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## Article

# Efficacy and Safety of *Echinacea purpurea* in Treating Upper Respiratory Infections and Complications of Otitis Media in Children: Systematic Review and Meta-Analysis

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**Abstract: Background:** *Echinacea purpurea* is widely utilized in dietary supplements, nutraceuticals, and herbal medicine, yet its effectiveness and safety for children remain debated. **Objective:** To evaluate the effectiveness and safety of *E. purpurea* in the treatment of upper respiratory tract infection (URTI) and otitis media (OM) in children. **Data sources:** Embase, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, PubMed from January 2000 to December 2023. **Methods:** This systematic review and meta-analysis were conducted and reported according to the PRISMA 2020 Checklist and Cochrane Training 2022 guidelines. **Results:** 9 randomized controlled trials with 1518 participants in the treatment group, 1651 participants in the placebo control group, met the selection criteria. Products derived from *E. purpurea* are highly diverse, utilizing different plant parts such as roots, leaves, and flowers, available in various dosage forms like capsules and extracts, and manufactured in numerous countries worldwide. Risk of bias was assessed according to the PEDro scale with 3 studies of excellent quality, 5 studies of high quality and 1 study of moderate quality. The meta-analysis found that *E. purpurea* significantly benefits URTI, reducing treatment duration (SMD = -0.19, 95% CI [-0.30; -0.09],  $p < 0.01$ ), incidence (RR = 0.81, 95% CI [0.75; 0.87]), and antibiotic use (RR = 0.18, 95% CI [0.13; 0.25],  $p < 0.01$ ). However, adverse events were moderately increased (RR = 1.38, 95% CI [1.08; 1.78]), though generally mild. For OM, *E. purpurea* lowered episode incidence (RR = 0.56, 95% CI [0.44; 0.73],  $p < 0.01$ ) but did not shorten treatment duration ( $p = 0.10$ ). Its effectiveness may be limited due to OM's bacterial etiology, often requiring antibiotics. While *E. purpurea* may help reduce recurrence, it is unlikely to speed recovery. Further research on optimal formulations and dosages is needed. The publication bias of pooled results as assessed by the funnel plot showed that the studies had certain bias, largely due to heterogeneity between studies. **Conclusion:** The meta-analysis of nine studies found that *E. purpurea* was effective in reducing the duration of treatment, the incidence of episodes, and antibiotic usage for URTI in children, with some

positive effects on OM. This study systematically evaluates the efficacy and safety of *E. purpurea* in treating URTI and OM in children, providing evidence-based insights to guide clinical decisions and inform healthcare professionals and parents considering its use. However, the safety profile remains unclear, particularly regarding adverse events. Further research is required to standardize methodologies and confirm these results.

**Keywords:** children; common cold; *Echinacea purpurea*; otitis media; upper respiratory tract infection

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## 1. Introduction

In recent years, there has been growing interest in the use of dietary supplements, nutraceuticals or herbal medicine to support health and well-being. *Echinacea purpurea*, a member of the *Echinacea* genus, is known by its immune-stimulating compounds, antioxidants, antibacterial, antiviral, and antiparasitic properties [1,2]. These attributes render it pertinent in various commercial formulations, often recommended for addressing respiratory issues, urinary tract infections, and chronic wounds [3,4].

Upper respiratory tract infection (URTI) are prevalent illnesses characterized by symptoms such as nasal congestion, runny nose, sore throat, cough, and mild fever [5,6]. Viral infections, including rhovirus, parainfluenza, respiratory syncytial virus, influenza, adenovirus, and coronaviruses are common causative agents transmitted through contact with infected individuals' nasal secretions and saliva [7]. The common cold is a prevalent form of URTI, primarily caused by viruses, with symptoms largely similar to those of URTIs. Weather changes, particularly during the cold season, often weaken the immune system and increase the risk of catching a cold, subsequently elevating the risk of upper respiratory tract infections.

Otitis media (OM) is a notable URTI complication, particularly in young children, often occurring after prolonged flu or cold episodes. Despite the challenges posed by the immature immune system in children, antibiotics are frequently prescribed for URTI and OM treatment, though their efficacy against viral infections [8,9].

To address medication side effects, natural products are increasingly preferred for pediatric conditions, with *Echinacea purpurea* emerging as a popular herbal supplement used to treat URTIs due to its immune-stimulating properties [1,10]. Despite its widespread use, multiple studies on efficacy of *E. purpurea* for treating URTIs show mixed results, and the effectiveness and safety of *E. purpurea* in pediatric populations remain unclear [11,12]. The widespread use of *E. purpurea* as a dietary supplement for immune support in children has garnered both endorsement and caution, given varying findings on its safety and efficacy. While some studies report only minor side effects, such as mild gastrointestinal discomfort or skin reactions, others underscore the importance of considering product variability and its potential impact on safety. This study aims to clarify the efficacy and safety profile of *E. purpurea* for managing URTIs and complications related to OM in children, with a focus on its role within nutrition and herbal supplementation.

Children and adults exhibit significant differences in immune responses to illnesses and treatments, including the use of *E. purpurea*. In children, the underdeveloped immune system heightens vulnerability to pathogens and potential side effects of therapeutic interventions. Conversely, adults possess a mature immune system, enabling more robust responses to stimuli with reduced risk. Active components in *E. Purpurea*, such as alkamides, polysaccharides, and phenolic acids, exert immunomodulatory effects but may overstimulate the immature immune systems of children, potentially leading to side effects such as rash, urticaria, or gastrointestinal disturbances, which are less common in adults [4,13,14]. Hence, research on *Echinacea* products must account for the unique physiological and immunological characteristics of pediatric populations, avoiding direct extrapolations from adult studies

## 2. Methods

**Study design:** The study adheres to the PRISMA 2020 checklist and Cochrane Training (Version 6.3, 2022) for a robust systematic review and meta-analysis, registered on PROSPERO (ID: CRD42024502333).

**Participants:** Randomized Controlled Trials (RCTs) evaluating efficacy of *E. purpurea* in treating URTIs and OM in children.

**Scope:** Unrestricted language search from January 2000 to December 2023, sourcing studies from Embase, Cochrane CENTRAL, ClinicalTrials.gov, and PubMed.

**PICOS Questions:**

**Population (P):** Children (1-12 years) with URTI or OM. **Intervention (I):** *E. purpurea*. **Comparison (C):** Placebo. **Outcome (O):** Treatment duration, the incidence of at least one episode, adverse events (AE), and antibiotic usage. **Study design (S):** RCTs

### *Search and Data Collection*

**Strategy:** Studies from January 2000 to December 2023 accessed via PubMed, Cochrane, ClinicalTrials.gov, and Embase. Keywords include *Echinacea purpurea*, children, Upper respiratory tract infection, common cold, and otitis media. The search strategy is detailed in Supplementary document 1. Data collection procedures followed the methodology previously outlined in reference [15].

### *Selection and Exclusion Criteria*

**Research inclusion:** A randomized, placebo-controlled trial assessing preparations containing *E. purpurea* for the prevention and/or treatment of URTI and/or OM complications in children. The study should provide comprehensive information on two groups: the treatment group and the control group, with outcomes measured in at least one of the following areas: duration of treatment, incidence rate of at least one episode, antibiotic usage rate, or adverse events. The participants are children under 12 years of age, with health status ranging from healthy to those with URTI, the common cold, or OM complications.

**Research exclusion:** Survey studies. Non-clinical research. Uncontrolled trials. Conference abstracts without comprehensive research papers. Studies lacking detailed information on the treatment and control groups, where results are presented only in graphs or figures without specific numerical data.

**Process:** Covidence tool [16] (Cochrane) used for study selection. Two independent reviewers screened studies, with discrepancies resolved by a third reviewer.

**Data collection:** Two variables considered: continuous (Mean $\pm$ SD) the results were analyzed using the relative risk (RR) outcome measure, offering insight into the relative probability of events occurring between two groups; and binary (N%) the analysis was conducted using the standardized mean difference (SMD), with different scales, providing a standardized measure of effect size. Extracted independently by two groups, discrepancies resolved by a fifth reviewer.

**Publication quality assessment:** The quality of the included studies was assessed using the PEDro scale [17], which comprises 11 items, 10 of which are scored. For this study, the PEDro scale was adapted to evaluate each criterion based on the information provided in the articles and the corresponding PEDro guidelines, with responses recorded as either 'Yes' or 'No.' Scores were categorized as follows: Low (0–3), Moderate (4–5), Good (6–8), and Excellent (9–10). A detailed summary table of the quality assessment for each study is provided, with comprehensive evidence for each criterion included in **Supplementary document 2**, in alignment with Cochrane recommendations. Any discrepancies during the assessment process were resolved through consultation with a third independent reviewer.

**Meta-analysis:** R Studio and meta packages used. Fixed and random-effects models applied, providing pooled effect estimates with risk ratios and standard mean differences. Heterogeneity assessed with  $I^2$ .

Although sensitivity analyses are typically recommended to assess the stability of results in meta-analyses, the limited number of studies in our dataset did not meet the minimum threshold for reliable sensitivity analysis outcomes.

**Bias evaluation:** Publication bias assessed using funnel plots and Egger regression test [18], evaluating asymmetry for continuous and binary variables.

3. Result

3.1. Study Selection

The process of selecting studies is detailed in Figure 1. The research team identified 131 studies through a thorough search of reliable sources. After using Covidence to semi-automatically eliminate duplicate studies, the number reduced to 104. These studies underwent further screening based on titles and abstracts, with 71 articles excluded for reasons outlined in Figure 1. Following careful full-text review, an additional 24 articles were excluded, including 2 studies involving subjects over 12 years old, 8 studies with inappropriate designs, 2 non-trial reports, 10 studies lacking outcome variables related to URTI or OM, and 2 studies found to be duplicates with different titles by the same author group. Finally, 9 RCTs were selected for conducting meta-analysis.

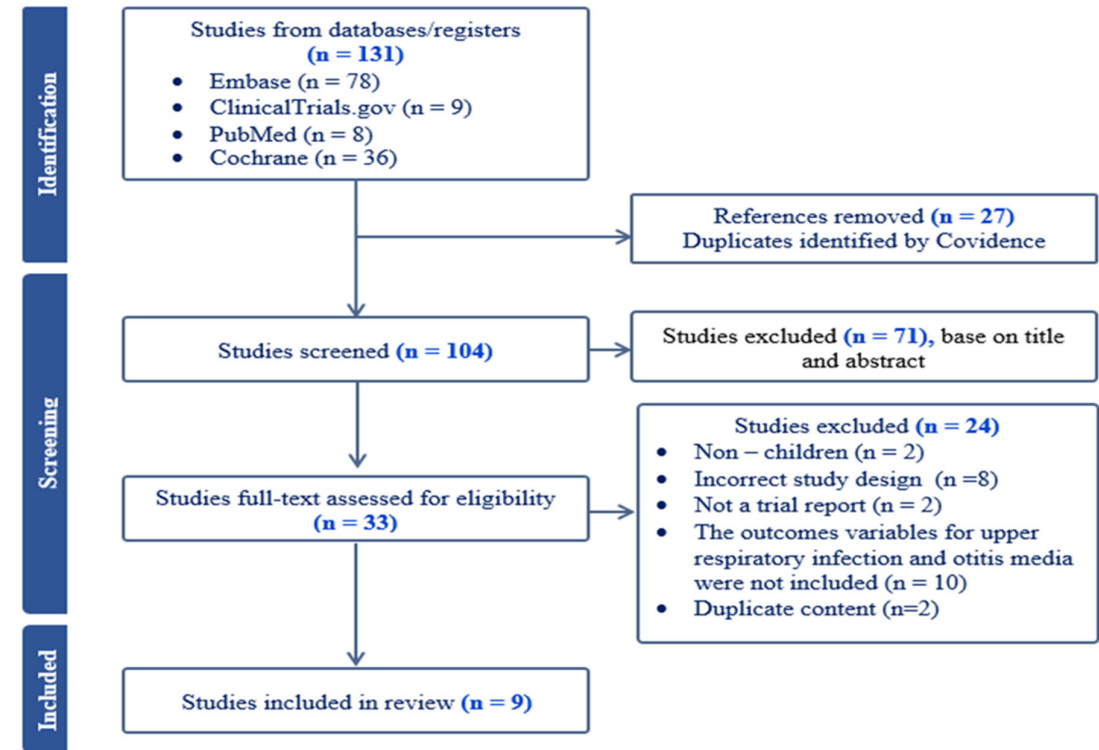


Figure 1. Flow diagram of study selection.

3.2. Study Characteristics

The characteristics of the studies are detailed in Table 1. The participants in the studies were healthy children aged 1-12 years. The studies utilized *E. purpurea* and a combination of *E. purpurea* and *E. angustifolia*, using various parts such as root and aerial part. Among the 9 RCTs, four studies used *E. purpurea* products manufactured in the United States [10,19–21], two RCTs used products from Switzerland [22,23], and the remaining three studies were from the United Kingdom, Russia, and Germany [24–26]. The predominant formulation was liquid dosage, with two RCTs in tablet form

[22,23] and two studies in nasal drop form [21,26]. Four studies used *E. purpurea* with alcohol [10,22,23,26], three studies used alcohol-free *E. purpurea* [20,24,25] and two studies used *Echinacea* with other supplements (vitamin C, propolis, and a few minor plant species, accounting for a small proportion) [19,21].

Table 1. Characteristics of included studies.

Study	Patient population	Species, part	Dose	Dosage form, Manufacturer	Patient number		Research group characteristics		Outcome
					Treatment	Placebo	Treatment	Placebo	
Barrett B., 2004 [24]	2-11 years URTI	<i>E. purpurea</i> aerial parts	Not reported	-Solution -England	337	370	Not reported	Not reported	- Treatment time - Adverse event
Cohen H.A., 2004 [19]	1-5 years -URTI and OM	<i>E. purpurea</i> aerial parts, <i>E. angustifolia</i> root	-1-3 years: 2x5 mL/day -4-5 years: 2x7,5mL/day	-Solution -USA	215	215	<i>Echinacea</i> , propolis, vitamin C	Propolis, vitamin C	- Treatment time - Number of times having at least one episode
Ogal M., 2021 [22]	4-12 years -URTI and OM	- <i>E. purpurea</i> root, aerial parts	- <i>Echinacea</i> : 3x400mg/day -Vitamin C: 3x50mg/day	-Tablet Switzerland	104	99	<i>Echinacea</i> , ethanolic	Vitamin C (axit ascorbic and canxi ascorbate)	- Treatment time - Adverse event - Number of times having at least one episode -Rate of antibiotic use
Taylor J.A., 2003 [20]	2-11 years URTI	- <i>E. purpurea</i> , the above-ground herb harvested at	-2-5 years: 7,5mL/day (2 x 3,75 mL/day) -6-11 years: 10mL/day (2x5mL/day)	-Solution -USA	337	370	<i>Echinacea</i> non-alcohol	Syrup	- Treatment time - Adverse event - Number

		floweri ng							r of times having at least one episode
Wahl R.A., 2008 [10]	1-5 years URTI and OM	-E. <i>purpurea</i> , the fresh roots and dried mature seeds	3x0,5mL/d ay during first 3 day, then 3x0,25mL/ day in the next 7 days	-Solution -USA	44	46	<i>Echinacea</i> , ethanol	Ethanol, filtered water, food coloring and thickeners	- Treatm ent time - Advers e events - Numbe r of times having at least one episode
G. Wikma n, 2004 [26]	4-11 years URTI	- E. <i>purpurea</i> (part not specifie d)	- <i>Echinacea</i> : 10 drops (3 times/day) - <i>Andrograph is paniculata</i> : 3x2 capsules/d ay	-Nasal drops -Russia  -Tablet - Sweden	94	39	<i>Echinacea</i> , ethanol, <i>Andrograp his paniculata</i> (N.)	Warm drinks, throat gargles, antiseptic nose drops, and paracetam ol at a dose of 500 mg 3 times a day in cases of fever and severe headache	- Advers e event -Rate of antibiot ic use
Weber W., 2006 [25]	2-11 years URTI	-E. <i>purpurea</i> , the above- ground plant parts harvest ed at floweri ng	-2-5 years: 87,75mg ( 2 x ¾ teaspoon/ day) -6-11 years: 117mg (2x1 teaspoon/d ay)	-Solution - Germany	263	261	<i>Echinacea</i> non- alcohol	Placebo liquid	- Treatm ent time - Advers e events - Numbe r of times having at least one episode
Weisha upt R., 2020 [23]	4-12 years URTI	-E. <i>purpurea</i> root	-Low dose: 3 capsules/d ay	-Tablet - Switzerla nd	79		<i>Echinacea</i> , ethanolic		- Treatm ent time



Total score	9/10	8/10	7/10	9/10	10/10	6/10	8/10	6/10	5/10
Study quality	Excellent	Good	Good	Excellent	Excellent	Good	Good	Good	Moderate

Note: \*Criterion 1 is not used to calculate the total PEDro score.

3.4. Results of Meta-Analysis

3.4.1. URTI Meta-Analysis

- The treatment time:

Performing a comprehensive analysis with five studies [19,20,22,23,25] evaluating the duration of URTI treatment using *E. purpurea* in children, as results shown in Figure 2A. The data indicated statistically significant analysis ( $p < 0.01$ ), with a standardized mean difference (SMD) of -0.19 and a confidence interval (CI) of 95% = [-0.30; -0.09]). There was a high heterogeneity among studies ( $I^2 = 91\%$ ). Surveys of studies using large numbers [20,25] showed results that improved URTI treatment time but were not statistically significant. However, studies by Cohen and Ogal both show clear effectiveness. Therefore, it was concluded that *E. purpurea* is effective in reducing the duration of URTI treatment in children.

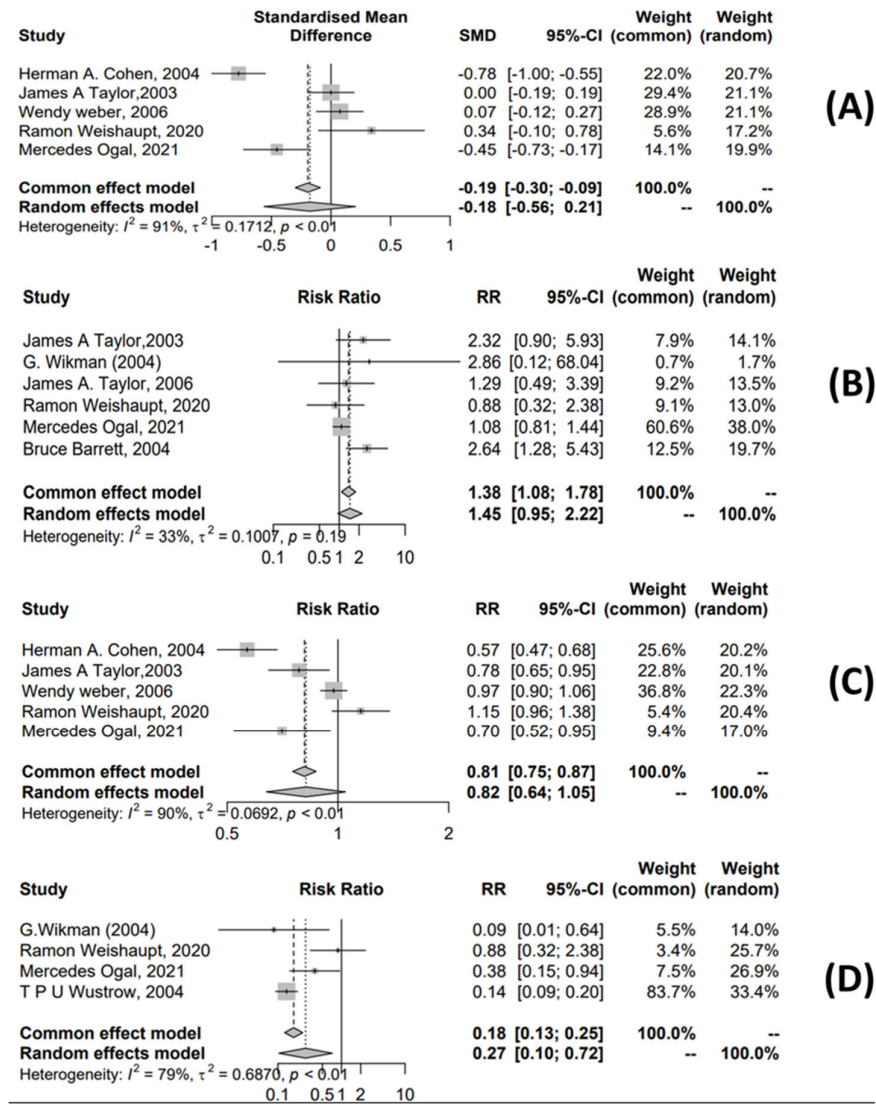


Figure 2. A meta-analysis on the effect of *Echinacea purpurea* in (A) the treatment time (B) Adverse event (C) the incidence of at least one (D) The antibiotic use rates of upper respiratory infections in children.

- Adverse event:

The meta-analysis of six studies [20,22–26] assessing the safety of *E. purpurea* in URTI treatment is presented in Figure 2B. The results indicated low heterogeneity ( $I^2 = 33\%$ ). The fixed-effect model with a risk ratio (RR) of 1.38; CI 95% = [1.08; 1.78], and the random-effect model with RR = 1.45; CI 95% = [0.95; 2.22]. Thus, the use of *E. purpurea* tends to be safe, causing fewer side effects than placebo, but no statistical significance with the p-value of 0.19 ( $> 0.05$ ).

To provide a comprehensive overview of safety, the research team synthesized and classified the adverse effects experienced by children in the studies. The severity classification was aligned for compatibility with a previously established grading system [27]. The summary table (Table 3) shows that most reported adverse effects were mild, with minimal and non-serious impact. Severe reactions were not reported in any of the studies included.

**Table 3.** Observed adverse reactions in children using *E. purpurea*.

Adverse reactions	Severity	Detailed description	References
Allergic reactions	Mild	Mild urticaria; itchiness; rash; choking	[20,22,25,26]
Gastrointestinal Issues	Mild-Moderate	Vomiting; diarrhea; stomachache	[20,22,23]
Infections	Moderate	Stomatitis; conjunctivitis	(23)
Fever	Mild	Some users may experience mild fever, though this is uncommon; scarlet fever	[22,23]
Dizziness	Mild	Some individuals may feel mild dizziness after taking <i>E. purpurea</i>	(23)
Drowsiness or Insomnia	Mild-Moderate	Some users may feel drowsy, while others might experience insomnia	(20)
Headaches	Mild-Moderate	Mild to moderate headaches may occur, particularly with prolonged use of <i>E. purpurea</i>	[20,22]

- The incidence of at least one:

Conducting a meta-analysis with five studies [19,20,22,23,25] (Figure 2C) revealed that the use of *E. purpurea* could significantly reduce the incidence of at least one episode of URTI in children ( $p < 0.01$ ). The data also showed a relative risk of RR = 0.81; CI 95% = [0.75; 0.87], and a random-effect model with RR = 0.82; CI 95% = [0.64; 1.05]. However, the heterogeneity among studies was very high ( $I^2 = 90\%$ ). Notably, one study indicated that the placebo group had a lower incidence than the intervention group [23].

- The antibiotic use:

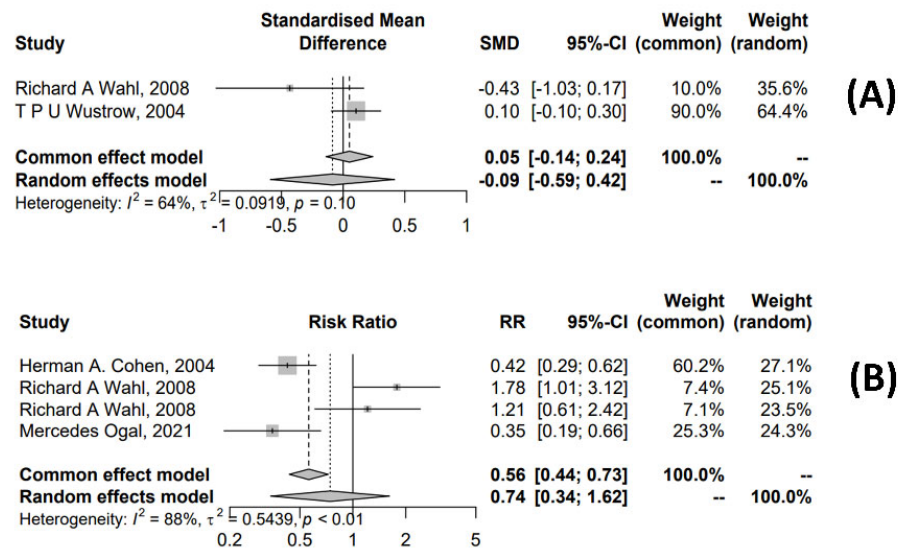
Four studies [21–23,26] evaluating the impact of *E. purpurea* on the antibiotic prescription rate in URTI treatment were comprehensively analyzed (Figure 2D). The results showed significant heterogeneity ( $I^2 = 79\%$ ), and the outcomes were statistically significant ( $p < 0.01$ ). The overall effect model with RR = 0.18; CI 95% = [0.13; 0.25], and the random-effect model with RR = 0.27; CI 95% = [0.10; 0.72] indicated a clear reduction in antibiotic usage with the use of *E. purpurea* in URTI treatment for children.

3.4.2. Meta-Analysis for OM Treatment

- Duration of treatment:

Conducting a meta-analysis of two studies [10,21] for data on the duration of OM treatment in children using *E. purpurea* showed inconclusive impact (Figure 3A). The heterogeneity was relatively moderate ( $I^2 = 64\%$ ), and the combined studies did not show statistically significant results ( $p = 0.10$ ).

> 0.05), with a SMD of 0.05 and a CI of 95% = [-0.14; 0.24]. The study with substantial weight [21] did not demonstrate a significant positive effect.



**Figure 3.** A meta-analysis on the effects of *Echinacea purpurea* and duration of treatment (A) and the incidence of at least one episode (B) for otitis media in children.

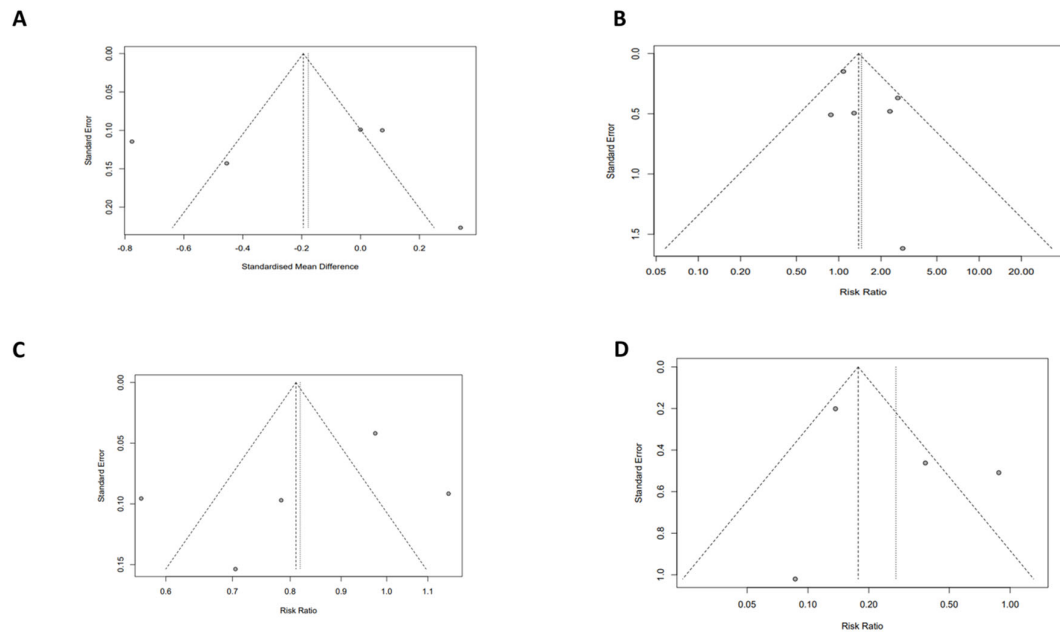
- The incidence of at least one:

Three studies [10,19,22] analyzing the rate of at least one episode of OM in children using *E. purpurea* were comprehensively analyzed (Figure 3B). The results indicated a statistically significant reduction in at least one episode of OM ( $p < 0.01$ ), with high heterogeneity among studies ( $I^2 = 88\%$ ). The overall effect model with  $RR = 0.56$ ;  $CI\ 95\% = [0.44; 0.73]$ , and the random-effect model with  $RR = 0.74$ ;  $CI\ 95\% = [0.34; 1.62]$  suggested a positive impact. The study with substantial weight [19,22] demonstrated a significant reduction in the rate of at least one episode of OM.

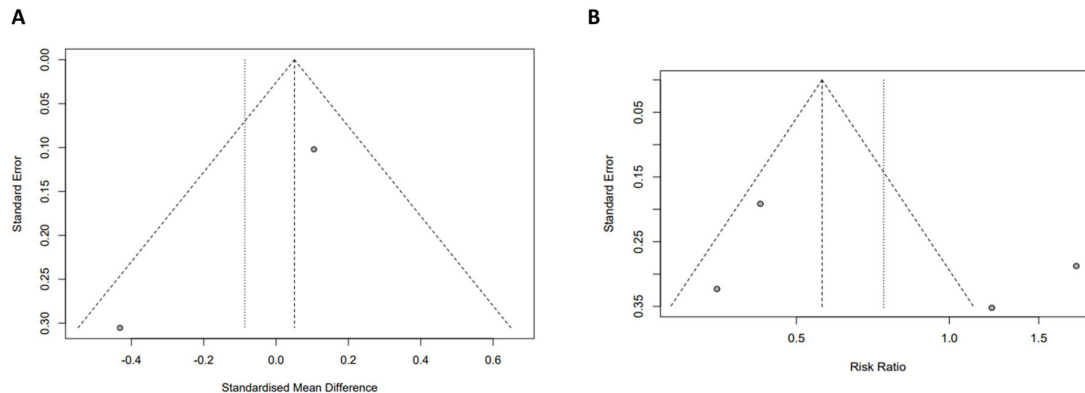
3.5. Quality Assessment of Meta-Analyses

For URTI analysis: Funnel plots for URTI studies (Figure 4) showed asymmetry, indicating potential publication bias. Evaluation of safety and antibiotic usage did not reveal significant publication bias.

For OM complications: Funnel plots for OM-related analyses (Figure 5) suggested potential publication bias, particularly in the analysis of OM treatment duration. The assessment of at least one episode of OM showed an asymmetrical funnel plot but with no significant publication bias.



**Figure 4.** Funnel plot on the (A): effect of *Echinacea purpurea* on the treatment time of upper respiratory infections in children, (B): safety of *Echinacea purpurea* in the treatment of upper respiratory infections in children, (C): relationship of *Echinacea purpurea* and the incidence of at least one upper respiratory tract infection in children, (D): effects of *Echinacea purpurea* and the rate of antibiotic use in the treatment of upper respiratory infections in children.



**Figure 5.** Funnel plot on the (A): effects of *Echinacea purpurea* and treatment time for otitis media in children, (B): relationship of *Echinacea purpurea* and the incidence of at least one otitis media in children.

## 4. Discussion

### 4.1. Study Findings

The aim of this study was to determine the effectiveness of *E. purpurea* in children with URTI and complications such as OM. After an exhaustive search of reliable sources, 131 records were identified. Following the removal of duplicates and meticulous screening of titles, abstracts, and full texts, 9 eligible studies were included in the comprehensive analysis.

The studies included in the analysis utilized various *E. purpurea* products derived from roots, seeds, above-ground parts, or the entire plant during flowering. All 9 studies employed *E. purpurea*, except for a 2004 study by Cohen et al. [19], which used a combination of the upper part of *E. purpurea* and the root of *E. angustifolia*. Factors such as the type of *E. purpurea* product, the part of the plant

used, and combinations with other supplements can significantly impact the efficacy of *Echinacea*. Specifically, studies using *E. purpurea* alone or in combination with *E. angustifolia*, and utilizing different parts of the plant such as the root or aerial parts, suggest that each part may uniquely affect the immune system. The root is generally considered to contain more active compounds, yet the aerial parts also exhibit certain effects [12]. Additionally, differences in chemical composition between *E. purpurea* and *E. angustifolia* may lead to variations in therapeutic effectiveness, warranting further analysis to identify the most suitable plant type or part for children. Moreover, combining *E. purpurea* with other supplements like vitamin C, honey, and various minor herbs appears to enhance its effects. This combination could potentially offer superior immune support compared to *Echinacea* alone [28]. This could inform future research and product development in the field.

The studies included in the analysis examined various *E. purpurea* products derived from roots, seeds, aerial parts, or the entire plant during flowering. Of the nine studies, all employed *E. purpurea*, except for one study by Cohen et al. (2004) [19], which used a combination of the aerial part of *E. purpurea* and the root of *E. angustifolia*. Factors such as the type of *E. purpurea* product, specific plant parts used, and combinations with other supplements can significantly influence the efficacy of *Echinacea*. Studies utilizing *E. purpurea* alone or in combination with *E. angustifolia*, and employing different plant parts, such as the root or aerial parts, suggest that each part may uniquely impact immune function. While the root is typically considered to contain higher levels of active compounds, the aerial parts also demonstrate certain beneficial effects [12]. Furthermore, differences in chemical composition between *E. purpurea* and *E. angustifolia* could lead to variations in therapeutic outcomes, warranting further analysis to determine the most appropriate plant type or part for pediatric use. Additionally, combining *E. purpurea* with supplements like vitamin C, honey, and other minor herbs appears to enhance its effects, potentially offering stronger immune support than *Echinacea* alone [28]. These insights could guide future research and product development in this field.

The products originated from different countries, with variations in formulations and dosages for different age groups. Liquid formulations were the predominant form, while tablet and nasal drop forms were also used. The formulation of *Echinacea* can significantly affect its absorption and duration of action. Liquid forms are typically absorbed more quickly, providing immediate effects, whereas tablets may offer prolonged effects due to slower absorption. Additionally, nasal drop formulations can directly target the respiratory system, which is particularly beneficial for treating symptoms like colds or respiratory infections. Optimizing the formulation for specific clinical situations is crucial. *E. purpurea* products from countries such as the United States, Switzerland, the United Kingdom, Russia, and Germany may yield different results due to varying manufacturing processes, including cultivation, harvesting, extraction, and formulation methods. For instance, studies showing better efficacy from a particular country could reflect the quality of the product or adherence to GMP standards in production. Furthermore, children aged 1-12 are a key demographic because their immune systems and development are still maturing. As a result, immune-supporting products like *E. purpurea* may have different effects compared to adults.

The risk of bias assessment using the PEDro scale indicated relatively high-quality studies, with 3 achieving excellent scores, 5 scoring high, and only 1 considered of moderate quality. Detail description of bias assessment can be located in Supplementary document 2.

The results of a meta-analysis of URTI in children show that *E. purpurea* helps reduce treatment time, reduces the incidence of at least one episode, and reduces the rate of antibiotic use which is relatively clear with p-values having statistical significance. Observation of studies on adverse events shows that using *E. purpurea* tends to be safer than the placebo group (the most common side effects are rash, and urticaria), however this result is not statistically significant (p-value > 0.05). A careful examination of individual studies with significant weight reveals that the incidence of rash and urticaria is higher in the *E. purpurea* group compared to the placebo group. Therefore, parents are advised to consult healthcare professionals and carefully consider before administering it to children.

For OM complications in children, a review of the significant weight studies found that *E. purpurea* was associated with a statistically significant reduction in the incidence of at least one

episode. Regarding treatment time, *E. purpurea* did not reduce the number of treatment days, but this result was not statistically significant.

The effectiveness of *E. purpurea* for OM may be limited due to the different pathophysiology of OM compared to URTI, as OM often has a bacterial rather than viral etiology, requiring antibiotic intervention in severe cases. These findings support the potential role of *E. purpurea* as an adjunctive treatment for URTI in children. In contrast, the analysis of OM complications yielded less conclusive results. The stronger effects for URTI may be due to its viral etiology, which aligns with *E. purpurea*'s immune-modulating properties. In contrast, OM often has a bacterial component, which may limit *E. purpurea*'s ability to reduce treatment duration once an infection occurs. These findings suggest that while *E. purpurea* may help reduce recurrence rates of OM, it is unlikely to accelerate recovery once an infection has occurred. Further research is needed to determine optimal formulations and dosages for OM treatment.

Publication bias assessment indicated some degree of bias in studies related to URTI treatment, potentially influenced by high heterogeneity. However, studies involving adverse events showed no significant publication bias, suggesting the accuracy of the findings.

#### 4.2. Significance of the Study

Our study not only focused on evaluating the effectiveness of *E. purpurea* in URTI but also investigated its impact on the significant co-occurring condition of OM. Given the high prevalence and infectious risk of these conditions in children, identifying an effective treatment is crucial for reducing symptom severity and duration. Additionally, the sensitivity of children aged 1 - 12 years to medication, coupled with incomplete development of certain organs, emphasizes the importance of safe and effective treatment choice [29,30].

The study results indicate that *E. purpurea* shows potential in reducing treatment duration, disease incidence, and the need for antibiotics in managing URTI in children. These findings suggest that *E. purpurea* could be a valuable adjunctive treatment option, helping to mitigate antibiotic overuse in pediatric care a crucial consideration given the rising concern over antibiotic resistance.

Moreover, the use of *E. purpurea* may contribute to reducing healthcare costs associated with URTI treatment, OM while providing safer and more effective options for healthcare providers in pediatric care. However, to ensure the safe and effective use of this herbal remedy, further in-depth studies are required to clarify safety concerns, particularly regarding potential adverse effects such as rash and urticaria.

Additionally, this research opens opportunities for the development of other herbal products and contributes to improving public health management by reducing the risk of antibiotic misuse. The findings may also encourage further clinical trials and research into other plant species, potentially leading to new herbal-based treatments that are both effective and safe for children.

It is noteworthy that most studies were conducted in Europe and North America. Future research assessing the efficacy of *E. purpurea* in Asian countries, where the plant is prevalent [31–33], would be intriguing, especially considering the high prevalence of respiratory diseases in Asian children [34,35].

#### 4.3. Differences from Previous Studies

As of the time of conducting this study, our investigation has concluded in five meta-analyses, including three scrutinies centered on the treatment of colds [36–38] and two on the management of URTI [11,39].

Regarding treatment time, the research results (Figure 2A) are similar to studies [36–38] which all show that using *E. purpurea* helps reduce URTI treatment time. In which a meta-analysis by Shah SA [38], showed that *E. purpurea* was effective in reducing the duration of colds by 1.4 days, the group of authors K Linde and colleagues [37] showed an improvement in symptoms. clearly over each period of 2 - 4 days and 5 - 10 days. Different from the results of the research group, David's results

showed that *E. purpurea* did not affect the duration of URTI treatment (SD = -0.12, CI 95% = [0.93; 1.22]) [11].

In assessing adverse events of trial products, scrutiny may be directed towards participant attrition rates, the incidence of adverse events or undesirable effects. The results (Figure 2B) show that *E. purpurea* tends to be safe, with few side effects when used in children (the most common side effects are rash and urticaria), but this result is not clear as indicated by the  $p$  value  $> 0.05$ , which is consistent with the studies of Marlies Karsch-Völck and K Linde [36,37] generally intimate a lower incidence of adverse effects in the *Echinacea* intervention group compared to the placebo cohort, albeit with an inconsistent clarity in this observation. Findings of Marlies Karsch-Völck [36] unveil a notable divergence in the frequency of patients reporting adverse effects between the placebo group (32.6%) and the treatment group (34.1%) (OR = 1.28, CI 95% = [1.02; 1.60],  $p = 0.03$ ). Sholto David's study again provided evidence that adverse events with *E. purpurea* were lower than placebo, with a larger number of participants experiencing at least one adverse event in the *E. purpurea* group (RR = 1.11, CI 95% = [0.94; 1.31]) [11].

Concerning the incidence of at least one episode of the common cold, RR outcomes of Marlies Karsch-Völck [36] do not evince a statistically significant effect relative to the placebo. Conversely, investigation of Shah SA demonstrates a conspicuous 58% reduction in the incidence of patients contracting the common cold (OR = 0.42, CI 95% = [0.25; 0.71],  $p < 0.001$  [38]. Other study of Linde similarly intimates a marginally lower risk of experiencing at least one cold episode with the *E. purpurea* preparation under scrutiny compared to the placebo (relative risk 0.80 to 0.88) [37]. Our study findings (Figure 2C) align with the conclusions drawn by Shah SA and K Linde, substantiating the premise that *E. purpurea* mitigates the incidence of at least one URTI infection in the pediatric demographic [37,38].

URTI is one of the common reasons for prescribing antibiotics to patients although the majority of URTI are caused by viruses and most resolve spontaneously unless due to complications such as acute OM with effusion, tonsillitis, sinusitis, so indiscriminate use of antibiotics is ineffective and inappropriate [40,41]. Research results (Figure 2D) show the positive effect of *E. purpurea* in reducing the rate of antibiotic use. Choosing *E. purpurea* is a solution that contributes to more treatment alternatives and helps reduce the overuse of antibiotics in children. These results are similar to the 2019 study of David's group [11].

*Echinacea purpurea* is also as the popular ingredient in dietary supplements and nutraceuticals primarily for its immune-enhancing effects [42]. Common forms of *Echinacea purpurea* supplements include capsules, tablets, tinctures, and teas [43]. Research has demonstrated various health benefits associated with its use. For instance, a study by Hao indicated that dietary supplementation with 200 mg/kg of *Echinacea purpurea* polysaccharide notably alleviated the reduction in colon length, weight loss, and histopathological damage in mice with dextran sulfate sodium-induced colitis [44]. Additionally, *E. purpurea* has been utilized as a nutritional supplement during the COVID-19 pandemic. A study in Saudi Arabia found that supplementing dairy products with *Echinacea* increased the proportion of participants using it for COVID-19 treatment, from 7.5% to 11.9% [45]. The active compounds in *E. purpurea*, such as polysaccharides, alkamides, and phenolic acids, are believed to stimulate the immune system by increasing the production of white blood cells and enhancing their activity [1,46].

In herbal supplement or medicine, *E. purpurea* is used not only for immune support but also for its anti-inflammatory and antioxidant properties [47,48]. The anti-inflammatory properties are largely attributed to the plant's alkamides and caffeic acid derivatives, which may help modulate the inflammatory response of the body [49]. Furthermore, antioxidant activity of *Echinacea* helps protect cells from oxidative stress, which is implicated in numerous chronic diseases [50,51].

The findings from this meta-analysis may significantly contribute to the field of nutrition by consolidating clinical information that supports guideline recommendations on dietary supplements and nutraceuticals to boost immune function and reduce antibiotic dependence, which is crucial given the growing concerns about antibiotic resistance [52]. For nutritional products, safety is

paramount. Guidelines that emphasize the importance of dietary supplements should be evidence-based [53], and our findings provide robust data to support recommendations for the appropriate use of *E. purpurea* in children, ensuring both efficacy and safety [52,54]. This endorsement by regulatory agencies further strengthens the role of *E. purpurea* in nutrition and treatment strategies to prevent and manage URTIs in children.

#### 4.4. Strengths and Limitations

This study is the first to comprehensively synthesize evidence on *E. purpurea* in children, contributes valuable insights for researchers and practitioners seeking safe and effective treatments. The homogeneity in intervention selection, participant criteria, and stringent target group selection enhances the robustness of the findings.

However, the limitation lies in the relatively small number of included studies, potentially limiting the persuasiveness of the conclusions. The research period spanned over 20 years, yet the number of eligible studies remained limited due to the lack of extensive research on *E. purpurea* in pediatric populations. While the small number of studies may affect statistical significance and trend detection, pooling individual studies with smaller sample sizes creates a larger composite sample, enhancing reliability for identifying significant associations. Each selected study meets strict quality and reliability standards, ensuring that the analysis is grounded in high-quality data.

The observed heterogeneity among studies also poses a challenge to result interpretation. The results (Figures 2A, 2C, 2D and 3A) show high heterogeneity ( $I^2$ ), limiting the findings due to variations in patient characteristics, product properties, dosage, formulation, and methodologies across studies. This diversity reflects clinical and scientific practice but challenges the consistency of results. Although subgroup analysis is commonly employed to address heterogeneity, it was not feasible in this study due to the limited number of studies and significant variability in study design. To improve the reliability and comparability of results, future studies should aim to standardize methods and variables. Sensitivity analysis should also be considered to assess the stability and robustness of aggregated results. However, for sensitivity analysis to be objective and effective, it typically requires a minimum of 10 studies [55]. To address these limitations, rigorous selection criteria were used, along with a thorough assessment of study quality using the PEDro scale. Heterogeneity ( $I^2$ ) has been transparently reported to provide context for the variability across studies. These limitations emphasize the need for further research with a larger and more homogeneous dataset to allow meaningful subgroup analyses.

To enhance the generalizability and applicability of findings, future studies should include diverse geographic regions to achieve a more comprehensive understanding of the efficacy of *E. purpurea* across various populations. Increasing statistical power through larger sample sizes is essential to provide more robust and conclusive evidence regarding its effectiveness in managing URTIs and OM in pediatric populations. Further research is needed to conduct a more nuanced investigation into the specific impact of *E. purpurea* on OM treatment duration to derive definitive conclusions in this area.

The ethical considerations surrounding the use of *E. purpurea* in children should not be overlooked. The variability in formulations, the potential for immune overstimulation, and the lack of standardized dosing present challenges that warrant caution. Given that mild adverse reactions such as rash and gastrointestinal discomfort have been reported, healthcare professionals should guide parents in making informed decisions. Regulatory bodies should also work towards establishing more stringent quality control measures to ensure the safe and effective use of *E. purpurea* in pediatric populations.

Long-term studies are critical for evaluating the sustained efficacy and safety of *E. purpurea*, particularly in children who experience recurrent respiratory infections. Investigating the efficacy of different *Echinacea* species and formulations is also crucial to understanding the variability in their therapeutic effects on pediatric respiratory health. Moreover, future research should include stratified analyses to assess age-related variations in safety and efficacy, comparing outcomes

between younger children (1–5 years) and older children (6–12 years). Longitudinal studies focusing on recurrent infections in children are recommended to comprehensively evaluate the long-term safety and effectiveness of *E. purpurea*. These multidimensional and rigorous approaches will provide a deeper and more precise understanding of *E. purpurea*'s role in pediatric healthcare, contributing to evidence-based guidance for its clinical application.

## 5. Conclusions

This meta-analysis highlights the potential of *E. purpurea* as a dietary intervention for managing pediatric URTIs and otitis media OM. The findings suggest that *E. purpurea* may effectively reduce treatment duration, the incidence of URTIs and OM episodes, and antibiotic usage. These results indicate that *E. purpurea* could contribute to mitigating the burden of pediatric respiratory infections while promoting antimicrobial stewardship and reducing reliance on synthetic medications.

From a nutritional perspective, *E. purpurea* offers a promising avenue for integrating phytotherapeutics into pediatric care. Its immune-modulating properties and natural origins align well with current trends in clinical nutrition, emphasizing safe and holistic approaches to health. However, significant concerns remain regarding the variability in formulations, inconsistent safety profiles, and limited data on long-term effects. Mild adverse events such as rash, urticaria, and gastrointestinal discomfort were noted, but the overall safety profile warrants further investigation.

Future research should prioritize rigorous and standardized methodologies to evaluate *E. purpurea* across diverse populations, stratify analyses by age groups, and explore its long-term impact. Additionally, studies should aim to better understand the nutritional and immunological mechanisms underlying its efficacy. These efforts will provide robust evidence to guide its integration into clinical nutrition practice.

In conclusion, while *E. purpurea* demonstrates significant potential as a nutritional intervention for pediatric respiratory health, its use must be informed by comprehensive research. Healthcare providers should carefully balance its benefits against unresolved safety concerns, ensuring that its application aligns with evidence-based nutritional strategies.

**Supplementary Materials:** Attached supplementary document 1 (search\_algorithm.docx). Attached supplementary document 2 (risk\_of\_bias\_assessment.xlsx)

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## Abbreviations

CI, confidence interval; OM, otitis media; RCT, randomized controlled trials; RR, risk ratio; SMD, standardized mean difference; URTI, upper respiratory tract infection.

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