


The therapeutic effects of naringenin on bronchial pneumonia in children

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Abstract

Bronchial pneumonia in children is a common infectious disease in toddlers and infants, which may cause hyperpyrexia, pulmonary moist rales, and even respiratory failure. Traditional drugs for bronchial pneumonia in children often lead to drug resistance and side effects. Recently, naringenin has been reported to be a potential treatment for several airway inflammatory diseases due to its anti-inflammatory and anti-microbial activities. The current clinical study aimed to evaluate the safety and therapeutic effect of naringenin in treating bronchial pneumonia in children. A total of 180 eligible patients were randomly assigned into naringenin (NAR) group and azithromycin (AZI) group. All participants were required to follow a 5-day oral administration, and their serum cytokine levels were measured during the clinical intervention. After the treatment, the disappearance time of clinical symptoms, and the incidences of complications and adverse reactions were compared between the two groups. Naringenin was able to inhibit inflammation, shorten the disappearance time of clinical symptoms, reduce the incidences of bronchial pneumonia complications and related adverse reactions, and improve the health conditions of the patients. Our results suggested that naringenin was safe and beneficial to children with bronchial pneumonia, providing new insights into the clinical application of naringenin.

KEYWORDS

bronchial pneumonia in children, children, naringenin, therapeutic outcomes

1 | INTRODUCTION

Bronchial pneumonia, also known as lobular pneumonia, is a common infectious disease in children, especially in toddlers and infants.¹ Bronchial pneumonia in children often occurs in winter and spring, when the weather is cold and unpredictable. Bronchial pneumonia in

children is usually induced by pathogenic infection, such as bacteria, viruses, molds, mycoplasma pneumoniae, as well as superinfection of viruses and bacteria.^{2,3} The primary clinical symptoms include high grade fever, cough, breathlessness, and permanent pulmonary medium or fine moist rales, even respiratory failure in some severe cases.⁴⁻⁶ Current available therapeutic drugs for the treatment of bronchial pneumonia

Abbreviations: AZI, azithromycin; COPD, chronic obstructive pulmonary disease; NAR, naringenin.

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include β -lactam antibiotics, macrolide antibiotics, aminoglycoside antibiotics, and neuraminidase inhibitors.^{2,7} Nevertheless, the long-term administration of antibiotics and inhibitors may result in drug resistance and side effects, such as intestinal flora imbalance.⁸ In addition, the application of ultrasonic nebulization as an adjuvant therapy may induce symptoms such as coughing and bronchospasm in infants and toddlers, and it is hard to operate because of the poor compliance of young children. Therefore, it is necessary to develop a new drug that is effective with fewer side effects for bronchial pneumonia in children.

Naringenin, the glycogen component of naringin, is a flavorless and colorless type of flavonoid. Naringenin has been shown with properties of scavenging free radicals, anti-oxidation, anti-inflammation, anti-atherosclerosis, cellular protection, as well as pharmacological functions, such as anti-microbial activities, inflammation resolving, and anti-cancer.⁹⁻¹² In China, oral liquid with the formulation containing naringin and relevant Chinese patent medicine injection has already been archived into pharmacopoeia. Moreover, several animal studies have already confirmed the efficacy of naringenin in treating airway inflammatory diseases, such as asthma and chronic obstructive pulmonary disease.¹³ However, naringin has not been used as a drug for the clinical treatment of bronchial pneumonia in children.

Due to the therapeutic potential of naringenin in various airway inflammatory diseases and the lack of new drugs for treating bronchial pneumonia in children, in this clinical trial, we aimed to evaluate the anti-inflammatory effect of naringenin in the clinical treatment of bronchial pneumonia in children. The results would help to elucidate the molecular mechanism of naringenin action, and provide theoretical insights into the clinical application of naringenin.

2 | MATERIALS AND METHODS

2.1 | Study design

The current study was conducted as a randomized controlled trial to lessen the potential confounding effects. A total of 186 children with bronchial pneumonia who were hospitalized between June 2019 and June 2020 in Zibo Central Hospital were recruited in this trial. The trial protocol was approved by ethics committee of Zibo Central Hospital. All statutory guardians of the participants were required to sign informed written consent before the participants were randomly assigned into the clinical trial.

2.2 | Inclusion criteria

Children were eligible to enter the clinical trial if they met the following six conditions: (a) age from 1.5 to 6 years; (b) the clinical symptoms were in accordance with the diagnostic criteria of bronchial pneumonia in children; (c) with normal gastrointestinal function; (d) free from antibiotic in the past 3 months; (e) had no allergic history of naringenin; and (f) both patients and their statutory guardians provided informed consent and voluntarily joined the study.

2.3 | Exclusion criteria

In the process of participant recruitment, children who met one of the following five exclusion criteria were excluded: (a) patients had severe diseases in the heart, brain, liver, kidney, and endocrine system, or were diagnosed with tuberculosis or tumors; (b) patients with atelectasis, bronchiectasis, pulmonary abscess, and bronchopulmonary dysplasia; and (c) patients with mental illness who failed to cooperate during the trial.

2.4 | Clinical intervention

The study flow diagram is shown in Figure 1. A total of 180 participants were randomly assigned into two groups: NAR group and AZI group.¹⁴ AZI group served as positive control. Patients in the NAR group received oral administration of naringenin tablets for 5 days, with the daily dosage of 5 mg/kg. Patients in the AZI group were given oral azithromycin tablets with 10 mg/kg per day for 5 days. Both drug tablets were crushed into powder and taken with water for better absorption effect.

2.5 | Enzyme-linked immunosorbent assay

Two milliliters of blood was collected from each patient from the left radial artery at four time points, including the day before the drug intervention (T0), 1 day after treatment (T1), 3 days after treatment (T2), and 5 days after treatment (T3).¹⁵ The serum was separated by centrifugation and stored in -20°C . The supernatant contents of IL-6, IL-8, IL-10, and TNF- α were measured by Enzyme-linked immunosorbent assay (ELISA) according to the manufactures' instructions. All kits were purchased from eBiosciences.

2.6 | Data collection

All basic information of the recruited children was collected through the hospital's electronic records. Additional data, such as family history of allergy and comorbidities, were extracted through a questionnaire before they joined in the clinical trial. Data of patient laboratory blood tests and diagnosis of clinical symptoms were also collected from the hospital's electronic records.

2.7 | Statistical analysis

The statistical analysis in the current study was performed using SPSS version 20. (SPSS Inc.). Data were expressed as mean \pm SD unless there was other statement. The count data were expressed by the number of positive cases and the positive rate. Measurement data and group comparing data were analyzed by Student *t* test and χ^2 -test, respectively. $p < .05$ was considered as statistically significant.

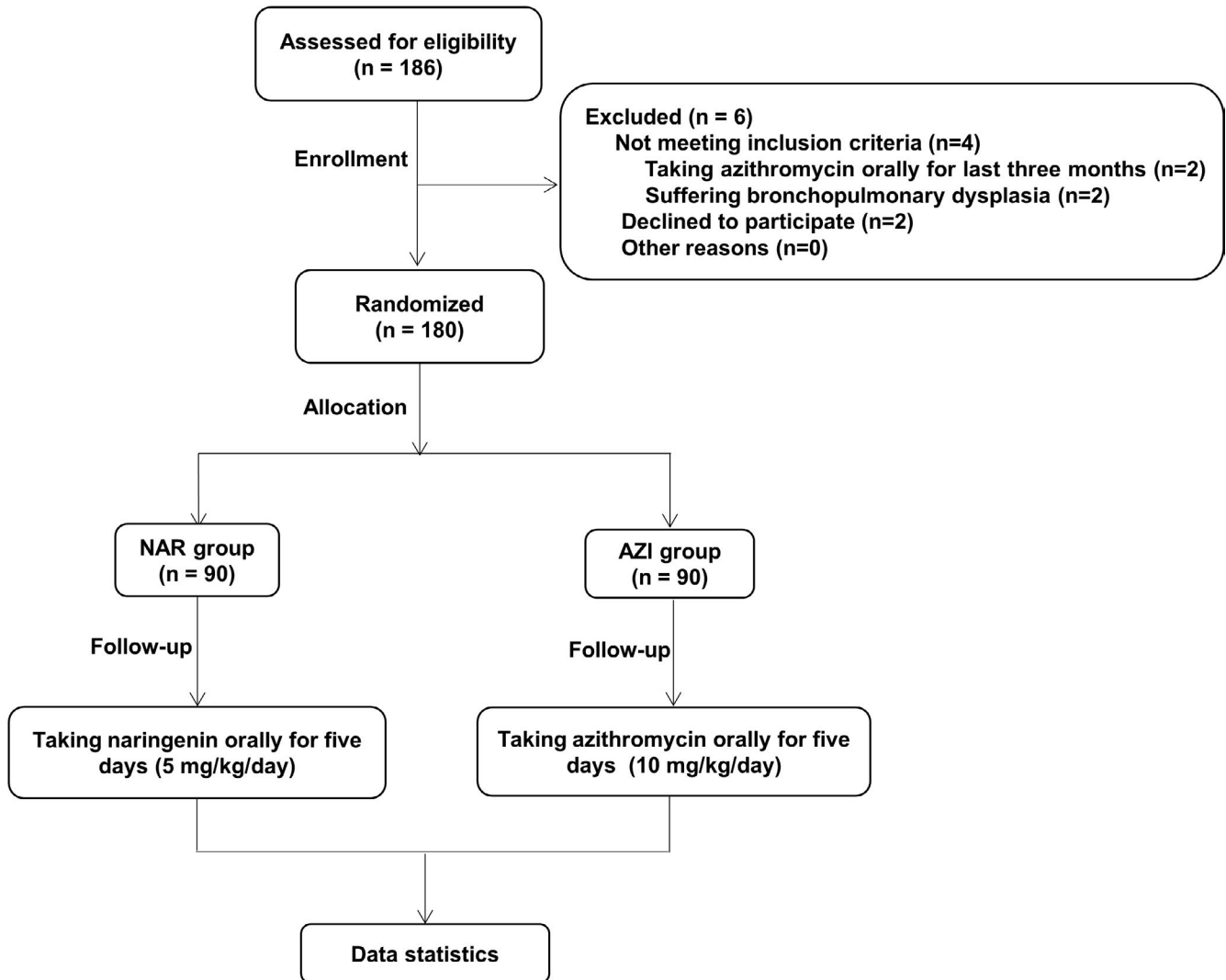


FIGURE 1 Flow diagram

3 | RESULTS

The flow diagram of this study is shown in Figure 1. A total of 186 children were enrolled into our trial for eligibility assessment. Six patients were excluded due to the presence of bronchopulmonary dysplasia, long-term antibiotic usage, and refusal to cooperate. The remaining 180 patients were randomly assigned into the NAR group ($n = 90$), which was the intervention group, and the AZI group ($n = 90$), which served as a positive control (Figure 1), respectively. All patients in the two groups were followed up and their clinical data were included into the analysis at the end of the trial.

3.1 | Participant demographic information and baseline characteristics

The basic information of the participants in both groups was summarized in Table 1. There were no significant differences in baseline characteristics between the two groups, with respect to age

(2.7 ± 1.2 years in NAR group and 2.6 ± 1.0 years in AZI group), gender ratio (M42/F48 in NAR group and M44/F46 in AZI group), or coexisting diseases (for patient number in NAR group vs. in AZI group, bronchial asthma 8 vs. 9, allergic rhinitis 11 vs. 13, anemia 9 vs. 8, and diarrhea 4 vs. 5). In addition, the clinical indicators, such as heart rate (94 ± 6 [number/min] in NAR group, 95 ± 8 [number/min] in AZI group), WBC counts (6.1 ± 1.3 vs. 6.3 ± 1.1 [$10^9/L$]), neutrophil numbers (8.9 ± 1.7 vs. 8.7 ± 1.3 [$10^9/L$]), and body temperature (38.2 ± 2.5 in NAR group, 38.4 ± 2.2 [$^{\circ}C$] in AZI group), were also found to be similar between the two groups.

3.2 | Naringenin reduces the serum levels of pro-inflammatory cytokines and elevates the levels of anti-inflammatory cytokines

All participants were required to draw 2 ml of blood from the left radial artery at the day before the drug intervention (T0), 1 day after treatment (T1), 3 days after treatment (T2), and 5 days after

TABLE 1 Comparison of the two groups of patients with basic information

Items/groups	NAR group (n = 90)	AZI group (n = 90)	p value
Age (years)	2.7 ± 1.2	2.6 ± 1.0	.56
Sex, n (%)			
Male	42 (46.7)	44 (48.9)	.28
Female	48 (53.3)	46 (51.1)	.25
Coexisting diseases			
Bronchial asthma (n)	8	9	.76
Allergic rhinitis (n)	11	13	.34
Anemia (n)	9	8	.58
Diarrhea (n)	4	5	.16
Indicators			
Heart rate, number/ min	94 ± 6	95 ± 8	.64
WBC counts, 10 ⁹ /L	6.1 ± 1.3	6.3 ± 1.1	.57
Neutrophils, 10 ⁹ /L	8.9 ± 1.7	8.7 ± 1.3	.29
Temperature (°C)	38.2 ± 2.5	38.4 ± 2.2	.81

Abbreviation: WBC, white blood cell. Data were expressed as mean ± SD.

TABLE 2 Comparison of the value of IL-6, IL-8, IL-10, and TNF- α between the two groups of patients

Index	Time points	NAR group (n = 90)	AZI group (n = 90)	p value
IL-6 (ng/ml)	T0	78.4 ± 12.3	78.9 ± 11.7	.87
	T1	64.9 ± 11.8*	72.1 ± 10.2	.14
	T2	45.3 ± 9.1**	68.3 ± 9.4	.04
	T3	34.9 ± 8.2***	53.5 ± 7.8*	.03
IL-8 (ng/ml)	T0	62.4 ± 10.3	61.7 ± 10.3	.69
	T1	42.9 ± 8.6*	57.1 ± 11.6	.28
	T2	17.4 ± 3.3***	50.4 ± 10.9*	.02
	T3	15.3 ± 2.7***	32.7 ± 10.9**	.04
IL-10 (ng/ml)	T0	14.0 ± 1.8	12.9 ± 3.2	.33
	T1	31.9 ± 4.6*	24.6 ± 8.4*	.05
	T2	43.7 ± 9.0**	27.5 ± 8.9*	.04
	T3	51.2 ± 15.4***	32.4 ± 6.7**	.03
TNF- α (ng/ ml)	T0	74.7 ± 16.3	73.9 ± 11.5	.73
	T1	42.9 ± 8.6**	67.2 ± 12.3	.04
	T2	35.8 ± 5.1**	55.7 ± 8.9*	.02
	T3	26.4 ± 3.6***	51.6 ± 10.2*	.01

Abbreviations: IL-10 interleukin-10; IL-6, interleukin-6; IL-8, interleukin-8; TNF- α , tumor necrosis factor- α . Data were expressed as mean ± SD.

* $p < .05$; ** $p < .01$; *** $p < .001$ compared with T0.

treatment (T3). The serum contents of IL-6, IL-8, IL-10, and TNF- α were determined by ELISA assay, and the results were summarized in Table 2. The serum concentrations of pro-inflammatory cytokines

IL-6, IL-8, and TNF- α were shown to be at relatively equal levels at T0 between NAR group and AZI group. Encouragingly, with drug administration from T0 to T3, the serum levels of these three pro-inflammatory cytokines exhibited sustained downregulation in both two groups. Moreover, the serum levels of IL-6, IL-8, and TNF- α in the NAR group showed more significant reduction at T1, T2, and T3 ($p < .05$), especially at T2 and T3, compared to the AZI group. IL-10 is a representative anti-inflammatory cytokine. The serum level of IL-10 increased obviously from T1 to T3 in both the NAR group and AZI group. However, IL-10 level in the NAR group was higher than the AZI group, especially at T3. These results suggested that naringenin was able to inhibit inflammatory response in children with bronchial pneumonia. Notably, the effects of naringenin were even superior than the positive drug candidate azithromycin.

3.3 | Naringenin shortens the disappearance time of clinical symptoms and improves the health conditions of the patients

The antipyretic time, cough disappearance time, and lung rale disappearance time of patients in the two groups were collected and analyzed to further evaluate the effectiveness of naringenin in treating bronchial pneumonia in children, and the results were summarized in Table 3. Overall, compared with the AZI group, the NAR group showed significantly lower symptom disappearance time in the following aspects: the antipyretic time in NAR group was 1.5 ± 0.2 days, which was significantly shorter than 3.8 ± 0.4 days in the AZI group ($p < .02$); the cough disappearance time in the two groups was 3.7 ± 0.5 days versus 5.6 ± 0.6 days ($p < .03$); as for lung rale disappearance time, 4.3 ± 1.2 days in the NAR group was also markedly shorter than 6.5 ± 1.4 days in the AZI group ($p < .04$). These data indicated that naringenin was potentially able to accelerate the recovery process from fever, coughing, and lung rale, thereby improving the treatment outcomes of the patients.

3.4 | Treatment with naringenin reduces the complication incidence of bronchial pneumonia

In order to assess the role of naringenin in controlling the complications of bronchial pneumonia in children, the incidences of bullae of lung, gastrointestinal hemorrhage, and proteinuria were statistically compared between the two groups (Table 4). In the AZI group, 10% of the patients have bullae of lung, while in the NAR group, the incidence of lung bullae was significantly lower, only 2.2% ($p < .04$). The incidence rate of gastrointestinal hemorrhage was also dramatically lower in the NAR group (1.1%) than the AZI group (12.2%, $p < .03$). In addition, only three patients (3.3%) have proteinuria in the NAR group, whereas 15 patients (16.7%) in the AZI group were diagnosed with proteinuria ($p < .01$). Taken together, fewer patients developed complications after the treatment of naringenin, which indicated that naringenin was able to reduce the incidence rate of complications in bronchial pneumonia.

3.5 | Adverse reactions and safety assessment

To estimate the safety profile of naringenin treatment, the most common treatment-related adverse events were analyzed in both groups, and the statistics were summarized in Table 5. Comparing with AZI group, the incidence rates of adverse events in the NAR group were markedly decreased in terms of nausea (1.1% vs. 11.1%, $p < .02$), vomiting (1.1% vs. 17.8%, $p < .01$), elevated urinary protein (3.3% vs. 11.1%, $p < .03$), leukopenia (1.1% vs. 15.6%, $p < .02$), and neutropenia (2.2% vs. 24.4%, $p < .01$). Furthermore, no diarrhea and rash occurred in patients treated by naringenin. These data confirmed that naringenin was a safe choice to treat bronchial pneumonia in children.

TABLE 3 Comparison of the value of antipyretic time, cough disappearance time, and lung rale disappearance time between the two groups of patients

Items/groups	NAR group (n = 90)	AZI group (n = 90)	p value
Antipyretic time (day)	1.5 ± 0.2	3.8 ± 0.4	.02
Cough disappearance time (day)	3.7 ± 0.5	5.6 ± 0.6	.03
Lung rale disappearance time (day)	4.3 ± 1.2	6.5 ± 1.4	.04

TABLE 4 Comparison of the incident of complications between the two groups of patients

Items/groups	NAR group (n = 90)	AZI group (n = 90)	p value
Bullae of lung	2 (2.2)	9 (10)	.04
Gastrointestinal bleed	1 (1.1)	11 (12.2)	.03
Proteinuria	3 (3.3)	15 (16.7)	.01

Data were expressed as n (%).

TABLE 5 Comparison of the incident of adverse reactions between the two groups of patients

Items/groups	NAR group (n = 90)	AZI group (n = 90)	p value
Nausea	1 (1.1)	10 (11.1)	.02
Vomiting	1 (1.1)	16 (17.8)	.01
Diarrhea	0 (0)	15 (16.7)	NA
Rash	0 (0)	9 (10.0)	NA
Elevated alanine aminotransferase	2 (2.2)	18 (20.0)	.01
Elevated urinary protein	3 (3.3)	10 (11.1)	.03
Leukopenia	1 (1.1)	14 (15.6)	.02
Neutropenia	2 (2.2)	22 (24.4)	.01

Data were expressed as n (%).

4 | DISCUSSION

This study demonstrated that naringenin exhibited therapeutic effect on children under 6 years suffering from bronchial pneumonia, with lower incidence of complications and higher safety. Naringenin might be a potential new drug for the clinical treatment of bronchial pneumonia in children in the near future.

In developing countries, bronchial pneumonia is one of the most common diseases for young children with high rates of hospitalization and mortality.¹⁶ Take China as an example, bronchial pneumonia in children occurs 0.06–0.27 per child a year, and about 1840 to 12 230 per million children fail to recover.^{17–19} Thus, developing early diagnosis and effective intervention are of great importance. Bronchial pneumonia in children is caused by microbe infections, and the pathogens include bacteria, virus, fungus, protozoa, and some noxious chemicals. The most reliable way to diagnose bronchial pneumonia in children is through chest X-ray and blood test.²⁰ Once children have bronchial pneumonia, they will suffer from high-grade fever, cough with yellow or green mucus, pain in the chest, pulmonary moist rales, breathlessness, and even respiration failure. Doctors usually give prescription after comprehensive evaluation of symptoms of individual patient.

Nowadays, available drugs for bronchial pneumonia in children are mainly antibiotics, such as β -lactam antibiotics and aminoglycoside antibiotics, as well as a certain amount of antivirals such as neuraminidase inhibitors and antifungal.²¹ It was recommended that every child diagnosed with bronchial pneumonia should receive antibiotics firstly since it is difficult to immediately determine the pathogens. According to the antibiotics treatment outcome reports in the United Kingdom, the first-generation cephalosporins are more effective to treat patients at preschool age.²² In the United States, penicillin and *Streptococcus pneumoniae* vaccine were verified to benefit children who were diagnosed with bronchial pneumonia.²³ However, increasing use of penicillin and cephalosporins can evoke tremendous safety concern because long-term administration of antibiotics often leads to drug resistance and imbalanced gastrointestinal function. Antibiotics resistance makes it even more difficult to treat infections and chronic diseases. Therefore, the use of antibiotics should be rationalized and novel drugs for bronchial pneumonia in children should be used.

In the past few years, naringenin, a colorless flavanone extracted from citrus fruit, has been widely used for its various pharmacological potentials, such as anti-diabetic, anti-inflammatory, anti-oxidant, and immunomodulatory capacities.²⁴ Manchope et al. found that naringenin activated Nrf2 in macrophages, inducing anti-oxidative reaction.²⁵ Felipe et al. reported that naringenin could inhibit NF- κ B activation and reduce the production of pro-inflammatory cytokines such as IL-1 and TNF- α ; thus, alleviating some inflammatory responses.²⁶ Naringenin was also shown to play a therapeutic role in chronic airway diseases, including asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and lung cancer, by regulating the expression of cytokines, differentiation of immune cells, and lung smooth muscle remodeling.^{27–29} Nevertheless, the therapeutic efficacy of naringenin in treating

bronchial pneumonia in children remains unclear. In the current study, we conducted a clinical trial to evaluate the safety and efficacy of naringenin in treating bronchial pneumonia in children.

A randomized controlled study was designed in this trial to lessen the possible confounding effects. A total of 180 children with bronchial pneumonia were enrolled and randomly assigned into the NAR intervention group and the AZI control group, and the blood factors and clinical outcomes were analyzed for comparing the therapeutic efficacy of naringenin. Our data revealed that naringenin reduced the serum contents of pro-inflammatory cytokines, including IL-6 and IL-8, while at the same time elevated the anti-inflammatory cytokine IL-10. In addition, patients in the NAR group exhibited shorter disappearance time of clinical symptoms, such as coughing and lung rale. Also, complications like bullae of lung, proteinuria, gastrointestinal bleeding, and other related adverse reactions occurred less often after treatment with naringenin. Our results have demonstrated that naringenin administration is a potential new therapy for bronchial pneumonia in children with higher safety and better curative effect.

Inevitably, our trial has several limitations. First of all, the data for this study were collected from the electronic records in our hospital, which were limited in quantity and might have some omissions. Secondly, bronchial pneumonia in children shared similar clinical manifestations with asthma; it was, therefore, unavoidable to interfuse a few cases of asthma because of the lack of specific biomarkers to distinguish these two diseases. But this interfusion was unbiased between the two groups; hence, it should have no effect on the final conclusion. Thirdly, the drug resistance of naringenin should have been assessed. Since our study was conducted from June 2019 to June 2020, and the intervention time was only 5 days, we have not received any resistance report to date. However, we will keep following up in the future. Another limitation in our study was the lack of a healthy control group in serum index analysis, mainly for T3 time point, which may help compare the patients' recovery state. Moreover, according to most of the literatures, the suggested dosage of naringenin was between 50 and 100 mg/kg. However, this dose of naringenin was mainly administrated in adults, little evidence was shown in children at pre-school age. Besides, the side effects remain unclear when treating patients with a large dose of naringenin. Therefore, for safety consideration, we choose a smaller dose (5 mg/kg) in our clinical intervention. In the future, we will optimize the dosage of naringenin in treating children with bronchial pneumonia. Nevertheless, this clinical trial verified that naringenin was able to treat bronchial pneumonia in children and improve the health conditions of the patients.

In addition, we still leave some questions for further studies. For example, what is the molecular mechanism of naringenin in alleviating bronchial pneumonia in children? Lawrence et al. reported that naringenin prevented degradation of I κ B in vitro, which is the endogenous inhibitor of NF- κ B p50/p65 subunits.³⁰ When I κ B is degraded by the proteasome, the p50/p65 subunit is released into the nucleus and promotes transcription of inflammation-related genes. Whereas when I κ B degradation is inhibited, NF- κ B transcription activity is also repressed; thus, relieving the excessive inflammation

responses. Besides, Shi et al. and Iwamura et al. showed that naringenin ameliorated chronic airway inflammation and continuous hyper-responsiveness, and slowed down the airway remodeling by reducing the proportion of CD4+ T cells, mainly T-helper 2 cells, which resulted in decreased IL-13 and IL-4, and reduced mucus production.^{31,32} According to these findings, we will aim to investigate the underlying mechanism of naringenin function in treating bronchial pneumonia in children in our future studies.

5 | CONCLUSION

In conclusion, our study assessed the therapeutic capacity of naringenin in treating bronchial pneumonia in children. Naringenin was found to be a safe drug candidate in treating bronchial pneumonia in children by inhibiting inflammation, alleviating clinical symptoms, reducing the incidence rates of bronchial pneumonia complications and related adverse reactions, and improving the health conditions of the patients. Our results provide a novel insight into the clinical application of naringenin.

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None.

DISCLOSURE

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

Wenjing Yao, Xiaopeng Zhang, Feng Xu, Chunxia Cao, Tongtong Liu, and Yuanyuan Xue performed the experiments, analyzed, and interpreted the data. Xiaopeng Zhang was the major contributor in writing the manuscript. All authors read and approved the final manuscript.

ETHICS STATEMENT

The trial protocol was approved by ethics committee of Zibo Central Hospital.

DATA AVAILABILITY STATEMENT

Data could be obtained upon request to the corresponding author.

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