Biologically Active Substances from the Genus *Artemisia*

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Received: June 20, 1997; Revision accepted: January 2, 1998

Abstract: *Artemisia* species, widespread in nature, are frequently utilized for the treatment of diseases such as malaria, hepatitis, cancer, inflammation, and infections by fungi, bacteria, and viruses. Furthermore, some *Artemisia* constituents were found to be potential insecticides and allelopathic chemicals. This genus is receiving growing attention presumably due to: (i) the diversified biology and chemistry of the constituents, (ii) the frequent application in traditional medical practice, and (iii) the rich source of the plant material. This review summarizes mainly the biological results obtained in the past decade. The significance and trends in this field are briefly discussed.

Key words: *Artemisia*, Compositae, biologically active substances.

Introduction

The genus *Artemisia* L., one of the largest genera belonging to the Compositae family consisting of more than 350 species, is predominantly distributed in the northern temperate region of the world in the 0–50 cm precipitation area. As summarized by different groups (1–3), many species have been used since ancient times as folk remedies for some treatment purposes (reducing phlegm, relieving cough, invigorating blood circulation, stopping pain, inducing sweat, diuresis, antihypertension, anthelminthic, antitoxic, and antiallergy). According to the literature, over 260 *Artemisia* species have been investigated to reveal that they contain many classes of secondary metabolites including terpenoids, flavonoids, coumarins, glycosides, sterols, and polyacetylenes.

During the intensive investigation of the chemical components of *Artemisia* genus, much renewed attention was paid to bioactive constituents. As reported, some substances from the genus were shown to be antimalarial, antiviral, antitumor, antipyretic, antihemorrhagic, anticoagulant, antianginal, antioxidant, antihepatitis, antiulcerogenic, antispasmodic, anticomplementary, and interferon-inducing. This article deals principally with bioactive constituents characterized in the past decade from *Artemisia* species in order to obtain a better understanding of the biological significance of this large genus.

Planta Medica 64 (1998) 295–302

Biologically Active Substances

Bioactive compounds found in this genus include mono- (**23–25**) and sesquiterpenoids (**1–22**), flavonoids (**26–57**), coumarins (**59–64**), isoprenylcoumaric acid derivatives (**65–68**), caffeoylquinic acids (**70–73**), acetylenes (**74–77**), sterols (**78**, **79**), a phenoxychromene (**57**), an acetophenone glucoside (**58**), a phenylpropene (**69**), methyl jasmonate (**80**), and γ-tocopherol (**81**). The plant sources and bioactivities are summarized in Table **1**, and the biologically active parts and fractions in Table **2**.

Antimalarial

Mainly due to the multidrug resistance developed by *Plasmodium* species, malaria remains a serious problem with approximately 300 million cases annually in the world (83, 84). As shown in Table **1**, the antimalarial constituents from *Artemisia* L. are sesquiterpenes, coumarins, and polymethoxyflavones. The renewed attention to artemisinin (**1**) and its related compounds indicate that the antimalarial mechanism of this class of drugs is based on an unusual mode of action leading to the alkylation of malaria-specific proteins (90). Quite interestingly, artemisinin was also detected in *A. apiacea* (87) and *A. lancea* (88). This disclosed clearly that the presence of artemisinin is not limited to *A. annua*. To some extent, screenings of other *Artemisia* species for the artemisinin-related compounds are desired for broadening the source of these valuable products particularly when the synthesis of them is very costly. Some flavonoids **26–29**, possessing weaker activities against *Plasmodium falciparum*, can potentiate the antiplasmodial activity of artemisinin (4). This finding suggested a possible way for increasing the effectiveness of artemisinin and its analogues. Other antimalarial constituents, 1(*S**)-hydroxy-α-bisaboloxide A acetate (**22**) and isofraxidin (**61**), were obtained from *A. abrotanum* (8). However, the mechanism and the dependence of the antimalarial activity on the structure are still obscure.

Antitumor

The antitumor natural products characterized from *Artemisia* genus include mono- and sesquiterpenes and phenolic compounds. Artemisinin (**1**) and its semi-synthetic analogues have been disclosed to possess stereochemistry-dependent cytotoxicity (86). A continuation of this topic is desired for the understanding of quantitative structure-activity relationships

Table 1 Bioactive substances from *Artemisia* species[1].

Plant Sources	Bioactive Compounds	References
A. abrotanum L.	antimalarial[2]: **22** and **61** (IC_{50}: 5.09 and 7.95 μg/ml, resp.)	(4)
	spasmolytic[3]: **44–46** (EC_{50}: 20–30 μM)	(5)
A. absinthium L.	antitumor[4]: **26**[4]	(6)
	antipyretic: **79**	(7)
A. annua L.	antimalarial: **1** (IC_{50}: 3×10^{-8} M), **3**, **26–29** (IC_{50}: $2.4–6.5 \times 10^{-5}$ M)	(8–10)
	antibacterial: **4**	(11)
	anti-inflammatory: **60**	(11)
	angiotensin-converting enzyme inhibitory: **47** (IC_{50}: 150 μM), **48**	(12)
	allelopathic: **1**, bis(1-hydroxy-2-methylpropyl)phthalate, ABA, Me-ABA	(13, 14)
	antitumor: **1** and **31**	(15)
A. argyi Levl. et Van.	antitumor[6]: **10–12**	(16)
	antihemorrhagic: **43**, β-sitosterol	(17)
	antispasmodic: **6**	(18)
A. austriaca Jacq.	*Aedes aegypti* repellent: 9-hydroxy-1,8-cineole	(19)
A. barrelieri	anti-inflammatory[7]: **15**[8], **17–19**	(20)
A. borealis Pall.	antimicrobial[9]: **74**, **75**	(21, 22)
	lavicidal[10]: **74**, **75**	(21)
A. caerulescens subsp. *gallica*	antipyretic (in rats): **13**, **14**, **20**	(23)
A. capillaris Thunb.	antitumor[11]: **30**, **57**	(24)
	antiviral: **77**	(25)
	antihepatitis: **33**, **34**, **59**, **63**, **64**	(26)
	anticoagulant: **60**, **62**	(27, 28)
	antianginal[12]: **62**	(29, 30)
	choleretic[13]: **62**, **65–67**	(31)
	antioxidant: **50–55**, **81**	(32, 33)
	immunosuppressive: **62** (10^{-6} M to 3×10^{-4} M)	(34)
	antifeedant: **69**, **76**, **77**	(35)
	plant growth regulatory: **68**[14], **78**[15], GA3, ABA	(36–38)
A. cina Berg. ex Pol.	antibacterial (*Bacillus subtilis* and *B. cereus*): **13**	(39)
A. douglasiana Bess.	hepatoprotective: **23**, **24**	(40)
	antiulcerogenic: **7**	(41)
A. giraldii Pamp.	antimicrobial[16]: **16**, **37–39**	(42, 43)
A. iwayomogi Kitam.	antioxidant: **70**	(44)
A. judaica	antispasmodic[17]: **30**	(45)
A. monosperma	antispasmodic[18]: **32**, **43**	(46)
A. motana Pamp.	hemostatic: **71–73**	(47)
A. myriantha Wall. ex Bess.	antitumor: **5**	(48)
A. nilagirica Pamp.	repellant to *Culex pipiens quinquefasciatus*: **77**	(49)
A. pacifica	antimicrobial[19]: **74**	(22)
A. princeps Pamp.	hemostatic: **71–73**	(47)
	cytotoxic: **21**, **40**, **42**, **49**	(94)
	anticoagulant[20]: sulfated polysaccharides[21]	(50)
	anticomplementary: neutral polysaccharides[22]	(51)

[1] *In vitro* activity unless stated otherwise.
[2] [^3H]-hypoxanthine incorporation assay.
[3] On carbacholine-induced contractions of the guinea pig trachea.
[4] In mice and rats with experimental tumors.
[5] Against melanoma B16.
[6] Inhibiting the growth of Sarcoma 100 cells in female BALB/cx DBA mice.
[7] Tested on carrageenan-induced rat paw edema.
[8] Prepared from **19** with zinc and acetic acid.
[9] On bioautographic assay and minimum amounts (in μg) of **74** required for the growth inhibition were: 1.25 (*Cladosporium cucumrinum*), 25 (*Candida albicans*), 25 (*Bacillus subtilis*), 50 (*Staphylococcus aureus*) and 100 (*Klebsiella pneumoniae*), and of **75**: 1.25 (*Cladosporium cucumrinum*).
[10] IC_{100}: 100 ppm, to larvae of *Aedes aegypt*.
[11] IC_{50} (μg/ml): **30**: 3.2 (Hela cells) and 0.54 (Ehrlich cells), **57**: 3.4 (Hela cells) and 0.03 (Ehrilich cells).
[12] Tested both *in vitro* (29) and *in vivo* (30).
[13] In Wistar rats.
[14] Promoting at 5×10^{-5} M rice root growth to 180 % of the control.
[15] Inhibiting completely at 8×10^{-6} M the germination of seeds of millet, pansy, cabbage and carrot.
[16] MIC (μg/ml): **16**: 50 (*Staphylococcus aureus*), 50 (*Candida tropicalis*), 75 (*Gecotrichun candidun*), 50 (*Aspergillus niger*), 75 (*A. flavus*).
[17] Reducing, at concentrations up to 3×10^{-4} M, the amplitude and tone of the phasic contractions of the isolated guinea-pig ileum.
[18] On isolated rat smooth muscle and in concentrations from 10^{-7} to 3×10^{-7} M.
[19] MIC (μg/ml) by the agar diffusion method: 25 [*Bacillus subtilis* (UA 2-27)], 50 [*Staphylococcus aureus* (UA 9-29)], 100 [*Klebsiella pneumoniae* (UA 3-9)] and [*Candida albicans* (UA 9-7)].
[20] The anticoagulant activity was assessed by measuring activated partial thromboplastin time of the tested sample.
[21] Prepared by the treatment of natural acidic polysaccharides with pyridine and chlorosulfonic acid complex.
[22] Structurally clear.

Table 1 Cont.

Plant Sources	Bioactive Compounds	References
A. scoparia Waldst. et Kit.	choleretic (in rats): *p*-hydroxyacetophenone	(52)
A. sieversiana Ehrhart er Willd.	antitumor[4]: **26**[5], **27**	(6)
A. stolonifera Komar.	cytostatic: **58**	(53)
A. subdigitata Mattf.	antianginal: **9**	(54)
A. sublessin-giana	antimicrobial: **35**, **36**, **41**, **56**	(55)
Krash. ex Poljak	enzyme regulator: **20**, **41**, **42**, **50**, **56**	(56, 57)
A. tridentata Nutt.	plant growth regulator: **80**	(58)
A. xanthochroa Krasch.	antitumor: **32**[5]	(6)

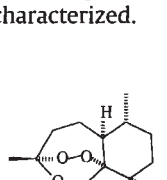
Table 2 Bioactive parts and fractions derived from *Artemisia* species.

Plant Sources	Bioactive Parts (Activities) or Fraction	References
Artemisia species	glycoproteins (interferon-inducing)	(59)
A. absinthium L.	aqueous MeOH extract (hepatoprotective)	(60)
A. afra	essential oils (antibiotic and antioxidant)	(61)
A. annua L.	extract (antipyretic)	(11)
A. apiacea Hance	acidic polysaccharides (anticoagulant)	(50)
A. arborescens	aqueous extract (antispasmodic)	(62)
A. asiatica Nakai ex Pamp.	essential oils (allelopathic)	(63)
A. asiatica Nakai ex Pamp.	essential oils (antibacterial)	(64)
nakai Pamp.	hot-water extract (antibacterial)	
A. capillaris Thunb.	HPLC fractions (cytocidal)	(23)
	ether, EtOAc and MeOH extracts (antioxidant)	(31)
A. cina Berg. ex Poljak.	total flavonoids (antitumor, antifungal)	(65)
A. dracunculus L.	essential oils (antifungal and antibacterial)	(66)
A. edgeworthii Balakr.	essential oils (antibacterial)	(66)
A. gmelini Web. ex Stechm.	essential oils (antifungal and antibacterial)	(66)
A. herba-alba	essential oils (antifungal and antibacterial)	(67, 68)
A. indica Willd.	extract (antifungal)	(69)
A. iwayomogi Kitam.	extract (hepatoprotective)	(70)
	polysaccharide parts (immunomodulating and antitumor)	(71)
A. jacutica	essential oils (anti-inflammatory)	(72)
	essential oils (antifungal and antibacterial)	(67)
A. laciniata Willd.	essential oils (antibacterial)	(66)
A. macrocephala Jacq. ex Bess.	essential oils (anti-inflammatory)	(72)
A. maritima L.	essential oils (antifungal and antibacterial)	(66)
A. molinieri	flavonoid fraction (antifungal)	(73)
A. moorcroftiana Wall. ex DC.	essential oils (antifungal and antibacterial)	(66)
A. nilagrica Pamp.	essential oils (antifungal and antibacterial)	(66)
A. parviflora Buch.-Ham. ex Rox.	essential oils (antifungal and antibacterial)	(66)
A. pontica L.	essential oils (anti-inflammatory)	(72)
A. princeps Pamp.	extract (antiaging)	(74)
A. princeps var. *orientalis* Hara	essential oils (allelopathic, antifungal and antibacterial)	(75)
	MeOH extract (anti-inflammatory and analgesic)	(76, 77)
	plant residues (allelopathic)	(78)
A. roxburghiana Bess.	essential oils (antifungal and antibacterial)	(66)
A. scoparia Waldst. et Kirt.	total flavonoids (antitumor)	(65)
	aqueous MeOH extract (hepatoprotective)	(79, 80)
	essential oils (antifungal and antibacterial)	(66)
A. selengensis Turcz. er Bess.	flavonoids (antifungal)	(73)
	polysaccharide parts (immunomodulating and antitumor)	(71)
	extract (hepatoprotective)	(81)
A. sieversiana Willd.	essential oils (anti-inflammatory)	(72)
A. stolonifera Komar.	flavonoids (antifungal)	(73)
A. sublessingiana Krasch. er Poljak.	total flavonoids (antifungal)	(65)
A. tournefortiana Reichb.	essential oils (antifungal and antibacterial)	(66)
A. tridentata Nutt.	dry leaves (repellent to beetles)	(82)

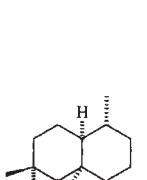
and the mode of action. However, this elegant work did exhibit the possibility that artemisinin-related compounds, in addition to being used as antimalarial drugs, could find application in the treatment of some cancers. Other sesquiterpenes, e.g., guaianolide (**5**), seco-guaianolides (**10–12**), and eudesmanolide (**21**), also showed antitumor activities (Table **1**). But more investigations are needed for the insight into the mechanism and the structure-activity relationship. Capillarisin (**57**), the only 2-phenoxychromene derivative found so far in the *Artemisia* genus, and its semi-synthetic analogues exhibited *in vivo* antitumor activities (24). A recent review described the distribution of 2-phenoxychromene compounds in the plant kingdom (95).

Antiviral

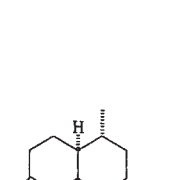
The antiviral constituents from *Artemisia* species were limited to plant sterols and acetylenes (25, 96). Furthermore, a few flavonoids like fisetin (**47**) and quercetin (**50**) were found to be inhibitors of HIV replication in H9 cells (89). To our knowledge, many *Artemisia* plants are being used for the treatment of the virus-related disease such as influenza indicating that more antiviral *Artemisia* constituents are to be characterized.



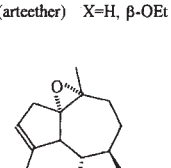
1 (artemisinin) X=O
2 (arteether) X=H, β-OEt



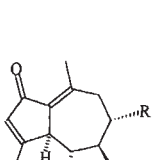
3 (arteannuin B)



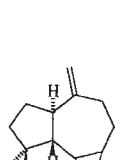
4 (artemisic acid)



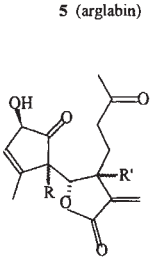
5 (arglabin)



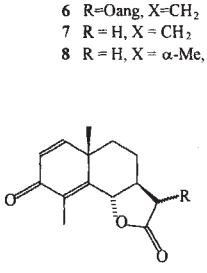
6 R=Oang, X=CH_2
7 R = H, X = CH_2
8 R = H, X = α-Me, H



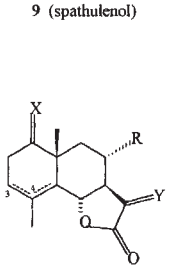
9 (spathulenol)



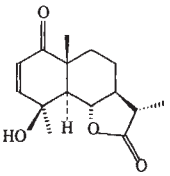
10 R = β-H, R' = α-H
11 R = β-H, R' = β-H
12 R = α-H, R' = α-H



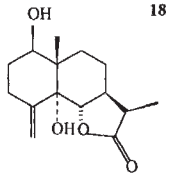
13 (α-santonin) R=α-Me
14 (β-santonin) R=β-Me



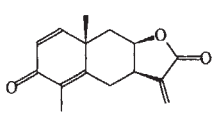
15 Δ^3, R = H, X = O, Y = H, α-Me
16 Δ^4, R = OH, X = O, Y = H, β-Me
17 Δ^4, R = H, X = O, Y = H, α-Me
18 Δ^4, R = H, X = H, β-OH, Y = H, α-Me



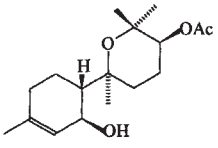
19 (barrelin)



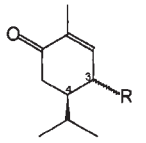
20 (arsubin)



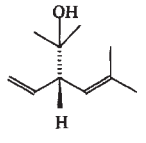
21 (yomogin)



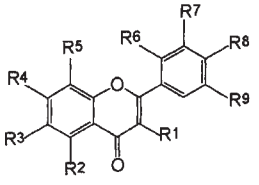
22 (1(S*)-hydroxy-a-bisaboloxide A acetate)



23 (3α-hydroxycarvotagenone) R = α-OH
24 (3β-hydroxycarvotagenone) R = β-OH



25 (sautolina alcohol)



	names	R1	R2	R3	R4	R5	R6	R7	R8	R9
26	artemetin	OMe	OH	OMe	OMe	H	H	OMe	OMe	H
27	chrysoplenetin	OMe	OH	OMe	OMe	H	H	OMe	OH	H
28	chrysoplenol-D	OMe	OH	OMe	OMe	H	H	OH	OH	H
29	cirsilineol	H	OH	OMe	OMe	H	H	OMe	OH	H
30	cirsimaritin	H	OH	OMe	OMe	H	H	H	OH	H
31	quercetagetin 6,7,3',4'-tetramethyl ether	OH	OH	OMe	OMe	H	H	OMe	OMe	H
32	eriodictyol 7-methyl ether	H	OH	H	OMe	H	H	OH	OH	H
33	eupatolitin	H	H	OMe	OMe	H	H	OH	OH	H
34	arcapillin	H	H	OMe	OMe	H	OH	H	OH	OMe
35		H	OH	OMe	OH	H	H	OMe	OH	H
36	chrysoeriol	H	OH	H	OH	H	H	OMe	H	H
37		H	OH	H	H	OMe	H	OMe	OMe	OH
38		H	H	OH	OH	H	H	OMe	OH	OMe
39		H	OH	H	OH	H	H	OMe	OH	OMe
40	genkwanin	H	OH	H	OMe	H	H	H	OH	H
41	hispidulin	H	OH	OMe	OH	H	H	H	OH	H
42	jaceosidin	H	OH	OMe	OH	H	H	OMe	OH	H
43	eupatilin	H	OH	OMe	OH	H	H	OMe	OMe	H
44		OMe	OH	OMe	OMe	H	H	OH	OMe	H
45		OMe	OH	OMe	OH	H	H	OH	OMe	H
46		OMe	OH	H	OH	H	H	OH	OMe	H
47	fisetin	OH	H	H	OH	H	H	OH	OH	H
48	patuletin 3,7-dirhamnoside	Orham	OH	OMe	Orham	H	H	OH	OH	H
49	acacetin	H	OH	H	OH	H	H	H	OMe	H
50	quercetin	OH	OH	H	OH	H	H	OH	OH	H
51	quercetin 3-O-galactoside	Ogal	OH	H	OH	H	H	OH	OH	H
52	quercetin 3-O-robinoside	Orob	OH	H	OH	H	H	OH	OH	H
53	isorhamnetin	OH	OH	H	OMe	H	H	OH	OH	H
54	isorhamnetin 3-O-galactoside	Ogal	OH	H	OMe	H	H	OH	OH	H
55	isorhamnetin 3-O-robinoside	Orob	OH	H	OMe	H	H	OH	OH	H
56	isorhamnetin 3-O-rutinoside	Orut	H	H	OH	H	H	OMe	OH	OH

* 2β,3-dihydro

Antihepatitis and hepatoprotective

Table **1** has indicated that antihepatitis and hepatoprotective constituents from *Artemisia* species were monoterpenes, flavonoids, and coumarins. Monoterpenes **23** and **24** from *A. douglasiana* showed a pronounced cytoprotective activity, and the preliminary investigation of the structure-activity relationship indicated that the presence of hydroxy groups in this pair of epimers could stop the activity (40). The extract of *A. capillaris* also had an intense suppressive activity in CCl_4-induced liver lesion in mice with the active components identified as eupatolitin (**33**), arcapillin (**34**), esculin (**59**), scopolin (**63**), and isoscopoletin-β-*O*-glucoside (**64**) (26). However, more pharmacological investigations are necessary for evaluating the potential as antihepatitis and hepatoprotective agent(s).

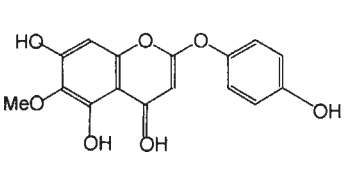
Antifungal

The search of novel antifungal agents has become an urgent task because the incidence of opportunistic systemic mycoses is increasing remarkably (97). As given in Table **1**, the anti-

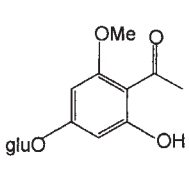
fungal constituents from *Artemisia* species include flavonoids, polyacetylenes, and sesquiterpenes. However, caution has to be taken in comparing their antifungal activities obtained on different bioassay models. The polyacetylenes **74** and **75** have been found to exhibit antifungal activity against plant and human pathogenic fungi. It seems that acetylation of the hydroxy groups can diminish the antifungal activity (21, 22). Further work in this respect will be helpful for understanding the dependence of the activity on the structure.

Antibacterial

Antibacterial substances characterized from *Artemisia* species were monoterpenes, flavonoids, and sesquiterpene lactones. A well-known antiprotozoal drug, α-santonin (**13**), showed a strong antibacterial activity (39). Artemisinic acid (**4**), a precursor for the semi-synthesis of artemisinin (**1**) (98), was shown to be antibacterial, too (11). This preliminary finding gave hints for broadening the applications of these two important *Artemisia* constituents.

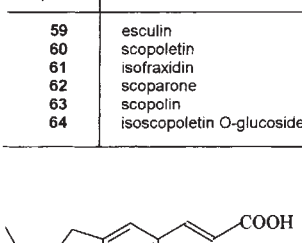


57 (capillarisin)

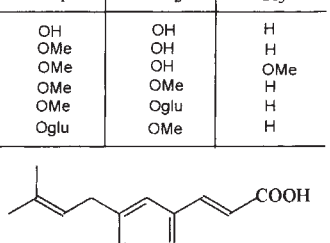


58

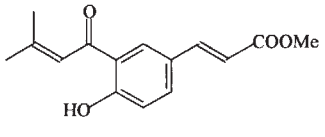
Compounds	Names	R_1	R_2	R_3
59	esculin	OH	OH	H
60	scopoletin	OMe	OH	H
61	isofraxidin	OMe	OH	OMe
62	scoparone	OMe	OMe	H
63	scopolin	OMe	Oglu	H
64	isoscopoletin O-glucoside	Oglu	OMe	H



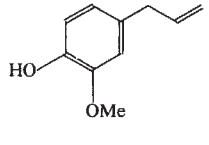
65 (artepillin)



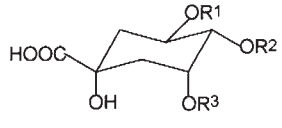
66 (capillartemisin B_1) R = OH
67 (artepillin C) R = H



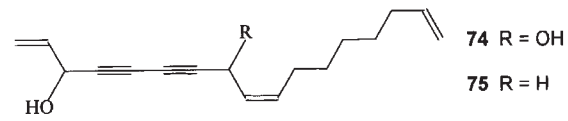
68 (capillarol)



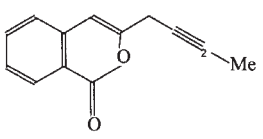
69 (methyleugenol)



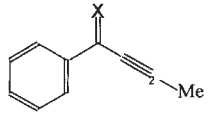
70 (chlorogenic acid) R^1 = caffeoyl, R^2 = R^3 = H
71 R^1 = R^2 = caffeoyl, R^3 = H
72 (neochlorogenic acid) R^1 = R^3 = caffeoyl, R^2 = H
73 R^1 = H, R^2 = R^3 = caffeoyl



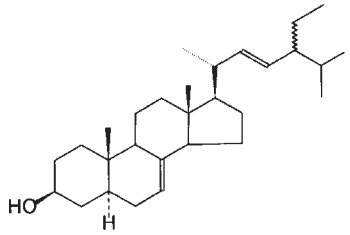
74 R = OH
75 R = H



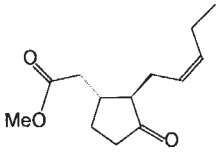
76 (capillarin)



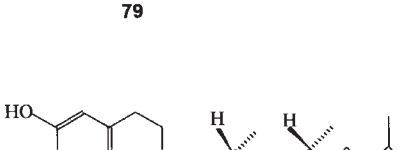
77 (capillin) X = O
78 (capillen) X = H_2



79



80 (methyl jasmonate)



81 (γ-tocopherol)

Anti-inflammation

As indicated by Tables **1** and **2**, the anti-inflammatory compounds found in the genus include mainly coumarins, sesquiterpene lactones, and essential oils. Barrelierin (**17**), artemalin (**18**), and barrelin (**19**) from *A. barrelieri*, and desoxyvulgarin (**15**) (obtained by reduction of barrelin with zinc and acetic acid) exhibited anti-inflammatory activities. Investigation of the structure-activity relationship showed that the α-methylene-γ-lactone moiety was not essential for the anti-inflammatory effect, but alterations in other parts of the molecule affected the activity substantially (20).

Antipyretic

α- and β-santonin (**13** and **14**) and arsubin (**20**) caused a decrease in rectal temperature of rats in a way similar to dopamine (23). The sterol 24-ζ-ethylcholesta-7,22-dien-3β-ol (**79**) was found to be antipyretic (7). However, more pharmacological attention is desired for assessing the potential as antipyretic agent(s).

Hemostatic, antihemorrhagic and anticoagulant

It seems that some polar constituents of the *Artemisia* species possess these activities. The hemostatic principles of *A. montana* and *A. princeps* were identified as 3,5-, 3,4-, and 4,5-di-*O*-caffeoylquinic acids (**71**–**73**) (47). This rationalized their

applications as hemostatic agents in traditional Chinese medical practice. Acidic polysaccharides from *A. apiacea* and *A. princeps* were shown to be anticoagulant (50). However, this investigation needs to be continued for the pharmaceutical potential of these products.

Spasmolysis and antianginal

Scoparone from *A. capillaris* was found to be a competitive antagonist of nor-epinephrine like nitroglycerine (29). But the mode of action and structure-activity relationship are to be highlighted. Furthermore, some flavonols like **30**, **32**, **44–46** also possessed spasmolytic activity (5, 45, 46). The results are not comparable since they were obtained on different models. Moreover, sesquiterpenes such as **6** and **9** were anti-spasmodic (54). More studies are needed for an insight into the mechanism and the structure-activity relationship.

Antiulcerogenic and choleretic

The guaianolide dehydroleucodin (**7**) from *A. douglasiana* was protective against gastric ulceration whereas deacetoxylmatricarin (**8**) from *A. mendozana* did not show any cytoprotective activity. Further comparative studies indicated that the α-methylene-γ-lactone unit was essential for the activity (41). As to choleretic substances, scoparone (**62**), artepillin (**65**), capillartemisin B_1 (**66**), and artepillin C (**67**) from *A. capillaris* were shown to be choleretic in Wistar rats (31). These findings rationalized that *A. capillaris*, called "Yingchenhao" in Chinese, is being often used for choleretic purposes.

Anticomplementary

Two acidic and three neutral polysaccharides from *A. princeps* were found to be anticomplementary. The two acidic ones had a rhamnogalacturonan main-chain which was mostly substituted with arabino-3,6-galactan and arabino-4-galactan at position four of rhamnose. Furthermore, the mode of action of the anticomplementary acidic heteroglycans has been also investigated (51).

Antioxidant

Antioxidant constituents characterized from *Artemisia* species were in most cases phenolic compounds. Chlorogenic acid (**70**) from *A. iwayomogi* was recently disclosed to possess an antioxidant activity comparable to that of L-ascorbic acid (44). A comparative study of its analogues such as **71–73** is desirable for their potential antioxidant activities.

Analgesic, antidiabetic and antiparasitic

The information about the constituents having these activities is quite limited (Tables **1** and **2**). What has been reported so far concerning these aspects are preliminary results such as bioassay of fractions (or even extracts) and ordinary phytochemical analyses.

Enzyme regulator

The enzyme regulators found in *Artemisia* species are mainly phenolic compounds. The flavonoids **47** and **48** from *A. annua* were capable of inhibiting the activity of angiotensin-converting enzyme. This observation may be of value in hypertension treatment (12). Flavonoids **40–42** and **50** as well as an eudesmanolide **20** from *A. sublessingiana* exerted modulating effects on the sodium, potassium-ATPase, and the results demonstrated the potential for new cardiotonic drugs (56, 57).

Interferon-inducing and immunomodulating

Many *Artemisia* species contain interferon-inducing glycoproteins with molecular weights ranging from 5×10^5 to 10×10^5 (59). The polysaccharide fractions from *A. selengensis* and *A. iwayomogi* were shown to have immunomodulating activity (71). These reports, together with anticoagulant and anticomplementary properties of polysaccharides discussed above, indicated the pharmaceutical significance of macromolecules of *Artemisia* species.

Antifeedant, insecticidal, and mosquito repellent

The antifeedant components from *Artemisia* genus are principally aromatic compounds with an unsaturated side chain. For example, the components from *A. capillaris* inhibiting the feeding to the larvae of the cabbage butterfly were methyleugenol (**69**), capillarin (**76**), and capillin (**77**) (34). The insect repellents of *Artemisia* origin are usually widespread volatile substances as exemplified by 9-hydroxy-1,8-cineole from *A. austriaca* and dimethyl phthalate in the oil of several *Artemisia* species (19, 99).

Allelopathy

The allelopathic chemicals detected in *Artemisia* species are acetylenes, mono- and sesquiterpenes. Artemisinin and its semi-synthetic analogues such as **2** were shown recently to be plant growth inhibitors (85). This work demonstrated the possibility that artemisinin-related compounds can be used as agricultural agent(s) such as herbicide. Capillin (**77**) from roots of *A. capillaris* was found to be a seed (millet, cabbage, pansy and carrot) germination inhibitor (35). In contrast to the growth inhibition, capillarol (**68**) from *A. capillaris* promoted at 5×10^{-4} M rice root growth to 180 % of the control (36). Since the side chain of **68** is quite similar to that of abscisic acid, it could be postulated that the α,β-unsaturated carbonyl moiety is involved in the plant growth promotion activity.

Conclusions

The growing significance of natural products in drug discovery and development is obvious as illustrated dramatically by Cragg et al. (93). In morphology, the *Artemisia* genus is endowed with head-like inflorescences and is considered to be one of the most evolutionary taxa in the Dicotyledonae. This advancement in taxonomy may increase the chemical diversity as the advanced species may synthesize more complex (cyclized, rearranged and/or oxygenated) secondary metabolites (1). This hypothesis has been reinforced by the reported phytochemical results describing the presence of diversified constituents in the *Artemisia* species. As the investigation continues, this genus may prove to be a richer source of lead compounds needed for the development of new chemotherapeutical and/or agricultural agents.

However, most of the reported biological studies of *Artemisia* constituents and extracts were carried out *in vitro*. Mean-

while, a lot of isolates from the genus have failed when tested biologically. More biological and chemical attention is highly desired.

Acknowledgements

Grants for RXT from the National Natural Science Foundation (No. 39670873 & 39725033) and the Doctoral Training Programme (No. 9628418) are gratefully acknowledged. The authors are very grateful to Prof. Dr. Adolf Nahrstedt (the editor-in-chief of the journal) for his encouragement and technical instructions about preparation of this manuscript.

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