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Review

Medicinal properties and conservation of *Pelargonium sidoides* DC.

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ABSTRACT

Ethnopharmacological relevance: Pelargonium sidoides DC. (Geraniaceae), a popular medicinal plant used in traditional medicine in the treatment of gastrointestinal ailments has been transformed into a phytopharmaceutical (EPs® 7360) for treating respiratory tract infections. The increasing international demand for *Pelargonium sidoides* has led to localised overexploitation of its wild populations in southern Africa. The aim of the review is to provide a synthesis of the current state of scientific knowledge on the phytochemical, pharmacological and toxicological properties of *Pelargonium sidoides* as well as the potential role of plant biotechnology in its conservation. The review highlights knowledge gaps in these research areas.

Materials and Methods: A comprehensive literature search involving mainly electronic and library sources of information were used to collate and synthesise published data.

Results: Experimental results from *in vitro* studies indicate that bioactive phytochemical constituents of *Pelargonium sidoides* may not possess a direct antimicrobial effect, but instead act by interfering with microbial binding to host cell receptors, inhibition of key enzymes and the production of antimicrobial effector molecules such as nitric oxide and interferons (IFNs) by the host cells. Furthermore, clinical evaluations in randomised, double-blind, placebo-controlled trials have demonstrated the beneficial effect of *Pelargonium sidoides* in the treatment of respiratory tract infections with few side effects. However, there is lack of adequate information on the safety evaluation of the plant. On the other hand, the increasing demand for *Pelargonium sidoides* has led to localised illegal harvesting of wild plants.

Conclusions: Pharmacological data reported in literature suggest that *Pelargonium sidoides* shows a beneficial effect in the treatment of respiratory tract infections. However, more studies are required to elucidate the mode of action of the active constituents exhibited in the treatment of respiratory tract infections and other health conditions caused by microbial attack. Furthermore, the pharmacological usefulness of *Pelargonium sidoides* must take cognisance of the broader context involving the need for conservation-friendly approaches in its utilisation. In this regard, plant biotechnology applications can play a meaningful role in a holistic conservation strategy.

Contents

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1. Introduction

Pelargonium sidoides DC. (Synonym: *Pelargonium sidaefolium* (Thunb.) R. Knuth; Common names: Umckaloabo, Uvendle, Kalwerbossie, Khoaara e nyenyane; Family: Geraniaceae) is a perennial geophyte predominantly found in the Eastern Cape Province of South Africa and the Lesotho highlands. The plant is adapted to a wide altitudinal range, spanning from near sea level in the Eastern Cape to 2746 m in the Lesotho highlands (Newton et al., 2013). The plant is widely used by local communities as a traditional medicine for curing various ailments, including diarrhoea, colic, gastritis, tuberculosis, cough, hepatic disorders, menstrual complaints and gonorrhoea (Brendler and van Wyk, 2008; Colling et al., 2010). The roots are also the main ingredient in a remedy used to treat a stomach ailment known as *instila* in infants (Hutchings et al., 1996). Powdered plant materials which are soaked in water are used as a facial cream in the treatment of skin pimples (Lewu et al., 2007). This indicates that *Pelargonium sidoides* may exhibit antibacterial properties. Probably the most compelling ethnobotanical use of *Pelargonium sidoides* has been in the treatment of tuberculosis, which subsequently led to its introduction in Europe in the late 1890s (Bladt and Wagner, 2007; Brendler and van Wyk, 2008). The traditional ethno-veterinary applications of *Pelargonium sidoides* include the use of root decoctions as an anthelmintic remedy in calves (Hutchings et al., 1996); boiled leaves to protect wounds against maggots; and the prevention of purging in horses (Brendler and van Wyk, 2008). An extract obtained by soaking the roots in water is administered orally in the treatment of dysentery in cattle (Lewu et al., 2007). Based on its medicinal properties in the treatment of respiratory-related ailments, *Pelargonium sidoides* has been formulated into phytopharmaceuticals, namely EPs® 7630 (Umckaloabo®, Dr. Willmar Schwabe GmbH & Co. KG Pharmaceuticals, Germany) and Linctagon® (Nativa, South Africa). The commercial success of Umckaloabo® is attributed to numerous factors, including > 15 years of extensive scientific and clinical research (Gericke, 2011). On the other hand, only negligible research (Bourdette, 2012; Motsamai, 2012) has been done to evaluate the efficacy and safety of Linctagon® (which mainly contains 350 mg *Pelargonium sidoides*, 500 mg Vitamin C, 50 mg bromelain, 80 mg quercetin, 5 mg zinc). This review provides a synthesis of the state of scientific knowledge on the pharmacology and safety evaluation of *Pelargonium sidoides* as well as exploring the potential of plant biotechnology applications in its conservation.

2. Phytochemistry

The extensive use of *Pelargonium sidoides* in traditional medicine coupled with its popularisation in modern medical systems in Europe have led to an upsurge in scientific exploration of its chemical composition in an effort to identify the active principles. This has resulted in a considerable body of literature exploring the phytochemical properties of *Pelargonium sidoides* (Gödecke et al., 2003, 2005; Hauer et al., 2010; Kayser and Kolodziej, 1995; Latté et al., 2000; Schoetz et al., 2008). Details of the phytochemistry of the plant were comprehensively summarised in an excellent review by Kolodziej (2007). However, identification of individual chemical constituents responsible for specific pharmacological activities has remained largely elusive. The chemical constituents of the root ethanolic extract of the plant consist largely of oligo- and polymeric proanthocyanidins, which are based on gallocatechin and epigallocatechin moieties (Theisen and Muller, 2012). The pharmacological efficacy of *Pelargonium sidoides* has been partly attributed to the biological activity of highly oxygenated coumarins (7-hydroxy-5, 6-di-methoxycoumarin; 6,8-dihydroxy-5,7-dimethoxycoumarin), gallic acid-derivatives, flavonoids, phenolic and hydroxycinnamic acid-derivatives (Kayser and Kolodziej, 1995; Kolodziej, 2007; Colling et al., 2010). Recently, 6-Methoxy-7-(sulfooxy)-2H-1-benzopyran-2-one and 6,8-Bis(sulfooxy)-7-methoxy-2H-1-benzopyran-2-one were identified in *Pelargonium sidoides* for the first time (Hauer et al., 2010). Most significantly, Hauer et al. (2010) characterised two novel compounds, 7-Hydroxy-6-methoxy-8-(sulfooxy)-2H-1-benzopyran-2-one and 8-Hydroxy-7-methoxy-6-(sulfooxy)-2H-1-benzopyran-2-one (Fig. 2). These novel compounds have to be screened for pharmacological activity as they may represent the individual active constituents that have so far remained elusive.

3. Pharmacological properties

It is interesting to note that the repertoire of health conditions for which *Pelargonium sidoides* is used has expanded beyond the original traditional uses against gastrointestinal disorders to include respiratory tract infections such as acute bronchitis, asthma, sinusitis and tonsilllopharyngitis. Accordingly, most of the experimental and clinical research has focused on the treatment of respiratory tract infections in line with the development of the phytopharmaceutical, EPs® 7630 (Umckaloabo®). In this regard, a wide array of pharmacological studies involving *in vitro* (Table 1), *in vivo* (Table 2) and randomised, double-blind, placebo-controlled clinical trials (Table 3) has been conducted. Concomitantly, a diverse range of test systems has been used to evaluate the pharmacological properties of *Pelargonium sidoides*. The approaches, which are characterised by different levels of complexity, including the antimicrobial microdilution assay, anti-adhesion assay using HEp-2 cells, penicillin/gentamicin-protection assay, neuraminidase inhibition assay, fibroblast-virus protection assay and reverse transcription-polymerase chain reaction (RT-PCR) assay have helped in deciphering the pharmacological efficacies as well as the possible modes of action involved in the healing processes.

3.1. In vitro studies

Pelargonium sidoides extracts have been tested and exhibited good activity against a number of viruses, including influenza A viruses (H1N1, H3N2), coxsackie A9 virus, human coronavirus, respiratory syncytial virus (RSV), parainfluenza virus 3 and herpes simplex viruses (HSV-1, HSV-2) (Table 1). However, the EPs® 7630 phytopharmaceutical had poor activity ($IC_{50} = > 100\ \mu g/ml$) against the highly pathogenic avian influenza A virus (H5N1) (Michaelis et al., 2011). Notably, the EPs® 7630 extract had high *in vitro* activity against H1N1 ($IC_{50} = 5.4\ \mu g/ml$) (Theisen and Muller, 2012) and H3N2 ($IC_{50} = 8.66\ \mu g/ml$) (Michaelis et al., 2011) attesting to its use in respiratory health conditions. The authors noted that the EPs® 7630 extract was more active against enveloped viruses compared to non-enveloped viruses (adenovirus 3, adenovirus 7 and human rhinovirus). Interestingly, antiviral bioactivity (EC_{50}) of isolated phenolic constituents against H1N1 increased in the order of complexity of their chemical chain structure as follows: epigallocatechin ($42.5\ \mu g/ml$) > gallocatechin ($28.4\ \mu g/ml$) > gallocatechin-(4β→8)-gallocatechin ($7.3\ \mu g/ml$) > epigallocatechin-(4β→8)-gallocatechin ($6.3\ \mu g/ml$) > oligo-/polymeric fraction ($2.8\ \mu g/ml$) (Theisen and Muller, 2012). The study reported a poor direct virucidal activity of EPs® 7630 ($250\ \mu g/ml$). Instead the authors discovered that the extract and its phenolic constituents imparted anti-viral activity by interfering with virus binding to host cell receptors and through inhibition of the neuraminidase enzyme. Furthermore, the control of viral infections may occur through the production of interferons (IFNs) by the host cells, suggesting that therapy by *Pelargonium sidoides* may be through the stimulation of the innate immune system (Kolodziej, 2007). Based on the current state of research using