

# ***Alternative Therapies for Acute Upper Respiratory Infections in Children***

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# ***Upper Respiratory Tract Infections (URIs)***

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- ***Children suffer 6 – 10 colds per year***
  - ***School children can suffer up to 12 colds per year***
- ***22 million school days lost annually***
- ***Symptoms of cold and flu account for more office visits than any other cause***
- ***\$2.9 billion spent on over-the-counter (OTC) cough and cold medicines (adults and children)***

# ***Common Types of URIs***

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- ***Rhinopharyngitis***  
***(Common Cold)***
- ***Sinusitis***  
***(rhinosinusitis)***
- ***Tonsillopharyngitis***
- ***Otitis Media***
- ***Laryngitis***
- ***Bronchitis***  
***(sometimes)***



***Conventional Treatments  
Leave Kids Out in the Cold***

# OTC Treatment Options

| <b><i>Treatment</i></b>             | <b><i>Symptom</i></b>                                | <b><i>Common Side effects</i></b>  |
|-------------------------------------|--|--|
| <b><i>Oral Decongestants</i></b>    | <b><i>Runny nose, nasal congestion, sneezing</i></b> | <b><i>Anxiousness, tachycardia, elevated blood pressure</i></b>                  |
| <b><i>Topical decongestants</i></b> | <b><i>Nasal Congestion</i></b>                       | <b><i>Rebound congestion if used longer than 3-4 days, throat irritation</i></b> |
| <b><i>Antihistamines</i></b>        | <b><i>Sneezing, runny nose, itchy eyes</i></b>       | <b><i>Older varieties are sedative, may thicken secretions</i></b>               |
| <b><i>Dextromethorphan</i></b>      | <b><i>Coughing</i></b>                               | <b><i>Limited effectiveness</i></b>  |
| <b><i>NSAIDS</i></b>                | <b><i>Headache, discomfort</i></b>                   | <b><i>Stomach irritation, Reye's syndrome</i></b>                                |
| <b><i>Acetaminophen</i></b>         | <b><i>Fever, discomfort</i></b>                      | <b><i>Liver toxicity</i></b>   |

# ***OTC Treatments No Better Than Placebo***

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- ***Cochrane Review of OTC medications for acute cough, including studies on 616 children, found that the following treatments were no more effective than placebo in treating cough in children:***

- Antitussives: dextromethorphan and codeine***

- Antihistamine/decongestants: brompheniramine/ phenylpropanolamine; brompheniramine/ phenylephrine/ propanolamine***

*Cochrane Database Syst Rev 2008:CD001831.*

- Antihistamines: clemastine,***

# ***Pediatric OTC Restrictions***

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- ***Pediatric OTC cough/cold medications not recommended for children under 4 years of age***
  - ***October 2008 - drug makers agreed to stop marketing to children < 4 years of age; January 2009, Canada set the bar at < 6 years of age***
- ***Although voluntary recall of pediatric OTC cough and cold medications was completed by drug companies, the FDA does not recommend use by children <6 yrs\****
- ***The American College of Chest Physicians strongly discourages use of OTC cough syrups in children <14 years old***

***\*Colorado Clinical Guidelines Collaborative (12/19/07)***

# ***New Guideline for Pediatric OTC Cough and Cold Medications***



## **Revised Product Labels for Pediatric Over-the-Counter Cough and Cold Medicines**

October 7, 2008, the Consumer Healthcare Products Association announced that the leading manufacturers of pediatric over-the-counter cough and cold medicines would voluntarily modify the labels on these products to state that they should not be used in children aged <4 years.\*

Previous product labels stated that these medicines should not be used in children aged <2 years. Existing products with these labels will not be removed immediately from store shelves but are expected to be replaced eventually with newly labeled products. Health-care providers should be aware of the new label and should alert parents and caregivers to this change.

Serious injuries and deaths have been reported among infants and children who received over-the-counter cough and cold medicines, but most adverse events resulted from overdoses or unsupervised ingestions (1--3). To promote child safety, the Food and Drug Administration and CDC have developed materials to educate parents, health-care providers, and consumers about how and when these products can be used safely. Additional information is available at <http://www.fda.gov/bbs/topics/news/2008/new01899.html>.

**Morbidity and Mortality Weekly Report. CDC. Available at:** <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5743a5.htm>

# ***Antibiotics – Often Unnecessary and Still Overused***

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- ***URIs are largely viral***
- ***In a Medicaid study, patients with URIs were more likely to return to the doctor if they received antibiotics***
- ***Even though antibiotic prescriptions have fallen, they are still overused for cough and cold symptoms***

*N Engl J Med* 2000;34.3:1917-24.  
*J Fam Med* 2009;41:182-7.

# ***URIs – Primarily Viral Infections***

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- ***Acute bronchitis - Fewer than 10% of patients have a bacterial infection identified as the cause***
- ***Acute sinusitis - Only 0.2 to 2% of viral respiratory tract infections lead to bacterial sinusitis. Current recommendations are for 7-10 days of monitoring and supportive treatment before antibiotic therapy***
- ***Tonsillitis: 30% of tonsillitis in children is caused by *Streptococcus pyogenes*; acute GABHS-negative is viral, self-limiting, and should be treated with supportive care only***

*Chest.* 2006;129(1 Suppl):95S-103S.

*Ann Intern Med.* 2001;134:495-497.

*Lancet* 2008;371:908-14.

Tonsillitis. Emedicine Health. [http://www.emedicinehealth.com/tonsillitis/page2\\_em.htm](http://www.emedicinehealth.com/tonsillitis/page2_em.htm).

***Alternative Therapies for  
Pediatric URIs  
An Evidence-Based View***

# ***Current “Evidence-Based” Line-up***

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- ***Vitamin C***
- ***Zinc***
- ***Echinacea (Echinacea combinations)***
- ***Andrographis***
- ***Ivy Leaf Extract***
- ***Pelargonium sidoides***

# ***Vitamin C***

# ***Cochrane Review 2007***

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- ***Vitamin C showed benefit for children in prophylaxis trials***
  - ***12 trial comparisons including 2434 episodes of illness (duration of 2 weeks to 9 months)***
  - ***Significant reduction in the duration of respiratory episodes – pooled estimate of 13.6% (compared to 8% in adults)***
  - ***For children <12 yrs, who experience colds more frequently, the pooled estimate of benefit suggests an average reduction in four symptom days from 28 to 24 days per year***
- ***No therapeutic trials on children***

# ***Vitamin C Questions***

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- ***Could a benefit perhaps be achieved in children through therapeutic supplementation alone?***
- ***Is there a dose dependent effect?***
  - ***While few trials have used doses higher than 1 g/day, a 1974 study with school children found that 2 g/day was about twice as effective as the results seen with 1 g/day in other studies***  
*New Engl J Med 1974;290:8-10.*

***Zinc***

# ***Zinc – Pediatric Studies***

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- ***Randomized, DB, PC trial with 129 children (ages 1 to 10 years; median age 5.2 yrs) with common cold (24-48 hrs within onset of illness) were treated with either 1.32 g zinc sulfate in 100 mL syrup (15 mL of Zn per 5 mL spoonful) or placebo b.i.d.***
- ***There was no difference in the median duration of all cold symptoms in either group (6 days). The total symptom severity score was significantly lower in the Zn group by day 2 (3.6 vs. 4.9). The mean score for cough and nasal symptoms was also significantly lower in the Zn group***
- ***AEs were similar in both groups (“bad taste” most common)***  
*Ped International 2007;49:842-7.*

# ***Zinc – Pediatric Studies, cont.***

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- ***DB, PC trial with 200 children (2 to 10 yrs; median age 5.6 yrs) – 15 mg of Zn sulfate daily for 7 months***
- ***Number of colds significantly reduced in the Zn group (1.2 vs. 1.7 colds per child;  $p = 0.003$ ). Mean cold-related absence from school was 0.9 days for the Zn group compared to 1.3 d for the placebo group ( $p = 0.04$ ) [Acta Paediatrica 2006;95:1175-81]***
- ***DB, PC intervention trial with 249 children (median age 13 yrs old) with common cold (first 24 hrs of symptoms). Treated with Zn gluconate lozenges – 10 mg 5 to 6 times per day.***
- ***Zn gluconate was not effective in shortening the severity or duration of the common cold [JAMA 1998;279:1962-7]***

# ***Echinacea***

# ***Echinacea – Pediatric Studies***

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- ***Randomized, DB, PC trial with 407 children (2 to 11 yrs old) – data on 707 URIs. *E. purpurea* (Echinacin) – 3.75 mL b.i.d. (2-5 yr olds) and 5 mL b.i.d. (6-11 yr olds) up to a maximum of 10 days\****
  - ***No difference in mean duration or severity of symptoms between groups. More frequent reports of rash in the echinacea group [JAMA 2003;290:2824-30]***
- ***Secondary analysis of data – incidence of URIs monitored over 4 months***
  - ***A second URI developed in 69.2% of children taking placebo vs. 55.8% in the echinacea group (28% decreased risk if recurrence; p = 0.01) [J Alternative Complement Med 2005;11:1021-6]***

# ***Echinacea Clinical Summary***

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- ***The remaining data on echinacea or echinacea combinations in children consists of obscure or poorly designed studies or large observational studies***
- ***One Israeli study found a combination of echinacea (*E. purpurea* [aerial part] and *E. angustifolia* [roots]; 50 mg/mL), propolis (50 mg/mL), and vitamin C (10 mg/mL) was effective in reducing the incidence of URIs in 328 children ages 1 – 5 years old. Dosage was 5.0 mL b.i.d for children 1-3 years; 7.5 mL b.i.d for children 4-5 years. Duration was 12 weeks. [Arch Ped Adolesc Med 2004;158:217-21]***

# ***Andrographis***

# ***Andrographis – Pediatric Study***

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- ***DB, PC trial comparing Kan Jang (fixed combination of andrographis [85 mg, 5.25 mg andrographolides] and eleuthero[9.7 mg] per tablet) and *E. purpurea* in 130 children ages 4-11 yrs with uncomplicated colds. Dosage of Kan Jang was 2 tablets t.i.d. (30 mg andrographolides per day). Treatment was for 10 days.***
- ***Compared to placebo and echinacea, the Kan Jang group had a greater decrease in symptom severity score at days 3 and 5. Notable decrease in nasal secretion and congestion. No AEs reported.***

***Phytotherapy Res 2004;18:47-53.***

# ***Ivy Leaf Extract***

# ***Ivy Leaf (*Hedera helix*)***

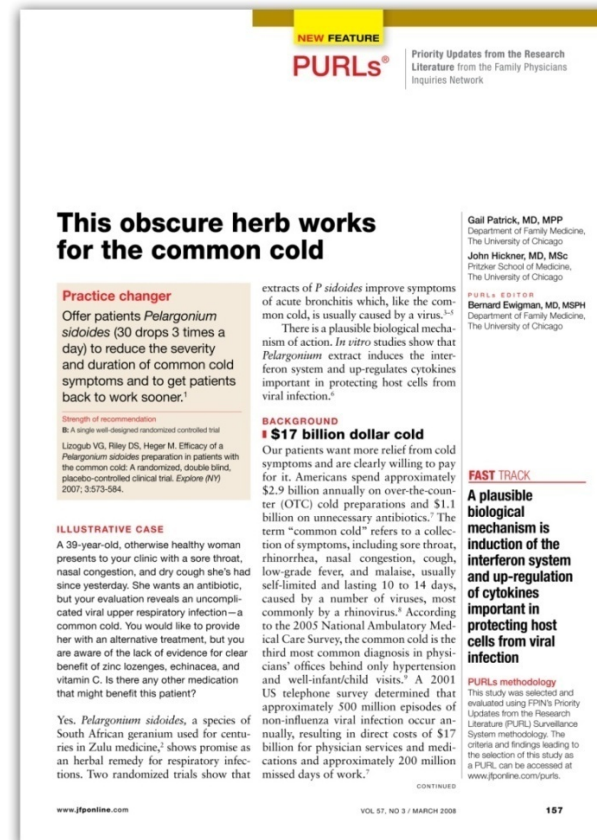
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- **German Commission E approves for “treatment of catarrhs of the respiratory passages and symptoms of chronic inflammatory bronchial conditions.**
- **Prospective, open-label, multi-center, post-marketing study, 5,181 children, ages 0 – 14. Patients had a clinical diagnosis of bronchitis. Treatment was a *H. helix* ivy leaf extract (5-7.5:1; ethanol 30% [w/w]). Dosage was 2.5 ml t.i.d for 0- 5 yrs old and 5 mL t.i.d. for 6-12 yrs old.**
- **Data is grouped together with results from adults and children < 12 yrs old. After 7 days, 95% of patients showed improvement and safety was rated as “very good”. [Phytomed 2009;16:17-24]**

***Pelargonium sidoides***  
***Extract***

# Journal of Family Practice, March 2008

- **“In the final analysis, we think that these findings justify recommending this (*Pelargonium sidoides*) to our patients.”**
- **“Our conclusion is that patients could be advised to purchase the medication to have on hand at home at the start of the cold season.”**
- **“More importantly, this degree of improvement in cold symptoms is dramatically better than other common OTC treatments, including vitamin C, echinacea, and zinc preparations.”**



# *Pelargonium sidoides*



# ***Pelargonium sidoides***

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- ***A member of the Geranium family and indigenous to South Africa***
- ***Most commonly found in grasslands***
- ***Medicinal preparations use the root***



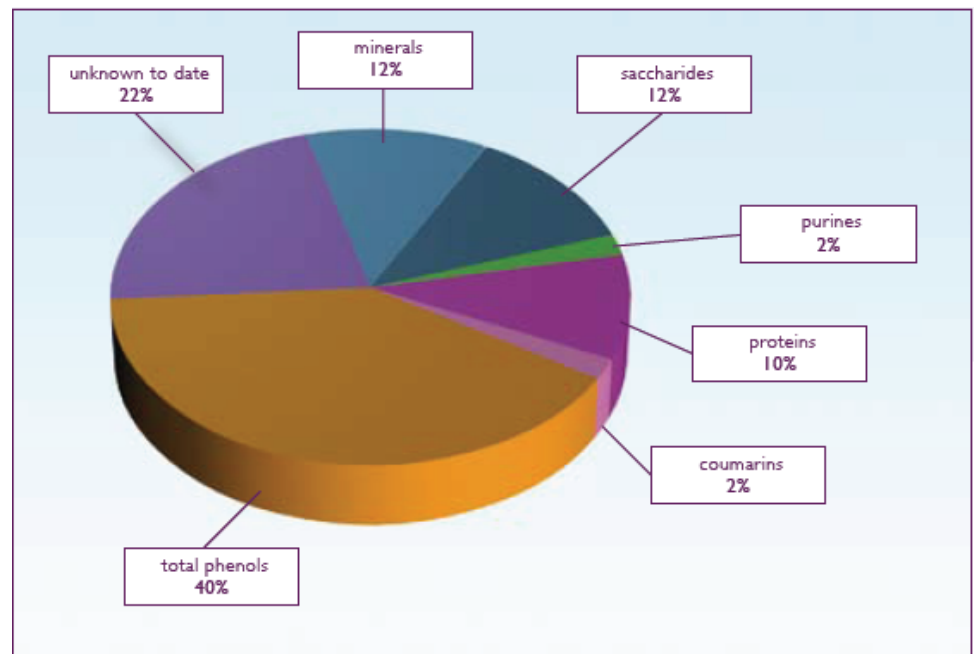
# ***Historical Overview***

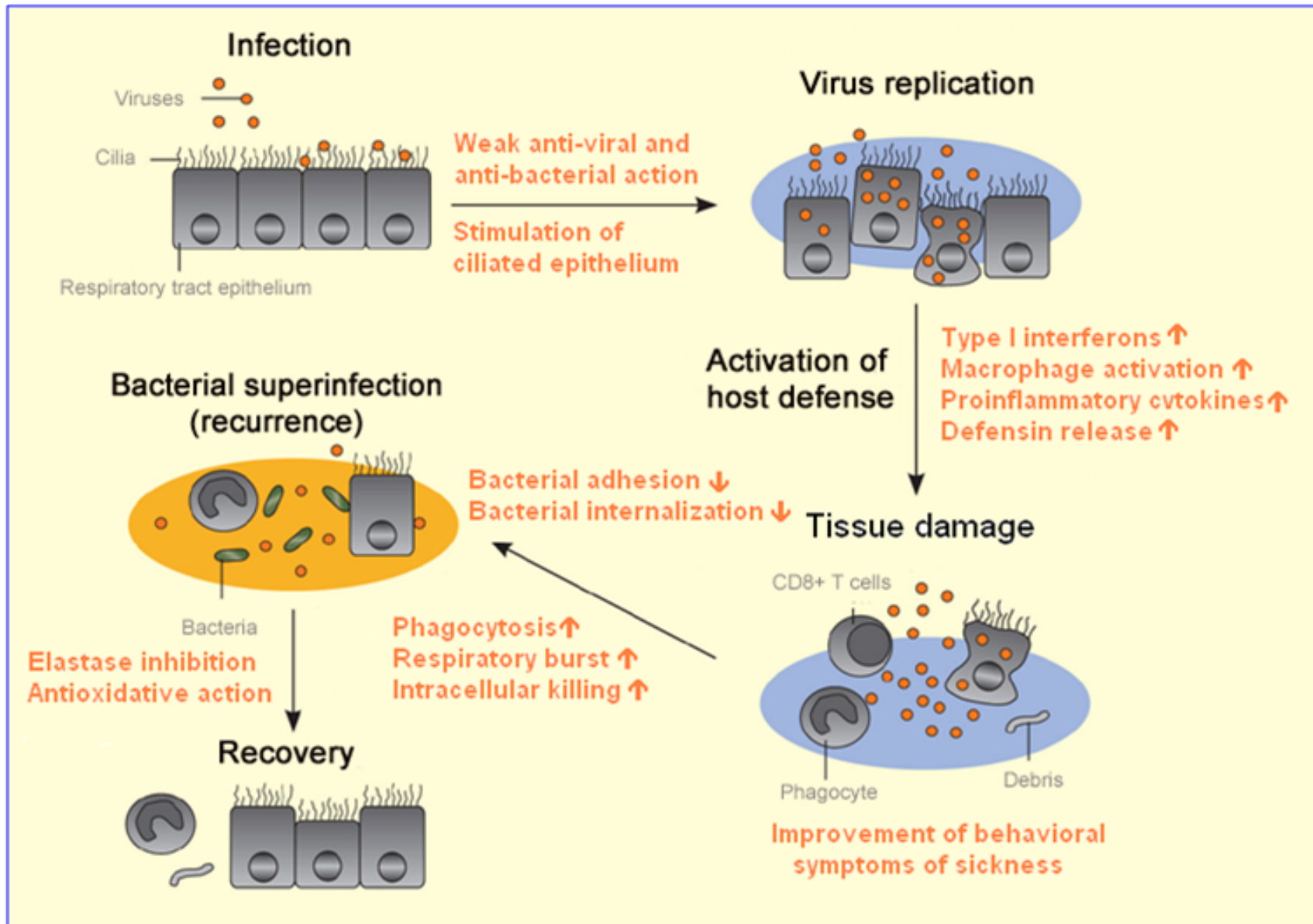
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- ***Long history of use by traditional healers in South Africa***
- ***Popularized throughout Europe by Charles Stevens as “Stevens’ Consumption Cure”***
- ***In 1972, the chemical identity of the *Pelargonium sidoides* root was discovered by German researchers. As research progressed, a proprietary extraction technique was developed and perfected to yield EPs 7630. It was determined that three year old rhizomes contain an optimal amount of active constituents.***

# EPs 7630 - Constituents

- *The EPs 7630 extract contains primarily polyphenols (mainly catechin and gallocatechin), proteins, minerals, and, in lower concentrations, 7-hydroxycoumarin derivatives.*
- *These coumarin derivatives differ in chemical structure from the known anti-coagulant coumarins and are not associated with anticoagulant activity.*

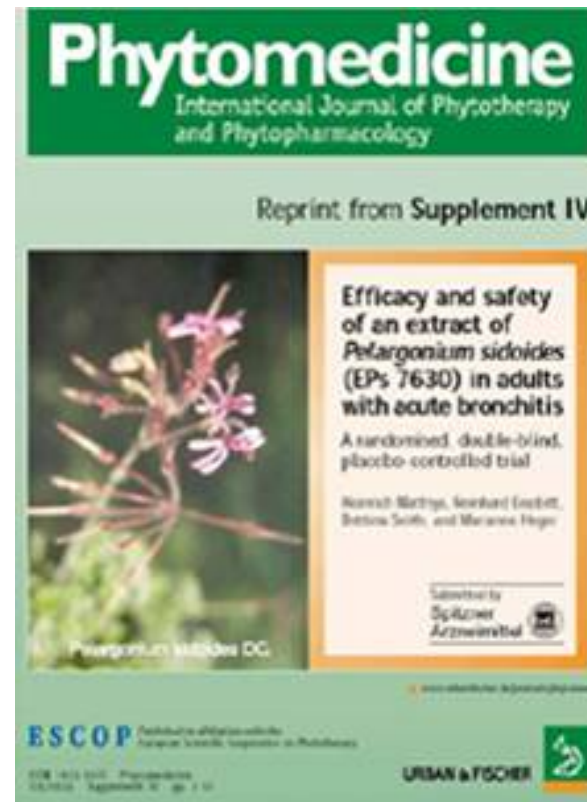




## Pathogenesis of URIs - Mode of Action of EPs7630

# ***Researched in Adults and Children***

- ***The efficacy and safety of EPs 7630 has been extensively studied***
  - ***Over 9,000 participants (including 3,900 children), of which 3,800 participated in placebo-controlled clinical studies***
- ***Evaluated on common cold, bronchitis, tonsillitis, and sinusitis***



# ***Acute Bronchitis***

# ***Acute Bronchitis – 2008 Meta-Analysis***

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*Pelargonium sidoides* for acute bronchitis: A systematic review and meta-analysis

Taofikat B. Agbabiaka\*, Ruoling Guo, Edzard Ernst

*Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, 25 Victoria Park Road, Exeter EX2 4NT, UK*

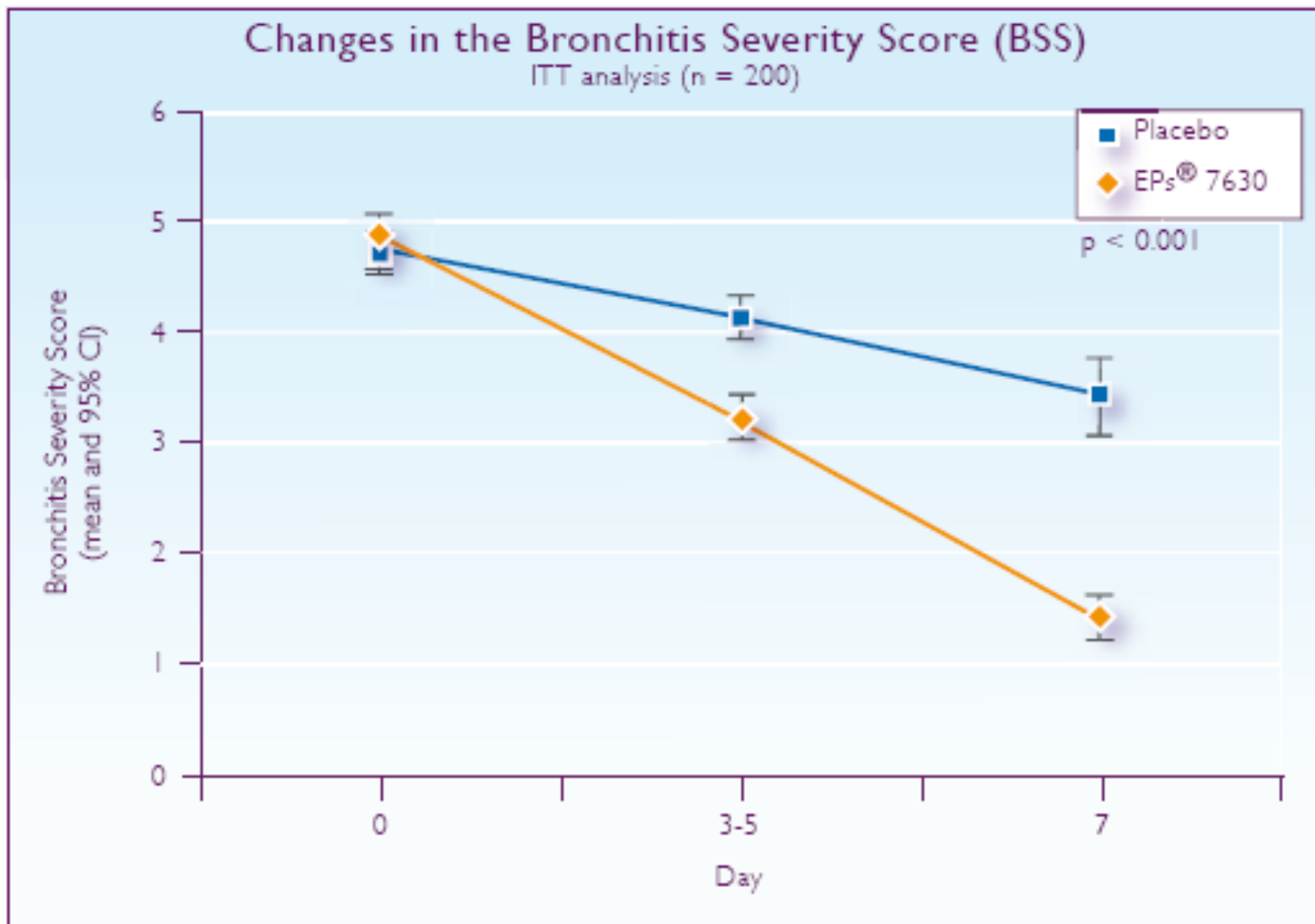
- ***"Current available data from 6 high quality randomised clinical trials suggest there is encouraging evidence that *P. sidoides* is effective compared to placebo for patients with acute bronchitis."***

# ***EPs 7630—Pediatric Bronchitis***

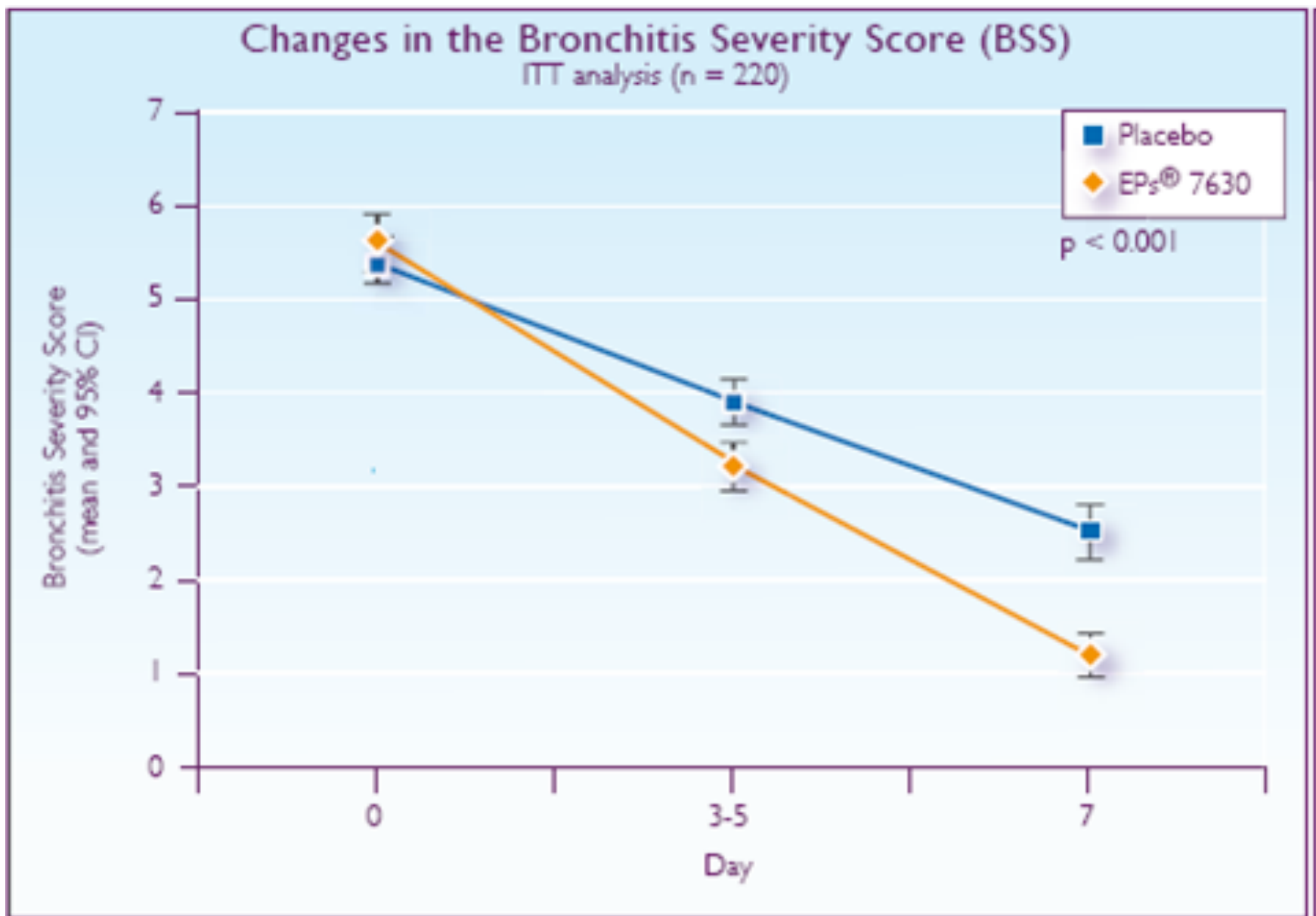
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- ***Combined analysis of two randomized, DB, PC trials with 420 children and adolescents (1-16 yrs old) with acute bronchitis. Treatment duration was 7 days with an interim visit at days 3-5.***
- ***Dosage:***
  - ***1-6 yrs old – 0.5 mL t.i.d.***
  - ***6-12 yrs old – 1.0 ml t.i.d.***
  - ***12-18 yrs – 1.5 mL t.i.d.***

***Planta Medica 2007;73;82; Zeitschrift Phytother 2008;29:38-9.***



***Decrease of BSS at day 7 was 3.4 points in the EPs 7630 group and 1.2 points in placebo***



***Decrease of BSS at day 7 was 4.4 points in the EPs 7630 group and 2.9 points in placebo***

## ***EPs 7630—Pediatric Bronchitis, cont.***

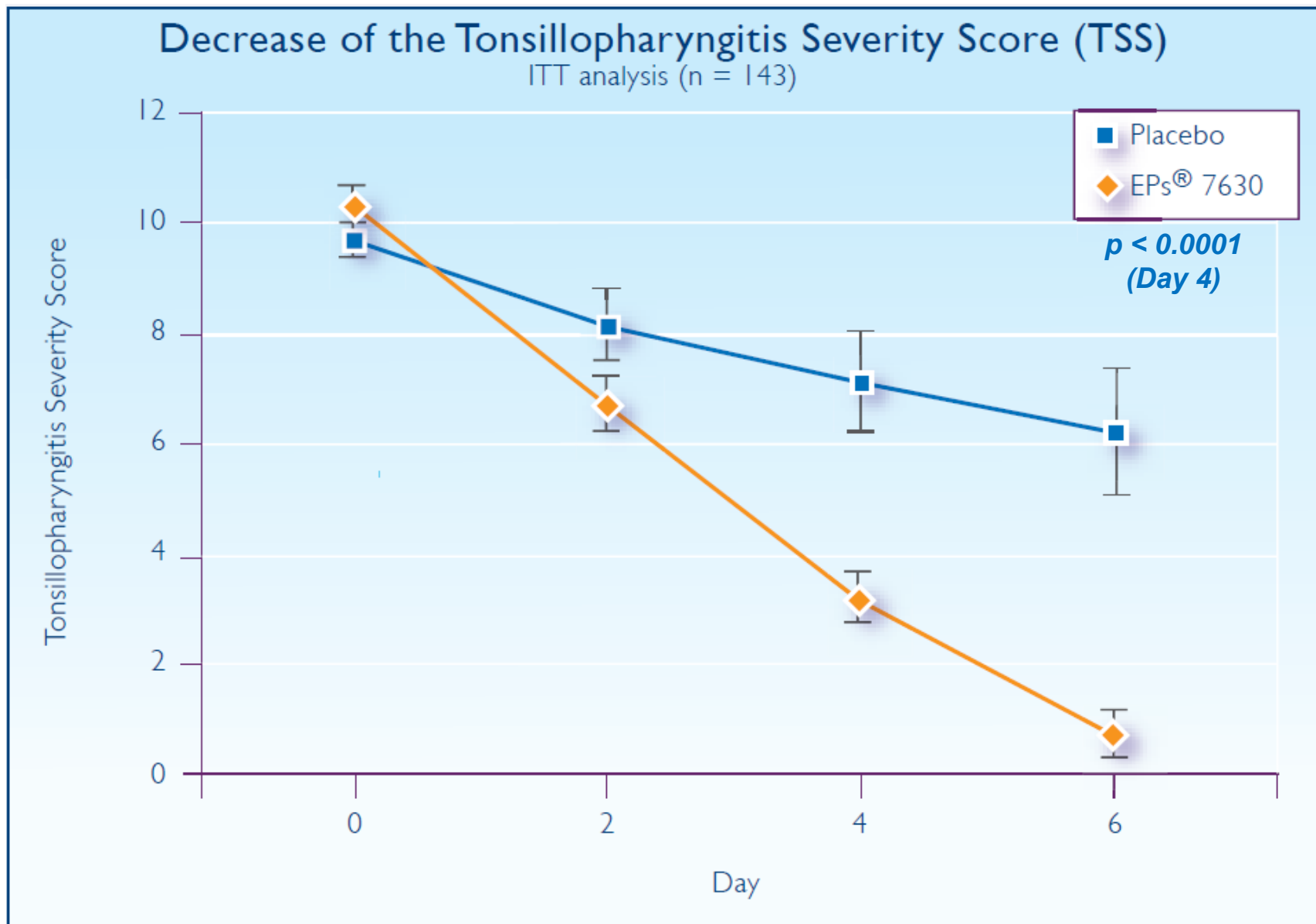
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- ***The EPs 7630 group demonstrated a significant decrease in BSS score at day 7 in both studies (3.4 vs. 1.2 and 4.4 vs. 2.9, respectively;  $p < 0.001$ )***
- ***Significant reduction in cough, dyspnea, and rales on lung auscultation noted in the EPs 7630 group compared to placebo.***
- ***No significant AEs found***

# ***Tonsillopharyngitis***

# ***EPs 7630—Pediatric Tonsillopharyngitis***

- ***Randomized, double-blind, placebo-controlled trial***
- ***143 children (ages 6-10 years) with non-GABHS tonsillopharyngitis ( $\leq 48$  hrs)***
- ***Given 20 drops (1 mL) of EPs 7630 or placebo t.i.d. for 6 days***
- ***Primary outcome was change in Tonsillopharyngitis Severity Score (TSS), which measures:***
  - ***Subjective features of sore throat and difficulty swallowing***
  - ***Objective measures of pharyngeal erythema and fever***



**Decrease of TSS at day 4 was 7.1 points in EPs 7630 group and 2.5 points in placebo**

# ***EPs 7630—Tonsillitis in Children***

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- ***TSS reduction significant ( $p < 0.0001$ ) at day 2:***
  - ***From 10.3 to 6.8 in EPs 7630 group***
  - ***From 9.7 to 8.2 in placebo group***
- ***Notable decrease in fever compared to placebo (less paracetamol consumed by children taking EPs 7630)***
- ***On day 6, 81% in EPs 7630 group were back at school vs. 21% in placebo group ( $p < 0.0001$ )***
- ***AEs occurred in 1 child taking EPs 7630 and 14 taking placebo. None were considered serious.***

# ***EPs 7630 Recommended Use, Safety, and Guidelines***

# ***EPs 7630 – Recommended Use***

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- ***Children 12 years and older***
  - ***1.5 mL three times per day***
- ***Children 6 to 12 years old***
  - ***1.0 mL three times per day***
- ***Children 2 to 6 years old***
  - ***0.5 mL three times per day***
  - ***ETOH-free cherry syrup available (2.5 mL t.i.d.)***

# ***EPs 7630 – Contraindications and Precautions***

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- ***Does not interact with antibiotics***
  - ***EPs 7630 does not affect liver metabolism except for a clinically irrelevant inhibition of CYP2C9. An effect on other tested cytochrome-P450 isoenzymes (including CYP3A4) has not been observed at clinically relevant concentrations.***
- ***Rare reports of allergic reactions – mainly rashes***

# ***EPs 7630 – Safety***

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- ***Approximately 304 million daily doses of EPs 7630 were sold between 1994 and 2006, predominantly in Germany.***
  - ***The incidence of side effects is extremely low - 0.53 per million defined daily doses (defined daily doses – DDD).***
  - ***The rate of side effects is 0.27 per million DDD for hypersensitivity reactions (especially redness and pruritus), 0.3 for gastrointestinal disorders and 0.05 for gingival hemorrhaging and nose bleeds.***

# ***EPs 7630 – Pediatric Safety***

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- ***There is extensive clinical research and post-marketing surveillance studies in children from 1 year of age and older***
- ***Large observational study with 2,099 patients with bronchitis\****
  - ***241 were ≤ 6 years of age (78 were infants < 2 years of age)***
  - ***Of the total of 28 adverse events, 3.1% were reported in children and 3.8% in infants (adverse events were largely minor and transitory with one case of a rash in one child)***
- ***Observational study of children with 742 children with acute bronchitis\*\****
  - ***13 AEs were reported and described as mild to moderate. In 8 cases, a causal relationship was not excluded. AEs included mild rash and diarrhea.***

***\*Phytomedicine2007;14:69-73.***

***\*\*Phytomedicine2007;14:60-4.***

# ***Proven Safety in Children***

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- ***“The addition of EPs 7630 to the practitioner’s therapeutic armamentarium could safely help decrease the inappropriate use of antibiotic therapy, especially in the setting of acute or acute-on-chronic bronchitis, in both children over age 2 years and adults.”***

***Russell H. Greenfield, M.D.***

***Assistant Clinical Professor of Medicine***

***The University of North Carolina at Chapel Hill***

***Questions?***