

Echinacea (*E. angustifolia* DC, *E. pallida*, *E. purpurea*)

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Synonyms/Common Names/Related Substances:

- American coneflower, Echinacin, Echinaforce®, Echinaguard®, black Sampson, black Susan, cock-up-hat, combflower, hedgehog, igelkopf, Indian head, Kansas snake root, kegelblume, narrow-leaved purple coneflower, purple coneflower, red sunflower, rudbeckia, scurvy root, snakeroot, solhat, sun hat.

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background:

- Echinacea species are perennials which belong to the Aster family and which originate in eastern North America. Traditionally used for a range of infections and malignancies, the roots and herb (above ground parts) of echinacea species have attracted recent scientific interest due to purported "immune stimulant" properties. Oral preparations are popular in Europe and the U.S. for prevention and treatment of upper respiratory tract infections (URI), and *Echinacea purpurea* herb is believed to be the most potent echinacea species for this indication.
- For URI *treatment*, numerous human trials have found echinacea to reduce duration and severity, particularly when initiated at the earliest onset of symptoms. However, the majority of trials, largely conducted in Europe, have been small or methodologically flawed. Although highly suggestive, the evidence cannot be considered definitive in favor of this use.
- For URI *prevention* (prophylaxis), daily echinacea has not been shown effective in human trials.
- Preliminary studies of oral echinacea for genital herpes and radiation-associated toxicity remain inconclusive. Topical *E. purpurea* juice has been suggested for skin and oral wound healing, and oral/injectable echinacea for vaginal *Candida albicans* infections, but evidence is lacking in these areas.
- The German Commission E discourages use of echinacea in patients with autoimmune diseases, but this warning is based on theoretical considerations rather than human data.

Scientific Evidence for Common/Studied Uses:

Indication	Evidence Grade	 GRADING SYSTEM LINK
Upper respiratory tract infections: treatment	<u>B</u>	
Upper respiratory tract infections: prevention	<u>C</u>	
Radiation-associated leukopenia	<u>C</u>	
Cancer	<u>C</u>	
Genital herpes	<u>D</u>	

Historical or Theoretical Uses which Lack Sufficient Evidence:

- Abscesses, acne, bacterial infections, bee stings, boils, burn wounds (1), candidiasis, diphtheria, dizziness, dyspepsia, catarrh, eczema (1), gingivitis, hemorrhoids, herpes labialis (2), HIV infection (3), insect bites (4;5;6), malaria, migraine headache, nasopharyngeal catarrh, pain, psoriasis, pyorrhea, recurrent vaginal candidiasis (8), rheumatism, septicemia, snake bites, skin ulcers (1), skin wounds (1), Staphylococcal infections, Streptococcal infections, syphilis, tonsillitis, typhoid, urinary tract infection, urinary disorders (9), whooping cough (10).

Expert Opinion and Historic/Folkloric Precedent:

- Natural medicine experts frequently recommend echinacea species oral extracts for treatment of the common cold, and for other conditions requiring "immune stimulation." It is occasionally recommended for topical treatment of wounds. Internal use of *Echinacea pallida* root and *E. purpurea* herb (above ground parts) has been approved by the German Commission E expert panel for supportive therapy of influenza-like infections.
- Despite a paucity of scientific evidence, the German Commission E has approved *E. purpurea* orally for supportive treatment of chronic respiratory infections, lower urinary tract infections, and for topical treatment of poorly healing wounds/chronic ulcerations. These indications are also noted in monographs published by the World Health Organization.
- Traditionally, echinacea roots and herbs were used by indigenous Americans for a wide variety of conditions, ranging from snakebites to malignancies.

Brief Safety Summary:

- **Likely Safe:** Echinacea is considered safe for internal use by most practitioners. Scientific evidence suggests safety when used orally or topically in recommended doses for a maximum of eight consecutive weeks.
- **Possibly Safe:** One small preliminary study suggests safety in pregnant women and children if taken as directed, although further evidence is warranted in this area.
- **Possibly Unsafe:** Echinacea may cause allergic reactions in atopic patients. Some experts discourage use in cancer patients, tuberculosis, leukocytosis, collagenosis, multiple sclerosis, AIDS, HIV infection, or autoimmune diseases, although this is based on theory rather than on human data, and there are no case reports of adverse events in such patients.
- **Likely Unsafe:** Echinacea may cause allergic reactions in patients with allergies to members of the *Asteraceae/Compositae* plant family (ragweed, chrysanthemum, marigold, daisy).

DOSING/TOXICOLOGY

General:

- Recommended doses are based on those most commonly used in available trials, or on historical practice (not necessarily proven efficacious). However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active component(s) of a product is, standardization may not be possible, and the clinical effects of different brands may not be comparable.
- Combination echinacea products, such as those containing goldenseal, may not be clinically active due to low echinacea concentrations.

Standardization:

- Some manufacturers standardize echinacea extracts to 4.0-5.0% echinacoside, while others standardize to cichoric acid. Because the active constituent(s) has not been identified, standardization may not be clinically relevant in predicting effectiveness.

Adult Dosing (18 years and older):

Oral:

- **Capsules (of powdered herb):** For treatment of upper respiratory tract infections, the dose recommended most often by experts is 500-1000mg three times/day, for 5-7 days (11). A total daily dose of 900mg/day has been shown superior to 450mg/day for improvement of cold/flu symptoms (12).
- **Expressed juice:** The dose recommended most often by experts is 6-9mL daily in divided doses, for 5-7 days.
- **Tincture (1:5):** The dose recommended most often by experts is 0.75 to 1.5mL, gargled then swallowed, 2-5 times/day, for 5-7 days (daily dose should have equivalent of 900mg dried echinacea root). Some herbalists prefer tinctures due to purported immune stimulation at the level of tonsillar lymphoid tissues when tinctures are gargled before swallowing.
- **Tea:** The dose recommended most often by experts is 2 tsp. (4g of echinacea) of coarsely powdered herb simmered in 1 cup of boiling water for 10 minutes, daily for 5-7 days. "Echinacea Plus®" tea, manufactured by Traditional Medicinals (equivalent of 1.275mg of dried herb and root per tea bag) has been shown to reduce upper respiratory tract infection symptoms when 5-6 cups are taken on the first day and titrated down by 1 cup/day for the next 5 days (13).

Topical:

- **Semisolid preparation:** For wound/ulcer healing, the dose recommended most often by experts is 15% pressed herb (non-root) juice semisolid preparation applied daily.

Parenteral:

- Parenteral preparations of echinacea are no longer approved for use in Germany, and are generally not available commercially. Severe reactions have been reported following parenteral use (14).

Pediatric Dosing (younger than 18 years):

Oral:

- In general, the dosage recommended for children is weight-based and calculated from the adult dosage (adult dose is based on 70kg male; dose should be reduced proportionately for child's weight).

Intramuscular/Parenteral:

- Three studies of 257 subjects total (infants to 14 year olds with whooping cough) found no adverse effects with 1-2 mL of squeezed aqueous extract (0.1g/2mL) given intramuscularly twice daily for 3-21 days (10;15;16;17;18;19). Safety of intramuscular preparations has not been established, and should be approached cautiously. Parenteral preparations of echinacea are no longer approved for use in Germany.

Toxicology:

- Symptoms after parenteral administration (not often recommended) have included shivering, fever, and muscle weakness, as documented in one human report of acute toxicity (20).
- *In vitro* toxic effects have been observed on cells at extremely high echinacea concentrations (8).
- The LD₅₀ of intravenous echinacea juice was found to be 50mL/kg in one animal study (21).

Allergy:

- **Oral and topical formulations:** Individuals with asthma or atopy may be predisposed to allergic reactions from oral/topical use of echinacea, consistent with IgE-mediated hypersensitivity (22). Anaphylaxis associated with echinacea has been reported in a 37 year-old woman with a history of atopy (23). She subsequently was found to have a positive skin prick test, and radioallergosorbent (RAST) testing confirmed IgE binding to echinacea. In a poorly described series of 23 case reports of IgE-mediated hypersensitivity reactions, causality was ascribed to echinacea as "certain" in two cases, and "probable" in ten cases. Adequate details of methodology were not provided (24). The same authors published a 2002 report from their referral center in Australia which documented four cases of anaphylaxis or bronchospasm following ingestion of echinacea, and one case of maculopapular rash (22). All five individuals subsequently reacted positively to skin prick and RAST testing for echinacea hypersensitivity. The authors also noted 26 cases reported to the Australian Adverse Drug Reactions Advisory Committee between 1979-2000 of urticaria, angioedema, bronchospasm, or anaphylaxis associated with echinacea use. More than six brands and multiple formulations (tea, tablets, liquid) were implicated. No deaths occurred.
- To determine the prevalence of echinacea sensitivity in the population at large, 100 atopic patients who had never taken echinacea were tested with skin prick tests, and a positive response was elicited in 20%, with negative controls (22;24).
- In a study of 1032 subjects who were patch tested topically with various plant extracts, two reacted to *E. angustifolia* (25).
- **Injections:** Five cases of severe reactions following injection of Echinacin® have been reported, characterized by angioedema, hypotension, anaphylactic shock, and rash; a 63-year-old patient developed bilateral hand swelling, erythema, and pruritis after oral ingestion of Esberitox® (14). Other cases of allergic reactions have been reported after parenteral use of echinacea products (26;27), and there is no supportive evidence from human trials to favor parenteral over oral use.
- Theoretically, individuals sensitive to members of the *Asteraceae/Compositae* plant family may be more likely to experience allergic responses (ragweed, chrysanthemums, marigolds, daisies, etc.).

Adverse Effects:

- **General:** Echinacea has been well tolerated in clinical practice and in trials, with few adverse events reported. In children, three studies of 257 subjects total (infants to 14 year olds with whooping cough) found no adverse effects with 1-2mL of squeezed aqueous extract (0.1g/2ml) given intramuscularly twice daily for 3-21 days (10;15;16;17;18;19).
- **Dermatologic:** Urticaria and allergic rashes have been reported (22). There is one published case of recurrent erythema nodosum in association with use of echinacea (28).
- **Neurologic/CNS:** Mild drowsiness and headache have been reported in <1% of study subjects (29). Dizziness has been rarely noted (22).
- **Cardiovascular:** One case of atrial fibrillation has been reported in association with echinacea use (22). Specific details are not available.
- **Gastrointestinal:** The most frequently cited adverse events from clinical trials are gastrointestinal, including transient mild nausea or vomiting (<1%), sore throat (<1%), and abdominal pain (<1%) (20). In one study, 13% reported adverse effects which were largely gastrointestinal, although the authors felt echinacea was the likely cause in only one case (additional details were not provided) (29). Seven cases of hepatitis associated with echinacea use were reported to the Australian Adverse Drug Reactions Advisory Committee between 1979-2000 (22). However, specific details of these cases are not available.
- **Genitourinary/Reproductive:** One *in vitro* study of zona free hamster oocytes concluded that

high concentrations of echinacea reduce the penetration of hamster sperm. At low concentrations, penetration was comparable to control. *In vitro* incubation of hamster sperm with echinacea for seven days indicated significant denaturation of sperm DNA and reduced viability (30).

- **Renal:** One case of acute renal failure has been reported in association with echinacea use (22). Specific details are not available.

Precautions/Warnings/Contraindications:

- Use cautiously in patients prone to atopic reactions, due to predisposition towards allergic reactions with oral/topical echinacea.
- Use caution with parenteral preparations of echinacea (no longer approved for use in Germany). Safety is not established, and in diabetics, parenteral administration may worsen glycemic control.
- Use tinctures cautiously with alcoholic patients and in patients taking disulfiram or metronidazole: many tinctures contain significant concentrations of alcohol (range: 15% to 90%).
- The German Commission E warns against use of echinacea in patients with AIDS/HIV, collagen vascular diseases, multiple sclerosis, or tuberculosis, due to theoretical adverse effects on immune function, although no specific trial data support this assertion.

Pregnancy & Lactation:

- In preliminary studies, oral echinacea has not appeared to pose a teratogenic risk. One controlled, prospective study of 206 pregnant women found no differences in the incidence of birth defects, gestational age, maternal weight gain, birth weight, pregnancy outcome, or fetal distress from echinacea use (31;32). In this study, different formulations were used by pregnant women: 58% used capsule/tablet (250-1000 mg/day) and 38% tinctures (5-30 drops/day) varying in alcoholic content from 25-45%. Duration of use varied but was typically continuous for 5-7 days. The statistical power of this study, however, was limited, leaving the possibility of undetected adverse gestational effects.
- The German Commission E expert panel considers oral echinacea in recommended doses safe for use in pregnancy and lactation. However, most experts do not recommend parenteral administration during pregnancy. Tinctures may be ill-advised due to 15-90% alcohol content, although the absolute quantity of alcohol ingested from tinctures at recommended doses is likely to be relatively small.
- Further data are warranted in this area.

INTERACTIONS

Echinacea/Drug Interactions:

- **Amoxicillin:** There is one poorly described case report of a 19-year-old patient ingesting amoxicillin and an unclear echinacea preparation who developed rhabdomyolysis, shock, and death; further details were not provided (14).
- **Disulfiram (Antabuse®):** Echinacea tinctures often contain high alcohol content (15-90%), and theoretically may elicit a disulfiram reaction.
- **Econazole Nitrate (Spectazole®):** There is preliminary evidence to suggest that use of echinacea with topical Econazole decreases the recurrence rate of vaginal Candida infections (33).
- **Hepatotoxic Agents:** Natural medicine practitioners often caution that echinacea may cause hepatotoxicity, and recommend avoiding concomitant use with other potentially hepatotoxic drugs (anabolic steroids, amiodarone, methotrexate, ketoconazole, etc.). However, there is no

clear evidence from basic science or human reports that echinacea causes significant liver toxicity. Some have noted that it lacks the 1,2 unsaturated necrine ring system that causes hepatotoxicity of pyrrolizidine alkaloids (34).

- **Immunosuppressant Drugs, [Oral Corticosteroids](#):** In theory, echinacea's immunostimulant properties may interfere with immunosuppressant therapy (including azathioprine, cyclosporin, and prednisone). This possibility has not been systematically studied in humans.
- **Metronidazole (Flagyl®):** A disulfiram reaction can occur when metronidazole and alcohol are used concomitantly. Due to the high alcohol content in some echinacea tinctures, this combination theoretically may cause such a reaction.

Echinacea/Herb/Supplement Interactions:

- **Immunostimulant Agents:** *Positive interaction:* Echinacea is sometimes used in combination products which are purported to synergistically stimulate the immune system. For example, Esberitox® (PhytoPharmica, Germany) contains *Echinacea purpurea*, *Echinacea pallida*, wild indigo root (*Baptisia tinctoria*), and thuja (white cedar). There is no available human evidence supporting these interactions.
- **Vitamin B:** While echinacea itself has not been found to interact with vitamin B, many echinacea preparations are coupled with goldenseal (*Hydrastis canadensis*), which is purportedly an antibiotic, and may decrease intestinal microflora and absorption of vitamin B. These preparations may have low levels of echinacea, and may not be efficacious against viral induced upper respiratory tract infections.
- **Kava:** Multiple reports of hepatotoxicity associated with kava use have been reported, believed to be most common with heavy or chronic use. Caution should be exercised with concomitant use of echinacea, which some natural medicine practitioners have warned may cause liver toxicity as well. However, there is no clear evidence from basic science or human reports that echinacea causes significant liver toxicity. Some have noted that it lacks the 1,2 unsaturated necrine ring system that causes hepatotoxicity of pyrrolizidine alkaloids (34). This potential interaction remains theoretical.

Echinacea/Food Interactions:

- Insufficient available evidence.

Echinacea/Lab Interactions:

- Insufficient available evidence.

MECHANISM OF ACTION

Pharmacology:

- Immunostimulatory properties of echinacea appear to target both non-specific and specific immune function. Non-specific effects include increases in macrophage proliferation and phagocytosis, as well as secretion of interferon, tumor necrosis factor, and interleukin-1 (*in vitro* and *in vivo*) (35;36;37;38;39;40). Specific immune responses include activation of alternate complement pathway components, and elevated levels/activity of T lymphocytes and natural killer (NK) cells (12;41;42). The echinacea species *E. purpurea* is believed to have the strongest potency on the immune system (43). Immunostimulation may depend on dosage and frequency of administration: Cell-mediated immunity can be stimulated by one therapeutic administration followed by a "free" interval of one week, but can be depressed by daily administration of higher doses (8). Other studies have failed to elicit these responses.
- In animal studies, *E. angustiflora* has exhibited anti-inflammatory (44) and antihyaluronidase activity, a likely function of its polysaccharide fraction (45), which may stimulate wound healing (46).

- In rats, an increase of primary and secondary antigen-specific IgG production has been seen with continuous echinacea treatment (47).
- Echinacea may possess microbiocidal activity against *Candida albicans*, *Listeria monocytogenes* (48), influenza virus (49), vesicular stomach virus, and herpes simplex virus (HSV-1 and HSV-2) (50). The relevance of these *in vivo* findings remains unclear.
- Constituents of the root oil of *E. angustiflora* and *E. pallida* have been shown to possess antitumor activity *in vivo* (51).

Pharmacodynamics/Kinetics:

- Insufficient available reliable data.

HISTORY

- Used in traditional medicine by Native Americans of the Great Plains region, there are nine known species of echinacea, all which grow east of the Rocky Mountains.
- Echinacea was adopted by central U.S. settlers in the 1800s. In the 1920s, American Eclectic physicians added echinacea to their pharmacopoeia. However, after the introduction of antibiotics, echinacea use fell out of favor.
- Echinacea's historical use against infections has found renewed interest due to recent rises in antibiotic resistance, and the limitations of available anti-viral drugs.

EVIDENCE TABLE

Condition	Study Design	Author, Year	N	Statistically Significant?	Quality of Study 0-2=poor 3-4=good 5=excellent	Magnitude of Benefit	ARR	NNT	Comments
Upper respiratory tract infection (URI) treatment	Randomized controlled (RCT), double-blind	Brinkeborn, 1999	246	Yes	5	Medium	25-35%	3-4	Examined severity but not duration of symptoms; higher concentration more effective.
URI treatment	RCT, double-blind	Brinkeborn, 1998	119	Yes	5	NA	NA	NA	This is a preliminary report of Brinkeborn, 1999 (same trial).
URI treatment	RCT, double-blind	Henneicke-von Zepelin, 1999	263	Yes	5	Small	NA	NA	Combination product Esberitox reduced severity & duration.
URI treatment	RCT, double-blind	Hoheisel, 1997	120	Yes	4	Medium	20%	5	Decreased duration & severity; subjective outcome.
URI treatment	RCT	Dorn, 1997	160	Yes	3	Large	NA	NA	Decreased duration & severity.
URI treatment	RCT	Lindenmuth, 2000	95	Yes	3	Small	NA	NA	Decreased duration & severity with early treatment.
URI treatment	RCT, double-blind	Thom, 1997	66	Yes	3	Large	NA	NA	Kanjan herbal mixture decreased duration of symptoms.
URI treatment	RCT: dosing trial	Braunig, 1992	180	Yes	2	Large	NA	NA	900mg/day more effective than 450mg. Methods poorly described.
URI treatment	RCT: dosing trial	Braunig, 1993	160	Yes	2	Large	NA	NA	Use of <i>Echinacea pallida</i> . Methods poorly described.
URI treatment	RCT, single blind	Scaglione, 1995	32	Yes	1	Medium	NA	NA	Cold-X (combination) reduced the # of

treatment		1995							tissues used & duration.
URI prevention	RCT, double-blind	Grimm, 1999	109	No	4	Small	9%	11	Level of statistical power questionable; no significant preventive effect; median symptom duration reduced by 1/3.
URI prevention	Equivalence trial, double-blind	Melchart, 1998	302	Yes	4	Small	6%	17	<i>E. angustiflora</i> vs. <i>E. purpurea</i> . No effect of echinacea vs. placebo on URI incidence, but positive subjective efficacy.
URI prevention	RCT, double-blind	Schoneberger, 1992	108	NA	3	Large	7%	14	Reduced incidence, severity and duration, but methods & statistics insufficiently described.
URI prevention	RCT	Berg, 1998	42	Yes	2	Medium	NA	NA	Methodologically weak study in male athletes prior to competition.
URI prevention	Controlled (not randomized or blinded)	Turner, 2000	117	No	1	None	13%	8	Poor statistical power; low content of pharmacologically active compounds.
URI prevention	RCT	Forth, 1981	95	Yes	1	Large	32%	3	Large preventive effect; methodologically weak.
Radiation-associated leukopenia	RCT	Bendel, 1988	50	No	1	None	NA	NA	No power calculation; unclear if sample size sufficient to sense differences.
Radiation-associated leukopenia	RCT	Sartor, 1972	48	Yes	1	Large	NA	NA	Combination product Esberitox reduced # days of radiation missed due to leukopenia.
Genital herpes	RCT	Vonau, 2001	50	No	4	NA	NA	NA	No effect of 6 months of combination product Esberitox.

EVIDENCE DISCUSSION

Upper Respiratory Tract Infection - Treatment

- Summary:** Oral echinacea is frequently recommended to reduce the duration and severity of upper respiratory tract infections (URI). Numerous trials have been conducted in this area, but have largely been of limited methodological quality (or used combination products). Nonetheless, the sum of existing positive evidence is highly suggestive - albeit not definitive. A sufficiently-sized, rigorously blinded study using doses previously found effective (*Echinacea purpurea* extract 900mg/day for 6-8 days) and using accepted outcome measures is warranted, in order to further characterize optimal timing, dosage, frequency of administration, and magnitude of benefit. Consideration should also be given to the possible differential efficacy of various echinacea species, and their different plant parts (root vs. above ground herb).
- Systematic reviews:** A systematic review of studies (before 1994) of echinacea for immunomodulatory indications (52) found six randomized, placebo controlled, double-blind trials examining efficacy in the treatment and prevention of URI (12;53;54;55;56;57). The authors concluded that, despite some evidence of immunomodulatory action of echinacea, no clear recommendations could be made for the treatment of URI with echinacea. Individual trials are discussed below.
- Barrett et al. published a similar review, but included trials published up to 1998 (58). Nine studies evaluating treatment efficacy (12;54;55;56;57;59;60;61), plus one unpublished trial (Galea. 1996) were identified. Most studies had significant methodological limitations. and often

used *ad hoc* symptom scores. The authors nevertheless concluded that the use of echinacea for treatment of early cold symptoms may be "cautiously supported," while long-term or preventive use was not recommended.

- Giles et al. presented a review of studies on echinacea efficacy in prevention and treatment of the common cold published since 1994 (62). Five such trials were included in the analysis (11;29;60;63;64). The authors concluded that the "efficacy of echinacea for treating common cold symptoms remains unclear, yet it appears a suitable alternative for suitable patients."
- A review of the efficacy of echinacea to prevent or treat the common cold (65) concluded that echinacea may be effective for preventing and treating the common cold, but more studies are needed to determine which preparations are most effective. All included randomized controlled trials are discussed in detail below.
- **Randomized trials (higher quality):** A well-conducted randomized, placebo controlled double-blind trial of 246 participants found that Echinaforce® (6.78mg *Echinacea purpurea* crude extract based on 95% herb and 5% root per tablet) and a 7X concentration (48.27mg) both significantly reduced severity of cold symptoms (29). Participants took two tablets three times daily after onset of symptoms, and were advised to continue until they "felt healthy" (7 days maximum). The primary endpoint was reduction in a 12-symptom complaint-index scale: improvement was documented for subjects who experienced reductions in complaint-index by >60% (physician scale) or >50% (patient scale). This otherwise methodologically strong study would have benefited from a more established, validated symptom-scale. Preliminary results of this trial in 119 patients were reported elsewhere (59).
- Braunig et al. conducted a randomized, placebo controlled, double-blind dosing trial on the efficacy of echinacea extract in the treatment of the common cold. In this study, 180 otherwise healthy patients with symptoms of the common cold were allocated to either placebo (no details provided), *Echinacea purpurea* radix 50% ethanolic extract 450mg/day, or 900mg/day (12). Randomization and blinding procedures, and treatment plans were not clearly described. At days 0, 3-4, and 8-10, cold symptoms (fatigue, sweats, teary eyes, stinging eyes, sore throat, ear aches, myalgia, headache) were assessed by a 4-point scale (0=not present, 1=mild, 2=moderate, 3=severe) and patients were clinically assessed. The two target variables were duration of illness, and reduction of symptoms. Only the higher dose of echinacea was superior to placebo in reducing symptoms ($p < 0.0001$). Although this finding is suggestive, the poor description of methods limits the usefulness of this study.
- A randomized, placebo controlled double-blind trial of 160 patients with symptoms of acute upper respiratory infection found an alcoholic extract of *Echinacea pallidae* radix to significantly reduce both severity and duration of upper respiratory tract infection symptoms (11). Neither the method of herb extraction nor a product name was specified. Ninety drops/day were given over 8-10 days (unclear whether one or several doses were given). Benefit of echinacea vs. placebo was reported in terms of illness length ($p < 0.0001$), overall symptom score ($p < 0.0004$), and "whole" clinical score ($p < 0.001$). However, limited information was provided regarding statistical analysis or measurement instruments. Although this study is suggestive, without further methodological details, results are difficult to interpret.
- A randomized, double-blind, placebo controlled study of 120 participants found the duration and severity of common cold symptoms to be significantly decreased with Echinaguard® (squeezed sap of *E. purpurea*) (60). The dose given was 20 drops in water every 2 hours for the first day, followed by 3 times daily (up to a total of 10 days). Efficacy was assessed by a short structured interview which included questions regarding the nature of illness ("real cold?"), fever, severity vs. previous episodes of common cold, onset of improvement, and duration of treatment. Fewer subjects in the Echinaguard® group experienced a "real cold" after initiation of treatment vs. placebo (40% vs. 60%, $p = 0.044$). Median time to improvement was significantly shorter in the Echinaguard® group than placebo (0 vs. 5 days, $p < 0.0001$). Limitations of this study include unclear standardization of the product used, and incomplete description of randomization, blinding, statistical analysis, dropouts, or validation of the measuring questionnaire.
- Lindenmuth and Lindenmuth conducted a randomized controlled trial of "Echinacea Plus" tea

vs. a placebo for upper respiratory tract symptoms (13). The tea contained the equivalent of 1.275mg of dried herb and root per tea bag. Participants were instructed to drink 5-6 cups of tea on the first day and titrate down by 1 cup/day for the next 5 days. The experimental group rated the effectiveness of echinacea tea as 4.1 on a 5-point scale (SD 0.96), while the control group rated their tea 2.8 (SD 0.095), with a p value <0.001. There was also a statistically significant (although small) difference in the number of days symptoms lasted and in the number of days before symptoms diminished in the treatment group vs. control. Statistical analysis may not have been appropriate (t-test for sum scores), but this methodological weakness would not likely explain the results. Therefore, echinacea tea, when taken at the first onset of symptoms, may be effective in relieving symptoms of the common cold and in abbreviating the course of the illness.

- In a well-conducted randomized, double-blind, placebo controlled multicenter trial, Henneicke-von Zepelin et al. examined the efficacy of the combination product Esberitox® (includes ethanolic-aqueous extracts of 2mg herba thujae occidentalis, 7.5mg *radix echinaceae*, 10mg *radix baptisiae tinctoriae*) (66). The study enrolled 263 patients with acute common colds who were not suffering from any chronic condition affecting immune system function. Patients received either Esberitox® N three tablets/day or placebo for 7-9 days. Primary outcomes were general well-being (Welzel-Kohnen color scale), physician evaluated symptom severity (clinical global impression item-1 [CGI-1]), and rhinitis score/bronchitis score (10-point scales). Patient follow-up was on days 0, 4, and 8. The "total efficacy value," a combination of all outcome measures, showed a >20% effect at study completion (p<0.05). The improvement in well-being was most prominent (33.9%, p=0.0048), followed by rhinitis score. Time to response, defined as a 50% decrease in symptom score, was significantly shorter in the treatment group vs. placebo (p=0.022). These findings suggest that an herbal combination containing echinacea significantly reduces the severity and duration of the common cold when given at the early onset of symptoms. However, the question of whether this effect is attributable to the echinacea component of Esberitox® cannot be addressed within the framework of this study.
- Thom and Wollan found a significantly faster improvement of cold symptoms with Kanjang, a mixture containing echinacea, Siberian ginseng, and Vasaka (67). Sixty-six patients with common cold symptoms were randomly assigned to either Kanjang (15mL three times daily, containing 4.5g/day of *E. purpurea radix*) or placebo. Improvement of cold symptoms was assessed by a 10-point Visual Analogue Scale (VAS) on days 2, 4, and 10 after onset of treatment. The difference between groups was most pronounced on day 4, when the average global efficacy VAS score was approximately 6 in the Kanjang group vs. 1 in the placebo group (p=0.001). As with other studies using combination products, this study does not permit specific inference regarding the efficacy of echinacea.
- **Lesser quality studies:** Braunig and Knick report a study evaluating the efficacy of *Echinacea pallida* for the treatment of URI (54). In this study, 180 otherwise healthy patients with symptoms of URI were randomly allocated to either *Echinacea pallida* radix (Pascotox®, 900mg/day) or placebo for 8-10 days. Outcome was measured by "overall clinical assessment" and by symptom scores as described for the prior study (12). Follow-up was at days 0, 3-4, and 8-10. Duration of illness was reduced from 13 to 10 days for bacterial infections and from 13 to 9 days for viral infections (neither the endpoint of illness, nor the basis for diagnosis of viral vs. bacterial infection was clearly defined). Improvement in total symptom score was faster with *Echinacea pallida* than with placebo (p<0.0001) and faster for viral vs. bacterial infections. The authors concluded that *Echinacea pallida* is effective in the treatment of URI and at least as effective as *Echinacea purpurea*. However, the poor description of methods limits the usefulness of this study.
- Scaglione and Lund evaluated the efficacy of an herbal mixture containing echinacea for the treatment of the common cold in a randomized, placebo controlled, single-blind trial (68). Thirty-two patients with cold symptoms, but otherwise healthy, were randomized to receive either four effervescent tablets/day of Cold-X® (Vitamin C 100mg, *Echinacea purpurea* root extract 20.1mg, eucalyptus leaf extract 12.3mg, fennel seed extract 10.3mg) or placebo (4 glucose tablets/day). Main outcome variables were duration of illness based on rhinorrhea and the

number of paper tissues used (measurement method not described). Overall number of tissues used was 882 in the echinacea group vs. 1168 in the control group. Mean duration of cold symptoms was 3.4 vs. 4.4 days respectively ($p < 0.01$; the statistical method used was incompletely described and may have been inappropriate). These findings suggest that treatment of the common cold with Cold-X® may be effective. However, due to the lack of double-blinding and the use of an herbal combination, no firm conclusions can be drawn.

Upper Respiratory Tract Infection - Prevention

- **Summary:** The evidence for echinacea's efficacy in the prevention of upper respiratory tract infections (URI) is equivocal. The available randomized controlled studies have substantial methodological weaknesses. Lack of statistical power may explain some of the negative results, which are largely based on moderate sample sizes and brief follow-up periods (person-time of observation may be insufficient). Even if there is a preventive effect of echinacea, it is likely small at best. A large well-designed longitudinal study is warranted in this area.
- **Systematic reviews:** A systematic review of studies (before 1994) of echinacea for immunomodulatory indications (52) found three randomized, placebo controlled and double-blind trials which examined the efficacy of echinacea in the prevention of URI (69;70;71). The authors concluded that, despite some evidence of immunomodulatory action of echinacea, no clear recommendations could be made for the prevention of URI with echinacea.
- Barrett et al. published a similar review, but included trials published up to 1998 (58). Four trials evaluating prevention efficacy were included (63;69;70;71). Most studies had significant methodological limitations, and often used *ad hoc* symptom scores. The authors concluded that the long-term or preventive use of echinacea should not be recommended.
- A review of the efficacy of echinacea to prevent or treat the common cold concluded that echinacea may be effective for preventing and treating the common cold, but more studies are needed to determine which preparations are most effective (65). All included randomized controlled trials are discussed in detail below.
- **Randomized trials (higher quality):** A double-blind, randomized, placebo controlled trial of 109 participants found that *E. purpurea* (fresh expressed juice of whole flowering plant harvested without roots), 4mL twice/day for eight weeks, did not significantly lower the incidence or severity of common colds (64). Although no preventive effect of *E. purpurea* juice was found, there was a statistically non-significant reduction in the duration of cold symptoms (4.5 days in the echinacea group vs. 6.5 days in the placebo group, $p = 0.45$). The size of this study, considering its prospective nature, may not have been adequate to detect small but significant benefits with sufficient statistical power. It was otherwise well-conducted.
- In a placebo controlled, non-randomized, unblinded experiment, Turner et al. investigated the effect of echinacea vs. placebo in 92 subjects challenged with rhinovirus type 23 (72). Subjects were treated for two weeks before and five days after inoculation with 300mg three times/day of echinacea ($n = 50$) or placebo ($n = 42$). A clinical diagnosis of a cold was subsequently made in 44% of echinacea subjects and 57% of placebo subjects. Mean symptom scores were lower in the echinacea group vs. placebo throughout the study (overall mean 13.6 vs. 11.4), and similar differences were observed for individual symptom scores (total rhinorrhea and mean nasal obstruction scales). However, none of the differences were statistically significant. A potential weakness is that almost no echinacosides or alkamides were found by high-pressure liquid chromatography in the echinacea preparation. In addition, the power of this study to detect a reduction in risk from 50% to 20% was only 75%.
- In a randomized, controlled, open trial, Forth and Beuscher examined the efficacy of two echinacea preparations to prevent URI (71). Ninety-five healthy subjects were randomly allocated to either Esberitox® liquid 25 drops three times daily, Esberitox® three tablets daily, or placebo. Esberitox® liquid includes ethanolic-aqueous extracts of herba thujae occidentalis (2mg), radix *echinaceae* (7.5mg), and radix baptisiae tinctoriae (10mg), while Esberitox® tablets add 20mg Vitamin C/tablet to these ingredients. Treatment duration varied from 3-17

weeks, and the main outcome measured was rhinitis. In both echinacea groups combined, two thirds did not suffer from URI, while in a placebo group this proportion was only one third ($p < 0.005$). The difference between the two echinacea groups was not statistically significant. Although these results suggest efficacy of echinacea, a proper statistical analysis would have compared the number of events per treatment time rather than the overall risk per group. It is unlikely, however, that this would have substantially changed the results.

- Melchart et al. conducted a randomized, placebo controlled, double-blind study comparing the efficacy of *E. angustiflora* vs. *E. purpurea* (63). In this equivalence trial, 302 healthy volunteers without signs of URI were randomly assigned to receive 1mL of extract from the root of either plant in 30% alcohol (twice daily from Monday-Friday, for 12 weeks), or placebo. There was no difference between the three treatment arms in terms of the main effect measure (time to first URI episode). However, the study may have been too small to detect small to medium-sized treatment effects due to low statistical power. Notably, 78% in the *E. angustiflora*, 70% in the *E. purpurea*, and 56% in the placebo group believed subjectively that they benefited from the treatment ($p = 0.04$). Although suggestive, the use of validated symptom indices might have been advantageous for identifying effects of either treatment.
- Schoneberger evaluated the potential of echinacea to prevent URI in a randomized, placebo controlled trial (70). In this study, 108 otherwise healthy patients "at risk for URI" were randomly allocated to receive *Echinacea purpurea* juice (4mL twice daily) or placebo juice for 8 weeks. Randomization and blinding methods were not described. Primary outcome variables were the number and severity of URI episodes. Secondary outcomes included time to first URI and URI duration. In the echinacea group, 23 URIs were observed (78% were mild) vs. 35 in placebo (63% were mild). The average duration of symptoms was 5.3 vs. 7.5 days, respectively. The proportion of URI-free patients was 35% vs. 27%. Although no statistical analysis was presented, the difference between the echinacea and placebo groups appeared to be substantial in terms of overall number, duration, and severity of URI.
- **Lesser quality studies:** Several trials of lower methodological quality have examined the effects of echinacea for the prevention of URI symptoms. In a 1974 study of 284 children attending a summer camp, Freyer treated half of subjects with an herbal combination containing echinacea (Esberitox®) and left the other half untreated (73). In the echinacea group, 30% contracted a cold vs. >50% in the no-treatment group. Although these findings are suggestive, the observational nature renders interpretation difficult. In an earlier (1965) study, children on a pediatric ward were given either oral Esberitox® (six weeks on average) or no treatment (74). Incidence, prevalence and number of febrile days were substantially lower in the Esberitox® group vs. control, but the lack of randomization or blinding limits the value of this study. In a 1961 study, Helbig enrolled 644 children hospitalized for non-URI causes, and randomly allocated them to Esberitox® or no treatment (75). Overall, there was no difference between the two groups. A post-study analysis limited to children hospitalized for >14 days found that fewer children treated with Esberitox® suffered from new common cold episodes, but no statistical analysis was presented. This method of historical data reshuffling cannot be considered valid. In a randomized, controlled trial in 42 male athletes given echinacea for 28 days prior to competition, subjects receiving echinacea were found to have lower serum and urine levels of soluble interleukin 2 receptors (sIL-2R), and significantly fewer respiratory infections vs. placebo (76). However, details of methodology and statistical analysis are limited.

Radiation Associated Leukopenia

- **Summary:** The evidence from a small number of randomized trials evaluating efficacy of echinacea in the treatment of radiation-induced leukopenia is equivocal. Studies have used the combination product Esberitox®, which includes ethanolic-aqueous extracts of *herba thujae occidentalis*, *radix echinaceae*, and *radix baptisiae tinctoriae*.
- **Evidence:** Bendel et al. randomly allocated 50 women receiving post-mastectomy radiation therapy to an herbal combination containing echinacea (Esberitox N®, 50 drops daily throughout the radiation treatment period) or to placebo (77). Effects on leukocyte counts and

other hematological parameters were assessed before and after radiation. No statistically significant differences were found. Despite the questionable statistical power of the study, the benefit of echinacea is likely to be small at best.

- In contrast, Sartor found a substantial effect of Esberitox® on radiation-induced leukopenia (78). Forty-eight patients undergoing six weeks of radiation therapy were assigned randomly to Esberitox® or no adjuvant treatment. In the Esberitox® group, 46% missed zero days of therapy because of leukocyte counts $<3000/\text{mm}^3$, vs. 18% in the untreated group. Although these proportions were not statistically compared, they are highly suggestive. The mean number of missed treatment days did not differ significantly, although these results are not interpretable due to an inadequate t-test.
- In a case series, Pohl found a statistically significant increase in leukocyte counts in 55 patients undergoing radiation therapy after treatment with Esberitox® (various doses and routes of administration) (7). This observational study is suggestive mechanistically but of limited clinical value.
- Additional weak evidence is provided by Bendel et al. in a randomized trial of 70 women receiving radiation therapy for breast cancer (79). No change in incidence of infection was noted, although bone marrow toxicity was reportedly lessened. The methodologic and histologic criteria were poorly described, weakening the clinical applicability of results.

Cancer

- **Summary:** There is insufficient evidence to recommend for or against the use of echinacea for any type of cancer. Only preliminary data from case series are available, without any evidence of benefit.
- **Evidence:** Cytokine levels were monitored in 35 brain tumor patients who were given 3mL/day of a 40% *E. angustifolia* herbal therapy. After four weeks, no change in white blood cell counts or cytokine production was noted. The clinical significance of these findings is unclear (80).
- Preliminary studies have been conducted to assess the safety of combination chemotherapy including Echinacin® (*E. purpurea*). In one study, 15 patients with advanced, metastatic colon cancer who had already undergone standard treatment with chemotherapy/surgery were given low-dose cyclophosphamide, thymostimulin, and Echinacin® (81). The mean survival time was four months. In a case series, five patients with advanced hepatocellular carcinoma were treated with a combination regimen including Echinacin®, and mean survival was 10 weeks (82).

Genital Herpes

- **Summary:** A small clinical trial assessing the potential benefit of oral echinacea for recurrent herpes genitalis found no effect. Conclusions cannot be considered definitive without further trials.
- Vonau et al. conducted a randomized, placebo controlled, cross-over trial to evaluate the therapeutic use of echinacea for recurrent genital herpes (83). Fifty patients were randomly allocated to a treatment sequence of either echinacea extract (800mg orally twice/day) for six months followed by placebo for six months, or vice versa. Number of recurrences and several indicators of disease status (Visual Analogue Scale of pain, CD4 counts, neutrophil counts) were assessed before and after treatments. No statistically significant differences were found between the groups. Although the sample size was relatively small, a relevant treatment benefit would likely have been detected if present.

PRODUCTS STUDIED

Brands used in statistically significant clinical trials:

- Echinacin® (Madaus AG, Germany) Echinaguard® (Nature's Way, USA) Echinaforce®

(Bioforce), EchinaFresh (Enzymatic Therapy), Esberitox® (Enzymatic Therapy), Esberitox® N, Pascotox®, Resistan®, Biracial® (Destiny BioMediX Corp).

- "Echinacea Plus®" tea (Traditional Medicinals): equivalent of 1.275mg of dried herb and root per tea bag.

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REFERENCES

1. Viehmann P. [Results of treatment with an Echinacea-based ointment]. *Erfahrungsheilkunde* 1978;27(6):353-358.
2. Bockhorst H, Gollnick N, Guran S, et al. [Therapy of herpes simplex in practice. Report on the treatment of herpes simplex labialis with Esberitox]. *ZFA (Stuttgart)* 1982;58(32):1795-1798. [View Abstract](#)
3. See D, Berman S, Justis J, et al. A phase I study on the safety of Echinacea angustifolia and its effect on viral load in HIV infected individuals. *J Amer Nutr Assoc* 1998;1(1):14-17.
4. Hill N, van Haselen RA. Clinical trial of a homeopathic insect after-bite treatment. *Hom Int R&D Newsletter* 1993;3/4:4-5.
5. Hill N, Stam C, Tuinder S, et al. A placebo controlled clinical trial investigating the efficacy of a homeopathic after-bite gel in reducing mosquito bite induced erythema. *Eur J Clin Pharmacol* 1995;49(1-2):103-108. [View Abstract](#)
6. Hill N, Stam C, van Haselen RA. The efficacy of Prrikweg gel in the treatment of insect bites: a double-blind, placebo-controlled clinical trial. *Pharm World Sci* 1996;18(1):35-41. [View Abstract](#)
7. Pohl P. [Treatment of radiation-induced leukopenia with Esberitox]. *Ther Ggw* 1970;109(6):902-906. [View Abstract](#)
8. Coeugnet EG, Elek E. Immunomodulation with *Viscum album* and *Echinacea purpurea* extracts. *Onkologie* 1987;10(3 Suppl):27-33. [View Abstract](#)
9. Timmermans LM, Timmermans LG, Jr. [Determination of the activity of extracts of Echinaceae and Sabal in the treatment of idiopathic megabladder in women]. *Acta Urol Belg* 1990;58(2):43-59. [View Abstract](#)
10. Baetgen D. Erfolge in der keuchhusten-behandlung mit *Echinacin*. *Therapiewoche* 1984;34:5115-5119.
11. Dorn M, Knick E, Lewith G. Placebo-controlled, double blind study of Echinaceae pallidae radix in upper respiratory tract infections. *Complement Ther Med* 1997;5:40-42.
12. Bräunig B, Dorn M, Limburg E, et al. Enhancement of resistance in common cold by *Echinacea purpurea* radix. *Zeitschrift für Phytotherapie* 1992;13:7-13.
13. Lindenmuth GF, Lindenmuth EB. The efficacy of echinacea compound herbal tea preparation on the severity and duration of upper respiratory and flu symptoms: a randomized, double-blind placebo-controlled study. *J Altern Complement Med* 2000;6(4):327-334. [View Abstract](#)
14. Anonymous. Immunallergische reaktionen nach echinacea-extrakten (*Echinacin*, *Exberitox N U.A.*). *Arzneitelegramm* 1991(April);39.
15. Heesen W. Unspezifische Behandlungsmöglichkeiten bei tuberkulösen Erkrankungen. *Erfahrungsheilkunde* 1964;13:210-217.
16. Volz G. Zur keuchhustenbehandlung mit Myo-Echinacin. *Ther Gegenwart* 1957;96:312-313.
17. Zimmermann O. Die therapie des keuchhusten mit Myo-Echinacin. *Hippokrates* 1969;6:223-235.
18. Barrett B, Vohmann M, Calabrese C. Information on additional echinacea trials. *J Fam Pract* 1999;48(12):1001-1002.

19. Ertel G, Manley H, McQueen C, et al. Information on additional Echinacea trials. *J Fam Pract* 1999;48(12):1001-1002. [View Abstract](#)
20. Parnham MJ. Benefit-risk assessment of the squeezed sap of the purple coneflower (*Echinacea purpurea*) for long-term oral immunostimulation. *Phytomed* 1996;3:95-102.
21. Mengs U, Clare CB, Poiley JA. Toxicity of *Echinacea purpurea*. Acute, subacute and genotoxicity studies. *Arzneimittelforschung* 1991;41(10):1076-1081. [View Abstract](#)
22. Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. *Ann Allergy Asthma Immunol* 2002;88(1):42-51. [View Abstract](#)
23. Mullins RJ. Echinacea-associated anaphylaxis. *Med J Aust* 1998;168(4):170-171. [View Abstract](#)
24. Mullins R. Allergic Reactions to Echinacea. *J Allergy Clin Immunol* 2000;105(1 part 2):s268-s269.
25. Bruynzeel DP, van Ketel WG, Young E, et al. Contact sensitization by alternative topical medicaments containing plant extracts. The Dutch Contact Dermatoses Group. *Contact Dermatitis* 1992;27(4):278-279. [View Abstract](#)
26. Bauer R. [Echinacea drugs--effects and active ingredients]. *Z Arztl Fortbild.(Jena)* 1996;90(2):111-115. [View Abstract](#)
27. Schonhofer PS, Schulte-Sasse H. [Are botanical immunostimulants effective and harmless?]. *Dtsch Med Wochenschr* 1989;114(46):1804-1806. [View Abstract](#)
28. Soon SL, Crawford RI. Recurrent erythema nodosum associated with Echinacea herbal therapy. *J Am Acad Dermatol* 2001;44(2):298-299. [View Abstract](#)
29. Brinkeborn RM, Shah DV, Degenring FH. Echinaforce and other Echinacea fresh plant preparations in the treatment of the common cold: A randomized, placebo controlled, double-blind clinical trial. *Phytomed* 1999;6(1):1-6.
30. Ondrizek RR, Chan PJ, Patton WC, et al. Inhibition of human sperm motility by specific herbs used in alternative medicine. *J Assist Reprod Genet* 1999;16(2):87-91. [View Abstract](#)
31. Gallo M, Sarkar M, Au W, et al. Pregnancy outcome following gestational exposure to echinacea: a prospective controlled study. *Arch Intern Med* 2000;160(20):3141-3143. [View Abstract](#)
32. Gallo M, Koren WA, Koren G. The safety of Echinacea use during pregnancy: a prospective controlled cohort study. Proceedings of the 11th International Conference of the Organization of Teratology. *Teratology* 1998;57:283.
33. Coeugnet E, Kuhnast R. Rezidivierende candidiasis. *Therapiewoche* 1986;36:3352-3358.
34. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998;158(20):2200-2211. [View Abstract](#)
35. Bauer R, Wagner H. Echinacea species as potential immunostimulatory drugs. In: Wagner H, Farnsworth NR, editors. *Economic and Medicinal Plant Research*. New York: Academic Press, 1991: 253-321.
36. Stimpel M, Proksch A, Wagner H, et al. Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fractions from the plant *Echinacea purpurea*. *Infect Immun* 1984;46(3):845-849. [View Abstract](#)
37. Mose JR. [Effect of Echinacin on phagocytosis and natural killer cells]. *Med Welt* 1983;34(51-52):1463-1467. [View Abstract](#)
38. Burger RA, Torres AR, Warren RP, et al. Echinacea-induced cytokine production by human macrophages. *Int J Immunopharmacol* 1997;19(7):371-379. [View Abstract](#)
39. Burger RA, Torres AR, Warren RP, et al. Echinacea purpurea induced cytokine production in human peripheral blood adherent mononuclear cells (PBAC). *J Allergy Clin Immunol* 1997;99(1, part 2):283.
40. Luettig B, Steinmuller C, Gifford GE, et al. Macrophage activation by the polysaccharide arabinogalactan isolated from plant cell cultures of *Echinacea purpurea*. *J Natl Cancer Inst* 1989;81(9):669-675. [View Abstract](#)
41. Jurcic K, Melchart D, Holzmann M. Two proband studies for the stimulation of granulocyte phagocytosis through echinacea extract containing preparations. *Zeitschrift fur phytoterapie* 1989;10:67-70.
42. See DM, Broumand N, Sahl L, et al. In vitro effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. *Immunopharmacology* 1997;35(3):229-235. [View Abstract](#)
43. Bodinet C, Willigmann I, Beuscher N. Host-resistance increasing activity of root extracts from Echinacea species. *Planta Med* 1993;59 (Suppl):a672-a673.
44. Traghi E, Tubaro A, Melis S, et al. Evidence from two classic irritation tests for an anti-inflammatory action of a natural extract, Echinacina B. *Food Chem Toxicol* 1985;23(2):317-319. [View Abstract](#)
45. Tubaro A, Traghi E, Del Negro P, et al. Anti-inflammatory activity of a polysaccharidic fraction of *Echinacea angustifolia*. *J Pharm Pharmacol* 1987;39(7):567-569. [View Abstract](#)
46. Tunnerhoff FK, Schwabe HK. Studies in human beings and animals on the influence of echinacea extracts on the formation of connective tissue following the implantation of fibrin. *Arzneim Forsch* 1956;6:330-334.

47. Rehman J, Dillow JM, Carter SM, et al. Increased production of antigen-specific immunoglobulins G and M following in vivo treatment with the medicinal plants *Echinacea angustifolia* and *Hydrastis canadensis*. *Immunol Lett* 1999;68(2-3):391-395. [View Abstract](#)
48. Steinmuller C, Roesler J, Grottrup E, et al. Polysaccharides isolated from plant cell cultures of *Echinacea purpurea* enhance the resistance of immunosuppressed mice against systemic infections with *Candida albicans* and *Listeria monocytogenes*. *Int J Immunopharmacol* 1993;15(5):605-614. [View Abstract](#)
49. Wacker A, Hilbig W. [Virus-inhibition by *echinacea purpurea* (author's transl)]. *Planta Med* 1978;33(1):89-102. [View Abstract](#)
50. Thompson KD. Antiviral activity of *Viracea* against acyclovir susceptible and acyclovir resistant strains of herpes simplex virus. *Antiviral Res* 1998;39(1):55-61. [View Abstract](#)
51. Voaden DJ, Jacobson M. Tumor inhibitors. 3. Identification and synthesis of an oncolytic hydrocarbon from American coneflower roots. *J Med Chem* 1972;15(6):619-623. [View Abstract](#)
52. Melchart D, Linde K, Worku F, et al. Immunomodulation with *echinacea* - a systematic review of controlled clinical trials. *Phytomed* 1994;1:245-254.
53. Dorn M. Milderung grippaler Infekte durch ein pflanzliches Immunstimulans [Treatment of influenza-like syndromes with a phytotherapeutic immunostimulatory preparation]. *Natur-und-Ganzheitsmedizin* 1990;2:314-319.
54. Bräunig B, Knick E. [Therapeutic experiences with *Echinacea pallida* in upper respiratory tract infections]. *Naturheilpraxis* 1993;1:72-75.
55. Vorberg G, Schneider B. Pflanzliches Immunstimulans verkürzt grippalen Infekt. Doppelblindstudie belegt die Steigerung der unspezifischen Infektabwehr [Phytotherapeutic immunostimulator decreases the duration of influenza-like syndromes. Double-blind trial proves the enhancement of unspecific immune defense]. *Ärztliche Forschung* 1989;36:3-8.
56. Reitz HD. Immunomodulatoren mit pflanzlichen Wirkstoffen: eine wissenschaftliche Studie am Beispiel Esberitox N [Immunomodulation with phytotherapeutic agents: a scientific study on the example of Esberitox]. *Notabene medici* 1990;20:362-366.
57. Vorberg G. Bei Erkältung unspezifische Immunabwehr stimulieren. [Stimulation of the immune defense in common colds]. *Ärztliche Praxis* 1984;36:97-98.
58. Barrett B, Vohmann M, Calabrese C. *Echinacea* for upper respiratory tract infection. *J Fam Pract* 1999;48(8):628-635. [View Abstract](#)
59. Brinkeborn R, Shah D, Geissbuhler S, et al. *Echinaforce* in the treatment of acute colds. Results of a placebo-controlled double-blind study carried out in Sweden. *Schweiz Zschr Ganzheits Medizin* 1998;10:26-29.
60. Hoheisel O, Sandberg M, Bertram S, et al. *Echinagard* treatment shortens the course of the common cold: a double blind, placebo controlled clinical trial. *European J Clin Research* 1997;9:261-269.
61. Dorn M. Milderung grippaler Effekte durch ein pflanzliches Immunstimulans. *Natur Ganzheitsmedizin* 1989;2:314-319.
62. Giles JT, Palat CT, III, Chien SH, et al. Evaluation of *echinacea* for treatment of the common cold. *Pharmacotherapy* 2000;20(6):690-697. [View Abstract](#)
63. Melchart D, Walther E, Linde K, et al. *Echinacea* root extracts for the prevention of upper respiratory tract infections: a double-blind, placebo-controlled randomized trial. *Arch Fam Med* 1998;7(6):541-545. [View Abstract](#)
64. Grimm W, Muller HH. A randomized controlled trial of the effect of fluid extract of *Echinacea purpurea* on the incidence and severity of colds and respiratory infections. *Am J Med* 1999;106(2):138-143. [View Abstract](#)
65. Melchart D, Linde K, Fischer P, et al. *Echinacea* for preventing and treating the common cold. *Cochrane Database Syst Rev* 2000;(2):CD000530. [View Abstract](#)
66. Henneicke-von Zepelin H, Hentschel C, Schnitker J, et al. Efficacy and safety of a fixed combination phytomedicine in the treatment of the common cold (acute viral respiratory tract infection): results of a randomised, double blind, placebo controlled, multicentre study. *Curr Med Res Opin* 1999;15(3):214-227. [View Abstract](#)
67. Thom E, Wollan T. A controlled clinical study of *Kanjang* mixture in the treatment of uncomplicated upper respiratory tract infections. *Phytother Research* 1997;11:207-210.
68. Scaglione F, Lund B. Efficacy in the treatment of the common cold of a preparation containing an *echinacea* extract. *International J Immunother* 1995;11(4):163-166.
69. Schmidt U, Albrecht M, Schenk N. Immunstimulas senkt Häufigkeit grippaler Infekte. Plazebokontrollierte Doppelblindstudie mit einem kombinierten *Echinacea*-Präparat mit 646 Studenten der Kölner Universität. [Immunostimulator decreases the frequency of influenza-like syndromes. Double-blind placebo-controlled trial on 646 students of the University of Cologne]. *Natur- und Ganzheitsmedizin* 1990;3:277-281.
70. Schöneberger D. [The influence of immune-stimulating effects of pressed juice from *Echinacea purpurea* on the course and severity of colds. Results of a double-blind study]. *Forum Immunologie* 1992;8(18):2-12.
71. Forth H, Beuscher N. [Effect on the frequency of banal cold infections by *esberitox*]. *ZFA (Stuttgart)* 1981;57(32):2272-2275. [View Abstract](#)

72. Turner RB, Riker DK, Gangemi JD. Ineffectiveness of echinacea for prevention of experimental rhinovirus colds. *Antimicrob Agents Chemother* 2000;44(6):1708-1709. [View Abstract](#)
73. Freyer HU. [Incidence of banal infections in childhood and possibilities of their prevention]. *Fortschr Med* 1974;92(4):165-168. [View Abstract](#)
74. Kleinschmidt H. Versuche zur herabsetzung der infektneigung bei kleinkindern mit esberitox. *Therapie ger Gegenwart* 1965;104:1258-1262.
75. Helbig G. Unspezifische Reizkörpertherapie zur Infektprophylaxe. *Medizinische Klinik* 1961;35:1512-1514.
76. Berg A, Northoff H, König D, et al. Influence of Echinacin (EC31) treatment on exercise-induced immune response in athletes. *J Clin Res* 1998;1:367-380.
77. Bendel R, Bendel V, Renner K, et al. [Supplementary treatment with Esberitox of female patients undergoing curative adjuvant irradiation following breast cancer]. *Strahlenther Onkol* 1988;164(5):278-283. [View Abstract](#)
78. Sartor KJ. [Efficacy of Esberitox in the treatment of radiation-induced leukopenia]. *Ther Ggw* 1972;111(8):1147-1150. [View Abstract](#)
79. Bendel R, Bendel V, Renner K, et al. [Additional treatment with Esberitox N in patients with chemo-radiotherapy treatment of advanced breast cancer]. *Onkologie*. 1989;12 Suppl 3:32-38. [View Abstract](#)
80. Elsasser-Beile U, Willenbacher W, Bartsch HH, et al. Cytokine production in leukocyte cultures during therapy with Echinacea extract. *J Clin Lab Anal* 1996;10(6):441-445. [View Abstract](#)
81. Lersch C, Zeuner M, Bauer A, et al. Nonspecific immunostimulation with low doses of cyclophosphamide (LDCY), thymostimulin, and Echinacea purpurea extracts (echinacin) in patients with far advanced colorectal cancers: preliminary results. *Cancer Invest* 1992;10(5):343-348. [View Abstract](#)
82. Lersch C, Zeuner M, Bauer A, et al. Stimulation of the immune response in outpatients with hepatocellular carcinomas by low doses of cyclophosphamide (LDCY), echinacea purpurea extracts (Echinacin) and thymostimulin. *Arch Geschwulstforsch* 1990;60(5):379-383. [View Abstract](#)
83. Vonau B, Chard S, Mandalia S, et al. Does the extract of the plant Echinacea purpurea influence the clinical course of recurrent genital herpes? *Int J STD AIDS* 2001;12(3):154-158. [View Abstract](#)



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