Mohammadhosseini, M, Frezza, C, Venditti, A and Sarker, SD

A systematic review on phytochemistry, ethnobotany and biological activities of the genus Bunium L.

Article

Mohammadhosseini, M, Frezza, C, Venditti, A and Sarker, SD (2021) A systematic review on phytochemistry, ethnobotany and biological activities of the genus Bunium L. Chemistry and Biodiversity, 18 (11). ISSN 1612-1872

A systematic review on phytochemistry, ethnobotany and biological activities of the genus *Bunium* L.

Majid Mohammadhosseini[a*], Claudio Frezza[b], Alessandro Venditti[c], and Satyajit D. Sarker[d]

a) Department of Chemistry, College of Basic Sciences, Shahrood Branch, Islamic Azad University, Shahrood, Iran
b) Dipartimento di Biologia Ambientale: "Sapienza" Università di Roma, Piazzale Aldo Moro 5, 00185 Rome (Italy)
c) Dipartimento di Chimica: "Sapienza" Università di Roma, Piazzale Aldo Moro 5, 00185 Rome (Italy)
d) Centre for Natural Products Discovery, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, James Parsons Building, Byrom Street, Liverpool L3 3AF, United Kingdom

*Correspondence: e-mail address: majidmohammadhosseini@yahoo.com; Phone: (++98)-23-32394530; Fax: (++98)-23-32394537

ABSTRACT

The aim of this review article is to present, for the first time, an appraisal of the phytochemical, ethnobotanical and pharmacological data on *Bunium* species. The literature search was conducted using the Scopus, Google Scholar and PubMed databases. The genus *Bunium* has been found to produce both essential oil (EO), mainly comprising monoterpenes and sesquiterpenes, and non-volatile components mainly coumarins and flavonoids. There are several pharmacological activities associated with the *Bunium* species, especially antioxidant, antibacterial and antifungal properties. The chemotaxonomic appraisal of the phytochemical pattern of the genus is in sink with the current classification of the family. Moreover, this review confirms the significant ethnobotanical and pharmacological potential of different *Bunium* species.

Keywords: Apiaceae, *Bunium* L., biological activities, ethnobotany, phytochemistry

Abbreviation list:

ABTS$^{\bullet+}$: 2;2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; *Alternaria alternata*: *A. alternata*; *Aspergillus flavus*: *A. flavus*; *Aspergillus niger*: *A. niger*; *Aspergillus parasiticus*: *A. parasiticus*; *Bacillus subtilis*: *B. subtilis*; BCLAB: β-Carotene-linoleic acid bleaching; BHA: Butylated hydroxyanisole; BHT: Butylated hydroxytoluene; BPEO: *B. persicum* essential oil; *Candida albicans*: *C. albicans*; CC: Column chromatography; *Colletotrichum acutatum*: *C. acutatum*; *Colletotrichum fragariae*: *C. fragariae*; *Colletotrichum gloeosporioides*: *C. gloeosporioides*; CUPRAC: Cupric Reducing Antioxidant Capacity; DPPH$^{\bullet}$: 1;1′-Diphenyl-1-picrylhydrazyl; EC$_{50}$: Median effective concentration; EO: Essential oil; *Escherichia coli*: *E. coli*; F.B.B.: Fruit-bearing branches; FRAP: Fe reducing antioxidant power; *Fusarium oxysporum*: *F. Oxysporum*; GLC: Gas-liquid chromatography; HD: Hydrodistillation; HD-SME: Hydrodistillation-headspace solvent microextraction; HPLC: High Performance Liquid Chromatography; HPLC-MS: HPLC coupled to Tandem Mass Spectrometry; HPSA: Hydrogen peroxide scavenging activity; IC$_{50}$: Median inhibitory concentration; ICPD: Instant controlled pressure drop; IR: Infra-red spectroscopy; LC: Liquid chromatography; LD$_{50}$: Median lethal dose; *Listeria gray*: *L. gray*; *Listeria monocytogenes*: *L. monocytogenes*; MAHD: Microwave-assisted hydrodistillation; MBC: Minimum bactericidal concentration; MD: Microdistillation; MFC: Minimum fungicidal concentration; MH:

Monotrerpene hydrocarbons; MIC: Minimum inhibitory concentration; MS: Mass spectroscopy; n.s.: Not specified; NH: Non-terpene hydrocarbons; NMR: Nuclear magnetic resonance spectroscopy; NR: Not reported; OM: Oxygenated monetrerpene; OS: Oxygenated sesquiterpenes; *Penicilium candidum*: *P. candidum*; *Penicillium notatum*: *P. notatum*; *Pseudomonas aeruginosa*: *P. aeruginosa*; PV: Peroxide value; *Salmonella typhi*: *S. typhi*; SCE: Supercritical extraction; SD: Steam distillation; SE: Solvent extraction; SH: Sesquiterpene hydrocarbons; SHWE: Superheated water-based extraction; SPME: Solid phase microextraction; *Staphylococcus aureus*: *S. aureus*; SXE: Soxhlet extraction; T.B.: Thickened branches; TBA: Thiobarbituric acid; TBHQ: Tertbutylhydroquinone; TLC: Thin layer chromatography; *Trichoderma harzianum*: *T. Harzianum*; UAE: Ultrasound-assisted extraction; UV: Ultraviolet spectroscopy; YEO: Yield of essential oil.

1. Introduction

Since prehistoric times, there has been a growing interest for the use of medicinal plants and herbs. In the literature, there are numerous reports accounting for the presence of several valuable bioactive compounds in plant materials possessing remarkable biological, pharmaceutical and medicinal activities. [1-5]

The genus *Bunium* L. comprises 212 arid or sub-arid geophytes from the family Apiaceae (*alt.* Umbelliferae), including 53 accepted species, 128 synonymous species and 31 unresolved species. [6] The name of the genus derives from the Greek term βούνιον (boúnion) meaning lump because of the typical big form of its tubers.

From the morphological standpoint, species of this genus are characterized by tuberiform storage roots, petioulate primary segments of bi- or tri-pinnatifid leaf blades, calyces without teeth and white petals with inflexed terminal lobes. The fruits appear to be rather uniform, but they present filiform ribs, special lignified elements in the mesocarp and an endosperm, which is flattened on the commissural side (Figure 1). [7] These morphological features make *Bunium* species quite similar to those of the genus *Carum* L. In fact, *Bunium* and *Carum* genera are taxonomically close and appear as useful herbs and aromatic plants, [8] which often grow under temperate, warm and dry, arid and semi-arid climatic conditions and usually on the mountainous slopes. [9, 10] The vernacular names of some of the *Bunium* species have been summarized in Table 1. The main habitats of *Bunium* species are in Jammu-Kashmir, Afghanistan, Baluchestan, India, Himachal Pradesh, Pamir Mountains, Tajikistan, Turkmenistan, Syria, Iran as well as in some European, and African countries. [11-16]

Figure 1: Photos of *Bunium* spp. highlighting flowers, leaves and stems.

Table 1

The vernacular names of some *Bunium* species

<table>
<tr><th>Bunium species</th><th>Country</th><th>Vernacular name(s)</th><th>Reference</th></tr>
<tr><td>B. cylindricum (Boiss. et Hohen.).</td><td>Iran</td><td>Kaji Zira</td><td>[17]</td></tr>
<tr><td>B. incrassatum (Boiss.) Batt. &Trab.</td><td>Algeria</td><td>Talghouda</td><td>[18]</td></tr>
<tr><td rowspan="13">B. persicum
(Boiss). B. Fedtsch</td><td>Iran</td><td>Wild caraway</td><td>[8]</td></tr>
<tr><td>India</td><td>Kalazira</td><td>[19, 20]</td></tr>
<tr><td>Iran</td><td>Black cumin (ZireSiah)</td><td>[14, 21]</td></tr>
<tr><td>Iran</td><td>ZirehKuhi</td><td>[22]</td></tr>
<tr><td>Iran</td><td>Mountainous Black Zira</td><td>[9, 23]</td></tr>
<tr><td>Germany</td><td>Zwartekomijin</td><td rowspan="8">[24]</td></tr>
<tr><td>Denmark</td><td>Sort kommen</td></tr>
<tr><td>France</td><td>Cumin noir</td></tr>
<tr><td>Japan</td><td>Burakku-kumin</td></tr>
<tr><td>Italy</td><td>Cuminonero</td></tr>
<tr><td>Nepal</td><td>Kalijira, Himalijira</td></tr>
<tr><td>Spain</td><td>Comino negro</td></tr>
<tr><td>Jammu-Kashmir</td><td>Zeur</td></tr>
</table>

In particular, 14 species are found in the flora of Iran [25] with 2 endemic species, namely *B. lurestanicum* Rech. f. and *B. wolffi* Kljuykov. [12, 26] In Turkey, 15 *Bunium* species are known, of which *B. fallax* Freyn, *B. nudum* (Post) H. Wolff and *B. pinnatifolium* Kljuykov are endemic. [27] In the Algerian flora, the genus *Bunium* comprises 7 species, of which 4 are endemic. [18] *B. persicum* (syn. *Carum persicum* Boiss.), is endemic in the central regions of Asia and in Northern India, instead [23, 28] Actually, some *Bunium* species are considered endangered, especially *B. persicum*, the seeds of which are extensively harvested for several purposes. [10]
This review article presents a systematic appraisal of the published literature on the genus *Bunium*. To conduct this study, the data available in the Scopus, Google Scholar and PubMed database were gathered under the title "*Bunium*" and lastly accessed in August 2021.

2. Phytochemistry of the genus *Bunium*

Bunium species are mainly known to biosynthesize volatile compounds composing the essential oil (EO) together with some metabolites of the polar fraction. In the following sub-sections, the metabolites, already identified to date, are presented.

2.1. Essential oil (EO) metabolites

EO a hydrophobic liquid, which is usually lighter than water and for its isolation, a number of classical and advanced methods have been reported in the literature to date. [29-32] The screening of the chemical profiles of the EOs usually leads to the identification of a wide range of natural compounds belonging to several classes (terpenoids, non-terpenoids) which are applied in different pharmacological and medical areas. [1, 2, 33-38]
Different species of the genus *Bunium* usually possess a pungent odor and are potential sources of secondary metabolites, mainly terpenoids, which constitute the EO found in their secretory glands. A large number of reports are found in the literature dealing with the quantitative and qualitative characterizations of various *Bunium* species. Accordingly, several studies focused on *B. persicum* essential oil (BPEO) profiles. As shown in Table 2, in many BPEO profiles, monoterpene hydrocarbons (MHs) are the major fractions of the characterized oils. In this sense, γ-terpinene and *p*-cymene were reported as the main constituents of BPEO samples. [39-42] On the other hand, some other profiles of BPEO are dominated by oxygenated monoterpenes (OMs), specifically cuminaldehyde. [13, 43] In addition, regardless of negligible differences in total amounts of natural compound groups, in some profiles, MHs and OMs were recognized as dominating groups with high prevalence of γ-terpinene. [43, 44]

Table 2: Essential oil (EO) components of different *Bunium* species

Bunium spp.	Organ studied	Country	Main compounds (%)	Number of identified compounds/ Total percentage	YEO [a]	Dominant class	Extraction/ Characterization methods	References
B. alpinum Waldst. & Kit.	Aerial parts	Algeria	Caryophyllene oxide (33.8%), humulene epoxide I (8.4%), *n*-pentacosane (6.4%), ledenoxide I (4.7%), 14-hydroxy-9-*epi*-(*E*)-caryophyllene (4.6%) and 2α-hydroxy-amorpha-4,7(11)-diene (4.4%)	24/87.3	0.10	OS [b]	HD [c]/ GC-MS [d]	[45]
B. badghysi (Korovin) Korovin	Seeds	Iran	β-Sesquiphellandrene (32.8%), germacrene D (21.3%), germacrene B (14.5%) and (*E*)-caryophyllene (7.5%)	16/93.1	0.57	SH [e]	HD/ GC-FID [f] and GC-MS	[26]
B. carioides (Boiss.) Hausskn. ex Bornm.	Seeds	Iran	β-Sesquiphellandrene (24.2%), germacrene D (13.5%) and germacrene B (13.1%)	13/77.2	0.09	SH	HD/ GC-FID and GC-MS	
	Aerial parts	Iran	(*E*)-Caryophyllene (26.6%), germacrene-D (22.1%), dillapiole (10.2%) and asaricin (7.5%)	30/92.3	0.14	SH	HD/ GC, GC-MS, and ^{13}C-NMR [g]	[8]
B. cylindricum (Boiss. et hohen.) Drude.	Aerial parts	Iran	Myristicin (43.1%), β-phellandrene (20.0%), β-pinene (15.6%) and α-pinene (10.7%)	14/100	0.09	MH [h] and NH [i]	HD/ GC and GC-MS	[46]
B. elegans (Fenzl) Freyn	Aerial parts	Turkey	Caryophyllene oxide (28.7%), myristicin (7.4%), caryophyllenol-II (4.1%), α-selinene (4.0%), hexadecanoic acid (3.7%), β-caryophyllene (3.0%), *iso*-caryophyllene oxide (3.0%), salvial 4(14)-en-1-ol (2.9%), humulen epoxide II (2.6%), spathulenol (2.6%) and germacrene D (2.5%)	29/76.7	3.7	OS	HD, GC-FID, GC-MS	[47]
		Iran	(*E*)-Caryophyllene (38.0%), germacrene-D (24.1%), (*Z*)-β-ocimene (5.9%) and α-pinene (4.1%)	19/91.4	0.13	SH	HD/ GC, GC-MS, and ^{13}C-NMR	[8]
B. ferulaceum Sm.	Fruits	Algeria	Caryophyllene oxide (31.0%), (*Z*)-β-farnesene (8.7%), β-caryophyllene	28/81.4	NR [j]	OS	SD [k]/ GC and GC-MS	[48]

			(7.2%) and germacrene B (5.8%)					
	F.B.B. [l]		Caryophyllene oxide (26.8%), nonacosane (11.6%), germacrene B (7.7%), β-caryophyllene (5.8%), (*Z*)-β-farnesene (5.1%), caryophyllenol II (4.8%) and spathulenol (2.5%)	40/85.2	NR	OS	SD/ GC and GC-MS	
	T.B. [m]		Nonacosane (44.7%), spathulenol (5.3%), eudesm-4(15),7-dien-1β-ol (4.4%), caryophyllenol II (4.1%), (*Z*)-β-farnesene (2.3%), germacrene B (1.2%) and β-caryophyllene (1.0%)	24/75.4%	NR	NH	SD/ GC and GC-MS	
	Areal parts	Algeria	Palmitic acid (18.4%), caryophylleneoxide (17.4%), β-eudesmol (14.0%), *n*-pentacosane (5.1%), 10-*epi*-α-muurolol (4.4%), hedycaryol (4.1%) and spatuleneol (4.0%)	31/97.2	0.09	OS	HD/ GC-MS	[45]
B. luristanicum Rech.f.	Aerial parts	Iran	*E*-Anethole (60.9%), limonene (9.7%), α-fenchyl acetate (5.2%), *p*-allylanisole (4.7%), γ-terpinene (2.9%), α-pinene (2.8%) and β-pinene (2.4%)	35/95.2	3.1	NH	HD, GC-MS	[49]
			E-Anethole (60.9%), limonene (9.2%), α-fenchyl acetate (5.2%), *p*-allylanisole (4.5%), α-pinene (2.5%), γ-terpinene (2.5%) and β-pinene (2.4%)	35/98.6	NR	NH	HD, GC-MS	
	Aerial parts	Iran	α-Pinene (16.2%),1.8-cineole (13.7%), myrcene(12.7%), camphor (8.2%), camphene (6.8%), α-terpinene (6.4%),borneol (5.5%), linalool (4.0%), 3-octanone (3.2%) and β-pinene (2.8%)	34/95.8	NR	MH	MAHD [n], GC-MS	[26]
	Seeds		Germacrene D (25.1%), (*E*)-caryophyllene (11.6%) and bicyclogermacrene (11.5%)	13/57	0.62	SH	HD/ GC-FID and GC-MS	

B. microcarpum (Boiss.) Freyn & Bornm.	Seeds	Iran	Elemicine (21.7%), germacrene D (12.7%), (*Z*)-β-ocimene (12.2%), limonene (11.8%) and β-pinene (9.6%)	23/90.1	1.99	MH	HD/ GC-FID and GC-MS	[26]
B. persicum (Boiss.) B. Fedtsch.	Fruits	Tajikistan	*p*-Mentha-1,4-dien-7-al (29.0%), γ-terpinene (25.7%), β-pinene (15.6%) and cuminaldehyde (11.7%)	22/98.1	3.33	MH and OM [o]	HD/ GC and GC-MS	[50]
	Fruits	Iran	Cuminaldehyde (27.0%), γ-terpinene (25.8%), *p*-cymene (12.1%), cuminyl alcohol (6.0%) and limonene (5.1%)	25/93.8	3.1	MH and OM	HD/ GC and GC-MS	[51]
	Seeds	Iran	γ-Terpinene (20.1%), cuminic aldehyde (16.6%), *p*-mentha-1,3-dien-7-al (15.1%) and *p*-mentha-1,4-dien-7-al (13.2%)	22/98.6	NR	OM and MH	HD HD-SME [p]/ GC-MS	[20]
			γ-Terpinene (29.3%), cuminic aldehyde (15.5%), *p*-mentha-1,3-dien-7-al (11.5%) and *p*-mentha-1,4-dien-7-al (13.4%)	17/99.8	NR	OM and MH	HD HD-SME / GC-MS	
	Seeds	Iran	(*E*)-Caryophyllene (27.8%), γ-terpinene (15.2%), cuminyl acetate (14.7%), cuminaldehyde (6.0%), *p*-cymene (5.2%), pinocarvyl acetate (4.4%), limonene (3.9%), α-methyl-benzene methanol (3.9%), croweacin (2.9%) and β-pinene (2.2%)	29/98.2	2.2	MH	HD/ GC-MS	[52]
	Fruits (Wild type)	Iran	γ-Terpinene (44.2%), *p*-cuminaldehyde (16.9%) and *p*-cymene (8.0%)	35/95.6	9.1	MH	HD/ GC and GC-MS	[40]
	Fruits (First year cultivation)		γ-Terpinene (40.8%), *p*-cuminaldehyde (14.1%) and *p*-cymene (9.5%)	35/95.0	6.2	MH	HD/ GC and GC-MS	
	Fruits (Second year cultivation)		γ-Terpinene (36.8%), *p*-cuminaldehyde (11.8%) and *p*-cymene (9.4%)	35/96.4	5.1	MH	HD/ GC and GC-MS	
	Fruits	Iran	Cuminaldehyde (33.0%), γ-terpinene (22.3%), γ-terpinen-7-al (15.4%), *p*-cymene (13.1%), α-terpinen-7-al (2.6%) and sabinene (1.8%)	15/91.5	8.5	OM and MH	HD/ GC and GC-MS	[13]
			γ-Terpinen-7-al (30.0%), γ-terpinene (23.2%),	17/96.7	3.5	OM and MH	HD/ GC and GC-MS	

			cuminaldehyde (15.7%), *p*-cymene (12.8%), limonene (5.9%), α-terpinen-7-al (3.3%) and sabinene (1.8%)					
			Cuminaldehyde (38.8%), γ-terpinene (16.5%), γ-terpinen-7-al (15.5%), *p*-cymene (14.2%), limonene (3.6%), α-terpinene-7-al (3.2%) and sabinene (1.2%)	14/95.4	7.0	OM and MH	HD/ GC and GC-MS	
			γ-Terpinene (32.9%), γ-terpinene-7-al (32.5%), cuminaldehyde (10.9%), *p*-cymene (5.3%), α-terpinen-7-al (4.6%), limonene (3.7%), sabinene (2.5%), α-pinene (1.3%), camphen (1.0%) and β-pinene (1.0%)	16/97.7	4.0	MH and OM	HD/ GC and GC-MS	
	Seeds	Iran	γ-Terpinene (44.2%), cuminaldehyde (16.9%), γ-terpinen-7-al (10.5%) and *p*-cymene (8%)	35/95.5	9.1	MH	HD/ GC and GC-MS	[53]
	Fruits	Iran	γ-Terpinene (46.1%), cuminal (23.9%) and *p*-cymene (15.9%)	10/99.8	2.0	MH	HD/ GC-MS	[54]
	Whole plant	Iran	γ-Terpinene (39.7%)	10/95.1	5.51	MH	HD/ GC and GC-MS	[14]
			γ-Terpinene (41.9%)	10/100	6.65	MH	HD/ GC and GC-MS	
			γ-Terpinene (41.8%)	10/99.9	3.12	MH	HD/ GC and GC-MS	
		India	Cuminaldehyde (37.1%)	9/98.3	1.92	OM	HD/ GC and GC-MS	
		Pakistan	γ-Terpinene (37.2%)	10/100	2.35	MH	HD/ GC and GC-MS	
	Seeds	Iran	γ-Terpinene (31.1%), cuminaldehyde (24.8%), *p*-cymene (16.2%), limonene (7.6%), β-pinene (3.3%) and elemicin (2.9%)	24/100	4.18	MH	HD/ GC and GC-MS	[55]
			Cuminaldehyde (28.2-29.2%), γ-terpinene (28.2-28.4%), *p*-cymene (14.7-16.5%), limonene (6.1-8.3%), β-pinene (2.1-2.7%) and elemicin (2.7-3.3%) [q]	24/100	4.31-4.73	MH	MAHD/ GC and GC-MS	
	Fruits	Iran	KF [r]: γ-Terpinene (26.3%), γ-terpinen-7-al (22.3%), cuminaldehyde (19.8%), *p*-cymene (14.2%) and limonene (6.2%)	19/99.3	2.3	MH	HD/ GC and GC-MS	[43]

			Ma [u]: γ-Terpinene (30.7%), γ-terpinen-7-al (25.6%), cuminaldehyde (17.3%), *p*-cymene (9.9%) and limonene (7.3%)	14/99.3	2.4	MH and OM	HD/ GC-FID and GC-MS	
			Cuminaldehyde (27.8%), γ-terpinene (23.0%), γ-terpinen-7-al (19.2%), *p*-cymene (13.5%) and limonene (5.8%)	23/100	NR	MH and OM	MD [s]/ GC and GC-MS	
			γ-Terpinene (32.0%), cuminaldehyde (27.2%), γ-terpinen-7-al (12.4%), *p*-cymene (11.0%) and limonene (5.6%)	37/99.5	-	MH	SPME [t] / GC and GC-MS	
	Fruits	Iran	*p*-Cymene (31.1%), cuminaldehyde (22.2%) and γ-terpinene (11.4%)	16/91.8	2.2	MH	HD/ GC-FID and GC-MS	[41]
	Seeds	Iran	2-Methyl-3-phenyl propanal (26.0%), 1-phenyl-1-butanol (20.7%) and γ-terpinene (21.9%)	21/99.0	4.1	NH	HD/ GC-FID and GC-MS	[56]
	Seeds	Iran	Cuminaldehyde (33.1%), γ-terpinene (17.2%) and *p*-cymene (12.8%)	24/100	1.97	OM	HD/ GC and GC-MS	[57]
	Fruits (Wild sample)	Iran	γ-Terpinene (30.8%), cuminaldehyde (20.5%), *p*-cymene (20.1%) and γ-terpinen-7-al (8.3%)	22/93.7	2.25	MH	HD/ GC-MS	[58]
			Cultivated sample: γ-Terpinene (27.6%), cuminaldehyde (21.1%), *p*-cymene (18.3%) and γ-terpinen-7-al (7.8%)	25/95.7	2.5	MH	HD/ GC-MS	
	Seeds	Iran	*p*-Cuminaldehyde (23.5%), α-methyl-benzenemethanol (14.6%), γ-terpinene (13.1%) and β-cymene (8.5%)	35/96.2	7.5	OM and MH	HD/ GC-MS	[59]
	Areal parts	Iran	γ-Terpinene (45.0%), cuminaldehyde (18.0%), *p*-cymene (15.0%) and limonene (11.0%)	10/98.7	2.5	MH	HD/ GC-MS	[42]
	Leaves	Iran	Cuminaldehyde (37.7%), γ-terpinene (17.1%), β-pinene (15.4%) and cuminyl alcohol (9.5%)	13/96.1	NR	OM and MH	HD/ GC-MS	[60]
	Fruits	Iran	γ-Terpinene (29.2-40.1%) [v], cuminic alcohol (16.4-28.4%), cumin aldehyde (9.0-18.9%), *p*-cymene (9.4-15.6%),	16-19/95.5-99.0%	3.1-7.9	MH	HD/ GC-FID and GC-MS	[61]

			safranal (3.4-7.9%) and limonene (3.7-6.4%)					
	Whole plant	Iran	γ-Terpinene (28.3%), cumin aldehyde (24.4%), γ-terpinen-7-al (13.8%), α-terpinen-7-al (10.4%) and *p*-cymene (9.5%)	25/100	2.8	MH	HD/ GC-MS	[44]
			γ-Terpinene (30.1-38.3%) [w], cumin aldehyde (12.8-18.9%), γ-terpinen-7-al (20.8-28.3%), α-terpinen-7-al (1.2-3.6%) and *p*-cymene (7.9-10.7%)	25/100	0.54-0.77	MH and OM	SCE [x]/ GC-MS	
	Seeds	Iran	γ-Terpinene (46.1%), cuminaldehyde (15.5%), cuminyl alcohol (7.4%), *p*-cymene (6.7%), limonene (5.9%), α-pinene (2.7%), β-pinene (2.5%) and α-terpineol (2.2%)	24/97.2	8.3	MH	HD/ GC-MS	[62]
	Seeds	Iran	γ-Terpinene (45.7%), cuminaldehyde (12.7%), limonene (10.6%), cuminyl alcohol (6.4%), *p*-cymene (5.6%), β-pinene (3.7%), α-methyl-benzene methanol (3.5%) and α-pinene (2.8%)	22/99.1	3.1	MH	HD/ GC-MS	[63]
			γ-Terpinene (38.0%), α-methyl-benzene methanol (25.6%), cuminaldehyde (11.5%), *o*-cymene (7.8%), limonene (6.8%), cuminyl alcohol (6.4%) and dillapiole (3.5%)	16/99.9	-	MH	SFE, GC-MS	
	Fruits	Iran	γ-Terpinene (24.0%), cuminaldehyde (20.1%), *p*-cymene (13.1%), α-propyl-benzene-methanol (13.0%), α-2-propenyl-benzenemethanol (6.0%), 2-methyl-1-methylene-3-(1-methylethenyl)-cyclopentane (3.6%), β-pinene (3.0%) and limonene (2.8%)	48/98.2	NR	MH	HD/ GC-MS	[64]
	Seeds	Himalaya	γ-Terpinene (40.4%), *p*-cymene (25.8%), cuminaldehyde (12.9%) and *p*-	31/97.9	0.52	MH	HD/ GC-FID, GC-MS	[65]

			mentha-1,3-dien-7-al (4.7%)					
B. wolffi Klyuikov	Seeds	Iran	Germacrene D (30.1%), β-selinene (11.6%) and β-pinene (8.1%)	23/73.4	1.90	SH	HD/ GC-FID and GC-MS	[26]

[a] YEO: Yield of essential oil; [b] OS: oxygenated sesquiterpenes; [c] HD: Hydrodistillation; [d] GC-MS: Gas chromatography coupled with mass spectrometry; [e] SH: Sesquiterpene hydrocarbons; [f] GC-FID: Gas chromatography with flame-ionization detection; [g] ^{13}C-NMR: Carbon-13 nuclear magnetic resonance; [h] MH: Monotrerpene hydrocarbons; [i] NH: Non-terpene hydrocarbons; [j] NR: Not reported; [k] SD: Steam distillation; [l] F.B.B.: Fruit-bearing branches; [m] T.B.: Thickened branches; [n] MAHD: Microwave-assisted hydrodistillation; [o] OM: Oxygenated monetrerpene; [p] HD-SME: Hydrodistillation-headspace solvent microextraction; [q] Over the range 180-540 W; [r] KF: Khajeh forest, Kelat, Khorasan Razavi province, Iran; [s] MD: Microdistillation; [t] SPME: Solid phase microextraction; [u] Ma: Mashhad, Khorasan Razavi province, Iran; [v] For eight populations of *B. persicum*(Boiss.) B. Fedtsch.; [w] Over 5 runs using supercritical extraction (SCE) method; [x] SCE: Supercritical extraction.

The mean oil yield obtained from BPEO samples (Table 2) is considerably higher than those of other *Bunium* species. Sesquiterpene hydrocarbons (SHs) have been reported as the main components of some *Bunium* species, *i.e.*, (*E*)-caryophyllene in *B. elegans* [8] and *B. caroides*, [8, 26] germacrene D in *B. lurestanicum* [26] and *B. wolffi* [26] as well as β-sesquiphellandrene in *B. badghayzi* [26] and *B. carioides*. [26] Furthermore, some oil profiles were dominated by oxygenated sesquiterpene (OSs), *e.g.*, caryophyllene oxide like EOs of *B. ferulaceum*, [48] *B. alpinum* [45] and *B. elegans*. [47] Non-terpene hydrocarbons (NHs) have been assigned as the main groups of natural compounds in some species. [48, 56] The structures of the main chemical constituents of essential of *Bunium* species are presented in Figure 2.

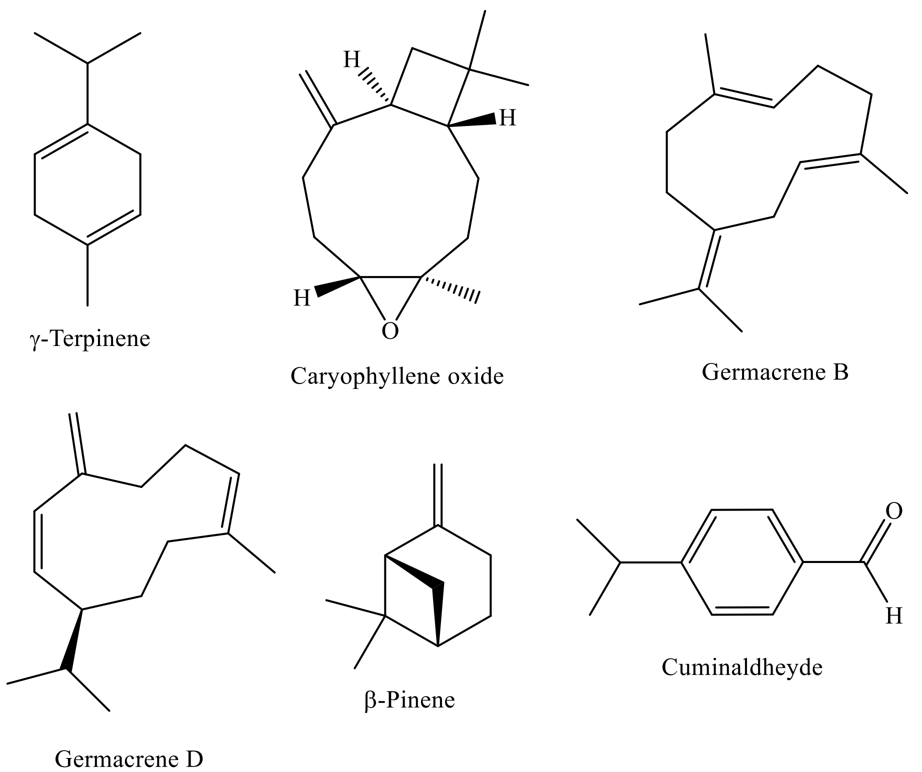


Figure 2: Chemical structures of the main components of *Bunium* species EOs.

Using a superheated water-based extraction (SHWE) approach along with hydrodistillation (HD) and Soxhlet extraction (SXE) methods, the EOs from the seeds of *Bunium* species have been isolated and subsequently characterized by GC-FID and GC-MS data analyses [66]. In accordance with this study and under optimized experimental conditions, the extraction efficiency of the SHWE technique was less than the traditional extraction methods (HD and SXE). However, SHWE offers such advantages like being more timesaving and having higher selectivity toward oxygen-containing natural compounds. This study showed that cuminaldehyde, α-terpinen-7-al and γ-terpinen-7-al had the highest frequency when using SHWE technique, whereas γ-terpinene, *p*-cymene, limonene and γ-terpinen-7-al were the dominant constituents identified in the EO obtained by HD approach. On the other hand, using the SXE-based method, γ-terpinene, γ-terpinen-7-al and cuminaldehyde were extracted as the major components of the obtained oil. Accordingly, OMs were found as the dominant constituent compounds of the chemical profiles obtained using SHWE technique, whereas a combination of MHs and OMs were reported as the most abundant constituents of the other characterized profiles of the EOs (SXE and HD).

Feyzi et al. [67] isolated BPEO from the relevant moist seeds using instant controlled pressure drop (ICPD) technique and compared the related profile with those obtained by classical HD, SXE and ultrasound-assisted extraction (UAE). Accordingly, cuminaldehyde, α-terpinen-7-al and γ-terpinen-7-al were the prevailing compounds using the ICPD strategy, while similar patterns were observed using the other techniques (HD, SXE and UAE) with high prevalence of γ-terpinene, cuminaldehyde and α-terpinen-7-al. Moreover, the yield of the obtained oil by ICPD was more than that of HD and UAE and only slightly lower than that obtained by SXE method.

2.2. Non-volatile metabolites

The non-volatile secondary metabolites reported from *Bunium* species are listed in Table 3, and the relevant molecular structures have been displayed in Figures 3-5.

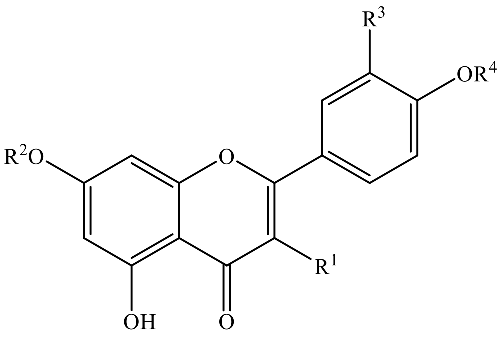
Table 3: Chemical constituents of *Bunium* spp. organs, isolated and identified by means of different methodologies

Bunium spp.	Studied organs	Collection site	Compounds	Extraction solvent	Isolation and identification methods	Reference
B. alpinum Waldst. & Kit.	Aerial parts	Algeria	*iso*-Quercitin	Ethyl acetate	CC [a], UV [b], NMR [c], MS [d]	[68]
B. brachyactis (Post) H.Wolff	Aerial parts	Turkey	Salvianic acid A, pantothenic acid, chlorogenic acid, *neo*-chlorogenic acid, *crypto*-chlorogenic acid, quinic acid, syringic acid, scopoletin,vicenin-2, orientin, *iso*-orientin, vitexin, *iso*-vitexin, cynaroside, *iso*-quercitrin, rutin, cosmosiin, diosmin, afzelin, naringenin, luteolin, apigenin, salcolin A, angelicin, salcolin B, esculin, esculetin, psoralen, bergapten, dillapiole, imperatorin, selinidin, indole-4-carbaldehyde, *N*-(2-phenylethyl)-acetamide, 4-acetamido-benzoic acid, naringenin-6,8-di-*C*-glucoside [f]	Methanol	HPLC-MS [e]	[69]
B. bulbocastanum L.	Tubers, Leaves and Flowers	n.s. [g]	Falcarinol, falcarinone, falcarinolone	Ethyl acetate	HPLC [h]	[70]
B. cylindricum (Boiss. & Hohen.) Drude	Seed oil	Pakistan [i]	Capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, petroselinic acid, oleic acid, linoleic acid, linolenic acid	*n*-Hexane	SXE [j], GLC [k]	[71]
	Aerial parts	Iran	Alkaloids, saponins, tannins, flavonoids	Methanol	Phytochemical screening	[72]
B. ferulaceum Sm.	Roots	Algeria	Oleic acid, β-sitosterol, scopoletin, scoparone, sucrose	Mixture of dichloromethane - methanol 1:1 *v/v*	CC, UV, NMR, MS	[18]
B. fontanesii (Pers.) Maire			β-Sitosterol			
B. hissaricum Korovin	Seed oil	Central Asia	Capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, petroselinic acid, octadec-7-enoic	Petroleum ether	GLC	[73]

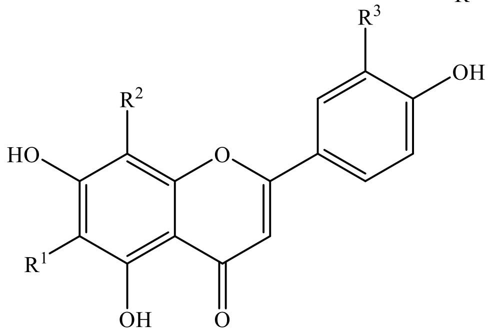
			acid, octadec-8-enoic acid [l]			
B. microcarpum (Boiss.) Freyn&Bornm.	Aerial parts	Turkey	Quinic acid, salvianic acid A, pantothenic acid, esculin, kynurenic acid, chlorogenic acid, *crypto*-chlorogenic acid, naringenin-6.8-di-*C*-glucoside, 4-hydroxy-mellein, vicenin-2, indole-4-carbaldehyde, orientin, *iso*-orientin, vitexin, *iso*-vitexin, cynaroside, narirutin, *iso*-quercitrin, rutin, cosmosiin, diosmin, bergapten, naringenin, luteolin, kaempferol, apigenin, salcolin A, angelicin, salcolin B, imperatorin [l]	Methanol	HPLC-MS	[69]
B. paucifolium DC.	Roots and Fruits	Turkey	5-Methoxy-6-geranyloxy-mellein, *cis*-2-acetoxy-5-methoxy-6-geranyloxy-mellein	Chloroform	CC, IR [m], UV, NMR, MS	[74]
	Fruits	Turkey	Desacyl-mehtyl-hallerin		CC, $\alpha_{[D]}$, IR, NMR, MS	[75]
B. persicum (Boiss.) B. Fedtsch.	Seeds	Iran	Kaempferol, caffeic acid, *p*-coumaric acid	Methanol	LC [n], TLC [o], UV, IR, NMR	[62]
	Fruits	India	Terpenoids, saponins, sterols, alkaloids, anthraquinones, tannins, flavonoids, carbohydrates, proteins	Several solvents	Phytochemical screening	[76]
	Seed oil	Pakistan [i]	Capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, petroselinic acid, oleic acid, linoleic acid, linolenic acid	*n*-Hexane	SXE, GLC	[71]
	Aerial parts	Iran	Alkaloids, saponins, tannins, flavonoids	Methanol	Phytochemical screening	[72]
B. pinnatifolium Kljuykov	Aerial parts	Turkey	Quinic acid, pantothenic acid, esculin, kynurenic acid, chlorogenic acid, *crypto*-chlorogenic acid, syringic acid, naringenin-6,8-di-*C*-glucoside, scopoletin, indole-4-carbaldehyde, ferulic acid, aromadendrin, hyperoside, *iso*-	Methanol	HPLC-MS	[69]

			quercitrin, rutin, astragalin, afzelin, quercetin, naringenin, kaempferol, apigenin, *iso*-rhamnetin, iso-imperatorin [l]			

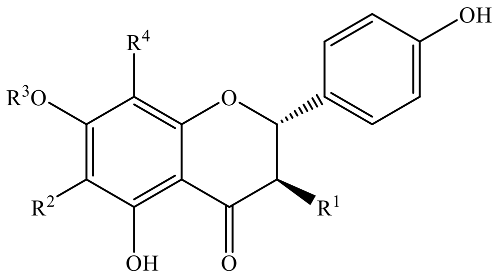
[a] CC: Column Chromatography; [b] UV: Ultraviolet Spectroscopy, [c] NMR: Nuclear Magnetic Resonance Spectroscopy; [d] MS: Mass Spectroscopy; [e] HPLC-MS: HPLC coupled to Tandem Mass Spectrometry; [f] Plus others not characterized; [g] n.s.: Not specified; [h] HPLC: High Performance Liquid Chromatography; [i] Purchased from a market; [j] SXE: Soxhlet Extraction; [k] GLC: Gas-Liquid Chromatography; [l] Plus other fatty acids and saccharides not characterized; [m] IR: Infra-Red Spectroscopy; [n] LC: Liquid Chromatography; [o] TLC: Thin Layer Chromatography



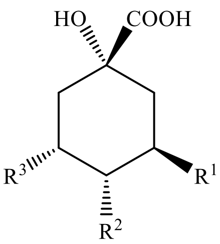
R^1 = *O*-β-D-Glc, R^2 = R^4 = H, R^3 = OH: *iso*-quercitin
R^1 = *O*-(α-L-Rha-(1-6)-β-D-Glc), R^2 = R^4 = H, R^3 = OH: rutin
R^1 = R^2 = R^4 = H, R^3 = OH: luteolin
R^1 = R^2 = R^3 = R^4 = H: apigenin
R^1 = R^3 = R^4 = H, R^2 = β-D-Glc: cosmosiin
R^1 = H, R^2 = *O*-(α-L-Rha-(1-6)-β-D-Glc), R^3 = OH, R^4 = Me:diosmin
R^1 = *O*-α-L-Rha, R^2 = R^3 = R^4 = H: afzelin
R^1 = OH, R^2 = R^3 = R^4 = H: kaempferol
R^1 = R^4 = H, R^2 = β-D-Glc, R^3 = OH: cynaroside
R^1 = *O*-β-D-Glc, R^2 = R^3 = R^4 = H: astragalin
R^1 = R^3 = OH, R^2 = R^4 = H: quercetin
R^1 = OH, R^2 = R^4 = H, R^3 = OMe: *iso*-rhamnetin
R^1 = *O*-β-D-Gal, R^2 = R^4 = H, R^3 = OH: hyperoside



R^1 = β-D-Glc, R^2 = H, R^3 = OH: *iso*-orientin
R^1 = β-D-Glc, R^2 = R^3 = H: *iso*-vitexin
R^1 = H, R^2 = β-D-Glc, R^3 = OH: orientin
R^1 = H, R^2 = β-D-Glc, R^3 = H: vitexin
R^1 = R^2 = β-D-Glc, R^3 = H: vicenin-2



R^1 = R^2 = R^3 = R^4 = H: naringerin
R^1 = R^3 = H, R^2 = R^4 = β-D-Glc: naringenin-6.8-di-*C*-glucoside
R^1 = R^2 = R^4 = H, R^3 = α-L-Rha-(1-6)-β-D-Glc: narirutin
R^1 = OH, R^2 = R^3 = R^4 = H: aromadendrin



R^1 = R^2 = R^3 = OH: quinic acid
R^1 = caffeic acid, R^2 = R^3 = OH: chlorogenic acid
R^1 = R^3 = OH, R^2 = caffeic acid: *crypto*-chlorogenic acid
R^1 = R^2 = OH, R^3 = caffeic acid: *neo*-chlorogenic acid

Figure 3: Chemical structures of the non-volatile compounds isolated from *Bunium* spp (part 1).

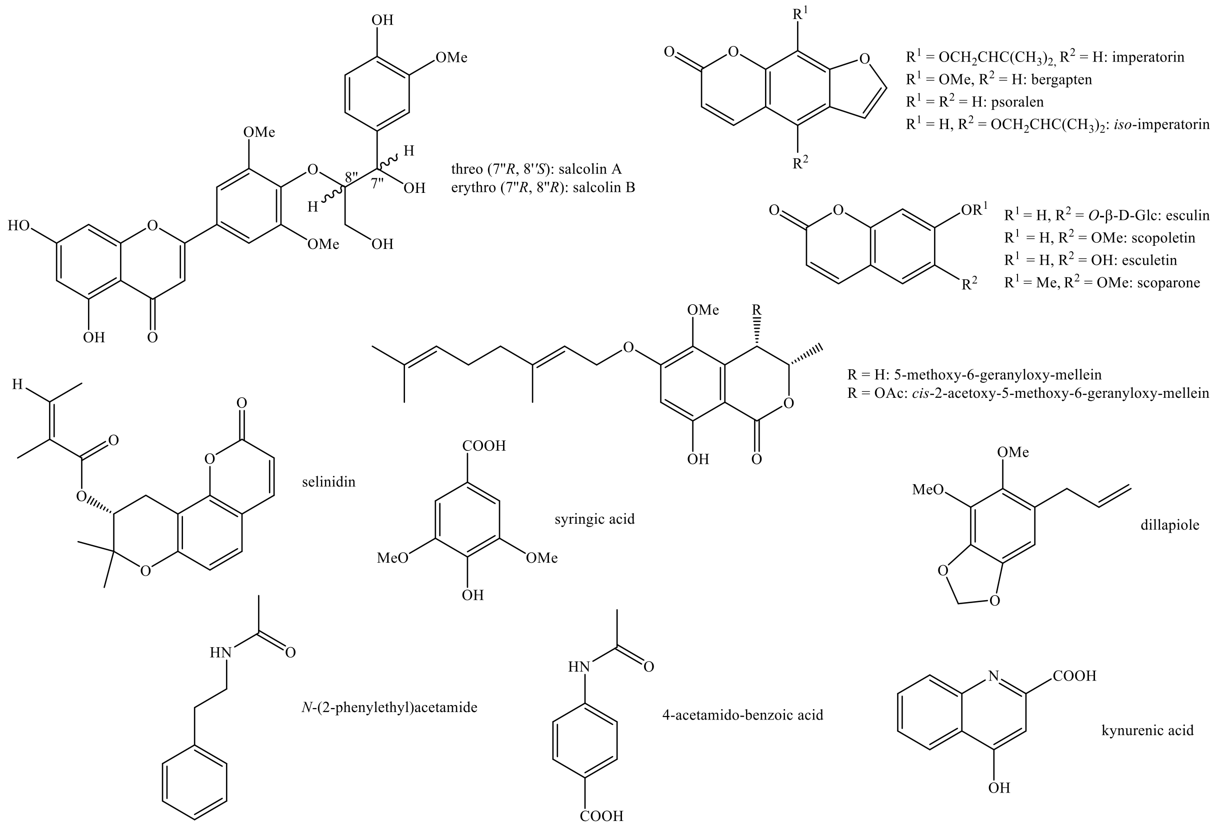


Figure 4: Chemical structures of the non-volatile compounds isolated from *Bunium* spp (part 2).

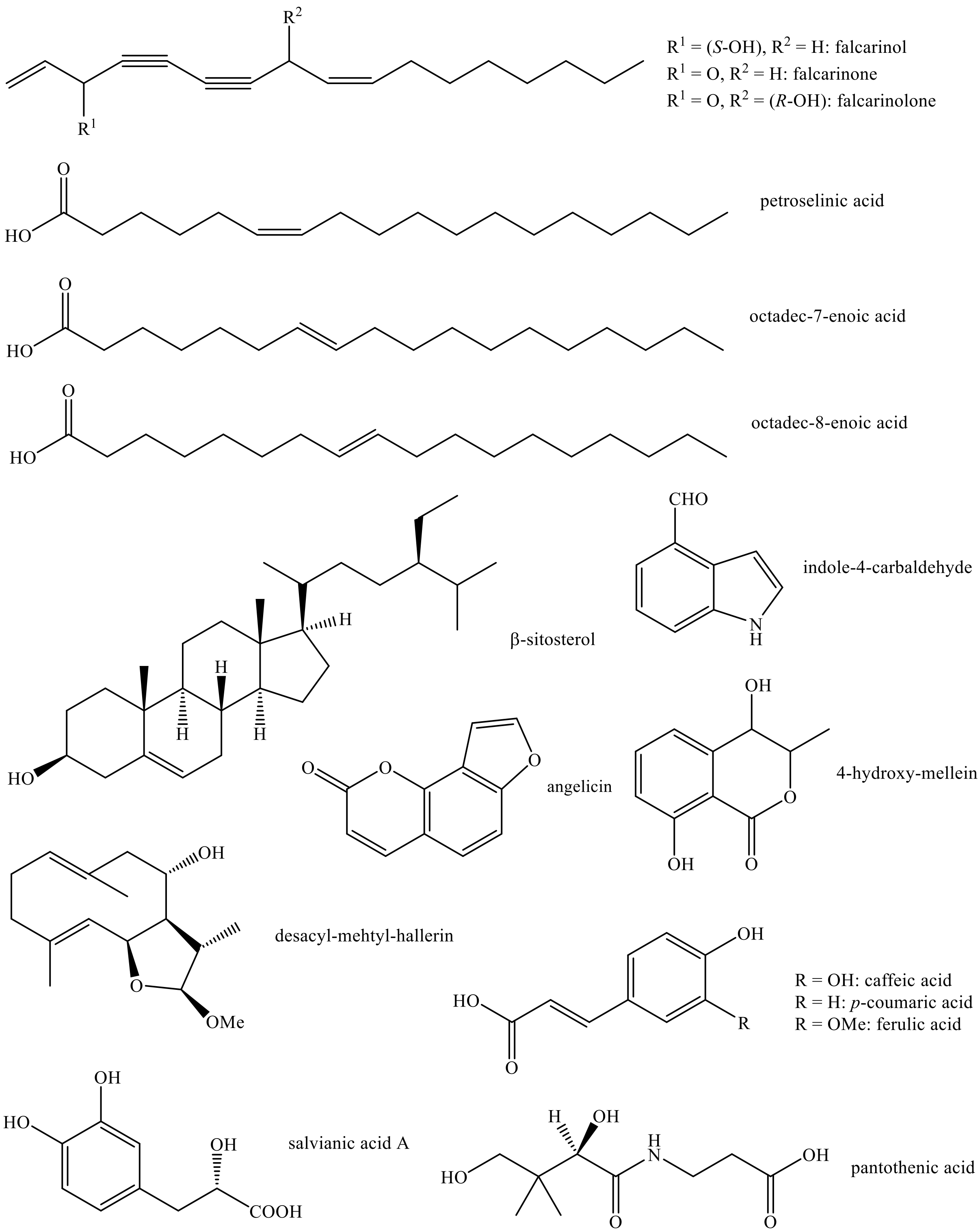


Figure 5: Structures of the non-volatile metabolites isolated from *Bunium* spp. (Part 3).

Not all the *Bunium* species have been studied for their polar fraction metabolites to date. In particular, these species are only 10 and, in most cases, one exemplar for each species has been taken into consideration. In one case, two different organs, deriving from the same studied exemplar, were separately analyzed for their phytochemical components, *i.e.*, the roots and the fruits of *B. paucifolium*. [77] In addition, for *B. persicum*, different organs coming from some samples collected in different areas of the world were studied, *i.e.*, the seeds from Iran, [62] the fruits from India [76] and the seed oil from Pakistan. [71] Several classes of natural compounds have been reported mainly comprising fatty acids, terpenoids, saponins, polyacetylenes, coumarins, anthraquinones, tannins, flavonoids, organic acids, saccharides and proteins (Table 3). For *B. alpinum*, [68] *B. fontanesii* [18] and *B. paucifolium* fruits, [75] only one compound was identified. All these results are extremely plausible since the phytochemical patterns are highly influenced by intrinsic and extrinsic factors like the genotype, the growth environment and the phytochemical analysis methods. For *B. cylindricum* aerial parts, [72] *B. persicum* fruits [76] and aerial parts, [72] only a phytochemical screening-based study has been established. In this context, they have been added to Table 3 even if these data are extremely vague and may be susceptible to errors given that phytochemical screening by itself is not always a reliable methodology. As for this point, the extraction method was always the SE except for *B. persicum* seed oil where the SXE was used. [71] HPLC-based techniques were the main methods used for the separation of the metabolites except for *B. alpinum*, [68] *B. ferulaceum* [18] and *B. paucifolium* [74, 75] where CC was used, *B. cylindricum* [71] and *B. hissaricum* [73] where GLC was used and *B. persicum* seeds where LC was utilized. [62] In all the cases in which CC was used, the methodology adopted for the identification of the compounds involved $\alpha_{[D]}$, IR, UV, NMR and MS, alone or together even partially. Roots, fruits, seeds, seed oil and the mixed organs as well as the generic aerial parts were considered, without any particular preference given to any plant organ. Most of the studied samples were collected in Turkey, whereas in two cases, *i.e.*, *B. alpinum* [68] and *B. ferulaceum*, [18] the collection site was in Algeria. For *B. cylindricum* [71] and *B. persicum* seed oil [71], the plant material was purchased from one market in Pakistan Therefore, the results obtained from the seeds of this species about the fatty acids composition should be reconfirmed also from a correctly identified sample. However, these whole results confirm that the main distribution of *Bunium* species is in Asia. On the other hand, the lack of information on the phytochemical patterns of *Bunium* species collected from other areas of the world, is a real limitation from the chemotaxonomic standpoint, given the impossibility to carry out phytochemical comparisons based also on the growth area, thus uncovering eventual different chemotypes. This may indeed represent a new research line. Lastly, for *B. bulbocastanum*, no information about the collection site was provided by the authors. [70]

3. Chemotaxonomic evalution of the *Bunium* genus within the Apiaceae family

The observed composition of both EOs and non-volatile fractions of *Bunium* species showed many similarities with other genera belonging to the Apiaceae family. In particular, in the case of the volatile metabolites, besides the most widespread hydrocarbon terpenoids already observed in the Apiaceae, for instance, in *Foeniculum vulgare* Mill. [78] and *Smyrnium olusatrum* L., [79] the presence of aldehydic derivatives in notable amounts is of utmost importance which might reflect the tendency of *Bunium* spp. to biosynthesize such derivatives. Aldehyde derivatives have been already reported among the volatile components recognized from other botanical entities that are classified in the Apiaceae such as *Prangos ferulacea* (L.) Lindl. from Iran, Turkey and Italy [80-86] as well as in *Coristospermum cuneifolium* Guss.. [87] The aldehydic derivatives might have a relevance in the systematics of the *Bunium* genus and in the Apiaceae family. For this reason, further studies of these aspects are essential in the future.

The non-volatile fraction comprises several compounds including flavonoids and other phenolics, which are quite common in the plant kingdom and their occurrence has been reported in other families [70, 88-94] implying they might have no chemotaxonomic relevance. On the other hand, the presence of acetylenes such as falcarinol, falcarinone and falcarinolone is interesting from the chemosystematic viewpoint. In fact, falcarinol-type polyacetylenes are widely distributed in the Apiaceae [70] as well as in chemotaxonomically close families such as the Asteraceae and the Araliaceae, [89] thus, representing peculiar chemotaxonomic markers. An additional phytochemical characteristic is the presence of coumarins, evidenced both as simple coumarins and structurally more complex derivatives, *e.g.*, linear and angular furano- and pyranocoumarins. The presence of this kind of compounds has been observed in many of the Apiaceae genera and some other herbal species such as *Ferula* spp., [95] *Peucedanum* spp., [96] *Ferulago galbanifera* (Mill.) W.D.J.Koch [97, 98] and *Coristospermum cuneifolium* Guss.. [99] This fact represents a distinctive phytochemical trait in these families and their biosynthetic pathway has been studied in *Apium graveolens* L.. [100] Furanocoumarins seem to have an ecological role being involved in the pattern of distribution and abundance of herbivore insects on the Apiaceae. [101] It should also be underlined that in many cases the presence of linear furanocoumarins is the main cause of phototoxicity. [102] Among pyranocoumarins, the presence of selinidin is important since it is a well-known metabolite in the Apiaceae having been reported in *Peucedanum austriacum* (Jacq.) W.D.J.Koch, in some *Angelica* L. species [103-105] as well as in *Glehnia littoralis* F. Schmidt ex Miq., [106] in *Zosima absinthifolia* Link [107] and in *Seseli gummiferum* Pall. ex Sm.. [108] So, the phytochemistry of the genus *Bunium* confirms the correct classification of the genus in the Apiaceae family. However, further relevant studies focusing on phytochemical, morphological and molecular aspects could be of primary importance for a more correct classification of the species which are currently of unresolved and/or problematic classification.

4. Ethnobotanical and medicinal uses of *Bunium* species

A large number of *Bunium* species are used in folklore medicine of different areas all over the world even if not all *Bunium* species have been studied in this sense. In particular, the most important relevant species is *B. persicum*. Some of the most common ethnobotanical uses of *Bunium* species are presented in Table 4. In the Persian folk medicine, it has been recommended as an effective drug for urinary and respiratory tract infections and digestive disorders (Table 4) [21, 23] and a parasite repellent. [21] In addition, it has also found some local therapeutic uses in many parts of Iran against nausea, [13] influenza, [13] constipation and convulsion, [23, 109, 110] dyspepsia, [19] diarrhea, [21] dysmenorrhea, [111] colic, [111] dyspnea, [112] as well as bronchodilatory and inflammatory bowel. [39, 113, 114] It has also been recognized as a powerful appetizer, [115, 116] anthelmintic, [20] antiseptic, [51, 115] diuretic [21] and digestive agent. [21] From long time ago, the Iranian local practitioners have frequently prescribed *B. persicum* for the skin youthfulness, lowering the infection of head skin and hair protection against nit. They believe that *B. persicum* can help to address the insomnia and to repel the free radicals from the human body. In addition, this herbal plant has been recognized to protect us against cancer and nervous diseases, like Parkinson (Table 4).

Table 4: Most important species of the genus *Bunium* and its traditional pharmacological uses

Bunium species/ organ	Country	Reference	Medicinal and folkloric applications
B. persicum (Boiss). B. Fedtsch/ whole plant	Iran	[15, 21, 51, 115]	For the treatment of gastrointestinal disorders involving indigestion, stomachache, diarrhea and to treat headache, urinary and respiratory tract infections and colic
			Appearing as a diuretic, flatulent, stimulant as well as strong antidiabetic, antiepileptic, antiseptic, anti-parasitic, antispasmodic, anticonvulsant and anti-asthma remedy
			To regulate liver function and body weight
			To increase the milk of lactating mothers
		[23]	To relieve terrible pains after delivery
		[21]	A parasite repellent
		[13, 110, 114, 116]	Used against insomnia, Parkinson, nausea, constipation, convulsion, inflammatory bowel, the blood lipids and cholesterol
B. persicum (Boiss). B. Fedtsch/seeds		[15, 116, 117]	Stimulant, toxic, to address stomach and intestine problems with expectorant, carminative, emmenagogue and galactogogue properties, to treat toothache, jaundice, epilepsy, diarrhea and dyspepsia as well as an appetizer
		[19, 118]	An adulterant to *Carum gracile* Lindl, as a spice, condiment and additive to foods and beverages
B. persicum (Boiss). B. Fedtsch/ fruits	Iran	[12, 54, 58, 115]	To treat flatulence, dyspepsia, indigestion, colic and dysmenorrhea; serving as effective anticonvulsant, diuretic, analgesic, anthelmintic and anti-asthma agent
	Central Asia	[116, 119]	To season dishes before the preparation of meat-based foods
B. bulbocastanum	Morocco	[120]	For the treatment of musculoskeletal and gynecological malfunctions
B. incrassatum Amo/ roots	Algeria	[18]	In local Algerian cookery
B. incrassatum Amo/tubers			As an astringent having a great potential against cough, bronchitis, diarrhea and hemorrhoids

In pregnant women, the common use of *B. persicum* is highly restricted since it may cause abortion. In the traditional medicine of Kerman, Iran, a mixture of powdered and dried *B. persicum*, along with five other medicinal plants, namely *Foeniculum vulgare* Mill. (named as Razianeh in Persian), *Achillea santolinoides* subsp. *wilhelmsii* (K.Koch) Greuter., *Glycyrrhiza glabra* L., *Nepeta cataria* L. and *Teucrium polium* L. is frequently used for the treatment of digestive disorders. [21] In addition, in the Persian culture, it is used in toothpastes due to its fresh odor. [121] In the Persian culinary, this species has been extensively employed to flavor rice for many years. [122] In addition, in Kashmir (India), the species is often used as a substituent of *Carum carvi* Linn. and is employed against menstrual disorders, anorexia, skin diseases and leucorrhea. [123] Its EO can suppress the first step of inflammation [109, 110] and is frequently used in confectionery to flavor goodies and baked biscuits as well as perfume industries. [20, 23] In the screening of the endemic medicinal plants of Iran, some gynecologic, [14, 112] lactagougue, [13] carminative and stimulant effects [11] have been attributed to this plant, as well.

In the literature, some therapeutic remedies have been mentioned also for its seeds involving antispasmodic, anti-epileptic, increasing milk in lactating mothers [116, 119] as well as lowering the blood lipids and cholesterol. [116] In fact, the seeds are edible possessing a pleasant odor and are excessively used as condiments and flavoring agents in Iranian cookery. [55] In the Ayurvedic system of medicine, seeds of *B. persicum* are employed as adulterant to *Carum gracile* Lindl. [118] From ancient time, Indian people have used *B. persicum* as a pungent and fragrant spice for the preparation of foods and beverages and as a condiment. [19] On the average, one thousand seeds of *B. persicum* have a mean weight of 2.0 g. [24] In the remote areas of Jammu as well as in Kashmir (India), its seeds are used against diarrhea, indigestion and dysentery. [124] In Pakistan, the decoction of the seeds of *B. persicum* is used against digestion problems, cold and cough [125] and as an antihistaminic agent. [126] In addition, its fruits are effective against hematomas, dysuria, kidney stones and hiccups [127] and are used against obesity and indigestion and considered as flavoring, galactogogue, carminative, calmative and appetizing agents. [128-130]

In the Central Asian regions, the fruits are employed for seasoning of dishes prior to the preparation of meat-based foods. [116, 119] These fruits have also been known to possess analgesic, [54] carminative and antiseptic properties. [58, 115] In particular, their decoction has strong analgesic, anti-inflammatory and antioxidant effects. [131] In Uzbekistan and Kyrgystan, their decoction is employed against kidney stone. [132] Moreover, in Pakistan, they are used together with the fruits of *Ammi visnaga* (L.) Lam. as powerful cardiotonic agents. [133] The dried fruits and seeds of this plant are considered as an additive and condiment to some food staffs like cheese, yogurt and baked rice. [15] In the Himalaya, its tubers are employed as a strong diuretic agent. [134]

The raw tubers of another *Bunium* species, *B. alpinum*, have been widely prescribed in the Adriatic Islands as well as in Eastern Albania. [135, 136] It is noteworthy that *B. bulbocastanum* aerial parts and roots are used in the Southern Mediterranean areas to treat asthma, pulmonary allergy, sore throat (pharyngitis) and bronchitis. [137] In addition, in Algeria, the whole plant is used against flatulence and intestinal worms, [138] whereas in several areas of the world, it is used as an astringent agent, as well. [139] Moreover, this species is one of the 13 medicinal plants composing Msahan, an herbal mixture from Morocco, which has been documented to be proper for health and to resolve musculoskeletal and gynecological malfunctions. [120] The tubers and the bulbs of this species are widely consumed as food in many regions of Italy as boiled vegetables or as ingredients of pies. [70, 140] The tubers are also eaten as raw material or crackers. [70, 141] *B. cylindricum* fruits are widely used in Iran and in Pakistan as a carminative remedy. [128-130] The infusion of the aerial parts of *B. elatum* (Batt.) Batt. is also used against intestinal gas and stomach colic in the North Eastern localities of Algeria. [142] The rhizomes of *B. elegans* is widely employed as raw material against urinary inflammations in Turkey. [143] *B. ferulaceum* has been widely used in the past against renal stones. [144] Also, *B. fontanesii* is used in the North Western areas of Algeria to treat allergy, bronchitis and cough. [145] *B. macuca* Boiss. tubers are used in the Granada province (Spain) against warts. [146] The roots of the Algerian *B. incrassatum*, as an economically valuable plant, are of great nutritional importance, particularly when added to potato. Table 4 shows that the dried tubers of *B. incrassatum* Amo have shown promising behavior against diarrhea, cough, bronchitis as well as inflammatory hemorrhoids and have been found as a stringent. [18] *B. paucifolium* tubers have been widely used as food in the Kahramanmaras region, Turkey. [147] In addition to this, in Spain, *B. balearicum* (Sennen) Mateo & López Udías, *B. macuca* and *B. pachypodum* P.W. Ball tubers are widely consumed as food. [148]

The phytochemical patterns associated with most of these species, both the EO composition and non-volatile compounds, provide a rationale for most of their applications in the traditional and folklore medicine. However, some uses have not been justified from the phytochemical standpoint. On one side, this is due to the lack of phytochemical analyses on all the *Bunium* species as well as all their organs used as drugs. On the other hand, this is also because some of the performed phytochemical analyses reported in literature for *Bunium* species are somewhat partial and basically focusing on specific classes of compounds or basing on a preliminary phytochemical screening, evidencing only the occurrence of some classes of natural compounds but not the specific substances which is not enough. In fact, the ethnobotanical uses should ideally be accompanied by a complete phytochemical analysis in order to fully understand the compounds responsible for such ethnopharmacological activities and also to verify any phytochemical variability, [149] but verifying the real non-toxicity of the plants is of primary importance due to the possible presence of toxic compounds. The traditional knowledge is effective in the treatment of a wide spectrum of persistent diseases but often not to a full extent. In literature, some works about the latter matter are present suggesting the possibility, in specific conditions, to use other species, which have been long deemed to be toxic because of some relevant phytochemical constituents, for ethnobotanical purposes. [150-152] On this subject, little is known and this must actually be the starting point for future investigations.

5. Biological activities

The extracts derived from different *Bunium* species are known to possess remarkable biological activities, which are discussed in the following subsections. Not all the biological properties have been studied and not all the *Bunium* species have been tested so far.

5.1. Antioxidant activity

Shahsavari et al. [52] assessed the antioxidant activity of BPEO using two assays, namely 1,1′-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) radical as well as β-carotene-linoleic acid bleaching (BCLAB) assays. Accordingly, the median effective concentration (EC_{50}) value obtained for $DPPH^{\bullet}$ assay was found to be as 0.88 mg/mL, whilst in the latter case (BCLAB), the inhibition percent of the EO (0.45%) and the standard used (BHT: 0.01%) were approximately the same. Moreover, following peroxide (PV) and thiobarbituric acid (TBA) values on the crude soybean oil, it was concluded that the BPEO induced significant reducing of the oxidation rate of the soybean oil at 60°C. In addition, its antioxidant activity (0.06%) was greater in comparison to butylated hydroxyanisole (BHA) (0.02%). Zangiabadi et al. [153] determined the *in vitro* $DPPH^{\bullet}$ radical scavenging activity of BPEO and reported the median inhibitory concentration (IC_{50}) value being 1.52 mg/mL. These authors also showed that it could be considered as an effective antioxidant agent in linseed oil and as a proper alternative to butylated hydroxytoluene (BHT) and tertbutylhydroquinone (TBHQ) as synthetic antioxidants.

Radical scavenging activities of BPEO seeds (Birjand region, Southern Khorasan Province, Iran) were monitored using the $DPPH^{\bullet}$ assay. [55] The IC_{50} of hydrodistilled EO was 9.31 mg/mL, while the EOs obtained using microwave-assisted hydrodistillation (MAHD) at 180, 360 and 540 W exhibited IC_{50} values of 8.62, 8.79 and 6.54 mg/mL, respectively.

To determine the influence caused by drought stress on BPEO, three relevant assays were used involving $DPPH^{\bullet}$, hydrogen peroxide scavenging activity (HPSA) and Fe^{3+} reducing antioxidant power (FRAP). [154] This study revealed a positive effect in antioxidant characteristics as well as the phenolic contents of BPEO. Considering the obtained results, drought stress finally gave rise to higher antioxidant capability of BPEO seeds.

Using the FRAP assay, the antioxidant activity of BPEO and *B. persicum* extracts were measured. [155] In this study, although the former one had the highest antioxidant capability (248.56 µmol trolox equivalent/g), the latter one showed a week antioxidant capability (48.53 µmol trolox equivalent/g).

The antioxidant activities of BPEO were evaluated using DPPH$^{\bullet}$ and and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS$^{\bullet+}$) assays. [156] Accordingly, within a concentration range of 2.5-10 mg/mL, an increase in antioxidant activity was noted from 24.3 to 35.2% for DPPH$^{\bullet}$ and from 29.2 to 60.5% for ABTS$^{\bullet+}$ assays.

The antioxidant activities relative to *B. persicum* were also studied by Sharififar et al. [62] In particular, the EO as well as the petroleum ether, chloroform, methanol and aqueous extracts were examined using DPPH$^{\bullet}$ and zone of β-carotene color retention assays considering BHT as the reference compound in all of the experiments. A perusal of the obtained results revealed that none of EO sample or the studied extracts resulted to be more effective with IC$_{50}$ values equal to 23.4, 45.7, 79.6, 36.1 and 49.8 µg/mL than BHT (20.3 µg/mL) when using the DPPH$^{\bullet}$ assay. Nevertheless, all of them were more effective than BHT in the other assay with retention zones equal to 26.2, 13.1, 4.2, 18.7 and 6.7 mm, respectively, against 30.4 mm.

The antioxidant activity, in the DPPH$^{\bullet}$, ABTS$^{\bullet+}$, Cupric Reducing Antioxidant Capacity (CUPRAC), FRAP, phosphomolybdenum and metal chelating assays, was also evaluated for the methanolic extracts of *B. brachyactis* (Post) Wolff, *B. microcarpum*, *B. pinnatifolium* and *B. sayai* Yıld. As shown in this study, *B. microcarpum* was reported to be the most effective extract for the first three assays with values equal to 69.66, 100.33 and 160.64 mg TE/g, respectively, followed by *B. pinnatifolium* extract with values equal to 51.89, 96.66 and 155.47 mg TE/g in the respective assays. The last extract was also the most effective in the FRAP and phosphomolybdenum assays with values equal to 128.23 mg TE/g and 1.53 mmol TE/g. Moreover, the least effective extract in all the assays except the last two ones, was that of *B. sayai* with numerical values equal to 41015, 68.66, 118.53 and 89.05 mg TE/g. In view of the observed results, it could be inferred that using FRAP and metal chelating activity assays, the highest potential were respectively due to *B. pinnatifolium* (128.23 mg TE/g) and *B. brachyactis* (52.61 mg EDTAE/g) extracts. However, *B. microcarpum* extract represented the least efficacy in the metal chelating activity and phosphomolybdenum assays with values equal to 15.66 mg EDTAE/g and 1.13 mmol TE/g. [69]

The methanol/dichloromethane (1:1 v/v), ethyl acetate and *n*-butanol extracts of *B. alpinum*, as well as the isolated compound, *i.e.*, *iso*-quercetin, were evaluated through the DPPH$^{\bullet}$ assay. The best result was obtained by the *n*-butanol extract with an EC_{50} value equal to 1.89 μg/mL, whereas the EC_{50} value for one of the isolated and characterized flavonoid compounds, namely quercetin-3-*O*-β-glucoside was equal to 0.28 μg/mL. All these values are lower but comparable to those observed for the relative standard, *i.e.*, Trolox having an EC_{50} value equal to 0.106 μg/mL. [68] *B. alpinum* methanol extract showed satisfactory antioxidant effects in the DPPH$^{\bullet}$ assay with an IC_{50} value equal to 21.85 μg/mL, while its EO showed no antioxidant activity, instead. [45]

Conversely, the *B. incrassatum* EO and methanol extract showed medium antioxidant activities using the DPPH$^{\bullet}$ assay with IC_{50} values equal to 38.52 and 55.77 μg/mL, respectively. [45] In addition, the antioxidant activity of *B. luristanicum* methanolic extract was evaluated in the DPPH$^{\bullet}$ assay, compared to BHT. The IC_{50} value of the extract was observed to be 89.2 μg/mL, while BHT showed an IC_{50} value of 26.5 μg/mL. [157]

5.2. Antibacterial activity

Khan et al. [158] reported the antibacterial activities of crude methanol extracts from the fruits of *B. bulbocastanum* against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis* and *Salmonella typhi*. Accordingly, remarkable antibacterial activity was noted *vs S. aureus* and moderate inhibition for the other bacterial strains. In addition, *n*-hexane fraction of MeOH extract of *B. bulbocastanum* L. showed high, moderate and low inhibition for *S. aureus*, *E. coli* and *B. subtilis*, respectively. However, under the conditions used in the tests, no activity was detected against *P. aeruginosa*. In addition, the $CHCl_3$ fraction of MeOH extract displayed moderate activity against *S. aureus*, low activity for *B. subtilis* and no activity for *P. aeruginosa* and *E. coli*. The EtOAC fraction of MeOH extract also showed moderate and low activity, respectively, against *B. subtilis* and *E. coli* and was found to be inactive *vs P. aeruginosa* and *S. aureus*. And, the aqueous fraction of methanol extract of *B. bulbocastanum* exhibited significant and moderate inhibition toward *B. subtilis* and *E. coli*. In this work, low activities were observed for this fraction versus *P. aeruginosa*, as well.

Masoudi et al. [46] presented no observed activity of *B. cylindricum* (Boiss. et Hohen.) crude oils against some bacterial strains like *S. aureus* (PTCC 1113), *Staphylococcus epidermidis*

(PTCC 1349), *S. saprophyticus* (PTCC 1379), as Gram-(+) bacteria along with *S. typhi* (PTCC 1185), *S. flexnery* (PTCC 1234) and *E. coli* (PTCC 1330) as Gram-(-) bacteria.

In another report, BPEO showed medium to low antimicrobial activity against *S. aureus* (ATCC 6538), *E. coli* (ATCC 25922), *Salmonella abony* (ATCC 6017) and *P. aeruginosa* (ATCC 27853) with MIC values ranging from 2000 to 8000 μg/mL. [65]

Bousetla et al. [18] tested the dichloromethane/methanol (1:1 v/v) crude extract of *B. incrassatum* against *E. coli*, *S. aureus*, *S. epidermis*, *Proteus mirabilis*, *Streptococcus pyogenes*, *P. aeruginosa*, *Klebsiella oxytoca*, *Enterobacter* spp. and *Seratia* spp. using the disk diffusion method at 1, 2, 4 and 8 mg/mL. The activity was observed against all the tested microbial strains only at 8 mg/mL. Considering the obtained results, at 1 mg/mL, the extract was active only against *S. aureus*. Furthermore, at 2 mg/mL, the extract was active only against *S. aureus* and *P. aeruginosa*, while at 4 mg/mL, the extract was not active only against *E. coli* and *P. mirabilis*. As for the growth inhibition zone values, all of them were found to increase with the concentration raising.

Recently, the EO of *B. incrassatum* and *B. alpinum* aerial parts showed notable antibacterial activities against a wide array of bacterial strains. [45]

The antibacterial activity of *B. brachyactis*, *B. microcarpum*, *B. pinnatifolium* and *B. sayai* methanol extracts was evaluated against *E. coli* (ATCC 35210), *P. aeruginosa* (ATCC 27853), *S. typhimurium* (ATCC 13311), *Proteous mirabilis* (human isolate), *Enterobacter cloacae* (ATCC 35030), *Bacillus cereus* (clinical isolate), *Micrococcus flavus* (ATCC 10240) and *S. aureus* (ATCC 6538). The related minimum inhibitory concentration (MIC) and the minimum fungicidal concentration (MFC) values showed that all the extracts were mostly less potent than the standard compounds, *i.e.*, streptomycin and ampicillin. In addition, the values of the different extracts were similar to each other except a few cases. The four species showed the highest activity against *P. myrabilis* and *E. coli* with MIC and minimum bactericidal concentration (MBC) values lower than 1 mg/mL. Besides, *B. brachyactis* extract was more efficient against *B. cereus*, *P. aeruginosa* and *S. typhimurium* with MIC and MBC values lower than ampicillin. On the other hand, *B. microcarpum* was more active against *P. mirabilis* with MIC and MBC values equal to 0.14 and 0.18 mg/mL, respectively. *B. pinnatifolium* also exhibited the highest antibacterial effect against *M. flavus* and *E. cloacae* with MIC and MBC values equal to 0.56 and 0.75 mg/mL, respectively. [69]

Using broth microdilution method, antibacterial activities of BPEO have been determined against a panel of six bacteria involving *E. coli*, *P. aeruginosa*, *B. cereus*, *S. aureus*, *S. epidermidis* and *E. faecalis* considering MIC and MBC values [122]. In this relation, the best

MIC and MBC values, as 4.0 and 15.0 µL/mL, respectively, were observed against *S. epidermidis* which were comparable to those obtained by ciprofloxacin (MIC = 4.0 µg/mL; MBC = 12 µg/mL) as standard.

Rabiey et al. [159] determined the highest level of BPEO with no unpleasant effect on sensory properties of fish fillets prior to its antimicrobial assessments against *L. monocytogenes* at 0.05, 0.02 and 0.04%. Regarding this attempt, the highest inhibition of *L. monocytogenes* was noted in fish peptone broth (FPB), while a significant decrease occurred in other two media, namely kutum broth (KB) as well as cold smoked kutum (SMK) broth. It has also been reported that impregnation of each broth with NaCl (4.0%) could significantly improve the BPEO efficiency under the optimized experimental conditions at low temperatures.

Taherkhani et al. [56] showed that BPEO (Black Zira) is able to improve the odor and flavor of Gouda cheese. The *in vitro* antibacterial effects of BPEO, *Cuminum cyminum* and *Carum copticum* oils from the Apiaceae family have been examined against a panel of food-borne pathogens, *e.g.*, *S. aureus B. cereus E. coli* O157:H7, *S. enteritidis* and *L. monocytogenes* using broth microdilution method. [53] According to the results of this study, both the MIC and MBC values were in the range of 0.18-3 mg/mL. As being reported in this study, the lowest MIC (0.18 mg/mL) and MBC (0.18 mg/mL) and hence the highest antibacterial activity of BPEO were observed against *B. cereus*. Moreover, regarding the less antibacterial effects of *B. persicum* (Boiss). B. Fedtsch and *Cuminum cyminum* L. volatile oil compared to those of *Trachyspermum ammi* (L.) Sprague oil, fractional inhibitory concentration (FIC) values of a combination of EOs of these two species were determined. As the obtained results in this report show, combination of the aforementioned EOs exerted more inhibition toward most pathogenic bacteria in comparison with the use of each EO alone.

Sharafati Chaleshtori et al. [155] studied MIC and MBC values of BPEO against two species of *Listeria* separated from seafood samples (*L. monocytogenes* and *L. gray*) using broth microdilution method. In accordance with this report, MIC values against *L. monocytogenes* and *L. gray* were respectively as 0.351 and 2.812 mg/mL. Furthermore, the MBC values toward these two *Listeria* species were, respectively, 0.703 and 5.625 mg/mL.

On the other hand, the ethanol extract of *B. persicum* (Boiss). B. Fedtsch showed remarkably less antibacterial activities toward *Listeria* species with MIC values of 247, 495, 495 and 990 mg/mL, respectively against *L. monocytogenes* and *L. gray*. More importantly, when treating *L. monocytogenes* and *L. gray* with MIC concentration of EO and extracts of *B. persicum* (Boiss). B. Fedtsch, a remarkable increase was noted in the trends of components release. The ethanol extract of this species was active against *P. aeruginosa*, *S. aureus* and *E. coli* with medium values of inhibition zone (10-14 mm). [160]

Noori et al. [22] reported the influences of some experimental variables, *e.g.*, pH, temperature, EO concentration and inoculum size on *L. monocytogenes* growth using brain heart infusion (BHI) broth in combination with parametric survival models. Accordingly, lower pHs and temperatures along with higher inoculum size exerted significant impacts on the initiation of growth of *L. monocytogenes*.

In the work by Ehsani et al. [156] dealing with the antibacterial activities of a set of food-borne pathogenic bacteria, remarkable and moderate sensitivity were observed, respectively, against Gram-(+) and Gram-(-) bacteria. In this report, antibacterial-based determinations were conducted using disk diffusion and microdilution methods. As being reported, using the former method on four bacterial strains, *e.g.*, *S. aureus*, *L. monocytogenes*, *S. typhimurium* and *E. coli* O157:H7, the highest and lowest inhibition zone diameter (IZD) were recorded for *S. aureus* and *S. typhimurium* strains, respectively. In addition, MIC values for Gram-(+) bacteria (*S. aureus* and *L. monocytogenes*) were 1.25 and 5.0 mg/mL, whereas the corresponding MBC values were 25 and 10 mg/mL. On the other hand, for both Gram-(-) bacteria involving *S. typhimurium* and *E. coli* O157:H7, MIC and MBC values were respectively as 10 mg/mL and 20 mg/mL accounting for less antibacterial effects of Gram-(-) bacteria compared to Gram-(+) bacteria. The lower sensitivity of Gram-(-) bacteria in comparison to Gram-(+) bacteria is related to the outer structure of their membranes, since in Gram-(-), the membrane is composed of hydrophilic polysaccharides serving as an obstacle for direct contact of bacterial cell with macromolecules as well as hydrophobic compounds; thereby giving rise to a higher resistance of Gram-(-) bacteria to EOs. [161]Additionally, the results of bacterial enumeration of *E. coli* O157:H7 and *L. monocytogenes* in Iranian white cheese revealed an increase in the number of counted colonies of both bacteria for all the tested cheese samples through the storage process. [160]

5.3. Antifungal activities

Mehni et al. [162] have shown that *B. persicum* exhibited some therapeutic impacts against *vulvovaginal candidiasis*. In this regard, the vaginal preparation consisting of clotrimazole and *B. Perscicum* Boiss (Black Zira) was found to have synergistic effect with clotrimazole and better address the symptoms and unpleasant effects of *V. candidiasis* like itching, soreness and irritation in respect to the treatment with clotrimazole added with placebo. However, it should be underlined that in this paper is not repreted in which form the plant materials were used (as they are, as extract obtained by organic solvent, hydrodistillate, etc..) and in which ratio with the standard drug clotrimazole. In addition, the BPEO was tested against different forms of *F. oxysporum* (F27, F37, F3, F6, F12 and F22) showing medium EC_{50} values. [64]

Using agar disc diffusion assay, Ghasemi Pirbalouti et al. [163] investigated the antifungal activities of BPEO against four fungal strains, namely *Aspergillus niger* (PTCC 5298), *A. fumigatus* (PTCC 5009), *A. flavus* (PTCC 5004) and *A. parasiticus* (PTCC 5018) in a concentration range of 8-256 μg/mL of the obtained oils. This study revealed weak to moderate antifungal activities of BPEO against *A. fumigatus*, while BPEO was found to be low or less active against the other tested fungal species.

Sekine et al. [164] determined the growth inhibition potential of 52 herbal samples (dried) including *B. persicum* using the disc pack method against *Fusarium oxysporum* as a soil-borne phytopathogenic fungus. In this report, among all the plant samples tested, the strongest inhibition was attributed to *B. persicum* with a mycelial growth inhibition percentage of 63%.

BPEO showed low antifungal activity against *C. albicans* (ATCC 10231) with an MIC value equal to 1000 μg/mL. [65] Moreover, it was tested at two concentrations (80 and 160 μg/mL) against *Colletotrichum acutatum*, *C. fragariae* and *C. gloeosporioides*. As reported, at 160 μg, BPEO demonstrated better activity against all the three species with growth inhibition zones of 9.0-10.0 mm. [65]

The ethanolic extract of this species was seen to be quite active against *Candida albicans* with a medium value of inhibition zone equal to 15 mm. [160] Using agar disc diffusion assay, the methanol extract of *B. bulbocastanum* and its organ fractions showed no antifungal activity against six fungal strains involving *Aspergillus niger*, *A. flavus*, *Penicillium notatum*, *Fusarium oxysporum*, *Trichoderma harzianum* and *Alternaria alternata*. [158] However, the methanol extract obtained from the fruits was active against *S. aureus* and *P. aeruginosa* with inhibition zone values of 12 and 15 mm, respectively. [165]

The crude extract (dichloromethane and methanol 1:1 v/v) of *B. incrassatum* was tested at different concentrations (0.25, 0.5, 1, 2, 4 and 8 mg/mL) against three fungal strains, *i.e.*, *A. flavus*, *Penicilium candidum* and *Candida albicans*. As reported, at the last two concentrations, the extract was active against all the strains. At 0.5, 1 and 2 mg/mL, the extract was active against *A. flavus* and *P. candidum* with medium growth inhibition zone values. Instead, at the concentration of 0.25 mg/mL, the extract was active against *A. flavus*. Again, for what concerns the growth inhibition zone values, they all were seen to increase with the concentration raising. [18]

More recently, Zengin et al. [69] have assessed the antifungal activity of *B. brachyactis*, *B. microcarpum*, *B. pinnatifolium* and *B. sayai* methanol extracts against *A. versicolor* (ATCC 11730), *A. fumigatus* (plant isolate), *A. terreus* (soil isolate), *A. niger* (ATCC 6275), *Penicillium ochrochloron* (ATCC 9112), *P. funiculosum* (ATCC 36839), *P. verrucosum* (food isolate) and *Trichoderma viride* (IAM 5061) using ketoconazole and bifonazole as positive controls. The obtained values of MIC and MFC showed that all the extracts were mostly less potent than the standard compounds. Nevertheless, in many cases, the values were highly comparable with those of the used standards and also very similar to each other except a few cases. Summarizing, *B. brachyactis* methanol extract showed the best activity against *A. versicolor, T. viride* and *P. funiculosum* with MIC and MFC values equal to 0.18 and 0.37 mg/mL, 0.02 and 0.03 mg/mL and 0.18 and 0.37 mg/mL, respectively. *B. brachyactis* methanol extract was more effective than ketoconazole against *A. versicolor* as well as more effective than both ketoconazole and bifonazole against *T. viride*. Indeed, *B. sayai* had no effect on *A. fumigatus* but was even more effective than ketoconazole against *A. fumigatus* with MIC and MFC values equal to 0.14 and 0.28 mg/mL, respectively. *B. pinnatifolium* was more effective against *P. ochrochloron* with MIC and MFC values equal to 0.275 and 0.37 mg/mL, respectively.

5.4. Larvicidal activity

A larvicidal activity testing on the genus *Bunium* was carried out by Vatandoost et al. [166] where they studied the larvicidal activity of BPEO as well as its methanol, petroleum ether and ethyl acetate extracts based upon a recommended method by WHO. [167] Regarding the results, both BPEO samples from cultivated and wild growing plants with lethal concentrations (LC_{50}) of 21.38 and 27.43 ppm exhibited the highest larvicidal activity, while methanol fractions of both samples of *B. persicum* had the lowest larvicidal activity.

5.5. Phytotoxic activity

Following the method given by McLaughlin et al. [168], the phytotoxicity of methanol extracts of *B. bulbocastanum* L. and its fractions was determined 1000 and 100 µg/mL. [158] Considering the respective results, at 1000 µg/mL, the phytotoxicity of the methanol extract along with its *n*-hexane, chloroform, ethyl acetate and aqueous fractions were respectively as 53.33%, 46.66%, 20.0%, 46.66% and 40.0%. However, at 100 μg/mL, the corresponding phytotoxicities were found to be respectively as 46.66%, 26.66%, 6.66%, 26.66% and 33.33%.

5.6. Hemagglutination activity

Khan et al. [158] investigated the potential hemagglutination activity of crude methanol extract of *B. bulbocastanum* L. and its fractions obtained after CC, against human erythrocytes of blood groups applying the suggested method by Naqvi et al. [169] It was concluded that that all the extracts of *B. bulbocastanum* L. were not able to agglutinate RBCs of the human blood groups accounting for the lack of phytolectins.

5.7. Anticonvulsant activity

Mandegary et al. [170] assessed the anticonvulsant activity of BPEO and *B. persicum* methanol extracts towards convulsions induced on pentylenetetrazole (PTZ) and maximal electroshock (MES). In this study, a group consisting of NMRI male mice with an average weight of 22.5 g were chosen and kept under normal diet. The mean outputs of this report were: i) mortality of BPEO at 5 g/kg dose, while being not mortal at 4 g/kg dose; ii) no mortality for BPEO at 2.5 mL/kg dose.

5.8. Hypoglycemic activity

Due to the remarkable hypoglycemic activity of its extracts, *B. persicum* has been recognized as an effective remedy against diabetes and obesity as reported by Statti et al. [171] In this report, the hypoglycemic activity was assessed via the trends of inhibition of α-amylase as one of the main agents for starch breakdown to simpler sugar units, *e.g.*, glucose, maltose and maltotriose. Accordingly, the highest inhibition was reported for the *B. persicum* *n*-hexane extract (72.3% ± 0.06) at a concentration of 250 μg/mL, whereas the corresponding MeOH extract exerted lower inhibition at most of the tested concentrations.

5.9. Cardiocirculatory activity

Khaksari et al. [172] have reported that aqueous extract derived from the aerial parts of freeze-dried *B. persicum* is able to increase the cardiocirculatory capacity. This study was conducted on 40 male hypercholesterolemic mice being classified into four categories. The obtained results of this work accounted for a notable increase of cardiorespiratory capacity over a normal six-week endurance training period.

5.10. Anti-inflammatory activity

In a recent report, the methanol extracts of *B. alpinum* and *B. incrassatum* were found to have anti-inflammatory effects by blocking albumin denaturation that contributes to the inflammation process. The albumin denutaration inhibitory average values were equal to 49.66 and 49.74 mg/mL, respectively, compared to 49.98 mg/mL for sodium diclofenac used as standard compound. Additionally, this activity was observed to be of concentration dependent type. [45]

5.11. Enzyme inhibitory activity

The enzyme inhibitory activity of *B. brachyactis*, *B. microcarpum*, *B. pinnatifolium* and *B. sayai* methanol extracts was evaluated against acetylcholinesterase (AChE), butyrylcholinesterase (BChE), tyrosinase, amylase, glucosidase and lipase. The results were expressed as milligrams of gallic acid equivalents per g of sample (GAE/g) and showed that the extract of *B. brachyactis* was the best BChE inhibitor with a value of 3.68 mg GAE/g. *B. sayai* extract was the best AChE inhibitor with a value equal to 3.53 mg GAE/g. Indeed, the four species had similar effects against tyrosinase and amylase with *B. brachyactis* as the best one in both cases (138.96 mg kojic acid equivalent per g of sample (KAE/g), 0.63 mmol ACAE/g). *B. microcarpum* extract was the best glucosidase inhibitor with a value equal to 11.96 mmol ACAE/g, whereas the best lipase inhibitor was *B. brachyactis* extract with a value equal to 95.74 mg OE/g. [69]

5.12. Mosquito-deterrent activity

BPEO was tested for its mosquito-deterrent activity against *Aedes aegypti*. It showed higher activity than the solvent control (ethanol) but lower than permethrin, a standard biting deterrent, used as a positive control. The reported median lethal dose (LD_{50}) value of this work was found to be 58.6 ppm *vs* 0.0034 ppm. [65]

6. Link between phytochemistry and biological activities

The biological assays performed on *Bunium* species EOs and extracts as reported in the literature, are all remarkable and reliable even if not all of them gave positive results. The methodologies applied for each assay are well-established and reliable. However, not all the explanations have been accurately provided. In particular, for some assays, values were not given. Nonetheless, we decided to include these data in this review, even if, in our opinion, their relevance is minimum. On the other hand, some biological assays were carried out without any phytochemical profiling, *i.e.*, the biological assays were performed without knowing the phytochemical patterns of the extracts derived from *Bunium* species. This latter point is extremely important since it may explain the biological results under the phytochemical standpoint. In all the cases where this was performed, the reported phytochemical patterns were found to be fully in accordance with the results from biological assays. Nevertheless, EOs are generally well-known to possess promising pharmacological activities [173] as well as all the non-volatile classes of compounds identified in *Bunium* species. [88, 174-176]
From the phytochemical standpoint, the effectiveness of extracts may be explained with the presence of flavonoids and phenolic metabolites such as caffeoylquinic derivatives which are known to be effective as antioxidants with different mechanisms ranging from the radical scavenging to the metal chelating properties. [177, 178] However, the lack of an extensive phytochemical background that explains the associated biological properties is a massive problem. Nowadays, in our opinion, it is no longer sufficient to say that one extract possesses a biological activity without giving information about its phytochemical pattern. In addition, it is not even sufficient to only establish the presence of some classes of natural compounds which may provide a hint but not the total explanation. More importantly, when considering that in a number of cases, the whole phytocomplex or some of its constituents, have a synergistic bioactivity. This can actually be another research line especially in relation to *Bunium* species.

7. Conclusions

In this review article, the chemical compositions of the EOs and non-volatile compounds of different *Bunium* species have been integrated and discussed. The chemotaxonomy of the genus is perfectly in accordance with the current phytochemical classification of the Apiaceae family for all the studied species. It is obviously important that further studies will be conducted also on those species of the genus with uncertain classification. *Bunium* species are widely used in the folklore medicine of several areas of the world and are able to exert a myriad of pharmacological activities as shown in this review article. However, it should be underlined that not all the *Bunium* species have been studied for many of their aspects and not all the possible explanations have been given. Therefore, this review article also means to encourage the phytochemical, chemotaxonomic, ethnobotanical and pharmacological studies on these species given their high potentialities and their unexplored aspects.

'Author Contribution Statement'

M. Mohammadhosseini generated the concept, wrote and edited the whole article. C. Frezza wrote the phytochemistry section. A. Venditti wrote the chemotaxonomy section. S.D. Sarker helped with the prepartion of the manuscript, and edited the article.

'Twitter text'

A systematic review on phytochemistry, ethnobotany and biological activities of the genus *Bunium* L. by M. Mohammadhosseini et al., Shahrood Branch, Islamic Azad University, Iran (without Account)

References

[1] M. Mohammadhosseini, 'The ethnobotanical, phytochemical and pharmacological properties and medicinal applications of essential oils and extracts of different *Ziziphora* species', *Ind. Crops Prod.* **2017**, *105*, 164-192.

[2] M. Mohammadhosseini, S. D. Sarker, A. Akbarzadeh, 'Chemical composition of the essential oils and extracts of *Achillea* species and their biological activities: A review', *J. Ethnopharmacol.* **2017**, *199*, 257-315.

[3] M. Mohammadhosseini, C. Frezza, A. Venditti, A. Akbarzadeh, 'Ethnobotany and phytochemistry of the genus *Eremostachys* Bunge', *Curr. Org. Chem.* **2019**, *23*, 1828-1842.

[4] M. Mohammadhosseini, A. Venditti, A. Akbarzadeh, 'The genus *Perovskia* Kar.: ethnobotany, chemotaxonomy and phytochemistry: a review', *Toxin Rev.* **2019**.

[5] M. Mohammadhosseini, C. Frezza, A. Venditti, B. Mahdavi, ' An overview of the genus *Aloysia* Palau (Verbenaceae): Essential oil composition, ethnobotany and biological activities', *Nat. Prod. Res.* **2021**.

[6] www.theplantlist.org.

[7] G. V. Degtjareva, E. V. Kljuykov, T. H. Samigullin, C. M. Valiejo-Roman, M. G. Pimenov, 'Molecular appraisal of *Bunium* and some related arid and subarid geophilic Apiaceae-Apioideae taxa of the Ancient Mediterranean', *Bot. J. Linn. Soc.* **2009**, *160*, 149-170.

[8] A. R. Jassbi, M. Mehrdad, M. Soleimani, M. Mirzaeian, A. Sonboli, 'Chemical composition of the essential oils of *Bunium elegans* and *Bunium caroides*', *Chem. Nat. Compd.* **2005**, *41*, 415-417.

[9] A. Ghahreman, 'Plant Systematic', Academic Publication, 1994.

[10] A. H. Saeidnejad, M. Khajeh-Hosseini, M. A. Askarzadeh, 'Breaking dormancy of seeds from eight populations of *Bunium persicum* (Apiaceae)', *Seed Sci. Technol.* **2013**, *41*, 452-457.

[11] A. Zargari, 'Medicinal Plants', Tehran University Press, Tehran, Iran, 1990.

[12] V. Mozaffarian, 'A Dictionary of Iranian Plant Names', Farhang Moaser Press, Iran, 1996.

[13] R. Omidbaigi, M. J. Arvin, 'Effect of growing locations on the essential oil content and chemical compositions of *Bunium persicum* Boiss wild growing in Iran', *J. Essent. Oil-Bear. Plants* **2009**, *12*, 34-40.

[14] F. Jahansooz, F. Sefidkon, A. Najafi, H. Ebrahimzadeh, M. S. Najafi, 'Comparison of essential oils of *Bunium persicum* (Boiss.) populations grown in Iran, Pakistan and India', *J. Essent. Oil-Bear. Plants* **2012**, *15*, 761-765.

[15] H. Hassanzadazar, B. Taami, M. Aminzare, S. Daneshamooz, '*Bunium persicum* (Boiss.) B. Fedtsch: An overview on phytochemistry, therapeutic uses and its application in the food industry', *J. Appl. Pharm. Sci.* **2018**, *8*, 150-158.

[16] K. Baser, T. Oezek, B. Abduganiev, U. Abdullaev, K. N. Aripov, 'Composition of the essential oil of *Bunium persicum* (Boiss.) B. Fedtsch. from Tajikistan', *J. Essent. Oil Res.* **1997**, *9*, 597-598.

[17] M. Sheidai, P. Ahmadian, S. Poorseyedy, 'Cytological studies in Iran Zira from three genus: *Bunium*, *Carum* and *Cuminum*', *Cytologia* **1996**, *61*, 19-25.

[18] A. Bousetla, A. Zellagui, K. Derouiche, S. Rhouati, 'Chemical constituents of the roots of Algerian *Bunium incrassatum* and evaluation of its antimicrobial activity', *Arab. J. Chem.* **2015**, *8*, 313-316.

[19] R. K. Thappa, S. Ghosh, S. G. Agarwal, A. K. Raina, P. S. Jamwal, 'Comparative studies on the major volatiles of Kalazira (*Bunium persicum* seed) of wild and cultivated sources', *Food Chem.* **1991**, *41*, 129-134.

[20] P. Salehi, F. Mohammadi, B. Asghari, 'Seed essential oil analysis of *Bunium persicum* by hydrodistillation- headspace solvent microextraction', *Chem. Nat. Compd.* **2008**, *44*, 111-113.

[21] M. Sadat-Hosseini, M. Farajpour, N. Boroomand, F. Solaimani-Sardou, 'Ethnopharmacological studies of indigenous medicinal plants in the south of Kerman, Iran', *J. Ethnopharmacol.* **2017**, *199*, 194-204.

[22] Z. Noori, S. Khanzadi, A. Jamshidi, H. A. Seifi, 'Modeling the effects of *Bunium persicum* (Black Zira) essential oil, pH, inoculums size and temperature on the growth of *Listeria monocytogenes*', *Iran. J. Vet. Res.* **2014**, *15*, 272-278.

[23] M. Mohammadhosseini, 'A Comprehensive Review on New Methods for Processing, Separation and Identification of the Essential Oils', Islamic Azad University of Shahrood Press, Shahrood, Iran, 2016.

[24] P. A. Sofi, N. A. Zeerak, P. Singh, 'Kala zeera (*Bunium persicum* Bioss.): A Kashmirian high value crop', *Turk. J. Biol.* **2009**, *33*, 249-258.

[25] K. Rechinger, J. Lemond, I. Hedge, 'Flora Iranica (Umbelliferae)', Akademische Druck Verlagsanstalt, Graz, Austria, 1987.

[26] F. Sefidkon, S. A. Gooshegir, A. Bahmanzadegan, M. Golipour, S. Meshkizadeh, 'Chemical composition of the essential oils of five Iranian *Bunium* species (*B. lurestanicum*, *B. microcarpum*, *B. badghayzi*, *B. wolffi* and *B. carioides*)', *J. Essent. Oil-Bear. Plants* **2014**, *17*, 13-17.

[27] B. Bani, G. V. Degtjareva, M. G. Pimenov, E. V. Kljuykov, N. Adigüzel, '*Bunium allioides* (Apiaceae), a new species from Turkey', *Ann. Bot. Fenn.* **2012**, *49*, 412-416.

[28] M. Azizi, G. Davareenejad, R. Bos, H. J. Woerdenbag, O. Kayser, 'Essential oil content and constituents of black zira (*Bunium persicum* [Boiss.] B. Fedtsch.) from Iran during field cultivation (domestication)', *J. Essent. Oil Res.* **2009**, *21*, 78-82.

[29] M. Mohammadhosseini, A. Akbarzadeh, G. Flamini, 'Profiling of compositions of essential oils and volatiles of *Salvia limbata* using traditional and advanced techniques and evaluation for biological activities of their extracts', *Chem. Biodivers.* **2017**, *14*.

[30] H. Hashemi-Moghaddam, M. Mohammadhosseini, Z. Azizi, 'Impact of amine- and phenyl-functionalized magnetic nanoparticles impacts on microwave-assisted extraction of essential oils from root of *Berberis integerrima* Bunge', *J. Appl. Res. Med. Aromat. Plants* **2018**.
[31] H. Hashemi-Moghaddam, M. Mohammadhosseini, M. Salar, 'Chemical composition of the essential oils from the hulls of *Pistacia vera* L. by using magnetic nanoparticle-assisted microwave (MW) distillation: Comparison with routine MW and conventional hydrodistillation', *Anal. Methods* **2014**, *6*, 2572-2579.
[32] H. Hashemi-Moghaddam, M. Mohammadhosseini, M. Basiri, 'Optimization of microwave assisted hydrodistillation on chemical compositions of the essential oils from the aerial parts of *Thymus pubescens* and comparison with conventional hydrodistllation', *J. Essent. Oil-Bear. Plants* **2015**, *18*, 884-893.
[33] M. Mohammadhosseini, 'Essential oils extracted using microwave-assisted hydrodistillation from aerial parts of eleven *Artemisia* species: Chemical compositions and diversities in different geographical regions of Iran', *Rec. Nat. Prod.* **2017**, *11*, 114-129.
[34] M. Nekoei, M. Mohammadhosseini, 'Chemical composition of essential oils of *Salvia leriifolia* by three different extraction methods prior to gas chromatographic-mass spectrometric determination: comparison of HD with SFME and HS-SPME', *J. Essent. Oil-Bear. Plants* **2017**, *20*, 410-425.
[35] A. Shafaghat, O. Ghorban-Dadras, M. Mohammadhosseini, M. Akhavan, M. Shafaghatlonbar, A. Panahi, 'A comparative study on chemical composition and antimicrobial activity of essential oils from *Tanacetum parthenium* (L.) Schultz. Bip. and *Tanacetum punctatum* (Desr.) Grierson. leaves from Iran', *J. Essent. Oil-Bear. Plants* **2017**, *20*, 1143-1150.
[36] M. Nekoei, M. Mohammadhosseini, 'Screening of profiles of essential oils from the aerial parts of *Sclerorhachis platyrachis* (Boiss.) Podlech ex Rech.f. using classical and microwave-based methods: Comparison with the volatiles using headspace solid-phase microextraction', *J. Essent. Oil-Bear. Plants* **2018**, *21*, 1199-1209.
[37] B. Mahdavi, T. Hajar, A. Ghodsi, M. Mohammadhosseini, M. Mehmandost, E. Talebi, 'Antidiabetic effect of *Sophora pachycarpa* seeds extract in streptozotocin-induced diabetic mice: a statistical evaluation', *J. Investig. Med.* **2021**, *0*, 1-7.
[38] Y. Zhang, B. Mahdavi, M. Mohammadhosseini, E. Rezaei-Seresht, S. Paydarfard, M. Qorbani, M. Karimian, N. Abbasi, H. Ghaneialvar, E. Karimi, 'Green synthesis of NiO nanoparticles using *Calendula officinalis* extract: Chemical charactrization, antioxidant, cytotoxicity, and anti-esophageal carcinoma properties', *Arab. J. Chem.* **2021**, *14*, 103105.

[39] F. Shakeri, M. H. Boskabady, 'A review of the relaxant effect of various medicinal plants on tracheal smooth muscle, their possible mechanism(s) and potency', *J. Ethnopharmacol.* **2015**, *175*, 528-548.

[40] M. Azizi, G. Davareenejad, R. Bos, H. J. Woerdenbag, O. Kayser, 'Essential oil content and constituents of black zira [*Bunium persicum* [Boiss.] B. Fedtsch.) from Iran during field cultivation (domestication)', *J. Essent. Oil Res.* **2009**, *21*, 193-194.

[41] B. Nickavar, A. Adeli, A. Nickavar, 'Analyses of the essential oil from *Bunium persicum* fruit and its antioxidant constituents', *J. Oleo Sci.* **2014**, *63*, 741-746.

[42] M. Khanavi, P. Laghaei, M. B. Isman, 'Essential oil composition of three native Persian plants and their inhibitory effects in the cabbage looper, *Trichoplusia ni*', *J. Asia-Pac. Entomol.* **2017**, *20*, 1234-1240.

[43] R. Chizzola, A. H. Saeidnejad, M. Azizi, F. Oroojalian, H. Mardani, '*Bunium persicum*: variability in essential oil and antioxidants activity of fruits from different Iranian wild populations', *Genet. Resour. Crop. Evol.* **2014**, *61*, 1621-1631.

[44] S. Zarrinpashne, S. Gorji Kandi, 'A study on the extraction of essential oil of Persian black cumin using static supercritical CO_2 extraction, and comparison with hydro-distillation extraction method', *Sep. Sci. Technol.* **2018**, *54*, 1778-1786.

[45] E. K. Hayet, L. Hocine, E. K. Meriem, 'Chemical composition and biological activities of the essential oils and the methanolic extracts of *Bunium incrassatum* and *Bunium alpinum* from Algeria', *J. Chilean Chem. Soc.* **2017**, *62*, 3335-3341.

[46] S. Masoudi, A. Monfared, A. Rustaiyan, F. Chalabian, 'Composition and antibacterial activity of the essential oils of *Semenovia dichotoma* (Boiss.) Manden., *Johreniopsis seseloides* (C.A.Mey) M.Pimen and *Bunium cylindricum* (Boiss. et Hohen.) Drude., three Umbelliferae herbs growing wild in Iran', *J. Essent. Oil Res.* **2005**, *17*, 691-694.

[47] G. Öztürk, B. Demirci, M. Çelik, K. BAŞER, 'Chemical composition of *Bunium elegans* (Fenzl) Freyn var. *elegans* essential oil', *Nat. Vol. Essent. Oils* **2020**, *7*, 26-29.

[48] A. Bousetla, M. Kurkcuoglu, B. Konuklugil, K. H. C. Baser, S. Rhouati, 'Composition of essential oil from *Bunium incrassatum* from Algeria', *Chem. Nat. Compd.* **2014**, *50*, 753-755.

[49] M. H. Meshkatalsadat, S. Zarei, 'Determination of volatile components of Bunium luristanicum Rech. F using MAHD and HD extraction twchniques and antioxidative activity of methanolic extract-A green chemistry approach', *Dig. J. Nanomat. Biostr.* **2011**, *6*, 515-521.

[50] K. H. C. Baser, T. Özek, B. E. Abduganiev, U. A. Abdullaev, K. N. Aripov, 'Composition of the essential oil of *Bunium persicum* (Boiss.) B. Fedtsch. from Tajikistan', *J. Essent. Oil Res.* **1997**, *9*, 106-108.

[51] A. Foroumadi, A. Asadipour, F. Arabpour, Y. Amanzadeh, 'Composition of the essential oil of *Bunium persicum* (Boiss.) B. Fedtsch. from Iran', *J. Essent. Oil Res.* **2002**, *14*, 161-162.

[52] N. Shahsavari, M. Barzegar, M. A. Sahari, H. Naghdibadi, 'Antioxidant activity and chemical characterization of essential oil of *Bunium persicum*', *Plant Foods Hum. Nutr.* **2008**, *63*, 183-188.

[53] F. Oroojalian, R. Kasra-Kermanshahi, M. Azizi, M. R. Bassami, 'Phytochemical composition of the essential oils from three Apiaceae species and their antibacterial effects on food-borne pathogens', *Food Chem.* **2010**, *120*, 765-770.

[54] V. Hajhashemi, S. E. Sajjadi, M. Zomorodkia, 'Antinociceptive and anti-inflammatory activities of *Bunium persicum* essential oil, hydroalcoholic and polyphenolic extracts in animal models', *Pharm. Biol.* **2011**, *49*, 146-151.

[55] S. Mazidi, K. Rezaei, M. T. Golmakani, A. Sharifan, S. Rezazadeh, 'Antioxidant activity of essential oil from Black Zira (*Bunium persicum* Boiss.) obtained by microwave-assisted hydrodistillation', *J. Agric. Sci. Tech.* **2012**, *14*, 1013-1022.

[56] P. Taherkhani, N. Noori, A. Akhondzadeh Basti, H. Gandomi, M. Alimohammadi, 'Antimicrobial effects of Kermanian black cumin (*Bunium persicum* Boiss.) essential oil in Gouda cheese matrix', *J. Med. Plants* **2015**, *14*, 76-85.

[57] M. Keramat, M. T. Golmakani, M. Aminlari, S. S. Shekarforoush, 'Comparative effect of *Bunium persicum* and *Rosmarinus officinalis* essential oils and their synergy with citric acid on the oxidation of virgin olive oil', *Int. J. Food Prop.* **2016**, *19*, 2666-2681.

[58] A. Rustaie, R. Keshvari, N. Samadi, F. Khalighi-Sigaroodi, M. R. S. Ardekani, M. Khanavi, 'Essential oil composition and antimicrobial activity of the oil and extracts of *Bunium persicum* (Boiss.) B. Fedtsch.: Wild and cultivated fruits', *Pharm. Sci.* **2016**, *22*, 296-301.

[59] A. Sanei-Dehkordi, H. Vatandoost, M. R. Abaei, B. Davari, M. M. Sedaghat, 'Chemical composition and larvicidal activity of *Bunium persicum* essential oil against two important mosquitoes vectors', *J. Essent. Oil-Bear. Plants* **2016**, *19*, 349-357.

[60] N. Khaledi, F. Hassani, 'Antifungal activity of *Bunium persicum* essential oil and its constituents on growth and pathogenesis of *Colletotrichum lindemuthianum*', *J. Plant Prot. Res.* **2018**, *58*, 431-441.

[61] F. Talebi, A. Misaghi, A. Khanjari, A. Kamkar, H. Gandomi, M. Rezaeigolestani, 'Incorporation of spice essential oils into poly-lactic acid film matrix with the aim of extending microbiological and sensorial shelf life of ground beef', *LWT* **2018**, *96*, 482-490.

[62] F. Sharififar, N. Yassa, V. Mozaffarian, 'Bioactivity of major components from the seeds of *Bunium persicum* (Boiss.) FEDTCH', *Pak. J. Pharma. Sci.* **2010**, *23*, 300-304.

[63] S. M. Pourmortazavi, M. Ghadiri, S. S. Hajimirsadeghi, 'Supercritical fluid extraction of volatile components from *Bunium persicum* Boiss. (black cumin) and *Mespilus germanica* L. (medlar) seeds', *J. Food Compos. Anal.* **2005**, *18*, 439-446.

[64] H. Behtoei, J. Amini, T. Javadi, A. Sadeghi, 'Composition and *in vitro* antifungal activity of *Bunium persicum*, *Carum copticum* and *Cinnamomum zeylanicum* essential oils', *J. Med. Plant Res.* **2012**, *6*, 5069-5076.

[65] I. Stappen, N. Tabanca, A. Ali, D. E. Wedge, J. Wanner, V. Gochev, V. Jaitak, B. Lal, V. K. Kaul, E. Schmidt, L. Jirovetz, 'Biological activity of *Bunium persicum* essential oil from western Himalaya', *Planta Med Int. Open* **2017**, *4*, e52-e58.

[66] S. V. Mortazavi, M. H. Eikani, H. Mirzaei, M. Jafari, F. Golmohammad, 'Extraction of essential oils from *Bunium persicum* Boiss. using superheated water', *Food Bioprod. Process.* **2010**, *88*, 222-226.

[67] E. Feyzi, M. H. Eikani, F. Golmohammad, B. Tafaghodinia, 'Extraction of essential oil from *Bunium persicum* (Boiss.) by instant controlled pressure drop (DIC)', *J. Chromatogr. A* **2017**, *1530*, 59-67.

[68] M. Lefahal, N. Zaabat, L. Djarri, M. Benahmed, K. Medjroubi, H. Laouer, S. Akkal, 'Evaluation of the antioxidant activity of extracts & flavonoids obtained from *Bunium alpinum* Waldst. & Kit. (Apiaceae) & Tamarix gallica L. (Tamaricaceae)', *Curr. Issues Pharma. Med. Sci.* **2017**, *30*, 5-8.

[69] G. Zengin, M. Y. Paksoy, M. Z. Aumeeruddy, J. Glamocilja, M. Sokovic, A. Diuzheva, J. Jekő, Z. Cziáky, M. J. Rodrigues, L. Custodio, M. F. Mahomoodally, 'New insights into the chemical profiling, cytotoxicity and bioactivity of four *Bunium* species', *Food Res. Int.* **2019**, *123*, 414-424.

[70] L. P. Christensen, K. Brandt, 'Bioactive polyacetylenes in food plants of the Apiaceae family: occurrence, bioactivity and analysis', *J. Pharm. Biomed. Anal.* **2006**, *41*, 683-693.

[71] B. Khalid, S. Hamid, L. Liaqat, J. I. Khan, 'Seed oils of Pakistani wild species of Umbelliferae family: *Ducrosia anethifolia*, *Bunium persicum*, *Bunium cylindricum* and *Ammi majus*; as potential industrial raw material', *Pak. J. Sci. Ind. Res.* **2009**, *52*, 260-263.

[72] B. Fazly Bazzaz, G. Haririzadeh, S. Imami, M. Rashed, 'Survey of Iranian plants for alkaloids, flavonoids, saponins, and tannins [Khorasan Province]', *Int. J. Pharmacogn.* **1997**, *35*, 17-30.

[73] G. A. Stepanenko, A. U. Umarov, A. L. Markman, 'A study of the oils of the family Umbelliferae', *Chem. Nat. Compd.* **1972**, *8*, 694-698.

[74] G. Appendino, H. Ç. Özen, J. Jakupovic, 'Prenylated isocoumarins from *Bunium paucifolium*', *Phytochemistry* **1994**, *36*, 531-532.

[75] G. Appendino, H. Cetin Özen, P. Lusso, M. Cisero, 'A sesquiterpene ketal from *Bunium paucifolium*', *Phytochemistry* **1991**, *30*, 3467-3468.

[76] R. Gani, Z. A. Bhat, M. A. Dar, M. A. Dar, 'Pharmacognostic and phytochemical characteristics of the fruits of *Bunium persicum* (Boiss.) B. Fedtsch, growing wild in Kashmir Valley, India', *Int. J. Pharm. Investig.* **2020**, *10*, 13-16.

[77] G. Appendino, H. Çetin Özen, J. Jakupovic, 'Prenylated isocoumarins from *Bunium paucifolium*', *Phytochemistry* **1994**, *36*, 531-532.

[78] M. Sabzi Nojadeh, M. Pouresmaeil, M. Younessi-Hamzekhanlu, A. Venditti, 'Phytochemical profile of fennel essential oils and possible applications for natural antioxidant and controlling *Convolvulus arvensis* L', *Nat. Prod. Res.* **2020**.

[79] F. Maggi, F. Papa, C. Giuliani, L. Maleci Bini, A. Venditti, A. Bianco, M. Nicoletti, R. Iannarelli, G. Caprioli, G. Sagratini, M. Cortese, M. Ricciutelli, S. Vittori, 'Essential oil chemotypification and secretory structures of the neglected vegetable *Smyrnium olusatrum* L. (Apiaceae) growing in central Italy', *Flav. Fragr. J.* **2015**, *30*, 139-159.

[80] A. Bertoli, L. Pistelli, I. Morelli, G. Spinelli, A. Manunta, 'Constituents of *Cachrys ferulacea* oils', *J. Essent. Oil Res.* **1998**, *10*, 533-536.

[81] M. A. Massumi, M. R. Fazeli, S. H. R. Alavi, Y. Ajani, 'Chemical constituents and antibacterial activity of essential oil of *Prangos ferulacea* (L.) Lindl. fruits', *Iran. J. Pharm. Sci.* **2007**, *3*, 171-176.

[82] F. Sümer Ercan, H. Baş, M. Koç, D. Pandir, S. Öztemiz, 'Insecticidal activity of essential oil of *Prangos ferulacea* (Umbelliferae) against *Ephestia kuehniella* (Lepidoptera: Pyralidae) and *Trichogramma embryophagum* (Hymenoptera: Trichogrammatidae)', *Turk. J. Agric. For.* **2013**, *37*, 719-725.

[83] M. Seidi Damyeh, M. Niakousari, 'Impact of ohmic-assisted hydrodistillation on kinetics data, physicochemical and biological properties of *Prangos ferulacea* Lindle. essential oil: Comparison with conventional hydrodistillation', *Innov. Food Sci. Emerg. Technol.* **2016**, *33*, 387-396.

[84] M. Seidi Damyeh, M. Niakousari, M. J. Saharkhiz, 'Ultrasound pretreatment impact on *Prangos ferulacea* Lindl. and *Satureja macrosiphonia* Bornm. essential oil extraction and comparing their physicochemical and biological properties', *Ind. Crops Prod.* **2016**, *87*, 105-115.

[85] M. Bruno, V. Ilardi, G. Lupidi, L. Quassinti, M. Bramucci, D. Fiorini, A. Venditti, F. Maggi, 'Composition and biological activities of the essential oil from a Sicilian accession of *Prangos ferulacea* (L.) Lindl', *Nat. Prod. Res.* **2019**.

[86] M. Bruno, V. Ilardi, G. Lupidi, L. Quassinti, M. Bramucci, D. Fiorini, A. Venditti, F. Maggi, 'The nonvolatile and volatile metabolites of *Prangos ferulacea* and their biological properties', *Planta Med.* **2019**, *85*, 815-824.

[87] A. Venditti, C. Frezza, G. Salutari, M. di Cecco, G. Ciaschetti, A. Oliva, M. De Angelis, V. Vullo, M. Sabatino, S. Garzoli, 'Composition of the essential oil of *Coristospermum cuneifolium* and antimicrobial activity evaluation', *Planta Med Int. Open* **2017**, *4*, e74-e81.

[88] F. Borges, F. Roleira, N. Milhazes, L. Santana, E. Uriarte, 'Simple coumarins and analogues in medicinal chemistry: Occurrence, synthesis and biological activity', *Curr. Med. Chem.* **2005**, *12*, 887-916.

[89] L. Hansen, P. M. Boll, 'Polyacetylenes in Araliaceae: Their chemistry, biosynthesis and biological significance', *Phytochemistry* **1986**, *25*, 285-293.

[90] V. Rao, L. Rao, 'Phytochemicals: Isolation, Characterisation and Role in Human Health', BoD–Books on Demand, 2015.

[91] C. Frezza, A. Venditti, M. Serafini, A. Bianco, in 'Phytochemistry, chemotaxonomy, ethnopharmacology, and nutraceutics of Lamiaceae', Elsevier, 2019.

[92] C. Frezza, A. Venditti, C. Toniolo, D. De Vita, I. Serafini, A. Ciccòla, M. Franceschin, A. Ventrone, L. Tomassini, S. Foddai, '*Pedicularis* L. genus: Systematics, botany, phytochemistry, chemotaxonomy, ethnopharmacology, and other', *Plants* **2019**, *8*, 306.

[93] C. Frezza, A. Venditti, D. De Vita, C. Toniolo, M. Franceschin, A. Ventrone, L. Tomassini, S. Foddai, M. Guiso, M. Nicoletti, 'Phytochemistry, chemotaxonomy, and biological activities of the Araucariaceae family—a review', *Plants* **2020**, *9*, 888.

[94] B. Salehi, A. Venditti, C. Frezza, A. Yücetepe, U. Altuntaş, S. Uluata, M. Butnariu, I. Sarac, S. Shaheen, S. A. Petropoulos, K. R. Matthews, C. S. Kiliç, M. Atanassova, C. O. Adetunji, A. O. Ademiluyi, B. Özçelik, P. V. T. Fokou, N. Martins, W. C. Cho, J. Sharifi-Rad, '*Apium* plants: Beyond simple food and phytopharmacological applications', *Appl. Sci.* **2019**, *9*.

[95] M. Mohammadhosseini, A. Venditti, S. D. Sarker, L. Nahar, A. Akbarzadeh, 'The genus *Ferula*: Ethnobotany, phytochemistry and bioactivities – A review', *Ind. Crops Prod.* **2019**, *129*, 350-394.

[96] F. Hadaček, C. Müller, A. Werner, H. Greger, P. Proksch, 'Analysis, isolation and insecticidal activity of linear furanocoumarins and other coumarin derivatives from *Peucedanum* (Apiaceae: Apioideae)', *J. Chem. Ecol.* **1994**, *20*, 2035-2054.

[97] S. Rosselli, A. M. Maggio, N. Faraone, V. Spadaro, S. L. Morris-Natschke, K. F. Bastow, K. H. Lee, M. Bruno, 'The cytotoxic properties of natural coumarins isolated from roots of *Ferulago campestris* (Apiaceae) and of synthetic ester derivatives of aegelinol', *Nat. Prod. Comm.* **2009**, *4*, 1701-1706.

[98] A. Basile, S. Sorbo, V. Spadaro, M. Bruno, A. Maggio, N. Faraone, S. Rosselli, 'Antimicrobial and antioxidant activities of coumarins from the roots of *Ferulago campestris* (Apiaceae)', *Molecules* **2009**, *14*, 939-952.

[99] A. Venditti, C. Frezza, V. Gatto Agostinelli, M. Di Cecco, G. Ciaschetti, M. Serafini, A. Bianco, 'Study on the molecular composition of an indigenous Italian species: *Coristospermum cuneifolium*(Guss.) Bertol', *Int. J. Indig. Med. Plants* **2016**, *48*, 1930-1938.

[100] V. Stanjek, J. Piel, W. Boland, 'Synthesis of furanocoumarins: mevalonate-independent prenylation of umbelliferone in *Apium graveolens* (Apiaceae)', *Phytochemistry* **1999**, *50*, 1141-1145.

[101] M. Berenbaum, 'Patterns of furanocoumarin distribution and insect herbivory in the Umbelliferae: plant chemistry and community structure', *Ecology* **1981**, *62*, 1254-1266.

[102] L. D. Scheel, V. B. Perone, R. L. Larkin, R. E. Kupel, 'The isolation and characterization of two phototoxic furanocoumarins (psoralens) from diseased celery', *Biochemistry* **1963**, *2*, 1127-1131.

[103] S. Milosavljević, D. Jeremić, M. Nevešćanin, G. Radovanović, P. Živanović, B. Todorović, V. Slavkovska, V. Vajs, 'Furo-and pyranocoumarins from plant species *Angelica silvestris* and *Peucedanum austriacum*', *J. Serb. Chem. Soc.* **1993**, *12*, 997-1001.

[104] M. Mohammadi, M. Yousefi, Z. Habibi, A. Shafiee, 'Two new coumarins from the chloroform extract of *Angelica urumiensis* from Iran', *Chem. Pharm. Bull. (Tokyo).* **2010**, *58*, 546-548.

[105] J. Zhang, L. Li, C. Jiang, C. Xing, S.-H. Kim, J. Lu, 'Anti-cancer and other bioactivities of Korean *Angelica gigas* Nakai (AGN) and its major pyranocoumarin compounds', *Anticancer Agents Med. Chem.* **2012**, *12*, 1239-1254.

[106] J. W. Lee, C. Lee, Q. Jin, E. T. Yeon, D. Lee, S.-Y. Kim, S. B. Han, J. T. Hong, M. K. Lee, B. Y. Hwang, 'Pyranocoumarins from *Glehnia littoralis* inhibit the LPS-induced NO production in macrophage RAW 264.7 cells', *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2717-2719.

[107] S. M. Razavi, G. Imanzadeh, F. S. Jahed, G. Zarrini, 'Pyranocoumarins from *Zosima absinthifolia* (Vent) link roots', *Russ. J. Bioorg. Chem.* **2013**, *39*, 215-217.

[108] A. Tosun, E. K. Akkol, E. Yeşilada, 'Anti-inflammatory and antinociceptive activity of coumarins from *Seseli gummiferum* subsp. *corymbosum* (Apiaceae)', *Zeitschrift für Naturforschung C* **2009**, *64*, 56-62.

[109] M. H. Boskabady, A. Moghadas, 'Inhibitory effect of *Bunium persicum* on histamine (H1) receptors of guinea pig tracheal chains', *Phytomedicine* **2004**, *11*, 411-415.

[110] M. H. Boskabady, A. Moghaddas, 'Antihistaminic effect of *Bunium persicum* on guinea pig tracheal chains', *Iran. Biomed. J.* **2004**, *8*, 149-155.

[111] M. Zendehdel, Z. Torabi, S. Hassanpour, 'Antinociceptive mechanisms of *Bunium persicum* essential oil in the mouse writhing test: Role of opioidergic and histaminergic systems', *Vet. Med.* **2015**, *60*, 63-70.

[112] Z. K. Turkish Journal of Agriculture and ForestryShinwari, S. S. Gilani, 'Sustainable harvest of medicinal plants at Bulashbar Nullah, Astore (Northern Pakistan)', *J. Ethnopharmacol.* **2003**, *84*, 289-298.

[113] M. H. Boskabady, M. Talebi, 'Bronchodilatory and anticholinergic effects of *Carum carvi* on isolated guinea pig tracheal chains', *Med. J. Islam. Repub. Iran* **1999**, *12*, 345-351.

[114] R. Rahimi, M. R. Shams-Ardekani, M. Abdollahi, 'A review of the efficacy of traditional Iranian medicine for inflammatory bowel disease', *World J. Gastroenterol.* **2010**, *16*, 4504-4514.

[115] G. Amin, in '*Bunium persicum*', Deputy of Research Ministry of Health and Medical Education, Tehran, Iran, 1991.

[116] A. Zargari, 'Medicinal Plants ', Tehran University Publication, Tehran, 1996.

[117] S. Sultana, F. A. Ripa, K. Hamid, 'Comparative antioxidant activity study of some commonly used spices in Bangladesh', *Pak. J. Biol. Sci.* **2010**, *13*, 340-343.

[118] S. G. Agarwal, V. N. Vashist, C. K. Atal, 'Terpenes and other components from *Bunium cylindricum* seeds', *Phytochemistry* **1974**, *13*, 2024-2025.

[119] M. H. Aqili Khorasani, 'Makhzan al Adviah ', Safa Publication, Tehran, 1991.

[120] I. Teixidor-Toneu, G. J. Martin, A. Ouhammou, R. K. Puri, J. A. Hawkins, 'An ethnomedicinal survey of a Tashelhit-speaking community in the High Atlas, Morocco', *J. Ethnopharmacol.* **2016**, *188*, 96-110.

[121] A. Arabzadeh, A. Azadi, S. Daneshamooz, S. Karami, M. Rezaei, 'Anti-halitosis tooth paste: From Persian manuscripts toward Clinic', *Res. J. Pharmacog.* **2018**, *5*, 15-23.

[122] G. R. Talei, Z. Mosavi, 'Chemical composition and antibacterial activity of *Bunium persicum* from west of Iran', *Asian J. Chem.* **2009**, *21*, 4749-4754.

[123] T. Srivastava, S. Rajasekharan, D. Badola, D. J. A. s. o. l. Shah, 'An index of the available medicinal plants, used in Indian system of medicine from Jammu and Kashmir state', *Anc. Sci. Life.* **1986**, *6*, 49-63.

[124] K. Bhardwaj, B. Bhushan, R. Kumar, S. Guleria, H. Kumar, 'Ethnomedicinal remedy for gastrointestinal disorders in rural and remote areas of Jammu and Kashmir: A review', *Biol. Forum* **2019**, *11*, 137-148.

[125] M. Ahmad, M. P. Z. Khan, A. Mukhtar, M. Zafar, S. Sultana, S. Jahan, 'Ethnopharmacological survey on medicinal plants used in herbal drinks among the traditional communities of Pakistan', *J. Ethnopharmacol.* **2016**, *184*, 154-186.

[126] W. Younis, H. Asif, A. Sharif, H. Riaz, I. A. Bukhari, A. M. Assiri, 'Traditional medicinal plants used for respiratory disorders in Pakistan: a review of the ethno-medicinal and pharmacological evidence', *Chin. Med.* **2018**, *13*, 1-29.

[127] Z. Memariani, R. Moeini, S. S. Hamedi, N. Gorji, S. A. Mozaffarpur, 'Medicinal plants with antithrombotic property in Persian medicine: a mechanistic review', *J. Thromb. Thrombolysis* **2018**, *45*, 158-179.

[128] M. Mojahedi, M. Naseri, R. Majdzadeh, M. Keshavarz, M. Ebadini, E. Nazem, M. S. Isfeedvajani, 'Reliability and validity assessment of Mizaj questionnaire: a novel self-report scale in Iranian traditional medicine', *Iran Red Crescent Med. J.* **2014**, *16*, 1-11.

[129] Aziz-UL-Ikram, N. B. Zahra, Z. K. Shinwari, M. Qaiser, 'Ethnomedicinal review of folklore medicinal plants belonging to family Apiaceae of Pakistan', *Pak. J. Bot.* **2015**, *47*, 1007-1014.

[130] M. S. Amiri, M. R. Joharchi, 'Ethnobotanical investigation of traditional medicinal plants commercialized in the markets of Mashhad, Iran', *Avicenna J. Phytomedicine* **2013**, *3*, 254.

[131] S. Ahmed, M. M. Hasan, Z. A. Mahmood, 'Antiurolithiatic plants: Multidimensional pharmacology', *J. Pharmacogn. Phytochem.* **2016**, *5*, 4.

[132] S. W. Eisenman, D. E. Zaurov, L. Struwe, 'Medicinal plants of central Asia: Uzbekistan and Kyrgyzstan', Springer Science & Business Media, 2012.

[133] A. Ali, L. Badshah, F. Hussain, 'Ethnobotanical appraisal and conservation status of medicinal plants in Hindukush Range, District Swat, Pakistan', *J. Herbs, Spices Med. Plants* **2018**, *24*, 332-355.

[134] S. Parveen, U. Jan, A. Kamili, 'Importance of Himalayan medicinal plants and their conservation strategies', *Aust. J. Herb. Med.* **2013**, *25*, 63.

[135] A. Pieroni, A. Nedelcheva, A. Hajdari, B. Mustafa, B. Scaltriti, K. Cianfaglione, C. L. Quave, 'Local knowledge on plants and domestic remedies in the mountain villages of Peshkopia (Eastern Albania)', *J. Mt. Sci.* **2014**, *11*, 180-193.

[136] Ł. Łuczaj, M. Jug-Dujaković, K. Dolina, M. Jeričević, I. Vitasović-Kosić, 'The ethnobotany and biogeography of wild vegetables in the Adriatic islands', *J. Ethnobiology Ethnomedicine* **2019**, *15*, 1-17.

[137] F. Senouci, A. Ababou, M. Chouieb, 'Ethnobotanical survey of the medicinal plants used in the Southern Mediterranean. Case study: The region of Bissa (Northeastern Dahra Mountains, Algeria)', *Pharmacog. J.* **2019**, *11*, 647-659.

[138] M. D. Miara, H. Bendif, M. A. Hammou, I. Teixidor-Toneu, 'Ethnobotanical survey of medicinal plants used by nomadic peoples in the Algerian steppe', *J. Ethnopharmacol.* **2018**, *219*, 248-256.

[139] A. Clapham, T. Tutin, E. Warburg, in 'Flora of the British Isles ', London, United Kingdom, Cambridge University Press, 1962.

[140] P. Guarrera, V. Savo, 'Wild food plants used in traditional vegetable mixtures in Italy', *J. Ethnopharmacol.* **2016**, *185*, 202-234.

[141] G. Mattalia, C. L. Quave, A. Pieroni, 'Traditional uses of wild food and medicinal plants among Brigasc, Kyé, and Provençal communities on the Western Italian Alps', *Genet. Resour. Crop. Evol.* **2013**, *60*, 587-603.

[142] M. D. Miara, H. Bendif, K. Rebbas, B. Rabah, M. A. Hammou, F. Maggi, 'Medicinal plants and their traditional uses in the highland region of Bordj Bou Arreridj (Northeast Algeria)', *J. Herbal Med.* **2019**, *16*, 1-17.

[143] U. Cakilcioglu, S. Khatun, I. Turkoglu, S. Hayta, 'Ethnopharmacological survey of medicinal plants in Maden (Elazig-Turkey)', *J. Ethnopharmacol.* **2011**, *137*, 469-486.

[144] S. Ahmed, M. M. Hasan, Z. A. Mahmood, 'Urolithiasis management and treatment: Exploring historical vistas of Greco-arabic contribution', *J. Pharmacogn. Phytochem.* **2016**, *5*, 167.

[145] B. Benarba, L. Belabid, K. Righi, A. amine Bekkar, M. Elouissi, A. Khaldi, A. Hamimed, 'Ethnobotanical study of medicinal plants used by traditional healers in Mascara (North West of Algeria)', *J. Ethnopharmacol.* **2015**, *175*, 626-637.

[146] G. Benítez, M. González-Tejero, J. Molero-Mesa, 'Pharmaceutical ethnobotany in the western part of Granada province (southern Spain): Ethnopharmacological synthesis', *J. Ethnopharmacol.* **2010**, *129*, 87-105.

[147] S. Demirci, E. E. Özkan, S. Demirci, 'Ethnobotanical studies of some Apiaceae plants in Kahramanmaras and a review of their phytochemical studies', *Istanbul J. Pharm.* **2014**, *44*, 241-250.

[148] P. Feeny, in 'Plant apparency and chemical defense', Springer, 1976.

[149] C. Toniolo, M. Nicoletti, F. Maggi, A. Venditti, 'HPTLC determination of chemical composition variability in raw materials used in botanicals', *Nat. Prod. Res.* **2014**, *28*, 119-126.

[150] A. Venditti, C. Frezza, E. Trancanella, S. M. M. Zadeh, S. Foddai, F. Sciubba, M. Delfini, M. Serafini, A. Bianco, 'A new natural neo-clerodane from *Teucrium polium* L. collected in Northern Iran', *Ind. Crops Prod.* **2017**, *97*, 632-638.

[151] A. Venditti, 'Secondary metabolites from *Teucrium polium* L. collected in Southern Iran', *Arab. J. Med. Arom. Plants* **2017**, *3*, 108-123.

[152] C. Frezza, A. Venditti, G. Matrone, I. Serafini, S. Foddai, A. Bianco, M. Serafini, 'Iridoid glycosides and polyphenolic compounds from *Teucrium chamaedrys* L', *Nat. Prod. Res.* **2018**, *32*, 1583-1589.

[153] M. Zangiabadi, M. A. Sahari, M. Barzegar, H. Naghdi Badi, '*Zataria multiflora* and *Bunium persicum* essential oils as two natural antioxidants', *J. Med. Plants* **2012**, *11*, 8-21.

[154] A. H. Saeidnejad, M. Kafi, H. R. Khazaei, M. Pessarakli, 'Effects of drought stress on quantitative and qualitative yield and antioxidative activity of *Bunium persicum*', *Turk. J. Bot.* **2013**, *37*, 930-939.

[155] F. Sharafati Chaleshtori, M. Saholi, R. Sharafati Chaleshtori, 'Chemical composition, antioxidant and antibacterial activity of *Bunium persicum*, *Eucalyptus globulus*, and Rose water on multidrug-resistant *Listeria* species', *J. Evid. Based Integ. Med.* **2018**, *23*.

[156] A. Ehsani, M. Hashemi, S. S. Naghibi, S. Mohammadi, S. Khalili Sadaghiani, 'Properties of *Bunium persicum* essential oil and its application in Iranian white cheese against *Listeria monocytogenes* and *Escherichia coli* O157:H7', *J. Food Saf.* **2016**, *36*, 563-570.

[157] M. H. Meshkatalsadat, R. Badri, S. Zarei, 'Hydro-distillation extraction of volatile components of cultivated *Bunium luristanicum* Rech.f. from west of Iran', *Int. J. Pharm. Res.* **2009**, *1*, 129-131.

[158] I. Khan, H. Ahmad, N. Ali, B. Ahmad, H. Tanoli, 'Screening of *Bunium bulbocastanum* for antibacterial, antifungal, phytotoxic and haemagglutination activities', *Pak. J. Pharma. Sci.* **2013**, *26*, 787-791.

[159] S. Rabiey, H. Hosseini, M. Rezaei, 'The hurdle effect of *Bunium persicum* essential oil, smoke and NaCl for controlling the *Listeria monocytogenes* growth in fish model systems', *J. Food Saf.* **2013**, *33*, 137-144.

[160] E. Menghani, A. Pareek, R. S. Negi, C. K. Ojha, 'Search for antimicrobial potentials from certain Indian medicinal plants', *Res. J. Med. Plant* **2011**, *5*, 295-301.

[161] H. Nikaido, 'Molecular basis of bacterial outer membrane permeability revisited', *Microbiol. Mol. Biol. Rev.* **2003**, *67*, 593-656.

[162] S. Mehni, S. T. Zahrani, M. T. Sarvtin, F. Mojab, M. Mirzaei, H. Vazirnasab, 'Therapeutic effects of *Bunium perscicum* Boiss (Black Zira) on *Candida albicans vaginitis*', *Biomed. Pharmacol. J.* **2015**, *8*, 1103-1109.

[163] A. Ghasemi Pirbalouti, B. Hamedi, R. Abdizadeh, F. Malekpoor, 'Antifungal activity of the essential oil of Iranian medicinal plants', *J. Med. Plant Res.* **2011**, *5*, 5089-5093.

[164] T. Sekine, M. Sugano, A. Majid, Y. Fujii, 'Antifungal effects of volatile compounds from black zira (*Bunium persicum*) and other spices and herbs', *J. Chem. Ecol.* **2007**, *33*, 2123-2132.

[165] S. Meher, I. Ali, A. Sami, M. Ismail, N. Naheed, S. Khan, V. Ahmad, 'Screening of some medicinal plants for antibacterial activity against conjunctivitis', *J. Anim. Plant Sci.* **2017**, *27*, 2069-2074.

[166] H. Vatandoost, A. Rustaie, Z. Talaeian, M. R. Abai, F. Moradkhani, M. Vazirian, A. Hadjiakhoondi, M. R. Shams-Ardekani, M. Khanavi, 'Larvicidal activity of *Bunium persicum* essential oil and extract against malaria vector, *Anopheles stephensi*', *J. Arthropod-Borne Dis.* **2018**, *12*, 85-93.

[167] Anonymous, 'Instructions for Determining the Susceptibility or Resistance of Mosquito Larvae to Insecticides', World Health Organization, Geneva, 1981.

[168] J. L. McLaughlin, C.-J. Chang, D. L. Smith, in 'Bench-top Bioassays for the Discovery of Bioactive Natural Products: An Update', Ed. Atta-ur-Rahman, 1991.

[169] S. Naqvi, D. Sheikh, K. Usmanghani, M. Shameel, R. Sheikh, 'Screening of marine algae of Karachi for haemagglutinin activity', *Pak. J. Pharma. Sci.* **1992**, *5*, 129-138.

[170] A. Mandegary, M. Arab-Nozari, H. Ramiar, F. Sharififar, 'Anticonvulsant activity of the essential oil and methanolic extract of *Bunium persicum* (Boiss). B. Fedtsch', *J. Ethnopharmacol.* **2012**, *140*, 447-451.

[171] G. Statti, M. R. Loizzo, F. Nadjafi, F. Menichini, 'Hypoglycaemic activity of two spices extracts: *Rhus coriaria* L. and *Bunium persicum* Boiss', *Nat. Prod. Res.* **2006**, *20*, 882-886.

[172] M. Khaksari, M. Ahmadi, H. Najafipour, N. Shahrokhi, 'Effect of *Bunium persicum* aqueous extract plus endurance exercise on cardiorespiratory capacity and serum lipid profile', *Avicenna J. Phytomedicine* **2014**, *4*, 118-126.

[173] B. Adorjan, G. Buchbauer, 'Biological properties of essential oils: An updated review', *Flav. Fragr. J.* **2010**, *25*, 407-426.

[174] Middleton E, Jr., 'Biological properties of plant flavonoids: An overview', *Int. J. Pharmacogn.* **1996**, *34*, 344-348.

[175] K.-H. Wagner, I. Elmadfa, 'Biological relevance of terpenoids', *Ann. Nutr. Metab.* **2003**, *47*, 95-106.

[176] M. Gil, D. Wianowska, 'Chlorogenic acids–their properties, occurrence and analysis', *Annales UMCS Sectio AA (Chemia)* **2017**, *72*, 61-104.

[177] G. Pandino, F. L. Courts, S. Lombardo, G. Mauromicale, G. Williamson, 'Caffeoylquinic acids and flavonoids in the immature inflorescence of globe artichoke, wild cardoon, and cultivated cardoon', *J. Agric. Food Chem.* **2010**, *58*, 1026-1031.

[178] T. Akihisa, K. Kawashima, M. Orido, H. Akazawa, M. Matsumoto, A. Yamamoto, E. Ogihara, M. Fukatsu, H. Tokuda, J. Fuji, 'Antioxidative and melanogenesis-inhibitory activities of caffeoylquinic acids and other compounds from Moxa', *Chem. Biodivers.* **2013**, *10*, 313-327.