Echinacea for Upper Respiratory Infection

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OBJECTIVES. To review the evidence regarding the effectiveness of orally ingested *Echinacea* extracts in reducing the incidence, severity, or duration of acute upper respiratory infections (URIs).

SEARCH STRATEGIES. Information from a wide range of sources was used as background material. More than 100 articles, books, and book chapters were reviewed for content and further references. Database searches, bibliographic reviews, and conversations with experts were carried out iteratively from January 1997 to February 1999.

SELECTION CRITERIA. Published or unpublished reports of all blinded placebo-controlled randomized trials of any *Echinacea* formulation used as a treatment or for the prevention of URIs.

DATA COLLECTION AND ANALYSIS. Review considerations included randomization, blinding, power, validity and clinical relevance of outcome measurements, inclusion and exclusion criteria, indistinguishability of treatment and placebo, and appropriateness of conclusions for the data presented.

MAIN RESULTS. Nine treatment trials and 4 prevention trials fitting the selection criteria were found. Eight of the treatment trials reported generally positive results, and 3 of the prevention trials reported marginal benefit. Methodologic quality of the majority of the trials was modest.

CONCLUSIONS. Evidence from published trials suggests that *Echinacea* may be beneficial for the early treatment of acute URIs. The influence of publication bias on those results is unknown. *Echinacea* preparations vary widely in composition, and are often found in combination with other potentially active constituents, making specific dose recommendations problematic. There is very little evidence supporting the prolonged use of *Echinacea* for the prevention of URIs.

KEY WORDS. Plant extracts; medicine, herbal; respiratory tract infections; botanicals; phytomedicine. *(J Fam Pract 1999; 48:628-635)*

CLINICAL QUESTION Are orally ingested *Echinacea* extracts effective in reducing the incidence, severity, or duration of acute upper respiratory infections?

Upper respiratory infection (URI), usually viral, with its common variants rhinosinusitis and pharyngitis, is the highest-incidence acute illness in the developed world.[1-3] According to estimates, the average adult in the United States has 2 to 4 colds per year; the average schoolchild has 6 to 10.[4] Although patients with complications, such as bacterial sinusitis, otitis media, streptococcal pharyngitis, bronchospasm, or pneumonia may benefit from antibiotic or inhaler treatment, medical science has little to offer for uncomplicated infections.[5-10] Nevertheless, antibiotics are frequently prescribed, despite convincing evidence of little or no benefit.[11-17] Clearly, there is great need for effective, safe, and affordable treatment.

Botanical extracts from plants of the genus *Echinacea* are among the most widely used herbal medicines throughout Europe and North America and are most commonly used for the prevention or treatment of URIs. *Echinacea* extracts are believed to affect URIs through "immunostimulating" activity. Symptom reduction through immunomodulation holds some theoretical and empirical promise.[18,19] If effective, such treatment could have an impact on the morbidity and loss of productivity associated with URIs, and the overuse of antibiotics and the effects of their sequelae in terms of costs, adverse effects, and antibiotic resistance.

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BACKGROUND

Echinacea was first used by Native Americans as a remedy for a wide variety of illnesses. It was mentioned in the *Flora Virginica* in 1762, the *Eclectic Dispensatory of the United States of America* in 1852, and the *National Formulary of the United States* from 1916 until 1950.[20,21] A 1909 editorial in the *Journal of the American Medical Association* stated that *Echinacea* was "deemed unworthy of future consideration," and it subsequently fell into many decades of disuse in the United States.[22] In Europe, however, *Echinacea* grew in popularity from its introduction in the 1920s to the present. Extracts from the leaves, flowers, and roots of *Echinacea purpurea* and its cousins *E pallida* and *E angustifolia* are currently sold under hundreds of brand names throughout Europe and North America. In Germany, *Echinacea* has been approved by the German regulatory

Commission E for treating respiratory and urinary tract infections.[23] More than 3 million physician prescriptions for *Echinacea* preparations are written each year.[24,25] More than 400 scientific studies, mostly German, have detailed *Echinacea*'s botany, chemistry, pharmacology, and clinical effects.[26-29]

In the United States, perhaps because of the regulatory climate,[30] herbal medicines are usually used without the advice or knowledge of a physician. Although precise estimates of the scope of *Echinacea* use in the United States are not available, several indicators point toward a large and growing pattern of use. Eisenberg and colleagues,[31] using a randomized national telephone survey, estimated that in 1990 34% of Americans had used some type of unconventional medicine, and 10% had seen a provider of herbal therapy. Using the same methods, these researchers[32] put the 1997 estimates at 42% and 15%, respectively. Another randomized national telephone survey in 1997 estimated that 17% of Americans used some type of herbal therapy.[33] A Gallup poll in 1997 estimated that 32% of Americans used herbal medicines, and a Harris poll in 1998 placed the figure at 37%.[34] According to recent market surveys, Americans spend close to $4 billion a year on herbal supplements.[34] Several surveys have indicated that *Echinacea* preparations are the leading botanical medicines in the United States, with close to 10% of the total herbal market.[34,35] Given its current popularity and reputation as scientifically justified, *Echinacea* will likely continue to be widely used.

Echinacea extracts are thought to have immunomodulating pharmacologic activity. Most notably, macrophage activation and enhanced phagocytosis have been reported in a number of studies.[36-42] Serum levels of properdin, a member of the complement system, increase after *Echinacea* administration.[43] Increased levels of tumor necrosis factor alpha, interleukins 1, 6, and 10, and of several other cytokines have also been variously reported.[44,45] Leukocytosis (especially granulocytes and macrophages) has been variably observed in tissue culture and live animal experiments.[43] *Echinacea* extracts given to mice before an injection with *Candida* and *Listeria* species have improved survival rates.[46,47] Anti-inflammatory effects have also been reported,[48-50] as have antibacterial, antiviral, and antiparasitical activities.[43,51] *Echinacea*'s pharmacologic effects appear to result from a combination of active ingredients rather than from a single agent. Various chemical constituents, including alkamides, caffeic acid derivatives (cicchoric acid), flavonoids, glycoproteins, isobutylamides, polyenes, and polysaccharides, have been identified and implicated as active constituents.[52,53] These phytochemicals occur at variable levels among the flowers, leaves, stems, and roots of the 3 medicinal species, *E purpurea*, *E angustifolia*, and *E pallida*.

METHODS

The goal of our search strategy was to locate, retrieve, and review the original reports of all blinded randomized trials of *Echinacea* for the prevention or treatment of acute URI. Throughout 1997 and 1998, we used MEDLINE and other bibliographic reference services to find relevant articles. Searches using variants of the key word "echinacea" were repeated on multiple occasions, covering all years available. More than 100 articles, books, and book chapters were reviewed for content and further references. Herbal medicine experts in the United States and Germany were contacted and questioned concerning their knowledge of published and unpublished controlled trials. All relevant original reports of randomized controlled trials (RCTs) were requested and reviewed in detail. Several of the RCTs we reviewed were not cited in MEDLINE. Retrieval of a few of the older German studies required personal contact with physicians and researchers in Germany, as medical libraries in the United States were unable to locate the studies. Seven of the RCTs were reviewed in the original German by a family physician fluent in the language. Review considerations included randomization, blinding, power, validity and clinical relevance of outcome measurements, inclusion and exclusion criteria, indistinguishability of treatment and placebo, and appropriateness of conclusions for the data presented. Because of dissimilarities in products, methods, and outcome measurements, meta-analysis was not a viable option.

RESULTS

Following the search strategy outlined above, reports of 13 blinded randomized studies were obtained and reviewed (Table). We found no meta-analyses of *Echinacea* trials. However, Melchart and colleagues[54] reviewed 26 prospective trials (18 randomized, 11 double-blind) testing *Echinacea* for a variety of indications. Some 30 of 34 reported outcomes in treatment groups were claimed to be superior to controls by the original authors. However, Melchart and coworkers concluded that only 22 of the 34 outcomes were reasonably demonstrated. Further, only 8 of the 26 trials earned 50% or better on the researchers' quality point-scoring system. Of the 12 URI trials, (6 prevention, 6 treatment), 9 were double-blinded,[55-63] but only 5 of these earned more than 50 quality points.[55-57,60,63] We reviewed all 9 randomized blinded URI trials identified by Melchart and coworkers, as well as 4 trials conducted subsequently.[64-66] Of the 13 trials we reviewed, 9 were treatment trials, and 4 were prevention trials. All studies were randomized and double-blinded. Eight of 9 treatment trials reported benefit. The study reporting no treatment benefit remains unpublished.[64] Two of the prevention trials reported marginal benefit.[58,60] A third

TABLE

Double-Blind Randomized Placebo-Controlled Trials of *Echinacea* Formulations for Respiratory Infections

Species (Product)	Plant Part	Reference	Purpose	N	Outcome Measure(s)*	Benefit	Limits
E purpurea (Echinaforce)	Herb and root	Brinkeborn, 1998	Treat	119	URI symptoms	Yes	AB
E purpurea (Echinagard)†	Herb	Hoheisel, 1997	Treat	120	URI symptoms	Yes	AB
E purpurea (2 doses *E purpurea* extract)	Root	Bräunig, 1992	Treat	180	Flu-like symptoms	Yes	AB
E pallida (*E pallida* extract)	Root	Bräunig, 1993	Treat	160	Flu-like symptoms	Yes	AB
E angustifolia (Resistan)‡	Herb and root	Dorn, 1989	Treat	100	URI symptoms and signs	Yes	AB
E angustifolia, pallida (Esberitox-N)§	Root	Reitz, 1990	Treat	150	URI symptoms and signs	Trend	ABC
E angustifolia, pallida (Esberitox)	Root	Vorberg, 1984	Treat	100	URI symptoms and signs	Trend	ABC
E angustifolia (*E angustifolia*)	Unknown	Galea, 1996	Treat	235	URI symptoms	No	ABD
E angustifolia (Resistan)‡	Herb and root	Vorberg, 1989	Treat	100	URI symptoms and signs	Yes	ABC
E angustifolia, E purpurea (3 arm)	Root	Melchart, 1998	Prevent	302	URI incidence	Trend	AC
E purpurea (Echinacin)	Herb	Schöneberger, 1992 Grimm, 1999	Prevent	109	URI incidence	Trend	ABC
E angustifolia (Resistan)‡	Herb and root	Schmidt, 1990	Prevent	646	URI incidence	Trend	ABC
E angustifolia, pallida (Esberitox)‖	Root	Forth, 1981	Prevent	95	URI incidence	Trend	ABC

E denotes *Echinacea*; URI, upper respiratory infection.
*Flu-like illnesses included fever, chills, and muscle aches along with upper respiratory symptoms.
†Echinagard, also called Echinacin, is a direct extract from the above-ground parts of *Echinacea purpurea.*
‡Resistan contains extracts of *Eupatorium, Baptista,* and *Arnica,* as well as *Echinacea angustifolia.*
§Esberitox-N contains extracts from *Babtista* and *Herba thujae,* as well as *Echinacea angustifolia* and *Echinacea pallida.*
‖Esberitox contains homeopathic dilutions of *Apis, Crotal, Silicea,* and *Lachesis* as well as the ingredients in Esberitox-N.
Note: Limitations: (A) lack of objective, validated measures; (B) no report of whether participants thought they took *Echinacea* or placebo; (C) trends rather than statistically and clinically significant benefits (insufficient power); and (D) insufficient dose.

was reported in 1992 to show benefit[61] — subgroup analyses found statistical significance — but was later reported as largely negative.[65] The authors of the fourth study (which we judged to be of the highest quality) found no statistically significant benefit, but noted that a 15% reduction in URI incidence attributable to *Echinacea* was consistent with their findings.[66]

Treatment Trials

The most recently reported *Echinacea* treatment trial was published by Brinkeborn and colleagues[66] in 1998. Approximately 119 participants were treated for 8 days with 3 doses of 2 tablets each of Echinaforce, a dried ethanolic extract of *E purpurea* (95% herb, 5% root). Ten symptoms and the "overall clinical picture" were assessed on a severity scale of 0 to 3 with a physician visit at the beginning of an acute URI (day 1 or 2 of symptoms) and again at day 8. An intention-to-treat analysis showed statistically significant benefit, with an indexed score dropping from 9.0 to 4.1 in the treatment group compared with 8.8 to 5.3 in the placebo group ($P = .045$). A per-protocol analysis of 87 of the participants yielded highly significant results ($P = .007$). Construction of the index was not described, and inclusion criteria, exclusion criteria, and verification of randomization and blinding were not properly reported.

Also recently published, and perhaps most convinc-

ing in its reported benefit, was the study by Hoheisel and coworkers[66] in 1997. This was a double-blind randomized placebo-controlled single-center clinical trial among adult factory workers in Sweden. The 120 participants were recruited at the first sign of URI, but before a full cold had developed. Participants were randomly given either placebo or active drug, and were followed up until symptoms had resolved. The active drug used was Echinagard, also called Echinacin, a commercial preparation made of juice from the aboveground parts of *E purpurea*. Participants were instructed to take 20 drops every 2 hours for the first day, and 3 times per day thereafter until symptoms resolved. The authors reported that 60% of the placebo groups, but only 40% of the *Echinacea* group, developed a "real cold." Among those who had a "real cold," the median time to resolution was 4 days in the *Echinacea* group and 8 days in the placebo group. Statistical significance was reached among all reported outcomes in an intention-to-treat analysis. The limitations of this study include: poorly defined inclusion and exclusion criteria, use of retrospectively defined criteria for progression from "first sign of a cold" to "real cold,"[65] and lack of evidence of indistinguishability between *Echinacea* and placebo.

In their 1992 article, Bräunig and coworkers[55] reported the results of a randomized double-blind trial of *E purpurea* root extract among 180 volunteers presenting with recent-onset influenza-like respiratory symptoms. There were 60 participants in each of the 3 groups: placebo, low-dose, and high-dose. The 2 treatment groups received twice daily doses of either 1 dropperful (about 4.5 mL) or 2 dropperfuls (about 9 mL) of juice extracted from *E purpurea* root. Primary end points were 8 symptoms (cough, sore throat, nasal symptoms, tearing, headache, fatigue, chills or sweats, and muscle aches) and 1 global indicator of severity, all rated on a 0 to 3 scale as either absent, mild, moderate, or severe, with measurements taken at time 0, after 3 to 4 days, and after 8 to 10 days. Although the low-dose regimen showed little improvement over placebo, the higher-dose group showed statistically significant improvement over placebo in several symptom scores, with positive trends in all measurements. Symptom scores in the treated group were 24% to 50% lower in the placebo group at 3 to 4 days, with the gap widening to 36% to 75% at 8 to 10 days. This study is singular in reporting a dose-dependency effect.

In their 1993 article, Bräunig and colleagues[56] described the results of a randomized double-blind clinical trial of *E pallida* root extract among 160 volunteers presenting with influenza-like respiratory infection. The dose used was equivalent to approximately 900 mg per day of dried extract. Symptom assessment was similar to that described above, with a 4-point none-to-severe rating scale assessed at days 3 to 4 and 8 to 10. The median duration of illness in the *Echinacea* group was 9.8 days, a statistically significant (P <.001) improvement over placebo (13 days). Interestingly, a physician assessment attempted to classify infections as viral or bacterial. A subgroup analysis showed greater benefit among patients with viral infections. White blood counts and differentials were not clearly different between the placebo and verum groups or the viral and bacterial groups.

Dorn's[57] trial consisted of recruiting 100 participants within 2 days of URI onset, and treating with either placebo or Resistan, a commercial preparation made primarily from *E angustifolia* herb and root, but also containing extracts from *Eupatorium perfoliatum*, *Baptisia*, and *Arnica*. Dosage was 30 cc for the first and second days, followed by 15 cc on the third through sixth days. Outcomes scored on a 0- to 3-point scale (none, mild, moderate, severe) included 7 self-reported symptoms and several physician-documented signs. These were assessed twice, at days 2 to 4 and 6 to 8. Three symptoms (sore throat, nasal drainage, and cough), and 1 sign (pharyngeal erythema), were reported as significantly superior to placebo (P <.01).

Vorberg and Schneider[63] reported a treatment trial in 1989 of Resistan among 100 participants suffering from URI. Patients were enrolled in the first 2 days of URI symptoms and randomly treated with either Resistan or an identical placebo. Symptom scores at days 3 and 8 were significantly improved (P < .01) in the treatment group when compared with placebo, with some benefit found in all assessed symptoms. An approximately 20% benefit at day 3 widened to an average 50% reduction at day 8. The authors concluded that there was a clear severity and duration benefit to *Echinacea* when compared with placebo.

Reitz[59] described the results of a trial of Esberitox-N among 150 participants with respiratory infections. Esberitox-N is a commercial preparation containing extracts from *E angustifolia* and *E pallida* roots, along with small amounts of *Baptisia* and *Thuja occidentalis* extracts. Participants were randomized to treatment or placebo (containing Vitamin C) for 8 weeks and were followed in a double-blinded manner for approximately 1 year. Outcomes measured at 7 and 14 days and monthly thereafter included 8 symptoms, 3 signs, and blood work, including a complete blood cell count and an immunoglobulin measurement. Reitz reported that the majority of symptoms and signs at 7 and 14 days were significantly better in the Esberitox group than with placebo, but provided little statistical analysis to support this claim. Relative improvements in nasal symptoms were noted most prominently. No differences in laboratory measurements were reported.

The 1984 trial by Vorberg[62] included 100 participants treated with either vitamin C as placebo or Esberitox. In addition to the ingredients in Esberitox-N, Esberitox contains homeopathic dilutions of *Apis*, *Crotal*, *Silicea*, and *Lachesis*. Outcomes were self-

reported symptoms and physician-reported signs, all assessed on a 0 to 3 scale of severity at days 3 and 10. Headache (P <.001), cough (P <.05), and subfebrile temperature (P <.01) differed significantly, favoring the Esberitox over the vitamin C group. Fatigue, sore throat, difficulty swallowing, nasal drainage, and physician-reported pharyngeal erythema and edema all trended toward benefit in the Esberitox group.

Of the 13 studies we reviewed, the one by Galea and Thacker[64] was singular because it reported no measurable benefit, was conducted in North America, and so far remains unpublished. This study treated a total of 190 undergraduate Canadian students with either placebo or a 250-mg capsule preparation of dried *E angustifolia* 3 times per day. Participants were recruited at first sign of URI and followed up by presence or absence of 8 symptoms for 10 days. No clear trends or statistically significant differences were found between the *Echinacea* and placebo groups. The relatively low dose and the lack of measures of severity may account for these negative findings.

A treatment trial of a capsulized mixture of dried powder made from the herb (25%) and root (25%) of *E purpurea* and the root of *E angustifolia* (50%) is currently under way at the Department of Family Medicine at the University of Wisconsin–Madison. Participants are recruited within 36 hours of first symptoms of URI. Capsulized dried plant material is taken in 1 g doses, 6 times on the first day and 3 times on each subsequent day. Symptom-based outcomes are measured daily using Likert-scale severity measures.

Prevention Trials

Melchart and colleagues[68] conducted a 3-arm prevention trial in which 302 volunteers took 50 drops of either placebo or 1 of 2 alcohol extracts from the root of either *E angustifolia* or *E purpurea* twice daily for 12 weeks. This was the first head-to-head trial of *Echinacea* preparations. Median time to onset of first URI was similar among the 3 groups. Compared with placebo, the relative risk of an infection was 0.80 in the *E purpurea* group and 0.87 in the *E angustifolia* group. These differences were not statistically significant, hence the null hypothesis that *Echinacea* is no better than placebo at preventing URI could not be rejected. The authors speculated that a larger study might be able to show an effect, as their study did not have the power to demonstrate a hypothetical 10% to 20% relative risk benefit.

Schöneberger and coworkers[61] conducted a trial in which 108 patients "with increased susceptibility to colds" were divided into treatment and placebo groups and followed for 8 weeks. Doses of 4 mL juice from the above-ground parts of *E purpurea* (Echinacin or Echinagard) were given twice daily for the entire 8-week period. The treatment group had 19 people (35%) without infections compared with 14 (26%) in the placebo group. Average duration of infection was 5.3 days in the treatment group compared with 7.5 days in the placebo group. When infections were grouped into 3 classes according to severity, the treatment group had fewer individuals in all 3 classes (33 vs 34 in mild; 8 vs 13 in moderate; 0 vs 3 in severe). Although these results were not statistically significant, all trends reported were in favor of *Echinacea* treatment. Grimm and Muller's 1999 analysis and interpretation of this trial[65] was less optimistic than Schöneberger's original report.

Schmidt and colleagues[60] reported a trial of Resistan as prevention of URI among 646 college students at the University of Cologne. Resistan was taken daily for 8 weeks, and students were monitored every 2 weeks and during each URI or flu-like infection. The symptoms assessed on a 0 to 3 scale were cough, sore throat, difficulty swallowing, nasal drainage, congestion, headache, muscle aches, and fatigue. Overall frequency of infection was 15% lower in the *Echinacea* group than in the placebo group, trending toward statistical significance (P = .08). A subgroup analysis of those patients judged to be especially prone to infection (3 or more colds per year for each of the previous 3 years) showed a statistically significant (P <.05) relative risk reduction in verum (27%) compared with placebo (15%).

Forth and colleagues[58] reported a study of 95 patients with URIs randomized to either Esberitox liquid, Esberitox tablet, or identical placebo. Participants took treatments 3 times daily from November until late February, filling out incidence and severity questionnaires every 14 days. A relative risk reduction of 38% (P <.005) was reported for nasal symptoms in the *Echinacea* tablet group compared with placebo. Other outcomes were reported as similar in all groups.

Data collection for a trial designed to study the efficacy of *Echinacea* for URI prevention was recently completed at Bastyr University in Seattle, Washington. Subjects who had experienced at least 3 respiratory infections in the 6 months before enrollment were treated with 8 mL *E purpurea* juice on an intermittent basis over 6 months and were followed in terms of incidence of URI and severity and duration of symptoms. Granolocyte and monocyte phagocytosis differences were assessed using an ex vivo laboratory model. Data analysis is currently under way, with results forthcoming.

Another prevention trial is under way at Oregon Health Sciences University. Explicit methods are not available.

DISCUSSION

In the treatment of acute URI, 8 of 9 randomized trials report some evidence of benefit of *Echinacea*. Although we attempted to review all trials, including

those that were not yet published, we only located 1 unpublished trial, which reported a negative result; therefore, the influence of publication bias remains unknown. Although there is a moderate degree of methodologic deficiency in all of the reviewed studies, and statistical significance is not reached for all outcomes, the published evidence supports the ability of *Echinacea* to decrease the severity and duration of acute URI. This evidence is not conclusive, however, and higher quality trials are needed. Future trials should include: (1) larger, more representative populations; (2) more precisely defined inclusion and exclusion criteria; (3) more precisely defined objective and validated outcomes measurement; (4) data to verify the inability of participants to distinguish placebo from drug; and (5) better characterization of the active constituents and mechanism of action.

Nevertheless, the current evidence suggests that *Echinacea* may work as an early treatment for uncomplicated acute URI. Hoheisel and coworkers[65] reported a 50% reduction in the proportion of people with first sign of a cold who went on to have a "real cold" (from 60% to 40%). Of those subjects who had a "real cold," those taking *Echinacea* had markedly shorter lengths of illness (from a median duration of 8 days to a median duration of 4 days). Brinkeborn and colleagues[66] reported a modest but statistically significant reduction in severity in what appears to be a moderately well-designed trial. The study by Dorn[57] and the 2 studies by Bräunig and coworkers[55,56] reported comparable clinical benefits, with 20% to 50% reductions in severity claimed. We interpret evidence from the highest quality trials to suggest that early dosing is important,[67] as is sufficient dosing.[55] The clinical significance of expected benefits cannot be precisely estimated.

The evidence for *Echinacea*'s ability to prevent rather than treat URI is not as promising. Published studies are few, of moderate quality, and report trends rather than statistically significant differences.[58,60,61] The most recent and best designed of these prevention trials reported nonsignificant trends toward benefits consistent with a 10% to 20% reduction in incidence.[68] We feel that the safety of long-term prophylactic dosing has not been sufficiently demonstrated, at least when valued against uncertain trends toward minor benefit. Neither expected benefits nor risks have been characterized properly, so no recommendations on preventive treatment can be made.

Despite equivocal clinical effects, the safety data on *Echinacea* are relatively strong, at least when compared with many other herbal medicines. In oral doses greater than 15 g per kg and intravenous doses greater than 5 g per kg, it has proved impossible to kill either a rat or a mouse, hence median lethal dose is so far incalculable.[67] Extended (4-week) dosing of rats and mice up to 8 g per kg per day has similarly failed to show adverse effects, with red blood cells, white blood cells, platelets, liver enzymes, creatinine, urea, cholesterol, triglycerides, blood glucose, and body weight as measured end points.[69] In a number of mutagenicity studies, no adverse effects were noted. An open-label trial with more than 1000 patients found the following side effects: unpleasant taste (1.7%), nausea or vomiting (0.5%), abdominal pain (0.3%), and diarrhea (0.3%).[29] During the years 1989 to 1995, 4 of 13 adverse events reported in association with *Echinacea* were thought to be causally related by the German authority. When compared with a denominator of several million patient courses, the reported adverse effect rate, and hence the estimated risk, is quite small. Serious allergic or anaphylactic events have been reported, however, so some caution is needed.[70]

There is currently no universally accepted standardization procedure to ensure comparability among products. Unfortunately, given the apparent multiple chemical nature of *Echinacea*'s mode of action and the unequal distribution of active constituents in the flowers, leaves, stems, and roots of the 3 medicinal species, it is difficult to determine exactly what kind of standardization would be optimal.[71] As there are a number of substances and mechanisms underlying *Echinacea*'s observed clinical effects, it seems possible that whole-extract dosing might indeed remain preferable to isolation and purification of single chemical entities. Still, as the concentrations of active ingredients are known to vary by species, among roots, leaves, and flowers, and most likely by season, soil type, and climate, and as there is very little research that tests one formulation against another, no recommendations regarding specific *Echinacea* products can be made.

RECOMMENDATIONS FOR CLINICAL PRACTICE

The use of *Echinacea* for the early treatment of the common cold can be cautiously supported. More evidence is needed before clear recommendations can be made regarding specific formulations or dosing. Extracts from *E purpurea*, *E angustifolia*, and *E pallida* roots, leaves, and flowers cannot at this point be distinguished from each other in terms of their apparent beneficial activity. If the decision is made to use an *Echinacea* product, we recommend that it be taken early in the course of a cold, several times per day, and discontinued as symptoms abate. We recommend that *Echinacea* not be taken routinely, chronically, or on a preventive basis. We note that no trials have included infants, children, or pregnant women, and recommend caution among those populations. We also note the theoretical contraindication among persons suffering from serious autoimmune disorders.

At the present time we conclude that the evidence suggests *Echinacea* taken early in the course of an ill-

ness may be safe and effective in reducing the severity and duration of the common cold. The evidence of *Echinacea*'s ability to prevent infection is inadequate to make any recommendations in this regard.

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