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

Monique Aucoin[a,*], Kieran Cooley[a,b,c,d], Paul Richard Saunders[a], Jenny Carè[b], Dennis Anheyer[d,e], Daen N. Medina[b,f], Valentina Cardozo[a], Daniella Remy[a], Nicole Hannan[g], Anna Garber[a]

[a] *Canadian College of Naturopathic Medicine, Toronto, Ontario, Canada*
[b] *Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, New South Wales, Australia*
[c] *Pacific College of Health Sciences, San Diego, California, United States*
[d] *National Centre for Naturopathic Medicine, Southern Cross University, Lismore, Australia*
[e] *Department of Internal and Integrative Medicine, Kliniken Essen-Mitte, University of Duisburg-Essen, Essen, Germany*
[f] *Torrens University, Sydney, New South Wales, Australia*
[g] *Griffith University, Gold Coast, Queensland, Australia*

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ABSTRACT

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.

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

* Corresponding author at: Canadian College of Naturopathic Medicine, Toronto, Ontario, Canada.
E-mail address: maucoin@ccnm.edu (M. Aucoin).

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Table 1
Summary of studies examining the effect of *Echinacea* spp. on respiratory tract infections in humans.

Author	Country, WHO Region	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Statistical method (s)	Study Population / Disease or Condition	Echinacea spp, part of plant	Form of supplement (juice, tincture, capsule)	Extraction Strength and Standardization	Dose	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Number Subjects, N in intervention and placebo	Measure of Outcome	Outcome
Grimm W et al. (1999)	Germany, European Region	Madaus AG, Cologne/ Philipps-University of Marburg, Germany	DBPC RCT	* A priori measures * Fisher's exact test for b/line categorical variable & incidence of AEs * Mann-Whitney U test for continuous demographic variables, infection incidence/ severity/ duration * Nonparametric Mann-Whitney U to estimate CIs for infection no./duration (normal distribution assumed) * Hochberg procedure adjusted for multiple testing * SAS and SPSS for as randomized, ITT & PP populations * Log rank test (for ITT) for main outcome measure * All other data; Kruskal-Wallis and x2 tests for exploratory inference statistics	Patients from a large general practice	Echinacea purpurea, whole flowering plant (no roots)	Freshly expressed juice 22 % alcohol identical to the commercially available Echinacin-Liquidum	Not provided	4 mL 2x/day	8 weeks	1. More than 3 respiratory airway infections or common colds in the preceding year 2. At least 12 years old 3. Gave written informed consent for study participation	1. Acute infections of any kind within 1 week of recruitment 2. Pregnancy or nursing 3. Use of immunostimulating drugs in preceding 4 weeks 4. Known allergy against coneflowers 5. Severe underlying disease or immunosuppression 6. Inability to give informed consent 7. Unreliability for follow-up as judged by the investigator	Placebo (alcohol/ water solution with artificial colour)	108, Echin = 54 Placebo = 54	# participants with one infection Mean no. of infections/patient Infection severity Desire to continue supplement Duration of infection Adverse events	No difference No difference No significant difference No difference No significant difference No significant difference
Melchart D et al. (1998)	Germany, European Region	The Center for Complem-entary Medicine Research; Bavarian Parliament; Plantapharmazie, Gottingen, Germany; Medizinische Klinik, Technische Universitat, Biometrisches Zentrum fur Therapiestudien	DBPC RCT three-armed study		4 military institutions & 1 industrial plant.	Echinacea purpurea roots OR Echinacea angustifolia roots	Extract in 30 % alcohol	1:11	2.5 mL 2x/ day	12 weeks from Monday to Friday	1. 18–65 years 2. Free of acute illness at the time of enrollment 3. written informed consent for study participation	1. Acute respiratory tract infection or other infections within the last 7 days 2. Serious progressive disease such as tuberculosis, multiple sclerosis, or acquired immunodeficiency syndrome 3. Systemic intake of corticosteroids, antibiotics, or immunostimulants in the previous 2 weeks 4. Allergy to the Compositae family 5. Pregnancy	Placebo coloured ethanolic solution	302, E august = 103 (3 drop outs) E purp = 103 (4 drop outs) Placebo = 96 (6 drop outs)	Time until first URTI (time to event) Number of participants with at least 1 infection Patient assessment Adverse events	No difference No significant difference Treatment groups believed they had more benefit from treatment than placebo (P = 0.04) No difference in frequency of AE reporting
Hall H et al. (2007)	USA, Region of the Americas	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)	DBPC RCT parallel group design	ANOVA performed on test data & salivary tests. Post hoc (Least Sig. Diff; LSD) used for significant main effects. Interactions subjected to simple main effects analysis, followed by post hoc (LSD) analysis. Independent samples *t* -test used for URTI incidence & duration SPSSX used for all analyses.	Non-smoking, active adults 19–46 years subjected to strenuous exercise testing	Echinacea purpurea	Capsule containing pressed juice	1.7–2.5:1	8 capsules/ day (2 with each meal and bedtime); each 800 g juice	28 days	1. Successful assessment of a medical history, present health status, and 12-lead resting ECG 2. Healthy, habitually active subjects 3. Gave written informed consent for study participation	1. Cigarette smoking 2. Respiratory disease, or signs and symptoms of URTI the preceding week 3. Taking any medications and/or dietary supplements 4. Exhibited contraindications to strenuous exercise 5. If unable to distinguish between allergies from the symptoms of a URTI on a pre-study intake form	Placebo prepared in-house; gelatin caps: sugar mixture (sugar, sucrose, cornstarch, brown sugar, molasses)	32, Echin = 18 Placebo = 14	s-IgA concentrations, saliva flow rate, and secretion rate of s-IgA (pre- and post-exercise at baseline and after 28 days of intervention) Number of URTI symptoms duration of URTI symptoms	Baseline: significant exercise induced reduction in s-IgA in both groups (Control –69 %; Ech – 43 %) & secretion rate of s-IgA (Control – 79 %; Ech – 53 %) ($p < 0.05$) End: placebo grp experienced decrease in s-IgA compared to Ech group (Control –45 %; Ech +7%) & secretion rate of s-IgA (Control –45 %; Experimental –7%, p = 0.004). No difference Reported URTI duration significantly decreased (placebo 8.6 days vs. Ech 3.4 days, p =<0.001)

O'Neil et al (2008)	USA, The Region of the Americas	grant 5 D39 HP 00023–09 from the Health Resources and Services Administration Border Health Education and Training Center. Medication used was donated by Natures Resource.	DBPC RCT	A prospective power analysis was calculated. Wilcoxon rank sum test was used to compare the treatment and placebo groups for each of the 8 symptoms over 8 weeks; with max poss symptom days @56. Missing data from drop out precluded intention -to treat- analysis	Volunteers recruited from hospital personnel; This population was expected to have more equitable exposure to cold/influenza.	Echinacea purpurea, 300 mg			3 capsules 2x/day daily, 300 mg per capsule	8 weeks	1. Healthy adults working in the University Medical Center Family Health Center including residents, staff, faculty, and nursing staff 2. Responded to flyer voluntarily 3. Gave written informed consent for study participation 4. 18–65 years of age	1. Known immune dysfunction 2. Undergoing immunosuppressive therapy 3. Pregnancy or lactation 4. Currently using echinacea 5. Allergies to echinacea and/or parsley	Parsley, 300 mg per capsule	90, Enrolled Placebo: n = 45; Echinacea: n = 45. Completed Placebo: n = 30; Echinacea n = 28	Number of days during that week in which they experienced sore throat, runny nose, headache, hoarseness, nasal congestion, muscle aches, cough, and fever	No difference in total symptoms or any induvial symptom.
															Number of days missed from work	The median total number of sick days was 9.0 for the echinacea group and 14.0 for the placebo group (p = 0.67).
															Medications used to treat symptoms	3 capsules BID of 300 mg Echinacea (exp grp) or parsley (control grp) for 8 weeks (total = 1800 mg/day)
															Number of capsules missed that week	Significant differences between drop-outs/ nonadherent and those who completed the study. Persons not included in the final analysis used fewer vitamins and herbs (p < 0.1) or fewer allergies (p = 0.3)
Jawad et al (2012)	UK, European Region	Unclear, possibly the product manufacturer	DBPC RCT	Chi-squared	Healthy adults observed for common cold	Echinacea purpurea (A Vogel Echinaforce), 95% her, 5% root	Liquid	95 % herba (DER = 1: 12) and 5% roots (DER = 1: 11) standardized to contain 5 mg/100 g of dodecatetraenoic acid isobutylamide	Prevention: 0.9 mL/dose 3x/day (2400 mg of extrat per day); during acute stages of a cold: 0.9 m 5x/day (4000 mg extract)	4 months (Oct to Nov 2009)	1. Adults in good physical health 2. Experience 2+ colds per year	1. Ineffective contraception 2. Participating in another study 3. Pregnancy or lactation 4. Currently using cold or antimicrobial medication 5. Alcohol or drug abuse 6. Psychiatric disorder, epilepsy, or suicidal ideation 7. Planned surgery 8. Serious chronic disease that could affect absorption, metabolism, and/or elimination 9. AIDS or another autoimmune disease 10. Diabetes 11. Steroid-treated asthma 12. Medically-treated allergy/atopy 13. Allergy to echinacea	drops similar shape, colour, odor, taste	755, ech 355, placebo 362	Safety/adverse events	No difference in AEs
															Number of colds	Significantly fewer colds in the tx group vs placebo, and fewer recurring episodes ($P < 0.05$, chi-square test)
															Days of having a cold	cumulated events (episodes and episode days) was 26 % lower in tx grp ($P < 0.05$, chi-square test)
															Concurrent medication	significantly fewer (-52 %) cold episodes were additionally treated with pain medication ($P < 0.05$, chi-square test)
															Lab confirmed viruses in nasal secretions	Fewer total viral infections detected (not statistically significant) Strongest effect was seen with membranous viruses, like Corona-, Influenza-, Parainfluenza-, Respiratory Syncytial- and Metapneumovirus with 24 and 47 detected infections in the Ech/placebo groups ($P < 0.05$).
Tiralongo E et al. (2012)	Australia, Western Pacific Region	Manufacturers of the interventions funded two of the authors leveraged from and Australian Government grant / Griffith University, Australia. Conflict statement not made.	DBPC RCT	Nonparametric Kolmogorov-Smirnov test for median differences in independent samples. 2 × 2 chi-squared test of independence and the Odds Ratio. t-tests and chi-square tests	Passengers travelling from Australia to America, Europe, or Africa and back again on commercial flights, of 15–25 hours flying time and < 12 h stopovers	Echinacea purpurea, Echinacea angustifolia, root		standardised to 4.4 mg alkylamides	1 tablet per day before and after travel; 2 tablets per day during travel; 112.5 mg Echinacea purpurea 6:1 extract (equivalent to 675 mg) and 150 mg E. angustifolia	1–5 weeks depending on travel duration; Varied, from 5 weeks (if 7 days of travel) to 9 weeks (if 35 days of travel)	1.18–65 years of age 2. In good general health 3. Suffered from no previous or current serious illness	1. Presence of a known plant allergy 2. Suffering from respiratory diseases (e.g., asthma, COPD) 3. Suffering from any other condition that could compromise the study or the participants health (e.g., autoimmune disease, cystic fibrosis) 4. Received flu vaccination within 20 days of starting the	Manufactured to match the Echinacea tablets in size, excipient, and colour	175, Echinacea n = 88 Placebo n = 87	Wisconsin Upper Respiratory Symptom Survey (WURSS-44) to assess upper respiratory symptom-related quality of life, administered: baseline, post travel, 4 week follow up.	4 weeks post travel: no difference in WURSS-44 scores (P = 0.18). During travel: the placebo group had border line significantly higher WURSS-44 scores compared to the Ech group (26 versus 13, P = 0.05). Significantly reduced percentage of respiratory disorder symptom-affected participants in the

Table 1 (*Continued*)

Author	Country, WHO Region	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Statistical method (s)	Study Population / Disease or Condition	Echinacea spp, part of plant	Form of supplement (juice, tincture, capsule)	Extraction Strength and Standardization	Dose	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Number Subjects, N in intervention and placebo	Measure of Outcome	Outcome
									4:1 extract (equivalent to 600 mg)			trial 5. Pregnant, planning pregnancy, or lactating 6. On regular treatment with Echinacea, antibiotics, corticosteroids, antihistamines, and/or immunosuppressants			Frequency of illness	Echinacea group compared to placebo (43 % versus 57 %, P = 0.05) during travel. 4 weeks post travel: significantly 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)
															Adverse events	Reported by 2 participants (1 in each group) during the trial. After trial cessation 2 participants in the Echinacea group reported adverse events.
Turner 2005	USA, region of the Americas	National Center for Complimentary and Alternative Medicine of the NIH	DBPC RCT	6 pairwise comparisons with between groups using chi-square analysis. Multiple logistic-regression analysis including covariates	Healthy volunteers exposed to rhinovirus experimentally	E. angustifolia root - 3 versions with supercritical CO2, 60 % ethanol or 20% ethanol	tincture		1.5 mL tincture containing 300 mg of echinacea root 3x/day	Either 1) 7 days before viral challenge (prophylaxis) or 2) starting at time of viral challenge (treatment) for 5 days	1. Healthy young adults 2. Susceptible to rhinovirus type 39 (based on Ab testing)	1. Existing antibodies to test virus at screening or at day 0	alcoholic beverage, denatonium benzoate and tap water	419, 7 groups (different extraction methods for herb + prophylaxis vs treatment options)	Rate of infection	No difference in outcome
															Severity of symptoms	No difference in outcome
															Volume of nasal secretions	No difference in outcome
															Polymorphonuclear leukocytes	No difference in outcome
															Interleukins	No difference in outcome
															Virus titers	No difference in outcome
Sperber	USA, region of the Americas	Madaus Aktiengesellschaft.	DBPC RCT	treatment group difference by students t or x2 analysis	healthy adults infected with rhinovirus 39	E. Purpura, pressed juice of the above-ground plant parts	tincture, 22 % alcohol (EchinaGuard)		2.5 mL tid (no equiv given)	7 days prior and 7 days after viral challenge	1. Susceptible to rhinovirus (based on Ab testing)	1. Conditions that would affect susceptibility to colds 2. Taking medication know to affect symptoms being measured 3. Pregnancy or lactation 4. Clinical or lab signs of infection at baseline	matching placebo - same taste, smell, appearance	48, 24 in each	Development of infection by measuring increase in Abs or culture virus	No difference
															Symptom diary	Colds developed in more placebo cases, but not statistically significant 58 % (CI 37–78) vs 82% (CI 60–94)
Isbaniah F et al. (2011)	Indonesia, South-East Asia Region	The study was supported by Frutarom Switzerland Ltd.'/ University of Indonesia, Persahabatan Hospital Indonesia, Totzke Scientific Geneva Switzerland, Frutarom Switzerland Ltd Switzerland	DBPC RCT, three arm, parallel group, single centre trial	* Continuous data: mean SD, differences tested with parametric & non-parametric analyses * ANOVA & Kruskal–Wallis test for between-group differences * Paired *t* -test & Wilcoxon-signed rank test for within-group diff between time-points * Kaplan–Meier plots and log-rank tests used for time-to-event	COPD Patients	Echinacea purpurea (L.) Moench (EP), aerial parts	Capsule from dried pressed juice		500 mg (or with 10 mg zinc, 15 ug selenium and 50 mg ascorbic acid (EP+))	14 days; At enrolment 500 mg ciprofloxacin bid for 7 days Then randomized to take in addition: Placebo OR EP 1/day 2 wks OR EP + 1/day 2 wks	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. Gave informed	1. asthma, a severe immune system disorder, a malignancy or haematologic disorder, an obstructive pulmonary disease caused by other reasons (e.g. tuberculosis), or any other disease with known impact on disease recovery such as diabetes mellitus, congestive heart disorder, cardiomyopathy, arrhythmia, severe hypertension or hepatic cirrhosis 2. An increase of > / = 12 % of the pulmonary function after using a bronchodilator, severe clinical symptoms in addition to cor pulmonale and heart	Composition not stated	120, Placebo n = 35 EP n = 36 EP + n = 37 108 completed the trial and included in analysis	Duration of exacerbation	' . . . duration of the exacerbation . . . significantly shorter in the EP + as compared with the other two groups.' [Placebo vs EP + p = 0.021, EP vs Placebo p = 0.242, EP + vs EP p = 0.001]
															CD4, CD8, TNF alpha, interleukins (IL) 1b, 6, and 10 before and after treatment	Significant differences in IL 1b (p = 0.106), IL6 (p = 0.253), IL10 (p = 0.234), CD8 abs (p = 0.182), CD8 rel (p = 0.266) found.
															Use/amount of bronchodilators during treatment	No difference
															Adverse events	'Study medication was safe and well tolerated with overall 15 adverse events one of which was serious. Among those, sleeping disorders were most frequent and likely related to the

											consent for study participation	failure, utilization of extra respiratory muscles, and oxygen dependence 3. Requirement for treatment with steroids or non-steroid anti-inflammatory drugs 4. Pregnancy or lactation 5. Hypersensitivity to Echinacea or ciprofloxacin				underlying disease.' (no statistical analysis completed)
Barrett BP et al. (2002)	USA, The Region of the Americas	U.S. Dept Health & Human Services and NIH, Shaklee Tecnica provided the products and monetary support (no role in design, conduct, reporting or submission for publication).	DBPC RCT	Frequency analysis, ANOVA, multivariate analysis, bootstrap resampling to calculate means and CIs, Cox multivariable proportional hazard regression. Study may be slightly underpowered: 150 participants provided at least 80 % power to detect a benefit of 2 days' duration. 148 participants enrolled, 142 completed and data presented for 142.	University student population, asked to make contact at first sign of cold/flu symptoms	E.angustif. root (50 %) and E. purp herb (25 %) and root (25 %) Additional ingred: 49 mg thyme, 31 mg pepper-mint, 3 mg citric acid	capsule		4 capsules 6 or 3 times per day (first day and subsequent days) Total of 6 g and 3 g Ech	Up to 10 days * In first 24 h (6 g Echinacea) * Thereafter (3 g Echinacea) until symptoms resolved or max 9 days	1. At least 18 years of age 2. Answer "Yes" to "Do you believe that you are coming down with a cold?" 3. Report at least 2 of 15 listed cold symptoms (at least 1 of which had to be in the respiratory tract) 4. Able & willing to adhere to the study protocol	1. Reported having any listed symptom for >36 h 2. Pregnancy 3. Currently using antibiotics, antihistamines, or decongestants 4. Had specified chronic diseases (autoimmune disease, chronic bronchitis, HIV infection, lupus, rheumatoid arthritis) at time of enrolment 5. History of asthma or allergic rhinitis and corresponding symptoms (itchy eyes, sneezing, wheezing) at the time of enrolment	Capsule: 333 mg alfalfa	148, Enrolled: Echin n = 73 Placebo n = 75 Completed: Echin n = 69 Placebo n = 73	Duration of illness Severity of 15 symptoms: productive cough, dry cough, cough impacting sleep, sore throat, hoarseness, scratchy throat, runny nose, plugged or stuffy nose, sneezing, headache, fever, sweats, muscle aches, loss of appetite, and feeling "run down" Global severity of illness	No difference No significant differences No difference
Dorn M et al. (1997)	UK/ Germany and UK; European region	Sponsorship not stated	DBPC RCT	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 & overall symptom scores	Consecutively seen patients in a family clinic with a clinical indication of URTI	Echinaceae pallidae radix	90 drops of liquid (no details of extraction method), in divided doses (not elaborated)		extract equivalent to 900 mg of Echinaceae pallidae radix per day	8–10 days	1. Clinical indication of URTI 2. Over 18 years 3. Total symptom score greater than 15	1. Ill for longer than 3 days prior to entry 2. Infection involving other organs 3. Treatments with drugs that may interfere with intervention 4. Presence of other significant diseases such as multiple sclerosis or polyarthritis 5. Suffering from pneumonia or fungal infections	Coloured aqueous alcoholic solutions mimicking & indistinguishable from verum treatment	160, Echin n = 80 Placebo n = 80	Duration of illness Clinical symptoms score Overall Symptoms	Illness days significantly lower in Echin group cw placebo for both bacterial and viral infections ($p < 0.0001$) significantly lower in Ech vs placebo ($p < 0.001$ in abstract) Significantly lower ($p < 0.0004$)
Goel V et al. (2005)	Canada, The Region of the Americas	3 authors were employed by the company suppling the intervention/ placebo which was also the sponsor	DBPC RCT	* Summation of daily symptom scores * Blood parameters computed by Students t-test (paired and unpaired) * SOD activity & neutrophil index computed by % change from baseline values, ANOVA using type 3 error were compared * Pearson correlation coefficients between symptom scores	Volunteers recruited through media ads in Edmonton and surrounding areas; at onset of cold	E. purpurea various parts, proprietary product Echinilin™	Concentrated water–ethanol extraction, purified to >95 % (verified), combined in 40 % ethanol to give	standardized alkamides/ cichoric acid/ polysaccharides at concentrations of 0.25/2.5/25.5 mg/mL	5 mL doses taken 8x on the first day, followed by 3x per day for the next 6 days	7 days, Day 1 throughout/ day Days 2–7 as above Doses diluted in half a glass of water. Participants instructed not to take other medication during treatment	1. Adults over 18 years 2. History of 2 or more common cold infections in the previous year	1. Vaccinated against influenza in the past 6 months 2. Had multiple sclerosis, tuberculosis, diabetes, cancer, lupus, asthma, fibromyalgia, HIV/ AIDS or cardiovascular disease 3. Were on immunosuppressive drugs such as corticosteroids or cyclosporin 4. Participants who used concomitant relief medication on a regular basis during study period (excluded from analysis)	Placebo contained similar ingredients, without the echinacea	62, Echin n = 25 Placebo n = 31 completed the study and did not use meds; 150 recruited, 62 caught cold, 6 used rescue medication (1 in ech, 5 in placebo)	Total symptom severity score (sore throat, runny nose, sneeze, stuffy nose, headache, achy muscles, hoarseness and cough)	Echin group demonstrated significantly lower scores by day 4 compared to placebo group, which was significantly lower by day 7 ($p < 0.05$). No significant effects on the distribution of CD3+, CD8+ and CD20+ cells. Decrease in CD4+ cells on day 3 ($p = 0.01$) and increase in the CD16+ (NK cells) on day 8 ($p = 0.05$) of echinacea treatment group. Both groups increased erythrocytic Cu Zn SOD activity

Table 1 (*Continued*)

Author	Country, WHO Region	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Statistical method (s)	Study Population / Disease or Condition	Echinacea spp, part of plant	Form of supplement (juice, tincture, capsule)	Extraction Strength and Standardization	Dose	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Number Subjects, N in intervention and placebo	Measure of Outcome	Outcome
Yale et al. (2004)	Canada, The Region of the Americas	Marshfield Clinic Research Foundation	DBPC RCT	and WBC differentials *Symptom scores were summarized with means of the 4-point severity scale *The Kaplan-Meier method was used to construct curves for time to symptom resolution in each group. *Brookmeyer and Crowley for median time to resolution *The Wilcoxon rank sum test was used to compare the time to resolution between the 2 groups.	Patients were recruited from the Marshfield Clinic system through advertisement in the Marshfield Clinic staff newsletter and through advertisements in local newspapers	E purpurea, aerial portion	freeze-dried pressed juice	standardized for a content of 2.4 % soluble -1,2-D-fructofuranosides	100 mg 3x/ day	Up to 14 days, 1 capsule 3 times daily for as long as their symptoms remained (max 14 days)	1. 18 years or older 2. Having acute sneezing and nasal discharge, with or without fever, occurring no less than 6 h and no longer than 24 h before enrollment 3. Free of cold symptoms and fever (temperature, 38.1 °C) for at least 2 weeks before enrollment 4. Having at least 2 of the following symptoms: sneezing, nasal discharge, nasal congestion, muscle aches, headache, sore or scratchy throat, hoarseness, or cough 4. No other primary sources of infection, including acute bacterial sinusitis, otitis media, and pneumonia 5. Using a reliable method of contraception, if a woman of childbearing age 6. Able to read, write, and understand English 7. Available for the 2-week period of the study 8. Gave written informed consent for study participation	1. Hypersensitivity to Echinacea or a history of allergy to plants of the Compositae family 2. Received antibiotics, antihistamines, decongestants, nasal sprays, or corticosteroids in the 48 h before enrollment 3. Used corticosteroids during the 8 weeks before enrollment 4. Had rales or rhonchi suggestive of a lower respiratory tract infection 5. History of allergic rhinitis due to seasonal allergy or ubiquitous environmental allergy 6. Bronchitis or sinusitis during the previous month 7. Had fever (temperature >/ = 38.1 °C) 8. Pregnancy or breastfeeding 9. Unable to complete a diary 10. Had an underlying immunodeficiency, renal failure (serum creatinine level 2.0 mg/dl [176.8 μmol/ L]), known bacterial infection, liver disease, eczema or allergic rhinitis, diabetes mellitus, congestive heart failure, or clinically active neoplastic disease 11. Had emphysema, asthma, or another chronic lung disease 12. Positive screening results for group A streptococcal pharyngitis 13. Active dependency on alcohol or other drugs 14. Known psychiatric disorders that might reduce the likelihood of successful completion of the protocol	lactose placebo capsule	128, Echinacea Group n = 63; Placebo n = 65	Symptom severity Time to resolution of symptoms Adverse events	No difference No difference Few adverse events were reported, with headache and dry mouth being the predominant adverse effects in both treatment groups
Goel V et al. (2004)	Canada; The Region of the Americas	Participants paid an honorarium on completion of the study.	DBPC RCT	*Repeated measures ANOVA with log transformation to adjust for	Volunteers were required to be in good general health, and to have	E. purpurea various parts, proprietary product Echinilin™	*water ethanol extraction of various parts Echinacea	standardized alkamides/ cichoric acid/ polysaccharides at concentrations	5 mL dose; 8 doses on first day, 3 doses on	7 Days	1. Volunteers aged 18−65 years 2. In good general health	1. Vaccinated against influenza in the past 6 months 2. Allergy to ragweed 3. Had multiple	placebo was made to look, taste, and smell like the echinacea extract but	282 enrolled, 128 caught a cold Echinacea n = 59 Placebo	Symptom severity	Mean severity scores (mean of 7 days) for all specific symptoms, except for cough, were found to be

				Type 3 error for interaction effects *one-way ANOVA for treatment effects *Pearson correlation for group differences.	contracted at least two infections of a cold in the past year; Start at onset of a cold		purpurea 40 % ethanol: 10 doses the first day, distributed equally throughout the day, followed by four doses per day for the next 6 days.	of 0.25/2.5/25.5 mg/mL	subsequent days		3. Contracted at least 2 infections of a cold in the past year 4. Responded to media advertisements and screened by phone 5. Gave written informed consent for study participation	sclerosis, tuberculosis, diabetes, cancer, lupus, asthma, fibromyalgia, HIV/AIDS, or cardiovascular disease 4.Taking immunosuppressive drugs such as corticosteroids or cyclosporine 5. Pregnancy and lactation	contained no detectable alkamides, cichoric acid, or polysaccharides.	n = 69 Total n = 128;	Duration Total daily symptom scores	significantly ower in the echinacea group ($p < 0.05$). (ITT and PP) PP analysis: the overall mean severity scores for runny nose, sore throat, stuffy nose, fatigue, headache, and chills, were found to be 27, 25, 22, 31, 39 and 44 % ($P < 0.05$) lower in the echinacea than in placebo, respectively. Illness resolved in 95 % of the subjects in the echinacea group by day 7 and only 63 % of the placebo ($p < 0.5$) Day 4, 50 % of the subjects in the echinacea (PP) group showed at least a 50 % reduction of their maximum TDSS
Schulten et al (2001)	Germany; European region	Madaus AG	DBPC RCT	*adaptive design with an interim analysis combined with a multiple testing procedure for a closed family of hypotheses, controlling the multiple a-level of 5 %, *interim analysis was intended to lead to either early termination in case of sufficient or missing treatment effects or continuation with a second independent trial step using the adaptively calculated sample size *3 priori : 1) days ill, 2) patients ill, 3)AUC for the modified Jackson score *Fisher's exact test	Adult male or female patients, employees of a German pharmaceutical company presenting with first sign s of URTI	Echinaceae purpureae (Ecbinacin, EC31J0 extract)	pressed juice, stabilised by ethanol	1.7–2.5: 1	5 mL 2xday	10 Days	1. Had an incipient infection of upper respiratory tract (subjective sensation of having a cold) 2. At least one of the following symptoms: sneezing, rhinorrhea, congestion of the nose, sore throat, cough, headache, malaise, or chilliness during previous 24 h	1. Acute respiratory tract infection during the week preceding the trial 2. Allergy to composites 3. Progressive systemic diseases (e.g. tuberculosis, multiple sclerosis, AIDS, HIV infections, other auto-immune diseases) 4. Pregnancy and lactation 5. Therapy with immunosuppressants in the week prior to the trial and during participation 6. Therapy with immunostimulants (herbal immunostimulants, cytokines, thymus fractions) 7. Zinc or antibiotics during two weeks before commencement of the trial	placebo	80, EC31J0 n = 41 Placebo n = 39	Duration of illness and Jackson score Severity of illness Patients who had developed a complete picture of a common cold Area under the curve (AUC) standardised to baseline with regard to the modified lackson score	Ech group: median time of illness was 6.0 days compared to 9.0 days; mean Jackson score decreased more rapidly in the Ech group than in the placebo group ($p = 0.01$) 61.0 % of the patients in the verum group assessed subjectively that their cold was "shorter than usual" compared to 28.2 % in the placebo group (two-sided $p = 0.007$) No statistically significant differences Fewer in Ech group (85.4 %) versus placebo (97.4 %); not statistically significant (Fisher's exact test: one-sided $p = 0.062$) AUC was smaller in the verum group (mean: 36.18, SD: 22.12) than in the placebo group (mean: 51.63, SD: 32.51), indicating a beneficial impact of the active treatment (one-sided $p = 0.008$)
Barrett 2010	USA, region of the Americas	National Center for Complimentary and Alternative Medicine of the NIH	4 ar m RCT, no treatment, placebo (blind), ech (blind), open label ech	* predecessor instrument WURSS-21 for a priori power calculations *Box–Cox transformation for skewed distribution *t test and the Mann–Whitney U test for group comparisons * general linear model for treatment effects	new-onset common cold, age 12–80 years	Mediherb tablets containing E. purpurea and E. anguslifolia; root	tablets		10.2 g of dried echinacea first 24 h, 5.1 g during next 4 days	5 days	Symptoms of cold in past 36 h with score of 2 or higher on Jackson criteria Must be min of 12 yrs and have parental permission if under 18.	istory of allergic rhinitis who reported sneezing or itching of the nose or eyes and those with a history of asthma who reported current cough, wheezing, or shortness of breath, pregnant, or history of auto-immune disdease or immune deficiency disease	inert ingredients	713, No pill group n = 173 Unblinded Echinacea Group n = 181 Blinded Placebo Group n = 176 Blinded Echinacea Group n = 183	Area-under-the-curve global severity, based on the Wisconsin Upper respiratory symptom survey Area-under-the-curve duration, based on the Wisconsin Upper respiratory symptom survey Psychosocial questionnaire Biomarkers of immune response and inflammation	Significantly lower in blinded and open-label echinacea Significantly lower in blinded and open-label echinacea No difference Not statistically significant
Lindenmuth GF et al (2000)	USA, Region of	Products donated by Traditional Medicinals®, Inc./	DBPC RCT although alternating	Means and standard	Nursing home employees, enrolled to the	E. purpurea and E. angustifolia;		(6:1)	equivalent to 1275 mg of dried	5 days of treatment, Drink 5–6	1. Nursing home employees	1. Pregnancy or breastfeeding 2. Known allergies to	Eater's Digest tea (ginger, cinnamon,	95, Echinacea n	Relief of symptoms	Significant difference in symptom relief Ech mean = 4.125, SD 5

Table 1 (*Continued*)

Author	Country. WHO Region	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Statistical method (s)	Study Population / Disease or Condition	Echinacea spp. part of plant	Form of supplement (juice, tincture, capsule)	Extraction Strength and Standardization	Dose	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Number Subjects, N in intervention and placebo	Measure of Outcome	Outcome
	the Americas	Rest Haven-York and York College of Pennsylvania. Conflict statement not made	assignment was used	deviations, *t* -test	study at the earliest symptoms of cold or flu: runny nose, scratchy throat, fever, etc	Leaves, flowers, and stems of plant			herb and root per tea bag - 5–6 cups per day	cups on the first day of symptoms titrating to 1 cup by the fifth day.		coneflowers or claiming to be allergic to many different flowering plants and pollens 3. Having acute infections and already taking antibiotics	peppermint, fennel seed, papaya leaf, rosehip, alfalfa leaf that 'at higher dosage. . . . might have an effect but in included amounts serve the purpose of flavor correctives.'	= 48 Placebo n = 47	Duration of symptoms	0.9593 Placebo mean = 2.787, SD 5 0.9541; t 5 6.814; p = 0.001 Significant difference in number symptom days Ech mean 5 4.333, SD 5 0.9302. Placebo mean = 2.340, SD 5 1.088; t 5 9.499; p = 0.001. Significant difference in days taken for relief of symptoms. Ech mean = 3.854, SD 5 0.9735 Placebo mean = 2.297, SD 5 1.204; t 5 6.865; p = 0.001. No side effects were reported by any of the subjects
															Days taken for relief of symptoms	
															Adverse events	

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 (TNF)α, 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.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$).tw. OR ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. OR PLACEBOS/ OR placebo$.tw. OR randomly allocated.tw. OR allocated adj2 random$).tw.) NOT (letter/ OR historical article/)) AND (*Echinacea* or *Echinacea angustifolia* or *Echinacea purpurea* or Echinace 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.

Author	Country, WHO regio	Sponsorship source/ association	Design	Study Population	Echinacea Spp	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects, N in intervention and placebo	Change in interferons (IFN)	Change in interleukins (IL)	Other safety outcomes
Barrett 2010	USA, Region of the Americas	National Center for Complementary and Alternative Medicine (NCCAM) f the National Institutes of Health (NIH). MediHerb provided the products and conducted phytochemical analysis but did not contribute financially	Placebo controlled RCT (4 ar m)	New onset common cold in people age 12–80	Extracts of E. purpurea and E. Angustifolia root	10.2 g of dried echinacea root first 24 h, 5.1 g during each of the next four days; 675 mg *E. purpurea* root standardized to 2.1 mg alkamides and 600 mg *E. angustifolia* root standardized to 2.1 mg alkamides	5 days	1. At least 1 of 4 symptoms (nasal discharge, nasal obstruction, sneezing or sore throat) 2. Score of 2 or higher on Jackson criteria	1. Use of antibiotics, antivirals, nasal steroids, decongestants, antihistamines, combination cold formulas, echinacea, zinc or vitamin C. 2. History of allergic rhinitis who reported sneezing or itching of the nose or eyes 3. History of asthma who reported current cough, wheezing or shortness of breath 4. Self-reported autoimmune and/or immune deficiency diseases 5. Pregnancy	Visual matched placebo containing identical amounts of exipients (calcium acid phosphate, cellulose, silica, sodium starch glycollate, hypromellose and magnesium stearate)	713 173 (no pill), 176 (blinded placebo), 183 (blinded Echinacea), 181 (unblinded Echinacea)	IL-8 in nasal rinse	No difference between Ech group and placebo	No differences between groups in adverse effects (rash, nausea, headache, diarrhea)
Dall'Acqua 2015	Italy, European Region	Farmaderbe, Pradamano (Udine) and Indena S.p.A. (Milan, Italy) for providing product	Open label	Healthy adults, both genders	Echinacea angustifolia	10 mg of lipophilic extract containing 1 mg of isolate dodeca-2E,4E,8Z,10E/Z-tetraenoic isobutylamides	Single dose	1. Healthy 2. Fasting at baseline	1. Dietary restrictions 2. Allergy to Compositae or Grossulariacee plants 3. Abnormal liver function 4. Use of medicines during the study	n/a	10	IL-2 IL-6 IL-8 IL-10 TNFα	Significant decrease from baseline $p < 0.05$ Significant decrease from baseline $p < 0.001$ Significant decrease from baseline $p < 0.001$ Increase from baseline $p = 0.001$ Statistically significant reduction $p = 0.002$	There was no reporting regarding adverse events
Dapas 2014	Italy, European Region		Open label pilot study; some ex vivo analysis	Healthy adults both genders	Echinacea angusifolia (triple standardized extract syrup Polinacea®)	10 mL daily	4 weeks	1. Healthy 2. No dietary restrictions 3. Fasting at baseline	1. Dietary restrictions 2. Allergy to Compositae or Grossulariacee plants 3. Abnormal liver function 4. Use of medicines during the study	n/a	10	Plasma IL-2 mRNA Plasma IL-6 mRNA Ex vivo lympohocyte IL-8 Ex vivo lympohocyte RNA TNFα	Increased ($p = 0.002$) Decreased ($p = 0.02$) Increased ($p < 0.001$) Decreased ($p = 0.02$)	No data reported on AE
Isbaniah F et al. (2011)	Indonesia, South-East Asia Region	The study was supported by Frutarom Switzerland Ltd.'/ University of Indonesia, Persahabatan Hospital Indonesia, Totzke Scientific Geneva Switzerland, Frutarom Switzerland Ltd Switzerland	DBPC RCT, three arm, parallel group, single centre trial	COPD Patients	Echinacea purpurea (L.	500 mg Echinacea purpurea (L.) Moench (EP), from dried pressed juice of the aerial parts or 500 mg EP with 10 mg zinc, 15 ug selenium and 50 mg ascorbic acid (EP +)	14 days; At enrolment 500 mg ciprofloxacin bid for 7 days Then randomized to take in addition: Placebo OR EP 1/day 2 wks OR EP + 1/day 2 wks	1. At least 40 years of age 2. Existing chronic obstructive pulmonary disease 3. An acute exacerbation episode (non-gradual increase	1. Asthma, severe immune system disorder, malignancy or haematologic disorder, obstructive pulmonary disease caused by other reasons (e.g. tuberculosis), or any other disease with known impact on disease recovery such as	Composition not stated	120 randomized 108 completed the trial and included in analysis Placebo n = 35 Echin n = 36 Echin + n = 37	Chemokines IL-1B IL6	No difference between Ech and placebo No difference between Ech and placebo No difference	one serious AE in ech grp: generalized erythema, resolved with antihistamine tx; mild Aes more common in ech grp, most common was insomnia

Table 2 (*Continued*)

Author	Country, WHO regio	Sponsorship source/ association	Design	Study Population	Echinacea Spp	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects, N in intervention and placebo	Change in interferons (IFN)	Change in interleukins (IL)	Other safety outcomes
								in at least 1 of the 3 major symptoms of dyspnea, sputum production and sputum purulence) supposedly caused by an acute infection 4. Gave written informed consent for study participation	diabetes mellitus, congestive heart disorder, cardiomyopathy, arrhythmia, severe hypertension or hepatic cirrhosis 2. An increase of >/ = 12 % of the pulmonary function after using a bronchodilator, severe clinical symptoms in addition to cor pulmonale and heart failure, utilization of extra respiratory muscles, and oxygen dependence 3. Requirement for treatment with steroids or non-steroid anti-inflammatory drugs 4. Pregnancy or lactation 5. Hypersensitivity to Echinacea or ciprofloxacin			IL10	between Ech and placebo No difference between Ech and placebo	
Turner 2005	USA, Americas	National Center for Complimentary and Alternative Medicine of the NIH	DBPC RCT	Healthy volunteers exposed to rhinovirus experimentally	E. angustifolia root - 3 versions with supercritical CO2, 60 % ethanol or 20 % ethanol	1.5 mL tincture containing 300 mg of echinacea root	Either 1) 7 days before viral chanllenge (prophylaxis) or 2) starting at time of viral challenge (treatment) for 5 days	1. Healthy young adults 2. Susceptible to rhinovirus type 39 (based on Ab testing)	1. Existing antibodies to test virus at screening or at day 0	alcoholic beverage, denatonium benzoate and tap water	419 7 groups (different extraction methods for herb + prophylaxis vs treatment options)	IL-8	No difference between Ech and placebo	reported that 2% had adverse events, mostly GI related; no mention of immune issues
Kim 2002	USA, Americas	Celestial Seasonings inc, Larex inc, Lee Dexter and associates	DBPC RCT	healthy volunteers	E. purpura and E. angustifolia	Standardized extact of E. purpura (1500 mg)or E. P + Ang OR ultra-refined EP + A (or larch arabinogalactan or Ech + larch)	4 weeks	1. Healthy females	1. Major illness and/or acute illness at enrollment or during study period 2. Taking immune-enhancing/altering supplements and/or medications	alfalfa and rice	48 8 in each of the 6 groups	TNFα	significant decrease from baseline in group taking ultra refined EPA (p = 0.04)	1 reported anxiety, nervousness and ht palpitations; 1 reported bilateral arthritic symptoms
Woelkar K. et al, (2006)	Austria, European Region	The study was supported by A. VogelBioforce AG, Switzerland.	randomized, single-dose, crossover study, placebo controlled	Healthy adults both genders (30.2 ± 3.6 (SD) years of age with abody mass index (BMI) of 22.3 ± 2.7 (SD))	E.purpurea	4 mL E.purpurea (Echinaforce®) tincture or 12 × 150 mg E. purpurea (Echinaforce®) tablets. *Echinaforce® = hydro-alcoholic extract made from Echinacea purpurea, 95 % herb and 5% roots. (Both doses contained the same amount (0.07 mg) of the major alkamides, dodeca-2E,4E,8Z,10E/Z-tetraenoicacid isobutylamides)	*Single dose (at 8:30a.m. after over-night fasting) *1-week washout period between administrations of 1 of the 2 different formulations.	1. Healthy adults 2.No special diet 3. Obliged to refrain from caffeine, alcohol and grapefruit juice 12 h before administration	1.Any progressive systemic illness including HIV, hepatitis B or C, tuberculosis, leukemia, connective tissue diseases, multiple sclerosis or other autoimmune diseases 2. History of relevant allergy, including allergy to plants of the species Compositae 3. Pregnancy	alcohol or lactose with 100 mL water at 8:30a.m. after over-night fasting	10 8 tested for each intervention, 2 tested with placebo	IL-8 TNF alpha in LPS pre-stimulated whole blood samples	Both forms led to a significant ($p < 0.01$) decrease in production in LPS pre-stimulated whole blood samples Both forms of medication, tincture and tablets, led to a significant ($p < 0.001$) decrease	No data reported on AE/safety
Ritchie M.R. et al (2011)	UK, European Region	This research was founded and sponsored	open label study; ex-vivo analysis	*Healthy subject with 2+ colds per year;	E.purpurea	*First 5 days: oral administration of 4 × 1-ml doses of	*10 days per study period (i.e. the stressful period and	1. Healthy adults 2. Aged 18–57 years 3. ≥ 2 colds	1. Use of any other medication during study periods	n/a	30 30 (but 2 subjects were	TNFα IL-1B	Decreased ($p < 0.05$)	"No adverse events were observed

		by A. Vogel, Bioforce AG, Switzerland	in reponse to LPS/SEB or Zymosan stimulation	subjects were studied once during a period of increased stress (during academic examinations) and again 5 weeks later)		Echinaforce® per day. *Following 3 days: oral administration of 10 × 1-ml doses of Echinaforce® per day. *Echinaforce® = hydro-alcoholic extract made from Echinacea purpurea, 95 % herb and 5% roots.	the non-stressful period). *2 days of baseline measurements followed by 5 days of 4 × 1 ml dose, followed by 3 days of 1 X 10 ml dose.	per year (not explicitly stated as inclusion criteria) 4. Experiencing heightened stress due to academic examination (assessed by the perceived stress score-10 questionnaire)	2. Vigorous physical activity during study periods 3. Excessive drinking or smoking during the study periods		excluded from the analysis for not strictly adhering to protocol)	IL-10 IL-8 in subgroup with low pre-treatment levels of IL8 IFN-y	significantly reduced from baseline ($p < 0.05$) increased from baseline ($p < 0.05$) significant stimulation of these factors upon treatment (30–49 % increases; $p < 0.05$) Increased in these levels in subgroup of subjects with low ($p < 0.05$)	aside from reddening of the skin at the puncture site"
Whitehead 2007	USA, americas	unclear	randomized-match, double-blind (first 12 randomized, rest assigned to make balanced groups base don baseline RBC count)	health adults	E. purpura (Puritan's Pride)	8000 mg/day	28 days	1. Healthy and active male students 2. Aged 18–30 years	1. On medications or diet supplements 2. Using tobacco 3. Having signs/ symptoms of cardiovascular or metabolic disease	wheat flour; both goups took a multi vitamin	24 12 Ech, 12 placebo	IL-3	increased at day 14 and 21 in ech group vs placebo (65 % and 73 % incr) $p = 0.011$	nothing reported
Schwarz 2002	Germany, European Region	Supported by equally distributed grantsfrom Shaper & Bruemmer and two of the authors (C. Bode andJ. C. Bode)	double blind placebo controlled cross over	healthy males	E. purpura, freshly expressed juice ; identical to the commercially available ESBERITOX mono ofSHAPER & BRUEMMER (Salzgitter, Germany)	not specified	14 days, washout, 14 days	1. Healthy men 2. Aged 20–40 years	1. Acute or chronic disease, atopic diathesis, or acute infection in last month 2. Taking any immunomodulating drugs (NSAIDs) 3. Smoking and/or excess alcohol intake 4. Obesity	control liquid	40	IL-1B TNFα production of monocytes cultured with LPS	no change in production No difference between Ech and control	not reported
Randolph 2003	Usa, americas	unclear	open label study	healthy adults	NUTRILITE Triple Guard Echinaceatablets	1518 mg/day	1518 mg for 2 days, 506 mg on third day	1. Adults aged 18–65 years 2. Non-smokers 3. Normally active 4. In good health based on interview and physical exam	None	None	6	gene expression of IFN-a2 IL-1B, gene expression IL-8 gene expression TNFa gene expression	increased steadily through day 12 in all subjects; achieved statistical significance on day 12 small down-regulation in some but not all subjects small down-regulation in some but not all subjects small down-regulation in some but not all subjects $p = 0.04$	not reported
Guiotto P. et al. (2008)	Italy, European Region	Financial support from the DALCO s.r.l. and the Region Friuli Venezia Giulia University of Trieste, Italy, Karl Franzens University, Graz, Austria, University	Stated as single blind study but there was no placebo so was open label	Healthy volunteers	Echinacea purpurea dry root extract	Single lozenge after overnight fasting. Dry extract containing dodeca-2E,4E,8Z,10E/Z-tetraenoic isobutylamides: 0.07 %,	Doses were administered in increasing order; wash-out period between treatments was 2 weeks. Blood samples (5 mL)	1. Abstinence from smoking, eating and drinking until the last blood sample was taken 180	1. 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	None	6	IL-12p70	Statistically significant decrease at all three dosage levels ($p = 0.016, 0.031$)	not reported

Table 2 (*Continued*)

Author	Country, WHO regio	Sponsorship source/ association	Design	Study Population	Echinacea Spp	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects, N in intervention and placebo	Change in interferons (IFN)	Change in interleukins (IL)	Other safety outcomes
		of Ljubljana, Slovenia, and Cellular Immunology Laboratory, IRCCS Burlo Garofolo, Trieste, Italy. Conflict declaration not made.				0.21 % and 0.9 % (w/w). No other details given.	collected in heparinised tubes were taken at 0 (before administration) and at 10, 20, 30, 40, 60, 120 and 180 min after each dose.	min after lozenge administration	of the study, except for oral contraceptives			IL-8	Statistically significant decrease at all three dosage levels (p = 0.016)	
												IL-6	Statistically significant decrease at all three dosage levels (p = 0.036, 0.016)	
												IL-10	Significant decrease at the higher dose of 0.90 mg (p = 0.022)	
												TNFα	significant decrease at the higher dose 0.90 mg (p = 0.036)	

pandemic influenza/ or Influenza C virus/ or influenza B/ or avian influenza/ or Influenza virus or SARS or MERS or respir$ or Middle East 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$).tw. OR ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. OR PLACEBOS/ OR placebo$.tw. OR randomly allocated.tw. OR allocated adj2 random$).tw.) NOT (letter/ OR historical article/)) AND (*Echinacea* or *Echinacea angustifolia* or *Echinacea purpurea* or *Echinace* or coneflower) AND (Cytokine$ or cytokine storm or cytokine release syndrome or chemokine$ or interferon$ or interleukin$ or tumor necrosis factor$ or colony-stimulating factor$)

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 method 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 dry 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 high 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 *ex vivo* blood samples were stimulated and immune response observed [26,27,28,29]. The studies assessed cytokines including TNFα (n = 9), IL-1B, IL-2, IL-3 IL-6, IL-8, IL-10, IL-12 and Interferon (IFN)α2.

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 URTI 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 3
Number of studies reporting increased or decreased levels of cytokines following *Echinacea* use.

Cytokine	Impact on Inflammation Levels and Cytokine storm (CS)	Studies reporting increased levels	Studies reporting no effect on levels	Studies reporting decreased levels
TNFα	Proinflammatory Key CS contributor		2 studies (5, 29)	7 studies (21-26)
IL-1B	Proinflammatory Key CS contributor		1 study (29)	2 studies (24, 27)
IL-6	Proinflammatory Key CS contributor		1 study (28)	3 studies (21, 25, 26)
IL-8	Proinflammatory	1 study(26) and 1 study, only in patients with low baseline levels (27)	2 studies (4, 8)	4 studies (21, 24, 25, 28)
IL-12	Proinflammatory			1 study (25)
IFN-α	Key CS contributor	1 study, only in patients with low baseline levels (27)		
IL-10	Anti-inflammatory Role in regulating pro-inflammatory responses	2 studies (21, 27)	1 study (5)	1 study (25)
IL-3	Not associated with CS	1 study (23)		
IL-2	Not associated with CS	1 study (26)		1 study (21)

supplementation with *Echinacea* in combination with zinc, selenium and ascorbic acid but not for *Echinacea* alone [5]. Seven of the studies using *Echinacea* at URTI 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 dodecatetraenoic acid, isobutylamide, alkylamides, cichoric acid and soluble -1,2-D-fructofuranosides [6,10,12–14].

3.3.2. 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.

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