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Effects of echinacea on the frequency of upper respiratory tract symptoms: a randomized, double-blind, placebo-controlled trial

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Background: Upper respiratory tract infection symptoms are a common cause of morbidity. Herbal preparations of the plant *Echinacea purpurea* have immune-enhancing properties.

Objective: To compare the frequency of upper respiratory tract symptoms in individuals receiving *E purpurea* capsules and those receiving placebo to evaluate the preventive efficacy of echinacea.

Methods: In a randomized, double-blind clinical trial, 90 volunteers recruited from hospital personnel were randomly assigned to receive 3 capsules twice daily of either placebo (parsley) or *E purpurea* for 8 weeks during the winter months. Upper respiratory tract symptoms were reported weekly during this period.

Results: Fifty-eight individuals were included in the final data analysis: 28 in the echinacea group and 30 in the placebo group. Individuals in the echinacea group reported 9 sick days per person during the 8-week period, whereas the placebo group reported 14 sick days ($z = -0.42$; $P = .67$). Mild adverse effects were noted by 8% of the echinacea group and 7% of the placebo group ($P = .24$).

Conclusion: Prophylactic treatment with commercially available *E purpurea* capsules did not significantly alter the frequency of upper respiratory tract symptoms compared with placebo use.

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INTRODUCTION

Upper respiratory tract infections are a common cause of morbidity, general discomfort, and missed days of work. Symptoms are more frequently encountered during the winter "flu season." More than 200 different viruses can cause common colds in adults, including rhinovirus (the most frequent cause), coronavirus, adenoviruses, respiratory syncytial virus, and parainfluenza viruses.[1] In the United States, on average, adults develop 2 to 4 colds and children 6 to 8 colds each year.[2]

Herbal preparations of the leaves and root of the plant *Echinacea purpurea* increase phagocytic cells in the spleen and bone marrow, acting as phytoimmune modulators or immune system enhancers.[3–5] In vitro studies support claims of immune modulation and indicate that this effect may be mediated by a modification of the activity of polymorphonuclear neutrophil granulocytes and macrophages.[6–9] Echinacea-containing preparations are extensively used for the treatment and prevention of infections and, apart from allergic reactions and an increased incidence of rash, are reported to be generally safe.[10–14]

Clinical trials[14–25] testing the ability of echinacea to prevent colds and ameliorate symptoms have had mixed results. A Cochrane Review[26] found that most available studies reported benefits from echinacea use, but variations in the preparations of echinacea used and methodological quality limited the conclusions. A recent meta-analysis[27] found that standardized echinacea extracts were effective in the prevention of symptoms of the common cold after clinical inoculation. Methodological shortcomings in studies of herbal medicines, including echinacea, have been noted by other researchers as well.[28] A meta-analysis[10] of studies published since 1997 suggested that echinacea was more effective at treating colds than at preventing them.

Although the efficacy of echinacea has not been conclusively demonstrated, there were more than 2.5 million prescriptions for echinacea preparations in Germany in 1993.[8] Use of nonprescription herbal remedies is undoubtedly higher, as almost 40% of patients in a US health maintenance organization indicated using herbal remedies, and echinacea ranks fifth in herbal medicine sales.[12,29] To address the methodological shortcomings identified in previous echinacea studies, we used a randomized, double-blind, placebo-controlled clinical trial designed to answer the following question: Does a commonly used echinacea preparation prevent or reduce upper respiratory tract infection symptoms?

METHODS

Sampling

This study was approved by the University of California San Francisco Institutional Review Board. This research was

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completed as part of the requirements for completion of the Family Medicine Residency Program at the University of California San Francisco–Fresno. For this reason, a convenience sample of healthy adults working in the University Medical Center Family Health Center, including residents, staff, faculty, and nursing staff, served as the participants in this study. This population was expected to have more equitable exposure to cold/influenza. Recruitment consisted of flyers distributed at the University Medical Center and the Family Health Center. Participation was voluntary, and participants were not reimbursed.

Ninety volunteers aged 18 to 65 years were recruited from hospital personnel in November and December 1998. The project was described, and written informed consent was obtained from each participant. Persons with known immune dysfunction, those undergoing immunosuppressive therapy, pregnant or lactating women, and persons with allergies to echinacea or parsley were excluded. Individual characteristics, such as age, race/ethnicity, tobacco use, presence of allergic rhinitis, use of other upper respiratory tract infection preventive measures (herbs, vitamins, or medications), and administration of the influenza vaccine, were recorded. Individuals currently using echinacea were not considered for the study, whereas those using other upper respiratory tract infection preventive measures were allowed to continue their use. Each participant was given an 8-week supply of medicine on enrollment.

Procedure

Participants were randomly assigned to either the experimental or the control group from a list generated using the random-number generator in a spreadsheet program (Microsoft Excel; Microsoft Corp, Redmond, Washington). Participants were asked to take 3 capsules 2 times daily for 8 weeks of either *E purpurea,* 300 mg per capsule, or parsley, 300 mg per capsule. This dose of echinacea was similar to that recommended by the manufacturer. Both types of capsules were provided by the same company and were indistinguishable in size, color, and smell. Capsules were provided in containers marked "A" or "B." Participants, the main investigator, and all persons involved in the study remained blinded to the identity of each group until data analyses were completed.

Participants were contacted by telephone once a week by a trained research assistant and asked to report the number of days during that week in which they experienced sore throat, runny nose, headache, hoarseness, nasal congestion, muscle aches, cough, and fever. Participants with symptoms were also asked about the number of days missed from work and any medications used to treat symptoms, (eg, aspirin, acetaminophen, vitamins, and cold formulas). The number of capsules missed that week and the perceived adverse effects were also recorded. Participants were defined as nonadherent and were excluded from data analysis if they missed more than one-third of the recommended dosage for 2 or more weeks. None of the persons in this study experienced serious adverse effects requiring disclosure of group assignment. Participants were told at the completion of data analyses whether they were in the experimental or placebo group.

Statistical Analysis

Data were entered into a database program (Microsoft Access; Microsoft Corp) and were analyzed using statistical analysis software (SAS for Windows, release 6.12; SAS Institute Inc, Cary, North Carolina). A prospective power analysis was calculated. Based on the assumption of an effect size of 14%, a sample size of 80 was calculated to provide sufficient power (0.80) to detect a difference of 30% (cold frequency SD = 0.5) to 60% (cold frequency SD = 1.0) between the 2 groups at $\alpha = .05$.

Missing data from dropped participants precluded an intention-to-treat analysis. A per-protocol analysis was performed.[30] Means and proportions were calculated for individual characteristics. χ^2 and t tests were used to test for differences between the groups after randomization. The median number of days with each individual symptom was reported owing to the nonnormal distribution of this information. The total number of days with symptoms was calculated by summing the maximum number of days reported with the most prevalent symptom in each week. Thus, the maximum possible total number of symptom days was 56. A Wilcoxon rank sum test was used to compare the treatment and placebo groups for each of the 8 symptoms and the total symptom days. We also compared the 2 groups each week separately for persons reporting symptoms of any kind vs no symptoms at all. χ^2 or Fisher exact tests were used to compare these data.

RESULTS

Ninety individuals were recruited for this study and randomly assigned to either the placebo or the echinacea group. Fifteen individuals in the echinacea group and 13 in the placebo group chose to leave the study, a 31% dropout rate (Fig 1). Six individuals leaving the study (3 from each group) re-

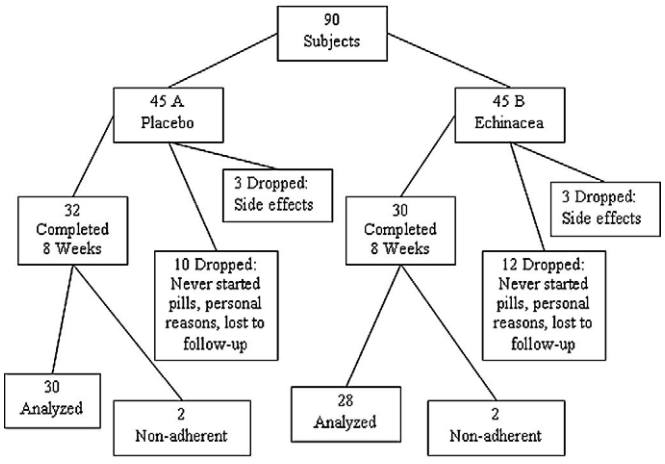

Figure 1. Randomization and participation results.

ported adverse effects that contributed to their study discontinuation. Each group also had 2 nonadherent individuals. There were no significant differences in individual characteristics, reason for dropout, or adherence between the 2 groups after randomization (data not shown). Fifty-eight individuals were included in the final analyses, 28 in the echinacea group and 30 in the placebo group. Table 1 has the individual characteristics for these groups and for individuals randomized but not analyzed. There were no significant differences between the echinacea and placebo groups in their demographic characteristics. There were significant differences between individuals who dropped out or were nonadherent and those who completed the study. Persons not included in the final analysis used fewer vitamins and herbs ($P < .01$) and reported fewer allergies ($P = .03$).

Table 2 summarizes the symptom information for the 2 groups during the 8-week period. Each of the 8 symptoms was compared separately for the 2 groups. No significant differences were found. The median total number of sick days was 9.0 for the echinacea group and 14.0 for the placebo group ($z = -0.42$; $P = .67$). Mild adverse effects were noted by 8% of the echinacea group and 7% of the placebo group ($P = .24$) (data not shown).

We compared the 2 groups each week for those reporting symptoms of any kind. Approximately 40% of the participants reported having symptoms most weeks, with no differences between the 2 groups (Fig 2). Of individuals in either group who reported symptoms, less than half treated those symptoms, and even fewer missed work because of them. The placebo group consistently reported symptoms during any given week more than the echinacea group and treated themselves more often. However, none of these differences were statistically significant.

Table 2. Incidence of Upper Respiratory Tract Symptoms in 8 Weeks by Treatment Group[a]

Symptom	Days with symptom, median (Q1-Q3), No.[b]		*P* value
	Echinacea group (n = 28)	Placebo group (n = 30)	
Cough	2.0 (0–8)	2.5 (0–8)	.66
Sore throat	2.5 (0–7)	1.5 (0–4)	.46
Runny nose	5.0 (0–10)	5.0 (1–14)	.39
Congestion	3.5 (0–10)	7.5 (2–16)	.11
Headache	0.0 (0–3.5)	1.0 (0–3)	.75
Muscle aches	0.0 (0–4)	0.0 (0–3)	.96
Fever	0.0 (0–1)	0.0 (0–1)	.63
Hoarseness	0.0 (0–2)	0.0 (0–1)	.20
Total sick days[c]	9.0 (3–29)	14.0 (3–21)	.67

[a] There were no statistically significant differences between the echinacea and placebo groups using the Wilcoxon rank sum test.
[b] Q1 is the number at the 25th percentile; Q3 is the number at the 75th percentile.
[c] Total sick days is the sum of the most prevalent symptom each week.

DISCUSSION

We found no difference in total symptom days or individual respiratory symptoms for patients taking prophylactic echinacea for 8 weeks compared with those taking parsley capsules. These findings are consistent with other recent studies that do not demonstrate the effectiveness of echinacea in preventing upper respiratory tract infections.

It is conceivable that echinacea actually reduces the total number of symptom days and that this study was simply too small to detect the underlying difference. Assuming the same variance as we observed, at a significance level of 5% and 80% power, group sizes of 28 and 30 participants provided numbers sufficient to detect only a prophylactic echinacea effect of 10 total symptom days. If we had retained and analyzed all the enrolled individuals, this detectable difference would have been reduced to 8 total symptom days. We saw an actual difference of 5 days in the median total number

Table 1. Demographic Characteristics of the 90 Study Participants[a]

Characteristic	Echinacea group (n = 28)	Placebo group (n = 30)	Dropped and nonadherent group (n = 32)
Age, mean, y	38	40	40
Smokers	3 (11)	4 (13)	5 (16)
Allergies[b]	7 (25)	5 (17)	1 (3)
Influenza vaccine	9 (32)	13 (43)	6 (19)
Vitamin/herb use[b]	15 (54)	12 (40)	4 (13)
Race/ethnicity			
Hispanic	8 (29)	6 (20)	13 (41)
White	14 (50)	19 (63)	12 (38)
Other	6 (21)	5 (17)	6 (19)
Unknown	0	0	1 (3)

[a] Data are given as number (percentage) except where indicated otherwise. Statistical tests compared the echinacea group with the placebo group and the echinacea and placebo groups with the dropped group. Age was tested using the *t* test; all other categorical data were tested using the χ^2 test.
[b] Statistically significant at the 5% level (the combined echinacea and placebo groups compared with the dropped group).

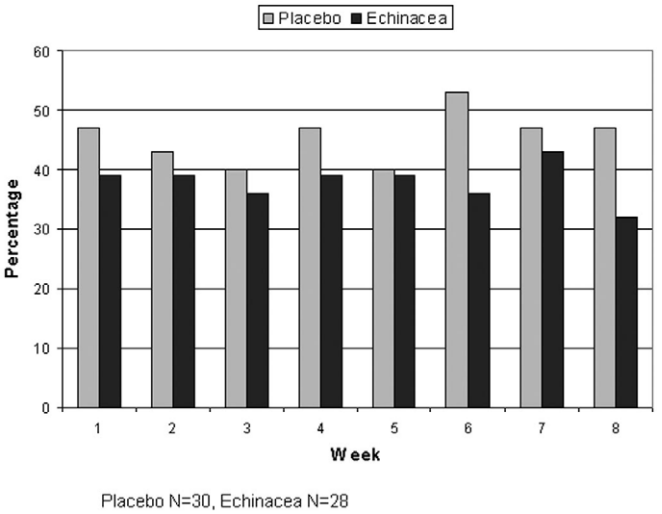

Figure 2. Participants with any respiratory problems.

of symptom days. The total number of symptom days ranged from 0 to 49 (of 56) in the echinacea group and from 0 to 41 in the placebo group. Assuming an actual reduction of 5 total symptom days with echinacea use, a per-group sample size of 111 would be required to detect this reduction at the same 80% power and 5% significance.

The relatively large number of unanalyzed individuals who dropped out or took less than one-third of the scheduled doses (32 of 90) may have biased the results. Excluded individuals were also different from study participants because they reported less herbal remedy use and fewer allergy symptoms. These differences suggest that the dropouts are people who are less afflicted with respiratory symptoms and less preoccupied with prevention. One might speculate that the burden of adherence to the protocol was excessive for this group. Dropouts and nonadherent participants were evenly distributed between the control and intervention groups.

Another limitation of this study is the use of health care professionals as participants, which makes it difficult to generalize these findings to other groups. We did not record participant sex or characterize the findings by this variable. Neither did we control for preventive measures that may have been taken by study participants and possibly biased the findings. Outcomes were not collected from those who dropped out, precluding an intention-to-treat analysis. However, the equal number of dropouts in both arms, coupled with the finding of no effect on symptom days in those taking echinacea, suggests that an intention-to-treat analysis would likely not have changed the conclusions.

Because this study used a dried plant extract, it can be argued that another echinacea formulation might have been more efficacious, but systematic reviews have failed to identify therapeutic distinctions between echinacea preparations.[18,19] This study involved the use of readily available over-the-counter products widely used by the public. Although none are suspected, if parsley has effects on respiratory symptoms, we could expect that findings might be different for the use of a truly inert placebo. A MEDLINE search of parsley and respiratory tract infections yielded no results.

Allopathic medicine has much to learn about alternative therapies. However, until further research is conducted that has greater power to detect differences in outcomes, that accounts for dropout rates, and that standardizes dose effects, the findings from this randomized controlled trial suggest that echinacea does not have a meaningful effect on respiratory tract infection symptoms.

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