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REVIEW ARTICLE

Bioactivity of the *Geranium* Genus: A Comprehensive Review

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Abstract: ***Background*:** Plants from the *Geranium* genus, which comprises about 400 species, have been used since ancient times in the practice of traditional medicines throughout the world. Therefore, herbal preparations based on *Geranium* species have found wide usage for the treatment of a variety of ailments. The aim of this work is to present a review, as comprehensive as possible, of the studies concerning different biological activities of *Geranium* species.

***Methods*:** Relevant data were obtained through systematic computer searches from major reputed scientific databases, particularly Web of Science and Scopus. Occasionally, information issued in primary sources not covered by these databases was also included provided published as peer-reviewed literature. This review covers the literature disclosed till the end of 2018.

***Results*:** Accompanying the increasing interest in herbal medicines in general, the evaluation of the biological properties of medicinal plants from the *Geranium* genus has been addressed thoroughly, mostly over the last two decades. *Geranium* species are endowed with a number of different biological activities. Herein, we present a survey of the results of the studies concerning these different biological activities.

***Conclusion*:** Most studies found in the literature effectively contribute to scientifically validate the beneficial properties of *Geranium* plants claimed by traditional medicines and medical herbalism and demonstrate that many of them possess evident therapeutic properties.

Keywords: *Geranium species*, medicinal plants, biological properties, species, herbalism, ailments.

1. INTRODUCTION

The use of plants as herbal medicines to treat the most varied ailments has run parallel to the development of human civilization. At the end of the last century, the World Health Organization estimated that about 80% of the world´s population depended on traditional medicines that largely involved the use of plant extracts or their active principles, for their primary healthcare needs [1]. Even presently, for millions of people, mainly in developing countries, traditional medicines in which herbal medicine is a core part are the main source of health care [2]. After a period in which the focus was on the use of synthetic drugs, the use and the popularity of herbal medicines, as one element of complementary and alternative medicines, is increasing worldwide [3, 4].

Although herbal preparations have been used for centuries and their properties recognized both by ancient traditional medicines and more contemporary herbalism practices, the scientific assessment of such alleged beneficial properties is essential for their corroboration. The main purpose of this work is to present a survey, as comprehensive as possible, of the scientific contributions to validate the use of plants from the *Geranium* genus with specific biological activities, both in traditional medicine and medical herbalism. Relevant data were obtained through systematic computer searches from major reputed scientific databases, particularly “Web of Science" and "Scopus”. Occasionally, information issued in primary sources not covered by these databases was also included provided published as peer-reviewed literature. Information disclosed in primary or secondary sources lacking these two requirements was not considered for inclusion in this review. Species that were not reported to be used in traditional medicine or herbalism practice but whose bioactivity is described based on *in vitro* or *in vivo* studies were also included in this survey in order to enlarge the body of knowledge on the biological activities of *Geranium* genus. This review covers the literature published until the end of 2018. The biological activities of *G. robertianum* were subject to a recent review and, therefore, only the information concerning this species which was published afterward was included herein [5].

The online database “The Plant List” was used to validate plant scientific names [6]. This helped to identify misspellings and the use of synonyms for different species. Species were excluded if there was confusion or imprecision in the botanical names. When an unequivocal validation was not possible, given the difficulty to retroactively clarify the correct name of the species studied, it was chosen to keep the name given by the authors in their work. Given the length of the manuscript, in the name of plants, the species authorities were omitted, and the designation of the genus abbreviated for simplicity.

2. BOTANICAL DESCRIPTION

The Geraniaceae family is composed of about 840 species [6]. These plants are annual or perennial herbs or shrubs that are distributed worldwide, mostly in temperate and subtropical regions [7, 8]. The species of this family are grouped into seven genera: *California*, *Erodium*, *Geranium*, *Hypseocharis*, *Monsonia*, *Pelargonium*

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and *Sarcocaulon*. The largest genus of this family is *Geranium,* comprising about 400 species [6], distributed throughout the world, mainly in temperate climates and in mountain conditions. The exceptions are only in tropical lowlands, deserts, and Polar Regions [9]. The name *Geranium*, which is derived from the Greek word "géranos" that means crane, results from the shape that the fruits of the species of this genus acquire resembling a crane beak [10]. These species, sometimes woody at the base, are herbaceous, annual, biennial or perennial plants. All have petiolate, palmately divided leaves, circular in form, with the divisions toothed or lobed. The flowers have five sepals, five equal petals that are often colored pink, purplish or bluish-pink, frequently with distinctive veining. Both the petioles and the sepals are usually hairy. The style divides into five stigmas, which open after the anthers have dehisced, thus avoiding self-pollination. The five mericarps, each containing a single seed, develop after fertilization of the flower. The method by which the seed discharge occurs is utilised to divide the genus *Geranium* into the three subgenera (*Geranium*, *Robertium,* and *Erodioideae*) [11].

3. MEDICINAL USES OF *GERANIUM* SPECIES

Geranium species have been used since ancient times in many parts of the world in the practice of different traditional medicine systems involving the use of herbal preparations, such as traditional Chinese medicine, Indian Ayurveda and various forms of indigenous medicine [12]. Accordingly, a relatively large number of plants from this genus have been reported for the treatment of a wide variety of conditions (Table **1**).

4. BIOLOGICAL ACTIVITY

Accompanying the increasing interest in herbal medicines in general, the evaluation of the properties of medicinal plants from the genus *Geranium* has been addressed thoroughly, mostly over the last two decades. It is now possible to find in the specialized literature many studies scrutinizing different biological properties of a relatively large group of species from this genus.

4.1. Anthelmintic Activity

Acharya *et al*. observed that the MeOH extract of *G. viscosissimum* leafs at a concentration of 50 mg/mL in DMSO was capable of 100% *in vitro* egg hatch inhibition of *Haemonchus contortus* (ED_{50} = 0.63 mg/mL) [93], a gastrointestinal nematode parasite that significantly constrains the profitability of livestock production systems [94].

A MeOH extract of *G. incanum*, obtained after sequential extraction of the plant with *n*-hexane, CH_2Cl_2 and EtOAc, was found to induce ~ 85% larval paralysis of *H. contortus* within 24 h of contact at a concentration of 20 mg/mL [95].

4.2. Antibacterial Activity

The antibacterial activity of the *Geranium* genus has been investigated in some extension. The extracts of about twenty species were tested against a large panel of representative Gram-positive (Supplementary Table **1**) [14, 26, 80, 96-117] and Gram-negative bacteria (Supplementary Table **2**) [14, 35, 92, 98-105, 108-113, 115-117], amongst which some important human pathogens, including methicillin-resistant *Staphylococcus aureus.* The studies involved mainly alcoholic and aqueous extracts of plants of various geographic origins. The disk diffusion test and the broth microdilution assay were the chief screening methods used to assess the antibacterial properties. The extracts were found to possess a broad spectrum of inhibitory activities, and, in the majority of cases, minimum inhibitory concentrations (MICs) were determined.

Contrary to the solid-liquid extracts, the antibacterial activity of essential oils from *Geranium* species has been much less explored. Several essential oils, obtained by hydrodistillation, were assayed against Gram-positive (Table **2**) and Gram-negative bacteria (Table **3**), including several plant pathogens. The majority of them displayed inhibitory activity and MICs were determined for all screened positive essential oils.

4.3. Anticancer Activity

The first investigation of the anticancer properties of a specimen from *Geranium* genus seems to have been carried out by Kosuge *et al.* with *G. nepalense* [41]. In a survey of ninety-one species of Chinese herbs with alleged anticancer properties, the MeOH and water extracts of *G. nepalense* were among the few to shown significantly *in vitro* cytotoxic activity against HeLa cervical cancer cells. Both extracts, at a concentration of 0.1 mg/mL, exhibited growth inhibition greater than 75%.

Kashiwada *et al.* found that an 80% aqueous acetone extract from *G. thunbergii*, possessed significant cytotoxicity against RPMI-7951 melanoma tumour cells (ED_{50} < 20 μg/mL) [123].

In a high-throughput screening of nearly nine hundred natural product extracts relative to paclitaxel for the antimitotic effect on the proliferation of MDA-MB-231 human breast carcinoma cells, an EtOH extract of *G. maculatum* showed to possess moderate growth inhibitory activity with an IG_{50} value of 0.0602 mg/mL [124]. Earlier, Mazzio and Soliman found that an EtOH extract of *G. maculatum* also exhibited cytotoxicity (LC_{50} = 1.170 mg/mL) against a Neuro 2-a murine neuroblastoma cell line [125].

Kim tested a 70% aqueous EtOH extract of *G. krameri* against a B16F10 murine melanoma cell line but observed relatively low cytotoxicity, with an ID_{50} value of 469.26 μg/mL [126].

Various aqueous (decoction and infusion) and organic extracts (*n*-hexane, CH_2Cl_2, EtOAc, acetone, and MeOH, obtained by successive extraction) from *G. robertianum* were tested against several human cancer cell lines: breast (MCF-7), non-small cell lung (NCI-H460), cervical (HeLa) and hepatocellular (HepG2) carcinomas [127]. All extracts revealed to possess cytotoxic activity, with GI_{50} values ranging from 45.68 to 236 μg/mL. Unlike the other extracts, for which the grown inhibition activity was very diverse amongst the different cell lines, the acetone extract was consistently the most cytotoxic for all the assayed cell cultures (GI_{50} from 57 to 60 μg/mL). Ellipticine, a potent antineoplastic agent, was used as a positive control, displaying GI_{50} values from 0.91 to 2.29 μg/mL.

An identical study by the same authors with *G. molle* against the same cell lines provided similar results with the acetone extract being the most cytotoxic one, exhibiting GI_{50} values from 50 to 85 μg/mL [128].

The bio-guided fractionation of some of the more active extracts of both *G. robertianum* and *G. molle* resulted in several fractions with improved cytotoxicity in comparison with the corresponding crude extracts [129, 130].

Şöhretoğlu *et al.* assessed the cytotoxic activity of different extracts of *G. psilostemon* and *G. tuberosum*, two plants widely used in traditional Turkish medicine, against a KB human epidermoid carcinoma cell line [131]. The extracts, resulting from initial extraction of the plants with 80% aqueous MeOH, followed by dissolution of the crude extracts in water and partition of the water-soluble fraction against petroleum ether, EtOAc and *n*-BuOH, showed dose-dependent cytotoxicity in the range of the concentrations tested (10 μg/mL - 0,1 μg/mL), being negligible below 10 μg/mL. At this concentration, both aqueous extracts of *G. psilostemon* and *G. tuberosum* exhibited a proliferative inhibition of ~ 65% and ~ 55%, respectively, comparable to that of doxorubicin, an antibiotic largely used in cancer chemotherapy, used as a positive control. The *n*-BuOH and EtOAc extracts showed cellular proliferation inhibition lower than 30% at the same concentration.

The anti-proliferative activity of 80% aqueous EtOH and EtOH extracts of *G. purpureum* was assessed against Hep G2 human hepatocellular carcinoma cells and compared with that displayed against a normal skin fibroblasts CRL-2522 cell line [108]. The

Table 1. Traditional uses of *Geranium* species.

Geranium Species	Country	Use	References
G. aculeolatum	Burundi	Ringworm, purulent rashes, diarrhoea	[13]
G. asphodeloides	Turkey	Wounds	[14]
G. ayavacense	Peru	Hypoglycaemic, astringent, ulcerative stomatitis, gastritis, gingivitis, gastric lesions	[15]
G. bellum	Mexico	Fever, pain, gastrointestinal disorders	[16]
G. canescens	Africa	Diarrhoea	[17]
G. carolinianum	China	Diarrhoea, rheumatic arthritis	[18]
G. berteroanum	Argentine	Hepatic and intestinal disorders, stomach problems	[19, 20]
G. core-core	Chile	Cataracts, shock, fever, astringent, toothache, inflammatory conditions	[21]
G. dissectum	Lebanon	Rheumatism	[22]
G. himalayense	India	Stomach ache	[23]
G. ibericum	Turkey	Wound healing	[24]
G. incanum	South Africa	Diarrhoea, menstruation	[17, 25]
G. koreanum	China	Itching, bruising, enteritis, chronic diarrhoea, liver disorders	[26]
G. lucidum	India	Diuretic, astringent	[23]
-	Spain	Wounds, cuts	[27]
G. macrorrhizum	Bulgaria, Poland, Romania	Antiviral, styptic in menorrhagia and haematuria, diarrhoea, dysentery, gastrointestinal ulcers	[12]
-	Bulgaria	Spasmolytic, cardiotonic, aphrodisiac, hypotensive agent, central depressive	[28, 29]
-	Serbia	Astringent, inflammation of gastric mucous membranes	[28]
-	Montenegro	Inflammation of the skin and mucous membranes	[30]
-	Bosnia and Herzegovina	Stomach disorders	[31]
G. maculatum	North America, Europe	Diarrhoea, dysentery, gastrointestinal ulcers, styptic in menorrhagia and haematuria, haemorrhoids, wounds, sores, bleeding	[12]
-	Canada	Duodenal ulcers, diarrhoea, haemorrhoids	[32]
G. mascatense	Pakistan	Diuretic, gastrointestinal disorders, diarrhoea, ulcers	[33]
-	India	Antiseptic, diuretic, astringent, liver disorders, fever	[23]
-	Nepal	Amoebic dysentery	[34]
G. maximowiczii	China	Rheumatism	[32]
G. mexicanum	Mexico, Venezuela	Laxative in infants, antispasmodic, rashes, wounds	[12]
-	Mexico	Diarrhoea, dysentery, stomach ache, purgative, tonsillitis, cough, whooping cough, urticarial, pruritus	[35-37]
G. molle	Portugal	Antiseptic, stomach ache, gingivitis, eye inflammation, uterus inflammation, cancer	[38]
-	India	Analgesic, astringent, wounds	[23]
G. nepalense	India	Antibacterial, diuretic, astringent, renal disorders, fever, toothache, ulcers, wounds, stomach disorders, jaundice, itching, eczema, diarrhoea, endometriosis	[12, 23, 39, 40]
-	China	Cancer, stomach ache, eyes problems, nose inflammation	[41, 42]
-	Pakistan	Renal infections, diarrhoea, cholera	[43, 44]
-	Nepal	Diarrhoea, endometriosis, shore throat, renal problems	[12, 45]
G. niveum	Mexico	Analgesic, purgative, infectious diarrhoea, gastrointestinal disorders, fever, kidney pain, urological problems, diabetes, skin tumours, dermatological conditions	[46-49]
G. phaeum	Bulgaria, Serbia	Astringent, inflammation of gastric mucous membranes, aphrodisiac	[28]

(Table 1) Contd....

Geranium Species	Country	Use	References
G. platyanthum	Japan, China	Rheumatism, numbness of limbs, pain	[12]
-	Korea	Enteritis, dysentery, diarrhoea	[50]
G. polyanthes	India	Ulcers, headache	[40]
G. pratense	China, Japan, Europe	Acute bacillary dysentery	[12]
-	Great Britain	Antihemorragic, astringent	[51]
-	India	Analgesic, pneumonia, swelling, liver and gastric disorders, cold, cough, fever, wounds, bruises	[23, 52-54]
G. purpureum	Portugal	Antiulcerative, analgesic, vulnerary, cancer, intestinal antispasmodic, gastric and hepatic protective, gastritis, sea-sickness, gall-bladder ailments, influenza, intestinal anti-inflammatory, renal antispas-modic, inflammations	[55, 56]
G. pusillum	India	Analgesic, astringent, wounds	[23]
G. rivulare	India	Insect bites, ulcers	[12]
G. robertianum	Europe, USA, China, Japan, North Africa, India, South America	Diarrhoea, haemorrhage, jaundice, dispersal of kidney and gall stones, mouthwash, burns, wounds	[12]
-	Montenegro	Diarrhoea, gastritis, inflammatory conditions of gallbladder, kidney and bladder, poorly healing wounds, rashes, sinuses diseases	[30]
-	Italy	Parasitosis of the scalp, mosquito repellent, mosquito bites, astringent, ovine, cattle and horses scabs, mouth and throat inflammations	[57-60]
-	Spain	Antipneumonic, antiecchymotic, antiherpetic, vulnerary, sore throat, cancer, lipomas, diarrhoea in animals	[61-63]
-	Israel	Cholesterol	[64]
-	Portugal	Diabetes, blood depurative, tumours, stomach ulcers, open sores	[65, 66]
-	Bosnia and Herzegovina	Male fertility improvement	[31]
-	Serbia	Intestinal ailments in animals	[67]
-	Mexico	Eyes, venereal diseases, mouth disorders, gastrointestinal disorders, cutaneous or connective tissue disorders	[68]
-	Morocco	Hypoglycaemic, tonic, antispasmodic, cancer	[69]
-	Africa	Diarrhoea	[17]
-	India	Astringent, haemostatic, tumours, ulcers, jaundice, fever, renal disorders	[23]
G. rotundifolium	India	Astringent, diuretic	[23]
-	Iran	Cold	[70]
-	Pakistan	Stomach ache, jaundice	[71]
-	Italy	Vulnerary, stomatitis, gastrointestinal complaints in cattle	[72]
G. ruizii	Peru	Diabetes, inflammation, chronic diarrhoea	[73]
G. sanguineum	Eastern Europe	Haemorrhage, diarrhoea	[12]
-	Bulgaria	Hypotensive, antivirus, immune-stimulant, sedative, CNS depressive, pruritus, itches, skin lesions, eruptive skin	[74, 75]
-	Italy	Stomatitis, astrigent	[74]
G. schiedeanum	Mexico	Fever, pain, gastrointestinal disorders	[76]
G. seemannii	Mexico, Caribbean, Central America	Diuretic, laxative, obesity	[77]
G. sessiliflorum	Peru	Uterine cancer, liver and kidney inflammation	[78]
G. sibiricum	India	Diuretic, astringent, wounds	[23]

(Table 1) Contd....

Geranium Species	Country	Use	References
-	Korea	Diarrhoea, intestinal inflammation, dermatitis, cancer	[79]
G. strictipes	China	Enteritis, diarrhoea, chronic gastritis	[80]
G. thunbergii	China, Japan	Inflammation of gastrointestinal system, diarrhoea, haematological and liver disorders	[23]
-	Japan	Diarrhoea, liver disorders, chronic gastroenterophaty, stomach ache	[81, 82]
G tuberaria	India	Urinary disorders	[83]
G. tuberosum	Cyprus	Cardiovascular, skin	[84]
-	Lebanon	Haemorrhoids, diuresis, diabetes, male sterility	[85]
G. wallichianum	India	Astringent, toothache, otorrhoea, ophthalmia, dysentery, diarrhoea, cough and cold, headache, wounds, leucorrhoea, backache, rheumatic pain, fever, cough, jaundice, body pain, styptic	[23, 86-88]
-	Pakistan	Hypotensive, uterine diseases, stomach disorders, tonic, gastric ulcers, jaundice, toothache, joint pains, diarrhoea, cholera, hepatitis, liver problems, kidney problems, chronic dysentery, leucorrhoea	[43, 44, 89, 90]
-	Nepal	Cough, cold, join pains, menstruation problems	[91]
G. wilfordii	China	Chronic rheumatism, gastrointestinal disorders, diarrhoea, dysentery	[12, 92]

Table 2. MIC (mg/mL) values of *Geranium* species essential oils against Gram-positive bacteria.

Plant	Part used	*Bacillus cereus* PCM 2019	*Bacillus cereus* 709 Roma	*Bacillus subtilis* ATCC 6633	*Bacillus subtilis* PCM 1949	*Clostridium perfringens* ATCC 19574	*Clostridium sporogenes* ATCC 19404	*Enterococcus faecalis* ATCC 29212	*Listeria monocytogenes* ATCC 43251	*Micrococcus flavus* ATCC 10240	*Mycobacterium smegmatis* ATCC 607	*Sarcina lutea* ATCC 9341	*Staphylococcus aureus* (clinical isolate)	*Staphylococcus aureus* ATCC 25923	*Staphylococcus aureus* PCM 2054	*Staphylococcus pseudintermedius* KP-Spi1	*Streptococcus agalactiae* KP-Sag1	*Streptococcus canis* KP-Sac1	References
G. asphodeloides	aerial parts	-	0.355[1]	-	-	-	-	-	-	-	0.355[2]	-	-	-	-	-	-	-	[118]
G. columbinum	aerial parts	-	-	14.0[3]	-	0.437[4]	3.50[5]	-	-	7.00[6]	-	7.00[7]	3.50[4]	1.750[3]	-	-	-	-	[119]
-	underground parts	-	-	12.0[3]	-	6.00[4]	12.0[5]	-	-	6.00[6]	-	-	6.00[4]	12.0[3]	-	-	-	-	-
G. lucidum	whole plant	-	-	13.4[3]	-	1.675[4]	6.70[5]	-	-	13.4[6]	-	13.4[7]	1.675[4]	3.35[3]	-	-	-	-	-
G. macrorrhizum	aerial parts	-	-	0.001	-	-	0.625	-	-	-	-	-	0.312	0.039	-	-	-	-	[120]
-	rhizomes	-	-	0.0004	-	-	2.5	-	-	-	-	-	0.625	2.5	-	-	-	-	-
G. psilostemon	aerial parts	-	4.220[1]	-	-	-	-	-	-	-	4.220[2]	-	-	-	-	-	-	-	[118]
G. purpureum	aerial parts	-	3.365[1]	-	-	-	-	-	-	-	3.365[2]	-	-	-	-	-	-	-	[118]
G. pyrenaicum	aerial parts	-	0.167[1]	-	-	-	-	-	-	-	0.335[2]	-	-	0.335[8]	-	-	-	-	[118]
G. robertianum	leaves	5[9]	-	-	5[9]	-	-	-	-	-	-	-	-		1.25[9]	2.5[9]	5[9]	2.5[9]	[121]
-	aerial parts	-	0.805[1]	-	-	-	-	-	-	-	0.805[2]	-	-	0.805[8]	-	-	-	-	[118]
G. sanguineum	whole plant	-	-	2.50[10]	-	-	2.50[11]	-	-	0.312[12]	-	5.00[10]	5.00[12]	5.00[12]	-	-	-	-	[122]
-	aerial parts	-	3.775[1]	-	-	-	-	-	-	-	1.887[2]	-	-	-	-	-	-	-	[118]

MIC - Minimum inhibitory concentration. - - No activity within the tested concentration range.
[1] Ampicillin (MIC = 15 µg/mL) was used as a reference compound. [2] Streptomycin (MIC = 4 µg/mL) was used as reference compound. [3] Chloramphenicol (MIC = 0.015 mg/mL) was used as reference compound. [4] Chloramphenicol (MIC = 0.062 mg/mL) was used as a reference compound. [5] Chloramphenicol (MIC = 0.250 mg/mL) was used as reference compound. [6] Chloramphenicol (MIC = 0.031 mg/mL) was used as reference compound. [7] Chloramphenicol (MIC = 0.125 mg/mL) was used as a reference compound. [8] Ampicillin (MIC = 35 µg/mL) was used as reference compound. [9] Tetracycline (MIC = 30 µg/mL) was used as a reference compound. [10] Tetracycline (MIC = 0.195 µg/mL) was used as a reference compound. [11] Tetracycline (MIC = 1.562 µg/mL) was used as reference compound. [12] Tetracycline (MIC = 0.098 µg/mL) was used as a reference compound.

Table 3. MIC (mg/mL) values of *Geranium* species essential oils against Gram-negative bacteria.

Plant	Part Used	*Escherichia coli* (clinical isolate)	*Escherichia coli* ATCC 8379	*Escherichia coli* ATCC 25922	*Escherichia coli* ATCC 35218	*Escherichia coli* PCM 2057	*Escherichia coli* Torlak 95	*Klebsiella pneumoniae* (clinical isolate)	*Klebsiella pneumoniae* ATCC 10031	*Pectobacterium carotovora* IOR-1815	*Pectobacterium carotovora* IOR-1822	*Pectobacterium atrosepticum* IOR-1825	*Pectobacterium atrosepticum* IOR-1826	*Proteus vulgaris* ATCC 8247	*Pseudomonas aeruginosa* ATCC 27853	*Pseudomonas aeruginosa* ATCC 43288	*Salmonella enteritidis* ATCC 13076	*Yersinia pseudotuberculosis* ATCC 911	References
G. asphodeloides	Aerial parts	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[118]
G. columbinum	Aerial parts	0.875[1]	-	-	-	-	14.0[2]	1.750[2]	14.0[2]	-	-	-	-	7.00[3]	0.875[4]	-	14.00[3]	-	[119]
-	Underground parts	12.0[1]	-	-	-	-	-	0.750[2]	-	-	-	-	-	12.0[3]	6.00[4]	-	-	-	-
G. lucidum	Whole plant	-	-	-	-	-	13.4[2]	0.873[2]	13.4[2]	-	-	-	-	13.4[3]	0.837[4]	-	13.4[3]	-	-
G. macrorrhizum	Aerial parts	2.5	-	0.312	-	-	-	0.625	-	-	-	-	-	-	-	-	-	-	[120]
-	Rhizomes	5	-	2.5	-	-	-	1.25	-	-	-	-	-	-	-	-	-	-	-
G. psilostemon	Aerial parts	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[118]
G. purpureum	Aerial parts	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[118]
G. pyrenaicum	Aerial parts	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[118]
G. robertianum	Leaves	-	-	-	-	10^5	-	-	-	10^5	10^5	10^5	10^5	-	-	-	-	-	[121]
-	Aerial parts	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[118]
G. sanguineum	Whole plant	0.312[6]	1.25[7]	5.00[8]	-	-	5.00[8]	2.50[7]	-	-	-	-	-	2.50[7]	-	-	5.00[6]	-	[122]
-	Aerial parts	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	[118]

MIC - Minimum inhibitory concentration. - - No activity within the tested concentration range.
[1] Chloramphenicol (MIC = 0.031 mg/mL) was used as a reference compound. [2] Chloramphenicol (MIC = 0.062 mg/mL) was used as a reference compound. [3] Chloramphenicol (MIC = 0.125 mg/mL) was used as a reference compound. [4] Chloramphenicol (MIC = 0.250 mg/mL) was used as a reference compound. [5] Tetracycline (MIC = 30 µg/mL) was used as reference compound. [6] Tetracycline (MIC = 0.195 µg/mL) was used as a reference compound. [7] Tetracycline (MIC = 0.390 µg/mL) was used as a reference compound. [8] Tetracycline (MIC = 1.562 µg/mL) was used as reference compound.

growth inhibition was found to be dose-dependent, but not significantly different in the two cell lines for each tested concentration.

G. macrorrhizum has been one of the most studied *Geranium* species concerning anticancer activity. Venskutonis *et al.* obtained an alcoholic extract of the plant by partition, between water and *n*-BuOH, of a 96% aqueous EtOH extract of the residue resulting from the initial extraction of the plant material with *tert*-butyl methyl ether, and found it to be cytotoxic *in vitro* against bovine leukemia virus-transformed lamb embryo kidney fibroblasts (line FLK) (LC_{50} = 112 µg/mL) [132]. Extraction of the residue remaining after extraction with 96% aqueous EtOH with water, yielded, after partition against *n*-BuOH, an aqueous fraction with even greater inhibitory activity (LC_{50} = 63 µg/mL). The prooxidant nature of the cytotoxicity displayed by the extract was evidenced since it was prevented by the antioxidant *N*,*N*'-diphenyl-*p*-phenylenediamine (DPPD) and was enhanced by *N*,*N*'-bis (2-chloroethyl)-*N*-nitrosourea (BCNU) which acts as a prooxidant. The *G. macrorrhizum* extract did not reveal genotoxicity *in vivo* in *Drosophila melanogaster*, although it showed to be genotoxic in cytogenetic tests *in vitro*. Sharopov *et al.* demonstrated that a MeOH extract of the leaves and roots of *G. macrorrhizum* exhibited moderate cytotoxic activity against human leukaemia CCRF-CEM and CEM/ADR 5000 cell lines, with IC_{50} values of 22.4 and 112.3 µg/mL, for the first cell line, and 98.3 and 154.2 µg/mL, for the second one, respectively [133]. As a comparison, the IC_{50} values determined for doxorubicin were, respectively, 2.3 µg/mL for the CCRF-CEM cells and 5.2 µg/mL for the CEM/ADR cells. A subcritical water extract from *G. macrorrhizum* leaves was also found to be cytotoxic *in vitro* for human cervix carcinoma - HeLa derivative (Hep2c), human rhabdomyosarcoma (RD) and murine fibroblast (L2OB) cells, with IC_{50} values ranging from 12.22 to 28.38 µg/mL [105]. Cisplatin, a standard chemotherapeutic agent effective for a great number of cancers, was used as a positive control with IC_{50} values from 0.72 to 1.4 µg/mL.

Recently, Herrera-Calderon *et al.* assessed the cytotoxicity of a 96% aqueous EtOH extract of *G. ruizii* against a relatively large number of human cancer cell lines: MCF-7 (breast), H-460 (non-small cell lung), HT-29 (colon), M-14 (melanoma), K-562 (myelogenous leukaemia) and DU-145 (prostate) [134]. The extract exhibited IC_{50} values from 75.13 to 196.54 µg/mL, showing relatively low toxicity in comparison to 5-fluorouracil, a well-known anticancer drug used as control (IC_{50} values from 0.33 to 4.08 µg/mL, except for the DU-145 cell line for which IC_{50} > 15.63 µg/mL).

4.4. Antidiarrhoeal Activity

Various *Geranium* species are used internally for the treatment of diarrhoeal conditions [12] but, conversely, the number of species that have been studied is relatively small. One of the mechanisms in diarrhea pathogenesis is secretory diarrhoea, which occurs when the secretion of water into the intestinal lumen exceeds absorption, a process that may easily lead to marked dehydration [135]. Extracts of the aerial parts of *G. mexicanum* were found to display antisecretory activity in Sprague-Dawley rats [136]. The aqueous extract of the plant showed 42.1% inhibition, comparable to that of lopera-

mide (43.3%), a standard drug for the treatment of a number of types of diarrhea. On the other hand, the MeOH extract showed much better antisecretory action than the antidiarrheal drug, displaying as much as 93.4% inhibition. Both the aqueous and the MeOH extract of the roots were devoid of antisecretory properties.

Alterations in intestinal motility usually increased propulsion, are observed in many types of diarrhea [135]. MeOH extracts of the roots of *G. mexicanum* showed 100% of inhibition of charcoal-gum acacia-induced hyperperistalsis in Sprague-Dawley rats (loperamide exhibited 34% inhibition at a dose of 10mg/Kg) [137]. Moreover, in what concerns antipropulsive properties, the MeOH extract of the aerial parts of the plant turned out to be inactive.

Amabeoku showed that the aqueous extract of the leaves of *G. incanum* possessed antidiarrhoeal and antipropulsive activities in castor oil-induced diarrhoea in albino mice, reducing the faecal output, the number of diarrhoeal episodes and the intestinal propulsion of charcoal meal, with a net effect similar to that of loperamide [17].

An aqueous extract of *G. ocellatum* leaves exhibited marked anti-diarrhoeal effect in castor oil-induced diarrhoea in Wistar rats, reducing the total number and the weight of wet faeces significantly. The inhibition of diarrhoea rats treated with the extract was 78.87%, comparable to that of loperamide (79.51%) [138].

4.5. Antifungal Activity

The antifungal properties of several species from the *Geranium* genus have also gained much attention. Solid-liquid extracts, mostly alcoholic and water extracts, of about a dozen species, were assayed against a panel of plant and human pathogenic fungi, including the most commonly found species in opportunistic mycoses such as *Aspergillus* and *Candida* (Supplementary Table **3**) [14, 98-106, 110, 111, 113, 114, 117, 139]. Almost all extracts were found to have antifungal activity.

The antifungal activity of essential oils from various *Geranium* species was also tested against several different fungi (Table **4**). The majority of them displayed inhibitory activity.

4.6. Antiglycation Activity

Non-enzymatic protein glycosylation (glycation) and the formation of advanced glycation end products (AGEs) contribute to the development or worsening of many degenerative diseases and aging of organisms [143]. In a survey of several Pakistani traditional medicinal plants to combat diabetes, Zia-ur-rehman *et al.* found that a 95% aqueous MeOH extract of *G. collinum* was capable of significant inhibition (~ 62%) of the formation of AGEs when compared with the positive control (quercetin-3-*O*-rutinoside, 86% inhibition) [144]. A similar extract of *G. wallichianum* did not inhibit AGE formation significantly (~ 3%).

4.7. Antihepatotoxic Activity

Radulović *et al.* reported a significant dose-dependent antihepatotoxic action of the MeOH extracts of the leaves and rhizomes of *G. macrorrhizum* in CCl_4-induced hepatotoxicity in Wistar rats, decreasing the levels of the enzymes aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), pseudocholinesterase (PCHE) and total bilirubin, and reducing the extent of morphological malformations of the liver [104].

The pre-treatment of Wistar rats with 70% aqueous acetone extracts of the aerial parts of *G. schiedeanum* showed to decrease and delay thioacetamide-induced liver injury, lowering the levels of AST and ALT [76]. This *G. schiedeanum* extract also exhibited a hepatoprotective effect on the damage caused by ethanol on partial post-hepatectomy liver regeneration in Wistar rats [145]. Vargas-Mendoza *et al.* observed that the pre-treatment of Wistar rats with the 70% aqueous acetone extract from *G. schiedeanum* stimulated

Table 4. Antifungal activity of *Geranium* species essential oils.[§]

Plant	Part Used	*Alternaria solani**	*Aspergillus fumigatus**	*Aspergillus niger* YP-001	*Aspergillus restrictus*[#]	*Candida albicans* ATCC 10231	*Candida albicans* ATCC 60193	*Fusarium solani**	*Macrophamina phaseolina**	*Penicillium chrysogenum**	*Rhizoctonia solani**	*Saccharomyces cerevisiae* ATCC 9763	*Saccharomyces cerevisiae* RSKK 251	*Sclerotium rolfsii**	References
G. asphodeloides	Aerial parts	-	-	-	-	-	-	-	-	-	-	-	-	-	[118]
G. columbinum	Aerial parts	-	0.109[1]	-	7.00[2]	0.437[3]	-	-	-	7.00[1]	-	0.437[4]	-	-	[119]
-	Underground parts	-	0.375[1]	-	12.0[2]	1.75[3]	-	-	-	12.0[1]	-	-	-	-	-
G. lucidum	Whole plant	-	0.837[1]	-	13.4[2]	0.837[3]	-	-	-	-	-	6.70[4]	-	-	[119]
G. macrorrhizum	Aerial parts	-	5	-	10	-	-	-	-	10	-	-	-	-	[120]
-	Rhizomes	-	5	-	10	-	-	-	-	10	-	-	-	-	-
-	Whole plant[9]	-	-	-	-	-	-	-	-	-	-	-	-	-	[140]
G. psilostemon	Aerial parts	-	-	-	-	-	4.220[5]	-	-	-	-	-	-	-	[118]
G. purpureum	Aerial parts	-	-	-	-	-	-	-	-	-	-	-	-	-	[118]
G. pyrenaicum	Aerial parts	-	-	-	-	-	0.335[5]	-	-	-	-	-	-	-	[118]
G. robertianum	Aerial parts	-	-	-	-	-	-	-	-	-	-	-	-	-	[118]
G. sanguineum	Whole plant	-	0.312[1]	-	-	5.00[6]	-	-	-	10.0[7]	-	2.50[8]	-	-	[122]
-	Aerial parts	-	-	-	-	-	3.775[5]	-	-	-	-	-	3775[5]	-	[118]
G. viscosissimum	Whole plant[9]	+	-	-	-	-	-	-	-	-	-	-	-	-	[141]
-	Whole plant[9]	-	-	-	-	-	-	+	+	-	+	-	-	+	[142]

[§] Numeric values correspond to MIC (minimum inhibitory concentration) (mg/mL). [#] Mattress dust isolate. * Strain not identified. + - With activity. - - No activity within the tested concentration range.

[1] Nystatine (MIC = 0.039 μg/mL) was used as a reference compound. [2] Nystatine (MIC = 0.078 μg/mL) was used as a reference compound. [3] Nystatine (MIC = 2.50 μg/mL) was used as a reference compound. [4] Nystatine (MIC = 1.75 μg/mL) was used as a reference compound. [5] Fluconazole (MIC < 8 μg/mL) was used as reference compound. [6] Nystatine (MIC = 6.250 μg/mL) was used as reference compound. [7] Nystatine (MIC = 0.390 μg/mL) was used as a reference compound. [8] Nystatine (MIC = 12.50 μg/mL) was used as a reference compound. [9] Presumably.

the endogenous antioxidant defense system, increasing the levels of catalase (Cat), superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR) in the liver of the rats, after intoxication with a sublethal dose of thioacetamide [146].

In a study aimed at scrutinizing the protective effect and related molecular mechanism of a MeOH extract of *G. koreanum* on $NaAsO_2$-induced cytotoxicity in HepG2 human liver cancer cells and liver damage in ICR mice, Akanda *et al.* found that co-treatment with the extract attenuated induced hepatotoxicity both *in vivo* and *in vitro* [147]. On HepG2 cells the *G. koreanum* extract significantly mitigates cell viability loss and the raise of reactive oxygen species (ROS) and lactate dehydrogenase (LDH) levels. *In vivo*, co-treatment with the extract resulted in a remarkable improvement of the histopathological changes caused by $NaAsO_2$, as well as of the liver function by reducing ALT and AST to nearly normal levels. Additionally, the study showed that the hepatoprotective activity was probably involved in the modulation of the mitogen-activated protein kinases (MAPK)(ERK1/2, JNK, p38)/caspase-3 signalling pathways.

4.8. Antihyperglycaemic Activity

Rodriguez *et al.* evaluated the hypoglycaemic activity of a 70% aqueous EtOH extract of *G. core-core* in normoglycaemic and alloxan-induced diabetic rats [21]. The results showed that a single oral dose of 500 mg/Kg, as well as the chronic administration of 250 mg/Kg (7 days), significantly reduced blood glucose levels both of normoglycaemic and alloxan-diabetic rats under glucose tolerance test conditions.

A 96% aqueous EtOH extract of *G. ruizii* showed the antihyperglycaemic effect on rats with experimental diabetes induced by alloxan at a dosage of 150 mg/Kg [148]. Moreover, it was found that the extract had a protective effect in the pancreas.

An aqueous extract of *G. ayavacence* also revealed to significantly decrease glycaemia in alloxan-induced diabetic rats at dosages of 300 and 500 mg/Kg, in a sustained way over a 24 h post-administration period [15].

Karato *et al.* observed that a MeOH extract of *G. dielsianum* was able to suppress blood glucose elevation after oral administration of sucrose, maltose and starch, but not of glucose, in hyperglycaemic (ddY) model mice, suggesting that the extract had no effect on glucose absorption but probably inhibited the carbohydrate-hydrolyzing enzymes involved in the metabolism of disaccharides [149]. The *in vitro* investigation of the effect of the extract on the activity of α-glucosidase from mouse small intestine showed that the enzyme, which breaks down starch and disaccharides to glucose, was inhibited in a dose-dependent manner, strongly indicating that the extract has an anti-hyperglycaemic effect by inhibiting α-glucosidase activity.

Curiously, the EtOAc soluble fraction of a 95% aqueous EtOH extract of *G. thunbergii* was found to exhibit considerable inhibitory activity against yeast α-glucosidase but only very weak inhibitory activity against mammalian α-glucosidase from rat intestinal acetone powder [150]. Yeast α-glucosidase is extensively used as a screening material for α-glucosidase inhibitors, but it is known that the results not always agree with those obtained with the enzyme from mammal origin [151].

Numonov *et al.* assessed the antihyperglycaemic activity of several aqueous and aqueous-EtOH extracts of the roots of *G. collinum* and found that they possessed promising inhibitory activities against yeast α-glucosidase, with IC_{50} values ranging from 0.07 to 1.98 μg/mL [152]. The 50% aqueous EtOH extract exhibited potent inhibitory activity, with an IC_{50} value of 0.07 μg/mL, considerably superior to that of acarbose (IC_{50} = 2.19 μg/mL), a α-glucosidase inhibitor commonly used as an antidiabetic agent. This extract also revealed potent inhibitory activity against the protein tyrosine phosphatase (PTB-1B), a key negative regulator of the insulin signaling pathway and a well-known target of type 2 diabetes whose inhibition is anticipated to preserve glucose homeostasis [153]. The observed IC_{50} value (0.10 μg/mL) was about 15 times lower than that of 3-(3,5-dibromo-4-hydroxybenzoyl)-2-ethyl-*N*-[4-(1,3-thiazol-2-ylsulfamoyl)phenyl]-1-benzofuran-6-sulfonamide (IC_{50} = 1.46 μg/mL), the positive control used and an established PTP-1B inhibitor.

Recently, an 80% aqueous MeOH extract from *G. asphodeloides* and several sub-extracts obtained by partition of the crude MeOH extract between water and, successively, *n*-hexane, EtOAc and *n*-butanol were shown to exhibit very potent inhibitory activity against yeast α-glucosidase (IC_{50} values from 0.85 to 11.65 μg/mL) compared with acarbose (IC_{50} = 40.47 μg/mL) [154]. The EtOAc sub-extract displayed the highest inhibitory effect with an IC_{50} value of 0.85 μg/mL.

4.9. Antihypertensive Activity

In a pharmacological study of several extracts of *G. macrorrhizum*, Petkov showed that some of them possessed an evident hypotensive action on anesthetized cats (acute experiments) and wakeful dogs (chronic experiments) with induced hypertension [155]. The EtOH extract of the whole plant and a MeOH fraction from the rhizome displayed strong and prolonged hypotensive effects. Several fractions from the total MeOH extract of the aerial parts of the plant also showed significant hypotensive action. The hypotensive activity was found to result mainly from a direct effect on the vascular smooth muscles.

The 70% aqueous EtOH extract of *G. pratense* was found to possess remarkable *in vitro* inhibitory activity against angiotensin I-converting enzyme (ACE I) (IC_{50} = 81 μg/mL), an enzyme of the renin-angiotensin system which plays a central role in the regulation of blood pressure [156].

Earlier, Hansen *et al.* verified that the aqueous extract of *G. core-core* was able to inhibit ACE activity by 33% [157].

4.10. Anti-inflammatory Activity

Küpeli *et al.* evaluated the anti-inflammatory activity of an aqueous fraction of *G. finitimum*, obtained by partition of a crude MeOH extract between water and $CHCl_3$, using three acute inflammation models in Swiss albino mice: carrageenan- and prostaglandin E2 (PGE_2)-induced paw oedema and 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced ear oedema [32]. In comparison with the anti-inflammatory drug indomethacin (at 10 mg/Kg), the extract, at a dosage of 100 mg/Kg, significantly inhibited both carrageenan- (26.6%, 3 hours post injection; 38% for indomethacin) and PGE_2-induced paw oedema (25.3%, 24 minutes post-injection; 13% for indomethacin), as well as the weight of TPA-induced ear oedema (42.4% after 4 hours of topical application, 59.7% for indomethacin).

A 50% aqueous EtOH extract of *G. wilfordii*, at a dose of 1.69 g/kg administered intragastrically for 5 days to Sprague-Dawley rats, significantly inhibited swelling in the carrageenan-induced paw oedema 1 hour post carrageenan injection, an effect considerably stronger than that of acetylsalicylic acid (0.1 mg/kg) used as positive control [158]. The pre-treatment of ICR mice with the same extract administered intragastrically (1.69 g/kg for 5 days) suppressed xylene-induce ear oedema by 33.3%, while acetylsalicylic acid (0.1 mg/kg) showed 35.6% reduction in swelling. The same authors demonstrated *in vitro*, using L929 murine fibrosarcoma cells, that the extract displayed activity against the expression of tumor necrosis factor-alpha (TNF-α), a key cell signalling protein in most inflammatory responses, in a dose-dependent manner, the inhibitory effect reaching 93.32% at a nontoxic dosage of 128 ug/mL.

Choi *et al.* examined the anti-inflammatory activity of a 50% aqueous EtOH extract of *G. thunbergii* in bone marrow-derived

macrophages (BMDM) activated by interferon-γ (INF-γ) and bacterial lipopolysaccharides (LPS) and found that the extract exerted a significant inhibitory effect on induced inflammation at non-toxic doses [159]. The anti-inflammatory effect seemed to be associated with the activation of the nuclear erythroid 2-related factor (Nrf2), a key transcription factor in anti-inflammatory systems. An EtOAc fraction of a 95% aqueous MeOH extract of *G. thunbergii*, obtained by the sequential partition of the later between water and various organic solvents, also showed anti-inflammatory effect on LPS-stimulated RAW 264.7 cells [160]. The fraction effectively suppressed NO production, in a dose-dependent way (> 60% inhibition at a concentration of 50 μg/mL), by down regulating inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression. Sung *et al.* investigated the effect of hot water extracts of *G. thunbergii* obtained with different extraction times on the expression of iNOS, COX-2, interleukin 1 β (IL-1β) and interleukin 6 (IL-6) in LPS-stimulated RAW 264.7 cells [161]. At 10 μg/mL, the most active extract, obtained by extracting the plant material at 90 ºC for 2 h, decreased the expression of those inflammatory mediators between 66 and 79%.

The oral administration of a 70% aqueous acetone extract of *G. bellum* to Wistar rats significantly suppressed the oedematous response to carrageenan-induced paw oedema, in a dose-dependent manner [162]. The observed oedema inhibition rates were 41.1 and 70.5%, at extract dosages of 150 and 300 mg/kg, respectively, after 6 hours of carrageenan injection. The commonly used nonsteroidal anti-inflammatory drugs indomethacin and diclofenac (at 30 mg/Kg) produced oedema inhibition rates of 42.8 and 47.2%, respectively, after the same post administration period.

A 99% aqueous EtOH extract of *G. sibiricum* was found to exhibit interesting anti-inflammatory activity in phorbol-12-myristate 13-acetate plus calcium inophore A23187 (PMACI) stimulated human mast cells (HMC-1) through modulation of pro-inflammatory cytokine interleukin-1β expression and NO production [79].

An EtOAc fraction of an aqueous extract of *G. nepalense* showed significant anti-inflammatory activity on TPA-induced ear oedema in Kumming mice at 2.5 g/Kg, similar to that of aspirin (0.6 g/kg) used as a positive control [163].

Piwowarski *et al.* demonstrated the anti-inflammatory action of an aqueous extract of *G. pratense* on human THP-1 cell line-derived macrophages [164]. It was shown that the plant's extract was a source of bioavailable gut microbiota metabolites, *i.e.* urolithins, which had an inhibitory action on the pro-inflammatory functions of the INF-γ and LPS stimulate macrophages.

Li *et al.* showed that an aqueous extract of *G. carolinianum* possessed anti-inflammatory properties *in vivo*, suppressing fresh egg white-induced acute paw oedema in Sprague-Dawley rats and dimethylbenzene-induced ear oedema in ICR mice, in a dose-dependent way [165]. The *G. carolinianum* extract orally premedicated at a dose of 500 mg/Kg displayed an anti-inflammatory effect even superior to that of indomethacin (5 mg/Kg) used as a positive control in the fresh egg white induced paw oedema test. At doses of 250 and 500 mg/Kg the extract also revealed significant inhibitory activity against acute inflammation induced by dimethylbenzene when compare to dexamethasone used as control.

A water extract of *G. robertianum* defatted with *n*-hexane was able to effectively decrease the production of NO by LPS-stimulated Raw 264.7 macrophages, at a concentration of 100 μg/mL [166]. The inability of the extract to modulate 5-lipoxygenase (5-LOX) activity and inducible nitric oxide synthase (iNOS) expression at this concentration suggested that its anti-inflammatory activity is based, at least partially, on its scavenging capacity against that radical.

Hernández-Guerrero *et al.* evaluated the anti-inflammatory activity of an aqueous extract of *G. seemannii* using the granuloma model in Wistar rats [167]. The extract at doses of 125, 250 and 500 mg/Kg presented anti-inflammatory activity similar to that of indomethacin at 5 mg/Kg, without producing, however, any macroscopic damage of the gastroduodenal mucosa of the rats.

Recently Nam *et al.* studied the anti-inflammatory activity of a CH_2Cl_2 fraction from *G. koreanum* obtained by the partition of a crude 70% aqueous ethanol extract between water and hexane, CH_2Cl_2, EtOAc and *n*-BuOH, presumably in this order [168]. Co-incubation of LPS-stimulated Raw 264.7 macrophage cells with the CH_2Cl_2 fraction (the most active one) at a concentration of 200 μg/mL decreased NO production by 89% and also significantly decreased the expression of the pro-inflammatory mediator iNOS. Pre-treatment of reflux esophagitis (RE)-induced rats with the CH_2Cl_2 fraction at 200 μg/mL resulted in a reduction of oesophageal mucosa damage to a condition similar to that of the normal control group. Moreover, at this concentration, the fraction improved oesophageal mucosa inflammation by inhibiting the expression of inflammatory proteins involved in nuclear factor κB (NF-κB) signalling pathways.

4.11. Antinociceptive Activity

Li *et al.* investigated the peripheral and central antinociceptive activity of an aqueous extract of *G. carolinianum* by monitoring mice exposed to chemical and thermal stimuli, respectively [165]. The *G. carolinianum* extract considerably reduced writhing reflexes, in a dose-dependent way, in mice subjected to the acetic acid-induced writhing test. At the higher dose tested (500 mg/kg), the diminution of writhing responses after intra-peritoneal acetic acid injection was more substantial than that observed in the mice pre-treated with the positive control indomethacin (5 mg/kg), suggesting that the extract possesses potent analgesic properties. The antinociceptive activity of the *G. carolinianum* extract was also demonstrated in the hot-plate test. Pre-treatment of mice with doses of 250 and 500 mg/kg of the extract significantly increased the latency period of mice when compared with the control group of animals, suggesting its central antinociceptive effect.

Küpeli *et al.* assessed the antinociceptive activity of an aqueous extract of *G. finitimum*, obtained by the partition of the crude MeOH extract between water and $CHCl_3$, and several of its fractions isolated by column chromatography in Swiss albino mice using the *p*-benzoquinone-induced abdominal constriction test [32]. At a dose of 100 mg/kg the aqueous extract and two flavonoid-rich fractions exhibited significant inhibition of writhing response in mice (21.3-32.0%) after intra-peritoneal injection of *p*-benzoquinone, when compared to that promoted by acetylsalicylic acid (48.3%) at the same dose, without causing apparent acute toxicity or gastric damage.

G. bellum was the object of a rather extensive study *in vivo* concerning its antinociceptive activity in classical models of pain [162]. A 70% aqueous acetone extract of the plant showed antinociceptive peripheral activity in Wistar rats both upon systemic and local administration, significantly inhibiting formalin-induced nociception. The inhibitory effect at a dose of 300 mg/kg and 800 μg/paw was comparable to that of the positive controls indomethacin (30 mg/kg, 800 μg/paw) and diclofenac (30 mg/kg, 200 μg/paw). In the acetic acid-induced writing test in CD1 albino mice the acetone-water extract at doses of 150 and 300 mg/kg showed significant inhibition of writhing frequency, in a dose-dependent manner, greater than that of indomethacin (10 mg/kg).

4.12. Antiobesity Activity

In a study aiming at discovering new potential anti-obesity agents, Roh and Jung screened the crude EtOH extracts from four-hundred plant species by monitoring the *in vitro* ability for the inhibition of porcine pancreatic lipase (PPL) [169]. *G. thunbergii*, one of the four more promising extracts, exhibited 31.4% inhibition of PPL (at 100 μg/mL), against 42% of Orlistat, a well-known antili-

pase agent used for long-term treatment of obesity. This extract also significantly reduced lipid accumulation in 3T3-L1 adipocytes, with relatively low toxicity to 3T3-L1 preadipocyte cells, further suggesting anti-obesity activity. The treatment of high-fat diet-induced obese C57bl76J mice with a 70% aqueous EtOH extract of *G. thunbergii* considerably reduced body weight gain, adipose tissue accumulation, adipocyte size and serum triglycerides, total cholesterol and low-density lipoprotein-cholesterol levels [170]. The levels of serum toxicological markers did not show meaningfully adverse toxic effects. The anti-obesity effects observed were mediated by altering the adipokine levels and downregulating the expression of transcription factors and lipogenic enzymes involved in lipid metabolism. The anti-obesity, as well as the anti-hyperlipidemic effects of an *n*-BuOH soluble fraction from a MeOH extract of *G. thunbergii*, have also recently been observed in high-fat diet-induced obese Sprague-Dawley rats [171].

4.13. Antioxidant Activity

The antioxidant capacity has been the most assessed bioactivity within the *Geranium* genus, encompassing about thirty studied species of diverse geographic origins (Table **5**). A number of analytical methods have been used to evaluate the antioxidant capacity of different *Geranium* extracts. The majority of the assessments have been performed by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay, which is the most extensively used *in vitro* method for antioxidant activity evaluation due to its rapidity, simplicity and low cost in comparison with other methods [195]. Other electron transfer-based assays such as 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), ferric reducing antioxidant power (FRAP) and reducing power have also been used in some extension.

Because each antioxidant assay has a different mechanism, redox potential, pH and solvent dependencies, *etc*. [196], there is no single method capable to provide unambiguous data about the total antioxidant capacity of a biological matrix. For that reason, it is considered that the best solution is to use simultaneously different assays for the same sample [197], a procedure that was followed in many studies of the antioxidant activity of *Geranium* species. Although the results of antioxidant capacity obtained for the different *Geranium* species and even for those obtained by different authors for the same single species are not comparable for the reasons pointed out above, the general trend observed among the investigated extracts was a significant antioxidant capacity. In many cases, comparisons with well-known antioxidants, either natural or synthetic, have been made that substantiate it.

The antioxidant properties of plants are intimately related to the presence of phenolic compounds [198]. In many *Geranium* species, a reliable direct correlation between antioxidant activity and the total content of phenolic compounds has been observed [104, 177, 180, 185, 194, 199].

Besides their role as scavengers of excessive injurious free radicals, there is recent evidence that polyphenolic compounds also have indirect antioxidant effects through induction of first-line defence antioxidant endogenous enzymes such as are superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GP) and glutathione reductase (GR) [200]. Sabuncuoğlu and Şöhretoğlu investigated the effects of EtOAc, *n*-BuOH, MeOH and water extracts of *G. tuberosum* on the levels of glutathione (GSH), an important tripeptide of the non-enzymatic antioxidant defence system, and on the activities of the enzymes SOD and CAT from human erythrocytes *in vitro* [201]. All extracts prevented H_2O_2-induced decrease of GSH levels and increased CAT and SOD activities, in a dose-depend manner, the EtOAc extract being the most potent antioxidant at 100 μg/mL, and possessing the highest polyphenol content (ca 450 μmol CE/g). However, apart from the MeOH extract at the concentration of 100 mg/mL, all other extracts did not improve resistance of human erythrocytes to H_2O_2-induced hemolysis.

In another study, a 70% aqueous EtOH extract of *G. collinum* roots increased SOD, CAT and GR activities, by factors ranging from 1.4 to 2.7, in erythrocytes from rats with alloxan-induced diabetes [202]. A significant decrease in erythrocyte membrane lipid peroxidation (LPO) was also observed.

4.14. Antiprotozoal Activity

The antiprotozoal activity in the *Geranium* genus seems to have been assessed only in two species. In a screening of the antiprotozoal potential of some Mexican medicinal plants, Calzada *et al.* found that the MeOH extract of the roots of *G. niveum* possessed significant *in vitro* activity against axenically grown trophozoites of *Entamoeba histolytica* HM1:IMSS (IC_{50} = 8.7 μg/mL), the protozoa causing amoebic dysentery, and *Giardia lamblia* IMSS:0989:1 (IC_{50} = 20.6 μg/mL), the microorganism responsible for giardiasis [47]. Metronidazole, an imidazolic antiprotozoal drug, was used as positive control presenting IC_{50} = 0.04 μg/mL for *E. histolytica* and IC_{50} = 0.21 μg/mL for *G. lamblia*.

G. mexicanum, an endemic species also used in Mexican traditional medicine, also possesses antiprotozoal properties. While the crude MeOH extract of the aerial parts of the plant presented weak *in vitro* activity against *E. histolytica* HM1:IMSS and *G. lamblia* IMSS:0989:1 (IC_{50} = 139.9 and 267.1 μg/mL, respectively) [203], the CH_2Cl_2-MeOH (1:1) extract of the roots was shown to be somewhat more active, with an IC_{50} value of 79.2 μg/mL for *E. histolytica* and 100.4 μg/mL for *G. lamblia* [36]. Suspension of the late crude dry extract in 9% aqueous MeOH and extraction with EtOAc furnished an EtOAc soluble fraction with improved antiprotozoal activity (*E. histolytica* IC_{50} = 66.7 μg/mL; *G. lamblia* IC_{50} = 63.7 μg/mL). In both cases, besides metronidazole, emetine was used likewise as control displaying IC_{50} = 1.05 μg/mL for *E. histolytica* and IC_{50} = 0.42 μg/mL for *G. lamblia*. The MeOH extract of the roots of *G. mexicanum* also exhibited activity against the flagellate protozoan *Trichomonas vaginalis* GT3, the etiological agent of trichomoniasis, with an IC_{50} value of 56.0 μg/mL [37].

4.15. Antipyretic Activity

Li *et al.* showed that an aqueous extract of *G. carolinianum* possessed significant antipyretic action, in a dose-dependent manner, in Sprague-Dawley rats with fever induced by intra-peritoneal injection of lipopolysaccharides (LPS) [165]. At doses of 250 and 500 mg/kg the extract displayed antipyretic effect similar to that of paracetamol at 100 mg/kg.

An aqueous extract of *G. ocellatum* leaves at a dose of 200 mg/kg also exhibited antipyretic activity in Brewer's yeast-induced pyrexia in rats, comparable to that of aspirin (100 mg/kg) [138].

4.16. Antiviral Activity

The antiviral potential of species from the *Geranium* genus has been assessed against influenza virus, herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), hepatitis B virus (HBV) and human immunodeficiency virus (HIV). The investigation of the anti-influenza activity of *Geranium* genus has been dominated by the studies conducted by Serkedjieva's research group with *G. sanguineum*. A MeOH extract of the plant, previously defatted with petroleum ether, which was termed polyphenolic complex, was found to be able to inhibit pronouncedly the reproduction of several strains of influenza A and B virus, both *in vitro* (CEF, MDCK and CAM cells) and *in ovo* (embryonated hen's eggs) [204]. It was shown that the inhibitory effect was dose-dependent, strain-specific and dependent on the biological test medium. The extract also reduced the mortality of mice in experimental lethal influenza A/Aichi/2/68 (H3N2) virus infection and prolonged the survival time of the infected animals. The selectivity of the anti-influenza activity of the polyphenolic complex *in vitro* was further confirmed against several other strains of subtypes H1N1, H2N2, H3N2, H3N8, H7N1 and H7N7 of influenza A virus (cultivated in CEF

Table 5. Antioxidant activity and total phenolics content of *Geranium* species.

Geranium Species	Part Used	Extract	Method	Antioxidant Activity	Total Phenolics Content	References
G. ayavacence	Whole plant	H_2O	DPPH (IC_{50})	19 µg/mL	-	[172]
-	-	-	PNRSA (IC_{50})	21 µg/mL	-	-
-	-	-	PRSA (IC_{50})	14 µg/mL	-	-
-	-	-	HRSA (IC_{50})	105 µg/mL	-	-
G. bellum	Aerial parts	EtOAc[1]	ABTS (% inhibition)[2]	~ 95[3]	-	[173]
-	-	MeOH[1]	ABTS (% inhibition)[2]	~ 40[3]	-	-
-	-	H_2O[1]	ABTS (% inhibition)[2]	~ 20[3]	-	-
G. caeruleum	Aerial parts	MeOH/H_2O (80/20)	DPPH (IC_{50})[4]	~ 30 µg/mL[3]	-	[174]
G. collinum	Aerial parts	EtOH/H_2O (70/30)	DPPH (IC_{50})	0.027 ± 0.002 mg/mL	131.7 ± 7.86 mg GAE/g	[175]
-	-	-	ABTS (IC_{50})	0.15 ± 0.01 mg/mL	-	-
-	-	-	FRAP	1852.75 ± 77.4 mmol Fe^{2+}/g	-	-
-	Roots	EtOH/H_2O (70/30)	DPPH (IC_{50})	0.045 ± 0.003 mg/mL	82.60 ± 4.94 mg GAE/g	-
-	-	-	ABTS (IC_{50})	0.19 ± 0.02 mg/mL	-	-
-	-	-	FRAP	1030.52 ± 58.9 mmol Fe^{2+}/g	-	-
-	Roots	H_2O	DPPH (IC_{50})[5]	15.17 ± 0.84 µg/mL	12.21 ± 0.10 mg GAE/g	[152]
-	-	EtOH/H_2O (30/70)	DPPH (IC_{50})[5]	10.89 ± 0.63 µg/mL	83.74 ± 0.18 mg GAE/g	-
-	-	EtOH/H_2O (50/50)	DPPH (IC_{50})[5]	11.21 ± 0.49 µg/mL	349.84 ± 0.21 mg GAE/g	-
-	-	EtOH/H_2O (70/30)	DPPH (IC_{50})[5]	12.69 ± 0.6µg/mL	180.14 ± 0.11 mg GAE/g	-
-	-	EtOH	DPPH (IC_{50})[5]	11.23 ± 0.7 µg/mL	100.42 ± 0.14 mg GAE/g	-
G. columbinum	Aerial parts	MeOH/H_2O (80/20)	DPPH (IC_{50})[4]	~ 30 µg/mL[3]	-	[174]
G. favosum	Whole plant	CH_2Cl_2[6]	DPPH (% inhibition)[7]	16.38 ± 0.00	0.254 ± 0.02 mg GAE/g	[176]
-	-	-	FCC (% inhibition)[8]	30.99 ± 0.03	-	-
-	-	EtOAc[6]	DPPH (% inhibition)[7]	12.17 ± 0.01	0.223 ± 0.12 mg GAE/g	-
-	-	-	FCC (% inhibition)[8]	13.13 ± 0.08	-	-
-	-	MeOH[6]	DPPH (% inhibition)[7]	92.06 ± 0.00	1.738 ± 0.05 mg GAE/g	-
-	-	-	FCC (% inhibition)[8]	4.25 ± 0.08	-	-
-	-	-	DMPD (% inhibition)[9]	55.73 ± 0.16	-	-
G. glaberrimum	Aerial parts	EtOAc[10]	DPPH (% inhibition)[11]	~ 90[3]	-	[99]
-	-	*n*-BuOH[10]	DPPH (% inhibition)[11]	~ 80[3]	-	-
-	-	H_2O[10]	DPPH (% inhibition)[11]	~ 5[3]	-	-
G. kikianum	Aerial parts	essential oil[12]	DPPH (IC_{50})[13]	69.7 ± 0.5 mg/mL	-	[177]
-	-	residual H_2O[12]	DPPH (IC_{50})[13]	0.20 ± 0.03 mg/mL	100.2 ± 1.7 mg GAE/g	-
G. krameri	Leaves	EtOH/H_2O (70/30)	DPPH (IC_{50})[16]	8.72 µg/mL	-	[126]
G. lasiopus	Aerial parts	EtOAc[10]	DPPH (% inhibition)[15]	80.143	-	[102]
-	-	*n*-BuOH[10]	DPPH (% inhibition)[15]	66.167	-	-
-	-	H_2O[10]	DPPH (% inhibition)[15]	2.447	-	-

(Table 5) Contd....

Geranium Species	Part Used	Extract	Method	Antioxidant Activity	Total Phenolics Content	References
-	Aerial parts	EtOAc[10]	H_2O_2-ILP (% inhibition)[16,17]	~ 70[3]	-	[178]
-	-	*n*-BuOH[10]	H_2O_2-ILP (% inhibition)[16,17]	~ 65[3]	-	
-	-	H_2O[10]	H_2O_2-ILP (% inhibition)[16,17]	~ 70[3]	-	
G. lucidum	Aerial parts	MeOH/H_2O (80/20)	DPPH (IC_{50})[4]	~ 45 µg/mL[3]	-	[174]
G. macrorrhizum	Aerial parts	MeOH/H_2O (80/20)	DPPH (IC_{50})[4]	10.58 µg/mL	-	[174]
-	Leaves	EtOAc	DPPH (% inhibition)[18]	26.9 ± 1.4	25.9 ± 0.2 mg mg GAE/g	[179]
-	-	Acetone	DPPH (% inhibition)[18]	44.6 ± 1.2	-	
-	-	MeOH	DPPH (% inhibition)[18]	91.7 ± 0.6	-	
-	-	-	ABTS (% inhibition)[18]	~ 100	-	
-	Leaves	MeOH	DPPH	178.7 ± 1.8 mg TE/g	160.2 ± 3.1 mg GAE/g	[104]
-	-	-	ABTS	323.3 ± 1.2 mg TE/g	-	-
-	-	-	IRA	84.2 ± 0.2 mg GAE/g	-	-
-	-	-	FRAP	1347.9 ± 46.7 µmol Fe^{2+}/g	-	-
-	-	-	CUPRAC	466.0 ± 4.1 mg TE/g	-	-
-	-	EtOH	DPPH	71.0 ± 0.5 mg TE/g	109.5 ± 3.8 mg GAE/g	-
-	-	-	ABTS	205.9 ± 1.0 mg TE/g	-	-
-	-	-	IRA	17.83 ± 0.3 mg GAE/g	-	-
-	-	-	FRAP	936.6 ± 26.3 µmol Fe^{2+}/g	-	-
-	-	-	CUPRAC	355.0 ± 6.5 mg TE/g	-	-
-	-	Acetone	DPPH	9.50± 0.09 mg TE/g	13.8 ± 0.5 mg GAE/g	-
-	-	-	ABTS	11.3 ± 0.09 mg TE/g	-	-
-	-	-	IRA	4.0 ± 0.3 mg GAE/g	-	-
-	-	-	FRAP	79.5 ± 3.7 µmol Fe^{2+}/g	-	-
-	-	-	CUPRAC	30.5 ± 0.4 mg TE/g	-	-
-	-	EtOAc	DPPH	4.2 ± 0.09 mg TE/g	6.2 ± 0.4 mg GAE/g	-
-	-	-	ABTS	5.7 ± 0.08 mg TE/g	-	-
-	-	-	IRA	2.1 ± 0.03 mg GAE/g	-	-
-	-	-	FRAP	30.4 ± 1.3 µmol Fe^{2+}/g	-	-
-	-	-	CUPRAC	21.1 ± 0.3 mg TE/g	-	-
-	Rhizomes	MeOH	DPPH	106.4 ± 1.8 mg TE/g	85.7 ± 1.3 mg GAE/g	-
-	-	-	ABTS	169. 5 ± 1.1 mg TE/g	-	-
-	-	-	IRA	42.4 ± 0.2 mg GAE/g	-	-
-	-	-	FRAP	632.1 ± 9.0 µmol Fe^{2+}/g	-	-
-	-	-	CUPRAC	268.9 ± 2.2 mg TE/g	-	-
-	-	EtOH	DPPH	50.0 ± 0.5 mg TE/g	50.6 ± 2.0 mg GAE/g	-
-	-	-	ABTS	72.2 ± 1.0 mg TE/g	-	-
-	-	-	IRA	11.6 ± 0.3 mg GAE/g	-	-

(Table 5) Contd....

Geranium Species	Part Used	Extract	Method	Antioxidant Activity	Total Phenolics Content	References
-	-	-	FRAP	355.3 ± 4.0 µmol Fe^{2+}/g	-	-
-	-	-	CUPRAC	207.5 ± 3.2 mg TE/g	-	-
-	-	Acetone	DPPH	20.4 ± 0.7 mg TE/g	22.4 ± 0.8 mg GAE/g	-
-	-	-	ABTS	20.3 ± 0.1 mg TE/g	-	-
-	-	-	IRA	8.5 ± 0.4 mg GAE/g	-	-
-	-	-	FRAP	108.3 ± 6.0 µmol Fe^{2+}/g	-	-
-	-	-	CUPRAC	49.8 ± 0.6 mg TE/g	-	-
-	-	EtOAc	DPPH	4.1 ± 0.2 mg TE/g	5.5 ± 0.06 mg GAE/g	-
-	-	-	ABTS	4.4 ± 0.05 mg TE/g	-	-
-	-	-	IRA	2.1 ± 0.07 mg GAE/g	-	-
-	-	-	FRAP	24.6 ± 0.8 µmol Fe^{2+}/g	-	-
-	-	-	CUPRAC	14.8 ± 0.08 mg TE/g	-	-
-	Leaves	subcritical H_2O	DPPH[19]	197.0 ± 4.3 mg TE/g	~ 140 mg GAE/g	[105]
-	-	-	FRAP[19]	148.32 ± 10.75 mg AAE/g	-	-
-	-	-	TAC[20]	31.65 ± 1.22 mg GAE/g	-	-
-	Leaves	MeOH	DPPH (IC_{50})[21]	14.1 µg/mL	-	[133]
-	-	-	ABTS (IC_{50})[22]	21.2 µg/mL	-	-
-	-	-	FRAP[23]	2419.8 µM Fe^{2+}/mg	-	-
-	Roots	MeOH	DPPH (IC_{50})[21]	5.5 µg/mL	-	-
-	-	-	ABTS (IC_{50})[22]	4.7 µg/mL	-	-
-	-	-	FRAP[23]	3566.4 µM Fe^{2+}/mg	-	-
-	Flowers	EtOH/H_2O (95/5)	DPPH	242.9 ± 0.1 mM TE/g	19.79 ± 0.11 mg GAE/g	[180]
-	-	-	FRAP	106.3 ± 0.4 mM TE/g	-	-
-	-	EtOH/H_2O (70/30)	DPPH	162.1 ± 0.4 mM TE/g	10.48 ± 0.03 mg GAE/g	-
-	-	-	FRAP	97.7 ± 0.2 mM TE/g	-	-
-	-	MeOH/H_2O (80/20)	DPPH	156.8 ± 0.3 mM TE/g	9.89 ± 0.05 mg GAE/g	-
-	--	-	FRAP	67.7 ± 0.2 mM TE/g	-	-
-	-	H_2O	DPPH	192.4 ± 0.1 mM TE/g	12.35 ± 0.07 mg GAE/g	-
-	-	-	FRAP	97.7 ± 0.5 mM TE/g	-	-
G. molle	Whole plant	H_2O (infusion)	DPPH (EC_{50})[24]	324 ± 9 µg/mL	79 ± 1 mg GAE/g	[128]
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	197 ± 8 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	54 ± 3 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	141 ± 1 µg/mL	-	-
-	-	H_2O (decoction)	DPPH (EC_{50})[24]	248 ± 4 µg/mL	63 ± 1 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	249 ± 9 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	144 ± 7 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	170 ± 6 µg/mL	-	-

(Table 5) Contd....

Geranium Species	Part Used	Extract	Method	Antioxidant Activity	Total Phenolics Content	References
-	-	*n*-Hexane	DPPH (EC_{50})[24]	1816 ± 126 µg/mL	13 ± 1 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	226 ± 4 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	98 ± 4 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	266 ± 5 µg/mL	-	-
-	-	CH_2Cl_2	DPPH (EC_{50})[24]	>10 000 µg/mL	6.15 ± 0.03 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	253 ± 11 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	130 ± 6 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[37]	265 ± 1 µg/mL	-	-
-	-	EtOAc	DPPH (EC_{50})[24]	128 ± 5 µg/mL	216 ± 2 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	212 ± 5 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	34 ± 2 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	51 ± 1 µg/mL	-	-
-	-	Acetone	DPPH (EC_{50})[24]	18.9 ± 0.5 µg/mL	497 ± 8 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	61 ± 3 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	6.5 ± 0.2 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	20.3 ± 0.2 µg/mL	-	-
-	-	MeOH	DPPH (EC_{50})[24]	135 ± 3 µg/mL	76 ± 5 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	274 ± 6 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	38 ± 2 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	105 ± 4 µg/mL	-	-
G. nepalense	Whole plant	EtOH/H_2O (70/30)	DPPH (IC_{50})	46.3 ± 0.84 µg/mL	169.4 ± 7.84 mg GAE/g	[181]
-	-	-	ABTS (IC_{50})	80.9 ± 0.77 µg/mL	-	-
-	-	-	SOD-like activity (IC_{50})	23.4 ± 1.25 µg/mL	-	-
G. niveum	Roots	MeOH/$CHCl_3$ (1/1)	DPPH (IC_{50})[28]	7.3 µg/mL	-	[48]
-	-	-	ABTS (IC_{50})[29]	17.8 µg/mL	-	-
-	-	-	SRSA (IC_{50})[30]	6.5 µg/mL	-	-
-	-	-	HRSA (IC_{50})[31]	0.2 µg/mL	-	-
		$CHCl_3$[32]	DPPH (IC_{50})[31]	92.0 µg/mL	-	-
-	-	-	HRSA (IC_{50})[31]	0.1 µg/mL	-	-
G. pratense	Leaves & flowers	H_2O	DPPH (% control)	13	-	[182]
-	-	-	SRSA (% control)	~5[3]	-	-
-	-	-	HRSA (% control)	27	-	-
G. psilostemon	Aerial parts	EtOAc[10]	DPPH (% inhibition)[11]	~ 80[3]	-	[99]
-	-	*n*-BuOH[10]	DPPH (% inhibition)[11]	~ 40[3]	-	-
-	-	H_2O[10]	DPPH (% inhibition)[11]	~ 20[3]	-	-
-	Aerial parts	EtOAc[10]	SRSA (IC_{50})	29.4 µg/mL	345.06. ±.0.12 mg GAE/g	[131]
-	-	-	NORSA (IC_{50})	98.4 µg/mL	-	-

(Table 5) Contd....

Geranium Species	Part Used	Extract	Method	Antioxidant Activity	Total Phenolics Content	References
-	-	-	ABTS[33]	0.371 ± 0.29 µM TE	-	-
-	-	*n*-BuOH[10]	SRSA (IC_{50})	29.4 µg/mL	281.08 ± 0.23 mg GAE/g	-
-	-	-	NORSA (% inhibition)[34]	~ 20[3]	-	-
-	-	-	ABTS[33]	0.301±0.30 µM TE	-	-
-	-	H_2O[10]	SRSA (% inhibition)[35]	~ 60[3]	224.64. ±.0.21 mg GAE/g	-
-	-	-	NORSA (% inhibition)[34]	~ 25[3]	-	-
-	-	-	ABTS[33]	0.284 ± 0.07µM TE	-	-
G. purpureum	Leaves	ground material	PF[36]	3.1	28.2 ± 0.1 mg GAE/g	[109]
-	-	MeOH	PF[36]	2.9	-	-
-	Aerial parts	H_2O	TAA	333.30 ± 15.0 mg AAE/g	219.52 ± 9.35 mg GAE/g	[108]
-	-	-	Reducing power	169.07 ± 3.21 mg Trolox/g	-	-
-	-	-	FRAP	467.24 ± 7.85 mg Trolox/g	-	-
-	-	-	DPPH (IC_{50})	211.57 ± 5.82 µg/mL	-	-
-	-	EtOH/H_2O (80/20)	TAA	472.04 ± 22.99 mg AAE/g	293.22 ± 14.28 mg GAE/g	-
-	-	-	Reducing power	295.51 ± 9.53 mg Trolox/g	-	-
-	-	-	FRAP	705.91 ± 15.21 mg Trolox/g	-	-
-	-	-	DPPH (IC_{50})	211.44 ± 10.33 µg/mL	-	-
-	-	EtOH	TAA	536.90 ± 21.67 mg AAE/g	326.90 ± 7.82 mg GAE/g	-
-	-	-	Reducing power	681.58 ± 20.18 mg Trolox/g	-	-
-	-	-	FRAP	783.48 ± 20.50 mg Trolox/g	-	-
-	-	-	DPPH (IC_{50})	197.16 ± 7.38 µg/mL	-	-
-	Aerial parts	EtOH	DPPH (IC_{50})[37]	1.700 ± 0.001 µg/mL	0.368 ± 0.002 mg GAE/mg	[183]
-	-	-	ABTS (IC_{50})[38]	259.89 ± 0.02 mM TE/mg	-	-
-	-	-	FCC (%)[39]	31.67 ± 0.95	-	-
-	Aerial parts	EtOAc[10]	DPPH (% inhibition)[15]	88.761	-	[102]
-	-	*n*-BuOH[10]	DPPH (% inhibition)[15]	40.390	-	-
-	-	H_2O[10]	DPPH (% inhibition)[15]	33.708	-	-
G. pyrenaicum	Aerial parts	MeOH/H_2O (80/20)	DPPH (IC_{50})[4]	13.61 µg/mL	-	[174]
G. robertianum	Whole plant	H_2O (infusion)	DPPH (EC_{50})[24]	65 ± 1 µg/mL	228 ± mg GAE/g	[127]
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	145 ± 8 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	7.24 ± 0.05 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	52 ± 1 µg/mL	-	-
-	-	H_2O (decoction)	DPPH (EC_{50})[24]	60 ± 1 µg/mL	212 ± 4 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	117 ± 4 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	7.3 ± 0.2 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	61 ± 3 µg/mL	-	-
-	-	*n*-Hexane	DPPH (EC_{50})[24]	877 ± 9 µg/mL	30.7 ± 0.5 mg GAE/g	-

(Table 5) Contd....

Geranium Species	Part Used	Extract	Method	Antioxidant Activity	Total Phenolics Content	References
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	178 ± 10 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	24 ± 1 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	234 ± 1 µg/mL	-	-
-	-	CH_2Cl_2	DPPH (EC_{50})[24]	1304 ± 71 µg/mL	3.8 ± 0.1 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	420 ± 36 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	262 ± 9 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	544 ± 6 µg/mL	-	-
-	-	EtOAc	DPPH (EC_{50})[24]	231 ± 3 µg/mL	176 ± 3 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	447 ± 19 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	37.2 ± 0.4 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	125 ± 1 µg/mL	-	-
-	-	Acetone	DPPH (EC_{50})[24]	54 ± 1 µg/mL	347 ± 4 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	110 ± 1 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	0.36 ± 0.04 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	40.4 ± 0.2 µg/mL	-	-
-	-	MeOH	DPPH (EC_{50})[24]	58 ± 1 µg/mL	268 ± 8 mg GAE/g	-
-	-	-	β-Carotene/linoleic acid (EC_{50})[25]	119 ± 1 µg/mL	-	-
-	-	-	TBARS (EC_{50})[26]	11.0 ± 0.4 µg/mL	-	-
-	-	-	Reducing power (EC_{50})[27]	48 ± 1 µg/mL	-	-
-	Leaves	MeOH/H_2O (99/1)	DPPH (IC_{50})[40]	64.56 µg/mL	-	[112]
-	Leaves	H_2O (decoction)[41]	DPPH (IC_{50})[42]	7.6 ± 0.6 µg/mL	-	[166]
-	-	-	ABTS (IC_{50})[43]	3.9 ± 0.6 µg/mL	-	-
-	-	-	HRSA (IC_{50})[44]	45.1 ± 2.4 µg/mL	-	-
-	-	-	FRAP (IC_{50})[45]	63.3 ± 5.4 µg/mL	-	-
-	-	-	TBARS (IC_{50})[46]	115.8 ± 16.1 µg/mL	-	-
-	-	-	ORAC	1.8 ± 0.1 µM TE/mg	-	-
-	-	-	NORSA (IC_{50})[47]	20.0 ± 0.9 µg/mL	-	-
-	Stems	H_2O (decoction))[41]	DPPH (IC_{50})[42]	17.3 ± 0.3 µg/mL	-	-
-	-	-	ABTS (IC_{50})[43]	5.8 ± 0.5 µg/mL	-	-
-	-	-	HRSA (IC_{50})[44]	59.8 ± 8.4 µg/mL	-	-
-	-	-	FRAP (IC_{50})[45]	93.5 ± 5.5 µg/mL	-	-
-	-	-	TBARS (IC_{50})[46]	210.4 ± 38.6 µg/mL	-	-
-	-	-	ORAC	1.3 ± 0.0 µM TE/mg	-	-
-	-	-	NORSA (IC_{50})[47]	24.2 ± 8.0 µg/mL	-	-
G. ruizii	Whole plant	EtOH/H_2O (96/4)	DPPH (% inhibition)[48]	23.7	-	[148]
-	Aerial parts	EtOH/H_2O (96/4)	DPPH (IC_{50})[49]	24.21 ± 2.14 µg/mL	35 ± 3.5 mg GAE/g	[134]
-	-	-	ABTS (IC_{50})[50]	32.45 ± 2.00 µg/mL	-	-

(Table 5) Contd....

Geranium Species	Part Used	Extract	Method	Antioxidant Activity	Total Phenolics Content	References
G. sanguineum	Aerial roots	MeOH[51]	DPPH (IC_{50})[52]	13.86 ± 0.84 µg/mL	34.60 % (w/w)	[184]
-	-	-	SRSA (IC_{50})[53]	26.0 µg/mL	-	-
-	-	-	β-Carotene/linoleic acid (% inhibition)[54]	88-89	-	-
-	Aerial parts	MeOH/H_2O (80/20)	DPPH (IC_{50})[4]	11.93 µg/mL	-	[174]
G. sibiricum	Whole plant	H_2O (decoction)	DPPH (IC_{50})[55]	2.92 µg/mL	169.46 mg GAE/g	[185]
-	-	-	SRSA (IC_{50})[56]	6.34 µg/mL	-	-
-	-	-	NORSA (IC_{50})[57]	6.11 µg/mL	-	-
-	-	-	β-Carotene/linoleic acid (IC_{50})[58]	4.58 µg/mL	-	-
-	-	-	XOD inhibition (IC_{50})[59]	266.14 µg/mL	-	-
-	-	-	Reducing power[60]	6.17 µg/mL	-	-
-	-	-	FRAP[61]	3.91 mmol Fe^{2+}/g	-	-
-	-	EtOH/H_2O (50/50)	DPPH (IC_{50})[55]	2.46 µg/mL	218.39 mg GAE/g	-
-	-	-	SRSA (IC_{50})[56]	5.18 µg/mL	-	-
-	-	-	NORSA (IC_{50})[57]	4.58 µg/mL	-	-
-	-	-	β-Carotene/linoleic acid (IC_{50})[58]	4.01 µg/mL	-	-
-	-	-	XOD inhibition (IC_{50})[59]	342.27 µg/mL	-	-
-	-	-	Reducing power[60]	5.79 µg/mL	-	-
-	-	-	FRAP[61]	6.67 mmol Fe^{2+}/g	-	-
-	-	Petroleum ether[62]	DPPH (IC_{50})[55]	48.34 µg/mL	130.78 mg GAE/g	-
-	-	-	SRSA (IC_{50})[56]	91.66 µg/mL	-	-
-	-	-	NORSA (IC_{50})[57]	58.43 µg/mL	-	-
-	-	-	β-Carotene/linoleic acid (IC_{50})[58]	70.16 µg/mL	-	-
-	-	-	XOD inhibition (IC_{50})[59]	> 500 µg/mL	-	-
-	-	-	Reducing power[60]	66.20 µg/mL	-	-
-	-	-	FRAP[61]	1.29 mmol Fe^{2+}/g	-	-
-	-	EtOAc[62]	DPPH (IC_{50})[55]	0.93 µg/mL	425.36 mg GAE/g	-
-	-	-	SRSA (IC_{50})[56]	3.32 µg/mL	-	-
-	-	-	NORSA (IC_{50})[57]	2.06 µg/mL	-	-
-	-	-	β-Carotene/linoleic acid (IC_{50})[58]	2.66 µg/mL	-	-
-	-	-	XOD inhibition (IC_{50})[59]	198.85 µg/mL	-	-
-	-	-	Reducing power[60]	1.64 µg/mL	-	-
-	-	-	FRAP[61]	17.76 mmol Fe^{2+}/g	-	-
-	-	*n*-BuOH[62]	DPPH (IC_{50})[55]	1.37 µg/mL	327.17 mg GAE/g	-
-	-	-	SRSA (IC_{50})[56]	3.35 µg/mL	-	-
-	-	-	NORSA (IC_{50})[57]	2.75 µg/mL	-	-
-	-	-	β-Carotene/linoleic acid (IC_{50})[58]	7.02 µg/mL	-	-
-	-	-	XOD inhibition (IC_{50})[59]	314.02 µg/mL	-	-

(Table 5) Contd....

Geranium Species	Part Used	Extract	Method	Antioxidant Activity	Total Phenolics Content	References
-	-	-	Reducing power[60]	2.14 µg/mL	-	-
-	-	-	FRAP[61]	13.22 mmol Fe^{2+}/g	-	-
-	-	H_2O[62]	DPPH (IC_{50})[55]	18.33 µg/mL	68.03 mg GAE/g	-
-	-	-	SRSA (IC_{50})[56]	29.71 µg/mL	-	-
-	-	-	NORSA (IC_{50})[57]	24.32 µg/mL	-	-
-	-	-	β-Carotene/linoleic acid (IC_{50})[58]	39.87 µg/mL	-	-
-	-	-	XOD inhibition (IC_{50})[59]	321.39 µg/mL	-	-
-	-	-	Reducing power[60]	25.59 µg/mL	-	-
-	-	-	FRAP[61]	2.5 mmol Fe^{2+}/g	-	-
-	Whole plant	H_2O[63]	FRAP	2.61 mmol Fe^{2+}/g	-	[186]
-	-	-	DPPH (IC_{50})	0.118 mg/mL	-	-
-	Whole plant	MeOH	DPPH (% inhibition)	92.9 ± 0.3	124.2 ± 0.3 µg GAE/mL	[114]
G. tuberosum	Aerial parts	EtOAc[10]	DPPH (% inhibition)[11]	~ 90[3]	-	[99]
-	-	*n*-BuOH[10]	DPPH (% inhibition)[11]	~ 75[3]	-	-
-	-	H_2O[10]	DPPH (% inhibition)[11]	~ 35[3]	-	-
-	Aerial parts	EtOAc[64]	H_2O_2-ILP (% of inhibition)[16]	~ 80[3]	-	[187]
-	-	*n*-BuOH[64]	H_2O_2-ILP (% of inhibition)[16]	~ 65[3]	-	-
-	-	H_2O[64]	H_2O_2-ILP (% of inhibition)[16]	~ 60[3]	-	-
-	Aerial parts	EtOAc[10]	SRSA (% inhibition)[35]	~ 70[3]	389.09 ± 0.84 mg GAE/g	[131]
-	-	-	NORSA (% inhibition)[34]	~ 25[3]	-	-
-	-	-	ABTS[33]	0.326 ± 0.28 µM TE	-	-
-	-	*n*-BuOH[10]	SRSA (% inhibition)[35]	~ 65[3]	271.86 ± 0.42 mg GAE/g	-
-	-	-	NORSA (% inhibition)[34]	~ 20[3]	-	-
-	-	-	ABTS[33]	0.300 ± 0.21 µM TE	-	-
-	-	H_2O[10]	SRSA (% inhibition)[35]	~ 60[3]	208.10 ± 0.82 mg GAE/g	-
-	-	-	NORSA (% inhibition)[34]	~ 20[3]	-	-
-	-	-	ABTS[33]	0.262 ± 0.34 µM TE	-	-
G. sylvicatum	Aerial parts	MeOH/H_2O (80/20)	DPPH (IC_{50})[4]	~ 30 µg/mL[3]	-	[174]
G. thunbergii	Stem, leaves	MeOH	IAC water-soluble substances	598.7 ± 10.9 µmol AA/g	53.3 ± 2.8 mg GAE/g	[188]
-	-	-	IAC lipid-soluble substances	296.3 ± 26.8 µmol Trolox/g	-	-
-	Stem, leaves	EtOH/H_2O (40/60)	IAC water-soluble substances	9.76 ± 0.14 mmol AAE/g	104 ± 2.4 mg GAE/g	[189]
-	-	-	IAC lipid-soluble substances	5.20 ± 0.04 mmol TE/g	-	-
-	Whole plant	*n*-hexane[65]	DPPH (% inhibition)[66]	13.43 ± 0.67	83.72 ± 5.04 mg GAE/g	[116]
-	-	-	ABTS (% inhibition)[67]	6.63 ± 0.33	-	-
-	-	$CHCl_3$[65]	DPPH (% inhibition)[66]	26.24 ± 1.01	148.83 ± 1.40 mg GAE/g	-
-	-	-	ABTS (% inhibition)[67]	21.36 ± 1.90	-	-
-	-	AcOEt[65]	DPPH (% inhibition)[66]	80.88 ± 1.34	604.28 ± 1.95 mg GAE/g	-
-	-	-	ABTS (% inhibition)[67]	80.12 ± 2.41	-	-

(Table 5) Contd....

Geranium Species	Part Used	Extract	Method	Antioxidant Activity	Total Phenolics Content	References
-	-	*n*-BuOH[65]	DPPH (% inhibition)[66]	73.48 ± 1.15	465.65 ± 4.88 mg GAE/g	-
-	-	-	ABTS (% inhibition)[67]	70.72 ± 1.28	-	-
-	-	H_2O[65]	DPPH (% inhibition)[66]	13.76 ± 3.80	98.52 ± 1.18 mg GAE/g	-
-	-	-	ABTS (% inhibition)[67]	15.54 ± 6.58	-	-
-	Whole plant	EtOH/H_2O (95/5)	DPPH (% inhibition)[68]	97.56	96.51 mg TAE/g	[115]
-	-	-	NORSA (% inhibition)[68]	59.74	-	-
-	Whole plant	H_2O (decoction)	DPPH (% inhibition)[69]	100	-	[190]
-	Whole plant	MeOH/H_2O (95/5)	DPPH (% inhibition)[70]	98.33	-	[191]
-	-	-	DCFH-DA (IC_{50})[71]	43.22 µg/mL	-	-
G. tuberosum	Aerial parts	MeOH/H_2O (80/20)	H_2O_2-ILP (% of inhibition)[17,72]	~ 50[3]	-	[192]
-	-	EtOAc[10]	H_2O_2-ILP (% of inhibition)[17,72]	~ 75[3]	-	-
-	-	*n*-BuOH[10]	H_2O_2-ILP (% of inhibition)[17,72]	~ 65[3]	-	-
-	-	H_2O[10]	H_2O_2-ILP (% of inhibition)[17,72]	~ 65[3]	-	-
-	Aerial parts	EtOAc[10]	DPPH (% inhibition)[15]	92.821	-	[102]
-	-	*n*-BuOH[10]	DPPH (% inhibition)[15]	74.040	-	-
-	-	H_2O[10]	DPPH (% inhibition)[15]	28.407	-	-
G. wallichianum	Roots	EtOAc[73]	DPPH (IC_{50})[74]	19.05 ± 0.90 µg/mL	-	[193]
-	-	*n*-BuOH[73]	DPPH (IC_{50})[74]	24.133 ± 0.56 µg/mL	-	-
-	-	H_2O[73]	DPPH (IC_{50})[74]	25.35 ± 1.20 µg/mL	-	-
G. wilfordii	Whole plant	MeOH/H_2O (80/20)	FRAP	347.33 ± 7.99 µmol Fe^{2+}/g	14.98 ± 0.64 mg GAE/g	[194]
-	-	-	ABTS	215.98 ± 4.10 µmol TE/g	-	-

AA - Ascorbic acid. AAE- Ascorbic acid equivalent. ABTS - 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid). BHA - 3-*tert*-Butyl-4-hydroxyanisole. BHT - 2,6-Di-*tert*-butyl-4-methylphenol. CUPRAC - Cupric reducing antioxidant capacity. DCFH-DA - Dichlorodihydrofluorescein diacetate. DMPD - *N*,*N*-Dimethyl-*p*-phenylenediamine. DPPH - 2,2-Diphenyl-1-picrylhydrazyl. EC_{50} - Extract concentration corresponding to 50% of antioxidant activity or 0.5 of absorbance in reducing power assay. FCC - Ferrous chelating capacity. FRAP - Ferric reducing antioxidant power. GAE - Gallic acid equivalent. H_2O_2-ILP hydrogen peroxyde-induced lipid peroxidation. HRSA - Hydroxyl radical scavenging activity. IAC - Integral antioxidant capacity. IC_{50} - Concentration at which inhibition is 50%. IRA - Iron (III) reduction activity. NORSA - Nitric oxide radical scavenging activity. ORAC - Oxygen radical absorbance capacity. PF - Protection factor. PNRSA - Peroxynitrite radical scavenging activity. PRSA - Peroxyl radical scavenging activity. SOD - Superoxide dismutase. SRSA - Superoxide radical scavenging activity. TAC - Total antioxidant capacity. TAE - Tannic acid equivalent. TBARS - Thiobarbituric acid reactive substances. TE - Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid) equivalent. XOD - Xanthine oxidase.

[1] Obtained, after defatting with *n*-hexane, by successive extraction with EtOAc, MeOH and H_2O. [2] Concentration of the extract: 1.5 mg/mL. AA (100% inhibition) was used as reference compound. [3] Estimated from bar chart. [4] Quercetin (IC_{50} = 3.1 µg/mL) was used as a reference compound. [5] AA (IC_{50} = 5.34 ± 0.42 µg/mL) was used as reference compound. [6] Obtained, after defatting with *n*-hexane, by successive extraction with CH_2Cl_2, EtOAc and MeOH. [7] Quercetin (90.13 ± 0.31 % inhibition) was used as a reference compound. [8] Quercetin (61.87 ± 0.98 % inhibition) was used as reference compound. [9] Quercetin (68.32 ± 0.99% inhibition) was used as a reference compound. [10] Obtained by successive partition of a crude MeOH/H_2O (80/20) extract between H_2O and petroleum ether, EtOAc and *n*-BuOH. [11] Concentration of the extract: 50 µg/mL. AA (~ 60% inhibition, estimated from bar chart) was used as reference compound. [12] Obtained by hydrodistillation. [13] BHT (IC_{50} = 0.21 ± 0.01 mg/mL) and thymol (1.9 ± 0.04 mg/mL) were used as reference compounds. [14] AA (IC_{50} = 5.65 µg/mL) was used as reference compound. [15] Concentration of the extract: 50 µg/mL. AA (57.623 % inhibition) was used as reference compound. [16] Concentration of the extract: 50 µg/mL. AA (~ 60 % inhibition, estimated from bar chart) and Trolox (~ 40% inhibition, estimated from bar chart) were used as reference compounds. [17] In human red blood cells. [18] Concentration of the extract: 2.5 mg/mL. [19] Extraction at 160ºC. [20] Extraction at 130ºC. [21] Caffeic acid (IC_{50} = 1.7 µg/mL) was used as reference compound. [22] Caffeic acid (IC_{50} = 2.0 µg/mL) was used as a reference compound. [23] Caffeic acid (3383.5 µM Fe^{2+}/mg) was used as reference compound. [24] Trolox (EC_{50} = 42 µg/mL) was used as reference compound. [25] Trolox (EC_{50} = 18 µg/mL) was used as a reference compound. [26] Trolox (EC_{50} = 23 µg/mL) was used as reference compound. [27] Trolox (EC_{50} = 41 µg/mL) was used as reference compound. [28] AA (IC_{50} = 54.6 µM) and resveratrol (IC_{50} = 323.9 µM) were used as reference compounds. [29] AA (IC_{50} = 57.0 µM) and resveratrol (IC_{50} = 5.8 µM) were used as reference compounds. [30] AA (IC_{50} > 1000 µM) and resveratrol (IC_{50} > 1000 µM) were used as reference compounds. [31] Resveratrol (IC_{50} = 0.4 µM) was used as reference compounds. [32] Obtained by partition of the crude MeOH/$CHCl_3$ (1/1) extract with $CHCl_3$ and H_2O. [33] Concentration of the extract: 50 µg/mL. [34] Concentration of the extract: 50 µg/mL. Quercetin (~ 60% inhibition, estimated from bar chart) was used as reference compound. [35] Concentration of the extract: 50 µg/mL. Quercetin (~ 75% inhibition, estimated from bar chart) was used as reference compound. [36] Determined by the Rancimat test using sunflower oil as substrate. [37] AA (IC_{50} = 3.000 ± 0.004 µg/mL) and BHT (IC_{50} = 9.000 ± 0.003 µg/mL) were used as reference compound. [38] BHT (IC_{50} = 252.02 ± 0.04) was used as reference compound. [39] Concentration of the extract: 50 µg/mL. EDTA (95.78 ± 0.20) was used as reference compound. [40] Trolox (IC_{50} = 2.08 µg/mL) was used as reference compound. [41] Defatted with *n*-hexane. [42] AA (IC_{50} = 4.8 ± 0.3 µg/mL) was used as reference compound. [43] AA (IC_{50} = 1.3 ± 0.2 µg/mL) was used as a reference compound. [44] Mannitol (IC_{50} = 196.2 ± 16.4 µg/mL) was used as reference compound. [45] BHT (IC_{50} = 20.0 ± 0.2 µg/mL) was used as reference compound. [46] Trolox (IC_{50} = 41.1 ± 5.2 µg/mL) was used as reference compound. [47] AA (IC_{50} = 285.7 ± 15.4 µg/mL) was used as reference compound. [48] Concentration of the extract: 1 µg/mL. AA (~ 30 % inhibition, estimated from bar chart) and Trolox (~70% inhibition, estimated from bar chart) were used as reference compounds. [49] AA (IC_{50} = 4.01 ± 1.26 µg/mL) was used as reference compound. [50] AA (IC_{50} = 5.00 ± 0.80 µg/mL) was used as a reference compound. [51] After defatting with petroleum ether. [52] BHT (IC_{50} = 19.81 ± 0.05 µg/mL) was used as reference compound. [53] SOD from bovine erytrocytes (IC_{50} = 1.04 µg/mL) and caffeic acid (IC_{50} = 4.9 µg/mL) were used as reference compounds. [54] BHT (~ 90% of inhibition, estimated from bar chart) was used as reference compound. [55] AA (IC_{50} = 9.5 µg/mL) was used as reference compound. [56] Trolox (IC_{50} = 21.54 µg/mL) was used as reference compound. [57] AA (IC_{50} = 1.03 µg/mL) was used as reference compound. [58] BHT (IC_{50} = 10.47 µg/mL) was used as a reference compound. [59] Allopurinol (IC_{50} = 1.72 µg/mL) was used as reference compound. [60] Extract concentration corresponding to 0.5 of absorbance. Trolox (IC_{50} = 0.96 µg/mL) was used as a reference com-

pound. [61] AA (IC_{50} = 11.38 mmol Fe^{2+}/g) was used as reference compound. [62] Obtained by successive partition of a crude EtOH/H_2O (50/50) extract between H_2O and petroleum ether, EtOAc and *n*-BuOH. [63] Microwave assisted enzymatic (cellulase) extraction. [64] Obtained from the partition of a crude MeOH extract between H_2O and petroleum ether, EtOAc and *n*-BuOH. [65] Obtained by successive partition of a MeOH/H_2O (95/5) extract between H_2O and *n*-hexane, $CHCl_3$, EtOAc and *n*-BuOH. [66] Concentration of the extract: 50 µg/mL. BHA (27.02 ± 3.57% inhibition) and AA (96.52 ± 0.29% inhibition) were used reference compounds. [67] Concentration of the extract: 50 µg/mL. BHA (87.70 ± 2.94% inhibition) and AA (99.05 ± 0.92% inhibition) were used as reference compounds. [68] Concentration of the extract: 1%. [69] Concentration of the extract: 0.77 mg/mL. α-Tocopherol, AA and cysteine (100% inhibition at 58.8, 68.8 and 128.6 µM, respectively) were used as reference compounds. [70] Concentration of the extract: 50 µg/mL. Quercetin (78.05% inhibition) was used as reference compound. [71] Using human keratinocytes (HaCaT). Quercetin (IC_{50} = 102.35 µg/mL) was used as a reference compound. [72] Concentration of the extract: 50 µg/mL. AA (~ 45% inhibition, estimated from bar chart) and Trolox (~ 60% inhibition, estimated from bar chart) were used as reference compounds.[73] Obtained by successive partition of a crude MeOH extract between H_2O and *n*-hexane, $CHCl_3$, EtOAc and *n*-BuOH. [74] BHA (IC_{50} = 8.0725 ± 0.65µg/mL) was used as a reference compound.

and MDCK cells) [205, 206]. At non-toxic concentrations, the polyphenolic complex reduced the expression of hemagglutinin (HA) on the surface of CEF cells infected with A/chicken/ Rostock/34 (H7N1), virus-induced cytopathic effect (CPE), infectious virus yield and plaque formation [206]. The results suggested that the early synthetic stages of replication were the most sensitive to the inhibitory action of the extract. Virus-specific protein synthesis was also selectively inhibited. The polyphenolic complex was found to stimulate the phagocytic activity of peritoneal macrophages and blood polymorphonuclear leucocytes isolated from ICR mice and showed a beneficial effect on spontaneous nitric oxide production by the peritoneal and alveolar macrophages [207]. In comparison with the normal parent virus, the *G. sanguineum* polyphenol-rich extract affected in lesser extension the expression of HA, neuraminidase (NA) and nucleoprotein (NP), virus-induced CPE, plaque formation and infectious virus yield of two variants of the avian influenza virus A/chicken/Germany/34 (H7N1) with reduced sensitivity to the extract cultivated in CEF cells [208]. The polyphenolic complex was shown to protect ICR mice from mortality in experimental influenza A/Aichi/2/68 (H3N2) virus infection alternatively through enhancement and restoration of the host immune response [209], regulation of the host lung protease activities [210] and exhibition of *in vivo* antioxidant and radical scavenging properties [211, 212]. A combined antiviral effect of the *G. sanguineum* polyphenolic complex and ε-aminocaproic acid, a protease inhibitor, was observed in MDCK cells and mice infected with influenza A/Aichi/2/68 (H3N2) virus [213]. Combinations of the polyphenolic complex and ε-aminocaproic acid in particular concentrations resulted in the synergistic inhibition of virus replication in the MDCK cells and the protection of mice against viral infection as determined by infectious parameters including lung virus titers, lung weight, mean survival time and mortality rates. The combined dosage of the polyphenolic complex and ε-aminocaproic acid to the infected mice was shown to revert the levels of lung protease and protease-inhibitory activity, which were increased due to the infection, back to normal. Serkedjieva *et al.* also investigated the combined protective effect of the *G. sanguineum* polyphenolic complex and a glycosylated Cu/Zn-containing superoxide dismutase produced by the fungus *Humicula lutea* 103 in experimental influenza A/Aichi/2/68 (H3N2) virus infection in ICR mice [214]. The result was a synergistically increased protection demonstrated by the significant reduction of infectious parameters, such as lung consolidation, lung virus titers, lung weights and mortality rates of infected animals, and the increase of survival times. Moreover, the levels of reactive oxygen species produced by alveolar macrophages as well as the levels of the lung antioxidant enzymes superoxide dismutase and catalase decreased to normal. A synergistic enhancement of the therapeutic efficacy in influenza A/Aichi/2/68 (H3N2) virus infection was also observed with the combined administration of the polyphenolic complex and vitamin C. The combined administration of the polyphenolic complex and rimantadine hydrochloride to human influenza virus A/Aichi/2/68 (H3N2)-infected MDCK cells was shown to reduce the risk of emergence of drug-resistant mutants [215]. The same effect was observed in the experimental influenza A/Aichi/2/68 (H3N2) virus infection in mice. Sokmen *et al.* reported that the *G. sanguineum* polyphenolic complex, as well as its *n*-BuOH soluble fraction, significantly reduced the virus-induced CPE and the production of HA in MDCK cells infected with influenza A/Aichi/2/68 (H3N2) virus [184]. In a murine model of experimental influenza infection with the same variant, the protection of the *n*-BuOH fraction was not relevant, while the EtOAc soluble fraction of the polyphenolic complex exhibited a significant protective effect *in vivo*, close to that of the whole extract. The aerosol administration of the polyphenolic complex proved to be very effective in experimental influenza A/Aichi/2/68 (H3N2) virus infection in ICR mice [216], reducing lung infectious virus titers and lung consolidation of the treated animals in comparison with the control.

The inhibitory effect of the polyphenolic complex obtained from *G. sanguineum* was also evaluated against HSV-1 reproduction *in vitro* (McIntyre and Kupka strains propagated in CEF and Vero cells) [204]. The extract was shown to display virucidal action against HSV-1 and reduced virus titer.

Serkedjieva and Ivancheva further explored the antiherpetic activity of *G. sanguineum* and studied the action of different polar extracts against HSV-1 (Kupka and KOS strains propagated in Vero and E6SM cells, respectively) and HSV-2 (G strain propagated in E6SM cells) [75]. The H_2O soluble fraction of a MeOH extract of the defatted (petroleum ether) aerial roots of the plant was the least toxic for the cell cultures and inhibited significantly the replication of both HSV-1 and HSV-2, with EC_{50} values from 3.6 to 6.2 µg/mL. The inhibitory effect was shown to be dose-dependent, strain-specific and to depend on the inoculum. It was observed that for the full expression of the antiviral effect, it was necessary the presence of the extract during the complete replicative cycle of the virus. In a preliminary assay *in vivo* the extract also delayed the development of herpetic vesicles in albino guinea pigs following infection with HSV-1 (Kupka strain) [75].

A polyphenol-rich extract from *G. carolinianum*, obtained by extraction of the aerial parts of the plant with 50% aqueous EtOH, followed by partition between $CHCl_3$ and H_2O and purification of the aqueous phase by macroporous resin D101 adsorption (elution with 50% aqueous EtOH), showed significant anti-HBV activity both *in vitro* and *in vivo* [18]. The extract effectively inhibited the expression of hepatitis B virus surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) in human HVB-transfected HepG2 2.2.15 cells, in a dose-dependent manner, with IC_{50} values of 46.85 µg/mL and 65.60 µg/mL, respectively. The antiviral effect was additionally confirmed by the decrease of the levels of HBV DNA in the HepG2 2.2.15 cells. In ducks infected with duck hepatitis B virus (DHBV) the polyphenolic extract, dosed intragastricly once a day for 10 days, reduced plasma and liver DHBV DNA levels, in a dose-dependent manner. Additionally, significant improvement of the ducks' livers was verified by histopathological analysis. Several organic fractions from a 95% aqueous EtOH extract of the aerial parts of *G. carolinianum*, obtained by sequential extraction of an aqueous solution of the crude ethanolic extract of the plant with different solvents (petroleum ether, $CHCl_3$, EtOAc, *n*-BuOH), also shown activity against HBV [217]. The extracts inhibited the expression of HBsAg and HBeAg in HepG2 2.2.15 cells with inhibition ratios from 29.0 to 75.8%, and from 18.6 to 56.0%, respectively. The EtOAc extract exhibited the highest anti-HBV activity and was also less toxic to cells.

The polyphenolic complex from *G. sanguineum*, which was extensively used in the studies against the influenza virus, was addi-

tionally shown to have an inhibitory effect on the reproduction of HBV *in vitro* [218].

In an *in vitro* screening of the inhibition ability of aqueous MeOH extracts of 70 plants against human immunodeficiency virus-1 reverse transcriptase, a key enzyme in the life cycle of the HIV-1, Mlinaric *et al.* found that the extract from *G. phaeum* was the second most potent, with an IC_{50} value of 0.067 mg/mL, after removal of tannins, which are regarded as non-specific enzyme inhibitors [219].

Earlier, Serkedjieva reported that the polyphenolic complex from *G. sanguineum* also inhibited the reproduction of HIV-1 *in vitro* [218].

4.17. Diuretic Activity

Although several species of the *Geranium* genus have been mentioned as diuretics, only *G. seemannii* seems to have been investigated regarding the ability to induce diuresis. Montejano-Rodríguez *et al.* showed that the administration by gavage of a defatted EtOH extract of the plant to Wistar rats significantly increased the urine output and electrolyte (sodium, potassium, and chloride) excretion, in a dose-dependent way, when compared to the control group [220]. The analogous action pattern between the EtOH extract and intraperitoneally administered furosemide, a standard diuretic drug, was considered suggestive of a similar mechanism of action.

4.18. Other Enzyme Inhibitory Activities

Sigurdsson and Gudbjarnason showed that a 45% aqueous EtOH extract from *G. sylvaticum* was capable of inhibiting acetylcholinesterase *in vitro*, an enzyme that has been the main target for the symptomatic treatment of Alzheimer's disease, with an IC_{50} = 3.56 mg/mL [221].

An EtOAc soluble fraction from a 95% aqueous EtOH extract of *G. thunbergii* was shown to exhibit potent *in vitro* inhibitory activity against β-secretase enzyme BACE1, in a concentration-dependent manner (69.39% at 50 μg/mL and 95.41% at 100 μg/mL) [222]. BACE1 is a promising therapeutic target for 'disease-modifying' approaches to the treatment of Alzheimer's disease by modulation of the deposition of extracellular amyloid β plaques [223].

One of the consequences of diabetes, as well as of galactosemia, is the development of cataracts through the polyol pathway in which the enzyme aldose reductase plays a central role [224]. Choi *et al.* found that the EtOAc soluble fraction of an EtOH extract of *G. thunbergii* inhibited rat lens aldose reductase activity with an IC_{50} = 2.64 μg/mL [225].

Ismail *et al.* observed that, contrary to the leaves of *G. wallichianum*, which were devoid of inhibitory activity, the extracts of rhizomes possessed varied activities against lipoxygenase and Jack Bean and *Bacillus pasteurii* ureases [117]. Lipoxygenases are dioxygenases enzymes that have been linked to the pathogenesis of various diseases, such as asthma and cancer [226]. Urease activity in human cells is implicated in the pathogenesis of clinical conditions such as peptic ulcers and gastric cancer [227]. The AcOEt fraction, obtained from an initial MeOH extract partitioned successively between water and different organic solvents of increasing polarity, showed the highest inhibitory activities against lipoxygenase (47.5%) and Jack Bean and *B. pasteurii* ureases (83 and 86%, respectively), considerably superior to those of the crude MeOH extract.

An EtOH extract of *G. purpureum* also revealed moderate anti-urease activity with 29.43% inhibition at a concentration of 12.5 mg/mL [183]. Thiourea, used as a positive control, exhibited 78.24% of inhibition at the same concentration.

4.19. Less Explored Activities

Recently, Boisvert *et al.* showed that a MeOH extract of *G. sibiricum* had a significant hair growth-promoting effect *in vitro*, by enhancing proliferation and migration of human dermal papilla cells (hDPCs), a primary cell type that regulates hair growth, superior to that of minoxidil [228]. *In vivo*, topical application of the *G. sibiricum* extract on shaved C57BL/6 mice for 3 weeks also shown to result in more significant hair growth than that obtained with minoxidil.

Starting from the observation that few plants can grow in the vicinity of *G. carolinianum* and *G. koreanum* plants, Qiu *et al.* investigated the allelopathic properties of their essential oils, obtained by hydrodistillation, against several weed species [229]. The essential oils were found to cause significant phytotoxicity on two important agricultural weeds: *Amaranthus viridis* and *Portulaca oleracea*.

CONCLUSION

The *Geranium* genus encompasses a number of species which are endowed with scientifically documented beneficial biological activities. Based on the studies undertaken to assess the corresponding biological activities, many species seem to possess evident therapeutic potential for a variety of diseases. Notwithstanding the different biological activities that have been addressed in some extension, to date their assessment appears to has been performed only *in vitro* and in small animal models. Despite some herbal medicines are efficacious, there is unquestionably a need for more reliable information regarding their efficacy and safety and the ultimate proof can only be achieved by some form of rigorous clinical research and standardization.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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