Review: Secondary Metabolites of Aquilaria, a Thymelaeaceae Genus

by Alfinda Novi Kristanti

Submission date: 09-Mar-2020 05:32PM (UTC+0800)
Submission ID: 1272168358
File name: 2018-Mini_Review.pdf (874.03K)
Word count: 7920
Character count: 39736

Send Orders for Reprints to reprints@benthamscience.ae

Mini-Reviews in Organic Chemistry, 2018, *15*, 36-55

REVIEW ARTICLE

Review: *S*econdary Metabolites of *Aquilaria*, a Thymelaeaceae Genus

Alfinda Novi Kristanti*, Mulyadi Tanjung and Nanik Siti Aminah

Department of Chemistry, Faculty of Science and Technology, Universitas Airlangga, Surabaya 60115, Indonesia

ARTICLE HISTORY

Received: November 15, 2016
Revised: June 21, 2017
Accepted: June 23, 2017

DOI:
10.2174/1570193X14666170721143041

Abstract: ***Background:*** Aquilaria, a genus belonging to the Thymelaeaceae, produces fragrant resinous agarwood, also known as eaglewood, which has been used as incense since old times. The intense fragrance is the result of the presence of a wide variety of secondary metabolites.

Objective: This genus was reported contained sesquiterpenes, chromones, flavonoids, benzophenones, diterpenoids, triterpenoids, and lignans.

Conclusion: Here, we review the different secondary metabolites that have been identified in Aquilaria to show their diversity and to allow comparison with other Thymelaeaceae genera.

Keywords: *Aquilaria*, Thymelaeaceae, sesquiterpene, chromone, flavonoid, benzophenone, diterpenoid, triterpenoid, lignan.

1. INTRODUCTION

The Thymelaeaceae are a family of dicotyledonous plants mainly found in the tropics and subtropics. They are mostly trees and shrubs, but include also a few vines and herbaceous plants. The family is especially diverse in the southern hemisphere, with many different species present in Africa and Australia [1]. Some species can also be found in Europe, and in parts of Asia and South America, but, in these latter regions, their diversity is much less [2]. Some genera are commercially grown for their sweet-scented and fragrant flowers. Other genera are cultivated for their hardwood, for their bark, which is a raw material for paper making, or for their odorous, highly resinous wood (agarwood), which is used for incense and perfume production.

Thymelaeaceae synthesize many, highly diverse secondary metabolites with a wide range of bioactivities, which has led to numerous applications of Thymelaeceae plant extracts in traditional medicine. For instance, in Kampo medicine in Japan, agarwood preparations are used as sedative, analgesic or digestive [3]. In China, *Aquilaria* leaves are applied topically to treat injuries such as fractures and bruises [4], and, in Korea, agarwood has been used for the treatment of cough, asthma, and as a sedative among others [5].

A completely different application exploits the strong fragrance of Thymeleaeceae plants, in particular of *Aquilaria* species. In Saudi Arabia and other Arabic countries, the wood of *Aquilaria* trees is used as incense at important religious occasions [5, 6]. Wood from closely related species is used during Budhist ceremonies in Asian countries such as Japan and India. Interestingly, the fragrant agarwood resin is not produced in normal wood tissues, but it is only formed when the plant is injured, *e.g.,* by wind, lighting, gnawing by ants or insects, or by microbial infection. These natural processes are slow and occur by chance, causing the agarwood to develop very slowly over decades. Therefore, agarwood is also produced artificially by burning, holing, cutting, or deliberate inoculation of the trees with fungi such as *Fusarium* spp [7-10]. Nevertheless, despite the artificial production, the demand for agarwood far exceeds the available supply, fostering a deep interest in the secondary metabolites that are responsible for the fragrance properties of agarwood

Widely studied *Aquilaria* species include *A. sinensis, A. malaccensis, A. crassna*, and *A. agallocha.* Depending on the region where these species grow, different names are used for the produced agarwood, such as Eaglewood, Gaharu, Kanankoh, Jinkoh, Chen Xiang or Tram [8, 9]. It is also called aloeswood or agalloch [8]. Each species produces agarwood with different fragrance properties, depending on the variety and quantity of the secondary metabolite content, especially sesquiterpenes and chromones. To assist in the search for alternative sources of agarwood-like fragrant resins, we review here the different secondary metabolites that have so far been characterized in *Aquilaria*.

There are two reviews that have been published that discussed about the same genus [11, 12]. These previous reviews did not discuss several classes of compounds such as diterpenoid, benzophenon, lignan and used references before 2011. Otherwise, this review was compiled using references, mostly published in 2001-2016. Some references which were dated before 2000 showed that the study of this genus had lasted for longtime. Another review published in 2016 discussed more on bioactivity of compounds contained in this genus [13].

2. PHYTOCHEMISTRY ASPECTS

2.1. Sesquiterpenes

The fragrant sesquiterpenes that have been found in the *Aquilaria* genus include compounds with a guaiane, eudesmane/selinane, eremophilane/nootkatane, agarofuran, vetispirane/agarospirane, or prezizane skeleton (Fig. **1**). Most of these sesquiterpenes are oxygenated [14-16].

*Address correspondence to this author at the Department of Chemistry, Faculty of Science and Technology, Universitas Airlangga, Surabaya 60115, Indonesia; E-mail: alfinda-n-k@fst.unair.ac.id

1875-6298/18 $58.00+.00

© 2018 Bentham Science Publishers

Mini-Reviews in Organic Chemistry

Almost all of these sesquiterpenes have been isolated from agarwood of several species of *Aquilaria*. For instance, guaiane sesquiterpenes were obtained from the agarwood of *A. agallocha* including α-guaiene (**1**), α-bulnesene (**2**), rotundone (**3**), 1,5-epoxy-nor ketoguaiene (**4**), as well as several guaia-1(10),11-diene derivatives (**5a-g**) [17, 18]. All reported guaiane sesquiterpenes were unsaturated guaianes with some of them being oxygenated.

An interesting guaiane sesquiterpene is 1,10-dioxo-4αH-5αH-7βH-11αH-1, 10-secoguaia-2(3)-en-12, 8β-olide (**7**), which exhibits anti-inflammatory activity with an IC_{50} value of 8.1 μM. This compound was isolated from *A. sinensis* agarwood, together with its derivatives 7βH-guaia-1(10)-en-12,8*b*-olide (**6**) and 1β-hydroxy-4βH-5βH-7βH-11αH-8,9-secoguaia-9(10)-en-8,12-olide (**8**) [19], Fig. (**2**).

The sesquiterpene 10-epi-γ-eudesmol (**9**), which has a eudesmane skeleton, has been isolated from the wood of *A. malac-*

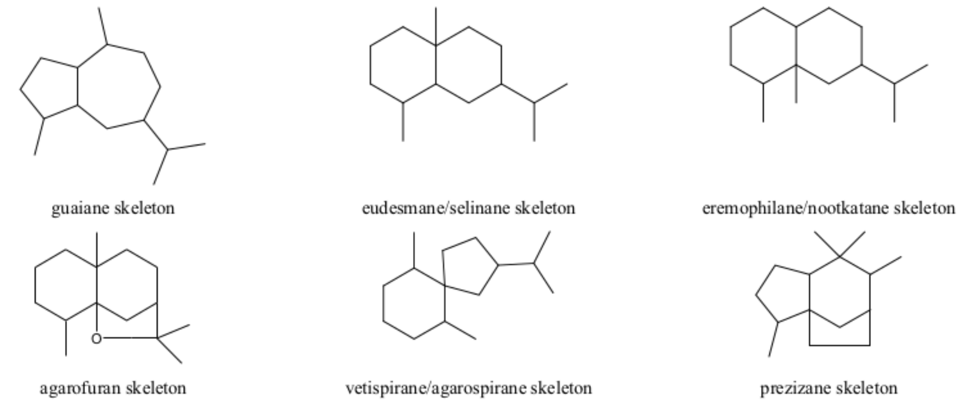


Fig. (1). Sesquiterpene skeletons present in the genus *Aquilaria.*

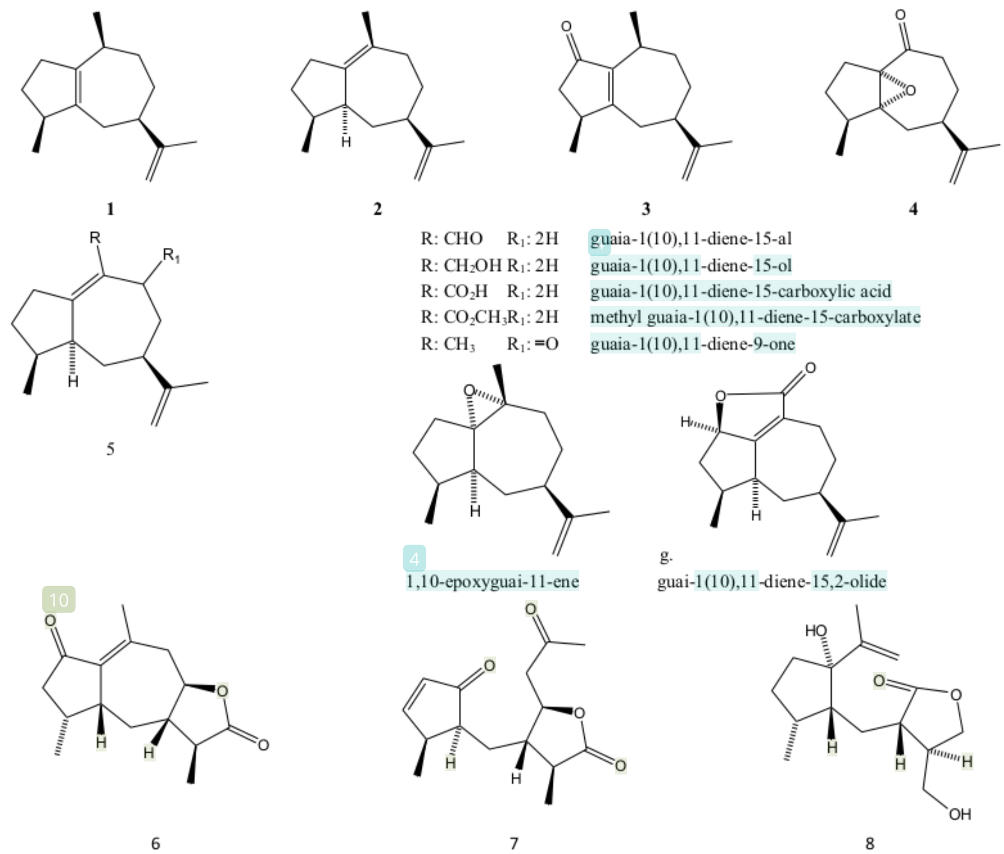


Fig. (2). Guaiane sesquiterpenes in *Aquilaria.*

censis [20]. Other eudesmanes, including selina-3,11-diene-9-one (**10**), selina-3,11-diene-9-ol (**11**), selina-3,11-diene-14-al (**12**), selina-4,11-diene-14-al (**13**), selina-3,11-diene-14-carboxylic acid (**14**), selina-4,11-diene-14- carboxylic acid (**15**), 9-hydroxyselina-4,11-diene-14-carboxylic acid (**16**) were isolated from agarwood of *A. agallocha* [18, 21]. In addition, *A. sinensis*, which had been subjected to artificial holing, produced several other eudesmane sesquiterpenes, such as 9-hydroxy-selina-3,11-diene-12-al (**17**), 9-hydroxy-selina-3,11-diene-14-al (**18**), 9-hydroxy-eudesma-3,11(13)-diene-12-methyl ester (**19**), 9-hydroxy-selina-4,11-diene-14-al (**20**), 8,12-dihydroxy-selina-4,11-diene-14-al (**21**), 3,4,4α,5,6,7,8,8α-octahydro-7-[1-(hydroxymethyl)ethenyl]-4α-methylnaphthalene-1-carboxaldehyde (**22**), 12,15-dioxo-α-selinen (**23**), 15-hydroxyl-12-oxo-α-selinen (**24**), eudesmane-1β,5α,11-triol (**25**), 7βH-eudesmane-4α,11-diol (**26**), and ent-4(15)-eudesmen-1α,11-diol (**27**) [22]. Compound **23** has also been isolated from *A. sinensis* by Zhao together with its isomer (**28**) [19]. In the same year, Wu *et al.* reported a new eudesmane sesquiterpene (**29**) that was isolated from 70% MeOH extract of *A. malaccensis* agarwood chips along with (**28**) and (**30**) [23], Fig. (**3**).

The agarofuran skeleton was the first reported sesquiterpene skeleton found in *Aquilaria*. Three different sesquiter-

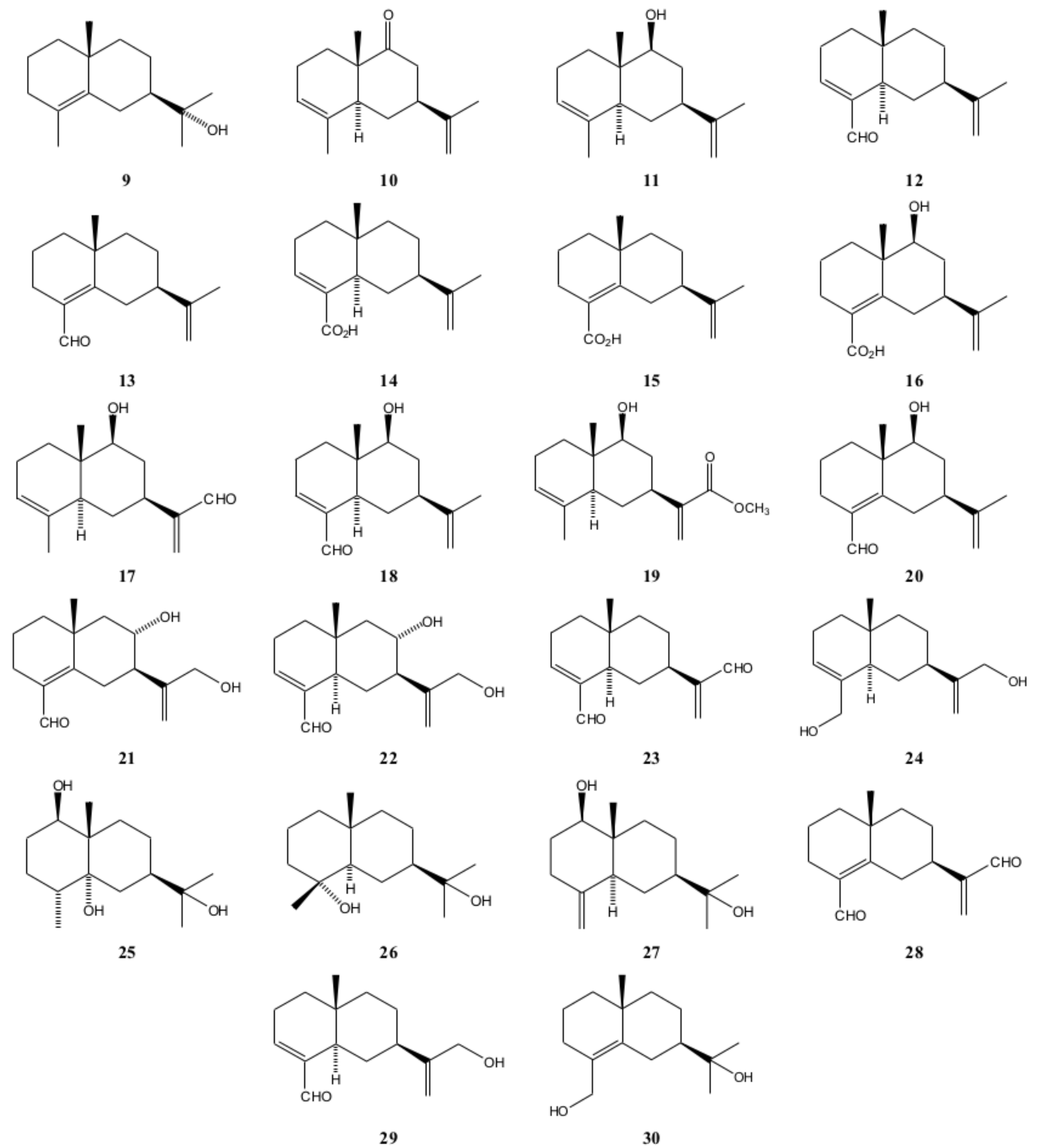
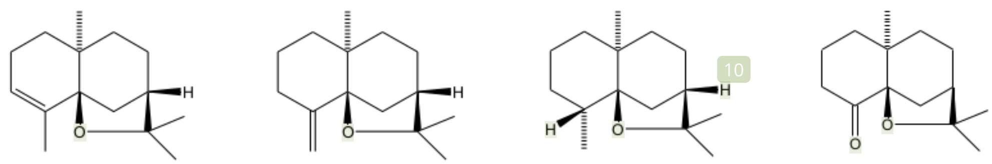


Fig. (3). Eudesmane sesquiterpenes in *Aquilaria.*

penes with this skeleton were isolated from agarwood oil, obtained from fungus-infected *A. agallocha* Roxb plants, and their structures and absolute configurations were determined by degradative studies and physical measurements. These sesquiterpenes were α-agarofuran (**31**), β-agarofuran (**32**) and dihydroagarofuran (**33**) [24]. β-agarofuran has also been isolated from finely powdered *A. agallocha* wood originating from Vietnam, together with another agarofuran and nor-ketoagarofuran (**34**) [25], Fig. (**4**).

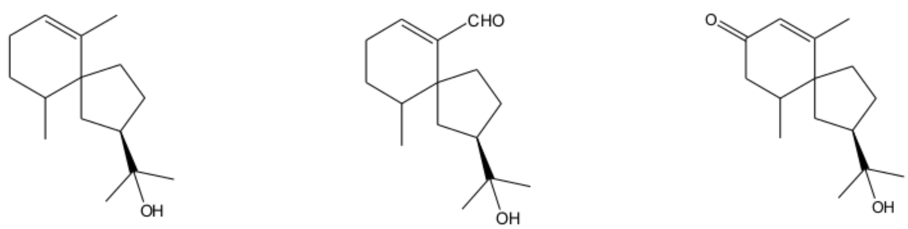
Another sesquiterpene skeleton present in *Aquilaria* plants is that of agarospirane. Some agarospirane sesquiterpenes that have been identified are agarospirol (**35**), isolated from agarwood of infected *A. agallocha* [26], oxo-agarospirol (**36**), isolated from *A. malaccensis* [20] and also found in *A. agallocha* agarwood [18, 25], and 1(10)-spirovetiven-11-ol-2-one (**37**), isolated from Vietnamese agarwood [8]. Zhao isolated compound **(36)** from *A. sinensis*, but named it baimuxinal [19] Fig. (**5**). This compound was also reported by Wu *et al.* in 2012, isolated from 70% MeOH extract of *A. malaccensis* agarwood chips [27], Fig. (**5**).

Sesquiterpenes with an eremophilane skeleton have also been identified in *A. agallocha* agarwood such as jinkoh eremol (**38**), kusunol (**39**), and dihydrokaranone (**40**) [25]. Alkhathlan *et al.* also successfully isolated the latter compound, but named it dehydrofukinone [6]. Ishihara *et al.* discovered the presence of the eremophilan sesquiterpene karanone (**41**) in agarwood from *A. agallocha* [17]. Two other eremophilan sesquiterpenes from *A. agallocha* were reported by Ishihara *et al.* in 1993, namely dehydrojinkoh-eremol (**42**) and neopetasane (**43**) [21]. The last compound, also reported by Wu *et al.* was isolated from 70% MeOH extract of *A. malaccensis* agarwood chips [27]. In 2014, Yang *et al.* published their research on the isolation and identification of compound (**43**), 7β-H-9(10)-ene-11,12-epoxy-8-oxoeremo-



31 32 33 34

Fig. (4). Agarofuran sesquiterpenes in *Aquilaria.*



35 36 37

Fig. (5). Agarospiran sesquiterpenes in *Aquilaria*.

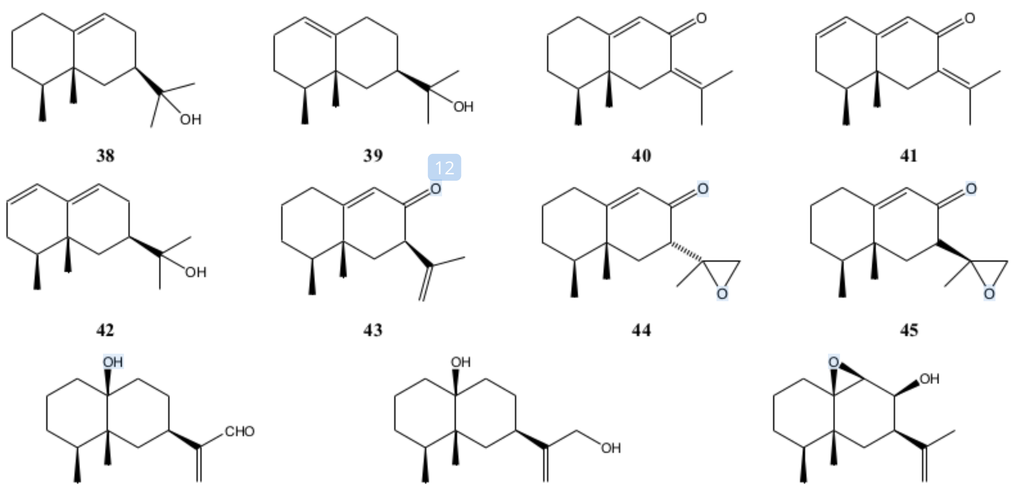
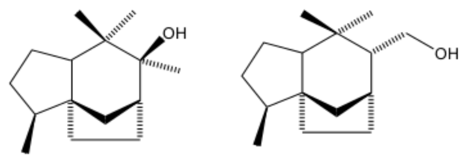


Fig. (6). Eremophilane sesquiterpenes in *Aquilaria.*

philane (**44**) and 7α-H-9(10)-ene-11,12-epoxy-8-oxoeremophilane (**45**) from Chinese agarwood (*A. sinensis* (Lour.) Gilg.) [16]. In 2012, Wu *et al.* reported the presence of three eremophilane sesquiterpenes (**46**), (**47**), and (**48**) isolated from 70% MeOH extract of *A. malaccensis* agarwood chips [23], Fig. (**6**).

The presence of prezizane sesquiterpenes in *Aquilaria* appears to be limited. Jinkohol (**49**) and jinkohol II (**50**) were present in agarwood from *A. malaccensis*. This finding was reported by Yoneda *et al.* in 1984 [25], Fig. (**7**). Previously, Nakanishi *et al.*. had already reported the existence of jinkohol in *Aquilaria sp.*(Indonesian agarwood) [14].



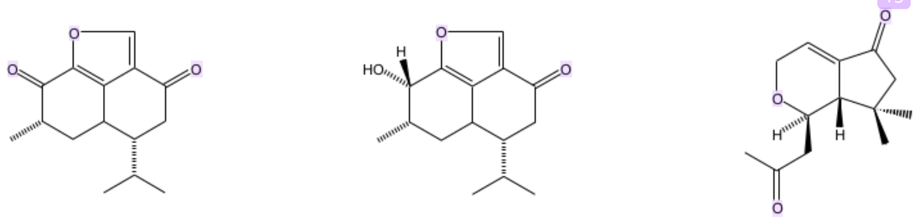
49 **50**

Fig. (7). Prezizane sesquiterpenes in *Aquilaria.*

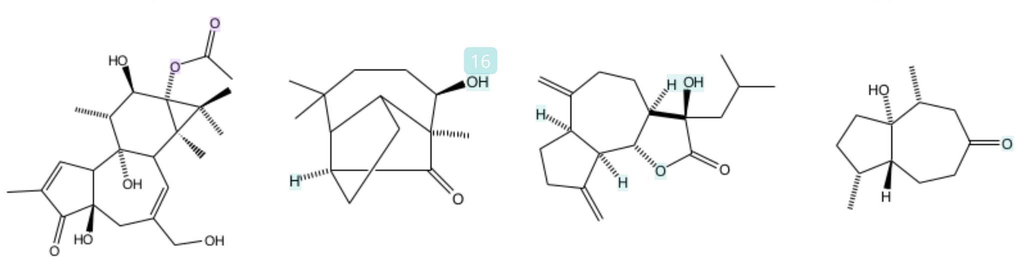
Miscellaneous sequiterpenes found in *Aquilaria* are gmelofuran (**51**) and 8β-dihydrogmelofuran (**52**), which were isolated from wood of *A. agallocha* [27]. Aquilarin B, a degraded sesquiterpene (**53**), as well as another sesquiterpene (**54**), both with a guaiane-like skeleton, were identified from the stem of *A. sinensis* [28, 29]. In addition, Yang *et al.* obtained two other compounds from Chinese eaglewood, with one of them also having a guaiane-like skeleton. These two compounds are 8β-hydroxy-longicamphenylone (**55**) and 11β-hydroxy-13-isopropyl-dihydro-dehydrocostus lactone (**56**) [30]. Another compound identified in Chinese eaglewood, *A. sinensis* (Lour.) Gilg., is the sesquiterpenoid derivative 1α-hydroxy-4α,10α-dimethyl-5βH-octahydro-azulen-8-one (**57**), which was isolated from a 95% ethanolic extract [19], Fig. (**8**).

2.2. Chromones

Another class of extensively reported secondary metabolites that have been isolated from *Aquilaria* species is the chromones, Fig. (**9**). All isolated chromones are derivatives of 2-(2-phenylethyl) chromone. The first two chromones identified (**58** and **59**) were isolated from *A. agallocha* wood [31], but the most simple chromone reported was 2-(2-phenylethyl)chromone or flidersiachromone (**60**) which was isolated for the first time from the ether extract of powdered agarwood of *A. malaccensis* along with 6-methoxy-2-[2-(3-methoxy-4-hydroxyphenyl)ethyl]chromone (**61**), 6,8-dihydroxy-2-(2-phenylethyl)chromone (**62**), 6-hydroxy-2-[2-(4-hydroxyphenyl)ethyl]chromone (**63**), 6-hydroxy-2-[2-(2-hydroxyphenyl)ethyl]chromone (**64**); 7-hydroxy-2-(2-phenylethyl)chromone (**65**), and 6-hydroxy-7-methoxy-2-(2-phenylethyl)chromone (**66**) [32]. Another 2-(2-phenylethyl) chromone derivative, namely 7,8-dimethoxy-2-[2-(3'-acetoxyphenyl)ethyl] chromone (**67**), was isolated from an acetone extract of Cambodian agarwood of *A. agallocha* along with two other chromones, 6-methoxy-2-(2-phenylethyl) chromone (**68**) and 6,7-dimethoxy-2-(2-phenylethyl) chromone (**69**) [6]. Then, Yang *et al.* obtained eight 2-(2-phenylethyl) chromone derivatives (**70-77**) from an EtOH extract of Chinese eaglewood from the *A. sinensis* [33]. Six 2-(2-phenylethyl) chromones were isolated from a 70% MeOH extract of *A. malaccensis* agarwood chips [23]. Two chromones was reported before and identified as compound (**58**) and (**59**) and four others were compound **78-81**. In the same year, 2012, Wu published again the report about some compounds contained in 70% MeOH extract of *A. malaccensis* agarwood chips. In that report, six chromones was isolated and identified [27]. Three compounds were reported before (**60**), (**68**) and (**69**), whereas three others had not been reported yet (**82-84**). In 2014, Li *et al.* reported the isolation of four 2-(2-phenylethyl)chromones (**85-88**), as well as other compounds that had been reported before, such as compounds **59**, **61**, **69, 76, 78, 79** and **84** from the EtOAc extract

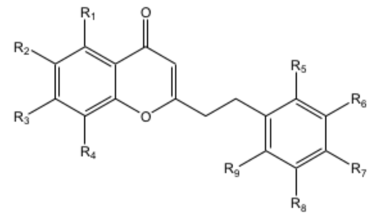


51 **52** **53**



54 **55** **56** **57**

Fig. (8). Miscellaneous sesquiterpenes in *Aquilaria.*



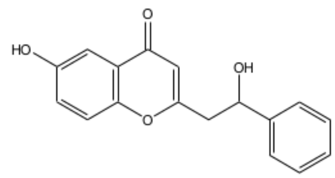
Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
58	H	H	H	H	H	H	OCH_3	H	H
59	H	OCH_3	H	H	H	H	OCH_3	H	H
60	H	H	H	H	H	H	H	H	H
61	H	OCH_3	H	H	H	OCH_3	OH	H	H
62	H	OH	H	OH	H	OCH_3	OH	H	H
63	H	OH	H	H	H	H	OH	H	H
64	H	OH	H	H	OH	H	H	H	H
65	H	H	OH	H	H	H	H	H	H
66	H	OH	OCH_3	H	H	H	H	H	H
67	OCH_3	H	H	OCH_3	H	OAc	H	H	H
68	H	OCH_3	H	H	H	H	H	H	H
69	H	OCH_3	OCH_3	H	H	H	H	H	H
70	H	OH	OCH_3	H	H	OH	OCH_3	H	H
71	H	OCH_3	OCH_3	H	H	OH	OCH_3	H	H
72	H	OCH_3	OH	H	H	OH	OCH_3	H	H
73	H	OCH_3	OCH_3	H	H	OCH_3	OH	H	H
74	H	OH	OH	H	H	H	OCH_3	H	H
75	H	OH	OCH_3	H	H	H	OH	H	H
76	H	OH	H	OH	H	OH	OCH_3	H	H
77	H	OH	H	H	H	OCH_3	OH	H	H
78	OH	OCH_3	H	H	H	H	OCH_3	H	H
79	H	H	OCH_3	H	H	H	H	H	H
80	OH	OCH_3	H	H	H	H	H	H	H
81	H	OCH_3	H	H	H	OCH_3	H	H	H
82	H	OCH_3	OH	H	H	H	OCH_3	H	H
83	H	OCH_3	OCH_3	H	H	H	OCH_3	H	H
84	H	OH	H	H	H	H	H	H	H
85	H	OCH_3	H	H	H	OH	OCH_3	H	H
86	OH	OCH_3	H	H	H	OH	OCH_3	H	H
87	H	OCH_3	H	H	H	H	OH	H	H
88	H	OH	H	H	H	H	OCH_3	H	H
89	H	OCH_3	OCH_3	H	H	H	OH	H	H
90	H	H	H	H	H	H	OH	H	H
91	H	H	H	OH	H	H	H	H	H

Fig. (9). Chromone basic skeleton.

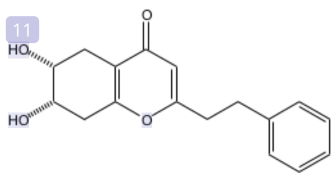
of Chinese agarwood induced by artificial holing originating from *A. sinensis* (Lour.) Gilg [9]. Phytochemical analysis of high quality Chinese agarwood from *A. sinensis* led to the isolation of three new 2-(2-phenylethyl) chromone derivatives (**89-91**) and two compounds that had been reported before [7]. In 2015, three 2-(2-phenylethyl) chromone derivatives were also isolated from the petioles and leaves of *A. sinensis*. The structures of these three chromones were elucidated and its structure were identical to compounds **58**, **61** and **63** [34].

In addition to having been isolated from *A. agallocha*, compound **68** was also obtained from withered wood of *A. sinensis,* together with three other chromones (**92**, **93** and **94**) [3]. The agarwood of the same plant gave also the 8-chloro-5,6,7-dihydroxy-2(3-hydroxy-4-methoxyphenylethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one chromone (**95**), which was isolated and identified by a Chinese research team [35]. Compound **93**, **94** and **95** belong to tetrahydrochromones. However, compound **94** and **95** are tetrahydrochromones that substituted by chloro in its structure. The presence of chloro in secondary metabolites structure is very rare. Meanwhile, compound **92** is unique because it is the only one chromone isolated and identified from *Aquilaria* that is hydroxylated in ethyl moiety. Subsequently, Dai *et al*.. isolated and structurally characterized two isomers of another tetrahydrochromones (**96** and **97**) from the EtOH extract of the withered wood of *A. sinensis* [36], Fig. (**10**).

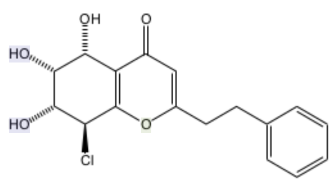
Three di-epoxy-tetrahydrochromones - oxidoagarochromones A (**98**), B (**99**), and C (**100**) - were isolated from agarwood that was artificially produced by intentional wounding of *A. crassna* [37]. Compounds **98** and **99** have also been obtained from Chinese agarwood of *A. sinensis* wounded by artificial holing [9]. In 2014, Li *et al.* reported the isolation of mono-epoxy-tetrahydrochromones (**101, 102** and **103**) [9], Fig. (**11**).



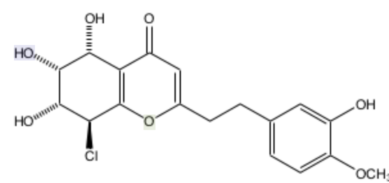
92



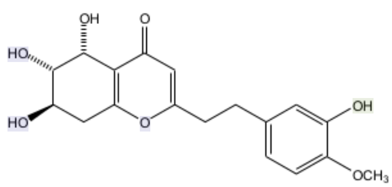
93



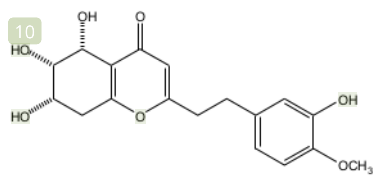
94



95

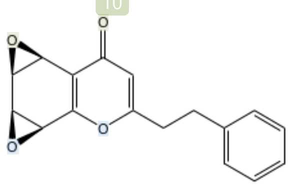


96

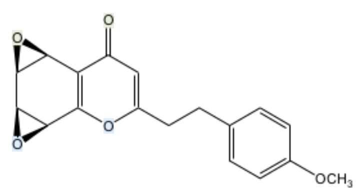


97

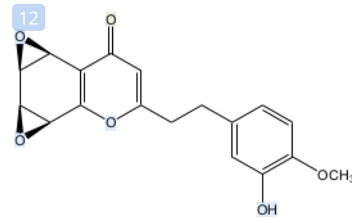
Fig. (10). Some tetrahydrochromones from *A. sinensis*.



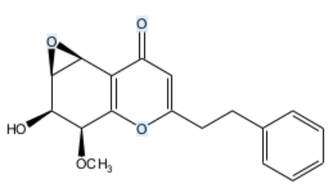
98



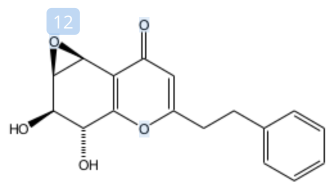
99



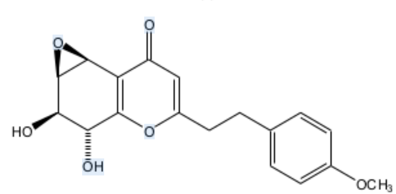
100



101

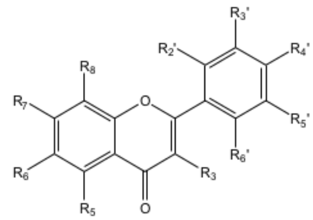


102



103

Fig. (11). Epoxy-tetrahydrochromones from *Aquilaria.*



Compound	R_3	R_5	R_6	R_7	R_8	$R_{2'}$	$R_{3'}$	$R_{4'}$	$R_{5'}$	$R_{6'}$
104	H	OH	H	OH	H	H	OH	OH	H	H
105	H	OH	H	OCH_3	H	H	H	OH	H	H
106	H	OH	H	OCH_3	H	H	OH	OH	H	H
107	H	OH	H	OCH_3	H	H	OH	OCH_3	H	H
108	H	OCH_3	H	OCH_3	H	H	OCH_3	OCH_3	H	H
109	H	OCH_3	H	OCH_3	H	H	H	OCH_3	H	H
110	OCH_3	OH	OCH_3	OCH_3	H	H	H	OCH_3	H	H
111	H	OH	H	OCH_3	H	H	H	OCH_3	H	H
112	H	OH	H	OCH_3	H	H	OCH_3	OCH_3	H	H
113	H	OH	H	OH	H	H	H	OCH_3	H	H

Fig. (12). Flavonoid basic skeleton.

2.3. Flavonoids

From the leaves of *A. sinensis*, several flavonoids, both as glycoside or aglycon, have been isolated and identified. Some aglycon flavonoids found in *Aquilaria* were luteolin **(104),** genkwanin (**105**), and hydroxygenkwanin (**106**) that were isolated by Qi *et al.* [38]. Cheng *et al.* identified several other aglycon flavonoids, such as 7,4'-dimethyl luteolin (**107**), 5,7,3',4'-tetramethoxy–flavone (**108**), 5,7,4'-trimethoxyflavone (**109**) and 5-hydroxy-3,4',6,7-tetramethoxyflavone (**110**) [39]. Furthermore, several aglycon flavonoids were also isolated from the stem of this plant, such as 5-hydroxyl-7,4'-dimethoxyflavone (**111**), 7, 3', 4'-trimethyl luteolin (**112**) and 5, 7-dihydroxyl-4'-methoxyflavone (**113**) [40], Fig. (**12**). All of aglycone flavonoids that has been reported belong to flavone, except compound **110** that was part of flavonol.

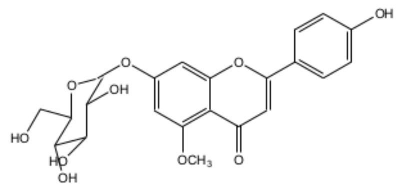
Flavonoids glycoside identified from *A. sinensis* were mono- or di-glycoside. This sugar moiety most often substituted the hydroxy group at position 5, but substitutions can also occur in positions 7 and 8. These flavonoids mono-glycoside were the 7–β–D-glucoside of 5-*O*-methylapigenin (**114**), the 5-β-D-glucoside of 7,3-di-*O*-methylluteolin (**115**) [38], aquilarisin (**116**), and hypolaetin 5-O-β-D-glucuronopyranoside (**117**) [41]. Several flavonoids glycoside were also isolated from the stem of this plant, such as 5-*O*-glucosides of 7,3',4'-tri-*O*-methylluteolin (lethedoside A) (**118**), 7-hydroxyl-4'-methyl-5-*O*-glucosideflavonoid (**119**) and 7, 4'-dimethyl-5-*O*-glucosideflavonoid (**120**) [40], Fig. (**13**).

Flavonoid di-glycoside reported from *Aquilaria* were 5-*O*-xylosylglucoside of 7-*O*-methylapigenin (**121**), 5-*O*-xylosylglucoside of 7,4'-di-*O*-methylapigenin (**122**) [38], aquisiflavoside (**123**) [42], aquilarinoside A_1 (**124**) and lethedioside A (= 5-*O*-xylosylglucosides of 7,3',4'-tri-*O*-methylluteolin) (**125**) [40], Fig. (**14**).

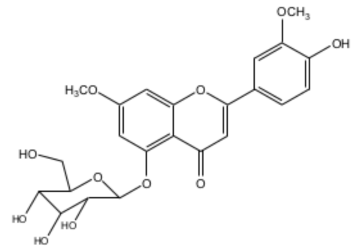
Besides flavonoids, the presence of several xanthons has been reported, particularly mangiferin (**106**) and aquilarixanthon (**107**) in *A. sinensis* [38, 41]. One isoflavonoid, formononetin (**108**), was also isolated and identified from the stem of this plant [40], Fig. (**15**).

2.4. Benzophenones

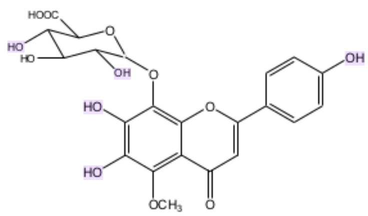
Such as flavonoids, *Aquilaria* benzophenone was also divided over the benzophenone aglycone and benzophenone glycoside. All benzophenone glycoside identified in *Aquilaria* are derivate of benzophenone iriflophenone (**129**) that was isolated from the leaves of *A. sinensis* along with the flavonoids described above [38]. An iriflophenone derivative, aquilarinoside A (**130**), was also obtained from the leaves of *A. sinensis*. Aquilarinoside A (**130**) was a benzophenone mono-glycoside with α-fructofuranose as a sugar moiety [38]. Some others iriflophenone mono-glycoside were iriflophenone 2-O-α-L-rhamnopyranoside (**131**) that was isolated from the leaves of *A. sinensis,* iriflophenone 3-C-β-D-glucoside (**132**) that were isolated from the petioles and leaves of *A. sinensis* [34] and another benzophenon that have been reported by other researchers and were identified as benzophenone C-glycoside (= 3C-β-D-glucopyranosyl-4',2,4,6-tetrahydroxybenzophenone (**133**) [39, 43]. Aquilarisinin (**134**) and iriflophenone 3,5-C-β-D-diglucopyranoside (**135**) that were isolated from the petioles and leaves of *A. sinensis* were exemples benzophenon iriflophenone di-glycoside [34]. In 2014, Sun *et al.* published four benzophenone glycosides, the aquilarinensides A-D (**136-139**), which



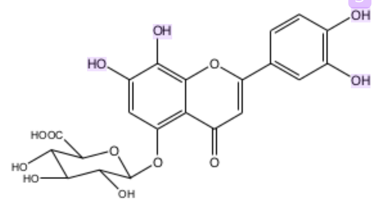
114



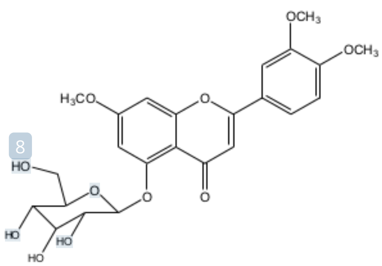
115



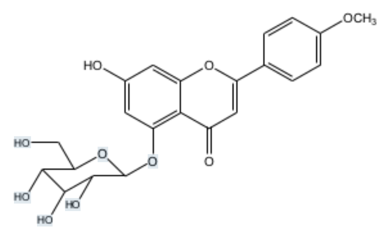
116



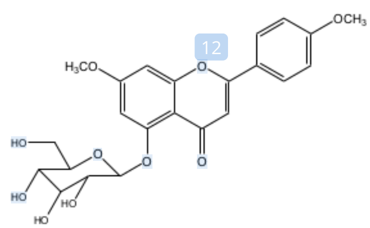
117



118

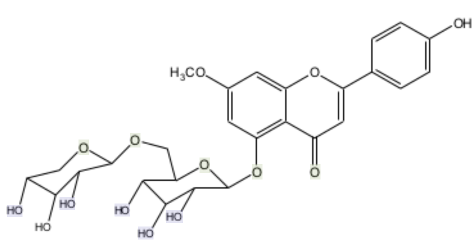


119

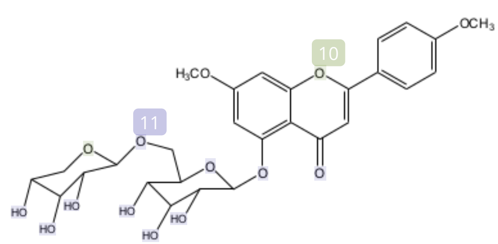


120

Fig. (13). Mono-glycoside flavonoids *in A. sinensis*.

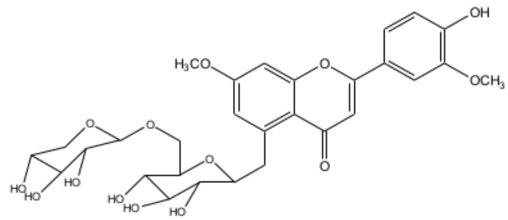


121

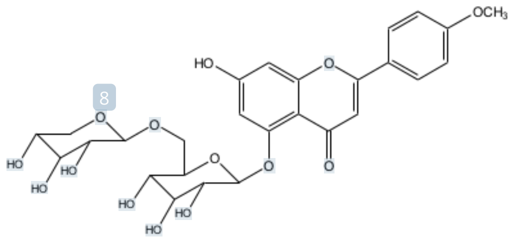


122

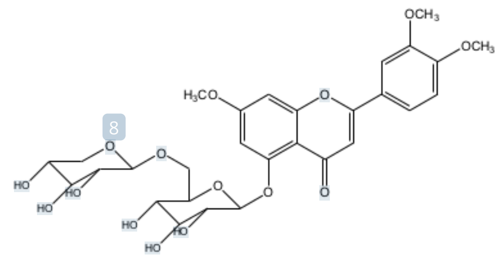
Fig. (14). Contd…



123

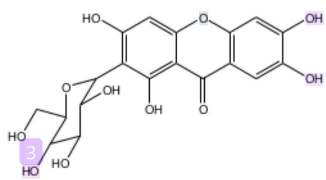


124

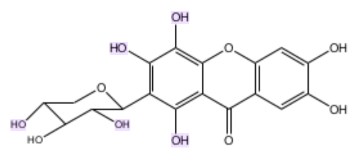


125

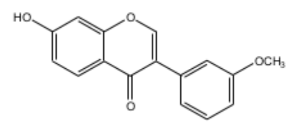
Fig. (14). Di-glycoside flavonoid in *A. sinensis.*



106



107



108

Fig. (15). *X*anthones and isoflavonoid in *A. sinensis.*

had also been isolated from the leaves of the same plant [44]. In addition to these four compounds, an iriflophenone glycoside with acetyl group (**140**) was also reported. Based on these structures, it can be seen that there are iriflophenone-O-glycoside and iriflophenone-C-glycoside. A sugar moiety could substitute hydroxyl group either at position 2 or 6, Fig. (**16**). Meanwhile for iriflophenone-C-glycoside, a sugar moiety could be substituted at position 3, 5 or 5'.

2.5. Diterpenoids

All diterpenoid compounds that so far have been isolated from *Aquilaria* species have an abietane and podocarpane skeleton. Seven abietane diterpenoids (aquilarabietic acids **141-147**) and one podocarpane diterpenoid (**148**) were obtained from the Chinese eaglewood, *A. sinensis* [45]. Meanwhile, a phorbol derivative - phorbol-13-acetate (**149**) - was isolated from the EtOH extract of the fresh stem of *A. sinensis* (Lour.) Gilg. [29]. Phorbol is a member of the tigliane family of diterpenes. Another phorbol compound had previously been isolated from the stem bark of the Thai *A. malaccensis* tree, namely 12-*O*-n-deca-2,4,6-trienoylphor-bol-13-acetate (**150**) [46], Fig. (**17**).

2.6. Triterpenoids

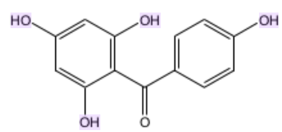
From the fruits of *A. sinensis*, five cucurbitacine triterpenoid compounds were isolated and identified as hexanocucurbitacin I (**151**), cucurbitacin I (**152**), cucurbitacin D (**153**), isocucurbitacin D (**154**), and neocucurbitacin B (**155**) [47]. Another cucurbitacine triterpenoid, namely dihydrocucurbitacine F (**156**), was isolated from the EtOH extract of the fresh stem of *A. sinensis* (Lour). Gilg. [29]. Furthermore, an aglycon cucurbitacine triterpenoid (**157**) were reported by Wang along with some cucurbitane triterpene glycosides (**158-161**) [34], Fig. (**18**).

Three triterpenoids with a tirucallane skeleton have also been identified in *A. sinensis*. They are aquilacalane A (24-methylenetirucall-7(8)-en-3β,25-diol) (**162**), aquilacallane B (24-methylene-25-methyltirucall-8(9)-en-3β-ol-7,11-dione (**163**), and 24-methylene-25-methyltirucall-7-en-3-one (wallenone) (**164**)). They were isolated from the leaves of *A. sinensis* [39, 48]. The presence of these two tirucallane triterpenoids (**162** and **163**) in the petioles and leaves of. *A. sinensis* have also reported by Wang [34], Fig. (**19**).

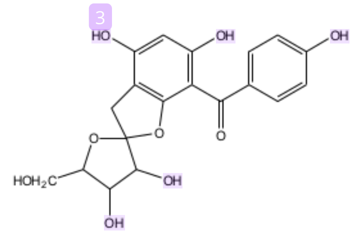
Oleanane triterpenoid skeletons were also found in *A. sinensis* such as those of 11-oxo-β-amyrin (**165**), hederagenin-an (**166**), 3β-acetoxyfriedelane (**167**) and ursolic acid (**168**). Their presence was reported by Cheng [39], Fig. (**20**).

2.7. Lignans

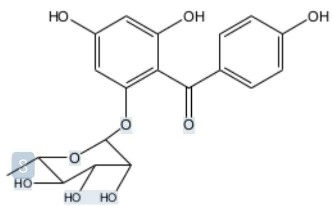
From the dried stems of *A. sinensis* that were collected in Qingyuan, Guangdong Province of China, seven lignans were isolated, including lignan aglycon and lignan glycoside [49]. They were identified as simulanol (**169**), syringaresinol



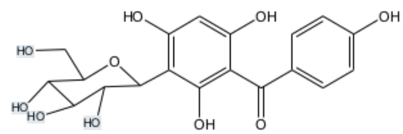
129



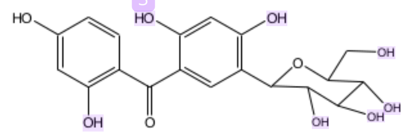
130



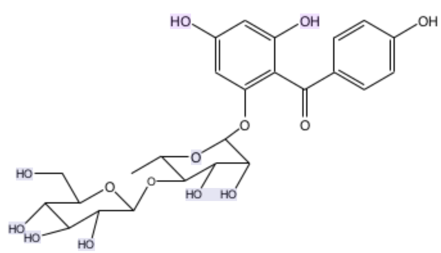
131



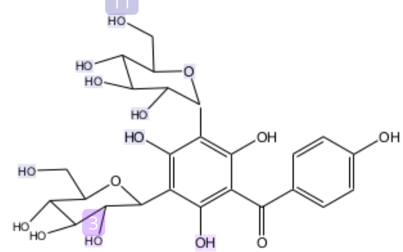
132



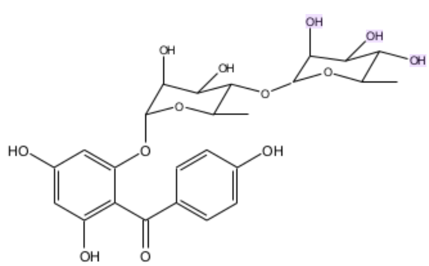
133



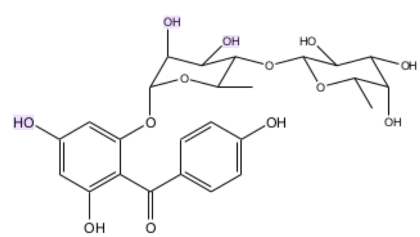
134



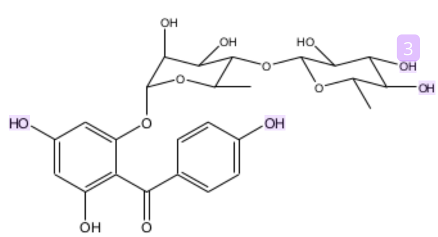
135



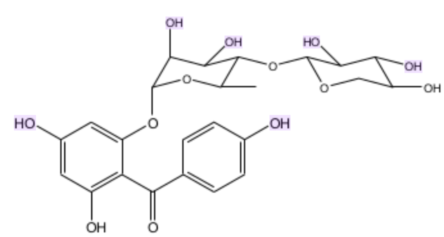
136



137

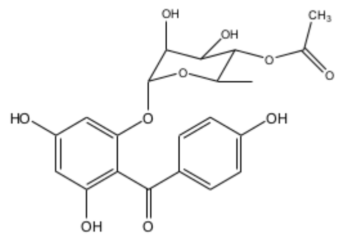


138



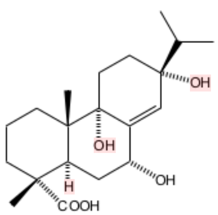
139

Fig. (16). Contd..

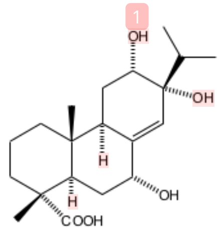


140

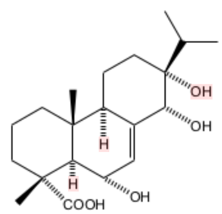
Fig. (16). Benzophenones in *Aquilaria.*



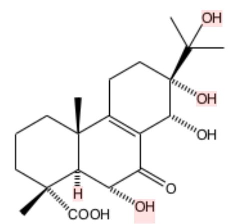
141



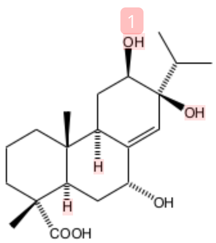
142



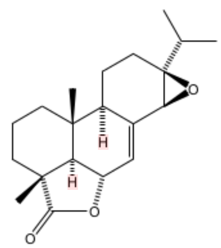
143



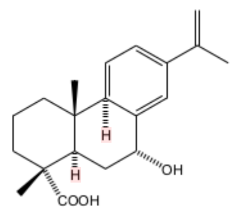
144



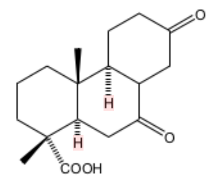
145



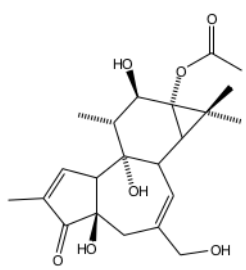
146



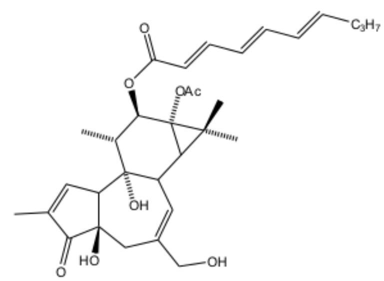
147



148

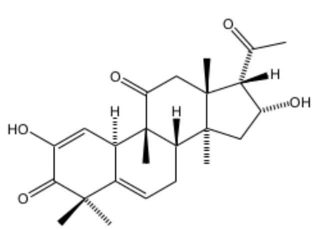


149

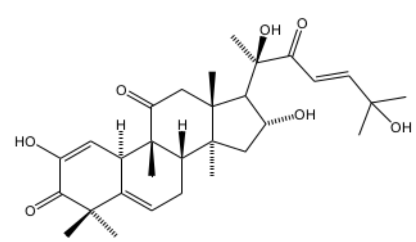


150

Fig. (17). Diterpenoides in *Aquilaria*.

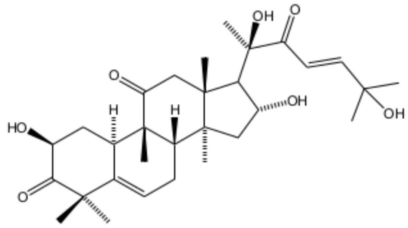


151

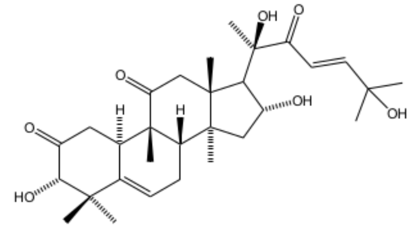


152

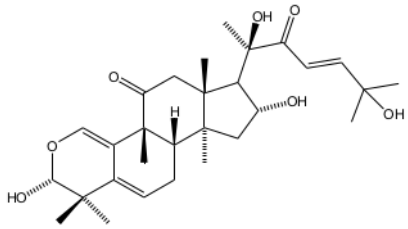
Fig. (18). Contd..



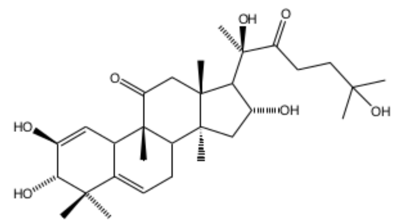
153



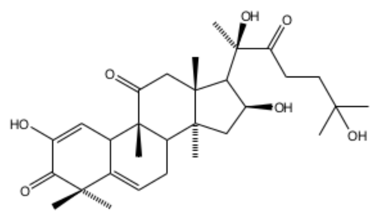
154



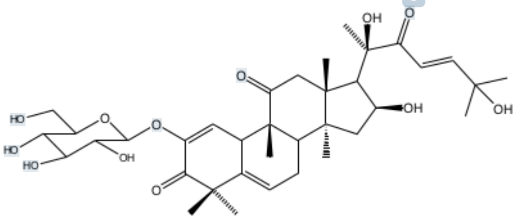
155



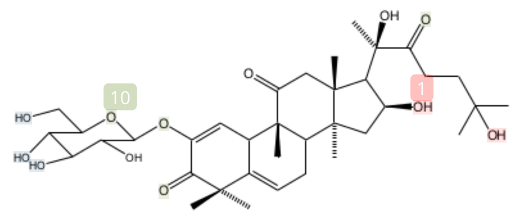
156



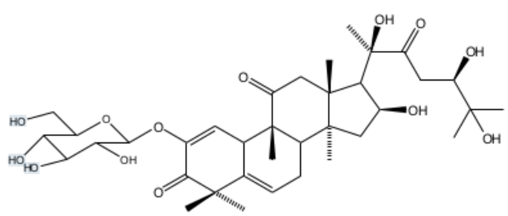
157



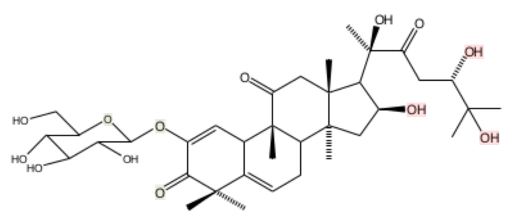
158



159

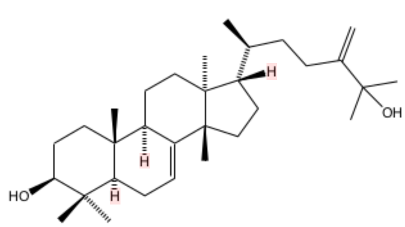


160

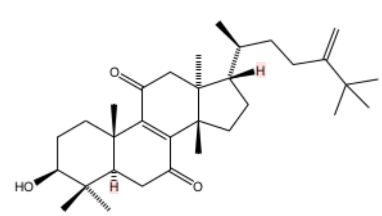


161

Fig. (18). Cucurbitacine triterpenoid in *Aquilaria.*

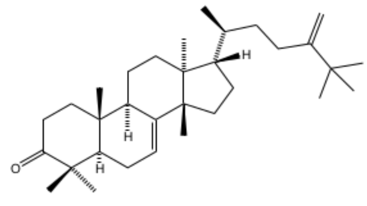


162



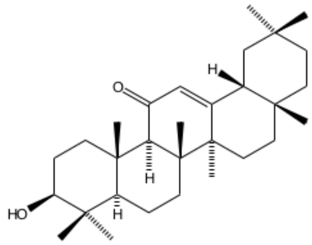
163

Fig. (19). Contd..

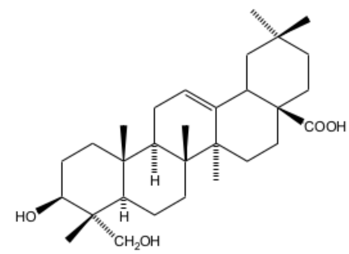


164

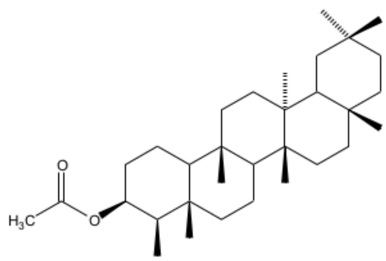
Fig. (19). Tirucallane triterpenoid in *Aquilaria.*



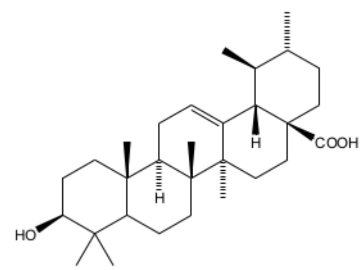
165



166



167



168

Fig. (20). Oleanane triterpenoides in *Aquilaria.*

(**170**), conicaol B (**171**), aquilaroside A (**172**), longifloroside A (**173**), conicaoside (**174**) and liriodendrin (**175**). These compounds are lignan derivatives with different skeletons, which are widely distributed in higher plants. Compounds **169**, **172** and **173** are common benzofuran-type lignan derivatives, but compounds **170** and **175** are di-tetrahydrofuran lignans, while compounds **174** and **171** represent tetrahydrofuran and dibenzylbutyrolactone types, respectively. A coumarinolignan, namely aquillochin (**176**), was isolated from the whole plant of *A. agallocha*. The structure was proposed by Bhandari *et al.* on the basis of chemical and physical characterization [50], Fig. (**21**).

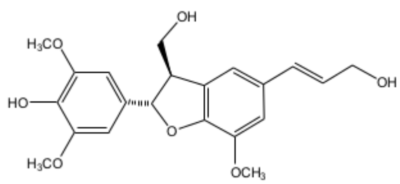
2.8. Miscellaneous

Several other compounds outside the compound classes discussed above are also found in *Aquilaria*. They include several nucleosides (**177**-**182**) and 4-hydroxyacetanilide (**183**). The nucleosides were isolated from the petioles and leaves of *A. sinensis*, whereas 4-hydroxyacetanilide (**183**) was obtained from a leaves extract of A. *malaccencis* [34, 51]. From the stem bark of *A. malaccensis* tree, the glyceride 1,3-dibehenyl-2-ferulyl glyceride (**184**) was isolated and identified [46], Fig. (**22**).

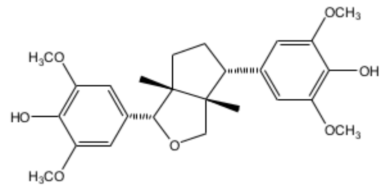
As *Aquilaria* plants are known as producers of high-quality fragrant material, then it is to be expected that these plants produce essential oils. 4-Phenyl-2-butanone, α-bulnesene, α-guaiene, agarospirol, ledene oxide-(II), elemol and γ-eudesmol were identified as the major chemical constituents of Malaysian agarwood (*A. malaccensis*) oils [52]. The composition of essential oils can be used to determine the quality of agarwood obtained from healthy, naturally infected, or artificially wounded trees. Such research has been done with agarwood from *A. agallocha* Roxb. [53].

Not only *Aquilaria* species, but also the fungi infecting them may produce fragrant compounds. For instance, from a fermentation of the endophytic Chinese eaglewood fungus HP-1, four compounds were isolated that were identified as 3α, 3β, 10β-trimethyl-decahydroazuleno [6, 7] furan-8, 9, 14-triol (**185**), 4-hydroxyphenylacetic acid (**186**), 4-hydroxyphenethyl alcohol (**187**) and 5-hydroxymethyl-2-furancarboxaldehyde (**188**) [54], Fig. (**23**).

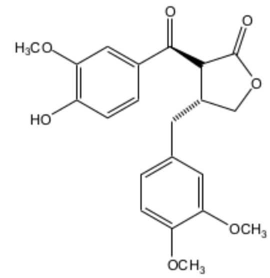
Table **1** provides a summary of secondary metabolites have been reported, along with parts of the plant and the species from which they were isolated.



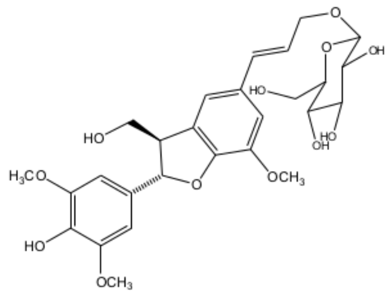
169



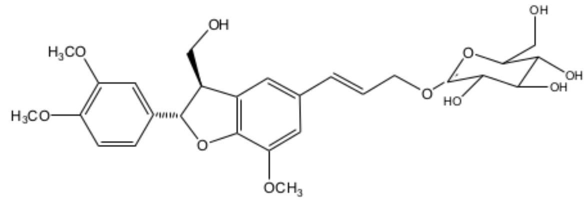
170



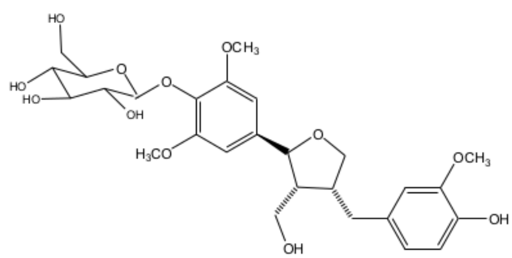
171



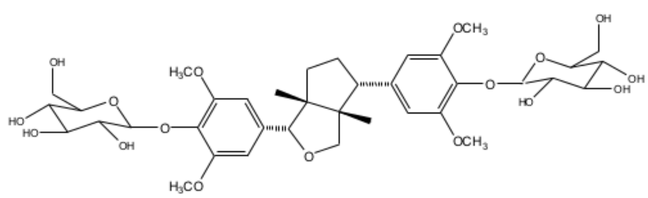
172



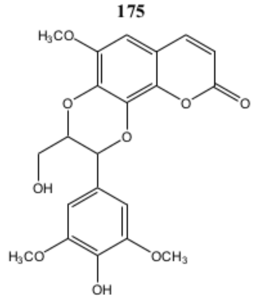
173



174

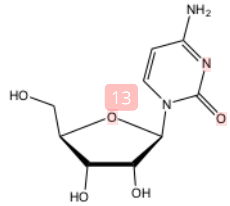


175

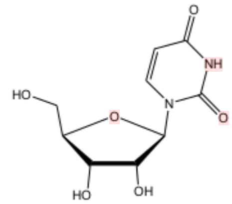


176

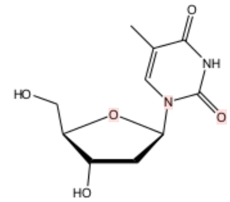
Fig. (21). Lignans in *Aquilaria.*



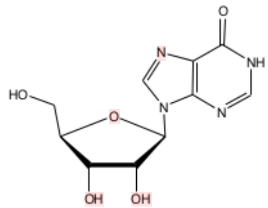
177



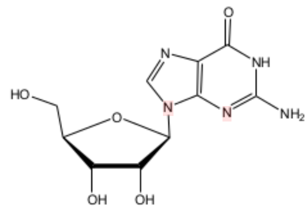
178



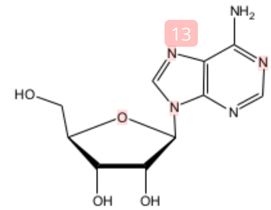
179



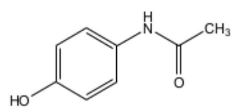
180



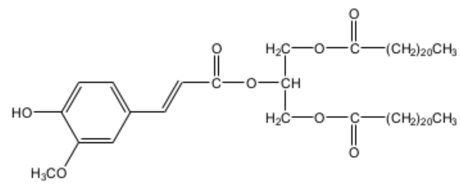
181



182

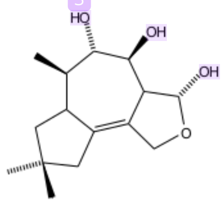


183

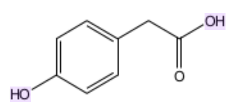


184

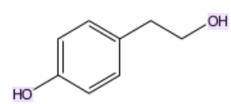
Fig. (22). Miscellaneous compounds in *Aquilaria.*



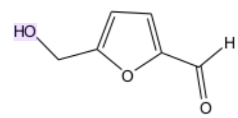
185



186



187



188

Fig. (23). Compounds producing by endophytic Chinese eaglewood fungus HP-1.

Table 1. Summary of secondary metabolites isolated from some *Aquilaria* species.

Secondary Metabolites	Part	*Species*	References
Guaiane Sesquiterpenes	Agarwood	*Aquilaria agallocha*	Ishihara, M. *et al.*
		Aquilaria sinensis	Zhao, H. *et al.*
Eudesmane Sesquiterpenes	Wood	*Aquilaria malaccensis*	Nakanishi, T. *et al.*
	Agarwood	*Aquilaria agallocha*	Ishihara, M. *et al.*
		Aquilaria sinensis	Li, W. *et al.* Zhao, H. *et al.*
		Aquilaria malaccensis	Wu, B. *et al.*
Agarofuran Sesquiterpenes	Agarwood	*Aquilaria agallocha*	Maheswari, M.L. *et al.*
	Wood		Yoneda, K. *et al.*

Table 1. (contd…)

Secondary Metabolites	Part	*Species*	References
Agarospirane Sesquiterpenes	Agarwood	*Aquilaria agallocha*	Varma, K.R. *et al.* Ishihara, M. *et al.* Yoneda, K. *et al.*
		Aquilaria malaccensis	Nakanishi, T. *et al.*
		Aquilaria sp. (Vietnam)	Ueda, J. *et al.*
		Aquilaria sinensis	Zhao, H. *et al.* Wu, B. *et al.*
Eremophilane Sesquiterpenes	Agarwood	*Aquilaria agallocha,*	Yoneda, K. *et al.* Alkhathlan, H.Z. *et al.* Ishihara, M. *et al.*
		Aquilaria malaccensis	Wu, B. *et al.*
		Aquilaria sinensis	Yang, D.L. *et al.*
Prezizane Sesquiterpenes	Agarwood	*Aquilaria malaccensis,*	Yoneda, K. *et al.*
		Aquilaria sp. (Indonesia)	Nakanishi, T. *et al.*
Miscellaneous Sesquiterpenes	Wood	*Aquilaria agallocha*	Wu, B. *et al.*
	Stem	*Aquilaria sinensis*	Pant, P. *et al.*
	Agarwood/ Eaglewood		Yang, L. *et al.* Zhao, H. *et al.*
Chromones	Wood	*Aquilaria agallocha*	Nakanishi, T. *et al.*
	Agarwood/ Eagle-wood	*Aquilaria* malaccensis,	Konishi, T. *et al.* Wu, B. *et al.*
		Aquilaria agallocha,	Alkhathlan, H.Z. *et al.*
		Aquilaria sinensis	Yang, L. *et al.* Li, W. *et al.* Yang, D.L. *et al.*
	Petioles And Leaves	*Aquilaria sinensis*	Wang, S.C. *et al.*
	Withered Wood		Yagura, T. *et al.*
Tetrahydrochromone	Withered Wood	*Aquilaria sinensis*	Yagura, T. *et al.* Dai, H.F. *et al.*
	Agarwood/ Eagle-wood		Liu, J. *et al.*
Di-Epoxy-Tetrahydrochromone	Agarwood	*Aquilaria crassna,*	Yagura, T. *et al.*
		Aquilaria sinensis	Li, W. *et al.*
Mono-Epoxy-Tetrahydrochromone	Agarwood	*Aquilaria sinensis*	Li, W. *et al.*
Aglycon Flavonoids	Leaves	*Aquilaria sinensis*	Qi, J. *et al.* Cheng, J.T. *et al.*
	Stem		Chen, D. *et al.*
Mono-Glycoside Flavonoids	Leaves	*Aquilaria sinensis*	Qi, J. *et al.* Feng, J. *et al.*
	Stem		Chen, D. *et al.*

Table 1. (contd…)

Secondary Metabolites	Part	*Species*	References
Di-Glycoside Flavonoids	Leaves	*Aquilaria sinensis*	Qi, J. *et al.* Yang, X.B. *et al.*
	Stem		Chen, D. *et al.*
Xanthons	Leaves	*Aquilaria sinensis*	Qi, J. *et al.* Cheng, J.T. *et al.*
Isoflavonoid	Stem	*Aquilaria sinensis*	Wu, Y. *et al.*
Aglycon Benzophenones	Leaves	*Aquilaria sinensis*	Qi, J. *et al.*
Mono-Glycoside Benzophenone	Leaves	*Aquilaria sinensis*	Qi, J. *et al.* Cheng, J.T. *et al.*
	Leaves and petioles		Wang, S.C. *et al.*
Di-Glycoside Benzophenone	Petioles and leaves	*Aquilaria sinensis*	Wang, S.C. *et al.*
	Leaves		Sun, G.J. *et al.*
Abietane And Podocarpane Diterpenoid	Agarwood	*Aquilaria sinensis*	Yang, L. *et al.*
Tigliane Diterpenoids	Stem	*Aquilaria sinensis*	Peng, K. *et al.*
	Stem bark	*Aquilaria malaccensis*	Gunasekera, S.P. *et al.*
Cucurbitacine Triterpenoids	Fruits	*Aquilaria sinensis*	Mei, W.L. *et al.*
	Stem		Peng, K. *et al.*
Aglycon And Glycoside Cucurbitane Triterpenoid	Petioles and leaves	*Aquilaria sinensis*	Wang, S.C. *et al.*
Tirucallane Triterpenoid	Petioles and leaves	*Aquilaria sinensis*	Cheng, J.T. *et al.* Wang, S.C. *et al.*
Oleanane Triterpenoid	Leaves	*Aquilaria sinensis*	Cheng, J.T. *et al.*
Benzofuran-Type Lignan (Aglycon And Glycoside)	Stem	*Aquilaria sinensis*	Wu, Y. *et al.*
Coumarinolignan	Whole plant	*Aquilaria agallocha*	Bhandari, P. *et al.*
Nucleosides	Petioles and leaves	*Aquilaria sinensis*	Wang, S.C. *et al.*
Acetanilide	Leaves	*Aquilaria malaccensis*	Afiffudden, S.K.N. *et al.*
Glyceride	Stem bark	*Aquilaria malaccensis*	Mei, W.L. *et al.*
Essential Oil	Agarwood	*Aquilaria malaccensis*	Tajuddin, S.N. *et al.*
		Aquilaria agallocha	Bhuiyan, M.N.I. *et al.*

CONCLUSION

The *Aquilaria* genus is very rich in different classes of natural products, such as sesquiterpenes, chromones, flavonoids, benzophenones, diterpenoids, triterpenoids and lignans. Hundreds of compounds have been identified in extracts from these plants, with *A. sinensis* as the most intensively studied source. Almost all parts of the *A. sinensis* plant have been investigated. Knowing the content of secondary metabolites from each part will be able to help understand the diversity of the usefulness of this plant. An example is the use of leaves that were reported to be used locally in trauma-related diseases such as fracture, bruise etc. It was also reported that agarwood has significant anticancer activities, analgesic and anti-inflammatory activities and antidepressant activities [55]. Research on the phytochemicals from this genus (*Aquilaria*) will continue certainly because there are still some species that have not been studied. There is a high possibility to find other compounds, even new compounds, from species that have not yet been studied. In addition, knowledge of the fragrant constituents of agarwood may be useful for the development of new fragrance products from other natural sources in the future.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors are thankful to the Directorate General of Higher Education, Ministry of Education and Culture, Republic of Indonesia, for supporting the research through funding of the PUPT Airlangga University research scheme year 2016.

The authors are also grateful to Prof. Bauke W. Djikstra from University of Groningen, Netherlands for manuscript correction.

REFERENCES

[1] Heywood, V.H.; Brummitt, R.K.; Culham, A.; Seberg, O. *Flowering Plant Families of The World*; Firefly Books: Ontario, Canada, **2007.**

[2] Heywood, V.H. *Les Plantes à Fleurs*; Editions Nathan: Paris, **1996.**

[3] Yagura, T.; Iro, M.; Kiuchi, F.; Honda, G.; Shimada, Y. Four new 2-(2-phenylethyl) chromone derivatives from withered wood of *Aquilaria sinensis*. *Chem. Pharm. Bull.*, **2003**, *51*(5), 560-564.

[4] Zhou, M.; Wang, H.; Suolangjiba, Kou, J.; Yu, B. Antinociceptive and anti-inflammatory activities of *Aquilaria sinensis* (Lour.) Gilg. leaves extract. *J. Ethnopharmacol*, **2008**, *117*, 345-350.

[5] Kim, Y.C.; Lee, E.H.; Lee, Y.M.; Kim, H.K.; Song, B.K.; Lee, E.J.; Kim, H.M. Effect of the aqueous extract of *Aquilaria agallocha* stems on the immediate hypersensitivity reactions. *J. Ethnopharmacol*, **1997**, *58*, 31-38.

[6] Alkhathlan, H.Z.; Al-Hazimi, H.M.; Al-Dhalaan, F.S.; Mousa, A.A. Three 2-(2-phenylethyl) chromones and two terpenes from agarwood. *Nat. Prod. Res.*, **2005**, *19*(4), 367-372.

[7] Yang, D.L.; Wang, H.; Guo, Z.K.; Dong, W.H.; Mei, W.L.; Dai, H.F. A new 2-(2-phenylethyl) chromone derivative in Chinese agarwood "Qi-Nan" from *Aquilaria sinensis*. *J. Asian Nat. Prod. Res.*, **2014**, *16*(7), 770-776.

[8] Ueda, J.; Imamura, L.; Tezuka, Y.; Tran, Q.L.; Tsuda, M.; Kadota, S. New sesuiterpene from Vietnamese agarwood and its induction effect on brain-derived neurotrophic factor mRNA expression *in vitro*. *Bioorg. Med. Chem.*, **2006**, *14*, 3571-3574.

[9] Li, W.; Cai, C.H.; Dong, W.H.; Guo, Z.K.; Wang, H.; Mei, W.L.; Dai, H.F. 2-(2-phenylethyl) chromone derivatives from Chinese agarwood induced by artificial holing. *Fitoterapia*, **2014**, *98*, 117-123.

[10] Gao, X.; Xie, M.; Liu, S.; Guo, X.; Chen, X.; Zhong, Z.; Wang, L.; Zhang, W. Chromatographic fingerprint analysis of metabolites in natural and artificial agarwood using gas chromatography-mass spectrometry combined with chemometric methods. *J. Chromatogr. B*, **2014**, *967*, 264-273.

[11] Naef, R. The volatile and semi-volatile constituents of agarwood, the infected heartwood of *Aquilaria* species: A review. *Flavour Fragr. J.*, **2011**, *26*, 73-89.

[12] Chen, H.Q.; Wie, J.H.; Yang, J.S.; Zhang, Z.; Yang, Y.; Gao, Z.H.; Sui, C.; Gong, B. Chemical constituents of agarwood originating from the endemic genus *Aquilaria* plants. *Chem. Biodivers.*, **2012**, *9*, 236-250.

[13] Hashim, Y.Z.H.; Kerr, P.G.; Abbas, P.; Salleh, H.M. *Aquilaria* spp. (agarwood) as a source of health beneficial compounds: A review of traditional use, phytochemistry and pharmacology. *J. Ethnopharmacol*, **2016**, *189*, 331-360.

[14] Nakanishi, T.; Yamagata, E.; Yoneda, K.; Miura, I. Jinkohol, a prezizane sesquiterpene alcohol from agarwood. *Phytochemistry*, **1981**, *20*(7), 1597-1599.

[15] Bajaj, Y.P.S. Medicinal and aromatic plant VIII (Biotechnology in agriculture and forestry), Springer-Verlag: Berlin, **2013**.

[16] Yang, D.L.; Wang, H.; Guo, Z.K.; Li, W.; Mei, W.L.; Dai, H.F. Fragrant agarofuran and eremophilane sesquiterpenes in agarwood "Qi-Nan" from *Aquilaria sinensis*. *Phytochem. Lett.*, **2014**, *8*, 121-125.

[17] Ishihara, M.; Tsuneya, T.; Uneyama, K. Guaiane sesquiterpenes from agarwood. *Phytochemistry*, **1991**, *30*(10), 3343-3347.

[18] Ishihara, M.; Tsuneya, T.; Shiga, M.; Uneyama, K. Three sesquiterpenes from agarwood. *Phytochemistry*, **1991**, *30*(2), 563-566.

[19] Zhao, H.; Peng, Q.; Han, Z.; Yang, L.; Wang, Z. Three new sesquiterpenoids and one new sesquiterpenoid derivative from Chinese eaglewood. *Molecules*, **2016**, *21*(3), 281-288.

[20] Nakanishi, T.; Yamagata, E.; Yoneda, K.; Nagashima, T.; Ichiro, K.; Yoshida, T.; Mori, H.; Miura, I. Three fragrant sesquiterpenes of agarwood. *Phytochemistry*, **1984**, *23*(9), 2066-2067.

[21] Ishihara, M.; Tsuneya, T.; Uneyama, K. Fragrant sesquiterpenes from agarwood. *Phytochemistry*, **1993**, *33*(5), 1147-1155.

[22] Li, W.; Cai, C.H.; Guo, Z.K.; Wang, H.; Zuo, W.J.; Dong, W.H.; Mei, W.L.; Dai, H.F. Five new eudesmane-type sesquiterpenoids from Chinese agarwood induced by artificial holing. *Fitoterapia*, **2015**, *100*, 44-49.

[23] Wu, B.; Lee, J.G.; Lim, C.J.; Jia, S.D.; Kwon, S.W.; Hwang, G.S.; Park, J.H. Sesquiterpenoids and 2-(2-phenylethyl)-4*H*-chromen-4-one (=2-(2-phenylethyl)-4*H*-1-benzopyran-4-one) derivatives from *Aquilaria malaccensis* agarwood. *Helv. Chim. Acta*, **2012**, *95*, 636-642.

[24] Maheswari, M.L.; Jain, T.C.; Bates, R.B.; Bhattacharyya, S.C. Terpenoids XLI. Structure and absolute configuration of α-agarofuran, β-agarofuran and dihydroagarofuran. *Tetrahedron*, **1963**, *19*, 1079-1090.

[25] Yoneda, K.; Yamagata, E.; Nakanishi, T.; Nagashima, T.; Kawasaki, I.; Yoshida, T.; Mori, H.; Miura, I. Sesquiterpenoids in two different kinds of agarwood. *Phytochemistry*, **1984**, *23*(9), 2068-2069.

[26] Varma, K.R.; Maheshwarsi, M.L.; Bhattacharyya, S.C. The constituent of Agarospirol, a sesquiterpenoid with a new skeleton. *Tetrahedron,* **1965**, *21*, 115-138.

[27] Wu, B.; Kwon, S.W.; Hwang, G.S.; Park, J.H. Eight new 2-(2-phenylethyl) chromone (=2-(2-phenylethyl)-4*H*-1-benzopyran-4-one) derivatives from *Aquilaria malaccensis* agarwood. *Helv. Chim. Acta*, **2012**, *95,* 1657-1665.

[28] Pant, P.; Rastogi, R.P. Agarol, a new sesquiterpene from *Aquilaria agallocha. Phytochemistry*, **1980**, *19*, 1869-1870.

[29] Peng, K.; Mei, W.L.; Zhao, Y.X.; Tan, L.H.; Wang, Q.H.; Dai, H.F. A novel degraded sesquiterpene from fresh stem of *Aquilaria sinensis. J. Asian Nat. Prod. Res.*, **2011**, *13*(10), 951-955.

[30] Yang, L.; Qiao, L.R.; Zhang, J.J.; Dai, J.G.; Guo, S.X. Two new sesquitrepene derivatives from Chinese eaglewood. *J. Asian Nat. Prod. Res.*, **2012**, *14*(11), 1054-1058.

[31] Nakanishi, T.; Inada, A.; Nishi, M.; Yamagata, E.; Yoneda, K. A new and a known derivatives of 2-(2-phenylethyl) chromone from a kind of agarwood ("kanankoh" in Japanese) originating from *Aquilaria agallocha. J. Nat. Prod.*, **1986**, *49*(6), 1106-1108.

[32] Konishi, T.; Konoshima, T.; Shimada, Y.; Kiyosawa, S. Six new 2-(2-phenylethyl) chromones from agarwood, *Chem. Pharm. Bull.,* **2002**, *50*(3), 419-422.

[33] Yang, L.; Qiao, L.; Xie, D.; Yuan, Y.; Chen, N.; Dai, J.; Guo, S. 2-(2-Phenylethyl) chromones from Chinese eaglewood. *Phytochemistry*, **2012**, *76*, 92-97.

[34] Wang, S.C.; Wang, F.; Yue, C.H. Chemical constituents from the petioles and leaves of *Aquilaria sinensis*. *Biochem. Syst. Ecol.*, **2015**, *61*, 458-461.

[35] Liu, J.; Wu, J.; Zhao, Y.X.; Deng, Y.Y.; Mei, W.L.; Dai, H.F. A new cytotoxic 2-(2-phenylethyl) chromone from Chinese eaglewood. *Chin. Chem. Lett*., **2008**, *19*, 934-936.

[36] Dai, H.F.; Liu, J.; Han, Z.; Zeng, Y.B.; Wang, H.; Mei, W.L. Two new 2-(2-phenylethyl) chromones from Chinese eaglewood. *J. Asian Nat. Prod. Res.*, **2010**, *12*(2), 134-137.

[37] Yagura, T.; Shibayama, N.; Ito, M.; Kiuchi, F.; Honda, G. Three novel diepoxy tetrahydrochromones from agarwood artificially produced by intentional wounding. *Tetrahedron Lett*., **2005**, *46*, 4395-4398.

[38] Qi, J.; Lu, J.J.; Liu, J.H.; Yu, B.Y. Flavonoids and a rare benzophenone glycoside from the leaves of *Aquilaria sinensis. Chem. Pharm. Bull.,* **2009**, *57*(2), 134-137.

[39] Cheng, J.T.; Han, Y.Q.; He, J.; WU, X.D.; Dong, L.B.; Peng, L.Y.; Li, Y.; Zhao, Q.S. Two new tirucallane triterpenoids from the leaves of *Aquilaria sinensis*. *Arch. Pharm. Res.*, **2013**, *36*, 1084-1089.

[40] Chen, D.; Bi, D.; Song, Y.L.; Tu, P.F. Flavonoids from the stems of *Aquilaria sinensis*. *Chin. J. Nat. Med.*, **2012**, *10*(4), 287-291.

[41] Feng, J.; Yang, X.W.; Wang, R.F. Bio-assay guided isolation and identification of a-glucosidase inhibitors from the leaves of *Aquilaria sinensis*. *Phytochemistry*, **2011**, *72*, 241-247.

[42] Yang, X.B.; Feng, J.; Yang, X.W.; Zhao, B.; Liu, J.X. Aquisiflavoside, a new nitric oxide production inhibitor from the leaves of *Aquilaria sinensis*. *J. Asian Nat. Prod. Res.*, **2012**, *14*(9), 867-872.

[43] Severi, J.A.; Lima, Z.P.; Kushima, H.; Monteiro, A.R.; Brito, S.; dos Santos, L.C.; Vilegas, W.; Hiruma-Lima, C.A. Polyphenols with antiulcerogenic action from aqueous aecoction of Mango leaves (*Mangifera indica L.*). *Molecules*, **2009**, *14*, 1098-1110.

[44] Sun, G.J.; Wang, S.; Xia, F.; Wang, K.Y.; Chen, J.M.; Tu, P.F. Five new benzophenone glycosides from the leaves of *Aquilaria sinensis* (Lour.). *Chin. Chem. Lett.*, **2014**, *25*, 1573-1576.

[45] Yang, L.; Qiao, L.; Ji, C.; Xie, D.; Gong, N.B.; Lu, Y.; Zhang, J.D.; Guo, S. Antidepressant abietane diterpenoids from Chinese eaglewood. *J. Nat. Prod.*, **2013**, *76*, 216-222.

[46] Gunasekera, S.P.; Kinghorn, A.D.; Cordell, G.A.; Farnsworth, N.R. Plant anticancer agents. XIX. Constituents of *Aquilaria malaccensis*, *J. Nat. Prod.*, **1981**, *44*(5), 569-572.

[47] Mei, W.L.; Lin, F.; Zuo, W.J.; Wang, H.; Dai, H.F. Cucurbitacins from fruits of *Aquilaria sinensis. Chin. J. Nat. Med.*, **2012**, *10*(3), 234-237.

[48] Schun, Y.; Cordell, G.A.; Cox, P.J.; Howie, R.A. Wallenone, a C32 triterpenoid from the leaves of *Gyrinops walla. Phytochemistry*, **1986**, *25*, 753-755.

[49] Wu, Y.; Liu, C; Li, H.F.; Sun, J.B.; Li, Y.Y; Gu, W; Wang, D.Y; Liu, J.G.; Hu, Y.L. A novel neolignan glycoside from *Aquilaria sinensis*. *Biochem. Syst. Ecol.*, **2014**, *55*, 41-45.

[50] Bhandari, P.; Pant, P.; Rastogi, R.P. Aquillochin, a coumarinolignan from *Aquilaria agallocha. Phytochemistry*, **1982**, *21*(8), 2147-2149.

[51] Afiffudden, S.K.N.; Alwi, H.; Hamid, K.H.K. Determination of 4-hydroxyacetanilide in leaves extract of *Aquilaria malaccensis* by high pressure liquid chromatograph. *Procedia, Soc. Behav. Sci.*, **2015**, *195*, 2726-2733.

[52] Tajuddin, S.N.; Muhamad, N.S.; Yarmo, M.A.; Yusoff, M.M. Characterization of the chemical constituents of agarwood oils from Malaysia by comprehensive two-dimensional gas chromatography-time-of-flight mass spectrometry. *Mendeleev Commun.*, **2013**, *23*, 51-52.

[53] Bhuiyan, M.N.I.; Begum, J.; Bhuiyan, M.N.H. Analysis of essential oil of eaglewood tree (*Aquilaria agallocha Roxb.*) by gas chromatography mass spectrometry. *Bangladesh J. Pharmacol.*, **2009**, *4*, 24-28.

[54] Zuo, W.J.; Jin, P.F.; Dong, W.H.; Dai, H.F.; Mei, W.L. Metabolites from the endophytic fungus HP-1 of Chinese eaglewood. *Chin. J. Nat. Med.*, **2014**, *12*(2), 151-153.

[55] Kang, Y.F.; Chien, S.L.; Wu, H.M.; Li, W.J.; Chen, C.T.; Li, H.T.; Chen, H.L.; Chao, D.; Chen, S.J.; Huang, C.T.; Chen, C.Y. Secondary metabolites from the leaves of *Aquilaria sinensis*. *Chem. Nat. Compd.*, **2014**, *50*(6), 1110-1112.

Review: Secondary Metabolites of Aquilaria, a Thymelaeaceae Genus

ORIGINALITY REPORT

19%	18%	9%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.skyehaven.net Internet Source	5%
2	www.minireviewsinorganicchemistry.com Internet Source	2%
3	mdpi.com Internet Source	2%
4	www.cropwatch.org Internet Source	2%
5	link.springer.com Internet Source	2%
6	eprints.nottingham.ac.uk Internet Source	2%
7	Rishu Kalra, Nutan Kaushik. "A review of chemistry, quality and analysis of infected agarwood tree (Aquilaria sp.)", Phytochemistry Reviews, 2017 Publication	1%
8	mp3freesongs.net Internet Source	

		1%
9	cropwatch.org Internet Source	1%
10	阿部 正人. "触媒的不斉分子内シクロプロパン化反応を基軸としたフロログルシン類の全合成研究", [出版者不明], 2012. Publication	1%
11	www-sor.inria.fr Internet Source	1%
12	Pigment & Resin Technology, Volume 41, Issue 5 (2012-09-01) Publication	<1%
13	Tereshchenko, Alexander. "Modulare Synthese neuer Pyridin-N-Oxid-Liganden - Darstellung von Komplexen und deren Einsatz in der Katalyse", Publikationsserver der Universität Regensburg, 2011. Publication	<1%
14	www.thieme-connect.com Internet Source	<1%
15	www.cinematography.net Internet Source	<1%
16	che1.lf1.cuni.cz Internet Source	<1%

17	www.freepatentsonline.com Internet Source	<1 %

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	On		

Review: Secondary Metabolites of Aquilaria, a Thymelaeaceae Genus

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13

PAGE 14

PAGE 15

PAGE 16

PAGE 17

PAGE 18

PAGE 19