Secondary metabolites of *Artemisia annua* and their biological activity

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***Artemisia annua* synthesizes and accumulates a variety of secondary metabolites. Some of the biologically active secondary metabolites substantiate the claim made in traditional system of medicine. The present review summarizes the information available on the secondary metabolites isolated from *A. annua*.**

ARTEMISIA annua (known as 'quinghao' in China) is an aromatic annual herb endemic to the northern parts of Chahar and Suiyuan provinces in China. However, the plant now grows wild in Europe and America[1–8]. It is cropped on a large scale in China, Vietnam, Turkey, Iran, Afghanistan and Australia. In India, it is being cultivated on an experimental basis in temperate as well as subtropical conditions[9–14]. *A. annua* is an important medicinal plant. The secondary metabolites isolated from the plant and their biological activities are reviewed.

Chemical constituents

The search for the concerned active compounds has led to isolation of the several sesquiterpenoids, flavonoids, coumarins, triterpenoids, steroids, phenolics, purines, lipids and aliphatic compounds and monoterpenoids from different plant parts of *A. annua*.

The phytochemicals isolated from different parts of the plants are listed in Table 1 (refs 15–154), which shows the percentage of the phytochemicals present in different plant parts in different countries.

Monoterpenoids

The essential oil constituents (monoterpenoids) of *A. annua* reported from various countries are listed in Table 2 (refs 155–169). The GC-MS analysis of the essential oil of *A. annua* characterized a large number of monoterpenoids. The yield of the oil generally ranges between 0.3 and 0.4%. Woerdenbag *et al.*[44] reported 4.0 and 1.4% essential oil (V/W) from the genotypes grown from Chinese and Vietnamese seeds, respectively in 1993. Artemisia ketone (63.9%), artemisia alcohol (7.5%), myrcene (5.1%), α-guainene (4.7%), and camphor (3.3%) were the main constituents found in Chinese oil. The Vietnamese oil contained camphor (21.8%), germacrene D (18.3%), α-caryophyllene (5.6%), trans-α-farnesene (3.8%), and 1,8-cineole (3.1%). No artemisia ketone was found in this analysis. In 1994, Woerdenbag *et al.*[28] reported maximum oil content before flowering period in the Vietnamese *A. annua* plants which contained 55% of monoterpenes.

Table 1. Compounds isolated from *Artemisia annua*

Sl no.	Compound	Plant part	Country	%	Ref.
Sesquiterpenes					
1	Abscisic acid (1)	AP	India	–	15
2	Abscisic acid methyl ester (2)	AP	India	–	15
3	Annuic acid, nor (3)	AP	India	–	16
4	Annulide (4)	AP	England (Cult)	0.0006	17
5	Annulide, iso (5)	LF	England (Cult) traces		17
6	Arteannuic acid (6)	LF	South Korea		18
		LF	USA	0.06	19
		LF	The Netherlands	0.4	20
		LF	The Netherlands	0.22	20
		LF	The Netherlands	0.66	20
	(Artemisinic acid)	HRC	Yugoslavia		21
		EP	India		22
		LF	Saudi Arabia (Cult)		23
		LF	Australia	0.18	24
		HRC	India		25
		SC	India (Cult)		26
		LF	Belgium (Cult)		27
		LF	The Netherlands (Cult)		24
		EP	The Vietnam		28
		AP	Switzerland (Cult)	0.006–0.02	29
		LF	USA-MS (Cult)	0.0053	30
		LF	Saudi Arabia (Cult)		31
		LF	USA-MD		32
		AP	China		33
		AP	India (Cult)		34
	(Artemisic acid)	EP	China		35
		EP	China		36
		EP	China		37
	(Artemisinin acid)	EP	Saudi Arabia		38
	(Artemisininic acid)	EP	China		39
	(Artemisinoic acid)	EP	China		40
7	Arteanuic acid, 11 (R)-dihydro: (7)	FL	China		41
		LF	The Netherlands		42
		LF	China		43
8	Arteannuic alcohol (8)	RT	Vietnam (Cult)		44

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Sl no.	Compound	Plant part	Country	%	Ref.
9	Arteannuin A (9)	EP	China		45
		EP	China		35
		AP	China		33
	(Qinghaosu I)	AP	India		16
		AP	India (Cult)		34
10	Arteannuin B (10)	HRC	Yugoslavia		21
		LF	Saudi Arabia (Cult)		31
		EP	China		45
		LF	USA-WV	0.02761	46
		SC	Europe	0.00065	47
		ST	The Netherlands	0.2	20
		HRC	India		25
		SC	India (Cult)		26
		LF	Belgium (Cult)		27
		EP	Vietnam		28
		LF	USA-MS (Cult)	0.0425	33
		LF	USA-MD		32
		LF	The Netherlands	0.15	20
		FL	The Netherlands	0.24	20
	(Qinghaosu II)	LF	China		48
	(Artemisinin B)	EP	Yugoslavia		49
		LF	USA-MD	0.06764	46
		LF	USA	0.07200	19
		EP	China		35
		AP	China		33
11	Arteannuin B, deoxy: EPI (11)	EP	USA-DC	0.015	50
		LF	Saudi Arabia	0.04933	23
		AP	England (Cult)	0.0018	51
12	Arteannuin B, dihydro (12)	LF	China		43
13	Arteannuin B, dihydro EPI: deoxy (13)	LF	China		43
		AP	England (Cult)	0.0004	51
14	Arteannuin C (14)	AP	India (Cult)	0.00214	52
15	Arteannuin D (15) (Qinghaosu IV)	–	China		53
16	Arteannuin E (16)	–	China		53
17	Arteannuin F (17) (Artemisilactone)	AP	China	0.0005	54
18	Artemisinin G (18)	LF	China	0.01	55
19	Arteannuin H (19)	LF	China	0.007	43
20	Arteannuin I (20)	LF	China	0.0055	43
21	Arteannuin J (21)	LF	China	0.0055	43
22	Arteannuin K (22)	LF	China	0.002	43
23	Arteannuin L (23)	LF	China	0.0075	43
24	Arteannuin M (24)	LF	China	0.0035	43
25	Arteannuin N (25)	LF	China	0.002	43
26	Artemisia dihydroxy-cadinolide 2-A (26)	AP	England (Cult)	0.0023	56
27	Artemisia secoca-dinane (27)	AP	England (Cult)	0.0023	56
28	Artemisin (28)	EP	France		57
29	Artemisinic acid methyl ester (29)	LF	China	0.0005	58
	(Artemisinonic acid methyl ester)	EP	China		40
30	Artemisinic acid, epoxy (30)	LF	China		59
		EP	China		60
	(Arteannuinic acid, epoxy)	EP	China		61
		AP	India (Cult)	0.00286	52
		LF	China		58
		EP	China		60
		SC	Taiwan	0.07	62
		EP	China		63
		LF	USA-MD		58
		AP	England (Cult)	0.001	51
31	Artemisinic acid, 6,7-dehydro (31)	LF	Saudi Arabia (Cult)	0.03733	23
32	Artemisinin (32)	EO	India (Cult)		64
		EP	USA (Cult)		65
		HRC	India		25
		SC	India (Cult)		26
		HRC	China		66
		HRC	China		67
		LF	Vietnam		68
		LF	China		69
		SH	Not stated		70
		LF	Saudi Arabia (Cult)		31
		CFE	USA-NY		71
		LF	Vietnam		72
		LF	USA		73
		LF	Vietnam		74
		EP	Vietnam		28
		LF	USA-MD		32
		LF	USA-OR (Cult)		75
		LF	USA-IN (Cult)		76
		LF	USA-IN (Cult)		77
		SC	Not stated		78
		LF	India (Cult)		10
		EP	Vietnam		79
		LF	Belgium (Cult)		27
		LF	China		80
		EP	China		81
		LF	China		82
		EP	Turkey		83
		EP	India		84
		LF	Vietnam		85
		LF	India		86
		PNS	China		87
		RT	USA-NY		8
		EP	Not stated		89
		LF	India (Cult)		9
		LF	USA-MS (Cult)		90
		AP	The Netherlands (Cult)		91
		SC	USA		92
		EP	China		63
		LF	China		93
		ST	China		94
		CT	China		95
		EP	China		35
		SC	Not stated		96
		LF	China		48
		AP	China		97
		AP	China		98
		AP	China		99
		SC	Europe	0.00095	47
		SC	USA (Cult)	0.001	100
		AP	Germany (Cult)	0.00133	101
		CT	Malaysia	0.0043	102
		AP	USSR	0.01–0.05	103
		EP	Australia (Cult)	0.01–0.5	104
		LF	USA-IN (Cult)	0.014–0.32	105
		EP	China	0.03–0.095	106
		SD	USA-IN (Cult)	0.04	107
		AP	Argentina	0.04–0.1	108
		AP	Belgium	Traces	108
		AP	USA-WA	0.04	108
		AP	Spain	0.04333	109
		FL	USA-DC (Cult)	0.05–0.37	110
		LF	USA	0.067–0.11	111
		LF	USA-MD	0.10024	46

Sl no.	Compound	Plant part	Country	%	Ref.
		LF	Malaysia (Cult)	0.12–0.39	112
		LF	USA-MS (Cult)	0.12125	30
		CT	Argentina	0.13	113
		FL	China	0.143	114
		ST	Not stated	0.16	115
		AP	France	0.16117	116
		FL	China	0.232	117
		AP	China	0.3–0.5	118
		LF	Argentina	0.31	119
		LF	China	0.53–0.59	120
		LF	China	0.58	125
		AP	Switzerland (Cult)	0.88–1.49	29
		LF	Japan (Cult)	1.12	122
		SC	Not stated	Traces	123
		PNS	China		87
		AP	Switzerland (Cult)		124
		AP	India		125
		SC	Not stated		88
		EP	India		126
		EP	China		39
		LF + ST	Chile	0.004	127
		LF	USA	0.044	19
		LF + ST	USA	0.06	128
		LF	China	0.6	129
		LF	China	0.6368	114
		LF	China	1.54	117
		ST	USA-IN (Cult) Traces		107
		HRC	Yugoslavia		21
		AP	China		33
		ST	The Netherlands	0.15	20
		AP	China	0.3–0.5	130
		LF	USA-IN (Cult)	0.15	107
		LF	USA-IN (Cult)	0.09	107
		LF	USA-IN (Cult)	0.08	107
		LF	The Netherlands	0.22	20
		AP	India (Cult)	0.00129	52
		FL	The Netherlands	0.28	20
33	Artemisinin, dehydro (33)	AP	USA-WV		131
		AP	USA		132
		LF	USA-OR (Cult)		75
		LF	China		121
		LF	USA-MD	0.04401	46
		LF	Belgium (Cult)		27
		EP	Vietnam		28
34	Artemisinin, deoxy (34)	LF	USA-MD		32
		EP	India		126
		–	China		133
35	Artemisinol (35)	EP	China		40
36	Cadin-4-en-11-ol, 3-iso-butyryl (36)	AP	India (Cult)		34
37	Cadin-4-ene,3-alpha-7-alhpa-diyhydroxy(37)	LF	China	0.0011	58
38	Cadina-4 (15)-11-dien-9-one (38)	AP	India (Cult)		34
39	Cadina-4 (7)-11-dien-12-al (39)	AP	India (Cult)		34
40	Eudesma-4 (15)-11-diene, 5-alpha-hydroxy (40)	LF	China	0.000355	58
Triterpenes					
41	Amyrenone, alpha	AP	India (Cult)		34
42	Amyrin, alpha	AP	India (Cult)		34
43	Amyrin, beta	AP	India (Cult)		34
44	Amyrin, beta: acetate	AP	Turkey		134
		AP	Spain	0.00166	109
45	Baurenol	AP	India (Cult)		34
46	Friedelan-3-beta-ol	LF	USA-MD		32
47	Friedelin	LF	USA-MD		32
48	Oleanolic acid	AP	India (Cult)		34
49	Taraxasterone	AP	India (Cult)		34
50	Taraxerol acetate	RT	India		135
Coumarins					
51	Aesculetin	AP	USSR		136
52	Coumarin	AP	China		33
		EP	China		60
		EP	China		63
		EP	China		60
		EP	China		35
		AP	England (Cult)	0.005	51
53	Eleutheroside B-1	LF + TW	Not stated		137
54	Fraxidin, iso	AP	Poland		138
55	Scopoletin	CT	Not stated		139
		EP	China		61
		EP	China		36
		EP	China		63
		AP	Poland		138
		AP	England (Cult)	0.0043	51
		AP	Spain	0.02	109
		EP	USSR		140
56	Scopolin	AP	India		141
		EP	USSR		140
57	Tomentin	LF + ST	China	0.0000105	142
Flavonoids					
58	Apigenin	LF+ ST	China	0.0000157	142
59	Artemetin	AP	USSR		143
		LF	England		144
60	Astragalin	AP	Spain	0.00016	109
		LF+ ST	China	0.000015	142
61	Axillarin	LF+ ST	China	0.0000052	145
62	Casticin	LF+ ST	China		145
		AP	USSR		143
		LF	England		144
		AP	Spain	0.002	109
		EP	Taiwan	0.01	85
		AP	England (Cult)	0.001	51
63	Chrysoeriol	LF+ ST	China	0.0000136	145
64	Chrysoplenetin	LF+ ST	China	0.00006	145
		LF	China		58
65	Chrysosplenetin	EP	India		146
		SC	Taiwan	0.06	62
		AP	USSR		143
		LF	England		144
		EP	Taiwan	0.04	62
		AP	England (Cult)	0.0033	51
66	Chrysosplenol	AP	India (Cult)	0.00314	52

Sl no.	Compound	Plant part	Country	%	Ref.
67	Chrysosplenol D	LF + ST	China	0.00018	145
		SC	Taiwan	0.06	62
		AP	Spain	0.03433	109
		EP	Taiwan	0.1	62
68	Chrysosplenol, 3′-methoxy	AP	India (Cult)	0.00114	52
69	Cirsilineol	SC	Taiwan	0.05	62
		LF+ ST	China	0.0001	145
		LF	England		142
		EP	Taiwan	0.01	62
70	Cirsiliol	LF+ ST	China	0.000074	145
71	Cirsimaritin	LF + ST	China	0.000076	145
72	Cynaroside	LF + ST	China	0.0000105	142
73	Eupatorin	LF	England		144
		LF + ST	China	0.00001	145
		EP	Taiwan	0.02	62
74	Flavone, 2′-4′-5-trihyd-roxy-5′-6-7-trimethoxy	LF + ST	China	0.0000121	145
75	Flavone, 3′-5-7-8-tetrahydroxy-3-4′-dimethoxy	LF + ST	China	0.000063	145
76	Flavone, 3-3′-5-trihydroxy-4′-6-7-trimethoxy	EP	China		61
		AP	India (Cult)	0.00171	52
77	Flavone, 3-5-dihydroxy-3′-4′-6-7-tetramethoxy	EP	China		37
		EP	China		61
78	Flavone′4-5-5′-trihydroxy-3-5-6-7-tetramethoxy	LF	England		144
79	Flavone, 5-hydroxy-3-4′-6-7-tetramethoxy	AP	England (Cult)	0.0011	51
80	Flavone, 5-hydroxy-3-4′-6-7-tetramenthoxy	EP	China		60
		EP	China		60
		LF	China		30
81	Kaempferide, Iso	LF + ST	China	0.0000105	142
82	Kaempferol	AP	Spain	0.00116	109
		LF + ST	China	0.0000315	142
83	Kaempferol, 6-methoxy: 3-O-beta-D-glucoside	AP	Spain	0.001	109
84	Luteolin	AP	Spain	0.00233	109
		LF+ ST	China	0.0000157	142
85	Luteolin-7-methyl ether	LF + ST	China	0.0000105	142
86	Pachypodol	LF	China		58
87	Patuletin	AP	Spain	0.0005	109
88	Patuletin-3-O-beta-D-glucoside	AP	Spain	0.09166	109
89	Penduletin	LF	England		144
		LF+ ST	China	0.0000078	145
		LF	China		58
90	Quercetagetin-3′-4′-6-7-tetramethyl ether	EP	Yugoslavia		147
		EP	China		63
		LF	USA-MD		32

Sl no.	Compound	Plant part	Country	%	Ref.
91	Quercetagetin-3-4′-dimethyl ether	LF + ST	China	0.0000052	145
92	Quercetagetin-3-dimethyl ether	LF + ST	China	0.000021	142
93	Quercetagetin-4′-6-7-trimethyl ether	EP	China		63
94	Quercetagetin-4′-methyl ether	LF + ST	China	0.000026	142
95	Quercetin	LF + ST	China	0.0000315	142
		AP	Spain	0.0005	109
96	Quercetin-3′-O-beta-D-glucoside	LF + ST	China	0.00013	142
97	Quercetin-3-methyl ether	LF + ST	China	0.0000052	145
98	Quercimeritrin	LF + ST	China	0.000036	142
99	Quercitrin, iso	AP	Spain	0.00083	109
		LF + ST	China	0.000031	142
100	Retusin	LF	China		58
101	Rhamnentin	LF + ST	China	0.000007	145
102	Rutin	AP	Spain	0.00166	109
103	Tamarixetin	LF + ST	China	0.0000052	145
Miscellaneous					
	(Alkane, Alkeneyne +)				
104	Annuadiepoxide	FL + LF	Germany (Cult)	0.023	148
105	Docosan-2-one	AP	Turkey		134
106	Hentriacontayl-triacontanoate	AP	India	0.22	149
107	Hexacosan-1-ol	AP	Turkey		134
108	Nonacosan-1-ol	LF + ST	India	0.0008	149
		EP	India		126
109	Nonacosane, n	AP	Turkey		134
110	Octacosan-1-ol	EP	China		37
		EP	India		126
111	Pentacosane, N	AP	Turkey		134
112	Ponticaepoxide +	RT	Not stated	Traces	150
		FL + LF	Germany (Cult)	0.0102	148
113	Triacontane,-2-29-dimethyl	LF + ST	India	0.00007	149
114	Triacosan-8-on-23-ol,2-methyl	LF + ST	India	0.00014	149
115	Tetratriacontane, n	AP	India		126
	(Alkaloids);				
116	Purine, 7-8-dihydro: 6-(3′-methyl-butyl-amino)-2-hydroxy	AP	India		151
117	Zeatin	AP	India		151
118	Zeatin, dihydro: riboside	AP	India		151
	(Benzenoids)				
119	Acetophenone, 2-4-dihydroxy-6-methoxy	AP	England (Cult)	0.0017	51
120	Annphenone	AP	India (Cult)	152	
121	Benzyl iso-valerate	EP	China		39
122	Resorcinol, 5-nona decyl:3-O-methylether	AP	England (Cult)	0.0036	51

Sl no.	Compound	Plant part	Country	%	Ref.
123	Phthalate, bis-(hydroxy-2-methyl-propyl)	AP	India		15
124	Xanthoxylin	AP	England (Cult)	0.0008	51
	(Diterpenes)				
125	Phytene-1-2-diol	AP	England (Cult)	0.0005	153
126	Phytol, trans				
127	Hentriacontan-1-ol-triacontanoate	EP	India		126
		AP	England (Cult)	153	
		AP	England (Cult)	0.0009	51
	(Monoterpenes)				
128	Fenchone	AP	India (Cult)		52
129	Myrcene alfa hydro peroxide	AP	Germany (Cult)	0.00018	154
130	Mycerene Beta Hydroperoxide	EP	Germany (Cult)	0.00133	154
		EP	China		60
		EP	India		126
		AP	India (Cult)		34
131	Tricyclene	AP	India (Cult)		52
	(Steroids)				
132	Sitosterol, beta	RT	India		135
		EP	China		60
		EP	China		37
133	Stigmasterol	RT	India		135
		EP	China		37
		AP	China		60
		EP	China		33
		LF	USA-MD		32
		EP	China		60
		EP	China		35
		AP	India (Cult)		34
		AP	India (Cult)	0.00400	52
		EP	India		126
	(Peptide alkaloid)				
134	Aurantinamide acetate	EP	China		60
	(Phenyl propanoid)				
135	Coumaric acid	AP	England (Cult)	0.002	51
	(Oxygen heterocycle)				
136	Chromene,2-2-6-trihydroxy	LF + ST	China	0.0000105	142
137	Chromene,2-2-dihydroxy-6-methoxy	LF+ ST	China	0.000015	142

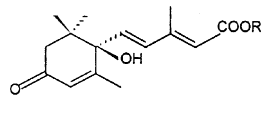
AP, Aerial part; ST, Stem; LF, Leaf; SD, Seed; FL, Flowers; TW, Twigs; RT, Root; SC, Suspension culture; EP, Entire plant; CR, Callus root; SH, Shoot; HRC, Hairy root culture; CFE, Cell-free extract Cult, Cultivated; PNS, Part not specified; CT, callus tissue.

In 1995, Hethelyi *et al.*[170] analysed Hungarian oil content from fresh flowering shoot which varies between 0.48 and 0.81%. The oil mainly consisted of artemisia ketone and artemisia alcohol, varing between 33 and 75% and 15 and 56%, respectively. The essential oil and its composition from the plants grown in Italy was also analysed.

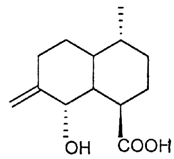
A. annua grown at Lucknow in India has been analysed for its essential oil constituents. The oil was found to contain artemisia ketone (58.8%), camphor (15.8%), 1,8-cineole (10.2%), and germacrene D (2.4%) as main constituents. The percentage of artemisia ketone was found to be less (52.3%) and 1,8-cineole more (13.1%) in the plants grown in the Himalaya region. The highest artemisia ketone containing genotype was reported from Bulgaria (80.9%), followed by the Netherlands variety (63.9%) and the US variety (63.1%)[34].

Biological activity

Biological activities reported for the compounds isolated from *A. annua* are antimalarial, antibacterial,



1. R=H
2. R=CH_3



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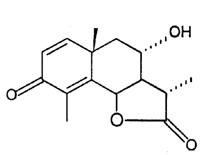

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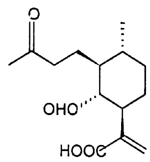
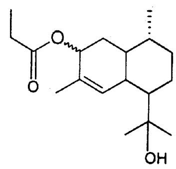


27.



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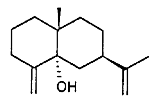

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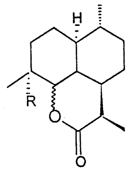
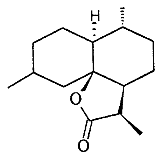
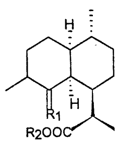


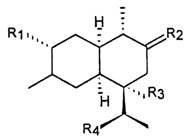
4. 5-α -O, 4 (15), 11 (13)-diene, R=H
5. 5-α -O, 3 (4), 11 (13)-diene, R=H
16. 5-β -O, 11 (13)-diene, R=OH
17. 5-α -O, 11 (13)-diene, R=OH
20. 5-α -O, 4 (15) - ene, R=H
21. 5-α -O, 3 (4) - ene, R=H



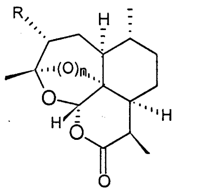
11. 4 (5), 11 (13)-diene
13. 4 (5) - ene
22. 5 β-OH, 3 (4) - ene
23. 5 β-OH, 4 (5) - ene
24. 5 β-OH, 4 - OH



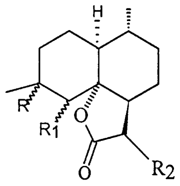
6. R_1 = HH, R_2 = H, 4 (5),11(13)-diene
7. R_1 = HH, R_2 = H, 4 (5) –ene
25. R_1 =O, R_2 = H, 3 (4) –ene
29. R_1 = HH, R_2 = CH_3, 4 (5),11(13)-diene
30. R_1 = HH, R_2 = H, 4,5 α-epoxy, 11(13)-ene
31. R_1 = HH, R_2 = H, 4 (5), 6 (7), 11(13)-triene



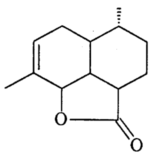
8. R_1,R_3 =H,R_2 =HH,R_4 =CH_2OH,4 (5),11(13)diene
35. R_1,R_3 =H,R_2 =HH,R_4 =CH_2OH,4 (5)- ene
37. R_1,R_3 =OH,R_2 =HH,R_4 =H,4 (5)- ene
38. R_1,R_3 =H,R_2 =O,R_4 =CH_3,4 (15),11(13)diene
39. R_1,R_3 =H,R_2 =HH,R_4 =CHO,4 (5), 7(11)diene



15. R=OH, n=1
32. R=H, n=2
33. R=H, n=2,11-13ene
34. R=H, n=1



10. R,R$_1$ =α- epoxy ; R$_2$ =CH$_2$
12. R,R$_1$ =α- epoxy ; R$_2$ =CH$_3$
14. R,R$_1$ =β- epoxy ; R$_2$ =CH$_2$
26. R,R$_1$ =OH ; R$_2$ =CH$_2$



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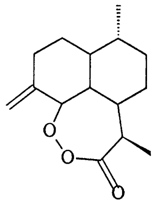

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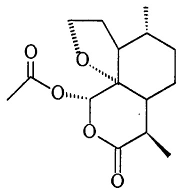

18

anti-inflammatory, angiotensin converting enzyme inhibitory, plant growth regulatory, cytokinin-like and antitumour. The various biological activities reported from different extracts of *A. annua* are summarized in Table 3 (refs 171–184).

Antimalarial

Artemisinin is a potent antimalarial even against chloroquine and quinine-resistant *Plasmodium falciparum* and other malaria-causing parasites. Its activity is based on an unusual mode of action, leading to the alkylation of malarial-specific proteins[185]. Some of the polymethoxyflavones found active in combination with artemisinin or which possess weaker activities against *P. falciparum* are: casticin[144], artemetin[144,186], chrysosplenetin, chrysosplenol-D and circilineol[186].

Table 2. Compounds isolated from essential oil of *Artemisia annua*

Sl. no.	Compound	Country	%	Compound type	Ref.
1	Artemisia alcohol	China (Cult)	7.5	–	155
		USA-CA	5.2	–	156
		China (Cult)	7.5	–	44
		Vietnam	0.1–0.6	–	28
		India (Cult)	0.155	–	34
2	Artemisia ketone	Bulgaria	–	Monoterpene	157
		France +++	52.50		158
		China ++	–		159
		Not stated	38.0	–	160
		USA-IN	68.5	–	161
		Vietnam	–	–	162
		Not stated	–	–	163
		USA-CA	35.7	–	56
		China (Cult)	63.9	–	44
		USSR	–	–	163
		England +	61.0	–	164
		China +	–	–	165
		China (Cult)	63.9	–	156
		Vietnam	0.1–4.4	–	28
		Indian (Cult)	58.84	–	34
3	Artemisia ketone, iso	Not stated		Monoterpene	163
		China			166
4	Benzyl isovalerate	China +		Benzenoid	165
5	Bicyclo (3,1,1) hept-2ene, 3-7-7-trimethyl	China +		Monoterpene	165
6	Bisabolene, beta sesquiterpene	China +	–	–	165
7	Borneol	Not stated	20.0	Monoterpene	160
		Not stated	–		167
		Vietnam	0.6–3.7	–	28
		China +	–		165
		England +	7.0	–	164
				–	
8	Borneol acetate	China	–	Monoterpene	39
				–	
9	But-2-en-1-al,3-methyl	Saudi Arabia	–	Alkanal to C4	168
10	Camphene	China	–	Monoterpene	166
		USSR	–	–	163

Sl. no.	Compound	Country	%	Compound type	Ref.
		Vietnam	0.3–1.9	–	28
		China ++			165
11	Camphene hydrate	USA-IN	12.0	Monoterpene	161
		India (Cult)	1.31		34
12	Camphor	Vietnam	21.8	Monoterpene	162
		Vietnam (Cult)	10.90		44
		France +++	27.5		158
		USA-IN	3.3		161
		China (Cult)	21.8		155
		Vietnam (Cult)	3.3		155
		China (Cult)	9.1–22.0		44
		Vietnam			28
		China			165
		Indian (Cult)	15.75		34
13	Camphor, (–)	China		Monoterpene	166
14	Caryophyllene	China +		Sesquiterpene	165
		Saudi Arabia			168
15	Caryophyllene oxide	India (Cult)	Traces	Sesquiterpene	34
16	Caryophyllene, beta	China ++		Sesquiterpene	159
		Vietnam (Cult)	5.6		44
		USSR			163
		China			166
		Vietnam (Cult)	5.6		155
		Vietnam	3.3–8.6		28
		India (Cult)	1.62		34
17	Caryophyllene, trans	China +		Sesquiterpene	165
18	Cedrol	Saudi Arabia		Sesquiterpene	168
19	Chrysanthenone	India (Cult)	Traces	Monoterpene	34
		China ++			165
		Vietnam	1.1–7.3		28
		India (Cult)	10.19		34
		England ++	3.0		164
20	Cineol, 1-4	Saudi Arabia		Monoterpene	168
21	Cineol, 1-8	India (Cult)		Monoterpene	169
		Vietnam			162
		USSR			163
		France +++	11.66		158
		USA-IN	22.8		161
		China ++			159
		Vietnam (Cult)	3.1		44
		USA-CA	31.5		156
		Not stated			167
		Vietnam (Cult)	3.1		155
22	Copaene	China +		Sesquiterpene	165
23	Copaene, alpha	Vietnam	0.1–0.3		28
		India (Cult)	0.14		34
24	Cubebene, beta	India (Cult)	0.15	Sesquiterpene	34
25	Cymene, para	USSR		Monoterpene	163
		China +			165
		Vietnam	0.1–1.5		28
26	Decan-2-one	China		Alkane	165
27	Elemene, beta			Sesquiterpene	163
28	Farnesene, beta	Vietnam		Sesquiterpene	162
		China			39
		India (Cult)	0.15		34
29	Farnesene, beta trans	Vietnam (Cult)	3.8	Sesquiterpene	44
		Vietnam	1.1–12.8		28
30	Farnesene, trans–beta	Vietnam (Cult)	0.38	Sesquiterpene	155
31	Fenchol	India (Cult)	Traces	Monoterpene	34
32	Germacrene D	Vietnam (Cult)	18.3	Sesquiterpene	44
		Vietnam (Cult)	18.3		155

Sl. no.	Compound	Country	%	Compound type	Ref.
		USA-CA	0.7		156
		Vietnam	0.3–18.9		28
		India (Cult)	2.39		34
33	Guaiene, alpha	China (Cult)	4.7	Sesquiterpene	155
		China (Cult)	4.7		44
34	Hepta-3-trans-5-diene-2-one, 6-methyl	India (Cult)	0.35	Alkene	34
35	Hex-2-en-al	China +		Alkene	165
36	Hex-cis-3-en-1-ol	China +		Alkene	165
37	Hex-trans-2-en-1-ol	China +		Alkene	165
38	Hexacosan-1-ol	Turkey		Alkane	134
39	Hexadecanoic acid ethyl ether	China +		Lipid	165
40	Hexan-1-ol acetate	China +		Alkane	165
41	Hexan-1-ol, 2-ethyl	China +		Alkene	165
42	Humulene	Vietnam	0.2–0.7	Sesquiterpene	28
43	Humulene, alpha	India (Cult)	Traces	Sesquiterpene	34
44	Limonene	China +		Monoterpene	165
		India (Cult)	0.235		34
45	Linalool	Vietnam	0.1–4.2	Monoterpene	28
46	Linalool acetate	England +	10.0	Monoterpene	164
47	Longipinene	India (Cult)	0.15	Sesquiterpene	34
48	Menthen-4-ol, para	Saudi Arabia		Monoterpene	168
49	Menthol	Bulgaria		Monoterpene	158
50	Menthol, 2-hydroxy	Saudi Arabia		Monoterpene	168
51	Myrcene	China (Cult)	5.1	Monoterpene	155
		USA-CA	4.6		156
		China (Cult)	5.1		44
		China +			165
		Vietnam	0.1–8.5		28
52	Myrtenal	India (Cult)	Traces	Monoterpene	34
53	Myrtenol	India (Cult)	0.15	Monoterpene	34
54	Nerolidol	Saudi Arabia		Sesquiterpene	168
55	Octan-1-ol	China +		Alkane	165
56	Pinene, alpha	USSR			163
		USA-CA	11.2	Monoterpene	156
		USA-IN	16.0		161
		Vietnam	0.1–1.4		28
		Not stated			163
		India (Cult)	0.39		34
57	Pinene, beta	China		Monoterpene	166
		USA-CA	1.8		156
		China + +			159
		USSR			163
		Not stated			163
		India (Cult)	1.93		34
		Vietnam	0.1–0.5		28
58	Pinocamphone	Not stated	15.0	Monoterpene	160
		Not stated			167
59	Pinocarveol, trans	USA-CA	1.1	Monoterpene	156
		USSR			163
60	Pinocarvone	USA-CA	1.3		156
		India (Cult)	1.85		34
61	Sabinene	USA-CA	2.5	Monoterpene	156
		USSR			163
		India (Cult)	0.695		34
		Vietnam	0.2–1.8		28
62	Sabinene, cis hydrate	India (Cult)	Traces	Monoterpene	34
63	Selinene, beta	USSR		Sesquiterpene	163
64	Thujone	England +	3.0	Monoterpene	164
65	Thujone, alpha	India (Cult)	Traces	Monoterpene	34
66	Thujone, iso	Not stated	9.0	Monoterpene	160
		England +	1.0		164
67	Terpinen-4-ol	China			165

Sl. no.	Compound	Country	%	Compound type	Ref.
		Vietnam India (Cult)	0.3–0.7 0.13	Monoterpene	28 34
68	Terpinene, alpha	USSR Vietnam India (Cult)	 0.2–2.1 1.16	 Monoterpene	163 28 34
69	Terpinene, gamma	USSR India (Cult)	 0.46	Monoterpene	163 34
70	Terpineol, alpha	China + Vietnam	 0.1–0.9		165 28
71	Thujene, alpha	India (Cult) +	0.39	Monoterpene	34
72	Ylangene	USSR		Sesquiterpene	163

+, Leaf essential oil; ++, Infl. essential oil; +++, Aerial part essential oil.

Table 3. Biological activities for extracts of *Artemisia annua*

Sl no.	Extract	Plant part	Country	IC50/ED50 conc. used	Species	Ref.
	Antimalarial activity					
1	Chloroform	SC	England	+ 18.5 mcg/ml	*Plasmodium falciparum*	171
2	Water ext.	”	”	+ 500.0 mcg/ml	”	”
3	Hexane ext.	”	”	+ 18.5 mcg/ml	”	”
4	Methanol ext	”	”	500 mcg/ml	”	”
5	Chloroform ext.	”	Taiwan	14.5 mcg/ml	”	62
6	Hexane ext.	LF	Belgium	++ 0.5 mg/ml		172
7	Methanol ext.	”	”	”	”	”
8	Ethanol ext.	LF	China	50.0 mg/kg	*P. berghei*	165
9	Decoction	EP	Myanmar	160.0 mg/kg	”	”
10	Ether ext.	”	”	40.0 mg/kg	”	”
11	”	”	”	++ 24.0 mg/kg	”	”
12	Pet ether ext.	”	”	40.0 mg/kg	”	”
13	”	”	”	++ 25.0 mg/kg	”	”
14	Chloroform ext.	CT	England	+ 6.0 mcg/ml	*P. falciparum*	171
15	Water ext.	”	”	500.0 mcg/ml	”	”
16	Hexane ext.	”	”	+ 18.5 mcg/ml	”	”
17	Methanol ext.	”	”	500.0 mcg/ml	”	173
18	Ethanol ext.	AP	”	+ 3.9 mcg/ml	”	174
	Antibacterial					
1	Decoction	EP	Taiwan	MIC 15.63 mg/ml	*Bordetella bronchiseptica*	175,
2	”	”	”	31.25 mg/ml	*Bacillus cereus*	176
3	”	”	”	”	*Micrococcus flavus*	
4	”	”	”	”	*Salmonella typhi*, Type2	
5	”	”	”	62.5 mg/ml	*B. subtilis*	
6	”	”	”	”	*Escherichia coli*	
7	”	”	”	”	*Klebsiella pneumoniae*	
8	”	”	”	”	*Pseudomonas aeruginosae*	
9	”	”	”	”	*Sarcina lutea*	
10	”	”	”	7.81 mg/ml	*Proteus vulgaris*	
11	”	”	”	”	*Staphylococcus aureus*	
12	”	”	”	”	*S. epidermidis*	
13	”	AP	Taiwan	15.6 mg/ml	*S. mutans*	
	Allergenic activity					
1	Water ext.	Fresh LF + ST	China	(Inhalation)	Human adult	177
2	”	”	”	(Intradermal)	”	
3	”	”	”	Nasal (–)	”	
4	”	”	”	Patch test	”	
	Mutagenic activity					
1	Water ext.	Fresh LF + ST	China	+++ 40.0 mg/plate	*Salmonella typhimurium* TA-100	178

Sl no.	Extract	Plant part	Country	IC50/ED50 conc. used	Species	Ref.
2	Water ext.	Fresh	China	+++ 40.0 mg/plate	*S. typhimurium* TA 98	
3	Water ext.	LF + ST	”	–	Mouse	
	Cholertic activity					
1	Water ext.	Dried LF	Japan	–	Rat	179
	Antiyeast activity					
1	Ethanol ext.	Dried LF	–	–	*Candida albicans*	180
	Antiviral activity					
1	Water ext.	Fresh EP	India	–	Tobacco mosaic virus	126
	Antipyretic activity					
1	–	–	–	–	Mouse	36
2	–	–	–	–	Rat	
	Anti-inflammatory					
1	–	–	–	–	Rat	36
2	–	–	–	–	Mouse	
	Analgesic activity					
1	–	–	–	–	Mouse	36
2	–	–	–	–	Rat	
	Cytotoxic activity					
1	Ethylacetate ext.	AP	Japan	+ 41.0 mcg/ml	HELA-3-3 cells	181
	Antimycobacterial activity					
1	Dichloromethane ext.	AP	Taiwan	+++ 0.1 mg/ml	*Mycobacterium aviom*	182
2	”	”	”	”	M.tuberculosis (VS-strain H 37 RV)	
	Chemiluminescence inhibition					
1	Ether ext.	AP	Vietnam	+ 20.0 mcg/ml	Polymorpho nuclear leucocytes	183
2	Ethylacetate ext.	”	”	25.0 mcg/ml	”	
3	Ethylacetate ext.	”	”	30.0 mcg/ml	”	
4	Water ext.	”	”	80.0 mcg/ml	VS	
5	Petroleum ether ext.	”	”	60.0 mcg/ml		
	Complement alternative pathway inhibition					
1	Ether ext.	AP	Vietnam	Conc. used	Serum-human	183
2	Etylacetate ext.	”	”	”	”	
3	”	”	”	”	”	
4	Water ext.	”	”	”	”	
5	Pet Ether ext.	”	”	”	”	
	Complement classical pathway inhibition					
1	Ether ext.	”	”	”	”	183
2	Etylacetate ext.	”	”	20.0 mcg/ml	”	
3	”	”	”	50.0 mcg/ml	”	
4	Water ext.	”	”	100.0 mcg/ml	Spleen (rat)	
5	Pet ether ext.	”	”	100.0 mcg/ml	Serum human	
	Lyphocyte proliferation inhibition					
1	Ether ext.	”	”	+ 40.0 mcg/ml	Lymphocyte	183
2	Etylacetate ext.	”	”	+ 75.0 mcg/ml	”	
3	”	”	”	+ 150.0 mcg/ml	Lymphocyte-T	
4	Water ext.	”	”	+ 240.0 mcg/ml	”	
5	Pet ether ext.	”	”	+ 100.0 mcg/ml	”	
	DNA polymerase inhibition					
1	Etylacetate ext.	”	China	Conc. used 10.0 mcg/ml	Hepatitis B virus	194

*VS chemiluminescence induced by Zymosan-stimulated PMN.
IC50 = +; ED50 = ++; Conc. used = +++.

Clinical studies: Artemisinin, artemether, and sodium artesunate were selected by the Chinese scientists for clinical evaluation during the early 1970s. A number of the tropical countries have started the clinical trials of artemisinin and its derivatives, which had good therapeutic effects and almost all patients were cured. Further, the treatment with artemisinin and derivatives was without any obvious side effects. More than 3000 malarial patients infected with *P. vivax* and *P. falciparum* were clinically cured by artemisinin and its derivatives. They are also effective in cerebral malaria. In general, the body temperature of patients becomes normal within 72 h and the asexual parasite formed was eliminated within 120 h[187,188].

Phase III multicentric clinical trails with arteether were conducted at 8 different centres in India in 267 patients of uncomplicated and 211 patients of complicated *P. falciparum*. These trails have established the efficacy of 3 days schedule with arteether. Recently, the drug has been cleared for marketing in India. Other artemisinin derivatives like artemether and artesunate have also been marketed in India after limited efficacy studies[189].

Artemisinin compounds offer a major advantage in the treatment of malaria due to some highly drug-resistant strains of *P. falciparum* in various parts of the world.

Antibacterial

Artemisinic acid, a well-known precursor for semisynthesis of artemisinin has shown antibacterial activity[190].

Anti-inflammatory

Scopoletin, a coumarin isolated from *A. annua* has been reported to possess anti-inflammatory activity[36]. Artemisinin, dihydro artemisinin and arteether have been found to exhibit marked suppression of humeral responses in mice at high dose level. These agents did not alter the delayed-type hypersensitivity response to sheep erythrocytes, and were not found to possess any anti-inflammatory activity when tested on carrageenan-induced oedema[191].

Angiotensin converting enzyme inhibitors

The flavonoid fisetin and patuletin-3,7-dirhamnoside, isolated from *A. annua* were found to be non-peptide angiotensin converting enzyme inhibitors[192].

Plant growth regulatory activity

Duke *et al.*[193] and Chen *et al.*[194] have found plant growth inhibitory activity in artemisinin, with potential as herbicide. Artemisinin reduced growth of the roots in lettuce and several weed species by about 50% at 33 µM. Later Bagchi *et al.*[195] have also reported plant growth regulatory activity in artemisinin and its one semi-synthetic derivative. The compounds bis(1-hydroxy-2-methylpropyl) phthalate, abscisic acid and abscisic acid methyl ester isolated from *A. annua* were also found to possess plant growth regulatory activity[125]. These results indicated that artemisinin or artemisinin-derived compounds can be used in agriculture, as herbicides.

Antitumour

In 1994, Zheng *et al.*[32] reported significant cytotoxic activity of artemisinin and quercetagetin-6,7,3′,4′-tetramethylether against P-388, A-549, Ht-29, MCF-7 and KB tumour cells. Deoxyartemisinin, artemisinic acid, arteannuin B, stigmasterol, friedelin, friedelin-3α-ol and artemetin were ineffective in the above system. In 1997 and 1998 Beekman *et al.*[196,197] found stereochemistry-dependent cytotoxicity in artemisinin and its semi-synthetic analogues.

Since artemisinin is a novel molecule by its chemical structure and mode of action, it is thus a new lead compound, which can be exploited for further drug development.

Conclusion

A. annua secondary metabolism appears to be a resource of many biologically active compounds. Artemisinin and its derivaties are already in extensive use for the control of drug-resistant malaria. *In vitro* studies on some of the other active compounds identified in *A. annua* will hopefully give new therapeutic and agricultural products of commercial importance.

1. Abba, G., *G. Bot. ltal*., 1995, **109**, 121.
2. Bodryg, M. V., *Rastil Ressy*, 1982, **18**, 558.
3. Park, J. M., Hu, W. S. and Staba, E. J., *Biotech. Bioeng*., 1989, **34**, 1209.
4. Huang, J., Xia and Zoand Wu, L. F., *Hua Hsueh Hsueh Pao*, 1987, **45**, 609.
5. Elias, P., *Preslia*, 1978, **53**, 225.
6. Ferakova, V., *Acta Fac. Rerum Nat. Univ. Comencanae. Bot*., 1973, **20**, 149.
7. Kucherezyk, H. and Marck, K., *An. Univ. Masiae Curiestelodowska Seet C Biot*, 1987, **39**, 173.
8. Leonova, T. G., *Bot. 2h* (*Leninger*), 1978, **63**, 75.
9. Singh, A., Vishwakarma, R. A. and Husain A., *Plant. Med*., 1988, **34**, 475.
10. Singh, A., Kaul, V. K., Mahagan, V. P., Singh, A, Mishra, L. N., Thakur, R. S. and Husain, A., *Indian J. Pharm. Sci*., 1986, **48**, 137.
11. Mathur, A. K. and Kumar, S., *J. Herb Spices Med. Plants*, 1996, **4**, 61–76.
12. Prasad, D., Kumar, D., Anuwar, M., Singh, D. V. and Jain, D. C., *J. Herbs Spices Med. Plants*, 1997, **5**, 49.

13. Ram, M., Gupta, M. M., Naqvi, A. A. and Kumar, S., *J. Essential Oil Res*., 1997, **9**, 193.
14. Ram, M., Gupta, M. M., Dwivedi, S. and Kumar, S., *Plant. Med*., 1997, **63**, 372.
15. Shukla, A., Abad Farooqui, A. H. and Shukla, Y. N., *Indian Drugs*, 1991, **28**, 376.
16. Misra, L. N., Ahmad, A., Thakur, R. S. and Jakupovic, J., *Phytochemistry*, 1993, **33**, 1461.
17. Brown, G. D., *Phytochemistry*, 1993, **32**, 391.
18. Kim, S. U. and Lim, H. J., *Hanguk Nonghwa Hakhoe Chi*, 1989, **32**, 178.
19. Roth, R. J. and Acton, N., *Plant. Med*., 1987, **53**, 501.
20. Woerdenbag, H. J., Pras, N., Bos, R., Visser, J. F., Hendriks, H. and Malingre, T. M., *Phytochem. Anal*., 1991, **2**, 215.
21. Weathers, P. J., Hemmavanh, D. D., Walcerz, D. B., Cheetham, R. D. and Smith, T. C., *In vitro Cell Dev. Biol. Plant*, 1997, **33**, 306.
22. Misra, L. N., Ahmad, A., Thakur, R. S., Lotter, H. and Wagner, H., *J. Nat. Prod*., 1993, **56**, 215.
23. EL-Feraly, F. S., AL-Meshal, I. A. and Khalifa, S. I., *J. Nat. Prod*., 1989, **52**, 196.
24. Vonwiller, S. C., Haynes, R. K., King, G. and Wang, H. J., *Plant. Med.*, 1999, **59**, 562.
25. Banerjee, S., Zehra, M., Gupta, M. M. and Kumar, S., *Plant. Med*., 1997, **63**, 467.
26. Gupta, M. M., Jain, D. C., Mathur, A. K., Singh, A. K. and Verma, R. K., *Plant. Med*., 1996, **62**, 280.
27. Vandenberghe, D. R., Vergauwe, A. N., Van Montagu, M. and Van Den Eeckout, E. G., *J. Nat. Prod*., 1995, **58**, 798.
28. Woerdenbag, H. J., Pras, N., Nguyen, G. C., Bui, T. B., Bos, R., Van Uden, W., Pham, V. Y., Nguyen, V. B., Batterman, S. and Lugt, C. B., *Plant. Med*., 1994, **60**, 272.
29. Kohler, M., Haerdi, W., Christen, P. and Veuthey, J. L., *Phytochem. Anal*., 1997, 223.
30. EL Sohly, N. H., Croom Jr., E. M., EL-Feraly, F. S. and EL-Sherei, M. M., *J. Nat. Prod*., 1990, **53**, 1560.
31. Elhag, H. M., EL-Domiaty, M. M., El-Feraly, F. S., Mossa, J. S. and El-Olemy, M. M., *Phytother. Res*., 1992, **6**, 20.
32. Zheng, G. Q., *Plant. Med*., 1994, **60**, 54.
33. Tian, Y., Wei, Z. X. and Wu, Z. H., *Chung TS'Ao Yao* , 1982, **13**, 249.
34. Ahmad, A. and Misra, L. N., *Phytochemistry*, 1994, **37**, 183.
35. Tian, Y., Wei, Z. and Wu, Z,. *Chung TS'Ao Yao* , 1982, **13**, 9–11.
36. Huang, L., Liu, J. F., Liu, L. X., Li, D. F., Zhang, Y., Niu, H. Z., Song, H. Y., Zhang, C. Y., Liu, X. C. and Tu, Y. Y., *Zhongguo Zhongyao Zazhi*, 1993, **18**, 44.
37. Tu, Y. Y., Zhu, Q. O. and Shen, X., *Chung Yao T'ung Pao*, 1985, **10**, 419.
38. El-Feraly, F. S., Al-Meshal, I. A., Al-Yahya, M. A. and Hifnawy, M. S., *Phytochemistry*, 1986, **25**, 2777.
39. Tu, Y. Y., Ni, M. Y., Chung, Y. Y. and Li, L. N., *Chung Yao T'ung Pao*, 1981, **6**, 31.
40. Zhu, D. Y., Zhang, S. G., Liu, B. N., Fan, G. J., Liu, J. and Xu, R. S., *Chung TS'Ao Yao* , 1982, **13**, 54.
41. Huang, J. J., Xia, Z. Q. and Wu, L. F., *Hua Hsueh Hsueh Pao*, 1987, **45**, 609.
42. Wallaart, T. E., Van Uden, W., Lubberink, G. M., Woerdenbag, H. J., Pras, N. and Quax, W. J., *J. Nat. Prod*., 1999, **62**, 430.
43. Sy, L. K., Brown, G. D. and Haynes, R., *Tetrahedron*, 1998, **54**, 4345.
44. Woerdenbag, H. J., Bos, R., Salomons, M. C., Hendrika, H., Pras, N. and Malingre, T. M., *Flavour Fragrance J*, 1993, **8**, 131.
45. Liu, J. M., Ni, M. Y., Fan, J. F., Tu, Y. Y., Wu, Y. L. and Chou, W. S., *Hua Hsueh Hsueh Pao*, 1979, **37**, 129.
46. Acton, N., Klayman, D. L., Rollman, I. J. and Novotny, J. F., *J. Chromatogr.*, 1986, **355**, 448.
47. Fulzle, D. P., Sipahimalani, A. T. and Heble, M. R., *Phytother. Res*., 1991, **5**, 149.
48. Chen, F. T., Xu, Q. C., Chen, H. R. and He, X. C., *Chung Yao T'ung Pao*, 1984, **9**, 6.
49. Stefanovic, M., Solujic, S., Jeremic, D., Jokic, A., Miljkovic, D. and Velimirovic, S., *Glas. Hem. Drus. Beograd*., 1977, **42**, 227.
50. Roth, R. J. and Acton, N. *Plant. Med*., 1987, **53**, 576.
51. Brown, G. D., *J. Nat. Prod*., 1992, **55**, 1756.
52. Misra, L. N., *Phytochemistry*, 1986, **25**, 2892.
53. Tu, Y. Y., Ni, M. Y., Zhong, Y. R., Li, L. N., Cui, Sl, Zang, M. Q., Wang, X. Z., J, Z and Liang, X. T., *Plant. Med*., 1982, **44**, 143.
54. Zhu, D. Y., Deng, D. A., Zhang, S. G. and Xu, R. S., *Hua Hsueh Hsueh Pao*, 1984, **42**, 937.
55. Wei, Z. X., Pan, J. P. and Li, Y., *Plant. Med*., 1992, **58**, 300.
56. Brown, G. D., *Phytochemistry*, 1994, **36**, 637.
57. Mengal, P., Zwegers, J. and Monpon, B., Patent-FR Demande, No. 7071166, 1994, p12.
58. Sy, L. K. and Brown, G. D., *Phytochemistry*, 1998, **48**, 1207.
59. Wu, Z. H. and Wang, Y. Y., *Hua Hsueh Hsueh Pao*, 1984, **42**, 596.
60. Tu, Y. Y., Yin, J. P., Ji, L., Huang, M. and Liang, X., *Zhongcaoyao*, 1985, 16, 200.
61. Liu, M. H., Li, K. L. and Wo, W. C., *Yao Hsueh T'ung Pao*, 1980, **15**, 39A.
62. Liu, K. C. S. C., Yang, S. L., Roberts, M. F., Elford, B. C. and Phillipson, J. D., *Plant Cell Rep*., 1992, **11**, 637.
63. Liu, H. M., Li, G. L. and Wu, H. Z., *Yao Hsueh Hsueh Pao*, 1981, **16**, 65.
64. Ram, M., Gupta, M. M., Dwivedi, S. and Kumar, S., *Plant. Med*., 1997, **63**, 372.
65. Ferreira, J. F. S and Janick, J., *Phytochemistry*, 1996, **41**, 97.
66. Liu, C. Z., Wang, Y. C., Ouyang, F., Ye, H. C. and Li, G. F. *Biotechnol. Lett*., 1997, **19**, 927.
67. Liu, C. Z., Wang, Y. C., Ouyang, F, Ye, H. C. and Li, G. F., *Biotechnol. Lett*., 1998, **20**, 265.
68. Chan, K. L., Yuen, K. H., Takayanagi, H., Janadasa, S. and Peh, K. K., *Phytochemistry*, 1997, **46**, 1209.
69. Wei, Z. X. and Tian, Y., Patent-Faming Zhuanli Shenqing Gongkai Shuomingshu, Pat. No. 87101346, 1988, p. 7.
70. Woerdenbag, H. J., Luers, J. F. J., Van Uden, W, Pras, N., Malingre, T. M. and Alfermann, A. W., *Plant. Med. Suppl*., 1992, **58**, A620.
71. Nair, M. S. R. and Basile, D. V., *Indian J. Chem*., 1992, **B31**, 880.
72. Sy, N. D., Hoan, D. B., Durg, N. P., Huong, N. V., Binh, L. N., Son, M. V. and Meshnick, S. R., *Am. J. Trop. Med. Hyg*., 1993, **48**, 398.
73. Ranasinghe, A., Sweatlock, J. D. and Cooks, R. G., *J. Nat. Prod*., 1993, **56**, 552.
74. Doan, H. D., Hang, A., Nguven, V. B. and Nguyen, N. T., *Tap Chi Duoc Hoc*, 1993, **1**, 9.
75. Duke, M. V., Paul, R. N., Elsohyly, H. N., Sturtz, G. and Duke, S. O., *Int. J. Plant Sci*., 1994, **155**, 365.
76. Ferreira, J. F. S., Simon, J. E. and Janick, J., *Plant. Med*., 1999, **61**, 167.
77. Ferreira, J. F. S., Charles, D. J., Wood, K., Janick, J. and Simon, J. E., *Phytochem. Anal*., 1994, **5**, 116.
78. Chen, P. K., Hua, H. and Yin, J. W., *Pgrsa q*., 1993, **21**, 151.
79. Bang, B. T., *Tap Chi Duoc Hoc*, 1993, **5**, 21.
80. Zhang, J. S., Fan, D. W. and Ma, X. B., Patent-Faming Zhuanli Shenqing Gongkal Shuomingshu, Pat. No. 1092073, 1994, p. 10.
81. Ge, F. H., Wang, H. B. and Liang, J. G., Patent-Faming Zhuanli Shenqing Gongkai Shuomingshu, 1095381, 1994, p. 6.
82. Xie, J. M. and Du, M. *Yunnan Daxue Xuebao Ziran Kexueban*, 1991, **13**, 280.
83. Cubukeu, B., Mericli, A. H., Ozhatay, N. and Damadyan, B., *Acta Pharm. Turc*., 1989, **31**, 41.

84. Jain, D. C., Mathur, A. K., Gupta, M. M., Singh, A. K., Verma, R. K., Gupta, A. P. and Kumar, S., *Phytochemistry*, 1996, **43**, 993.
85. Nguyen, T. D., Pham, D. T., Hoang, V. P. and Trinh, X. G., *Tap Chi Hoa Hoc*, 1995, **33**, 41.
86. Gupta, M. M., Jain, D. C., Verma, R. K. and Gupta, A. P., *J. Med. Aromat. Plant Sci*., 1996, **18**, 5.
87. Anon, K., *O Hsueh T'ung Pao*, 1977, **22**, 142.
88. Nair, M. S. R., Acton, N., Klayman, D. L., Kendrick, K., Basile, D. V. and Mante, S., *J. Nat. Prod*., 1986, **49**, 504.
89. Crom Jr., E. M., *Pharma Weekbl*., 1987, **9**, 220.
90. El-Feraly, F. S. and El Sohly, H. N., Patent-US. 4952603, 1990, p. 4.
91. Pras, N., Visser, J. F., Batterman, S., Woerdenbag, H. J., Malingre, T. M. and Lugt, C. B., *Phytochem. Anal*., 1991, **2**, 80.
92. Haigh, J. R. and Linden, J. C., *Genetic Eng. Biotechnol*., 1991, **11**, 22.
93. Zhu, H. S., *Yao Hsueh T'ung Pao*, 1980, **15**, 6.
94. Koch, H., *Pharm. Int*., 1981, **2**, 184.
95. He, X. C., Zeng, M. Y., Li, G. F. and Liang, Z., *Chih Wu Hsueh Pao*, 1983, **25**, 87.
96. Nair, M. S. R., Acton, N., Klayman, D. L., Kendrick, K. and Mante, S., Abst. Int. Res. Cong. Nat. Prod., 7–12 July 1985, Abstr. No. 102.
97. Teng, X. H., Phillipson, J. D. O. and Neill, M. J., *Fitoterapia*, 1987, **85**, 336.
98. Anon, *Chung-Hua I Hsueh Tsa Chih* (English edn), 1979, **92**, 811.
99. Proc. US–China Pharmacology Symposium, 29–31 October 1979, National Academy of Sciences, Washinton, DC, 1980, p. 137.
100. Whipkey, A., Simon, J. E., Charles, D. J. and Janick, J. J., *Herbs Spices Med. Plants*, 1992, **1**, 15.
101. Rucker, G., Mayer, R. and Manns, D., *Plant. Med*., 1986, **3**, 245.
102. Teo, C. K. H., Bana, N. A., Jinadasa, S. U. A., Chan, K. L. and Gan, E. K., Appl. Plant *in vitro* Technol. Proc. Int. Symp., 1993, 165.
103. Kasymov, S. Z., Ovezdurdyev, A., Yusupov, M. I., Sham' Yanov, I. D. and Malikov, V. M., *Chem. Nat. Comp*., 1987, **22**, 599.
104. Laughlin, J. C., *Trans. R. Soc. Trop. Med. Hyg*., *Supp1*., 1994, **88**, 21.
105. Ferreira, J. F. S., Simon, J. E. and Janick, J., *Plant. Med*., 1995, **64**, 351.
106. Zhang, X. O. and Xu, L. X., *Yao Hsueh Hsueh Pao*, 1985, **20**, 383.
107. Charles, D. J., Simon, J. E., Wood, K. V. and Heinstein, P., *J. Nat. Prod*., 1950, **53**, 157.
108. Liersch, R., Soicke, H., Stehr, C. and Tullner, H. U., *Plant. Med*., 1986, **5**, 387.
109. Marco, J. A., Sanz, J. F., Bea, J. F. and Barbera, O., *Pharmazie*, 1990, **45**, 382.
110. Acton, N., Klayman, D. L. and Rollman, I. J., *Plant. Med*., 1985, **5**, 445.
111. El Sohly, H. N., Hala, N., Croom, E. M. and EL Sohly, M. A., *Pharm. Res*. 1987, **4**, 258.
112. Chan, K. L., Teo, C. K. H., Jinadasa, S. and Yuen, K. H., *Plant. Med.*, 1995, **61**, 285.
113. Paniego, N. B., Maligne, A. E. and Giulietti, A. M., *Biotechnol. AGR. For.*, 1993, **24**, 64.
114. Zhao, S. S. and Zeng, M. Y., *Plant. Med*., 1985, **3**, 233.
115. Woerdenbag, H. J., Luers, J. F. J., Van Uden, W. M., Pras, N., Malingre, T. M. and Alfermann, A. W., *Plant Cell Tissue Org. Cult.*, 1993, **32**, 247.
116. Rey, J. P., Levesque, J. and Pousset, J. L., *J. Chromatogr.*, 1992, **605**, 124.
117. Zhao, S. S. and Zeng, M. Y., *Yaowu Fenxi Zazhi* , 1986, **6**, 324.
118. Bruce-Chwatt, L. J., *Br. Med. J.*, 1982, **284**, 767.
119. De Lampasona, M. E. P., De Delfini, M. L. T. and De Riscals, E. C., *An Asoc. Quim Argent* ., 1990, **78**, 333.
120. Luo, H. M., Chao, P. P., Yu, C. C., Tai, C and Liu, C. W., *Yao Hsueh T'ung Pao*, 1980, **15**, 6.
121. Wei, Z. X., Patent-Faming Zhuanli Shenqing Gongkai Shuomingshu, Patent No. 1047503, 1990, p. 20.
122. Jaziri, M., Diallo, B., Vanhaelen, M., Homes, J., Yoshimatsu, K. and Shimomura, K., *Phytochemistry*, 1983, **33**, 821.
123. Woerdenbag, H. J., Pras, N., Van Uden, W., De Boer, A., Batterman, S., Visser, J. F. and Malingre, T. M., *Nat. Prod. Lett*., 1992, **1**, 121.
124. Maillard, M. P., Wolfender, J. L. and Hostettmann, K, *J. Chromatogr.*, 1993, **647**, 147.
125. Shukla, A., Abad Farooqi, A. H., Shukla, Y. N. and Sharma, S., *Plant Growth Regul*., 1992, **11**, 165.
126. Khan, M., Jain, D. C., Bhakuni, R. S., Zaim, M. and Thakur, R. S., *Plant Sci*., 1991, **75**, 161.
127. Brown, G. D., *J. Nat. Prod*., 1994, **57**, 328.
128. Klayman, D. L., Lin, A. J., Acton, N., Scovill, J. P., Hoch, J. M., Milhous, W. K. and Theoharides, A. D., *J. Nat. Prod*., 1984, **47**, 715.
129. Haynes, R. K. and Vonwiller, S. C., *Trans. R. Soc. Trop. Med. Hyg*., 1994, **88**, 23.
130. Anon, WHO Document TDR/Chemal-Swg, Pat No. (4)/(Qhs)/ 81.3, 1981, p. 19.
131. Acton, N and Klayman, D. L., *Plant. Med*., 1985, **5**, 441.
132. Klayman, D. L., Acton, N. and Lin, A. J., Princess Congress I, Thailand, 10–13 December 1987, Abstr CI-8.
133. Zhou, W. S. and Xu, X. X., *Pharm. Ind*., 1987, **18**, 470.
134. Ulubelen, A. and Halfon, B., *Plant. Med*., 1976, **29**, 258.
135. Agrawal, P. K. and Bishnoi, V., *Indian J. Chem*., 1996, **B35**, 86.
136. Aleskerova, A. N., *Izv. Akad. Nauk. Az. SSR Biol. Nauk* ., 1985, **2**, 25.
137. Plouvier, V., *CR Acad. Sci. Ser. III* , 1985, **301**, 117.
138. Danielak, R. and Borkowski, B., *Diss Pharm. Pharmacol*, 1970, **22**, 231.
139. Brown, G. D., *J. Nat. Prod*., 1994, **57**, 975.
140. Rakhmankulov, U., Kasymov, S. Z., Taizhanov, K., Korotkova, E. E. and Sidyakin, G. P., *Rastit. Resur*., 1979, **15**, 79.
141. Agarwal, P. K., Singh, A. K., Bhakuni, R. S. and Jain, D. C., *Curr. Res. Med. Aromatic Plants*, 1995, **17**, 321.
142. Yang, S. L., Roberts, M. F., O'Neill, M. J., Bucar, F. and Phillipson, J. D., *Phytochemistry*, 1995, **38**, 255.
143. Baeva, R. T., Nabizade, L. I., Zapesochnaya, G. G. and Karryev, M. O., *Chem. Nat. Comp*., 1988, **24**, 256.
144. Yang, S., Roberts, M. F. and Phillipson, D., *J. Pharm. Pharmacol. Suppl*., 1988, **40**, 106.
145. Shilin, Y., Roberts, M. F. and Phillipson, J. D., *Phytochemistry*, 1989, **28**, 1509.
146. Bhardwaj, D. K., Jain, R. K., Jain S. C. and Manchanda, C. K., *Proc. Indian Natl. Sci. Acad*., 1985, **A51**, 741.
147. Djermanovic, M., Jokic, A., Mladenovic, S. and Stefanovic, M., *Phytochemistry*, 1985, **14**, 1873.
148. Manns, D. and Hartmann, R., *J. Nat. Prod*., 1992, **55**, 29.
149. Bhakuni, R. S., Jain, D. C., Shukla, Y. N. and Thakur, R. S., *J Indian Chem Soc*., 1990, **67**, 1004.
150. Bohlmann, F., Arnot, C. and Bornowski, H., *Chem Ber*., 1960, **93**, 1937.
151. Shukla, A., Farooqi, A. H. A. and Shukla, Y. N., *J. Indian Chem. Soc*., 1997, **74**, 59.
152. Singh, A. K., Pathak, V. and Agrawal, P. K., *Phytochemistry*, 1997, **44**, 555.
153. Brown, G. D., *Phytochemistry*, 1994, **36**, 1553.
154. Rucker, G., Mayer, R. and Manns, D., *J. Nat. Prod*., 1987, **50**, 287.
155. Woerdenbana, H. J., Bos, R., Salomons, M. C., Hendriks, H., Pras, N. and Malingre, T. M., *Plant. Med. Suppl.*, 1992, **58**, A682.

156. Libbey, L. M. and Sturtz, G., *J. Essential Oil Res.*, 1989, **1**, 201.
157. Toleva, P. D., Ognyanov, I. V., Karova, E. A. and Georgiev, E. V., Int Congress Essential Oils (PAP) 6th Allured Publ Corp., 1974, vol. 117, p. 7.
158. Chalchat, J. C., Garry, R. P., Michet, A., Gorunovic, M. and Stosic, D., *Acta Pharm. Jugosl.*, 1991, **41**, 233.
159. Liu, Q., Yang, Z., Sa, G. and Wang, X., *Chih Wu Hsueh Pao*, 1988, **30**, 223.
160. Banthorpe, D. V., Charlwood, B. V., Greaves, G. M, and Voller, C. M., *Phytochemistry*, 1977, **16**, 1387.
161. Charles, D. J., Cebert, E. and Simon, J. E., *J. Essential Oil Res.*, 1991, **3**, 33.
162. Nguyen, X. D., Leclercq, P. A., Dinh, H. K. and Nuuyen, M. T., *Tap Chi Duoc Hoc*, 1990, **2**, 11.
163. Dembitskii, A. D., Krotova, G. I., Kuchukhidze, N. M. and Yakobashvili, N. Z., *Maslo-zhir. Promst.*, 1983, **3**, 31.
164. Banthorpe, D. B., Baxendale, D., Gatford, C. and Williams, S. R., *Plant. Med.*, 1971, **20**, 147.
165. Hu, S., Xu, Z., Pan, J. and Hou, Y., *J. Res. Educ. Ind. Med*., 1993, **3**, 9.
166. Zhong, Y. and Cui, S., *Chung Yao T'ung Pao*, 1983, **8**, 31.
167. Allen, K. U., Banthorpe, D. V., Charlwood, B. V. and Voller, C. M., *Phytochemistry*, 1977, **16**, 79.
168. Alkhathalan, H. Z., Al-Zoman, M. M., Basha, R. M. and Mousa, A. A., *Al-Orient J. Chem.* 1991, **7**, 204.
169. Fulzele, D. P., Heble, M. R. and Rao, P. S., *J. Biotechnol.*, 1995, **40**, 139.
170. Hethelyi, E. B., Cseko, I. B., Grosy, M., Mark, G. and Palinkas, J. J., *J. Essential Oil Res.*, 1995, **7**, 45.
171. Tawfiq, N. K., Anaderson, L. A., Roberts, M. F., Phillipson, J. D., Bray, D. H. and Warhurst, D. C., *Plant Cell Rep.*, 1989, **8**, 425.
172. Francois, G., Docchez, C., Jaziri, M. and Laurent, A., *Plant. Med. Suppl*., 1993, **59**, A677.
173. Lwin, M., Maun, C. and Aye, K. H., *Trans. R. Soc. Trop. Med. Hyg.*, 1991, **85**, 449.
174. O' Neill, M. J., Bray, D. H., Boardman, P., Phillipson, J. D. and Warhurst, D. C., *Plant. Med.*, 1985, **5**, 394.
175. Chen, C. P., Lin, C. C. and Namba, T., *Shoyakugaku Zasshi*, 1987, **3**, 215.
176. Chen, C. P., Lin, C. C. and Namba, T, *J. Ethnopharmacol.*, 1989, **27**, 285.
177. Leng, X. and Ye, S. T., *Asian PAC J. Allergy Immunol*., 1987, **5**, 125.
178. Yin, X. J., Liu, D. X., Wang, H. and Zhou, Y., *Mutat. Res*., 1991, **260**, 73.
179. Okuno, I., Uchida, K. and Namba, T., *Yakugaku Zasshi*, 1984, **104**, 384.
180. Scharfenberger, M., *Chimia*, 1998, **52**, 641.
181. Takatsuki, S., Narui, T., Ekimoto, H., Abuki, H., Niijima, K. and Okuyama, T., *Nat. Med*., 1996, **50**, 145.
182. Cantrell, C. L., Fischer, N. H., Urbatsch, L., Mc Guire, M. S. and Franzblau, S. G., *Phytomedicine*, 1998, **5**, 137.
183. Kroes, B. H., Quaries, H. C., Van Ufford, Q., Tinbergen-De Boer, R. L., Van Den Berg, A. J. J., Beukelman, C. J., Labadie, R. P. and Van Dijk, H., *Phytother. Res.*, 1995, **9**, 551.
184. Ghisalberti, E. L., Skelton, B. W. and White, A. H., *Aust. J. Chem.*, 1995, **48**, 1771.
185. Fesen, M. R., Pommier, Y., Leteurtre, F., Heroguchi, S., Yang, J. and Kohn, K. W., *Biochem. Pharmacol.*, 1994, **48**, 595.
186. Cubukcu, B., Bray, D. H., Warhust, D. C., Mericli, A. H., Ozhalay, N. and Sariyar, G., *Phytother. Res.*, 1990, **4**, 203.
187. Xuan De Wo and Chia-Chiang Shen, *Med. Res. Rev*., 1987, **7**, 29.
188. Zeffer, H., Hight, H. J. and Klayman, D. C., *Progress in the Chemistry of Organic Natural Products* (eds Herz, W. *et al.*), Springer, New York, 1997, vol. 72, p. 121.
189. Jain, D. C., Bhakuni, R. S., Gupta, M. M., Sharma, R. P., Kahol, A. P., Dutta, G. P. and Kumar, S. J., *Sci. Ind. Res.*, 2000, **59**, 1.
190. Roth, R. S. and Acton, N., *J. Nat. Prod.*, 1989, **52**, 1183.
191. Tavlik, A. F., Bishop, S. J., Ayalp, A. and EL-Feraly, F. S., *Int. J. Immunol. Pharmacol.*, 1990, **12**, 385.
192. Lin, J. Y., Chen, T. S. and Chen, C. S., Jpn-Kokai Tokkyo Koho Jp, Patent No. 06135830, 1994.
193. Duke, S. O., Vaughn, K. C., Croom Jr., E. M. and Elsohly, H. N., *Weed Sci*., 1987, **35**, 499.
194. Chen, P. K., Leather, G. R. and Klayman, D. L., *Plant Physiol.*, 1987, **83**, 406.
195. Bagchi, G. D., Jain, D. C. and Kumar, S., *Phytochemistry*, 1997, **45**, 1131.
196. Beekman, A. C., Barentesen, A. R. W., Woedenbag, H. J., Wden, W. V., Pras, N., Konings, A. W. T., El-Feraly, F. S., Galal, A. M. and Wikstrom, H. V., *J. Nat. Prod.*, 1997, **60**, 325.
197. Beekman, A. C., Wierenga, P. K., Woedenbag, H. J., Uden, W. V., Pras, N., Konings, A. W. T., El-Feraly, F. S., Galal, A. M. and Wikstrom, H. V., *Plant. Med.*, 1997, **64**, 615.

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