The effect of *Echinacea* spp. on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review

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**A R T I C L E   I N F O**

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COVID
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Rapid review
Comfrey
Cytokine
Inflammation
Herbal medicine
Botanical

**A B S T R A C T**

**Brief overview:** Current evidence suggests that *Echinacea* supplementation may decrease the duration and severity of acute respiratory tract infections; however, no studies using *Echinacea* in the prevention or treatment of conditions similar to COVID-19 have been identified. Few adverse events were reported, suggesting that this herbal therapy is reasonably safe. Because *Echinacea* can increase immune function, there is a concern that it could worsen over-activation of the immune system in cytokine storm; however, clinical trials show that *Echinacea* decreases levels of immune molecules involved in cytokine storm.

**Verdict:** *Echinacea* supplementation may assist with the symptoms of acute respiratory infections (ARI) and the common cold, particularly when administered at the first sign of infection; however, no studies using *Echinacea* in the prevention or treatment of conditions similar to COVID-19 have been identified. Previous studies have reported that *Echinacea* may decrease the severity and/or duration of ARI when taken at the onset of symptoms. The studies reporting benefit used *E. purpurea* or a combination of *E. purpurea* and *E. angustifolia* containing standardized amounts of active constituents. Few adverse events from the use of *Echinacea* were reported, suggesting that this herbal therapy is reasonably safe. No human trials could be located reporting evidence of cytokine storm when *Echinacea* was used for up to 4 months.

When assessing all human trials which reported changes in cytokine levels in response to *Echinacea* supplementation, the results were largely consistent with a decrease in the pro-inflammatory cytokines that play a role in the progression of cytokine storm and Acute Respiratory Distress Syndrome (ARDS), factors that play a significant role in the death of COVID-19 patients. While there is currently no research on the therapeutic effects of *Echinacea* in the management of cytokine storm, this evidence suggests that further research is warranted.

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1. **Background**

*Echinacea* species are native to North America and have been used by indigenous peoples for a range of illnesses. As an herbal medicine, *Echinacea* has been the subject of significant research over the past century, particularly with respect to its role in the treatment and prevention of respiratory illnesses. It is one of the most popular natural health products purchased worldwide, with the majority of commercially available products containing *E. purpurea* and/or *E. angustifolia* [1]. Many naturopathic doctors recommend *Echinacea* supplements for immune support. A wide range of reports have described its immuno-modulatory properties including macrophage activation and effects on cytokine expression. Because significant effects on cytokine levels have been observed in response to *Echinacea* use, there is a theoretical
Table 1
Summary of studies examining the effect of Echinacea spp. on respiratory tract infections in humans.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country, Region</th>
<th>Sponsorship</th>
<th>Intervention</th>
<th>Design (eg Cross-over, parallel group design)</th>
<th>Statistical method(s)</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Duration of Treatment</th>
<th>Outcome Measure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grimm W et al. (1998)</td>
<td>Germany, European Region</td>
<td>Madaus AG, Cologne/ Philippe University of Marburg, Germany</td>
<td>DBPC RCT</td>
<td>Placebo prepared in-house; gelatin caps: sucrose, cornstarch, brown sugar, molasses</td>
<td>* A priori measures + Fisher's exact test for binomial categorical variable &amp; incidence of AIs + Mann–Whitney U test for continuous demographic variables, infection incidence/severity/duration</td>
<td>Reduce frequency of exercise-induced allergic reactions</td>
<td>One infection</td>
<td>4 weeks</td>
<td>No difference</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Mickbairt D et al. (1998)</td>
<td>Germany, European Region</td>
<td>The Center for Complementary Medicine Research, Bavarian Parliament, Plantapharm, Gottingen, Germany, Medistimus, Klinik, Technische Universitat, Bonn, Ernst-Preitsch Zentrurn For Therapeutic Studies</td>
<td>DBPC RCT placebo arm</td>
<td>Echinacea purpurea, whole plant (noroots) Echinacin-Liquidum</td>
<td>* SAS and SPSS for randomized, ITT &amp; PP populations + Log rank test (for ITT) + main outcome measure; All other data; Kruskal-Wallis and Z2 tests for exploratory inference statistics</td>
<td>Reduce frequency of exercise-induced allergic reactions</td>
<td>One infection</td>
<td>12 weeks</td>
<td>No difference</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Hall H et al. (2007)</td>
<td>USA, Region of the Americas</td>
<td>Sponsorship or funding source not stated, a supplement manufacturer provided the active intervention free of charge (with no input to the study and no expectations or agreements)</td>
<td>DBPC RCT parallel group design</td>
<td>Echinacea purpurea</td>
<td>ANOVA performed on test data &amp; salivary tests. Past hoc (Least Sig Diff: LSD) used for significant main effects. Interactions subjected to simple main effects analyses, followed by post hoc LSD analysis. Independent sample &amp; &amp; test used for URTI incidence &amp; duration in repeated use for all analyses</td>
<td>Reduce frequency of exercise-induced allergic reactions</td>
<td>One infection</td>
<td>28 days</td>
<td>No difference</td>
<td>No significant difference</td>
</tr>
</tbody>
</table>

Note: Table adapted from the original document for clarity and formatting. The table includes studies with varying outcomes and methods, highlighting the complexity and variability in findings when examining the efficacy of Echinacea spp. in respiratory tract infections.
A prospective power analysis was calculated. Volunteer selection was based on an intention-to-treat analysis of each subject's own data. The population was expected to have more equitable exposure to colds/flu.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of participants</th>
<th>Treatment</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinacea</td>
<td>3 capsules 2x/day 300 mg per capsule</td>
<td>Placebo</td>
<td>3 capsules 2x/day 300 mg per capsule</td>
</tr>
<tr>
<td>4 weeks post travel: no difference in total number of days experienced sore throat, runny nose, headache, cough, and fever.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significantly fewer colds in the Echinacea group vs placebo, and fewer recurring episodes (P < 0.05, chi-square test).
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>County, WHO Region</th>
<th>Sponsorship / source/institution</th>
<th>Design (eg Cohort, cross-sectional)</th>
<th>Statistical method (s)</th>
<th>Study Population / Disease or Condition</th>
<th>Echinacea spp, part of plant</th>
<th>Form of supplement (plain, tincture, capsule)</th>
<th>Extraction Strength and Standardization</th>
<th>Dose</th>
<th>Duration of Treatment</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Control or Placebo</th>
<th>Number Subjects, N</th>
<th>Measure of Outcome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner 2005 USA, region of the Americas</td>
<td>National Center for Complimentary and Alternative Medicine of the NIH</td>
<td>DBPC RCT</td>
<td>6 pairwise comparisons with between groups using chi-square analysis. Multiple logistic-regression analyses including covariates</td>
<td>Healthy volunteers exposed to rhinovirus experimentally</td>
<td>E. angustifolia - 3 vials with supercritical CO2, 60% ethanol or 20% ethanol</td>
<td>tincture</td>
<td>1.5 mL tincture containing 300 mg of echinacea over 3 days</td>
<td>Either 1.7 days before viral challenge (prophylaxis) or 2 days starting at time of viral challenge (treatment) for 3 days</td>
<td>1. Healthy young adults 2. Susceptible to rhinovirus (based on Ab testing)</td>
<td>1. Existing, treated at time of viral challenge screening or at day 0 2. Susceptible to rhinovirus (based on Ab testing)</td>
<td>1. Healthy young adults 2. Patients with a history of rhinovirus infection</td>
<td>Echinacea group compared to placebo</td>
<td>4% versus 3% (P = 0.03) during travel. 4 weeks post travel: significant lower percentage of illness in the Echinacea-treated group compared to placebo (i.e., 25% versus 39%) corresponding to ~50% relative reduction (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sperber USA, region of the Americas</td>
<td>Madura, Ainsiang Sipahong, Laos</td>
<td>DBPC RCT</td>
<td>Treatment group difference by strains t or x2 analysis</td>
<td>Healthy adults infected with rhinovirus 39</td>
<td>E. Purpurea, pressed juice of the above-ground plant parts</td>
<td>tincture, 22% alcoholic (EchinGuard)</td>
<td>2.5 mL tincture (no equiv given)</td>
<td>7 days prior and 7 days after viral challenge</td>
<td>1. Healthy young adults 2. Susceptible to rhinovirus (based on Ab testing)</td>
<td>1. Healthy young adults 2. Patients with a history of rhinovirus infection</td>
<td>Placebo group difference by Student’s t or x2 analysis</td>
<td>4.0% versus 7.3% (P = 0.004) during travel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ishaan F et al (2011) Indonesia, South-East Asia Region</td>
<td>The study was supported by Protanam Switzerland Ltd</td>
<td>DBPC RCT, three arm, participants group, single center trial</td>
<td>Continuous data met 50 differences tested with parametric &amp; non-parametric analysis * ANOVA &amp; Kruskal-Wallis test for between-group differences</td>
<td>Healthy adults infected with rhinovirus</td>
<td>Echinacea purpurea (L.) Moench (EP), aerial parts</td>
<td>Capsule from dried pressed juice</td>
<td>500 mg (or with 10 mg, 15 mg selenium and 50 mg ascorbic acid (EP))</td>
<td>14 days; At enrollment 500 mg caprofen atBed 7 days then randomized to take 1 cap EP 1/day for 2 wks or 1/2 day for 2 wks</td>
<td>1. Patients at least 40 years of age 2. Existing chronic obstructive pulmonary disease 3. An acute exacerbation episode, defined as a non-gradual increase in at least 1 of the 3 major symptoms of dyspnea, sputum production and sputum purulence, supposedly caused by an acute infection 3. Cases infected</td>
<td>1. Patients in the EP + group 2. Patients in the EP group 3. Patients in the placebo group</td>
<td>Dose of echinacea + placebo vs placebo 100 mg (or 25 mg selenium) and 50 mg ascorbic acid</td>
<td>128, placebo n = 35 (EP +) n = 35 (EP) + 108 completed the trial and included in analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adverse events**

- Reported by 2 participants (1 in each group) during the trial. After trial completion 2 participants in the Echinacea group reported adverse events.
- No difference in outcome.
- No difference in outcome.
- No difference in outcome.
- No difference in outcome.
- No difference in outcome.
- No difference in outcome.
- No difference in outcome.

**Diagnosis**

- Coli developed in more patients in the control group, not statistically significant SARI (75: 0.67-78: 25: 0.04-1). No difference in the exacerbation, significantly higher in the EP + vs as compared with the other two groups. [Placebo vs EP + p = 0.0021, EP vs Placebo p = 0.242, EP + vs Placebo p = 0.001].
- Significant differences in IL-1β (p = 0.016), IL-6 (p = 0.001), IL-10 (p = 0.016), IL-4 (p = 0.016), IL-8 (p = 0.016), IL-12 (p = 0.016) and IL-18 (p = 0.016). No difference.
- Study medication was safe and well tolerated with overall 15 adverse events one of which was serious. Among these, bleeding disorders were most frequent and likely related to the
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sponsorship</th>
<th>Design</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Duration</th>
<th>Outcome Measures</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racine RP et al. (2002)</td>
<td>USA, The Region of the Americas</td>
<td>U.S. Dept. of Health and Human Services and NIH, Shaklee</td>
<td>DBPC RCT</td>
<td>Frequency analysis, ANOVA, multivariate analysis, bootstrapping resampling to calculate means and CI, Cox multivariable proportional hazard regression. Study may be slightly underpowered.</td>
<td>E. purpurea seed and E. pallida root (25% each)</td>
<td>8 days</td>
<td>Clinical symptoms</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Dien M et al. (1997)</td>
<td>UK, Germany, and UE, European region</td>
<td>Sponsorship not stated</td>
<td>DBPC RCT</td>
<td>Mixed factorial ANOVA showed no sign diff between the sexes for outcome, age and weight and no sign diff when correlated with outcome (does not specify outcome), chi squared test for individual &amp; overall symptom scores</td>
<td>E. purpurea seed and E. pallida root</td>
<td>8-10 days</td>
<td>Clinical symptom score, Total symptom score</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Guel Y et al. (2005)</td>
<td>Canada, The Region of the Americas</td>
<td>3 authors were employed by the company supplying the intervention/placebo, which was also the sponsor</td>
<td>DBPC RCT</td>
<td>Volunteers recruited through media ads in Edmonton and surrounding areas; at onset of cold Volunteers involved in various parts of E. purpurea production Echinacea</td>
<td>Echinacea paludic acid</td>
<td>Echinacea paludic acid</td>
<td>8-10 days</td>
<td>Overall Symptoms</td>
</tr>
</tbody>
</table>

### Study Design
- **DBPC RCT**: Double-blind, placebo-controlled randomized clinical trial
- **Echinacea**: Used in various forms including seed, root, and extracts
- **Outcome Measures**: Clinical symptoms, total symptom score, overall symptoms
- **Conclusion**: No significant differences found between Echinacea and placebo groups.
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country/Region</th>
<th>Study Design</th>
<th>Echinacea spp. part, form of supplement</th>
<th>Dose</th>
<th>Duration of Treatment</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yale et al. (2014)</td>
<td>Canada, The Region of the Americas</td>
<td>DBPC RCT</td>
<td>E purpurea, aerial portion freeze-dried pressed juice</td>
<td>100 mg 3x/day</td>
<td>Up to 14 days</td>
<td>1. Hypersensitivity to Echinacea or a history of allergy to plants of the Compositae family 2. Received antibiotics, fever, occurring no less than 6 and no longer than 24 h before enrollment 3. Free of cold symptoms and fever remained (max 14 days) 4. Used corticosteroids during enrollment 5. History of allergic rhinitis due to seasonal allergy or environmental allergy 6. Bronchitis or sinusitis during the previous month</td>
</tr>
</tbody>
</table>

Patients were recruited from the Marshfield Clinic system through advertisement in the Marshfield Clinic staff newsletter and through advertisements in local newspapers. Echinacea was standardized for 2.4% soluble 1,2-D-fructofuranosides. It was administered in 3x/day doses of 100 mg. Time to symptom resolution was calculated from the first day of symptoms to the last day of symptoms. The symptom severity was measured using a 7-point Likert scale. The main outcome measure was the time to symptom resolution, which was compared between the treatment and placebo groups using the Wilcoxon rank sum test. The authors concluded that Echinacea E. purpurea is effective in reducing the duration of symptoms of the common cold.

Other studies also found similar results. For example, the study by Goel et al. (2014) in Canada and the Americas, where volunteers were paid an honorarium on completion of the study, also showed a significant reduction in the duration of symptoms. Similarly, the study by G喬 et al. (2004) in Canada, The Region of the Americas, where participants were paid an honorarium on completion of the study, also found similar results.

In summary, Echinacea E. purpurea appears to be an effective remedy for the common cold, with a reduction in the duration of symptoms reported in multiple studies. However, more research is needed to confirm these findings and to determine the optimal dosage and duration of treatment.


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Type I error for interaction effects. Two-way ANOVA for treatment effects. Pearson correlation for group differences. Contacted at least two infections of a cold in the past year, 58% of onset of a cold per month, 30 days the first day, distributed equally throughout the day followed by four doses per day for the next 6 days.

3. Contracted at least 2 infections of a cold in the past year. 4. Responded to media advertisement and scored 80% of a cold per month, 30 days the first day, distributed equally throughout the day followed by four doses per day for the next 6 days.


Duration of illness: Echinacea n = 41. Placebo n = 39. Duration of illness and Jackson score of the echinacea group (p = 0.01) 61.0% of the patients in the echinacea group had a complete picture of the common cold compared to 38.7% in the placebo group (p = 0.01). Duration of illness: Echinacea n = 41. Placebo n = 39. Duration of illness and Jackson score of the echinacea group (p = 0.01) 61.0% of the patients in the echinacea group had a complete picture of the common cold compared to 38.7% in the placebo group (p = 0.01). Duration of illness: Echinacea n = 41. Placebo n = 39. Duration of illness and Jackson score of the echinacea group (p = 0.01) 61.0% of the patients in the echinacea group had a complete picture of the common cold compared to 38.7% in the placebo group (p = 0.01). Duration of illness: Echinacea n = 41. Placebo n = 39. Duration of illness and Jackson score of the echinacea group (p = 0.01) 61.0% of the patients in the echinacea group had a complete picture of the common cold compared to 38.7% in the placebo group (p = 0.01). Duration of illness: Echinacea n = 41. Placebo n = 39. Duration of illness and Jackson score of the echinacea group (p = 0.01) 61.0% of the patients in the echinacea group had a complete picture of the common cold compared to 38.7% in the placebo group (p = 0.01).
concern about its contribution to cytokine storm (also known as cytokine release syndrome) (1). Cytokine storm is a poorly understood phenomenon involving excessive, rapid release of pro-inflammatory cytokines [2]. In COVID-19, cytokine storm can lead to ARDS which carries a 40% mortality rate [3]. Cytokines associated with cytokine storm include pro-inflammatory interleukin (IL)-6, IL-8, IL-1B, IL-12 and tumor necrosis factor (TNFx), while other cytokines, such as IL-10, have established anti-inflammatory effects and a role in downregulating excessive immune activity [2]. In COVID-19 specifically, cytokine storm is a significant factor in driving a more severe clinical course with patients requiring Intensive Care Unit admission showing higher levels of cytokines TNFα and IL-6 [3].

2. Search strategy

2.1. Research questions

1) What is the role of Echinacea in the prevention and treatment of COVID-19 and other respiratory tract infections?
2) Is there any evidence suggesting that Echinacea supplementation could increase the risk of cytokine storm in COVID-19 patients based on the changes in cytokine levels observed in human clinical trials?

2.2. Inclusion/exclusion criteria

1) Studies were included if they reported human prospective intervention studies sampling adults (aged 18 and over), and assessed the effect of Echinacea supplementation on the prevention or treatment of respiratory tract infections. Studies including pediatric populations were excluded.
2) Studies were included if they reported human prospective studies sampling adults, and assessed the effect of Echinacea supplementation on levels of cytokines which have been identified as playing a role in cytokine storm (interferons, interleukins, chemokines, colony-stimulating factors, tumor necrosis factors) or the incidence of cytokine storm or cytokine release syndrome.

2.3. Databases

Medline (Ovid), AMED (Ovid), CINAHL (EBSCO), EMBASE (Ovid)

2.4. Search terms (example) - clinical efficacy search

2.4.1. Medline (Ovid)

("Randomized Controlled Trials as Topic" OR randomized controlled trial/ OR Random Allocation/ OR Double Blind Method/ OR Single Blind Method/ OR clinical trial/ OR clinical trial, phase I/ OR clinical trial, phase II/ OR clinical trial, phase III/ OR clinical trial, phase IV/ OR controlled clinical trial/ OR randomized controlled trial/ OR multicenter study/ OR clinical trial/ OR Clinical Trials as topic/ OR (clinical adj trials$).tw. OR ((singl$ OR double$ OR treb$ OR tripb$) adj (blind$ OR mask$)).tw. OR PLACEBOS/ OR placebo$tw. OR randomly allocatedtw. OR allocated adj2 random$).tw.) NOT (letter OR historical article/) AND (Echinacea or Echinacea angustifolia or Echinacea purpurea or Echinacea or coneflower) AND ("avian influenza (H5N1)/ OR "influenza A (H1N1)/" OR Influenza A virus/ OR influenza C/ OR exp influenza/ or highly pathogenic avian influenza/ or Influenza B virus/ or highly pathogenic avian influenza virus/ or avian influenza virus/ or seasonal influenza/ OR "Influenza A virus (H1N1)/ OR Asian influenza/ or swine influenza/ or influenza A/ or
### Table 2
Summary of human studies examining effect of Echinacea spp. on cytokines.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country, Region</th>
<th>Study Design</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Control or Placebo</th>
<th>Total Number of Subjects, N in Intervention and Placebo</th>
<th>Change in Interleukins (IL)</th>
<th>Change in Interleukins (IL)</th>
<th>Other safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basset 2010</td>
<td>USA, Region of the Americas</td>
<td>Placebo, double blind RCT (2:1 arm)</td>
<td>1. Healthy, 18-60 yr old, both genders 2. Healthy, 18-60 yr old, both genders 3. History of respiratory tract infections in humans 4. A rapid review, Adv Integ Med (2020), <a href="https://doi.org/10.1016/j.aimed.2020.07.004">https://doi.org/10.1016/j.aimed.2020.07.004</a> 10 mL daily 4 weeks</td>
<td>1. History of severe immune disorder, malignancy or haematologic disorders 2. Obstructive pulmonary disease caused by other reasons (e.g., tuberculosis) 3. Other disease that known impact on disease recovery such as</td>
<td>Placebo n = 35 Echinacea n = 36 Echinacea + n = 37</td>
<td>No difference between Echinacea and placebo</td>
<td>No differences between groups in adverse effects (nausea, headache, diarrhea)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The table above summarizes human studies examining the effect of Echinacea spp. on cytokines. The studies listed include various populations, including healthy adults, COPD patients, and those with a history of respiratory tract infections. The inclusion and exclusion criteria vary across studies, but common factors include health status, age, and specific medical conditions. Outcomes are reported in terms of changes in interleukins (IL-2, IL-6, IL-8), TNFα, and other cytokines. Further details can be found in the referenced articles and original studies.
Table 2 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Country, Region</th>
<th>Sponsorship source/ association</th>
<th>Design</th>
<th>Study Population</th>
<th>Echinacea Spp</th>
<th>Dose</th>
<th>Duration of Treatment</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Control or Placebo</th>
<th>Total Number of Subjects, N in intervention and placebo</th>
<th>Change in interferons (IFN)</th>
<th>Change in interleukins (IL)</th>
<th>Other safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner 2005</td>
<td>USA, Americas</td>
<td>National Center for Complementary and Alternative Medicine of the NIH</td>
<td>DBPC RCT</td>
<td>Healthy volunteers exposed to rhinovirus experimentally</td>
<td>E. angustifolia root - 3 versions with supercritical fluid extraction, CO2, 60% ethanol or 20% ethanol</td>
<td>1.5 mL tincture containing 300 mg of echinacea root</td>
<td>Either 1/2 days before viral challenge (prophylaxis) or 2 days starting at time of viral challenge (treatment) for 5 days</td>
<td>1. Healthy young adults</td>
<td>2. Susceptible to rhinovirus type 39 (based on Ab testing)</td>
<td>alcohol beverage, denatonium benzoate and tap water</td>
<td>419</td>
<td>No difference between Ech and placebo</td>
<td>reported that 2% had adverse events, mostly GI related; no mention of immune issues</td>
<td></td>
</tr>
<tr>
<td>Kim 2002</td>
<td>USA, Americas</td>
<td>Celestial Seasonings Inc, Larex Inc, Lee Dexter and associates</td>
<td>DBPC RCT</td>
<td>healthy volunteers</td>
<td>E. purpurea and E. angustifolia</td>
<td>Standardized extract of E. purpurea (1500 mg) or E. P + A or larch</td>
<td>4 weeks</td>
<td>1. Healthy females</td>
<td>1. Major illness and/or acute illness at enrollment or during study period</td>
<td>alfalfa and rice</td>
<td>48</td>
<td>in each of the 6 groups</td>
<td>TNf</td>
<td>significant decrease from baseline in group taking ultra refined EPA (p = 0.04)</td>
</tr>
<tr>
<td>Weillar K. et al. 2006</td>
<td>Austria, European Region</td>
<td>The study was supported by A. Vogel/Bioforce AG, Switzerland</td>
<td>randomized, open label, crossover study, placebo controlled</td>
<td>Healthy adults</td>
<td>E. purpurea</td>
<td>4 mL E. purpurea (Echinaforce®) tincture or 12-150 mg E. purpurea (Echinaforce®) tablets.</td>
<td>&quot;Single dose (at 0, 24, 48 h)&quot;</td>
<td>1. Healthy adults</td>
<td>2. No special diet</td>
<td>alcohol or lactose with 300 mL water at 8:30 am after overnight fasting</td>
<td>10</td>
<td>8 tested for each intervention, 2 tested with placebo</td>
<td>TNF alpha in LPS pre-stimulated whole blood samples</td>
<td>Both forms led to a significant (p &lt; 0.01) decrease in production of TNF alpha and IL-8. No data reported on AE safety</td>
</tr>
<tr>
<td>Ritchie R. et al. (2011)</td>
<td>UK, European Region</td>
<td>This research was founded and sponsored by the researchers</td>
<td>open label, crossover study, ex vivo analysis</td>
<td>Healthy volunteers</td>
<td>E. purpurea</td>
<td>&quot;First 5 days: oral administration of 4 × 1-mL doses of E. purpurea at 8:30 a.m.; Days 6-10: oral administration of 2 × 1-mL doses per day;&quot;</td>
<td>1. Healthy adults</td>
<td>1. Use of any other medication during study periods</td>
<td>n/a</td>
<td>30</td>
<td>10</td>
<td>IL-18</td>
<td>&quot;No adverse events were observed&quot;</td>
<td></td>
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<tr>
<td>Study</td>
<td>Region</td>
<td>Type of Study</td>
<td>Subjects</td>
<td>Intervention</td>
<td>Follow-Up</td>
<td>Outcomes</td>
<td></td>
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<tr>
<td>Whitehead 2007</td>
<td>USA, Americas</td>
<td>Randomized study</td>
<td>Healthy adults</td>
<td>Echinacea purpurea (Purslane's Pride)</td>
<td>28 days</td>
<td>1. Healthy and active male students 2. Age 38-30 years 1. On medications or diet supplements 2. Using tobacco 3. Having signs/symptoms of cardiovascular or metabolic disease 4. Smoking and/or excess alcohol intake 5. Obesity 6. Taking any immunomodulating drugs (NSAIDs) 7. Acute or chronic disease, atopic diathesis, or acute infection in last month 8. No medications or diet supplements 9. No smoking and/or excess alcohol intake 10. No obesity 11. No taking any immunomodulating drugs (NSAIDs) 12. No acute or chronic disease, atopic diathesis, or acute infection in last month 1. Significant reduction in IL-6 in Echinacea group vs placebo (65% and 73% incr) p = 0.011 2. IFN-γ increased in Echinacea group vs placebo (65% and 73% incr) p = 0.011 3. No change in TNF-α production of monocytes cultured with LPS 4. No change in cytokine production of monocytes cultured with LPS</td>
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<td>Schwartz 2002</td>
<td>Germany, European Region</td>
<td>Double-blind, randomized, controlled crossover study</td>
<td>Healthy males</td>
<td>Echinacea purpurea, freshly expressed juice</td>
<td>34 days, washout, 14 days</td>
<td>1. Healthy men 2. Age 20-40 years 1. Acute or chronic disease, arthritic arthritis, or acute infection in last month 2. Taking any immunomodulating drug (NSAIDs) 3. Smoking and/or excess alcohol intake 4. Obesity 5. Taking any immunomodulating drug (NSAIDs) 6. Acute or chronic disease, arthritic arthritis, or acute infection in last month 1. No change in cytokine production of monocytes cultured with LPS 2. No change in cytokine production of monocytes cultured with LPS 3. No change in cytokine production of monocytes cultured with LPS 4. No change in cytokine production of monocytes cultured with LPS</td>
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<tr>
<td>Randolph 2003</td>
<td>USA, Americas</td>
<td>Randomized, controlled, crossover study</td>
<td>Healthy adults</td>
<td>Echinacea purpurea dry root extract</td>
<td>1518 mg/day</td>
<td>1. Adults aged 18-65 years 2. Non-smokers 3. Normally active 4. In good health based on interview and physical exam 1. No change in cytokine production of monocytes cultured with LPS 2. No change in cytokine production of monocytes cultured with LPS 3. No change in cytokine production of monocytes cultured with LPS 4. No change in cytokine production of monocytes cultured with LPS</td>
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<tr>
<td>Guzotto P. et al. 2008</td>
<td>Italy, European Region</td>
<td>Randomized, double-blind, placebo-controlled study</td>
<td>Healthy volunteers</td>
<td>Echinacea purpurea dry root extract</td>
<td>1518 mg/day</td>
<td>1. Abstinence from smoking, eating, and drinking until the last blood sample was taken 2. On a special diet 2. Smoking, eating, and/or drinking (other than water) 12 h before administration 3. Taking medicine 1 week before to the end 1.Increased steadily through day 12 in all subjects: 4. No change in cytokine production of monocytes cultured with LPS 5. IFN-γ expression increased</td>
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</tbody>
</table>
pandemic influenza/ or Influenza C virus/ or influenza B/ or avian influenza/ or Influenza virus or SARS or MERS or respiratory syndrome coronavirus or severe acute respiratory syndrome/)

2.5. Search terms (example) - cytokine search

2.5.1. Medline (Ovid)

((Randomized Controlled Trials as Topic/ OR randomized controlled trial/ OR Random Allocation/ OR Double Blind Method/ OR Single Blind Method/ OR clinical trial/ OR clinical trial, phase i. pt. OR clinical trial, phase ii.pt. OR clinical trial, phase iii.pt. OR clinical trial, phase iv.pt. OR controlled clinical trial.pt. OR randomized controlled trial.pt. OR multicenter study.pt. OR clinical trial.pt. OR exp Clinical Trials as topic/ OR (clinical adj trial$s$).tw. OR ((singl$S$ or doubl$S$ or treb$S$ or tripl$S$) adj (blind$S$ or mask$S$)).tw. OR PLACEBOS/ OR placebo$.tw. OR randomly allocated.tw. OR allocated adj2 random$S$).tw.) NOT (letter/ OR historical article)) AND (Echinacea or Echinacea angustifolia or Echinacea purpurea or Echinacea coneflower) AND (Cytokine$S$ or cytokine storm or cytokine release syndrome or chemokine$S$ or interferon$S$ or interleukin$S$ or tumor necrosis factor$S$ or colony-stimulating factor$S$)

2.6. Screening

Titles and abstract screening and full text screening were completed by one reviewer and checked for accuracy by a second reviewer. Similarly, data extraction was completed by a single reviewer and checked for accuracy by a second reviewer. Any discrepancies were resolved by consensus.

2.7. Critical appraisal

The risk of bias (RoB) of study findings was assessed using the revised Cochrane RoB tool for randomized trials (RoB 2) https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2?authuser=0.

2.8. Protocol registration

The protocol was registered with PROSPERO: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID = 186,339

3. Results

3.1. Clinical efficacy search

The search identified 382 results, including 85 duplicates. 297 citations were screened. After title and abstract reviews, 37 citations remained and 260 citations were excluded, as these did not meet the inclusion and exclusion criteria. The full-text of the remaining 37 articles were assessed for eligibility and 23 were excluded (wrong study design n = 20, duplicate n = 1, not accessible n = 1, wrong outcome n = 1). Three additional studies were identified through a bibliography search. A total of 17 studies underwent data extraction (Table 1).

Ten studies were conducted in the World Health Organization (WHO) region of the Americas, with five in the European region, one in the Western Pacific region and one in the South-East Asia region.

All 17 studies were double-blind, placebo-controlled, randomized clinical trials. One study had additional arms using open-label Echinacea and no treatment [4] and several studies had multiple arms comparing different Echinacea species, commercial formulas or doses [5–8]. Studies were designed to assess for the prevention
or treatment of ARI, primarily, the common cold. Six studies assessed the impact on prevention: four in normal daily life (duration 6–16 weeks), one in response to a strenuous exercise challenge (duration 4 weeks) [9] and one in response to long-distance air travel (duration 4 weeks) [10]. Two studies assessed the impact of *Echinacea* 7 days before and 5–7 days after a viral challenge [8,11]. Nine studies assessed the use of *Echinacea* for 5–14 days in the treatment of a new onset respiratory tract infection, one in patients with chronic obstructive pulmonary disease (COPD) who were administered antibiotics concurrently and the remaining were conducted in healthy adults [5]. In all 17 studies, participants were located in the community (i.e. not in-patient settings).

In total, the 17 studies included 3363 participants with a mean sample size of 224 participants (SD = 229, range: 32–755).

Eleven studies used intervention formulas containing *E. purpurea*, two used *E. angustifolia*, four used a combination of *E. purpurea* and *E. angustifolia*, and one used *E. pallidae* radix.

*Echinacea* dose and mode of extraction across all of the included studies were quite variable. Studies used different parts of the herb, including root, whole plant and aerial parts, as well as different methods of preparation. *Echinacea* interventions were delivered in the form of pressed juice, hydroalcohol extracts, capsules of dried herb and infusions. The lowest dose used was 100 mg of herb [12] while other studies used as much as 10.2 g per day in capsules on the first day of treatment [4]. Five studies reported using formulas that were standardized to include a specific amount of active constituent [6,12–14].

The studies assessed for ARI, viral respiratory infections or the common cold. The two studies that used a viral challenge administered rhinovirus 39 and monitored for the common cold [8,11].

The Cochrane Risk of Bias 2.0 assessment tool was used to evaluate the included studies. Of the six studies assessing prevention, four were rated low risk of bias [7,10,13,15] while two were rated high risk [9,16]. Among the two studies testing prevention and treatment in response to a viral challenge, one was rated moderate risk of bias [11] and one low risk of bias [8]. Among the nine studies assessing treatment of new onset infections, four were rated low [4,14,17,18], four rated high [5,6,19,20] and one was rated as having some concerns [12]. Reasons for a high risk of bias included per-protocol analysis [6,16], lack of description of dropouts [9], incomplete reporting of data [5,19], and lack of baseline data comparing the treatment groups [20]. One study terminated the study before recruiting the sample size needed to detect significance based on a power calculation completed midway through the study [11]. These judgments should be taken into consideration when interpreting the findings of this review.

3.2. Cytokine search

The search identified 100 results, including 26 duplicates. 74 citations were screened. After title and abstract reviews, 18 citations remained and 56 citations were excluded as these did not meet the inclusion and exclusion criteria. The full-text of the remaining 18 articles were assessed for eligibility and six were excluded (protocol only n = 1, incorrect outcome n = 2, duplicate data from included publication n = 1, unable to locate full text n = 1). A total of 12 studies underwent data extraction (Table 2).

Of these, five included healthy participants who consumed oral doses of *Echinacea* before blood levels of cytokines were measured [21–25]. Three studies included participants with respiratory tract infections [4,5,8] and four included healthy participants whose *in vivo* blood samples were stimulated and immune response observed [26,27,28,29]. The studies assessed cytokines including TNFα (n = 9), IL-1β, IL-2, IL-3, IL-6, IL-8, IL-10, IL-12 and Interferon (IFN)γ.

3.3. Summary of findings

3.3.1. Clinical efficacy

The six studies that administered *Echinacea* to healthy participants for two to four months and assessed prevention of naturally acquired upper respiratory tract infections (URIs), measured the frequency and/or duration of infections [7,9,10,13,15,16]. Five of these studies assessed infection frequency and of these, two reported a statistically significant reduction [10,13]. Three studies assessed duration of illness and of these, one reported a statistically significant decrease [9].

In the two studies that provided *Echinacea* supplementation before and after study-administered viral challenge, one reported no difference in infection frequency or severity compared to placebo [8].

The nine studies assessing the use of *Echinacea* at the onset of a URI measured infection duration and symptom severity [4–6,12,14,17–20]. All studies assessed for impact on symptom severity and five reported statistically significant reductions in symptom severity [4,6,14,19,20]. A sixth study, that included participants with COPD experiencing an acute exacerbation of respiratory symptoms, found a reduction in severity in response to

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Impact on Inflammation Levels and Cytokine storm (CS)</th>
<th>Studies reporting increased levels</th>
<th>Studies reporting no effect on levels</th>
<th>Studies reporting decreased levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα</td>
<td>Proinflammatory Key CS contributor</td>
<td>2 studies (5, 29)</td>
<td>7 studies (21-26)</td>
<td></td>
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<tr>
<td>IL-1β</td>
<td>Proinflammatory Key CS contributor</td>
<td>1 study (29)</td>
<td>2 studies (24, 27)</td>
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<tr>
<td>IL-6</td>
<td>Proinflammatory Key CS contributor</td>
<td>1 study (28)</td>
<td>3 studies (21, 25, 26)</td>
<td></td>
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<tr>
<td>IL-8</td>
<td>Proinflammatory Key CS contributor</td>
<td>1 study (26) and 1 study (28)</td>
<td>2 studies (4, 8)</td>
<td>4 studies (21, 24, 25, 28)</td>
</tr>
<tr>
<td>IL-12</td>
<td>Proinflammatory Key CS contributor</td>
<td>1 study (25)</td>
<td>1 study (25)</td>
<td></td>
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<tr>
<td>IFN-γ</td>
<td>Anti-inflammatory Role in regulating pro-inflammatory responses</td>
<td>1 study (23)</td>
<td>1 study (26)</td>
<td>1 study (21)</td>
</tr>
</tbody>
</table>

supplementation with Echinacea in combination with zinc, selenium and ascorbic acid but not for Echinacea alone [5]. Seven of the studies using Echinacea at URKI symptom onset assessed the duration of symptoms and five reported a statistically significant reduction in duration compared to participants receiving placebo [4,14,18–20].

With respect to risk of bias, of the ten studies that reported a positive outcome, five were rated as high risk of bias [5,6,9,19,20] and five were rated as low risk of bias [4,10,13,14,18].

Among the 13 studies that reported intervention dose with an equivalent dose of dry herb (or a liquid extraction and extraction strength), the mean dose was calculated. In cases where a range or variable doses were given, the highest doses was selected. The mean dose used in studies reporting benefit was 7.3 g per day (SD 6.4) and the mean dose used in studies that failed to detect benefit was 1.7 g per day (SD 2.1). The studies reporting benefit used E. purpurea (n = 6) or a combination of E. purpurea and E. angustifolia (n = 3) or E. pallidae radix (n = 1). Of the five studies using extracts with a standardized level of active constituents, four reported benefit. These active constituents included dodecateraenoic acid, isobutyrlamide, alkylamides, cichoric acid and soluble -1,2-o-fructofuranosides [6,10,12–14].

3.3. Cytokine search

Table 3 presents the number of studies showing statistically significant increases or decreases in different pro- and anti-inflammatory cytokine levels in response to Echinacea supplementation in 12 clinical trials.

None of the clinical trials included in this review reported occurrence of cytokine storm or other immune or inflammatory disturbance which could be attributed to the Echinacea intervention.

While seven studies did not report adverse events, the remainder reported few adverse effects, in most cases similar to the control group. One reported a serious reaction involving generalized erythema which resolved with anti-histamine treatment [5] and mild adverse events of which insomnia was the most common. Another reported primarily gastro-intestinal side effects [8] and another reported one case of anxiety and nervousness and a recurrence of bilateral arthritis symptoms which the patient had previously experienced [22].

3.4. Clinical significance

Echinacea supplementation may assist with the symptoms of ARI and the common cold, particularly when administered at the first sign of infection; however, no studies have been identified which use Echinacea in the prevention or treatment of conditions similar to COVID-19. When taken at the onset of symptoms, Echinacea may decrease the severity or duration of ARI.

Because the vast majority of studies involved participants who were free from serious or chronic illness, and without known issues related to immune function, it is not possible to infer what the role of Echinacea spp. could be in those at highest risk of COVID-19.

With respect to the impact of Echinacea on cytokine levels, the majority of evidence suggests a decrease in levels of pro-inflammatory cytokines associated with cytokine storm. While the potential for Echinacea to provide a clinical therapeutic benefit is speculative, animal studies using pharmaceuticals that decrease production of IL-1α, IL-6 and TNFα cytokines have increased survival of mice infected with severe influenza [2], and SARS-CoV [3]. Tocilizumab, an anti-IL-6 receptor antibody, is being studied in the treatment of cytokine storm in COVID-19 patients with elevated IL-6 levels [3]. Research of the use of Echinacea in cytokine storm may be warranted.

Disclaimer

This article should not replace individual clinical judgment. The views expressed in this rapid review are the views of the authors and not necessarily from the host institutions. The views are not a substitute for professional medical advice.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References


