

Effectiveness of an Herbal Preparation Containing Echinacea, Propolis, and Vitamin C in Preventing Respiratory Tract Infections in Children

A Randomized, Double-blind, Placebo-Controlled, Multicenter Study

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Objective: To evaluate the effectiveness and safety of a preparation containing echinacea, propolis, and vitamin C in the prevention of respiratory tract infections in children during a 12-week winter period.

Design: Randomized, double-blind, placebo-controlled study.

Subjects: Four hundred thirty children, aged 1 to 5 years, were randomized to an herbal extract preparation (n=215) or a placebo elixir (n=215).

Intervention: Administration of an herbal preparation (Chizukit) containing 50 mg/mL of echinacea, 50 mg/mL of propolis, and 10 mg/mL of vitamin C, or placebo (5.0 mL and 7.5 mL twice daily for ages 1 to 3 years and 4 to 5 years, respectively) for 12 weeks.

Results: Significant mean \pm SD reductions of illnesses were seen in the Chizukit group in the number of illness episodes, 138 vs 308 (55% reduction); number of episodes per child, 0.9 ± 1.1 vs 1.8 ± 1.3 (50% reduction, $P<.001$); and number of days with fever per child, 2.1 ± 2.9 vs 5.4 ± 4.4 (62% reduction, $P<.001$). The total number of illness days and duration of individual episodes were also significantly lower in the Chizukit group. Adverse drug reactions were rare, mild, and transient.

Conclusion: A preventive effect of a product containing echinacea, propolis, and vitamin C on the incidence of respiratory tract infections was observed.

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AT THE TIME OF THE PASSAGE of the Dietary Supplements Health and Education Act in 1994, the annual expenditures for herbal medicines in Europe, Japan, and the United States and Canada were \$6 billion, \$2.1 billion, and \$1.5 billion, respectively.¹ In the United Kingdom, the amount exceeds £40 million.² Since then, consumer sales of herbal products have grown by about 10% to 15% per year.

Some herbal or natural products are believed to affect certain immunological factors. Echinacea, one of the most popular herbal medicines in Europe and the United

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States, is considered an immune stimulant and is usually used for the prevention and treatment of upper respiratory tract infection. Several researchers have demonstrated its cytokine-modulating and macrophage and natural killer cell activity in vitro and in animal studies.³⁻¹¹ However, the chemical properties of echinacea contain-

ing preparations may differ according to the species (*Echinacea purpurea*, *Echinacea pallida*, or *Echinacea angustifolia*) and plant parts (roots, leaves, or whole plants) used, the method of extraction, and the presence of other plant extracts. Propolis is a natural resinous product collected by honeybees from various plant sources and is also used for the management of respiratory infections. After the resin is masticated and salivary enzymes are added, the partially digested material is mixed with beeswax and used in the hives.^{12,13} Propolis is composed of 50% resin and vegetable balsam, 30% wax, 10% essential and aromatic oils, 5% pollen, and 5% other substances (minerals).¹⁴ Its putative antimicrobial activities have been attributed to flavones^{14,15} and its anticancerous activities to caffeic acid phenethyl ester.¹⁶ Propolis has also been shown to have a general anti-inflammatory activity, an antiviral effect on herpes simplex virus type 1^{17,18} and influenza virus,¹⁹ and a suppressive effect on the replication of human immunodeficiency virus type 1.²⁰ Experimental studies indicate that vitamin C may have effects on the

immune system. Ascorbic acid has been reported to increase the proliferative responses of T lymphocytes in vitro^{21,22} and to induce the production of interferon in cell culture.^{23,24} Vitamin C concentrations are up to 100 times greater in phagocytes and lymphocytes than in plasma, suggesting a physiological role in these immune system cells.²⁵

Despite the widespread use of echinacea and propolis, their efficacy remains controversial.^{26,27} Clinical results supporting their effectiveness in the treatment and prevention of upper respiratory tract infection have been published primarily in German and only from trials among adults.²⁷ The objective of the present study was to investigate the effectiveness of a preparation containing echinacea extract, propolis, and vitamin C (Chizukit; Hadas Corp Ltd, Yokneam, Israel) in preventing upper respiratory tract infections in children.

METHODS

SUBJECTS

A randomized, double-blind, placebo-controlled design was used. The study was performed during the winter between November 1, 1999, and March 30, 2000. It took place at 10 primary care pediatric community clinics in Israel. The study sample consisted of 430 children aged 1 to 5 years, 215 each randomized to placebo elixir or active Chizukit groups. The sample size calculation was based on a previous study²⁸ that showed a crude rate of 17.8% reports of flulike and acute respiratory symptoms during a winter period. Although that population (mean age, 28 years) was not restricted to children, other characteristics, such as membership in the Israeli Health Insurance System, seasonality, and 12 weeks' observation, were similar to those among the population of the present study. Assumptions for the calculation were based on a 0.18 probability of colds in the placebo group, estimating that we had 90% power with $\alpha = .05$ to detect a relative risk of 0.5.

Under these conditions, the minimum sample size for each group is 134 subjects. Adding 50% to accommodate probable dropouts, the sample size increased to 201. Although it is expected that a population of children in a clinical trial will report more events than the general population, reducing the sample size needs, we added an extra 10% (13.4 subjects) in case the reported rate in children was lower. Therefore, the final calculated sample size was 215 subjects for each trial group. Exclusion criteria were presence of acute upper respiratory tract infection or other infections within the 7 days before consideration for the study, cystic fibrosis, immunodeficiency syndromes (acquired or congenital), anatomic abnormalities of the respiratory tract (acquired or congenital), malabsorption, or use of immunostimulating or immunosuppressive drugs within 4 weeks before inclusion in the study. Eligible patients were randomly assigned to receive 12 weeks' treatment with placebo elixir or active Chizukit, a preparation containing an extract of 50 mg/mL of echinacea (upper plant parts of *E purpurea* and roots of *E angustifolia*), 50 mg/mL of propolis, and 10 mg/mL of vitamin C. Chizukit is a standard combination widely used in Israel as an over-the-counter drug. Group allocation was done according to a computer-generated randomization list in blocks of 4. The medication or placebo was administered following the company recommendations, twice daily, in a dosage of 5.0 mL for children aged 1 to 3 years and 7.5 mL for children aged 4 to 5 years. If an episode of acute illness occurred during the study, the dosage was increased to 5.0 mL and 7.5 mL, respectively, 4 times daily during the episode only. The medication or placebo was packed in boxes containing 5 bottles of 250 mL

each. The boxes and bottles were identical, and the Chizukit and placebo extracts were indistinguishable by appearance, color, or flavor. The Chizukit and the placebo were supplied directly by the manufacturer, and all randomization lots were stored in a sealed envelope at the pharmacy of the company, to be opened only in the event of an emergency.

At the outset of the study, the parents were given the first box of Chizukit or placebo and were instructed to administer it according to schedule. They also received a diary card to record any acute episodes of respiratory tract illness, specific symptoms (fever, runny nose, and nighttime and daytime cough, if more than usual), use of antipyretic or antibiotic agents, absence from day care or kindergarten, and physician office visits (other than those scheduled). Follow-up visits were conducted at 4, 8, and 12 weeks to hand out new medication, collect data on respiratory morbidity and adverse drug reaction, and monitor compliance. All other visits because of respiratory symptoms were considered *unscheduled physician visits*. The participants were asked to contact the study physicians in the event of symptoms of upper respiratory tract infection to confirm the existence of the acute episode of respiratory illness. The final registration of an illness episode was made only if such a confirmation was done. We define an *adverse drug reaction* as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, that predicts hazard from future administration and warrants prevention or specific treatment, alteration of the dosage regimen, or withdrawal of the product.²⁹ In addition, a study coordinator weekly telephoned the parents to obtain information regarding the occurrence of acute respiratory episodes, symptoms, and use of additional prescribed medication (antipyretics, antibiotics, and decongestants). An episode of *acute illness* was defined as the appearance after at least 5 symptom-free days of 1 or more major signs together with at least 1 minor sign, as follows: *major signs*, fever greater than 38°C, acute otitis media, tonsillopharyngitis with severe redness or exudates, and auscultatory finding compatible with pneumonia; and *minor signs*, hoarseness or stridor, conjunctivitis, cough, and runny nose (significantly more than usual). The *duration of an episode* was measured from the onset of symptoms to the return to the basic condition, based on parental assessment.

The local ethics committee of the Schneider Children's Medical Center of Israel approved the study. All parents gave informed consent to participate before starting the study.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS for Windows, version 10.0 (SPSS Inc, Chicago, Ill). The differences between proportions test was used to determine the significance of differences in nominal variables (number [percentage] of children with ≥ 1 episodes in **Table 1**, and incidence of respiratory system infection in **Table 2**) between the groups, and a *t* test was used to compare the mean number of days with symptoms and means of the other variables. For the relevant variables, mean \pm SD and 95% confidence intervals were calculated.

RESULTS

Three hundred twenty-eight children completed the study, 160 (82 boys) in the Chizukit group and 168 (91 boys) in the placebo group. The mean ages of the groups were 38.3 ± 18.6 months and 38.9 ± 20.6 months, respectively. Ninety-nine children (23%) dropped out, 55 from the Chizukit group and 44 from the placebo group. Among all dropouts, the reasons for withdrawal from the study were unpleasant taste (27 subjects and 22 subjects from

Table 1. Primary Outcome Data*

Variable	Chizukit (n = 160)	Placebo (n = 168)	Reduction, %	P Value
Total No. of episodes	138	308	55	...
Total No. of illness days	423	1040	59	...
No. (%) of children with ≥1 episodes	85 (53.1)	150 (89.3)	43	<.001†
No. of episodes per child	0.9 ± 1.1	1.8 ± 1.3	50	<.001‡
Days of illness per child	2.6 ± 4.2	6.2 ± 5.0	58	<.001‡
Duration of individual episodes	1.6 ± 1.9	2.9 ± 1.6	45	<.001‡

*Data are mean ± SD unless otherwise indicated. Chizukit is an herbal preparation. See text for detail.

†Difference between proportions test.

‡t Test.

Table 2. Incidence of Respiratory System Infection

Diagnosis	No. (%)		Reduction, %	P Value†
	Chizukit* (n = 160)	Placebo (n = 168)		
Upper respiratory tract infection	79 (47.4)	158 (94.0)	50	<.001
Acute otitis media	31 (19.4)	73 (43.5)	68	<.001
Pneumonia	13 (8.1)	38 (22.6)	66	<.001
Tonsillopharyngitis	10 (6.3)	25 (14.9)	60	.01

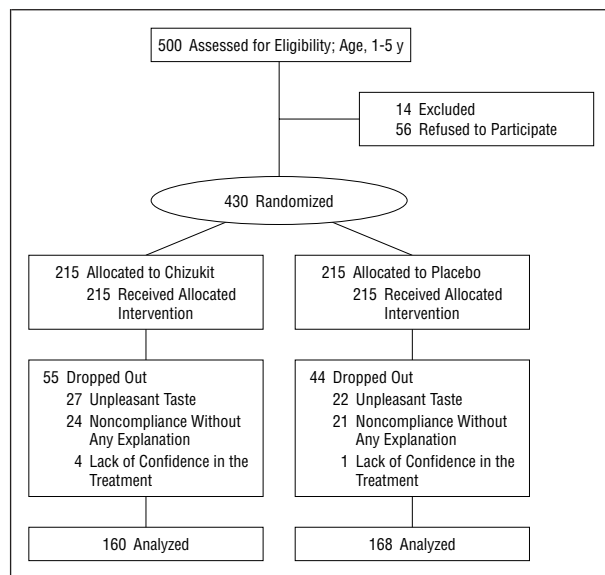
*Chizukit is an herbal preparation. See text for details.

†Difference between proportions test.

the Chizukit and placebo groups, respectively), lack of confidence in the treatment (4 subjects and 1 subject), and noncompliance without any explanation (24 subjects and 21 subjects). Because all of the differences between the Chizukit and placebo groups (rate of withdrawal and reasons for it) were not significant (*P* approaching 1.00 for all) and because all dropouts occurred during the first week of the study, we performed an efficacy study instead of an intention-to-treat analysis. The **Figure** shows the subject progress through the phases of the trial.

The primary outcome data are presented in Table 1. The number of children who experienced 1 or more respiratory tract illness episodes during the 12 weeks of the study, the total number of episodes, and the mean number of episodes per child were significantly lower in the Chizukit than the placebo group (by 43%, 55%, and 50%, respectively). The total number of illness days and duration of individual episodes were also significantly lower in the Chizukit group. Similar findings were noted when the children 3 years and younger and those older than 3 years were analyzed separately (data not shown).

The secondary outcome data are presented in **Table 3**. The number of days of fever and of use of antipyretics (acetaminophen) and antibiotics, the number of unscheduled visits to the physician's office for respiratory tract illnesses, and the number of days absent from day care or kindergarten were significantly lower in the Chizukit than the placebo group (by 62%, 53%, 50%, 36%, and 49%, respectively). In addition, the incidence of rhi-



Flow diagram of subject progress through the phases of the trial. Chizukit is an herbal preparation. See text for details.

nit and daytime and nighttime cough (more than usual), according to parental report, was lower by 22%, 30%, and 36%, respectively, in the Chizukit group, but these differences did not reach statistical significance, except for nighttime cough (*P* = .03). The respiratory system diseases diagnosed during the study are summarized in Table 2. Upper respiratory tract infection was the most frequent, followed by acute otitis media. There were few cases of pneumonia and tonsillopharyngitis. The incidence of each of the diseases was significantly lower in the Chizukit group.

Adverse drug reactions were observed in 9 patients (5.6%) in the Chizukit group and 7 (4.2%) in the placebo group (*P* = .54). All were mild gastrointestinal and palatability symptoms that were transient and did not require discontinuation of treatment.

COMMENT

The results of the present study demonstrate, for the first time, that an herbal preparation containing an extract of echinacea, propolis, and vitamin C has a significant beneficial effect on the incidence and severity of respiratory tract infections in young children (as in adults). Recently, Mark et al⁸ reviewed the use of echinacea in the pediatric population and described their trial evaluating the effect of echinacea in preventing recurrent otitis media.

Several studies^{3,6,30,31} have investigated the effectiveness of various preparations of echinacea extracts for the treatment and prevention of respiratory tract infection in adults. Barret et al³¹ reviewed the evidence on orally administered echinacea extracts for acute upper respiratory tract infections and concluded that they may be beneficial for the early treatment of existing illness but not for prevention. The same conclusion was reached by Melchart⁶ and Gunning³² and their colleagues. However, Schoneberger,³³ in an 8-week trial, noted a shorter duration of illness and a trend toward fewer study participants with infection, indicating a possible preven-

Table 3. Secondary Outcome Data*

Variable	Chizukit (n = 160)	Placebo (n = 168)	Reduction, %	P Value†
Fever				
Total No. of days with	340	902	62	...
Days per child	2.1 ± 2.9	5.4 ± 4.4	...	<.001
Antipyretics				
Total No. of days used	380	815	53	...
Days used per child	2.4 ± 3.5	4.9 ± 3.9	...	<.001
Antibiotics				
Total No. of days used	541	1084	50	...
Days used per child	3.4 ± 5.6	6.5 ± 8.0	...	<.001
Unscheduled visits to physician				
Total No. of visits	333	519	36	...
Visits per child	2.1 ± 2.1	3.1 ± 2.8	...	<.001
Absence from day care or kindergarten				
Total days	367	718	49	...
Days per child	2.3 ± 4.6	4.3 ± 5.6	...	<.001
Rhinitis				
Total No. of days with	771	993	22	...
Days per child	4.8 ± 8.6	5.6 ± 8.143
Daytime cough, more than usual				
Total No. of days	642	914	30	...
Days per child	4.0 ± 7.0	5.4 ± 7.608
Nighttime cough, more than usual				
Total No. of nights	424	667	36	...
Nights per child	2.7 ± 5.1	4.0 ± 6.003

*Data are mean ± SD unless otherwise indicated. Chizukit is an herbal preparation. See text for details.

†t Test.

tive effect. In other placebo-controlled trials, Schmidt and colleagues³⁴ found a 15% lower frequency of infection in subjects given echinacea ($P=.08$), Forth and Beuschler³⁵ reported a relative risk reduction of 38% in nasal symptoms ($P<.005$), and Henneicke-von Zepelin et al³⁶ reported a superiority of echinacea preparation over placebo in the treatment of the common cold. On the other hand, Turner et al³⁷ found no significant difference in the occurrence of infection or severity of illness in a group of 92 volunteers challenged with rhinovirus type 23 and treated with echinacea for 5 days compared with control subjects.

Propolis has been shown to have anti-inflammatory¹⁴ and antiviral¹⁷⁻²⁰ activity. Crisan et al³⁸ reported a lower incidence of rhinopharyngeal infection and symptoms in a group of preschool children treated with a propolis preparation for 5 months. The authors suggest that the decrease in the local virus and bacterial carriage rate in the nasopharynx was attributable to the anti-inflammatory and decongestive properties of the product.

We do not believe that the low dose of vitamin C in the Chizukit preparation by itself plays a role in the prevention of respiratory tract illness. However, some additive effects to echinacea and propolis immunomodulation cannot be ruled out.

The safety data on echinacea are relatively strong.³⁹⁻⁴¹ It also appears to be well tolerated, with a low frequency of adverse effects, such as unpleasant taste, nausea or vom-

What This Study Adds

Complementary therapies are commonly used and have increased in popularity. Echinacea and propolis are widely used for the treatment and prevention of upper respiratory tract infection in adults and children.

The present study demonstrates that an herbal extract preparation containing echinacea, propolis, and vitamin C may be beneficial for the prevention of respiratory tract infections in children. Advice regarding the use of herbal extracts, especially for children, is recommended.

iting, abdominal pain, and diarrhea.⁴² This was also observed in the present study. However, serious allergic or anaphylactic events have been reported in rare cases,^{43,44} so caution is advised for patients with a history of hypersensitivity to products from the daisy family (sunflower seeds and ragweed).

Melchart et al⁵ suggested that echinacea may be beneficial for individuals who already have an immune disorder but that it has little or no effect on a healthy immune system. The use of immunostimulants in the prevention of upper respiratory tract infection is controversial.⁴⁵ Berber and Del-Rio-Navarro⁴⁶ conducted a meta-analysis study and reported that immunostimulants can reduce the incidence of acute upper respiratory tract infection in children but cannot prevent all these infections. Therefore, they suggest that the use of immunostimulants for prevention must be limited to children with high susceptibility to these kinds of infections or to overexposed children attending day care centers, kindergartens, or elementary schools. We assume that the beneficial effect of the Chizukit preparation in this study was due to the immunomodulatory action of its components. The immunostimulating properties of echinacea may decline with continued use. Therefore, some authors suggest that preparations containing echinacea not be taken for longer than 8 to 12 consecutive weeks.⁴⁷⁻⁴⁹ After a drug holiday, it may be restarted.

One limitation of the present study is the lack of appropriate quality control and standardization, because the active components of the preparations are not known. In addition, the safety of long-term prophylactic use was not tested.

The present study suggests that an herbal extract preparation containing echinacea, propolis, and vitamin C is beneficial for the prevention of respiratory tract infections in children. However, considering that this is the first trial conducted in young children, conclusions must be made with caution. Additional studies are needed in larger samples to confirm our findings and to rule out potential adverse effects in general or specific populations at risk, such as allergic children or those receiving cotherapy or having different morbidities, before the preparation can be recommended for routine clinical use.

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