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Echinacea products are widely used to treat and prevent colds and other infections. Three randomized, placebo-controlled trials found no benefit of echinacea-only products in preventing upper respiratory infections (URIs). However, six of seven randomized, placebo-controlled trials did a benefit for several extracts echinacea in treating URIs— E. pallida root, E. purpurea root, and E. purpurea pressed juice (NOTE: trials of E. purpurea root found no effect). Echinacea extracts contain alkylamides, caffeic acid derivatives, ketoalkenes/ketoalkynes glycoproteins, and polysaccharides; it is unknown which compounds are most active. Echinacea products have been associated with allergic skin reactions, asthma, urticaria/angioedema, and anaphylaxis.

Echinacea for the Prevention and Treatment of Upper Respiratory Infections

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Echinacea extracts are widely sold for treating and preventing infections. Echinacea, also called purple coneflower, is a member of the daisy Compositae/Asteraceae) family. The three Echinacea species used commercially are *E. purpurea, E. angustifolia,* and *E. pallida.* Preparations include root extracts, pressed juice of *E. purpurea* herb (ie, aerial parts), and mixtures of both herb and root. Many single-herb and mixed-herb products are available. Single-herb products tested in the clinical trials available in the United States include two fresh-pressed *E. purpurea* products: Echinaforce® (Bioforce), a hydroalcoholic extract (65% ethanol; extract ratio 9:1) of fresh herb (95%) and root (5%), and Echinaguard® or Echinacin (Madaus), an extract of *E. purpurea* herb in a 20% ethanol base. This review discusses all randomized, controlled trials of echinacea-only products for treating colds or URIs (Table 1). Sources include MEDLINE, IBIDS, and the author's own files.

Clinical Trials

Three randomized, placebo-controlled trials of echinacea-only products for the prevention of URIs were identified. None of these trials found a benefit. A three-armed trial of 302 subjects in which 289 were analyzed compared *E. angustifolia* root extract to *E. purpurea* root extract and placebo (50 drops twice daily, five

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TABLE 1

Randomized Controlled Trials of Echinacea for the Prevention or Treatment of Upper Respiratory Infections

PREVENTION	n	Treatment	Outcome Measures	Results
Melchart, 1998	302/289;214 complied fully	*E. angustifolia* root extract, *E. purpurea* root extract vs. placebo, 2×50 drops daily 5x/wk × 12 weeks	Time to first URI, number of participants with at least one infection, global assessment	Negative (time to occurrence first URI and number with infection; global assessment better in the experimental groups ($p = 0.04$)
Grimm, 1999; Schoneberger, 1992	109/108 analyzed	*E. purpurea* extract (Echinacin) 4 mL bid × 8 wks vs. placebo,	Incidence and severity of colds and respiratory infections	Negative (incidence, duration, and severity)
Turner, 2000	117/92 completed	300 mg tid (4% phenolic mixture of *E. purpurea* and *E. angustifolia*) containing 0.16% cichoric acid) vs. placebo, 14 days prior and 5 days after rhinovirus challenge	Viral infection, illness severity	Negative (infection and clinical colds)
TREATMENT				
Barrett, 2002	148/142 completed	6 doses (each dose contained *E. angustifolia* root 500 mg, *E. purpurea* root 250 mg, and *E. purpurea* herb 250 mg) vs. placebo (1332 mg alfalfa/dose) on Day 1, then 3 doses daily until symptoms resolved or until Day 10	Self-assessed symptom severity (9-point Likert scale for 15 symptoms) and duration of self-reported symptoms	Negative for duration, symptom severity, adverse effects
Schulten, 2001	80/70 analyzed	*E. purpurea* extract (Echinacin®, 5 mL bid) vs. placebo, × 10 days	Number of days with illness (modified Jackson score), proportion of patients with a "complete picture of the common cold," subjective assessment	Significantly decreased number of days with symptoms to 6 days in treated group vs. 9 days in placebo group (by log rank test, one-sided ($p = 0.0112$); no significant difference in proportion of patients with "complete" cold; significantly more thought their cold was "shorter than usual" (two-sided $p = 0.007$)
Lindenmuth, 2000	95/all completed (early symptoms of cold or flu)	Echinacea Plus tea® (*E. purpurea* herb, *E. angustifolia* herb, and a dry extract of *E. purpurea* root in a 6:1 ratio) vs. placebo, 5-6 cups/day titrating down to 1 cup/day over 5 days	Self-assessed questionnaire on effectiveness for symptom relief (1-5 scale from not effective to excellent); days with symptoms; time to symptom change	Improvement in all measures: symptom relief (treatment mean 4.125, SD 0.9593 vs. placebo 2.787, SD 0.9541, $t = 6.814$ $p < 0.001$); number of days with symptoms (4.333, SD 0.9302 vs. 2.34, SD 1.088, $t = 9.499$, $p < 0.001$); days to symptom change (3.854, SD 0.9735 vs. 2.297, SD 1.204, $t = 6.865$, $p < 0.001$).
Dorn, 1997, Braunig, 1993	160/?160 (viral or bacterial URIs)	*E. pallida* root 900 mg/day vs. placebo × 8-10 days	Length of illness, symptom relief	Decreased duration of illness and decreased overall symptom scores (both $p < 0.0001$)

TABLE 1
(Cont'd)

PREVENTION	n	Treatment	Outcome Measures	Results
Brinkeborn, 1999	559 randomized while well; 246 fell ill, used treatment, and returned for follow-up)	4 groups: Echinaforce 2 tabs tid (6.78 mg) *E. purpurea* root 5% herb 95%) vs. concentrate (48.27 mg same) vs. *E. purpurea* root extract (26.9 mg) vs. placebo	Symptom relief by 12-symptom complaint index assessed by doctor and patient	Significant reduction in 12-symptom index by doctor's record by Echinaforce and concentrate vs placebo $p < 0.05$; no significant reduction in *E. purpurea* root group) by patient assessment in ITT analysis, only the Echinaforce concentrate significantly reduced complaint index ($p = 0.01$)
Hoheisel, 1997	120/120	Echinagard (pressed juice of *E. purpurea* herb; drops every 2 hours × 1 day, then up to 20 drops 3x/day) vs. placebo	Development of a "real" cold, time to improvement	Fewer developed clinical colds (24/60 in the treatment group vs. 36/60 in the control group) $p = 0.044$; time to improvement shorter among those with colds (by about 2 days, $p < 0.001$
Braunig, 1992	180/?180 (influenza-like URI)	3 groups: *E. purpurea* root extract 90 drops (450 mg) vs. *E. purpurea* root extract 180 drops (900 mg) vs. placebo, each daily × 8-10 days	Duration of illness, symptom relief	Clinical scores by physicians were significantly better ($p < 0.0001$) in the 180 -drop dose group compared to both the 90-drop dose group and the placebo group, low dose was not better than placebo, symptom scores also apparently better in the high-dose group *p* value not apparent from translation)

times per week for 12 weeks). No difference was noted among the groups in the time to occurrence of the first URI, nor in the proportion of groups that developed URIs.[1] Another trial tested pressed juice of *E. purpurea* herb extract (4 mL twice daily for 8 weeks) in 109 subjects and found no benefit on the incidence, duration, or severity of colds or URIs.[2,3] The only trial of experimentally induced colds found no effect of an echinacea extract containing 0.16% cichoric acid on the incidence of experimentally induced infection or colds.[4]

In contrast, all but one randomized, placebo-controlled trials of echinacea-only products identified for the treatment of URIs found a benefit in at least one treated group. Seven trials, with a total of more than a thousand subjects, tested various echinacea extracts: *E. pallida* root,[5,6] *E. purpurea* pressed juice (Echinagard® and Echinacin®,[7,8] *E. purpurea* root,[9,10] two doses of Echinaforce® (containing *E. purpurea* root 5%, herb 95%)[10] and Echinacea Plus® tea (containing *E. purpurea* herb, *E. angustifolia* herb, and *E. purpurea* root dry extract) and a mixture of *E. angustifolia* root, *E. purpurea* root, and *E. purpurea* herb.[11,12] Most formulations (all except for two extracts of E. purpurea root and the mixture of *E. angustifolia* root[9,10] with *E. purpurea* root and herb[12]) were significantly better than placebo in the primary outcome measures. Most trials examined duration

of symptoms. The Hoheisel study, sometimes classified as a prevention trial, told participants to take echinacea at the first onset of symptoms and found a significant reduction in the proportion of subjects who developed a "real cold," as well as a shorter duration of symptoms among those who fell ill.

The Barrett 2002 study is the only treatment trial that found no effect at all. This trial, however, is highly problematic because of the choice to use alfalfa as a "placebo." Alfalfa contains L-canavanine, a non-protein amino acid known to affect the immune system. In humans, alfalfa has been linked to flares of quiescent systemic lupus erythematosus (SLE) and reversible SLE-like syndrome in those without a history of SLE.[13] An agent that may affect the immune system is obviously not an inappropriate placebo for a study of infection.

Formulations, Active Constituents, and Mechanisms of Action

Extracts of *E. purpurea* root may be inferior to *E. pallida* root or *E. purpurea* herb. The Brinkeborn study, a four-armed study of 559 subjects that compared placebo to Echinaforce® (two potencies) and *E. purpurea* root extract, found that the *E. purpurea* root extract was not superior to placebo. The Braunig 1992 trial compared two doses of *E. purpurea* root extract (90 drops daily vs. 180 drops daily) to placebo and found a benefit only in the high-dose group; this trial has been criticized as not truly blinded.[13]

Although alkylamides are believed to be the most active constituents of echinacea, caffeic acid derivatives (ie, cichoric acid, echinacoside), ketoalkenes/ketoalkynes glycoproteins, and polysaccharides may also be active. Compounds vary in type and ratio among plant parts and species, so the most effective constituent(s) remain to be determined.[14] Although "standardized" extracts of echinacea are available, preparations are standardized to different compounds, some of which are of questionable significance. Echinacoside, a caffeic acid derivative, is most often used to "standardize" commercial echinacea preparations. While echinacoside may be suitable for standardizing extracts made from the roots of *E. angustifolia* and *E. pallida,* the roots of *E. purpurea* lack echinacoside. Cichoric acid, another caffeic acid derivative used to "standardize" extracts, is regarded as the most active constituent of fresh-squeezed juice preparations, but remains unsuitable for standardizing extracts since only traces exist in the roots of *E. angustifolia.*

The predominant mechanism of action of echinacea extracts appears to be through stimulation of phagocytosis. A double-blind study in 24 healthy men found that an ethanolic *E. purpurea* root extract increased phagocytosis significantly more than the placebo.[15] Stimulation of phagocytosis was demonstrated in most *in vitro* assays. Echinacea extracts may also enhance natural killer cell activity. In *in vitro* assays utilizing peripheral blood mononuclear cells from three groups of subjects (healthy, with AIDS, or with chronic fatigue syndrome), *E. purpurea* whole-plant extract increased antibody-dependent cellular cytotoxicity against human herpes virus-6 infected H9 cells and enhanced natural killer cell function in all groups.[16] Although parenteral administration of several polysaccharides has stimulated macrophage cytotoxicity, these polysaccharides would be unlikely to survive oral administration.[14]

Adverse Reactions/Interactions

With oral products, an unpleasant taste is the most common side effect. Allergic skin reactions may also occur. Adverse events attributed to echinacea include 4 cases of anaphylaxis, 12 cases of acute asthma, and 10 cases of urticaria/angioedema reported to the Australian Adverse Drug Reactions Advisory Committee. Three of five cases evaluated by the reviewers had positive skin prick tests.[17] Parenteral administration of *E. purpurea* juice may cause shivering, fever, and muscle weakness.[18] A case report documents four episodes of erythema nodosum, over 18-month period, that were temporally associated with use of echinacea (an unidentified preparation) in a 41-year-old, healthy man, who was also taking St. John's wort and occasional loratidine.[19] He remained free of episodes for 1 year after discontinuing echinacea. Theoretical concerns that echinacea may worsen symptoms of autoimmune disease have been raised, but no such cases have been reported.

A controlled study compared 206 women who reported gestational use of echinacea to the Motherisk program (112 reported first trimester use) with 206 controls. No significant differences ex-

isted between groups for major or minor malformations.[20]

Discussion

Little research has been done on therapies for the prevention and treatment of colds. A MEDLINE search on cold and the randomized, controlled trials that have been conducted between 1995 and 2001 revealed 40 trials, 29 of which were for therapies to prevent or treat colds. More trials (four) have been completed on echinacea preparations than on any other therapy, except zinc (also four). To date, most reviews of echinacea have included combinations of echinacea with other herbs (most commonly *Baptisia tinctoria* and *Thuja occidentalis*); sometimes homeopathic components are also included.[21,22,23] One paper reviewed echinacea-only products but only included trials conducted between 1994 and 1999.[24] Mixing studies of combination-herb products with single-herb products clouds the picture. Even when echinacea is assessed alone, preparations made from different species and plant parts predictably have different effects. These diverse products should be viewed as distinct phytopharmaceuticals.

In summary, evidence supports the efficacy of echinacea extracts for reducing the duration of symptoms associated with URIs, but atopic patients may experience adverse reactions, including anaphylaxis. The evidence from these trials does not suggest that echinacea is beneficial in preventing URIs. Preparations made from pressed juice of *E. purpurea* herb (eg, Echinacin® and others) or *E. pallida* root appear superior to those made from *E. purpurea* root. Notably, these trials bear out the conclusions of the German Commission E, which is the body that evaluated herbal products for the German government before disbanding in 1995. Before most of these trials were published, Commission E had issued positive monographs on *E. pallida* root and *E. purpurea* herb and concluded that evidence of efficacy for other extracts was insufficient. The most active constituents have not been identified, so standardized products of echinacea are no guarantor of effectiveness. The use of echinacea to prevent URIs should be discouraged.

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