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REVIEW

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Chemical Constituents and Biological Properties of Genus *Doronicum* (Asteraceae)

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The genus *Doronicum*, belonging to tribe Senecioneae (Fam. Asteraceae), is found mainly in the Asia, Europe and North Africa. This genus of plant has always been used in traditional medicinal treatments due to the many biological properties shown such as killing parasitic worms and for relieving constipation, as well as to improve heart health, to alleviate pain and inflammation, to treat insect bites, etc. According to the World Flora the genus *Doronicum* contains 39 subordinate taxa.[1–3] The purpose of this article, which covers data published from 1970 to 2021 with more than 110 articles, aims to carry out a complete and critical review of the *Doronicum* genus, examining traditional uses and reporting the antioxidant, antimicrobial, anti-inflammatory and antitumor activity shown from crude extracts or essential oils, and from single isolated compounds. Furthermore, critical considerations of the published data have been highlighted by comparing them with the results obtained from species of other genus belonging to the Asteraceae family.

Keywords: *Doronicum* ssp. (Asteraceae), secondary metabolites, essential oils, ethnopharmacology, biological properties.

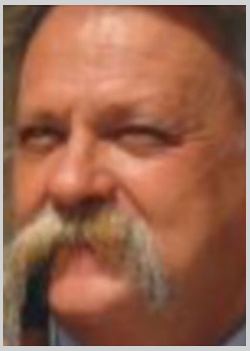
1. Introduction

The Doronicum genus which, now, by means of morphological, chemical and genetic studies, is part of the Senecioneae tribe (Fam. Asteraceae),[4–7] includes 26 species and 4 subspecies distributed in Asia, Europe and the North Africa,[7] from Iran to Turkey with some species growing in the Himalayas.[8]

All the members of this genus are perennial, rhizomatous herbs, bearing one to several radiate, yellow-flowered capitula. The involucre is composed of two or three rows of similar bracts. Cypselae are cylindric to obovate- cylindric with 10 longitudinal ribs and bear a pappus of white-tinted minutely scabrous capillary bristles. The plants occur in open or forested habitats from sea level up to 5000 m in elevation.[7]

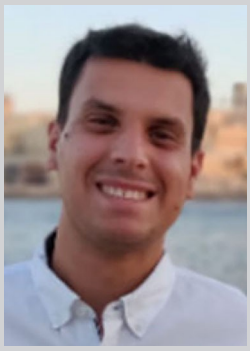
Several articles have been published both on the phytochemistry and biological properties of species belonging to this genus. In the present article, the volatile and non-volatile secondary metabolites, the biological activities and the traditional uses of *Doronicum* taxa are reviewed. *Table 1* reports the taxa of *Doronicum* investigated so far, their synonyms and the accepted botanical names.

Our research focused on the *Doronicum* terms, including all synonyms, and considering the chemical variability and multiple biological properties of the extracts and isolated molecules in this genus. Articles from the 1970s to the present day were considered, using PubMed, SciFinder, Science Direct, Scopus, Web of Science and Google Scholar as a search database. No restrictions have been set for languages.

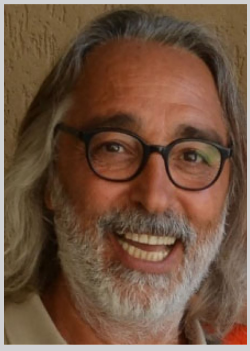


Prof. Maurizio Bruno completed his studies in Chemistry in 1980 at the University of Palermo. From 1985 to 1986 he worked at the Florida State University with Prof. Werner Herz and from 1987 to 1988 at the Imperial College, London, with Prof. Steven Ley. He was appointed to the faculty of Engineering as full professor of Organic Chemistry (2000-present). From 2002 he has been included in the ISI list as one of the most cited researchers in the world. In 2005 the President of the Italian Republic appointed him as 'Commendatore dell'Ordine al Merito della Repubblica Italiana' for his contributions to the scientific research. From 2010 to 2012 he was President of the Società Chimica Italiana - Sez. Sicilia. He works in natural organic products chemistry on natural and semi-synthetic terpenoids with antifeedant and insecticidal activities. Lately he is interested in sesquiterpenes from Compositae, in natural and semi-synthetic compounds with anti-HIV and cytotoxic activity and in the extraction and analysis of essential oils with antibacterial and antifungal properties to be applied also as food protectors. His interests include also investigations on plants used as food and the determination of their biological properties. He was editor of a thematic issue on terpenoids published in Natural Product Communications and he is co-editor of several international scientific journals. He is the author of more than 370 articles published in international journals and over 200 conference proceedings.

Aurora Modica studied Conservation and Restoration of Cultural Heritage at the University of Palermo, discussed a thesis about the restoration of ancient photographs and proposing an experimental study on a particular mechanism of cellulose degradation, called foxing. She's author or coauthor of seven research articles and eight conference presentations, about diagnostic analysis on cultural heritage, instrumental analytical techniques to identify the chemical composition and conservation state of photographic and article materials, organic waste recovery to obtain hand-made article or microcrystalline cellulose as filler for biodegradable polymer composites through green procedures, essential oils composition and properties. Is currently attending a post-graduate scholarship for research activities, entitled 'Development of experimentation protocols in the field of the health characterization of extracts from food matrices',



Natale Badalamenti completed his studies in Chemistry in 2018 at the University of Palermo. Between January and July 2019, he is a scholarship winner at the University of Malta, Dip. of Chemistry, under the supervision of Prof. Giovanna Bosica. He currently undertaking a PhD under the supervision of Dist. Prof. Maurizio Bruno and Prof. Antonella Maggio. He is the author of 17 scientific researches and speaker at three international congresses. His research interests include method and strategy development for the semi-synthesis of terpenoid natural products.



Prof. Vincenzo Ilardi Date of birth 06.01.961; degree in Agricultural Science in 1989. Associate Professor since 2004 at the School of Basic and Applied Sciences (formerly Faculty of Science) of the University of Palermo (disciplinary scientific sector 05/A1-Botany), at the Department of Earth and Marine Sciences (DISTEM). At the same University, he obtained the qualification of Doctor in 'Plant Resources' (XI cycle) in 1999, with a final dissertation entitled 'Surveys on Manna Ashes in Sicily aimed at the restore and conservation of the varietal heritage'. From 2001 to 2003, he held a research grant entitled 'Biological, autoecological and culture observations on exotic species of potential interest in wood arboriculture', at the Department of Botany (University of Palermo). As a professor, he worked within the Faculty of Science and of Architecture of the University of Palermo, where he held the courses in General Ecology, Plant Ecology, Landscape Ecology, Phytogeography, Management of protected areas, Utilization and improvement of forests and pastures, Ethnobotany, Environmental and Applied Botany.

Table 1. *Doronicum* taxa studied so far and their synonymous (accepted botanical name in bold).

Taxa	Synonymous	Ref.
***D. altaicum* Pall.**	*Arnica altaica* (Pall.) Turcz.; *Aronicum altaicum* (Pall.) DC.; *D. bargusinense* Serg.	[9]
***D. austriacum* Jacq.**		[10]
***D. austriacum* subsp. *giganteum* (Griseb.) Stoj. & Stef.**	*D. pardalianches* var. *giganteum* Griseb.; *D. orphanidis* Boiss.	[10]
D. bithynicum subsp. *sparsipilosum* J.R.Edm.	***D. macrophyllum* subsp. *sparsipilosum* (J.R.Edm.) Alv.Fern**	[9]
***D. carpathicum* (Griseb. & Schenk) Nyman**	*Aronicum carpathicum* (Griseb. & A.Schenk) Schur; *Aronicum scorpioides* var. *carpaticum* Griseb. & Schenk; *D. grandiflorum* subsp. *carpaticum* (Griseb. & A.Schenk) Rouy	[9]
***D. columnae* Ten.**	*D. cordifolium* Sternb. & Hoppe; *D. wulfenianum* Poir.	[10]
***D. corsicum* (Loisel.) Poir.**	*Arnica corsica* Loisel.; *Aronicum corsicum* (Loisel.) DC.	[10]
***D. grandiflorum* Lam.**	*D. halleri* Tausch; *D. portae* Chabert; *D. pyrenaicum* (Godr.) Rivas Mart.; *D. scorpioides* Lam.; *D. viscosum* (Freyn & Gaut.) Nyman; *Aronicum scorpioides* (Lam.) W. D. J. Koch; *Aronicum viscosum* Freyn & Gaut.; *Aronicum scorpioides* var. *pyrenaicum* Godr.	[10]
D. hookeri C.B.Clarke ex Hook.f	***Nannoglottis hookeri* (Hook.f.) Kitam**	[9]
***D. hungaricum* Rchb. f.**	*D. longifolium* Griseb. & Schenk; *D. hungaricum* subsp. *praehungaricum* Pénzes	[10]
D. macrolepis Freyn & Sint.	***D. macrophyllum* Fish**	[10]
***D. macrophyllum* Fish**	*D. balansae* Cavill.; *D. macrolepis* Freyn & Sint.	[10]
***D. oblongifolium* DC.**		[10]
***D. orientale* Hoffm.**	*D. caucasicum* M. Bieb.; *Arnica cordata* Wulfen	[9]
***D. pardalianches* L.**	*D. cordatum* Lam; *D. matthioli* Tausch; *Arnica scorpioides* L.	[10]
D. roylei DC.	***D. kamaonense* (DC.) Alv.Fern.**; *Fullartonia kamaonensis* DC.	[9]

2. Compounds Isolated from *Doronicum* Species

2.1. Non Volatile Compounds

Aerial part and root extracts of the *Doronicum* species have been shown to contain pyrrolizidine alkaloids, flavonoids, terpenes and aromatic compounds such as benzofurans and thymol derivatives with esters groups (acetyl, isobutyryl, angeloyl, 2-methylbutyryl and isovaleryl). The occurrence of these metabolites is reported in *Table 2*, whereas their structures are depicted in *Figures 1–4*.

The thymol derivatives are largely present in the family Asteraceae,[29] particularly within the tribes Senecioneae, Eupatorieae, Inuleae and Helenieae. The occurrence thymyl and 8,9-dehydrothymyl isobutyrate in the extract of *Arnica amplexicaulis*[30] and of 10-acetoxy-8,9-epoxythymyl isobutyrate from *Arnica sachalinensis*, two species closely related to *Doronicum*[31–33] has been reported. Other thymol derivatives containing acetyl, isobutyryl, tigloyl, 2-methylbutyryl and isovaleryl groups in their structures have been shown to be present in the genus *Schkuhria*,[34] *Inula*,[35–37] *Stoebe*,[38] *Marshallia*,[39] *Eriophyllum*,[40] *Mikania*,[41] *Ageratina* and *Sclerolepis*.[42–44] These derivatives were largely represented in some *Doronicum* taxa: *D. austriacum* (**24**, **25**),[11] *D. corsicum* (**22**, **46**, **48**–**51**),[16] *D. hungaricum* (**28**–**31**),[19] *D. macrophyllum* (**24**–**26**, **43**),[21] and *D. pardalianches* (**20**–**21**, **23**–**27**, **47**–**49**) (*Figure 2*).[20] On the other hand *D. grandiflorum*,[17] *D. hookeri*,[18] *D. oblongifolium*,[24] and *D. orientale*,[15,26] devoid of thymol derivatives, were shown to be rich in flavonoids. Flavonoids were also present in *D. pardalianches*,[15] *D. macrophyllum*[24] and *D. corsicum*.[15] It is quite interesting to evidence the presence of tremetone derivatives (**32**–**42**) in *D. austriacum*,[11–12] *D. hungaricum*,[19] *D. macrophyllum*[21] and *D. pardalianches*[20] and of pyrrolyzidine alkaloids (**70**–**73**) in *D. columnae*[14] and *D. macrophyllum* (*Figure 3*).[22]

Finally, two coumarins (**79** and **80**) (*Figure 3*) were identified in the roots of *D. macrophyllum*[25] and several carotenoids (**81**–**88**) were detected in the flowers of *D. carpathicum* (*Figure 4*).[13]

2.2. Essential Oils

Regarding the composition of the essential oils obtained from different parts of *Doronicum* species of different geographic origin, several articles have been published. *Table 3* reports the composition of the taxa studied so far. Leaves and flowers, together with all the aerial parts, are the different parts used for the hydrodistillation of essential oils, characterized mainly by a high content of sesquiterpene hydrocarbons. In

Table 2. Metabolites of *Doronicum* taxa.

Taxa	Origin	P.*	Flavonoids	Aromatic	Terpenes	Alkaloids	Other	Ref.
D. austriacum	n.r.	n.r		**24**, **25**, **35**, **36**, **39**, **40**			**74**	[11]
	Austria	r.		**32**–**34**				[12]
D. carpathicum	Romania	fl.					**81**–**88**	[13]
D. columnae	Poland	lv.				**73**		[14]
D. corsicum	France	a.p.	**9**, **16**					[15]
	France	a.p.		**22**, **46**, **48**–**51**				[16]
D. grandiflorum	France	a.p.	**2**, **4**, **5**, **6**, **8**, **10**–**15**					[15]
	France	a.p.		**44**, **45**				[17]
D. hookeri	India	fl.	**3**, **7**, **19**					[18]
D. hungaricum	Germany	r.		**28**–**31**, **35**, **39**			**74**	[19]
	Germany	a.p.		**29**–**31**	**66**			[19]
D. macrophyllum	Germany	a.p			**65**			[20]
	Germany	r.		**24**–**26**, **33**, **37**, **39**–**41**	**57**, **58**, **63**		**74**	[21]
	Germany	a.p		**37**–**40**, **42**, **43**	**57**, **58**, **60**, **62**, **63**, **68**, **69**		**74**	[21]
	Azerbaidzhan	r.				**70**–**72**		[22]
	Azerbaidzhan	r.			**67**			[23]
	Azerbaidzhan	a.p.	**1**, **10**, **13**, **14**, **16**					[24]
	Azerbaidzhan	r.					**79**, **80**	[25]
D. oblongifolium	n.r.	a.p.	**13**, **14**					[24]
D. orientale	France	a.p.	**9**, **16**					[15]
	Turkey	a.p.	**13**, **17**, **18**	**54**–**56**				[26]
D. pardalianches	Germany	r.		**20**, **21**, **23**–**27**, **33**, **34**, **37**, **39**–**42**, **47**–**49**, **52**, **53**	**57**–**59**, **62**, **65**		**74**	[20]
	Germany	a.p		**36**-**38**, **40**, **42**, **53**	**57**, **60**–**65**		**74**	[20]
	France	a.p.	**9**, **16**					[15]
	Italy	r.					**75**–**78**	[27]
	Italy	lv.					**75**, **76**, **78**	[27]
	–	r.				**72**		[28]

*Plant part = vegetative parts; r. = roots; a.p. = aerial parts; lv. = leaves; fl = flowers.

fact it was the main class in *D. austriacum* subsp. *giganteum*,[46] *D. bithynicum* subsp. *sparsipilosum*,[47] *D. macrolepis*[47,48] and *D. orientale*[47] with germacrene D, (*E*)-β-caryophyllene, α-humulene and farnesene derivative as main components.

Only the oil of *D. corsicum*[16] was shown to be rich of oxygenated monoterpenes whereas a high content of oxygenated sesquiterpenes was detected in *D. altaicum*.[45]

3. Ethnopharmacology and Biological Properties

Root extracts of *D. austriacum* were historically used in alpine medicine for killing parasitic worms and for relieving constipation, as well as to improve heart health.[49] Macrophages J774A.1 and C6 astrocytes has been used to assess the anti-inflammatory and antioxidant strength of dichloromethane extract and of its principal compounds. Ratings of nitrotyrosine formation, nitric oxide and reactive oxygen species has been considered in the same study. Furthermore, 3-(4,5-dimethyltiazol-2yl)-2,5-phenyl-2H-tetrazolium bromide (MTT) tests were carried on studying the anti-proliferative activity, showing meaningful results in inhibiting

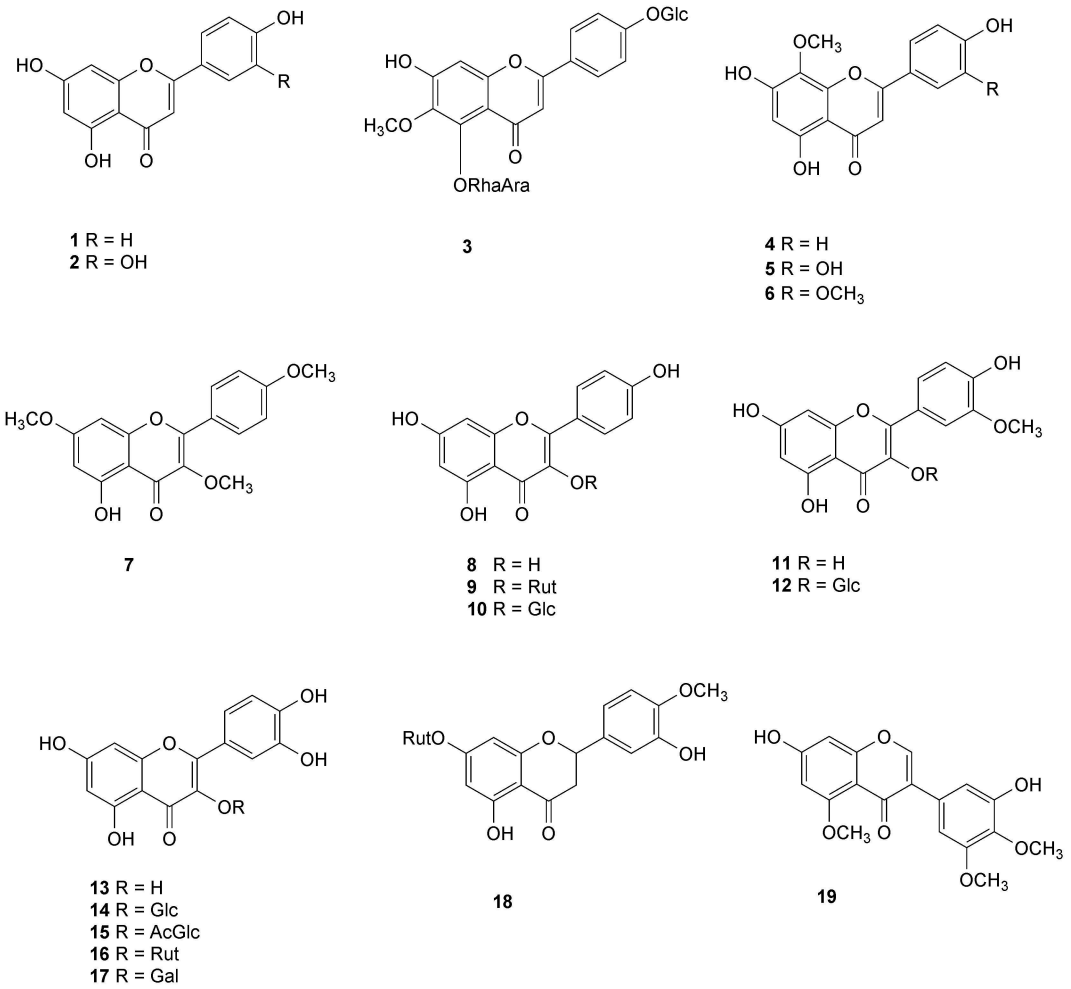


Figure 1. Chemical structures of flavonoids **1**–**19** isolated from species of the genus *Doronicum*.

pro-oxidative and pro-inflammatory mediators. Nitric oxide and reactive oxygen species were inhibited by the tremetone derivative **32**–**34**, found in the extract, especially 6,12-dihydroxy-(−)-2*S*-tremetone (**32**) (*Figure 2*). The activity of benzofurans is probably responsible for its anti-inflammatory properties. *D. austriacum* extract has been proved not to interest cellular viability.[12] Tremetone derivatives, occurring in *Doronicum* taxa (*Table 2*), are largely and exclusively represented also in several other genus of plants of Asteraceae family and many of them have been shown to possess very interesting biological properties. Their occurrence is listed in *Table 4* and *Figures 5*–*7* report their structures.

Ageratina altissima (syn. *Eupatorium rugosum*, *E. urticaefolium*), known as 'white snakeroot', and *Isocoma pluriflora*, (syn. *Aplopappus heterophyllus*, *Isocoma wrightii*), known as 'rayless goldenrod' were shown to cause 'trembles' and 'milk sickness' in livestock and humans by consuming milk from affected animals, respectively.[77] It was noted that after ingesting the plant, for several days, a significant number of animals developed a disease characterized by reluctance to move and fine muscle tremors of the nose, flanks and legs, especially after exercise or activity. The affected animal often has tachypnea, tachycardia, a stiff gait and altered posture because poisoned animals stand in an arched back position. Nursing young often develop the disease before their dam as the toxins are

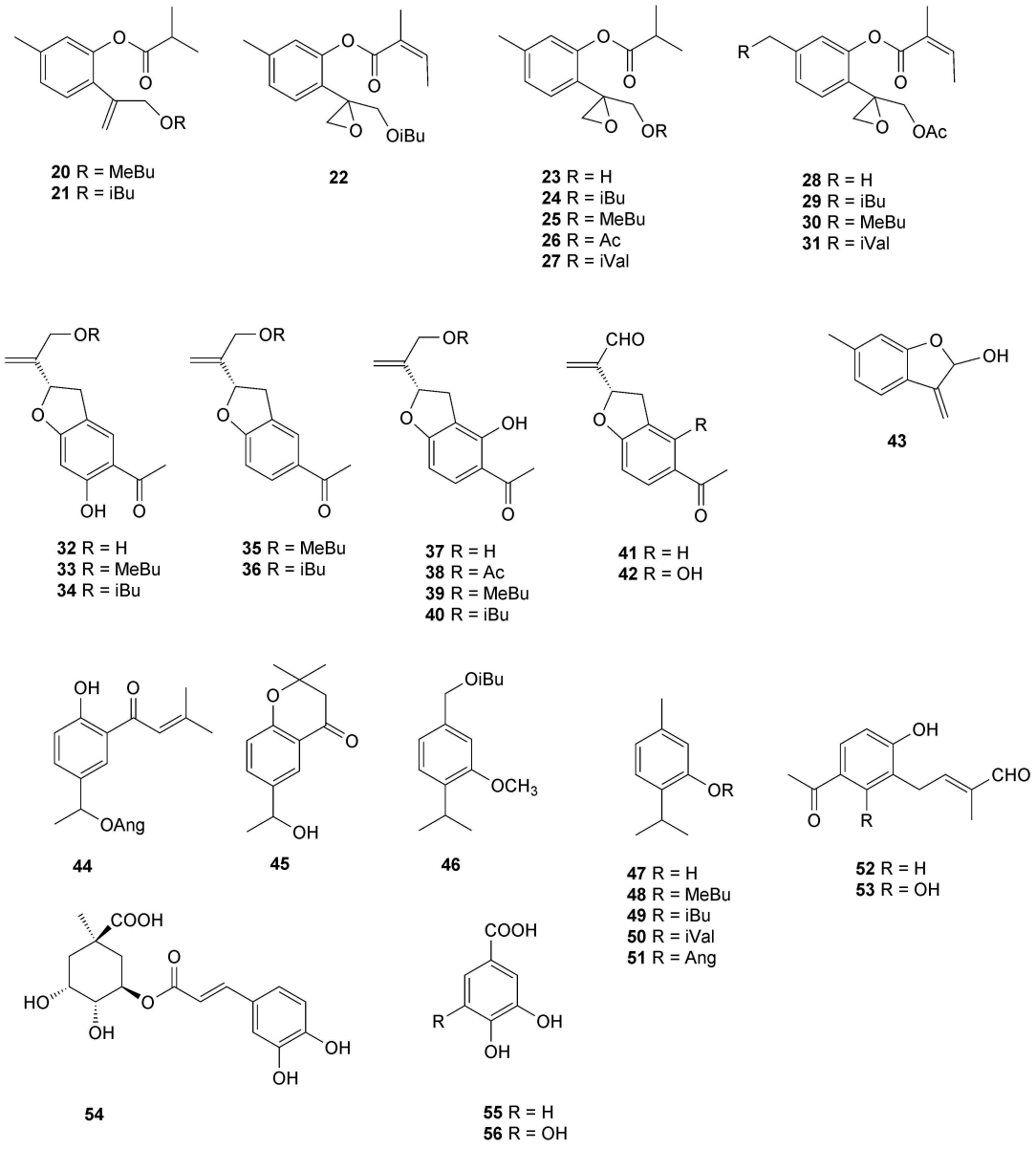


Figure 2. Chemical structures of aromatic compounds **20**–**56** isolated from species of the genus *Doronicum*.

eliminated through the milk. It was discovered in the 1920s that the toxin in question was tremetol, which later was demonstrated to be a complex mixture of alcohols and ketones, including benzofuran ketones, such as 3-oxyangeloyl-tremetone (**92**), tremetone (**89**), dehydrotremetone (**162**), and 6-hydroxytremetone (**90**)[83] and the last three of them were shown to be all toxic in the goldfish bioassay (*Figure 5*).[84]

Tremetone (**89**), isolated from white snakeroot was toxic to murine melanoma ($B16F_1$) cells and five other mammalian cell lines, deducing that it could be the toxic component in both white snakeroot and rayless goldenrod. It is noteworthy that tremetone (**89**) is unstable and convert to nontoxic dehydrotremetone (**162**) in dried plant and plant extracts. This could be the reason why toxicity of white snakeroot and rayless goldenrod it is a sporadic and unpredictable event and doesnot always occur.[85–87] An interesting evidence is that neither sheep nor cockerels developed any disease when treated with synthetic tremetone.[84,88]

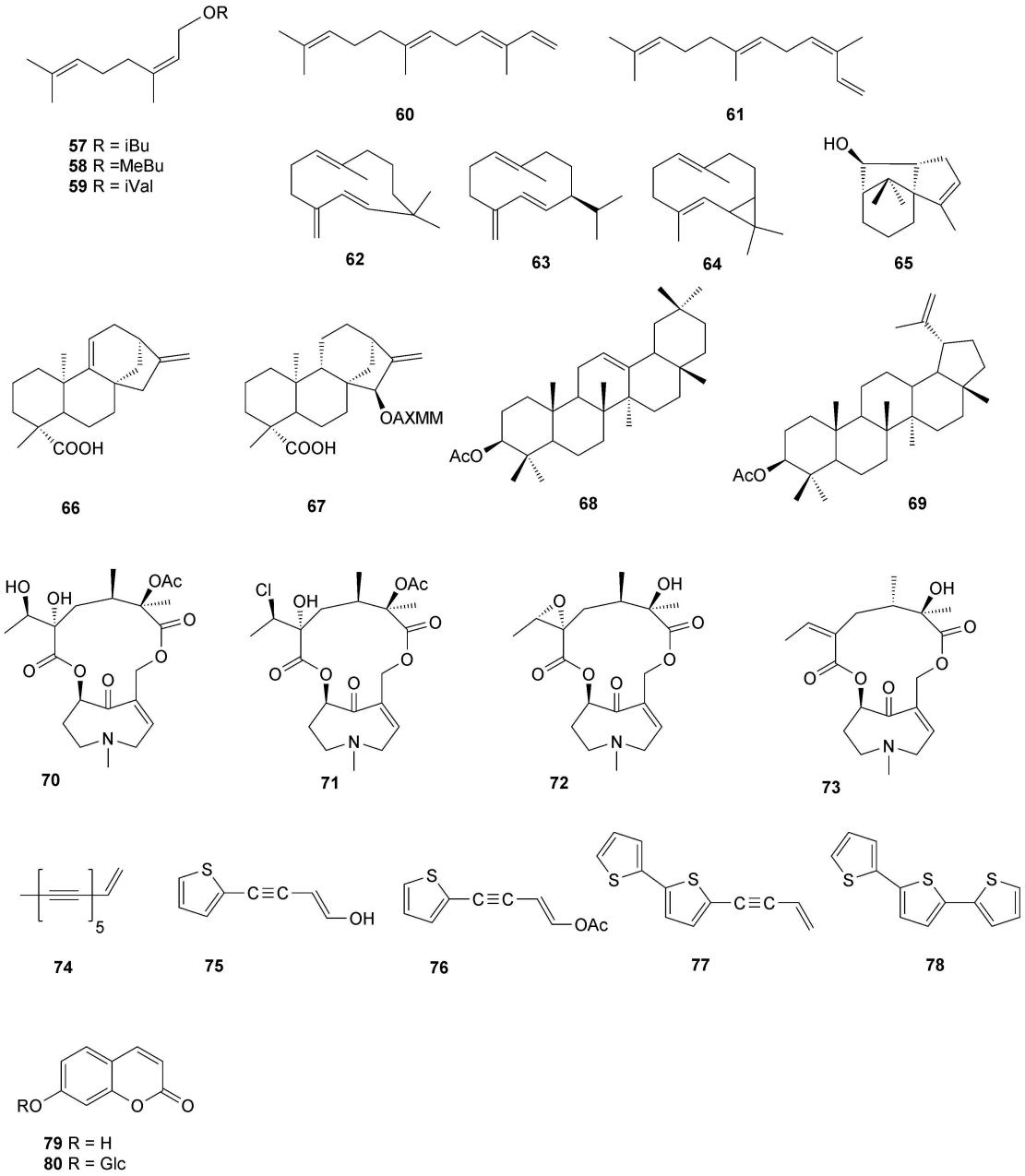


Figure 3. Chemical structures of terpenoids **57**–**69**, alkaloids **70**–**73** and compunds of other classes **74**–**80** isolated from species of the genus *Doronicum*.

On the other hands, studies with benzopyrans and benzofurans isolated from this plant showed that dehydrotremetone (**162**) has a notable larvicidal effect against the dengue vector *Aedes aegypti* L. (0.03 ± 0.001 ng/μL).[89]

Another study on extracts from the aerial parts of some *Asteraceae* collected in Chile tested the plant growth inhibitory effects of the tremetones **89**, **106**, **107** and **115**–**117** (*Figure 5*), measuring the effects on seedling growth, germination, and respiration of ryegrass, lettuce, green tomato, and red clover weedy target species. Like some other compounds detected in the extract, also tremetones **89**, **106**, **107** and **115**–**117** proved to interfere with the dicot preemergence properties, showing effects on radicle inhibition analogous to those of ovatifolin, a known natural growth

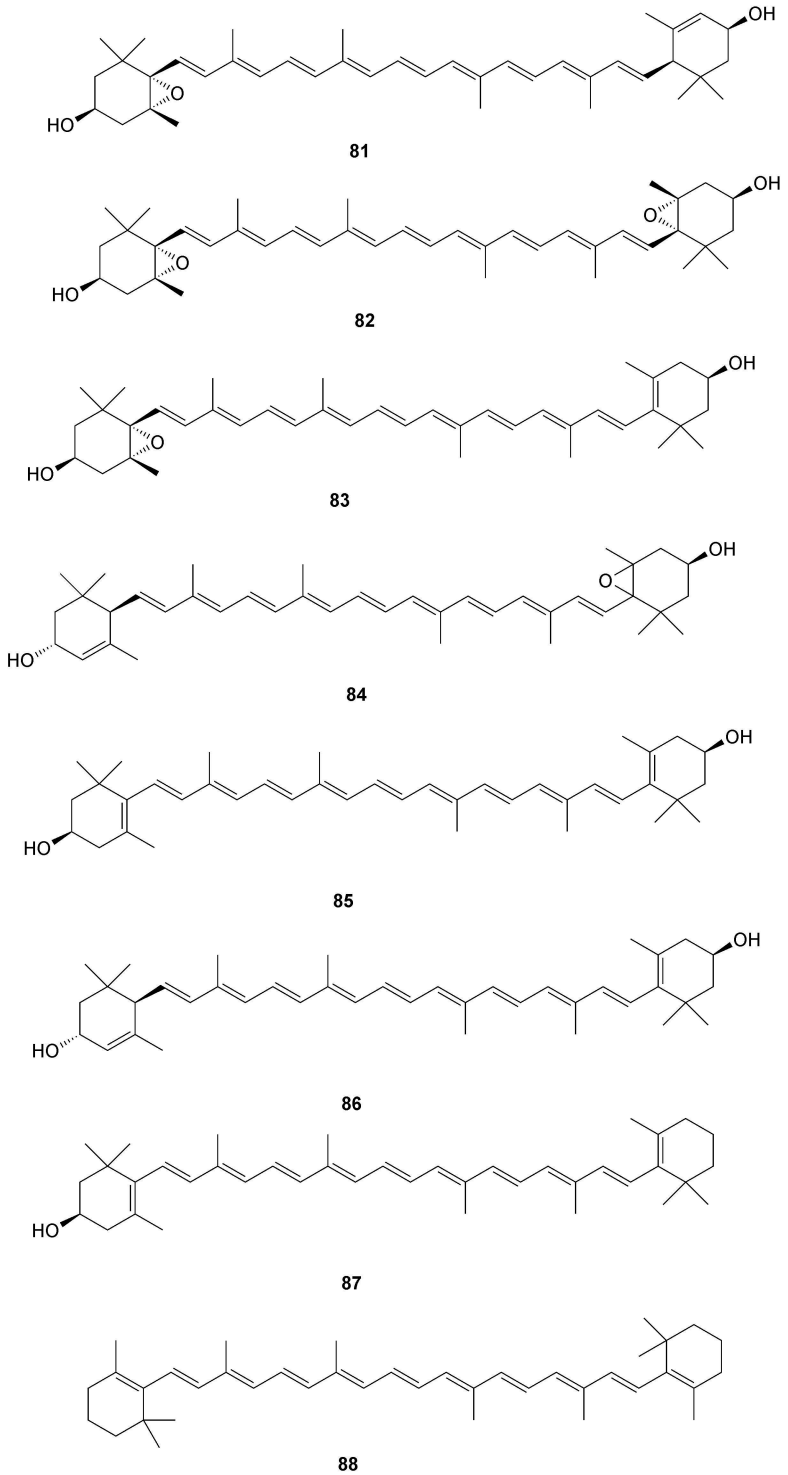


Figure 4. Chemical structures of carotenoids **81**–**88** isolated from *Doronicum carpathicum* (Griseb. & Schenk) Nyman.

inhibitor. Moreover, tremetones also showed inhibition of H^+ uptake and oxygen uptake respiration in isolated chloroplasts and mitochondria, respectively.[57]

Allelopathy is a biological phenomenon by which some bioactive molecules or biochemicals, produced by an organism, have the power to influence the germination, growth and reproduction on

Table 3. Main components (>2%) and classes of the essential oils of *Doronicum* taxa.

Taxa	Origin	Parts	Compounds	MH	OM	SH	OS	O	Ref.
D. altaicum	Kazakhstan	ap, MSD-SPME	eupatoriochromene (38.0), 8-acetyl-7-hydroxy-2,2-dimethyl-2H-chromene (8.2, eudesma-4(15),7-dien-1-ol (6.0), hexahydrofarnesyl acetone (3.4), spathulenol (2.7), torilenol (2.4), propionic acid (2.4).	0	4.4	4.7	73.5	6.6	[45]
D. austriacum subsp. *ganteum*	Serbia	ap, HD	germacrene D (50.8), β-caryophyllene (9.1), α-humulene (5.5), (*Z*,*E*)-α-farnesene (5.2), germacrene D-4-ol (3.9), bicyclogermacrene (3.8), (*E*,*E*)-α-farnesene (2.9), (*Z*)-3-hexenol (2.1).	0	0.3	81.6	11.1	0.1	[46]
D. bithynicum subsp. *sparsipilosum*	Turkey, Aladag-Bolu	fl, HD	(*E*)-β-farnesene (47.5); β-elemene (12.4), α-zingiberene (11.3), (*E*)-caryophyllene (9.1), germacrene D (7.5), selin-11-en-4-α-ol (4.2).	0	0	88.7	5.1	3.9	[47]
	Turkey, Aladag-Bolu	lv, st, HD	(*E*)-β-farnesene (55.4); α-zingiberene (11.7), β-elemene (5.8), (*E*)-caryophyllene (7.6), selin-11-en-4-α-ol (5.3), germacrene D (5.7).	0.1	0.5	88.4	6.1	1.3	[47]
D. corsicum	Corsica	ap, HD	modhephene (11.6), (*E*)-β-caryophyllene (9.9), 10-isobutyryloxy-8,9-epoxythymol angelate (9.8), thymyl angelate (8.7), thymyl methyl oxide (4.6), 7-β-(H)-silphiperfol-5-ene (3.4), 2,5-dimethoxycymene (2.7), thymyl 2-methylbutyrate (2.5), germacrene D (2.1).	0.5	36.7	38.2	4.1	0.9	[16]
D. macrolepis	Turkey, Artabel/ Gümüşhane	ap, HD	(*E*,*E*)-α-farnesene (21.5), *trans*-β-ocimene (12.8), δ-cadinene (9.5), caryophyllene oxide (8.2), α-cubebene (6.4), thymol (4.4), oplopenone (3.7), β-phellandrene (2.7), pentadecanal (2.7), 2-pentyl-furan (2.5).	18.4	5.5	43.3	13.6	10.8	[48]
	Turkey, Uzungöl-Trabzon	fl, HD	(*E*)-caryophyllene (24.3), germacrene D (11.7), α-humulene (12.3), methyl linoleate (5.1), methyl tetradecanoate (3.7), caryophyllene oxide (3.5), α-copaene (3.3), tetradecanoic acid (3.3), α-pinene (2.6), methyl hexadecanoate (2.6), α-phellandrene (2.4), (*Z*)-β-ocimene (2.4), β-pinene (2.0).	9.4	0.7	54.7	5.4	19.1	[47]
	Turkey, Uzungöl-Trabzon	lv, st, HD	(*E*)-caryophyllene (52.7), germacrene D (10.8), α-humulene (10.7), caryophyllene oxide (4.9), α-cadinol (2.1).	1.1	0.6	79.6	7.0	2.6	[47]
D. orientale	Turkey, Abant	fl, HD	(*E*)-β-farnesene (41.1); α-zingiberene (18.7), β-elemene (4.9), germacrene D (8.6), (*E*)-caryophyllene (8.2), (*E*,*E*)-α-farnesene (4.0).	0	0.1	86.0	1.6	2.5	[47]
	Turkey, Abant	lv, st, HD	(*E*)-β-farnesene (35.7); germacrene D (20.5), β-elemene (11.9), selin-11-en-4-α-ol (10.4), (*E*)-caryophyllene (7.8), α-zingiberene (2.6).	0	0.3	88.7	11.2	1.6	[47]

ap = aerial parts; fl = flowers; lv = leaves; st = stems; HD = hydrodistillation; MSD-SPME = microsteam distillation with solid-phase microextraction; MH = monoterpene hydrocarbons; OM = oxygenated monoterpenes; SH = sesquiterpene hydrocarbons; OS = oxygenated sesquiterpenes; O = others.

another.[90,91] Tremetones are among those compounds known as mitochondrial respiration inhibitors, partially inhibiting ATP synthesis, H^+-uptake, photosystem II, and electron transport in a concentration-dependent manner from 1 to 500 mm. Likely, the presence of an oxygenated function at certain strategic positions (hydroxy, methoxy and epoxy substituents) significantly enhances the inhibitory effects of these compounds as energetic inhibitors.[57]

On the other hand tremetone derivatives can have different properties, some of which are non-toxic and with good potential as promising drugs. For example, a recent study in mouse model proved that *p*-coumaroyloxytremetone (**153**) has gastroprotective activity (76%), higher than the control drug lansoprazole (72%).[76]

Some tests with tremetone (**89**) and methoxytremetone (**103**) showed morphine-like analgesic properties. A decrease of the analgesic effect in animals that have previously been injected with the morphine antagonist naloxone suggests a potential role for these compounds on opiate receptors, even

Table 4. Occurrence of tremetone derivatives in Asteraceae taxa.

Species	Compounds	Ref.
Ageratina altissima (L.) R.M.King & H.Rob ***(syn. Eupatorium rugosum Houtt.; E. urticaefolium Reichard)*** White Snakeroot	**89**, **162**, **90**, **91**, **92**	[50,51]
	89, **162**, **90**, **171**	[52]
Haplopappus heterophyllus (A. Gray) S.F.Blake (syn. *Isocoma pluriflora* (Torr. & A. Gray) Greene, *Isocoma wrightii* A. Gray) Rayless goldenrod	**89**, **162**, **90**, **92**	[50,51,53]
	91, **92**, **89**, **162**, **118**, **168**	[54]
Anaphalis sinica Hance	**119**	[55]
Aster exilis Elliot	**130**	[56]
Baccharis sp.	**89**, **115**, **117**, **106**, **107**, **116**	[57]
Bahianthus viscidus (Baker) R.M.King & H.Rob	**123**, **124**, **127**, **128**, **129**, **163**	[58]
Campuluclinium megacephalum (Mart. ex Baker) R.M.King & H.Rob.	**110**	[59]
Critonia quadrangularis (DC.) R.M.King & H.Rob.	**148**	[60]
Disynaphia halimifolia (DC.) R.M.King & H.Rob.	**133**, **134**, **135**, **164**	[61]
Encelia canescens Lam.	**163**, **93**, **94**, **113**, **166**	[62]
Eupatoriadelphus fistulosis(Barret.) K. et R,	**163**, **167**, **132**, **131**	[63]
Fleishmanniopsis leucocephala (Benth) K. et R.	**169**, **159**	[63]
Grosvenoria rimbachii (B.L.Rob.) R.M.King & H.Rob.	**93**, **95**, **96**, **97**, **98**, **99**, **100**, **101**, **102**	[64]
Helianthella quinquenervis (Hook.) A.Gray	**103**, **105**	[65]
Helichrysum italicum subsp. *microphyllum* (Willd.) Nyman	**108**, **109**, **111**, **112**	[66]
Helichrysum srirlingii F. Mucll.	**149**	[67]
Heliopsis helianthoides (L.) Sweet	**170**	[68]
Ligularia przewalskii (Maxim.) Diels	**104**	[69]
Madia sativa Molina	**158**	[70]
Microglossa pyrifolia (Lam.) Kuntze	**160**, **161**, **154**–**157**	[71]
Minuria leptophylla DC.	**138**–**144**	[72]
Morithamnus crassus R.M.King, H.Rob. & G.M.Barroso	**120**–**126**, **163**	[73]
Ophryosporus axilliflorus (Griseb.) Hieron.	**145**, **146**, **147**	[74]
Ophryosporus heptanthus (Sch.Bip. ex Wedd.) R.M.King & H.Rob.	**90**	[75]
Parastrephia quadrangularis (Meyen) Cabrera	**151**, **152**	[76]
Parastrephia lepidophylla (Wedd.) Cabrera	**89**, **162**, **90**, **163**, **92**, **103**	[77]
	89, **103**, **153**	[78]
Platypodanthera melissaefolia (DC.) R.M.King & H.Rob.	**114**	[79]
Symphyopappus reticulatus Baker	**136**, **137**, **165**	[80]
Verbesina eggersii Hieron.	**169**	[81]
Xenophyllum poposum (Phil.) V.A.Funk	**90**	[82]

though its mode of action it is not still perfectly clear.[77]

Tremetone (**89**) also showed extremely anti-inflammatory activity, confirming that acetophenones have notable bioactivities acting as leukotriene antagonist.[74]

Antibacterial properties are another interesting feature of some tremetone derivatives and in particular 6-hydroxytremetone (**90**) proved its efficacy against four fungal strains (*Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton rubrum*) and also a bacterial one, that is *Stafhyloccoccus aureus*.[82] Also the antifungal properties of the tremetone derivative **119** against *Valsa mali*, *Elsinoe ampelina* and *Gibberella saubinetii* was determined and compared to the commercial fungicide carbendazim.[55]

Himalayan traditional medicine proposes roots of *D. hookeri* Hook (Leopardi's Bane) to make cardiac and nervine preparations.[92,93] Grown in Lachen, Tungu and Sikkim, Nepal, Bhutan, Tibet between 12,000 to 14,000 ft, its roots are known as '*Darunaj-aqrabi*' in Unani. It is also used in traditional folk medicine as exhilarant and to treat gastric problems, like meteorism.[92] The methanolic extract of *D. hookeri* roots showed free radical scavenging, antioxidant and reducing activities, due to high phenolic content. In particular, scavenging is similar to the standard BHT

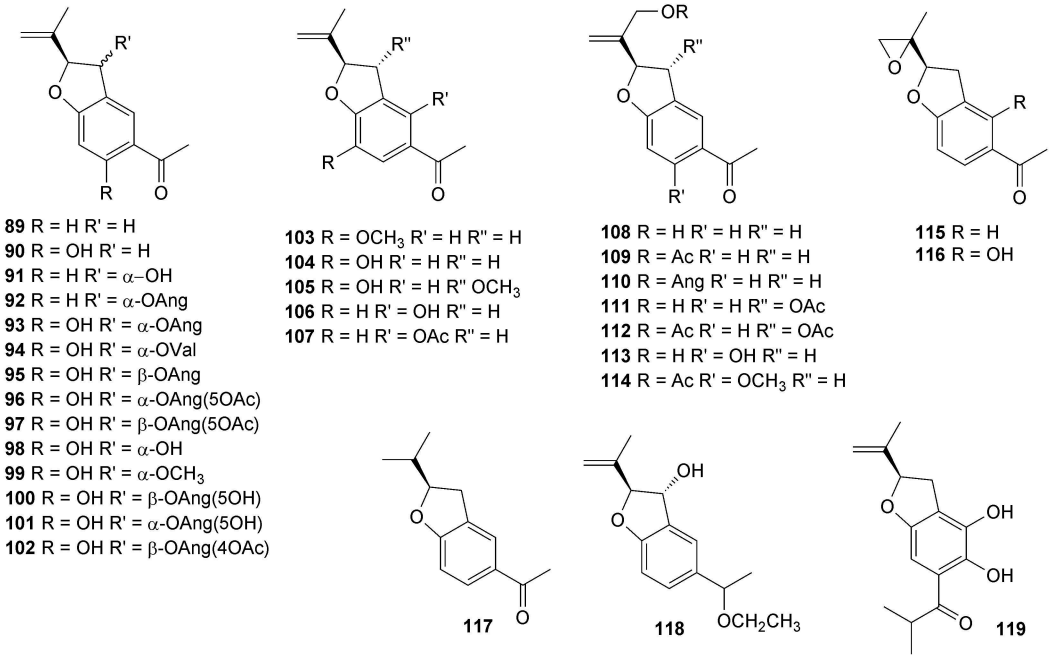


Figure 5. Chemical structures of tremetone derivatives **89**–**119** isolated from Asteraceae species.

(butylated hydroxytoluene) (~85%) at concentration 0.5 mg/mL in DPPH (2,2-diphenyl-1-picryhydrazyl) assay, while the inhibition to azinobis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt radical cation ($ATBS^+$) at concentration above 0.3 mg/mL is more than 90%.[94] On the contrary, dichloromethane extract shows a lower reducing power activity, although has high level of flavonoids and proved its efficiency in chelating metals (78.684 ± 0.659% at 0.5 mg/mL), and in scavenging activities of nitric oxide (52.232 ± 0.934% at 0.15 mg/mL) and superoxide radical (59.882 ± 0.772% at 0.5 mg/mL). Comparing different *D. hookeri* roots extracts it turns out that the dichloromethane and methanolic extracts show high free radical scavenging and reducing activities and DHME high total antioxidant capacity and ferric antioxidant power values, but methanol is confirmed to be the most promising way to isolate antioxidative compounds.[94] The same extracts also were demonstrated to have efficient antimicrobial activities against *Candida albicans* (MTCC 10231) and *Saccharomyces cerevisiae* (ATCC 9763) (500 μg/mL).[95,96]

Another interesting species of *Doronicum* with various medical applications, growing wild in Turkey, is *D. macrolepis*.[97] Its essential oil has been shown to have good antioxidant and antimicrobial properties, for example against *E. coli* (at 4 mg/mL), *E. faecium*, *Y. pseudotuberculosis*, *C. albicans* and *C. tropicalis* (at 32 mg/mL), and it is also capable of inhibiting enzymes activity. Flowers ethyl acetate extract (262.4 mg trolox equivalent/g (TE/g) of extract) of *D. macrolepis* is effective in scavenging using ABTS method, while stems ethanol extract (486.5 mg TE/g of extract) and roots ethyl acetate extract (480.6 mg TE/g of extract) has given good results using DPPH method. Furthermore, flowers ethyl acetate extract can inhibit α-amylase, flowers ethanol extract α-glucosidase and stems ethyl acetate extract cholinesterase.[48]

In Afyonkarahisar, Inner-West Anatolia, flowers and leaves of *Doronicum orientale* Hoffm. Sarıçiçek were used as fodder or bait for animals.[98] Roots of the same plant, also called *'Tiger herb'*, has been used fresh to treat infertility,[99] while decoction of aerial parts of *D. orientale* Hoffm. has been used as diuretic.[100] The methanol extract of Turkish *D. orientale* could represent a valid alternative when dealing with oxidative stress, thanks to its high levels of hesperidin (**18**), chlorogenic acid (**54**), hyperoside (**17**), protocatechuic acid (**55**), gallic acid (**56**) and quercetin (**13**).[26] Other studies reported the antioxidant properties of *D. orientale*[101] and also showed to be capable of inhibit *Streptococcus pyogenes*, using both aqueous and ethanol extracts.[102]

Some other *Doronicum* species have been reported to have significant ethno-biological properties. In Spain, a lotion called '*arnica*' made from *D. grandiflo-*

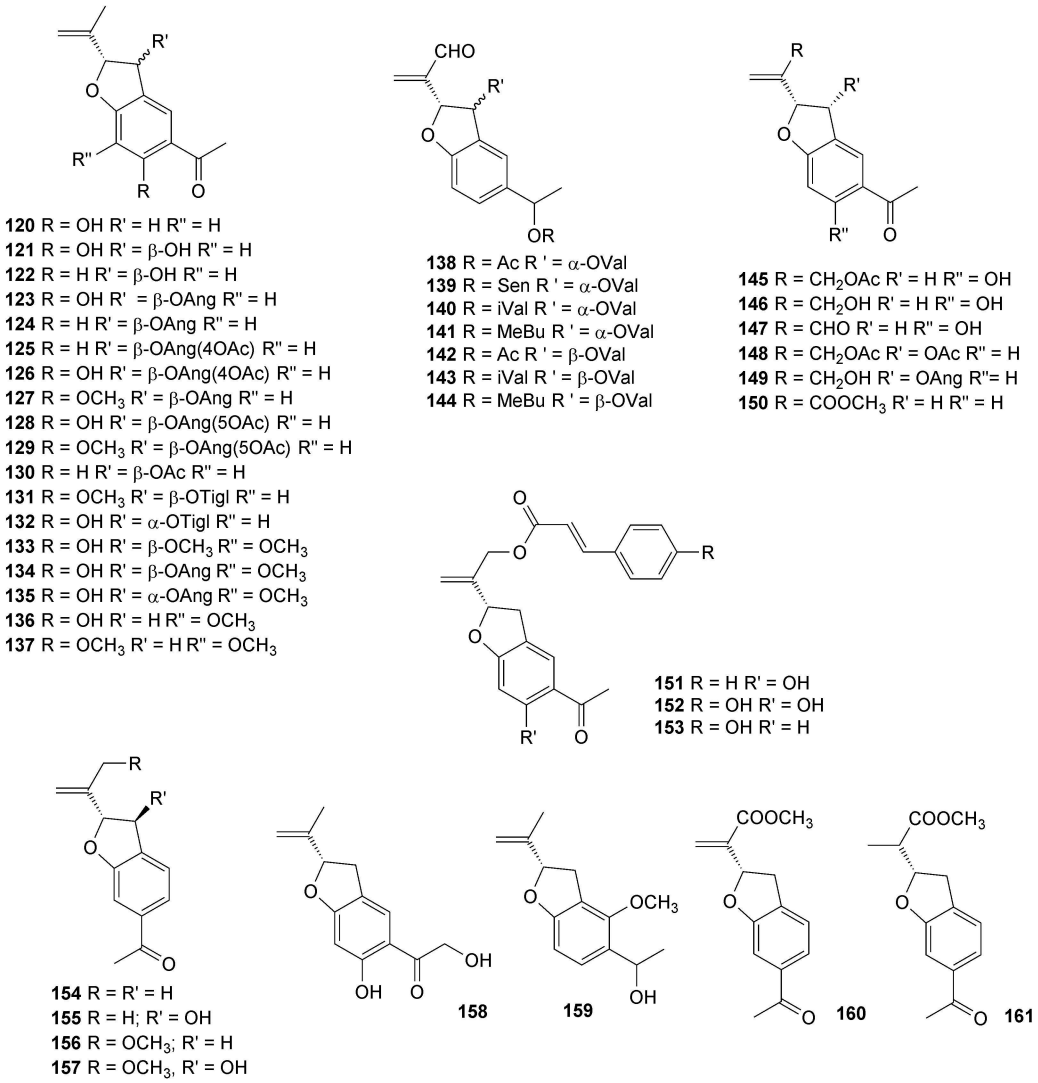


Figure 6. Chemical structures of tremetone derivatives **120**–**161** isolated from Asteraceae species.

rum, using just the flowers, is applied topically to alleviate pain and inflammation.[103]

Pyrrolizidine alkaloids (PAs) are secondary metabolites found in more than twelve unrelated botanical families all over the world. About 3% of the world's flowering plants contain more than 600 PAs, and some of them seem to be related to chronic toxicity, especially those found in Asteracee, Boraginaceae, Fabaceae and Orchidaceae families.[104] *In vitro* and *in vivo* studies have shown that PAs can produce DNA adducts, cross-linking and breaks, with consequent gene mutations and chromosomal aberrations.[105] Mutated cells bearing alkylated DNA bases may proliferate, leading to the development of cancers. These are dangerous effects, given that phytochemicals and traditional medicine are widely used by the world population due to their remarkably low costs,[106] although the World Health Organization (WHO) recommends minimizing PA exposure to humans as much as possible.[107] Some countries, like Germany and United Kingdom, recommended a daily total PA intake of not more than 7 ng/kg bodyweight applying a margin of exposure (MOE) of 10,000.[108] Applying the same MOE as above reported, this result in a recommended threshold of 23.7 ng/kg body weight per day.[109]

Pyrrolizidine alkaloids are primarily derived from *L*-ornithine or *L*-arginine, derivatives of 1-methylpyrrolizidine, consisting of two fused five-membered rings with bridgehead nitrogen. When hydroxylated, the PAs can be either saturated or contain a double bond between the 1 and 2 positions. The position of

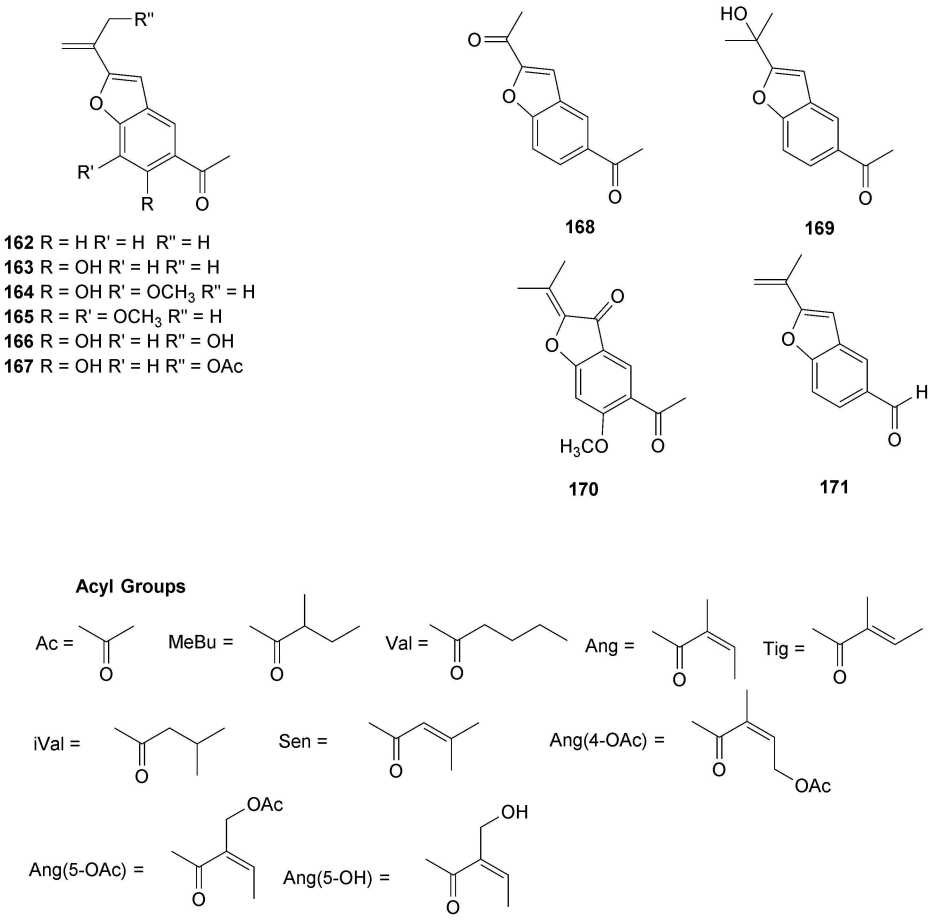


Figure 7. Chemical structures of dehydrotremetone derivatives **162**–**171** isolated from Asteraceae species.

the double bond is an important determinant in the hepatotoxicity of PAs.[110] Although they are not proven human carcinogens, pyrrolizidine alkaloids are genotoxic and mutagenic, and they cause cancer in rats.[111] They are also responsible for numerous livestock losses in northwestern US[112] and potentially harmful for horses, which are highly susceptible to pyrrolizidine alkaloid-induced hepatotoxicity.[113] They may also act synergistically with aflatoxins and hepatitis viruses in causing human liver cancers.[107]

Some of the most common PAs are floridanine (**70**) otosenine (**72**), senkirkine (**73**) and doronine (**71**) (*Figure 3*), that have been identified in some *Doronicum* taxa (*Table 2*). The last one, with chemical structure of 6′-chlorodeoxyfloridanine, identified in 1976, took its name from *Doronicum macrophyllum*, the species from which it was isolated for the first time.[22]

Senkirkine (**73**) and senecionine, 1,2-unsaturated PAs commonly found, for example, in *Tussilago farfara* L., Asteraceae, may cause damage to the liver and even liver cancer in humans.[114]

There are different types of food products that can be a source of PAs. For example, milk from animals that consume PA-containing plants have proven to contain PAs as well. Furthermore, it seems that plant pollen, rich in PAs, can be transferred by bees, contaminating their honey, while eggs from poultry eating grain with PAs could lead to potential health risks for humans.[115]

Senkirkine (**73**), together with seneciphylline, has shown to produce 4.4% sex-linked recessive lethal (2541 chromosomes tested) against 0.17% in control in males of *Drosophila melanogaster*. Brood pattern analysis with senkirkine (**73**) showed maximum sensitivity in the late spermatid stage of spermatogenesis, which agrees with evidence that pyrrolizidine alkaloids act as indirect mutagens.[116] Senkirkine (**73**) produces genotoxicity in mouse and hamster hepatocytes.[117] It also induces mutagenicity in *Salmonella typhimuriun* in the presence of mammalian microsomes.[118] In 20

male rats fed with 10% of the LD_{50} dose of senkirkine (**73**) twice weekly for 4 weeks, nine rats developed liver tumors.[119] Genotoxicity of senkirkine (**73**) was also studied with the sister-chromatid exchange assay in V79 Chinese hamster cells. Exposure to this pyrrolizidine alkaloid, in the presence of co-cultured primary chick embryo hepatocytes, resulted in a high induction of SCEs.[120]

D. pardalianches, growing in India and containing otosenine (**72**),[28] has been used to treat nervous depression, melancholia and to prepare tonics to improve cardiac health, as well as to cure scorpion bites. In the Himalayas area, from Kashmir to Garhwal, the roots of *D. roylei* have been used for typical dizziness due to altitude.[92]

The alkaloid extracts of *D. austriacum* showed inhibits the growth of mouse fibroblasts *in vitro* and the growth of mouse mammary carcinoma *in vivo*.[121]

4. Conclusions and Outlook

An accurate and detailed investigation on the literature data on *Doronicum* genus has shown the occurrence of pyrrolizidine alkaloids, flavonoids, terpenes and aromatic compounds such as benzofurans and, mainly, thymol derivatives with esters groups. The essential oils obtained and analyzed from the different species of *Doronicum* genus showed a large presence of hydrocarbon sesquiterpenes, with germacrene D, (*E*)-β-caryophyllene, α-humulene and farnesene derivatives as main components. One of the most interesting classes of compounds in this genus is that of tremetone derivatives, compounds found in most plants belonging to the Asteraceae family, are known as mitochondrial respiration inhibitors, partially inhibiting ATP synthesis, H+-uptake, photosystem II, and electron transport in concentration-dependent manner, resulting in excellent plant growth inhibitors and interesting insecticides against multiple disease vectors. The several derivatives of tremetone Although several studies have been carried out on its biological properties and the results have confirmed their traditional uses in popular medicine more investigations are required since many extracts and pure compounds have been not tested.

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Author Contribution Statement

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