

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.

Monoterpeneoids

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

Sl no.	Compound	Plant part	Country	%	Ref.	Sl no.	Compound	Plant part	Country	%	Ref.
67	Chrysosplenol D	LF + ST	China	0.00018	145	91	Quercetagelin-3-4'-dimethyl ether	LF + ST	China	0.0000052	145
		SC	Taiwan	0.06	62	92	Quercetagelin-3-dimethyl ether	LF + ST	China	0.000021	142
		AP	Spain	0.03433	109	93	Quercetagelin-4'-6-7-trimethyl ether	EP	China		63
		EP	Taiwan	0.1	62	94	Quercetagelin-4'-methyl ether	LF + ST	China	0.000026	142
68	Chrysosplenol, 3'-methoxy	AP	India (Cult)	0.00114	52	95	Quercetin	LF + ST	China	0.0000315	142
69	Cirsilineol	SC	Taiwan	0.05	62	96	Quercetin-3'-O-beta-D-glucoside	LF + ST	Spain	0.0005	109
		LF+	China	0.0001	145	97	Quercetin-3-methyl ether	LF + ST	China	0.000013	142
		ST	England		142	98	Quercimeritin	LF + ST	China	0.000052	145
		EP	Taiwan	0.01	62	99	Quercitrin, iso	AP	Spain	0.000036	142
70	Cirsiliol	LF+	China	0.000074	145	100	Retusin	LF	China	0.00083	109
71	Cirsimarin	ST	China	0.000076	145	101	Rhamnentin	LF + ST	China	0.000031	142
		LF + ST	China			102	Rutin	AP	Spain	0.00166	109
72	Cynaroside	LF + ST	China	0.0000105	142	103	Tamarixetin	LF + ST	China	0.0000052	145
		LF	England		144	<i>Miscellaneous</i> (Alkane, Alkeneyne +)					
		LF +	China	0.00001	145	104	Annuadiepoxyde	FL + LF	Germany (Cult)	0.023	148
		ST	China			105	Docosan-2-one	AP	Turkey		134
73	Eupatorin	EP	China		61	106	Hentriacontyl-triacontanoate	AP	India	0.22	149
		AP	India (Cult)	0.00171	52	107	Hexacosan-1-ol	AP	Turkey		134
74	Flavone, 2'-4'-5-trihydroxy-5'-6-7-trimethoxy	LF + ST	China	0.0000121	145	108	Nonacosan-1-ol	LF + ST	India	0.0008	149
		LF	China			109	Nonacosane, n	EP	Turkey		126
75	Flavone, 3'-5-7-8-tetrahydroxy-3-4'-dimethoxy	LF + ST	China	0.000063	145	110	Octacosan-1-ol	EP	China	0.37	134
		EP	China			111	Pentacosane, N	EP	India		126
76	Flavone, 3-3'-5-trihydroxy-4'-6-7-trimethoxy	AP	China		61	112	Ponticaepoxide +	RT	Not stated	Traces	134
		AP	India (Cult)	0.00171	52	113	Triacontane,-2-29-dimethyl	FL + LF	Germany (Cult)	0.0102	148
77	Flavone, 3-5-dihydroxy-3'-4'-6-7-tetramethoxy	EP	China		37	114	Triacosan-8-on-23-ol,2-methyl	LF + ST	India		126
		EP	China		61	115	Tetratriacontane, n	AP	Turkey		134
78	Flavone'4-5-5'-trihydroxy-3-5-6-7-tetramethoxy	LF	England		144	116	(Alkaloids); Purine, 7-8-dihydro: 6-(3'-methyl-butyl-amino)-2-hydroxy	AP	India		126
		AP	England (Cult)	0.0011	51	117	Zeatin	AP	India		134
79	Flavone, 5-hydroxy-3-4'-6-7-tetramethoxy	EP	China		60	118	Zeatin, dihydro: riboside	AP	India		126
		EP	China		60	119	(Benzenoids)	AP	India (Cult)		134
80	Flavone, 5-hydroxy-3-4'-6-7-tetramethoxy	LF	China		30	120	Acetophenone, 2-4-dihydroxy-6-methoxy	AP	India (Cult)		126
		LF	China			121	Anphenone	AP	India	152	134
81	Kaempferide, Iso	LF + ST	China	0.0000105	142	122	Benzyl iso-valerate	EP	China	0.00007	149
		AP	Spain			123	Resorcinol, 5-nona-decyl:3-O-methylether	AP	England (Cult)	0.0036	151
82	Kaempferol	AP	Spain	0.00116	109	124					151
		LF + ST	China	0.0000315	142	125					151
83	Kaempferol, 6-methoxy: 3-O-beta-D-glucoside	AP	Spain	0.001	109	126					151
		AP	Spain			127					151
84	Luteolin	AP	Spain	0.00233	109	128					151
		LF + ST	China	0.0000157	142	129					151
85	Luteolin-7-methyl ether	LF + ST	China	0.0000105	142	130					151
		LF	China			131					151
86	Pachypodol	LF	China		58	132					151
		AP	Spain	0.0005	109	133					151
87	Patuletin	AP	Spain	0.09166	109	134					151
		AP	Spain			135					151
88	Patuletin-3-O-beta-D-glucoside	LF	China		58	136					151
		LF	China			137					151
89	Penduletin	LF	England		144	138					151
		LF + ST	China	0.0000078	145	139					151
90	Quercetagelin-3'-4'-6-7-tetramethyl ether	EP	Yugoslavia		147	140					151
		EP	China		63	141					151
91	Quercetagelin-3'-4'-6-7-tetramethyl ether	LF	USA-MD		32	142					151

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

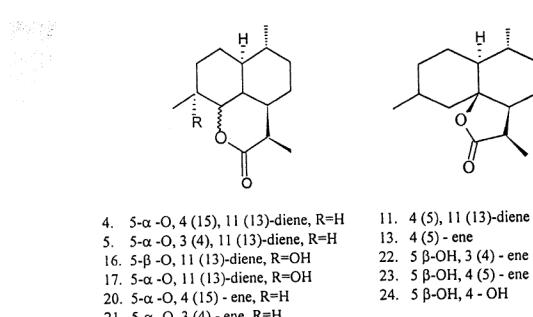
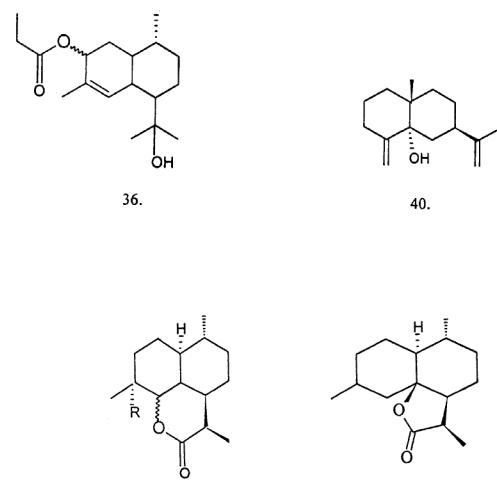
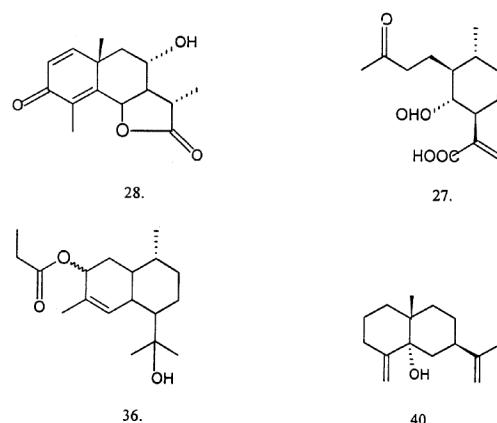
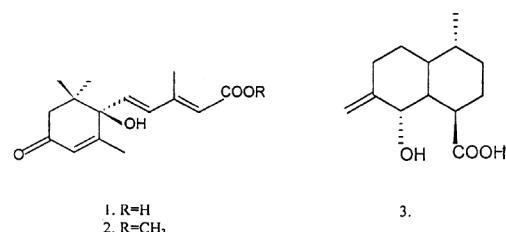
In 1995, Hethelyi *et al.*¹⁷⁰ analysed Hungarian oil content from fresh flowering shoot which varies between 0.48 and 0.81%. The oil mainly consisted of artemisia ketone and artemisia alcohol, varying between 33 and 75% and 15 and 56%, respectively. The essential oil and its composition from the plants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

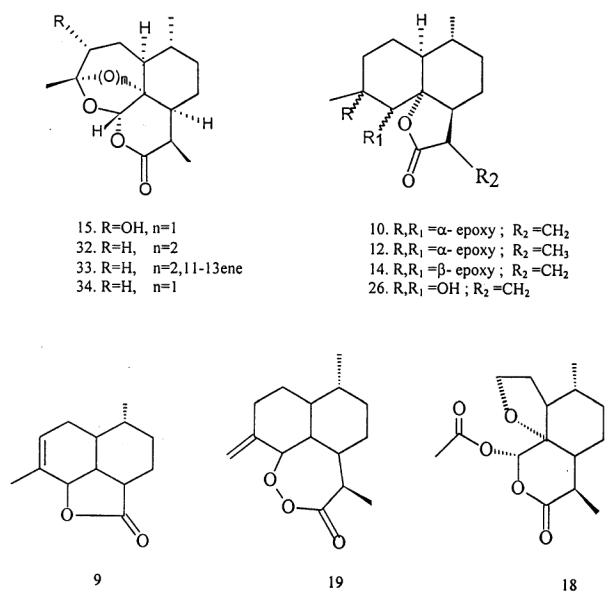
A. annua grown at Lucknow in India has been analysed for its essential oil constituents. The oil was found to contain artemisia ketone (58.8%), camphor (15.8%), 1,8-cineole (10.2%), and germacrene D (2.4%) as main constituents. The percentage of artemisia ketone was found to

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,





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 proteins¹⁸⁵. Some of the polymethoxy-flavones found active in combination with artemisinin or which possess weaker activities against *P. falciparum* are: casticin¹⁴⁴, artemetin^{144,186}, chrysosplenitin, chrysosplenol-D and circilineol¹⁸⁶.

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
3	Artemisia ketone, iso	China (Cult)	63.9	Monoterpene	156
		Vietnam	0.1–4.4		28
4	Benzyl isovalerate	Indian (Cult)	58.84	Monoterpene	34
		Not stated	—		163
5	Bicyclo (3,1,1) hept-2ene, 3-7-7-trimethyl	China	—	Monoterpene	166
		China +	—		165
6	Bisabolene, beta sesqui- terpene	China +	—	Monoterpene	165
		Not stated	—		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
		Saudi Arabia	—		—
9	But-2-en-1-al,3-methyl	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.
33	Guaiene, alpha	USA-CA	0.7	Sesquiterpene	156
		Vietnam	0.3–18.9		28
		India (Cult)	2.39		34
34	Hepta-3-trans-5-diene-2-one, 6-methyl	China (Cult)	4.7	Alkene	155
		China (Cult)	4.7		44
34	Humulene, alpha	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		Monoterpene	163
		USA-CA	11.2		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
58	Pinocamphone	Vietnam	0.1–0.5	Monoterpene	28
		Not stated	15.0		160
59	Pinocarveol, trans	Not stated	15.0	Monoterpene	167
		Not stated	1.1		156
60	Pinocarvone	USA-CA	1.1	Monoterpene	163
		USSR			156
61	Sabinene	USA-CA	1.3	Monoterpene	34
		India (Cult)	1.85		163
62	Sabinene, cis hydrate	USA-CA	2.5	Monoterpene	156
		USSR			163
		India (Cult)	0.695		34
		Vietnam	0.2–1.8		28
63	Selinene, beta	India (Cult)	Traces	Monoterpene	34
		USSR			163
64	Thujone	England +	3.0	Monoterpene	164
		India (Cult)	Traces		34
65	Thujone, alpha	Not stated	9.0	Monoterpene	160
		England +	1.0		164
66	Terpinen-4-ol	China			165

Sl. no.	Compound	Country	%	Compound type	Ref.
		Vietnam	0.3–0.7	Monoterpene	28
		India (Cult)	0.13		34
68	Terpinene, alpha	USSR			163
		Vietnam	0.2–2.1	Monoterpene	28
		India (Cult)	1.16		34
69	Terpinene, gamma	USSR		Monoterpene	163
		India (Cult)	0.46		34
70	Terpineol, alpha	China +			165
		Vietnam	0.1–0.9		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.
<i>Antimalarial activity</i>						
1	Chloroform	SC	England	+ 18.5 mcg/ml	<i>Plasmodium falciparum</i>	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	<i>P. berghei</i>	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	<i>P. falciparum</i>	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
<i>Antibacterial</i>						
1	Decoction	EP	Taiwan	MIC 15.63 mg/ml	<i>Bordetella bronchiseptica</i>	175,
2	"	"	"	31.25 mg/ml	<i>Bacillus cereus</i>	176
3	"	"	"	"	<i>Micrococcus flavus</i>	
4	"	"	"	"	<i>Salmonella typhi</i> , Type2	
5	"	"	"	62.5 mg/ml	<i>B. subtilis</i>	
6	"	"	"	"	<i>Escherichia coli</i>	
7	"	"	"	"	<i>Klebsiella pneumoniae</i>	
8	"	"	"	"	<i>Pseudomonas aeruginosa</i>	
9	"	"	"	"	<i>Sarcina lutea</i>	
10	"	"	"	7.81 mg/ml	<i>Proteus vulgaris</i>	
11	"	"	"	"	<i>Staphylococcus aureus</i>	
12	"	"	"	"	<i>S. epidermidis</i>	
13	"	AP	Taiwan	15.6 mg/ml	<i>S. mutans</i>	
<i>Allergenic activity</i>						
1	Water ext.	Fresh LF + ST	China	(Inhalation)	Human adult	177
2	"	"	"	(Intradermal)	"	
3	"	"	"	Nasal (-)	"	
4	"	"	"	Patch test	"	
<i>Mutagenic activity</i>						
1	Water ext.	Fresh LF + ST	China	+++ 40.0 mg/plate	<i>Salmonella typhimurium</i> TA-100	178

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Sl no.	Extract	Plant part	Country	IC50/ED50 conc. used	Species	Ref.
2	Water ext.	Fresh LF + ST	China	+++ 40.0 mg/plate	<i>S. typhimurium</i> TA 98	
3	Water ext.		"	-	Mouse	
<i>Choleric activity</i>						
1	Water ext.	Dried LF	Japan	-	Rat	179
<i>Antiyeast activity</i>						
1	Ethanol ext.	Dried LF	-	-	<i>Candida albicans</i>	180
<i>Antiviral activity</i>						
1	Water ext.	Fresh EP	India	-	Tobacco mosaic virus	126
<i>Antipyretic activity</i>						
1	-	-	-	-	Mouse	36
2	-	-	-	-	Rat	
<i>Anti-inflammatory</i>						
1	-	-	-	-	Rat	36
2	-	-	-	-	Mouse	
<i>Analgesic activity</i>						
1	-	-	-	-	Mouse	36
2	-	-	-	-	Rat	
<i>Cytotoxic activity</i>						
1	Ethylacetate ext.	AP	Japan	+ 41.0 mcg/ml	HELA-3-3 cells	181
<i>Antimycobacterial activity</i>						
1	Dichloromethane ext.	AP	Taiwan	+++ 0.1 mg/ml	<i>Mycobacterium aviom</i>	182
2	"	"	"	"	M.tuberculosis (VS-strain H 37 RV)	
<i>Chemiluminescence inhibition</i>						
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		
<i>Complement alternative pathway inhibition</i>						
1	Ether ext.	AP	Vietnam	Conc. used	Serum-human	183
2	Ethylacetate ext.	"	"	"	"	
3	"	"	"	"	"	
4	Water ext.	"	"	"	"	
5	Pet Ether ext.	"	"	"	"	
<i>Complement classical pathway inhibition</i>						
1	Ether ext.	"	"	"	"	183
2	Ethylacetate 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	
<i>Lymphocyte proliferation inhibition</i>						
1	Ether ext.	"	"	+ 40.0 mcg/ml	Lymphocyte	183
2	Ethylacetate 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	"	
<i>DNA polymerase inhibition</i>						
1	Ethylacetate 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 trials with arteether were conducted at 8 different centres in India in 267 patients of uncomplicated and 211 patients of complicated *P. falciparum*. These trials 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 studies¹⁸⁹.

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 activity¹⁹⁰.

Anti-inflammatory

Scopoletin, a coumarin isolated from *A. annua* has been reported to possess anti-inflammatory activity³⁶. 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 oedema¹⁹¹.

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 inhibitors¹⁹².

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 activity¹²⁵. 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 derivatives 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.

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