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An Evidence-Based Systematic Review of Umckaloabo (*Pelargonium sidoides*) by the Natural Standard Research Collaboration

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ABSTRACT. An evidence-based systematic review, including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

KEYWORDS. Adverse effects, umckaloabo (*Pelargonium sidoides*), dosing, evidence-based, interactions, pharmacodynamics, pharmacology, pharmacokinetics, systematic review

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SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Search Strategy

To prepare this Natural Standard review, electronic searches were conducted in several databases, including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT. Search terms included the common name(s), scientific name(s), and all listed synonyms. Hand searches were conducted of 20 additional journals (not indexed in common databases) and bibliographies from 50 selected secondary references. No restrictions were placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) were consulted for access to additional references or ongoing research.

Selection Criteria

All literature was collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, human data). Standardized inclusion/exclusion criteria were utilized for selection.

Data Analysis

Data extraction and analysis were performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertained to each review section (defining inclusion/exclusion criteria and analytic techniques, including the validated measures of study quality). Data were verified by a second reviewer.

Review Process

A blinded review was conducted by multidisciplinary research–clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addressed conflicts and consulted experts when applicable. The authors of studies were contacted when clarification was required.

Synonyms/Common Names/Related Substances

6,7,8-trihydroxycoumarin, 8-hydroxy-5,6,7-trimethoxycoumarin, African geranium, catechin, coumarin, coumarin sulphates, ellagitannins, EPs 7630®, gallic acid, gallocatechin, Geranien (German), geranium, geranium root, Kalwerbossie

(German), Kapland-Pelargonie (German), Kap-Pelargonie (German), O-galloyl-C-glucosylflavones, Pelargonien (German), *Pelargonium*, *Pelargonium reniforme*, *Pelargonium reniforme* Curtis, *Pelargonium* root, *Pelargonium sidoides*, *Pelargonium sidoides* DC, *Pelargonium sidoides* extract, polyphenols, proanthocyanidins, rabassam, Rabassamin (German), scopoletin, South African geramium, tannins, umckalin.

Note: An ethanolic extract of the roots of *Pelargonium sidoides* and *Pelargonium reniforme* has been marketed in Germany under the name "Umckaloabo" since 1983.

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- *Pelargonium sidoides*, also known as umckaloabo, is a member of the Geranium family and is native to South Africa.
- For centuries the roots of *Pelargonium sidoides* DC have been used in traditional South African medicine for the treatment of respiratory diseases (Conrad, Kolodziej, & Schulz, 2007; Trun, Kiderlen, & Kolodziej, 2006), diarrhea, dysmenorrhea, and hepatic disorders (Kolodziej, Kayser, Radtke, Kiderlen, & Koch, 2003; Noldner & Schotz, 2007).
- In modern times, an aqueous formulation of the roots of *Pelargonium sidoides*, called EPs 7630®, has been examined in clinical trials as a potential treatment for bronchitis (acute) (Chuchalin, Berman, & Lehmacher, 2005; Matthys & Heger, 2007b; Matthys, Eisebitt, Seith, & Heger, 2003; Matthys, Kamin, Funk, & Heger, 2007; Schulz, 2007), acute pharyngitis (acute non-group A beta-hemolytic streptococcal tonsillopharyngitis) (Bereznoy, Riley, Wassmer, & Heger, 2003), and the common cold (Lizogub, Riley, & Heger, 2007).

Scientific Evidence for Common/Studied Uses

Bronchitis	A
Acute pharyngitis	B
Common cold	B

The Natural Standard evidence-based validated grading rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and historic/folkloric precedent are not included in this assessment and are reflected in a separate section of each review ("Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from more than two properly randomized controlled trials (RCTs), OR evidence from one properly conducted RCT and one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit and with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1–2 properly randomized trials, OR evidence of benefit from more than one properly conducted meta-analysis, OR evidence of benefit from more than one cohort/case-control/nonrandomized trials and with supporting evidence in basic science, animal studies, or theory.
C (unclear or conflicting scientific evidence)	Evidence of benefit from more than one small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from more than one cohort/case-control/nonrandomized trials and without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/nonrandomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from more than one properly randomized, adequately powered trial(s) of high-quality design by objective criteria.*
Lack of evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

*Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al. (1996), in which a score below 4 is considered to indicate lesser quality methodologically.
†Listed separately in reviews in the "Historical or Theoretical Uses which Lack Sufficient Evidence" section.

Historical or Theoretical Uses which Lack Sufficient Evidence

Anorexia (Noldner & Schotz, 2007), antibacterial (Beil & Kilian, 2007; Kolodziej & Kiderlen, 2007; Kolodziej et al., 2003; Trun et al., 2006; Wittschier, Faller, & Hensel, 2007a), coughs (Lewu, Grierson, & Afolayan, 2006), depression (Noldner & Schotz, 2007), diarrhea (Noldner & Schotz, 2007), dysmenorrhea (Noldner & Schotz, 2007), fatigue (Lewu et al., 2006), fever (Lewu et al., 2006), immunomodulation (Kolodziej & Kiderlen, 2007; Trun et al., 2006), liver disease (Noldner & Schotz, 2007), and tuberculosis (Lewu et al., 2006).

Expert Opinion and Historic/Folkloric Precedent

- The name *umckaloabo* is derived from two independent Zulu words: "umkhuhlane," meaning fever and cough-related diseases, and "uhlabo," meaning pleurisy-related chest pain (de Boer, Hagemann, Bate, & Meyboom, 2007).

- Umckaloabo is not currently listed as having generally recognized as safe (GRAS) status with the US Food and Drug Administration (FDA).

Brief Safety Summary

- Likely Safe: When used orally or appropriately, for short-term, for acute bronchitis. A specific extract of South African geranium (Umckaloabo, EPs 7630®, Schwabe GmBh, Germany) in doses of 4.5 ml per day (30 drops), orally, has been safely used for up to 7 days (Chuchalin et al., 2005).
- Possibly Safe: In children, when used orally and appropriately, for short periods. A specific extract of South African geranium (Umckaloabo, EPs 7630®, Schwabe GmBh, Germany) in doses of 3 ml per day (20 drops) has been safely used in children aged 6–10 years for up to 7 days (Bereznoy et al., 2003).
- Possibly Unsafe: In patients with liver disease or who are using hepatotoxic agents, as umckaloabo contains coumarin, which may cause hepatotoxicity (Kolodziej et al., 2003). In patients with blood disorders or who are using anticoagulants or antiplatelets, as umckaloabo contains coumarin, and concurrent use may increase bleeding risks (Kolodziej et al., 2003). In patients with heart conditions, as umckaloabo may cause tachycardia or circulatory failure (de Boer et al., 2007). In patients with asthma or other respiratory conditions, as umckaloabo has been reported to cause bronchospasm or dyspnea in humans (de Boer et al., 2007).
- Likely Unsafe: In patients with a known allergy/hypersensitivity to umckaloabo, its constituents, or members of the plant family *Geraniaceae*.

DOSING/TOXICOLOGY

General

Doses are based on those most commonly used in available trials or in historical practice. However, with natural products the optimal doses necessary to balance efficacy and safety are often not clear. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. The standardization may not be possible, and the clinical effects of different brands may not be comparable because the active components of a product are often not clear.

Standardization

There is no well-known standardization for umckaloabo.

Dosing

Adult (age ≥ 18 years)

Oral

- General: Anecdotal information suggests one tablet (10, 20, or 30 mg), with food, thrice daily for up to 10 days. Thirty drops of a specific extract (EPs 7630®, Schwabe

GmBh, Germany) thrice daily for 10 days has also been used for various respiratory tract conditions (Chuchalin et al., 2005; Lizogub et al., 2007; Matthys & Heger, 2007b; Matthys et al., 2003).
- Bronchitis (acute): Thirty drops of EPs 7630® solution (total 4.5 ml over three doses) (Umckaloabo, EPs 7630®, Schwabe GmBh, Germany), thrice daily for 7–14 days (Chuchalin et al., 2005; Matthys & Heger, 2007b; Matthys et al., 2003).
- Common cold: Thirty drops of *Pelargonium sidoides* extract thrice daily (total 4.5 ml) for up to 10 days (Lizogub et al., 2007).

Children (age ≤ 18 years)

Oral

- Acute pharyngitis (acute non-group A beta-hemolytic streptococcal tonsillopharyngitis): Twenty drops, thrice daily (total approximately 3 ml) of EPs 7630® solution (Umckaloabo, EPs 7630®, Schwabe GmBh, Germany) for 7 days in children aged 6–10 years (Bereznoy et al., 2003).

Toxicology

- No serious adverse effects were observed in any clinical trial that was related to umckaloabo (Chuchalin et al., 2005; Matthys & Heger, 2007b; Matthys et al., 2003) even when administered to children between the ages of 6 and 10 years (Bereznoy et al., 2003).
- Umckaloabo contains coumarin as one of its main constituents (Kolodziej et al., 2003). According to secondary sources, coumarin is moderately toxic to the liver and kidneys, with an LD50 of 275 mg/kg, which is relatively low compared to related compounds.

PRECAUTIONS/CONTRAINDICATIONS

Allergy

- Avoid with known allergy/hypersensitivity to umckaloabo, its constituents, or members of the *Geraniaceae* family.
- As of June 9, 2006, the Uppsala Monitoring Center (UMC), a division of the World Health Organization (WHO), received a total of 50 case reports of suspected allergic reactions to umckaloabo (de Boer et al., 2007). The majority were skin-related (i.e., skin rashes with itching) (N = 34), and out of these patients 17 had accompanying angioedema or systemic involvement (e.g., bronchospasm or dyspnea, diarrhea, tachycardia, or circulatory failure). Three patients developed conjunctivitis.

Adverse Effects/Post-Market Surveillance

- General: Overall, umckaloabo appears to be well tolerated when used on short-term basis. Few adverse effects have been reported that include skin rashes (Bereznoy

et al., 2003; Matthys et al., 2003) with itching (de Boer et al., 2007), sometimes with accompanying angioedema or systemic involvement (e.g., bronchospasm or dyspnea, diarrhea, tachycardia, or circulatory failure), conjunctivitis (de Boer et al., 2007), and gastrointestinal irritation (Bereznoy et al., 2003; Matthys et al., 2003).
- Cardiovascular: As of June 9, 2006, UMC, a division of the WHO, received a total of 50 case reports of suspected adverse reactions to umckaloabo, including tachycardia or circulatory failure (de Boer et al., 2007).
- Dermatologic: As of June 9, 2006, UMC, a division of the WHO, received a total of 50 case reports of suspected adverse reactions to umckaloabo (de Boer et al., 2007). The majority were skin-related (i.e., skin rashes with itching) (de Boer et al., 2007). Adverse events following administration of umckaloabo in clinical trials have been minimal and largely consist of skin rashes (Bereznoy et al., 2003; Matthys et al., 2003).
- Gastrointestinal: Adverse events following the administration of umckaloabo in clinical trials have been minimal and largely consist of gastrointestinal irritation (Bereznoy et al., 2003; Matthys et al., 2003) or diarrhea (de Boer et al., 2007).
- Ocular/Otic: As of June 9, 2006, UMC, a division of the WHO, received a total of 50 case reports of suspected adverse reactions to umckaloabo, including conjunctivitis (de Boer et al., 2007).
- Pulmonary/Respiratory: As of June 9, 2006, UMC, a division of the WHO, received a total of 50 case reports of suspected adverse reactions to umckaloabo, including bronchospasm or dyspnea (de Boer et al., 2007).

Precautions/Warnings/Contraindications

- Avoid in patients with a known allergy/hypersensitivity to umckaloabo, its constituents, or members of the plant family *Geraniaceae*. Umckaloabo has been shown to occasionally cause skin rashes in humans (Bereznoy et al., 2003; Matthys et al., 2003).
- Use cautiously in patients with liver disease or who are using hepatotoxic agents, as umckaloabo contains coumarin, which may cause hepatotoxicity (Kolodziej et al., 2003).
- Use cautiously in patients with blood disorder or who are using anticoagulants or antiplatelets, as umckaloabo contains coumarin, and concurrent use may increase the risk of bleeding (Kolodziej et al., 2003).
- Use cautiously in patients with heart conditions, as umckaloabo may cause tachycardia or circulatory failure (de Boer et al., 2007).
- Use cautiously in patients with asthma or other respiratory conditions, as umckaloabo has been reported to cause bronchospasm or dyspnea in humans (de Boer et al., 2007).

Pregnancy and Lactation

- Not recommended due to lack of sufficient data. Information concerning umckaloabo is currently lacking in the National Library of Medicine's Drugs and Lactation Database (LactMed).

INTERACTIONS

Umckaloabo/Drug Interactions

- Antibiotics: Based on in vitro study, umckaloabo may exert antibacterial effects against a wide range of gram-negative and gram-positive bacteria (Beil & Kilian, 2007; Conrad et al., 2007b; Kayser & Kolodziej, 1997; Kolodziej & Kiderlen, 2007; Kolodziej et al., 2003; Neugebauer, Mickenhagen, Siefer, & Walger, 2005; Wittschier et al., 2007a, 2007b). The effects of umckaloabo with antibiotics are not well understood.
- Anticoagulants/antiplatelets: Based on in vitro study, umckaloabo contains coumarin, a natural anticoagulant, as one of its main constituents (Kolodziej et al., 2003). Theoretically, concurrent use of anticoagulants or antiplatelets and umckaloabo may increase the risk of bleeding.
- Cardiovascular agents: Based on human case reports, umckaloabo may cause tachycardia, and theoretically may alter the effects of cardiovascular agents (de Boer et al., 2007).
- Hepatotoxic agents: Umckaloabo contains coumarin (Kolodziej et al., 2003), which may cause hepatotoxicity when consumed in large amounts. Theoretically, concurrent use of hepatotoxic agents and umckaloabo may increase the risk of liver damage.
- Immunosuppressants: Based on in vitro studies, umckaloabo may have immunostimulant effects (Chuchalin et al., 2005; Conrad, Hansmann, Engels, Daschner, & Frank, 2007a; Kayser & Kolodziej, 1997; Kayser, Kolodziej, & Kiderlen, 2001; Koch & Lanzendörfer-Goossens Wohn, 2002; Kolodziej et al., 2003, 2005). Theoretically, umckaloabo may interfere with the effects of immunosuppressants.
- Laxatives: Based on human study, umckaloabo may cause a laxative effect (de Boer et al., 2007). Theoretically, concurrent use of umckaloabo and laxatives may cause additive effects.

Umckaloabo/Herb/Supplement Interactions

- Antibacterials: Based on in vitro study, umckaloabo may exert antibacterial effects (Beil & Kilian, 2007; Conrad et al., 2007b; Kayser & Kolodziej, 1997; Kolodziej & Kiderlen, 2007; Kolodziej et al., 2003; Neugebauer et al., 2005; Wittschier et al., 2007a, 2007b). The effects of umckaloabo with antibacterial agents are not well understood.
- Anticoagulants/antiplatelets: Based on in vitro study, umckaloabo contains coumarin, a natural anticoagulant, as one of its main constituents (Kolodziej et al., 2003). Theoretically, concurrent use of anticoagulants or antiplatelets and umckaloabo may increase the risk of bleeding.
- Cardiovascular herbs and supplements: Based on human case reports, umckaloabo may cause tachycardia, and theoretically may alter the effects of cardiovascular agents (de Boer et al., 2007).
- Hepatotoxic agents: Umckaloabo contains coumarin (Kolodziej et al., 2003), which may cause hepatotoxicity when consumed in large amounts. Theoretically, concurrent use of hepatotoxic agents and umckaloabo may increase the risk of liver damage.
- Immunosuppressants: Based on in vitro studies, umckaloabo may have immunostimulant effects (Chuchalin et al., 2005; Conrad et al., 2007a; Kayser & Kolodziej, 1997;

Kayser et al., 2001; Koch & Lanzendörfer-Goossens Wohn, 2002; Kolodziej et al., 2003, 2005). Theoretically, umckaloabo may interfere with the effects of immunosuppressants.
- Laxatives: Based on human study, umckaloabo may cause a laxative effect (de Boer et al., 2007). Theoretically, concurrent use of umckaloabo and laxatives may cause additive effects.

Umckaloabo/Food Interactions

Insufficient evidence available.

Umckaloabo/Laboratory Interactions

- Bacterial cultures: Based on in vitro study, umckaloabo may exert antibacterial effects against a wide range of gram-negative and gram-positive bacteria (Beil & Kilian, 2007; Conrad et al., 2007b; Kayser & Kolodziej, 1997; Kolodziej & Kiderlen, 2007; Kolodziej et al., 2003; Neugebauer et al., 2005; Wittschier et al., 2007a, 2007b).
- Coagulation panel: Based on in vitro study, umckaloabo contains coumarin, an anticoagulant, as one of its main constituents (Kolodziej et al., 2003).
- Heart rate: Based on human case reports, umckaloabo may cause tachycardia (de Boer et al., 2007).
- Immune panel: In vitro studies indicate that *Pelargonium sidoides* may increase immune function (Chuchalin et al., 2005; Kayser & Kolodziej, 1997; Kayser et al., 2001; Koch & Lanzendörfer-Goossens Wohn, 2002; Kolodziej et al., 2003, 2005).
- Liver function tests: Umckaloabo contains coumarin (Kolodziej et al., 2003), which may cause hepatotoxicity and elevated liver enzymes when consumed in large amounts.

Umckaloabo/Nutrient Depletion

Insufficient available data.

MECHANISM OF ACTION

Pharmacology

- Constituents: The active ingredients of the South African geranium, or umckaloabo, are found in the root and are thought to be coumarins, including scopoletin, 6,7,8-trihydroxycoumarin, 8-hydroxy-5,6,7-trimethoxycoumarin, coumarin sulphates, and coumarin glycosides; hydrolyzable tannins such as umckalin, catechin, gallocatechin, gallic acid, O-galloyl-C-glucosylflavones, ellagitannins, and other polyphenols; and proanthocyanidins (Kolodziej et al., 2003).
- Antibacterial effects: An acetone root extract of umckaloabo seems to have antibacterial activity against several gram-positive and gram-negative bacterial pathogens and some Leishmania parasites in vitro (Kayser & Kolodziej, 1997; Kolodziej & Kiderlen, 2007; Kolodziej et al., 2003) and this effect may be due to an ability of *Pelargonium sidoides* to prevent bacteria from attaching to cells in the mucous membranes (Beil & Kilian, 2007; Conrad et al., 2007b; Wittschier et al., 2007a, 2007b).

- Anecdotal information suggests that most of the coumarins found in *Pelargonium sidoides* contain a methoxy function at the C7 position and an OH group at either the C6 or C8 position and that this is primarily responsible for its antibacterial activity (Fukuda, Kishii, Takei, & Hosaka, 2001).
- Anticoagulant effects: Based on in vitro study, umckaloabo contains coumarin, an anticoagulant, as one of its main constituents (Kolodziej et al., 2003).
- Cytotoxic effects: In vitro studies showed that, compared with controls, EPs 7630® increased phagocytosis, oxidative burst, and intracellular killing of human peripheral blood phagocytes (Conrad, Hansmann et al., 2007).
- Immunomodulatory effects: Anecdotal information suggests that gallic acid and other phenols present in large amounts in *Pelargonium sidoides* may possess immunomodulatory effects, possibly through stimulation of release of tumor necrosis factor (TNF), stimulate interferon activity, and increase natural killer cell activity, thereby increasing immune activity (Chuchalin et al., 2005; Kayser & Kolodziej, 1997; Koch & Lanzendörfer-Goossens Wohn, 2002; Kolodziej et al., 2003). Tannins found in *Pelargonium sidoides* may induce nitric oxide synthase and cytokine gene expression in vitro, thereby inducing an immune response against bacterial pathogens (Kayser et al., 2001; Kolodziej et al., 2005).
- In vitro studies show that extracts of *Pelargonium sidoides* and some isolated constituents exerted significant immunomodulatory properties via functional bioassays including an in vitro model for intracellular disease. Assays also confirmed the protein production of TNF-alpha, IL-1 alpha, and IL-12, which indicates an increased immune response (Kayser et al., 2001; Kolodziej & Kiderlen, 2007; Kolodziej et al., 2003, 2005; Trun et al., 2006).
- Respiratory effects: In vitro, EPs 7630® was determined to significantly and concentration dependently increase ciliary beat frequency (CBF), which is an important parameter of mucociliary system's defense mechanism (Neugebauer et al., 2005).

Pharmacodynamics/Kinetics

- Insufficient evidence available.

HISTORY

- The use of *Pelargonium sidoides* extract is based on traditional use by Zulu healers in the Eastern Cape province of South Africa, and has been known to modern science since the 1890s. The word *umckaloabo* is derived from the two Zulu words, "umkhuhlane" (fever and cough-related illnesses) and "uhlabo" (chest pain-related to pleurisy) (de Boer et al., 2007). In the early 1920s, the Englishman Charles Stevens traveled to South Africa for the treatment of his tuberculosis. He turned to a Basuto tribal healer who gave him a medicine derived from umckaloabo. He eventually recovered from his illness.
- *Pelargonium sidoides* forms a rosette-like plant with crowded leaves. It is very similar to some forms of *Pelargonium reniforme*, but is easily distinguished by its blackish rather than pink petals. Active ingredients from both species are located in the root.
- Extracts of the root have been available in German pharmacies since 1983 without prescription and have found widespread usage for sinus, throat, and respiratory tract infections.

NATURAL STANDARD EVIDENCE TABLE

Condition Treated	Study Type	Author, Year	N	Are Results Statistically Signifi-cant?	Quality of Study (0–2 = poor, 3–4 = good, 5 = excellent)	Magnitude of Benefit (How Strong Is the Effect?)	Absolute Risk Reduction	No. of Patients Needed to Treat for One Outcome	Comments
Bronchitis	Randomized controlled trial (RCT)	Matthys, 2007	217	Yes	5	Medium	NA	NA	Subjects received 30 drops of the proprietary extract of *Pelargonium sidoides*, EPs 7630®, which is contained in umckaloabo, thrice daily for 7 days.
Bronchitis	RCT	Matthys et al., 2003	468	Yes	5	Medium	NA	NA	Subjects received 30 drops of the proprietary extract of *Pelargonium sidoides*, EPs7630®, which is contained in umckaloabo, thrice daily, for 7 days.
Bronchitis	RCT	Chuchalin et al., 2005	124	Yes	5	Medium	NA	NA	Subjects received 30 drops of the proprietary extract of *Pelargonium sidoides*, EPs7630®, which is contained in umckaloabo, thrice daily, for 7 days.
Bronchitis	RCT	Schultz, 2007	124	Yes	3	Medium	36	3	Subjects received a liquid herbal drug preparation from the roots of *Pelargonium sidoides.*
Bronchitis	Open, multicenter, prospective, observational study	Matthys, 2007	2099	No	NA	Medium-large	NA	NA	Subjects received the proprietary extract of *Pelargonium sidoides*, EPs 7630®, which is contained in umckaloabo, for 14 days.

NATURAL STANDARD EVIDENCE TABLE

Condition Treated	Study Type	Author, Year	N	Are Results Statistically Signifi-cant?	Quality of Study (0–2 = poor, 3–4 = good, 5 = excellent)	Magnitude of Benefit (How Strong Is the Effect?)	Absolute Risk Reduction	No. of Patients Needed to Treat for One Outcome	Comments
Bronchitis	Open, multicenter, prospective, outcomes trial	Matthys, 2007	205	NA	NA	NA	NA	NA	Subjects received the proprietary extract of *Pelargonium sidoides*, EPs7630®, which is contained in umckaloabo. Total symptom scores were observed to improve, and a majority of subjects subjectively reported their condition as much improved.
Acute pharyngitis	RCT	Bereznoy et al., 2003	143	Yes	5	Large	NA	NA	Subjects received 20 drops of the proprietary extract of *Pelargonium sidoides*, EPs7630®, which is contained in umckaloabo, thrice daily, for 6 days. Acute non-group A beta-hemolytic streptococcal tonsillopharyngitis.
Common cold	Randomized, placebo-controlled, double-blind, multicenter, prospective, parallel group, phase-III clinical trial	Lizogub et al., 2007	103	Yes	5	Medium	NA	NA	Subjects received either 30 drops of the liquid herbal drug preparation or placebo, thrice daily (4.5 ml per day), for a maximum of 10 days.

EXPLANATION OF COLUMNS IN NATURAL STANDARD EVIDENCE TABLE

Condition

It refers to the medical condition or disease targeted by a therapy.

Study Design

Common types included in study design are given below:

- Randomized controlled trial (RCT): An experimental trial in which participants are randomly assigned to receive either an intervention being tested or placebo. Note that the Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- Equivalence trial: It is an RCT that compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- Before and after comparison: A study that reports only the change in outcome in each group of study, and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- Case series: A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.
- Case-control study: A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary and alternative medicine literature.
- Cohort study: A study that assembles a group of patients with certain baseline characteristics (e.g., use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary and alternative medicine literature.
- Meta-analysis: A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none of which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcome measures or therapies may differ from study to study, hindering direct comparison.
- Review: An author's description of his or her opinion based on personal and non-systematic review of the evidence.
- Systematic review: A review conducted according to pre-specified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.
- P: Pending verification.

Author, Year

Author and year identify the study being described in a row of a table.

N (Number)

The total number of subjects included in a study (treatment group plus placebo group). Some studies initially recruit a larger number of subjects, but do not use all of them because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as "N." N includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of dropouts that are not included in the analysis are considered to be weaker evidence for efficacy. (For systematic reviews the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.) P = pending verification.

Is Statistically Significant?

Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as *p*-values). P = pending verification.

Quality of Study

A numerical score between 0 and 5 is assigned as a rough measure of study design/reporting quality (0 being the weakest and 5 being the strongest). This number is based on a well-established and validated scale developed by Jadad et al. (1996). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" sections of reviews).

- A Jadad score is calculated using the seven items in the table given below. The first five items are indications of good quality, and each counts as one point toward an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Magnitude of Benefit

This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant "NA" for "not applicable" is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, the Natural Standard defines the magnitude of benefits in terms of the standard deviation (SD) of the outcome measures. Specifically, the benefit is considered

- large, if SD $>$ 1,
- medium, if SD = 0.5 to 0.9,
- small, if SD = 0.2 to 0.4.

Jadad Score Calculation Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double-blind?	0/1
Was the method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/−1
Deduct one point if the study was described as double-blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

P = pending verification.
In many cases, studies do not report the SD of change of the outcome measures. However, the change in the SD of the outcome measures (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled SD,

- Effect Size = (Mean Treatment−Mean Placebo)/SDp.

Absolute Risk Reduction (ARR)

This describes the difference between the percentage of people in the control/placebo group experiencing a specific outcome (control event rate), and the percentage of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, ARR equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies ([control event rate–experimental event rate]/control event rate). Many studies do not include adequate data to calculate the ARR, in such cases "NA" is entered into this column. P = pending verification.

Number Needed to Treat

This denotes the number of patients who would need to use the therapy under investigation, for the period described in the study, in order for one person to experience the specified benefit. It is calculated by dividing 1 by ARR (1/ARR). P = pending verification.

Comments

When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, no intention to treat, etc.), notable

study design elements (crossover etc.), dosing, and/or specifics of study group/subgroups (age, gender, etc). More detailed description of studies is found in the "Evidence Discussion" section that follows the "Evidence Table" in the Natural Standard reviews.

EVIDENCE DISCUSSION

Bronchitis

- Summary: Umckaloabo has been recommended for treatment of acute bronchitis. Several RCTs have shown that *Pelargonium sidoides* (EPs 7630®) (Umckaloabo) is effective in reducing symptoms associated with acute bronchitis. The sum of existing positive evidence is highly suggestive, albeit not definitive. A sufficiently sized, randomized, placebo-controlled, double-blind, multicenter trial using doses found effective in other clinical trials (*Pelargonium sidoides* (EPs 7630®; 30 drops, thrice daily for a total of 45 ml per day, for 7 days) showed that the experimental treatment improved acute bronchitis symptoms.
- Evidence: Matthys and Heger (2007b) conducted a randomized, placebo controlled, double-blind, multicenter trial to examine the effectiveness of an herbal drug preparation from the roots of *Pelargonium sidoides* (EPs 7630®) (Umckaloabo) in the treatment of acute bronchitis. In all 217 patients between the ages of 18 and 66 years with bronchitis (acute) were given 30 drops of EPs 7630® solution thrice daily (45 ml per day) (N = 108) or 30 drops placebo thrice daily for a period of 7 days (N = 109). Outcome measures included individual change in bronchitis symptom score (BSS) over 7 days, individual symptoms, patient satisfaction, and adverse events. The BSS score decreased in the EPs 7630® group by 7.6 ± 2.2 points and by 5.3 ± 3.2 points in the placebo group after 7 days. This result was significant for the EPs 7630® group ($p < .0001$). Also, compared to placebo, the EPs 7630®-treated group showed improvements in individual symptoms, and no adverse events were recorded during the course of the trial.
- Matthys et al. (2003) conducted a randomized, placebo-controlled, double-blind trial to evaluate the efficacy and safety of an extract of *Pelargonium sidoides* (EPs 7630®) in patients with bronchitis (acute). In all 468 patients with acute bronchitis were referred by 36 primary care physicians (investigators) from the outpatient care setting receiving EPs 7630® (N = 233) or placebo (N = 235) (30 drops thrice daily or 45 ml per day) for 7 days. Outcome measurements included the change in BSS (cough, sputum, rales/rhonchi, chest pain at cough, dyspnea) on day 7. Patients treated with EPs 7630® showed a 5.9 ± 2.9-point BSS decrease from baseline to day 7, whereas the placebo group showed a 3.2 ± 4.1-point BSS decrease from baseline to day 7. The 95% confidence interval (CI) for the difference of effects between the two treatment groups (EPs 7630® minus placebo) was (−3.359; −2.060), showing that treatment with EPs 7630® was more effective compared to placebo on day 7 ($p < .0001$). The patients' inability to work decreased in the EPs 7630®-treated group to 16% compared to 43% in the placebo group ($p < .0001$). In addition, the duration of illness was shorter for patients treated with EPs 7630® compared to placebo ($p < .001$). The onset of treatment effect was recognized in 53.6% of EPs 7630®-treated patients compared to 36.2% of patients that received placebo within the first 4 days ($p < .0001$). No significant adverse events were recorded during the trial.

- Chuchalin et al. (2005) conducted a randomized, placebo-controlled, double-blind trial to evaluate the efficacy and safety of a *Pelargonium sidoides* preparation (EPs 7630®). In all 124 patients with acute bronchitis from six outpatient clinics received EPs 7630® (N = 64) or placebo (N = 60) (30 drops thrice daily or 45 ml per day) for 7 days. Outcome measures included the change of BSS on day 7. The decrease of BSS from baseline to day 7 was 7.2 ± 3.1 points with EPs 7630® and 4.9 ± 2.7 points with placebo. The 95% CI for the difference of effects between the two treatment groups (EPs 7630® minus placebo) was calculated as (1.21, 3.56), showing a significant improvement of EPs 7630® compared with the placebo on day 7 ($p < .0001$). The Onset of treatment effect was observed in 69% of EPs 7630®-treated patients within the first 4 days compared to only 33.3% of patients given placebo ($p < .0001$). No significant adverse events were observed in either group.
- Schultz et al. (2007) conducted a randomized, double-blind, placebo-controlled trial to examine the effects of a liquid herbal drug preparation from the root of *Pelargonium sidoides* for acute bronchitis. The reduction in BSS (cough, sputum, rales/rhonchi, chest pain at cough, dyspnea) symptoms was 7.2 ± 3.1 points with the treatment group, and 4.9 ± 2.7 in the placebo group ($p < .0001$). Adverse effects were experienced in both treatment and placebo groups. They were not, however, classified as being serious.
- Matthys et al. (2007) conducted a multicenter, prospective, open observational trial to evaluate the efficacy and safety of treatment with EPs 7630® in patients with acute bronchitis. A total of 299 patients (age range: 0–93 years) from 440 sites with productive cough for less than 6 days without indication for treatment with antibiotics were given EPs 7630® solution in an age-dependent dosage for 14 days. Outcome measures included the mean change in BSS (cough, sputum, rales/rhonchi, chest pain at cough, dyspnea) from baseline to patient's individual last observation. The mean BSS of all patients decreased from 7.1 ± 2.9 points at baseline to 1.0 ± 1.9 points at patients' last visit. When children were analyzed separately, treatment with EPs 7630® resulted in a decrease of mean BSS from 6.3 ± 2.8 points to 0.9 ± 1.8 points, and the analysis of less than 3-year-old children showed a decrease of mean BSS from 5.2 ± 2.5 points to 1.2 ± 2.1 points. Adverse events occurred in 1.2% of all patients. Although the results of this study are promising, lack of true control group, randomization, placebo group, and blinding limits the usefulness of this study.
- Matthys and Heger (2007a) conducted a prospective, open, multicenter outcomes study to examine the efficacy and tolerability of EPs 7630® (Umckaloabo) for acute bronchitis or acute exacerbation of chronic bronchitis. In all 205 patients with acute bronchitis or acute exacerbation of chronic bronchitis received EPs 7630® (Umckaloabo). Outcome measures included the change in the total score of five symptoms typical for bronchitis (cough, expectoration, wheezing, or whistling on expiration, chest pain during coughing, and dyspnea) in addition to other symptoms, including hoarseness, headache, aching limbs, and fatigue. On average, at the start of the treatment, the total score of the typical bronchitis symptoms amounted to 6.1 ± 2.8 points and decreased by 3.3 ± 3.8 points to 2.8 ± 2.6 points by the final examination on day 7. By the end of the trial, approximately 61% of the patients rated their health condition as much improved or free from symptoms. Adverse events occurred in 16 patients; however, there were no serious adverse events in any of the patients. The majority of the patients (78%) were satisfied with the treatment. Although the results of this study are promising, lack of a true control group, randomization, placebo group, and blinding limits the usefulness of this study.

Acute Pharyngitis

- Summary: Umckaloabo has been recommended for treatment of acute pharyngitis (acute non-group A beta-hemolytic streptococcal tonsillopharyngitis). One randomized, placebo-controlled, double-blind trial in children showed that *Pelargonium sidoides* (EPs 7630®) was in fact effective in reducing symptoms associated with acute pharyngitis (acute non-group A beta-hemolytic streptococcal tonsillopharyngitis). However, although these results are promising until more randomized trials with large sample sizes are conducted, there is insufficient evidence to draw a firm conclusion pertaining to the use of umckaloabo in treating acute pharyngitis.
- Evidence: Bereznoy et al. (2003) conducted a randomized, placebo-controlled, double-blind trial to examine the effectiveness of *Pelargonium sidoides* (EPs 7630®) extract for the treatment of acute non-group A beta-hemolytic strep (non-GABHS) tonsillopharyngitis in children. In all 143 children, aged 6–10 years, with non-GABHS tonsillopharyngitis presented from six study sites in four pediatric and ENT primary care outpatient clinics received EPs 7630® (N = 73) or placebo (N = 70) (20 drops thrice per day or 30 ml per day) for 6 days. Outcome measures included the decrease in the tonsillopharyngitis severity score (TSS) from baseline (day 0) through day 4. In children treated with EPs 7630, a decrease in TSS from baseline (day 0) through day 4 was 7.1 ± 2.1 points and 2.5 ± 3.6 points for those who received the placebo ($p < .0001$). No adverse events occurred that were related to the study medication. Although the results of this study are promising, a lack of blinding limits the usefulness of this study.

Common Cold

- Summary: Umckaoabo has been recommended for the treatment of common cold. One randomized, placebo-controlled, double-blind trial in adults showed that *Pelargonium sidoides* was in fact effective in reducing symptoms associated with the common cold; however, although these results are promising until more randomized trials with large sample sizes are conducted, there is insufficient evidence to draw a firm conclusion pertaining to the use of umckaloabo in treating the common cold.
- Evidence: Lizogub et al. (2007) conducted a randomized, placebo-controlled, double-blind, multicenter, prospective, parallel group, phase III clinical trial 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. In all 103 male and female adult patients with at least two major and one minor cold symptom from eight outpatient departments received either 30 drops of the liquid herbal drug preparation or placebo, thrice a day (4.5 ml per day), for a maximum of 10 days. Outcome measures included the sum of symptom intensity differences (SSID) of the cold intensity score (CIS) from day 1 to day 5. From baseline to day 5, the mean SSID improved by 14.6 ± 5.3 points in the *Pelargonium sidoides* group compared with 7.6 ± 7.5 points in the placebo group ($p < .0001$). After 10 days, 78.8% versus 31.4% in the *Pelargonium sidoides* extract group versus placebo group were clinically cured ($p < .0001$). The mean duration of inability to work was significantly lower in the *Pelargonium sidoides*-treated group (6.9 ± 1.8 days) compared to the placebo group (8.2 ± 2.1 days; $p = .0003$).

Brands Used in Human Studies

- EPs 7630® is a unique proprietary extract of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany (Bereznoy et al., 2003; Chuchalin et al., 2005; Matthys & Heger, 2007b; Matthys et al., 2003) and is the extract found in Umckaloabo.

Brands Shown to Contain Claimed Ingredients through Third-Party Testing

- Consumer laboratory: Not applicable.
- Consumer reports: Not applicable.
- Natural products association: Not applicable.
- NSF International: Not applicable.
- US Pharmacopeia: Not applicable.

Select Patents Outside the United States

- Not applicable.

US Patents

- 20090061027: Composition for the prevention and treatment of common cold diseases.
- 20060263448: Use of extracts from roots of *Pelargonium sidoides* and *Pelargonium reniforme*.
- 20070014877: Use of extracts from *Pelargonium* species.
- 7211567: Composition for preventing and treating type-I allergy.

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