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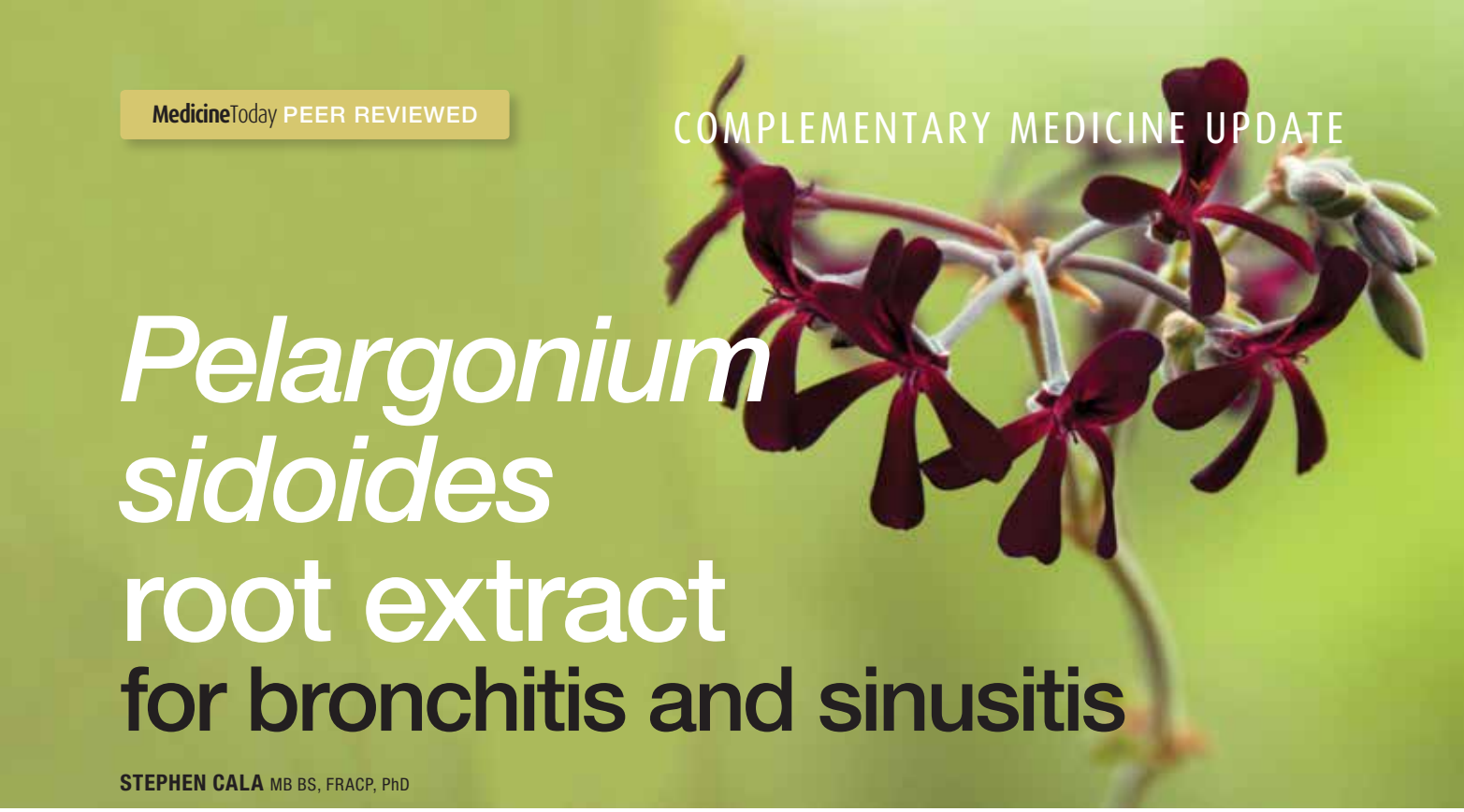

Pelargonium sidoides root extract for bronchitis and sinusitis

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Pelargonium sidoides **root extract EPs 7630 is registered in Australia for the treatment of the generally self-limiting conditions acute bronchitis and acute sinusitis. It has been shown to improve recovery time and relieve symptoms.**

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Acute respiratory infections (ARIs) are divided into those of the upper respiratory tract, such as tonsillitis/pharyngitis, sinusitis, otitis media and the common cold, and those of the lower respiratory tract, such as acute bronchitis.[1] These infections involve acute mucosal inflammation, oedema and mucus hypersecretion. Symptoms include cough, fever, congestion, increased secretions and discharge, and sore throat. The majority of ARIs are caused by viruses and are self-limited.

In adults and older children, a common cold tends to last about one week, but coughs may persist for up to three weeks; in young children symptoms, tend to last 10 to 14 days.[1] Acute bronchitis may take up to three weeks to resolve. Based on observations in general practice, the median time for symptoms associated with acute bronchitis to resolve following consultation varies between five days (for dyspnoea) and 11 days (for cough). Subjective complaints may persist for four weeks or more in a minority of patients. Patients with acute sinusitis usually have symptoms for a median duration of seven days, and 50 to 80% of patients are considered cured after two weeks (based on symptom resolution), although complete resolution may take up to 12 weeks in the remainder.

ARIs are among the most common acute diseases in the community, particularly in winter, and are a common reason for consultation in general practice.[1] Both children and adults often receive an empiric antibiotic prescription, although the limited effectiveness of this approach in a predominantly viral disease is well documented. Also, the increasing prevalence of community-acquired infections with antibiotic-resistant bacteria is stimulating strategies to reduce antibiotic prescribing.[2] An effective alternative approach to the treatment of patients with ARIs is needed therefore.

One possible such alternative is *Pelargonium sidoides* root extract EPs 7630, which a Cochrane Collaboration meta-analysis considers, on the basis of the limited evidence from the very few clinical trials with acceptable methodology, might offer symptom relief in patients with acute bronchitis, rhinosinusitis and the common cold.[1] This root extract was recently included on the Australian Register of Therapeutic Goods (ARTG) for the treatment of acute bronchitis and acute sinusitis. The background of this herbal remedy and the evidence supporting its use are discussed in this article.[1]

WHAT IS PELARGONIUM SIDOIDES ROOT EXTRACT?

P. sidoides, whose common names include umckaloaba and South African geranium, is a South African plant belonging to the Geraniaceae family.[1] A herbal remedy derived from its roots is sold in various countries as Umckaloabo, Umckabo, Umcka, Kaloba and Zucol.

A product made from the root of this plant was first marketed in 1897 in the UK by Major Charles H. Stevens as 'Stevens' Consumption Cure' for its supposed antituberculous properties; it lost popularity, however, with the advent of antibacterial therapy. A liquid alcohol-containing preparation (drops) of *P. sidoides* root extract was approved for the treatment of acute bronchitis in Germany in December 2005, and subsequently in several other countries. This liquid preparation of the root extract is now one of the most frequently prescribed childhood medications in Germany. Other preparations – tablets, syrups for children and quick dissolving lozenges (US market) – are also available. The Cochrane review found the tablet form may be less effective than the alcoholic extract but the number of trials was not sufficient to confirm this.[1]

The chemical profile identity of *P. sidoides* root was first discovered in Germany in 1972, and research yielded the ethanolic root extract known as EPs 7630. This extract contains characteristic groups of substances, namely polyphenols, proteins, purines, minerals, saccharides and, in lower concentrations, 7-hydroxycoumarin derivatives. The polyphenols mainly comprise the monomeric flavan-3-ols catechin and gallocatechin. Some of the substances in the root extract have not yet been identified.

WHAT IS THE POSSIBLE MODE OF ACTION?

In vitro research has found weak antibacterial effects of EPs 7630 but these are unlikely to be relevant in vivo. It has been shown in vitro that EPs 7630 interferes with the adherence to and invasion of human epithelial cells by *Streptococcus pyogenes*, potentially preventing bacterial superinfection.[3,4]

Other hypotheses for the mode of action of EPs 7630 include similar effects on viral adherence and immunomodulation. This extract may also have mucolytic properties (it improves cilia function in vitro) and stimulate nonspecific defence mechanisms such as interferon synthesis and pro-inflammatory cytokines, natural killer (NK) cells, phagocytosis, adhesion molecules and chemotaxis.[5] It is also regarded as a cough expectorant.

WHAT IS THE EVIDENCE SUPPORTING ITS USE?

Studies have shown EPs 7630 to significantly improve recovery time and relieve symptoms in patients with acute bronchitis and acute sinusitis.

Two multicentre, prospective, randomised, double-blind, placebo-controlled studies of adults (n for EPs 7630-treated groups = 108 and 64) with acute bronchitis demonstrated that after seven days, use of EPs 7630 significantly decreased the Bronchitis Severity Score (BSS) compared with placebo.[6,7] (The BSS scores the five most important symptoms of acute bronchitis, namely cough, sputum, crackles/wheeze, chest pain and dyspnoea, using a five-point verbal rating scale from 0 [absent] to 4 [very severe].) More patients taking EPs 7630 experienced a reduction in symptom severity at seven days compared with placebo. At day 7, 45% of patients takin EPs 7630 were assessed by physicians as being completely recovered compared with 6% of those taking placebo, with complete recovery or major improvement in 90% of those taking EPs 7630 and in 65%, of those taking placebo.[6]

Use of EPs 7630 also significantly decreased the BSS from baseline to day 7 compared with use of placebo in a trial in 200 patients aged 1 to 18 years with acute bronchitis (BSS score, 3.4 *vs* 1.2 points, $p<0.0001$).[8]

A multicentre, prospective, randomised, double-blind, placebo-controlled, parallel-group trial of 103 adults with acute sinusitis demonstrated a greater reduction in Sinus Severity Score (SSS) and major symptom improvement at day 7 with use of EPs 7630 (n = 51) compared with placebo.[9] (The SSS is based on a five-point verbal rating scale – from 0 [absent] to 4 [very severe] – of the six symptoms headache, maxillary pain, maxillary pain worsened by posture, nasal obstruction, purulent nasal secretion, and purulent nasal discharge in the middle meatus or post-nasal space.)

The available data on EPs 7630 were subjected to a Cochrane Collaboration meta-analysis in 2009, which was updated in 2013.[1] Based on the limited evidence from the very few clinical trials with acceptable methodology, this considered that the *P. sidoides* root extract EPs 7630 might offer symptom relief in patients with acute bronchitis, rhinosinusitis and the common cold but the clinical relevance of these effects remains uncertain.

The Cochrane review found that adverse events were slightly more common in the EPs 7630-treatment groups than in the control groups, but none were serious.[1]

As well as gastrointestinal complaints such as nausea, vomiting, diarrhoea and heartburn (0.13 cases per million daily doses) allergic skin reactions with pruritus and urticaria (0.27 cases per million daily doses) and nose/gum bleeding (0.05 cases per million daily doses) were reported in the included trials.[3]

Concerns have also arisen because the studies included in the Cochrane review were all performed by the same investigator (the manufacturer) and on a similar protocol and in similar settings (multicentre and outpatient, in Ukraine or Russia).[1] This narrow spectrum limits the applicability of the evidence. More well-designed, placebo-controlled studies in patients with acute bronchitis, rhinosinusitis and the common cold from other investigators and/or other parts of the world (Germany, Bulgaria, Japan, Korea) are in progress and will provide a better evidence base for the clinically relevant efficacy of the preparation in patients with ARIs.

REGISTRATION OF KALOBA ORAL LIQUID

Kaloba oral liquid was listed on the ARTG in December 2011 for the following indications:

- treatment of acute bronchitis in adults
- treatment of acute bronchitis in children over 2 years of age (with medical supervision for children 2 to 6 years of age)
- treatment of acute sinusitis in adults.

USING PELARGONIUM SIDOIDES ROOT EXTRACT

The approved daily dose of Kaloba oral liquid, 1 mL of which contains the equivalent of 91 mg dry *P. sidoides* root, is listed below.

- For acute bronchitis:
  - adults and adolescents over 12 years of age, 30 drops (= 1.35 mL) three times daily
  - children 6 to 12 years of age, 20 drops (= 0.9 mL) three times daily
  - children 2 to 5 years of age, 10 drops (= 0.45 mL) three times daily.
- For acute sinusitis:
  - adults, 60 drops (= 2.7 mL) three times daily.

The product should not be used in children under 2 years of age, during pregnancy or while breastfeeding, and is contraindicated in patients with hypersensitivity to the active ingredient or an increased risk of bleeding, and in those taking anticoagulants. The duration of treatment should not exceed one week for acute bronchitis and three weeks for acute sinusitis. It is important to reassess the patient post-ARI to exclude chronic lung disease.

The ARTG preferred the descriptor 'mild to moderate' rather than 'acute' bronchitis because the severity of bronchitis is difficult to assess as most patients would improve after seven days without treatment. Conventionally, if the condition lasts longer than 10 days then antibiotics are usually prescribed even though studies have shown their benefit is minimal.

Given that the standard medical treatment is to wait until symptoms are well established before antibiotics are prescribed, the ARTG agreed that Kaloba is probably harmless and may relieve conditions where few alternative effective treatment options are available. They also required an advisory statement to inform consumers of symptoms of significant concern, such as those of pneumonia (fever, dyspnoea, haemoptysis) and that it is not to be used in children younger than 2 years of age.

CONCLUSIONS AND RECOMMENDATIONS

P. sidoides root extract EPs 7630 (marketed in Australia as Kaloba) is useful to help limit the symptoms, severity and duration of acute bronchitis and sinusitis in otherwise normal patients in conjunction with realistic advice about the duration of these self-limiting respiratory infections. Its use can be part of patient self-management of these conditions.

Discussion of the treatment presents another opportunity to explain to patients the importance of both immunisation for vaccine-preventable ARIs and cessation of smoking. Patients should be reassessed after resolution of the bronchitis or sinusitis to exclude chronic lung disease. MT

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COMPETING INTERESTS: Dr Cala has received an honorarium for participation on a medical advisory panel sponsored by Blackmores for evaluation of scientific data regarding Kaloba prior to its introduction into the Australian market and participation in GPCE seminar and workshops.