Chapter 17

Umckaloabo: From a Patent Remedy to a Modern Herbal Pharmaceutical based on *Pelargonium sidoides* with Clinically Proven Efficacy

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*Pelargonium sidoides* has a long-standing tradition in the treatment of diseases, starting with ethnobotanical records from the mid 19th century. *Pelargonium sidoides* is native to the coastal regions of South Africa. In the first half of the 20th century, a product made from the root (Umckaloabo) was successfully used in Europe for the treatment of tuberculosis. Various metabolites including phenolic and cinnamic acids, tannins, flavonoids and coumarins were characterized in *P. sidoides*. In the late 20th century Umckaloabo was developed into a safe and efficacious herbal pharmaceutical for the treatment of upper respiratory tract infections, specifically acute bronchitis in children. EPs® 7630 (Umckaloabo®), an ethanolic root extract (1:9-11) of *P. sidoides* roots, showed antibacterial, antiviral, and immunomodulatory properties in a vast number of investigations. These activities seem to account for its therapeutic effect. In Germany, Umckaloabo is a fully licensed medicinal product ranging among the most widely bought self-medications. Numerous clinical trials with EPs® 7630 have confirmed its efficacy and safety.
This species is native to the coastal regions of South Africa. 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 in South African traditional medicine to treat coughs, upper respiratory tract irritations, tuberculosis, and gastrointestinal complaints. In the first half of the 20th century, a product made from the root (Umckaloabo) was used in Europe for the treatment of tuberculosis. In the late 20th century Umckaloabo was developed into a safe and efficacious herbal pharmaceutical for the treatment of upper respiratory tract infections, specifically acute bronchitis in children. Various metabolites including phenolic and cinnamic acids, tannins, flavonoids and coumarins were characterized in *P. sidoides*. Activities against pathogens which are primarily responsible for respiratory tract infections and the immunomodulatory potential provide the rational basis for its therapeutic use. Numerous clinical trials with an ethanolic root extract (1:9-11) of *P. sidoides* roots, referred to as EPs® 7630 (Umckaloabo®) have confirmed its efficacy and safety.

**Umckaloabo, the patent remedy**

**Ethnobotany**

The ethnobotany of South African *Pelargonium* species and specifically *P. sidoides* has been extensively reviewed (1). Early recordings of the traditional uses of *Pelargonium* species refer predominantly to indications such as diarrhoea and dysentery owing to the astringent nature of their roots (2-8). Harvey and Sonder (9), in their treatment of *P. sidoides* [as *P. reniforme* Curtis var. *sidaefolium* (Thunb.) Harv.], stated the species as useful as an astringent in dysentery. The most detailed account of the value and uses of *P. sidoides* is that of Smith (10). Phillips (11) reported that the roots of are used to treat colic in Lesotho. Watt and Breyer-Brandwijk (12) reviewed ethnobotanical data for several *Pelargonium* species. The claim that the roots of *P. sidoides*/*P. reniforme* have been utilized for the therapy of tuberculosis in traditional medicine of South Africa (13,14) could not be substantiated by other sources.

**Etymology of 'Umckaloabo'**

The etymology of "Umckaloabo" has been discussed in detail in (1). “Umckaloabo” is the name introduced by Charles Henry Stevens for his tuberculosis medicine. Attempts to explain the origin of the word umckaloabo remain hitherto inconclusive. One interpretation was offered by Bladt (13) claiming it to be a derivation from isiZulu umKhulane, a term for various ailments with symptoms like fever, cough etc., and uHlabo, stinging breast pain. Doke and Vilakazi (15) refer to umkhuhlana (sic!) as a collective term for naturally occurring diseases accompanied by fever such as colds, influenza, pneumonia, pleurisy and malaria. According to Callaway (16) the term uhlabo is
derived from isiZulu / isiXhosa ukuhlaba, to stab or a stabbing pain, referring to pleurodynia or pleurisy. The legitimacy for quoting the isiZulu / isiXhosa words, however, is questionable, as the ethnicity of Stevens’ healer and hence the language he used is uncertain. The term Umckaloabo may thus be an invention of Stevens.

History of commercialization

In 1897, the then 17-year old Charles Henry Stevens from Birmingham, UK, was diagnosed with pulmonary tuberculosis and sent by his doctor to South Africa to recover. There he met a local healer, Mike Kijitse, who prescribed a root concoction which drove his condition into complete remission within three months. On his arrival back in the UK he was pronounced cured. Over the next 10 years Stevens returned to South Africa and involved himself in various unsuccessful ventures to commercialize his "discovery". In 1907 he brought quantities of the root back to England and established the "Stevens Co." in London, UK, in order to market his cure in England. Not without success, his company accounts for 1908 reveal takings of £4,415 (17, 18).

The industrialization of the 19th century signalled a dramatic increase in urban population, particularly in England. Cramped unhealthy conditions and inhuman working hours and inadequate nutrition were the result. The infectious and resistant Tuberculosis (TB) bacteria had found ideal breeding grounds as the exhausted, haggard bodies of the industrial proletariat had nothing to fight back with. Under these circumstances, the “white plague” was responsible for claiming the lives of hundreds of thousands. Every fifth death was due to TB. The only cures the medical establishment in Europe had come up with to date were fresh air, rest and good food, i.e. an illusion for most of its victims. Robert Koch discovered the bacterium responsible for TB in 1882 but the development and widespread application of useful medication would take another 60 years.

The medical establishment of the time was not oblivious to Stevens’ activities, the founder being a layperson and the disease in question the no. 1 national epidemic. Stevens (and others selling various “suspicious” treatments) did not have to wait long for the BMA’s (British Medical Association’s) response: In 1909 it published “Secret Remedies – what they contain and what they cost”, a book in which “Stevens’ Consumption Cure” was denounced as “quackery” and the origin of the plant used called into question (19-22).

While Stevens carried on selling his remedy, he felt an increasing impact of the BMA publication, impairing his sales in the UK and his attempts to take his remedy abroad. In 1912 he brought libel action against the BMA, an unprecedented step. While in the first trial the jury could not agree on a verdict, he was defeated in 1914, when despite numerous expert witnesses for Stevens, the jury found in favour of the BMA (supported by a recently published government report), the case was dismissed and Stevens ordered to pay the costs of £2,000. Both trials were extensively covered in both national and international press (23-31). An appeal in 1915 was refused.

War intervened. Stevens served with distinction, being promoted to the rank of major (19). After the war production and marketing of Umckaloabo (or
"Stevens' Cure") continued and Stevens' business extended as far as the US and India.

In January 1920, the Swiss physician Dr Adrien Sechehaye heard about Stevens Consumption Cure from a patient. He began gathering information about it to use the treatment on his TB patients. After curing a young woman, he went on to treat some 800 patients in the next nine years (and further into the 1960s). He frequently reports to the Medical Society on his successes and eventually publishes a selection of case reports concluding the cure to be an advance in the treatment of tuberculosis (17,32-40).

As part of his "marketing strategy", Stevens published (or had published) numerous polemics and books of case reports. These books were published by Fraser & Co. in London, a publisher who – located conveniently close to Stevens' business - never published anything but 'Umckaloabo literature' and thus may well have been run or at least 'sponsored' by Stevens (41-43). By 1931, Stevens employed 50 people manufacturing and distributing his remedy (lozenges, an extract and capsules) (44). The US authorities, meanwhile, debarred the remedy from the mails (45).

Stevens' lobbying kept the public interest up and the authorities busy. Even though he never received any official recognition for his remedy, there are numerous records for attempts being made by the medical establishment to identify it (46). Publicity also helped maintaining the success of his business (47). Then war disrupted supply routes. Stevens died aged 62 in 1942. Sechehaye continued treating tuberculosis patients with Umckaloabo until well into the 1960s (48-54).

As early as the 1930 Stevens' remedy had attracted attention throughout central Europe ("his" books were translated into German, Italian, Rumanian etc., cf. (55)). When the arrival of modern antibiotics resulted in the interest in the remedy waning, Stevens' son eventually sold the business to a drug manufacturer in Germany. There it appeared unchanged in the German National Formulary (Rote Liste), but without being actively marketed. Despite repeated attempts (56-58), it took until well into the 1970s for the plant ingredient of the remedy finally to be identified, when the mystery was finally resolved by Dr. Sabine Bladt, a pharmacist of Munich University (13,14,59-62). At this point the drug received renewed interest and pharmacological research was initiated and an ethanolic root extract (1:9-11) of Pelargonium (EPs® 7630) developed.

Marketing of the remedy as a treatment for bronchitis and symptoms of common cold started in the 1990s while research into the compounds and their mechanisms of action continued. Studies were initially observational, but later developed into fully fledged clinical trials (63-77).

In December 2005, the Federal Institute for Drugs and Medical Devices (BfArM, Bonn) approved a new license for the use of Umckaloabo (EPs® 7630) as a drug (78,79). It is a fully licensed liquid herbal medicine on the German market (€80,000,000 turnover in 2006). The drug is listed in the European Pharmacopoeia (80,81).

A preparation of P. sidoides mother tincture is marketed in the Ukraine, Russia and Latvia as Umkalor. A further preparation - meanwhile registered under the Traditional Herbal Products Directive - is available in the United Kingdom of Great Britain and Northern Ireland (82). Various liquid and solid
preparations are available as herbal supplements in North America and Mexico. A variety of liquid and dry forms of mono-preparations and herbal combinations that include *P. sidoides* are available in South Africa and adjacent countries, e.g. Linctagon, Phyto Nova Cough Syrup and Natura Pentagen.

Proprietary extracts of *Pelargonium sidoides* and their preparations, as well as the use thereof, are to date protected by a total of seven patents in various countries (83-89).

**Umckaloabo, the pharmaceutical**

**Botanical identity and habitat**

Taxonomy and description of *P. sidoides* vs. *P. reniforme* have been reviewed (1). Confusion about the correct identity of *P. sidoides* stems largely from Harvey and Sonder (9) including it as a variety within a broader concept of *P. reniforme*. Whether or not the name *P. reniforme* includes *P. sidoides* is thus not always clear. This is also reflected in the fact that into the late 1990s EPs® 7630 was referred to as an extract of *P. sidoides/P. reniforme* (90). This does, however, not necessarily imply use of both species as the taxonomy of *P. sidoides* vs. *P. reniforme* remained doubtful until revision (91,92). The correct scientific name of the species is *P. sidoides* DC. Dreyer and Marais (92) summarised the diagnostic differences between the two species.

The dried product can easily be adulterated with the very similar-looking *P. reniforme*, as morphological distinction of the dried product is extremely difficult. Chemical analysis, however, provides a reliable identification method, as *P. sidoides* contains umckalin and its 7-O-Methylether, which are absent in *P. reniforme*.

*P. sidoides* occurs in the Republic of South Africa throughout the Eastern Cape, Lesotho, Free State and southern and south-western Gauteng. *P. sidoides* is found at altitudes ranging from near sea level to 2300m in Lesotho. Most of the material is still wild-crafted in the Eastern Cape Province, but significant quantities of raw material will soon be produced from cultivated, seed-propagated plants.

**Chemistry**

A comprehensive study of all the chemical constituents of both underground and areal parts of *P. sidoides* and *P. reniforme* was done by Kolodziej (93). He also summarised earlier publications (67,72,94-103,172). However, further research may be warranted as these investigations were based on single samples of *P. sidoides* and *P. reniforme*, thus not taking into account possible geographical, phenotypical and genotypical patterns. A summary of main constituents in the roots and herb including constituents shown to be contained in Umckaloabo, an aqueous ethanolic extract of *P. sidoides* roots
(EPs® 7630) is given in Table I. A detailed account of the constituents of EPs® 7630 has been presented (104,105).

A yield of 0.52% (of dry weight) essential oil was obtained from the leaves of *P. sidoides* by hydrodistillation (106) and 102 components could be identified by GLC and GC-MS analyses.

**Table I. Main constituents of Pelargonium sidoides root, herb and of EPs 7630**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Roots</th>
<th>Herb</th>
<th>EPs® 7630</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenolic acids, phenylpropanoids and derivatives</strong></td>
<td></td>
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<tr>
<td>Gallic acid</td>
<td>+</td>
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<tr>
<td>Gallic acid methyl ester</td>
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<tr>
<td>Gallic acid ethyl ester</td>
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</tr>
<tr>
<td>Shikimic acid</td>
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<tr>
<td>Shikimic acid 3-0-gallate</td>
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<td>+</td>
<td></td>
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<tr>
<td>Glucogallin</td>
<td>+</td>
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<tr>
<td>Protocatechuic acid</td>
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<tr>
<td><strong>Coumarins, coumarin glycosides and coumarin sulfates</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7-Hydroxy-6-methoxycoumarin (Scopoletin)</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>6,7,8-Trihydroxycoumarin</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6,8-Dihydroxy-7-methoxycoumarin</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>7-Hydroxy-5,6-dimethoxycoumarin (Umckalin)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7,8-Dihydroxy-6-methoxycoumarin (Fraxetin)</td>
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</tr>
<tr>
<td>8-Hydroxy-5,6,7-trimethoxycoumarin</td>
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<tr>
<td>7-Acetoxy-5,6-dimethoxycoumarin</td>
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<tr>
<td>5,6,7-Trimethoxycoumarin</td>
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<tr>
<td>6,8-Dihydroxy-5,7-dimethoxycoumarin</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>5,6,7,8-Tetramethoxycoumarin (Artelin)</td>
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<tr>
<td>Umcalkelin-7-ß-D-glucoside</td>
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<td>Fraxetin-7-ß-D-glucoside</td>
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<td>Magnolioside</td>
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<tr>
<td>Isofraxoside</td>
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<tr>
<td>6,7-Dihydroxycoumarin-8-sulfate</td>
<td>+</td>
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<tr>
<td>5,6-Dimethoxycoumarin 7-sulfate</td>
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<td>6-Hydroxy-5,7-dimethoxycoumarin 8-sulphate</td>
<td>+</td>
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<td></td>
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<tr>
<td>8-Hydroxy-5,7-dimethoxycoumarin 6-sulphate</td>
<td>+</td>
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</tbody>
</table>

*Source: Modified from (93)*
### Table I. continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>Roots</th>
<th>Herb</th>
<th>EPs® 7630</th>
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<tr>
<td><strong>Flavonoids</strong></td>
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<tr>
<td>Isoorientin</td>
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<td></td>
<td></td>
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<tr>
<td>Isoorientin 2&quot;-O-gallate</td>
<td>+</td>
<td></td>
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<tr>
<td>Isovitexin</td>
<td>+</td>
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<td></td>
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<tr>
<td>Isovitexin 2&quot;-O-gallate</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quercetin</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Taxifolin 3-O-β-D-glucoside</td>
<td>+</td>
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<tr>
<td>Orientin</td>
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<tr>
<td>Orientin 2&quot;-O-gallate</td>
<td>+</td>
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<tr>
<td>Dihydrokaempferol 3-O-β-D-glucoside</td>
<td>+</td>
<td></td>
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<tr>
<td>Luteolin 7-O-β-D-glucoside</td>
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<td></td>
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<tr>
<td>Vitexin</td>
<td>+</td>
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<tr>
<td>Vitexin 2&quot;-O-gallate</td>
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<tr>
<td>Epigallocatechin-3-O-gallate</td>
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<tr>
<td><strong>Flavan-3-ols / Hydrolysable Tannins</strong></td>
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<tr>
<td>Catechin</td>
<td>+</td>
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<tr>
<td>Gallocatechin</td>
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<tr>
<td>Proanthocyanidins</td>
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<tr>
<td><strong>Others</strong></td>
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</tr>
<tr>
<td>β-Sitosterol</td>
<td>+</td>
<td></td>
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<tr>
<td>(+)-Cyclolariciresinol-2a-β-D-glucoside</td>
<td></td>
<td></td>
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<tr>
<td>4,6-Dihydroxyacetophenone 2-O-β-D-glucoside</td>
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<tr>
<td>4-Allyl-2,5-dimethoxyphenol-1-β-D-glucoside</td>
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</tbody>
</table>

**Pharmacology**

A detailed account of the pharmacological properties of *P. sidoides* and/or EPs® 7630 has been given (1). The following overview summarizes this information.
Antibacterial properties

Antibacterial activity of extracts and isolated constituents of *P. sidoides* was evaluated against three gram-positive and five gram-negative bacteria (107). Most compounds exhibited antibacterial activities. Further investigations complement these findings (108).

EPs® 7630 shows a synergistic indirect antibacterial effect in group A-streptococci through inhibition of bacterial adhesion to human epithelial cells as well as induction of bacterial adhesion to buccal epithelial cells (109-111). The antiadhesive effect of EPs® 7630 was confirmed for *Helicobacter pylori* growth and adhesion to gastric epithelial cells (112, 113). Umckaloabo significantly stimulated phagocytosis and oxidative burst. Intracellular killing was also enhanced (114-120).

Modulation of epithelial cell-bacteria interaction through EPs® 7630 may protect mucous membranes from microorganisms evading host defence mechanisms. This provides a rationale for the treatment of upper respiratory tract infections with EPs® 7630 (121).

Anti-mycobacterial activity for hexane extracts of roots of *P. reniforme* and *P. sidoides* was established (122-124). As no significant effect on the bacterial growth of two strains of mycobacteria by extracts and fractions of *P. sidoides* could be shown (101), it was postulated that an antitubercular effect may be achieved indirectly by stimulation of immune response. This assumption was supported by Mativandlela et al. (125, 126) as none of the compounds
isolated from *P. sidoides* showed any significant activity against *M. tuberculosis*.

**Immunomodulatory properties**

Extracts and isolated constituents of *P. sidoides* were investigated for their effects on nonspecific immune functions in various bioassays (98,107,127). Results imply indirect activity, possibly through activation of macrophage functions. Activation was confirmed through the presence of tumour necrosis factor (TNF-alpha) and inorganic nitric oxides (iNOS). TNF-inducing potencies for EPs® 7630 as well as interferon-like activities were also observed (128,129). Interferon (IFN)-beta production increased and natural killer cell mediated cytotoxicity was enhanced in MG-63 human osteosarcoma cells preincubated with Umckaloabo (130).

Kolodziej et al. (131,132) investigated polyphenol-containing extracts of *P. sidoides* and simple phenols, flavan-3-ols, proanthocyanidins and hydrolysable tannins for gene expressions (iNOS, IL-1, IL-10, IL-12, IL-18, TNF-alpha, IFN-alpha/gamma). All extracts and compounds were capable of enhancing the iNOS and cytokine mRNA levels in parasitized cells. EPs® 7630 induced low mRNA levels in non-infected cells, but considerably up-regulated transcript expressions in infected cells (133). Production of IFN-gamma mRNA was also stimulated. Similar profiles were obtained for the methanol-insoluble fraction and gallic acid. Significant immunomodulatory properties for EPs® 7630, extracts and isolated constituents of *P. sidoides* were demonstrated in various functional bioassays (134).

EPs® 7630 stimulates host defence through enhancing the release of antimicrobial peptides (135).

**Effects on the mucociliary system**

EPs® 7630 significantly increased ciliary beat frequency in a dose-dependent manner (136,137).

**Effects on symptoms of sickness behaviour**

EPs® 7630 showed inhibition of sickness behaviour in a dose-dependent manner (138,139).

**Antiviral properties**

An inhibitory effect of an aqueous root extract of *P. sidoides* against herpes simplex virus type 1 and 2 was shown in a plaque reduction assay and high antiviral activity against both herpes viruses could be demonstrated in viral suspension tests (140).
Toxicology, adverse effects, precautions, contraindications, interactions

Toxicity of coumarins present in the crude drug and/or extracts can be considered negligible (NOEL >750 mg/kg body weight). No hepatotoxic activity could be established for coumarins present in EPs® 7630 (72,103,141,142). In controlled clinical trials with over 7,200 adults and children mild adverse events, consisting of gastrointestinal complaints and skin rashes, occurred in <15% of subjects (79,143). A total of 34 hypersensitivity reactions have been recorded through the World Health Organisation (WHO) international pharmacovigilance programme and may be associated with EPs® 7630 (144).

Roots et al. (145) investigated a potential interaction of a P. sidoides extract (EPs® 7630) with penicillin V in a placebo-controlled, double-blind trial with 28 healthy humans. No interaction was shown. Interaction with anticoagulants and antiplatelet drugs could be ruled out as the coumarins so far identified in EPs® 7630 do not appear to possess anticoagulant characteristics (146).

The extract of P. sidoides root (EPs® 7630) is contraindicated during pregnancy and lactation as no specific data on its effect on pregnant or lactating women is available.

Clinical evidence of efficacy

Results for a total of 20 clinical trials have thus far been published, 7 of which were observational studies, the remaining 13 were randomized, double-blind and placebo-controlled. For 6 of those 13 trials, only preliminary results have been published. For more detailed information see Table II. In several instances, more than one publication presents the results for one and the same trial/study; Table II summarizes and combines the various references. All trials have been carried out using a P. sidoides extract (EPs® 7630) in liquid or solid forms.

The data derived from these trials has been evaluated in two reviews (147,148). Akbabiaka et al. (147) focused on Pelargonium sidoides for acute bronchitis and identified 6 studies (90,149-151) and two unpublished trials referred to as "Kieser (2007a)" and "Kieser (2007b)". Results for the latter two were initially presented by Kamin (152) and are thus referred to this reference for the purpose of this overview) which met their inclusion criteria (randomized trials against a control intervention, excluding trials which admitted patients with pre-existing chronic bronchitis and/or infectious diseases), two of which were/are unpublished. Methodological quality of the trials reviewed was good; a Jadad score of 5 was calculated for three trials. Akbabiaka et al. (147) concluded that there was encouraging evidence for the efficacy of P. sidoides in the treatment of acute bronchitis vs. placebo.

Timmer et al. (148) reviewed the efficacy of P. sidoides extract for acute respiratory tract infections and identified 12 trials meeting their inclusion criteria (randomized trials against a control intervention with complete resolution of symptoms as primary outcome criteria). Four trials were excluded from the analyses due to high risk of bias. They reviewed eight trials
While the evidence from trials with acceptable methodology was considered limited and more trials are called for, both reviews concluded treatment with *P. sidoides* offered relief from the symptoms of acute respiratory tract infection, and specifically from acute bronchitis in children. Taking into account additional data from observational studies and post-market surveillance, results support the use of Umckaloabo (EPs® 7630) as a possible alternative to antibiotics for the acute treatment of these conditions. Overall safety and a very low incidence of side effects have been confirmed.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial type/Size (verum / placebo)</th>
<th>Results (References)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infections, acute or chronic</td>
<td>Observational study 166</td>
<td>166 children and adolescents aged 1-19 were treated for up to three weeks, median 7 days. Primary outcome criteria were change in symptoms and evaluation of efficacy and tolerability on a four point scale after completion of the treatment. Improvement of all related symptoms (cough n=62, fever n=47, with complete remission in 50% and 85% respectively) could be observed, in 2/3 of patients no further treatment was required. Tolerability was described as &quot;good&quot; or &quot;very good&quot; in more than 90%. Adverse effects were not reported. (64)</td>
</tr>
<tr>
<td>Upper respiratory tract infections, acute or chronic</td>
<td>Observational study 641</td>
<td>641 patients were included aged &lt;10 to 60 and treated for up to &gt;14 days, median 12 days. Significant improvement of symptoms were observed after 7 days (n=240) and 14 days (n=305) respectively. In 85% treatment could be concluded after 2 weeks. In 88.9% efficacy was assessed as &quot;good&quot; or &quot;very good&quot;. Tolerability was described as &quot;good&quot; or &quot;very good&quot; in 639 cases. Adverse effects were not reported, in 7 cases new or aggravated symptoms were reported. (65)</td>
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<tr>
<td>Bronchitis, acute</td>
<td>Observational study 259</td>
<td>259 children aged up to 12 years were included and treated for up to three weeks, median 14 days. Cough, expectoration, rattling and chest pain were assessed in a 5-level, verbal rating scale. Overall success of therapy was also assessed in a 5-level rating scale. A remission or improvement of &gt;80% of symptoms was observed after conclusion of the treatment. Overall remission could be observed in 57.9%, overall improvement in 32%. Tolerability was described as &quot;good&quot; or &quot;very good&quot; in 96.5%. Adverse effects were reported in 6 cases and included mild exanthema and gastrointestinal complaints. (72)</td>
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<tr>
<td>Indication</td>
<td>Trial type/Size</td>
<td>Results (References)</td>
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<tr>
<td>Bronchitis, acute</td>
<td>Observational study 742</td>
<td>742 children (0 to 12 years) were included and treated according to age (0-2, 2-6, &gt;6) with 15/30/60 drops of Umekaloabo for up to 14 days. Overall outcome measure was the sum of five Bronchitis Severity Score symptoms. Bronchitis Severity Score decreased from 6.0+-3.6 points at baseline to 2.7+-2.5 points after 7 days and to 1.4+-2.1 points after 14 days. Complete or partial remission of symptoms was observed in 90.2%. Tolerability was described as &quot;very good&quot; in 94.9%, 8 patients experienced non-serious adverse effects including aggravation of symptoms, mild exanthema, gastrointestinal complaints, unrest and dyspnoea. (70,155)</td>
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<tr>
<td>Bronchitis, acute</td>
<td>Randomized controlled trial 60 (30/30)</td>
<td>60 children aged 5-14 were included and treated for 7 days with Umekaloabo (30), or with acetylcysteine (30). Changes in Bronchitis Severity Score were evaluated. Score base value was 7 (+/-3) points and decreased in the Umekaloabo group by 7 (+/-2) points, in the acetylcysteine group by 6 (+/-3) points. Total remission of symptoms after 7 days was observed in 76.7% (Umekaloabo) and 56.7% (acetylcysteine). Tolerability was assessed as &quot;very good&quot; by 53.3% (Umekaloabo) and 46.7 (acetylcysteine). Adverse effects were not reported. (90)</td>
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<tr>
<td>Angina catarrhalis</td>
<td>Randomized controlled trial 60 (30/30)</td>
<td>60 children aged 6-10 were included, 30 of which were treated with Umekaloabo, 30 received symptomatic treatment (Priessnitz' cure and gargling with apple vinegar) over a period of 10 days. Target criteria were change in angina-related symptoms and tolerability. By day 4, improvement of symptoms had reached the response criteria in 23 cases in the Umekaloabo group vs. 9 cases with symptomatic treatment. Tolerability was assessed as &quot;good&quot; or &quot;very good&quot; by 100% in the Umekaloabo group after 10 days vs. 63.4% in the symptomatic treatment group. Adverse effects were not reported. (156)</td>
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<tr>
<td>Indication</td>
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<tr>
<td>Non-GABHS tonsillopharyngitis in children</td>
<td>Randomized, placebo-controlled double-blind trial 143 (73/70)</td>
<td>143 children aged 6-10 years with a Tonsillopharyngitis Severity Score $\geq$ 8 points were included. EPs® 7630 or placebo were given (20 crops 3 times daily) for 6 days. Score decreased from baseline to day 4 7.1 $\pm$ 2.1 points with EPs® 7630, and 2.5 $\pm$ 3.6 points with placebo. The 95% confidence interval for the difference between the groups was [2.7; 4.9] and showed significant superiority in efficacy of EPs® 7630 ($P &lt; 0.0001$). 4 and 43 withdrawals for reasons other than complete recovery were reported for the Umckaloabo and placebo groups respectively. Tolerability was assessed as &quot;good&quot; or &quot;very good&quot; for almost all cases in both groups. Adverse events were reported for 15 patients (EPs® 7630 1 patient, placebo 14), however, were neither classified as serious nor related to the medication. (157,158)</td>
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<tr>
<td>Bronchitis, acute</td>
<td>Randomized, placebo-controlled double-blind trial 468 (233/235)</td>
<td>468 adults with Bronchitis Severity Score $\geq$ 5 points were included. EPs® 7630 or placebo were given (30 drops 3 times daily) for 7 days. Decrease from baseline to day 7 was 5.9 $\pm$ 2.9 points with EPs® 7630, and 3.2 $\pm$ 4.1 points with placebo. The 95% confidence interval for the difference of effects between the treatment groups showed significant superiority in efficacy of EPs® 7630 on day 7 ($p &lt; 0.0001$). Tolerability was assessed as &quot;good&quot; or &quot;very good&quot; by 96.1% in the EPs 7630 group vs. 88.1% in the placebo group. Non-serious adverse events occurred in 36 patients (EPs® 7630 20 patients, placebo 16 patients). Most commonly reported were ear and labyrinth disorders and gastrointestinal disorders. (149)</td>
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<tr>
<td>Indication</td>
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<tr>
<td>Bronchitis, acute</td>
<td>Randomized, placebo-controlled double-blind trial 124 (64/60)</td>
<td>124 adults with Bronchitis Severity Score $\geq 5$ were included. 64 patients received 30 crops EPs® 7630, 60 patients received placebo three times daily for 7 days. Decrease of Bronchitis Severity Score from baseline to day 7 was $7.2 \pm 3.1$ points with EPs® 7630 vs. $4.9 \pm 2.7$ points with placebo. The 95% confidence interval for the difference of effects between treatment groups showed a significant superiority of EPs® 7630 ($P &lt; .0001$). Treatment effect was recognized in 68.8% of patients in the EPs® 7630 group vs. 33.3% of patients in the placebo group ($P &lt; .0001$) within the first 4 days. 3 and 4 withdrawals were recorded for the verum and placebo group, respectively. Tolerability was assessed as &quot;good&quot; or &quot;very good&quot; by 98.4% in the EPs 7630 group vs. 96.7% in the placebo group. Non-serious adverse events occurred in 25 of 124 patients (EPs® 7630 15 patients, placebo 10 patients). (78,150,159,160)</td>
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<tr>
<td>Sinusitis, acute bacterial maxillary</td>
<td>Randomized, placebo-controlled double-blind trial 272</td>
<td>272 patients with radiologically confirmed acute bacterial maxillary sinusitis were treated with 3x 60 drops EPs® 7630 or placebo, respectively, for a maximum of 3 weeks. Primary outcome criteria were sinusitis symptoms. Symptoms decreased from $14.4 \pm 1.8$ points by $7.0 \pm 3.2$ points in the verum group, while the baseline value of $13.9 \pm 1.7$ in the placebo group remained unchanged ($p=0.0001$). No serious adverse events were recorded. (151)</td>
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<tr>
<td>Sinusitis, acute bacterial maxillary</td>
<td>Randomized, placebo-controlled double-blind trial 103 (51/52)</td>
<td>103 patients with radiologically confirmed acute bacterial maxillary sinusitis were treated with 3x 60 drops EPs® 7630 or placebo, respectively, for a maximum of 22 days. Primary outcome criteria were the change in Sinusitis Severity Score after 7 days. Score decreased by 5.5 points in the verum group, and 2.5 points in the placebo group ($p=0.00001$). Complete recovery at treatment end was observed in 32 and 4 patients in the verum and placebo group, respectively. No serious adverse events were recorded. (153,161)</td>
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<tr>
<td>Sinusitis</td>
<td>Observational study 361</td>
<td>361 patients aged 1-94 were included and treated with EPs® 7630 (days 1 and 2 30 drops 12 times daily (children 20 drops), thereafter 30 drops 3 times daily (children 20 drops) for 28 days, patients with chronic sinusitis received a prophylactic treatment for another 8 weeks of 30/20 drops two times daily (adults/children). Within 4 weeks 80.9% of the patients became symptom-free or experienced improvement in symptoms. Success rate was over 90% for each individual symptom. Tolerability was assessed as &quot;good&quot; or &quot;very good&quot; by 95.8%. 17 patients reported non-serious adverse events, mostly gastrointestinal complaints. (152)</td>
</tr>
<tr>
<td>Bronchitis, acute</td>
<td>Observational study 205</td>
<td>205 patients with a mean age of 42 +/-16 were included and treated with 3x 30 drops EPs® 7630 daily for 7 days. Change in the total score of 5 Bronchitis Severity Score symptoms was the outcome measure. Total score of bronchitis symptoms was 6.1 +/-2.8 points at baseline and decreased by 3.3 +/-3.8 points to 2.8 +/-2.6 points by the final examination on day 7. 60.5% of the patients assessed their health as much improved at the end of the study. Non-serious adverse events occurred in a total of 16 patients, mostly gastrointestinal complaints. (163)</td>
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<tr>
<td>Bronchitis, acute</td>
<td>Observational study 2099</td>
<td>2099 patients (0-93 years) were treated with an age-dependent dose of EPs® 7630 for 14 days. Change of the Bronchitis Severity Score was the primary outcome criterion. Score decreased from 7.1 +/-2.9 points at baseline to 1.0 +/-1.9 points at patients’ individual last visit. Children showed decrease of score from 6.3 +/-2.8 points to 0.9 +/-1.8 points. Children &lt;3 years showed a decrease of score from 5.2 +/-2.5 points to 1.2 +/-2.1 points. Compliance was assessed as &quot;good&quot; in 96.4%. Mostly non-serious adverse events occurred in 26 patients, mostly gastrointestinal complaints. (164)</td>
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### Table II. Continued.

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<tr>
<td>Bronchitis, acute</td>
<td>Randomized, placebo-controlled double-blind trial 217 (108/109)</td>
<td>217 patients (18 to 66 years) were included. 108 (109) patients received 30 drops of EPs® 7630-solution (placebo) 3x times daily for 7 days. Bronchitis Severity Score decreased by 7.6 +/- 2.2 points in the EPs® 7630 group and by 5.3 +/- 3.2 points in the placebo group. Time to remission was significantly shortened in the verum group. The 95% confidence interval for difference between effects showed highly significant superiority of EPs® 7630 (p &lt; 0.0001). 47 non-serious adverse events were recorded. <em>(151,165-167)</em></td>
</tr>
<tr>
<td>Bronchitis, acute</td>
<td>Randomized, placebo-controlled double-blind trials 399 (298/101)</td>
<td>399 children aged 6-18 are included and treated with 30, 60 and 90mg EPs® 7630 tablets and placebo, respectively. Primary outcome criterion is the mean change of the Bronchitis Severity Score. The two higher dosages showed significant improvement vs. placebo (score decreased -3.6/-4.4/-5.0 vs. -3.3, p&lt;0.001 for 60/90mg. Non-serious adverse events are reported in 18 patients, mostly gastrointestinal complaints. <em>(147</em>,148**,152,168)* referred to as Kieser (2007b), **referred to as Anonymous 2</td>
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<tr>
<td>Bronchitis, acute</td>
<td>Randomized, placebo-controlled double-blind trials 405 (101,101,101,102)</td>
<td>405 patients aged &gt;18, mean 40, were included. Patients were divided up into 4 groups receiving 3 times daily one tablet of 10, 20 or 30mg EPs® 7630 or placebo for 7 days. Decrease of Bronchitis Severity Score and typical symptoms was observed. Decrease was significant in all 3 verum groups vs. placebo (score decreased -4.3/-6.1/-6.3 vs. -2.7, p&lt;0.001 for 30/60/90mg. 3 times 20mg daily appears to correspond to 3 times 30 drops, dose increase beyond 60mg daily does not appear to increase efficacy. Non-serious adverse events are reported in 18 patients, mostly gastrointestinal complaints. <em>(147</em>,148**,152,169,170)* referred to as Kieser (2007a), **referred to as Anonymous 3</td>
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<tr>
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<tr>
<td>Bronchitis, acute</td>
<td>Randomized, placebo-controlled double-blind trials 200</td>
<td>200 children and adolescents aged 1-18 were included. Patients received EPs® 7630 solution or placebo three times daily 10/20/30 drops (age groups 1-6/6-12/&gt; 12-18) for 7 days. Decrease in Bronchitis Severity Score and typical symptoms were observed. Difference of reduction in score and other symptoms was significant (p &lt; 0.0001) in verum (-3.4) vs. placebo (-1.2). Non-serious adverse events related to verum were recorded in 31 cases (6 possibly related to therapy), mostly gastrointestinal complaints. (148, 152, 168, 171) *referred to as Anonymous 1</td>
</tr>
<tr>
<td>Bronchitis, acute</td>
<td>Randomized, placebo-controlled double-blind trials 220</td>
<td>220 children and adolescents aged 1-18 were included. Patients received EPs® 7630 solution or placebo three times daily 10/20/30 drops (age groups 1-6/&gt; 6-12/&gt; 12-18) for 7 days. Decrease in Bronchitis Severity Score and typical symptoms were observed. Difference of reduction in score and other symptoms was significant (p &lt; 0.0001) in verum (-4.4) vs. placebo (-2.9). Non-serious adverse events related to verum were recorded in 2 cases (unrelated to therapy). (148, 152, 168, 171) *referred to as Anonymous 4</td>
</tr>
<tr>
<td>Cold, common</td>
<td>Randomized, placebo-controlled double-blind trial 103 (52/51)</td>
<td>103 adult patients aged 18-55 with cold symptoms (maximum symptom score of 40 points) were included. Patients received either 30 drops EPs® 7630 or placebo 3 times daily for 10 days. Outcome criterion was the sum of symptom intensity differences of the cold intensity score from day 1-5. From baseline to day five, the mean score improved by 14.6 +/- 5.3 points with EPs® compared to 7.6 +/- 7.5 points with placebo (p &lt; 0.0001). 8 patients were withdrawn (4/4). Tolerability was assessed as &quot;good&quot; to &quot;very good&quot; in 94.2% for verum vs. 82.4% for placebo. Non-serious adverse events occurred in 3 patients (2/1), one possibly related to verum (mild epistaxis). (154)</td>
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</table>
Conclusions

*Pelargonium sidoides* has a long-standing tradition in the treatment of diseases, starting with ethnobotanical records from the mid 19th century and followed by the enthusiastic perseverance of Charles Henry Stevens and Adrien Sechehaye in the first half of the 20th century.

In Germany, a fully licensed medicinal product containing a special extract of *P. sidoides* root is now among the most widely bought self-medication products. EPs® 7630 (Umckaloabo®), showed in vitro antibacterial, antiviral, and immunomodulatory properties in several studies. These activities seem to account for its therapeutic effect in patients suffering from acute bronchitis, tonsillopharyngitis, sinusitis and symptoms of the common cold. Efficacy and safety have been proved in numerous clinical trials.

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