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Review Article

Traditional Uses, Botany, Phytochemistry, and Pharmacology of *Pelargonium graveolens*: A Comprehensive Review

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ABSTRACT

Pelargonium graveolens (PG) is a popular medicinal plant, widely used in Africa for centuries to treat various diseases. Because of its wide exploitation, the therapeutic studies of *P. graveolens* keep penetrating. This research engulfs a comprehension of all previous studies related to this medicinal herb, where it summaries and evaluates the traditional uses, the botany, the phytochemistry, the pharmacology, and the toxicology of *P. graveolens*. A literature review was conducted through the classic books of herbs, medicine, PhD papers, and online scientific databases, searching up to January 2022. This review analyzes all literature on the research subject. Our main findings are: (1) more than 290 biochemical components have been identified from *P. graveolens*, counting terpenoids, flavonoids, steroids, alkaloids and other composites. (2) Terpenoids are the most significant biologically active matter detected in this plant. (3) Extracts and compounds of *P. graveolens* exert a wide range of pharmacological effects. Study of the plant's toxicological effects has also been restricted as well. *P. graveolens* has potential in the treatment of numerous ailments, particularly cancers and diabetes. Current investigations confirmed that much traditional uses of *P. graveolens* has been corroborated by current studies. However, contemporary reports on its pharmacological impacts are not deep enough, and its underlying mechanisms for the cure of tumours and diabetes should be further elucidated.

***Keywords*:** *Pelargonium graveolens*, Pharmacological activity, Traditional usages, Flavonoids, Alkaloids.

Introduction

Pelargonium graveolens, also known as, Rose-scented geranium, is a herbaceous flowering plant belonging to the Geraniaceae family,[1] native to southern Africa,[2,3] that has been introduced to Australia, eastern Africa, New Zealand, the Middle East and the islands of Madagascar, St. Helena, Europa and North Africa.[4] Surprisingly, this plant is not only a decorative plant, but it also has high medicinal properties.[5,6] In South Africa, *P. graveolens* extract is intricated in approximately 50 patents of health products, used for the treatment of numerous maladies such as alopecia, diabetes, asthma, tumours, inflammation, fever, pain and skin disorders.[7] *P. graveolens* was first documented by the French botanist, Charles L'Heritieron, and discoursed in subsequent generations of traditional African medicine monographs.[8] But in terms of its function, the indications mainly revolve around healing of wounds and other skin disorders. In modern studies on infected skin wounds, pharmacodynamic studies have confirmed that *P. graveolens* is effective in the treatment of infected male Wistar rats.[9] Today, with the rising prevalence of diabetes, the medicinal value of this plant is receiving increased consideration. The clinical application of *P. graveolens* is in constant growth in tandem with the advancement of chemical composition and pharmacological research. Moreover, the product is inexpensive, widely available, and has promising clinical applications.

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A large number of modern studies, ranging from botany to phytochemistry and pharmacology, have confirmed that *P. graveolens* has a wide range of pharmacological effects, including hypoglycemic, anti-tumor, anti-inflammatory, hepatoprotective, antioxidant and antibacterial.[5] Phytochemical research has also identified more than 290 chemical substances in *P. graveolens*, including flavonoids, terpenoids, alkaloids and so on. Conversely, limited articles have reviewed the inclusive research on *P. graveolens*. According to the accessible data, only its phytochemical and antibacterial activities have been investigated. This may not be sufficient for researchers to fully comprehend this plant. Researchers have insulated many new chemical components from *P. graveolens* in recent years, and conducted more in-depth studies on its anti-diabetic, anti-tumour, anti-inflammatory and hepatic-protecting pharmacological activities. Among them is an increase in research on biologically active ingredients and the analogous appliance of action. Additionally, from the standpoint of ethnopharmacology, its traditional uses should also be entirely esteemed. Moreover, it is of interest to improve medicinal plant quality control through homogeneous parting and analysis techniques. By providing an overview of botany, phytochemistry, and pharmacology, this paper delivers a comprehensive review of a wild plant that has sparked widespread intrest-*Pelargonium graveolens*, and challenges to guide readers to a better and more in-depth discernment of this remedial plant as well as provide overall information for better research and development of *P. graveolens*. The necessary traditional literature on *P. graveolens* were recovered from African medicine books to pursue the presentation in ethnopharmacology. A literature search was conducted by using online scientific databases, such as Web of Science, Google Scholar, CNKI, SciFinder, Science Direct, Scopus, Pubmed, NDLS and others utilizing different search terms such as "*Pelargonium graveolens*", "Geranium", "clinical observations", "traditional use", "phytochemistry", "pharmacology" and "toxicology". Additional information is collected from a series of related PhD publications in Korea and China via CNKI and NDLS database. Geranium's botanical name has been validated by http://www.theplantlist.org/, and is in legal condition. In addition to presenting information on the plant's

traditional uses, pharmacological reactions, and mechanisms, the botanical description and phytochemical compounds are introduced as well. The study of ethnopharmacology can widen contemporary pharmacology's innovative ideas. Diverse types of phytochemical compounds derived from *P. graveolens* as well as various medicinal attributes of the plant or plant parts, are detailed in different sections.

Pelargonium graveolens, taxonomy and botanical aspects
Taxonomy
The genus (*Pelargonium*) is comprised of approximately 283 recognized species.[10] Referring to the National Center for Biotechnology Information (NCBI), William Aiton reported on *Pelargonium graveolens* in Hortus Kewensis in 1789. Brawner mentioned in his comprehensive book in 2003 that *P. graveolens* was first classified by Linnaeus in the genus *Geranium* 1753. While the French botanist Charles L'Heritier initially described pelargoniums as a separate genus in 1787, this nomenclature was not broadly recognized for many years later, and pelargoniums were long connected with the common term geraniums.[8] *Geraniospermum terebintaceum* (Spreng.) *Kuntze and Geranium graveolens* (L'Hér.) *Thunb* as are listed as synonyms of *Pelargonium graveolens* in the World Checklist of Selected Plant Families (WCSP- in review). Morphologically, *P. graveolens* has several local forms that can be distinguished by other characteristics without affecting taxonomic identification.[11] The Genus *Pelargonium* is currently a member of the the *Geraniaceae* world-wide family, Order Geraniales The scientific names listed below are acceptable: *Geranium terebinthinaceum* Cav. and *Pelargonium terebinthinaceum* by iNaturalist and Tropicos considers *Pelargonium intermedium Kunth* to be a synonym of *P. graveolens*. This species has been studied and published primarily under the three Latin names: *Pelargonium graveolens, Pelargonium roseum* and *Pelargonium species.*

Botanical aspects
Pelargonium graveolens (Fig. 1) is an evergreen shrub plant with woody shoots at the base becoming softer towards the tips. It is a strongly aromatic perennial treated as an annual.[12] This shrub is ubiquitous in locations with low rainfall and low humidity,[4,13] in a multiplicity of surroundings, from rocky slopes to grasslands, forests and along streams, geranium naturally grows on roadside weed, ancient pastures, rock fissures on top of plains, riverbanks, and woods of limestone.[3,4] *Pelargonium graveolens* in particular, is the most widely spread of the ten *Pelargonium* species recognized in Algeria.[14]
Perennial development is perceived in damp, somewhat shaded environments. It is a perennial medium-lived shrub that grows to be around 4.9 feet (1.5 m) tall and 3.3 feet (1 m) wide. The roots are brown and flexible, with a strong stem that surfaces from the earth. The leaves are concentrated to scanty pubescent, tomentose, or hairy and have deeply cut blades. The plant blooms for roughly 6 months from late summer through mid-winter and blossoms almost continuously until it dies. Glomerulus flowers are white or pinkish with red streaks, and seeds ensure reproduction.[8] *Pelargonium graveolens* flowers all year round and provides nectar to bees and wasps making it useful for pollination in agro-ecosystems.[15, 16]

Traditional uses
Pelargonium graveolens has been used medicinally for centuries in Africa. The chief use is to treat digestive issues, wounds and respiratory diseases. Nevertheless, there are limited reports about its medical use outside Africa. With regard to the traditional medicine references, people use three methods to prepare different extracts from whole or partial plants: decoction, infusion, and juice. The root decoction, as depicted in Table 1, has been utilized to treat gastrointestinal diseases and respiratory tract infections, while the aerial portions are employed to treat skin diseases. The pertinent pharmacological underpinning for these indications is, in spite of that, frequently missing.
P. graveolens leaves are classified as a category 1 herb by the Botanical Safety Handbook, "if handled properly".[17] There is no information on contraindications to geranium. There are a few reports that topical geranium oil can cause contact dermatitis or sensitization (*Pelargonium sp.*),[6,18,19] or that handling the plant,[20-22] while other reports showed that the oil is non-allergenic and non-irritating.[18,19] Nevertheless, reports of adverse reactions are rare [6]. Aside from its medical significance, clear cosmetic values of geranium also have been confirmed. The powdered leaves were reportedly used as a deodorants by African members of African tribes.[6] In the Victorian era, the lemon leaf of geranium became a popular addition to finger bowls,[23,24] and table-top water bowls were used to keep hands clean and refreshed during meals. Geranium oil can be found in a wide range of commercial cosmetics, such as detergents, soaps, lotions, creams and perfumes.[25, 26]

Chemical constituents
Primary metabolites
Primary metabolites are key components for maintaining normal physiological processes. They include (carbohydrates, nucleotides, proteins, amino acids, ethanol, etc.) and their derivatives, some of which are converted into coenzymes (e.g. vitamins).[41]
Geranium comprises many primary metabolites. The ethanolic extract, for example, has a significant amount of carbohydrates (74 ± 8.27 mg glucose equivalent/g dw), and a maximum yield of protein was estimated (41.25 ± 0.49 mg/g dw), while the determination of chlorophylls was (2.24 ± 0.05 mg/g dw).[42] Amino-acids were quantified by Ali *et al*. as (387.72 $mg.g^{-1}$ DW).[43] The cells of plants like *P. graveolens* are known to contain high concentrations of polysaccharides.[44] The crude *Pelargonium graveolens* polysaccharide (CPGP) accounted for 87.27 % and had a total sugar content of 6.43%.[45] A total reducing sugars in the leaves was estimated to be approximately in the leaves (5.58 ± 0.13 mg/g fr wt, for total sugars, 2.43 ± 0.10 mg/g fr wt, for reducing sugars).[46]

Figure 1: Different parts of *Pelargonium graveolens* L'Hér. (1): aeriel parts – (2): Flowers and leaves – (3) Roots and stem.
Perennial development is perceived in damp, somewhat shaded environments. It is a perennial medium-lived shrub that grows to be around 4.9 feet (1.5 m) tall and 3.3 feet (1 m) wide. The roots are brown and flexible, with a strong stem that surfaces from the earth. The leaves are concentrated to scanty pubescent, tomentose, or hairy and have deeply cut blades. The plant blooms for roughly 6 months from late summer through mid-winter and blossoms almost continuously until it dies. Glomerulus flowers are white or pinkish with red streaks, and seeds ensure reproduction.[8] *Pelargonium graveolens* flowers all year round and provides nectar to bees and wasps making it useful for pollination in agro-ecosystems.[15, 16]

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Table 1: The traditional uses of *Pelargonium graveolens*

Traditional use	Part used	Mode of use	Population or geographic zone	References
Skin disorders				
Wounds	Aerial parts	Unspecified	Turkey (Atça) and Iran	[27, 28]
	Leaves	Pounded	South Africa	[29]
Wounds and boils	Leaves	A paste	Xhosa (Eastern Cape of S. Africa)	[7]
Skin sores	Leaves	Unspecified	Guatemala	[30]
		Wash	Botswana	[2]
Skin eruptions of cattle	Whole plant	Lotion	Botswana	[2]
Alopecia areata	Flowers	EO	Portugal	[31]
Entire body - general maladies				
Fever	Roots	Decoction (bath)	Natives of Lesotho	[11, 30]
Internal pain	Leaves	Mixed with two species	Central Chile	[32]
Headache	Leaves	Mixed with vinegar and salt	New Mexico	[33]
Backache	Roots	Infusion	Shona (Zimbabwe)	[2]
Earache	Warmed leaves	Inserted into the ear	New Mexico	[33]
Bruises and sprains	Leaves	Poultice	South-West Cape	[2]
Cervical cancer	EO	Applied locally	Hangzhou, China	[34]
		Unspecified	Ecuador	
Vision disorders				
Sore eyes	Leaves	Juice (eyewash)	East Africa	[2]
Night blindness (vitamin A deficiency)	Leaves	Unspecified	South America	[35]
Central and peripheral nervous system disorders				
Neuralgia	Leaves	EO	North America	[36]
Digestive system disorders				
Diarrhoea	Roots	Infusion (enema)	Zulu (S. Africa)	[2]
	Tuber	Decoction (boiled in milk)	South African Cape	
Dysentery, nausea	Leaves	Tea	Boers of S. Africa	[37]
			South Africa	[30]
Colic			Lesotho	[37]
Intestinal cramping and gas	Leaves	Infusion	South Africa	[29]
Constipated children	Leaves	Juice	Central Chile	[32]
Stomach cramps and vomiting	Leaves	Infusion	South African Cape	[2]
Hyperglycemia	Leaves	Decoction	Tunisia	[38]
Respiratory system disorders				
Cough, Carretones, Pencahue.	Flowers	Infusion	Central Chile	[32]
Colds, coughs and upper respiratory infections	Leaves and twigs	Decoction (inhalation)	South Africa	[4, 7, 11]
Sinusitis				[29]
Asthma	Unspecified	Burned and inhaled	Zulus, Boers and Cape Malays of Africa	[2]
Tuberculosis	Roots	Decoction	England and Switzerland	[39, 40]

El-Kareim *et al.* emphasized the existence of sugars including sucrose, fructose and glucose, and in lower amounts raffinose, galactose, mannose and xylose in smaller levels.[47] The crude protein of *P. graveolens* was measured at three cuttings treated with α–tocopherol and stigmasterol and the highest values were (2.190 mg/g fresh wt), while the highest Lipid peroxidation (TBARS) content was (2.470 n.mol MDA/g fresh wt).[48] The extract of acetone presented also a considerable content of lipid (0.07 ± 0.004 mg/g dw).[42] Besides, a putative transit peptide of 65 amino acids was successfully isolated from this species.[49] Concerning lipids, phospholipids, phytosterols and carotenoids have also been identified.[50-52] Regarding enzymes, farnesylpyrophosphate synthase (FPP), geranyl pyrophosphate (GPP), Secretory anionic isoperoxidase (PA1), and cationic isoperoxidase (PC3) was purified from *P. Graveolens.*[53-55]

Secondary metabolites

Secondary metabolites, are not required for plant growth, development, or reproduction. Secondary metabolites are a diverse group of active chemicals produced biosynthetically from primary metabolites.[56] For a given plant species growing in different areas, they vary in quality and quantity.[57,58] They are primarily involved in ecological interactions between plants and their environment, and they contribute to plant species defence and competitiveness plans.[56] These specialized metabolites frequently exhibit biological and medicinal features that are of great interest to humans.[59] Terpenoids, phenolic compounds and alkaloids are the three types of secondary metabolites explored in plants.[60] This plant is the most studied in its genera, owing to its extensive distribution and ease of collecting, as well as its noticeable biological activities. The geranium metabolome is mostly composed of terpenoids found in the essential oil, as well as other phenolic chemicals. A recent review on geranium highlights the "various biological activity discussions" reached. Asgarpanah and Ramezanloo recognized Barratta as the first to publish a work seeking to extract its essential oil and analyze its chemical composition in their work.[61] Much earlier in the same century, in 1957, Naves reported the first chemical analysis of *P. graveolens* EO,[62] upgraded later in 1969 by Kami *et al.*[63] The majority of the natural compounds of geranium are biosynthesized in glandular trichomes and accumulate in plastids located in plant cells.[64] Herein, the varied categories of secondary metabolites that are predominantly biosynthesized in geranium will be covered below.

Terpenoids of the essential oil

There are different ways to extract essential oils. The most prevalent extraction process is the hydro-distillation using a Clevenger equipment, which takes 3–4 h to extract a considerable quantity of EO. Other methods for obtaining volatile compounds include steam distillation and supercritical fluid extraction (SFE) under specified conditions. Because of their high efficiency, low energy consumption, short process length, and low environmental effect, microwave-assisted extraction (MAE) and ultrasound-assisted extraction (UAE) are regarded as the most promising extraction procedures.[65] In a different study, Junming and his team. utilised solid-phase microextraction (SPME).[66] The most often utilized method for identifying and quantifying geranium's volatile components is gas chromatography (GC) combined with mass spectrometry (MS).[67] The two-dimensional gas chromatography with quadrupole mass spectrometric detection (GC×GC-qMS) approach has also demonstrated to be to be rapid and sensitive for analyzing *P. graveolens* essential oil.[68]

Singh investigated geranium EO in 1916. At that moment, he discovered that this essential oil is the basic medium for the manufacture of rhodinol "citronellol" **(2)** and its esters.[68] Aside from phenolic compounds, the constituents of essential oils represent the most important chemical groupings, with hundreds of them having been identified. *P. graveolens* EO accounts for 0.15–0.34% (v/w) in green matter in harvests each year.[69,70] Terpenoids are bonded through head-to-tail bonds of isoprene units. Their biosynthesis occurs in nature by two distinct biochemical pathways: the 2C-methyl-d-erythritol-4-phosphate (MEP) pathway, discovered by Lichtenthaler, Rohmer, Arigoni, and Seto in the 1990s/2000s, and the mevalonic acid (MVA) pathway, discovered in the 1950s by Lynen, Bloch, and Cornforth, starting with the condensation of the five-carbon monomer isopentenyl diphosphate (IPP) to its isomer dimethylallyl diphosphate (DMAPP) (IPP).[105,106] It takes place, at least in part, in capitate glandular trichomes.[107] The essential oil of geranium is mostly formed by monoterpenes and sesquiterpenes. Each class is further classified into oxygenated terpenes and non-oxygenated terpenes. Oxygenated monoterpenes exist in a higher concentrations than non-oxygenated monoterpenes, with an average concentration ranging from (64.3-74.2%).[92, 108] Monoterpenes are predominantly represented by geraniol **(5)**, linalool **(7)**, and isomenthone **(93)** with up 83.0% (Tables 2 and 3). Anyhow, a variety of minority non-oxygenated terpenes including alcohols, aldehydes, acids, ketones or esters can be found in the essential oil of various cultivars.[63,72,82,86,87,92] Sesquiterpenes are represented by oxygenated and non-oxygenated compounds, but the non-oxygenated are the most abundant compounds of the essential oil, including δ-selinene **(202)** (up to 8.15%), *β*-caryophyllene **(160)** (up to 7.2%), guaia-6, 9-diene **(183)** (up to 6.58%), and α-humulene **(189)** (up to 6.1%) (Table. 4). Each cultivar of geranium contains an essential oil with its own chemical composition. Indeed, different cultivars of geranium growing on the same geographical area, with identical soil and climatic conditions, are able to produce different essential oils,[109,110] we talk about genetic chemotypes. Some terpenoids are chemical markers for cultivars identification,[111] citronellol **(2)**, geraniol **(5)**, linalool **(7)**, citronellyl formate **(33)**, geranyl formate **(51)**, isomenthone **(93)**, 10-epi-*γ*-eudesmol **(122)** and guaia-6, 9-diene **(183).**[112, 113] The cultivation area and the agroclimatic regions is also important parameter, which leads to changes in the essential oil composition. For example, a significant differences existed between the oil produced from plants grown in higher and lower altitude regions in India, especially in monoterpene contents.[77] Citronellol **(2)** dominated in some samples, geraniol **(5)** was the major terpene in others.[77] The complex composition of essential oils from geranium was collected in different localities in Palestine.[114] Many compounds have been found with considerable changes in the composition of the main terpenes. Other essential oil components found in geranium EO include hemiterpene esters, acids, aliphatic hydrocarbons and miscellaneous.[63, 90, 92, 99] Sulfur containing compounds, such as mintsulfide, and dimethyl sulfide were also detected in trace levels.[38, 63] These latter compounds are not exhaustively listed in this review.

Phenolic compound of geranium

Flavonoids and derivatives

Flavonoids are the most diverse and widely distributed phenolic compounds with different metabolic functions in plants. Structurally, they have a common basic frame consisting on three units organized in C6–C3–C6.[116] Flavonoids are synthetized through the combination of the phenylpropanoid and polyketide pathways. The starting point is the transformation of phenylalanine into p-coumaroyl CoA via cinnamic acid using the enzymes: phenylalanine ammonia lyase (PAL), cinnamate 4-hydroxylase (C4H), and 4-coumaroyl CoA ligase (4CL). Tyrosine ammonia lyase (TAL) converts the amino acid tyrosine directly to 4-coumaric acid in some plants. The activity of chalcone synthase (CHS) marks the start of the specific flavonoid pathway.[117] This enzyme is responsible for forming the two phenyl rings of the flavonoid skeleton from one p-coumaroyl-CoA and three malonyl-CoA molecules received via the polyketide pathway to form the two phenyl rings (C6- C3-C6). Chalcone isomerase (CHI), catalyzes The production of the heterocyclic C-ring, resulting in naringenin (flavanone) as an intermediate molecule.[117] It is from this basic frame that all other flavonoids will be formed. Geranium contains flavonoids from five different families: flavonols, flavanones, flavones, flavan-3-ols including some glycosides derivatives (Table 6, 7 and 8). Additionally, phenolic acids, anthocyanins, coumarins and tannins were also discovered.[54,118-120] The most flavonoids were found in the leaves, flowers and herbs of the ornemental and the medicinal plant.[121-123]

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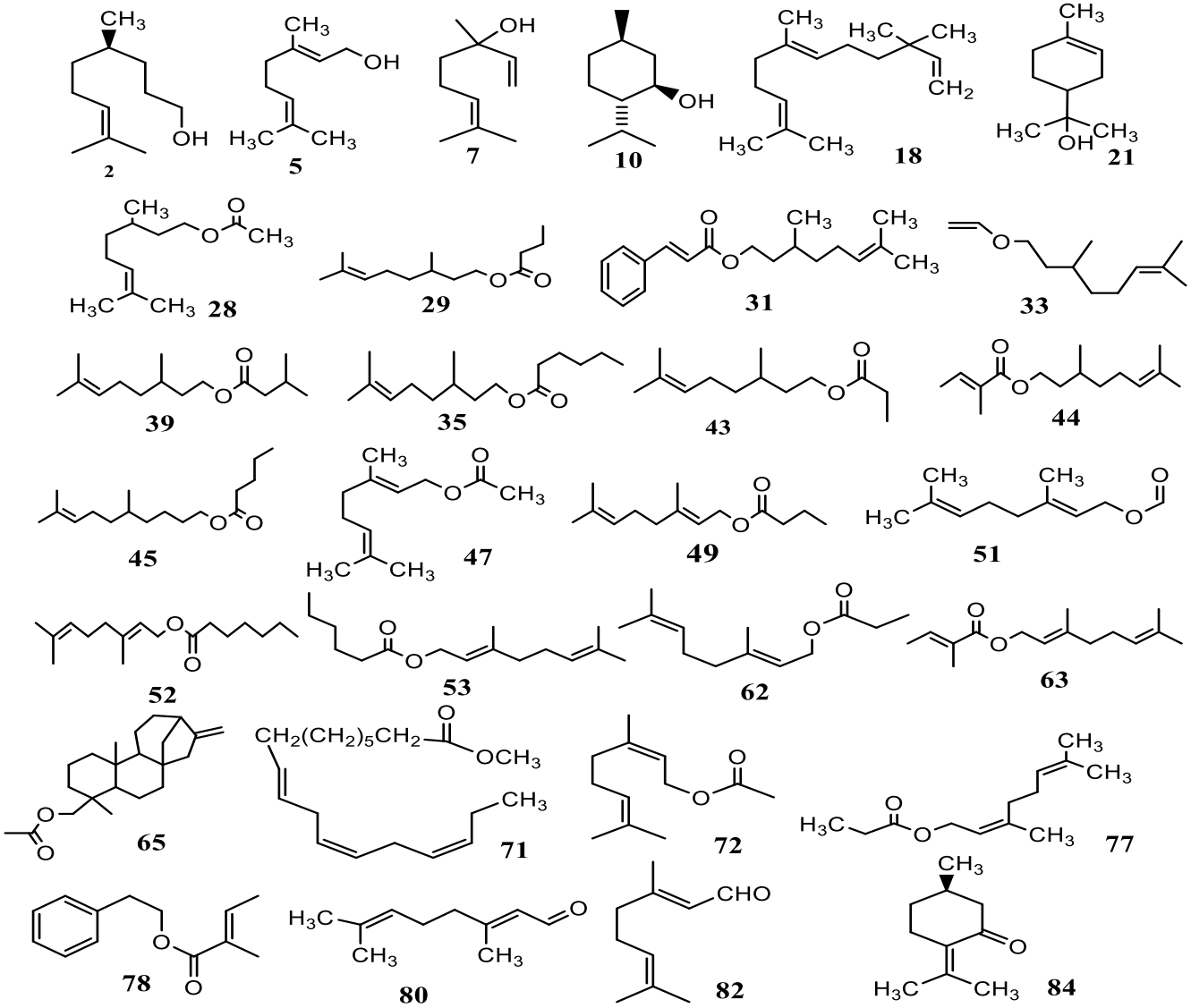
Table 2: Oxygenated monoterpenes found in *Pelargonium graveolens* (uniquely components with yields super than 1% are depicted).



N°	Name	Amount %	References
Alcohols			
1	Borneol	0.3	[71]
2	Citronellol	0.05-33.4	[38, 68, 71-99]
3	Elemol	0.2-0.40	[38, 92]
4	Eugenol	0.2-0.60	[100]
5	Geraniol	0.1-43.64	[38, 68, 71-73, 77-80, 82-98, 100, 101]
6	Lavandulol	0.1	[87]
7	Linalool	0.8-50.6	[38, 68, 71-73, 75, 77-85, 87-101]
8	Epoxylinalool	0.4	[72]
9	3-p-Menthanol	0.14	[38]
10	Menthol	0.2-1.2	[71-73, 86, 92, 98, 99]
11	Isomenthol	0.1-0.3	[71, 97]
12	Neomenthol	0.3	[71, 86]
13	neo-Isomenthol	0.6	[68, 71]
14	Menthomenthol	0.17	[91, 93]
15	8-Hydroxy-neomenthol	0.1	[97]
16	p-Menth-1-ene-8-ol	0.14	[101]
17	Myrtanol	0.22-2.23	[98, 99]
18	Nerolidol	0.6-1.6	[75]
19	Nerol	0.1-3.08	[38, 68, 77, 80, 83, 86, 87, 89]
20	Neo-isopulegol	0.1	[68, 97, 100]
21	α-terpineol	0.02-4.8	[38, 68, 71-73, 75, 80, 82, 84, 86, 90-94, 96-98, 100, 102]
22	Terpinen-4-ol	0.15	[68, 90]

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Oxides			
23	Geranic oxide limetol	0.2	[72]
24	cis-Linalool oxide	0.2-0.37	[68, 71, 80, 82-84, 86, 87, 89, 90, 92, 97, 98, 100, 101]
25	trans-Linalool oxide	0.1-0.18	[68, 71, 80, 83, 84, 86, 87, 89, 90, 92, 97, 98, 100, 101]
26	Nerol oxide	0.02	[102]
Carboxylic acids and esters			
27	Bornyl acetate	0.1-0.2	[71, 86]
28	citronellyl acetate	0.18-3.67	[68, 71, 80, 83, 86, 87, 89, 90, 94, 96-99, 101]
29	Citronellyl butanoate	0.3-1.5	[87, 92, 97, 100]
30	Citronellyl butyrate	0.07-1.7	[68, 80, 83, 84, 86, 90, 92, 94, 96, 98]
31	Citronellyl cinnamate	1.78	[99]
32	Citronellyl ester	1.1	[97]
33	Citronellyl formate	0.1-28.2	[38, 68, 71, 72, 74, 77, 79, 80, 82-85, 87-91, 93-96, 98, 100, 103]
34	Citronellyl heptanoate	0.3	[68, 97]
35	Citronellyl hexanoate	2.64	[68, 99]
36	Citronellyl isobutyrate	0.2	[97]
37	Citronellyl isoheptanoate	0.1-0.2	[86]
38	Citronellyl isohexanoate	0.1-0.2	[86]
39	Citronellyl isovalerate	0.1-10.41	[97, 99]
40	Citronellyl octanoate	0.3	[68, 97]
41	Citronellyl pentanoate	0.3	[97]
42	Citronellyl propanoate	0.3-1.0	[68, 87, 92, 94, 100]
43	Citronellyl propionate	0.03-1.4	[38, 71, 80, 83, 90, 96-98, 101]
44	Citronellyl tiglate	0.1-2.4	[80, 83, 84, 86, 90, 92, 96-98, 100]
45	Citronellyl valerate	0.1-1.4	[83, 86, 96, 99]
46	Ethyl geranate	0.2	[92]
47	Geranyl acetate	0.17-4.52	[68, 71, 80, 84, 86, 89-94, 96, 98, 101]
48	Geranyl butanoate	0.2-1.2	[87, 92, 97, 100]
49	Geranyl butyrate	0.1-3.50	[68, 78, 80, 82, 86, 88, 90, 94, 98, 99, 101]
50	Geranyl ester	0.5	[97]
51	Geranyl formate	0.03-27.6	[38, 71, 77-80, 83-85, 87-98, 100, 103]
52	Geranyl heptanoate	0.05-2.93	[68, 86, 89, 90, 97, 99]
53	Geranyl hexanoate	0.4-1.65	[68, 86, 97, 99, 101]
54	Geranyl isobutanoate	0.3	[92]
55	Geranyl isobutyrate	0.1-0.32	[84, 90]
56	Geranyl isoheptanoate	0.1	[86]
57	Geranyl isovalerate	0.1-0.5	[84, 86, 96]
58	Geranyl octanoate	0.3	[68, 86]
59	Geranyl-2-methylbutanoate	0.4	[97]
60	Geranyl pentanoate	0.7	[97]
61	Geranyl propanoate	0.6-0.8	[68, 92, 97]
62	Geranyl propionate	0.15-2.3	[71, 80, 84, 86, 89-91, 93, 95, 96, 98, 101]
63	Geranyl tiglate	1.1-4.99	[38, 68, 80, 83-85, 87, 89-94, 96-101, 103, 104]
64	Geranyl valerate	0.09-0.4	[68, 84, 86, 90, 92, 96]
65	Kauren-19-yl-acetate	1.43	[99]
66	Lavandulyl acetate	0.76	[38]
67	Lavandulyl-2-methylbutanoate	0.1	[97]
68	Linalyl propionate	0.06	[90]
69	Methyl citronellate	1.0	[92]
70	Methyl geranate	0.1	[97]
71	Methyl linolenate	1.87	[99]
72	Neryl acetate	0.2-2.32	[38, 84, 86, 87, 90, 91, 98, 99, 101]
73	Neryl formate	0.19-0.2	[80, 89, 92, 97]
74	Neryl hexanoate	2.98	[99]
75	Neryl isobutanoate	0.5	[87]
76	Neryl propanoate	1.5	[87]
77	Neryl propionate	4.79	[99]
78	Phenylethyl tiglate	0.3-2.3	[38, 68, 75, 80, 83-90, 92, 96, 98, 101]
Aldehydes and ketones			
79	1,8-cineol	0.03	[102]
80	Citral	0.38-2.4	[38, 72, 73, 91, 93, 95, 98]
81	Citronellal	0.2	[68, 92]
82	Geranial	0.37-3.0	[68, 71, 80, 84, 87, 90, 92, 96, 100]
83	Neral	0.04-0.9	[68, 80, 86, 92, 94, 96, 97]
84	Pulegone	1.3-1.9	[83]

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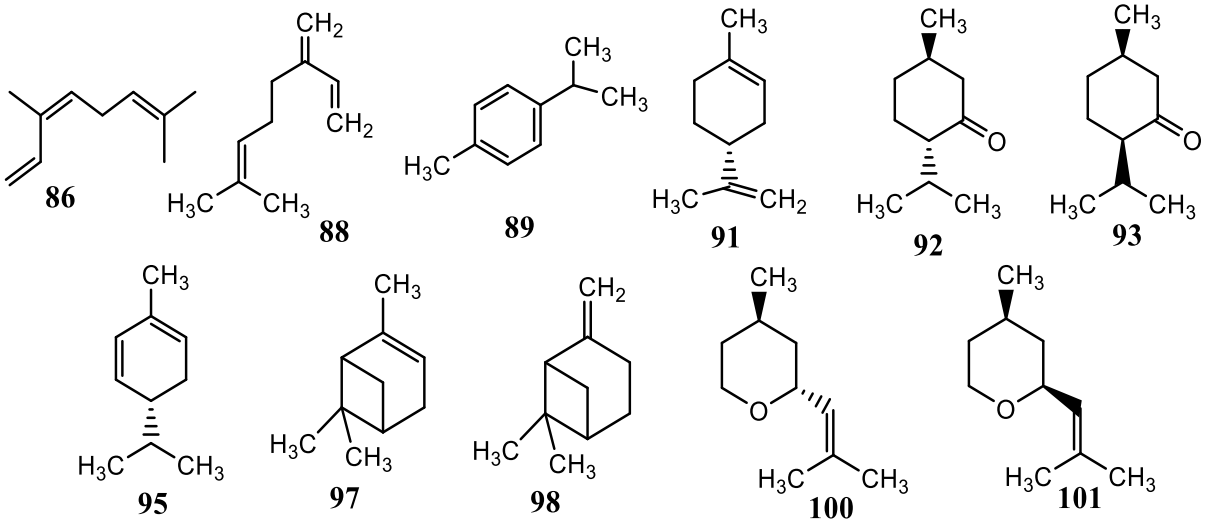
Table 3: Non-oxygenated monoterpenes found in *Pelargonium graveolens* (uniquely components with yields super than 1% are depicted).



N°	Name	Amount %	References
Acyclic monoterpene hydrocarbons			
85	6-Methyl-5-haptene-2-one	tr-0.9	[68, 72, 82, 86, 100]
86	cis-Ocimene	0.12-6.0	[38, 68, 71, 75, 80, 82-84, 86, 87, 90, 91, 93, 95, 102]
87	trans-Ocimene	0.24-0.6	[38, 68, 71, 75, 80, 82-84, 86, 87, 90, 102]
88	Myrcene	0.2-5.0	[38, 63, 68, 71, 72, 75, 76, 80, 82, 84, 86, 87, 89, 90, 97, 98, 100, 102]
Monocyclic monoterpenes			
89	p-Cymene	0.04-1.1	[68, 71, 72, 75, 80, 82, 84, 86, 87, 90, 96, 97, 99, 100, 102]
90	m-Cymene	tr	[92]
91	Limonene	0.19-7.3	[63, 68, 71, 72, 75, 78, 80, 82-84, 86, 87, 89, 90, 97-101]
92	Menthone	0.34-7.6	[38, 68, 71-73, 75-78, 80, 82-84, 86-89, 91-95, 97-102, 104]
93	Isomenthone	3.3-83.0	[68, 71, 72, 75-80, 83-91, 93-98, 100-103]
94	Perillene	tr	[102]
95	α-Phellandrene	0.09-13.0	[38, 68, 75, 80, 82, 83, 86, 87, 90, 92, 100, 102]
96	β-Phellandrene	0.7-0.9	[68, 71, 75, 83, 86, 96, 100]
97	α-Pinene	0.2-9.6	[38, 63, 68, 71, 72, 75, 76, 78, 83, 84, 86, 87, 89-98, 100-102]
98	β-Pinene	0.12-3.6	[63, 75, 78, 80, 82, 83]
99	Piperitone	0.1-0.8	[68, 71, 75, 83, 86, 96, 100]
100	cis- Roseoxide	0.05-1.19	[68, 71, 72, 77, 80, 83-85, 87-94, 96-98, 100]
101	trans- Roseoxide	0.04-1.77	[38, 68, 71, 72, 77, 80, 83, 84, 87-98, 100]
102	γ-Terpinene	tr	[97]
103	Terpinolene	0.1-0.2	[68, 84, 87, 90]
Bicycle monoterpenes			
104	Camphene	tr	[63, 92]
105	δ –3- Carene	0.07	[91, 93]
106	1,8-epoxy-p-menth-2-ene	Tr	[102]
107	Sabinene	Tr-0.17	[63, 71, 83, 84, 90]
108	Tricyclene	0.2-0.4	[75]

Flavanones and flavones and flavan-3-ols

In many plants, the enzyme chalcone isomerase (CHI) with a ketone group on the C4 position cyclizes an unstable chalcones to the corresponding 4', 5, 7-trihydroxyflavanone. Flavanones are the progenitors of all other flavonoid classes, making them the foundation of flavonoid.[124] Flavones are formed from flavanones by a set of enzymes known as flavone synthase introducing a double bond between the C-2 and C-3 sites (FNS).[125] The flavanones geranium are represented by the prenylated molecule, cirsimaritin **(210)** and hesperidin **(212).**[126] In geranium, the few abundance of flavanones may be related to the following prenylation and methylation of the A-ring, as well as the plant's hydrophobic cellular environment, which would tend to hinder isomerization into flavanones.[127] Flavanone hexoside **(211)**, the only glycoside flavanone that has been isolated up to now in geranium.[120] Some minor flavones have also been identified in geranium as diosmetin **(213)** and luteolin **(214)** in leaves extracts.[123, 128] Depending on the stereochemistry of the asymmetric carbons on the C3-ring, flavan-3-ols may have two distinct biosynthetic antecedents. They are among the last molecules generated in the flavonoid pathway. They can be produced by reducing flavan-3,4-diols formed from the initial reduction of dihydroflavonols; or by reducing an anthocyanidol after oxidation of flavan-3,4-diol.[129] In Geranium, flavan-3-ols are represented, among others, by catechin **(206)** presented with an important amount (9.80 $.10^{-3}$ mg/g f.t), epigallocatechin **(207)**, dimer **(208)** and trimer epigallocatechin **(209)**.[120, 126]

Flavonols and their glycosides

Flavonols derive from flavanones after two reaction steps (Fig. 3). First, the C3 position on the central ring is hydroxylated by the flavanone 3-hydroxylase (F3H) to form a dihydroflavonol. In a second step, a flavonol synthase (FLS), introduces a double bond between the C2 and C3 positions.[131] In more than 90% of cases, the first ring of the flavonols is hydroxylated at the C5 and C7 positions; other substitutions may vary and may also be glycosylated.[132] Aglycones of flavonols encountered in geranium are the common quercetin **(219)**, myricetin **(218)**, kaempferol **(217)**, and ayanin **(215).**[123, 133, 134]

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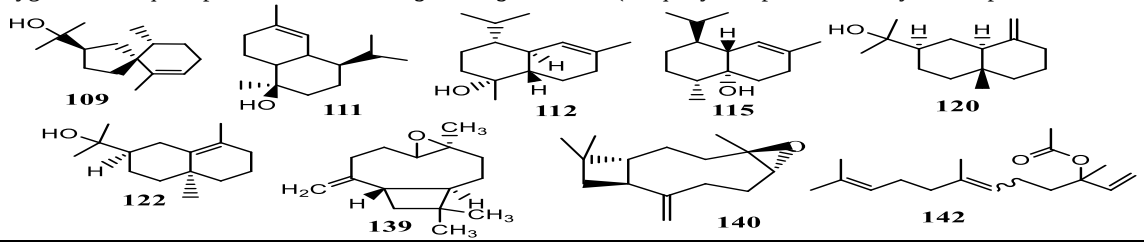
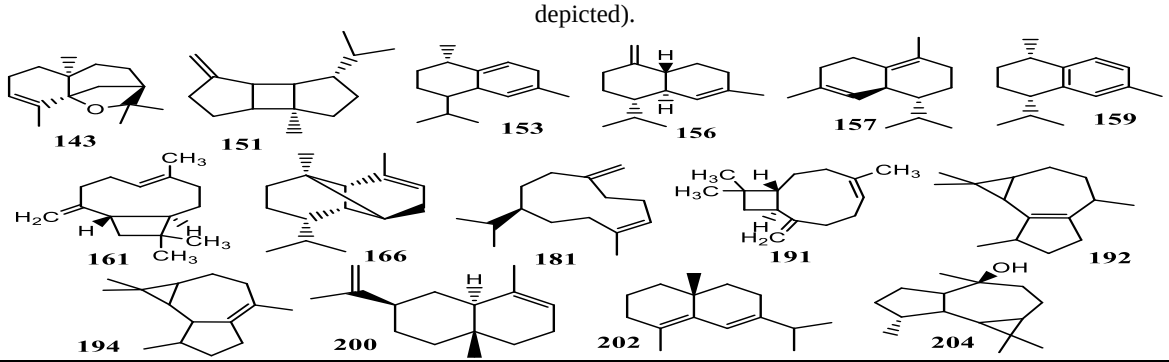
Table 4: Oxygenated sesquiterpenes found in *Pelargonium graveolens* (uniquely components with yields super than 1% are depicted).



N°	Name	Amount %	References
Alcohols			
109	Agarospirol	0.46-1.14	[38, 101]
110	α-Cadinol	0.3-0.6	[92, 93, 97]
111	*epi*-α-Cadinol	0.5-1.1	[92]
112	τ- Cadinol	0.07-1.21	[90, 91, 93]
113	Caryophylla-4(12),8(13)-dien-5-ol	0.4	[97]
114	α-Costol	0.2	[82]
115	Cubenol	0.26-1.44	[98, 99]
116	1-*epi*-Cubenol	0.2-0.99	[82, 97, 99, 100]
117	1,10-di-*epi*-Cubenol	0.2-0.4	[92, 97]
118	Cubedol	0.12	[98]
119	α- Eudesmol	0.1-0.65	[86, 88]
120	β- Eudesmol	0.1-1.3	[84, 86, 92, 95, 98, 100]
121	γ-Eudesmol	0.12-0.3	[68, 92, 93, 96, 100]
122	10-epi-γ-Eudesmol	0.7-8.27	[68, 80, 83, 84, 86, 89, 90, 92, 95, 96, 98, 101]
123	2Z, 6E-Farnesol	0.6-1.0	[92]
124	Globulol	0.2-1.67	[92, 98, 101]
125	Guaiol	0.12	[98]
126	Heptaminol	2.92	[99]
127	Hinesol	0.2-0.4	[68, 92, 100]
128	neo-Isopulegol	0.1	[97]
129	Junenol	0.2	[97]
130	Ledol	0.15	[91, 93]
131	Maaliol	0.1	[97]
132	α- Muurolol	0.4-0.70	[86]
133	τ- Muurolol	0.6	[97]
134	(E)-Nerolidol	0.1-3.2	[83, 86, 90, 92]
135	Spathulenol	0.1-0.5	[86, 92, 97, 98]
136	Valerianol	0.4-1.2	[92, 100]
137	Viridiflorol	0.5	[97]
Epoxides			
138	Alloaromadendrene oxide	0.2	[98]
139	Caryophyllene oxide	0.1-3.7	[86, 94, 96-98]
140	Caryophyllene epoxide	3.63	[99]
141	Humulene epoxide II	1.0	[97]
Esters			
142	Nerolidyl acetate	2.18	[99]

Table 5: Non-oxygenated sesquiterpenes found in *Pelargonium graveolens* (uniquely components with yields super than 1% are depicted).



N°	Name	Amount %	References
143	α- Agarofuran	0.19-1.28	[38, 68, 91-93, 95, 100]
144	α- Amorphene	Tr-0.29	[38, 92, 97]
145	δ- Amorphene	tr	[92]
146	Aristolene	0.45	[101]
147	Aromadendrene	0.68-0.1	[38, 68, 91-93, 95, 97, 98]

148	allo-Aromadendrene	0.1-0.69	[68, 71, 86, 90, 96, 97, 100]
149	trans-α-Bergamotene	0.10	[68, 115]
150	Bicyclogermacrene	0.20	[92]
151	β-Bourbonene	0.1-3.14	[38, 68, 71, 80, 82, 84, 87, 90-93, 95-98, 100, 101]
152	Cadalene	0.2	[97]
153	Cadina-1,4-diene	0.25-1.4	[91-93]
154	α- Cadinene	0.56	[90]
155	β- Cadinene	0.33	[98]
156	γ-Cadinene	0.1-2.89	[75, 84, 86, 90, 92, 95, 97, 98, 101]
157	δ- Cadinene	0.2-3.2	[38, 68, 86, 91-96, 98, 100]
158	α-Calacorene	0.2	[97]
159	Calamenene	0.1-1.3	[68, 82, 84, 96-98]
160	α -Caryophyllene	0.37-0.9	[95, 96]
161	β-Caryophyllene	0.15-7.2	[68, 71, 78, 80, 82-84, 86, 88, 90, 92, 94, 96, 100]
162	γ -Caryophyllene	0.6	[96]
163	(E)-Caryophyllene	0.33-1.63	[38, 87, 91, 95, 97, 98, 101]
164	(Z)-Caryophyllene	0.1	[97]
165	α- Cofaene	0.5	[94]
166	α-Copaene	0.10-1.60	[68, 71, 80, 84, 86, 87, 90-93, 95-97, 99-101]
167	β-Copaene	0.2-0.4	[75, 97]
168	α-Cubebene	0.11-0.96	[38, 68, 71, 84, 86, 91, 93, 95-98, 100, 101]
169	β-Cubebene	0.18-0.64	[38, 95, 98]
170	β-Cuvebene	0.32	[38]
171	β-Elemene	0.1-0.6	[75, 92, 97, 98]
172	γ- Elemene	0.05-0.38	[90, 92, 98]
173	trans-β-Elemenone	0.1-0.8	[92]
174	Epizonaren	0.24-0.42	[38, 95]
175	(E)-β-Farnesene	0.13	[90]
176	2-epi-β-Funebrene	tr	[92]
177	Furopelargone A	0.5	[115]
178	Furopelargone B	0.4-0.9	[86, 87]
179	Germacrene A	tr	[92]
180	Germacrene B	1.25-0.4	[68, 92, 101]
181	Germacrene D	0.06-4.33	[38, 68, 71, 75, 76, 80, 82-87, 91, 93-96, 98, 100, 101]
182	Germacrone	0.1-6.1	[92]
183	Guaia-6,9-diene	0.06-6.58	[71, 80, 83-88, 90, 92, 96, 98, 100]
184	α- Guaiene	0.1-0.5	[68, 92, 96, 98, 100]
185	cis-β- Guaiene	0.2-0.21	[97, 98]
186	α- Gurjunene	0.1-0.55	[38, 97]
187	γ –Gurjunene	0.9	[92]
188	α-Himachalene	1.57	[99]
189	α-Humulene	0.08-6.1	[38, 68, 71, 80, 82, 84, 86, 87, 90-94, 97, 98, 101]
190	14-Hydroxy-9-epi-(E)-caryophyllene	0.6	[97]
191	Isocaryophyllene	3.77	[99]
192	Isoledene	0.47-1.18	[38, 95, 98]
193	Isolongifolene	0.54	[95]
194	Ledene	0.5-3.10	[38, 82, 91, 93, 98]
195	cis-Muurola-3,5-diene	0.4	[97]
196	cis-Muurola-4(14),5-diene	0.1	[97]
197	α- Muurolene	0.1-0.44	[38, 84, 86, 92, 95-97]
198	γ-Muurolene	0.1-0.8	[68, 71, 86, 92, 98]
199	Selina-3,7(11)-diene	0.1	[92]
200	α- Selinene	0.04-6.6	[82, 90, 96]
201	β- Selinene	Tr-0.31	[38, 82, 86, 98]
202	δ-Selinene	8.15-8.69	[38, 91, 93]
203	Valencene	0.32	[93]
204	Viridiflorol	2.35	[95]
205	α- Ylangene	0.04-0.36	[68, 80, 84, 88, 90, 96, 97]

In the majority of situations, their hydroxylated substitutions form heterosidic linkages (Table 7). A number of quercetin, myricetin and kaempferol glycosides were recently identified in geranium using HPLC–PDA–ESI–MS/MS, however the nature of sugars has not been thoroughly elucidated. Further, flavonol glycosides have been revealed as the most abundant category of flavonoids in leaves.[122] They can also be detected in rose.[121]

Phenolic acids

On the aromatic ring, phenolic acids have at least one hydroxyl group and one carboxylic function. In strict sense, this phrase refers to compounds in the C6-C1 range. There are, however numerous variants of C6–C1 to C6–C3. They can be unesterified, esterified, or glycosylated. The basic structure remains constant; the variation is due to the position and the amount of substituents in the aromatic ring.[135] The most common phenolic acids are derived from benzoic acid (C6–C1) or cinnamic acid (C6–C3), and are referred to as hydroxybenzoic acids or hydroxycinnamic acids, respectively.[136] Their metabolic origin is determined by the precursors. The phenylpropanoid route produces hydroxycinnamic acids by first converting L- phenylalanine to cinnamic acid, which is subsequently hydroxylated to make p-coumaric acid.[136] Caffeic acid **(255)**, ferulic acid **(259)**, and rosmarinic acid (260) are the most common hydroxycinnamic acids in geranium.[118,128] Hydroxybenzoic acids can be produced in in a variety of pathway.

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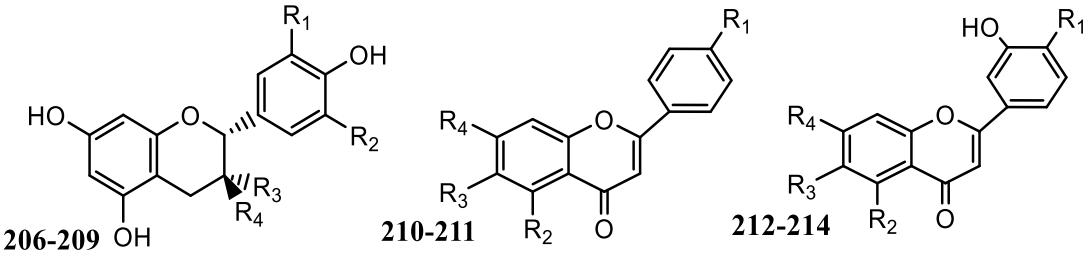
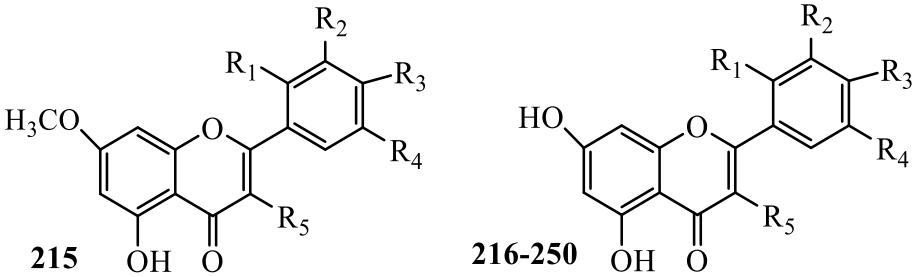
Table 6: Flavan-3-ols, flavonones and flavones found in *P. graveolens*



N°	Name	R_1	R_2	R_3	R_4	Amount (Mg/g f.t)	References
Flavan-3-ols							
206	Catechin	H	OH	H	OH	$9.80 .10^{-3}$	[126, 130]
207	Epigallocatechin	OH	OH	OH	H	-	[120, 130]
208	Epigallocatechin dimer	OH	OH	$O(Cat)_1$	H	-	[120]
209	Epigallocatechin trimer	OH	OH	$O(Cat)_2$	H	-	[120]
Flavanones							
210	Cirsimaritin	OH	OH	OCH_3	OCH_3	-	[121]
211	Flavanone hexoside	H	H	H	Hexoside	-	[120]
212	Hesperidin	OCH_3	OH	H	Man-Glu	$3.0 .10^{-6}$	[126]
Flavones							
213	Diosmetin	OCH_3	OH	H	OH	-	[128]
214	Luteolin	OH	OH	H	OH	-	[123]

Table 7: Flavonols and their glycosides found in geranium (Glu glucose, Rha rhamnose, Gal galactose).



N°	Name	R_1	R_2	R_3	R_4	R_5	Amount (Mg/g f.t)	References
Flavonols								
215	Ayanin	H	H	OCH_3	OH	OCH_3	-	[134]
216	Isorhamnetin	H	OCH_3	OH	H	OH	-	[38]
217	Kaempferol	H	H	OH	H	OH	$1.04 .10^{-6}$	[123, 133]
218	Myricetin	H	OH	OH	OH	OH	-	[120, 123, 126, 133]
219	Quercetin	H	OH	OH	H	OH	$2.29 .10^{-6}$	[123, 126, 133]
Flavonol Glycosides								
220	Astragalin (Kaempferol 3,7-di-O-glu)	H	H	OH	H	Glu	-	[38]
221	Hyperoside (Quercetin 3-O-gal)	H	H	OH	OH	O-Gal	-	[120]
222	Kaempferol 3-O-glu	H	H	OH	H	O-Glu	$89.0 .10^{-3}$	[38, 120, 121]
223	Kaempferol hexoside	H	H	OH	H	Hexoside	$14.7 .10^{-3}$	[121]
224	Kaempferol-hexose-rha	H	H	OH	H	Hex-Rha	-	[133]
225	Kaempferol -O-pentose -O-glucuronic acid	H	H	OH	H	O-Pent-O-Glu	$19.7 .10^{-3}$	[121]
226	Kaempferol 3-O- rha-glu	H	H	OH	H	O-Rha-Glu	-	[38, 121]
227	kaempferol-3,4´-dimethyl ether	H	H	OCH_3	OH	OCH_3	-	[134]
228	kaempferol-3,7- dimethyl ether	H	OCH_3	OH	H	OCH_3	-	[134]
229	Kaempferol-3-methyl ether	H	H	OH	H	OCH_3	-	[134]
230	Kaempferol 3-O-pentoside	H	H	OH	H	O-Pent	-	[120, 121]
231	Myricetin 3-O-gal	H	OH	OH	OH	O-Gal	-	[120]
232	Myricetin 3-O-glu	H	OH	OH	OH	O-Glu	-	[120]
233	Myricetin 3-O-glu-rha	H	OH	OH	OH	O-Glu-Rha	-	[38]
234	Myricetin-hexose	H	OH	OH	OH	Hexose	-	[133]
235	Myricetin-pentose	H	OH	OH	OH	Pentose	-	[133]
236	Myricetin-rhamnose	H	OH	OH	OH	Rha	-	[133]
237	Myricetin 3-O-rhamnosyl (1 → 6) hex	H	OH	OH	OH	O-Rha-O-hex	-	[120, 133]

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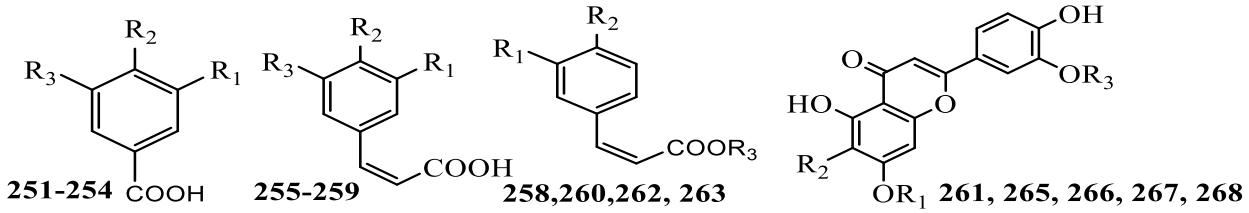
238	Myricitrin (Myricetin 3-O-rha)	H	OH	OH	OH	O-Rha	-	[120]
239	Quercetin-3-O-arabinoside	H	OH	OH	H	O-Ara	-	[121]
240	Quercetin-3-O-hexoside	H	OH	OH	H	O-hex	$7.0 .10^{-3}$	[121]
241	Quercetin 3-O-pent-glu	H	OH	OH	H	O-pent-glu	-	[38]
242	Quercetin 3-O-glu	H	OH	OH	H	O-glu	$7.4 .10^{-3}$	[38, 120, 121]
243	Quercetin 3-O-pentosyl (1 → 2) hex	H	OH	OH	H	O-pent- hex	-	[120, 133]
244	Quercetin 3-O-pent	H	OH	OH	H	O-pent	-	[38, 120, 133]
245	Quercetin 3-O-rham (1 → 6) hexoside	H	OH	OH	H	O-Rha-hexoside	-	[120]
246	Quercetin-hexose-rha	H	OH	OH	H	O-hex- Rha	-	[121, 133]
247	Quercetin-3,3- dimethyl ether	H	H	OH	OCH_3	OCH_3	-	[134]
248	Rutin (quercetin-3-rutinoside)	H	OH	OH	H	O- Rhu	14.0	[38, 121, 122, 126]
249	Retusin (quercetin-3, 7, 3,4-tetramethyl ether)	H	OCH_3	OCH_3	H	OCH_3	-	[134]
250	Trifolin (Kaempferol 3-*O*-gal)	H	H	OH	H	O-Gal	-	[120]

Table 8: Phenolic acid derivatives detected in geranium



N°	Name	R_1	R_2	R_3	Amount (Mg/g f.t)	References
Benzoic acid derivatives						
251	Benzoic acid	H	H	H	16.76	[118]
252	Gallic acid	OH	OH	OH	$0.61 .10^{-6}$	[126, 138]
253	Protocatechuic acid	OH	OH	H	-	[128]
254	Methylated protocatechuic acid hexose	Hex	OCH_3	H		[120]
Cinnamic acid derivatives						
255	Caffeic acid	OH	OH	H	0.6902	[118, 126]
256	Coumaric acid hexose ester	H	O-hex	H	-	[120]
257	Coumaric acid pentose ester	H	O-pent	H	-	[120]
258	p-Coumaroylquinic acid	H	OH	O-coumaroyl	-	[128]
259	Ferulic acid	OCH_3	OH	H	0.0824	[118]
260	Rosmarinic acid	OH	OH	2,4-dihydroxyphenyl ester	-	[128]
Glycoside derivatives						
261	Acacetin- 7-O-β-D-glucoside	oxychromenone	H	CH_3	-	[138]
262	Caffeoyl glucarate isomers	OH	OH	trihydroxyhexanedioic acid	-	[133]
263	Caffeoyl hexoside	OH	OH	O-hexoside	-	[121]
264	Hexose	-	-	-	$5.3 .10^{-3}$	[121]
265	Luteolin acetylglucuronide	H	H	dihydroxyoxane-2-carboxylic acid	-	[128]
266	Luteolin *p*-coumarylglucoside	H	H	coumarylglucoside	-	[128]
267	Luteolin 3′-O-glucuronide	H	O-Glu	H	-	[128]
268	Scutellarein-7-O-β-glucuronide	O-Glu	OH	H	-	[121]

For the most basic, they are biosynthesized from dehydroshikimic acid at the start of the shikimate pathway; others are formed by a CoA ligase converting cinnamoyl-CoA ahead in the phenylpropanoid pathway.
The addition of various ingredients is subsequently catalyzed by different enzymes.[137] Among the hydroxybenzoic acids found in geranium are benzoic acid **(251)**, gallic acid **(252)** and protocatechuic acid **(253)**.[126, 128,138] Different phenolic acid derivatives identified in geranium is summarized in Table 8.

Tannins
Flavan-3-ol monomers can produce oligomers or polymers with variable binding modes and degrees of polymerization, known as proanthocyanidins or condensed tannins, the most common of which is a catechin derivatives (prodelphinidin) **(271).**[123,139] Table 9 listes the tannins found in geranium. Cinnamate 4-hydroxylase, a P450 monooxygenase, catalyzes the conversion of cinnamic acid to 4-coumaric acid.

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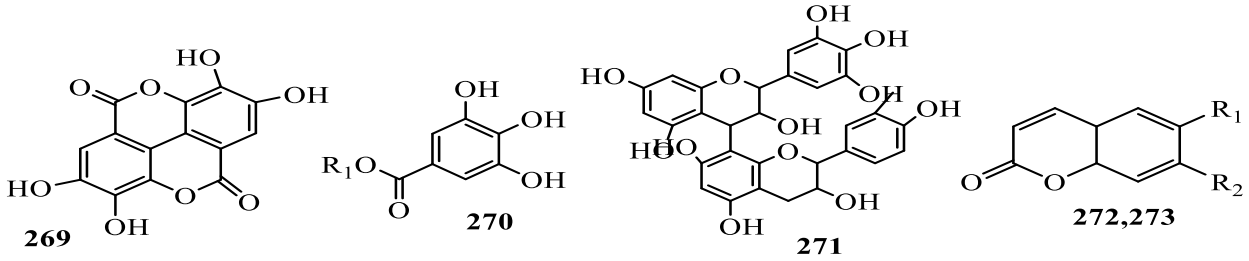
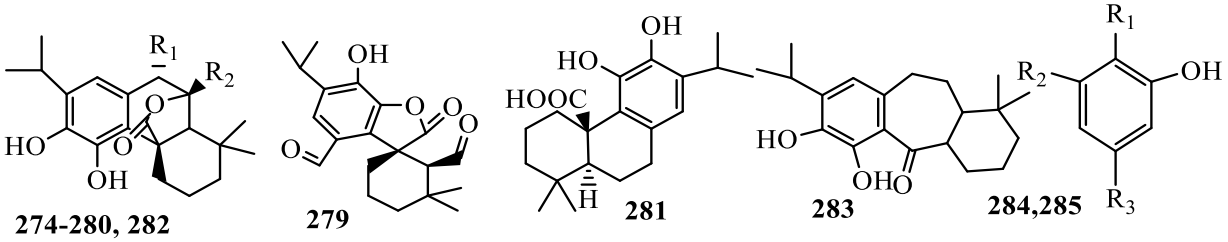
Table 9: Tannins and coumarins identified in geranium



N°	Name	R_1	R_2	R_3	Amount	References
Tannins						
269	Ellagic acid	-	-	-	-	[123]
270	Glucogallin	Glu	-	-	-	[120]
271	Prodelphinidin				-	[123]
Hydroxycoumarins						
272	Esculetin	OH	OH	-	-	[54]
273	Scopoletin	OCH_3	OH	-	-	[54]

Table 10: More phenolic compounds identified in geranium



N°	Name	R_1	R_2	R_3	Amount	References
Diterpene lactones						
274	Carnosol	H	H	-	-	[128]
275	Epirosmanol	OH	H	-	-	[128]
276	6,7-Dimethoxy-7 Epirosmanol	OCH_3	OCH_3	-	-	[128]**Error! Bookmark not defined.**
277	11,12-Dimethyl Rosmanol	CH_3	CH_3	-	-	[128]
278	7-Methyl- Rosmanol	OH	H	-	-	[128]
279	Rosmadial	-	-	-	-	[128]
280	Rosmanol	OH	H	-	-	[128]
Benzenediol abietane						
281	Carnosic acid	-	-	-	-	[128]
282	Isorosmanol	H	OH	-	-	[128]
283	Rosmaridiphenol	-	-	-	-	[128]
Dihydrochalcone						
284	Phloretin hexoside	O-hex	OH	OH	-	[120]
Phenol esters						
285	Guaiacol	OCH_3	H	H	-	[54]

This enzyme fraction was shown to slowly convert cinnamic acid to co-coumaric acid but to be more active in converting p-coumaric acid and ferulic acid to scopoletin **(273)**.[140] The hydroxylation of umbelliferone by a P450 monooxygenase was used to investigate the synthesis of esculetin **(272)**.[140]

Other phenolics found in geranium

Recently, various lactone and chalcone compounds have been discovered in geranium.[120, 128] The presence of some abietanes was noted in leaves and herbs: isorosmanol **(282)** and rosmaridiphenol **(283),** as well as a phenol ester: guaiacol **(285)**.[54] Table 10 lists more phenolic compound groupings.

Alkaloids and nitrogen components

Alkaloids sensus stricto, are molecules that behave like bases, have at least one nitrogen in their heterocycle, and are biosynthetically derived from amino acids.[141] They have high pharmacological qualities in general; some of them are utilized to cure cancer or have beneficial effects on the brain.[142] Richard *et al.* (2011) have first noticed some alkaloids in geranium. Arassu *et al.* (2014) recently isolated four alkaloids, including dimeric alkaloids vinblastine and vincristine **(297–298)** (Table 11). Ajmalicine **(286)** is one of the most important monoterpenoid indole alkaloids is found in geranium. Aside from the above information and the articles reported from authors about alkaloids, very little is known about their amounts and none was fully elucidated, despite its widespread identification and characterisation.

Pharmacological and toxicological reports

Pharmacological reports

According to a review of the literature survey, *Pelargonium graveolens* has been studied in a variety of pharmacological domains, including analgesic, antiinflammatory, antibacterial, antifungal, antidiarrheal, antiviral, and anti-oxidant effects. The known pharmacological trials with detailed conditions are listed in tables Table 12, 13, 14 and 15. This review summarizes the more relevant activities of this compounds. Emphasis is placed on essential oil and terpenoids.

Activity against harmful microorganisms

PG's antipathogenic microorganism actions have received more attention, and its antibacterial, antiviral, and antifungal properties have been well investigated and proven. Importantly, oxygenated compounds have been recognized as the primary active in this plant (Table 12).

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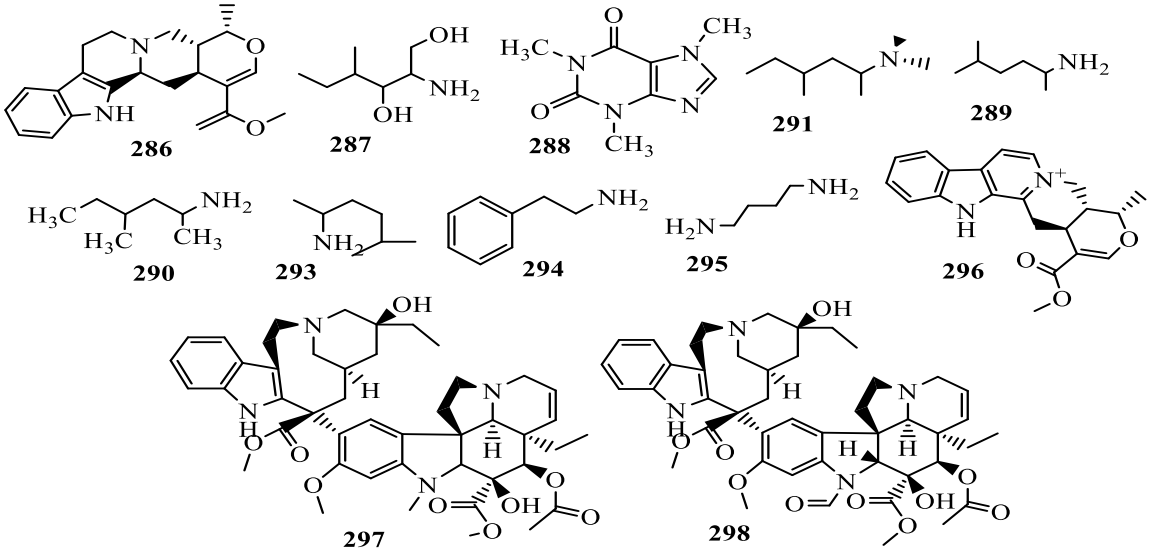
Table 11: Alkaloids and nitrogen compounds identified in geranium



N°	Name	Amount	References
286	Ajmalicine	-	[143]
287	2-Amino-4-methylhexane	-	[144]
288	Caffeine	-	[144]
289	1,3-dimethylamylamine	-	[144, 145]
290	1,3-dimethylpentylamine	2 ng/g	[144, 146]
291	Geranamine	-	[144]
292	Methylhexaneamine	-	[144]
293	4-Methyl-2- hexylamine	-	[144]
294	Phenylethylamine	-	[144]
295	Putrescine	40 mg L^{-1}	[147]
296	Serpentine	-	[143]
297	Vinblastine	-	[143]
298	Vincristine	-	[143]

Table 12: Anti-pathogenic microorganism activities of geranium

Pathogenic microorganism	Extract/ compounds	*In vivo/ In vitro*	Mechanism	Minimal active concentration/dose	Reference
Acinetobacter baumannii	EO	*in vitro*	Not mentioned	MIC = 0,4-1,75 % (V/V)	[149]
Adenovirus	EO	*in vitro*	Prevent viral entrance into the host cell by interacting with viral attachment factors and/or membrane fusion proteins.	Positive control against serial concentrations of AdV (30 µL) (10^4-10^9 PFU/mL)	[121]
	Eth-ex			+ (10^4-10^8 PFU/mL)	
Aeromonas hydrophila	EO	*in vitro*	Injuring membranes by increasing membrane lipid fluidity and modifying membrane protein structure.	8.89 µg/ml	[161]
Bacillus cereus	EO	*in vitro*	Not mentioned	10 mg/ml	[93]
	EtOac			0.039 mg/ml	
	MeOH			0.156 mg/ml	
Bacillus subtilis	EO		Not mentioned	5 mg/ml	[93]
	EtOAc			0.156 mg/ml	
	MeOH			0.078 mg/ml	
Citrobacter freundii	EO	*in vitro*	Not mentioned	MIC = 1-2 % (V/V)	[149]
Citrobacter koseri	EO	*in vitro*	Not mentioned	MIC = 1-2 % (V/V)	[149]
COVID-19	EO	*in vitro*	Inhibition of ACE2 and TMPRSS2 receptor activation in SARS-COV2 virus–host epithelial cells without cytotoxicity.	IC_{50} = >200 µg/mL Selected Dose = 50 µg/mL	[136]
Enterobacter cloacae	EO	*in vitro*	Not mentioned	MIC = 1-1,75 % (V/V)	[149]
Enterobacter sakazakii	EO	*in vitro*	Not mentioned	MIC = 0,3-1,5 % (V/V)	[149]
Enterococcus faecalis	EO	*in vitro*	Not mentioned	2.5 mg/ml	[93]
	Etoac			1.25 mg/ml	
Escherichia coli	Eth-ex	*in vitro*	DNA cleavage	25.00 mg/mL	[162]

Helicobacter pylori	MeOH	*in-vitro and in vitro*	chelating the co-factor nickel of the pathogen	MIC=15.63 µg/ml IC_{50}= 31.05 µg/mL for urease	[153, 154]
Influenza virus	EO	*in vitro*	Activities Against Viral HA (Hemagglutinin) and NA (Neuraminidase) proteins of the influenza virus	TC_{50}= 67.46 (µL/mL)	[163]
Klebsiella oxytoca	EO	*in vitro*	Not mentioned	MIC =1,5-3 % (V/V)	[149]
Klebsiella pneumoniae	EO	*in vitro*	interference with the lipid bilayer of the bacterium by virtue of its hydrophobic property destruction of the genetic material, leading to the death of the bacteria	MIC = 5 µL/mL)	[164]
Listeria monocytogenes	EO EtOac MeOH	*in vitro*	Not mentioned	2.5 mg/ml 2.5 mg/ml 0.156 mg/ml	[93]
Lymphatic filariasis	EO	*in vitro*	Acute toxicity against the larvae of the filariasis vector Culex quinquefasciatus	LC_{50} = 98.4 µL/L	[165]
Mariniluteicoccus fla vus	EO	*in vitro*	Interfering with the development of Z-rings in order to inhibit the cell division protein.	MIC = 0.12 mg/mL	[151]
Micrococcus luteus	EO EtOac MeOH	*in vitro*	Not mentioned	10 mg/ml 2.5 mg/ml 0.31 mg/ml	[93]
Proteus mirabilis	EO	*in vitro*	inhibiting MDR efflux systems in bacteria	MIC = 0.25 mg/mL	[166]
Pseudomonas aeruginosa	EO	*in vitro*	DNA cleavage	MIC = 1,75-2 % (V/V)	[149, 162]
	ext			MIC= 0.78 mg/mL	
Ross River virus infection RRV - T48	EO	*in vitro*	Inhibition viral RRV-renLuc replication and infectivity	CC_{10} = 533 µg.mL^{-1}	[158]
Salmonella enterica	EO EtOac MeOH	*in vitro*	Not mentioned	5 mg/ml 0.312 mg/ml 0.078 mg/ml	[93]
Salmonella typhimurium	acetone extract	*in vitro*	Stimulation of the HaCaT cells Regulation of the immune response	1.56 mg/mL	[152]
Staphylococcus aureus	EO	*in vitro*	different mechanisms of drug resistance, within prevents biofilm formation	0.25-2.5 µL/mL	[150]
Staphylococcus epidermidis	EO	*in vitro*	Not mentioned	MIC = 0,05-0,85 % (V/V)	[149]
Staphylococcus saprophyticus	EO	*in vitro*	Not mentioned	MIC = 0,1-1 % (V/V)	[149]
Streptococcus agalactiae	EO	*in vitro*	Destroying the structure of the bacterial cell membrane and impeding protein and DNA synthesis.	MIC= 0,01-0,2 % (V/V)	[149, 162]
	EtEx			0.78 mg/mL	
Streptococcus salivarius	EO	*in vitro*	inhibition of biofilm strains	0.36 mg/mL	[148]
Streptococcus sanguinis	EO	*in vitro*	inhibition of biofilm strains	2.22 mg/mL	[148]

Antibacterial effect

Antibacterial activities of geranium are exploited historically against food spoilage pathogens. The food industry still uses it for the same reasons, in addition to the plant's role in the flavour of aliments. The volatile oil and different extracts of geranium was screened against 31 microorganisms of significant importance (Table 12). A high antimicrobial potential of geranium EO has been proved, in some cases exceeding that of traditional medications,[148] although the results and conclusions were mainly based on ATCC strains. Geranium EO high in monoterpenes and sesquiterpenes has long been known to have antibacterial properties against Gram-positive bacteria. Gram-positive (G+) bacteria including *Streptococcus agalactiae*, *Staphylococcus aureus, S. epidermidis, S. saprophyticus, S. salivarius, Streptococcus sanguinis, Bacillus cereus, B. subtilis, Enterococcus faecalis, Listeria monocytogenes, Mariniluteicoccus flavus* and *Micrococcus luteus* can be inhibited by Geranium EO.[148-151] Besides, antibacterial potential against Gram-negative strains is mainly linked to non prenylated flavonoids such as flavonols, flavan-3-ols and tannins, phenolic acids which is enhanced by the degree of hydrophobicity of these compounds, contributing to their interaction with the bacterial membrane.[121] Geranium EO contributes to antibacterial activities to a lesser level, with a slight-to-moderate activity against some Gram-negative bacteria such as *Acinetobacter baumannii, A. hydrophila, Citrobacter freundii, C. koseri, Enterobacter cloacae, E. sakazakii, E. coli, Helicobacter pylori, Klebsiella oxytoca, K. pneumonia, Proteus mirabilis, P. aeruginosa, Salmonella enterica,* and *Salmonella typhimurium*.[149,152-154] Previous research linked the effects of *P. graveolens* and its active constituents to the cell membrane damage, the inhibition of protein and DNA synthesis. The of Geranium extracts had a higher antibacterial effect against G+ bacteria than against G- bacteria, which can be explicated by the pathogens' differing cell membrane architecture.[155]

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Table 13: Cardiovascular system protection effects of geranium

Pharmacological effects	Extract/ compounds	Material or model	Mechanism	Dose	Reference
Lipid lowering effect	EO	the effect of SNP protozoan model (T. pyriformis)	Increase lipid peroxidation and catalase and SOD enzymatic activity.	Reducing SOD release by 69.1% SOD = 1414.66 ± 5.50 µmol/mg protein CAT = 120.66 ± 1.15 µmol/mg protein	[174]
Hypolipidemic Effect	Geraniol	Measuring the total serum cholesterol in NIH female mice bearing the nu/nu genotype.	A549 heteroplastoma inhibited 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and reduced blood cholesterol levels.	cholesterol synthesis reduced by 55% in A549 cells compared to controls (29 ± 7 vs. 13 ± 4 dpm/µg cellular protein)	[173]
Synergetic cholesterol-lowering effects	Linalool	HC diet mice HepG2 Human cell	Reduce Binding of SREBP-2 to the HMGCR promoter	*in-vivo*: 120 mg/mouse/; in vitro: 0.5 mM	[172]
Anti-hyperlipidemia	Linalool	3T3-L1 cell line of mice	Inhibition of lipid production	(At C= 100 µg/mL)	[175]
Treating obesity	EO	High fat and high carbohydrate diet Male wistar rats with body weight 180 to 220 g,	Reducing the abdominal fat deposits and adiposity index without e difference in organ to body weight ratios	400 mg/kg /6 weeks	[176]
Healing atherosclerosis and other chronic inflammatory processes.	medicinal plant decoction	*in-vitro* model of RAW 264.7 murine macrophages exposed to pro-atherogenic conditions	preventing foam cell formation by different mechanisms	Cell viability = (40 µg plant mash/mL)	[133]
Anti-atherosclerosis	EO	*ex-vivo* model using macrophages derived from human monocytes (THP-1 cells) *In-vivo* model using brine shrimp.	Inhibiting oxidation and inflammation cytokine IL-6 and TNF-α	LC_{50}= 13.8 µg/mL LC_{50}= 13.8 µg/mL	[170]
Hepatoprotective activity	Eth Ex	treatment of mice with CCl_4 at dose of 500 mg/kg/day	prevent the liver injury induced by free radicals	Preservation of liver in 37.5 and 50 % of animals	[120]

Antiviral effect

Previous research has shown that *P. graveolens* inhibits respiratory syncytial virus, influenza virus, coronavirus and H1N1 neuraminidase (NA-1). Geranium oil with 0.3% inhibited influenza type A (H1N1) virus by 80% in-vitro and by 95% after 30 min of vapor exposure. It has not, however, been shown to be effective against influenza virus type A (H3N2).[156] Because ACE2 has unique mechanisms of enzymatic action and tissue distribution, inhibiting ACE2 or TMPRSS2 receptors could be a possible target for SARS-CoV prophylaxis. Thus, geranium essential oil decreased ACE2 activity substantially without causing cytotoxicity.[157] In addition, studies showed that the inhibitory effects of geranium against Ross River virus infection RRV-T48 with a CC_{10} equal to 533 $\mu g.mL^{-1}$.[158] Furthermore, Geranium may also inhibit adenovirus-signaling pathways that are required for virus gene expression by preventing viral entrance into A549 cells via specific interactions with viral attachment factors.[121] Geranium was also effective against yellow fever virus.[158]

Antifungal effect

Geranium had a mild inhibitory impact on *Candida albicans* when used alone; however, when combined with fluconazole, it resulted in 73.28 and 69.51 percent mortality of C. albicans cells after 3 h incubation and allowed for four to eightfold decreases in effective doses compared to MIC values.[159] Geranium's antifungal activity is based on its capacity to impede mitochondrial function, produce reactive oxygen species (ROS), limit growth and AFB1 synthesis, and target the cell wall integrity pathway.[160]

Cardiovascular system protection effects

Cardiovascular diseases (CVDs) affecting the heart or blood arteries are the main cause of death globally. CVDs are expected to kill about 23 million individuals per year by 2030.[167] Importantly, geranium has been shown to have considerable antiatherosclerotic, antihyperlipidemic, antidiabetic, and antihepatic steatotic effects on major CVD risk variables. Polyphenols in geranium have been proven in a recent research to protect against CVDs, such as, myocardial ischemia-reperfusion damage, heart failure, arrhythmia, and hypertension.[120, 168] (Table 13). Gernium showed also hepatoprotective activity induced by free radicals.[120] However, the precise mechanism responsible for the protection needs further investigation which could a warrant research in the future.

Anti-atherosclerotic effect

Atherosclerosis (AS) is most typically found in the subendothelial space (intima) of arteries and is caused by endothelial dysfunction and subendothelial lipoprotein retention.[169] Geranium and its primary terpenoids, including linalool and geraniol have been shown to diminish Dil-ox-LDL Uptake by RAW 264.7 Macrophages, reduce lipopolysaccharide-Induced NFkB activation in RAW-Blue Macrophages,[133] and halting chronic inflammatory processes reactions via preventing foam cell formation by different mechanisms,[170] Targeting macrophage, metabolism metabolism and responses to oxidative stress and inflammation in atherosclerosis may therefore, constitute a therapeutic strategy for addressing this condition. The accumulation of foam cells in the subendothelial region is a critical phase in the onset and progression of AS.

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Table 14: Antidiabetic effects of geranium

Pharmacological effects	Extract	Material or mode	Mechanism	Dose	Reference
hypoglycemic activity	EO	EO effects on blood glucose and hepatic glycogen levels in normal and alloxan-induced diabetic wistar rats.	Antioxidative stress via down regulating GPx and up-regulating cu-Zn SOD and CAT.	150 mg/kg 30 day	[38]
Antihyperglycemic activity	AE	*in vitro:* glucose oxidase method *in vivo:* Oral starch tolerance tests and oral glucose tolerance tests in Sprague-Dawley rats.	α-amylase and α-glucosidase inhibitors In vitro: dual inhibition of α-amylase and α-glucosidase Acute postprandial antihyperglycemic by reducing the overall glycemic excursions in OGTTs	*in-vitro* IC_{50}= 84.7 µg/ml In vivo 250 mg/kg, 165-min	[178]
Treating diabetic neuropathy	Nano emulsion	Murine RAW 264.7 cells	Deacrising the levels of IFNγ and caspase-3	MIC = 1.82 µg/ml	[180]

The formation of foam cells in the subendothelial area is a necessary phase in the development of AS. Geranium proved its efficacy to to inhibit foam cell development as well as lipid and cholesterol build-up.

Anti-hyperlipidemic effect

Hyperlipidaemia, described as elevated levels of blood lipids, is a well-known risk factor for cardiovascular diseases. The main fundamental mechanism of hyperlipidaemia resistance is related to suppressing and boosting lipid consumption, conversion, and excretion.[171] Linalool may lower plasma cholesterol levels by inhibiting the expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), a hepatic cholesterol production marker.[172] Moreover, geraniol altered cholesterogenesis by reducing the amount of expression of membrane-related Ras proteins in hetero-transplanted animals without affecting overall Ras protein levels.[173] Geranium could prevent oxidation of various low-density lipoprotein (LDL) forms by causing lipid peroxidation and enhancing catalase and SOD enzymatic activity.[174] According to the experimental findings shown above, entire plant extracts often have significantly greater hypolipidemic activity than single isolated components. The presence of polyphenols in the various extracts may account for this bioactivity. This characteristic may support the *P. graveolens's* traditionally claimed helpful effect in cardiovascular disease.[2]

Antidiabetic effects

Diabetes mellitus (DM) is now defined as altered lipid, protein, and carbohydrate metabolism, as well as an elevated risk of vascular disease consequences.[177] The reports explored *P. graveolens's* antidiabetic properties as well as possible action mechanisms.[38, 178] The current study clearly demonstrates that geranium and its components not only have significant hypoglycemic effects, reduce lipid peroxidation processes and boost antioxidant defense mechanisms.[175, 179] Geranium exerts anti-diabetic properties because it improves glucose metabolism and insulin resistance (IR), and it may aid in the prevention of diabetes problems caused by oxidative stress (Table 14). Diabetes is directly linked to inflammation and oxidation. Geranium therapy resulted in lower levels of proinflammatory cytokines such as TNF-a, IL-6, iNOS, and COX-2.[180] Notably, the combined inhibitory activity of geranium-based α-amylase and *in vitro* α-glucosidase was verified by a highly substantial and strong acute antihyperglycemic trend in starch-fed rats.[178] More importantly, its extract did not improve postprandial glycemic response to glucose load in fasting rats. Overall, *P. graveolens* represents a promising and significant plant option for combination medication therapy of prediabetes and type 2 diabetes. Insulin resistance (IR) is a pathological condition in which cells fail to respond to insulin's normal activity. IR raises the risk of pre-diabetes and type 2 diabetes. For 13 days, geranium at 65 mg/kg/day was helpful against IR syndrome symptoms and improved levels of IR indices such as body weight, hyperglycemia, hyperinsulinemia, and hypercholesterolemia.[28]

Anticancer effects

Cancer is the world's second largest cause of death, killing 10 million people by 2020. According to the World Health Organization, cancer is responsible for approximately one in every six deaths worldwide.
Geranium has been found in studies to be beneficial against several human malignancies, including bladder cancer, breast cancer, cervical cancer, cholangiocarcinoma, colon cancer, stomach cancer, leukemia, lung cancer, melanoma, and myeloma (Table 15). Geranium and its active components can help prevent cancer by decreasing tumor cell growth, causing apoptosis, limiting migration and invasion, and improving immunological function.

Inducing apoptosis

Geranium promotes apoptosis in human colon cancer cell line HT-29, leukemia cell lines ATL and MT-2, and breast cancer MCF-7 cells by creating ROS. Geranium induces apoptosis by using a variety of apoptosis-regulating signals. Geranium inhibits survivin production in MCF-7 gastric cancer cells by raising levels of apoptosis-related markers p53, caspase-3, mir-21, mir-92a, Bcl-2, and ki-67.[181] Linalool also boosted the expression of pro- apoptotic proteins (Bax and Bak) while decreasing the expression of anti-apoptotic factors (Bcl-2 and Bcl-xl) in the human glioblastoma U87-MG cell line, activating the intrinsic apoptosis pathway.[182] *In vitro* and *in vivo* models of S-180 tumor-bearing mice demonstrate that linalool's apoptotic and anti-proliferative actions are caused by increased ROS generation and reduced antioxidant enzyme activity.[183]

Cell cycle arrest

Geranium prevented the proliferation of T24 urinary bladder cells cancer by reducing the number of cells in the S and G2/M phases.[184] Geranium inhibits colon adenocarcinoma growth by inducing G2/M phase arrest.[185] Linalool, another geranium component, can also cause cell cycle halt in certain cancers,[186] demonstrated that linalool at 20, 40, and 80 µM concentrations triggered sub-G1 cell cycle arrest, resulting in DNA damage, in human prostate cancer cells (DU145) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Likewise, a recent article confirmed linalool's lethal activity in DU145 and PC-3 (human Caucasian prostate cancer) prostate cancer cells.[187] Furthermore, it inhibited the proliferation of melanoma MV3 cells with moderate cytotoxicity and produced cell cycle arrest at the G2/M transition, which was associated with attenuated CDK6 gene expression and MMP2 expression.[188]

Inhibiting tumour metastasis

MMPs and urokinase-type plasminogen activator (uPA) play key roles in tumor metastasis and angiogenesis, and inhibiting uPA and MMP can decrease cancer cell migration and invasion. Geranium inhibits MMP-2, MMP-9, and MMP-1 melanoma and breast cancer cells via the p38 MAPK, P13K-Akt, and NFjB signaling pathways.[189, 190] By stimulating cytokines, interferon (IFN), lymphocyte-activated killer cell synthesis, and natural killer (NK) cell proliferation, medicinal herbs can boost the body's immune function and promote tumor cell apoptosis.

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Table 15: Anticancer activities of geranium

Pharmacological effects	Extract	Material or mode	Mechanism	Dose	Reference
Treating breast cancer	EO	MCF-7 cells	Induction of cell cycle arrest and apoptosis	60 ± 2.1 µg/ml	[181]
		MDA-MB-231 cells	Anti-metastatic function anti-angiogenesis and cytotoxic potentials	4 µL/mL	[188]
		MCF-7 cells	Regulation of the AMPK/mTOR pathway	42.8, 90.2 and 73.9 µg/ml	[190]
Treating melanoma	EO	B16F10 cells	Inhibition of L-tyrosin hydroxylation and L-DOPA oxidation enzyme activity.	dose-dependent manner	[191]
		MV3 cells	Anti-metastatic function anti-angiogenesis and cytotoxic potentials	4 µL/mL	[188]
		SK-MEL-3	antioxidative activity and decreasing the tyrosinase activity	XTT_{50}= 45 µU/mL	[189]
Treating lung cancer	EthEx	A549 cells	growth inhibitory effect and larvicidal activities	46.72 µg/ml	[193]
Treating leukemia	EO	ATL cells	Inhibition of MT-2 caspase-dependent apoptotic cell death and constitutive Nκ-B activation.	IC_{50} = 0.022（v/v %)	[194]
		HL-60 cells (acute myeloid)	inhibition of promyelocytic leukemia cells	LC_{50} = 86.5 µg/ml	[101]
		NB4 cells		LC_{50} = 62.5 µg/ml	
Treating lung cancer	EO	NCI-H460 cells	Inducing cytotoxicity and DNA damage	GI_{50} = 81.4 ± 2.03 µg/ mL	[185]
Treating colon carcinoma	EO	HCT-15 cells	Inducing cytotoxicity and DNA damage	GI_{50} = 63.7 ± 1.39 µg/ mL	[185]
Treating colon adenocarcinoma	EO	HT-29 cells	suppress the prolifieration by inducing apoptosis	IC_{50} = 195.33 ± 5.4 µg/ml	[184]
Treating gastric cancer	EO	AGS cells	Anti-metastatic function anti-angiogenesis and cytotoxic potentials	4 µL/mL	[188]
Treating cervical carcinoma	EO	HeLa cells	Inducing cytotoxicity and DNA damage	GI_{50} = 70.9 ± 0.04 µg/ mL	[185]
Treating hepatocellular carcinoma	EO	HepG2 cells	Inducing cytotoxicity and DNA damage	GI_{50} = 93.9 ± 2.99 µg/ mL	[185]
Treating urinary bladder carcinoma	EO	T24 cells	Inhibition cell proliferation	IC_{50} = 270.13 ± 7.1 µg/ml	[184]

Importantly, geranium extract inhibited the phosphorylation of mTOR and its downstream effector 4E-BP1 in MCF-7 breast cancer cells.[190] Furthermore, geranium was able to reduce L-tyrosine hydroxylation and L-DOPA oxidation in B16F10 melanoma cells and tumor cell proliferation, implying that the mechanism may include the caspase-1/IL-1b inflammatory signaling axis being down-regulated.[191] Linalool has been demonstrated to reduce the expression of proliferation markers, such as NF-κB, TNF-α, IL-6, COX-2, prevent the overexpression of angiogenic factors such as vascular endothelial growth factor (VEGF), Transforming growth factor beta 1 (TGF-beta1) and increase apoptosis by inhibiting mutant p53 while simultaneously reducing anti-apoptotic factor (Bcl-2).[192] In the pharmaceutical industry, new drugs for cancer treatment are urgently needed. According to the current study, phytochemicals, particularly monoterpenes, interfere with many intracellular signaling pathways to promote autophagy and death in various types of cancer cells. Geranium exhibits anticancer properties in a range of cancer cell lines and via various biological processes. Geranium essential oil, in particular demonstrated potent cytotoxicity with LC_{50} values of 62.50 µg/ml in the NB4 cell line and 86.5 µg/ml in the HL-60 cell line. The components may be used in molecularly targeted therapy and palliative care for a variety of malignancies and inflammatory illnesses, when

NF-κB is activated. More research is needed to fully comprehend the mechanism of action of its extract in cancer cells. Furthermore, it might be interesting to investigate the effects of geranium in tumor-bearing animal models.

Toxicological reports

Pelargonium graveolens with caution should be used according to acute toxicity studies. Boukhatem *et al.* (2013) investigated the essential oil of the entire plant and reported an LD_{50} of 1,000 mg/kg body weight in mice (intra-peritoneal treatment) when geranium EO was given GRAS status (Generally Recognized As Safe) and and was allowed for food by the US Food and Drug Administration (FDA).[96]

The toxicity of various *Pelargonium* species was investigated in *vitro*. Lalli *et al.* measured toxicity using the IC_{50} value.[195] *Pelargonium graveolens* a relatively high IC_{50} value, indicating that it is relatively non-toxic. Besides, it was discovered that *P. graveolens* essential oil had a high protective effect against oxidative stress damage and that a daily dose of 67 mg/kg was adequate to minimize protein oxidation in the testis as well as oxidative stress and lipid peroxidation. This oil also improved sperm quality.[196] Toxicological studies did not detailed toxicity data, i.e, the organs impacted and the effects on biological parameters. There is currently no information on adverse reactions or toxicity associated with the use of *Pelargonium graveolens* in humans, other than the warning for the use of geranium during pregnancy.

Conclusion

Numerous reports designate that *Peargonium graveolens* comprehend significant secondary metabolites. So far, the investigation reports claim that *P. graveolens* is rich in terpenoids. Currently, modern pharmacological studies have confirmed the main traditional use of PG. Consequently, it is necessary to more study the chemical composition of additional components of this herb. In addition, *P. graveolens* along with its various active components has a broad-spectrum antibacterial activity, exhibiting as bacteriostasis at measly concentrations and sterilization at high ones. Moreover, PG, a natural chemical with either anti-inflammatory or anti-tumour activities, demonstrates a considerable potential for cancer curing. As a result, more investigations are needed to study the pharmacokinetics and characteristics of *P. graveolens*, and further supplementary research are needed to assess the possible efficacy and potential toxicity of PG and its active constituents on target organs.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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