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REVIEW

Echinacea Reduces the Risk of Recurrent Respiratory Tract Infections and Complications: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: Respiratory tract infections are common, and these infections occur frequently in children, susceptible adults, and older persons. The risk for recurrences and complications relates not only to the presence of viruses but also to immune function. Therefore, modulation of the immune system and antiviral interventions such as echinacea might reduce the risk of recurrences and possibly the development of complications.

Methods: MEDLINE, EMBASE, CAplus, BIOSIS, CABA, AGRICOLA, TOXCENTER, SCISEARCH, NAHL, and NAPRALERT were searched for clinical trials that studied recurrent respiratory infections and complications on treatment with echinacea extracts in a generally healthy population. Two independent reviewers selected randomized, placebo-controlled studies of high methodological quality and a Jadad score of $\geq$4. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated according to a fixed effect model.

Results: Six clinical studies with a total of 2458 participants were included in the meta-analysis. Use of echinacea extracts was associated with reduced risk of recurrent respiratory infections (RR 0.649, 95% CI 0.545–0.774; $P < 0.0001$). Ethanolic extracts from echinacea appeared to provide superior effects over pressed juices, and increased dosing during acute episodes further enhanced these effects. Three independent studies found that in individuals with higher susceptibility, stress or a state of immunological weakness, echinacea halved the risk of recurrent respiratory infections (RR 0.501, 95% CI 0.380–0.661; $P < 0.0001$). Similar preventive effects were observed with virologically

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confirmed recurrent infections (RR 0.420, 95% CI 0.222–0.796; $P = 0.005$). Complications including pneumonia, otitis media/externa, and tonsillitis/pharyngitis were also less frequent with echinacea treatment (RR 0.503, 95% CI 0.384–0.658; $P < 0.0001$).

Conclusion: Evidence indicates that echinacea potently lowers the risk of recurrent respiratory infections and complications thereof. Immune modulatory, antiviral, and anti-inflammatory effects might contribute to the observed clinical benefits, which appear strongest in susceptible individuals.

Keywords: Complications; Echinacea; Meta-analysis; Recurrences; Respiratory tract infections

INTRODUCTION

Respiratory tract infections (RTIs) are common and demonstrate a high propensity to recur. Adults and children experience up to 5 and 12 infections, respectively, for a total of up to 4–11 recurrent infections within a single cold season [1].

These infections can be debilitating and immune depleting, with physical damage of the airway epithelium that can increase risk of further infection [2–6]. Infections are associated with reduced salivary immunoglobulin (Ig) A and interferon-gamma (IFN-γ) secretion, which otherwise would provide immunity against recurrences [7, 8]. Without intervention, infections tend to recur and in turn increase the risk for complications [9].

Therapeutic options for acute infections are scarce and no therapies have shown benefit in reducing recurrences to justify continuation of prophylactic after acute treatment. Echinacea extracts could present an interesting solution here. Traditionally, these extracts have been used to support the immune system, and newer studies indicate immunomodulatory effects via interaction with endocannabinoid receptors (CB2R). In particular, tumor necrosis factor-alpha (TNF-α) was down-regulated in contrast to an increased production of IFN-γ or macrophage chemotactic protein-1 (MCP-1) during treatment with echinacea [10, 11]. Direct antiviral and anti-inflammatory effects further add to the pharmacodynamic profile of echinacea, suggesting its potential for treating recurrent infections and complication prevention [12].

In 2007, Shah and colleagues [13] performed a meta-analysis of the incidence and duration of common colds in randomized placebo-controlled clinical studies investigating echinacea containing products for treatment and/or prophylaxis, and reported a significant benefit for echinacea in reducing common cold rates [odds ratio (OR) 0.42; $P < 0.001$]. They also reported a reduced infection duration of 1.4 days ($P < 0.01$). We previously reported significant benefit with 7–14 days pre-treatment plus 5 days post-inoculation treatment with echinacea in prevention of rhinovirus-induced colds, studying exclusively experimentally induced infections, and identified a 55% higher likelihood for clinical colds with placebo ($P < 0.05$) [14]. Only the early acute phase was observed and recurrent infections or complications resulting therefrom were not studied. Likewise, a very recent update on Cochrane review found a risk ratio (RR) of 0.83 [95% confidence interval (CI) 0.75–0.92; $P < 0.001$] when evaluating participants with at least one cold episode, i.e., the occurrence of first infections. This analysis also regarded studies on artificially induced infections as well as unpublished reports without restriction for methodological quality [15].

The aim of this meta-analysis, therefore, was to evaluate studies reporting the risk of recurrent RTIs and of complications following a treatment period with echinacea.

METHODS

Two reviewers (AS, PK) independently conducted a systematic literature research of MEDLINE, EMBASE, CAplus, BIOSIS, CABA, AGRICOLA, TOXCENTER, SCISEARCH, NAHL, and NAPRALERT and the search terms *echinacea*, *black Sampson*, *coneflower*, and *Roter Sonnenhut* with no restriction for year or publication status. Articles were further evaluated for human subjects treated with echinacea under randomized, placebo-controlled conditions and information concerning recurrent RTIs [16–21]. Some studies explicitly stated the number of recurrent infections [17, 18, 21] while others gave the total number of episodes and the number of first infections and/or the number of participants with ≥1 episode [16, 19, 21]. In the latter case, the number of recurrent RTIs was deduced by subtracting the number of first episodes from the total number of infections. When different echinacea preparations were applied in parallel within a single study, we pooled the data from the echinacea arms [19]. All studies included generally healthy volunteers without underlying health conditions or allergies to plants of the composite family. The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

In a next step, articles were assessed for suitability for analysis using quality of reporting of meta-analyses criteria [22]. The quality of the included studies was assessed by Jadad score considering randomization procedure and blinding efficacy as well as traceability of study subjects during the trial [23]. Only high-quality studies with a total Jadad Score of ≥4 were selected for analysis to control the risk of bias. Included studies were evaluated and assessed by AS, PK, and SJ. In case of disagreement, consensus was sought and resolved. This study was conducted according to recommendations from the PRISMA group for reporting of meta-analyses [24].

The primary outcome was recurrent infection risk, e.g., the total of second, third, fourth, and fifth episodes under echinacea or placebo continuous treatment for 2–4 months [17–21] or in one study, during a surveillance period (4 months) of repetitive acute treatments, each over 10 days [16]. In addition, the number of participants experiencing recurrent infections (with >1 infection per investigation period) was displayed as a confirmatory variable. This analysis integrated data on RTIs and complications that followed a treatment period with echinacea.

A formal meta-analysis was conducted by pooling results from eligible studies. The ratios of recurrent infection and complication incidences under echinacea or placebo were compared to the ratios of the underlying populations and 95% CIs were calculated for the RRs. Results from the particular studies were combined using the calculated weighted means of the log-RRs [25]. Because of the rather small number of included studies, a fixed-effects model was used at first to calculate overall estimators and tests for difference, assuming that the characteristics of patients contributing data were the same as those in the total population. Results were compared to calculations using a random-effects model

referring to a more conservative approach, which allows for a greater influence of variability in treatment difference estimates. Quantitative heterogeneity of effect differences between trials was estimated using a chi square test as proposed by Hedges and Olkin [26] and was considered significant if $P < 0.1$.

Complications developing under placebo and echinacea were deduced by cumulating the total reports on conjunctivitis, sinusitis, otitis media/externa, tonsillitis, pharyngitis, bronchitis, and pneumonia from every clinical study. RRs were deduced as described above. The associated intake of antibiotics was estimated from days under treatment with this therapeutic class.

Finally, safety was assessed by calculating total numbers of adverse events reported during the observation period as well as study subjects experiencing adverse events. The occurrence of severe adverse events was separately expressed. The validated program MetaSub version 1.3.4 (IDV, Gauting/Munich, Germany) was used in this analysis.

RESULTS

Of 949 hits for search term "echinacea," 681 non-clinical studies and 167 non-human studies were excluded based on title inspection (Fig. 1). Abstracts of the remaining 101 articles were scanned and 89 excluded because they did not include RTIs as indications, studied pharmacodynamic effects, lacked appropriate placebo control, or had inappropriate endpoints. Twelve clinical trials qualified for further investigation. One clinical trial by Berg and colleagues [27] was rejected because of low methodological quality (Jadad score = 3). Similarly, clinical trials by Turner et al. [28, 29] and Sperber et al. [30] were excluded

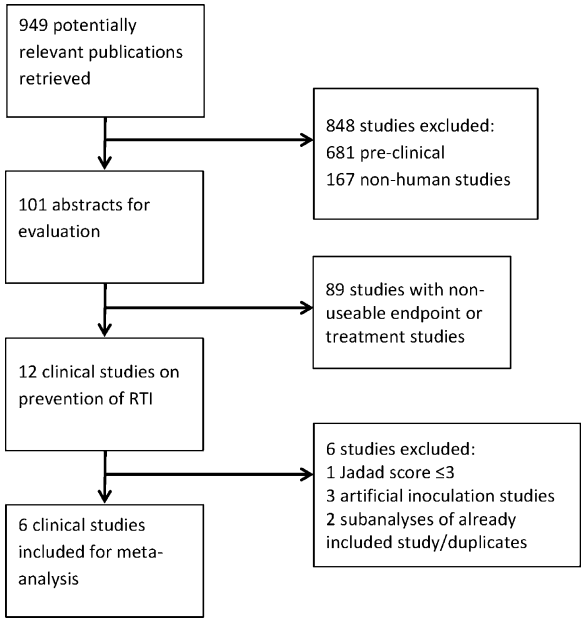

Fig. 1 Description of included and excluded studies. *RTI* respiratory tract infection

because they investigated experimentally induced infections in which the post-treatment period was not surveyed. Schöneberger's report [31] and the analysis by Weber et al. [32] were used supportively for discussion of pharmacodynamics but were not included in the primary meta-analysis because they relied on subgroups of original papers [16, 17]. Finally, data from the six clinical trials were extracted for meta-analysis [16–21]. Melchart et al. [19] tested two echinacea preparations (*Echinacea angustifolia* and *Echinacea purpurea*). In our analysis, we pooled the incidence of recurrent infections and safety data from the two arms for comparison to placebo.

Principally, the two reviewers (AS and PK) agreed on the selections with the exception of the Berg study, which finally was rejected because of inappropriate blinding and sample-size calculations [27]. Our methodology was very similar to that of the Shah meta-analysis [12], but here we followed a more restrictive approach and excluded the studies by Turner

et al. [28, 29], Sperber et al. [30], Berg et al. [27], and Hoheisel et al. [33] because of the above-mentioned reasons but included the newer trials by Jawad et al. [21] and qualitatively discussed Heinen-Kammerer et al. [34].

Table 1 summarizes the clinical studies that were of appropriate methodological quality (Jadad score $\geq$4) and for which data regarding recurrent infections and complications were available. The studies varied in echinacea preparations and doses administered. Four studies employed ethanol/glycerol extractions from *E. purpurea*/*E. angustifolia* (500–4000 mg extract/day), and two used pressed juices from *E. purpurea* (6200–10,000 mg/day). Extracts present a rather lipophilic spectrum of active substances (e.g., alkylamides, polyacetylenes) while pressed juices contain many hydrophilic arabinogalactans and polysaccharides [35]. Supplementary treatments were not permitted except in the trials by Cohen et al. [20] and Schmidt et al. [18] (Table 1). In all clinical studies, cold symptoms were self-reported during the observation period by the treated subject prior to RTI confirmation by a physician or study staff. Jawad et al. [21] was the largest clinical study with 757 subjects. In that study, RTIs were identified based on definition by Jackson and colleagues [36]. All six studies defined RTIs based on symptoms, but Jawad et al. [21] also reported virally confirmed RTIs, providing a specific case definition, which was separately analyzed.

As Table 2 demonstrates, effect sizes of individual studies on recurrent RTI varied (RRs), but all trials reported lower incidence for recurrent infections in echinacea-treated versus placebo-treated groups. Only studies by Cohen et al. [20] and Jawad et al. [21] yielded significant benefits, with an average RR of 0.498 (95% CI 0.386–0.642; $P < 0.0001$). Pooling all included clinical studies still yielded an overall RR of 0.649 (95% CI 0.545–0.774) on the level of $P < 0.0001$ (Table 2; Fig. 2). The largest two clinical studies by Jawad et al. [21] and Schmidt et al. [18], both testing echinacea alcoholic extracts, showed effects that were similar to the overall calculated RR, i.e., RR = 0.663 and 0.734, respectively. Heterogeneity between study results was indicated with $I^2 = 72\%$ ($P = 0.0069$). Because all single results were positive, the reason for heterogeneity was quantitative rather than qualitative. In a more conservative approach employing the random-effects model, the results (overall RR of 0.640, 95% CI 0.451–0.910; $P = 0.0129$) were consistent with the fixed-effects model for which data are presented (Table 2).

We next examined numbers of participants experiencing at least one recurrent RTI. For this analysis, we retrieved data from the four studies for which such data were available [17, 19, 21, 32]. Table 2 shows that the protective effect for echinacea (RR 0.769, 95% CI 0.598–0.990; $P = 0.041$) approximates the estimates from the overall incidences of RTIs. This analysis included patient-related data from Melchart et al. [19], which showed a slightly different picture for *E. angustifolia* than for *E. purpurea*, but the weight effect of the difference was small on the overall analysis because of low sample size.

Despite the robustness of the results, we decided to perform subgroup analyses to investigate the sensitivity of our analyses. As noted in the Methods, the tested echinacea preparations varied. The test preparations were therefore grouped into lipophilic extracts (which included the studies performed by Jawad et al. [21], Cohen et al. [20], and Schmidt et al. [18]) and those using the pressed juices [16, 17]. RR for prevention of recurrent infections with echinacea alcoholic extracts was 0.542 (95% CI 0.432–0.679;

Table 1 Description of included studies and assessment of methodological quality according to Jadad scoring

Study	Echinacea species	Extraction method	Supplement	Duration of treatment/ observation	Daily dose/ amount of echinacea	Patient number	Cold definition	Jadad score
Schmidt et al. [18]	EA	Ethanolic extract	Eupatorium/baptisia	2 months	1 × 12 ml/1440 mg[a]	609	Patient reported, confirmed by physician	4
Grimm et al. [17]/ Schoeneberger [31]	EP	Pressed juice	None	2 months	2 × 4 ml/6200 mg[b]	108/66 with weak immune response	Patient reported, confirmed by physician	5
Melchart et al. [19], three-arm study	EP	Ethanolic extract	None	3 months	2 × 50 drops/1800 mg[c]	99 (90 placebo)	Patient reported, confirmed by physician	4
	EA	Ethanolic extract	None		2 × 50 drops/1800 mg[c]	100 (90 placebo)		
Cohen et al. [20]	EP + EA	Glycerol extract	Propolis + vitamin C	3 months	2–4 × 5–7.5 ml/ 500–1500 mg	328	Patient reported, confirmed by physician	4
Taylor et al. [16]/ Weber et al. [32]	EP	Pressed juice	None	10 days/ 4 months	7.5–10 ml/ 7500–10,000 mg	407/401	Study staff confirmed	5
Jawad et al. [21]	EP	Ethanolic extract	None	4 months	2.7–4.5 ml/ 2400–4000 mg	717	Patient reported, confirmed by Jackson method	5
						717	Virally-confirmed infections	

EA Echinacea angustifolia, *EP Echinacea purpurea*

[a] With 120 mg/ml EA extract

[b] Product contains 22% ethanol for stabilization

[c] At 20 drops/ml and $\delta = 0.9$ g/ml

Table 2 Incidence of recurrent infections and number of participants experiencing recurring infections for the individual studies

Study	*N*		Incidence of recurrent infections		Ratio of incidences	Number of subjects with recurrent infections (>1 infection)		Ratio of patients with recurrent infections
	Echinacea	Placebo	Echinacea	Placebo	RR (95% CI) *P* value	Echinacea	Placebo	RR (95% CI) *P* value
Schmidt et al. [18]	303	306	32	44	0.734 (0.453–1.190) $P = 0.182$	N/a	N/a	–
Grimm et al. [17]/ Schoenberger [31]	54	54	14	18	0.778 (0.352–1.720) $P = 0.480$	7	8	0.875 (0.296–2.582) $P = 0.796$
Melchart et al. [19], three-arm study	99 (EP) 100 (EA)	90	– –	– –	– –	4 7	6	0.829 (0.297–2.312) $P = 0.712$
Cohen et al. [20]	160	168	53	158	0.352 (0.241–0.515) $P < 0.0001$	N/a	N/a	N/a
Taylor et al. [16]/ Weber et al. [32]	200/197	207/204	137/-	163/-	0.870 (0.645–1.173) $P = 0.229$	-/110	-/142	0.802 (0.584–1.101) $P = 0.082$
Jawad et al. [21]	355	362	65	100	0.663 (0.469–0.936) $P = 0.009$	28	43	0.664 (0.404–1.093) $P = 0.090$
Overall (fixed effect)	1271	1187	301	483	0.649 (0.545–0.774) $P < 0.0001$	156	199	0.769 (0.598–0.990) $P = 0.041$
Heterogeneity	Chi^2 14.129 P 0.0069 I^2 72%					Heterogeneity		Chi^2 0.477 P 0.924 I^2 0%
Random effects	RR (95% CI) 0.640 (0.451–0.910) P 0.0129					Random effects		RR (95% CI) 0.769 (0.598–0.990) P 0.041

CI confidence interval, *N/a* not available, *RR* relative risk

$P < 0.0001$) while for pressed juices, the RR was 0.858 (95% CI 0.649–1.135; missing statistical significance in the latter with $P = 0.283$).

These analyses employed a patient-reported and symptomatic assessment of RTIs, but Jawad et al. [21] provided data on virally confirmed infections, using an objective measure. In the echinacea group, 54 nasal secretions from 355 subjects tested positive for respiratory viruses in comparison to 74 infections from 362 placebo recipients. Of those, 14 and 34 samples, respectively represented recurring viral infections in the echinacea and placebo groups, which corresponds to an RR of 0.420 (95% CI 0.222–0.796; $P = 0.005$).

The literature discusses several factors leading to increased susceptibility to RTIs. Patient subgroups with risk factors including exposure to stress (perceived stress score, PSS-10), being an active smoker, poor sleep, with presumed immune weakness due to low T4/T8 ratio <1.5, and a history of >2 colds/year were separately analyzed in two clinical trials [21, 31]. The risk for contracting recurrent RTI in these groups was lower with a RR of 0.501 (95% CI 0.380–0.661; $P < 0.0001$) than for the total population. Overall estimates must be considered with caution, however, because effects from the different groups are based on two clinical trials, not the six independent studies (Fig. 3).

Complications including conjunctivitis, sinusitis, otitis media/externa, tonsillitis/pharyngitis, bronchitis, and pneumonia were reported in three studies [17, 20, 21]. As Table 3 shows, the overall complication incidence was effectively reduced by 50% with echinacea (RR 0.503, 95% CI 0.384–0.658; $P < 0.0001$). The reduction of pneumonia was most prominent at a 64.9% decrease ($P < 0.0001$). Similar reductions were observed for otitis media/externa and tonsillitis/pharyngitis ($P < 0.0001$ and $P = 0.021$, respectively). Complication reduction finally was associated with a decreased need for antibiotics, which was noted in two placebo-controlled studies and in one study comparing echinacea with

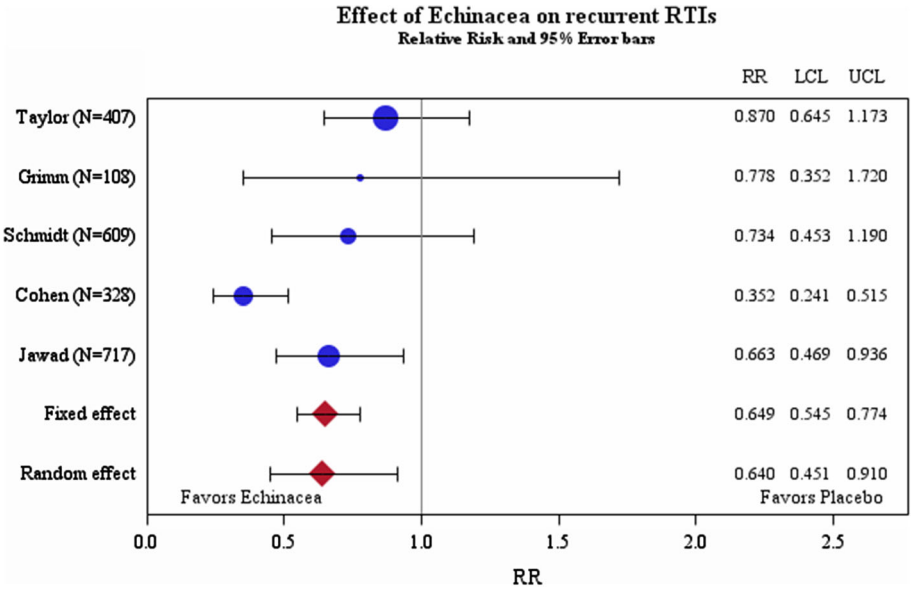

Fig. 2 Effect of echinacea on recurrent RTIs as demonstrated by RR. *Error bars* indicate the 95% confidence intervals. *LCL* lower confidence limit, *RR* relative risk, *RTI* respiratory tract infection, *UCL* upper confidence limit

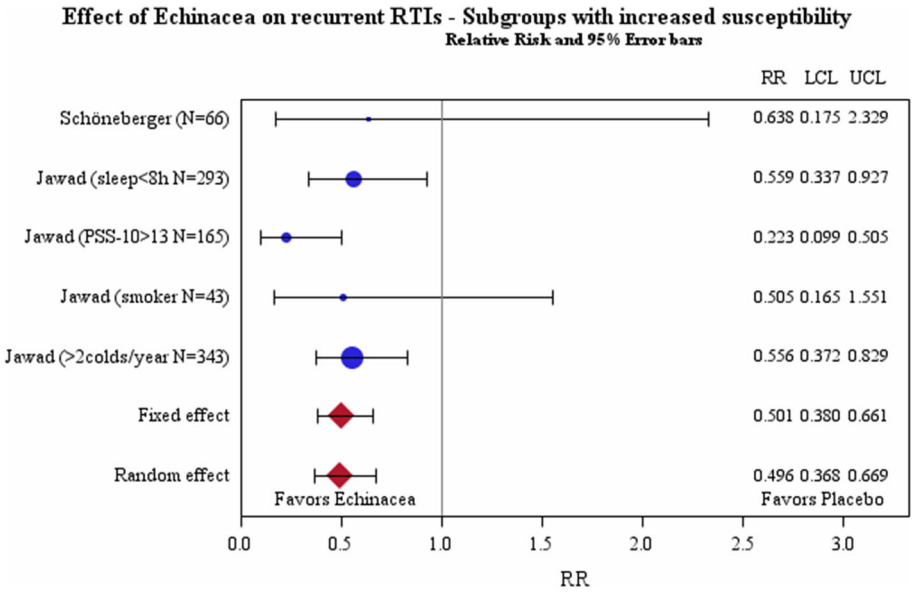

Fig. 3 The RR of recurring infections between echinacea and placebo in subgroups with increased susceptibility to RTIs. *LCL* lower confidence limit, *PSS* perceived stress score, *RR* relative risk, *RTI* respiratory tract infection, *UCL* upper confidence limit

standard treatment. Cohen et al. [20] reported a total of 1084 days with antibiotic use in the placebo group ($n = 168$) compared to 541 days in the echinacea group ($n = 160$), corresponding to a 50% reduction [20]. Unpublished results cited in Jawad et al. [21] were 7 days with antibiotic treatment under echinacea and 33 days for placebo (personal communication).

Safety profile data were available either as total adverse events or as number of subjects experiencing one or more adverse events and from a total of 1440 echinacea-treated subjects and 1326 subjects receiving placebo. Overall, 491 adverse events occurred with echinacea in comparison to 474 with placebo. Most affected the gastrointestinal tract and were mild and transient; only two severe adverse events (stridor) occurred with echinacea and one (glandular fever, requiring hospitalization) in the placebo group (Table 4). No differences in laboratory biochemical and hematological parameters were identified in 4 months with echinacea prevention. Finally, personal assessments of tolerability were mostly assessed as "good" or "very good" [21].

DISCUSSION

RTIs belong to the most frequent illnesses worldwide. With an average of 2.5 episodes per year, we experience approximately 200 infections in our life, lasting for 4–5 years in total [37]. Recurrences therefore are a significant medicinal issue, especially in susceptible populations [1]. Depending on an individual's immunological condition, these infections can produce serious complications, morbidity, and even mortality. In view of the high risk for recurrences and complications, an effective management of RTI's might benefit from going beyond treatment of acute symptoms of infection in order to prevent the consequences of infections, which finally are a main reason for prescription of antibiotics [37].

Table 3 Cumulated number of complications including conjunctivitis, sinusitis, otitis media/externa, tonsillitis, pharyngitis, bronchitis, and pneumonia

Complication	Echinacea ($N = 569$)	Placebo ($N = 584$)	Relative risk (95% confidence interval) *P* value
Conjunctivitis	2	3	0.684 (0.114–4.110)
			$P = 0.676$
Sinusitis	4	5	0.821 (0.219–3.073)
			$P = 0.768$
Otitis media/ externa	31	74	0.430 (0.278–0.664)
			$P < 0.0001$
Tonsillitis/ pharyngitis	37	61	0.623 (0.407–0.952)
			$P = 0.021$
Bronchitis	10	17	0.604 (0.274–1.330)
			$P = 0.201$
Pneumonia	13	38	0.351 (0.185–0.666)
			$P < 0.0001$
Total	97	198	0.503 (0.384–0.658)
			$P < 0.0001$

The study aim was to review the existing literature and estimate in a meta-analysis echinacea's preventive effect on recurrent respiratory infection and complications. Data on recurrent infections were available from six clinical trials and a total of 2458 participants, who received a variety of echinacea extracts for up to 4 months [16–21]. Despite heterogeneity of treatment and dosage ranges, in all studies, the risk for recurrent infections was reduced with echinacea compared to placebo. The overall number of recurrent infections correlated well with the number of participants experiencing recurrent episodes as well as with the number of virologically confirmed recurrent infections.

The heterogeneous treatment modes could be considered as a potential weakness of this analysis. On the other hand, the variation in effects might serve to optimize therapy. The studies by Cohen et al. [20] and Jawad et al. [21] provided a statistically significant effect when analyzed individually and prevented approximately 50% of recurrences. Both applied alcoholic extracts prepared from echinacea herb and roots continuously over 3 and 4 months and doubled the dose of echinacea during acute treatment, reflecting an already proposed "mixed" therapeutic intervention combining preventive and acute treatment [38]. One study looked specifically at recurrent infections during repeated acute therapies [16]. Although the overall benefit was lower than for the combined acute and prevention approach, even short-term therapy with echinacea appeared to support immunological processes with beneficial effect on recurrent infections. We hypothesize, that increased dosing upon treatment of an initial "trigger" infection (in addition to basic prevention) could reduce inflammatory tissue damage (airway reactiveness), which otherwise would lead to further infections and complications.

Several pharmacological properties of echinacea could be responsible for the observed effects. The support of particular immune functions potentially increases resistance to viral infections [10, 11]. Two studies tested the preventive benefits in a subgroup with reported risk factors to infection like stress, poor sleep, and infection susceptibility [18, 21]. In all subgroups, superior effects were observed compared to the overall study population, further indicating possible immune supportive influence. In addition, antiviral effects are attributed to echinacea [12], which have been observed in vitro as well as in a clinical study by Jawad et al. [21]. Considering the heterogeneity of investigated extracts, the observed preventive benefits are likely to be a combination of pharmacodynamic effects that contribute to overall outcomes to various extents.

Table 4 Number of AEs, patients experiencing AEs and SAEs as per safety collectives of the respective studies

Study	*N*		Number of AEs		Patients with AEs		Number of SAEs	
	Echinacea	Placebo	Echinacea	Placebo	Echinacea	Placebo	Echinacea	Placebo
Schmidt et al. [18]	322	324	12	10	12	10	0	0
Grimm et al. [17]	55	54	N/a	N/a	11	7	0	0
Melchart et al. [19] (EP)	103	96	13	12	10	11	0	0
Melchart et al. [19] (EA)	103		21		18		0	
Cohen et al. [20]	215	215	N/a	N/a	9	7	0	0
Taylor et al. [16]	263	261	152	146	N/a	N/a	2	0
Jawad et al. [21]	379	376	293	306	177	172	0	1
Overall	1440	1326	491	474	237	207	2	1

AEs adverse events, *EA Echinacea angustifolia*, *EP Echinacea purpurea*, *N/a* not available, *SAEs* serious adverse events

Only one study [21] provided a detailed chemical analysis of the tested product, which makes overall recommendations for standardization on the basis of marker substances difficult. On the level of manufacturing procedures lipophilic extracts appeared to outperform hydrophilic pressed juices, but definite conclusions are limited due to the low number of referenced studies. It would be highly desirable that future research focusses on chemically standardized extracts.

A very recent Cochrane review compared echinacea with placebo in the prevention of first infections (participants with at least one cold episode) [15]. Nine prevention trials were evaluated, including artificial inoculation studies [28–30]. Most of these studies did not report recurrences as well as complications following the analyzed first infection. Results were not significant on the single study level but an exploratory meta-analysis pooling all trials yielded a reduced risk of experiencing first cold infections (RR 0.83, 95% CI 0.75–0.92; $P < 0.001$). Despite heterogeneity of tested preparations, the result was highly consistent across included studies. Whereas the effect on first infections was considered small by the authors, our data indicate an increased benefit upon long-term echinacea prevention (2–4 months) on recurrent infections (RR = 0.649) as well as complications (RR = 0.503).

This meta-analysis investigated for the first time the potential reduction in recurrent RTIs and complications by comparing echinacea with placebo treatment. The identified effects might be an underestimation of the overall benefit because the placebo effect in cold studies is substantial [39]. One non-controlled, open study estimated the gross benefit of echinacea prevention for recurrent infections [34]. A total of 213 patients with an initial infection were treated with standard therapy including analgesics, expectorants, and conventional cough, rhinitis, and sinusitis therapies. Another 782 patients received echinacea in addition to this standard therapy. Throughout the 3-month surveillance period, 15.1% (88/584) of echinacea recipients developed recurrent infections in comparison to 34.9% (53/152) in the reference group ($P = 0.001$). Overall, the risk for recurrent

episodes was 2.3 times higher in the absence of echinacea. With echinacea supplementation the frequency of prescription of antibiotics and anti-infectives was reduced from 14.3% to 4.4% [34].

In parallel with the recurrent RTIs, complications were significantly reduced from an overall number of 197 events in the placebo group to 97 in the echinacea group, a magnitude similar to the recurrence effects.

Safety is critical, especially in therapies applied over a long period of time. In this regard, echinacea demonstrated a very positive picture. The vast majority of reported events were mild and transient and not significantly different between echinacea and placebo groups. Laboratory values remained stable, and the overall assessment by patients was (very) good in general.

CONCLUSIONS

Echinacea presents an effective option for the longer term management of recurrent RTIs and related complications. Differences in efficacy may exist, possibly explained by differences in preparation methods. People with presumed lower immune function and a consequently high susceptibility might benefit most. In parallel with the reduced risk for infections, complications like pneumonia, otitis, or tonsillitis are prevented, as well as the associated need for antibiotic therapy. Finally, the good safety profile allows for long-term prevention with echinacea.

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