Resveratrol plus carboxymethyl-β-glucan for children with respiratory diseases

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POINT OF VIEW

Introduction

Respiratory infections, ranging from common colds to more severe respiratory illnesses, can impact the child's well-being, leading to symptoms, such as nasal congestion, coughing, and fever. Moreover, respiratory infections can contribute to school absences and medical visits, creating a substantial socio-economic burden for families[1]. Resveratrol, a natural polyphenol found in various plant sources like grapes, berries, and peanuts, has emerged as a subject of considerable scientific interest. This compound has garnered attention not only for its antioxidant properties but also for its potential anti-inflammatory and antiviral effects[2,3]. Studies have suggested that resveratrol may play a crucial role in modulating immune responses, with a particular emphasis on its ability to attenuate inflammatory processes[4]. The compound has been associated with the stimulation of phagocytosis by professional phagocytes, direct activation of natural killer (NK) cells, and the release of cytokines[5]. β-Glucans, derived from fungi, cereals, and bacteria, are large polysaccharides known as “biological response modifiers”. They stimulate the immune system, offering benefits like anticancer, antiviral, and wound healing effects[6]. They enhance resistance to infections by the stimulation of phagocytosis, the direct activation of NK cells, and the release of cytokines[7]. Used in pharmaceuticals for drug delivery, the introduction of carboxymethylation to these biopolymers enhances their solubility in aqueous environments without compromising their biological activities[8]. The stability of resveratrol can be enhanced by combining it with a modified version of β-glucan, specifically carboxymethyl-β-glucan (CM-glucan), in a water-based solution while preserving its biological properties[3,8]. Recent research explores the antiviral potential efficacy of a solution containing resveratrol and carboxymethyl-β-glucan in children with respiratory diseases, revealing synergistic anti-inflammatory effects through cytokine modulation[4,9].

Materials and Methods

A comprehensive literature review was conducted to evaluate the clinical evidence supporting the action of resveratrol and carboxymethyl-β-glucan in children with respiratory diseases. Our research specifically

sought out randomized clinical trials in children that explored the utilization of solutions incorporating resveratrol and carboxymethyl-β-glucan (Linfovir® plus spray and nasal drops, Noos srl) in the management of respiratory diseases among children. Through this search, five randomized clinical trials were identified.

Results

A study conducted by Varricchio et al. employed a real-life, randomized design and involved 82 children (49 boys, with an average age of 8.1 ± 2.6 years) who were dealing with acute rhinopharyngitis and recurrent respiratory infections (RRIs). After a 10-day course of anti-infective and anti-inflammatory treatment for acute rhinopharyngitis, participants were randomly assigned (ratio 1:1) to receive either resveratrol plus carboxymethyl-β-glucan or a saline isotonic solution. The treatments were administered over 20 days, and assessments were conducted for days with respiratory symptoms, fever, medication use, medical visits, and school absences. Follow-up visits occurred at 30, 60, and 90 days after treatment initiation. The results indicated that the active compound significantly decreased the number of days with nasal congestion ($p < 0.001$), runny nose ($p < 0.001$), sneezing ($p < 0.001$), coughing ($p = 0.002$), fever ($p < 0.001$), medication usage ($p < 0.001$), medical visits ($p < 0.001$), and school absence ($p < 0.001$). This preliminary real-life study suggests that an aerosolized mixture comprising resveratrol and carboxymethyl-β-glucan could potentially offer preventative benefits for children with RRIs[10]. In a study conducted by Baldassare et al., eighty-nine infants with respiratory infection symptoms were randomly assigned to either the group receiving the nasal resveratrol/carboxymethyl-β-glucan solution or the group receiving the nasal saline solution. Physicians and parents assessed all patients using the Canadian Acute Respiratory Illness and Flu Scale (CARIFS) at enrollment, after 48 hours, seven days, and 30 days. Additionally, nasal swabs were collected at enrollment, after 48 hours, and after one week. The results indicated an improvement in the CARIFS score in both groups. Notably, the study group reported reduced episodes of sneezing and coughing after seven days of follow-up ($p < 0.05$)[11]. In a study by Indolfi et al., the researchers aimed to assess the effectiveness of nasal solutions containing resveratrol and carboxymethyl-β-glucan in reducing

wheezing in non-atopic children with RRIs. The prospective single-blind study involved 39 children, who were randomized into two groups: one received the resveratrol plus carboxymethyl-β-glucan solution, while the other received a saline placebo. The results demonstrated a significant reduction in the number and severity of wheezing episodes in the resveratrol plus carboxymethyl-β-glucan group compared to the placebo group. Specifically, the resveratrol plus carboxymethyl-β-glucan group had fewer wheezing days and episodes, reduced hospital visits, and less need for oral corticosteroids. These findings suggest that nasal resveratrol could be a promising intervention for managing wheezing in non-atopic children when administered at the onset of upper respiratory tract infections (URTI) symptoms. The treatment was generally well-tolerated, with only mild and transient nasal irritation reported as a side effect[12]. In a research by Miraglia et al., 68 children diagnosed with allergic rhinitis caused by Parietaria pollen were enrolled. The participants were divided into two groups, with one receiving treatment through an intranasal device containing a combination of resveratrol and carboxymethyl-β-glucan. In contrast, the other group was administered a placebo over two months. The findings indicated a noteworthy decrease in nasal symptoms, including itching, sneezing, rhinitis, and nasal congestion, among children who underwent the resveratrol and carboxymethyl-β-glucan treatment, accompanied by a reduction in the usage of antihistamines[13]. In an another study conducted by Miraglia et al., it was observed that the application of a nasal spray containing resveratrol and carboxymethyl-β-glucan to a cohort of 76 children with persistent allergic rhinitis resulted in a notable reduction in nasal symptoms and respiratory infection-related effects compared to a placebo-treated control group[14]. The findings revealed a statistically significant decrease in Total Symptom Score (TSS), severity of cough and wheezing, β2-agonist usage, days with fever, and school absences within the actively treated group in comparison to the placebo group. This outcome suggests a potential efficacy of the nasal spray formulation containing resveratrol and carboxymethyl-β-glucan in mitigating both allergic symptoms and respiratory infections in children with persistent allergic rhinitis[14].

Discussion

In recent years, the exploration of novel therapeutic approaches for pediatric respiratory diseases has gained significant attention. Among these, the combination of resveratrol and carboxymethyl-β-glucan has emerged as a promising intervention, exhibiting potential anti-inflammatory and antiviral effects. The use of formulations containing resveratrol and carboxymethyl-β-glucan shows promising results in children with respiratory diseases. These formulations, explored through a series of clinical trials, demonstrate a significant reduction in symptoms related to respiratory infections and allergic rhinitis **(Table 1)**. This suggests potential benefits in both preventive and therapeutic contexts, indicating a potential role for resveratrol in treating respiratory infections[15]. Despite these promising findings, it's important to acknowledge the limitations of current research. The studies are based on small sample sizes and single-center trials with a focus on short-term outcomes, which could introduce biases and limit the generalizability of the findings. The limited follow-up duration raises questions about the sustained efficacy and safety of this combination therapy. For this reason, long-term studies are essential to determine whether the benefits observed are maintained over time and to assess any delayed adverse effects. In addiction, while the reviewed studies reported a positive safety profile with only mild and transient nasal irritation reported as a side effect, none provided extensive data on adverse effects, necessitating caution in interpreting the results. Moreover, the efficacy of resveratrol and CM-glucan was notable, but it is crucial to compare these results with those of standard treatments for respiratory infections and allergic rhinitis. For this reason, it's important to emphasize that this natural multi-component compound is not a pharmaceutical drug and should not replace established therapies for respiratory infections. Instead, it can be considered an additional treatment, complementing standard approaches[2]. Future investigations involving larger cohorts, multicenter studies, and comparative studies with standard treatments could provide more robust evidence of effectiveness and help identify potential variations in treatment response among diverse populations.

Conclusion

The combination of resveratrol and carboxymethyl-β-glucan has demonstrated significant efficacy in

reducing symptoms associated with respiratory infections and allergic rhinitis in children, highlighting its potential both as a preventive and therapeutic option. While the treatment was generally well-tolerated, with only minor side effects such as transient nasal irritation, the current data on adverse effects remains limited, necessitating caution. Moreover, the existing research is constrained by small sample sizes and studies conducted in single centers, focusing predominantly on short-term outcomes. This limitation raises concerns about potential bias and restricts the generalizability of the findings. Consequently, there is a critical need for long-term studies with larger, multicentric samples to confirm the treatment's efficacy and safety over time and to compare it against standard therapies for respiratory infections and allergic rhinitis. It is essential to emphasize that this nutraceutical is intended to complement, rather than replace, established standard therapies for respiratory infections in children. Based on these concepts, the combination of resveratrol plus carboxymethyl-β-glucan could considered a valuable add-on strategy complementary to pharmacological standard treatments.

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146 **Table 1. Studies on resveratrol plus carboxymethyl-β-glucan.**

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Study [ref,]	**Study design**	**Patients**	**Treatments**	**Outcomes**	**Follow-up**	**Main results**	**Funding**	**Registr N°**
Varricchio et al. [10]	RCT	82 children (8.1 ± 2.6 years) with acute rhinopharyngitis and recurrent respiratory infections	Resveratrol 0.05% and carboxymethyl-b-glucan 0.33% vs. saline isotonic solution nebulized (12 drops/day for 20 days).	nasal symptoms, medication use, medical visits, school absences	Follow-up at 30, 60, and 90 days	Reduction of symptoms in the active group ($p < 0.001$)	Not specified	Not specified
Baldassarre et al. [11]	RCT	100 infants (0 to 6 months), with acute respiratory illness	Resveratrol 0.05% and carboxymethyl-b-glucan 0.33% vs. saline isotonic solution (3 drops in each nostril, 4 times a day for 7 days)	sneezing and cough, nasal biomarkers	30 days follow-up	Reduction of symptoms in the active group ($p < 0.05$)	No	NCT 03683108
Indolfi et al. [12]	RCT	39 preschoolers with recurrent wheezing	Resveratrol 0.05% and carboxymethyl-b-glucan 0.33% vs. saline isotonic solution (two sprays per nostril, 3 times a day for 7 days)	wheezing, hospital visits, medications use	180 days follow-up	reduction of wheezing, hospital admissions, and drugs in the active group ($p < 0.001$)	No	Not specified
Miraglia del Giudice et al. [13]	RCT	68 children (mean age 7.9 years) with seasonal allergic rhinitis	Resveratrol 0.05% and carboxymethyl-b-glucan 0.33% vs. saline isotonic solution (two sprays per nostril, 3 times/day for 2 months)	nasal symptoms, rescue medication use (cetirizine)	60 days follow-up	Reduction of symptoms in active group ($p < 0.001$)	Yes	NCT 02130440
Miraglia del Giudice et al. (2014)[14]	RCT	76 children (mean age 9.5 years) with persistent allergic rhinitis	Resveratrol 0.05% and carboxymethyl-β-glucan 0.33% vs. saline isotonic solution (two sprays per nostril 3 times/day for 2 months.	nasal symptoms, respiratory infections	Up to 2 months	reduction of TSS, cough and wheezing, β2-agonist use, days with fever, school absences in active group ($p < 0.001$)	Yes	NCT 02130440

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Author Contributions

All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable

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Conflict of Interest

The authors declare no conflict of interest.

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