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GERANIUM PLANTS OF ISRAEL AND PALESTINE: DIVERSITY OF INGREDIENTS WITH HIGH MEDICINAL ACTIVITIES

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ABSTRACT

Geranium genus is part of the Geraniaceae plant family. *Geranium* species are beautiful flowering plant. The species of Israel and Palestine were scarcely studied and published. Most of the published studies focused on chemical compositions. The traditional medicine and ethnobotany extensively utilized these plants. Very few review articles were published about these plants, which is another "strange" fact. Moreover, there was very limited number of publications about the archaeological findings that link these plants with ancient human societies. Antimicrobial and antioxidant activities were significantly published, compared with other medicinal activities and other properties that were rarely published or not at all. Important natural products structures will be presented in figures. The discussion section will mainly focus on the known activities of some of these natural products, in a comparative presentation with other plants. Finally, and based on our literature survey, conclusions and recommendations for future research will be drawn.

KEYWORDS: Geraniaceae, *Geranium*, antimicrobial, antioxidant, ethnomedicine, chemical composition, enzyme inhibition, Palmatine, Columbamine, Geranioside.

1) Introduction: Taxonomy and Published Review Articles

The *Geranium* plant genus, commonly known as Cranesbill, is part of the Geraniaceae plant family, named غرنوقيات in Arabic and גרניים in Hebrew. It is very important to clarify that the plant genus of *Geranium* does not include species commonly named Geraniums which are actually part of the plant genus of *Pelargonium*, sometimes commonly named Storksbills.

The numbers of genera and species included in the Geraniaceae plant family are very highly debated. V.C. Graça ahc cited the numbers of 5-11 genera and around 750 species.[1]

According to S. Esfandani-Bozchaloyi ahc, the genus *Geranium* is the largest among the genera of Geraniaceae plant family and it includes around 430 species.[2] In the reviewed regions, the Geraniaceae plant family consists of five genera, and the *Geranium* genus includes nine species: *Geranium columbinum*, *G. dissectum*, *G. libani*, *G. libanoticum*, *G. lucidum*, *G. molle*, *G. purpureum*, *G. rotundifolium* and *G. tuberosum*.[3]

To the best of our literature search, we found only two significant review articles about the *Geranium* genus: V.C. Graça ahc[4] and B. Alshehri.[5]

2) Ethnobotany and Ethnomedicine of *Geranium* Plants of Israel and Palestine

Traditional medicine and ethnobotany made extensive uses of the *Geranium* plants of Israel and Palestine, mainly outside of this region. The number of publications of folk uses of these plants exceeds the number of modern research publications about them. A summary of ethnobotanical and ethnomedicinal uses of *Geranium* plants of the RR is presented in **Table 1**.

Table 1: Ethnobotany and Ethnomedicine of *Geranium* Plants of Israel and Palestine.

Species	Country/Region; Plant Parts; Method; Uses; Reference
G. columbinum	Georgia; NI; food[6] Turkey; NI; extract; gynecological disorders[7] Ukraine; (mentions in traditional medicine texts)[8]
G. dissectum	Italy; leaves; infusion; anti-hemorrhoids[9] Turkey; leaves; food[10]
G. libanoticum	Turkey; leaves; infusion; intestinal pain[11]
G. lucidum	Bulgaria; NI; pastry fillings[12] India; whole plant; NI; diuretic, astringent[13] Kosovo;whole plant; macerated in olive oil (topical); eczema[14] Pakistan; leaves, roots; NI; NI[15] NI; NI; food[16]
G. molle	Croatia; leaves; food[17] Turkey; NI; extract; gynecological disorders[7] Leaves; food (nutritional composition is presented)[18]
G. purpureum	Italy; leaves; decoction, infusion, poultice; infections, inflammations of oral cavity, tuberculosis, brush[19] Portugal; aerial parts; infusion; anti-ulcer, vulnerary, anticancer, intestinal antispasmodic, digestive, gastric analgesic, hepatic protector, sea-sickness, gall-bladder ailments, gastritis, influenza, intestinal anti-inflammatory, renal antispasmodic[20,22] NI; infusion (tea, soup); stomach/liver/bladder pain, colitis[21] Turkey; NI; extract; gynecological disorders[7] Aerial parts; food[23] Flowers; infusion; diuretic, anti-inflammatory[24] Global; (example of urban ethnopharmacology)[25]

G. rotundifolium	Georgia; NI; food [6] Iran; bulb; decoction; intestinal infections, diarrhea[26] Aerial parts; decoction; adult squirt, intestinal infections[27] Morocco; leaves, decoction; cold[28] Pakistan; NI; NI; food, medicinal[16] Roots; mixed with sugar and milk; joints pain, antispasmodic, urine blockage, cooling effect, epilepsy[29,31,36,37] NI; NI; medicinal (no details)[30,39] Aerial parts; food[32] Roots; mixed with milk; stomach ache, jaundice[33] Whole plant (fresh); juice; astringent, diuretic[34,41] Roots; infusion; mouth/stomach ulcer, hemorrhoids[35] Flowers, leaves; powder; astringent, diuretic[38] Leaves; eaten fresh, powder; sore throat, bleeding, nephritis, bruises[40] Whole plant; food[42] Spain; aerial parts; ointment; wound healing (veterinary)[43]
G. tuberosum	Lebanon; whole plant; decoction; hemorrhoids[44] Turkey; whole plant; black color due[45]

3) Published Activities-Properties of *Geranium* Plants of Israel and Palestine

The number of publications about the activities-properties of the *Geranium* plants of Israel and Palestine is relatively very low, compared with other families and genera that we reviewed so far. The only property that was published in relatively usual intensity is the chemical composition, but not for all species. A summary of these findings is presented in **Table 2**.

Table 2: Published Activities-Properties of *Geranium* Plants of Israel and Palestine.

Activity-Property, Testing Method(s), Result(s), Reference
Geranium columbinum Whole plant or aerial parts ethanolic extract was tested for **antibacterial** activity against *S. aureus* and found inactive.[46,47] EOs (hydrodistillation) of aerial parts and roots were separately prepared and tested for **antimicrobial** activity (against 14 bacterial and 5 fungal strains), resulting higher activity for roots EO. They were also analyzed for chemical composition by GC-MS, where the major component was hexadecanoic acid, 17.6% in aerial parts EO and 60.8 in roots EO.[48] Whole plant acetone extract was analyzed for phenolic composition and the following compounds were detected: luteolin, kaempferol, quercetin (**Figure 1**) and quercetin 3-methyl ether.[49] Aerial parts EO (hydrodistillation) was analyzed with GC-MS resulting previously known compounds.[50]
Geranium dissectum Leaves EO (hydrodistillation) was tested for **antimicrobial** activity (against *S. aureus*, *P. aeruginosa*, *S. Typhi*, *L. innocua*, *C. albicans* and *A. niger*) showing moderate to notable activity. It was analyzed (GC-MS) for chemical composition where the major components were (%): β-citronellol 25.45, geraniol 13.83, 1-menthone 9.46, L-linalool 8.2 and α-gurjunene 9.08 (**Figure 2**).[51]
Geranium libani **No published studies about medicinal activities-properties or chemical composition**

Geranium libanoticum

No published studies about medicinal activities-properties or chemical composition

Geranium lucidum

Whole plant EO (hydrodistillation) was tested for **antimicrobial** activity (against 14 bacterial and 5 fungal strains), showing significant activity. It was also analyzed for chemical composition by GC-MS, where the major component was hexadecanoic acid, 32.3%.[48]

Whole plant acetone extract was analyzed for phenolic composition and thirteen compounds were detected, including myricetin (**Figure 3**)[49]

Aerial parts EO (hydrodistillation) was analyzed with GC-MS resulting previously known compounds.[50]

Aerial parts 80% aqueous methanolic extract was analyzed for TFC and TPC. It had significant **antimicrobial** (against four bacterial and one fungal strains), **anti-inflammatory** (inhibition of protein denaturation) and **antioxidant** (DPPH method) activities.[52]

Aerial parts were separately extracted with water (cold and hot) and 80% aqueous ethanol, and all extracts were analyzed for TFC, TTC and GCC. All extract had clear **antifungal** activity against *P. chrysogenum*, *T. mentagrophytes*, *M. Canis* and *F. oxysporeum*.[53]

Aerial parts 80% aqueous ethanolic extract was analyzed using HPLC affording four alkaloids: Palmatine, Columbamine, *pseudo*-Columbamine (**Figure 3**) and Geraniin; and five glycosides: Geranioside A, Geranioside B, Quercetin 4-*O*-β-glucopyranoside, Quercetin 3-*O*-β-glucopyranoside and Kaempferol- 3-*O*-β-glucopyranoside.[54]a

Flowering aerial parts were separately extracted with boiling water (decoction) and 80% aqueous ethanol, and both extracts had **hepatoprotective** effect measured by an *in vitro* model of metabolic dysfunction-associated steatotic liver disease, in palmitic acid-treated HepG2 cells. Extracts were qualitatively analyzed resulting the detection of previously known compounds.[55]

a) In this article, table 1, page 4, Geraniin is listed as an alkaloid, which is not. Its molecular formula is $C_{41}H_{28}O_{27}$, so it does not contain nitrogen atom/s. See in PubChem.

Geranium molle

Aerial parts were analyzed for GCC, polar compounds (mainly saccharides and short-chained organic acids) and fatty acids (C_6-C_{24}). They were separately extracted with *n*-hexane, DCM, ethyl acetate, acetone, methanol and water, and the extracts were analyzed for TFC and TPC. These extracts were tested for **antioxidant** (CUPRAC, DPPH, FRAP and β-carotene bleaching methods), **anticancer** (against four cancer cell lines) and **hepatotoxic** (in PLP2 cell) activities. The acetone extract was analyzed for bioactive compounds yielding previously known phenolics.[56]

Follow up of previous study by the same research group. In this research acetone and methanolic extracts were tested again for the same activities (**anticancer**, **antioxidant**) and more extensively analyzed for chemical compositions. Results showed that many compounds contained in one extract were not contained in the other. One on the compounds that was present in both extracts is 3-*p*-Coumaroylquinic acid (**Figure 4**).[57]

Follow up of previous study afforded the isolation and structure elucidation of four active **anticancer** compounds: Apigenin-6-C-β-D-glucoside, Luteolin-6-C-β-D-glucoside (**Figure 4**), 2,3-Dygalloyl-4,6-HHDP-α-D-glucose and 2,3-Dygalloyl-4,6-HHDP-β-D-glucose.[58]

Geranium purpureum

Aerial parts 80% aqueous ethanolic extract was analyzed using HPLC affording four alkaloids: Palmatine, Columbamine, *pseudo*-Columbamine (**Figure 3**) and Geraniin (see note a in "*Geranium lucidum*" above); and five glycosides: Geranioside A, Geranioside B, Quercetin 4-*O*-β-glucopyranoside, Quercetin 3-*O*-β-glucopyranoside and Kaempferol- 3-*O*-β-glucopyranoside.[54]

Flowering aerial parts were separately extracted with boiling water (decoction) and 80% aqueous ethanol, and both extracts had **hepatoprotective** effect measured by an *in vitro* model of metabolic dysfunction-associated steatotic liver disease, in palmitic acid-treated HepG2 cells. Extracts were qualitatively analyzed resulting the detection of previously known compounds.[55]

Aerial parts were separately extracted with ethanol, water and 80% aqueous ethanol. Three extracts were analyzed for TFC, TPC, and tested for **antioxidant** activity (DPPH, FRAP, TAC and TRPA methods). It was also tested for **antibacterial** (against *B. cereus*, *E. coli*, *E. faecalis*, *L. monocytogenes*, *P. aeruginosa*, *S. aureus*) and **antiproliferative** activity (against Hep-G2 cells). Analysis (HPLC) of methanolic extract for single phenolics indicated that the major component was gallic acid. The zinc content of the crude plant material was determined, 12.11 mg/kg.[59]

Aerial parts were separately extracted DMSO, methanol, ethanol, acetone and ethyl acetate. The extracts were tested for **antimicrobial** activity against 14 bacteria species and *C. albicans*.[60]

Leaves were extracted with 62.5% aqueous methanol and was analyzed for TPC and was analyzed (HPLC) for phenolic acids and flavonoids where the major components were (mg/100 g dry extract): caffeic acid 20 and Quercetin, Hydroxytyrosol (**Figure 5**) 11.2, respectively. **Antioxidant** activity was tested using with DPPH method and **antibacterial** activity was tested against six bacterial strains.[61]

Aerial parts EOs were obtained using two methods, solid phase microextraction (EO1) and hydrodistillation (EO2). Both oils were tested for **antimicrobial** activity (against eight bacterial and two fungal species, with ampicillin, streptomycin and fluconazole as standard drugs). Oils were analyzed for complete chemical compositions resulting major compounds (%): caryophyllene 21.7 in EO1 and hexadecanoic acid 36.2 in EO2.[62]

Aerial parts ethanolic extract was analyzed for TFC, TPC and TTC. It was tested for **antioxidant** activity (ABTS, DPPH and ferrous chelating methods), and **urease inhibition** activity. It was very partially and qualitatively analyzed for chemical composition resulting the detection of previously known compounds.[63]

Aerial parts 80% aqueous ethanolic extract was chromatographed affording a new compound, 1-Octyl-4′-isovaleroyl-neohesperoside (**Figure 5**), along with several previously known compounds.[64]

Aerial parts methanolic extract was chromatographed yielding two new compounds, Geranioside A (kaempferol 3-[3-(*α*-rhamnopyranosyl)-4-oxy-5-hydroxy-6-methyl-3,4-dihyropyran-2*H* -2-pyranoside]) and Geranioside B (quercetin 3-[3-(*α*-rhamnopyranosyl)-4-oxy-5-hydroxy-6-methyl-3,4-dihyropyran-2*H* -2-pyranoside]) (**Figure 5**), together with several other previously known phenolics.[65]

EO (hydrodistillation) was obtained from flowering whole plant and analyzed for chemical composition. New compounds were not reported and hexadecanoic acid was the major component, 33.5%.[66]

Aerial parts 80% aqueous methanolic extract was prepared and fractionized with ethyl acetate, *n*-butanol and water. These fractions were tested for **antioxidant** (DPPH method) and **antimicrobial** (against four bacterial and three fungal strains) activities.[67]

Geranium rotundifolium

Whole plant acetone extract was analyzed for phenolic composition and thirteen compounds were detected, including luteolin, kaempferol, myricetin and some of their derivatives.[49]

Leaves and stems 50% methanolic extract was analyzed for TFC, TPC and alkaloids content. No antioxidant tests are reported.[68]

Aerial parts EO (hydrodistillation) was analyzed with GC-MS for chemical composition. New compounds were not reported and the major components (%) were: α-terpinyl acetate 39.3 and pulegone 27.7 (**Figure 6**, stereochemistry is not reported).[69]

Aerial parts 70% aqueous ethanolic extract was fractionized with several solvents (not reported) and the ethyl acetated fraction was chromatographed affording eleven phenolics including (mg/100 g dry extract): Afzelin 5.39, Juglanin 7.95, Avicularin 8.90 and Astragalin 9.74 (**Figure 6**).[70]

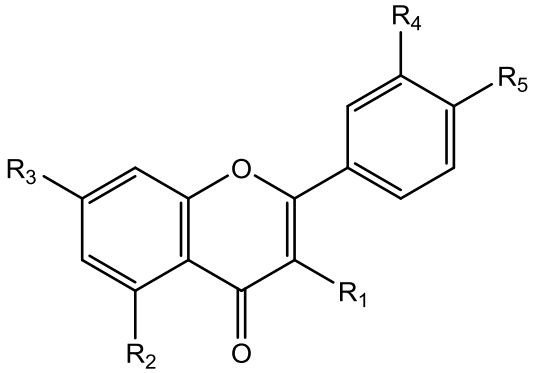
Geranium tuberosum

Aerial parts 80% aqueous methanolic extract was prepared and fractionized with ethyl acetate, *n*-butanol and water. These fractions were tested for **antioxidant** (DPPH method) and **antimicrobial** (against four bacterial and three fungal strains) activities.[67]

Aerial parts 80% aqueous methanolic extract was prepared and partitioned with PE, ethyl acetate and *n*-butanol, and was analyzed for TPC. The extract and the three fractions were tested for **antioxidant** (enhancement of GSH, SOD and catalase) and **antihemolytic** (H_2O_2-induced) activities.[71]

Leaves and roots were separately extracted with methanol and both extracts had significant **antimicrobial** activity against six bacterial and two fungal species. Both extracts also had **enzyme inhibition** activity (AChE, BuChE, XO). Leaves extracts were more active.[72]
Aerial parts 80% aqueous methanolic extract was prepared and fractionized with PE, ethyl acetate and *n*-butanol. These fractions were tested for **antioxidant** (H_2O_2-induced lipid peroxidation). The ethyl acetate fraction was chromatographed yielding ten previously known phenolics.[73]
Aerial parts were extracted with DCM and the extract was analyzed for detailed chemical composition. New compounds were not reported but four rare cyclobutene derivatives were isolated and characterized (**Figure 7**).[74]

* Unless indicated otherwise, solvent mixtures are volume/volume, v/v.



R_1= H, R_2=R_3=R_4=R_5= OH , Luteolin
R_1=R_2=R_3=R_5= OH, R_4= H, Kaempferol
R_1=R_2=R_3=R_4=R_5= OH , Quercetin
Ref. 49

Figure 1: Natural products isolated from Geranium columbinum.

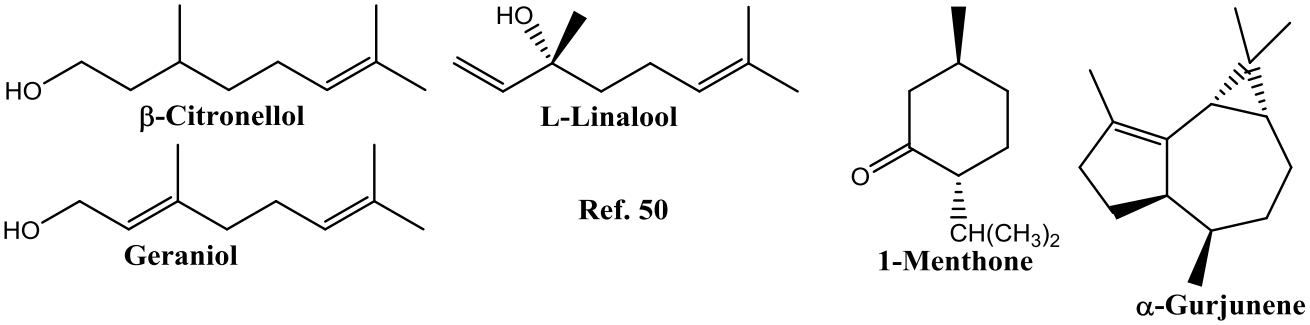
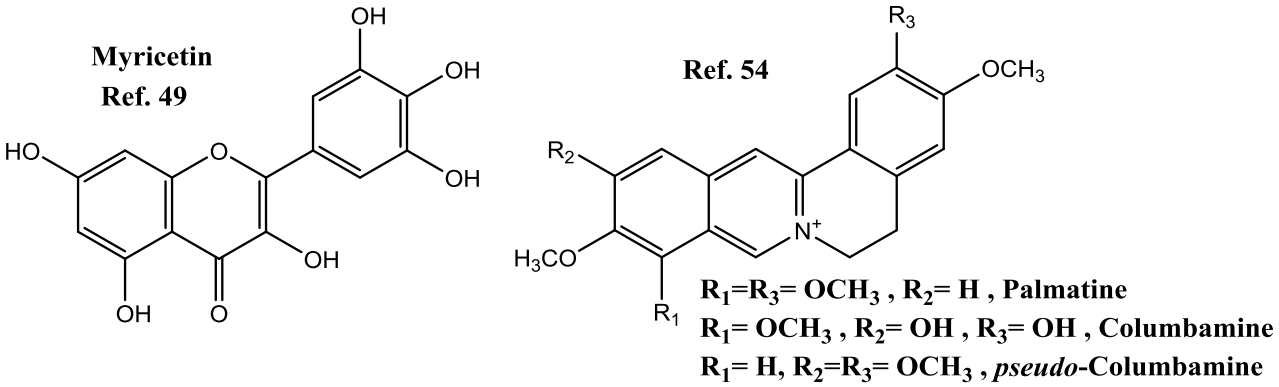


Figure 2: Natural products isolated from *Geranium dissectum.*



R_1=R_3= OCH_3 , R_2= H , Palmatine
R_1= OCH_3 , R_2= OH , R_3= OH , Columbamine
R_1= H, R_2=R_3= OCH_3 , *pseudo*-Columbamine

Figure 3: Natural products isolated from *Geranium lucidum.*

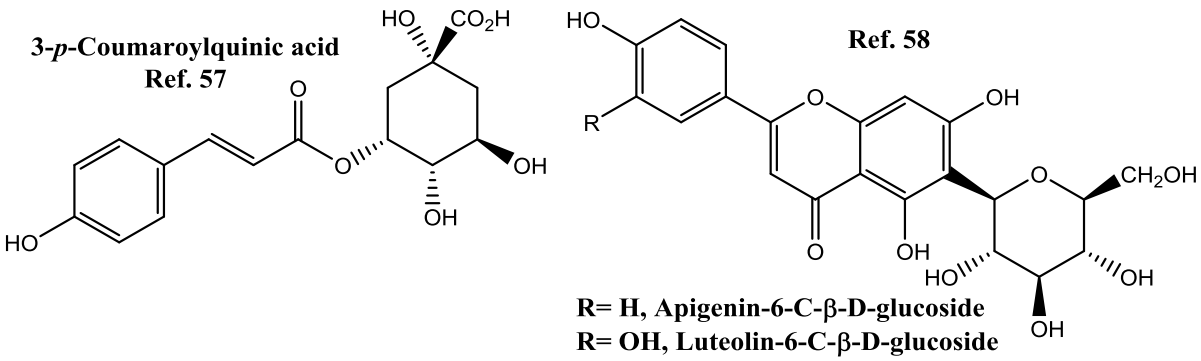


Figure 4: Natural products isolated from *Geranium molle.*

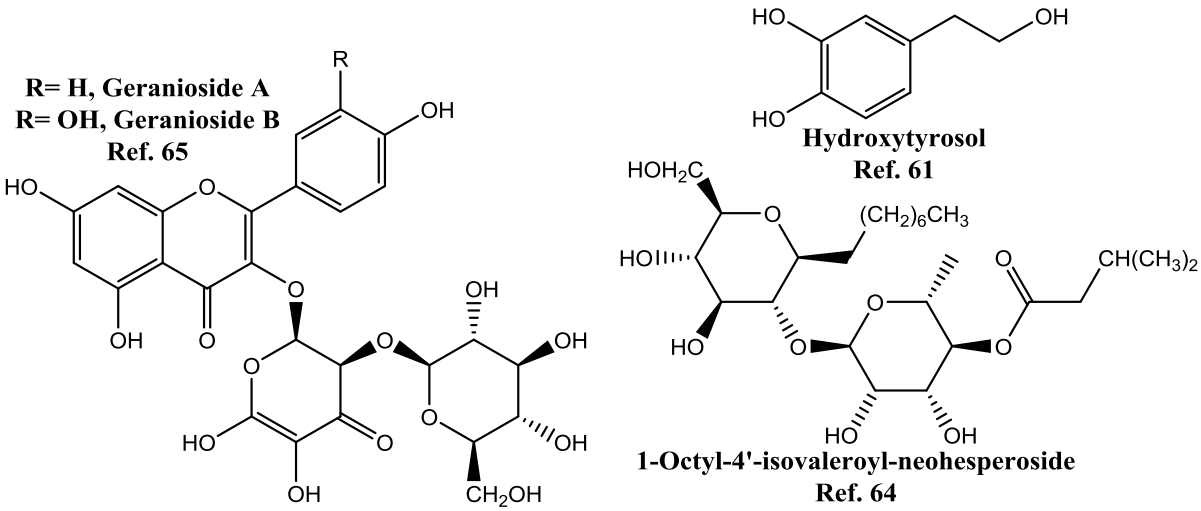


Figure 5: Natural products isolated from *Geranium purpureum.*

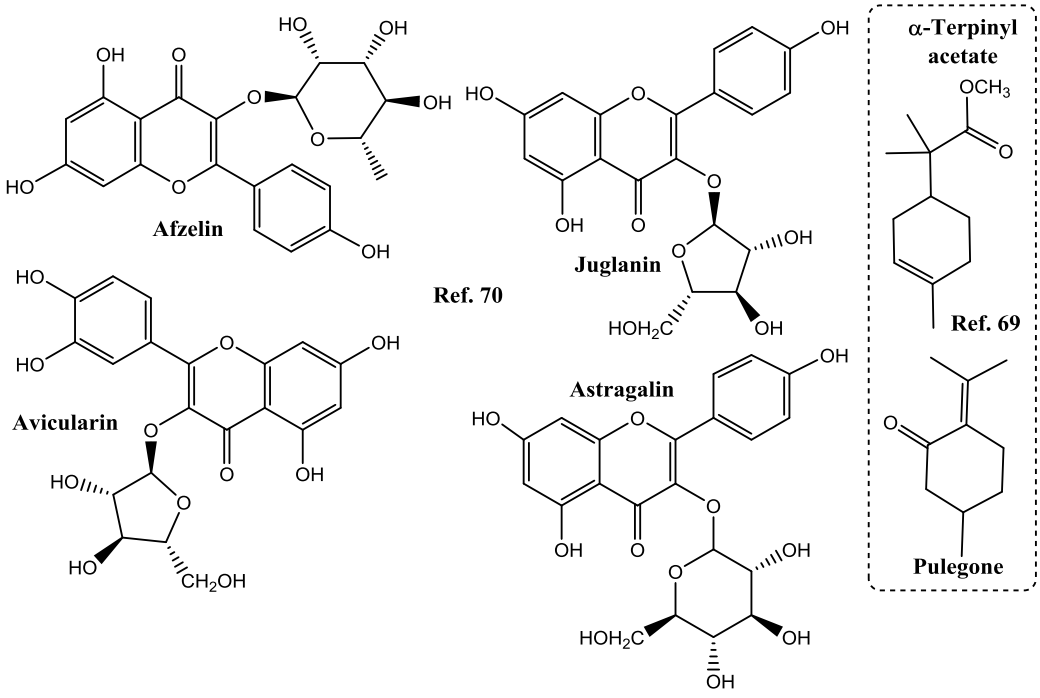
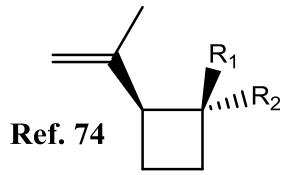


Figure 6: Natural products isolated from *Geranium rotundifolium.*



1, R_1= CH_3 R_2= CH_2CH_2OH
2, R_1= CH_3 R_2= CH_2CH_2OAc
3, R_1= CH_2CH_2OH, R_2= CH_3
3, R_1= CH_2CH_2OAc, R_2= CH_3

Figure 7: Natural products isolated from *Geranium tuberosum*.

4) DISCUSSION

The notably low number of publications about the medicinal activities-properties of the *Geranium* species of Israel and Palestine as can be seen in **Table 1**, is way lower when indirect properties are concerned. This scarcity is in contrary to the richness of publications about active natural products found in these plants, as presented below. Anyhow, M.A. Sajad ahc reported that *Geranium rotundifolium* has notable capacity to remove zinc from contaminated soil, phytoremediation.[75]

In three seemingly contradicting reports, C,L. Quave ahc reported twice that *Geranium columbinum* were inactive against *Staphylococcus aureus*[46,47], while N. Radulovic ahc reported that the essential oil (EO) of the same species (and *Geranium lucidum*) was notably active.[48] In fact, these reports are not contradicting since the tested plant products is not the same. Moreover, these reports are consistent with many studies that reported higher antimicrobial activity of EOs compared with extracts of the same plant species.[76-78]

The richness and the diversity of natural products contained in these plants are surprizing, as can been seen in the cited studies and **Figures 1-7**. Elaboration on the activities of these compounds could go far beyond the objectives of this review article. Among these natural products, this could be done for Geranioside A, Geranioside B (**Figure 5**), *pseudo*-Columbamine and Columbamine (**Figure 3**). Columbamine for example was published for anticancer[79-81] and antifungal activities.[82] And due to the importance of Columbamine and the natural availability of Berberine, the first was prepared using the second as starting material, as early as 1967.[83]

But the focus of this part is Palmatine, a natural product with numerous medicinal activities. Some of them, carefully selected, will be presented below. Palmatine is a protoberberine alkaloid that was isolated from several plant species. Despite some structural differences, Palmatine and Berberine (**Figure 8**) had allosteric potential.[84]

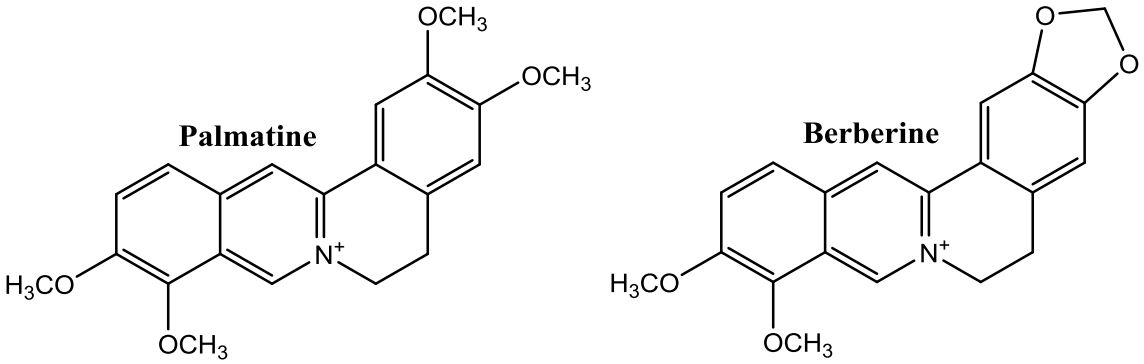


Figure 8: Palmatine and Berberine.

And like Berberine, Palmatine has large number of medicinal activities, especially anticancer. Selected activities are shown in **Table 3**.

Table 3: Selected Medicinal Activities of Palmatine.

Activity	Major Discovery; Reference
Analgesic	Inhibiting the expression of calcitonin gene-related peptide in the trigeminal ganglion[85] Reduction of pain transmission by inhibiting the BDNF/TrkB* pathway and suppressing ERK1/2 phosphorylation[86]
Anticancer	Coparison with Berberine activity against rhabdomyosarcoma[87] Inhibits the growth of human estrogen receptor-positive breast cancer cells and acts synergistically and additively with Doxorubicin[88] Suppresses acute myeloid leukemia by inducing pyroptosis via ROS/PI3K/AKT signaling[89] Inhibition of the PI3K/AKT pathway in canine mammary gland tumor CMT‑U27 cells[90] Binding mode to DNA[91] Inhibition of colorectal cancer[92]
Anticonvulsant	Synergistic effect with Berberine against Pentylenetetrazole-induced seizures in Zebrafish[93] Effective in two models: against seizures chemically induced (Zebrafish) and radiation induced (mice)[94]
Antidiabetic	Reduction of blood glucose and oxidative stress in STZ-induced diabetic rats[95] Ameliorates high fat diet induced impaired glucose tolerance[96] *In vitro* and *in-silico* studies of effect of Palmatine o α-amylase, α-glucosidase and dipeptidyl peptidase-IV[97]
Antifeedant	By binding to five neuroreceptors and inhibition of three enzymes[98]
Anti-inflammatory	Acting synergistically with Berberine as ligands of α7 nAChR, regulate inflammation and phagocytosis of microglial cells[84] Inhibition of inflammatory cytokines[92] Attenuates inflammation in mice submitted to permanent focal cerebral ischemia induced by middle cerebral artery occlusion[99]
Antimicrobial	Inhibits *Helicobactor pylori* that causes gastric damages[100] Inhibits several species of *Helicobactor pylori* and a mechanism of action is proposed: inhibition of ureases of the bacteria[101] Synergism with Berberine against *Pseudomonas aeruginosa* isolated from burn infections[102] Antifungal activity against *Candida* spp. resistant to azoles in planktonic cells and biofilm[103]
Antioxidant	*In vitro*: ABTS, DPPH, CUPRAC, FRAP, NO radical scavenging and lipid peroxidation

	inhibition; *in vivo*: effect on oxidant/antioxidant enzymes[104] Tested with DPPH method[124]
Antiulcer	Gastroprotective activity against acetic acid-induced ulcer with proposed mechanism of increasing Prostaglandin E2 and reducing Platelet-activating factor[105] Protection against intestinal epithelial cell injury and alleviating intestinal barrier dysfunction[106]
Antiviral	Effect against West Nile virus by inhibition of NS2B-NS3 protease activity[107] Inhibition of Zika virus and Japanese by disrupting virus binding, entry, and stability[108] Inhibition of infectious bronchitis virus through regulation of NF-κB/IRF7/JAK-STAT signalling pathway and apoptosis[109] Enhancing resistance to Micropterus salmoides rhabdovirus in largemouth bass through innate immune activationand viral suppression[110]
Antiatherosclerosis	Effect was due to regulating the gut microbiota-phenylalanine metabolism axis[111]
Cardioprotective	Alleviation of acute myocardial infarction by activation of pAMPK/Nrf2 signaling pathway in mouse model[112]
Determination	Simultaneous determination of Berberine, Palmatine, Matrine, Catechin and Baicalin in Funing Shuan (Chinese herbal mixture)[113] Determination with flow-injection post-chemiluminescence method in pharmaceutical samples and biological fluids[114]
Hepatoprotective	Improves the blood flow and mitotic activity in thioacetamide-traumatized livers of female rats[115] Inhibition of potassium and calcium currents in isolated rat hepatocytes[116] Alleviation of gentamicin-induced hepatotoxicity in rats by inhibition of oxidative stress[117]
Nephroprotective	Alleviation of gentamicin-induced nephrotoxicity in rats by inhibition of oxidative stress[117] Effects were achieved mainly by uric acid modulating targeting Keap1-Nrf2/NLRP3 axis[118]
Neuroprotective	Alleviates neuronal damage and memory deficits in mice submitted to permanent focal cerebral ischemia induced by middle cerebral artery occlusion[99] Inhibition of AChE[104] Inhibition of MAO[119] Memory enhancement (mice) by inhibiting AChE, involvement of GABA-benzodiazepine pathway, and antioxidant activity[120] The hydrochloride administration improves cognitive dysfunction in STZ-induced diabetic rats[121]* Sedative and hypnotic by increasing 5-hydroxytryptamine[122] Enhancement of antioxidant defense and small heat shock protein expression in A***β***-transgenic *Caenorhabditis elegans*[123] Alleviation of AlCl_3-induced oxidative stress in mice[124] * Accurately, the compound is Palmatine chloride, not hydrochloride. The nitrogen atom in Palmatine is quaternary is positively charged, so it can not bind to a proton or any other positively charged ion, but it does (and must) bind to a negatively charged ion, i.e. chloride in the neutral molecule.
Antiosteoporotic	Attenuates osteoclast differentiation through inhibition of RANKL and OPG expression by osteoblasts[125] Increases osteoclast apoptosis via the NOS system in RAW 2264.7 cells[126]

* For abbreviations in this table, please refer to the cited article

The brief descriptions presented in **Table 3** above were mostly copied-pasted (and slightly edited in most citations) from either the titles or the abstracts of very carefully selected

publications. But in addition to these cited articles, large number of publications was not included since they present similar information included in those that were cited. However, other class of articles was not included in **Table 3** because they do not publish activities or the activity emerge from Palmatine products, yet they include valuable information. Here are two examples. J. Li ahc studied the pharmacokinetics of Palmatine in rat after oral and intravenous administration by UPLC-MS/MS.[127] Z. Jiang ahc prepared Palmatine-loaded electrospun poly (ε-caprolactone)/gelatin nanofibrous scaffolds that had notable wound healing activity in rabbit ear model.[128]

Finally, to demonstrate the fact that Palmatine was published in many more publications than those we cited, it is sufficient to consider very selected review articles that were published about this compound. Five of them are presented in **Table 4**.

Table 4: Selected Published Review Articles about Palmatine.

Author(s)	Short Description, reference
S. Chaves ahc	Mini review, 5 pages, 34 references, general[129]
J. Long ahc	Medium size, 9 pages, 140 references, general[130]
S. Ogechi Ekeuku ahc	Medium size, 12 pages, 97 references, activity against metabolic syndrome and its complications[131]
D. Tarabasz, W. Kukula-Koch	Comprehensive; 17 pages, 132 references, extended presentation of pharmacokinetics[132]
Z. Shi ahc	Comprehensive, 30 pages, 132 references, general, highly illustrated with many very helpful figures[133]

5) CONCLUSIONS

1) *Geranium* plants of Israel and Palestine have high medicinal potential.

2) *Geranium* plants of Israel and Palestine contain a great diversity of natural products.

3) All *Geranium* species of the RR were not sufficiently studied.

4) Some of these species were not published at all for medicinal activities-properties.

5) Very intense research efforts are needed to close the information gaps.

Abbreviations: ABTS 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), ahc and her/his colleagues, AChE acetylcholine esterase, BuChE butyrylcholine esterase, CUPRAC cupric reducing antioxidant capacity, DPPH 2,2-Diphenyl-1-picrylhydrazyl, DCM dichloromethane, DMSO dimethyl sulfoxide, EO essential oil, FRAP ferric reducing activity, GSH glutathione, HPLC high performance liquid chromatography, MAO monoamine oxidase, NI not indicated, PE petroleum ether, RR reviewed region, SOD superoxide dismutase, STZ streptozotocin,

TAC total antioxidant capacity, TFC total flavonoid content, TPC total phenolic content, TRPA total reducing power ability, TTC total tannins content, XO xanthine oxidase

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