The importance of Pelargonium species, most notably Pelargonium reniforme and Pelargonium sidoides, in traditional medicine in the southern African region is well documented. A modern aqueous-ethanolic formulation of the roots of P. sidoides (EPs 7630) is successfully employed for the treatment of ear, nose and throat disorders as well as respiratory tract infections.

To provide a scientific basis of its present utilisation in phytomedicine. EPs 7630, extracts were evaluated for antibacterial activity and for their effects on nonspecific immune functions. The samples exhibited merely moderate direct antibacterial capabilities against a spectrum of Gram-positive and Gram-negative bacteria. Functional bioassays including an in vitro model for intracellular diseases, a fibroblast lysis assay (tumour necrosis factor [TNF] activity), a fibroblast-virus protection assay (TNF activity) and a biochemical assay for nitric oxides revealed significant immunomodulatory properties.

Gene expression experiments not only confirmed functional data, they also clearly showed differences in the response of infected macrophages when compared to that of noninfected cells. Protein production of TNF-a, IL-1α and IL-12 was confirmed, while FACS analyses reaffirmed the cytokines IL-1α and IL-12 at the singular cell level. This supports the improvement of immune functions at various levels, validating the medicinal uses of EPs 7630.

**PHARMACODYNAMIC PROPERTIES**

The antibacterial activity of extracts and isolated constituents was evaluated by Kaysen and Klotz (1997) against three gram-positive (Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus 1451) and five gram-negative bacteria (Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae). Minimum inhibitory concentrations varied between 200-1000μg/ml, depending on the extracts and microorganisms tested, indicated weak antibacterial activity. Further investigations by Lewu et al (2006) confirmed these findings. The demonstrated weak antibacterial activity in comparison with the activities of antibiotics cannot adequately explain the documented clinical efficacy of Pelargonium-containing herbal medicines in the treatment of respiratory tract infections.

Conrad et al (2007) investigated the impact of a root extract of Pelargonium sidoides on the activity of human peripheral blood phagocytes and on host-bacteria interaction. Phagocytosis was increased in a concentration-dependent manner and intracellular killing was enhanced. Furthermore, investigations provided strong evidence for bacterial anti-adhesion activity (Conrad et al, 2006), suggesting that the mechanism whereby these extracts exercise antibacterial activity apparently includes various mechanisms. Hansmann (2005) also investigated the influence of a Pelargonium root extract on the function of human phagocytes. Candida albicans was used as the target organism. Significant stimulated phagocytosis and oxidative burst were observed while intracellular killing was hardly influenced. Mickenhagen et al (2004) and Neugebauer et al (2005) investigated the influence of Pelargonium root extract on the stimulation of ciliary beat frequency (an important defence mechanism of the mucociliary system) in ciliated cell cultures of human nasal epithelium in vitro. Three concentrations of the extracts were tested, which significantly increased ciliary beat frequency in a dose-dependent manner.


Wittschier et al (2007) incubated intact human stomach tissue with fluorescent-labelled Helicobacter pylori. Pre-treatment of bacteria with Pelargonium extract showed a dose-dependent antiadhesive effect. No direct cytotoxicity against Helicobacter pylori could be established. Bell and Kilian (2007) showed that EPs 7630 inhibited Helicobacter pylori growth and adhesion to gastric epithelial cells in a dose-dependent manner. Intracellular killing was also enhanced. EPs 7630 also reduced GAS adhesion to HEP-2 cells significantly, but increased GAS adhesion to BEC, due to different viabilities of the types of epithelial cell investigated. This variety in modulation of epithelial cell–bacteria interaction through EPs 7630 may help to protect mucous membranes from microorganisms which evade host defense mechanisms and/or overcome antibiotic treatment. These results provide a rationale for the treatment of upper respiratory tract infections with EPs 7630.

Agbabiaka and Ernst, (2008) reported that findings of randomised clinical trials confirmed the effectiveness of Pelargonium sidoides in treating acute bronchitis. Meta-analysis of four placebo-controlled trials suggested that root extracts significantly reduced bronchitis symptom scores in patients with acute bronchitis by day seven. No serious adverse events were reported. Lizogub et al (2007) performed a randomised, double blind, placebo-controlled clinical trial which showed that a liquid preparation from the roots of Pelargonium sidoides represented an effective treatment for the common cold. It significantly reduces the severity of symptoms and shortens the duration of the common cold compared with placebo. The herbal drug is well tolerated.

**Antimycobacterial properties**

Taylor (2003) as well as Sessell and Taylor (2004) established anti-mycobacterial activity for hexane extracts of roots of Pelargonium reniforme and Pelargonium sidoides. They claimed that several mono- and diunsaturated fatty acids are the active compounds (with oleic acid and linoleic acid being considered the most active, having MICs of approximately 2g/ml). Gödecke (2005) tested extracts and fractions of Pelargonium sidoides against two strains of mycobacteria. Since no significant effect on the bacterial growth could be shown, it was assumed that the effective use of the plant in tubercular conditions.
may be due to an activation of the immune system. This assumption was supported by Mativandlela et al. (2006, 2007), who investigated various extracts and isolated compounds from Pelargonium sidoides root with regards to their antimycobacterial and especially their antitubercular activities. Strains of Moraxella catarrhalis, Aspergillus niger, Rhizopus stolonifer, Fusarium oxysporum, Haemophilus influenza, Mycobacterium tuberculosis and M. smegmatis were exposed to acetone and ethanol root extracts, as well as four coumarins and two flavonoids isolated from Pelargonium sidoides. Significant activity could be shown for ethanol extract against Aspergillus niger and Fusarium oxysporum but limited activity against Rhizopus stolonifer and Mycobacterium tuberculosis. None of the isolated compounds showed any activity against Mycobacterium tuberculosis.

**Immunomodulatory properties**

Kayser et al. (1997, 2001, 2003) investigated extracts and isolated constituents of Pelargonium sidoides for their effects on nonspecific immune functions in various bioassays. No significant activity against extracellular, promastigote Leishmania donovani, could be shown. However, all extracts and compounds significantly reduced the intracellular survival of Leishmania donovani. This implies indirect activity, possibly through activation of leishmanicidal macrophage functions. Activation was confirmed through the presence of tumour necrosis factor (TNF-alpha) and inorganic nitric oxides (iNO). Synthesis of the latter is a known mechanism of macrophages against microorganisms.

Kolodziej et al. (2003) and Janecki et al. (2007) observed TNF inducing potencies for EPs 7630 as well as interferon-like activities in supernatants of sample-activated bone marrow-derived macrophages in several functional assays. Various subfractions of EPs 7630 were tested for their NO-, TNF- and interleukin (IL)-12-inducing capacity. EPs 7630 induced significant TNF levels in non-infected and GFP transfectected-Leishmania major-infected macrophages. Production of NO and IL-12, however, were negligible, while flow cytometry indicated a decrease in parasites in cells treated with EPs 7630. This suggests that radical scavengers or low but efficient NO levels may be present in EPs 7630.

Koch et al. (2002) further investigated if and how EPs 7630 interferes with interferon (IFN)-beta synthesis in MG-63 human osteosarcoma cells. IFN-beta production increased in cells preincubated with Umckaloabo. Enhancement of natural killer cell mediated cytotoxicity was also found. Umckaloabo thus enhanced but did not induce IFN-beta production.

Kolodziej et al. (1999, 2005) investigated polyphenol-containing HNP 1–3 and BPI. Thus EPs 7630 seem to stimulate host defence through enhancing the release of antimicrobial peptides.

**Effects on the mucociliary system**

Mickenhagen et al. (2004) and Neugebauer et al. (2005) presented investigations into the stimulation of ciliary beat frequency (an important defence mechanism of the mucociliary system) in ciliated cell cultures of human nasal epithelium with Eps 7630 in vitro. Three concentrations of Eps 7630 (1, 30, 100g/ml) were tested, which significantly increased ciliary beat frequency in a dose-dependent manner.

**Effects on symptoms of sickness behaviour**


**CLINICAL EVIDENCE OF EFFICACY**

A total of 18 clinical trials have thus far been conducted, several of which were randomised, double-blind and placebo-controlled. EPs 7630 has been shown to effectively shorten the severity and duration of acute bronchitis and tonsillitis, most notably in children. Results from trials with adults and children support the use of this product as a possible alternative to antibiotics for the acute treatment of these conditions. Research also focuses on the treatment of symptoms of sickness behaviour and of acute bronchitis.

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**Why Flugon?**

Flugon combines a unique combination of plant extracts and vitamins that has shown to have strong antibacterial, antiviral, mucolytic and immunomodulatory activities.

The cornerstone ingredient in Flugon, *Pelargonium sidoides*, has shown in clinical trials to both shorten the duration and severity of upper respiratory tract infections. **Indication:** In acute and chronic inflammation with or without viral infections of the respiratory tract, for example: Bronchitis, Sinusitis, Tonsillitis, Ear and Throat infections, Colds and Flu.

Flugon can also be used as a supplementary measure in antibacterial therapy.

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**FLUGON**

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In vitro evaluation of antibacterial and immunomodulatory activities of Pelargonium sidoides, Pelargonium sidoides, and the reduced herbdrug preparation (Flu Flugon), Herbert Koenenberger, Alfred F. Koberlegi.
The common cold is a viral infection with symptoms such as sneezing, sore throat, and running nose. It is one of the most prevalent illnesses in the world, and although commonly caused by rhinoviruses, antibiotics are often prescribed unnecessarily. Therefore, it is of utmost importance to evaluate alternative treatments such as herbal medications, whose efficacy and safety is proven by pharmacological and clinical studies. The aim of the present study was to evaluate the efficacy of a liquid herbal drug preparation from the roots of Pelargonium sidoides compared with placebo in adult patients with the common cold.

**Design:** The study was designed as a multicentre, prospective, randomised, double-blind, parallel group, placebo-controlled phase III clinical trial with an adaptive group–sequential design.

**Setting:** The study took place in eight outpatient departments affiliated with hospitals.

**Patients:** One hundred thirty male and female adult patients with at least two major and one minor or with one major and three minor cold symptoms (maximum symptom score of 40 points), present for 24 to 48 hours, and who gave provision of informed consent were randomised to receive either 30 drops (1.5mL) of the liquid herbal drug preparation Eps or placebo three times a day.

**Intervention:** Patients received randomised treatment for a maximum period of 10 days.

**Measurements:** The primary outcome criterion was the sum of symptom intensity differences (SSID) of the cold intensity score (CIS) from day one to day five. The CIS consists of the following 10 cold symptoms: nasal drainage, sore throat, nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, muscle aches, and fever.

**Results:** From baseline to day five, the mean SSID improved by 14.6 ± 5.3 points in the Eps group compared with 7.6 ± 7.5 points in the placebo group. This difference was statistically significant (P < 0.0001). The mean CIS decreased by 10.4 ± 3.0 points and 5.6 ± 4.3 points in Eps and placebo-treated patients, respectively. After 10 days, 78.8% versus 31.4% in the Eps vs. placebo group were clinically cured (CIS equals zero points or complete resolution of all but a maximum of one cold symptom; P < 0.0001). The mean duration of inability to work was significantly lower in the Eps treatment group (8.9 ± 1.8 days) than in the placebo group (8.2 ± 2.1 days; P = 0.0003). Treatment outcome (rates of complete recovery or major improvement from disease [integrative medicine outcomes scale]) was assessed better in the Eps treatment group than in the placebo group by both the investigator and the patient on day five (P < 0.0001).

**Adverse events** occurred in three of 103 patients (2.9%), with two of 52 (3.8%) and one of 51 (2.0%) patients in the Eps and placebo group, respectively. All adverse events were assessed as nonserious. At the end of treatment, all patients (100%) in the active treatment group judged the subjective tolerability of Eps as good or very good.

**Conclusions:** Eps represents an effective treatment of the common cold. It significantly reduces the severity of symptoms and shortens the duration of the common cold compared with placebo. The herbal drug is well tolerated.