INTRODUCTION

Currently, allergic diseases have a great impact on the health of children. The childhood incidence rates of asthma, eczema or dermatitis, and allergic rhinitis are increasing gradually, and this increase is even evident in adults.

Atopic dermatitis (AD) is a chronic recurrent inflammatory skin disease characterized by severe itching and eczema-like lesions. It usually occurs in infancy and childhood. A Chinese epidemiology survey in 2014 reported that the prevalence of AD among children from 1 to 7 years old was 12.94% and the trend declined when they are growing up. Its etiology is related to heredity, immunity, and skin barrier function.

According to reports from the World Health Organization, the number of asthma sufferers worldwide has reached 235 million, and as such, asthma represents one of the most common diseases in children. WHO also released the report that the number of deaths caused by asthma was 383,000 in 2015.
The placebo group experienced a mean of 1.43 number of infectious episodes in patients with recurrent respiratory tract infections. The multicenter clinical trial, bacterial lysate treatment could reduce the number of infectious episodes in patients with recurrent respiratory tract infections. Another meta-analysis included 53 studies to assess the efficacy of bacterial lysate treatment on allergic disease as well as the degree of influence of bacterial lysate on each disease could be assessed. In addition, our research includes not only an evaluation of clinical symptoms but also some serum markers of immunity as well as indicators of lung function.

Pathogenesis of allergic diseases was proven to involve immune imbalance so that it is believed that some bacterial lysates promote immune responses by increasing immunoglobulin and cellular immunity. Bacterial lysates consist of inactivated bacterial extracts from pathogenic respiratory bacteria. Most of them are divided into two types, either PCBL (polyvalent chemical bacterial lysate) or PMBL (polyvalent mechanical bacterial lysate (PMBL)). OM-85 is the most common PCBL used in current studies. It is a lysate of 21 strains of eight bacteria which may boost immunologic responses. Ismigen was the PMBL used in the included studies. This orally/or sublingually administered immunomodulator can activate immunologic defense reactions by increasing IgA and IgG, elevating levels of the Th-1-specific cytokine IFN-γ, and reducing the Th2-specific cytokine IL-4. Some studies have shown that administration of bacterial lysate could reduce episodes in patients with recurrent respiratory infections. According to the result of a double-blind, placebo-controlled, multicenter clinical trial, bacterial lysate treatment could reduce the number of infectious episodes in patients with recurrent respiratory tract infections. The placebo group experienced a mean of 1.43 (95% CI [1.01, 1.86]) episodes in the 8-month study period, while 0.86 (95% CI [0.54, 1.19]) episodes were recorded in the bacterial antigen-treated group. The mean days of antibiotic usage in the treated group was 1.24 compared with 2.83 in the placebo group. Another meta-analysis included 53 studies to assess the efficacy of OM-85 in pediatric patients with recurrent respiratory tract infection found that bacterial lysates could reduce the frequency of respiratory infection.

However, the effect of bacterial antigen treatment on allergic disease remains controversial. Some studies have shown bacterial lysate treatment could reduce asthma attack in terms of duration of coughing and wheezing compared with the control group but others have reported that no significant difference was observed in the number of allergic episodes between treated and placebo groups. For AD, a study by Bodemer and colleagues demonstrated that a 20% reduction in occurrence of repeated events was observed in the OM-85-treated group compared with placebo. Conversely, the result from a randomized placebo-controlled trial including 606 newborns revealed that the prevalence of AD was no difference between the bacterial lysate and placebo groups after 3 years' follow-up. However, it was noted that a significant difference was observed in the group of infants with single heredity for atopy. Feeding bacterial lysate early in life is likely to reduce the occurrence of AD in infants with single atopic family history.

Therefore, the aim of our study was to investigate the clinical efficiency of bacterial lysate treatment on allergic disease as well as assess the extent of its influence.

### METHODS

#### 2.1 Data sources

We conducted a systematic literature search to identify potential articles from PubMed, EMBASE, Cochrane, China National Knowledge Infrastructure(CNKI), Chinese Biomedical database (CBM), and Wanfang databases. The search was performed using key terms, "OM-85." All identified articles were imported in Endnote, and selection was based on a three-step procedure, first screening by title, then by abstract, and finally by assessing full texts.

Two reviewers (LCM and CDT) conducted article screening independently, and any disagreements were resolved by discussion.

#### 2.2 Inclusion and exclusion criteria

In order to be included in this review, studies had to meet all of the following criteria: (1) study design: RCTs without language restriction; (2) participants: children and adults receiving a diagnosis of any type of allergic disease (asthma, dermatitis, allergy rhinitis); (3) intervention group: patients treated with at least one course of bacterial lysate alone, or participants received treatments of bacterial lysate combined with routine allergic disease treatment; (4) comparison group: patients treated with routine therapy for allergic disease or placebo only; and (5) outcome assessment: each study must provide the effective or invalid number. The primary outcome refers to effective/invalid numbers in the bacterial lysate and control groups individually. According to the guide for management and prevention of asthma, asthma symptoms could be assessed as...
well controlled, partly controlled, or not controlled, by frequency of asthma attack during the day, the efficiency of treatment, activity limitation, or night waking due to asthma. Partly controlled and well controlled were regarded as effective outcomes, and not controlled was defined as an invalid outcome. The effectiveness of treatment on dermatitis and rhinitis was assessed as improvement or no improvement by questionnaire or clinical observation. Secondary outcomes included serum immunoglobulin levels (IgG, IgA, or IgM), or T lymphocyte subtypes (CD3+, CD4+, or CD8+). FEV1 levels or side effects of treatment would be analyzed if mentioned by at least two articles.

Trials were excluded if (1) the study design was not an RCT; (2) no primary outcome number was available; (3) bacterial lysate and other treatments were administered to the experiment group while giving conventional treatment to the control group; and (4) external use of bacterial lysate was applied rather than oral or injected.

2.3 | Statistical analysis

In the meta-analysis of RCTs, dichotomous data were expressed as a relative ratio (RR) with 95% confidence intervals (CI). Continuous data were expressed as mean difference (MD) with 95% CI. Subgroup analysis was performed when at least two studies were concerned. The I² statistic was used to assess heterogeneity. When I² was between 25% and 50%, it was regarded as low heterogeneity. Moderate heterogeneity and high heterogeneity were reflected by I² between 50% and 75%, and 75% and 100%, respectively. When I² was below 25%, it was regarded as no heterogeneity. All analyses were performed using StataMP-64. The risk of bias was also assessed by the Cochrane risk bias assessment tool.

3 | RESULTS

3.1 | Study characteristics

A total of 231 references were searched, and after three-step selection, 19 articles were finally included, of which 15 studies were published in Chinese and four in English (Figure 1). One thousand seven hundred and twenty-eight patients were recruited in this study, of which 881 and 841 belonged to the bacterial lysate treatment and control groups, respectively. Out of those 19 articles, 17 studies used OM-85 treatment as intervention therapy. The remaining two studies used polyvalent bacterial lysate (PBL) and killed mycobacterium vaccae as their intervention treatment. Twelve RCTs described results in asthma, four for dermatitis, and three for rhinitis. All 19 studies reported the number of symptom improvement. Five studies and six studies analyzed the level change of T-cell subgroups and interleukins, respectively. Two studies showed the level of serum immunoglobulin and four studies involved the change of FEV1. Only two studies reported the adverse events. Four RCTs included adults, while the remaining 15 studies concerned children (Table 1).

3.2 | Assessing the risk of bias in included studies

Randomization methods were reported in 19 studies. Results of some studies were assessed by questionnaire, whereby the non-blinding of outcome assessment may lead to overestimation of results. In addition, as bacterial lysate usually took at least 3 months to show its effect, some studies with shorter follow-up times may mask the real effect which leads to underestimated results. And, in some studies, the methodology was described in insufficient detail to assess the risk of bias (Figure 2A,B).
| Study          | Publisher year | Type     | T/C | Intervention                        | Followed | Age (year) | Endpoint |
|---------------|----------------|----------|-----|-------------------------------------|----------|------------|----------|
| Yang Xing     | 2017           | Asthma   | 44/44 | OM-85 Budesonide Aerosol           | 21 days   | T:6.28 ± 1.31 C:6.35 ± 1.17 | 1, 2, 3, 5, 6 |
| Cao Jian      | 2016           | Asthma   | 36/36 | OM-85 Terbutaline                  | 10 days   | T:35.4 ± 8.7 C:39.9 ± 10.4  | 1, 4      |
| Zhang Tian    | 2018           | Asthma   | 48/47 | OM-85 placebo, routine therapies   | 3 months  | T:6.2 ± 0.5 C:5.8 ± 0.7    | 1, 3      |
| Chengyang     | 2015           | Asthma   | 67/54 | OM-85 Pulmicort Respules           | 21 days   | T:5.2 ± 2.2 C:5.4 ± 1.3    | 1, 2, 3   |
| Yang F        | 2017           | Asthma   | 43/43 | OM-85 Pulmicort Respules           | 3 weeks   | T:5.3 ± 2.06 C:5.02 ± 1.82 | 1, 2      |
| Jiang Yuan    | 2012           | Dermatitis | 20/20 | OM-85 Loratadine tablets          | 3 months  | 3-12        | 1        |
| Jiang Yuan    | 2013           | Dermatitis | 46/45 | OM-85 Ebastine tablets           | 4 weeks   | T:40 ± 3 C:39 ± 3          | 1, 6      |
| Su Huixia     | 2017           | Asthma   | 65/65 | OM-85 placebo                      | 12 months | T:8.59 ± 1.38 C:8.64 ± 1.40 | 1, 3      |
| Zhang Hua     | 2019           | Asthma   | 44/44 | OM-85 Pulmicort Respules           | 1 month   | T:6.73 ± 0.82 C:6.65 ± 0.74 | 1, 5      |
| Tang Yuqi     | 2017           | Asthma   | 44/43 | OM-85 Dipropionate powder          | 4 months  | T:7.8 ± 2 C:7.6 ± 1.9     | 1, 3, 5   |
| Wu Huanting   | 2019           | Asthma   | 49/49 | OM-85 Pulmicort Respules           | 3 months  | T:7.43 ± 2.62 C:7.31 ± 2.71 | 1, 3      |
| Cai Jierong   | 2020           | Asthma   | 37/37 | OM-85 Pulmicort Respules           | 6 months  | T:2.13 ± 0.46 C:2.21 ± 0.57 | 1, 4      |
| Cai Weiwei    | 2019           | Asthma   | 44/44 | OM-85 Laboratoire GlaxoSmithKline  | 3 months  | T:46.52 ± 3.2 C:47.62 ± 4.1 | 1, 2, 5   |
| Hou Jie       | 2019           | Asthma   | 45/45 | OM-85 Terbutaline                  | 2 weeks   | T:7.72 ± 2.16 C:7.13 ± 1.86 | 1, 2      |
| Xu Huai Yuan  | 2016           | Dermatitis | 72/72 | OM-85 Ebastine tablets           | 3 months  | T:13-58 C:14-61          | 1        |
| Chen J        | 2017           | Rhinitis | 48/48 | OM-85 intranasal saline           | 3 months  | 4-12         | 1        |
| G. Banche     | 2006           | Rhinitis | 26/15 | PMBL placebo treatment           | 3 months  | T:7-76 C:5-78         | 1        |
| Berth-Jones J | 2006           | Dermatitis | 54/49 | Killed mycobacterium vaccae      | 6 months  | 5-16         | 1        |
| Zagar S       | 1988           | Rhinitis | 29/22 | OM-85 placebo treatment          | 6 months  | T:6.52 ± 0.96 C:6.81 ± 0.80 | 1        |

Note: Endpoints: 1. Improvement of symptoms; 2. the level of T-cell subgroup; 3. the level of interleukins; 4. the level of serum immunoglobulin; 5. the level of FEV1; 6. adverse event.
3.3 | Allergy symptom improvement

A total of 19 RCTs reported improvement of allergic symptoms by assessing symptom control. There were 881 patients in the bacterial lysate-treated group and 847 children in the control group. As shown in Figure 3, allergic symptom improvement was 24% higher in the bacterial lysate group than in the control group. Asthma symptom control (RR: 1.22, 95% CI [1.14, 1.26]) was 22% higher in the bacterial lysate-treated group compared with controls. In addition, the effect size of dermatitis was 1.08 (95% CI 1.0–1.17) which seems to be a small improvement. However, there are only four studies concerned dermatitis treatment. None of the analyses reached statistical significance. Therefore, there was insufficient evidence to conclude that bacterial lysate treatment benefits for dermatitis patients.

On the other side, the total I² was 68.7%, which was regarded as moderate heterogeneity. After subgroup analysis by disease type, moderate heterogeneity was found in rhinitis studies. Conversely, lower heterogeneity was observed in asthma and dermatitis studies.

3.4 | Level of T-cell subgroup

After bacterial lysate treatment, the experimental group showed significantly increased CD3+ (SMD = 1.47, 95% CI [1.2, 1.74]), CD4+ (SMD = 1.57, 95% CI [1.33,1.81]), CD4/CD8 (SMD = 0.91, 95% CI [0.67, 1.15]), and Th1 (SMD = 0.48, 95% CI [0.22, 0.74]) cells and significantly decreased CD8+ (SMD = −0.71, 95% CI [−0.95, −0.47]) and Th2 (SMD = −0.61, 95% CI [−0.88, −0.35]) cells (Figure 4).

3.5 | Levels of interleukins

This subgroup analysis showed (Figure 5) that after bacterial lysate treatment, IFN-γ (SMD = 1.0, 95% CI [0.81, 1.19]), IL-2 (SMD = 1.07, 95% CI [0.73, 1.4]), and IL-12 (SMD = 2.4, 95% CI [2.04, 2.76]) were significantly increased, while other factors such as IL-4 (SMD = −0.87, 95% CI [−1.07, −0.68]) and IL-5 (SMD = −2.63, 95% CI [−3.14, −2.13]) were decreased.
### 3.6 Level of serum immunoglobulin

The studies regarding IgA and IgM showed high heterogeneity and all used random-effects models to analyze the data. After bacterial lysate treatment, IgA (SMD = 1.67, 95% CI [1.33, 2.01]) and IgG (SMD = 1.00, 95% CI [0.69, 1.31]) were significantly increased, but there were no differences in IgM levels (SMD = 0.05, 95% CI [−0.25, 0.36]) between the two groups (Figure 6).

### 3.7 FEV1

The studies regarding FEV1 showed no heterogeneity. The bacterial lysate treatment significantly improved the FEV1 (SMD = 0.53, 95% CI [0.32, 0.74]) (Figure 7).

### 3.8 Adverse events

Only two RCTs reported the rate of adverse events. Dizziness, lethargy, nausea, and diarrhea were reported during treatment in both groups, with the results showing that the adverse event rate was not significantly different in the bacterial lysate-treated group compared with controls (RR = 1.27, 95% CI [0.51, 3.09]).

### 3.9 Funnel plot of study

From the funnel plot (Figure 8), small-study effect was evident in this study.

There was small-study effect in this study.
This meta-analysis based on 19 studies comparing bacterial lysate treatment with a control group showed a 24% improvement in allergy symptom control. Additionally, the improvement of asthma symptoms was 22% higher following bacterial lysate treatment, while rhinitis improvement was three times higher in the bacterial lysate-treated group compared with controls. However, there was no difference between bacterial lysate and control groups in dermatitis patients. Moreover, the levels of immunoglobulin (IgA and IgG) were higher in the treated group compared with the control group. Bacterial lysate treatment improved the levels of T lymphocyte subtypes (CD3+, CD4+, CD4+/CD8+, Th1) and decreased CD8+ and Th2 T-cell numbers. Similarly, the bacterial lysate also elevated the levels of IFN-γ, IL-2, and IL-12 while decreasing the levels of IL-4 and IL-5. It was noted that the FEV1 also increased after bacterial lysate treatment, indicating improved lung function.

**FIGURE 4** The level of T-cell subgroup in bacterial lysate and control group
Some studies showed the ability of bacterial lysate to prevent respiratory tract infection and asthma exacerbations. One meta-analysis of OM-85 in pediatric recurrent respiratory tract infections showed that OM-85 could not only reduce the frequency of respiratory infections (MD = −2.22, 95% CI [−2.75, −1.90]) but also reduce the duration of wheezing (MD = −3.37 days, 95% CI [−4.52, −2.22]). The trends identified in the present study for IgA, IgG, CD3, and CD4 were similar with this meta-analysis. Another meta-analysis included 5 studies showed the use of bacterial lysate decreased both wheezing episodes (mean difference −2.35 (−3.03−1.67)) and asthma exacerbations (mean difference −0.9 (−1.23−0.57)). The result was similar to our study.

Two further meta-analysis studies investigated the effect of OM-85 on respiratory infection and showed that bacterial lysate was beneficial in the prevention of infection in children but presented no data regarding wheezing or allergic disease. Nevertheless, some searches proposed that the decrease in upper respiratory infection may lead to the reduction in asthma exacerbations.

The occurrence of allergic diseases is usually accompanied by an imbalance of the immune system, with skewing away from Th1 and

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**Figure 5** The change of IL-4, IFN-γ, IL-5, IL-2, IL-12 in bacterial lysate and control group

| Study ID | SMD (95% CI) | % Weight |
|----------|--------------|----------|
| **IL-4** |              |          |
| Cheng yang (2015) | -4.62 (-5.31, -3.93) | 7.99    |
| Su huixia (2017)  | -1.16 (-1.53, -0.78)  | 27.33   |
| Tangyuqi (2017)   | 1.06 (0.61, 1.51)    | 18.72   |
| Wuhuanting (2019) | 1.10 (0.68, 1.53)    | 20.86   |
| Zhangtian (2018)  | -1.98 (-2.47, -1.49) | 15.89   |
| Yang xing (2017)  | -3.25 (-3.89, -2.61) | 9.21    |
| **Subtotal** (I-squared = 98.5%, p = 0.000) | -0.87 (-1.07, -0.68) | 100.00 |
| **IFN-γ** |              |          |
| Cheng yang (2015) | 2.59 (2.11, 3.08)    | 15.17   |
| Su huixia (2017)  | 1.28 (0.90, 1.66)    | 25.19   |
| Tangyuqi (2017)   | 0.12 (-0.30, 0.54)   | 20.32   |
| wuhuanting (2019) | 0.13 (-0.27, 0.52)   | 22.89   |
| Yang xing (2017)  | 1.41 (0.94, 1.88)    | 16.43   |
| **Subtotal** (I-squared = 95.1%, p = 0.000) | 1.00 (0.81, 1.19) | 100.00 |
| **IL-5** |              |          |
| Yang xing (2017)  | -4.82 (-5.65, -3.99) | 36.84   |
| Cheng yang (2015) | -5.46 (-6.24, -4.68) | 41.94   |
| Tangyuqi (2017)   | 6.74 (5.65, 7.84)    | 21.21   |
| **Subtotal** (I-squared = 99.4%, p = 0.000) | -2.63 (-3.14, -2.13) | 100.00 |
| **IL-2** |              |          |
| Tangyuqi (2017)   | 1.02 (0.57, 1.46)    | 54.71   |
| Wuhuanting (2019) | 1.13 (0.63, 1.62)    | 45.29   |
| **Subtotal** (I-squared = 0.0%, p = 0.744) | 1.07 (0.73, 1.40) | 100.00 |
| **IL-12** |              |          |
| Yang xing (2017)  | 2.85 (2.25, 3.44)    | 36.30   |
| Cheng yang (2015) | 2.14 (1.69, 2.59)    | 63.70   |
| **Subtotal** (I-squared = 70.6%, p = 0.065) | 2.40 (2.04, 2.76) | 100.00 |
FIGURE 6  The change of IgA, IgM, IgG in bacterial lysate and control group

FIGURE 7  The change of FEV1 in bacterial lysate and control group
toward Th2. Therefore, many treatments are expected to increase levels of Th1 effectors and reduce Th2 to achieve an immune response that is more Th1-prone. Consistent with this, increased levels of Th1-type cytokines (IFN-γ and IL-2) and decreased levels of Th2-type cytokines (IL-4, IL-5, IL-10) were observed in our study. It could be concluded that bacterial lysate regulates the immune response by altering T-cell subgroups and immune cells. This finding was consistent with other studies, which claimed that OM-85 could induce an immune response shift from Th1/Th2 to Th1. The mechanism by which bacterial lysates stimulate immune responses may concern pathogen recognition receptor ligands containing common motifs shared by pathogenic and commensal bacteria. Furthermore, the changes in gut microbiome diversity following oral administration of bacterial lysates may contribute to immune interactions and influence the immune response.

A major strength of our study is the identification of the effective extent of bacterial lysate therapy on allergic diseases. As three allergic diseases (asthma, allergic rhinitis, and dermatitis) were included in our study, the degree of influence of bacterial lysate on each disease could be assessed. In addition, our research includes not only an evaluation of clinical symptoms but also some serum markers of immunity as well as indicators of lung function which can help to evaluate diseases, such as asthma, comprehensively.

However, there remain some limitations related to our study. Firstly, there were 12 RCTs regarding asthma, but only three studies concerned rhinitis and four were related to dermatitis. And the number of studies analyzing some serum indicators was small so that the evidence was not strong enough to draw conclusions. Secondly, due to the extent of unclear and high-risk bias in methodology and study design, the strength of the overall result may be low. Furthermore, the heterogeneity was moderate to high. After subgroup analysis on disease type, moderate heterogeneity was observed in the rhinitis group. The funnel plot of the present study showed asymmetry which means there was a small-study effect. Invalid effective studies are also less frequently published.

5 | CONCLUSION

Our study showed improvement of allergic disease symptoms when bacterial lysate combined with routine treatment was administered. However, because of some high-risk bias and unclear methodologies, these results still require confirmation by high-quality and large sample size studies in the future.

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CONFLICT OF INTEREST
The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS
Chengmei Li: Formal analysis (lead); Methodology (lead); Software (lead); Writing-original draft (lead). Hua Zhou: Conceptualization (equal). Wei Zhang: Resources (equal). Datian Che: Supervision (lead).

ETHICAL APPROVAL
All analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

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