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MAJOR GENERA OF PAPAVERACEAE (POPPY) PLANT FAMILY IN ISRAEL AND PALESTINE. PART I: *FUMARIA* (FUMITORY)

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ABSTRACT

Fumaria is one of the genera included in the Papaveraceae plant family. All the species of this family have notable alkaloid content, and *Fumaria* alkaloids will be presented and discussed. Traditional medicine used these plants for a variety of purposes. The presence of the *Fumaria* plants in the reviewed region (RR) is very highly debated, and this will be introduced and discussed as well. Modern research studied some of these species extensively but not enough for others. The medicinal properties-activities that were published are of a high diversity, and these will be presented in easy-to-use tables. Significant previous published review articles about *Fumaria* plants of RR with be presented compared with this review article. The structures of most of the natural products that were isolated from these plants will be shown in separate figures. The indirect products of these plants and some other properties will be introduced in the discussion section.

KEYWORDS: Papaveraceae, *Fumaria*, hepatoprotective, alkaloids, ethnomedicine, chemical composition, *Fumaria officinalis*, *Fumaria parviflora*, review articles, nanoparticles.

ABBREVIATIONS

ABTS 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), ahc and her/his colleagues, AChE acetylcholine esterase, BHA butylated hydroxyanisole, BHT butylhydroxytoluene, BuChE butyrylcholine esterase, CUPRAC cupric reducing antioxidant capacity, DPPH 2,2-Diphenyl-1-picrylhydrazyl, DCM dichloromethane, DEE diethyl ether, EO essential oil,

FRAP ferric reducing activity power, GCC general chemical composition, GC-MS gas chromatography mass spectrometry, GPx glutathione peroxidase, HDL high density lipoprotein, HPLC high performance liquid chromatography, LC-MS liquid chromatography mass spectrometry, LDL low density lipoprotein, LPS lipopolysaccharide, MDA malondialdehyde, NI not indicated, NMR nuclear magnetic resonance (spectroscopy), NPs nanoparticles, PBD phosphomolybdenum (assay), PE petroleum ether, RR reviewed region, SOD superoxide dismutase, STZ streptozotocin, TAC total antioxidant capacity, TEAC Trolox equivalent antioxidant capacity, TFC total flavonoid content, TG triglycerides, TLC thin layer chromatography, TPC total phenolic content, TTC total tannins content.

1. Taxonomy and Presence of Wild Papaveraceae and *Fumaria* Plants in the RR

Fumaria with Fumitory or Fumewort as common names in English, شاهترج in Arabic and עשנן in Hebrew, is one of the plant genera that comprise the Papaveraceae (Poppy, خشخاشية, פרגיים, English, Arabic, Hebrew, respectively) plant family. According to H-W. Peng ahc, this is a medium size plant family that includes about 48 genera and 920 species.[1] P.C. Gupta ahc stated that the *Fumaria* plant genus globally includes about 40 species.[2]

However, according to the very reliable website of "Flora of Israel and Adjacent Areas" (Israel), in the RR the Papaveraceae plant family includes 9 genera and 38 species. In this series of review articles, three genera will be published: *Fumaria*, *Glaucium* and *Papaver*. This website shows that eleven wild *Fumaria* species are native to the RR, and these are: *Fumaria asepala*, *F. bracteosa*, *F. capreolata*, *F. densiflora*, *F. gaillardotii*, *F. judaica*, *F. kralikii*, *F. macrocarpa*, *F. officinalis*, *F. parviflora*, *F. petteri*.[3]

But this taxonomy is extremely debated by most notable botanical website: Florapal (Palestine). According to this website, there are no *Fumaria* plants in the reviewed region. Here is a screenshot of this website, section "Species Lists", letter F, that was taken on the 15th of September 2025, presented as **Figure 1**.[4]

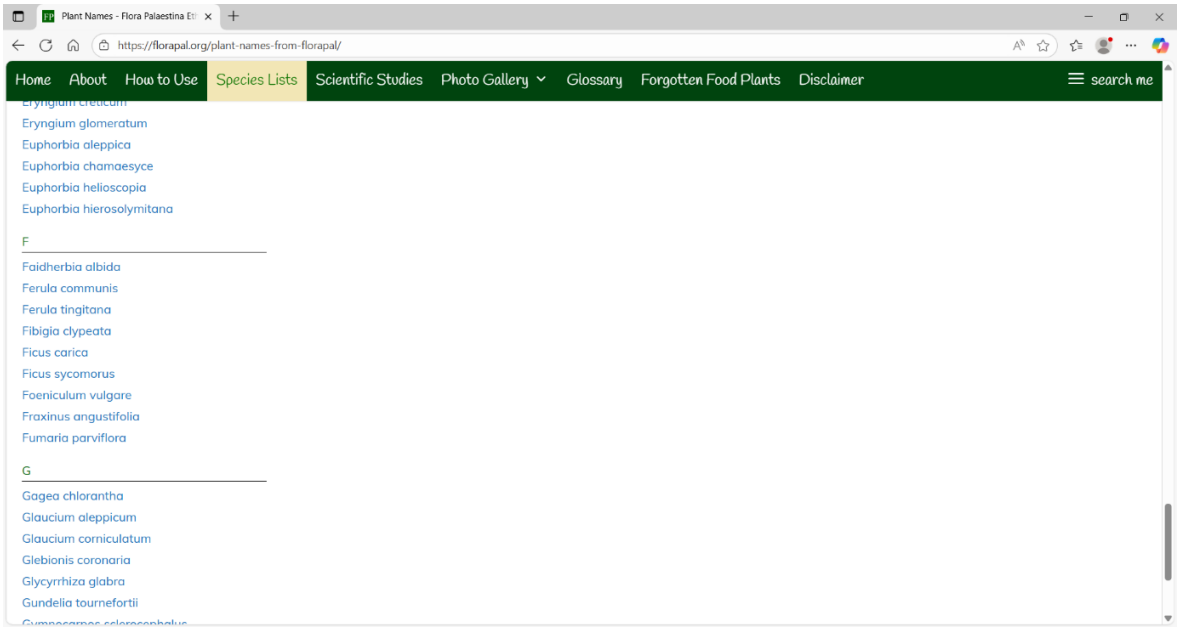


Figure 1: Screenshot of "Species Lists" of website Florapal, 15/09/2025.

This website was lately published by S. Sallon ahc as "*Florapal* an ethnobotanical website of Flora Palaestina reflects changing patterns of plant use in this region during the mid-20th to 21st century".[5] It is clearly not. Moreover, three of the authors of this article co-authored a research article that reported the AChE inhibition activity of Palestinian indigenous flora.[6] Contradicting the data on Florapal website, in this article three *Fumaria* species are listed, including *F. vaillanti*, which is not included in "Flora of Israel and Adjacent Areas" and consequently, it is not included in our review article.

2. Notable Published Review Articles about *Fumaria* Genus and Species

Our literature search for previously (until 15/09/2025) published review articles about *Fumaria* plant genus ant its plants resulted in around twenty five publications. Most of them focus on either *F. officinalis* or *F. parviflora*. A few more review articles present *Fumaria indica* which is not native to the RR. After carefully examining them, we found that fifteen of them are relevant to our review article. These are presented in **Table 1**.

Table 1: **Selected published review articles about *Fumaria* until 15/09/2025.**

Author(s)	Pages	References	Major topic(s), Ref.
P.L. Rajagopal ahc	20	62	*Fumaria*, medicinal activities, no presentation of ethnomedicinal uses and natural products and their structures [7]
R. Zhang ahc	18	159	Alkaloids in *Fumaria* species, comprehensive, detailed lists and structures, brief ethnomedicinal

			presentation [8]
F. Kiumarsi & A. R. Derakhshan	17	54	Treatment of gastro and hepatic problems with *Fumaria*, comprehensive, ethnomedicinal uses and components structures are presented [9]
P. Goetz ahc	5	36	*Fumaria officinalis*, mini review, brief presentation of most relevant topics [10]
S. Sajjad ahc	6	53	*Fumaria officinalis*, mini review, brief presentation of most relevant topics [11]
R. Dutta ahc	7	49	*Fumaria officinalis*, mini review, brief presentation of most relevant topics. No structures of active components [12]
A.E. Al-Snafi	9	85	*Fumaria officinalis*, mini review, brief presentation of most relevant topics. No structures of active components [13]
R. Aguiar	8	44	*Fumaria officinalis*, mini review, brief presentation of most relevant topics. No structures of active components [14]
Y. Prokopenko ahc	50	75	*Fumaria officinalis*, very comprehensive and very detailed [15]
S. Kumar ahc	8	42	*Fumaria parviflora*, mini review, brief presentation of most relevant topics [16]
A.E. Al-Snafi	11	83	*Fumaria parviflora*, medium length review, brief presentation of most relevant topics. No structures of active components [17]
P.K. Tayade & M. Jadhav	8	15	*Fumaria parviflora*, mini review, brief presentation of most relevant topics. No structures of active components [18]
F.N. Jamaldeen ahc	14	73	*Fumaria parviflora*, comprehensive and detailed [19]
N. Kumar ahc	5	24	*Fumaria parviflora*, mini review, brief presentation of most relevant topics [20]
A. Sharma ahc	15	77	*Fumaria parviflora*, comprehensive and detailed[21]

3. Ethnobotanical Uses of *Fumaria* Plants of Israel and Palestine

Traditional societies used the *Fumaria* species of the RR for broad range of purposes. Among the eleven species, we found documented (published) frequent uses of four species and a single publication for each one of other three species. It is important to pay attention to the fact that none of these articles was published about traditional uses in the RR. These uses include various treatments of medical problems and for nutritional goals. Summary of this data is presented in **Table 2**.

Table 2: Ethnobotanical Uses of *Fumaria* Plants of Israel and Palestine.

Fumaria Species	Country; Plant part(s); method(s); use(s); reference
F. asepala	**Iran**; leaves; decoction; carminative, Stomach-ache, depurative, against fever [22,28] Aerial parts; powder with Henna; migraine, hand schism, mange [23] Leaves; powder; topical; sores [24] Aerial parts; NI; children jaundice [25] Shoots; NI; migraine, hypertension [26] Whole plant; decoction; eczema, hand chap [27] Whole plant; powder applied externally; itching, skin allergy; decoction; liver diseases; mixed with Henna, hair colour [29] Aerial parts; infusion; head and face itching, allergy, face acne [30] Aerial pars; NI; itching [31] **Turkey**; flowers; infusion applied externally; fungal infections [32]
F. capreolata	**Algeria**; NI; NI; bile flow production an flow regulation, stimulation of liver and spleen, worming [33] Aerial parts; decoction, infusion, cream; mainly skin diseases, rarely hypotensive, diuretic [34] **Italy**; NI; NI but used externally, skin disorders, enhance sweat; purifying digestive system [35] **Turkey**; aerial parts; NI; bile enhancer, eczema, antifungal [36]
F. gaillardotii	**Turkey**; aerial parts; NI; different purposes (no details) [36]
F. judaica	**Libya**; NI; NI; diuretic [37]
F. macrocarpa	**Greece**; NI; NI; NI but mentioned in the book "About the Antidotes" composed by Nikolaos Myrepsos in 1339[38]
F. officinalis	**Greece**; NI; NI; NI but mentioned in the book "About the Antidotes" composed by Nikolaos Myrepsos in 1339[38] **Iran**; aerial pars; NI; itching[31] **Italy**; NI; NI but used externally, skin disorders, enhance sweat; purifying digestive system[35] **Morocco**; roots, decoction; hyperthyroidism[39] Roots; decoction; diabetes[40] Aerial parts; NI; hypertension, cardiac diseases[41] **Pakistan**; aerial parts; NI; blood purification, laxative, skin antiallergy[42]
F. parviflora	**India**; whole plant; NI; fever, influenza, skin itching[43] **Iran**; whole plant; decoction, poultice; jaundice, skin diseases, allergy, cold, hypertension, coolant, aromatic water[44] NI; NI; jaundice, skin rash, liver detoxification, skin itching[45] **Oman**; aerial parts; NI; anthelmintic, laxative, skin disorders[46]

4. Published Medicinal Properties-Activities of *Fumaria* Plants of Israel and Palestine

Modern research investigated the medicinal properties-activities of the *Fumaria* species of the RR. But expectedly, some of these plants were notably studied while others were partially or fully "ignored". Modern research confirmed the traditional uses and reported many more. A summary of these findings is shown in **Table 3**.

Table 3: **Medicinal Properties-Activities of *Fumaria* Plants of Israel and Palestine.**

***Fumaria* species**	**Property-Activity, Method, Results, Reference**
F. asepala	Whole plant 80% aqueous methanolic extract were tested for **anticancer** activity against BEAS-2B, SH-SY5Y, HCT116 and A549 cell lines. Results showed activity against most of these cells.[47] Whole plant 80% aqueous methanolic extract was tested for **antimicrobial** (three bacterial and three fungal species), showing activity only against one of them.[48] Leaves and stems ethanolic extract was tested for **antibacterial** activity against *S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa*. Results were moderate to high activity.[49] Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species. The links between single alkaloids and single species are not indicated. These alkaloids were tested for **antimicrobial** and **antiviral** activities showing moderate to high potency.[50] Fruits, leaves, roots and stems were separately extracted with 96% aqueous ethanol and the resulting extracts were chromatographed yielding alkaloid fractions. These fractions were tested for **antifungal** activity. Results showed high efficiency, and the effect was due to genetic influence. The major alkaloids that were isolated are Protopine, Sanguinarine, Parfumine and Allocryptopine (**Figure 2**).[51] Aerial parts were separately extracted with methanol and ethyl acetate, and the extracts were tested for **antioxidant** activity, using DPPH, superoxide anion scavenging and lipid peroxidation methods. Both extracts showed high activities.[52] Whole plant ethanolic extract was chromatographed affording Protopine, Allocryptopine and Sanguinarine, in addition to Cryptopine, Stylopine, Scoulerine and Bicuculline (**Figure 2**).[53] Whole plant methanol-chloroform (1:1) extract had significant **enzyme inhibition** (AChE, BuChE) activity.[54] Whole plant methanolic extract had significant **enzyme inhibition** (AChE, BuChE and carbonic anhydrase I and II) activity.[55] Aerial parts EO (hydrodistillation) was tested for **antimicrobial** (against five bacterial strains and *Candida albicans*) and **antioxidant** (TAC method) activities, showing significant results in both tests. EO was analyzed (GC-MS) and the major components were (%): thymol 20.42, benzyl benzoate 15.89, phytol 20.74 and Hexahydrofarnesyl acetone (**Figure 2**) 12.92.[56] Aerial parts methanolic extract had moderate **antimicrobial** activity against seven bacterial species and *C. albicans*.[57]
F. bracteosa	Whole plant alkaloid extract was chromatographed yielding Protopine and Bicuculline (**Figure 2**), in addition to Adlumidine (optical isomer of Bicuculline) and Hydrastine (**Figure 3**).[58]
F. capreolata	Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species (see *F. asepala*). These alkaloids were tested for **antimicrobial** and **antiviral** activities showing moderate to high potency.[50]

	Whole plant ethanolic extract was chromatographed affording Protopine, Sanguinarine, Cryptopine, Stylopine, Scoulerine and Bicuculline (**Figure 2**), in addition to Fumaritine, Capnoidine and Coptisine (**Figure 4A**).[53] Whole plant methanol-chloroform (1:1) extract had significant **enzyme inhibition** (AChE, BuChE) activity.[54] Aerial parts ethanolic extract had **analgesic** (acetic acid writhing test) and **anti-inflammatory** (xylene or 12-O-tetradecanoylphorbol-13-acetate-induced) activities in mice.[59] Aerial parts alkaloid extract had **anti-inflammatory** activity against dinitrobenzene sulfonic acid-induced colitis, *in vitro* (intestinal epithelial CMT93 cells) and *in vivo* (mice). Effect was measured with several biomarkers. The extract was analyzed (liquid chromatography) and the main alkaloids were (mg/g): Parfumine 3.18, Protopine 9.27, Stylopine 12.67 (**Figure 2**), and Isoboldine 4.5, Coreximine 2.32, Cheilanthifoline 3.04, Dehydrocheilanthifoline 0.69, Fumariline 1.18, Coptisine 11.04, Corysamine 0.88 (**Figure 4A**).[60] Follow up of previous research: aerial parts alkaloid extract had **anti-inflammatory** activity against dextran sodium sulfate-induced colitis in mice. Effect was measured with several biomarkers.[61] Earlier study by the same research group: aerial parts alkaloid extract had **anti-inflammatory** activity against LPS-induced inflammation in RAW 264.7 cells. It also had **antinociceptive** activity tested by acetic acid-induced writhing and formalin-induced paw licking methods. Each effect was measured with several biomarkers.[62] Aerial parts 70% aqueous ethanolic extract had **anti-inflammatory** activity against carrageenan-induced inflammation in mice. Partial GCC is presented.[63] Aerial parts methanolic (alkaloid) extract was tested for **antioxidant** activity using DPPH, FRAP and linoleic acid peroxidation methods. The methanolic extract was analyzed with GC-MS resulting the detection of significant amounts (%) of five alkaloids: Protopine 50.6, Stylopine 22.9, Fumariline 8, Fumaritine 3.7 in addition to Fumaricine 2, Protoberberine 3.2 and Fumarofine (traces). (**Figure 4A**).[64] Aerial parts 90% aqueous ethanolic extract was analyzed for TPC and tested for **antioxidant** activity (DPPH, FRAP and β-carotene bleaching methods; with BHA, BHT and ascorbic acid as reference antioxidants). Fresh and dry plant material as well as the extract were analyzed for GCC.[66] Aerial parts methanolic (alkaloid) extract was tested for **antioxidant** activity using ABTS, DPPH, FRAP and hydrogen peroxide scavenging methods. It was also tested for **acute toxicity** in mice and erythrocytes resulting no toxicity in both tests.[67] Aerial parts ethanolic (alkaloid) extract had ameliorative **antiulcer** activity in acetic acid-induced colitis in mice.[68] Aerial parts methanolic (alkaloid) extract was fractionized and analyzed affording eleven alkaloids: Pallidine, N-methylcoclaurine, Reticuline, “Simple Isoquinoline”, Magnoflorine (**Figure 4B**), Sanguinarine, Protopine, Scoulerine, Isoboldine, Dehydrocheilanthifoline and Coptisine. In addition, choline was also isolated.[69] Whole plant ethanolic (alkaloid) extract was chromatographed yielding

	nine previously known alkaloids (%): Protopine 0.11, Cryptopine 0.09, Allocryptopine 0.09, Fumaritine 0.1, Stylopine 0.09, Scoulerine 0.05, Coptisine 0.05, Capnoidine 0.12, and Sanguinarine 0.05.[70] Aerial parts ethanolic (alkaloid) extract was chromatographed yielding nine previously known alkaloids (%): Isoboldine 4, Sanguinarine 2, Bicuculline 2, Protopine 45, Fumariline 4, Parfumine 12, Cheilanthifoline 5, Scoulerine 4 and Stylopine 6.[71] Aerial parts ethanolic (alkaloid) extract was analyzed with GC-MS yielding six previously known alkaloids (% of total alkaloid content): Fumarophycine 2 and Dihydrosanguinarine 2 (**Figure 4B)**, in addition to Protopine 71, Stylopine 10, Parfumine 5 and Fumariline 11.[72] Aerial parts methanolic (alkaloid) extract was qualitatively analyzed with GC-MS yielding eight previously known alkaloids: Protopine, Protoberberine, Stylopine, Fumariline, Fumarophycine, Fumaritine, Fumarofine and Fumaricine. [73] Aerial parts were extracted for alkaloids using methanol-DCM (1:1) and the extract was comparatively and qualitatively analyzed with two methods yielding 24 precisely identified compounds: N,N-dimethylcoclaurine, Coclaurine, Demethyleneberberine, Jatrorubine, Impatien C, 8-Oxocoptisine (**Figure 4B**), in addition to Pallidine, Fumaritine, N-methylcoclaurine, Magnoflorine, Reticuline, Parfumine, Parfumidine, Isoboldine, Coreximine, Cheilanthifoline, Dehydrocheilanthifoline, Cryptopine, Protopine, Fumariline, Stylopine, Coptisine, Corysamine, Dihydrosanguinarine. [74] Fruits 60% ethanolic extract had moderate **AChE inhibition** activity and no **antioxidant** activity (DPPH method).[6] Aerial parts 70% aqueous ethanolic extract was analyzed for TFC, TPC and total hydroxycinnamic acids content. It was also analyzed (HPLC-MS) for phenolic components where six known compounds were detected. The extract had notable **antioxidant** (ABTS and TEAC methods) and **diuretic** (in saline-loaded rats) activities.[75] Aerial parts methanolic extract had **anticancer** (against human hepatocellular carcinoma cancer cell lines Hep3B and HepG2) and **antioxidant** (DPPH and PBD methods) activities.[76] Aerial parts methanolic extract was partially analyzed for alkaloids and phenolic acids. Crude extracts and five of its components (Fumarophycine, *O*-Methylfumarophycine, Protopine, Caffeic acid and Protocatechuic acid) were tested for **antioxidant** activity, using DPPH and lipid peroxidation methods.[86] a) The presented structure of Fumarofine in this article is mistaken[65]
F. densiflora	Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species (see *F. asepala*). These alkaloids were tested for **antimicrobial** and **antiviral** activities showing moderate to high potency.[50] Whole plant methanol-chloroform (1:1) extract had significant **enzyme inhibition** (AChE, BuChE, in high dose) activity.[54] Aerial parts ethanolic (alkaloid) extract was analyzed with GC-MS yielding six previously known alkaloids (% of total alkaloid content): Sinactine 2 and Adlumine 3 (**Figure 5A)**, in addition to Protopine 76, Cryptopine 8, Parfumine 5 and Dihydrosanguinarine 6.[72]

	Leaves 60% ethanolic extract had high **AChE inhibition** and **antioxidant** (DPPH method) activities.[6] Twenty-two alkaloids were isolated from aerial parts ethanolic (alkaloid) extract. Two of these alkaloids, Parfumine and Fumaritine, had dose-dependent **effect on isolated perfused mouse heart and ilium**. Two alkaloids were isolated for the first time from a natural source, N-methyl-5-hydroxystylopine chloride and Fumaricine N-oxide; Norfumaritin was isolated for the second time from natural source, and Norjuziphine was isolated for the first time from this plant (**Figure 5A**).[77] Aerial parts ethanolic (alkaloid) extract was chromatographed affording eight alkaloids, one of them was new, Densiflorine (**Figure 5A**).[78] Whole plant ethanolic (alkaloid) extract was chromatographed yielding fourteen previously known compounds: N-methylhydrasteine, Fumaridine, Adlumidine (**Figure 5A**); in addition to Protopine, Hydrastine, Parfumine, Fumaritine, Cheilanthifoline, Cryptopine, Fumariline, Parfumidine, Scoulerine, Isosalutaridine (Pallidine), and Bicuculline. [79] Whole plant ethanolic (alkaloid) extract was chromatographed affording Fumadensine, Fumaramine, Adlumidiceine (**Figure 5A**), Palmatine (**Figure 5B**), in addition to Coptisine, Sinactine, Protopine, Cryptopine and Densiflorine.[80] Flowering aerial parts methanolic extract had **gastroprotective** activity in on primary cultures of rat hepatocytes intoxicated with CCl_4. This effect is associated with the alkaloids contained in the extract. Analysis of the extract afforded twenty alkaloids where 18 were previously presented, in addition to Fumaritridine, Corytuberine, Fumaflorine (and its methyl ester) and *cis*-*N*-methylstylopinium iodide (**Figure 5B**).[81] Interestingly, the same research group published a year after the previous article, the isolation of Fumaflorine as a new compound. [82] Whole plant 85% aqueous ethanolic extract was fractionized with PE, chloroform, ethyl acetate and methanol. The crude extract and fractions were analyzed for TFC and TPC. They also had significant **antioxidant** activity (DPPH, FRAP, Fe^{+2} chelating, xanthine oxidase inhibition methods).[83] Aerial parts 85% aqueous ethanolic extract was tested for **antiparasitic** activity (against malarial *Plasmodium falciparum* and human African trypanosomiasis *Trypanosoma bruceirhodesiense*). It was also partially analyzed (HPLC) for phenolic acid composition.[84] Whole plant was separately extracted with *n*-hexane, ethyl acetate, ethanol, methanol and water. The extracts were tested for **toxicity** against Brine shrimp (*Artemia salina*), and the *n*-hexane and ethyl acetate extracts were toxic.[85] Aerial parts methanolic extract was partially analyzed for alkaloids and phenolic acids. Crude extracts and five of its components (Fumarophycine, *O*-Methylfumarophycine, Protopine, Caffeic acid and Protocatechuic acid) were tested for **antioxidant** activity, using DPPH and lipid peroxidation methods.[86]
F. gaillardotii	Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species (see *F. asepala*). These alkaloids were tested for **antimicrobial** and

	antiviral activities showing moderate to high potency.[50] Whole plant ethanolic (alkaloid) extract was analyzed affording: N-methylhydrastine (**Figure 6**), in addition to Protopine, Fumaritine, Fumaricine, Stylopine and Bicuculline.[87]
F. judaica	Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species (see *F. asepala*). These alkaloids were tested for **antimicrobial** and **antiviral** activities showing moderate to high potency.[50] Whole plant methanol-chloroform (1:1) extract had significant **enzyme inhibition** (AChE, BuChE) activity.[54] Aerial parts ethanolic (alkaloid) extract was chromatographed yielding Stylopine, Cheilanthifoline, Coptisine, Protopine, Parfumine and Bicuculline.[88] Whole plant ethanolic (alkaloid) extract was analyzed affording (%): Protopine 0.18, Adlumidine 0.l7, Allocryptopine 0.11, Stytopine 0.11, Fumaritine 0.07, Coptisine 0.04 and Scoulerine 0.03. [89]
F. kralikii	Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species (see *F. asepala*). These alkaloids were tested for **antimicrobial** and **antiviral** activities showing moderate to high potency.[50] Whole plant methanol-chloroform (1:1) extract had significant **enzyme inhibition** (AChE, BuChE) activity.[54] Whole plant 85% aqueous ethanolic extract was fractionized with PE, chloroform, ethyl acetate and methanol. The crude extract and fractions were analyzed for TFC and TPC. They also had significant **antioxidant** activity (DPPH, FRAP, Fe^{+2} chelating, xanthine oxidase inhibition methods).[83] Aerial parts 85% aqueous ethanolic extract was tested for **antiparasitic** activity (against malarial *Plasmodium falciparum* and human African trypanosomiasis *Trypanosoma bruceirhodesiense*). It was also partially analyzed (HPLC) for phenolic acid composition.[84] Leaves ethanolic (alkaloid) extract was chromatographed yielding a new compound, Norfumaritine (**Figure 7**), which is the demethylation product of Fumaritine.[90] Aerial parts (plants were collected from three different locations) ethanolic (alkaloid) extract was analyzed affording Stylopine, Sinactine, Chelianthifoline, Scoulerine, Protopine, Cryptopine, Dihydrofumariline, Fumaricine, Parfumidine, Fumaritine, Fumariline, Parfumine, Fumarofine, Fumarophycine, *O*-methylfumarophycine and Dihydrosanguinarine.[91] Aerial parts 70% aqueous ethanolic extract was tested for **antioxidant** activity using ABTS, CUPRAC, DPPH and FRAP methods. It was analyzed for TFC, TPC and phenolic composition where ten known compounds were detected.[92] Aerial parts methanolic extract was fractionized with chloroform and water. The combined polar fractions were analyzed using GC-MS detecting 8 monosaccharides, 5 organic (non-amino) acids, 5 lipids and 8 amino acids. The structure of Threonic acid is shown in **Figure 7**.[93] Aerial parts methanolic (alkaloid) extract was chromatographed yieldingProtopine, Fumarophycine, Berberine, Adlumidiceine,

	Coptisine, *O*-methylfumarophycine, Cryptopine, Stylopine, and Canadine (**Figure 7**).[152]
F. macrocarpa	Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species (see *F. asepala*). These alkaloids were tested for **antimicrobial** and **antiviral** activities showing moderate to high potency.[50] Whole plant methanol-chloroform (1:1) extract had significant **enzyme inhibition** (AChE, BuChE) activity.[54] Whole plant ethanolic (alkaloid) extract was analyzed affording (%) Protopine 0.16, Sinactine 0.13, Adlumine 0.13. Cryptopine 0.11, Fumariline 0.11 and Coptisine 0.07.[94] Aerial parts ethanolic (alkaloid) extract was analyzed yielding Fumariline, Parfumine and Bicuculline.[95]
F. officinalis	Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species (see *F. asepala*). These alkaloids were tested for **antimicrobial** and **antiviral** activities showing moderate to high potency.[50] Aerial parts ethanolic (alkaloid) extract was analyzed with GC-MS yielding nine previously known alkaloids (% of total alkaloid content): Sinactine 6, Adlumine 2, Protopine 42, Cryptopine 11, Parfumine 3, Fumariline 3, Fumarophycine 24, Fumaritine 6 and Dihydrosanguinarine 2.[72] Aerial parts 70% aqueous ethanolic extract was analyzed for TFC, TPC and total hydroxycinnamic acids content. It was also analyzed (HPLC-MS) for phenolic components where seven known compounds were detected. The extract had notable **antioxidant** (ABTS and TEAC methods) and **diuretic** (in saline-loaded rats) activities.[75] Flowering aerial parts methanolic extract had **gastroprotective** activity in on primary cultures of rat hepatocytes intoxicated with CCl_4. This effect is associated with the alkaloids contained in the extract.[81] Whole plant was separately extracted with *n*-hexane, ethyl acetate, ethanol, methanol and water. The extracts were tested for **toxicity** against Brine shrimp (*Artemia salina*), and the *n*-hexane extract was toxic.[85] Aerial parts methanolic extract was partially analyzed for alkaloids and phenolic acids. Crude extracts and five of its components (Fumarophycine, *O*-Methylfumarophycine, Protopine, Caffeic acid and Protocatechuic acid) were tested for **antioxidant** activity, using DPPH and lipid peroxidation methods.[86] Aerial parts 70% aqueous ethanolic extract was tested for **antioxidant** activity using ABTS, CUPRAC, DPPH and FRAP methods. It was analyzed for TFC, TPC and phenolic composition where ten known compounds were detected.[92] Aerial parts methanolic extract was fractionized with chloroform and water. The combined polar fractions were analyzed using GC-MS detecting 8 monosaccharides, 5 organic (non-amino) acids, 7 lipids and 10 amino acids.[93] Leaves were separately extracted with PE, chloroform, ethyl acetate and methanol. The extracts were tested for **antioxidant** activity using superoxide scavenging method (reference: ascorbic acid). The

	a**ntiasthmatic** activity of ethyl acetate and methanolic extracts was tested using two methods: histamine-induced in guinea pig ileum and acetyl choline in guinea pig trachea. The **anti-inflammatory** activity of these two extracts was tested against ovalbumin-induced inflammation in the animals. **Acute toxicity** and ***in vivo* antioxidant** (measured with three biomarkers) activities of the methanolic extract were measured in the same animals.[96] Leaves were separately extracted with 70% aqueous ethanol and water, and the extracts were analyzed for TFC, TPC and TTC. They were tested for **anticancer** (against MCF-7 cancer cells), **antibacterial** (against ten bacterial strains), **antioxidant** (using DPPH and PBD methods), **anti-inflammatory** (haemoglobin denaturation) and **antidiabetic** (haemoglobin glycosylation) activities. The extracts were analyzed for phenolic composition yielding known compounds. Leaves were also extracted for total alkaloid content.[97] Aerial parts 70% aqueous ethanolic extract was analyzed for GCC. It had **antihyperlipidemic** activity in high fat diet-induced in rats. Effect was measured with five biomarkers.[98] Aerial parts ethanolic (alkaloid) extract was tested for **antidiabetic** (alloxan-induced in mice), **anti-inflammatory** (carrageenan-induced) activities, with a proposed mechanism of action. Authors refer these activities to most active components of the extract, Stylopine and Sanguinarine.[99] Aerial parts were separately extracted with *n*-hexane, chloroform, methanol and water, and GCCs of these extracts were determined. The **antioxidant** activity was tested using DPPH method. The **antidiabetic** activity was tested *in vivo* (alloxan-induced in rats) and *in vitro* (α-amylase inhibition).[100] Aerial parts ethanolic (alkaloid) extract was analyzed affording 17 compounds including Jatrorrhizine (**Figure 8**). The extract was tested for **anti-inflammatory** activity using two methods. *In vivo* (against carrageenan-induced paw edema in mice, and *in vitro* (bovine serum albumin denaturation). The alkaloids were tested *in silico* (molecular docking) resulting highest possible potency in Protopine, Bicuculline, Stylopine (highest), and coptisine.[101] Aerial parts 60% aqueous ethanolic extract was defatted with PE and partitioned with ethyl acetate yielding flavonoid-rich fraction. This fraction was tested for **antioxidant** (lipid peroxidation method) and **anti-inflammatory** (bovine serum albumin denaturation) activities. The **nephroprotective** activity was tested against permethrin-induced kidney damage in rats.[102] Whole plant was separately extracted with chloroform, ethyl acetate, acetone and methanol. The extracts were tested for **antibacterial** activity against twelve bacterial strains resulting no effect.[103] Aerial parts aqueous extract was analyzed for TPC and phenolic composition where caffeic and rosmarinic acids were the major components. The extract was tested for **antimicrobial** (against seven microbial species, showing moderate effect against four) and **antioxidant** (using ABTS and DPPH methods) activities.[104] Aerial parts 95% aqueous ethanolic (alkaloid) extract was partitioned

	with several solvents, and the crude extract and the fractions were analyzed for total alkaloid content. They were tested for **antibacterial** (against three bacterial species) and **antioxidant** (using six methods) activities. The crude extract was analyzed (GC-MS) for alkaloid composition detecting: Protopine 34.48%, Bicuculline 18.63%, Cryptopine 6.70%, Sinactine, Adlumine, Fumaritine, Fumariline, Stylopine, Parfumine, Fumarophycine and Corlumine (**Figure 8**).[105] Leaves were separately extracted with PE, chloroform, ethyl acetate and methanol, and the extracts were analyzed for GCC, TFC and TPC. They were tested for **antioxidant** activity using DPPH and hydrogen peroxide scavenging methods, with ascorbic acid as reference.[106] Flowering aerial parts were extracted with 70% aqueous ethanol using three methods: maceration, ultrasound-assisted and microwave-assisted. The **antioxidant** capacity of the extract was tested using ABTS, CUPRAC, DPPH and FRAP methods. Microwave-assisted extracts were most potent.[107] Aerial parts 70% aqueous ethanolic extract was analyzed for TFC, TPC and partial chemical composition using HPLC. The extract was teste for **antioxidant** (DPPH method), **antiulcer** (ethanol-induced gastric ulcer and gastric acid secretion in rats) and **acute toxicity** (rats) activities. Molecular docking was performed for four phenolic compounds contained in the extract with three synthetic reference molecules.[108] Leaves were successively extracted with PE, chloroform and methanol. The combined extracts were analyzed for GCC and tested for **antioxidant** activity using DPPH method. The **antiaging** activity was tested *in vitro* (enzyme inhibition: hyaluronidase, collagenase and elastase) and *in vivo* (topical cream application in skin irritation and UV light exposure in mice). [109] Leaves ethanolic extract had **Immunoprotective** activity in ethanol-induced immunosuppression in mice and in cells. Effect was measured by several biomarkers including oxidative-antioxidative. [110] Aerial parts 70% aqueous ethanolic extract had **antitoxicity** effect against fluoxetine-induced testicular damage in male rats. Effect was measured with several physical and histological biomarkers.[111] Fruits ethanolic extract had **aphrodisiac** effect in female rats, where effect was measured by frequency of sexual activity. In addition, extract GCC is presented.[112] Whole plants alkaloid extract was obtained using ion exchange method. The crude extract and its components (Protopine, Cryptopine, Fumaritine, Sanguinarine, Sinactine, and Stylopine) had **anti-arrhythmic** activity in mice and rabbits. Quinidine and Ethmosine were used as standard drugs.[113] Mineral composition (13 elements) was tested by a list of complete results is not presented.[114] Aerial parts were separately extracted for alkaloids and phenolics and both extracts were chromatographed yielding previously known compounds, five alkaloids and eight phenolics.[115] Aerial parts 95% ethanolic (alkaloid) extract was chromatographed affording 20 compounds: two new compounds, Fumaranine, and Fumarostrejdine, and three previously known that were not presented so

	far in this article, O-methylfumarofine, N-methylcorydaldine and Corydamine (**Figure 8**). All others are presented in the other figures. All the alkaloids were tested for **enzyme inhibition** (AChE, BuChE and prolyl oligopeptidase) where ten compounds were active.[116] Aerial parts were successively extracted with PE, chloroform and ethanol. The ethanolic extract was tested for **hepatoprotective** activity in carbon tetrachloride-induced rats, showing good results. The three extracts were analyzed for GGC, but results are not reported. In addition, the article uses wrong term of "photochemical screening" instead of "phytochemical screening".[117] Leaves were separately extracted with 70% aqueous ethanol and pure methanol. Both extracts were tested for **antiparasitic** activity against adult *Schistosoma mansoni*, *Fasciola hepatica*, and *Echinostoma caproni* in vitro. The hydroethanolic extract had weak activity while the methanolic was inactive.[118] Plant part, alcohol name and alcohol concentration are not reported, but the resulting extract/s had positive effect on rabbits' kidneys.[119] Aerial parts were successively extracted with PE, chloroform and ethanol. The ethanolic extract was tested for **acute toxicity** in mice (not toxic) and for **muscle relaxation** in in stressed rats. The stress was induced by rota rod and traction tests, and positive effect was indicated in both. Very partial GCCs of the three extracts are reported.[120] Whole plant 70% aqueous ethanolic extract was used to prepare a cream in combination with silymarin, and this cream had **anti-moderate-eczema** activity in human patients.[121] Aerial parts were extracted with 50 and 70% aqueous ethanol, and these extracts were analyzed for TFC, TTC and total alkaloid content. The **skin protection** of these extracts was tested in keratinocyte model resulting positive effect. **Antioxidant** activity was tested with ABTS, CUPRAC, DPPH, FRAP and H_2O_2 scavenging methods. Extracts were also analyzed for chemical compositions resulting 21 phenolics.[122] Aerial parts ethanolic (alkaloid) extract was prepared in basic, neutral and acidic forms. The three extracts were tested for **acute toxicity** in mice resulting slight effect.[123]
F. parviflora	Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species (see *F. asepala*). These alkaloids were tested for **antimicrobial** and **antiviral** activities showing moderate to high potency.[50] Whole plant methanol-chloroform (1:1) extract had significant **enzyme inhibition** (AChE, BuChE) activity. [54] Whole plant methanolic extract had moderate **antimicrobial** activity against seven bacterial species and *C. albicans*.[57] Aerial parts ethanolic (alkaloid) extract was analyzed with GC-MS yielding eight previously known alkaloids (% of total alkaloid content): Parfumidine 7 (**Figure 9A**), in addition to Sinactine 2, Adlumine 3, Protopine 57, Cryptopine 5, Parfumine 14, Fumariline 10, and Dihydrosanguinarine 2.[72] Aerial parts methanolic extract had **anticancer** (against human hepatocellular carcinoma cancer cell lines Hep3B and HepG2) and **antioxidant** (DPPH and PBD methods) activities.[76]

	Whole plant 85% aqueous ethanolic extract was fractionized with PE, chloroform, ethyl acetate and methanol. The crude extract and fractions were analyzed for TFC and TPC. They also had significant **antioxidant** activity (DPPH, FRAP, Fe^{+2} chelating, xanthine oxidase inhibition methods).[83] Aerial parts 85% aqueous ethanolic extract was tested for **antiparasitic** activity (against malarial *Plasmodium falciparum* and human African trypanosomiasis *Trypanosoma bruceirhodesiense*). It was also partially analyzed (HPLC) for phenolic acid composition.[84] Aerial parts methanolic extract was partially analyzed for alkaloids and phenolic acids. Crude extracts and five of its components (Fumarophycine, *O*-Methylfumarophycine, Protopine, Caffeic acid and Protocatechuic acid) were tested for **antioxidant** activity, using DPPH and lipid peroxidation methods.[86] Flowers, leaves, stems and roots were separately extracted with water and the extracts were applied for **allelopathic** activity against *Lolium rigidum*. Leaves extract was most active.[124] Whole plant was tested for **anticancer** activity against MCF-7 cancer cells, showing moderate effect. The extract was chromatographed yielding 19 compounds. Molecular docking was performed for these components resulting highest potency for Bidenlignasides A and B. Structures of eight of the isolated compounds (Berberine, Bidenlignaside A, Bidenlignaside B, Bowdichione, Friedelin-3,4-lactone, Stepharanine, Syringaresinol and Tembetarine), including Bidenlignasides A and B are shown in **Figure 9A**.[125] Aerial parts methanolic extract had **antidiabetic** activity in STZ-induced diabetic rats. Effect was measured with several biomarkers especially blood glucose concentrations.[126] Whole plant *n*-butanol extract had **antidiabetic** activity in alloxan-induced diabetic rats. Effect was measured with several biomarkers mainly blood glucose levels.[127] Hydroalcoholic extract had positive effect in type II diabetics.[128,129] Leaves 96% aqueous ethanolic extract had **antidiabetic** (in STZ-induced diabetic rats) and **hepatoprotective** activities. Effects were measured by blood lipids (cholesterol, HDL, LDL, TG) and oxidative stress biomarkers (SOD, GPx, MDA).[130] Aerial parts 70% aqueous ethanolic extract had **antihyperlipidemic** activity in high fat-fed rats.[131] Whole plant 70% aqueous ethanolic extract had **anti-inflammatory** effect in carrageenan-induced paw edema in rats.[132] Leaves aqueous and ethanolic extracts had **anti-inflammatory** activities in rats. Inflammation was induced by carrageenan (paw) and cotton pallet (granuloma). Effects were measured with several parameters, especially inflammatory biomarkers.[133] Whole plant 50% aqueous methanolic extract had **antimicrobial** (against four bacterial strains, *E. coli*, *P. aeruginosa*, *S. aureus*, *E. faecalis*, and four fungal species, *C. albicans*, *A. niger*, *C. lunata*, *A. alternata*). It also had **antioxidant** activity (DPPH method).[134] Aerial parts 70% aqueous methanolic extract had **antibacterial** (against five species) and **antioxidant** (DPPH method) activities. Analysis of the

	extract using GC-MS afforded 21 compounds where the major component was 4H-pyran-4-one (**Figure 9A**), 13.26%.[135] Flowers, leaves, roots and stems were separately extracted with *n*-hexane, chloroform, ethyl acetate and methanol (16 extracts). All extracts were tested for **antibacterial** (seven species) activity.[136] Whole plant methanolic extract was chromatographed and a new compound was isolated and characterized: *n*-Octacosan-7-ol (**Figure 9A**), which is mistakenly named N-octacosan-7β-ol in the article title. This compound was tested for **antimicrobial** (against four bacterial and two fungal strains), **antiparasitic** (against *Leishmania donovani*) activity. Its **cytotoxicity** was tested on mammalian macrophages isolated from mice (nontoxic).[137] Whole plant methanolic extract had **antinociceptive** activity tested with formalin and hot plate tests, in rats. **Acute toxicity** test (mice) showed that the extract was relatively nontoxic (indomethacin reference).[138] Fruits, leaves, roots and stems were separately extracted with ethanol and the four extracts were analyzed for TFC and TPC. The **antioxidant** activities of the extracts were tested with DPPH method.[139] Whole plant aqueous extract had **antioxidant** activity tested with DPPH and H_2O_2 scavenging methods, and **hepatoprotective** activity against CCl_4-induced liver damage in rats.[140] Whole plant 96% aqueous ethanolic extract had protective effect **against oxidative stress** and **testis tissue damage** in STZ-induced diabetic male rats. Each one of the effects was measured using three different parameters.[141] Whole plant aqueous and ethanolic extracts were tested for **antiparasitic** activity against gastrointestinal nematodes of sheep. Tests were performed *in vitro* (eggs) and *in vivo* (larvae).[142] Roots and stems were separately extracted with *n*-hexane, chloroform, ethyl acetate and methanol, and the eight extracts were analyzed for GCC. Each one of the extracts was tested for **antiparasitic** effect against southern root-knot nematode *Meloidogyne incognita*. Test were performed *in vitro* (eggs) and *in vivo* (nematodes on the plants).[143] Whole plant aqueous extract had **antiparasitic** (antileishmanial) activity, *in vitro* (promastigotes, uninfected/infected macrophages with amastigotes) and *in vivo* (infected mice).[144] Whole plant ethanolic extract had **antiparasitic** (against *Leishmania major*) separately on in synergistic effect with Amphotericin B. Effect was tested *in vitro* (standard strain) and *in vivo* (infected mice). Expression of miR146a-5p and miR499 levels were the major biomarkers measured to detect the effect of treatment.[145] Aerial parts had **antiparasitic** effect against *Fasciola* species in naturally infected buffaloes.[146] Whole plant *n*-hexane extract was chromatographed resulting the isolation and characterization of Nonacosane-10-ol and 23a-Homostigmast-5-en-3β-ol (**Figure 9A**). These compounds had **antiparasitic** activity against *Meloidogyne incognita*. The effect was tested *in vitro* (eggs) and *in vivo* (juveniles).[147] Leaves ethanolic extract had **antitoxicity** activity against lead-induced testicular damage in male rats. Effect was measured with oxidative stress

	biomarkers (GPx. MDA, SOD), and sperm parameters. [148] Aerial parts were successively extracted with PE DEE, benzene, chloroform, ethyl acetate and 95% aqueous ethanol. The combined extracts were chromatographed affording, among other compounds *n*-Pentatriacontane, $CH_3(CH_2)_{33}CH_3$. In addition, inorganic salts and fumaric acid contents were determined. [149] Whole plant ethanolic (alkaloid) extract was chromatographed yielding 35 alkaloids, where three of them were new: Fumaramidine, Fumariflorine and Parviflorine (**Figure 9B**).[150] Follow up of previous study resulted the isolation of a new alkaloid, the enantiomer of Corlumine presented in **Figure 8**. Seven previously known alkaloids were also isolated.[151] Aerial parts methanolic (alkaloid) extract was chromatographed yielding Protopine, Adlumidiceine, Dihydrofumariline, Parfumine, Fumariline, Cryptopine, Stylopine, 8-Oxocoptisine, Sanguinarine, Coptisine, In addition, Oxysanguinarine (**Figure 9B**) was also isolated from this species for the first time.[152] Leaves and twigs of cultivated plant methanolic (alkaloid) extract was analyzed affording Rhoeagenine (**Figure 9B**) and other previously known alkaloids.[153] Fumaric acid content in various parts of the plant was determined.[154] Aerial parts EO (hydrodistillation) was analyzed using GC-MS yielding 29 compounds, and the five major components (%) were: 3-Isothujopsanone 5, Farnesyl acetate 8 (**Figure 9B**), in addition to Octadecane 13.2, Hexadecanoic acid 23.2 and Methyl-9,12-octadecadionate 7.5.[155] Aerial parts methanolic extract was chromatographed affording five new compounds (**Figure 9B**): (5αH,11αH)-8-oxo-homoiridolide (Comp. 1), *n*-docosanyl-2-*O*-β-*D*-glucopyranosyl salicylate (Comp. 2), 2-methyl-6-hydroxymethylenedodecan-10-oyl-12,15-olide14-*O*-β-*D*-xylopyranoside (Comp. 3), 4-oxo-stigmast-5-en-3β-ol-*D*-glucopyranoside (Comp. 4) and salicylic acid-*O*-β-*D*-xylopyranoside (Comp. 5). Several previously known were also isolated.[156] Whole plant contents of Protopine and *β*-Sitosterol were determined.[157] Follow up of the research cited as reference 156: whole plant methanolic extract was chromatographed affording six new compounds (**Figure 9B**). Several previously known were also isolated.[158] Authors of this publication claim that they isolated “new flavonoids” from the aerial parts 85% aqueous methanolic extract. Practically, they presented only one as such: kaempferol-3-O-rhamnoside.[159] This compound was isolated many years before this research and numerous articles were published about its isolation, activities and uses. See[160] These articles reported TFC, TPC and/or GCC.[161,162] Whole plant methanolic extract was analyzed affording three new compounds (**Figure 9C**): *n*-propyl-3,4-dioxymethylene benzene (comp. 1), 5β, 6, 7, 8, 9, 10β-hexahydrocoumarin (comp.2) and 2,6-dimethyl dodecan-10-oyl-12,15-olide (comp. 3). Several previously known were also isolated.[163] *

	* In the title of this article, it is stated that aerial parts were extracted, but in the experimental section it is clearly written that the whole plant was used. Whole plant/aerial parts 80%/90% aqueous ethanolic extract had **Hepatoprotective** activity against CCl_4-induced damages in rat liver. Effect was measured with several biomarkers, especially oxidant-antioxidant. Silymarin was positive control.[164,165,166] Leaves 70% aqueous methanolic extract was tested for **Hepatoprotective** activity against Isoniazid and Rifampicin-induced liver injury in Rats. Silymarin was reference. Effect was measured with five parameters. Extract **acute toxicity** was tested and found nontoxic.[167] Aerial parts 80% aqueous ethanolic extract had **hepatoprotective** activity against vincristine-induced hepatotoxicity in male rats. Effect was measured with oxidant-antioxidant biomarkers.[168] Whole plant 95% aqueous methanolic extract was tested for **Hepatoprotective** activity against Isoniazid and Rifampicin-induced liver injury in Rats. Effect was measured with five parameters.[169] Aerial parts 70% aqueous ethanolic extract had **hepatoprotective** activity against high fat-induced liver damages in rats. Effect was measured with eight parameters, mainly blood lipid levels.[170] Whole plant 80% aqueous ethanolic extract had **hepatoprotective** activity on carbon tetrachloride-treated HepG2 cells. Effect was measured with several parameters, mainly cell viability.[171] Aerial parts aqueous extract was tested in breastfeeding infants for **anti-colic** activity in comparison with Simethicone, where the extract had stronger effect, that was measured with several parameters like crying, stooling, constipation, diarrhea and regurgitation. The extract was also analyzed for fumaric acid content.[172] Aerial parts 70% aqueous methanolic extract had **prokinetic** and **laxative** activities in mice, and **spasmodic** effect in guinea pig isolated ileum but not in rabbit isolated ileum. Carbachol was reference dug and atropine was used to block the spasmodic effect in order to study the mechanism of action.[173] Whole plant encapsulated powder was administered to haemodialysis patients for **treatment** of **Uremic Pruritus**, compared with Gabapentin.[174] Whole plant powder was administered to haemodialysis patients for **treatment** of **Uremic Pruritus**, compared with Gabapentin. Effects of both treatments were approximately equal.[175] Whole plant 50% aqueous ethanolic extract had **preservative** activity in stored *Rutilus kutum*. Effect was measured with various parameters, textural and chemical, mainly oxidant-antioxidant.[176] Whole plant methanolic extract had positive effects on **spermatogenesis** of male rats, qualitative and quantitative.[177] Follow up of previous research: whole plant ethanolic extract had positive effect in male rats **reproductive system**: testis volume, blood vessels and spermatogenesis.[178] Leaves ethanolic extract had positive effects on male rats **reproductive system**, morphology and spermatogenesis.[179]

	Whole plant powder was supplemented (250 mg/kg/day by gavage for 8 weeks) to **treat Varicocele** (induced by partial occluding of the left kidney vein). Positive effects were observed in sexual organs physical health, sex hormones, spermatogenesis and oxidant-antioxidant biochemicals.[180] Aerial parts 80% aqueous ethanolic extract was analyzed for TPC. It was used to prepare a cream (4%) for **treatment of eczema**, showing significant amelioration.[181] Whole plant was defatted with PE and extracted with methanol, and the resulting extract was analyzed for TFC and TPC. It was used to prepare a formulation, in combination with extract of *Glycyrrhiza globra* showing significant stability and pH.[182] Long term use of aerial parts 70% aqueous ethanolic extract proved toxic to rats, where toxicity was verified by several biomarkers. This includes lower concentrations than higher ones that were confirmed toxic in previous studies, that stated that this extract is safe.[183] HPLC analysis of aerial parts of cultivated plants yielded 15 alkaloids that were tested for **acute toxicity** and **wound healing**, both *in vitro*. Eight of these alkaloids had wound healing activity and the most active was Sanguinarine. The isolated alkaloids that were previously mentioned are: Hydrastine, Bicuculline, Protopine, Coptisine, Dihydrosanguinarine, Fumaramidine, Sanguinarine, Fumaramine, Dihydrofumariline, 8-Oxocoptisine and Norjuziphine. In addition, N-methylstylopine, Noroxyhydrastinine, Lahorine and Microcarpine were also isolated (**Figure 9C**).[184]
F. petteri	Forty Isoquinoline alkaloids were isolated from fourteen *Fumaria* species where ten of them are native to the RR, including this species (see *F. asepala*). These alkaloids were tested for **antimicrobial** and **antiviral** activities showing moderate to high potency.[50] Whole plant methanol-chloroform (1:1) extract was had significant **enzyme inhibition** (AChE, BuChE) activity.[54] Aerial parts ethanolic (alkaloid) extract was analyzed with GC-MS yielding eight previously known alkaloids (% of total alkaloid content): Dihydrofumariline 7 (**Figure 10**), in addition to Sinactine 10, Protopine 37, Cryptopine 5, Parfumine 7, Fumariline 20, Fumarophycine13 and Dihydrosanguinarine 2.[72]

*Unless stated otherwise, percentages of solvent mixtures are V/V.

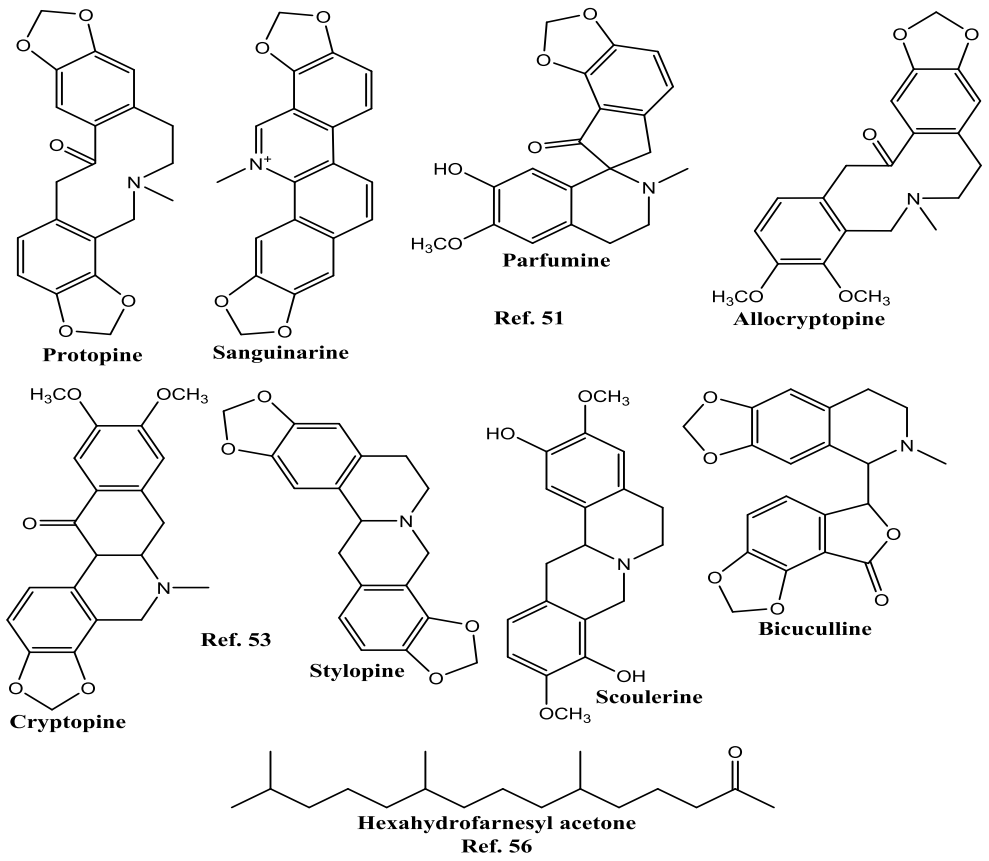


Figure 2: Natural products isolated from *F. asepala.*

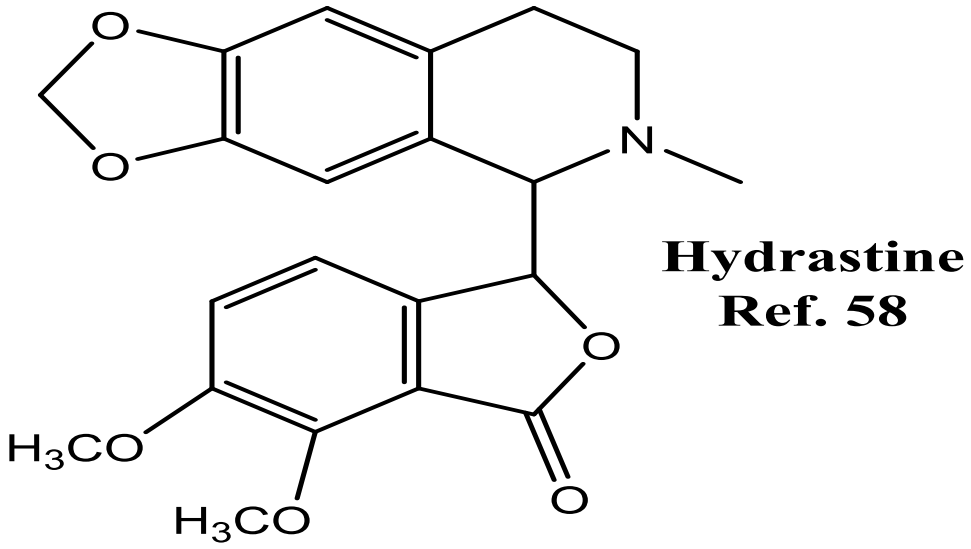


Figure 3: Natural products isolated from *F. bracteosa.*

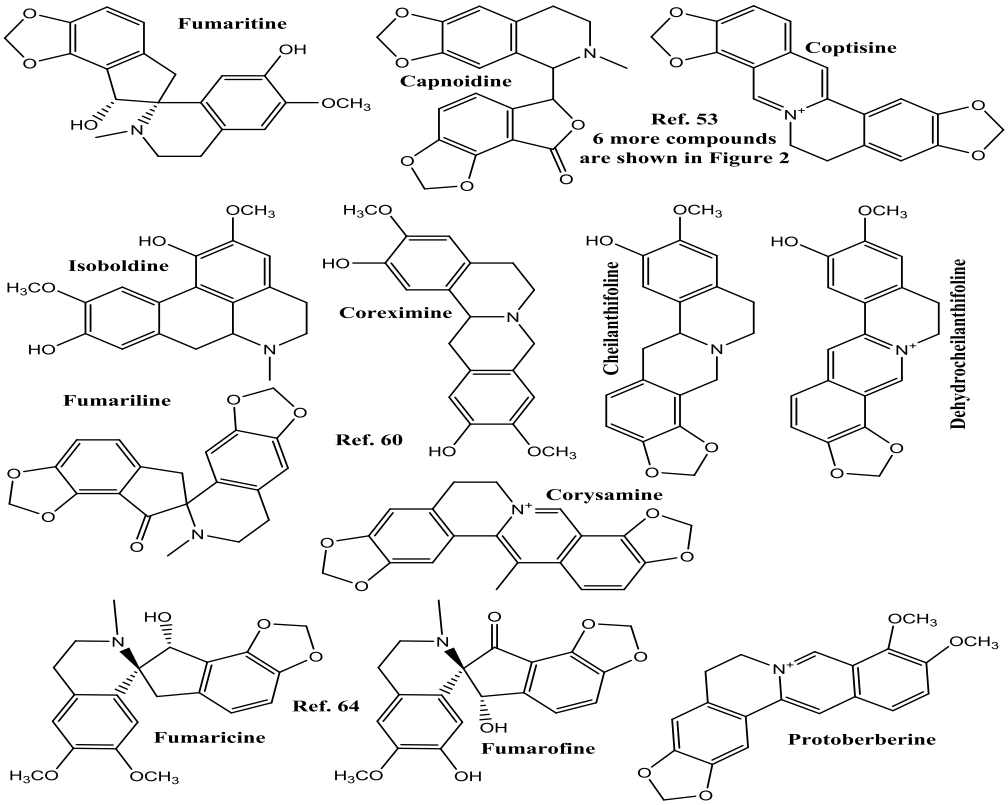


Figure 4A: Natural products isolated from *F. capreolata.*

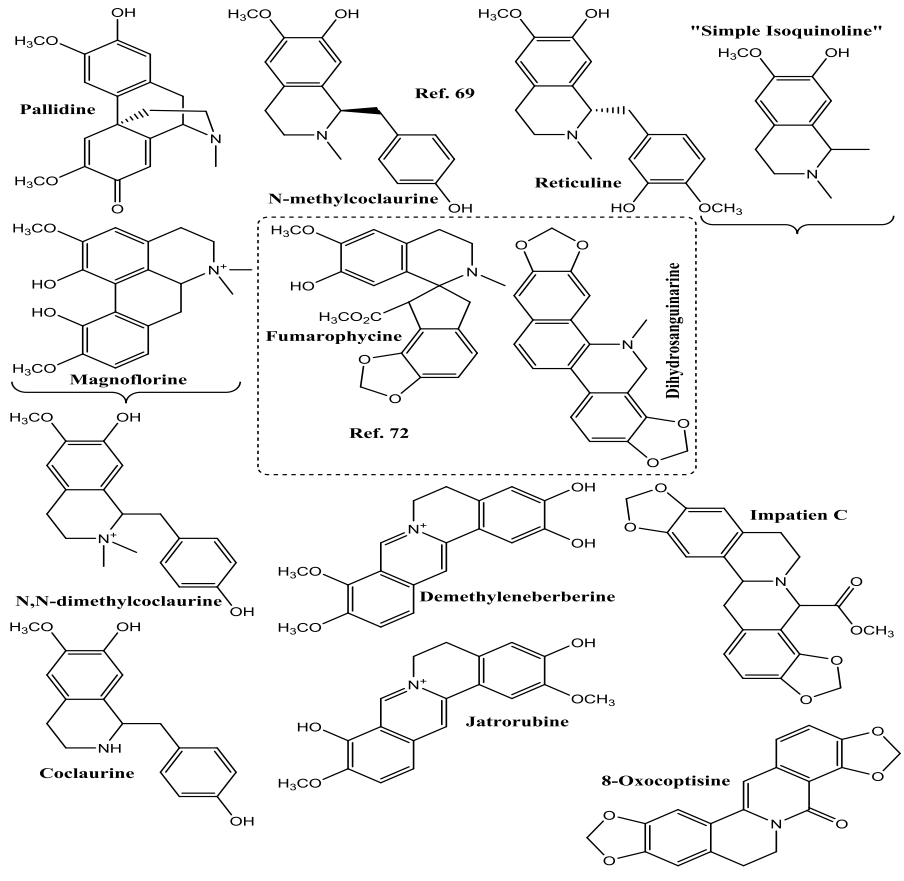


Figure 4B: Natural products isolated from *F. capreolata.*

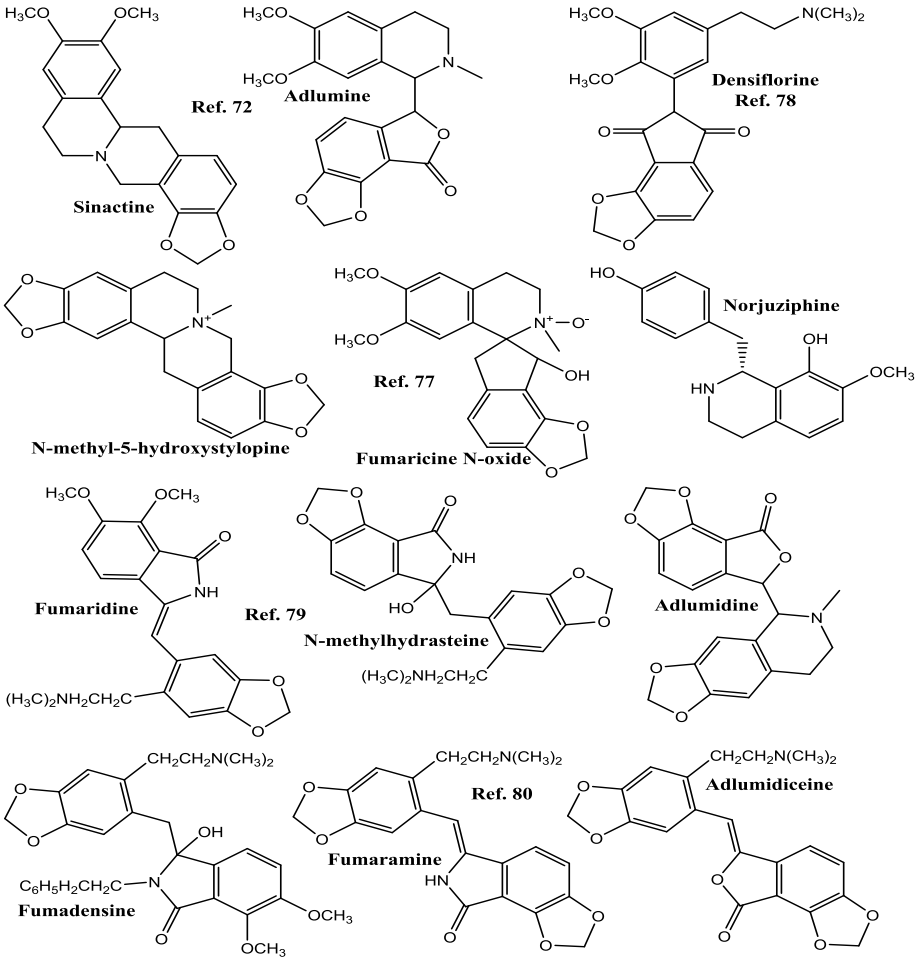


Figure 5A: Natural products isolated from *F. densiflora.*

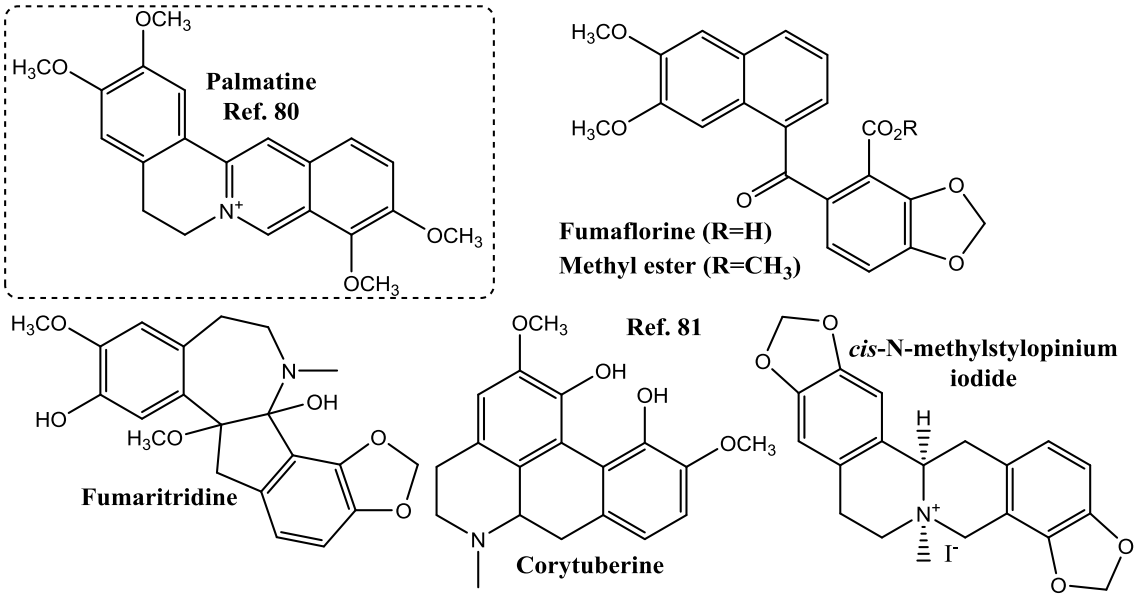


Figure 5B: Natural products isolated from *F. densiflora.*

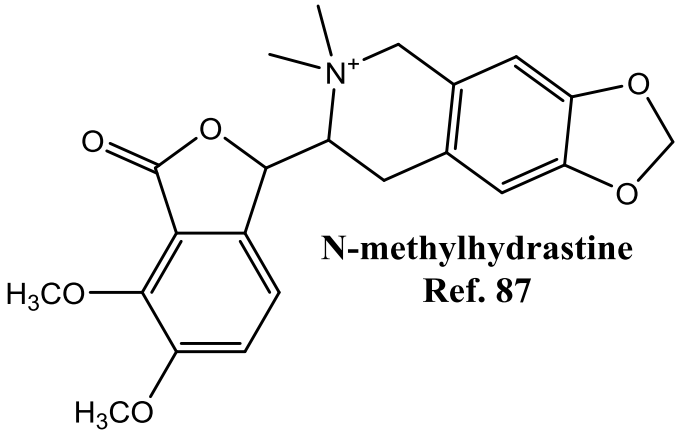


Figure 6: Natural products isolated from *F. gaillardotii.*

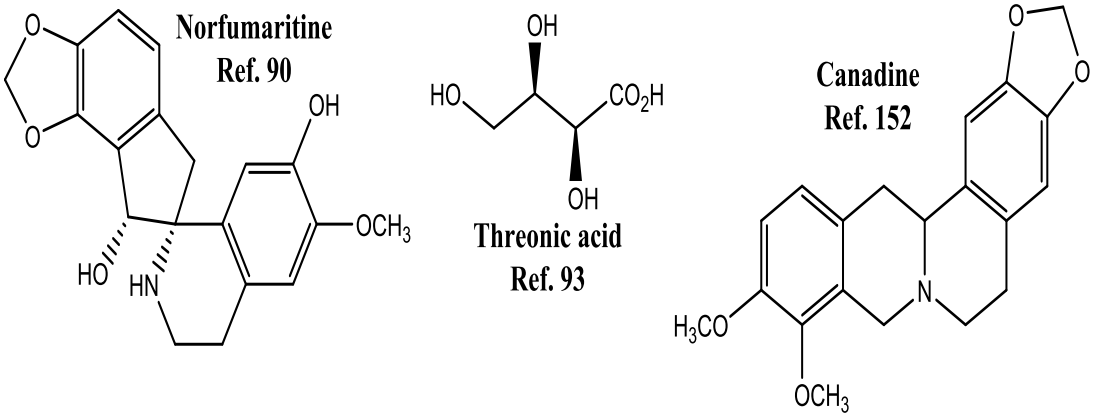


Figure 7: Natural products isolated from *F. kralikii.*

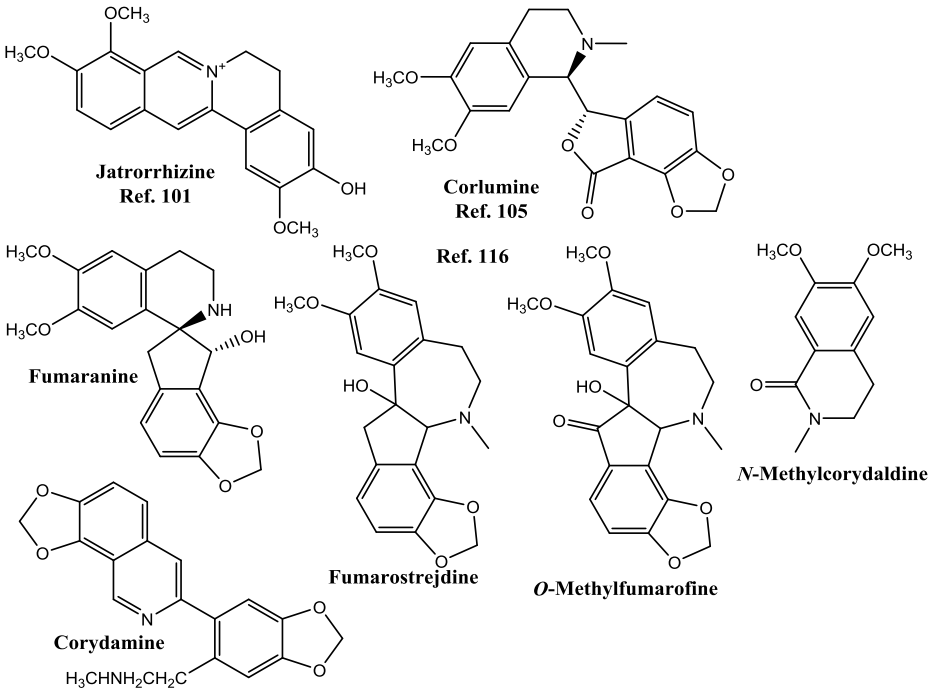


Figure 8: Natural products isolated from *F. officinalis.*

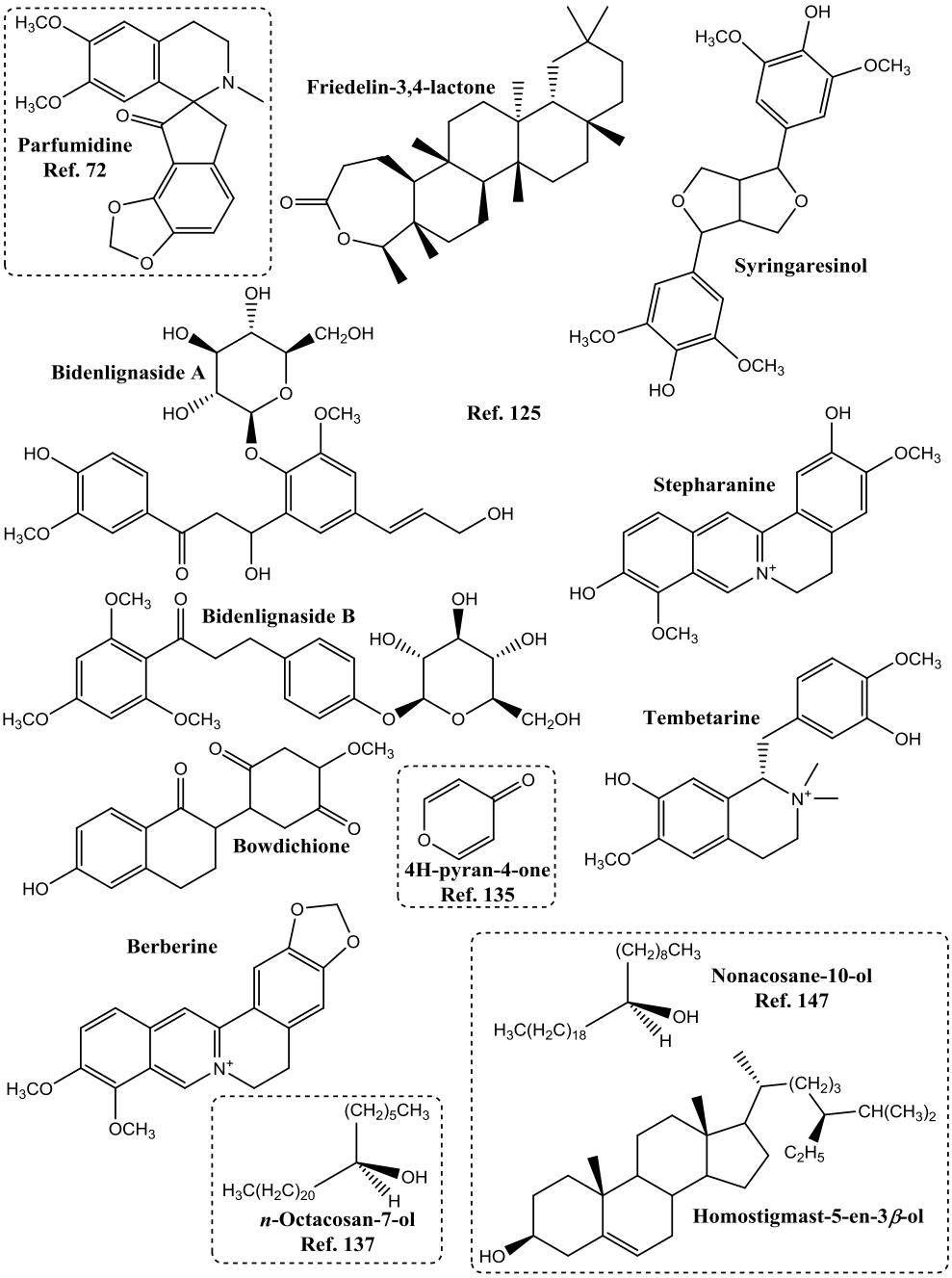


Figure 9A: Natural products isolated from *F. parviflora.*

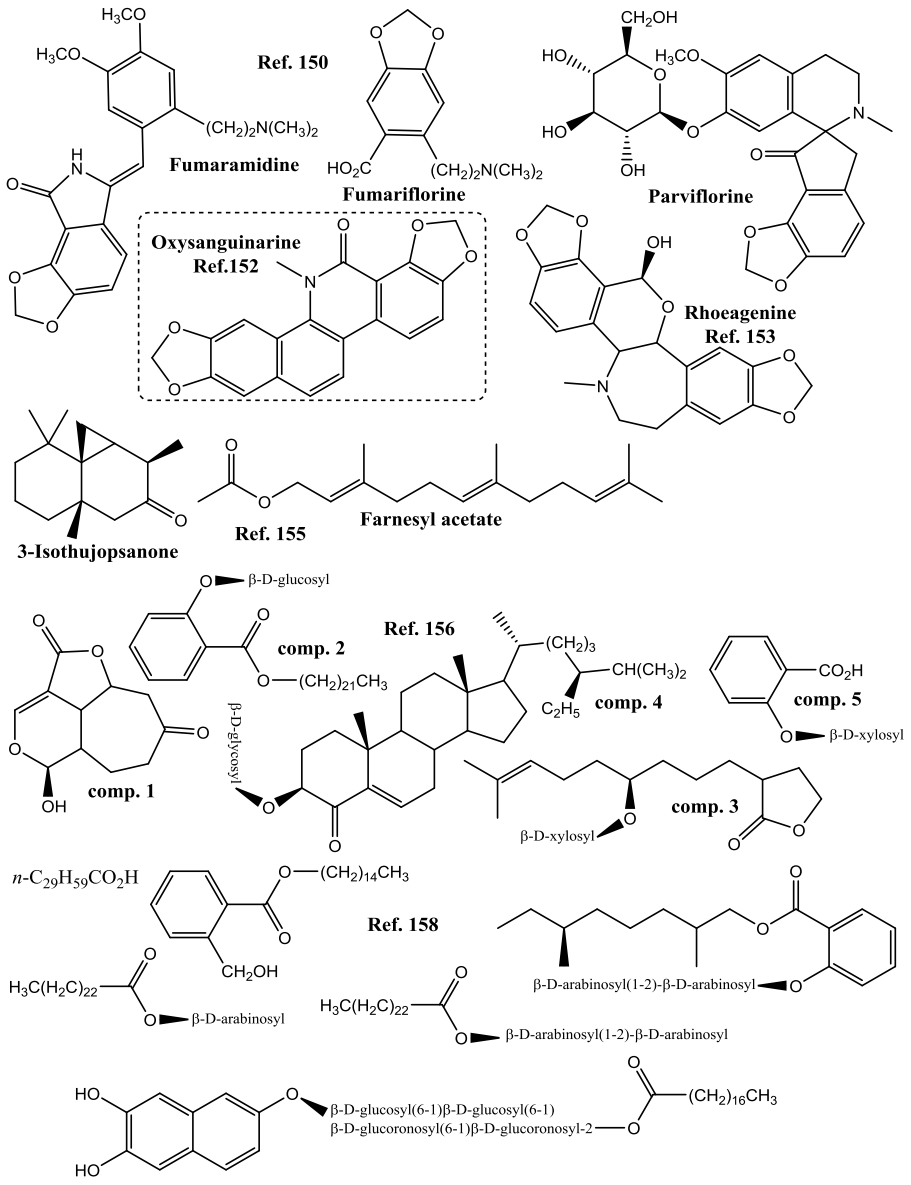


Figure 9B: Natural products isolated from *F. parviflora.*

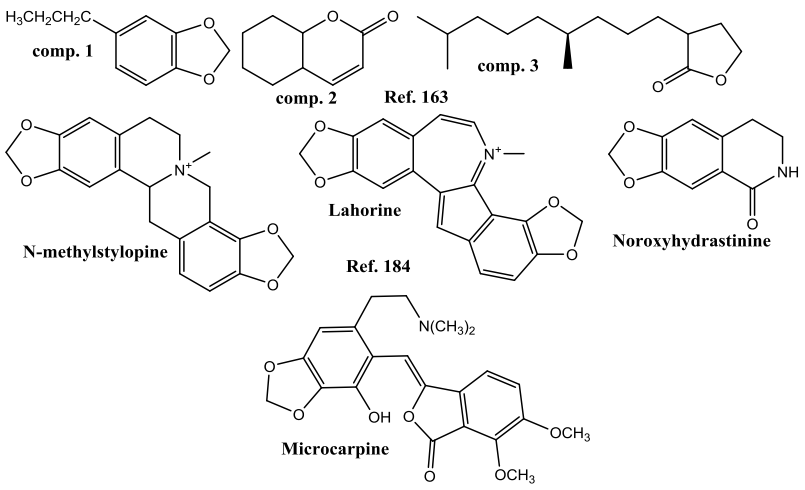
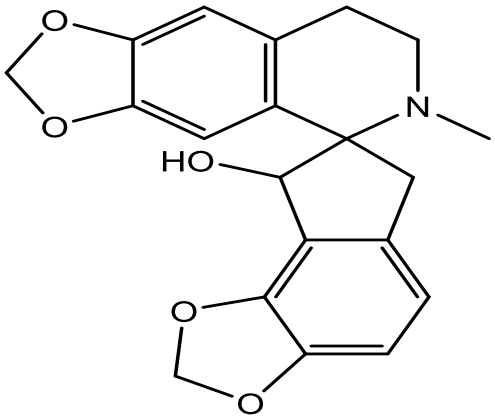


Figure 9C: Natural products isolated from *F. parviflora.*

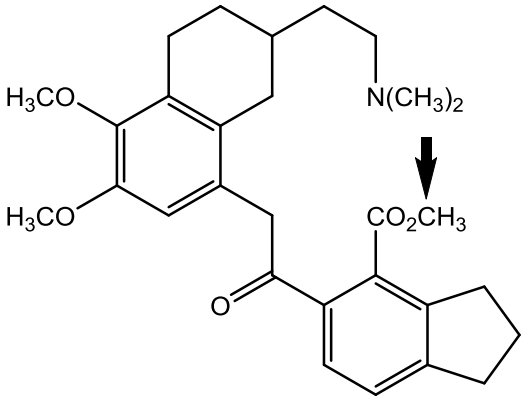


Dihydrofumariline
Ref. 72

Figure 10: Natural products isolated from *F. petteri.*

5. DISCUSSION

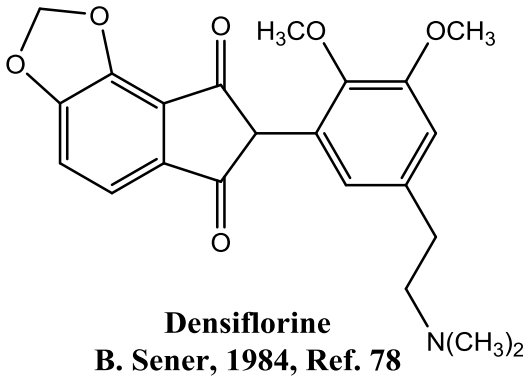
Reviewing *Fumaria* plants of Israel and Palestine was a challenging yest very interesting task, mainly due to the presence and great diversity of alkaloids in these species. Most of these alkaloids are present in all species with obvious differences in their concentrations. Because of this fact, it is emphasized in many articles that some compounds were isolated from certain species for the first time, indicating that these compounds were previously known. One of the best examples of these articles was published by J. Sousek ahc.[185] This work was published in 1999, and it does not report previously unknown natural products. Authors analyzed the alkaloid and organic acids content of eight *Fumaria* species, four of them native to the RR: *F. capreolata*, *F. densiflora*, *F. officinalis* and *F. parviflora*. The analysis aimed to qualitatively and quantitatively detect the presence of Isoquinoline alkaloids Adlumiceine (**Figure 11**), Adlumidiceine, Coptisine, Corytuberine, Cryptopine, Fumaricine, Fumariline, Fumaritine, Fumarophycine, *O*-methylfumarophycine, Palmatine, Parfumine, Protopine, Sinactine, Stylopine, and *N*-methylstylopine. A detailed table (table 1 in the cited article) is provided that includes even the dates of harvesting the plants. In a second table (table 2 in the cited article), alkaloids isolated for the first time from each species are presented. This presentation is very highly helpful.



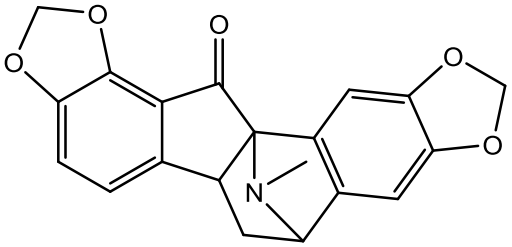
Adlumiceine (methyl ester)

Figure 11: Structure of Adlumiceine (methyl ester).

The published reports about *Fumaria densiflora* include contradicting presentations. B. Şener published in 1984 the structure of Densiflorine that she isolated as a new compound from this species, and its structure is presented in **Figure 5A**.[78] This structure is identical to that presented in many chemical databases such as PubChem (PubChem CID 343060).[186] But a year earlier (1983), M.E. Popova ahc reported the isolation of the same compound as a new natural product and presented a notably different structure.[187] And to increase the confusion, the same compound is presented in PubChem with a different PubChem CID (177184)[188], which is identical to the structure presented by M.E. Popova ahc. Both structures are shown in **Figure 12**.



Densiflorine
B. Sener, 1984, Ref. 78
PubChem CID 343060, Ref. 186



Densiflorine
M.E. Popova ahc, 1983, Ref. 187
PubChem CID 177184, Ref. 188

Figure 12: Two different reported structures of Densiflorine.

In a recent work, A.H. Roni ahc performed molecular docking of several compounds as antiviral agents, including Densiflorine, and the presented a structure like that presented by M.E. Popova ahc.[189]

Following the mentioned above contradictory concerning the structure of Densiflorine, it is important to highlight analytical efforts that add more information about natural products, their structures and their isolation. In the work of M.H. Abu Zarga ahc that reported the isolation and characterization of Fumadensine (**Figure 5A**) as a new compound from *Fumaria densiflora*[80], they included its decomposition with Trifluoroacetic acid (TFA). This was done as additional way of confirming its structure. See **Figure 13**.

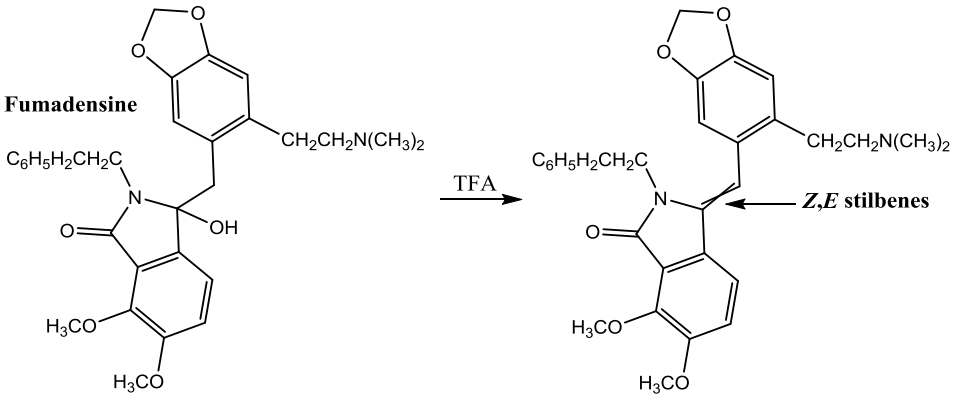


Figure 13: Decomposition of Fumadensine with TFA (Ref. 80).

T. Fafal and M.A. Önür published an outstanding article in 2007 about Ddetermination of protopine in *F. densiflora* by TLC-densitometric and spectrophotometric method.[190] In addition to the efficiency and accuracy of this method, the authors presented all the alkaloids that were isolated from 18 *Fumaria* species. They presented the information in two very clear tables, qualitative and quantitative.

In 1938, R.H. Manske published the alkaloid composition of *Fumaria officinalis*.[191] He reported (quantitatively) the isolation and characterization of seven alkaloids: Aurotensine, Tetrahydrocoptisine, Cryptocavine (**Figure 14**), Protopine, Sinactine and two new alkaloids that he indicated them with molecular formulas and symbols F36 and F37. The structures of the alkaloids were not presented. However, the structure of Cryptocavine was debated, and in 1955, A.F. Thomas ahc (a research group headed by R.H. Manske) resolved the debate and the similarity to the structure of Cryptopine by chemical modifications.[192]

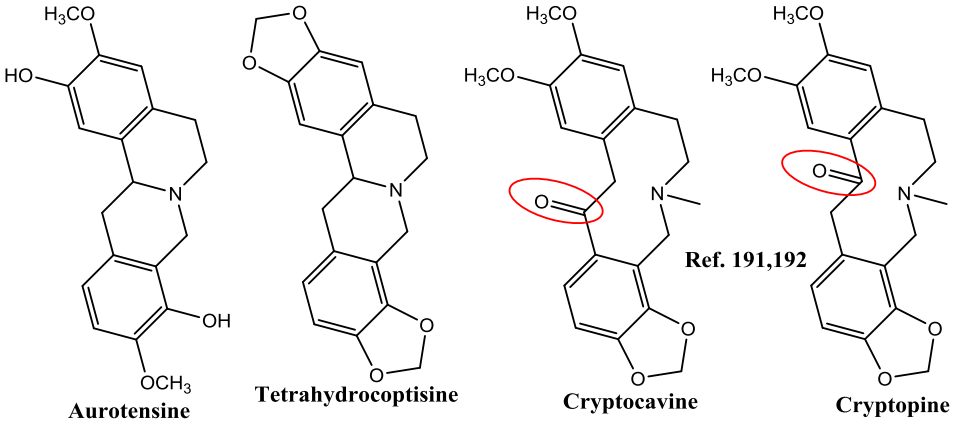


Figure 14: Alkaloids isolated from *Fumaria officinalis.*

Additional clarity to the structures of alkaloids isolated from *Fumaria officinalis* was presented by C. Seger ahc (2004). They published a comprehensive ^{1}H and ^{13}C-NMR peak assignment of Adlumine, Corlumine, Corydamine, Cryptopine, Fumarophycine, *O*-methylfumarophycine, Hydrastine, Parfumine, Protopine and Sinactine.[193]

The extraction of *Fumaria officinalis* was thoroughly studied and improved by several research groups. S. Khamtache-Abderahimi ahc published the optimization of phenolic compounds extraction, affording higher yields of TFC and TPC, and consequently, the antioxidant capacity measured with ABTS and DPPH methods.[194] In a recent work, G. Mammadova and P. Koseoglu-Yilmaz improved the extraction (HPLC) of Fumaric acid.[195] R. Ashowen Ahmoda ahc investigated the effect of heating on the yields of extraction and optimized this method for polyphenols and flavonoids in *F. officinalis*.[196]

Of all *Fumaria* species of the RR, *Fumaria parviflora* is the most studied and published (**Table 3**). But one of the "strangest" articles about this plant was published by A. Bhargava ahc.[197] They analyzed whole plant methanolic extract by special method of HPLC yielding 42 compounds arranged in four tables. Strangely enough, under the column title of "assigned substance", all 42 entries are "unknown".

Fumaria parviflora is considered a medicinal plant in most parts of its natural habitat. But in some cases, it becomes hazardous weed, and some studies were published about its control. One of these articles was published by B. Hajjaj ahc, where they investigated the control of this plant that infest wheat crop, by two synthetic herbicides, Florasulam and 2,4-D (2,4-Dichlorophenoxyacetic acid).[198]

M. Tashakorizadeh ahc investigated the effect of copper (ancient copper mine) and drought on growth and essential oil yield and composition.[199] Drought had major effect on both parameters, suggesting that this plant can not tolerate drought stress, and its phytoremediation was clearly limited. This research was followed up and three additional articles were published by the same research group.[200,201,202]

In a very recent research, V. Ramezani ahc tested the aerial parts aqueous extract in breastfeeding infants for anti-colic activity in comparison with Simethicone, where the extract had stronger effect.[172] This achievement is questionable. Simethicone is a polydimethylsiloxane mixed with silicon dioxide (**Figure 15**).[203]

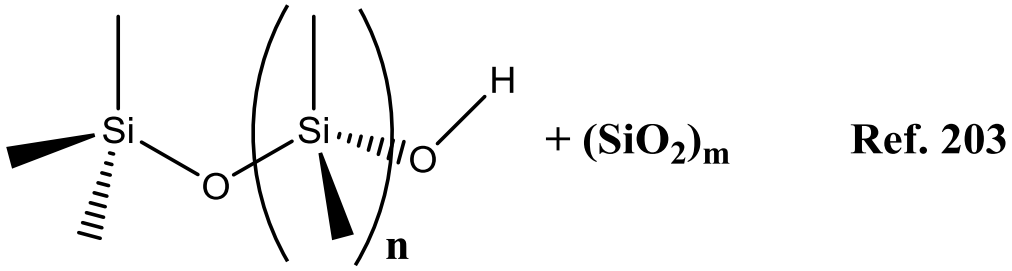


Figure 15: Structure of Simethicone.

Reference drugs usually have proven activity, and this is not the case of Simethicone. In 1994, T.J. Metcalf ahc published a research that was carried out to "determine the efficacy of simethicone in the treatment of infant colic" [204] They concluded that "Simethicone is no more effective than placebo". Moreover, C. Evans and W.P. Lorentz published a research that used a mixture of plants to treat infant colic showing notable ameliorative effect.[205] They compared their findings to Simethicone and even mentioned that some other synthetic medications are more effective Simethicone.

To conclude this part of the discussion, a summary of published *Fumaria* extract assisted preparations of nanoparticles (NPs) and their activities, is presented in **Table 4**.

Table 4: NPs prepared with *Fumaria* plants (of the RR) and their medicinal activities.

Species	NP	Property-Activity, reference
F. officinalis	Ag	Antibacterial [206]
	Fe_3O_4	Absorbing material, antioxidant [207]
	Mn	Anticancer [208]
	Extract loaded on Chitosan	Wound healing [209]
	Ni	Anticancer[210]
	Zn	Antileukemia[211]

	ZnO	Antibacterial, antioxidant[212]
F. parviflora	Ag	Antibacterial, antioxidant[213]
	Ag	Anticancer[214]
	Ag	Antibacterial[215]
	Extract coated with Maltodextrin and/or gum Arabic	Antioxidant[216]
	Extract loaded on Chitosan	Antiparasitic[217]
	ZnO	Antibacterial, antioxidant[218]

6. CONCLUSIONS

1) *Fumaria* plants of Israel and Palestine were partially investigated and published.
2) A research effort is needed to achieve the completion of this research.
3) *Fumaria* plants of Israel and Palestine contain an amazing diversity of alkaloids.
4) These alkaloids must be tested for drug development.
5) It is vitally important to share species data among scholars in the RR.

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