



## Review

A historical, scientific and commercial perspective on the medicinal use of *Pelargonium sidoides* (Geraniaceae)T. Brendler<sup>a</sup>, B.-E. van Wyk<sup>b,\*</sup><sup>a</sup> Plantaphile, Immanuelkirchstrasse 32, 10405 Berlin, Germany<sup>b</sup> Department of Botany and Plant Biotechnology, University of Johannesburg, P.O. Box 524, Auckland Park 2006, South Africa

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## ABSTRACT

**Ethnopharmacological context:** A detailed review of the ethnobotany and commercial history of *Pelargonium sidoides* is presented, together with a brief summary of pre-clinical and clinical scientific results that support the use of the plant in modern, evidence-based phytomedicines. The aim is to identify the main factors responsible for the success in product development.

**Materials and methods:** The literature studied includes all modern scientific papers and also old documents and books that are no longer readily accessible.

**Results:** Available ethnobotanical information shows that several tuberous *Pelargonium* species (including *Pelargonium sidoides*) are important traditional medicines with a rich ethnobotanical history. A summary of the interesting history of the commercial development of Stevens' Cure or Umckaloabo in Europe is presented. Scientific evidence for the efficacy of the product, mainly as a treatment for acute bronchitis, is reviewed. These include numerous *in vitro* studies as well as 18 clinical studies. The botanical identity of the plant and its complex mixture of coumarins and other chemical constituents are summarised.

**Conclusions:** The use of *Pelargonium* stems or tubers for a variety of ailments (including the complications of dysentery) is an important but hitherto under-estimated part of traditional medicine in southern Africa. Key elements in the successful development of *Pelargonium sidoides* from a profound traditional remedy to a highly successful phytomedicine include the choice of species, a favourable cost–benefit ratio, innovative marketing over many years, good scientific evidence of the botanical and chemical identity of the product and convincing proof of concept.

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## 1. Introduction

*Pelargonium sidoides* DC. (Geraniaceae) is one of several geophytic species of the genus that are important traditional medicines in South Africa. These plants, often referred to by their original Khoi-Khoi name *rabas*, were amongst the first to be recorded by early explorers such as van der Stel (1685) and Thunberg (1773). The fleshy, bright red tubers or rhizomes have been widely used by different cultural groups, mainly to treat diarrhoea and dysentery. *Pelargonium sidoides* stands apart from the rest of the genus, not only in the dark, maroon-red to black petals, but also in the fact that it has been developed into a highly successful, evidence-based phytomedicine.

The aim of this paper is to record the interesting historical development of the plant, from a highly prized local ethnomedicine to a fully licensed herbal medicine for treating acute bronchitis. A second aim is to briefly review the scientific evidence that has contributed to the acceptance and popularity of the product. *Pelargonium sidoides* is a potential role model for several other products currently being developed, and it may be useful to reflect on the critical elements that are required for successful commercialisation.

## 2. Historical and commercial perspectives

### 2.1. Ethnobotany

Of the 35 indigenous medicinal plants that have been accurately recorded at the Cape in the period 1650–1800, no fewer than six are species of *Pelargonium* (Scott and Hewett, 2008). Those used specifically for their astringent roots were included in the writings and herbaria of N.L. Burman and C.P. Thunberg (Scott and Hewett, 2008): *Pelargonium myrrhifolium* (L.) L'Herit. var. *myrrhifolium*, *Pelargonium pinnatum* (L.) L'Herit. and *Pelargonium triste* (L.) L'Herit. (Table 1). During his visit to Cape Town in 1773, Thunberg specifically noted that “Many gerania, with their red and pulpos roots, grew in the sandy plains near the town; and as these roots are of an astringent nature, the country people used them in the diarrhoea and dysentery” (Forbes, 1986). Although common names were unfortunately not recorded at the time, these plants are widely known, to this day, as *rabas* or *rooirabas*.

*Pelargonium antidysentericum* (Eckl. & Zeyh.) Kostel. is an interesting example of a plant named for its ethnomedicinal use. Ecklon and Zeyher (1835) recorded the name (“*t'namie*”) and uses of this important traditional medicine of the Nama people (Table 1). The large red tuber was used in milk decoctions to treat anaemias and weaknesses, with repeated doses given in the case of dysenteric fevers. The importance of red-rooted *Pelargonium* species is also reflected in the recording of the common names for these plants by Simon van der Stel in his diary of the expedition to Namaqualand in 1685 (De Wet and Pheiffer, 1979) as *areé* (Griqua) or *heijtame* (Nama). It is here suggested that *heijtame* and *t'namie* are probably the same word, the difference resulting from two separate attempts at transliterating the dental click of the original Nama name. It persists to this day as the name of the Hantam or Hanteyme Moun-

tain (“the mountain of the red bulb”) at Calvinia (Smith, 1966). The Calvinia-Nieuwoudtville region, still known as the Hantam district, is one of the main distribution areas of *Pelargonium antidysentericum*.

Pappe (1847, 1850, 1857) included four species of *Pelargonium* in his materia medica of the Cape colonists, three of which have tuberous stems or roots: *Pelargonium grossularioides* (listed by the old name *Pelargonium anceps*), *Pelargonium triste* and *Pelargonium antidysentericum*.

In his treatment of *Pelargonium sidoides* [as *Pelargonium reniforme* Curtis var. *sidaefolium* (Thunb.) Harv.] for the Flora Capensis, Harvey and Sonder (1860) named Dr Atherstone as the authority for the statement that the species is useful as an astringent in dysentery. Dr William Guybon Atherstone was an innovative medical doctor, naturalist and later member of the Cape parliament (Gunn and Codd, 1981). He obtained his M.D. in Heidelberg in 1839 and joined the practise of his father (who was Dr John Atherstone, the District Surgeon of Albany, based in Grahamstown).

The most detailed account of the value and uses of *Pelargonium sidoides* (at the time regarded as a mere variety of *Pelargonium reniforme*) is that of Smith (1895). Smith noted that dysentery differs from diarrhoea in being “attended by inflammation and fever” and other complications. He also noted that “As these maladies proceed from many different causes, and commonly enough involve complications, it cannot be supposed that a simply drug can be relied on to cure them. At the same time singular benefit has often been derived from certain plant substances, when the usual course of medicine has failed, as if they aid the curative powers of nature to rally and overcome the disease”. He then lists *Pelargonium reniforme*/*Pelargonium sidoides* as the first of five species used in this context [the others being, in order of appearance, *Sutherlandia frutescens* (L.) R.Br., *Rubia petiolaris* DC., *Solanum capense* L. and *Cassia mimosoides* L., which is now *Chamaecrista mimosoides* (L.) Greene]. The two varieties are described, and the one with “flowers a dark port-wine colour” is specifically referred to: “Whether for good reason or not, the latter is the more highly esteemed”. Smith (1895) then recorded three patients for whom the cut roots (“boiled in milk for a considerable time”) have cured dysentery-related complications “where the usual course of medicine has failed”.

An independent record from Lesotho is that of Phillips (1917), who reported that the roots of “*Pelargonium reniforme*” (this is *Pelargonium sidoides*; *Pelargonium reniforme* sensu stricto does not occur in Lesotho) are used to treat colic. The Sesotho vernacular name, *khoaara e nyenyane*, literally means “growing attached to stones or rocks”.

Kling (1923) listed the use of “*rooi rabassan*” to ease childbirth and to treat amenorrhoea. From the context it is almost certain that he referred to the *rooi rabassam* of Pappe (1847, 1850, 1857), which is *Pelargonium grossularioides* (“*Pelargonium anceps*”) and not *Pelargonium sidoides* as Watt and Breyer-Brandwijk (1962) have assumed.

Watt and Breyer-Brandwijk (1962) reviewed available ethnobotanical data for several *Pelargonium* species, including *Pelargonium reniforme* and *Pelargonium sidoides* [as *Pelargonium sidaefolium* (Thunb.) R. Knuth]. They also reported the use of “*Pelargonium sidaefolium*” roots by Zulu and Swazi people to treat

**Table 1**  
Summary of available ethnobotanical information on southern African tuberous *Pelargonium* species

Species	Vernacular name	Author(s) and date	Recorded uses
<i>Pelargonium antidysentericum</i> (Eckl. & Zeyh.) Kostel.?	areé (Griqua), heijtame (Nama)	Simon van der Stel, 1685 (De Wet and Pheiffer, 1979)	Not recorded
<i>Pelargonium antidysentericum</i>	t'namie (Nama)	Ecklon and Zeyher (1835)	Large red tuber used in milk decoctions to treat anaemias and weaknesses, with repeated doses given in the case of dysenteric fevers
<i>Pelargonium antidysentericum</i>	t'namie (Nama)	Pappe (1847, 1850, 1857)	Dysentery
<i>Pelargonium antidysentericum</i>	naniewortel, nanieknol (Afrikaans)	Kling (1923)	Root boiled in milk to treat diarrhoea and dysentery
<i>Pelargonium antidysentericum</i>	D/kanie (D/for the dental click, Nama)	Laidler (1928)	Boiled in milk and used as astringent
<i>Pelargonium grossularioides</i> (L.) L'Herit. [syn. <i>Pelargonium anceps</i> DC.]	roode rabassam (Dutch)	Pappe (1847, 1850, 1857)	Stems used by Cape Malay people for "suppression of the catamenia" (amenorrhoea) and to promote parturition in pregnant women
<i>Pelargonium grossularioides</i>	rooi rabassan (Afrikaans)	Kling (1923)	Stems used of to ease childbirth and to treat amenorrhoea
<i>Pelargonium grossularioides</i>	rabass (Nama), rooiwortel, rooistorm (Afrikaans)	Laidler (1928)	Roots used by Afrikaners as decoction or infusion in brandy; roots used for anaemias and weaknesses; repeated doses given during fevers
<i>Pelargonium grossularioides</i>	rabas; kxwara, makorotswana (Sesotho)	Watt and Breyer-Brandwijk (1962)	As above (Pappe)
<i>Pelargonium luridum</i> (Andr.) Sweet	ishagua, isandhla sonwabu, uvendle, inyonkuku (isiZulu)	Watt and Breyer-Brandwijk (1962), Hutchings et al. (1996)	In addition to diarrhoea and dysentery, the roots are used to treat colic and fever
<i>Pelargonium myrrhifolium</i> (L.) L'Herit. var. <i>myrrhifolium</i>	Not recorded	N.L. Burman (1759) cited in Scott and Hewett (2008):	Root used for menstrual disorders, as tonic and as treatment for tuberculosis, colic and earache
<i>Pelargonium pinnatum</i> (L.) L'Herit.	Not recorded	N.L. Burman (1759) cited in Scott and Hewett (2008):	Roasted root used as appetite stimulant
<i>Pelargonium reniforme</i> Curtis	rabassam or rabas (Dutch/Afrikaans), i-Yeza lezikali (isiXhosa)	Smith (1895)	Dysentery "attended by inflammation and fever" and other complications. Boiled leaves to protect wounds against maggots; roots to prevent purging in horses
<i>Pelargonium reniforme</i>	rabas, rooirabas, rabassam; iyeza-lezikhali, kubalo (isiXhosa)	Watt and Breyer-Brandwijk (1962)	Used in the Eastern Cape to treat liver complaints in calves and sheep, and as a remedy for diarrhoeas, dysenteries, colic and fever
<i>Pelargonium reniforme</i>	iYeza lezikhali, iKhubalo (isiXhosa)	Batten and Bokelman (1966)	Uses as in Smith (1895); Xhosa people use the root for liver complaints in sheep and calves; Europeans use it to treat asthma
<i>Pelargonium reniforme</i>	rabas, rooirabas	Smith (1966)	Diarrhoea and dysentery
<i>Pelargonium reniforme</i>	"Umckaloabo"	Bladt (1974, 1977)	Tuberculosis (source unrecorded)
<i>Pelargonium sidoides</i> DC. [as <i>Pelargonium reniforme</i> Curtis var. <i>sidaefolium</i> (Thunb.) Harv.	Not recorded	Harvey and Sonder (1860)	Useful as an astringent in dysentery
<i>Pelargonium sidoides</i>	rabassam or rabas (Dutch/Afrikaans), i-Yeza lezikali (isiXhosa)	Smith (1895)	Dysentery "attended by inflammation and fever" and other complications. Boiled leaves to protect wounds against maggots; roots to prevent purging in horses
<i>Pelargonium sidoides</i>	khoaara e nyenyane (Sesotho)	Phillips (1917)	Roots used in Lesotho to treat colic
<i>Pelargonium sidoides</i>	kalwerbossie (Afrikaans)	Watt and Breyer-Brandwijk (1962)	Roots used by Zulu (?) and Swazi people (?) to treat gonorrhoea, diarrhoeas and dysenteries
<i>Pelargonium sidoides</i>	kalwerbossie (from Free State Province northwards)	Smith (1966)	Plants mixed with equal parts of <i>Ziziphus mucronata</i> L. and used in decoctions as remedy for worms in calves (Afrikaans: <i>kalwers</i> )
<i>Pelargonium sidoides</i>	Not recorded	Sanderson (ca. 1860, cited in Smith, 1966)	Used by Khoi people in eastern Free State Province as a cure "of some diseases"
<i>Pelargonium sidoides</i>	"Umckaloabo"	Bladt (1974, 1977)	Tuberculosis (?)
<i>Pelargonium sidoides</i>	kalwerbossie	Hutchings et al. (1996)	Plant used by Xhosa people in Transkei to treat a prolapsed rectum, severe diarrhoea and a stomach ailment in babies known as <i>intisila</i>
<i>Pelargonium sidoides</i>	icwayiba (isiXhosa)	Matsiliza and Barker (2001)	Used in Grahamstown region as a gripe water for infants; also gonorrhoea, (severe) diarrhoea, dysentery, a prolapsed rectum and stomach condition in babies known as <i>intisila</i>
<i>Pelargonium sidoides</i>	uvendle, ikhubalo (isiXhosa)	Lewu et al. (2007)	Plant used in Amatola region of the Eastern Cape to treat dysentery in cattle

Table 1 (Continued)

Species	Vernacular name	Author(s) and date	Recorded uses
<i>Pelargonium triste</i> (L.) L'Herit.	Not recorded	C.P. Thunberg (1785) cited in <a href="#">Scott and Hewett (2008)</a> ; <a href="#">Pappe (1847, 1850, 1857)</a>	Root used to treat diarrhoea, dysentery, renal calculi and acid urine
<i>Pelargonium triste</i>	Not recorded		For diarrhoea and dysentery; vermifuge
<i>Pelargonium</i> species (unidentified)	<i>ubala</i> (isiZulu)	<a href="#">Hutchings et al. (1996)</a>	Roots used by Zulu people to treat a sore throat

gonorrhoea, diarrhoeas and dysenteries but these can hardly be traditional uses, as *Pelargonium sidoides* does not occur naturally in KwaZulu-Natal and Swaziland.

In the northern parts of the distribution range of *Pelargonium sidoides* (from the Free State Province northwards), the name *kalwerbossie* is used ([Smith, 1966](#)) because the plants were used as a remedy for worms in calves. This use was also recorded by [Burt Davy](#) (cited in [Watt and Breyer-Brandwijk, 1962](#)). [Sanderson](#) (ca. 1860, cited by [Smith, 1966](#)) recorded an unspecified medicinal use of *Pelargonium sidoides* by Khoi people in the eastern part of the Free State Province.

[Batten and Bokelman \(1966\)](#) gave the common names of *Pelargonium reniforme* as *iYeza lezikhali* and *iKhubalo* and repeated the medicinal and ethnoveterinary uses reported by [Smith \(1895\)](#). They added that the Xhosa people use the root for liver complaints in sheep and calves and that Europeans use it to treat asthma. *Pelargonium sidoides* is also described and illustrated (under the name *Pelargonium sidaefolium*) but no uses are recorded.

It is claimed that the roots of *Pelargonium sidoides*/*Pelargonium reniforme* have been utilized in traditional medicine of South Africa for the therapy of tuberculosis ([Bladt, 1974, 1977](#)) but the source or accuracy of this information is not provided. [Matsiliza and Barker \(2001\)](#) recorded the isiXhosa name *icwayiba*. Their ethnobotanical survey in the Grahamstown region revealed the traditional use of *Pelargonium sidoides* as a gripe water for infants (“upset stomach”, ... “with air in the intestine”). The crushed root is mixed with water and a teaspoonful of the red infusion is taken orally. [Hutchings et al. \(1996\)](#) repeated the Zulu uses of [Watt and Breyer-Brandwijk \(1962\)](#) but added some valuable new records of uses by the Xhosa people in Transkei. In interviews with 42 *Pelargonium* harvesters from 10 rural settlements in the Amatola region of the Eastern Cape, [Lewu et al. \(2007\)](#) recorded the isiXhosa names *uvendle* and *ikhubalo*.

An unidentified species of *Pelargonium* with the Zulu name *ubala* is mentioned by [Hutchings et al. \(1996\)](#), the roots of which are used by Zulu people to treat a sore throat. The name *uvendle* is given as one of several isiZulu names for *Pelargonium luridum* (Andr.) Sweet. This popular medicine, usually called *ishaqu* or *isandhla sonwabu*, is another tuberous species, similar to *Pelargonium sidoides* in general appearance and in its traditional uses ([Table 1](#)). In addition to diarrhoea and dysentery, the roots of *ishaqu* are used to treat colic and fever ([Watt and Breyer-Brandwijk, 1962](#); [Hutchings et al., 1996](#); [Van Wyk et al., 1997](#); [Van Wyk and Gericke, 2000](#)).

It is interesting to note the traditional uses of tuberous *Pelargonium* species listed in [Table 1](#) mainly involve ailments of the gastro-intestinal tract (diarrhoea and dysentery) and rarely respiratory conditions. Notable exceptions are [Smith \(1895\)](#) who makes a strong case that *Pelargonium sidoides* should be regarded as a general tonic. The treatment of anaemias, weakness and fever ([Table 1](#)), using *Pelargonium antidysentericum* or *Pelargonium grossularioides* is also noteworthy in the context of recent pre-clinical and clinical research, as is the explicit citation from [Burman in 1759 \(Scott and Hewett, 2008\)](#) that *Pelargonium myrrhifolium* is used as a tonic to treat tuberculosis and colic. Further, independent support for the idea of *Pelargonium sidoides* as a colic remedy was presented by [Phillips \(1917\)](#), who recorded only this use in Lesotho. It is impor-

tant to note that Basutoland (now the Kingdom of Lesotho) is given by [Anonymous \(1931a\)](#) as the origin of both the “native medicine man” (who treated Stevens) and the origin of the “native plant” claimed to be locally known as “Umckaloabo”.

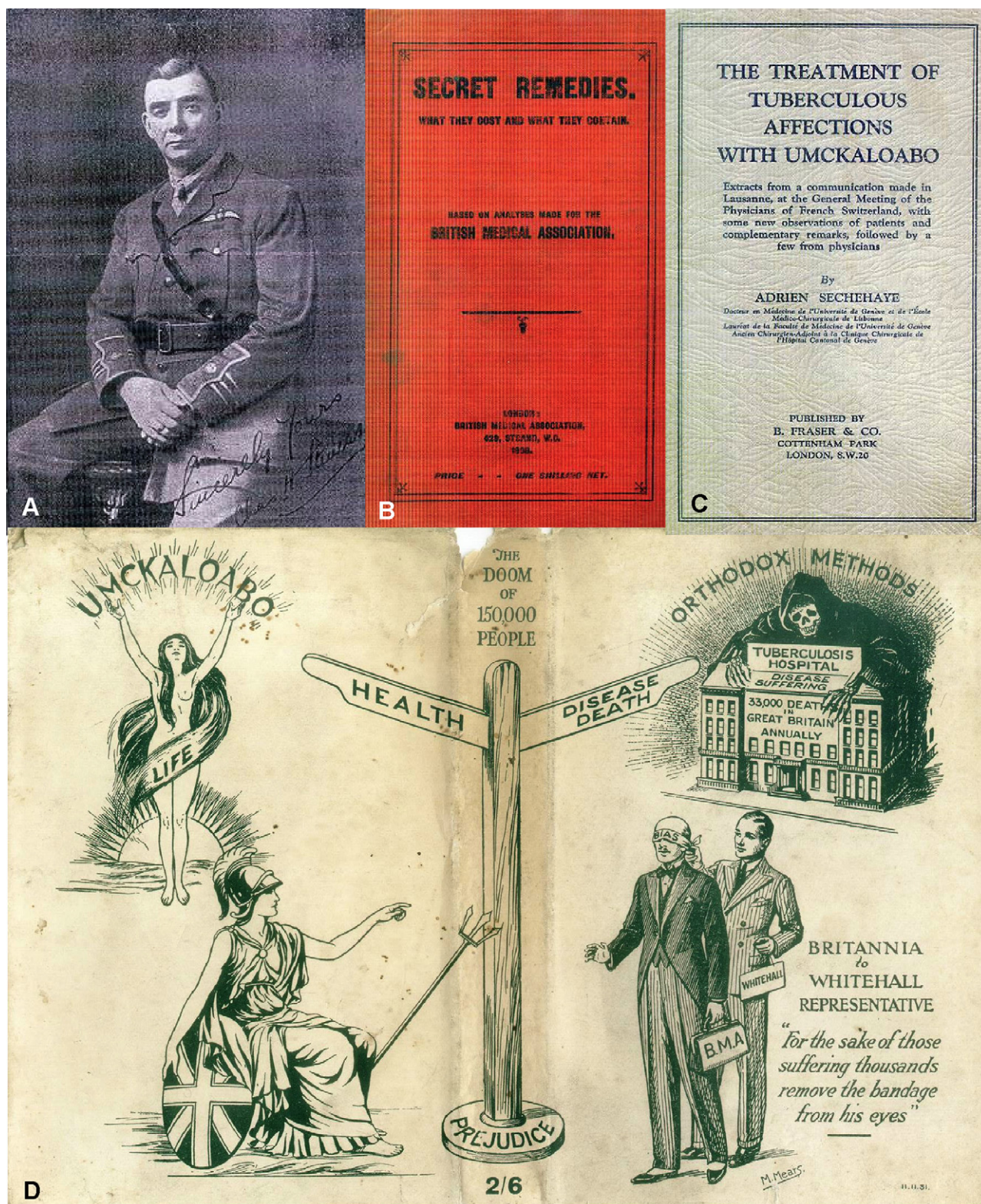
## 2.2. Etymology of “Umckaloabo”

“Umckaloabo” is the name used by Stevens for his tuberculosis medicine, a name that has persisted to this day. All contemporary attempts to explain the origin of the name refer to [Bladt \(1974\)](#). Accordingly, it is claimed to be a derivation from isiZulu *umKhulane*, a term for various ailments with symptoms like fever, cough, etc., and *uHlabo*, stinging breast pain. Other sources refer to *umkhuhlana* (sic!) as a collective term for naturally occurring diseases accompanied by fever such as colds, influenza, pneumonia, pleurisy and malaria ([Doke and Vilakazi, 1958](#)). *Uhlabo*, the name of a disease, is derived from isiZulu/isiXhosa *ukuhlaba*, to stab, for being accompanied by a stabbing pain or stitch in the side. It is applied either to pleurodynia or pleurisy ([Callaway, 1870](#)). The isiXhosa name *ikhubalo* is similar, but not convincingly so. The legitimacy for quoting the isiZulu/isiXhosa words, however, is questionable, as the ethnicity of Stevens' healer and hence the language he used (and Stevens misquoted) remains uncertain. Further confusion is caused by [Smith \(1895\)](#) and later authors, who recorded the vernacular name (in isiXhosa) as *ieyeza lezikhali*, *ikhubalo*, *uvendle* and *icwayiba*. The term *Umckaloabo* may indeed be an invention of Stevens, based on South African languages, intended to create a sufficiently mysterious image for his remedy in order to further its marketability.

## 2.3. History of commercialisation

A summary of the history of Charles Henry Stevens ([Fig. 1A](#)) and “Stevens' Cure” is given in [Table 2](#). Umckaloabo was a secret remedy said to have been introduced from Lesotho ([Anonymous, 1931a](#)). However, South Africa, the Gold Coast and Liberia are given in the same book as the three sources of material of this mysterious plant, which was said to belong to the family Polygonaceae. It may therefore be speculated that it could have been a species of *Rumex* (a genus widely used in traditional medicine in South Africa). All these “facts” may have been invented in an attempt to protect the secrecy of the medicine and its source of raw material. It took until well into the 1970s for the plant ingredient of the remedy finally to be identified. In the early 1990s the product was “relaunched”, this time supported with data on efficacy and safety, provided by scientific investigations. A comprehensive list of clinical studies is given in [Table 3](#), together with the relevant sources of information. Various metabolites in the tuberous rhizomes of *Pelargonium sidoides*, including phenolic and cinnamic acids, tannins, flavonoids and coumarins were isolated and characterized (see later). Furthermore, the composition of the essential oil has been analysed. Antibacterial activities against pathogens which are primarily responsible for respiratory tract infections, and the immunomodulatory potential of the product provide the rational basis for its current therapeutic use. Several clinical trials with an ethanolic root extract (1:9–11) of *Pelargonium sidoides* roots,





**Fig. 1.** The history of Umckaloabo (*Pelargonium sidoides*): (A) Charles Henry Stevens, ca. 1925; (B) cover of British Medical Association (1909b) – Secret Remedies: What they Cost and What they Contain published by the British Medical Association, London; (C) Cover of Sechehaye (1930) – The treatment of tuberculous affections with Umckaloabo, Fraser & Co., London; (D) Dust jacket of Anonymous (1931b) – The Doom of 150,000 People, Reason Publishing Co., London.

referred to as EPs® 7630 (Umckaloabo®) have confirmed its efficacy in conditions such as acute bronchitis (see Table 3). In recent years (Table 2), Umckaloabo has become a popular, lucrative and fully licensed herbal medicine.

#### 2.4. Production and raw material identification

Most of the material is still wild-crafted in the Eastern Cape Province, but crop development has progressed to a point where



**Table 2**  
Chronological review of main historical events in the commercial development of *Pelargonium sidoides*

Period	Events	Literature references
1897–1907	Charles Henry Stevens (Fig. 1A) from Birmingham, UK is sent to South Africa by his doctor in order to recover from pulmonary tuberculosis. There he meets a local healer who treats him with a root concoction. Three months later he feels well, returns to the UK and is pronounced free of TB. Stevens returns to South Africa and makes various unsuccessful attempts to commercialize his “discovery”.	Sechehaye (1930), Helmstädter (1996).
1908–1909	Stevens returns to the UK and sets up a company in Wimbledon to prepare and sell his remedy with some success (his company accounts for 1908 reveal takings of £4415). Soon the British Medical Association (BMA) takes notice and in “Secret Remedies: What they Cost and What they Contain” (Fig. 1B) they accuse him of quackery and fraud.	Newsom (2002), British Medical Association (1908, 1909a, 1909b).
1910–1914	Stevens carries on selling his remedy but feels 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. The jury could not agree on a verdict. The trial continued in 1914, when despite numerous expert witnesses in favour of 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.	American Medical Association (1910, 1913, 1914, 1915, 1919), British Medical Association (1912a, 1912b, 1912c, 1914a, 1914b, 1914c), Stevens (1912), UK Government Report (1914).
1915–1919	Stevens keeps up his efforts to sell his remedy (“Stevenson’s Cure”) and his business grows continuously. However, war intervenes; Stevens serves with distinction, being promoted to the rank of major.	Newsom (2002).
1920–1931	In 1920 the French-Swiss physician Adrien Sechehaye starts using Stevens’ cure to treat TB patients. Over the following 10 years he treats more than 800 patients, 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 TB. These books (see Fig. 1C) are published by Fraser & Co. in London (a publisher who—located conveniently close to Stevens’ business never published anything but ‘Umckaloabo literature’ and may thus well have been ‘sponsored’ by Stevens). By 1931, Stevens employs 50 people manufacturing and distributing his remedy (lozenges, an extract and capsules). The US authorities, meanwhile, debar the remedy from the mails. Stevens also keeps lobbying for his remedy, confronting the authorities and seeking recognition.	Sechehaye (1920, 1921, 1922, 1923, 1924, 1926, 1928, 1929, 1930, 1931a, 1931b), Anonymous (1931a, 1931b), American Medical Association (1930). The dust jacket of Anonymous (1931b) is shown in Fig. 1D.
1932–1960	Stevens’ lobbying keeps the public interest up, the authorities busy (while he never received any recognition for his remedy, there are numerous records for attempts being made by the medical establishment to identify it) and also helps maintaining the success of his business. War disrupts supply routes. Stevens dies aged 62 in 1942 and his son eventually sells the business to a drug manufacturer in Germany. There it appears unchanged in the German National Formulary (Rote Liste), but without being actively marketed. Sechehaye continues treating TB patients with Umckaloabo until well into the 1960s.	Canadian Medical Association (1932a, 1932b), Dudan (1932); Sechehaye (1933, 1934, 1936, 1938, 1951, 1959), Kew Archive File No.121317 (1936ff), Bojanowski (1937). The cover of Sechehaye (1936) is shown in Fig. 1C.
1961–1990	Despite repeated attempts, the remedy remains unidentified until 1974, when the mystery is finally resolved by Dr. Sabine Bladt, a pharmacist of Munich University. At this point the drug receives renewed interest and pharmacological research is initiated.	Hörhammer (1961), Anonymous (1962), Zimmermann (1965), Bladt (1974, 1977), Bladt and Wagner (1988, 2007), Wagner et al. (1974), Wagner and Bladt (1975), Taylor et al. (2005), Newsom (2002), Ernst (2002), Moss (2002), Maynard (2002).
1991–2000	Marketing of the remedy as a treatment for bronchitis and symptoms of common cold starts in the early 1990s while research into the compounds and their mechanisms of action continues. Studies were initially observational, but later developed into fully fledged clinical trials.	Karl (1992), Heil and Reitermann (1994), König (1995), Marschewski (1995), Kolodziej (2000b), Kolodziej et al. (1995), Haidvogel et al. (1996), Dome and Schuster (1996), Kayser (1997)
2001–2008	Based on science, proven efficacy and safety, clinical trials and patents, the remedy is marketed in Germany and abroad with great success, with annual turnover in Germany rising from €8 mil. in 2001 to €80 mil. in 2006. Umckaloabo received a full market authorization by the German drug regulatory agency in 2005. The drug is listed in the European Pharmacopoeia.	Kolodziej (2001), Kolodziej and Schulz (2003, 2004a, b), European Directorate for the Quality of Medicines & HealthCare (2005), European Pharmacopoeia (2008), Schulz (2006).

significant quantities of raw material will soon be produced from cultivated, seed-propagated plants (Fig. 2A). The tuberous roots (the structure is actually partly root and partly stem/rhizome) are sliced and dried (Fig. 2B and D). In view of the consistently high demand for wild-crafted *Pelargonium sidoides*, Lewu et al. (2006) determined conditions suitable for clonal propagation. Socioeconomic aspects of wild-crafting *Pelargonium sidoides* in the Eastern Cape region of South Africa are discussed by Lewu et al. (2007a). The production figures given for 10 rural centres show an estimated total of 26,354 kg, harvested over a period of 4 weeks. At a total price of US\$ 13,915.35, this represents an average of about 53 US cents per fresh kg and an average weekly earning per harvester of about US 13.81.

White et al. (2008) developed a method for the purification of root umckalin and quantification of concentrations in wild and cultivated plants by HPLC. Root umckalin concentration in wild plants was shown to be inversely related to the average annual rainfall and directly related to soil pH. An attempt to

gain high umckalin concentrations in greenhouse-cultivated plants through water stress yielded no significant results. Greenhouse-cultivated control plants, however, yielded umckalin concentrations similar to wild plants, with considerably higher growth rates.

The product may be adulterated with the very similar-looking *Pelargonium reniforme* (the two species often grow side by side) but both the potential risks and the impact of adulteration on international trade seem relatively unimportant. Morphological distinction of the dried product is extremely difficult and chemical analysis is the only reliable method. Whereas *Pelargonium sidoides* contains umckalin and its 7-*O*-methylether (=5,6,7-trimethoxycoumarin), these coumarins are characteristically low or absent in *Pelargonium reniforme* (see later). Coumarins are the most prominent compounds in extracts of *Pelargonium* species, detectable by TLC because of their strong UV fluorescence at 366 nm (Kayser and Kolodziej, 1995) and therefore useful for quality control purposes.

**Table 3**List of clinical trials on *Pelargonium sidoides* or the proprietary extract known as Umckaloabo or EPs® 7630

Reference(s)	Indication	Trial type; trial size (verum/placebo)
Heil and Reitermann (1994)	Upper respiratory tract infections, acute or chronic	Observational; 166 children
Dome and Schuster (1996)	Bronchitis, acute	Observational; 259 children
Haidvogel et al. (1996)	Bronchitis, acute	Observational; 742 children
Blochin et al. (1999)	Bronchitis, acute	Randomized, controlled; 60 children (30/30)
Blochin and Heger (2000)	Angina catarrhalis	Randomized, controlled; 60 children (30/30)
Bereznoy et al. (2003); see also Heger and Bereznoy (2002)	non-GABHS tonsillo-pharyngitis in children	Randomised, placebo-controlled double-blind; 143 children (73/70)
Matthys et al. (2003)	Bronchitis, acute	Randomised, placebo-controlled double-blind; 468 adults (233/235)
Chuchalin et al. (2005); Golovatiouk and Chuchalin (2002); see also Schulz (2006, 2007b), Kamin, (2007)	Bronchitis, acute	Randomised, placebo-controlled double-blind; 124 adults (64/60)
Schapowal and Heger (2007)	Sinusitis	Observational; 361 adults and children
Matthys and Heger (2007a)	Bronchitis, acute	Observational; 205 patients
Haidvogel and Heger (2007)	Bronchitis, acute	Observational; 742 children
Matthys and Heger (2007a)	Bronchitis, acute	Observational; 2099 patients of 0–93 years old
Matthys and Heger (2007b); see also Schulz (2007a), Matthys and Funk (2008)	Bronchitis, acute	Randomised, placebo-controlled double-blind; 217 patients of 18–66 years old (108/109)
Schulz (2008b) Report on an unpublished dose-finding trial presented at the “Phytopharmaka und Phytotherapie” congress in February 2008.)	Bronchitis, acute	Randomised, placebo-controlled double-blind; 405 adults (101, 101, 102/102) 3 times daily one tablet of 10, 20 or 30 mg EPs® 7630 or placebo.
Schulz (2008c); see also Kamin (2007)	Bronchitis, acute	Randomised, placebo-controlled double-blind; 200 and 220 children and adolescents
Lizogub et al. (2007)	Cold, common	Randomised, placebo-controlled double-blind; 103 adults (52/51)
Agbabiaka et al. (2008); see also Kamin (2007) Report on two unpublished trials referred to as ‘Kieser 2007a’ and ‘Kieser 2007b’.	Bronchitis, acute	Randomised, placebo-controlled double-blind; trial 1: 405 adults (303/102); trial 2: 399 children (298/101)

All of these trials reported efficacy, with limited or no side effects.

**Fig. 2.** *Pelargonium sidoides*. (A) commercial plantation; (B) harvested raw material; (C) flowering plant with leaves and flowers; (D) the tuberous root in cross section. Photographers: Van Wyk (A, B, D), A. Oskolski (C).



## 2.5. Standardisation and dosage

Ethanollic extracts are used in a proprietary herbal tincture known as Umckaloabo. Infusions or decoctions are traditionally used but dosage information on the crude herb is not available. Qualitative standardisation has been attempted in a [European Pharmacopoeia \(2008\)](#) monograph.

The recommended dose of EPs® 7630, a root extract from *Pelargonium sidoides*, for adults and children over the age of 12 years is 30 drops (1.5 ml) three times per day for 7 days. Children ages 6–12 years may take 20 drops (1.0 ml) three times per day. Observational studies have suggested that children under the age of 6 years may take 0.5 ml three times per day ([Haidvogel and Heger, 2007](#); [Matthys et al., 2007](#); [Schulz, 2008b, c](#); [Agabiakia et al., 2008](#)).

## 2.6. Products, patents and regulatory aspects

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 ([Erdelmeier et al., 2003](#); [Chatterjee et al., 2006](#); [Koch et al., 2006](#); [Germer et al., 2006](#); [Kohnen, 2007](#); [Schneider and Ploch, 2007](#); [Beil et al., 2008](#)). Noteworthy is [Kohnen \(2007\)](#), describing a method of extraction by means of ethanol-free solvents or an ethanol-free solvent mixture, thus opening the potential for creating an ethanol-free liquid preparation, which may be particularly suitable for children. [Germer et al. \(2006\)](#) describe the potential use of the trisubstituted benzopyranones, constituents present in *Pelargonium sidoides*, for use in the treatment or prophylaxis of conditions related to oxidative stress and/or inflammatory reactions.

In December 2005, the Federal Institute for Drugs and Medical Devices (BfArM, Bonn) approved a new license for the use of Umckaloabo as a drug ([Conrad et al., 2007c](#)). It is a fully licensed liquid herbal medicine on the German market and Germany is still by far the largest market (€80,000,000 turnover in 2006). The preparation of solid formulations is under way, as seen in the dose-finding trials with tablets ([Schulz, 2008b](#)).

A preparation of *Pelargonium sidoides* mother tincture is marketed in the Ukraine, Russia and Latvia as Umkaloar. An unlicensed solid preparation 'Pelargonium' is available in the United Kingdom of Great Britain and Northern Ireland (UK). In the European Union (EU), the implementation of new, EU-wide, regulations on (traditional) herbal medicines over the next few years will have an important impact. Unlicensed products may need to be taken off the market, unless a manufacturer undertakes full drug development and/or licensing procedures. While this is unlikely to have any immediate impact on the German market, preparations of *Pelargonium sidoides* roots may lend themselves to be registered/licensed as traditional herbal medicines in other European countries due to their long history of traditional use. Various liquid and solid preparations are available as herbal supplements in North America and Mexico. Since preparations are marketed as a herbal (food) supplement in most markets outside Germany, no health claims (or only weak claims) can be made. A variety of liquid and dry forms of mono-preparations and herbal combinations that include *Pelargonium sidoides* are available in South Africa and adjacent countries, e.g. Linctagon, Phyto Nova Cough Syrup and Natura Pentagon.

In order to assess the popularity of these remedies, we conducted a number of Google searches (May 2008) with the following keywords and keyword combinations. Umckaloabo (mostly Germany/Europe): 1,010,000 hits; EPs 7630: 83,000 hits; Umcka (the Americas) 44,100 hits; Um(c)kaloar (Eastern Europe) 1200 hits; the South African products together ca. 2000 hits; "*Pelargonium sidoides*" 25,400 hits. [Newsom \(2002\)](#) also conducted a Google search for Umckaloabo and reported only 266 hits!

## 3. Scientific perspectives

### 3.1. Botanical identity and relationships

There has been some confusion about the correct identity of *Pelargonium sidoides*, mainly because [Harvey and Sonder \(1860\)](#) included it (as a variety) within a broad concept of *Pelargonium reniforme*. It is therefore not always clear in the literature if the name *Pelargonium reniforme* includes *Pelargonium sidoides* or not (i.e. whether the name is used in a broad or narrow sense). [Van der Walt and Vorster \(1988, p. 129\)](#) clearly illustrated and discussed the diagnostic differences between *Pelargonium reniforme* and *Pelargonium sidoides*. The correct scientific name of the species is *Pelargonium sidoides* DC. [syn. *Pelargonium sidaefolium* Thunb., *Pelargonium reniforme* Curtis var. *sidaefolium* (Thunb.) Harv.]. *Pelargonium reniforme* Curtis sensu stricto was described and illustrated by [Van der Walt \(1977\)](#) and comprises two subspecies ([Dreyer and Marais, 2000](#)): subsp. *reniforme*, with long internodes of 5–15 mm long and relatively short petioles (mostly 20–40 mm) and subsp. *velutinum* (Eckl. & Zeyh.) Dreyer, with short internodes of 1–5 mm (rarely up to 7 mm) and long petioles that are mostly 50–90 mm long.

In a taxonomic revision of *Pelargonium sidoides* and its seven closest relatives, [Dreyer and Marais \(2000\)](#) included a key that summarised the diagnostic differences between the two species: *Pelargonium sidoides* has maroon to black and linear to spatulate petals ([Fig. 2](#)), with green sepals having white margins; in contrast, *Pelargonium reniforme* has pink to purple, oblanceolate to ovate petals and red sepals with pink margins. They are nevertheless closely related, being the only two species of the group [section *Reniformia* (Knuth) Dreyer] with terete petioles (i.e., there is no adaxial groove). [Dreyer and Marais \(2000\)](#) described this new section on the basis of flower morphology, pollen surface sculpturing and the basic chromosome number of  $x=8$  (in all other sections and groups of *Pelargonium*,  $x=9, 10, 11, 17$  or  $19$ ). Molecular systematic studies (e.g. [Bakker et al., 2004](#)) have confirmed that the section is monophyletic.

Detailed distribution maps ([Dreyer and Marais, 2000](#)) showed that the species is endemic to South Africa and Lesotho. In South Africa, it is widely distributed, including the extreme eastern boundary of the Western Cape Province, almost the entire Eastern Cape Province, as well as parts of the Free State, North-West Province, Gauteng and Mpumalanga Province. It typically grows in short, open grassland, often in rocky places in sandy to loamy soil derived from quartzite, shale or basalt. The altitude ranges from near sea level to more than 2300 m in Lesotho. Most of the distribution area receives rainfall of about 200–800 mm per year, mainly in summer (November to March). *Pelargonium reniforme* has a much narrower distribution range and is more or less confined to the Eastern Cape Province.

No biosystematic studies are available. [Lewu et al. \(2007b\)](#) studied morphological variation in three populations of *Pelargonium sidoides* but a wider survey is required to gain insight into morphological, chemical and genetic variability in the species over the entirety of its rather wide distribution range.

### 3.2. Chemistry

A comprehensive study of all the chemical constituents of both underground and areal parts of *Pelargonium sidoides* and *Pelargonium reniforme* was done by [Kolodziej \(2007\)](#). He also summarised earlier papers by [Kayser and Kolodziej \(1995, 1997\)](#), [Kayser \(1997\)](#), [Kolodziej and Kayser \(1998\)](#), [Latté et al. \(2000\)](#), [Kolodziej \(2000a\)](#), [Kayser et al. \(2001\)](#), [Kolodziej et al. \(2002\)](#), [Gödecke et al. \(2003, 2005\)](#) and [Gödecke \(2005\)](#). As result, another review here would serve no purpose.



The extreme complexity of the metabolites in *Pelargonium sidoides* and *Pelargonium reniforme* is reflected in the presence of numerous coumarins, coumarin glycosides, coumarin sulphates, flavonoids, proanthocyanidins, phenolic acids and phenylpropanoid derivatives (Kolodziej, 2007). A novel diterpene, called reniformin, was found in the roots of *Pelargonium reniforme* (but apparently not in *Pelargonium sidoides*). Umckalin, 5,6,7-trimethoxycoumarin and other coumarins were known to be useful marker compounds for *Pelargonium sidoides*, as they appear to be absent in *Pelargonium reniforme*. The study of Kolodziej (2007) however, also suggests that various coumarin glycosides and coumarin sulphates are confined to *Pelargonium sidoides*. This is interesting, as it may explain the ethnobotanical preference for *Pelargonium sidoides*, as clearly stated by Smith (1895).

The antibacterial and antiviral effects are attributed to gallic acids and other phenolic compounds, while the immunomodulatory activity is considered to be due to a combination of phenolic compounds and the numerous coumarins (umckalin and derivatives).

A yield of 0.52% (of dry weight) essential oil was obtained from the leaves of *Pelargonium sidoides* by hydrodistillation (Kayser et al., 1998) and 102 components could be identified by GLC and GC–MS analyses. Sesquiterpenes (approximately 60%) constituted the largest fraction, with caryophyllene (2.3%) and caryophyllene epoxide (13%) being the most abundant compounds. The oil further contained monoterpenes (16%) and phenylpropanoids (9%), with methyleugenol (4.3%) and elemicin (3.6%) as the most abundant compounds in the latter group.

Schötz and Nöldner (2007) and Schötz et al. (2008) give a detailed account of the constituents of EPs® 7630, an aqueous ethanolic extract of *Pelargonium sidoides* roots. The extraction method yields a specific range of constituents markedly different from those obtained from extraction with non-polar solvents. Six main groups of constituents can be found in EPs® 7630, purine derivatives (2%), benzopyranones (2%), peptides (10%), carbohydrates (monomeric and oligomeric) (12%), minerals (12%) and substituted and unsubstituted oligomeric prodelphinidins (40%).

### 3.3. Pharmacology

#### 3.3.1. Antibacterial and antifungal properties

The antibacterial activity of extracts and isolated constituents (scopoletin, umckalin, 5,6,7-trimethoxycoumarin, 6,8-dihydroxy-5,7-dimethoxycoumarin, (+)-catechin, gallic acid and its methyl ester) of *Pelargonium sidoides* was evaluated by Kayser and Kolodziej (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*). (+)-Catechin proved ineffective. All other compounds exhibited antibacterial activities with minimum inhibitory concentrations (MICs) of 200–1000 µg/ml. MICs varied with extracts and microorganisms tested. Further investigations by Lewu et al. (2006) complement these findings.

Daschner et al. (2004) established a synergistic indirect antibacterial effect of a *Pelargonium sidoides* extract (EPs® 7630) in group A-streptococci (GAS) through inhibition of bacterial adhesion to human epithelial cells (HEp-2) as well as induction of bacterial adhesion to buccal epithelial cells (BEC).

Hansmann (2005) investigated the influence of Umckaloabo on the function of human phagocytes. Phagocytosis, burst and intracellular killing were observed, with *Candida albicans* as the target organism. Umckaloabo significantly stimulated phagocytosis and oxidative burst while intracellular killing was hardly influenced.

It was postulated that an already known increase in adhesion of particles caused by Umckaloabo goes along with an increase in phagocytosis. *In vitro* observations on cytokine production and cell surface receptor expression by Thäle et al. (2007) highlight EPs® 7630 as a potent modulator of macrophage activity. Dorfmueller et al. (2005) further examined the impact of *Pelargonium sidoides* extract (EPs® 7630) on the interaction of GAS with HEp-2. *Pelargonium sidoides* extract inhibited adhesion of GAS to HEp-2. Pre-incubation of GAS with EPs® 7630 also inhibited adhesion. Carrapatoso (2005) examined the influence on adhesion of *Streptococcus pyogenes* to human BEC using flow cytometry and a microscopic count of cells with bacteria. Umckaloabo significantly increased adhesion of bacteria to BEC.

Wittschier et al. (2007a) incubated intact human stomach tissue with fluorescent-labelled *Helicobacter pylori*. Pre-treatment of bacteria with *Pelargonium* extract showed a dose-dependent anti-adhesive effect. No direct cytotoxicity against *Helicobacter pylori* could be established. Beil and Kilian (2007) showed that EPs® 7630 inhibited *Helicobacter pylori* growth and adhesion to gastric epithelial cells in a dose-dependent manner.

Conrad et al. (2007a,b; 2008a,b,c) investigated the impact of therapeutically relevant concentrations of 0–30 µg/ml EPs® 7630 on the activity of human peripheral blood phagocytes (PBP) and on host–bacteria interaction. A flow cytometric assay was used to determine phagocytosis, oxidative burst and adhesion of GAS on human HEp-2 and BEC. Intracellular killing was analysed in a penicillin/gentamicin-protection assay. EPs® 7630 increased the number of phagocytosing PBP in a concentration-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 defence mechanisms and/or overcome antibiotic treatment. These results provide a rationale for the treatment of upper respiratory tract infections with EPs® 7630—see also Wittschier et al. (2007b).

#### 3.3.2. Antimycobacterial properties

Taylor (2003a, b) as well as Seidel 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 2 g/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*.

### 3.3.3. 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-transfected-*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 extracts of *Pelargonium 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 parasitised cells. Trun et al. (2006) carried out gene expression analyses using the reverse transcription-polymerase chain reaction for the iNOS and the cytokines IL-1, IL-12, IL-18, TNF- $\alpha$ , IFN- $\alpha$ , and IFN- $\gamma$  in non-infected and in *Leishmania major*-infected RAW 264.7 cells. EPs® 7630 induced low mRNA levels in non-infected cells, but considerably up-regulated transcript expressions in infected cells. Production of IFN- $\gamma$  mRNA was also stimulated. Similar profiles were obtained for the methanol-insoluble fraction (MIF) and gallic acid. The methanol-soluble fraction and umckalin did not show any significant gene-inducing capabilities. These results indicate that the inducing principle may be located in the MIF.

Kolodziej and Kiderlen (2007) investigated effects on non-specific immune functions by EPs® 7630, extracts and isolated constituents of *Pelargonium sidoides*. Significant immunomodulatory properties could be established in various functional bioassays. Gene expression experiments (iNOS, IFN- $\alpha$ , IFN- $\gamma$ , TNF- $\alpha$ , IL-1, IL-10, IL-12, IL-18) not only confirmed these data but also showed response differences of infected macrophages compared to non-infected cells.

Koch and Wahn (2007) investigated potential effects of EPs® 7630 on the release of antimicrobial peptides from neutrophils. The neutrophil granulocyte, containing antimicrobial peptides and proteins with a wide range of antimicrobial as well as chemotactic, immunomodulating and wound healing activity [such as bactericidal/permeability-increasing protein (BPI) and defensins], is a key cellular component of immune response. EPs® 7630 at concentrations between 0.3 and 30  $\mu$ g/ml was added to heparinized whole human blood samples. Analysis of plasma for BPI and human neutrophil peptides (HNP) 1–3 content after 5 h incubation revealed a significant dose-dependent increase in the release

of HNP 1–3 and BPI. Thus EPs® 7630 seem to stimulate host defence through enhancing the release of antimicrobial peptides.

### 3.3.4. 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, 100  $\mu$ g/ml) were tested, which significantly increased ciliary beat frequency in a dose-dependent manner.

### 3.3.5. Effects on symptoms of sickness behaviour

Nöldner and Koch (2004) and Nöldner and Schötz (2007) studied the inhibition of sickness behaviour (anorexia, listlessness, reduced activity) by EPs® 7630 in male NMRI mice induced by a cytokine-inducer (lipopolysaccharide). Oral administration of EPs® 7630 antagonised the above-mentioned effects in a dose-dependent manner.

### 3.3.6. 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. Table 3 provides a list of these studies, with comprehensive literature references. EPs® 7630, an extract of *Pelargonium sidoides*, has been shown to effectively shorten the severity and duration of acute bronchitis and tonsillopharyngitis, 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 maxillary sinusitis. Overall safety and a very low incidence of side effects have been confirmed.

### 3.3.7. Toxicology, adverse effects, precautions, contraindications, interactions

The cytotoxicity of coumarins present in the crude drug and/or extracts can be considered negligible (Kayser, 1997; Kolodziej et al., 1997; Kolodziej, 2002). To date, there are no contraindications or known drug interactions with the root extract (EPs® 7630). Schulz (2008a) and Conrad et al. (2007c) summarised efficacy and safety-related findings for EPs® 7630. Controlled clinical trials all demonstrated that EPs® 7630 is well-tolerated and safe. In studies with over 7000 adults and children suffering from acute bronchitis, acute tonsillopharyngitis, or acute maxillary sinusitis, adverse events occurred in 1–15% of subjects. These events have been reported as largely mild, consisting of gastrointestinal complaints and skin rashes. With regards to a potential risk related to the coumarin content, a NOEL value of more than 750 mg/kg body weight was established in toxicological studies in dogs and rats. A daily intake of 60 mg (3  $\times$  30 drops) of extract would be equivalent to 4 and 1 mg/kg body weight (15 kg for a child or 60 kg for an adult, respectively) translating into a safety factor of more than 100. No hepatotoxic activity could be established for 7-hydroxycoumarin derivatives (the only coumarins present in EPs® 7630) (Loew and Koch, 2008).

A theoretical risk of interactions with anticoagulants and antiplatelet drugs could not be confirmed as the coumarins so far identified in EPs® 7630 do not appear to possess anticoagulant characteristics. Koch and Biber (2007) administered EPs® 7630 to rats and observed changes in coagulation parameters and interactions with anti-coagulants of the coumarin type (warfarin). After 2 weeks of oral application of EPs® 7630, no impact on coagulation parameters was observed. Treatment with warfarin, however,



resulted in a significant lowering of coagulation parameters. Co-treatment with EPs® 7630 and warfarin did not show any effect of EPs® 7630 over the efficacy of warfarin, neither did it influence the pharmacokinetics of warfarin.

A total of 34 case reports of allergic (hypersensitivity) reactions have been recorded through the World Health Organisation (WHO) international pharmacovigilance programme, which may be associated with the use of *Pelargonium* extract, all originating from Germany (De Boer et al., 2007). While such reactions appear to be limited to Germany, these may assume a more general interest, as products containing *Pelargonium* are now also marketed in other countries. The extract of *Pelargonium sidoides* root (EPs® 7630) is contraindicated during pregnancy and lactation as no specific data on its effect on pregnant or lactating women is available.

Treatment of infections of the upper respiratory tract, particularly tonsillitis, often requires administration of antibiotics. Roots et al. (2004) investigated a potential interaction of a *Pelargonium sidoides* extract (EPs® 7630) with penicillin V in a placebo-controlled, double-blind trial with 28 healthy humans. EPs® 7630 and penicillin V were administered for 7 and 8 days, respectively. None of the target parameters showed any statistically significant difference between verum and placebo. Adverse reactions linked to the herbal extract were not recorded.

#### 4. Conclusion

Tannin-containing plant remedies are traditionally used to treat diarrhoea, hence the emphasis on the treatment of this condition in the published ethnobotanical literature for *Pelargonium sidoides*. However, closer examination reveals a much wider use, including colic, anaemia, weakness and complications related to dysentery. The traditional uses of the roots of *Pelargonium myrrhifolium* as tonic and treatment for tuberculosis, as recorded by Burman in 1759 (Scott and Hewett, 2008) is particularly noteworthy. We conclude that the use of *Pelargonium* tubers in traditional medicine is poorly recorded and much more important than the rather meagre ethnobotanical record would seem to suggest. There are striking similarities in traditional uses in the Western Cape (for *Pelargonium triste* and other species; Khoi-Khoi/Afrikaans: *rabas*, *rabassam*, *rooi rabas*, *rooiwortel*, *t'namie*, *heyntame*), in Zululand (for *Pelargonium luridum*; isiZulu: *ishaqua*, *isandhla sonwabu* or *uvendle*), in the Eastern Cape (for *Pelargonium reniforme* and *Pelargonium sidoides*, isiXhosa: *iyeza lezikhali*, *ikhubalo*, *uvendle* or *icwayiba*) and in Lesotho for *Pelargonium sidoides* (Sesotho: *khoara e nyenyane*).

*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 Sechehayé in the first half of the 20th century. It is clear that care should be taken when reading and interpreting the literature on commercially important plants, as the distinction between scientifically accurate facts and misinformation given for marketing reasons is not always clear. Nevertheless, the commercialisation process turned out to be highly successful. In Germany, a fully licensed medicinal product containing a special extract of *Pelargonium sidoides* root is now among the most widely bought self-medication products.

The underground parts of *Pelargonium sidoides* are known to contain a wealth of highly oxygenated coumarins and numerous other phenolic and polyphenolic compounds. The study of Kolodziej (2007), excellent and detailed as it may be, was based on single samples of *Pelargonium sidoides* and *Pelargonium reniforme*, so that possible geographical, phenotypical and genotypical patterns remain as a challenge for future research. It may also be interesting to extend the study of coumarins and coumarin

derivates to other red-rooted species of *Pelargonium* with a recorded history of ethnomedicinal use. It is likely that the efficacy in treating respiratory ailments is due to the activities and interactions of several components rather than that of a single main constituent.

EPs® 7630, a root extract of *Pelargonium sidoides* (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 has been proved in numerous clinical trials. With research into new applications and new pharmaceutical formulations under way, and with governments tightening the rules which govern the licensing of herbal medicinal products, *Pelargonium sidoides*/Umckaloabo is well positioned for commercial growth while at the same time enjoying a science-based reputation of being a safe and efficacious remedy.

This review was aimed at exploring the variables that play a role in the successful transformation of a traditional medicinal plant into a world class phytomedicine. The following key factors came to light: (1) the choice of species—a profound indigenous southern African remedy that has a long history of use by different cultural groups (and that appears to be a hitherto unrecorded “generic” concept, relating to several tuberous species of the genus *Pelargonium*); (2) the large differential between revenue for the finished product and the cost of raw material (a universal prerequisite for any profitable business); (3) innovative marketing by enthusiastic, pioneering individuals over a period of many years (in competitive but lucrative First World markets); (4) scientific clarification of the botanical and chemical identity of the product (that contributed to consistency and quality); (5) proof of concept, through *in vitro* pharmacological studies and several controlled clinical trials.

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