

Echinacea purpurea Therapy for the Treatment of the Common Cold

A Randomized, Double-blind, Placebo-Controlled Clinical Trial

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Background: *Echinacea purpurea* stimulates the immune response and is promoted to reduce symptom severity and the duration of upper respiratory tract infections. We sought to determine the efficacy of a standardized preparation of *E purpurea* in reducing symptom severity and duration of the common cold.

Methods: A randomized, double-blind, placebo-controlled design was used. Patients received either 100 mg of *E purpurea* (freeze-dried pressed juice from the aerial portion of the plant) or a lactose placebo 3 times daily until cold symptoms were relieved or until the end of 14 days, whichever came first. Symptoms (sneezing, nasal discharge, nasal congestion, headache, sore or scratchy throat, hoarseness, muscle aches, and cough) were scored subjectively by the patient and recorded daily in a diary. Kaplan-Meier curves were used to estimate the survival function of time to resolution in each group. The Wilcoxon rank sum test was used to compare time to resolution between the 2 groups.

Results: One hundred twenty-eight patients were enrolled within 24 hours of cold symptom onset. Group demographic distribution was comparable for sex, age, time from symptom onset to enrollment in the study, average number of colds per year, and smoking history. No statistically significant difference was observed between treatment groups for either total symptom scores (P range, .29-.90) or mean individual symptom scores (P range, .09-.93). The time to resolution of symptoms was not statistically different (P = .73).

Conclusions: Some studies have concluded that *Echinacea* effectively reduces the symptoms and duration of the common cold. We were unable to replicate such findings. Further studies using different preparations and dosages of *E purpurea* are necessary to validate previous claims.

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IN RECENT YEARS, A GROWING NUMBER of people have turned to alternative forms of health care, including massage, acupuncture, homeopathy, energy healing, megavitamins, and herbal medicines.¹ A recent study² has shown that more than 42% of the people in the United States have tried some form of alternative medicine, increasing 8% over a 7-year period and amounting to \$27 billion spent out-of-pocket in 1997. Several factors have been reported as contributing to the increasing trend of alternative medicine, including a growing skepticism over the effectiveness of conventional medicines,³ personal adoption of a holistic orientation to health and health care, poor health status, long-term health problems,⁴ and the ability to reduce the frequency of primary care physician visits.⁵

Herbal medicine is one of the fastest-growing alternative therapies. Eisenberg et al² estimated a 12% increase in the use

of herbal medicines from 1990 to 1997, corresponding to 15% use in the United States during 1997. The uses of herbal medications range from the treatment and prevention of common illnesses to cancer treatment and prevention.^{6,7}

One of the most prevalent acute illnesses in the United States is the common cold, accounting for 40% of all time lost from employment and 30% of time lost from education.⁸ Most adults contract 2 to 4 colds per year, whereas children can have as many as 10 colds per year, producing substantial expenditures for physician office visits and over-the-counter cold and cough remedies, totaling more than \$3.5 billion per year.^{8,9} The infection is self-limiting. It usually resolves within 7 days, but many colds persist for up to 3 weeks and are due to various viruses. Although it is known that rhinovirus infections cause 10% to 40% of colds,⁸ with coronavirus, parainfluenza virus, adenovirus, echovirus, and coxsackievirus accounting for the

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remainder of cases,^{10,11} these viruses produce clinically indistinguishable disease,^{12,13} making specific viral diagnosis difficult. Available remedies act only to alleviate the cold symptoms (sneezing, nasal stuffiness and discharge, sore or scratchy throat, cough, hoarseness, headache, fever, and myalgia), and have no true therapeutic benefit toward eliminating the viral challenge.^{9,14,15}

Echinacea, an herb widely used to treat and prevent common illnesses,¹⁶ has been shown to have immunostimulatory properties.¹⁷ *Echinacea* is a member of the Compositae family of plants, and is commonly referred to as the coneflower, purple coneflower, black-eyed Susan, and narrow-leaved coneflower. Of the 9 species in this family, 3 are of medicinal interest (*Echinacea angustifolia*, *Echinacea pallida*, and *Echinacea purpurea*), and are commonly used to treat viral upper respiratory tract infections.¹⁸ *Echinacea* causes an increase in numbers of circulating white blood cells, activation of phagocytosis by human granulocytes, and elevation of body temperature,¹⁹ resulting primarily from the aerial portion of *E purpurea*¹⁷ and the root portion of *E pallida*.²⁰ Previous research suggests that *Echinacea* may be most effective at lessening the severity and duration of the common cold when taken early in the illness,^{21,22} and has little to no preventative benefit.²³ A review²⁴ of 5 randomized clinical trials investigating the immunomodulatory activity of *Echinacea* concluded that *Echinacea* may be an efficacious immune stimulator, but that there is insufficient evidence to recommend clear therapeutic regimens. Another review²⁵ encompassing 6 clinical trials of *Echinacea* concluded there is insufficient evidence to make recommendations about the preparation or dose to be used to achieve effective immunomodulation.

In this study, we tested a standardized dose of *E purpurea*, prepared from the aerial portion of the plant, for effectiveness at reducing the severity of symptoms and the duration of the common cold when treatment is started within 24 hours of the onset of cold symptoms.

METHODS

PATIENTS

Patients were recruited from the Marshfield Clinic system through advertisement in the Marshfield Clinic staff newsletter and through advertisements in local newspapers. Patients were enrolled after completing an informed consent process approved by the Institutional Review Board of the Marshfield Clinic Research Foundation.

Patients were included in the study if they (1) provided written informed consent; (2) were 18 years or older; (3) presented with acute sneezing and nasal discharge, with or without fever, occurring no less than 6 hours and no longer than 24 hours before enrollment; (4) were free of cold symptoms and fever (temperature, $<38.1^{\circ}\text{C}$) for at least 2 weeks before enrollment; (5) exhibited at least 2 of sneezing, nasal discharge, nasal congestion, muscle aches, headache, sore or scratchy throat, hoarseness, or cough; (6) had no other primary sources of infection, including acute bacterial sinusitis, otitis media, and pneumonia; (7) used a reliable method of contraception, if a woman of childbearing age; (8) were able to read, write, and understand English; and (9) were available for the 2-week period of the study.

Exclusion from the study occurred if the patient (1) had a known hypersensitivity to *Echinacea* or a history of allergy

to plants of the Compositae family; (2) received antibiotics, antihistamines, decongestants, nasal sprays, or corticosteroids in the 48 hours before enrollment; (3) used corticosteroids during the 8 weeks before enrollment; (4) had rales or rhonchi suggestive of a lower respiratory tract infection; (5) had a history of allergic rhinitis due to seasonal allergy or ubiquitous environmental allergy; (6) had bronchitis or sinusitis during the previous month; (7) had a fever (temperature, $\geq 38.1^{\circ}\text{C}$); (8) was pregnant or breastfeeding; (9) was unable to complete a diary; (10) had an underlying immunodeficiency, including the human immunodeficiency virus, AIDS, tuberculosis, multiple sclerosis, collagen vascular disease, renal failure (serum creatinine level >2.0 mg/dL [>176.8 $\mu\text{mol/L}$]), known bacterial infection, liver disease (aspartate aminotransferase or bilirubin level, >2 times normal), eczema or allergic rhinitis, diabetes mellitus, congestive heart failure, or clinically active neoplastic disease (not being clinically remissive for at least 1 year or receiving chemotherapy); (11) had emphysema, asthma, or another chronic lung disease; (12) exhibited positive screening results for group A streptococcal pharyngitis; (13) showed active dependency on alcohol or other drugs; or (14) had known psychiatric disorders that might reduce the likelihood of successful completion of the protocol.

ECHINACEA PREPARATION

The placebo and *Echinacea* (EchinaFresh, an *Echinacea* extract made from the aerial portion of *E purpurea* and standardized for a content of 2.4% soluble β -1,2-D-fructofuranosides) were provided by Enzymatic Therapy, Green Bay, Wis.

STUDY DESIGN

Within 24 hours of the self-reported onset of symptoms, patients were scheduled for the first visit during which the study inclusion and exclusion criteria were reviewed; informed consent was obtained; a brief medical history was collected; and a medical examination, including patient height, weight, blood pressure, oral temperature, and current symptom score (based on a modification of the criteria of Jackson et al²⁶), was performed. In addition, a pharyngeal swab specimen for the rapid streptococcal antigen detection test was obtained and a urine pregnancy test for women of childbearing age was performed. Instructions for the treatment plan were given, diary recording explained, questions answered, and treatment dispensed.

The patients were given capsules containing either 100 mg of freeze-dried pressed juice from a pure standard extract of the aerial portion of *E purpurea* or an identical-appearing lactose placebo capsule, and instructed to take 1 capsule 3 times daily for as long as their symptoms remained or until 14 days had elapsed from the time of enrollment, whichever came first. Treatments and group assignments remained blinded to patients and investigators, with the exception of the clinical pharmacist.

Patients were encouraged not to take any other cold remedies, including antihistamines, decongestants, cough suppressants, corticosteroids, or isotonic sodium chloride solution during the study. Acetaminophen was allowed, if needed. Patients were required to maintain a daily diary, recording whether symptoms of sneezing, nasal discharge, nasal congestion, headache, sore or scratchy throat, hoarseness, muscle aches, and cough were present.

The subjective symptom score scale used was as follows: 0 indicates absent; 1, mild (symptoms were minor); 2, moderate (symptoms caused noticeable discomfort); and 3, severe (symptoms caused marked discomfort, interfering with usual activities).

The total symptom score was defined as the sum of the individual symptom scores, and served to quantify the sever-

ity of the cold. Asymptomatic was defined as a total symptom score of 0 or 1. Cold resolution required that the subject be asymptomatic for at least 12 hours or asymptomatic on the final diary record and at the exit interview.

Compliance was measured at each office visit by counting medication capsules and reviewing data entries in the diary. On days 3, 6, 10, and 13, if still actively enrolled, the study coordinator contacted the participants to answer questions, review possible adverse effects, and assess compliance with instructions and medications. Participants were scheduled for follow-up visits on days 7 and 14, and were asked to schedule a follow-up visit within 1 day of symptom resolution, if less than 7 days. Participants with symptoms persisting beyond day 7 were asked to return to the clinic within 1 day of symptom resolution or on day 14, whichever came first.

At the final follow-up visit, the patient diary forms were reviewed and collected and patients were asked if they had any difficulties following the treatment plan. Compliance with treatment was measured by pill counting and questioning about the use of additional medications (with the exception of acetaminophen). Patients were asked to compare the treatment with previous ones for the common cold and whether they would use the assigned medication again for the common cold. Patients were also asked which treatment they believe they received, the active *E purpurea* or the placebo control.

The cold symptom impact on daily functioning was assessed to determine when patients were able to return to normal daily activities. Medication adverse effects and number of cigarettes smoked were also recorded.

This study was designed to recruit 120 patients, providing 79% power to detect a reduction in the median duration from 7 to 4 days. For the daily total symptom score, the study also had approximately 88% power to detect a reduction of 25%.

STATISTICAL ANALYSIS

Descriptive data were summarized according to a randomized group. Symptom scores were summarized with means of the 4-point severity scale (0 indicates none; 1, mild; 2, moderate; and 3, severe), across patients and symptoms for overall scores and across patients and days (1-7 only) for individual symptoms. In the computation and comparison of total symptom scores and individual symptom scores, when a symptom score was missing, it was imputed as the mean for the same symptom on the previous and subsequent records. If only one adjacent record was missing, it was carried over. If both adjacent records were missing, the total symptom score was coded as missing.

The Kaplan-Meier method was used to construct curves for time to symptom resolution in each group. The confidence limit for the median time to resolution was based on the formula proposed by Brookmeyer and Crowley.²⁷ The Wilcoxon rank sum test was used to compare the time to resolution between the 2 groups. Total symptom scores during the first 7 days and 8 individual symptom scores were compared using the Wilcoxon rank sum test. A difference between groups with $P < .05$ was considered statistically significant.

RESULTS

A total of 128 patients were enrolled in the study. The ages of the participants ranged from 18 to 62 years (mean, 38 years). Of the participants, 14.1% were men and 85.9% were women. The participants reported an average of 15 hours elapsing from the time since symptoms were first noticed to enrollment in the study (range, 2-24 hours). Patients reported an average of 2 colds in the year be-

Patient Demographic Data*

Variable	Placebo Group (Given Lactose) (n = 65)	Active Treatment Group (Given <i>Echinacea purpurea</i>) (n = 63)
Sex		
Male	16.9	11.1
Female	83.1	88.9
Age, mean, y	37.7	37.9
Time to enrollment, mean, h	15.3	15.2
No. of colds in the previous year, mean	2.0	2.2
Smoking history		
Never smoked	64.6	73.0
Previous smoker	23.1	19.1
Current smoker	12.3	7.9

*Data are given as percentage of each group unless otherwise indicated.

fore this study (range, 0-10 colds). Of the subjects, 10.1% were active smokers, 21.1% had smoked previously, and 68.8% had never been smokers (**Table**).

When comparing total symptom scores and individual symptom scores, most patients in our study resolved their cold symptoms by day 7 and, therefore, data from days 8 to 14 of the study are not included. Patients adhered to the recommendation not to take any cough or cold medications other than Tylenol or acetaminophen. Only 16 (12.5%) of the patients reported that they had taken a decongestant at some time during the study. When asked, at the end of the trial, whether the patient believed he or she received the active medication or the placebo, 23.0% of patients in the control group and 24.1% of patients in the *E purpurea* medication group guessed they received the active *E purpurea* medication, with 36.9% and 53.2%, respectively, being uncertain of the medication he or she had been assigned.

A comparison of the total symptom scores for each of the first 7 days showed no statistically significant difference between the placebo control group and the active *E purpurea* group (P range, .29-.90). Individual symptom scores were analyzed by taking the mean treatment group score over days 1 to 7 using daily mean symptom values for each patient. Individual symptom scores were compared between groups using the Wilcoxon rank sum 2-sample test, and did not reveal a statistically significant difference between groups (P range, .09-.93).

Only a few adverse events were reported, with headache and dry mouth being the predominant adverse effects in both treatment groups (**Figure 1**), although this may not accurately reflect adverse events because headache is also a frequent symptom of the common cold.

A comparison of the time to resolution of symptoms did not show a statistically significant difference ($P = .73$) between treatment groups (**Figure 2**).

COMMENT

In this study, we examined whether starting *Echinacea* therapy within the first 24 hours of cold symptom onset would significantly reduce the severity of symptoms and shorten duration. A 100-mg dose of *E purpurea* was taken

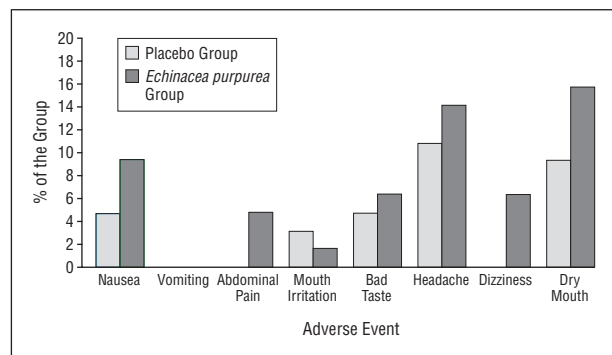


Figure 1. A comparison of adverse events reported by the 2 treatment groups.

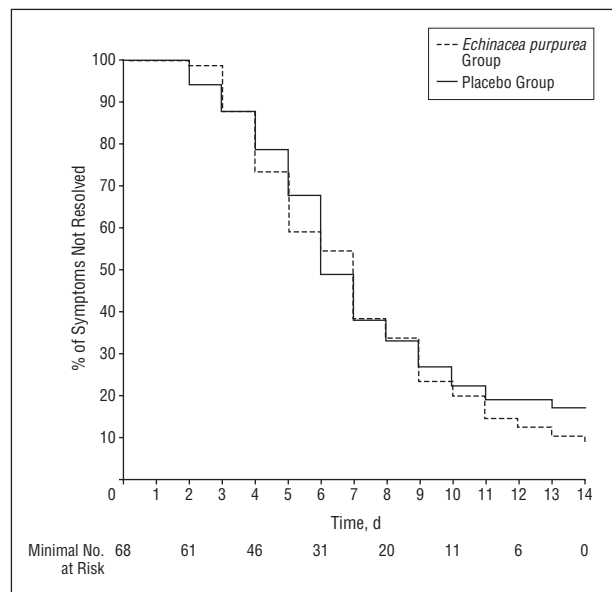


Figure 2. A comparison of time to symptom resolution between the groups. The Kaplan-Meier method was used to construct curves. The Wilcoxon rank sum test was used to compare time to resolution between groups ($P=.73$). Confidence limits for the median time to resolution were based on the formula proposed by Brookmeyer and Crowley.²⁷

3 times daily by patients for 7 days or until symptoms were relieved, but no longer than 14 days. Initial upper respiratory tract infection (common cold) symptoms were confirmed by the collaborating physician within the first 24 hours of self-reported onset of symptoms, and relief of symptoms was confirmed within 1 day of the patient's self-reported recovery. Patients recorded daily symptom severity in a journal using a 4-point severity score index (0 indicates no symptoms; and 3, severe and debilitating symptoms) designed by us. We were unable to reproduce a statistically significant reduction of symptom severity or duration, as demonstrated by Barrett et al.²⁸ We did not observe any statistically significant differences between treatment groups when we analyzed the mean total symptom scores for each of the first 7 days of treatment, nor did we observe any statistically significant difference between groups for individual symptoms when patients' daily mean symptom scores were averaged and analyzed by group. The overall time to resolution of symptoms did not show a statistically significant difference between treatment groups.

Echinacea has been reported to have immunostimulatory properties¹⁷ that can reduce the duration and lessen the symptoms of the common cold.^{21,22,24} Of 9 treatment trials reviewed by Barrett et al,²⁸ 8 reported benefit in reducing the symptoms of upper respiratory tract infections, although additional studies have shown little to no effect of *Echinacea* therapy on common cold symptoms.

In a trial of a proprietary preparation of *E purpurea* (Echinagard) in patients with acute upper respiratory tract infection symptoms,²¹ the researchers concluded that *E purpurea* therapy (specifically, Echinagard) begun at the first sign of cold symptoms inhibited cold progression and resulted in quicker relief of symptoms than placebo. Cold duration was decreased from 8 days for the placebo group to 4 days for the active *E purpurea* group. Unfortunately, the dosage used in this study was not specified and the symptoms and presence of a true cold were not verified by a physician until 10 days of the study had elapsed, questioning whether true colds were present in all patients included and whether the results and assumptions garnered from this study are accurate.

A recent study by Barrett et al²⁹ using a dried mixture of *E angustifolia* roots and *E purpurea* herb and root found no reduction in the severity or duration of upper respiratory tract symptoms when given within the first 24 hours. Grimm and Muller³⁰ were also unable to show a significant reduction in the severity or duration of upper respiratory tract infections when patients were treated with the expressed juice of the whole flowering *E purpurea* plant, minus the roots. This study observed a decrease in duration of 2 days in the *E purpurea*-treated group, from 6½ days with placebo to 4½ days with *E purpurea*. This decrease in duration was not statistically significant ($P=.45$).

It is unlikely that treatment group demographics or patient assumptions about what treatment they received had any impact on the speed of recovery or the perception of symptom severity. There were an equal number of patients in both groups who believed they had received the active medication, and the distribution of patients between treatment groups was comparable for sex, age, time from symptom presentation to enrollment in the study, number of colds in the year before this study, and smoking history (Table).

Doses of 150 to 300 mg of dried *E purpurea* extract taken in solid oral dosage form 3 times daily have been recommended for the effective treatment of the common cold.^{17,31} Doses as low as 13 mg of *E purpurea* extract (95% herb and 5% root) taken 3 times a day up to 7 days have been effective in the treatment of the common cold. It is unlikely that the dose used in this study was too low to produce immunostimulation sufficient to eliminate the virus more quickly than placebo.³²

The full potential of *E purpurea* may depend on the inclusion of other portions of the plant in the preparation. This is supported by a 1999 study³² that found a crude extract of *E purpurea* made from 95% herb and 5% root, taken 3 times daily until symptoms cleared, produced a relative reduction of symptom severity that was significantly higher than that of a placebo ($P=.02$). However, a recent study²⁹ using the whole plant *Echinacea* (consisting of 50% *E angustifolia* root, 25% *E purpurea*

root, and 25% herb) found no benefit in the reduction of symptom scores.

Few adverse events were observed, with headache and dry mouth being most prevalent. However, this may not be an accurate measure for headache as an adverse effect, because headache is a common symptom of the common cold.

One limitation of our study, as is the case with others,^{29,30} is the modest sample size. We enrolled 128 patients in our study, a sample size that may not be large enough to detect a smaller treatment effect of *Echinacea*.

The *Echinacea* preparation used in our study is a well-tolerated, but ineffective, therapy for the common cold. Further investigation would be necessary to determine whether the dosage and composition (flowers, leaves, roots, and/or a combination of species) can be adjusted to produce an immunostimulation that might be adequate to eliminate a viral challenge presented by the organisms responsible for the common cold.

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