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REVIEW

Genus *Pelargonium*: General Aspects, Potential Pharmacological Applications, Extraction Methods and Applications in Industry

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ABSTRACT

***Pelargonium* is a genus belonging to the Geraniaceae family, found within the Angiospermae division, the Dicotyledoneae class, and the Geraniales order. It is the second biggest genus of the family; it has about 280 taxa. In the past, *Pelargonium* species were characterized by presenting large and red roots, from which preparations were used in the treatment of diarrhea, dysentery, anemia, and weakness. This article is a bibliographic search carried out in different databases that focus on chemical and physical features of *Pelargonium* and also some of the extraction methods. Currently, there are a variety of studies that affirm the different properties of the species of the genus *Pelargonium*, among which the activities stand out: antituberculous, antioxidant, antitumor, antibacterial, antifungal, antiviral, and immunomodulatory. Therefore, they are used in both the pharmaceutical and food industries. The most relevant species of this genus is *Pelargonium sidoides*, which has a broad range of biological properties, from which a standardized hydroalcoholic root extract was formulated, known as EPs® 7630, which has been authorized by the EMA and is listed in the European Pharmacopoeia. It is important to continue with the clinical studies to be able to analyze the other properties that *Pelargonium* has in order to contribute to the pharmaceutical industry.**

Keywords: *Pelargonium*, *P. reniforme*, *P. sidoides*, root.

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1. Introduction

Pelargonium L'Héritier in Aiton is a genus belonging to the Geraniaceae family and the Angiospermae division, the Dicotyledoneae class, and the Geraniales order. It is considered a brother genus of Geranium, Erodium, Monsonia, Hypseocharis, Rhynchotheca, and Sarcocaulon (Blerot *et al*., 2016). It has a great variety of floral morphologies and life forms, representing the second-largest genus of the Geraniaceae family, with around 280 taxa. It is morphologically different from the rest of the family since it has a hypanthium consisting of a spur of nectar adhered to a nectary. It usually features a zygomorphic floral symmetry (Reyes, 2010; Roeschenbleck *et al*., 2014).

The main distribution of the genus, which is 90%, is located in southern Africa. The most remarkable species diversity is located in the southwestern area of South Africa, where the rainfall comes exclusively during the winter. There is a distribution of species outside of southern Africa, which populate mountain habitats throughout the Rift Valley in West Africa and South Australia, Madagascar, the Arabian Peninsula, Anatolia, and New Zealand (Roeschenbleck *et al*., 2014).

The mild climate with low humidity is ideal for the *Pelargonium*'s growth. These species grow in short grassland areas and, in some cases, with shrubbery and trees in stony soils, which vary in their composition of sand, clay, shale, and basalt (Saraswathi *et al*., 2011). Furthermore, they can adapt to different climates and soils (tropical, subtropical, mediterranean, or arid), making their global distribution easier (Blerot *et al*., 2016). *Pelargonium*'s growth ways range from annual herbaceous plants and shrubbery to stem succulents and geophytes (Roeschenbleck *et al*., 2014). They can reach more than a meter in height (Reyes, 2010).

The stems are thick, with more ramifications at the base, and pairs of green stipules in a triangulated shape attached to the bud area. The leaves join the stem through

a long petiole (Reyes, 2010), and it has a great variety of shapes and sizes. They can be covered with fine hairs and rugged, sticky, or velvety texture. The leaf's borders can be "curly" or "crusty" in some species. The flowers are asymmetrical pentamerous, and they are presented in pseudo-umbels, with 5 to 10 foils. In addition, they can feature different colors that range from white, pink, mallow, lavender, pale yellow, and burgundy to a combination of them (Saraswathi *et al*., 2011). These flowers are hermaphrodites, present 2 to 7 fertile stamens, and are pollinated by several animals, such as bees, flies, butterflies, hawks, and birds (Blerot *et al*., 2016).

The initial cariological research suggested a division of the genus into two significant clades, one with large chromosomes (>1.5 μm in length) and another with small chromosomes (<1.5 μm in length). Other studies have established the genus division into five compatible clades (A1, A2, B, C1, and C2). The clades A and B correspond to the small chromosomic clades, and clade C corresponds to the large chromosomic clade. Moreover, through floral morphology, leaf components, and nuclear markers analysis, it has been possible to establish the existence of four main clades (A, B, C1, and C2) instead of five. However, the classification of *Pelargonium* is still not considered a challenge (Blerot *et al*., 2016).

In 2014, a sub-generic division of *Pelargonium* was exposed, a division composed of the sub-genera *Magnipetala, Paucisignata, Parvulipetala*, and *Pelargonium*. At the same time, every one of these is subdivided into different phylogenetically arranged sections. The Reniformia section, belonging to the Parvulipetala sub-genus, contains species such as *P. sidoides* DC and *P. reniforme* Curtis, which are the most recognized of the genus due to their applications as traditional remedies (Roeschenbleck *et al*., 2014).

Around 35 indigenous medicinal plants were described in Cape Town during the years 1650 to 1800, of which six belonged to the *Pelargonium* genus. These presented big, red roots, from which formulations were developed to treat diarrhea, dysentery, anemia, and weakness. Some of these red-rooted *Pelargonium* were identified as *Pelargonium myrrhifolium* (L.) *L'Herit. var. myrrhifolium*, *Pelargonium pinnatum* (L.) *L'Herit., Pelargonium triste* (L.) *L'Herit*. and *Pelargonium* antidysentericum (Brendler & van Wyk, 2008).

In 1867, the Englishman Charles Henry Stevens, who suffered from tuberculosis, travelled to South Africa to cure his illness. During this trip, the man met Kagaitse, a Zulu healer, who offered him boiled root preparation, which he had to take twice a day. After three months of treatment, Stevens overcame tuberculosis and introduced this natural medicine to England. However, it was not relevant due to the lack of knowledge regarding the plant's botanical origin, chemical composition, and pharmacological activities. Eventually, Dr. Sechehaye gathered information about the plant and began to treat tuberculosis patients with the preparation utilized by Stevens. In 1930, he published the results of the treatments for the first time. He came to the conclusion that, in many tuberculosis cases, excluding acute or complicated cases, it was possible to establish healing effects from the preparation of the *Pelargonium*. Subsequently, after a detailed analysis of the plants' roots components, it was possible to identify that the herbal preparation used consisted of a mixture of *Pelargonium reniforme* and *Pelargonium sidoides* (Aquines & Tassano, 2015; Bladt & Wagner, 2007).

For many years, efforts have been made to adequately document the therapeutic benefits of the *Pelargonium* species. This has been mainly achieved with *Pelargonium sidoides*, which facilitated the production of a standardized hydroalcoholic extract of the species' roots, known as EPs® 7630, and commercialized by Spitzner Arzneimittel, Ettlingen, Germany. This extract received full market authorization from the German medicine regulation agency in 2005 and is, up to this day, listed in the European Pharmacopoeia (Brendler & van Wyk, 2008). The research backs up the use in respiratory tract infections, such as acute bronchitis (Kolodziej, 2011).

Traditionally, the rhizomes and herbs of the *Pelargonium* species have been mainly used to treat conditions like diarrhea, colic, gastritis, cough, soreness, tuberculosis, liver diseases, abdominal disorders, period pains, and gonorrhea. The leaves have been utilized to remedy wounds, abscesses, neuralgia, infections, ringworms, ulcers, and rashes. It has been used to protect wounds from worms in animals and prevent purges in horses. Furthermore, the roots have been employed in animals to treat dysentery and as an anthelmintic remedy (Moyo & Van Staden, 2014; Saraswathi *et al*., 2011).

The *Pelargonium* plants have been helpful in popular medicine since they have been used to control menstrual problems, hematuria, hemorrhoids, syphilis, herpes, menopausal problems, cellulitis, dry skin, fluid retention, and ulcers. They have also been employed in childhood affections like chickenpox, measles, and mumps. Besides, geranium oils derived from *Pelargonium* have been used to control constipation, insomnia, anxiety, high cholesterol, high blood pressure, congestion, hemorrhoids, indigestion, among others (Saraswathi *et al*., 2011).

Generally, the preparation of the plant is made by decoction, although it is also usual to chew pieces of the plant, grind them up and mix them with the foods. Another common practice involves boiling the tubercle in milk or elaborating creams from grinding the vegetable material (Moyo & Van Staden, 2014; Saraswathi *et al*., 2011).

2. Materials and Methods

To carry out the article, a bibliographic search was carried out in the databases: Elsevier, ResearchGate, Taylor & FrancisOnline, PubMed, Ovid, ScienceDirect, SpringerLink, WileyOnlineLibrary, PlosOne, Ebsco, Proquest, and Google Patents. The publication dates of the articles comprised the period from 2002 to 2019. Keywords were used; *Pelargonium*, *P. sidoides, P. reniforme*, EPs® 7630, taxonomy, history, pharmacological, alimentary, extraction, and formulation. Review articles, meta-analysis, preclinical studies, clinical studies, patents, and thesis were used.

3. Results and Discussion

3.1. Potential Pharmacological Applications

The indole alkaloids elaeocarpidine and its isomer 20-H epielaeocarpidine have been identified in some *Pelargonium* species. There have been found, as well, the flavonols and coumarins; scopoletin, 7-hydroxy-5,6-dimethoxycoumarin, as well as its methyl ether and glucoside. In addition, other compounds have been identified, such as common organic acids, ellagitannins, cinnamic acid derivatives, and phytosterols. Besides, approximately 230 compounds of the *Pelargonium* essential oils have been detected, these being a complex blend of monoterpenes and sesquiterpenes and compounds like alcohol, esters, aldehydes, ketones, and phenols. Other kinds of chemical products are included, such as flavonoids and derivatives of salicylic acid (Kolodziej, 2007; Saraswathi *et al*., 2011).

Due to its medicinal properties, *P. sidoides* is the most important *Pelargonium* species in the pharmaceutical industry and is botanically related to *P. reniforme* curt (Schoetz *et al*., 2008). The species used for the production of essential oils are also of great relevance, with these being often known as "geranium oils"*; P. graveolens, P. radens*, and *P. capitatum*.

Traditionally, both *P. sidoides* and *P. reniforme* have been used to treat a great variety of ailments. However, *P. sidoides* has had greater relevance in the health area nowadays. Therefore, it has been harvested on a large scale to be exported to Europe and other regions, aiming to explore and apply its medicinal properties in the medicine manufacturing process (Victor & Aphane, 2014).

Morphologically, *P. sidoides* differ from *P. reniforme* in flowers and leaves. *P. reniforme* has pink-colored flowers and lanceolate petals with distinctive stripes and reniform type leaves, whereas *P. sidoides* presents rope-shaped leaves and flowers with a dark red color, which are commonly observed in almost black color (Kolodziej, 2007; Victor & Aphane, 2014).

Regarding the plants' chemical composition, it has been identified that both species roots show important variations in the types of coumarins they contain, although they share the scopoletin, 6,7,8-trihydroxycoumarin and 8-hydroxy-5,6,7-trimethoxycoumarin coumarins; therefore, these compounds can be used as chemical markers. Besides, *P. sidoides* show coumarin sulfates and glucosides and the umckalin compound, which is considered a characteristic metabolite of the species, whereas *P. reniforme* has the reniformin compound, a unique metabolite of the species (Kolodziej, 2007; Schoetz *et al*., 2008).

P. graveolens is an aromatic and erect bush with an approximate 1.3 m height and 1 m length. It presents carved and soft to the touch leaves, which have numerous glandular trichomes and small pink-colored flowers (Blerot *et al*., 2016). The main components are geraniol, linalool, citronellyl formate, menthone, isomenthone, and nerol (Szutt *et al*., 2019). Besides, *P. capitatum* is a slightly scented sub-shrub with approximately 1 m in height and 1.6 m in length. It presents hairy leaves with interspersed glandular trichomes. Their main components are caryophyllene, viridiflorol, 10-epi-gamma-eudesmol, citronellyl formate, and citronellol. Finally, *P. radens* is an erect bush, approximately 1.5 m in height and less than a meter in width. It has leaves that are hard to touch with many interspersed glandular trichomes. The main components are citronellic acid, menthone, and isomenthone (Blerot *et al*., 2016; Lalli *et al*., 2006).

3.2. Pharmacological Properties of Pelargonium

3.2.1. Anti-Tuberculosis

During the year 2009, it was identified that compounds such as quercetin-3-d-glucoside, myricetin, gallic acid, and methyl gallate, which exist in *P. reniforne's* aqueous extract, were capable of modulating the intracellular survival of the mycobacteria *M. fortuitum* and *M. tuberculosis*, which are present in murine peritoneal macrophages. (Kim *et al*., 2009) Another study determined that a raw root extract of *P. sidoides* exhibited an increased inhibition of *M. tuberculosis* growth. (Kolodziej *et al*., 2003) It has also been seen that acetone, chloroform, and ethanol extracts of *P. reniforme's* roots present activity against *M. tuberculosis*, although to a lesser extent than the standard anti-tuberculosis medicine (Mativandlela *et al*., 2006).

On the contrary, it has been described that the umckalin, scopoletin, 6,8-dihydroxy-5.7-dimethoxy-2H.-benzopyran-2-one,6,8-dihydroxy-7-methoxy-2H.-benzopyran-2-one, catechin, and epigallocatechin compounds, isolated from the butanolic root extract of *P. sidoides* do not exhibit any activity against *M. tuberculosis*, and they present no activity against THP-1 macrophage cell lines, which are infected with the bacteria. As a result, it is supposed that the described cases on the effective use of the plant against tuberculosis can be due to indirect effects or due to an immune system activation (Mativandlela *et al*., 2006).

3.2.2. Antioxidant

The antioxidant activity of a mother tincture of *P. sidoides* has been confirmed, attributed to gallic acid, trihydroxycoumarin, dihydroxycoumarin sulfates, proanthocyanidins, and phenolic glycosides. Furthermore, due to the presence of hydrolyzable flavonoids and tannins, it has been informed of the antioxidant activity of *P. reniforme*. These compounds protect the cells of the reactive oxygen species (ROS) and eliminate the superoxide radicals, nitric oxide, and peroxyl (Latté & Kolodziej, 2004).

On the other hand, the raw acetone extracts of *P. botulinum* and *P. crispum* have proven to execute a potent antioxidant activity attributed to the flavonoid derivatives (Lalli *et al*., 2008). It has been established that the hydrosols obtained from the stems and leaves of *P. graveolens* show significant antioxidant activity. Besides, it reaches even ten times more activity than the thymol due to the phenolic derivatives. Therefore, formulations of this species are promising food supplements (Ćavar & Maksimović, 2012).

3.2.3. Antitumor

The solid anticancer activity of a commercial *P. sidoides* mother tincture has been proven, this being against the lymphoblast cellular line of human T leukemic cells. The blocking of the G0/G1 phases of the cell cycle and

apoptosis have been identified. Due to the presence of polyphenolic compounds in the plant (Pereira *et al*., 2015). Besides, it has been observed that the methanolic extract of *P. quercetorum* has a significant antiproliferative effect against the lung cancer cell lines (Aztopal *et al*., 2015). The tetracosane, heneicosane, and 2-methyl eicosan are the most abundant compounds in this species;thereby, it is believed that they are responsible for said activity. Moreover, anticancer activity has been confirmed with *P. graveolens'* essential oil in human promyelocytic leukemia cells. Said activity can be due to the presence of monoterpenes, such as citronellol and transgeraniol (Fayed, 2009).

3.2.4. *Antibacterial*

Studies have shown that the root extract of *Pelargonium sidoides* has strong antibacterial properties against one of the periodontal pathogens, *Aggregatibacter actinomycetemcomitans*. This effect is mediated by compounds like oxygenated coumarins, flavonols, and prodelfinidines. In addition, the antibacterial activity of root methanolic extracts of *P. reniforme* and *P. sidoides* has been proven, which had an inhibitory activity over microorganisms responsible for this activity. It is believed that antibacterial efficiency is achieved by inhibiting bacterial adhesion (Kolodziej & Kiderlen, 2007).

It has been informed that the commercial extract of *P. sidoides*, EPs® 7630, inhibits the growth of *Streptococcus pyogenes*, *Proteus mirabilis*, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus epidermidis* (Jekabsone *et al*., 2019). Another study has proven that this commercial extract presents inhibitory activity against *Helicobacter pylori* by reducing the bacterial density due to the block of the adhesion of the bacteria to the host's gastric cells. It was suggested that the negatively charged extract components are responsible for the effect (Beil & Kilian, 2007).

The essential oil of *P. graveolens* has shown antimicrobial activity against *Salmonella enteritidis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis*. An antimicrobial effect has been observed, more effective than chloramphenicol and amoxicillin. It looks like β- citronellol, a prominent part of the oil, and its likely synergistic effect with other components is responsible for the antibacterial effect (Ghannadi *et al*., 2012).

3.2.5. *Antifungal*

It has been seen that aerial and root part extracts of *P. sidoides* present anticryptococcal activity and antipathogenic properties in virulence factors against *Cryptococcus neoformans*. These effects are mediated by the inhibition of the laccase and urease activities and the reduction in the size of the fungus capsule. It is believed that some of the compounds responsible for the activity are: isoorientin, orientin, vitexin, and luteolin 7- O-β-D-glucoside. Besides, compounds like gallic acid, fraxetin, and scopoletin, present in this plant, have reports of activity against *Candida albicans* (Samie *et al*., 2019).

The main compounds of the rose-scented oil from the *Pelargonium* species' leaves, citronellol, linalool, geraniol, isomenthone, geranyl formate, and citronellyl formate, have proven activity against *Candida albicans* and *Cryptococcus neoformans* (Rath *et al*., 2015). Also, the *Pelargonium zonale* stem's extract has indicated an inhibition of the activity against *Candida albicans*, through changes in the morphology of the fungal cells and the cellular metabolic activity (Lewtak *et al*., 2014).

3.2.6. *Antiviral*

The EPs® 7630 medicine has proven antiviral activity against several viruses, especially the ones responsible for respiratory diseases, such as respiratory syncytial virus, human coronavirus, parainfluenza virus, and coxsackie virus, as well as the seasonal influenza A virus strains (H1N1, H3N2), through the inhibition of the activity of neuraminidase and hemagglutination (Theisen & Muller, 2012). However, this preparation is inactive against other viruses, such as; adenoviruses, rhinoviruses, and measles. Said antiviral effects are attributed to the gallic acids and other phenolic compounds present in the plant (Brendler & van Wyk, 2008).

The aqueous extract of *P. sidoides* has proven to be capable of inhibiting the replication of the HSV-1 and HSV-2 virus (Michaelis *et al*., 2011). Furthermore, this aqueous extract showed a potent anti-HIV-1 activity by directly interfering with the viral infectivity and blocking the virus's particles union to the objective cells. It has been determined that said activity was mediated by multiple low-cytotoxic polyphenolic compounds present in the plant (Helfer *et al*., 2014).

3.2.7. *Inmunomodulatory*

Recent studies have informed that EPs® 7630 can increase innate immune defense by activating monocytes, inducing proinflammatory cytokines, and modulating their mediator production capacity and neutrophils and Th17 and Th22 adaptive cell generation (Witte *et al*., 2015). In addition, it has been established that this extract can stimulate the host's defense by enhancing the liberation of antimicrobial peptides. Besides isolated *P. sidoides*, simple phenols, flavan-3-ols, proanthocyanidins, and hydrolyzable tannins compounds could enhance the ARNm of iNOS y cytokines levels in parasitized cells (Brendler & van Wyk, 2008). Moreover, geraniol, the main compound of the *Pelargonium*'s essential oils, has proved the prevention of graft rejection in live models, mediated by a reduction in the immune system's response. It has also been proven, in live models, to exercise suppression regarding the adherence of neutrophils induced by TNF-α (Chen & Viljoen, 2010).

3.3. *Pelargonium Applications in Pharmaceutical and Food Area*

Nowadays, the preparation of EPs® 7630 is made from the *P. sidoides* roots' ethanolic extract (11% w/w), and it is the most popular medicinal product obtained from *Pelargonium* species in the pharmaceutical industry. This has been the object of many chemical studies, clinical and non-clinical, from which it has been awarded immunomodulatory, antiviral, and antibacterial properties mainly. In addition, it is found in a film-coated tablet fashion, which

contains the dry extract, which is prepared from the liquid extract. It contains six main compound groups: purine (2%), coumarins (2%), peptides (10%), carbohydrates (12%), minerals (12%), and oligomeric prodelfinidines derivatives (EMA, 2018). At present, it is indicated for the treatment of acute bronchitis. It offers an effective alternative in treating this condition in cases where an antibiotic is not required (Chuchalin *et al*., 2005).

Numerous clinical essays have informed about the use of this formulation to treat the common cold in adults. It has been proven that early administration reduces the severity of the symptoms and the duration of the illness (Chuchalin *et al*., 2005). Furthermore, its effectiveness has been reported regarding the early treatment of acute respiratory tract infections in kids, quickly decreasing the symptoms and, as a result, the risk of bacterial superinfection (Careddu & Pettenazzo, 2018). Moreover, some studies have proven the prevention of asthma attacks during viral superior respiratory tract infections, a significant reduction of cough frequency, a high secretolytic activity, and the reduction of trachea and bronchi injuries (Bao *et al*., 2015; Tahan & Yaman, 2013). Some mechanisms that describe said activities are the activation of macrophages and the resultant increase in nitric oxide production, the modulation of the production of inflammatory mediators, the inhibition of the adhesion proteins on the bacterial surface, and the increase in the ciliary motility of the respiratory epithelium (Careddu & Pettenazzo, 2018).

In the wide variety of clinical studies that have been made, there has not been a report on serious side effects regarding the use of this formulation. The indications have mainly included allergic reactions and, to a lesser extent, gastrointestinal pain, nervous, respiratory, and mediastinal system problems, ear discomfort, and epistaxis. Furthermore, satisfactory tolerability of the treatment has been established in both adults and children (Matthys *et al*., 2003).

One of the main precautions regarding using the extract is to avoid the administration on patients with a known hypersensitivity to the ethanolic extract of *P. sidoides*, its compounds, or members of the plant family Geraniaceae (Ulbricht *et al*., 2010).

Besides, the essential oils obtained from the *Pelargonium* species or compounds isolated from these are frequently used in domestic and cosmetic products. Due to the pleasant scents they present, they are employed in the formulation of; massage oils, skin care creams, makeup, soaps, deodorants, toothpaste, and other cosmetic or pharmaceutical formulations based on natural products (Alcedo, 2018; Saraswathi *et al*., 2011). The terpene-free *Pelargonium* oils are used as fragrances in the production of floral bouquets or as a base for synthetic rose compounds. In addition, and due to the limited production and high prices of rose-based products, they are used as substitutes for rose attar. The oil-isolated compound, rhodinol, is widely used in perfumery and aromatherapy (Preddy, 2015).

Another use of the *Pelargonium* essential oils is its insecticidal and repellent activity. The oil-isolated geraniol is used in pest control or as a natural repellent, specifically against mites, mosquitoes, and ticks. It also presents low mammalian toxicity and good biodegradability, ideal properties in these products (Chen & Viljoen, 2010).

Pelargonium essential oils are also used in the food industry as flavorings and preservatives. The isolated compound citronellol is used as a natural flavor in products such as yogurt, drinks, desserts, jams, tobacco products, and chewing gum (Blerot *et al*., 2016). Other compounds are used as preservatives in products such as; dairy, dehydrated, processed, vegetables, and fruits. Also, the aerial sections of *P. graveolens* are used to extract additives used in tea and various foods. The FDA approved this oil, and it is considered safe, being used in concentrations below 0.001% in finished products (Preedy, 2015).

It is worth noting that the most common adverse effect of the *Pelargonium* essential oils are the dermal reactions, such as skin irritation and sensitization, due to the skin being the primary route of exposure for these products (Chen & Viljoen, 2010).

3.4. Pelargonium Extraction Methods

3.4.1. Procedure for the Preparation of Extracts of Pelargonium sidoides and Pelargonium reniforme

The roots of *Pelargonium sidoides* and *Pelargonium reniforme* undergo percolation or a two-stage maceration. Percolation and double maceration are carried out with mixtures at different proportions of water:ethanol, such as 10%–92% w/w ethanol or 10%–60% w/w ethanol. The extracts obtained, after drying, have a total phenolic content of 15%–18% (Erdelmeier *et al*., 2007).

Percolation examples (Erdelmeier *et al*., 2007):

1) 1 kg of dried roots of *Pelargonium sidoides* is placed in 2 kg of 35% w/w ethanol for 24 hours and then transferred to a glass column. It is percolated for 10 hours with 8 kg of 5% w/w ethanol. The drug residue is squeezed lightly, and the extract is filtered through a Seitz Supra 1500 filter and concentrated by evaporation to dryness.
2) 40 g of dried roots of *Pelargonium sidoides* are placed in 80 g of an extraction solvent (11% w/w or 35% w/w ethanol) for 22 hours and then transferred to a glass column. It is percolated for 3 to 4 hours with 320 g of the solvent used for the extraction, the drug residue is squeezed lightly, and the extract is concentrated by evaporation to dryness.
3) 40 g of dried roots of *Pelargonium sidoides* are placed on a glass column and percolated for 8 hours with 400 g of 11% w/w ethanol. The drug residue is squeezed lightly; the extract is filtered through a Seitz Supra 1500 filter and concentrated to dryness.

Maceration example (Erdelmeier *et al*., 2007):

1) 20 g of dried Pelargonium sidoides roots are macerated with 140 g of an extraction solvent (11%, 20%, 35%, 60%, 90% w/w ethanol-water or water) at 50 °C for 30 minutes. The extract is separated by filtration, and the drug residue is macerated for a second time in the same way. After solid/liquid separation, the extract solutions are mixed and dried.

3.4.2. Procedure for the Preparation of Dry Extracts of Pelargonium sidoides y Pelargonium reniforme

Two solvents are used; solvent A composed of 10 parts of 96% ethanol, 20 parts of 85% glycerol, and 70 parts of water. And solvent B composed of 10 parts of 85% glycerol, 10 parts of xylitol and 80 parts of water (Herrmann & Thöle, 2010).

Examples (Herrmann & Thöle, 2010):

1) 28 kg of ethanol (35% w/w) are added to 14 kg of the ground root of *Pelargonium sidoides* and stored at room temperature for 20 hours. The mixture is percolated with 112 kg of ethanol (6% w/w) for 10 hours and then filtered. Later, 50 kg of the liquid extract is dried at 50 °C under a vacuum. Then, 1 g of each of the dry extracts obtained is mixed with 100 ml of solvent A or B after mixing with 4.55 g of a carrier substance.
2) 28 kg of ethanol (35% w/w) are added to 14 kg of ground *Pelargonium sidoides* root and stored at room temperature for 20 hours. The mixture is percolated with 112 kg of ethanol (6% w/w) for 10 hours and then filtered. Subsequently, 1.25 kg of mannitol is dissolved in 15.4 kg of the liquid extract. It is dried at 50 °C under a vacuum. Then, 5.55 g of each of the obtained dry extracts (corresponding to 1 g of the native portion and 4.55 of mannitol) are mixed with 100 ml of solvent A or B.
3) 28 kg of ethanol (35% w/w) are added to 14 kg of the ground root of *Pelargonium sidoides* and stored at room temperature for 20 hours. It is percolated with 112 kg of ethanol (6% w/w) for 10 hours and filtered. Subsequently, 1.19 kg of sucrose is dissolved in 14.7 kg of the liquid extract. It is dried at 50 °C under a vacuum. Then, 5.55 g of each obtained dry extract (corresponding to 1 g of the native portion and 4.55 of sucrose) are mixed with 100 ml of solvent A or B.
4) 28 kg of ethanol (35% w/w) are added to 14 kg of the ground root of *Pelargonium sidoides* and stored at room temperature for 20 hours. The mixture is percolated with 112 kg of ethanol (6% w/w) for 10 hours and filtered. Subsequently, 1.34 kg of maltodextrin is dissolved in 16.5 kg of this liquid extract. It is dried at 50 °C under a vacuum. Then 5.55 g of each of the obtained dry extracts (corresponding to 1 g of the native portion and 4.55 of maltodextrin) are mixed with 100 ml of solvent A or B.

3.4.3. Procedure for the Preparation of Essential Oil of Pelargonium odoratissimum

The vegetable material of *Pelargonium odoratissimum* is placed in a volatile oil extractor, then distilled water is added according to a solid-liquid ratio of 1:10–20 and is then soaked for 1 to 3 hours, occasionally shaking it. Then, the wet distillation is done, and after 3 to 6 hours, the essential oil is gathered through drying using anhydrous sodium sulfate. After the sealing, a transparent, yellow, and usable form of the volatile oil is obtained and preserved at −4 °C. This product can be used as an essence in makeup and laundry products or as a medicinal essence (Chen *et al*., 2015).

3.4.4. Procedure for the Preparation of the Rose-Scented Pelargonium Essential Oil

350 kg of *Pelargonium* leaves are placed in a false bottom in the distillation tank, and steam is poured into the false bottom. The vapors formed are passed through a cohabation column and condensed in a horizontal shell and tube heat exchanger. The distillate and collected oil are separated in a receiver/separator. The distillate is recycled to the distillation tank through the cohobation column from the receiver/separator. After completing the 4 hours of distillation, steam is injected into the steam jacket to boil the residual water that collects at the bottom of the alembic. The process continues for another 4 hours. The collected oil is dried over anhydrous sodium sulfate (Babu & Kaul, 2005).

3.5. Pelargonium Pharmaceutical Formulations

3.5.1. Formulation of Hedera Helix Extract, Pelargonium sidoides Extract and Zingiber officinale Extract

The formulation aims to administer orally, parenterally, ocularly, nasally, buccally, sublingually, and topically, with the oral being the preferred route. The volume of *Zingiber officinale* must be preferably 0%, 1%–4% w/v. The formulation contains at least one propolis extract, *Glycyrrhiza glabra*, and *Echinacea purpurea* (Cifter *et al*., 2014):

1) If the formulation contains propolis extract, the weight ratio of the *Hedera helix, Pelargonium sidoides, Zingiber officinale*, and propolis extracts is 6:10:4:1, respectively.
2) If the formulation contains *Glycyrrhiza glabra*, the weight ratio of the *Hedera helix, Pelargonium sidoides, Zingiber officinale*, and *Glycyrrhiza glabra* extracts is 7:12:5:5, respectively.
3) If the formulation contains *Echinacea purpurea* the weight ratio of the *Hedera helix, Pelargonium sidoides, Zingiber officinale*, and *Echinacea purpurea extracts* is 7:12:5:8, respectively.
4) If the formulation contains *Hedera helix, Pelargonium sidoides, Zingiber officinale*, propolis, and *Glycyrrhiza glabra* extracts, the weight ratio is 6:10:4:1:4, respectively.
5) If the formulation contains *Hedera helix, Pelargonium sidoides, Zingiber officinale*, propolis, and *Echinacea purpurea* extracts, the weight ratio is 6:10:4:1:7, respectively.
6) If the formulation contains *Hedera helix, Pelargonium sidoides, Zingiber officinale*, *Glycyrrhiza glabra*, and *Echinacea purpurea extracts*, the weight ratio is 7:12:5:5:8, respectively (Nadjib *et al*., 2010).

The formulation must also contain 10%–25% w/v sorbitol, citric acid monohydrate, and sodium citrate dehydrate with a weight ratio of 1:2, 0.05%–2% eucalyptus, 0.005%–10% w/v of a sweetener such as; sucralose, saccharin sucrose, fructose, glucose, sorbitol, or a mixture of these, and solvents such as; propylene glycol, glycerin, water or ethanol or a mixture of them (Cifter *et al*., 2014).

One method to elaborate the formulation consists of adding every solvent to the fabrication container and mixing until obtaining a homogeneous mixture (A mixture). Then, add the inactive ingredients to the container carrying the A mixture and mix until obtaining a homogeneous mixture (B mixture). Then incorporate the extracts of the herb-based substances into the B mixture and mix until obtaining a homogeneous mixture (C mixture). Finally, the C mixture can become a different dosage (Cifter *et al*., 2014).

3.5.2. Formulation of Emulsion for Topical Use, Based on Aromatic Water of Pelargonium graveolens

A semi-solid formulation of the hydrophilic emulsion type is made. The oil phase (30%) contains; 10%–15% paraffin oil, 5% white wax, 4% stearic acid, 4% cetyl alcohol, and 1%–2% cetostearyl alcohol. And the aqueous phase (70%) contains; 65% geranium hydrosol (aromatic geranium water), 4%–5% glycerin, and 0.3%–2% triethanolamine. The protocol used is that of a conventional emulsion, where the two phases (oily and aqueous) are prepared at 70 °C separately and mixed by applying agitation. Then, a preservative is added to guarantee sterility, and it is packaged in aluminum tubes (Nadjib *et al*., 2010).

3.5.3. Solid Formulation Made from Pelargonium sidoides Extracts and Silicic Acid Compounds

As a first step, the extract of *Pelargonium sidoides* is made. The plant's dried roots are cut to a size of about 10 mm or less, dipped in 35% ethanol. 5.3% ethanol is added in a volume of approximately eight times that of the dried root. Subsequently, the liquid extract is filtered. Then, it is sterilized at 120–121 °C for 30 seconds and cooled (Choi *et al*., 2016).

The development of the solid formulation that includes extract of *Pelargonium sidoides* and a compound of silicic acid consists of; placing the previously made extract in conjunction with a silicic acid compound in a high-speed mixer and mixing them together to adsorb the extract of *Pelargonium sidoides* on the silicic acid compound. Subsequently, microcrystalline cellulose, hydrated lactose, and povidone are added and mixed. The obtained mixture is dried and sieved. Then, croscarmellose sodium, colloidal silicon dioxide, and sodium stearyl fumarate are added to the sieved product and mixed. The obtained mixture is compressed in a tableting machine. Finally, coating the tablets with Opadry is performed (Choi *et al*., 2016).

3.5.4. Formulation of Herbal Supplements Made from Geranio Pelargonium

One or more crushing plants of the Geranium or *Pelargonium* genus are used, and water and alcohol are added to obtain a mixture that is then refluxed. The mixture is extracted to separate the essential oil phase from the aqueous phase. The aqueous phase is concentrated and dried to obtain a powder. The purified essential oil is combined with the powder to obtain the extract. This method (or modifications thereof) can be used to obtain an extract containing at least 1% methylhexaneamine (Akrong *et al*., 2012). Examples (Akrong *et al*., 2012):

1) Dietary supplement for appetite suppression: It is prepared as a powder to mix with water and consumed twice a day. One serving (about 8 g) contains 6 g Inulin Root (*Cichorium intybus*), 150 mg Anhydrous Caffeine, 10 mg Psyllium Powder Seed Husk (*Plantago ovata*), 10 mg Oat Powder (*Avena sativa*), 5.3 mg of methylhexaneamine (obtained from the extract of Geranium or *Pelargonium*), excipients and flavorings.
2) Pre-exercise supplement: Prepared as a powder to administer before exercise, 1 to 3 servings (tablespoon/serving) contain; 120 mg of caffeine, 5.3 mg of methylhexaneamine (obtained from Geranium or *Pelargonium* extract), 1 g of B-alanine, 1 g of citrulline, and 1 g of creatine.

4. Conclusion

Pelargonium is a genus with many species, widely characterized in taxonomy, phylogeny, distribution, and traditional uses. Among the most relevant *Pelargonium* species are *Pelargonium sidoides* and *Pelargonium reniforme*, which have a wide range of biological properties and are therefore helpful in the pharmaceutical and food areas, especially the standardized pharmacological extract EPs® 7630 that is currently widely used in the health area, mainly as immunomodulatory and antiviral. However, it is necessary to carry out more clinical studies that contribute to evaluating the other pharmacological properties that have been described, and based on this, analyze different pharmaceutical formulations with the potential to be introduced in the pharmaceutical industry.

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Conflict of Interest

The author declares that there is no conflict of interest.

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