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Extract of *Pelargonium sidoides*: South African Herbal Remedy Successfully Treats Acute Bronchitis and Tonsillopharyngitis

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Although antibiotics continue to be used for the treatment of acute bronchitis and tonsillopharyngitis, there is a growing consensus among medical professionals worldwide that the preferred course of therapy for both conditions is to treat the symptoms without resorting to antibiotics. With the exception of acute tonsillopharyngitis due to group A beta-hemolytic streptococcus (GABHS), recent clinical guidelines recommend that patients with GABHS-negative tonsillopharyngitis be told about the self-limiting nature of the illness and treated with supportive care only.^{1,2} Although acute bronchitis is predominantly caused by viral infections, some reports have placed the use of antibiotics in clinical practice at as high as 70%.³ Overuse of antibiotics may lead to gastrointestinal disorders, allergic reactions, and the development of resistant organisms.

While there are many traditional herbal remedies used for acute bronchitis and tonsillopharyngitis, few clinical trials have been performed to support their efficacy. One exception has been the development of an extract of pelargonium (*Pelargonium sidoides* DC, Geraniaceae) roots, referred to as EPs® 7630 (Umckaloabo®, manufactured by Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany, and registered by ISO Pharmaceuticals, Ettlingen, Germany). In recent years, the ethanolic root extract (1:9-11) has become a popular herbal medicine in Germany, approved for the treatment of acute bronchitis, acute tonsillopharyngitis, as well as acute sinusitis. Clinical trials support its efficacy.

Pelargonium sidoides is native to the coastal regions of South Africa.⁴ The plant is notable for its narrow, deep red flowers and its large, heart-shaped leaves. Along with the closely related *P. reniforme* Curt, the root has been used for centuries by the Zulu to treat coughs, upper respiratory tract irritations, tuberculosis, and gastrointestinal complaints.⁵

In the late nineteenth century, a product made from the root gained some popularity in England as a cure for tuberculosis.

Active Constituents and Pharmacology

The primary constituents of the root of *P. sidoides* include coumarins, tannins of the proanthocyanidin type, and simple phenolic compounds.⁶ Although the mechanism of action of the root extract is somewhat unclear, in vitro studies suggest that it may be related to antimicrobial⁷ and immunomodulatory^{8,9} properties that have been demonstrated for the tannins (e.g., catechin, gallic acid, and gallic acid) and coumarins (e.g., umckalin). The immunomodulatory actions are mediated by the release of tumor necrosis factor alpha and nitric oxide as well as the stimulation of interferon and an increase of natural killer cells.¹⁰

Clinical Overview

The subject of 9 randomized trials conducted on a total of 1,477 patients (680 of them children ages 6 to 12 years) to date, EPs 7630 has been shown to safely and effectively shorten the severity and duration of acute bronchitis and tonsillopharyngitis.⁶ Perhaps most notable has been the rapid recovery noted for children with GABHS-negative tonsillopharyngitis—the clinical trial reviewed below demonstrated a clinically significant effect by the second day of treatment. On a practical note, the product used in these trials is palatable and easy to deliver to young children. Results from trials with adults and children support the introduction of this product made from a traditional herb with a long history of use. The product offers health care professionals an alternative to antibiotics for the acute treatment of these conditions. New research is also focusing on the use of the product in acute maxillary sinusitis.

Acute Non-GABHS Tonsillopharyngitis

In a randomized, double-blind, placebo-controlled trial, 143 children ages 6-10 years, with non-GABHS tonsillopharyngitis received either *P. sidoides* root extract (EPs 7630) or a placebo at a dose of 20 drops (1 mL) 3 times per day for 6 days.¹¹ Children enrolled in the study were diagnosed less than 48 hours prior to starting the trial with a negative rapid test for GABHS and a Tonsillopharyngitis Severity Score (TSS) \geq 8 points. In the case of fever (\geq 38.5° C), acetaminophen suppositories (500mg) were allowed from day 0 to day 4. The main outcome measure

was change in TSS from baseline (day 0) to day 4. TSS measures two subjective features of acute tonsillopharyngitis—sore throat and functional impairment (difficulty swallowing). It also objectively measures symptoms of inflammation—pharyngeal erythema and fever. Each symptom was assessed by an investigator using a 4-point rating scale ranging from 0 to 3 (0 = absent; 1 = mild; 2 = moderate; 3 = severe). Secondary outcome criteria included: (1) response criteria based on the TSS; (2) change of individual symptoms and further complaints including headache; (3) treatment outcomes according to the Integrative Medicine Outcome Scale (IMOS; complete recovery, major improvement, slight to moderate improvement, no change, deterioration); and (4) patient activity level. Following the enrollment day (day 0), controlled examinations occurred on days 2, 4, and 6. At each visit the investigator recorded clinical status, reviewed the patient's diary, documented the consumption of acetaminophen, and recorded information about adverse events.

There was a statistically significant decrease in the primary outcome criteria (change in TSS from day 0 to day 4) in the EPs 7630 group compared with the placebo group. The decrease of TSS from baseline (day 0) to day 4 was 7.0 ± 2.4 points in the EPs 7630 group and 2.9 ± 2.4 points in the placebo group ($p < 0.0001$). On day 2, TSS decreased from 10.3 ± 1.2 to 6.8 ± 2.2 in the EPs 7630 group compared to 9.7 ± 1.4 to 8.2 ± 2.8 in the placebo group ($p < 0.0001$)—suggesting an early response in the EPS 7630 group.

A TSS of < 5 points on day 4 was seen in 76.7% of patients in the EPs 7630 group compared with 34.3% of subjects in the placebo group ($p < 0.0001$). A decrease of at least 5 points by day 4 was seen in 91.8% in the EPs 7630 group compared with 35.7% in the placebo group. Rapid recovery, defined as fulfillment of secondary response criteria 1 and 2, was observed in 75.3% in the EPs 7630 group and 32.9% in the placebo group ($p < 0.0001$). There was also an improvement seen in the activity level of subjects in the EPs 7630 group, but not in the placebo group. By day 6, the number of patients returning to school was 80.8% in the EPs 7630 group compared with 21.4% in the placebo group ($p < 0.0001$). Subjects in the EPs 7630 group consumed less acetaminophen than did subjects in the placebo group. No serious adverse events were reported.

Acute Bronchitis

To determine the efficacy of EPs7630 for treating acute bronchitis, 468 adult male and female subjects (age \geq 18 years) diagnosed with acute bronchitis \leq 48 hours and having a Bronchitis Severity Score (BSS) \geq 5 points were recruited for a randomized, double-blind, placebo-controlled trial.¹² Patients received either EPs 7630 or a placebo at a dose of 30 drops (1.5 mL) 3 times per day for 7 days. In the case of fever (\geq 39° C), acetaminophen tablets (500mg) were allowed.

The primary outcome measure was the change in the BSS on day 7 in relation to the baseline score. BSS measures the following features of acute bronchitis—cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnea. (Note: rales refers to an abnormal or pathological respiratory sound heard on auscultation [i.e., listening to the sounds of internal organs as a diagnostic method]; rhonchi refers to a coarse rattling sound usually caused by a secretion in the bronchial tubes.) Each symptom was scored by an investigator using a 5-point rating scale ranging from 0 to 4 (0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe). Secondary outcome measures included: (1) prospective defined response criteria based on the BSS (A: BSS < 3 points; B: decrease of BSS \geq 7 points; C: A+B); (2) treatment outcome according to the Integrative Medicine Outcome Scale (IMOS); (3) onset of treatment effect; (4) consumption of paracetamol (acetaminophen); (5) change of individual symptoms of BSS and further symptoms; (6) patients' health status using the health-related quality of life questionnaires (SF-12 Health Survey, EQ-5D); and (7) questions about the complaints and satisfaction with treatment using the Integrative Medicine Patient Satisfaction Scale (IMPSS). Safety was assessed with respect to frequency, nature, and severity of adverse events. Tolerability of treatment was also assessed by investigators and patients, as well as by laboratory tests. Following enrollment (day 0), controlled examinations occurred on day 3, 4, or 5, and on day 7. At each visit the investigator recorded clinical status, reviewed the patient's diary, documented the consumption of acetaminophen, and recorded the number of adverse events. On day 7, there was a final assessment, which included laboratory tests and sputum analysis.

On day 7, BSS had decreased by 5.9 ± 2.9 in the EPs 7630 group and by 3.2 ± 4.1 in the placebo group compared to baseline. The 95% confidence interval (CI) for the difference of effects between the two treatment groups (EPs 7630 minus placebo) was calculated as $[-3.359; -$

2.060], showing a significant superiority of EPs 7630 over the placebo by day 7 ($p < 0.0001$). This statistically significant difference was observed as early as the first follow-up visit (day 3, 4, and 5) with a BSS score of 4.8 ± 2.3 points in the EPs 7630 group compared with 6.2 ± 3.0 in the placebo group ($p < 0.0001$).^{*} In patients with the highest BSS at baseline (defined as a BSS ≥ 8 points), there was a statistically significant decrease in the BSS in the EPs 7630 group (6.8 ± 2.7) compared with the placebo group (4.5 ± 4.2) at day 7 ($p < 0.0001$). A BSS of < 3 points (response criteria A) was observed in 64% of patients in the EPs 7630 group compared with 37.9% in the placebo group ($p < 0.0001$). A decrease of BSS of at least 7 points (response criteria B) was observed in 43.3% of patients in the EPs 7630 group compared with 23.0% of patients treated with the placebo at day 7 ($p < 0.0001$). Rapid recovery (defined as response criteria C) was observed in 34.3% of EPs 7630 patients compared with 20.4% receiving the placebo ($p < 0.0001$). There was a statistically significant improvement in the individual symptoms of rales/rhonchi and chest pain during coughing in the EPs 7630 group compared with the placebo group ($p < 0.0001$). In the EPs 7630 group, cough disappeared or improved in 89.2% of patients compared with 56.6% of patients in the placebo group ($p < 0.0001$), and sputum disappeared or improved in 66% of patients in the EPs 7630 group compared with 47.7% of those in the placebo group ($p < 0.0002$). On day 7, fever had disappeared in 96.9% of patients in the EPs 7630 group compared with 58.4% of those in the placebo group ($p < 0.0001$). Patients in the EPs 7630 group were able to return to work nearly two days earlier than the placebo-treated group ($p < 0.0001$). Adverse events were mild and similar in both groups—8.6% in the EPs 7630 group and 6.8% in the placebo group. These events included ear-nose-throat (ENT) and respiratory complaints (likely due to the existing condition), as well as mild gastrointestinal upset.

Recommended Use and Safety

To date, acute bronchitis and acute non-GABHS tonsillopharyngitis have been the primary conditions studied in controlled clinical trials. The recommended dose of EPs 7630 for adults and children over the age of 12 years is 30 drops (1.5 mL) 3 times per day for 7 days. Children ages 6 to 12 years may take 20 drops (1.0 mL) 3 times per day. Unpublished observational studies have suggested that children under the age of 6 years may take 0.5 mL 3 times per day.⁶ Dosage and duration of

treatment for persons suffering from acute maxillary sinusitis should become clearer with the results of a recently completed clinical trial awaiting publication.

Controlled clinical trials such as the two reviewed above demonstrate that EPs 7630 is well-tolerated and safe for the short-term treatment of acute bronchitis and tonsillopharyngitis. Open-label, observational studies with over 2,500 adults and children suffering from acute bronchitis, acute tonsillopharyngitis, or acute maxillary sinusitis have found adverse events occurring in 1.2% to 15.5% of subjects.⁶ In only 1.6% of these cases was there a probable or possible connection made to EPs 7630. Adverse events have been largely mild, consisting of gastrointestinal complaints and skin rash.

The extract of *P. sidoides* root (EPs 7630) is contraindicated during pregnancy and lactation as no specific data on pregnant or lactating women are available. To date, there are no other contraindications or known drug interactions with the root extract.

*Editor's note: The hard copy version of *HerbalGram* 63 contained an error in this sentence. This online version of *HerbalGram* 63 contains the corrected sentence.

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