population and the PPS population after the log-rank test ($P = 0.0018$ and $P = 0.0027$).

3.2.2.2. Proportion of afebrile patients. The proportions of afebrile patients after treatment were 92.4%, 89.7%, and 71.4% in the high-dose group, low-dose group and placebo control group, respectively, in the FAS analysis and 96.0%, 89.3% and 76.5%, respectively,

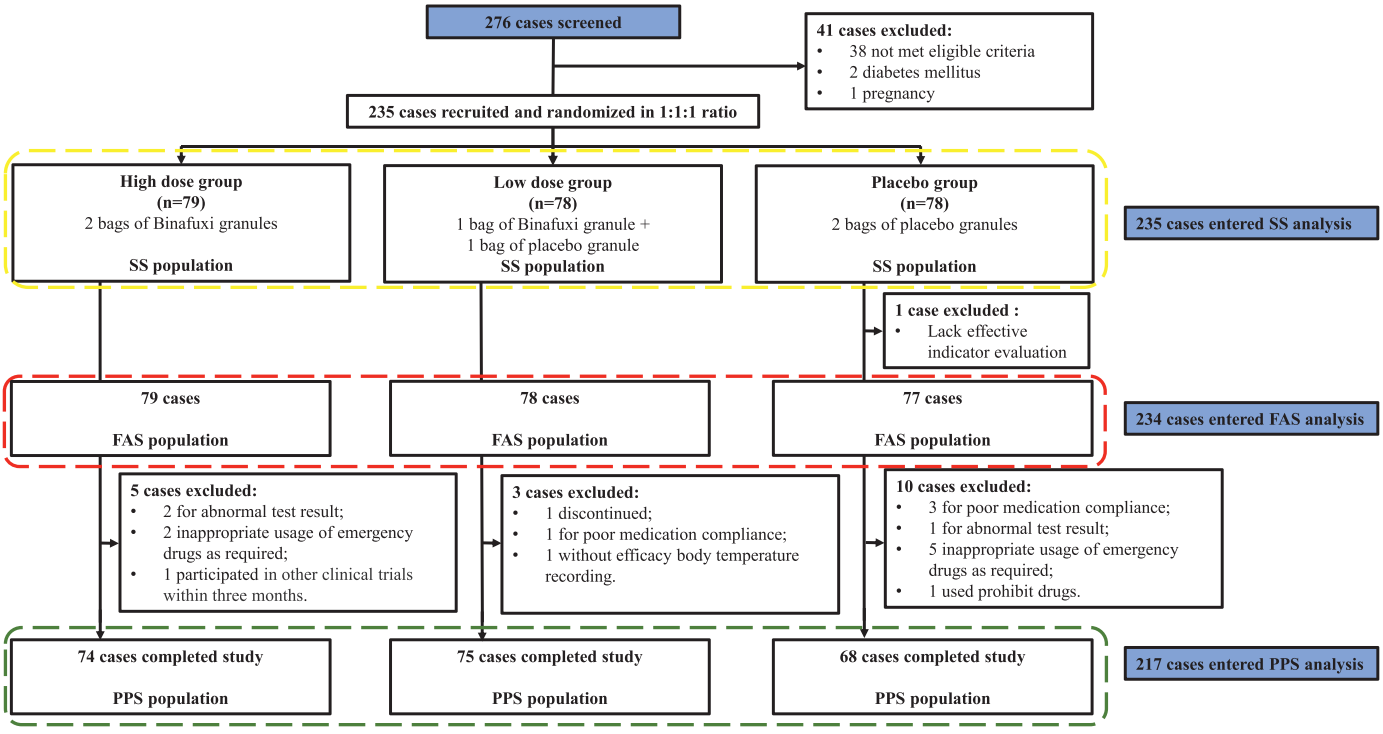

Fig. 1. flowchart of the study. FAS: full analysis set; SS: safety set; PPS: per-protocol set.

Table 2
Baseline demographics, clinical characteristics and compliance assessment (FAS analysis).

	High-dose (n = 79)	Low-dose (n = 78)	Placebo (n = 77)	P
Age (year)	35.5 ± 14.8	34.3 ± 13.0	34.1 ± 12.6	0.79
Gender: male (n, %)	40.5	37.2	35.1	0.78
Combined diseases (n, %)	12 (11.4%)	6 (6.4%)	11 (6.5%)	0.30
Gastritis, gastric ulcer	1 (1.3%)	0 (0.0%)	0 (0.0%)	
Fatty liver disease	1 (1.3%)	1 (1.3%)	0 (0.0%)	
Coronary heart disease	4 (5.1%)	0 (0.0%)	3 (3.9%)	
Hypertension	4 (5.1%)	1 (1.3%)	6 (7.7%)	
Arrhythmia	0 (0.0%)	2 (2.6%)	0 (0.0%)	
Cerebral infarction	1 (1.3%)	0 (0.0%)	0 (0.0%)	
Old pulmonary lesions: nodules, tuberculosis	1 (1.3%)	0 (0.0%)	1 (1.3%)	
Renal cyst and kidney stone	0 (0.0%)	1 (1.3%)	1 (1.3%)	
Anemia	0 (0.0%)	1 (1.3%)	0 (0.0%)	
With allergic history (%)	1.39	6.41	6.41	0.21
Body temperature (°C)	38.0 ± 0.4	37.9 ± 0.3	37.9 ± 0.4	0.10
Average course of fever (hour)	19.9 ± 9.7	20.9 ± 10.7	22.9 ± 10.3	0.17
Total symptom score	19.3 ± 5.9	18.5 ± 6.5	19.9 ± 7.6	0.42
Concomitant medication use				
Total cases (n, %)	3 (3.8%)	2 (1.3%)	6 (7.8%)	0.28
Total frequency of drug use	5	2	18	
Peptic ulcer	1	0	0	
Antihypertensive	2	0	5	
Coronary heart disease drug	2	1	4	
Antiarrhythmic drug use	0	1	2	
Antibiotics	0	0	5	
Vitamin C	0	0	1	
Dexamethasone	0	0	1	
Compliance assessment				
Average bags of test drug taken	11.8 ± 1.2	11.9 ± 0.6	11.8 ± 0.7	0.84
Average days of test drug taken	2.9 ± 0.4	3.0 ± 0.2	3.0 ± 0.2	0.80

Data are presented as mean ± SD or n (%). FAS: full analysis set; TUM: traditional Uighur medicine.

Table 3
Proportion of afebrile subjects at different time points, symptoms disappearance and TUM symptom score (FAS analysis).

	High-dose (n = 79)	Low-dose (n = 78)	Placebo (n = 77)	Statistics (F or CMH)	P value
Temperature returned to normal, n (%)					
24h	54 (68.4)	47 (60.3)	35 (45.5)	10.9	0.0044
48h	72 (91.1)	70 (89.7)	55 (71.4)	15.9	0.0004
72h	73 (92.4)	70 (89.7)	55 (71.4)	17.3	0.0002
Symptom's disappearance, n (%)					
All symptoms	43 (54.4)	33 (42.3)	16 (20.8)	22.0	<0.0001
Fever	77 (97.5)	77 (98.7)	66 (85.7)	14.2	0.0008
Nasal congestion	47 (85.5)	51 (91.1)	40 (69.0)	12.5	0.0019
Nasal discharge	41 (82.0)	43 (74.1)	33 (55.9)	14.2	0.0008
Sore throat	58 (81.7)	56 (82.4)	38 (55.1)	19.6	<0.0001
Cough	40 (69.0)	36 (70.6)	27 (45.0)	13.4	0.0012
Headache	60 (95.0)	59 (95.2)	43 (71.7)	20.7	<0.0001
Dry mouth, thirsty	61 (81.3)	50 (77.0)	52 (70.3)	2.6	0.2741
Sweating	42 (95.5)	27 (81.8)	34 (91.9)	4.2	0.1222
Sore limbs	61 (98.4)	50 (89.3)	46 (80.7)	11.8	0.0027
TUM symptom score, (mean ± SD)					
Baseline	19.3 ± 5.9	18.5 ± 6.5	19.9 ± 7.6	0.9	0.4200
4th day	1.8 ± 3.1	2.1 ± 3.0	4.6 ± 4.2*#	15.5	<0.0001
Score changed	−17.5 ± 6.2	−16.5 ± 6.0	−15.3 ± 8.3	2.0	0.139
Clinical effective, n (%)	71 (89.9)	71 (91.0)	47 (61.0)*#	35.3	<0.0001
Emergency drug used, n (%)	2 (2.5)	0 (0.0)	11 (14.3)	17.1	0.0002

Data are presented as mean ± SD or n (%). The symptoms disappearance rate was analyzed in participants with specific symptoms at baseline. *: Compared with high-dose group, P value<0.05; #: Compared with low-dose group, P value<0.05. TUM: traditional Uighur medicine; CI: confidence interval; FAS: full analysis set; CMH: Cochran–Mantel–Haenszel test.

in the PPS analysis (Table 3 and Supplementary Table 4. The difference among groups was statistically significant (P = 0.0002 in the FAS analysis and P = 0.0004 in the PPS analysis).

3.2.2.3. Time to symptom disappearance. According to the log-rank test, the time to disappearance of all symptoms and that of individual symptoms of fever, nasal congestion, sore throat, and headache were significantly different among groups in both the FAS analysis and the PPS analysis (P < 0.05) (Supplementary Table 5). In terms of the time to disappearance of all symptoms and individual symptoms of fever, nasal congestion, sore throat and headache, the high-dose group showed a better effect than the low-dose group and the placebo control group. The time to disappearance of sore throat in the low-dose group was shorter than that in the high-dose group and placebo control group (Supplementary Table 5).

3.2.2.4. Rate of symptom disappearance. On the fourth day of the study, the disappearance rate of all symptoms and that of individual symptoms of fever, nasal congestion, nasal discharge, sore

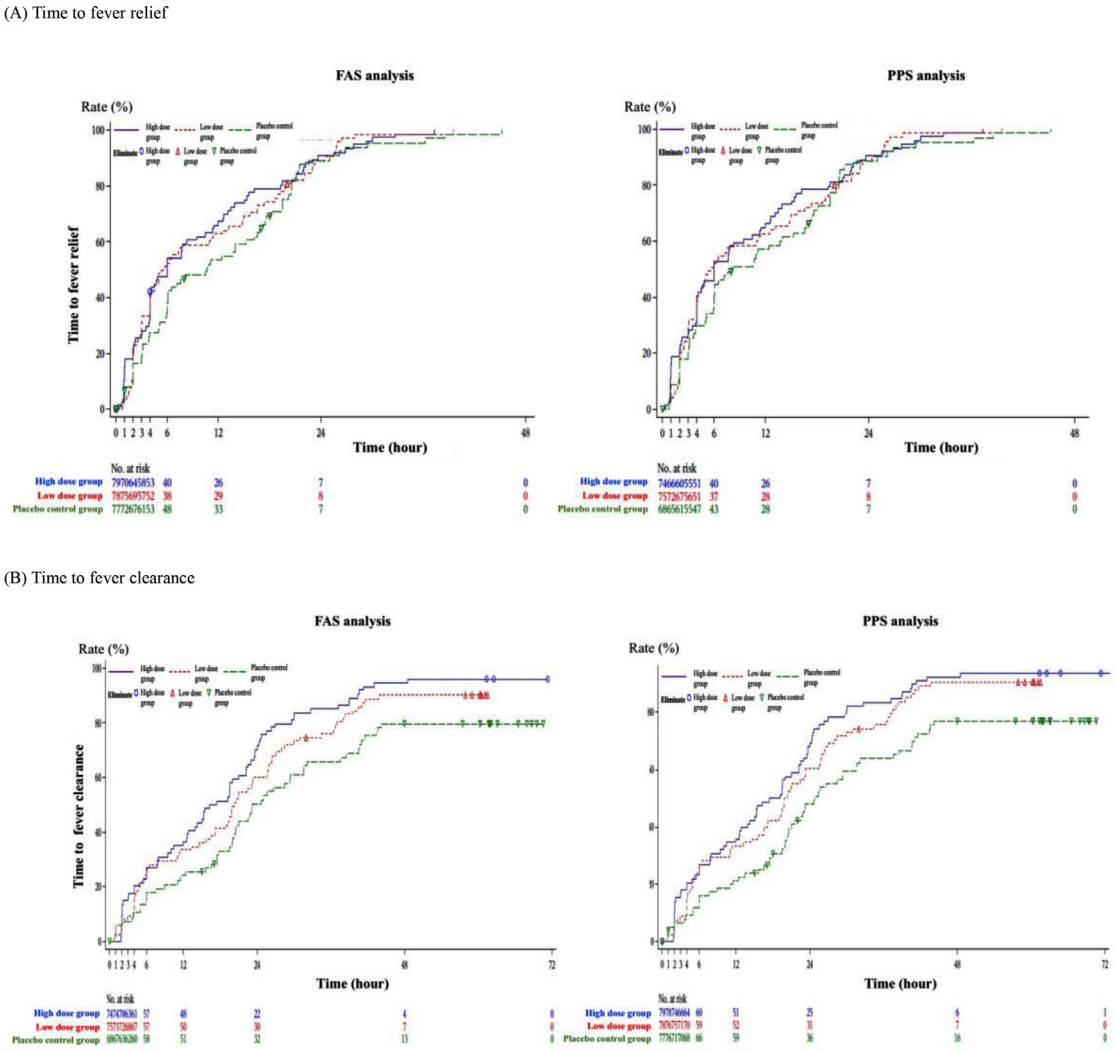

Fig. 2. Kaplan-Meier curves of time to fever relief and time to fever clearance. FAS: full analysis set; PPS: per-protocol set.

throat, cough, headache and sore limbs were significantly different among groups in both the FAS analysis and the PPS analysis (Table 3 and Supplementary Table 6 and Table 7).

3.2.2.5. Effective rate. The change of TUM symptom score from baseline to post-treatment was not significantly different among three groups (Table 3 and Supplementary Table 8). The effective rate in the high-dose group was higher than that in the placebo group ($P < 0.0001$ in the FAS and PPS analyses) and the low-dose group compared with the placebo group ($P < 0.0001$ in the FAS and PPS analyses), while it was similar in the high-dose group and the low-dose group ($P = 0.80$ in the FAS analysis and $P = 0.72$ in the PPS analysis).

3.2.2.6. Emergency drug usage. During the trial, the proportions of emergency drugs used by patients in the high-dose group, low-dose group and placebo control group were 2.5%, 0.0% and 14.3%, respectively, in the FAS analysis ($P = 0.0002$) and 0.0%, 0.0% and 6.8%, respectively, in the PPS analysis ($P = 0.0013$) (Table 3 and Supplementary Table 8). Two patients in the high-dose group and four patients in the placebo group were excluded from the PPS analysis for inappropriate use of ibuprofen as required because they took ibuprofen when their body temperature had not reached 39.0 °C or they took ibuprofen to alleviate dysmenorrhea instead of fever.

3.3. Safety assessment

Throughout the analysis, a total of 111 AEs with 75 participants (31.9%) were recorded (Table 4). Among them, 35 participants (44.3%) with 51 cases of AEs were in the high-dose group, 26 subjects (33.3%) with 40 cases of AEs were in the low-dose group, and 14 subjects (18.0%) with 20 cases of AEs were in the placebo group. The main AEs were gastrointestinal disorders (26.0%) and laboratory abnormalities (6.4%), among which diarrhea was the most common AEs. Two significant AEs (2.6%) (manifested as bacterial tonsillitis and positive urine leukocytes) occurred in the placebo control group; these were found not to be drug-related AEs after evaluation (Table 4, Supplementary Table 9 and 10). No serious AEs were reported during the study. All the AEs were cured naturally except for one case who developed bacterial tonsillitis and then received antibiotic therapy.

A total of 45 cases involving 33 participants (41.8%), 36 cases involving 26 participants (33.3%), and 17 cases involving 12 participants (15.4%) were recorded as drug-related AEs in the high-dose group, low-dose group, and placebo group, respectively (Supplementary Table 7). All drug-related AEs were mild to moderate, except for one (1.3%) in the low-dose group who suffered from severe diarrhea. All AEs were cured naturally by the end of the study.

Table 4
Overall AEs rate among three groups in safety set.

Type of AEs	High-dose (n = 79)		Low-dose (n = 78)		Placebo (n = 77)		Total (n = 235)	
	Times	Cases (rate,%)	Times	Cases (rate,%)	Times	Cases (rate,%)	Times	Cases (rate,%)
All	51	35 (44.3)	40	26 (33.3)	20	14 (18.0)	111	75 (32.0)
Drug related	45	33 (41.8)	36	25 (32.1)	17	12 (15.4)	98	68 (28.9)
Significant	0	0	0	0	2	2 (2.6)	2	2 (0.9)

Note: There were no serious AEs, serious drug related AEs, and AEs leading to dropout.

4. Discussion

4.1. Summary of the main results

The results showed a significant dose-dependent antipyretic effect of Binafuxi granules, manifested as a shortened fever course, improved clinical symptoms, an increased afebrile rate, and less antipyretic usage. Our study also revealed that Binafuxi granules dose-dependently relieved symptoms of the common cold, including cough, nasal congestion, and nasal discharge.

4.2. Agreements and disagreements with other studies or reviews

The common cold is a widespread disease, and there are a large number of articles reports the latest treatment progress of common cold every year. The effective treatments for the common cold are intranasal ipratropium, analgesics, decongestants, antihistamines and zinc, while the ineffective treatments for the common cold are antibiotics, antivirals, intranasal corticosteroids, steam, vitamins D and E, echinacea.[24] As alternative and over-the-counter treatment, Binafuxi granules could effectively shorten the symptom course of the common cold, especially alleviate fever.

There are limited articles focus on common cold with fever. Most of the currently published articles related to the common cold with fever are integrative medicine researches.[25-27] Kangbingdu Oral Liquid is composed of 9 herbs (Radix isatidis, Rhizoma phragmitis, Radix Rehmanniae, Radix Curcumae, Rhizoma Anemarrhenae, Rhizoma acori tatarinowii, Herba pogostemonis, Fructus Forsythiae, and Gypsum fibrosum). After 3 days of taking Kangbingdu Oral Liquid, the fever reduction rate reached 66.5%, and the rate was further increased to 95.16% after 7 days medication.[25] Compared with Kangbingdu Oral Liquid, the antipyretic effect of Binafuxi granules was more predominant, for the afebrile rate was 92.4% after 3 days medication.

Shufeng Jiedu capsule is an oral Chinese herbal medicine and composed by Fallopia japonica (Houtt.), Forsythia suspense (Thunb.), Isatis indigotica (Fort.), Bupleurum chinense (DC.), Patrinia scabiosaefolia (Fisch.), Verbena officinialis (L.), Phragmites communis (Trin.) and Glycyrrhiza uralensis (Fisch.).[26] It shows significant antipyretic effects on patients with common cold. However, it is incompatible with Binafuxi granules for different recruited populations and treatment cycles.

4.3. Potential mechanisms

Binafuxi granule is composed of six herbs, making it complicated to explore the potential mechanism of treating common cold with fever. Modern pharmacological studies reveal some working mechanisms of individual traditional Uyghur herbs, which help to explain the clinical effect of the compound prescription. As the pathogenesis of the common cold involves a complex interplay between replicating viruses and the host's inflammatory response,[3] the antipyretic effect of Binafuxi granules may be largely attributed to the component of *Viola kunawarensis* Royle, as it has been proven to have anti-inflammatory and antiviral effects. In influenza A virus H1N1 infections, *Viola kunawarensis* Royle inhibited MDCK cell lesions *in vitro* and reduced the mortality and inflammatory responses of mice *in vivo*.[8] The antipyretic effect of *Viola kunawarensis* Royle in mice intraperitoneally injected with *Escherichia coli* or *Staphylococcus aureus* was related to a reduction in peritoneal capillary permeability and inflammatory exudation.[7] *Glycyrrhiza uralensis* Fisch. and *Rosa rugosa* Thunb have been proven to relieve cough,[13,28] and *Fomes officinalis* Ames significantly inhibits NO production in lipopolysaccharide-treated RAW 264.7 cells.[29]

In our study, the main adverse event was diarrhea. All drug related diarrheas were cured naturally, without serious AEs, which might be caused by *Convovulus scammonia* L..[14] Based on traditional TCM theory, lung and large intestine are external and internal related, and inducing diarrhea is a treatment to cure lung disease by expelling lungs external evil from the body through intestines. Inducing diarrhea also draw antipyretic effect. So, drug related diarrheas in our study were a method of reducing fever.

4.3. Implications for practice and research

In our study, Binafuxi granules have predominant antipyretic effects, as well as outstanding effects on alleviating symptoms of the common cold. As an over-the-counter drug, it is convenient and effective to reduce fever. Due to *Convovulus scammonia* L., diarrhea is the main adverse event. Although all the drug related diarrheas were cured naturally, Binafuxi granules are still potential to cause increased frequency of bowel movements and fluid electrolyte disorders. For following clinical trials or practice, the dosage for patients with habitual diarrhea may need to taper.

It is complicated to clarify the action mechanisms of Binafuxi granules in treating common cold with fever. Systems pharmacology, a comprehensive method based on the concept of "disease-gene–target-medicine", has been largely used to investigate the complex pharmacological mechanisms of TCM.[30] With the wide application of systems pharmacology, the pharmacological mechanism of Binafuxi granules should be explored in further research.

4.4. Strength and limitations

Fever is a common manifestation of respiratory disease, especially the common cold and influenza.[24] However, current treatment for the common cold is supportive and symptomatic, limited research focused on antipyretic effect of test drug.[27,31] To our knowledge, this is the first randomized, double-blind, placebo-controlled trial to report the efficacy and safety of Uighur medicine in treating the common cold with fever. In our study, compared with placebo control group, Binafuxi granules could significantly short fever course, increase afebrile rate, and relieve symptoms of the common cold, including cough, nasal congestion, and nasal discharge.

There are some limitations in our study. The improvement in symptom scores after medication may have reflected the therapeutic effect of Binafuxi granules. However, we only compared the symptom scores at baseline and on the fourth day, and more time points should be set for the comparison of symptom scores to fully evaluate the effect of Binafuxi granules.

In summary, Binafuxi granules are safe and effective for the common cold with fever in terms of shortening the course of fever and improving clinical symptoms. Based on the current study, a multicenter, randomized, phase III clinical study is well prepared to further evaluate Binafuxi granules under the same conditions.

4.5. Conclusions

Binafuxi granules can dose-dependently shorten the fever course and improve clinical symptoms in patients suffering from the common cold with fever. This treatment is generally well tolerated, with diarrhea being the main adverse event.

CRediT authorship contribution statement

XM Liu: Study design and development, ethics application, trial registration, data interpretation, writing - original draft. **J Min:** Study design, protocol development, study performance and reporting, writing - original draft. **B She and Y Chen:** Investigation, methodology, project administration. **J Li, L Huang and J Chen:** Preparation and testing of Binafuxi granules and placebo and coordination of each center to complete the project. **A Luo, M Yang, T Li, YQ Wu, HL Zhong and DH Chen:** Data interpretation, data analysis and manuscript draft, writing the original draft. **W Liu:** Protocol development, study supervision. **HL Jiang and B Mao:** Co-corresponding authors, who contributed equally to the study design, protocol development, study supervision, writing - review & editing.

All authors critically reviewed the content and approved the final version. The contents of this manuscript are not under consideration for publication elsewhere.

Declaration of competing interest

The property right of Binafuxi granules belongs to the organizing institution (Xinjiang Yinduolan Pharmaceutical Co., Ltd.), which applied for an invention patent (Compound of Chinese traditional medicine for treating common cold with heat syndrome, and its preparation method and application. No. CN201910775844.6) in 2019. As an organizing institution, Xinjiang Yinduolan Pharmaceutical Co., Ltd., provided financial support for the project research. West China Hospital of Sichuan University is the leading investigating hospital for the Binafuxi granules phase II clinical trial, researchers from which designed the study and were responsible for the data analyses and the decision for manuscript submission. The organizing institution, as well as the authors from the organizing institution, who are J Li, L Huang and J Chen, had no role in the design of this study and does not have any responsibility for analyses, interpretation of the data, or the decision to submit results. The authors declare that they have no competing interests.

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Ethical statement

This study was reported in compliance with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement and adhered to the principles of the Declaration of Helsinki. This study has been registered with the Chinese Clinical Trial Registry (ChiCTR-IIR-17,013,379). Ethical approval for the study was provided by the Ethics Committee of Clinical Trials and Biomedicine of West China Hospital of Sichuan University (IRB-2017–5). All participants provided informed written consent.

Data availability

Datasets generated and/or analyzed during this study may be obtained from the organizing institution (Xinjiang Yinduolan Pharmaceutical Co., Ltd., Xinjiang, China) upon reasonable request.

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Supplementary materials

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