REVIEW

Chemical Constituents of Agarwood Originating from the Endemic Genus *Aquilaria* Plants

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Contents

1. Introduction. – The genus *Aquilaria* belongs to Thymelaeceae, and comprises *ca.* 15 species which are distributed in Southeast Asia. Eight such species have been reported for the formation of agarwood [1]. Agarwood, also known as '*chenxiang*' in Chinese and called '*aloeswood*', '*agalloch*', '*eaglewood*', '*jinkoh*', '*gaharu*', or '*Kanan-*

koh' in different regions, is a fragrant wood. Being a highly valuable non-timber product from Asian tropical forests, agarwood is used for incenses, perfumes, traditional medicines, and other products in the world market. Agarwood cannot be generated in normal wood tissues, but might be formed when the *Aquilaria* plants are injured by insects, physical cuts, bacterial infections, or chemical stimulation [2]. Nowadays, the demand for agarwood far exceeds the supply, and the eight *Aquilaria* species have declined to the threatened level according to the *IUCN Red List* [3]. Studies on the chemical constituents of agarwood started half a century ago. Different from the healthy wood of *Aquilaria* plants, except for fatty acids and alkanes, agarwood contains sesquiterpenes and 2-(2-phenylethyl)-4*H*-chromen-4-one derivatives, characteristic chemical constituents that have never been detected in the normal tissues of the original plants [4][5].

Here, we review the progress achieved in phytochemical studies of agarwood, list the compounds isolated from agarwood over the past few decades, and introduce the biological activities of the components isolated from agarwood in recent years.

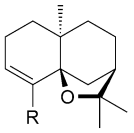
2. Chemical Constituents. –The chemical constituents **1**–**132** of agarwood originating from the genus *Aquilaria* include sesquiterpenes, 2-(2-phenylethyl)-4*H*-chromen-4-one derivatives, aromatics, triterpenes, *etc*. Their structures are shown below, and their names and the corresponding plant sources/origins are compiled in the *Table*. Sesquiterpenes and 2-(2-phenylethyl)-4*H*-chromen-4-one derivatives are the two predominant constituents in agarwood.

2.1. *Sesquiterpenes.* Sesquiterpenes in agarwood are divided into several categories depending on their skeleton.

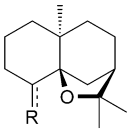
2.1.1. *Agarofurans.* From 1959 to 1965, *Battacharrya* and co-workers investigated the essential oil extracted from the fungus-infected agarwood (*A. agallocha* Roxb.), and obtained six agarofuran-type compounds, **1**–**6** [6][11]. The C=C bond in β-agarofuran was of methylenic character (>C=CH) [6]. From the volatile oil of the agarwood originating from *A. sinensis* (Lour.) Gilg, *Yang et al.* [8][12][13] isolated four new agarofuran compounds, **7**–**10**. Later, compounds **11**–**14** were isolated from the agarwood oil from *A. agallocha* [14][15]. Their structures were confirmed through synthesis.

2.1.2. *Agarospiranes. Battacharrya* and co-workers [16] isolated sesquiterpenoid compound **15** with a new agarospirane skeleton from the fungus-infected agarwood (*A. agallocha*). It is a well-known constituent of agarwood oil. Compounds **16** and **17** were found along with compound **15** in agarwood (*A. sinensis*) [17]. Phytochemical investigation of the oil distilled from agarwood (*A. malaccensis*), collected in Cambodia, led to the isolation of two new agarospirane-type compounds, **18** and **19** [18]. Compounds **20**–**23** with the vetispirane-skeleton are included here, as the vetispirane-skeleton is similar to the agarospirane-skeleton [19]. In 2006, *Ueda et al.* [20] isolated a new spirovetivane-type sesquiterpene, **24**.

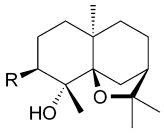
2.1.3. *Guaianes.* In total, 15 guaianes, **25**–**39**, have been isolated from the agarwood originating from different *Aquilaria* species. *Xu et al.* [9] isolated compounds **25** and **26**, as well as compounds **2**, **16**, **17**, and **58**. *Ishihara et al.* [10][21–23] characterized a series of newly identified compounds **27**–**36** with guaiane skeleton in agarwood (Kanankoh) oil from *A. agallocha* (Vietnam), as well as two known compounds **37** and **38**. Among



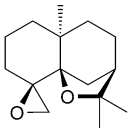
1 R = Me
8 R = CH_2OH



2 R = CH_2=
3 R = α-Me
4 R = O=
7 R = α-CH_2OH
9 R = β-CH_2OH
10 R = β-COOH
11 R = H
12 R = α-OH



5 R = H
6 R = OH



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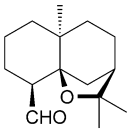

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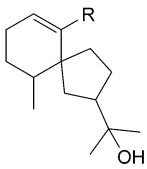
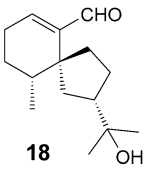


15 R = Me
16 R = COOH
17 R = CHO



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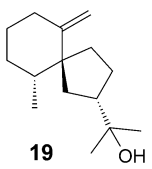

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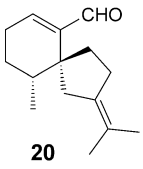

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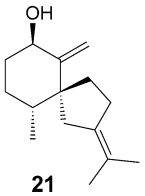

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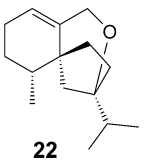

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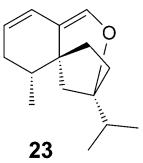

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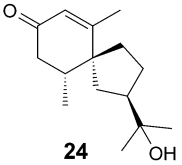

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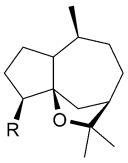

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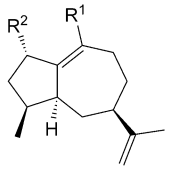
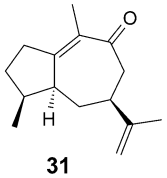
26 R = CHO



27 R^1 = CHO, R^2 = H
28 R^1 = CH_2OH, R^2 = H
29 R^1 = COOH, R^2 = H
30 R^1 = COOMe, R^2 = H
35 R^1 = COOH, R^2 = OH
38 R^1 = Me, R^2 = H



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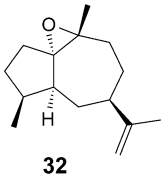

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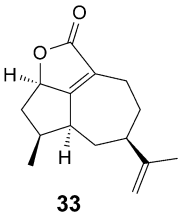

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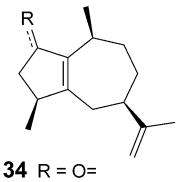
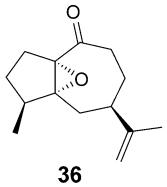


34 R = O=
37 R = H



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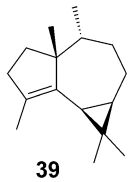

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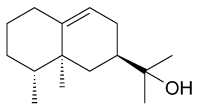

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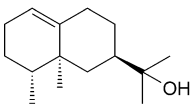

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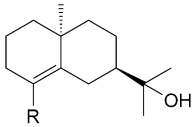
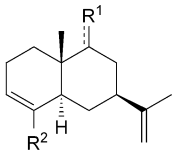
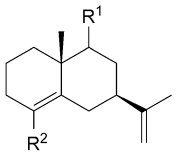


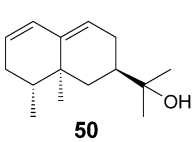
42 R = Me
51 R = H



43 R^1 = O=, R^2 = Me
44 R^1 = OH, R^2 = Me
45 R^1 = H, R^2 = CHO
47 R^1 = H, R^2 = COOH



46 R^1 = H, R^2 = CHO
48 R^1 = H, R^2 = COOH
49 R^1 = OH, R^2 = COOH



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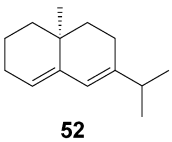

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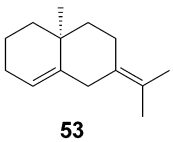

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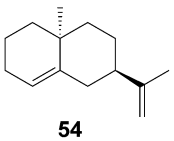

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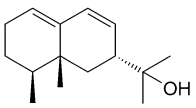

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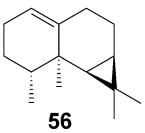

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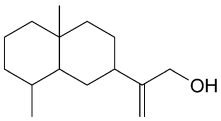

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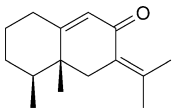

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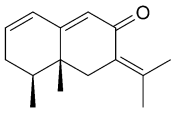

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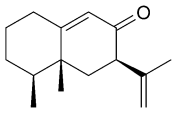

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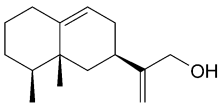

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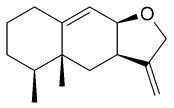

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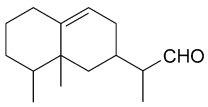

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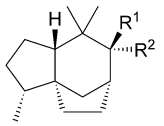
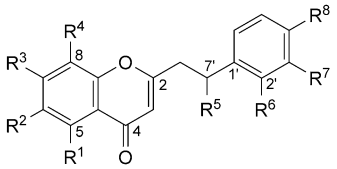
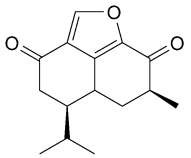


64 R^1 = OH, R^2 = Me
65 R^1 = H, R^2 = CH_2OH





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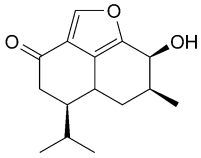

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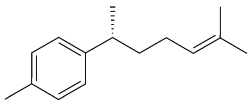

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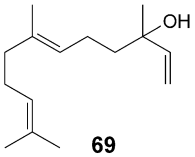

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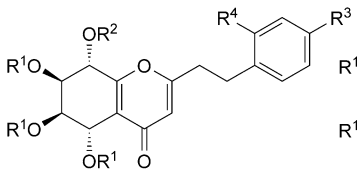
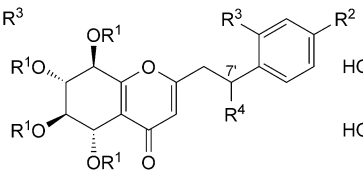
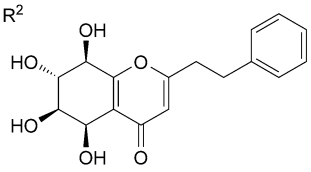
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
70	H	H	H	H	H	H	H	H
71	H	OH	H	H	H	H	H	H
72	H	MeO	H	H	H	H	H	H
73	H	MeO	H	H	H	H	MeO	H
74	H	MeO	MeO	H	H	H	H	H
75	H	OH	H	H	H	H	H	MeO
76	H	H	H	H	H	H	H	MeO
77	H	MeO	H	H	H	H	H	MeO
78	OH	H	H	OH	H	H	H	H
79	OH	H	H	OH	H	H	H	MeO
80	H	MeO	MeO	H	H	H	H	MeO
103	H	MeO	H	H	H	H	MeO	OH
104	H	OH	H	OH	H	H	H	H
105	H	OH	H	H	H	H	H	OH
106	H	OH	H	H	H	OH	H	H
107	H	H	OH	H	H	H	H	H
108	H	H	OH	MeO	H	H	H	H
109	OH	MeO	H	H	H	H	H	H
110	H	H	H	H	OH	H	H	H
116	MeO	H	H	MeO	H	H	AcO	H
117	H	OH	H	OH	H	H	MeO	OH
118	H	MeO	H	H	H	H	MeO	OH
119	H	OH	H	H	H	H	MeO	OH



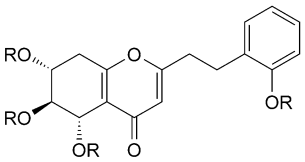
	R^1	R^2	R^3	R^4
81	H	H	H	H
82	Ac	Ac	MeO	H
90	H	Me	H	H
91	H	H	H	OH



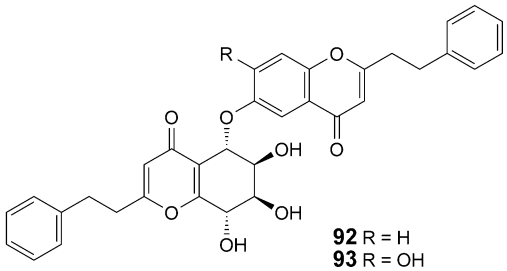
	R^1	R^2	R^3	R^4
83	H	H	H	H
84	H	MeO	H	H
85	H	H	OH	H
86	H	H	H	α-OH
87	H	H	H	β-OH



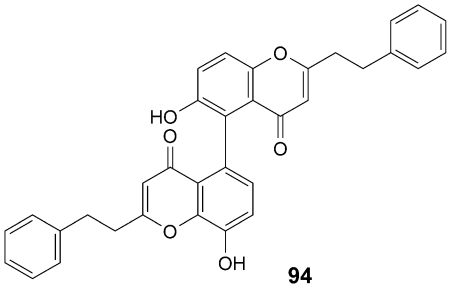
88



89 R = Ac



92 R = H
93 R = OH



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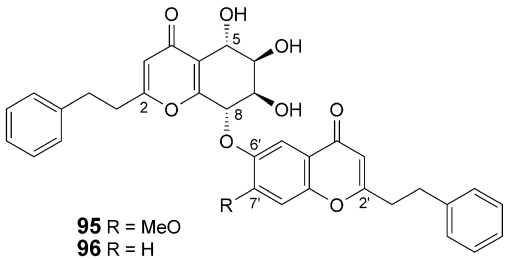
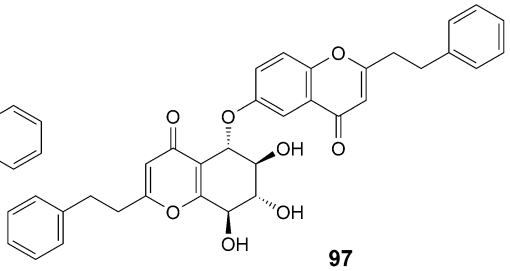


95 R = MeO
96 R = H



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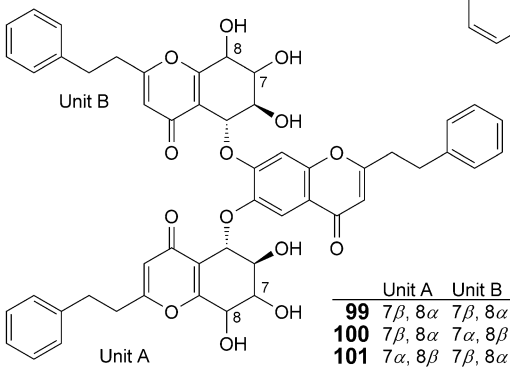
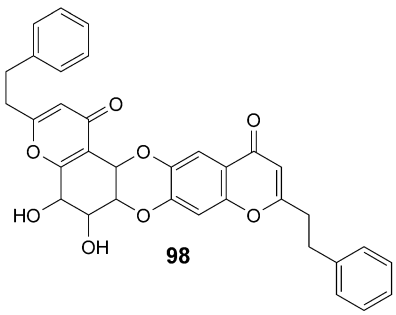


	Unit A	Unit B
99	7β, 8α	7β, 8α
100	7β, 8α	7α, 8β
101	7α, 8β	7β, 8α



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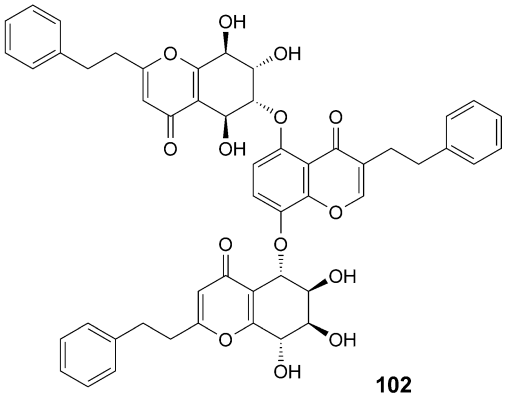

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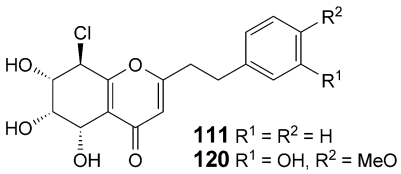
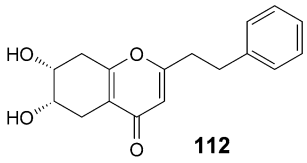


111 $R^1 = R^2 = H$
120 $R^1 = OH$, $R^2 = MeO$



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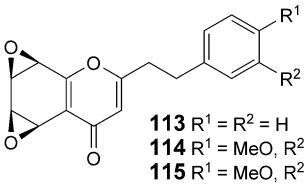
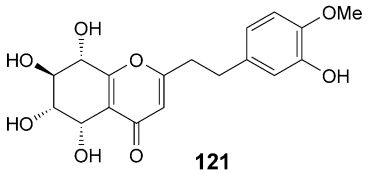


113 $R^1 = R^2 = H$
114 $R^1 = MeO$, $R^2 = H$
115 $R^1 = MeO$, $R^2 = OH$



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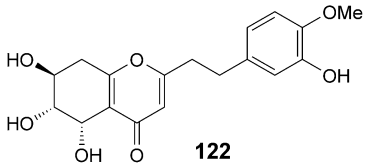

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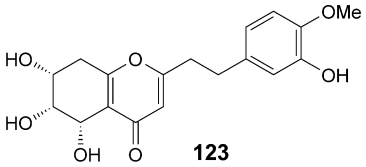

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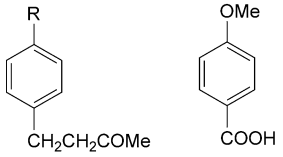
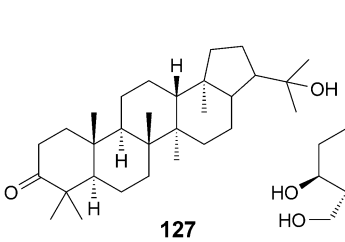


124 R = H
125 R = MeO

126



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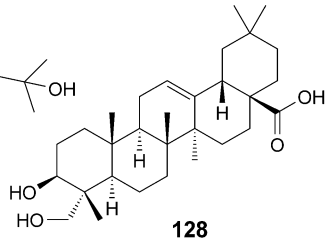

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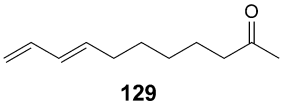

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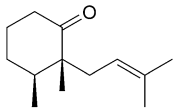

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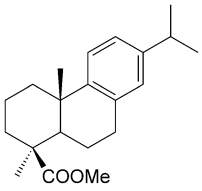

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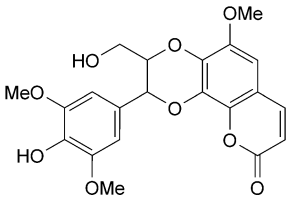

132

Table. *Chemical Constituents of Agarwood Originating from the Genus* Aquilaria

No.	Compound class and name	Source or origin	Ref.
	Agarofurans (*Sesquiterpenes*)		
1	α-Agarofuran	*A. agallocha* (India)/ *A. malaccensis* (Indonesia)	[6][7]
2	β-Agarofuran	*A. agallocha* (India/Vietnam)/ *A. sinensis* (China)	[6][8–10]
3	Dihydroagarofuran	*A. agallocha* (India)	[6]
4	Norketoagarofuran	*A. agallocha* (India)	[11]
5	Dihydro-4-hydroxyagarofuran	*A. agallocha* (India)	[11]
6	Dihydro-3,4-dihydroxyagarofuran	*A. agallocha* (India)	[11]
7	Baimuxinol	*A. sinensis* (China)	[12]
8	Dehydrobaimuxinol	*A. sinensis* (China)	[12]
9	Isobaimuxinol	*A. sinensis* (China)	[8]
10	Baimuxifuranic acid	*A. agallocha* (India)	[13]
11	(3*R*,5a*S*,9a*R*)-Octahydro-2,2,5a-trimethyl-2*H*-3,9a-methano-1-benzoxepine	*A. agallocha* (India)	[14]
12	(3*R*,5a*S*,9*R*,9a*R*)-Octahydro-2,2,5a-trimethyl-2*H*-3,9a-methano-1-benzoxepin-9-ol	*A. agallocha* (India)	[14]
13	Epoxy-β-agarofuran	*A. agallocha* (India)	[15]
14	(3*R*,5a*R*,9*S*,9a*S*)-Octahydro-2,2,5a-trimethyl-2*H*-3,9a-methano-1-benzoxepine-9-carbaldehyde	*A. agallocha* (India)	[15]
	Agarospiranes (*Sesquiterpenes*)		
15	Agarospirol	*A. agallocha* (India)	[16][17]
16	Baimuxinic acid	*A. agallocha* (India)	[17][9]
17	Baimuxinal	*A. agallocha* (India)	[17][9]
18	Oxoagarospirol	*A. malaccensis* (Cambodia)	[18][7]
19	Isoagarospirol	*A. malaccensis* (Cambodia)	[18]
20	Vetaspira-2(11),6-dien-14-al	*A. agallocha* (India)	[19]
21	Vetaspira-2(11),6(14)-dien-7-ol	*A. agallocha* (India)	[19]
22	2,14-Epoxyvetispir-6-ene	*A. agallocha* (India)	[19]
23	2,14-Epoxyvetispira-6(14),7-diene	*A. agallocha* (India)	[19]
24	(4*R*,5*R*,7*R*)-11-Hydroxyspirovetiv-1(10)-en-2-one	*A. agallocha* (Vietnam)	[20]
	Guaianes (*Sesquiterpenes*)		
25	Sinenofuranol	*A. sinensis* (China)	[13][9]
26	Sinenofuranal	*A. sinensis* (China)	[9]
27	(−)-Guaia-1(10),11-dien-14-al	*A. agallocha* (Vietnam)	[10][21]
28	(−)-Guaia-1(10),11-dien-l4-ol	*A. agallocha* (Vietnam)	[21]
29	(−)-Guaia-1(10),11-dien-14-oic acid	*A. agallocha* (Vietnam)	[21]
30	Methyl guaia-1(10),11-dien-14-oate	*A. agallocha* (Vietnam)	[21]
31	(+)-Guaia-1(10),11-dien-9-one	*A. agallocha* (Vietnam)	[21]
32	(−)-l,l0-Epoxyguai-11-ene	*A. agallocha* (Vietnam)	[20][21]
33	(−)-Guaia-1(10),11-dien-14,2-olide	*A. agallocha* (Vietnam)	[21]
34	(−)-Rotundone	*A. agallocha* (Vietnam)	[21]
35	(−)-2α-Hydroxyguaia-1(10),11-dien-14-oic acid	*A. agallocha* (Vietnam)	[22]
36	(+)-1,5-Epoxynorketoguaiene	*A. agallocha* (Vietnam)	[23]
37	α-Guaiene	*A. agallocha* (Vietnam)	[10]
38	α-Bulnesene	*A. agallocha* (Vietnam)	[10]
39	α-Gurjunene	Vietnam	[24]
	Eudesmanes (*Sesquiterpenes*)		
40	Jinkoheremol	*A. malaccensis* (Indonesia)	[25]
41	Kusunol	*A. malaccensis* (Indonesia)	[10][25]
42	(−)-10-Epi-γ-eudesmol	*A. malaccensis* (Indonesia)	[7]

Table (cont.)

No.	Compound class and name	Source or origin	Ref.
43	(−)-Selina-3,11-dien-9-one	*A. agallocha* (Vietnam)	[10]
44	(+)-Selina-3,11-dien-9-ol	*A. agallocha* (Vietnam)	[10]
45	(−)-Selina-3,11-dien-14-al	*A. agallocha* (Vietnam)	[23]
46	(+)-Selina-4,11-dien-14-al	*A. agallocha* (Vietnam)	[23]
47	(−)-Selina-3,11-dien-14-oic acid	*A. agallocha* (Vietnam)	[23]
48	(+)-Selina-4,11-dien-14-oic acid	*A. agallocha* (Vietnam)	[23]
49	(+)-9-Hydroxyselina-4,11-dien-14-oic acid	*A. agallocha* (Vietnam)	[23]
50	Dehydrojinkoheremol	*A. agallocha* (Vietnam)	[23]
51	2-[(2*R*,4a*S*)-1,2,3,4,4a,5,6,7-Octahydro-4a-methylnaphthalen-2-yl]propan-2-ol	*A. agallocha* (India)	[14]
52	(8a*S*)-1,2,3,7,8,8a-Hexahydro-8a-methyl-6-(1-ethylethyl)naphthalene	*A. agallocha* (India)	[14]
53	(4a*S*)-1,2,3,4,4a,5,6,7-Octahydro-4a-methyl-2-(1-methylethylidene)naphthalene	*A. agallocha* (India)	[14]
54	(2*R*,4a*S*)-1,2,3,4,4a,5,6,7-Octahydro-4a-methyl-2-(1-methylethenyl)-naphthalene	*A. agallocha* (India)	[14]
55	Valenca-1(10),8-dien-11-ol	*A. agallocha* (India)	[19]
56	Calarene	*A. agallocha* (Vietnam)	[24]
	Eremophilanes (Sesquiterpenes)		
57	Agarol	*A. agallocha* (India)	[26][27]
58	Dihydrokaranone	*A. malaccensis* (Cambodia)/ *A. agallocha* (Vietnam)	[9][10] [18][28]
59	Karanone	*A. malaccensis* (Cambodia)	[10][18]
60	Neopetasane	*A. agallocha* (Vietnam)	[23]
61	Eremophila-9,11(13)-dien-12-ol	*A. agallocha* (India)	[19]
62	8,12-Epoxyeremophila-9,11(13)-diene	*A. agallocha* (India)	[19]
63	Valenc- or eremophil-9-en-12-al (tentative)	*A. agallocha* (India)	[19]
	Prezizaanes (*Sesquiterpenes*)		
64	Jinkohol	*A. agallocha*/*A. malaccensis* (Indonesia)	[25][29]
65	Jinkohol-II	*A. malaccensis* (Indonesia)	[25]
	Others (*Sesquiterpenes*)		
66	Gmelofuran	*A. agallocha* (India)	[30]
67	8βH-Dihydrogmelofuran[a])	*A. agallocha* (India)	[27][30]
68	ar-Curcumene	*A. malaccensis* (Cambodia)	[18]
69	Nerolidol	*A. malaccensis* (Cambodia)	[18]
	*2-(2-Phenylethyl)-4*H*-chromen-4-one derivatives*		
70	2-(2-Phenylethyl)-4*H*-chromen-4-one	*A. agallocha* (Vietnam, Kalimantan)/*A. malaccensis* (Indonesia)/ *A. sinensis* (China)	[10][31] [32][33]
71	6-Hydroxy-2-(2-phenylethyl)-4*H*-chromen-4-one (AH_3)	*A. agallocha* (Kalimantan)/ *A. sinensis* (China)	
72	6-Methoxy-2-(2-phenylethyl)-4*H*-chromen-4-one (AH_4)	*A. agallocha* (Kalimantan)/ *A. sinensis* (China)	[28][33] [34]
73	6-Methoxy-2-[2-(3-methoxyphenyl)ethyl]-4*H*-chromen-4-one (AH_5)	*A. agallocha* (Kalimantan)/ *A. sinensis* (China)	[33][34]
74	6,7-Dimethoxy-2-(2-phenylethyl)-4*H*-chromen-4-one (AH_6)	*A. agallocha* (Kalimantan)/ *A. sinensis* (China)	[33][34] [28]
75	6-Hydroxy-2-[2-(4-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. sinensis* (China)	[35]

Table (cont.)

No.	Compound class and name	Source or origin	Ref.
76	2-[2-(4-Methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. agallocha* (Kalimantan)	[10][36][33]
77	6-Methoxy-2-[2-(4-methoxyphenyl)ethyl]-4*H*-chromen-4-one	Vietnam	[10][37][32]
78	5,8-Dihydroxy-2-(2-phenylethyl)-4*H*-chromen-4-one (AH_7)	*A. agallocha* (Kalimantan)	[38]
79	5,8-Dihydroxy-2-[2-(4-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. sinensis* (China)	[39]
80	6,7-Dimethoxy-2-[2-(4-methoxyphenyl)ethyl]-4*H*-chromen-4-one (AH_8)	*A. agallocha* (Kalimantan)	[28][38]
81	Agaroretrol (AH_1)	*A. agallocha* (Kalimantan)	[40]
82	5α,6β,7β,8α-Tetraacetoxy-5,6,7,8-tetrahydro-2-[2-(4-methoxyphenyl)ethyl)]-4*H*-chromen-4-one (AH_{1A})	*A. agallocha* (Kalimantan)	[41]
83	(5*S*,6*R*,7*S*,8*R*)-5,6,7,8-Tetrahydro-5,6,7,8-tetrahydroxy-2-(2-phenylethyl)-4*H*-chromen-4-one (Isoagarotetrol) (AH_2)	*A. agallocha* (Kalimantan)	[40]
84	5,6,7,8-Tetrahydro-5α,6β,7α,8β-tetradydroxy-2-[2-(4-methoxyphenyl)ethyl]-4*H*-chromen-4-one (AH_{2a})	*A. agallocha* (Kalimantan)	[41]
85	5,6,7,8-Tetrahydro-5α,6β,7α,8β-tetradydroxy-2-[2-(2-hydroxyphenyl)ethyl]-4*H*-chromen-4-one (AH_{2b})	*A. agallocha* (Kalimantan)	[41]
86	(5*S*,6*R*,7*S*,8*R*,7′*R*)-Hydroxyisoagarotetrol	*A. agallocha* (Kalimantan)	[42]
87	(5*S*,6*R*,7*S*,8*R*,7′*S*)-Hydroxyisoagarotetrol	*A. agallocha* (Kalimantan)	[42]
88	(5*R*,6*R*,7*S*,8*R*)-5,6,7,8-Tetrahydro-5,6,7,8-tetrahydroxy-2-(2-phenylethyl)-4*H*-chromen-4-one (AH_{16})	*A. agallocha* (Kalimantan)	[43]
89	(5*S*,6*S*,7*R*)-5,6,7-Triacetoxy-2-[2-(2-acetoxyphenyl)ethyl]-5,6,7,8-tetrahydro-4*H*-chromen-4-one (AH_9)	*A. agallocha* (Kalimantan)	[38]
90	5,6,7,8-Tetrahydro-5α,6β,7β-trihydroxy-8α-methoxy-2-(2-phenylethy)-4*H*-chromen-4-one (AH_{17})	*A. agallocha* (Kalimantan)	[44]
91	5,6,7,8-Tetrahydro-5α,6β,7β,8α-tetrahydroxy-2-[2-(2-hydroxyphenyl)ethyl]-4*H*-chromen-4-one (AH_{23})	*A. agallocha* (Kalimantan)	[44]
92	2-(2-Phenylethyl)-6-{[(5*S*,6*S*,7*R*,8*S*)-5,6,7,8-tetrahydro-6,7,8-trihydroxy-4-oxo-2-(2-phenylethyl)-4*H*-chromen-5-yl]oxy}-4*H*-chromen-4-one (AH_{10})	*A. agallocha* (Kalimantan)/ *A. sinensis* (China)	[33][45][46]
93	7-Hydroxy-2-(2-phenylethyl)-6-{[(5*S*,6*S*,7*R*,8*S*)-5,6,7,8-tetrahydro-6,7,8-trihydroxy-4-oxo-2-(2-phenylethyl)-4*H*-chromen-5-yl]oxy}-4*H*-chromen-4-one (AH_{15})	*A. agallocha* (Kalimantan)	[46][47]
94	6,8′-Dihydroxy-2,2′-bis(2-phenylethyl)-4*H*,4′*H*-5,5′-bichromene-4,4′-dione (AH_{11})	*A. agallocha* (Kalimantan)	[45][46]
95	7-Methoxy-2-(2-phenylethyl)-6-{[(5*S*,6*R*,7*R*,8*S*)-5,6,7,8-tetrahydro-5,6,7-trihydroxy-4-oxo-2-(2-phenylethyl)-4*H*-chromen-8-yl]oxy}-4*H*-chromen-4-one (AH_{12})	*A. agallocha* (Kalimantan)	[46]

Table (cont.)

No.	Compound class and name	Source or origin	Ref.
96	2-(2-Phenylethyl)-6-{[(5*S*,6*R*,7*R*,8*S*)-5,6,7,8-tetrahydro-5,6,7-trihydroxy-4-oxo-2-(2-phenylethyl)-4*H*-chromen-8-yl]oxy}-4*H*-chromen-4-one (AH_{13})	*A. agallocha* (Kalimantan)	[46]
97	2-(2-Phenylethyl)-6-{[(5*S*,6*S*,7*S*,8*R*)-5,6,7,8-tetrahydro-6,7,8-trihydroxy-4-oxo-2-(2-phenylethyl)-4*H*-chromen-5-yl]oxy}-4*H*-chromen-4-one (AH_{14})	*A. agallocha* (Kalimantan)/ *A. sinensis* (China)	[33][46]
98	AH_{21}	*A. agallocha* (Kalimantan)	[48]
99	AH_{18}	*A. agallocha* (Kalimantan)	[47]
100	AH_{19a}	*A. agallocha* (Kalimantan)	[49]
101	AH_{19b}	*A. agallocha* (Kalimantan)	[49]
102	AH_{20}	*A. agallocha* (Kalimantan)	[44]
103	2-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-6-methoxy-4*H*-chromen-4-one	*A. malaccensis* (Indonesia)	[32]
104	6,8-Dihydroxy-2-(2-phenylethyl)-4*H*-chromen-4-one	*A. malaccensis* (Indonesia)	[32]
105	6-Hydroxy-2-[2-(4-hydroxyphenyl)ethyl]-4*H*-chromen-4-one	*A. malaccensis* (Indonesia)	[32]
106	6-Hydroxy-2-[2-(2-hydroxyphenyl)ethyl]-4*H*-chromen-4-one	*A. malaccensis* (Indonesia)	[32]
107	7-Hydroxy-2-(2-phenylethyl)-4*H*-chromen-4-one	*A. malaccensis* (Indonesia)	[32]
108	7-Hydroxy-8-methoxy-2-(2-phenylethyl)-4*H*-chromen-4-one	*A. malaccensis* (Indonesia)	[32]
109	5-Hydroxy-6-methoxy-2-(2-phenylethyl)-4*H*-chromen-4-one	*A. sinensis* (China)	[33]
110	6-Hydroxy-2-(2-hydroxy-2-phenylethyl)-4*H*-chromen-4-one	*A. sinensis* (China)	[33]
111	(5*S*,6*S*,7*S*,8*R*)-8-Chloro-5,6,7,8-tetrahydro-5,6,7-trihydroxy-2-(2-phenylethyl)-4*H*-chromen-4-one	*A. sinensis* (China)	[33]
112	(6*S*,7*R*)-5,6,7,8-tetrahydro-6,7-dihydroxy-2-(2-phenylethyl)-4*H*-chromen-4-one	*A. sinensis* (China)	[33]
113	(5*R*,6*R*,7*R*,8*R*)-5,6 : 7,8-Diepoxy-5,6,7,8-tetrahydro-2-(2-phenylethyl)-4*H*-chromen-4-one	*A. crassna* (Vienam)/ *A. sinensis* (China)	[50]
114	(5*R*,6*R*,7*R*,8*R*)-5,6 : 7,8-Diepoxy-5,6,7,8-tetrahydro-2-[2-(4-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. crassna* (Vienam)/ *A. sinensis* (China)	[50]
115	(5*R*,6*R*,7*R*,8*R*)-5,6 : 7,8-Diepoxy-5,6,7,8-tetrahydro-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. crassna* (Vienam)/ *A. sinensis* (China)	[50]
116	2-[2-(3-Acetoxyphenyl)ethyl]-5,8-dimethoxy-4*H*-chromen-4-one	*A. agallocha* (Cambodia)	[28]
117	6,8-Dihydroxy-2-[2-(4-hydroxy-3-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. sinensis* (China)	[51]
118	2-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-6-methoxy-4*H*-chromen-4-one	*A. sinensis* (China)	[51]
119	6-Hydroxy-2-[2-(4-hydroxy-3-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. sinensis* (China)	[52]
120	(5*S*,6*S*,7*S*,8*R*)-8-Chloro-5,6,7,8-tetrahydro-5,6,7-trihydroxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. sinensis* (China)	[53]
121	(5*S*,6*S*,7*R*,8*S*)-5,6,7,8-Tetrahydro-5,6,7,8-tetrahydroxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. sinensis* (China)	[54]

Table (cont.)

No.	Compound class and name	Source or origin	Ref.
122	(5*S*,6*R*,7*S*)-5,6,7,8-Tetrahydro-5,6,7-trihydroxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. sinensis* (China)	[55]
123	(5*S*,6*R*,7*R*)-5,6,7,8-Tetrahydro-5,6,7-trihydroxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-4*H*-chromen-4-one	*A. sinensis* (China)	[55]
	Aromatics		
124	Benzylacetone	Review/*A. sinensis* (China)	[8][24][31]
125	(*p*-Methoxybenzyl)acetone	Review/*A. sinensis* (China)	[8][31]
126	Anisic acid	*A. sinensis* (China)	[8]
	Triterpenes		
127	22-Hydroxyhopan-3-one	*A. sinensis* (China)	[56]
128	Hederagenin	*A. sinensis* (China)	[52]
	Others		
129	(*E*)-Undeca-8,10-dien-2-one	*A. agallocha* (Vietnam)	[15]
130	(2*R*,3*S*)-2,3-Dimethyl-2-(3-methylbut-2-en-1-yl)-cyclohexanone	*A. agallocha* (Vietnam)	[15]
131	Methyl abieta-8(14),9(11),12-trien-19-oate	*A. agallocha* (Cambodia)	[28]
132	Aquillochin	*A. agallocha* (India)	[57]

[a]) Compound '*agarol*' recommended by *Pant et al.* [30] is actually known as 8*β*H-dihydrogmelofuran [27].

them, compound **27** was the main component of ether extracts. Compound **35** was found as a biosynthetic intermediate of compound **33**. *Takemoto et al.* isolated compound **39** from the agarwood oil produced in Vietnam [24].

2.1.4. *Eudesmanes.* From the benzene extract of agarwood collected in Indonesia and imported *via* Singapore (*Aquilaria* sp.; probably *A. malaccensis* BENTH.), a new eudesmane compound **40**, and two known eudesmane compounds, **41** and **42**, were obtained [7][25]. Eight novel eudesmane compounds, **43**–**50**, were isolated by *Ishihara et al.* in a sample of agarwood extract produced in the laboratory from *A. agallocha* of the Vietnamese origin [10][23]. *Näf et al.* found four eudesmol-type compounds, **51**–**54**, and one compound with the valencane skeleton, **55** [14][19]. *Takemoto et al.* isolated compound **56** together with compound **39** mentioned above [24].

2.1.5. *Eremophilanes.* Only a few eremophilane sesquiterpenes, *i.e.*, **57**–**63**, have been found in agarwood [7][17][18][24].

2.1.6. *Prezizaanes.* Two prezizaane-type sesquiterpenes, **64** and **65**, were isolated from the agarwood originating from *A. malaccensis* [22][26].

2.1.7. *Others.* Compounds **66**–**69** are included here, as they do not belong to any of the above classes [18][19][30].

2.2. *2-(2-Phenylethyl)-4*H*-chromen-4-one Derivatives.* 2-(2-Phenylethyl)-4*H*-chromen-4-one derivatives are also among major constituents in agarwood. They have been obtained from only a few plant species: *Eremophila georgei*, *Bothriochloa ischaemum*

(Gramineae) and the agarwood originating from *Aquilaria* spp. (Thymelaeaceae) [58]. More than 40 2-(2-phenylethyl)-4*H*-chromen-4-one derivatives have been isolated from agarwood. The review of *Yang* [31] on 2-(2-phenylethyl)-4*H*-chromen-4-one derivatives **70**–**102** [34–49] covered the literature up to 1998. We will compile the new 2-(2-phenylethyl)-4*H*-chromen-4-one derivatives found after 1998.

Konishi et al. [32] described six new chromones, **103**–**108**, isolated from the Et_2O extract of agarwood (*A. malaccensis*), as well as a known compound **70**. *Yogura et al.* [33] reported four new chromone derivatives, **109**–**112**, together with seven known chromones, **70**–**74**, **92**, and **99**, from the MeOH extract of withered wood of *A. sinensis*. Three new diepoxy tetrahydrochromones, **113**–**115**, were isolated from the agarwood artificially produced by intentional wounding of *A. crassna* [50]. They are assumed to be involved in the biosynthesis of chromone derivatives in agarwood. *Alkhathlan et al.* [28] reported chromone **116** together with two known 2-(2-phenylethyl)-4*H*-chromen-4-one derivatives, **72** and **80**, from the acetone extract of the agarwood of the Cambodian origin (*A. agallocha*). In the past five years, seven new compounds, **117**–**123**, were isolated by Chinese researchers from agarwood (*A. sinensis*) [51–55].

2.3. *Aromatics.* Three aromatic compounds, **124**–**126**, were found in agarwood [8][24][31]. Benzylacetone was considered to be associated with the resin formation [59].

2.4. *Triterpenes.* Only two triterpenes, **127** and **128**, have been reported in agarwood (*A. sinensis*) [52][56].

2.5. *Others.* A linear C_{11}-dienone, **129**, and a C_{13}-isoprenoid, **130**, were detected by *Näf et al.* [15]. Compound **130** may be a degradation product of compound **58** [15]. *Alkhathlan et al.* [28] first isolated diterpenoid compound **131** from agarwood. *Bhandari et al.* [57] confirmed the presence of a coumarinolignan, **132**, in *A. agallocha*.

3. Biological Activities. – 3.1. *Central Nervous System (CNS) Activity.* Agarwood is used as a sedative in oriental medicine. Compound **16** showed an anesthetic effect on mice [17]. Benzylacetone was reported to have an effective constituent for cough relief, and the (2-phenylethyl)chromone derivatives exhibited anti-allergic effects [31]. It has been reported that the benzene extract of agarwood could reduce spontaneous motility, prolong the hexobarbiturate-induced sleeping time, hypothermia, and analgesia in mice [60]. Jinkoh-eremol and agarospirol, obtained from the benzene extract, also showed positive effects on the central nervous system by peritoneal and intracerebroventricular administration [61].

Ueda et al. [20] found that the newly isolated compound **24** could significantly induce BDNF exon β–V mRNA expression. In 2008, *Takemoto et al.* showed that the inhalation of agarwood oil vapor, the main constituents of which were benzylacetone (agarwood oil from a Hong Kong market), or α-gurjunene and (+)-calarene (agarwood oil made in Vietnam), could sedate mice [24].

3.2. *Antimicrobial Activity.* The essential oil of agarwood has been shown to possess antibacterial activities against different pathogens. The agarwood oil from *A. sinensis* showed significant antibacterial activity against *methicillin-resistant Staphylococcus aureus* (MRSA) [62]. The extracts of dried agarwood (*A. crassna*) powder by H_2O distillation, supercritical fluid extraction (SFE) and SFE with EtOH as the cosolvent, respectively, exhibited antimicrobial activities against *S. aureus* and *Candida albicans*,

but were not sensitive to *Escherichia coli* at 2 mg/ml, the maximum concentration of the study [63].

3.3. *Antitumor activity.* 2-(2-Phenylethyl)-4*H*-chromen-4-one derivative **120** showed cytotoxicity against the human gastric cancer cell line (SGC-7901) *in vitro* by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay [53].

3.4. *Antioxidative Activity.* The AcOEt extract of the heartwood of *A. agallocha* had a strong antioxidant effect on human blood haemolysate *in vitro* [64].

4. Conclusions. – Of the 132 constituents isolated from agarwood, sesquiterpenes and 2-(2-phenylethyl)-4*H*-chromen-4-one derivatives account for 52 and 41%, respectively. Agarwood originating from different *Aquilaria* plants share some common compounds but still have several different compounds. The difference in chemical composition might serve to chemically distinguish different kinds of agarwood and thus enables species identification. From this review, we can see that the compounds in agarwood are very complex. However, some of the skeletons show a strong structure–evolution relationship, such as the skeleton of guaianes, eremophilanes, and eudesmanes. Up to now, the mechanism of how agarwood are formed is still unclear. The isolated compounds could serve as clues in searching for some important metabolic synthases [65]. Various biological activities of crude extracts of agarwood or the isolated compounds have been revealed, including CNS, antimicrobial, antitumor, and antioxidative activities. The phytochemistry of agarwood of different origins and produced by different agar-formation techniques needs to be systematically studied, and the bioactivities of the isolated compounds have to be further investigated.

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