An Overview of Agarwood, Phytochemical Constituents, Pharmacological Activities, and Analyses

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ABSTRACT

Agarwood is a resin-impregnated heartwood obtained from the plants belongs to the genera, *Aquilaria, Daphne, Gonystylus, Gyrinops* and *Wikstroemia*. It is traditionally used for the production of perfume and incense stick, and pharmaceutical applications. Agarwood usually induced by the natural (traditional), conventional, and non-conventional methods. The major groups of phytochemicals identified in agarwood extracts are sesquiterpenes, 2-(2-phenylethyl)-4H-chromen-4-one derivatives (PECs), and aromatic compounds. These phytochemicals are showed various pharmalogical properties such as anti-inflammatory, cytotoxic, neuroprotective, anti-diabetic, anti-bacterial, etc. Several analytical techniques are applied to analyze the agarwood phytochemicals including sesquiterpenes, which exists mostly in the form of essential oils, and the fragrance constituents of PECs. The present review summarize the agarwood traditional uses, induction methods, phytochemical constituents, potential pharmacological activities, along with analyses methods. This review was carried out by searching various scientific databases, including Google Scholar, PubMed, Elsevier, ACS publications, Taylor and Francis, Wiley Online Library, MDPI, Springer, Thieme, and ProQuest. The present review provides a scientific basis for future studies and necessary information for the development of agarwood based therapeutic agents.

Keywords: Agarwood; Traditional uses; Induction methods; Chemical constituents; Biological activities; Analyses

INTRODUCTION

Agarwood, known as aloeswood or eaglewood, is an aromatic dark resin-impregnated heartwood obtained from wounded tree species of the Thymelaeaceae family [1]. The plant family Thymelaeaceae contains 54 genera, including *Aquilaria, Daphne, Gonystylus, Gyrinops and Wikstroemia* [1]. The species of the genus *Aquilaria, Gonystylus*, and *Gyrinops* produce agarwood [1]. In particular, the genus *Aquilaria* contains 57 species, among these 21 are accepted in the plant list [1]. So

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far, fifteen species of *Aquilaria* and nine species of Gyrinops are reported as agarwood producing plants [2]. Agarwood (resin)-producing species are found from the forests of Southeast Asia including, Bangladesh, Bhutan, China, India, Indonesia, Laos, Malaysia, Myanmar, Singapore, Taiwan, Thailand, and Vietnam [1,2]. They are usually found in lowland tropical forests with optimal sunlight, shade and moisture. Agarwood-producing species have a small flower similar to that of 'jasmine', and the fruit is bitter [3].

Healthy *Aquilaria* tree does not produce agarwood [2]. The healthy wood is white, soft, even-grained and not having a perfumed smell, as compared with the dark, hard and heavy scented characterictics resin-impregnated agarwood [2]. The agarwood resin developed through pathological, wounding and non-pathological mechanisms [4]. The formation of agarwood occurs naturally in response to natural injuries such as lightning, insects and mold attacks [4]. The deposited resin around the wounds over the years accumulate and eventually forms agarwood [4]. Therefore, Agarwood is termed as the resin-impregnated pieces of wood [4], and its formation is related to the self-defense mechanism of *Aquilaria* trees in response to biotic and abiotic stresses [1,2]. Stresses trigger the defense responses of *Aquilaria* species, which in turn initiate the secondary metabolite biosynthesis and the accumulation of agarwood resin [1,2].

The prominent species of agarwood producing *Aquilaria* species are, *A. beccariana* Tiegh., *A. crassna* Pierre ex Lecomte, *A. filaria* (Oken) Merr., *A. hirta* Ridl., *A. khasiana* Hallier f., *A. malaccensis* Lamk., *A. microcarpa* Baill., *A. rostrata* Ridl., *A. sinensis* (Lour.) Spreng., and *A. agallocha* [5]. Among these *A. agallocha*, *A. crassna*, *A. malaccensis*, and *A. sinensis* gain significant attention due to their therapeutic uses in traditional Southeast Asian medical systems [5]. Accordingly, these species appear frequently in the literature, particularly *A. crassna*, *A. malaccensis* and *A. sinensis* [1,5]. The agarwood producing *Aquilaria* species and their native place are presented in Table 1. With the increasing demand for agarwood, the population of agarwood species is declining rapidly in the wild. Currently, the genus *Aquilaria* is listed as endangered species and protected under Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) regulation [1]. The index of CITES species listed A. agallocha Roxb. as a synonym of *A. malaccensis* Lamk [1]. *A. malaccensis* Lamk., is also synonym to *Aquilariella malaccensis* (Lam.) Tiegh., and Agallochum malaccense (Lam.) Kuntze [6]. The International Union for Conservation of Nature and Natural Resources (IUCN) Red List of Threatened Species is listed *A. crassna* as critically endangered, and *A. malaccensis* and *A. sinensis* as vulnerable [7].

Species	Place of origin (Native)
Aquilaria apiculata Merr	Philippines
Aquilaria baillonii Pierre ex Lecomte	Cambodia, Thailand, Laos, Vietnam
Aquilaria banaensis P.H.H6	Vietnam
Aquilaria beccariana Tiegh	Indonesia
Aquilaria citrinicarpa (Elmer) Hallier f.	Philippines
Aquilaria crassna Pierre ex Lecomte	Thailand, Cambodia, Vietnam
Aquilaria cumingiana (Decne) Ridl	Malaysia
Aquilaria khasiana Hallier f.	India
Aquilaria malaccensis Lam.	India, Myanmar, Malaysia, Indonesia, Philippines
Aquilaria microcarpa Baill	Indonesia
Aquilaria parvifolia (Quisumb) Ding Hon	Philippines
Aquilaria rostrata Ridl	Malaysia
Aquilaria rugosa Kiet Kessler	Vietnam

Aquilaria sinensis (Lour.) Gilg	China
Aquilaria subintegra Ding Hon	Thailand
Aquilaria urdanetensis (Elmer) Hallier f.	Philippines
Aquilarla yunnanensis S.C. Huang	China

Table 1: Agarwood producing *Aquilaria* species and their place of origin.

1.1. Traditional uses

Agarwood is known as "wood of God" because of religious practices [4]. The word "aloes" which means agarwood is found in the Sanskrit poet, Kâlidâsa, dated back to c. 4th–5th century CE [4]. Agarwood is considered the finest natural incense and has been used in many cultures, such as the Arabian, Chinese, Indian, and Japanese cultures [8]. Agarwood also associated with religious history, rituals and ceremonies in Buddhism, Christianity, Hinduism, and Islam [8]. It is known as gaharu in the Indonesia and Malaysia, jin-koh in Japan, chen xiang (沉香) in Chinese, agar in India, chim-hyuang in Korea, kritsana noi in Thailand, tram huong in Vietnam, and oud in the Middle East [8]. Agarwood is widely used as therapeutic perfumes, traditional medicine, religious purposes and aromatic food ingredient (Table 3) [3]. In the traditional Chinese and Ayurvedic medicines as an aphrodisiac, sedative, cardiotonic and carminative, as well as to treat gastric problems, coughs, rheumatism and high fever [9]. Agarwood is a traditional Chinese medicine included in the 2020 edition of Chinese Pharmacopoeia [10]. In traditional Arabian medicine, agarwood essential oil is used for aromatherapy [3]. In Thailand, agarwood has been used for a long time as a traditional treatment for infectious diseases such as diarrhea and skin diseases [3]. Additionally, *A. crassna* extract has been using as the ingredient of Ya-hom, a traditional Thai herbal formulation for the treatment of fainting by targeting the cardiovascular system.

1.2. Grading system

The market price of agarwood has commercial attention. However, the grading process of agarwood is largely depends on the human experience from the age-old practices of each country [1]. In general, the classification of agarwood oil quality is based on wood physical properties, long lasting aroma when burnt, color, resin content, high fixative properties and consumer perception, etc [1]. The higher the grade of agarwood, the richer the layers of aroma [1]. The best agarwood fragrance is mellow and sweet, full of penetration and persistence, and the powdery waxy material on the surface can be scraped off and kneaded it into a ball [1]. Its aroma is regarded as a symbol of high quality. Complexity and variability in agarwood composition are major challenges associated with its grading process. The morphological grading system of agarwood is shown in Table 2.

Observational Feature	Grading Categary		
	A	**B**	**C**
Sense of oiliness	Strong	Strong	Mild
Aroma	Strong, feel sweet and cool	Less potent odor, feel sweet and slightly spicy	Mild aroma, feel slightly sweet, salty
Resin density	High dense, compact, sink in water when soaked	Dense, less compact, half-sinkage in water	Light and not dense, full-floating on water
Weight	Hard texture, brittle, and not hollowed	Texture little hard, little brittle, slightly hollow	Loose texture, not brittle, and hollow

Table 2: Assesment of agarwood quality using grading system.

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1.3. Economical value

Agarwood is a valuable, non-timber forest product used different societies for medicinal, aromatic, cultural and religious purposes [8]. As the wealth of the consumer countries are gradually increased in recent decades, the market's demand for agarwood started to exceed its supply [1]. The market value of agarwood derivative products is dependent on the classification or grading of agarwood, which is determined by a cumulative factor of the fragrance strength and longevity, resin content, geographical origin and purity (for oil) [8]. Global agarwood prices can be ranging from US$20 – 6,000 per/kg for the wood chips depending on its quality or US$ 10,000 per/kg for the wood itself [1]. High quality wood is used as incense in Arabian households and for the 'koh-doh' incense ceremony in Japan [8]. High-quality agarwood products can reach prices as high as US$100,000/kg. In the form of oud oil which is distilled from agarwood for perfumery, can be sold for US $1500 per 11.7 g [1,9]. The annual global market for agarwood has been estimated to be in the range of US$ 6 – 8 billion [1,9]. Agarwood has commercial importance in three categories i.e. perfume production, incense stick, and pharmaceuticals as described below [8].

1.3.1. Perfume

Agarwood oil is an essential oil obtained by water and steam distillation of agarwood [1]. Agarwood oil is a yellow to dark amber, viscous liquid with a characteristic balsamic and woody odour [9,11]. It is used in luxury perfumery for application. Agarwood perfumes are commonly prepared in both alcoholic and non-alcoholic carriers [9,11]. Agarwood perfume has a unique smell obtained from fragrance essential oil and aromatic compound [11]. The oil is also used as a fragrance in the production of cosmetics and personal care products, such as soaps and shampoos [9,11]. Agarwood resin is a key ingredient in old and new Arabic perfume products, and used as an element within high-quality perfumes in Arabic, Japanese and Indian cultures [4]. Traditionally in the Middle East, agarwood oil is used as a scent, and Minyak attar (water-based) [4]. "Attar" is an example of a water-based perfume containing agarwood oil, which is traditionally used by Muslims to lace prayer clothes [4]. Agarwood oil is one of the most important ingredients in Chinese perfume industry; additionally it became a prominent in the modern western perfume and fragrance industry.

1.3.2. Incense stick

Burning agarwood produces fragrance, which is used as incense for ceremonial purposes in Buddhism, Confucianism and Hinduism [11]. The incense also functions as an insect repellent [4,8]. The aromatic compounds are the main chemical components in agarwood smoke and create an atmosphere of peace and serenity [1,4]. It scent heavenly, woody nuance, balsamic and warm aura of bittersweet when the chromones break into low molecular weight at high temperature [1,4]. In Taiwan, the agarwood stick is used in traditional festivals or ceremonies to bring safety and good luck to the believer [11]. The agarwood incense stick is used in the bathroom as a customary sense, during Ramdan prayer by the Muslim, and Puja celebration by the Hindu religious practice [11].

1.3.3. Pharmaceutical use

Agarwood plays a vital role in the field of medicine, contains various chemical components, including several sesquiterpenes, 2-(2-phenylethyl)chromens (PECs), and aromatic compounds, etc [3,6,12]. These compounds display various biological properties such as anticancer, anti-inflammatory, antioxidant, antibacterial, antifungal, antidiabetic, and so on [3,6,12]. Traditionally agarwood is prescribed to treat pleurisy by the Sahih Muslim, relieve pain, arrest vomiting, and asthma [6,12]. *A. malaccensis* products are an essential source in the field of Ayurveda for treating various diseases such as appetizer, analgesic, antipyretic, antihistaminic, styptic, carminative, cytotoxic, insecticidal, general tonic, etc [6,11,12]. Agarwood materials have also been formulated into a balm (muscle rub) and candle wax [11]. The pharmaceutical and traditional use of agarwood in different countries/locations are presented as in Table 3.

Place	Traditional use	Preparations/route of intake
Bangladesh	Treatment of rheumatism	Agarwood taken orally
China	Treatment of circulatory disorders, abdominal pain, vomiting, dyspnea, asthma	Heartwood in Chinese medicines, and Heartwood decoction
India	Treatment of diarrhoea, dysentery, vomiting, anorexia, mouth and teeth diseases, facial paralysis, shivering, sprains, bone fracture	Heartwood in Ayurvedic formulation such as Chawanprash, Arimedadi Taila and Mahanarin Taila
Indonesia	Treatment of joint pain, Sedation, detoxification, treatment of stomachaches, incense sticks	Wood burned and smoke held over the affected area
Japan	Stomachic and sedative agent	Infusion or decotion
Korea	Treatment of cough, acroparalysis, croup, asthma, stomachic agent, tonic, sedative and expectorant	Infusion or decotion
Malaysia	Tonic, stimulant and carminative agent after childbirth	Heartwood mixed with coconut oil
	Treatment of rheumatism and body pains	Heartwood decoction (mixed with other types of woods)
	Treatment of small pox	Heartwood prepared into Ointment
Philippines	Stop bleeding of the wounds	Bark and roots
	Treatment of malaria (substitute for quinine)	Bark, wood and fruits
Thailand	Treatment for diarrhoea, dysentery and skin diseases, antispasmodic and cardiovascular function enhancer in fainted patient	Traditional medicinal preparation 'Krisanaglun
	Treatment of fainting, nausea and vomiting	Folk medicine 'Ya–Hom'
Tibet	Treatment of nervous and emotional disorders Cardioprotective agents	Infusion or decotion

Table 3: The pharmaceutical and traditional use of agarwood in different countries/locations.

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1.3.4. Other uses

The uses of agarwood is not restricted to incense and perfumery. Solid pieces of agarwood are carved into natural art sculptures, beads, bracelets and boxes [4,11]. The wood of *A. agallocha* is used as decorative ornaments (China), 'joss sticks' (China and India), and flea and louse repellents (India), whereas the bark has been used to manufacture paper (China) [1,4]. In India, the wood of *A. malaccensis* used as fuel for fumigation, and the bark has been used to make cloth and rope [11].

1.4. Agarwood induction methods

Agarwood is a valuable non-timber product, and its demand is much greater than its supply. The agarwood (resin) induction mechanism is not fully understood or elucidated. High demand of quality agarwood in conjunction with the depletion of the wild *Aquilaria* trees, leads to the artificial induction of agarwood resin formation. Modern artificial agarwood formation techniques are mainly biochemical methods, such as chemical reagent invasion and bacteria inoculation (Figure 1) [2].

1.4.1. Natural (Traditional) methods

Naturally, agarwood formation is often linked to the physical wounding or damage of *Aquilaria* trees caused by thunder strike, animal grazing, pest and disease infestations [13]. These events expose the inner part of the trees toward pathogenic microbes, which evoke the defense mechanism of *Aquilaria* to initiate the resin production [13]. This natural formation process of agarwood has greatly inspired the development of diverse artificial induction methods (Figure 1). For example, the microbial species of *Actinobacteria* sp., *Acidobacteria* sp., *Aspergillus* sp., *Alcaligenes* sp., *Bacillus* sp., *Chaetomium* sp., *Curvularia* sp. *Fusarium* sp. *Lasiodiploidia* sp., *Penicillium* sp., *Proteobacteria* sp., *Pseudomonas* sp., and *Trichoderma* sp. are involved in the agarwood formation [1,13]. For more details, please refer the recent review article [221].

1.4.2. Conventional methods

Various conventional methods are applied to initiate agarwood resin formation. The techniques often involved the physical penetration into the trunk (wounding), mechanical wounding, axe chopping, nailing, holing, burning, insertion of a microbial (mainly fungal) concoction (pathology) and response of the tree towards the administered stress (non-pathological) [2,5]. Many pure-culture strains of fungi such as *Aspergillus niger*, *A. fijiensis, Chaetomium* sp., *Fusarium solani, Lasiodiplodia* sp. (*L. hormozganensis*), *Gongronella butleri*, *Saitozyma podzolica*, *Cladorrhinum bulbillosum*, *Humicola grisea*, *Penicillium* sp., *Trichoderma lentiforme*, *Phaeoacremonium rubrigenum*, and *Tetracladium marchalianum* are isolated from natural agarwood are found to be effective biological agents to induce agarwood formation in healthy *Aquilaria* trees [14-16]. For more details, please refer the recent review article [221]. Therefore, fungal-interaction induction methods coupled with the application of biological inoculum are developed for agarwood induction [2,5]. The advantage of using fungal inoculum is that it is generally believed to be safe for handling and eco-friendly. However, fungal inoculation will normally give rise to localized and inconsistent quality of agarwood due to the different fungal consortium used [2,5]. As a solution, laborious holing process and long incubation time is required to maximize the colonized surface area on the tree to produce better quality of agarwood [17]. The fungal infected Aquilaria trees are reported to deposit agarwood resin around the infected sites as barrier to prevent further fungal intrusion [13,14]. Agarwood resin deposition accompanied with color changes of internal tissues occured within a year by injuring the trees [8]. Although it is cost effective and requires only personnel with little or no scientific knowledge on agarwood, but these conventional induction methods usually result in inferior quality and uncertain yield of agarwood. Mass cultivation and large plantation of Aquilaria trees using these conventional methods have greatly resolved the shortage of agarwood supply in the global market.

1.4.3. Non-conventional methods

Artificial induction of agarwood formation is the use of chemical, insect and pathogen-inducing techniques is increasingly common in agarwood induction [18]. Chemical inducers normally comprise of phytohormones, salts, minerals and biological-derived substances [2,18,19]. Various chemical induction approaches are developed, including cultivated agarwood kit (CA-kit), the whole-tree agarwood inducing technique (Agar-Wit) and biologically agarwood-inducing technique (Agar-bit). CA-kit is a combined method based on physical wounding and chemical induction, where the inducing agent is applied into the *Aquilaria* tree via an aeration device inserted into the wound [2]. Agar-Wit is a transpiration-assisted chemical treatment to form an overall wound in the tree, where the preloaded inducer in a transfusion set is distributed via plant transpiration [18]. Similarly, Agar-bit method adopts the idea of distributing the inducing reagent

by plant transpiration, except that the reagents are injected directly into the stems of the tree [20]. Chemical inducers are suitable for mass production of agarwood with easier quality control than biological inoculum. However, in spite of the fast results and high yields, the application of chemical inducers still poses skepticism of toxicity on both human and environment. All of these induction techniques in any case mimic the natural processes of agarwood formation, which have their own strengths and weaknesses. The agarwood induction methods are presented in Figure 1. On the other hand, *in vitro* culture of various parts of *Aquilaria* spp. and *Gyrinops* spp. are studied at various tissue culture laboratories [2]. The tissue culture techniques identified the key regulator genes of *Aquilaria* spp. and *Gyrinops* spp. involved in the agarwood production [2].

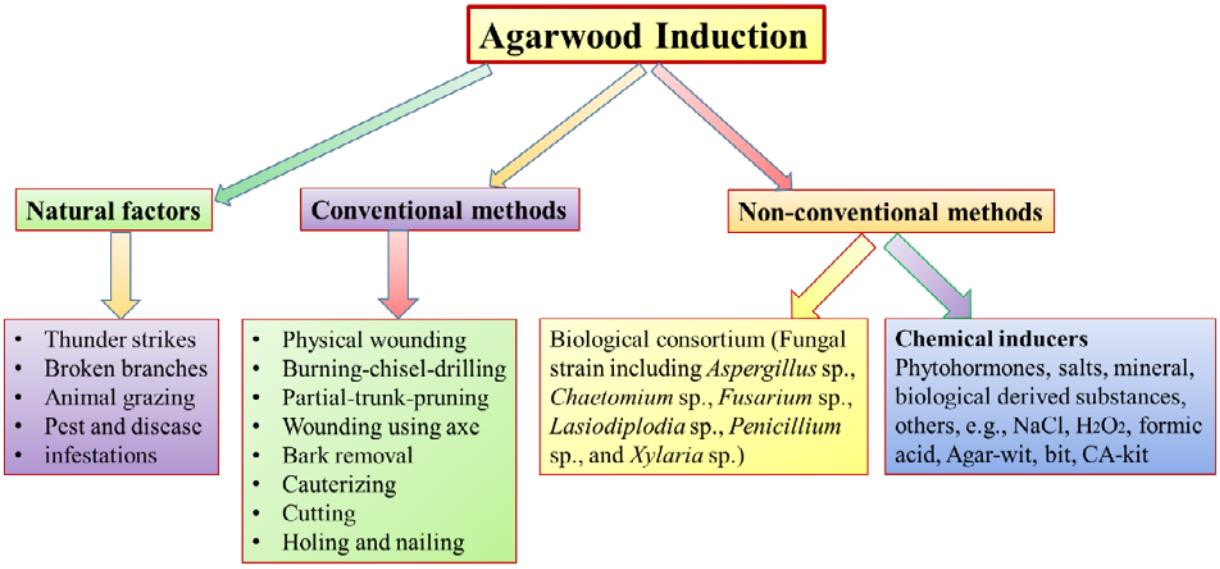

Figure 1: Schematic presentation of Agarwood induction techniques.

2. PHYTOCHEMICAL CONSTITUENTS OF AGARWOOD

The chemical constituents of healthy *Aquilaria* trees without resin-formation differ from the resin-impregnated portions of the plants [6,12]. The phytochemical analysis of agarwood resin has been the subject of many studies [1,6,12]. The types and derivatives of chemical constituents in agarwood are extremely wide and diverse, indicating the different types of fragrance properties of agarwood from different species and regional sources [1,6,12]. Agarwood resin constituents were isolated using solvent extraction, with subsequent purification via column chromatography and structural elucidation using spectroscopic techniques, including NMR [1,6,12]. Essential oils are produced by the hydrodistillation of resin followed by GC-MS or the newer technique of supercritical fluid extraction (SFE) [21]. The chemical constituents in agarwood may vary considerably in terms of quality, source plant origin, extraction methods, agarwood induction method, or agarwood-formation process, collection time, analytical approach etc [1,6,12]. The agarwood chemical constituents produced by Aquilaria species including *A. sinensis*, *A. malaccensis* (syn. A. agallocha), *A. crassna*, *A. filaria*, and *Gyrinops salicifolia*, as well as an unidentified *Aquilaria* spp [1,6,12]. Previous chemical investigations of agarwood species resulted in the isolation and structure characterization of several sesquiterpenes, 2-(2-phenylethyl)-4H-chromen-4-one derivatives (PECs), and aromatic compounds are the main characteristic chemical constituents [6,12,22]. The types of agarwood chemical constituents are described below.

2.1. Sesquiterpenoids

Sesquiterpenes are composed of three isoprene units. They are mainly distributed in plants existing mostly in the form of volatile constituents present in essential oils. The constituents of agarwood essential oil is mainly composed of sesquiterpenoids, and low abundant of volatile aromatic metabolites, which gives an unique and fragrant-smelling property of agarwood [1]. The sesquiterpenes isolated from agarwood exhibit various types (Figure 2), including acoranes **(A)**, agarospiranes **(B)**, cadinanes **(C)**, eudesmanes **(D)**, eremophilanes **(E)**, guaianes **(F)**, humulanes **(G)** and prezizaanes **(H)**, zizaanes **(I)**.

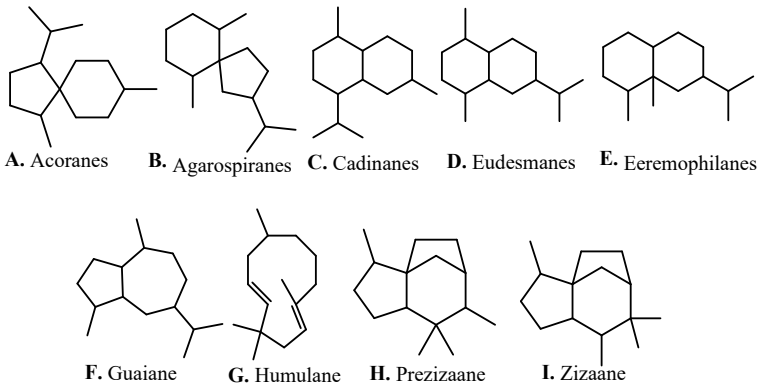

Figure 2: Types of sesquiterpenes from agarwood.

2.1.1. A. Acoranes

The spiro sesquiterpenes, acoranes (**A1-A3**), are reported from the agarwood of *A. sinensis* (Figure 3). The compounds **A2** and **A3** are a pair of stereoisomers.

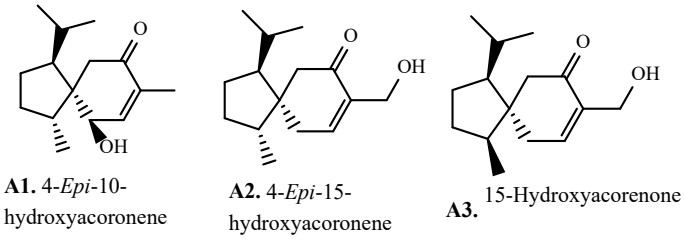

Figure 3: Chemical structures of acorane-type sesquiterpenes from agarwood.

2.1.2. B. Agarospiranes (vetispiranes)

The spirocyclic sesquiterpenes, agarospiranes are reported in agarwood from *A. sinensis*, *A. malaccensis* and *A. agallocha* (Figure 4, and Table 4). The first agarospirane sesquiterpene discovered in agarwood is agarospirol (**B1**) from the agarwood of *A. agallocha* [23]. The allyl ether 2,14-epoxy-vetispir-6-ene (B10) and enol ether 2,14-epoxy-vetispira-6(14),7-diene (B11) are reported from the essential oil of *A. agallocha* [24]. Vetispira-2(11),6(14)-dien-7-ol (**B8**) and vetispira-2(11),6-dien-14-al (**B9**) might be artefacts [25]. The sesquiterpenes, agarospiranes have limited distribution and are mainly found in the agarwood species of *A. agallocha*, *A. malaccensis*, and *A. sinensis* (Figure 4, Table 4). Phytochemical examination of 95% ethanol extract of *A. agallocha* agarwood, resulted in the isolation of agarospirane-type sesquiterpenes (agarospiranic aldehyde A, and B, **B13**, **B14**) [26].

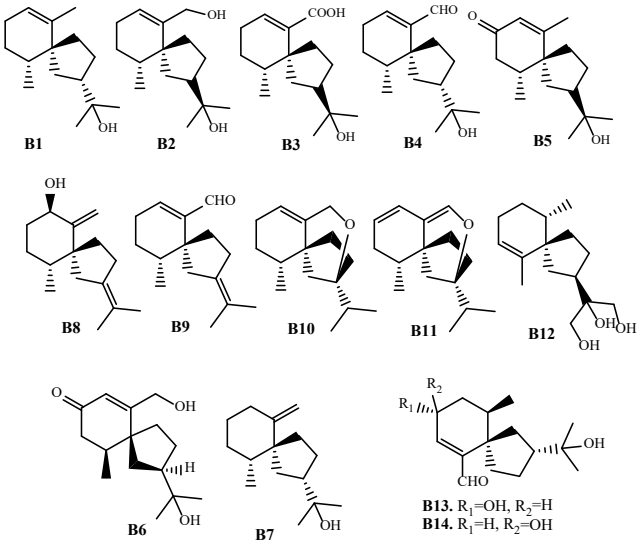

Figure 4: Chemical structures of agarospirane-type sesquiterpenes from agarwood.

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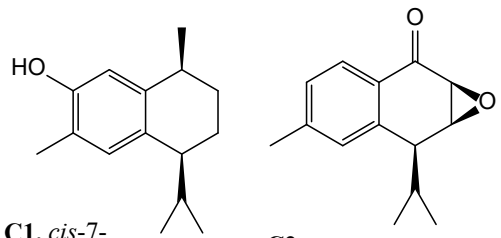
No.	Name	Source	Ref.
B1	Agarospirol	*A. agallocha* *A. malaccensis* *A. sinensis*	27,23 28 29
B2	Baimuxinol	*A. sinensis*	30
B3	Baimuxinic acid	*A. sinensis*	30
B4	Baimuxinal [Oxoagarospirol]	*A. sinensis* *A. malaccensis* *A. agallocha*	29, 31,32 33,34, 35
B5	(4*R*,5*R*,7*R*)-1(10)-spirovetiven-11-ol-2-one	*Kyara-Vietnam*	36
B6	2-Oxo-12-hydroxy-hinesol	*A. sinensis*	37
B7	Isoagarospirol		25
B8	Vetispira-2(11),6(14)-dien-7-ol	*A. agallocha*	24
B9	Vetispira-2(11),6-dien-14-al	*A. agallocha*	24
B10	2,14-Epoxy-vetispir-6-ene	*A. agallocha*	24
B11	2,14-Epoxy-vetispira-6(14),7-diene	*A. agallocha*	24
B12	*rel*-(2*R*,5*R*,10*S*)-6(7)-Spirovetiven-11,12,13-triol	*Aquilaria spp.*	38

Table 4: Agarospirane-type sesquiterpenes from agarwood.

2.1.3. C. Cadinanes

Two (**C1** and **C2**), decalin skeleton containing cadinane-type bicyclic sesquiterpenes are reported from agarwood of *A. sinensis* (**C1**) [39], and *A. crassna* (**C2**) [40], respectively. These two sesquiterpenes differ from eudesmane-type sesquiterpenes by the position of the isopropyl substituents and two methyl groups (Figure 5).



C1. *cis*-7-Hydroxycalamenen

C2. 8,9-epoxycalamenen-10-one

Figure 5: Chemical structures of cadinane-type sesquiterpenes from agarwood.

2.1.4. D. Eudesmanes (selinanes)

The main types of sesquiterpene found in agarwood are eudesmane-type sesquiterpenes, which are a class of bicyclic sesquiterpenes with a decalin skeleton. These compounds are widely distributed in the agarwood species of *A. agallocha, A. crassna, A. malaccensis*, and *A. sinensis*, as well as in *G. salicifolia* [12,25,416]. The eudesmane-type sesquiterpenes of agarwood are presented as Figure 6, and Table 5. Most of agarwood eudesmanes (**D1–D36**) contains an isopropenyl group or 2-hydroxyisopropyl group at the C-7 position, while the methyl groups at C-4 or C-11 are often oxidized to form CHO, COOH, or CH_2OH groups. The eudesmanes (**D3, D6, D7, D11, E19, E20** and **E27**) possessing an oxidation at C-9 or C-15, and an isopropenyl group at the C-7 position are reported from the acetone extract of the Vietnamese agarwood called kanankoh (A. agallocha) [35,42]. The sesquiterpenes, agarofurans, valencanes and agarospiranes (vetispiranes) biosynthetic precursor (–)-10-epi-γ-eudesmol (**D21**) is isolated from *A. malaccensis* [33]. The nor-eudesmane derivatives **D37–D40** are reported from the commercial agarwood oil (*A. agallocha*) [43]. The agarofuran sesquiterpenes **D41–D55** has a *trans*-decalin structure, and a *β*-oriented isopropoxy bridge [12,44]. The compounds **D44, D48, D49, D51, D53** and **D54** are isolated from the agarwood of *A. agallocha* [45,46]. The sesquiterpenes **D41, D43, D45**, and **D46** are obtained from the volatile oil of *A. sinensis* [47–49]. The nor-agarofuran derivatives (**D52, D54** and **D55**, which lack the methyl group at C-4 are only reported from agarwood of *A. agallocha* [43,46]. A recent study reported that the phytochemical examination of 95% ethanol extract of *A. agallocha* agarwood, resulted in the isolation of eudesmane-type sesquiterpenes (agalleudesmanol A-I, **D56–D64**) [26]. Chemical examination of the ethyl ether extract of *Aquilaria* spp. collected in Thailand, resulted in the isolation and structure determination of eudesmane sesquiterpenes, **D65**, **D66**, and **D67** [50].

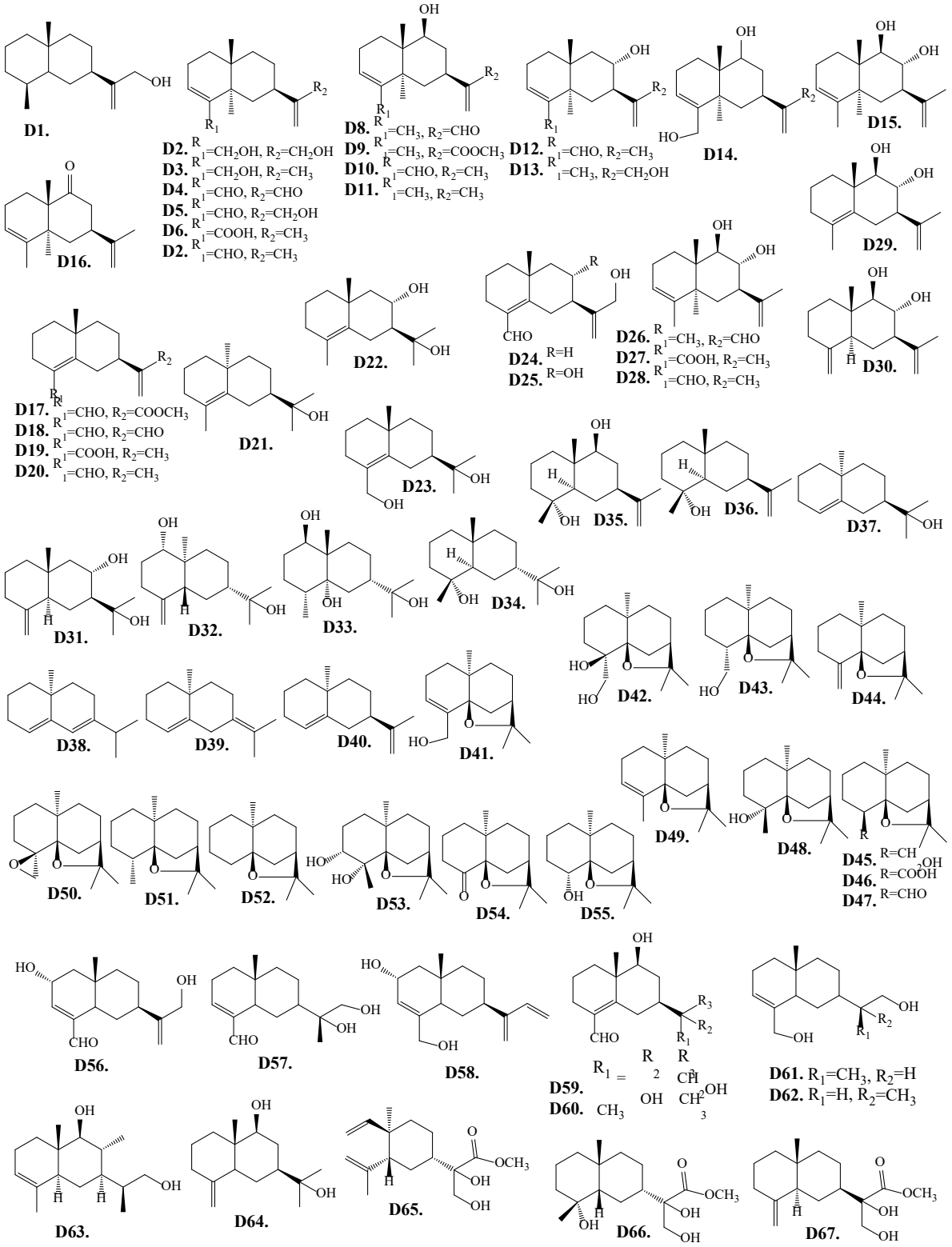


Figure 6: Chemical structures of eudesmane-type sesquiterpenes from agarwood.

No.	Name	Source	Ref.
D1.	Agarol- [11(13)-Eudesmen-12-ol]	*A. agallocha*	51
D2.	15-Hydroxyl-12-oxo-α-selinen	*A. sinensis*	52
D3.	Selina-3,11-dien-14-ol	*A. agallocha*	23
D4	12,15-Dioxo-α-selinen	*A. sinensis*	32,52,53
	[Selina-3,11-diene-12,15-dial]	*G. salicifolia*	54
D5	(4aβ,7β,8aβ)-3,4,4a,5,6,7,8,8a-Octahydro-7-[1-(hydroxymethyl) ethenyl]-4a-methylnaphthalene-1-carboxaldehyde	*A. malaccensis*	55
		A. sinensis	30,31,52
D6	Selina-3,11-dien-14-oic acid	*A. agallocha*	42
D7	(−)--Selina-3,11-dien-14-al	*A. agallocha*	42
D8	(5S,7S,9S,10S)-(+)-9-hydroxy-selina-3,11-dien-12-al	*A. sinensis*	31,52
D9	(5S,7S,9S,10S)-(+)-9-hydroxy-eudesma-3,11(13)-dien-12-methyl ester	*A. sinensis*	31,52
D10	(5S,7S,9S,10S)-(−)-9-hydroxy-selina-3,11-dien-14-al	*A. sinensis*	52
D11	(5S,7S,9S,10S)-(+)-selina-3,11-dien-9-ol	*A. agallocha*	35
D12	Petafolia A	*A. sinensis*	30
D13	(+)-8α-Hydroxyeudesma-3,11(13)-dien-14-al	*A. sinensis*	31
D14	Selina-3,11-dien-9,15-diol	*A. sinensis*	31
D15	(+)-Eudesma-3,11(13)-dien-8α,9β-diol	*A. sinensis*	56
D16	(5S,7S,10S)-(−)-Selina-3,11-dien-9-one	*A. agallocha*	35
D17	Methyl-15-oxo-eudesmane-4,11(13)-dien-12-oate	*A. crassna*	57
D18	12,15-Dioxo-selina-4,11-dine- [Selina-4,11-diene-12,15-dial]	*A. malaccensis*	55
		A. sinensis	31,32
D19	Selina-4,11-dien-14-oic acid	*A. agallocha*	42
D20	Selina-4,11-dien-14-al	*A. agallocha*	42
D21	(−)-10-epi-γ-eudesmol	*A. malaccensis*	33
D22	Eudesma-4-en-8,11-diol	*A. crassna*	57
		A. malaccensis	55
D23	Eudesma-4-en-11,15-diol	*A. sinensis*	31
		A. crassna	57
D24	12-hydroxy-4(5),11(13)-eudesmadien-15-al	*A. sinensis*	31, 30
D25	(7S,8R,10S)-(+)-8,12-dihydroxy-selina-4,11-dien-14-al	*A. sinensis*	52
D26	(+)-9β-hydroxyeudesma-4,11(13)-dien-12-al	*A. sinensis*	31
D27	9-hydroxy-selina-4,11-dien-14-oic acid	*A. agallocha*	42
D28	(7S,9S,10S)-(+)-9-hydroxy-selina-4,11-dien-14-al	*A. sinensis*	31,52,30
D29	(+)-eudesma-4,11(13)-dien-8α,9β-diol	*A. sinensis*	31
D30	(+)-eudesma-4(14),11(13)-dien-8α,9β-diol	*A. sinensis*	31
D31	5-desoxylongilobol	*A. sinensis*	31
		A.crassna	40
D32	Ent-4(15)-eudesmen-1α,11-diol	*A. sinensis*	52
D33	Eudesmane-1β,5α,11-triol	*A. sinensis*	52
D34	(−)-7β-H-eudesmane-4α,11-diol	*A. sinensis*	52

D35	(4R,5R,7S,9S,10S)-(–)-eudesma-11(13)-en-4,9-diol	*A. sinensis*	52
D36	Selin-11-en-4α-ol	*A. sinensis*	31,30
D37	(2R,4aS)-2-(4a-methyl-l,2,3,4,4a,5,6,7-octahydro-2-naphthyl)-propan-2-ol	*A. agallocha*	43
D38	(S)-4a-methyl-2-(1-methylethy1)-3,4,4a,5,6,7-hexahydronaphthalene	*A. agallocha*	43
D39	(S)-4a-methyl-2-(1-methylethylidene)-1,2,3,4,4a,5,6,7-octahydronaphthalene	*A. agallocha*	43
D40	(2R,4aS)-4a-methyl-2-(1-methylethenyl)-l,2,3,4,4a,5,6,7-octahydronaphthalene	*A. agallocha*	43
D41	Dehydrobaimuxinol	*A. sinensis*	29,47
D42	4-Hydroxyl-baimuxinol	*A. sinensis*	58
D43	Baimuxinol	*A. sinensis*	29,47
D44	β-Agarofuran	*A. agallocha*	35,45
		A. sinensis	29,48,59
D45	Isobaimuxinol	*A. sinensis*	48
D46	Baimuxifuranic acid	*A. sinensis*	31,49
D47	(1S,2R,6S,9R)-6,10,10-trimethyl-ll-oxatricyclo[7.2.1.01,6]dodecane-2-carbaldehyde	*A. agallocha*	27
D48	4-hydroxy-dihydro-agarofuran	*A. agallocha*	46
D49	α-Agarofuran	*A. agallocha*	45
		A. malaccensis	33
D50	Epoxy-β-agarofuran	*A. agallocha*	27
D51	Dihydro-β-agarofuran	*A. agallocha*	45
D52	(1R,6S,9R)-6,10,10-trimethyl-11-oxatricyclo[7.2.1.0]dodecane	*A. agallocha*	43
D53	3,4-dihydroxy-dihydro-agarofuran	*A. agallocha*	46
D54	Nor-ketoagarofuran	*A. agallocha*	46
D55	(1R,2R,6S,9R)-6,10,10-trimethyl-11-oxatricyclo[7.2.1.0]dodecan-2-ol	*A. agallocha*	43
D56	Agalleudesmanol A	*A. agallocha*	26
D57	Agalleudesmanol B	*A. agallocha*	26
D58	Agalleudesmanol C	*A. agallocha*	26
D59	Agalleudesmanol D	*A. agallocha*	26
D60	Agalleudesmanol E	*A. agallocha*	26
D61	Agalleudesmanol F	*A. agallocha*	26
D62	Agalleudesmanol G	*A. agallocha*	26
D63	Agalleudesmanol H	*A. agallocha*	26
D64	Agalleudesmanol I	*A. agallocha*	26
D65	5β,7β-H-elema-1,3-dien-11,13-dihydroxy-11-methyl ester	*Aquilaria sp.*	50
D66	5β,7β-H-4α-hydroxy-eudesma-11,13-dihydroxy-11-methyl ester	*Aquilaria sp.*	50
D67	5α,7α-H-4(14)-ene-eudesma-11,13- dihydroxy-11-methyl ester	*Aquilaria sp.*	50

Table 5: Eudesmane-type sesquiterpenes from agarwood

2.1.5. E. Eremophilanes (valencanes)

The chemical structures of eremophilane-type sesquiterpenes from agarwood consist two six-membered rings (**E1** to **E38**) are presented in Figure 7, and Table 6. The reported eremophilanes contain a tri-oxygenated isopropyl group (**E6, E14, E23, E24, E29, E33**, and **E34**), and an 11-methyl ester functionality (**E24, E29**, and **E34**). The *G. salicifolia* compound, *rel*-4b,5b,7b-eremophil-9-en-12,8a-olide (**E11**) is the only one of an eremophilane containing an 8,12-lactone ring [60]. The *A. agallocha* essential oils compound **E36** exhibits a nor-skeleton of eremophilane [27], which might be a degradation product of major agarwood compound, dihydrokaranone (**E25**). The eremophilanes, (+)-(4*S*,5*R*)-karanone (**E22**) and (+)-(4*S*,5*R*)-dihydrokaranone (**E25**) are unsaturated and conjugated ketones. These two compounds present in most of the essentials and extracts of *Aquilaria* species, except for *A. malaccensis* from Indonesia, and are characteristic constituents of agarwood [25]. The compounds **E16** and **E26** are a pair of epimers at C-7, and have strong long-lasting pennyroyal-like minty smell [58]. Chemical examination of the ethyl ether extract of *Aquilaria* sp. collected in Thailand, resulted in the isolation and structure determination of eremophilane sesquiterpenes, **E40**, and **E41** [50].

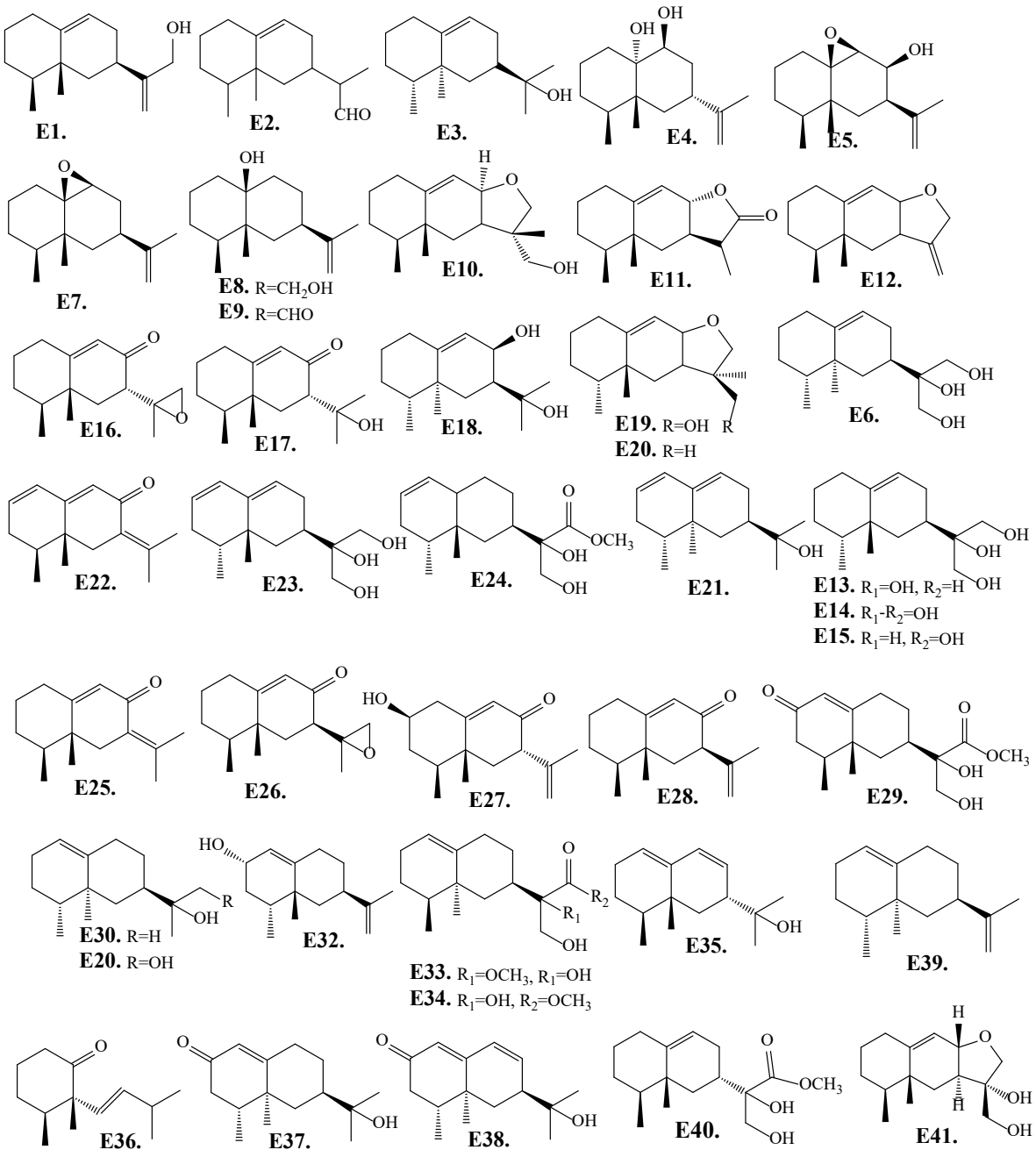


Figure 7: Chemical structures of eremophilane-type sesquiterpenes from agarwood.

No.	Name	Source	Ref.
E1.	Eremophila-9,11(13)-dien-12-ol	*A. agallocha*	24
E2.	Valenc- or eremophil-9-en-12-al (tentative)	*A. agallocha*	24
E3.	Jinkoh-eremol	*A. malaccensis*	28
E4	(1β,3α,4aβ,5β,8aα)-4,4a-dimethyl-6(prop-l-en-2-yl) octahydronaphtha-lene-1,8a(1H)-diol	*A. crassna*	57
E5	(1aβ,2β,3β,4aβ,5β,8aβ)-octahydro-4a,5-dimeth-yl-3-(1-methylethenyl)-3H-naphth[1,8a-b]oxiren-2-ol	*A. malaccensis*	55
E6	Eremophil-9-ene-11,12,13-triol	*Aquilaria spp.*	38
E7	(+)-9β,10β-epoxyeremophila-11(13)-en	*A. sinensis*	31
E8	(1β,4aβ,7β,8aβ)-octahydro-7-[1-(hydroxymethyl) ethenyl]-1,8a-dimethylnaphthalen-4a(2H)-ol	*A. malaccensis* *A. sinensis*	55 31,61
E9	2-[(2β,4aβ,8β,8aβ)-decahydro-4α-hydroxy-8,8a-di-methylnaphthalen-2-yl]prop-2-enal	*A. malaccensis* *A. sinensis*	55 31
E10	11,13-dihydroxy-9(10)-ene-8β,12-epoxyemophilane	*A. crassna* *Aquilaria spp.*	40 38
E11	rel-4β,5β,7β-eremophil-9-en-12,8α-olide	*G. salicifolia*	60
E12	8,12-epoxy-eremophila-9,11(13)-diene	*A. agallocha*	24
E13	Eremophil-9(10)-ene-11,12-diol	*G. salicifolia*	41
E14	4β,7α-H-eremophil-9(10)-ene-11,12,13-triol	*G. salicifolia*	41
E15	4β,7α-H-eremophil-9(10)-ene-12,13-diol	*G. salicifolia*	41
E16	7β-H-9(10)-ene-11,12-epoxy-8-oxoeremophilane	*A. sinensis*	58
E17	Ligudicin C	*A. sinensis*	53, 62
E18	(–)-Eremophila-9-en-8β,11-diol	*A. sinensis* *A. crassna*	31 57
E19	4β,7α,8α-H-eremophil-9(10)-ene-8,12-epoxy-11α,13-diol	*G. salicifolia*	41
E20	Cyclodebneyol	*A. sinensis*	37
E21	Dehydro-jinkoh-eremol	*A. agallocha*	42
E22	(+)-(4S,5R)-Karanone	*A. agallocha*	35
E23	4β,7α-H-eremophil-1(2),9(10)-dien-11,12,13-triol	*G. salicifolia*	41
E24	4β,7α-H-11,13-dihydroxy-eremophil-1(10)-ene-11-methyl ester	*G. salicifolia*	41

E25	(+)-(4S,5R)-dihydrokaranone- [7(11)-eremophilen-8-one]	*A. sinensis*	30,53,59,29,62
		A. agallocha	35,53
E26	7α-H-9(10)-ene-11,12-epoxy-8-oxoeremophilane	*A. sinensis*	58,61,62
		A. crassna	40
E27	Petafolia B	*A. sinensis*	30
		A. agallocha	42
E28	Neopetasane- [Eremophila-9,11-dien-8-one]	*A. malaccensis*	34
		A. sinensis	30,53,58,61,62
E29	(4S,5R,7R)-11,12-dihydroxy-eremophila-1(10)-ene-2-oxo-11-methylester	*A. crassna*	62
		A. malaccensis	24
E30	Kusunol- [Valerianol]	*A. agallocha*	25
		A. sinensis	29,61
E31	2-[(2β,8α,8aα)-8,8a-dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl]propane-1,2-diol	*A. crassna*	57
E32	(+)-trans-Nootkatol	*G. salicifolia*	41
E33	2-[(2β,8β,8aα)-8,8a-dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-yl]-3-hydroxy-2-methoxypropanoic acid	*A. crassna*	57
E34	Methyl crassicid	*A. crassna*	63
E35	Valenca-1(10),8-dien-11-ol	*A. agallocha*	24
E36	2,3-dimethyl-r-2-(3-methyl-2-butenyl)-1-cyclohexanone	*A. agallocha*	27
E37	11-hydroxy-valenc-1(l0)-en-2-one	*A. sinensis*	30,31,61
E38	(+)-11-hydroxyvalenc-1(10),8-dien-2-one	*A. sinensis*	31
E39	Valencene	*A. malaccensis*	64
E40	7β-H-9(10)-ene-emophane-11,13-dihydroxy-11-methyl ester	*Aquilaria sp.*	50
E41	7α-H-11α,13-dihydroxy-9(10)-ene-8α,12-epoxyemophane	*Aquilaria sp.*	50

Table 6: Eremophilane-type sesquiterpenes of agarwood.

2.1.6. F. Guaianes

The sesquiterpene guaianes are structurally coupled with a five- and seven-membered ring structures, and are consisting of a 4,10-dimethyl-7-isopropenyl moiety. The isolated and structure identified guaianes (**F1–F47**) from the species of *Aquilaria* and *Gyrinops* are presented as in Figure 8, and Table 7. The guaianes **F2–F11**, and **F13** bearing a 7-isopropenyl moiety are considered as the characteristic components from the agarwood of *A. agallocha*, namely kanankoh. The characteristic compound of kanankoh, (–)-guaia-1(10),11-dien-15-al (**F7**) has a pleasant *β*-damascenone-like woody and floral note with a slight cooling side note [35,36]. Among the kanankoh compounds, the isolates **F3, F4, F6, F7, F10** and **F11** are functionalized at **C-14**, which is rarely encountered in nature. The compound, (+)-1,5-epoxy-nor-ketoguaiene (**F13**) is a nor-guaiane with 14 carbons lacking the methyl group at C10. On the other hand, the tricyclic scaffold patchoulenetype compounds F14–F16 are isolated from the agarwood of *A. malaccensis* [66]. The *A. sinensis* agarwood compound F19 possesses a 5/6/7 ring system of guaiane skeleton through C1–C11 linkage. It is interesting to note that the agarwood species A. sinensis is a rich source for various interesting chemical structures. The compounds **F17–F31** and **F33** are reported from the agarwood of *A. sinensis* [59]. The guaiane-furans (**F20–F25**) are reported from a agarwood variety of *A. sinensis*, namely "Lv Qi-Nan" in Chinese [67]. These compounds possess a 5,11-epoxy ring with stereoisomers, and are functionalized at C15 (Figure 8, Table 7). Furthermore, the guaianes **F33** and **F34**, with cleavage of the seven-membered core ring also obtained from the agarwood of *A. sinensis* [32]. Additionally, the guaianes, **F28, F32** and **F38**, which are possessing a bridge in the seven-membered ring structure are also reported from the agarwood of *A. sinensis*[61,68]. Among the guaiane sesquiterpenes bearing five-membered lactone, the compounds **F35–F37** and **F41** are reported from the agarwood of *A. filaria* and *G. salicifolia*. These compounds have typical conjugated double bonds within the seven-membered ring, as well as a five-membered *α,β*-unsaturated lactone [41,68]. Phytochemical examination of *A. malaccensis* resulted in the isolation of guaiane-type sesquiterpenes **F43–F47** [69].

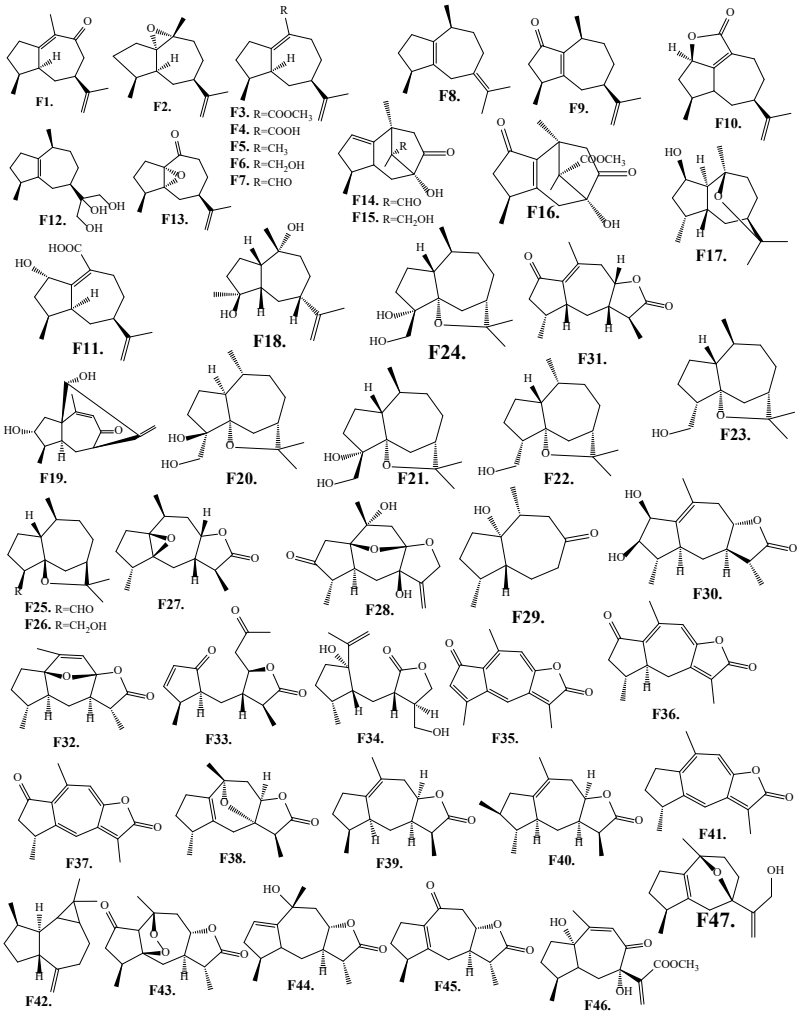


Figure 8: Chemical structures of guaiane-type sesquiterpenes from agarwood.

No.	Name	Source	Ref.
F1.	(+)-Guaia-1(10),11-dien-9-one	*A. agallocha*	55
F2.	(-)-1,10-epoxyguai-11-ene	*A. agallocha*	55
F3.	Methyl guaia-1(10),11-diene-15-carboxylate	*A. agallocha*	35, 55
F4	(-)-Guaia-1(10),11-diene-15-carboxylic acid	*A. agallocha*	55
F5	α-Bulnesene	*A. agallocha*	35
F6	(-)-Guaia-1(10),11-dien-15-ol	*A. agallocha*	55
F7	(-)-Guaia-1(10),11-dien-15-al	*A. agallocha*	35, 55
F8	α-Guaiene	*A. agallocha*	35
F9	(-)-Rotundone	*A. agallocha*	55
F10	(-)-Guaia-1(10),11-dien-15,2-olide	*A. agallocha*	55
F11	(-)-2α-hydroxyguaia-1(10),11-dien-15-oic acid	*A. agallocha*	70
F12	(+)-12,13-dihydroxyguaiol	*Aquilaria spp.*	38
F13	(+)-1,5-epoxy-nor-ketoguaiene	*A. agallocha*	42
F14	Auranticanol A	*A. malaccensis*	66
F15	Chamaejasmone D	*A. malaccensis*	66
F16	Chamaejasmone E	*A. malaccensis*	66
F17	α-Kessyl alcohol	*A. sinensis*	71
F18	*Epi*-guaidiol A	*A. sinensis*	37
F19	Qinan-guaiane-one	*A. sinensis*	71
F20	Qinanol E	*A. sinensis*	67
F21	Qinanol C	*A. sinensis*	67
F22	Qinanol A	*A. sinensis*	67
F23	Qinanol B	*A. sinensis*	67
F24	Qinanol D	*A. sinensis*	67
F25	Sinenofuranal	*A. sinensis*	59
F26	Sinenofuranol	*A. sinensis*	59, 67
F27	1,5;8,12-diepoxyguaia-12-one	*A. sinensis*	61
F28	3-Oxo-7-hydroxylholosericin A	*A. sinensis*	61
F29	1α-hydroxy-4α,10α-dimethyl-5βH-octahydro-azulen-8-one	*A. sinensis*	32
F30	Qinanlactone	*A. sinensis*	71
F31	7βH-Guaia-1(10)-en-12,8β-olide	*A. sinensis*	32
F32	1,8-Epoxy-5H-guaia-9-en-12,8-olide	*A. filaria*	68
F33	1,10-dioxo-4αH-5αH-7βH-11αH-1,10-secoguaia-2(3)-en-12,8β-olide	*A. sinensis*	32

F34	1α-hydroxy-4βH-5βH-7βH-11αH-8,9-secoguaia-9(10)-en-8,12-olide	*A. sinensis*	32
F35	2-Oxoguaia-1(10),3,5,7(11),8-pentaen-12,8-olide	*G. salicifolia*	41
		A. filaria	68
F36	(4R,5S)-3-Oxo-5,6-dihydro-gweicurculactone	*A. filaria*	68
F37	(4R)-3-Oxo-gweicurculactone	*A. filaria*	68
F38	1(5)-Ene-7,10-epoxy-guaia-12-one	*A. filaria*	68
F39	Guaianolide	*G. salicifolia*	41
		A. filaria	68
F40	4β,5α,7α,8α-H-3β-hydroxy-1(10)-ene-8,12-epoxy-guaia-12-one	*G. salicifolia*	41
F41	(–)-Gweicurculactone	*G. salicifolia*	41
F42	Aromadendrene	*A. malaccensis*	72
F43	2-Oxo-5β,10β-peroxyl-1αH,4αH,7αH,8βH-guaian-8α,12-olide	*A. malaccensis*	69
F44	10α-hydroxy-4αH,5αH,7αH,8βH-guaia-1(2)-en-8α,12-olide	*A. malaccensis*	69
F45	4αH,7αH-14-nor-guaia-1(5)-en-8α,12-olide	*A. malaccensis*	69
F46	1α,7α-dihydroxy-8oxo-4αH,5αH-guaia-9(10),11(13)-dien-12-oate	*A. malaccensis*	69
F47	7β,10β-epoxy-4αH-guaia-1(5),11(13)-dien-12-ol	*A. malaccensis*	69

Table 7: Guaiane-type sesquiterpenes isolated from agarwood species.

2.1.7. G. Humulanes

Four humulane-type sesquiterpenes (**G1–G4**) are reported from the agarwood of *A. sinensis* and *A. malaccensis* (Figure 9) [31,66]. The compounds, quilanols A and B (**G1** and **G2**) possess an unprecedented macrocyclic humulene structure with a bicyclic 7/10 ring system [66]. The sesquiterpene *β*-caryophyllene (**G5**) is reported from from the essential oil of *A. crassna* [73]. Phytochemical examination of *A. malaccensis* resulted in the isolation of humulene-type sesquiterpenes **G6–G9** [69].

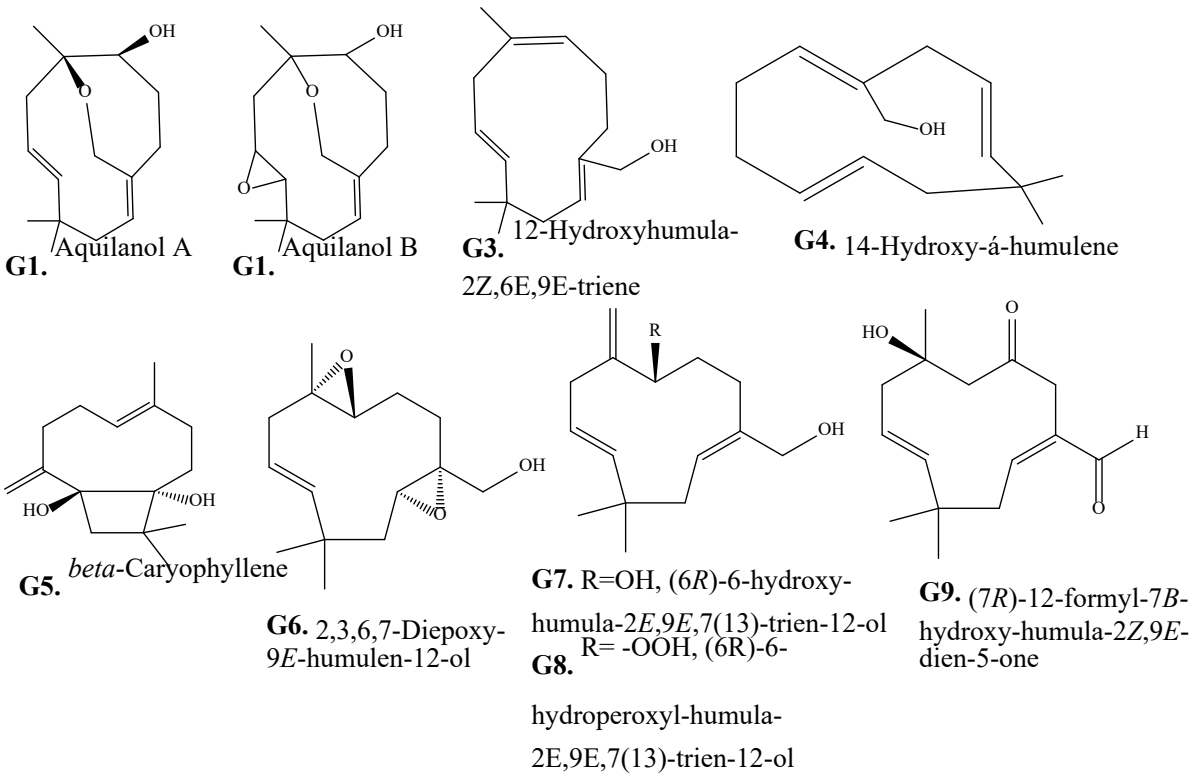


Figure 9: Chemical structures of humulane-type sesquiterpenes from agarwood.

2.1.9. H. Prezizaanes

The tricyclic prezizaanetype sesquiterpenes jinkohol II (**H1**) and jinkohol (**H11**) are reported from the agarwood of *A. malaccensis* [25,28,74]. Then the prezizaane-type sesquiterpenes (**H1–H17**), are reported from the agarwood of *Aquilaria* spp. collected in Thailand (Figure 10 and Table 8).

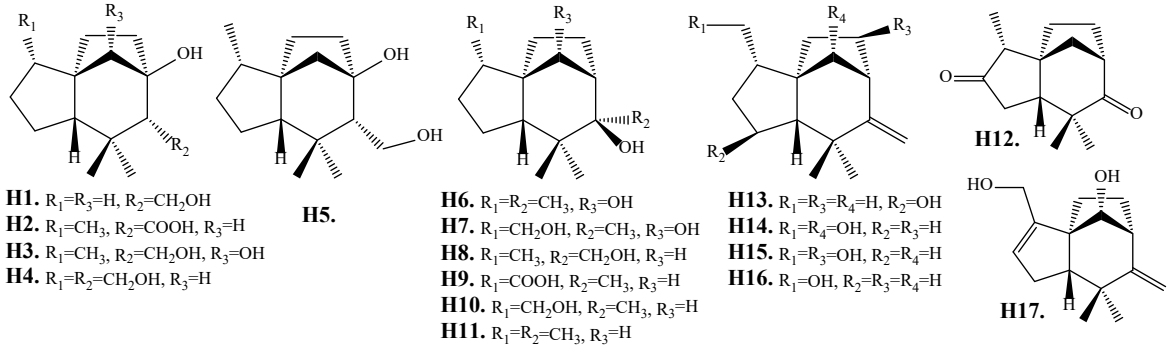


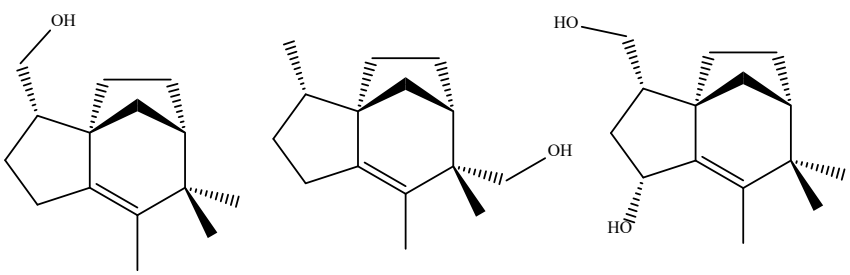
Figure 10: Chemical structures of prezizaane-type sesquiterpenes from agarwood.

No.	Name	Source	Ref.
H1.	Jinkohol II	*A. malaccensis*	28
		Aquilaria spp.	75
H2.	Jinkoholic acid	*Aquilaria spp.*	75
H3.	Aquilarene E	*Aquilaria spp.*	76
H4	Aquilarene D	*Aquilaria spp.*	76
H5	Agarozizanol B	*Aquilaria spp.*	75
H6	Agarozizanol C	*Aquilaria spp.*	75
H7	Aquilarene C	*Aquilaria spp.*	76
H8	Agarozizanol D	*Aquilaria spp.*	75
H9	Aquilarene B	*Aquilaria spp.*	76
H10	Aquilarene A	*Aquilaria spp.*	76
H11	Jinkohol	*A. malaccensis*	74
		Aquilaria spp.	75
H12	Aquilarene F	*Aquilaria spp.*	76
H13	Aquilarene G	*Aquilaria spp.*	76
H14	Agarozizanol A	*Aquilaria spp.*	75
H15	Aquilarene I	*Aquilaria spp.*	76
H16	Aquilarene H	*Aquilaria spp.*	76
H17	Aquilarene J	*Aquilaria spp.*	76

Table 8: Prezizaane-type sesquiterpenes from agarwood.

2.1.10. I. Zizaanes

Three tricyclic sesquiterpenes of the zizaane skeleton (**I1–I3**) are reported from agarwood of *Aquilaria* spp., collected from Thailand (Figure 11) [75].



I1. Isokhusenol **I2.** Agarozizanol E **I3.** Agarozizanol F

Figure 11: Chemical structures of zizaane-type sesquiterpenes from agarwood.

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2.1.11. J. Other sesquiterpenoids

In addition to the aforementioned sesquiterpenoids, the species of the agarwood also resulted in the isolation and structure determination different minor sesquiterpenes (Figure 12, Table 9). For example, the eudesmane skeleton compound, 12-hydroxy-dihydrocyperolone (**J1**) is obtained as a new one from the agarwood of *G. salicifolia* [60]. The daphnauranols B–D (**J2–J4**) exhibiting a rare 5/6/7 ring system were obtained from the agarwood of *A. malaccensis* [66]. Furthermore, the agarwood of *A. malaccensis* also resulted in the isolation and chemical structure identification of tricyclic cadinene-rearranged-sesquiterpenoids with a 6/6/5 ring system, malacinones A and B (**J6** and **J7**) [77]. On the other hand, the compound 1,5,9-trimethyl- 1,5,9-cyclododecatriene (**J5**) is obtained from the from the agarwood of *A. sinensis* [61].

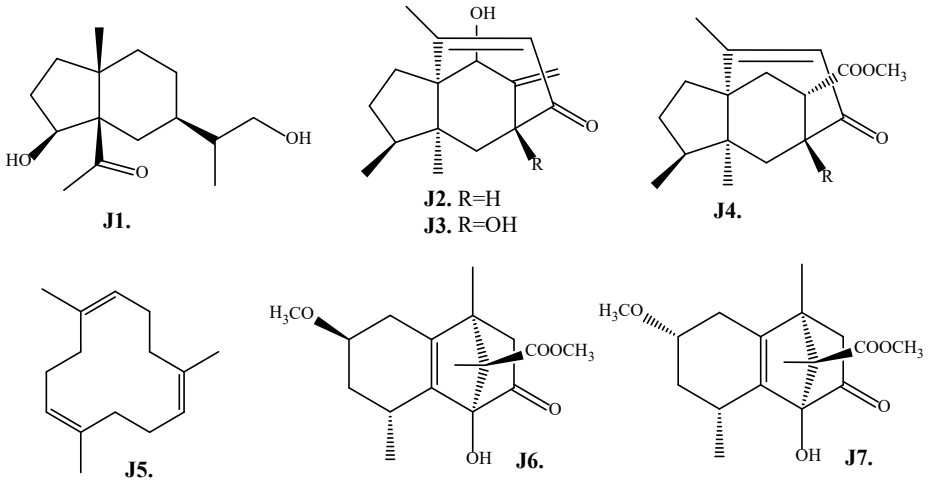

Figure 12: Chemical structures of other sesquiterpenes from agarwood.

No.	Name	Source	Ref.
J1	12-Hydroxy-dihydrocyperolone	*G. salicifolia*	60
J2	Daphnauranol C	*A. malaccensis*	66
J3	Daphnauranol B	*A. malaccensis*	66
J4	Daphnauranol D	*A. malaccensis*	66
J5	1,5,9-Trimethyl-1,5,9-cyclododeca-triene	*A. sinensis*	61
J6	Malacinone B	*A. malaccensis*	77
J7	Malacinone A	*A. malaccensis*	77

Table 9: Other sesquiterpenes from agarwood.

All these isolation and structure identification reports indicating that agarwood is a rich source for various sesquiterpenes including, acorane, agarospirane, cadinane, eudesmane, eremophilane, guaiane, humulane, prezizaane, or zizaane, etc. Among the reported sesquiterpenes of agarwood, eremophilanes, eudesmanes, and guaianes are widely distributed in various agarwood species. Most of these sesquiterpenes are reported from the agarwood species of *A. agallocha, A. crassna, A. malaccensis*, and *A. sinensis*. Additionally, these sesquiterpenes also reported from the other species of agarwood including *A. filaria, G. salicifolia,* and an unidentified *Aquilaria* spp.

2.2. 2-(2-phenylethyl)chromones (PECs)

2-(2-phenylethyl)chromones (PECs) is a member of the class of chromones, which are substituted by a 2-phenylethyl group at C2 position [78]. These compounds has structural resembling with flavonoids, which bears only phenyl group at C-2 position, instead of 2-phenylethyl group present in PECs [78]. PEC derivatives are other major group of constituents in agarwood species [6,12]. The PECs are responsible for the fragrances odor of agarwood burning or heating [12]. The natural PECs are reported from plant species of *Eremophila georgei, Bothriochloa ischaemum* (Gramineae), and agarwood of *Aquilaria* spp [6,12]. Depending on the molecular skeleton, PECs are mainly divided into monomeric 2-(2-phenylethyl)chromone, dimeric 2-(2-phenylethyl)chromones, sesquiterpenoid-4*H*-chromones and benzylacetone-4*H*-chromones, and trimeric chromones as described below.

2.2.1. Monomeric 2-(2-phenylethyl)chromone

Following the characteristic structure of the chromone skeleton, monemeric PECs are subdivided into four groups as *Flindersia* type 2-(2-phenylethyl)chromones (FPECs), 5,6,7,8-tetrahydro-2-(2-phenylethyl) chromones (TPECs), mono-epoxy-5,6,7,8-tetrahydro-2-(2-phenylethyl) chromones (EPECs), and diepoxy-5,6,7,8-tetrahydro-2-(2-phenylethyl) chromones (DPECs) (Figure 13).

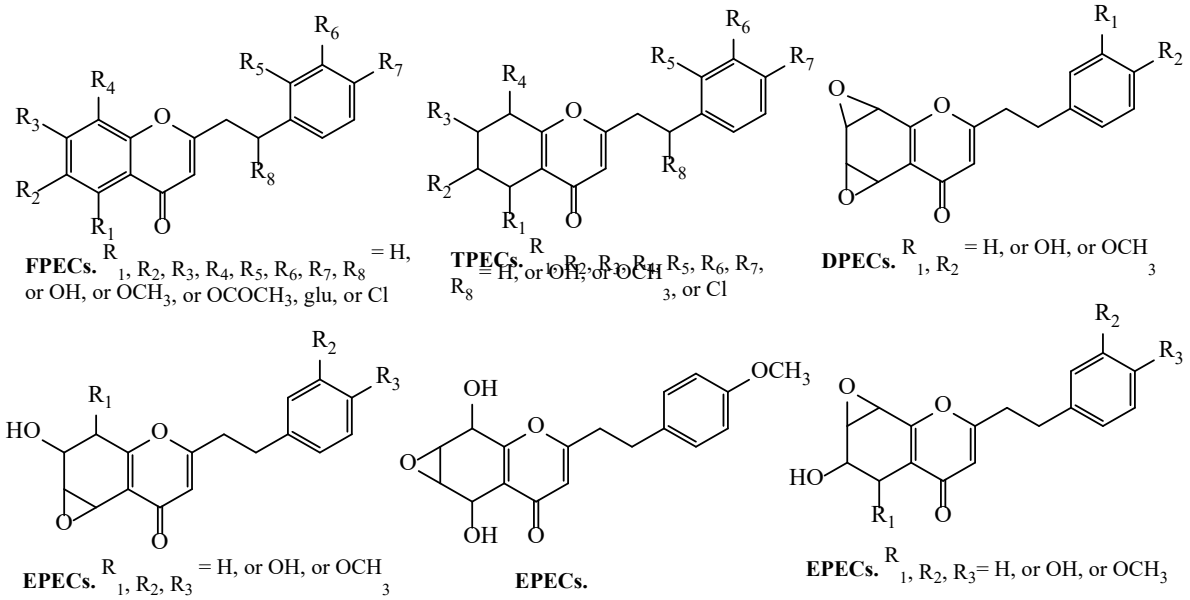

Figure 13: Chemical structures of monomeric 2-(2-phenylethyl)chromones types of agarwood.

2.2.1a. Flindersia type 2-(2-phenylethyl)chromones (FPECs)

The FPECs are the most abundant PECs in agarwood species (**1–86**). Additionally, a new FPEC (**85a**) is reported from the MeOH extract of agarwood *Jink* [79]. The chemical structures of FPECs are presented in Figure 14, and their natural source in Table 10.

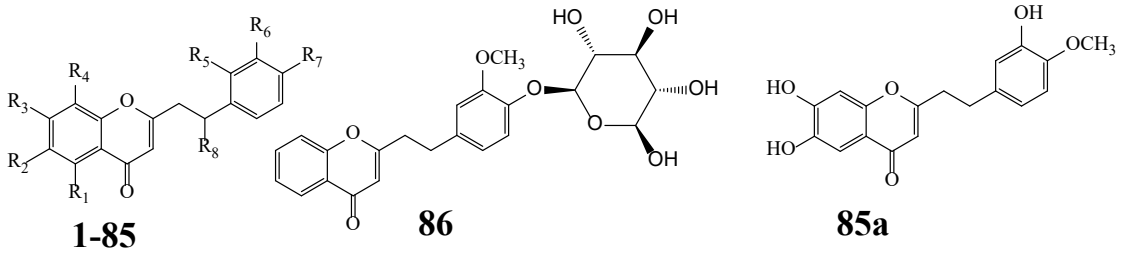

Figure 14: Skeleton of Flindersia type 2-(2-phenylethyl)chromones from agarwood.

No.	Name	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Source	Ref.
1	2-[2-(4-hydroxyphenyl)ethyl]chromone [Qinanone D]	H	H	H	H	H	H	OH	H	*A. sinensis*	80,81
2	2-[2-(3-hydroxyphenyl)ethyl]chromone [Qinanone E]	H	H	H	H	H	OH	H	H	*A. sinensis*	80
3	2-[2-(2-hydroxyphenyl)ethyl]chromone [Qinanone F]	H	H	H	H	OH	H	H	H	*A. sinensis* *A. malaccensis*	80 82
4	8-hydroxy-2-(2-phenylethyl)chromone	H	H	H	OH	H	H	H	H	*A. sinensis* *A. filaria* *A. malaccensis*	83 84 82
5	7-hydroxy-2-(2-phenylethyl)chromone	H	H	OH	H	H	H	H	H	*A. malaccensis*	78
6	6-hydroxy-2-(2-phenylethyl)chromone	H	OH	H	H	H	H	H	H	*Kalimantan* *A. sinensis* *A. malaccensis* *A. filaria* *G. crassna* *Aquilaria spp.*	86 53,80,87,88 34,82 84 89 90
7	5-hydroxy-2-(2-phenylethyl)chromone	OH	H	H	H	H	H	H	H	*A. sinensis* *A. malaccensis*	91 82
8	(S)-2-(2-hydroxy-2-phenylethyl) chromone	H	H	H	H	H	H	H	S-OH	*A. crassna* *A. filaria*	89 84
9	(R)-2-(2-hydroxy-2-phenylethyl) chromone	H	H	H	H	H	H	H	R-OH	*A. crassna* *A. sinensis* *A. filaria*	89 92,93 84
10	2-(2-phenylethyl) chromone [flidersiachromone]	H	H	H	H	H	H	H	H	*Vietnam* *A. agallocha* *A. sinensis* *A. malaccensis* *A. filaria* *Aquilaria spp.*	94 35 37,62,80,91,92,95 34,82,85 68,84 90
11	7-methoxy-2-(2-phenylethyl)-4H-chromen-4-one	H	H	OCH_3	H	H	H	H	H	*A. malaccensis* *A. sinensis*	82,96 53,62,91

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12	6-methoxy-2-(2-phenylethyl)chromone [AH4]	H	OCH_3	H	H	H	H	H	H	*Kalimantan* *A. sinensis* *A. agallocha* *A. malaccensis* *Aquilaria spp.*	86 29,95 97 34,82 90
13	2-[2-(4-methoxyphenyl)ethyl]chromone	H	H	H	H	H	H	OCH_3	H	*Vietnam* *A. agallocha* *A. malaccensis* *A. sinensis*	94 35,98 82,96 80,91,99
14	5,8-dihydroxy-2-(2-phenylethyl)chromone [AH_7]	OH	H	H	OH	H	H	H	H	*Kalinantan* *A. sinensis*	100 91,99,101
15	5-hydroxy-2-[2-(2-hydroxyphenyl)ethyl] chromone	OH	H	H	H	OH	H	H	H	*A. crassna*	102
16	5,6-dihydroxy-2-(2-phenylethyl)chraomone	OH	OH	H	H	H	H	H	H	*A. crassna* *A. malaccensis*	103 82
17	6-hydroxy-2-[2-(4-hydroxyphenyl)ethyl] chromone	H	OH	H	H	H	H	OH	H	*A. malaccensis* *A. sinensis* *A. filaria* *G. salicifolia* *A. crassna*	85 81,87 84 54 102
18	6-hydroxy-2-[2-(2-hydroxyphenyl)ethyl] chromone	H	OH	H	H	OH	H	H	H	*A. malaccensis* *A. sinensis*	85 80,92,87
19	6,7-dihydroxy -2-(2-phenylethyl) chromone	H	OH	OH	H	H	H	H	H	*G. salicifolia* *Aquilaria spp.* *A. sinensis* *Jinko*	54 104 37 79
20	6,8-dihydroxy-2-(2-phenylethyl)chromone	H	OH	H	OH	H	H	H	H	*A. malaccensis* *A. sinensis* *A. filaria* *Aquilaria spp.*	85 88,92,99 84 104
21	2-[2-hydroxy-2-(4-hydroxyphenyl)ethyl] chromone	H	H	H	H	H	H	OH	OH	*A. sinensis*	83
22	6-hydroxy-2-(2-hydroxy-2-phenylethyl) chromone	H	OH	H	H	H	H	H	OH	*A. sinensis*	95, 93
23	6-methoxy-7-hydroxy-2-(2-phenylethyl) chromone	H	OCH_3	OH	H	H	H	H	H	*A. sinensis*	93,105

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24	6-hydroxy-5-methoxy-2-(2-phenylethyl)chromone	OCH_3	OH	H	H	H	H	H	H	*A. sinensis*	62
25	5-hydroxy-6-methoxy-2-(2-phenylethyl)chromone	OH	OCH_3	H	H	H	H	H	H	*A. sinensis* *A. malaccensis*	95 82,96
26	6-hydroxy-7-methoxy-2-(2-phenylethyl)chromone	H	OH	OCH_3	H	H	H	H	H	*A. malaccensis* *A. sinensis* *A. filaria*	85 53,62 84
27	6-hydroxy-2-[2-(4-methoxyphenyl)ethyl] chromone	H	OH	H	H	H	H	OCH_3	H	*A. sinensis* *A. crassna* *A. filarial* *A. malaccensis*	80,81,88,99 106 84 82
28	6-methoxy-2-[2-(4-hydroxyphenyl)ethyl] chromone [Aquilarone H]	H	OCH_3	H	H	H	H	OH	H	*A. sinensis*	88,107
29	6-methoxy-8-hydroxy-2-(2-phenylethyl) chromone	H	OCH_3	H	OH	H	H	H	H	*A. crassna*	108
30	6-methoxy-2-[2-(2-hydroxyphenyl)ethyl] chromone	H	OCH_3	H	H	OH	H	H	H	*A. crassna*	103
31	6-methoxy-2-[2-(3-hydroxyphenyl)ethyl] chromone	H	OCH_3	H	H	H	OH	H	H	*A. sinensis*	88,107
32	2-[2-(3-hydroxy-4-methoxyphenyl)ethyl] chromone [Qinanone A]	H	H	H	H	H	OH	OCH_3	H	*A. sinensis*	80
33	2-[2-(3-methoxy-4-hydroxyphenyl)ethyl] chromone [Qinanone B]	H	H	H	H	H	OCH_3	OH	H	*A. sinensis* *A. crassna*	80,81 89
34	7-hydroxy-2-[2-(4-methoxyphenyl)ethyl] chromone	H	H	OH	H	H	H	OCH_3	H	*A. sinensis*	62
35	2-[2-(2-hydroxy-4-methoxyphenyl)ethyl] chromone [Qinanone C]	H	H	H	H	OH	H	OCH_3	H	*A. sinensis*	80
36	7-methoxy-2-[2-(4-hydroxyphenyl)ethyl] chromone	H	H	OCH_3	H	H	H	OH	H	*A. sinensis* *A. crassna*	62 109
37	6-hydroxy-8-chloro-2-(2-phenylethyl) chromone	H	OH	H	Cl	H	H	H	H	*A. sinensis* *A. filaria* *A. crassna* *A. malaccensis*	91,93,110 84 63 111

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38	2-[2-hydroxy -2-(4-methoxyphenyl) ethyl]chromone	H	H	H	H	H	H	OCH_3	OH	*A. sinensis* *A. crassna*	90 89
39	5,8-dihy-droxy-2-[2-(4-me-thoxyphenyl)ethyl] chromone	OH	H	H	OH	H	H	OCH_3	H	*A. sinensis* *G. salicifolia*	105 111
40	6,7-dime-thoxy-2-(2-phenyleth-yl)chromone [AH6]	H	OCH_3	OCH_3	H	H	H	H	H	*Kalinantan* *A. sinensis* *A. agallo-cha* *Kyara 1st (Vietnam)* *A. malac-censis* *A. crassna* *A. filaria* *Aquilaria spp.*	86 53,62,112 88,92,95 83,105 97 36 34,82 106 84 90
41	5,8-dihydroxy-6-me-thoxy-2-(2-phenyleth-yl)chromone	OH	OCH_3	H	OH	H	H	H	H	*A. sinensis*	113
42	6-me-thoxy-2-[2-(3-me-thoxyphenyl)ethyl] chromone [AH5]	H	OCH_3	H	H	H	OCH_3	H	H	*Kalimantan* *A. sinensis* *A. malac-censis*	86 53,112,95 82,96
43	2-me-thoxy-2-[2-(4-me-thoxyphenyl)ethyl] chromone	H	OCH_3	H	H	H	H	OCH_3	H	*A. agallo-cha* *A. sinensis* *A. malac-censis*	35,98 29,112,88 96
44	6,8-dihy-droxy-2-[2-(4-me-thoxyphenyl)ethyl] chromone	H	OH	H	OH	H	H	OCH_3	H	*A. sinensis* *Aquilaria spp.*	99,114 104
45	6-hydroxy-2-[2-(3-hy-droxy-4-methoxyphenyl) ethyl]chromone [Aquilarone I]	H	OH	H	H	H	OH	OCH_3	H	*A. sinensis* *Aquilaria spp.*	80,81,93,107 90
46	6-hydroxy-7-me-thoxy-2-[2-(4-hydrx-oyphenyl)ethyl] chromone	H	OH	OCH_3	H	H	H	OH	H	*A. sinensis* *G. salicifolia* *Aquilaria spp.*	93,115 111 116
47	6-hydroxy-2-[2-(3-me-thoxy-4-hydroxyphenyl)ethyl] chromone	H	OH	H	H	H	OCH_3	OH	H	*A. sinensis* *Aquilaria spp.* *Aquilaria spp.*	80,93,114,117 104 75
48	6,7-dihy-droxy-2-[2-(4-me-thoxyphenyl)ethyl] chromone	H	OH	OH	H	H	H	OCH_3	H	*A. sinensis* *G. salicifolia* *Aquilaria spp.*	114,115 54 104

49	5-hydroxy-8-methoxy-2-[2-(4-methoxyphenyl)ethyl] chromone	OH	H	H	OCH_3	H	H	OCH_3	H	*A. sinensis*	99
50	5-hydroxy-6-methoxy-2-[2-(3-methoxyphenyl)ethyl] Chromone	OH	OCH_3	H	H	H	OCH_3	H	H	*A. sinensis*	53
51	5-hydroxy-7-methoxy-2-[2-(4-methoxyphenyl)ethyl] chromone	OH	H	OCH_3	H	H	H	OCH_3	H	*A. sinensis*	113
52	6-hydroxy-5-methoxy-2-[2-(4-methoxyphenyl)ethyl] chromone	OCH_3	OH	H	H	H	H	OCH_3	H	*A. sinensis*	53
53	6-hydroxy-8-chloro-2-[2-(4-hydroxyphenyl) ethyl]chromone	H	OH	H	Cl	H	H	OH	H	*Aquilaria spp.*	116
54	5-Hydroxy-6-methoxy-2-[2-(4-methoxyphenyl)ethyl] chromone	OH	OCH_3	H	H	H	H	OCH_3	H	*A. malaccensis* *A. sinensis*	96 88
55	6,7-dimethoxy-2-[2-(3-hydroxyphenyl)-ethyl] chromone	H	OCH_3	OCH_3	H	H	OH	H	H	*A. sinensis*	81
56	6-methoxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl] chromone	H	OCH_3	H	H	H	OH	OCH_3	H	*A. sinensis* *A. crassna* *Aquilaria spp.*	88 106 90
57	6-methoxy-7-hydroxy-2-[2-(4-methoxyphenyl)ethyl] chromone	H	OCH_3	OH	H	H	H	OCH_3	H	*A. malaccensis* *A. sinensis* *A. crassna*	34 81,99,114 102,108
58	6-hydroxy-2-[2-(3,4-dimethoxyphenyl)ethyl] chromone	H	OH	H	H	H	OCH_3	OCH_3	H	*A. sinensis*	81,114
59	6,7-dimethoxy-2-[2-(2-hydroxyphenyl)ethyl] chromone	H	OCH_3	OCH_3	H	OH	H	H	H	*A. sinensis*	53,92
60	6-methoxy-2-[2-(3-methoxy-4-hydroxyphenyl)ethyl] chromone	H	OCH_3	H	H	H	OCH_3	OH	H	*A. malaccensis* *A. sinensis* *A. crassna* *Aquilaria spp.*	85 53,92,88,105 106 104

61	6-hydroxy-7-methoxy-2-[2-(4-methoxyphenyl)ethyl] chromone	H	OH	OCH_3	H	H	H	OCH_3	H	*A. sinensis* *G. salicifolia* *A. filaria*	114 54 84
62	7-hydroxy-2-[2-(3-methoxy-4-hydroxyphenyl)ethyl] chromone	H	H	OH	H	H	OCH_3	OH	H	*A. sinensis*	81
63	(R)-6,7-dimethoxy-2-(2-hydroxy-2-phenylethyl)chromone	H	OCH_3	OCH_3	H	H	H	H	R-OH	*A. sinensis*	93,114
64	(S)-6,7-dimethoxy-2-(2-hydroxy-2-phenylethyl)chromone	H	OCH_3	OCH_3	H	H	H	H	S-OH	*A. sinensis*	93,114
65	6,7-dimethoxy-2-[2-(4-hydroxyphenyl)ethyl] chromone [Qinanone G]	H	OCH_3	OCH_3	H	H	H	OH	H	*A. sinensis*	81,83,92,114
66	6,7-dimethoxy-2-[2-(4-methoxyphenyl)ethyl] chromone [AH8]	H	OCH_3	OCH_3	H	H	H	OCH_3	H	*Kalinantan* *A. sinensis* *A. malaccensis* *A. crassna*	100 29,53,56,62 34 102
67	7-chloro-8-hydroxy-2-[2-(4-methoxyphenyl) ethyl]chromone	H	H	Cl	OH	H	H	OCH_3	H	*A. sinensis*	53
68	8-chloro-6-hydroxy-2-[2-(4-methoxyphenyl) ethyl]chromone	H	Cl	H	OH	H	H	OCH_3	H	*A. sinensis* *A. crassna*	93,110 63,106
69	5,8-dihydroxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl] chromone	OH	H	H	OH	H	OH	OCH_3	H	*G. salicifolia*	54
70	5,6-dihydroxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl] chromone	OH	OH	H	H	H	OH	OCH_3	H	*A. sinensis*	62
71	5,8-dimethoxy-2-[2-(3-acetoxyphenyl)ethyl] chromone	OCH_3	H	H	OCH_3	H	$OCO-CH_3$	H	H	*A. agallocha*	97
72	6-methoxy-2-[2-(3,4,5-trihydroxyphenyl)ethyl] chromone	H	OCH_3	H	H	OH	OH	OH	H	*A. sinensis*	113

73	6,8-dihydrx-oy-2-[2-(3-hy-droxy-4-methoxyphe-nyl)ethyl]chromone	H	OH	H	OH	H	OH	OCH_3	H	*A. sinensis*	107,115
74	6,8-dihy-droxy-2-[2-(3-me-thoxy-4-hydroxyphe-nyl)ethyl]chromone	H	OH	H	OH	H	OCH_3	OH	H	*A. sinensis*	118
75	8-chloro-6-hydroxy-2-[2-(3-hydroxy-4-me-thoxyphenyl)ethyl] chromone	H	OH	H	Cl	H	OH	OCH_3	H	*A. sinensis* *A. crassna*	92,93,114 106
76	2-[2-(4-glucosy-loxy-3-methoxyphe-nyl)ethyl]chromone	H	H	H	H	H	OCH_3		glu	*A. sinensis*	119
77	5-Methoxy-6-hy-droxy-2-[2-(3-hy-droxy-4-methoxyphe-nyl)ethyl]chromone	OCH_3	OH	H	H	H	OH	OCH_3	H	*A. sinensis*	114
78	6,7-dime-thoxy-2-[2-(3-me-thoxy-4-hydroxylphe-nyl)ethyl]chromone	H	OCH_3	OCH_3	H	H	OCH_3	OH	H	*A. sinensis* *Aquilaria spp.*	81,114,115 90
79	6-methoxy-7-hy-droxy-2-[2-(3-hy-droxy-4-methoxyphe-nyl)ethyl]chromone	H	OCH_3	OH	H	H	OH	OCH_3	H	*A. sinensis* *G. salicifolia* *Aquilaria spp.*	115 111 75
80	5-hydroxy-6,7-dime-thoxy-2-[2-(4-me-thoxyphenyl)ethyl] chromone	OH	OCH_3	OCH_3	H	H	H	OCH_3	H	*A. sinensis*	91
81	6,7-dime-thoxy-2-[2-(3-hy-droxy-4-methoxyphe-nyl)ethyl]chromone	H	OCH_3	OCH_3	H	H	OH	OCH_3	H	*A. sinensis* *A. crassna*	81,114,115 102
82	6-hydroxy-7-me-thoxy-2-[2-(3-hy-droxy-4-methoxyphe-nyl)ethyl]chromone	H	OH	OCH_3	H	H	OH	OCH_3	H	*A. sinensis* *G. salicifolia* *Aquilaria spp.* *Aquilaria spp.*	81,107,114 111 90 75

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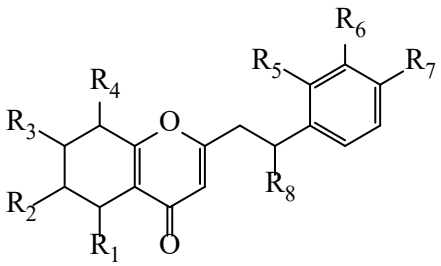
83	7-hydroxyl-6-methoxyl-2-[2-(4-hydroxyl-3-methoxylphenyl) ethyl]chromone	H	OCH_3	OH	H	H	OCH_3	OH	H	*A. sinensis*	120
84	5-hydroxy-6-methoxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chromone	OH	OCH_3	H	H	H	OH	OCH_3	H	*A. sinensis* *A. crassna*	88 102
85	6-hydroxy-7-methoxy-2-[2-(3-methoxy-4-hydroxyphenyl)ethyl]chromone [Aquilarone G]	H	OH	OCH_3	H	H	OCH_3	OH	H	*A. sinensis* *Aquilaria spp.*	107 90
85a	6,7-dihydroxy-2-[2-(3'-hydroxy-4'-methoxyphenyl)ethyl] chromone	-	-	-	-	-	-	-	-	*Jinko*	79
86	6-methoxy-2-[2-(3,4,5-trihydroxyphenyl)ethyl] chromone	H	OCH_3	H	H	OH	OH	OH	H	*A. sinensis*	113

Table 10: *Flindersia* type 2-(2-phenylethyl)chromones from agarwood species.

The commonly observed substituents in FPECs core structure are hydroxy and methoxy groups, and are substituted at C-6, followed by C-7, C-5 and C-8. The methoxy functional groups appear more frequently at C-7 than hydroxyl groups. However, it is interesting to note that five chlorinated FPECs (**37, 53, 67, 68** and **75**), are reported from the agarwood species (Figure 14, Table 10). It is also reported the only glycosylated FPEC (**76**) from *A. sinensis*. The only acetyl FPEC (**71**) reported from the agarwood of *A. agallocha*.

2.2.1b. 5,6,7,8-tetrahydro-2-(2-phenylethyl)chromones (TPECs)

The isolated and structure identified highly oxidized TPECs (**87–135**) from agarwood species are presented as Figure 15, and Table 11. Further, chemical examination of whole-tree agarwood-inducing technique (Agar-Wit) from 8 years old A. sinensis, resulted in the isolation of TPEC compounds **135a, 135b**, and **135c** (Figure 14) [121].



TPECs (85 - 135c)

Figure 15: General chemical structure of TPECs from agarwood species.

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No.	Name	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Source	Ref.
87	(6S,7S,8S)-6,7,8-trihydroxyl-2-(3-hydroxyl-4-methoxyphenylethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one.	H	*α*-OH	*α*-OH	*α*-OH	H	OH	OCH_3	H	*A. sinensis*	120
88	(6S,7S,8S)-6,7,8-trihydroxyl-2-(4-hydroxyl-3-methoxyphenylethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one	H	*α*-OH	*α*-OH	*α*-OH	H	OCH_3	OH	H	*A. sinensis*	120
89	6,7-dihydroxy-5,6,7,8-tetrahydro-2-(2-(4-methoxy phenyl)ethyl) chromone	H	*α*-OH	*α*-OH	H	H	H	OCH_3	H	*A. crassna*	122
90	6,7-dihydroxy-2-(2-phenylethyl)-5,6,7,8-tetrahydrochromone	H	*α*-OH	*α*-OH	H	H	H	H	H	*A. sinensis* *Aquilaria spp.*	95 90
91	(6S,7S,8R)-6,7-dihydroxy-8-chloro-5,6,7,8-tetrahydro-2-(2-(3-hydroxy-4-methoxyphenyl)ethyl)chromone	H	*α*-OH	*α*-OH	*β*-Cl	H	OH	OCH_3	H	*A. crassna*	122
92	(5S,6R,7R)-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenylethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one	*α*-OH	*α*-OH	*α*-OH	H	H	OH	OCH_3	H	*A. sinensis*	91,123
93	rel-(5R,6S,7R)-5,6,7,8-tetrahydro-5,6,7-trihydroxy-2-[2-(4-methoxyphenyl) ethyl]-4H-1-benzopyran-4-one	*α*-OH	*α*-OH	*β*-OH	H	H	H	OCH_3	H	*A. malaccensis*	34
94	(6R,7S,8S)-6,7,8-trihydroxy-2-(4-hydroxyl-3-methoxyphenylethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one.	*β*-OH	*β*-OH	*β*-OH	H	H	OCH_3	OH	H	*A. sinensis*	91

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95	rel-(5R,6S,7R)-5,6,7,8-tetrahydro-5,6,7-trihydroxy-2-(2-phenylethyl)-4H-1-benzopyran-4-one	*α*-OH	*α*-OH	*β*-OH	H	H	H	H	H	*A. malaccensis*	34
96	(5S,6S,7R)-5,6,7-trihydroxy-2-[2-(hydroxylphenyl)ethyl]-5,6,7,8-tetrahydrochromone [AH9]	*α*-OH	*β*-OH	*α*-OH	H	OH	H	H	H	*Kalimantan*	100
97	(5S,6R,7S)-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenylethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one	*α*-OH	*α*-OH	*β*-OH	H	H	OH	OCH_3	H	*A. malaccensis*	34
98	Agarotetrol [AH1]	*α*-OH	*β*-OH	*β*-OH	*α*-OH	H	H	H	H	*A. agallocha* *Kalimantan* *Aquilaria spp. A. sinensis*	124 125 104 126, 127
99	Aquilarone B	*α*-OH	*α*-OH	*α*-OH	*β*-OH	H	H	H	H	*A. sinensis* *Aquilaria spp.*	107,127 90
100	Tetrahydrochromone B	*β*-OCH_3	*α*-OH	*α*-OH	*β*-OH	H	H	H	H	*A. sinensis*	127
101	5α,6β,7β-trihydroxy-8α-methoxy-2-(2-phenylethyl)-5,6,7,8-tetrahydrochromone [AH17]	*α*-OH	*β*-OH	*β*-OH	*α*-OCH_3	H	H	H	H	*Kalimantan* *A. sinensis*	128 127
102	(5R,6R,7S,8R)-2-(2-phenylethyl)-tetrahydroxy-5,6,7,8-tetrahydrochromone [AH16]	*β*-OH	*β*-OH	*α*-OH	*β*-OH	H	H	H	H	*Kalimantan* *A. sinensis*	129 126
103	Isoagarotetrol [AH2]	*α*-OH	*β*-OH	*α*-OH	*β*-OH	H	H	H	H	*Kalimantan* *A. sinensis* *Aquilaria spp.*	125 95 90

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104	(5R,6S,7S,8R)-2-[2-(4-methoxyphenyl) ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone	*β*-OH	*α*-OH	*α*-OH	*β*-OH	H	H	OCH_3	H	*Aquilaria spp.*	90
105	5α,6β,7α,8β-tetrahydroxy-2-[2-(4-methoxyphenyl)ethyl]-5,6,7,8-tetrahydrochromone [AH2a]	*α*-OH	*β*-OH	*α*-OH	*β*-OH	H	H	OCH_3	H	*Kalimantan* *A. sinensis* *Aquilaria spp.*	130 37,87 90
106	(5S,6R,7S,8R,7'R)-7'-hydroxyisoagarotetrol	*α*-OH	*β*-OH	*α*-OH	*β*-OH	H	H	H	R-OH	*Kalimantan*	131
107	8-chloro-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydrochromone	*α*-OH	*α*-OH	*α*-OH	*β*-Cl	H	H	H	H	*A. sinensis* *Aquilaria spp.*	53,95 90
108	5α,6β,7α,8β-tetrahydroxy-2-[2-(2-hydroxyphenyl)ethyl]-5,6,7,8-tetrahydrochromone [AH2b]	*α*-OH	*β*-OH	*α*-OH	*β*-OH	OH	H	H	H	*Kalimantan* *A. sinensis* *Aquilaria spp.*	130 56 90
109	5α,6β,7β,8α-tetrahydroxy-2-[2-(2-hydroxyphenyl)ethyl]-5,6,7,8-tetrahydrochromone (AH_{23})	*α*-OH	*β*-OH	*β*-OH	*α*-OH	OH	H	H	H	*Kalimantan*	128
110	5α,6β,7β,8α-tetrahydroxy-2-[2-(4-methoxyphenyl)ethyl]-5,6,7,8-tetrahydrochromone[AH1A] [4'-methoxy-agarotetrol]	*α*-OH	*β*-OH	*β*-OH	*α*-OH	H	H	OCH_3	H	*Kalimantan* *A. sinensis* *Aquilaria spp.*	130 127,132 116
111	Aquilarone C	*α*-OH	*α*-OH	*α*-OH	*β*-OH	H	H	OCH_3	H	*A. sinensis* *Aquilaria spp.*	91,107 90
112	(5S,6S,7S,8S)-8-chloro-5,6,7-trihydroxy-2-(phenylethyl)-5,6,7,8-tetrahydrochromone	*α*-OH	*α*-OH	*α*-OH	*α*-Cl	H	H	H	H	*A. sinensis*	91

113	(5S,6R,7S,8R,7'S)-7'-hydroxyisoagarotetrol	α-OH	β-OH	α-OH	β-OH	H	H	H	S-OH	*Kalimantan*	131
114	Aquilarone F	α-OH	β-OH	β-OH	α-OH	H	H	OH	H	*A. sinensis* *Aquilaria spp.*	107 90
115	(5R,6S,7S,8R)-2-[2-(4-hydroxy-3-methoxyphenyl)ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone	β-OH	α-OH	α-OH	β-OH	H	OCH_3	OH	H	*Aquilaria spp.*	90
116	Tetrahydrochromone G	β-OCH_3	β-OH	β-OH	α-OH	H	H	OCH_3	H	*A. sinensis*	127
117	Aquilarone E	α-OH	β-OH	β-OH	α-OH	H	OH	OCH_3	H	*A. sinensis*	107, 127
118	(5R,6S,7S,8R)-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone	β-OH	α-OH	α-OH	β-OH	H	OH	OCH_3	H	*Aquilaria spp.*	90
119	Tetrahydrochromone F	α-OCH_3	α-OH	α-OH	β-OH	H	H	OCH_3	H	*A. sinensis* *A. crassna*	127 102
120	(5R,6S,7S,8R)-5,6,7-trihydroxy-8-methoxy-5,6,7,8-tetrahydro-2-(2-(4-methoxyphenyl)ethyl)chromone	β-OH	α-OH	α-OH	β-OCH_3	H	H	OCH_3	H	*A. crassna*	122
121	Tetrahydrochromone E	α-OH	β-OH	β-OH	α-OCH_3	H	H	OCH_3	H	*A. sinensis*	127
122	5,6,7,8-tetrahydroxy-2-(3-hydroxy-4-methoxy phenethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one	α-OH	β-OH	β-OH	α-OH	H	OH	OCH_3	H	*A. sinensis*	133
123	Aquilarone D	α-OH	β-OH	α-OH	β-OH	H	OH	OCH_3	H	*A. sinensis* *Aquilaria spp.*	56,107 90

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124	Aquilarone A	*α*-OH	*α*-OH	*α*-OH	*β*-OH	H	OH	OCH_3	H	*A. sinensis* *Aquilaria spp.*	107,127 90
125	Tetrahydrochromone A	*α*-OCH_3	*β*-OH	*β*-OH	*α*-OH	H	H	OCH_3	H	*A. sinensis*	127
126	(5R,6R,7R,8R)-8-chloro-5,6,7-trihydroxy-2-(4-methoxyphenethyl)-5,6,7,8-tetrahydrochromone	*β*-OH	*β*-OH	*β*-OH	*β*-Cl	H	H	OCH_3	H	*A. sinensis*	91
127	rel-(5R,6S,7S,8R)-8-chloro--5,6,7,8-tetrahydro-5,6,7-trihydroxy-2-[2-(4-methoxyphenyl)ethyl]-4H-1-benzopyran-4-one	*α*-OH	*β*-OH	*β*-OH	*α*-Cl	H	H	OCH_3	H	*A. malaccensis* *A. sinensis*	34 127
128	(5R,6R,7R,8S)-8-chloro-5,6,7-trihydroxy-2-(4-methoxyphenethyl)-5,6,7,8-tetrahydrochromone	*β*-OH	*β*-OH	*β*-OH	*α*-Cl	H	H	OCH_3	H	*A. sinensis* *Aquilaria sp*	91 75
129	Tetrahydrochromone I	*α*-OCH_3	*α*-OH	*α*-OH	*β*-Cl	H	H	OCH_3	H	*A. sinensis*	127
130	Tetrahydrochromone D	*α*-OCH_3	*β*-OH	*β*-OH	*α*-Cl	H	H	OCH_3	H	*A. sinensis*	127
131	Tetrahydrochromone C	*α*-OCH_3	*β*-OH	*β*-OH	*α*-OH	H	OH	OCH_3		*A. sinensis*	127
132	Tetrahydrochromone H	*α*-OCH_3	*α*-OH	*α*-OH	*β*-OH	H	OH	OCH_3	H	*A. sinensis*	127
133	Tetrahydrochromone J	*α*-OCH_3	*α*-OH	*α*-OH	*β*-Cl	H	OH	OCH_3	H	*A. sinensis*	127
134	8-chloro-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4H-chromon-one	*α*-OH	*α*-OH	*α*-OH	*β*-Cl	H	OH	OCH_3	H	*A. sinensis*	134

135	rel-(5R,6S,7S,8R)-8-chloro-5,6,7,8-tetrahydro-5,6,7-trihydroxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-4H-1-benzopyran-4-one	*α*-OH	*β*-OH	*β*-OH	*α*-Cl	H	OH	OCH_3	H	*A. malaccensis* *A. sinensis*	34 37
135a	(5S,6R,7S,8S)-8-chloro-5,6,7-trihydroxy-2-[2-(4'-methoxyphenylethyl)]-5,6,7,8-tetrahydrochromone	*α*-OH	*β*-OH	*α*-OH	*α*-Cl	H	H	OCH_3	H	*A. sinensis*	121
135b	(5S,6R,7S,8S)-8-chloro-5,6,7-trihydroxy-2-(2-phenylethyl)-5,6,7,8-tetrahydrochromone	*α*-OH	*β*-OH	*α*-OH	*α*-Cl	H	H	H	H	*A. sinensis*	121
135c	(5S,6R,7R,8S)-8-chloro-5-ethoxy-6,7-dihydroxy-2-[2-(3'-hydroxy-4'-methoxyphenylethyl)-5,6,7,8-tetrahydrochromone	*α*-OCH_2CH_3	*β*-OH	*β*-OH	*α*-Cl	H	OH	OCH_3	H	*A. sinensis*	121

Table 11: 5,6,7,8-tetrahydro-2-(2-phenylethyl)chromones (TPECs) reported from agarwood.

Among the reported TPECs, the compound, agarotetrol (**98**) is a common metabolite found in different samples of agarwood. The Chinese Pharmacopeia (2015 edition), identified agarotetrol (**98**) as a marker compound of agarwood, and standardized the contents needs to be higher than 0.10%. Most of the reported TPECs are oxidized at C-5, C-6, C-7 and C-8 positions, either with hydroxy or methoxy functional groups. It is observed that the reported TPECs at C-6 and C-7 are usually substituted with hydroxyl groups, while the methoxy group at C-5 or C-8. Some of the reported TPECs contains a chlorine substituent at the C-8 position. It is interesting to note that the TPECs **106** and **113** are ethoxy derivatives.

2.2.1c. Mono-epoxy-5,6,7,8-tetrahydro-2-(2-phenylethyl)chromones (EPECs)

Various epoxy-substituted PECs are reported from agarwood species (Figure 16, Table 12). The epoxy group is usually located either at C-5 and C-6, or at C-7 and C-8. However, the EPEC **141** carries an epoxy group located at C-6 and C-7 [135]. Similar to the structures of TPECs, the C-5, C-6, C-7 and C-8 positions of EPECs are oxidized and carry hydroxy or methoxy or epoxy groups, while the methoxy groups usually located at C-5 or C-8. In this connection, the EPECs **136–138** are reported from *A. malaccensis* [34], whereas **136–144**, and **148–150** are reported from the agarwood of *A. sinensis* (Table 12). The EPECs **136** and **144** are obtained from the agarwood of *A. crassna* [108].

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2.2.1d. Diepoxy-5,6,7,8-tetrahydro-2-(2-phenylethyl) chromones (DPECs)

Various DPECs compounds (**145–151**), are reported from the species of agarwood (Figure 16, Table 12). The DPECs (**145–147**) are obtained from the agarwood of *A. crassna*, *A. malaccensis* and *A. sinensis* (Table 12).

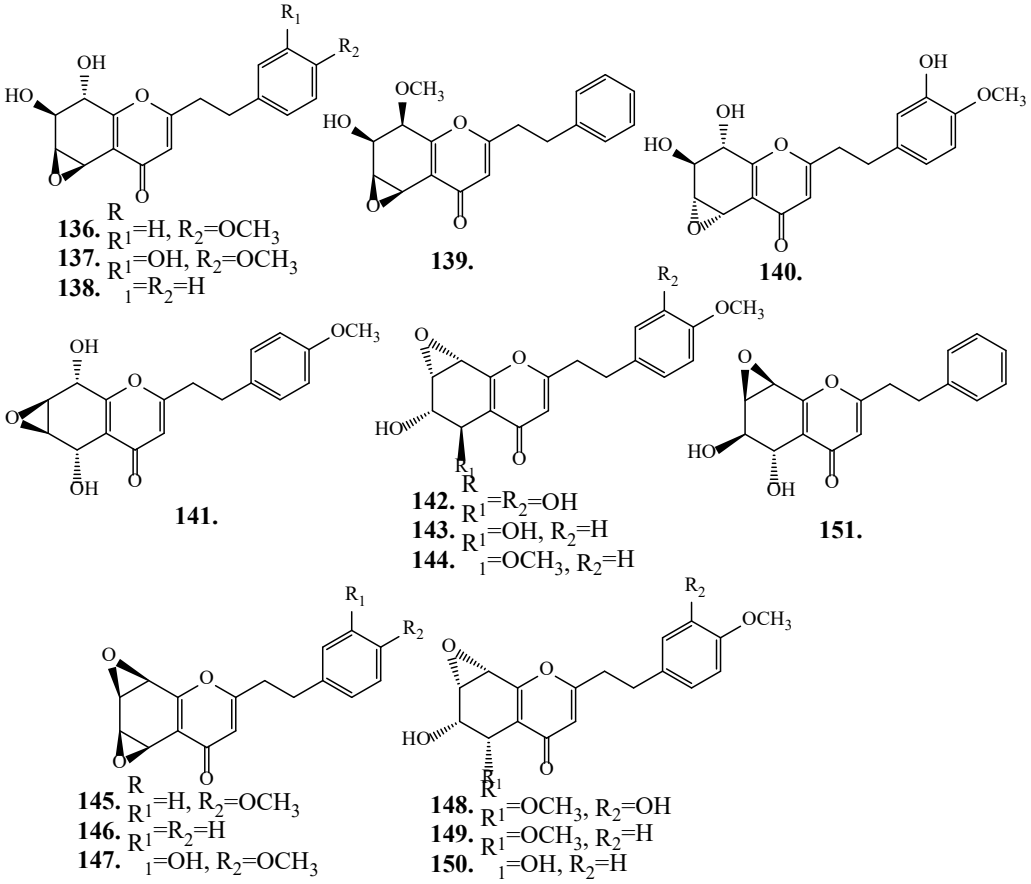


Figure 16: Chemical structures of EPECs and DPECs of agarwood.

No.	Name	Source	Ref.
136	*rel-(1aR,2R,3R,7bS)*-1a,2,3,7b-tetrahydro-2,3-dihydroxy-5-[2-(4-methoxyphenyl)ethyl]-7H-oxireno[f] [1]benzopyran-7-one	*A. malaccensis* *A. sinensis* *A. crassna*	34 91 108
137	*rel-(1aR,2R,3R,7bS)*-1a,2,3,7b-tetrahydro-2,3-dihydroxy-5-[2-(3-hydroxy-4-methoxyphenyl) ethyl]-7H-oxireno[f][1]benzopyran-7-one	*A. malaccensis* *A. sinensis*	34 88
138	*rel-(1aR,2R,3R,7bS)*-1a,2,3,7b-Tetrahydro-2,3-dihydroxy-5-(2-phenylethyl)-7H-oxireno[f] [1] benzopyran-7-one	*A. malaccensis* *A. sinensis*	34,82 53,88
139	5,6-epoxy-7β-hydroxy-8β-methoxy-2-(2-phenylethyl)chromone	*A. sinensis*	88
140	5α,6α-Epoxy-7β,8α,3'-trihydroxy-4'-methoxy-2-(2-phenylethyl)chromone	*A. sinensis*	113
141	*(5S,6R,7S,8S)*-2-[2-(4'-methoxyphenyl)ethyl]-6,7-epoxy-5,8-dihydroxy-5,6,7,8-tetrahydrochromone	*A. sinensis*	135

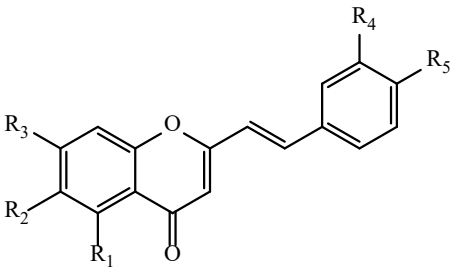
142	Tetrahydrochromone M	*A. sinensis*	127
143	Tetrahydrochromone L	*A. sinensis*	127
144	*(5R,6S,7S,8S)*-2-[2-(4'-methoxyphenyl)ethyl]-7,8-epoxy-5-methoxy-6-hydroxy-5,6,7,8-tetrahydrochromone	*A. sinensis*	135
		A. crassna	108
145	Oxidoagarochromone B	*A. crassna*	136
		A. malaccensis	34
		A. sinensis	53,88
146	Oxidoagarochromone A	*A. crassna*	136
		A. malaccensis	34
		A. sinensis	53,88
147	Oxidoagarochromone C	*A. crassna*	136
		A. malaccensis	34
		A. sinensis	127
148	*(5S,6S,7S,8S)*-2-[2-(3'-hydroxy-4'-methoxyphenyl)ethyl]-7,8-epoxy-5-methoxy-6-hydroxy-5,6,7,8- tetrahydrochromone	*A. sinensis*	135
149	*(5S,6S,7S,8S)*-2-[2-(4'-methoxyphenyl)ethyl]-7,8-epoxy-5-methoxy-6-hydroxy-5,6,7,8-tetrahydrochromone	*A. sinensis*	135
150	*(5S,6S,7S,8S)*-2-[2-(4'-methoxyphenyl)ethyl]-7,8-epoxy-5,6-dihydroxy-5,6,7,8-tetrahydrochromone	*A. sinensis*	135
151	Tetrahydrochromone K	*A. sinensis*	127

Table. 12: EPECs and DPECs from agarwood species.

The C-4' position of the phenylethyl moiety in both EPECs and DPECs are without substitution, or substituted with a methoxy group (Figure 16). Alternatively, both EPECs and DPECs are substituted at C-3' with a hydroxyl and/or C-4' with a methoxyl group (Figure 16).

2.2.1e. Other PECs

From the agarwood species of *A. crassna, A. filaria, A. sinensis,* and *G. salicifolia*, seven 2-(2-phenylethenyl)chromones (PEECs) are reported (Figure 17). The compounds PEECs are possess a styryl moiety instead of a phenylethyl moiety at C-2 of chromones. The chemical structures and names are presented as in Figure 17 and Table 13.



152. R_1=R_2=R_3=H, R_4=OCH_3, R_5=OH
153. R_1=R_3=R_4=H, R_2=OCH_3, R_5=OH
154. R_1=OH, R_2=R_3=R_4=H, R_5=OCH_3
155. R_1=R_3=H, R_2=R_4=OCH_3, R_5=OH
156. R_1=R_3= H, R_2=R_5=OH, R_4=OCH_3
157. R_1=R_4=OH, R_2=R_3=H, R_5=OCH_3
158. R_1=R_4=H, R_2=R_3=OCH_3, R_5=OH

Figure 17: Chemical structures of 2-(2-phenylethenyl)chromones (PEECs) from agarwood.

No.	Name	Source	Ref.
152	(*E*)-2-[2-(3-methoxy-4-hydroxyphenyl)ethenyl]chromone	*A. crassna*	109
153	(*E*)-6-methoxy-2-[2-(4-hydroxyphenyl)ethenyl]chromone	*A. crassna*	109
154	5-hydroxy-2-[2-(4-methoxyphenyl)ethenyl]chromone	*G. salicifolia* *A. filaria*	54 68
155	(*E*)-6-methoxy-2-[2-(3-methoxy-4-hydroxyphenyl)ethenyl] chromone	*A. crassna*	109
156	6-hydroxy-2-[2-(3-methoxy-4-hydroxyphenyl)ethenyl]chromone	*A. sinensis* *Aquilaria spp.*	37,115 116
157	5-hydroxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethenyl]chromone	*G. salicifolia*	137
158	6,7-dimethoxy-2-[2-(4-hydroxyphenyl)ethenyl]-4H-chromen-4-one	*A. sinensis*	92

Table 13: 2-(2-phenylethenyl)chromones (PEECs) from agarwood.

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2.2.2. Dimeric 2-(2-phenylethyl)chromones (DIPECs)

The agarwood species of *A. sinensis* and *A. crassna* are rich source for the compounds DIPECs (Figure 18, Table 14). The DIPECs are isolated and purified by silica gel column chromatography and semi-preparetive HPLC and so on. The chemical structures of DIPECs are identified by spectroscopic data. The single C–C bond linked DIPECs (**159–162**), which are composed of two FPECs (unit A and unit B) through a C5–C5' linkage, are reported from the agarwood "Jinko" from Kalimantan (Figure 18, Table 14). Further, chemical examination of whole-tree agarwood-inducing technique (Agar-Wit) from 8 years old *A. sinensis*, resulted in the isolation of a single C–C bond linked DIPEC, aqulisinone A (**162a**, Figure 18) [121]. The reported remaining DIPECs are linked with a C–O–C bond (Table 14). Most of these C–O–C bond linked DIPECs are composed of a TPEC unit (unit A) and a FPEC unit (unit B) (Figure 18, Table 14). In the DIPECs **167–187**, the linkage position of unit A is situated at C-8, while the linkage position of unit B is usually at C-7' or at C-6', except for dimer **176** (Figure 18). The DIPECs 195 and 196 are composed of two EPEC units, which are connected through a C5–O–C6' linkage (Figure 18). It is observed that the DIPECs unit A usually linked at C5 or C8. The reason might be that the conjugated C5 and C8 of 4*H*-pyran-4-one yielded the stable intermediate carbocations as compared with C6 and C7. The DIPECs AH_{10}–AH_{15}, and AH_{21} (**164–166, 168**, and **169**) are reported from the agarwood "Jinko" from Kalimantan (Table 15). Further, AH_{10} (**166**) and AH_{14} (**165**) are also reported from the withered wood of *A. sinensis* grown in Taiwan [95]. A recent study reported the new DIPECs **198a–198d** from the MeOH extract of agarwood *Jinko* [79]. The DIPEC compounds, aquilasinenones L and M (**198e** and **198f**) are reported from the artificial agarwood originating from *A. sinensis* [138].

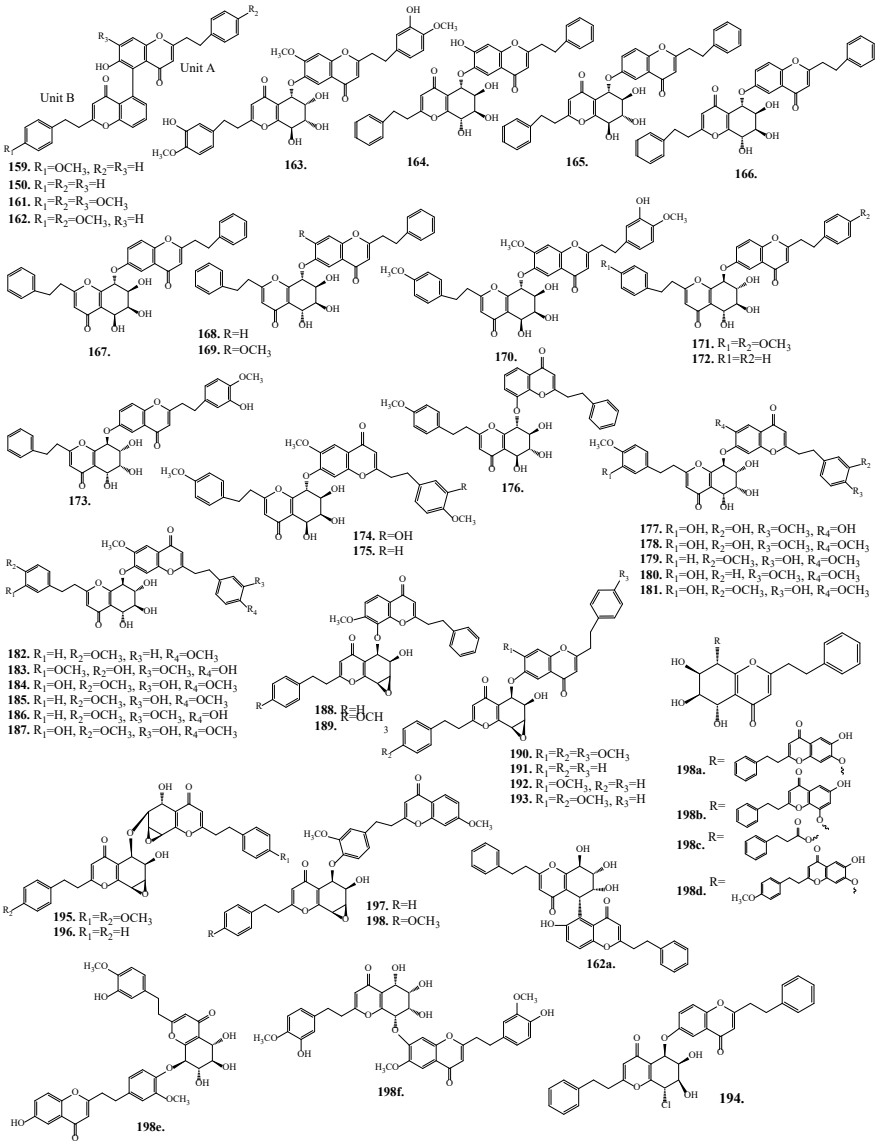

Figure 18: Chemical structures of dimeric 2-(2-phenylethyl)chromones from agarwood.

No.	Name	Source	Ref.
159	Aquisinenone O	*A. sinensis*	139
160	2,2'-di-(2-phenylethyl)-8,6'-dihydroxy-5,5'-bichromone [AH_{11}]	*Kalimantan*	140
		A. sinensis	139
161	7,4'-dimethoxyaquisinenone O	*A. sinensis*	139
162	Crassin A	*A. crassna*	141
		A. sinensis	139
162a	Aqulisinone A	*A. sinensis*	121

Table 14: Dimeric 2-(2-phenylethyl)chromones with C–C bond of agarwood.

No.	**Name**	**Source**	**Ref.**
163	Aquilasinenone K	*A. sinensis*	142
164	(5S,6S,7R,8S)-2-(2-phenylethyl)-6,7,8-trihydroxy-5,6,7,8-tetrahydro-5-[2-(2-phenylethyl)-7-hydroxy-chromonyl-6-oxy]chromone [AH_{15}]	*Kalimantan*	143
165	(5S,6R,7S,8S)-2-(2-phenylethyl)-6,7,8-trihydroxy-5,6,7,8-tetrahydro-5-[2-(2-phenylethy)chromonyl-6-oxy]chromone [AH14]	*Kalimantan*	144
		A. sinensis	39,95
166	(5S,6S,7R,8S)-2-(2-phenylethyl)-6,7,8-trihydroxy-5,6,7,8-tetrahydro-5-[2-(2-phenylethy)chromonyl-6-oxy]chromone [AH10]	*Kalimantan*	140
		A. sinensis	95
167	(5R,6R,7R,8S)-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydro-8-[2-(2-phenylethyl)chromonyl-6-oxy]chromone	*A. sinensis*	145
168	(5S,6R,7R,8S)-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydro-8-[2-(2-phenylethy)chromonyl-6-oxy]chromone [AH13]	*Kalimantan*	144
169	(5R,6R,7R,8S)-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydro-8-[2-(2-phenylethy)-7-methoxychromonyl-6-oxy]chromone [AH12]	*Kalimantan*	144
170	Aquisinenone N	*A. sinensis*	139
171	(5S,6R,7S,8R)-2-[2-(4-methoxyphenyl)ethyl]-5,6,7-trihydroxy5,6,7,8-tetrahydro-8-{2-[2-(4'''-methoxyphenyl)ethyl]chromonyl-6-oxy}chromone	*A. sinensis*	145
172	(5S,6R,7S,8R)-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydro-8-[2-(2-phenylethyl)chromonyl-6-oxy]chromone	*A. sinensis*	145
173	Aquilasinenone J	*A. sinensis*	142
174	Aquisinenone M	*A. sinensis*	139
175	Crassin D	*A. sinensis*	139

176	Crassin B	*A. sinensis*	141
177	Aquilasinenone C	*A. sinensis*	142
178	Aquilasinenone B	*A. sinensis*	142
179	Aquilasinenone E	*A. sinensis*	142
180	Aquilasinenone D	*A. sinensis*	142
181	Aquilasinenone A	*A. sinensis*	142
182	Crassin C	*A. crassna*	141
183	Aquilasinenone H	*A. sinensis*	142
184	Aquilasinenone G	*A. sinensis*	142
185	Aquilasinenone I	*A. sinensis*	142
186	(5S,6R,7S,8R)-2-[2-(4-methoxyphenyl)ethyl]-5,6,7-trihydroxy-5,6,7,8-tetrahydro-8-{6-methoxy-2-[2-(3'''-methoxy-4'''-hydroxyphenyl)ethyl]chromonyl-7-oxy} chromone	*A. sinensis*	145
187	Aquilasinenone F	*A. sinensis*	142
188	Aquisinenone H	*A. sinensis*	139
189	4'-methoxyaquisinenone	*A. sinensis*	139
190	4',7'',4'''-trimethoxyaquisinenone I	*A. sinensis*	139
191	Aquisinenone I	*A. sinensis*	139
192	7''-methoxyaquisinenone I	*A. sinensis*	139
193	4',7''-dimethoxyaquisinenone I	*A. sinensis*	139
194	Aquisinenone L	*A. sinensis*	139
195	4',4'''-dimethoxyaquisinenone K	*A. sinensis*	139
196	Aquisinenone K	*A. sinensis*	139

197	Aquisinenone J	*A. sinensis*	139
198	4'-methoxyaquisinenone J	*A. sinensis*	139
198a	(5S,6R,7R,8S)-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydro-8-[6'-hydroxy-2-(2-phenylethyl)chromonyl-7'-oxy]chromone [diaquilariachrome A]	*Jinko*	79
198b	(5S,6R,7R,8S)-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydro-8-[6'-hydroxy-2-(2-phenylethyl)chromonyl-8'-oxy]chromone [diaquilariachrome B]	*Jinko*	79
198c	(5S,6R,7R,8S)-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydro-8-(3-phenyl-propionyloxy)chromone	*Jinko*	79
198d	(5S,6R,7R,8S)-2-(2-phenylethyl)-5,6,7-trihydroxy-5,6,7,8-tetrahydro-8-{6'-hydroxy-2-[2-(4'''-methoxyphenyl)ethyl]chromonyl-7'-oxy}chromone [diaquilariachrome C]	*Jinko*	79
198e	Aquilasinenones L	*A. sinensis*	138
198f	Aquilasinenones M	*A. sinensis*	138

Table 15: Dimeric 2-(2-phenylethyl)chromones with C–O–C bond of agarwood.

Additionally, double linked 2-(2-phenethyl)chromone dimers (DLPECs) also reported from the species of agarwood. The reported compounds chemical structures (Figure 19) are presented in Table 16. These compounds are composed of a TPEC unit (unit A) and an FPEC unit (unit B) (Figure 19). In most of the DLPECs, the linkage position of unit A is usually at C5 and C7, while the same in unit B is C6' and C7', might be duce to the 6,7-dihydroxy-FPECs provides two adjacent hydroxyl groups to form the two C–O–C bonds (Figure 19). In the TPEC unit, the C–O–C bond linked at C7, while the same for the C–C bond is at C5. On the other hand, in the FPEC unit, the C–C bond linked at C5', C7' or C8' of the chromone moiety (**205–215**), or at C2''', C3''' or C4''' of the phenylethyl moiety (**216–224**) (Figure 19, Table 16). Among these DLPECs, six compounds (199–204) are linked through two C–O–C bonds to form a seven or six-membered oxygen-carrying heterocyclic ring (Figure 19, Table 16). Six new DLPECs (204a–204f) are reported from the EtOAc extract of artificial agarwood originating from *A. sinensis* [146]. On the other hand, the DLPECs 205–224 contains an unusual 3,4-dihydro-2H-pyran ring connected to two PEC monomeric moieties through a C–O–C bond and a C–C bond (Figure 19, Table 17). Three new C–O–C bond DLPECs, crassin I– K (**224a–224c**) (Figure 19, Table 17), reported from the artificial holing agarwood originating from *A. sinensis* [147].

No.	Name	Source	Ref.
199	Crassin E	*A. crassna*	148
200	Crassin F	*A. crassna*	148
201	Crassin G	*A. crassna*	148
202	AH_{21}	*Kalimantan*	149
203	(+)-4'-Methoxyaquisinenone G	*A. sinensis*	150

204	(–)-Aquisinenone G	*A. sinensis*	150
204a	(–)-3'''-hydroxy-4'''-methoxy-aquisinenone G	*A. sinensis*	146
204b	(+)-3'''-hydroxy-4'',4'''-dimethoxy-aquisinenone G	*A. sinensis*	146
204c	(+)-3''-hydroxy-4'',4'''-dimethoxy-aquisinenone G	*A. sinensis*	146
204d	(+)-4'''-hydroxy-4'',3'''-dimethoxy-aquisinenone G	*A. sinensis*	146
204e	3'''-hydroxy-4''-demethoxy-crassin G	*A. sinensis*	146
204f	3'''-hydroxy-crassin G	*A. sinensis*	146

Table 16: Double linked 2-(2-phenylethyl)chromones with double C–O–C bonds.

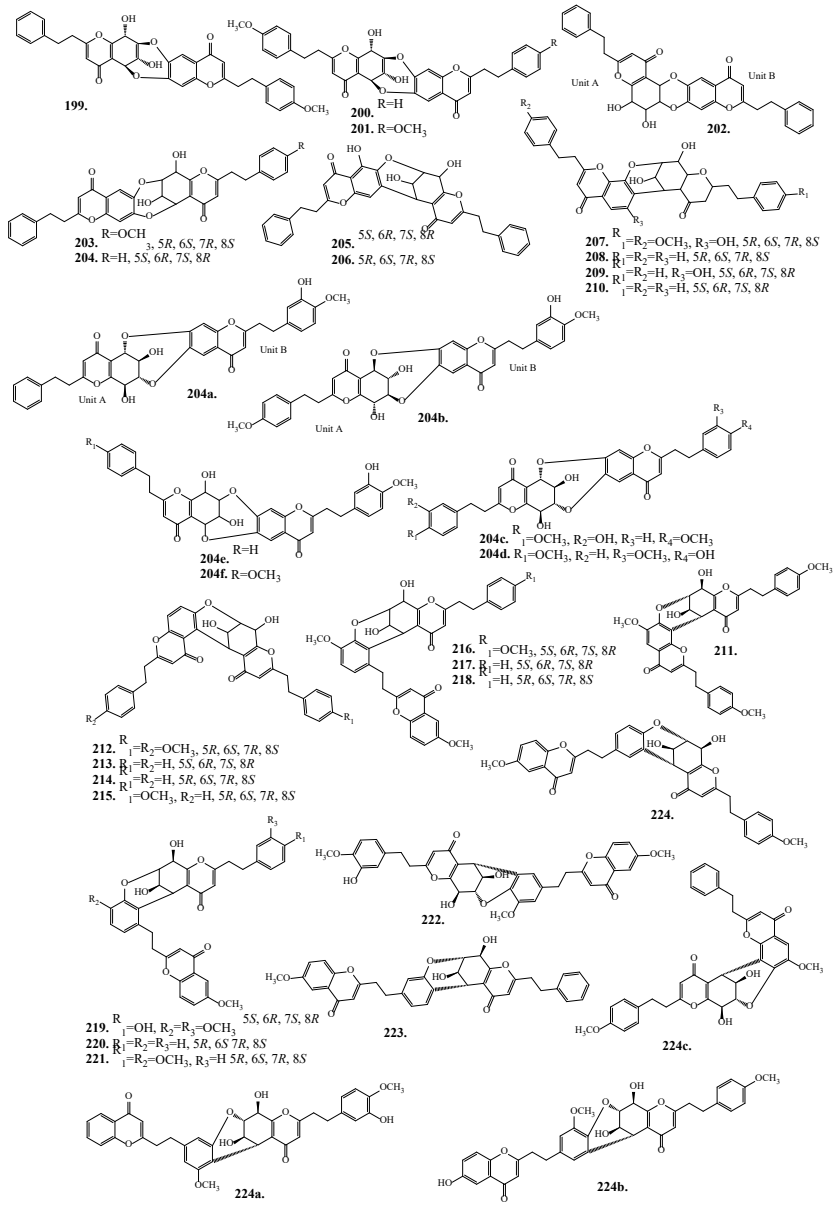

Figure 19: Chemical structures of agarwood double linked 2-(2-phenylethyl)chromones.

No.	Name	Source	Ref.
205	(–)-Aquisinenone C	*A. sinensis*	150
206	(+)-Aquisinenone C	*A. sinensis*	150
207	(+)-6''-hydroxy-4',4'''-dimethoxyaquisinenone B	*A. sinensis*	150
208	(+)-Aquisinenone B	*A. sinensis*	150
209	(–)-6''-hydroxyaquisinenone B	*A. sinensis*	150
210	(–)-Aquisinenone B	*A. sinensis*	150
211	Aquisinenone P	*A. crassna*	151
212	Aquisinenone Q	*A. crassna*	151
213	(+)-Aquisinenone A	*A. sinensis*	150
		A. crassna	151
214	(–)-Aquisinenone A	*A. sinensis*	150
		A. crassna	151
215	(–)-4'-methoxyaquisinenone A	*A. sinensis*	150
216	(–)-Aquisinenone D	*A. sinensis*	150
		A. crassna	151
217	(–)-4'-demethoxyaquisinenone D	*A. sinensis*	150
		A. crassna	106
218	(+)-4'-demethoxyaquisinenone D	*A. sinensis*	150
		A. crassna	106
219	3'-hydroxyaquisinenone D	*A. crassna*	122
220	Aquisinenone R	*A. crassna*	151
221	(+)-Aquisinenone D	*A. crassna*	151
222	Crassin H	*A. crassna*	148
223	(–)-Aquisinenone F	*A. sinensis*	150
224	(+)-Aquisinenone E	*A. sinensis*	150
224a	Crassin I	*A. sinensis*	147
224b	Crassin J	*A. sinensis*	147
224c	Crassin K	*A. sinensis*	147

Table 17: Double linked 2-(2-phenylethyl)chromones with C–O–C and C–C bonds.

2.2.3. Sesquiterpenoid-4H-chromones (STCs) and benzylacetone-4H-chromones (BACs)

It is reported that the rare sesquiterpenoid-4H-chromone derivatives (STCs, **225–234**) are reported from the species of agarwood (Figure 20, Table 18). These STCs are composed of a PEC (unit A) and a sesquiterpene moiety (unit B) linked together by an ester bond or an ether bond (Figure 20, Table 18). The *A. crassna* agarwood collected in Laos contains STCs of **225–230**, which are composed by the coupling of a sesquiterpene moiety (unit B) at the C-8 position of the TPEC (unit A) by an ester bond [152]. The only qinanmer STC **231** is a sesquiterpenoid-4H-chromone reported from the Chinese agarwood "Lv Qi-Nan" of *A. sinensis*.[126] The Cambodian variety of A. crassna agarwood resulted the STCs of **232–234**, which are formed by the sesquiterpene moiety connected to the EPEC through an ether bond [151]. Furthermore, the benzylacetone-4*H*-chromone derivatives **235** and **236** are reported from the agarwood of *G. salicifolia* [137]. These STCs are consisting an unusual 3,4-dihydro-2*H*-pyran ring, which is formed by a C–O–C bond and a C–C bond at C-7 and C-5, respectively (Figure 20).

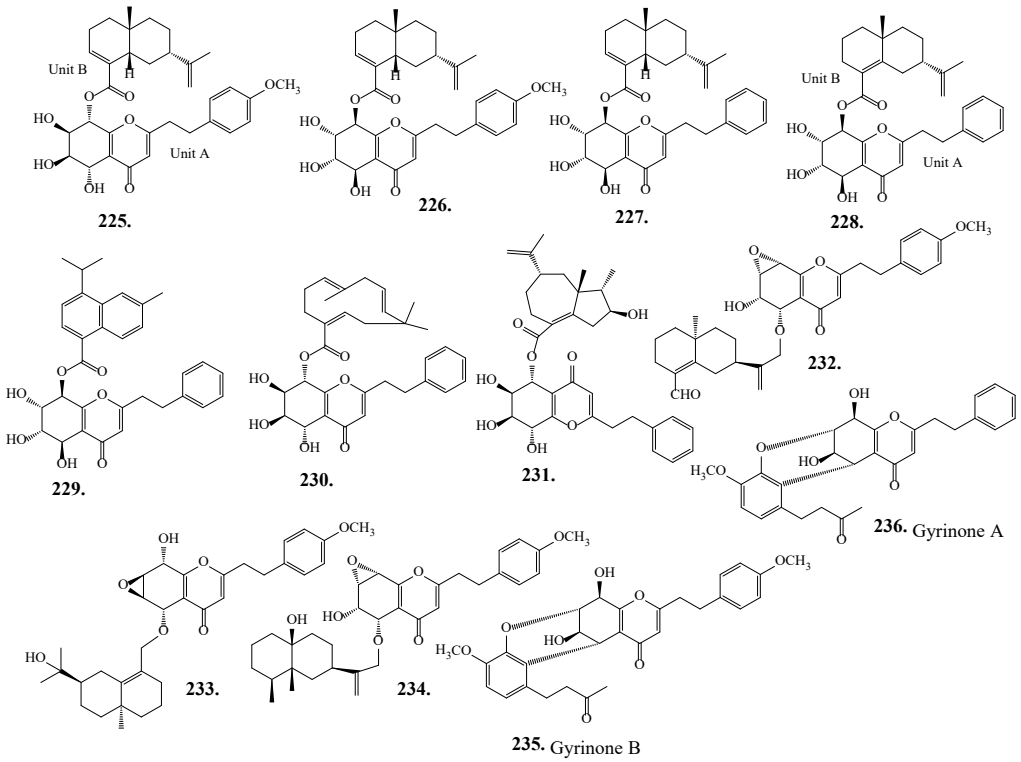

Figure 20: Sesquiterpenoid-4*H*-chromones and benzylacetone-4*H*-chromones of agarwood.

No.	Name	Source	Ref.
225	Aquilacrassnin D	*A. crassna*	152
226	Aquilacrassnin C	*A. crassna*	152
227	Aquilacrassnin B	*A. crassna*	152
228	Aquilacrassnin A	*A. crassna*	152
229	Aquilacrassnin F	*A. crassna*	152
230	Aquilacrassnin E	*A. crassna*	152
231	Qinanmer	*A. sinensis*	126
232	Xcrassin C	*A. crassna*	151
233	Xcrassin A	*A. crassna*	151
234	Xcrassin B	*A. crassna*	151

Table 18: Sesquiterpenoid-4H-chromones from agarwood

2.2.4. Trimers

The trimeric 2-(2-phenethyl)chromone compounds, AH_{19b} (237), AH_{20} (**238**), AH_{18} (**239**), and AH_{19a} (**240**) are reported from the agarwood "Jinko" from Kalimantan (Figure 21 and Table 19). The trimers 237, 239 and 240 are composed of two TPEC units (unit A and unit B) connected with a 6,7-dihydroxy-2-(2-phenethyl)chromone moiety (unit C) through a 5C–O–6C bond and a 5C–O–7C bond, respectively. The trimer **238** is composed of two TPEC units (A and B) with a 5,8-dihydroxy-2-(2-phenylethyl)chromone (unit C) through a 5C–O–8C bond and a 6C–O–5C bond, respectively (Figure 21).

No.	Name	Source	Ref.
237	AH_{19b}	*Kalimantan*	153
238	AH_{20}	*Kalimantan*	128
239	(5*S*,6*S*,7*R*,8*S*)-2-(2-phenylethyl)-6,7,8-trihydroxy-5,6,7,8-tetrahydro-5-[2-(2-phenylethyl)chromonyl-6,7-dioxy]chromone [AH_{18}]	*Kalimantan*	143
240	AH_{19a}	*Kalimantan*	153

Table 19: Tri-2-(2-phenylethyl)chromones of agarwood.

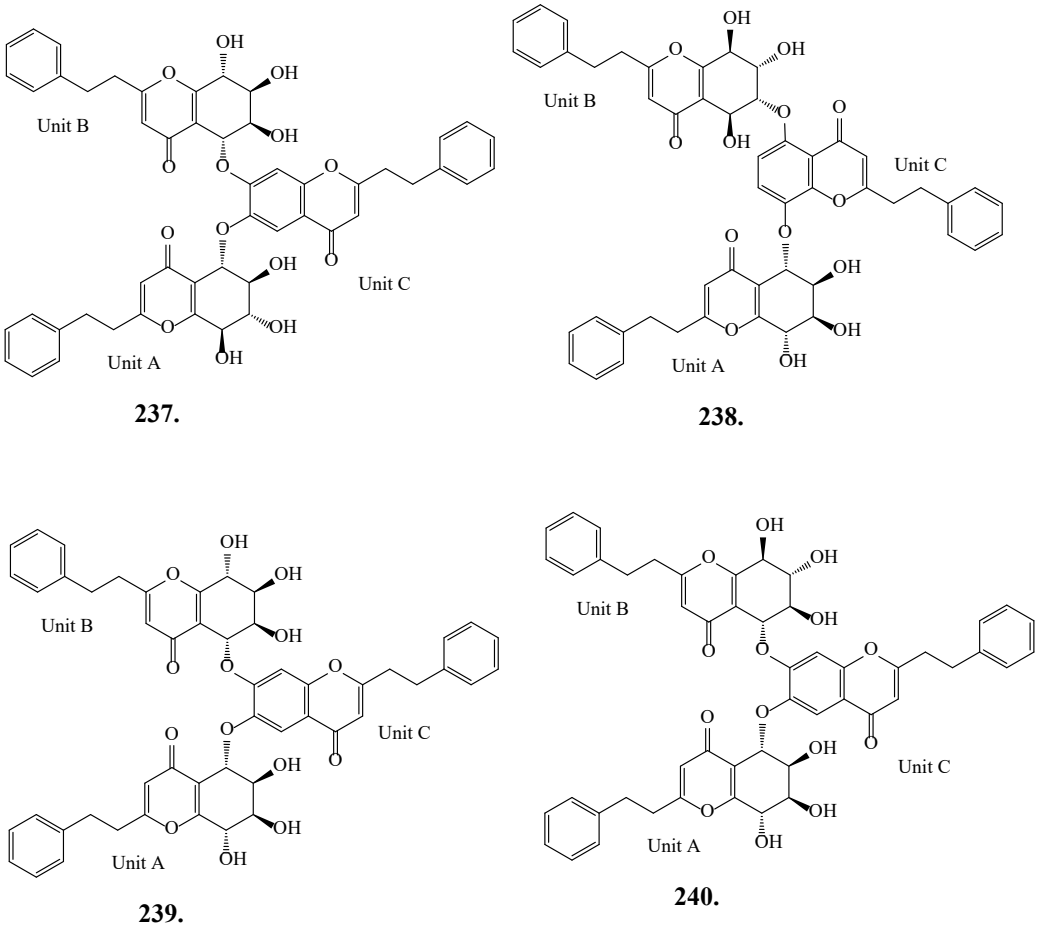

Figure 21: Chemical structures of agarwood tri-2-(2-phenylethyl)chromones.

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2.2.5. Phenolics and miscellaneous compounds

The volatile oils of agarwood contains various phenylbutanoids including, anisylacetone (**P5**), zingerone (**P6**), and benzylacetone (**P7**) (Figure 22) [29,48,154,155]. These phenylbutanoids generally are substituted with 3', or 4'-OCH_3, or 4'-OH, or withour any substitution (Figure 22). In this connection, it is interesting to note that the volatile aromatic compounds are reported from the smoke of agarwood, which might be the degradation products of chromones and lignins. Further, the phenylpropanoid such as 4'-methoxycinnamic acid (**P1**), 4'-methoxy-phenylpropionic acid (**P4**), anisic acid (**P8**), 3-hydroxy-4-methoxy phenylpropionic acid methyl ester (**P9**), and cinnamaldehyde (**P15**) are also reported from agarwood essential oils [24,48,56,65,155,156]. Additionally, the phenolic compounds including syringin (**P10**), and **P11** – **P14** are also reported from the species of agarwood (Figure 22).

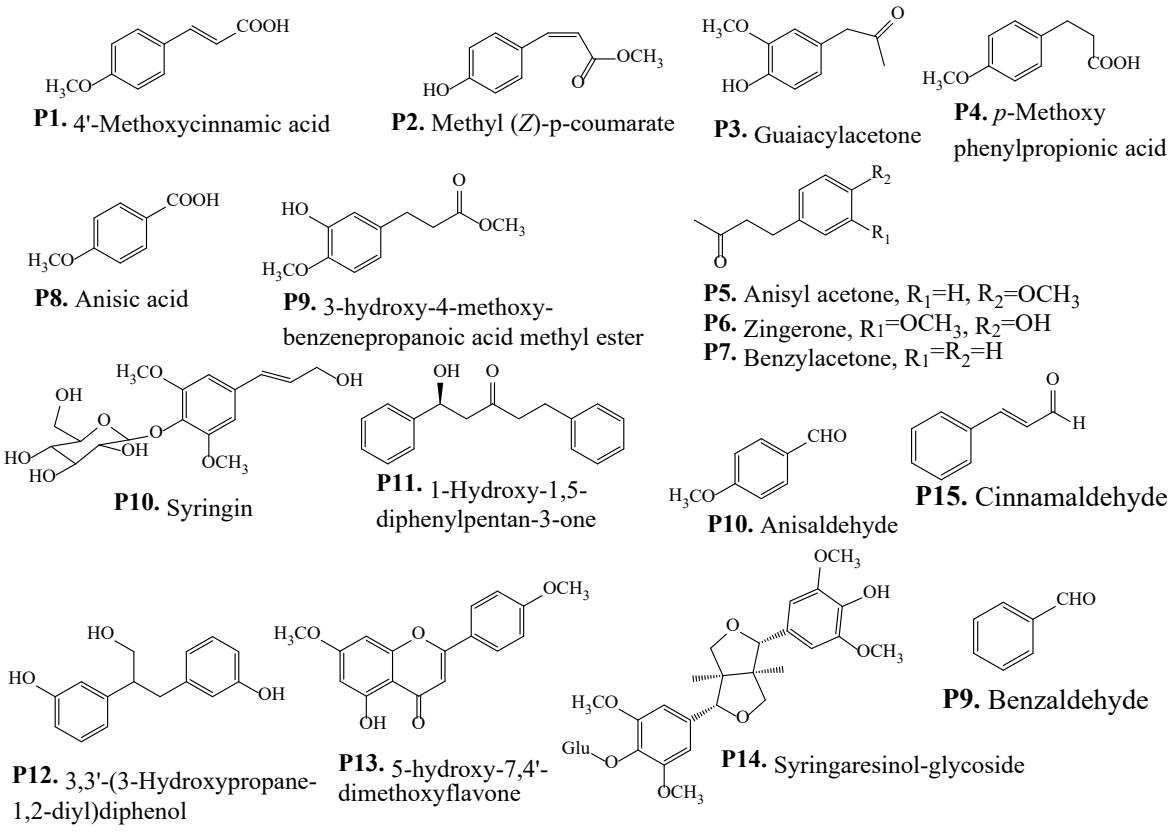

Figure 22: Phenolic compounds of agarwood.

On the other hand, the oxygen-containing triterpenoids, 3β-olean-12-ene-3,23-diol (**M1**), 3-oxo-22-hydroxyhopane (**M2**) and hederagenin (**M3**) (Fig. 23) are reported from the agarwood of *A. sinensis*[47,53,61,117,155].

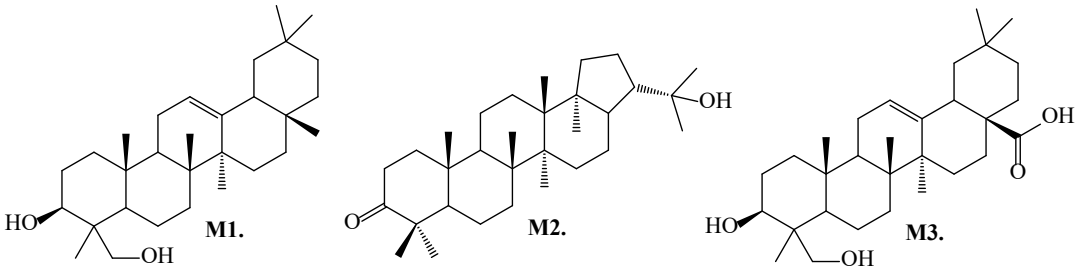

Figure 23: Chemical structures of agarwood triterpenoid compounds.

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2.3. Chemical constituents of Taiwan agarwood *Excoecaria formosana*

Excoecaria formosana (Syn: *Excoecaria crenulata* var. *formosana* Hayata), is a species of flowering plant in the family Euphorbiaceae. It is a shrub and mainly distributed in Tonkin, Indo-China, the southern part of Taiwan in thickets and forests along the seashores. The resin of *Excoecaria* is used as a substitute for agarwood incense. Chemical investigations on this plant resulted in the isolation of structurally diverse compounds. The halimane-type diterpenoids, formosins A–C (**N1–N3**), and and clerodane-type diterpenoids formosins D–F (**N4–N6**), are isolated from the 95% ethanolic extract of the twigs of *E. formosana* [157]. The whole plant of *E. formosana* led to the isolation of various metabolites; one apocarotenoid, seven benzenoids, cerebrosides, three coumarins, six coumarinolignans, three diterpenes, two flavonoids, six steroids, and eight galloyl glucosides (**N7–N50**, Figure 24, Table 20) [158].

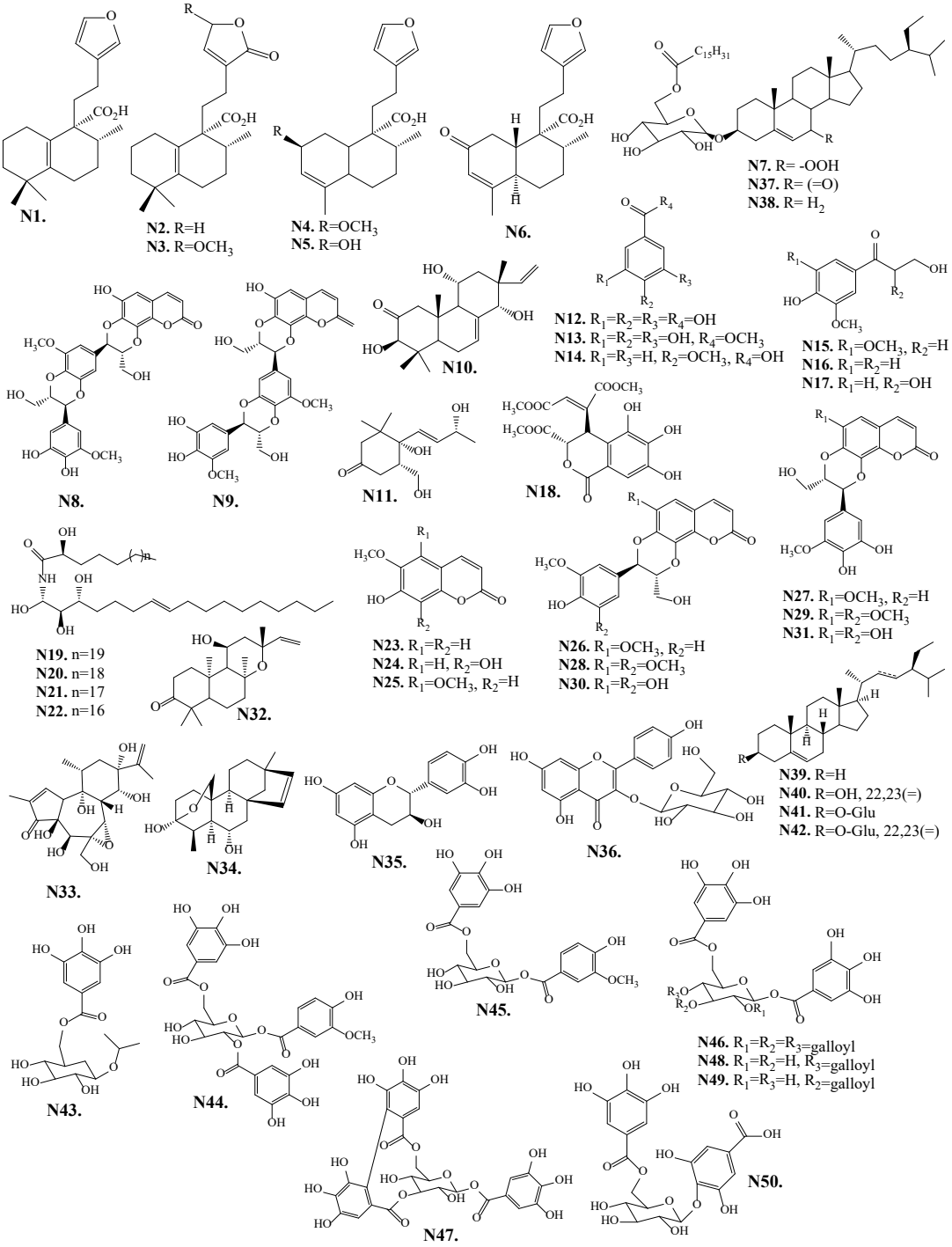

Figure 24: Chemical structures of Excoecaria formosana constituents.

No.	Name	Source	Ref.
N1	Formosin A	*E. formosana*	157
N2	Formosin B	*E. formosana*	157
N3	Formosin C	*E. formosana*	157
N4	Formosin D	*E. formosana*	157
N5	Formosin E	*E. formosana*	157
N6	Formosin F	*E. formosana*	157
N7	7*α*-hydroperoxysitosterol-3-*O*-*β*-D-(6-*O*-palmitoyl)glucopyranoside	*E. formosana*	158
N8	Excoecoumarin A	*E. formosana*	158
N9	Excoecoumarin B	*E. formosana*	158
N10	Excoeterpenol A	*E. formosana*	158
N11	Deglucosyl lauroside B	*E. formosana*	158
N12	Gallic acid	*E. formosana*	158
N13	Methyl gallate	*E. formosana*	158
N14	4-methoxybenzoic acid	*E. formosana*	158
N15	3-hydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)propan-1-one	*E. formosana*	158
N16	3-hydroxy-1-(4-hydroxy-3-ethoxyphenyl)propan-1-one	*E. formosana*	158
N17	2,3-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)propan-1-one	*E. formosana*	158
N18	(2*S*,3*R*)-4*E*-dehydrochebulic acid trimethyl ester	*E. formosana*	158
N19	Gynuramide I	*E. formosana*	158
N20	Gynuramide II	*E. formosana*	158
N21	Gynuramide III	*E. formosana*	158
N22	Gynuramide IV	*E. formosana*	158
N23	Scopoletin	*E. formosana*	158
N24	Fraxetin	*E. formosana*	158
N25	6-hydroxy-5,7-dimethoxycoumarin	*E. formosana*	158
N26	Cleomiscosins A	*E. formosana*	158
N27	Cleomiscosins B	*E. formosana*	158

N28	Cleomiscosins C	*E. formosana*	158
N29	Cleomiscosins D	*E. formosana*	158
N30	Malloapelin A	*E. formosana*	158
N31	Malloapelin B	*E. formosana*	158
N32	*ent*-11*α*-hydroxy-3-oxo-13-*epi*-manoyloxide	*E. formosana*	158
N33	Excoecafolin D	*E. formosana*	158
N34	Agallochin I	*E. formosana*	158
N35	(+)-catechin	*E. formosana*	158
N36	Kaempferol-3-*O*-*β*-D-glucoside	*E. formosana*	158
N37	6'-(stigmast-5-en-7-one-3-*O*-*β*-glucopyransidyl)hexadecanoate	*E. formosana*	158
N38	(6'-*O*-palmitoyl) sitosterol-3-*O*-*β*-D-glucoside	*E. formosana*	158
N39	*β*-sitosterol	*E. formosana*	158
N40	Stigmasterol	*E. formosana*	158
N41	3-*O*-*β*-D-glucopyranosyl β-sitosterol	*E. formosana*	158
N42	3-*O*-*β*-D-glucopyranosyl stigmasterol	*E. formosana*	158
N43	Isopropyl *O*-*β*-(6'-*O*-galloyl)glucopyranoside	*E. formosana*	158
N44	4-hydroxy-3-methoxyphenol 1-*O*-*β*-D-(2',6'-di-*O*-galloyl)glucoside	*E. formosana*	158
N45	3-methoxy-4-hydroxyphenyl 1-*O*-*β*-D-(6'-*O*-galloyl)glucopyranoside	*E. formosana*	158
N46	1,2,3,4,6-penta-*O*-galloyl-*β*-D-glucose	*E. formosana*	158
N47	Corilagin	*E. formosana*	158
N48	1,4,6-tri-*O*-galloyl-*β*-D-glucose	*E. formosana*	158
N49	1,3,6-tri-*O*-galloyl-*β*-D-glucose	*E. formosana*	158
N50	Gallic acid 4-*O*-*β*-D-(6'-O-galloyl)-glucose	*E. formosana*	158

Table 20: Chemical constituents of *Excoecaria formosana*.

3. PHARMACOLOGICAL ACTIVITIES OF AGARWOOD

The agarwood-isolated compounds/extracts showed various pharmacological activities including, anti-inflammatory, anti-allergic, anti-diabetic, anti-cancer, anti-oxidant, anti-ischemic, anti-microbial, and effects on the central nervous system [3,6,12,25]. The details are described below.

3.1. Anti-inflammatory activity of agarwood compounds/extracts

Inflammation is a vital biological phenomenon that occurs in response to internal and external injurious stimuli to mitigate foreign triggers, initiate damaged tissue repair and restore the normal body homeostasis [159]. Although the healthy body requires limited inflammation, however, excessive inflammation can cause chronic and degenerative diseases such as diabetes, atherosclerosis, rheumatoid arthritis, cancer and cardiovascular diseases [159]. Nitric oxide (NO) is a pro-inflammatory mediator that plays a vital role in the process of inflammation [160]. Further, nuclear factor (NF)-κB and tumor necrosis factor (TNF)-α are the key cytokines involved in promoting and triggering the inflammatory process [160].

Therefore, inhibitors of NO, TNF-α, and NF-κB release may be considered as therapeutic targets for various inflammatory related ailments [160]. Agarwood compounds/extracts are examined for their anti-inflammatory activity through inhibition of NO, TNF-α, and NF-κB release in activated macrophages and neutrophils. Agarwood essential oil has an anti-inflammatory function, significantly reducing the skin thickness, ear weight, oxidative stress, and pro-inflammatory cytokines production in the 12-O-tetradecanoylphorobol-13 acetate (TPA)-induced mouse ear inflammation model [161]. The results of NO inhibitory production are summarized in Table 21.

The sesquiterpenoids, **E17, E26** and **E28** (Figure 7), are reported as inhibitors of NF-kB activation in the activated RAW264.7/Luc-P1 cell line, however, these compounds had not affect the NO release in LPS activated RAW264.7 macrophages (Table 21). Further, the sesquiterpenoids **D4** (Figure 6), and **E28** (Figure 7), at a concentration of 50 μM, suppress the superoxide anion generation in fMLP-activated human neutrophils [53]. On the other hand, among the reported PECs, the compounds **11**, **16** and **48** (Figure 14), inhibited the LPS-induced NO production in RAW264.7 macrophages and NF-kB activation in the RAW264.7/Luc-P1 cell line [62]. The authors reported that the presence of a 6-methoxy moiety increased the activity, while the C4' hydroxylation decreased. The PECs **9, 37, 47** and **75** reduced the release of TNF-α in LPS-activated RAW264.7 cells.93 Further, the PECs **6, 26, 52, 60, 66** (Figure 14), and **146** (Figure 16), suppressed the superoxide anion generation in fMLP-activated human neutrophils [53]. The structure–activity relationship (SAR) analysis indicated that the C2'-hydroxy and C4'-methoxy enhanced the activity. Furthermore, the chlorinated PEC **127** (Figure 15), reduced the expression of various inflammatory mediators, such as iNOS, COX2 TNF-α, IL-6, IL-1β, and PGE2 in LPS-activated RAW264.7 macrophage. A mechanistic study revealed that compound **127** selectively suppressed phosphorylation of STAT1/3 and ERK1/2 and activation of NF-kB/MAPK/STAT pathways [162]. A recent study reported that the alcohol extracts of agarwood alleviates the occurrence and development of gastric ulcers via inhibiting oxidation and inflammation [163].

No.[a]	NO inhibition (IC_{50}, μM)	Ref.	No.[a]	NO inhibition (IC_{50}, μM)	Ref.	No.[a]	NO inhibition (IC_{50}, μM)	Ref.
D5	7.2	31	**99**	5.12	107	**192**	1.6	139
D8	7.1	31	**107**	4.5	91	**193**	5.8	139
D12	3.2	30	**111**	7.71	107	**194**	8.1	139
D18	12.8	31	**112**	3.8	91	**195**	0.6	139
D24	14.2	30	**114**	13.09	107	**196**	0.7	139
D43	2.5	30	**117**	22.6	107	**203**	8.0	150
E7	53.8	31	**123**	22.26	107	**204**	11.4	150
E9	9.3	31	**124**	9.01	107	**207**	10.5	150
E25	12.5	30	**126**	7.3	91	**208**	8.8	150
E37	17.3	30	**128**	4.5	91	**210**	8.6	150
F33	8.1	32	**138**	1.6	91	**213**	11.5143	150
14	6.4	91	**140**	84	113	**214**	7.6	150
28	5.95	107	**159**	7.6	139	**215**	9.3	150
45	7.59	107	**160**	7.4	139	**216**	7.0	150
51	4.6	113	**161**	2.3	139	**217**	8.5	150
73	7.94	107	**174**	37.1	139	**218**	8.5	150
82	6.59	107	**188**	4.3	139	**223**	12.0	150
85	7.94	107	**191**	1.8	139	**D56**	5.46	26

D57	14.07	26	**D59**	45.49	26	**B13**	52.25	26
B14	62.57	26	**F43**	66.0	69	**F44**	76.8	69
F45	62.7	69	**F46**	18.8	69	**F47**	72.8	69
G6	89.5	69	**G7**	68.5	69	**G8**	74.8	69
G9	84.3	69	**135a**	3.46	121	**135b**	12.52	121
135c	> 40	121	**162a**	35.45	121			

[a]Compound number

Table 21: Inhibitory effect of agarwood compounds on LPS-induced nitric oxide (NO).

3.2. Cytotoxic potential of agarwood compounds/extracts

Agarwood compounds are tested to examine their cytotoxicity in various cancer cell lines such as A549 (human lung), human hepatoma carcinoma cell lines, BEL-7402 and SMMC-7721, Hela (human cervical), K562 (human myeloid leukemia), KB (epidermoid carcinoma), KB-VIN [vincristine (VIN)-resistant KB], MGC-803 (human gastric cancer), OV-90 (human ovarian), breast cancer cell lines, MCF-7 and MDA-MB-231, and SGC-7901 (human gastric). The tested compounds showed weak or moderate cytotoxicity (Table 22).

No.[a]	IC_{50} (cell line)	Ref.
E11	17.85 μg/mL (K562), 21.82 μg/mL (BEL-7402)	60
F32	33.8 μM (K562)	68
F36	45.1 μM (K562)	68
F38	48.6 μM (K562)	68
6	26.2 μM (A549), 19.2 μM (KB-VIN)	84
17	47.0 μM (K562), 37.95 μg/mL (SMMC-7721), 35.25 μg/mL (MGC-803), 26.98 μg/mL (OV-90), 33.8 μM (A549), 36.6 μM (KB-VIN), 29.0 μM (MCF-7)	54,84,81
19	18.1 μM (K562), 20.1 μM (BEL-7402)	54
33	31.59 μg/mL (SMMC-7721), 33.12 μg/mL (MGC-803), 30.77 μg/mL (OV-90)	81
41	13.20 μM (K562), 25.91 μM (BEL-7402), 23.51 μM (SGC-7901), 22.00 μM (A549), 30.55 μM (HeLa)	116
46	45.38 μM (K562), 35.42 μM (SGC-7901), 33.31 μM (A549)	116
48	22.21 μM (SGC-7901), 8.36 μM (K562), 5.76 μM (BEL-7402)	54, 114
55	30.01 μg/mL (SMMC-7721), 35.25 μg/mL (MGC-803), 26.98 μg/mL (OV-90)	81
56	61.31 μM (K562), 28.53 μM (BEL-7402), 17.63 μM (SGC-7901), 49.42 μM (HeLa)	102
57	37.64 μM (SGC-7901), 27.08 μg/mL (SMMC-7721), 31.17 μg/mL (MGC-803), 33.51 μg/mL (OV-90)	81, 114
58	21.40 μg/mL (SMMC-7721), 36.42 μg/mL (MGC-803), 35.38 μg/mL (OV-90)	81
60	43.65 μg/mL, 14. 96 μM (K562)	106, 102
61	17.8 μM (SGC-7901), 13.9 μM (K562), 31.9 μM (BEL-7402), 25.8 μM (A549), 26.1 μM (KB), 21.9 μM (KB-VIN), 38.1 μM (MDA-MB-231), 28.7 μM (MCF-7)	54, 84
62	18.82 μg/mL (SMMC-7721), 25.35 μg/mL (MGC-803), 31.60 μg/mL (OV-90)	81
65	20.01 μg/mL (SMMC-7721), 31.34 μg/mL (MGC-803), 36.64 μg/mL (OV-90)	81

78	24.85 μg/mL (SMMC-7721), 28.60 μg/mL (MGC-803), 30.40 μg/mL (OV-90)	81
81	31.06 μg/mL (SMMC-7721), 28.24 μg/mL (MGC-803), 22.54 μg/mL (OV-90)	81
84	11.83 μM (K562), 25.02 μM (BEL-7402), 29.29 μM (SGC-7901), 44.11 μM (HeLa)	102
110	35.11 μM (BEL-7402), 32.95 μM (SGC-7901)	116
134	14.6 mg/mL (SGC-7901)	134
136	46.1 μM (SGC-7901), 43.8 μM (A549)	108
152	2.87 μM (K562), 4.75 μM (BEL-7402), 9.91 μM (SGC-7901), 22.43 μM (A549), 13.86 μM (HeLa)	116
153	40.81 μM (K562), 44.18 μM (BEL-7402)	109
175	73.5 μM (K562)	141
182	70.9 μM (K562)	141
199	44.68 μM (BEL-7402)	148
200	42.10 μM (BEL-7402)	148
213	34.20 μM (SGC-7901), 37.99 μM (K562), 36.26 μM (HeLa)	151
214	11.59 μM (SGC-7901), 22.97 (A549), 10.93 μM (K562), 12.88 μM (HeLa)	151
227	25.7 μM (BEL-7402), 30.6 μM (HeLa)	152
228	33.9 μM (K562), 29.9 μM (BEL-7402), 26.7 μM (HeLa), 46.3 μM (A549)	152
230	24.8 μM (BEL-7402), 30.9 μM (SGC-7901), 17.6 μM (HeLa), 32.0 μM (A549)	152
232	31.50 μM (SGC-7901), 49.0 μM (A549), 22.12 μM (K562), 30.75 μM (HeLa)	151
234	39.95 μM (SGC-7901), 28.67 μM (K562), 29.34 μM (HeLa)	151

[a]Compound number

Table 22: Cytotoxicity potential of agarwood compounds in various cancer cell lines.

3.3. Neuronal activity of agarwood compounds/extracts

It is known that agarwood traditionally used as a sedative and analgesic agent [3]. The pharmacological studies reported that agarwood extracts as well as pure compounds showed neuroprotective activity [3,6,12]. For example, the benzene extract of *A. malaccensis* agarwood reduced spontaneous motility, prolonged hexobarbiturate-induced sleeping time, and decreased rectal temperature, while the petroleum ether, chloroform, or water extracts did showed the similar effect [164]. A bio-guided isolation of a benzene extract yielded the jinkoh-eremol (**E3**, Figure 7) and agarospirol (**B1**, Figure 4) are the main active constituents [165,166]. The agarwood essential oil sedated mice through vapor inhalation, and identified the main volatile compounds are benzylacetone, α-gurjunene, and (+)-calarene [167]. The 70% EtOH extract of Vietnamese agarwood induced the expression of brain-derived neurotrophic factor (BDNF) mRNA in rat cultured neuronal cells, and identified the sesquiterpene **B5** (Figure 4), is responsible active compound to the observed biological potential [36]. The PEC compound **73** (Figure 14), showed neuroprotective activity in P12 pheochromocytoma, and human U251 glioma cells against glutamate-, and corticosterone-induced neurotoxicity [115]. The alcohol extract of agarwood produced by whole-tree agarwood-inducing technique, and the volatile oil combined with pentobarbital sodium showed hypnotic effect. These tested agents prolonged the sleeping time, and increased the rate of falling asleep in mice [168]. In addition, it is also found that the agarwood essential oil showed sedative-hypnotic effects through the GABAergic system [169]. Agarwood essential oil ameliorates restrain stress-induced anxiety and depression by inhibiting HPA axis hyperactivity [170]. The diterpenoids of agarwood showed antidepressant activity through the synaptic reuptake of serotonin and norepinephrine [171]. A recent study reported that the low molecular weight aromatic compounds (LACs) obtained from the headspace-solid phase

microextraction (HS-SPME) of *Kyara* grade (highest-grade agarwood in Japan), showed strongest sedative activity in mice [172]. Agarwood smoke from Kynam agarwood, showed anti-anxious and anti-depressant effects associated with the increase of serotonin levels in mice [173]. Furthermore, agarwood compounds are reported as as promising therapeutic agents to combat Alzheimer's disease through inhibition of acetylcholinesterase (AChE) activity (Table 23). The AChE inhibitory potential of agarwood compounds are presented in Table 23.

No.[a]	Inhibition rate(%)	Ref.	No.[a]	Inhibition rate (%)	Ref.	No.[a]	Inhibition rate (%)	Ref.
D22	21.2	57	**2**	24.1	80	**81**	19.6	114
E15	33.3	41	**3**	14.3	80	**82**	21.6	41
E16	274.8 μM (IC_{50})	58	**6**	19.3	88	**83**	41.47	120
E18	32.7	57	**8**	15.8	89	**84**	33.6	88
E26	491.4 μM (IC_{50})	58	**9**	17.4	89	**87**	41.27	120
E28	158.3 μM (IC_{50})	58	**14**	38.0	111	**88**	32.11	120
E29	42.9	40	**20**	11.4	41	**100**	17.5	127
E33	15.2	57	**21**	20.3	83	**105**	10.61	37
F17	19.5	71	**27**	16.3	80	**125**	19.1	127
F19	19.4	71	**28**	23.5	88	**135**	21.10	37
F21	19.1	67	**32**	10.0	80	**139**	31.5	88
F22	63.1	59	**35**	17.0	80	**142**	15.8	118
F23	15.0	67	**33**	14.9	80	**143**	35.9	118
F26	24.1	67	**37**	26.9	80	**146**	47.9	127
F30	31.0	71	**38**	25.4	83	**148**	155.6μM (IC_{50})	135
F35	54.2	41	**39**	24.0	41	**149**	441.6μM (IC_{50})	135
F40	35.3	41	**40**	10.8	100	**151**	47.4	127
F41	46.2	41	**42**	10.1	88	**163**	16.82	142
B6	16.35	37	**44**	12.2	114	**167**	44.01	145
C1	49.9	39	**47**	15.0	80	**171**	10.85	145
A1	44.5	71	**60**	22.0	106	**172**	24.57	145
A2	20.8	71	**62**	35.0	109	**173**	16.80	142
1	18.6	80	**65**	10.0	83	**185**	15.66	142
E41	48.33	50						

[a]Compound number

Table 23: Acetylcholinesterase inhibitory activity of agarwood compounds (at 50 μg/mL).

3.4. Anti-diabetic activity of agarwood compounds/ extracts

Diabetes mellitus (DM), known as diabetes is a serious, chronic, and complex metabolic disorder [174]. The DM complications affect people both in the developing and developed countries. There are several classes of therapeutic antidiabetic drugs such as sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinediones, and non-sulfonylureas secretagogues [174]. The agarwood compounds are reported as α-glucosidase inhibitors. For example, A. filaria sesquiterpenoid, guaianolide (**F37**) reported as an inhibitor of α-glucosidase with an IC_{50} value of 253.2 μM [68]. Further, the prezizaane sesquiterpenoids, **H1**, **H4**, and **H11** (Figure 10), and zizaane sesquiterpenoids, **I1** and **I3** (Figure 11), are reported to possess the inhibitory effect against α-glucosidase [76]. On the other hand, the PECs compounds **11** and **12** (Figure 14), shown to promote the secretion of adiponectin as PPARγ agonists

during adipogenesis in human bone marrow mesenchymal stem cells [82]. The *A. sinensis* PEC compounds **47, 48** and **65** (Figure 14), reported as inhibitors of α-glucosidase with IC_{50} values of 90, 50 and 150 μM, respectively [114].

3.5. Antibacterial activities of agarwood compounds/ extracts

The sesquiterpenoids and 2-(2-phenylethyl) chromones (PECs) of *A. crassna* and *A. sinensis* are examined for their antibacterial activity against *Staphylococcus* aureus and *Ralstonia solanacearum* using disk agar diffusion method (Table 24). The PECs of *A. sinensis* agarwood showed antibacterial activity against *S. aureus*, and methicillin-resistant *S. aureus* (MRSA) (Table 24) [99]. The sesquiterpene β-caryophyllene (G5, Figure 9), showed superior antibacterial activity against Gram-positive human pathogenic bacteria than that of Gram-negative bacteria [73]. The extracts of *A. crassna* agarwood, aqueous, SFE, and SFE with ethanol as the co-solvent, are showed antimicrobial activities against *S. aureus* and *Candida albicans*, but are not against *Escherichia coli* [175].

No.[a]	*S. aureus*	*R. solanacearum*	Ref.
D4	20.02	11.02	52
D5	9.12	8.98	52
D8	12.90	18.20	52
D9	14.20	10.15	52
D10	8.10	Not active	52
D31	12.35	16.90	40
6	Not active	6.80	89
54	9.10	Not active	88
56	10.01	Not active	88
145	14.95	12.09	88
146	12.75	15.40	88
P4	11.20	7.81	155

[a]Compound number

Table 24: Antibacterial activity (Inhibition zone in mm) of agarwood compounds

3.6. Effect of agarwood compounds/extracts on cardiovascular System

It is reported that 50% ethanolic extract of Bawei Chenxiang powder enhanced the hypoxia tolerance of cardiomyocytes [176]. The Tibetan Bawei Chenxiang powder showed a protective effect on the ratmodel of myocardial ischemia [177]. The agarwood alcohol extract ameliorates isoproterenol-induced myocardial ischemia by inhibiting oxidation and apoptosis [178]. The agarwood of *A. crassna* showed noticeable cardioprotective activities. For example, *A. crassna* extract reduced simulated ischemia induced cell death in cardiac myoblast cell line, H9c2 [179], as well as isolated adult rat ventricular myocytes [180]. Additionally, the ethyl acetate extract of *A. crassna* protect the heart from myocardial ischemia/reperfusion injury through attenuation of p38 MAPK phosphorylation [181]. Further, it is also reported the cytoprotective effect of *A. crassna* extract on actin cytoskeleton organization, in cardiac cell subjected to simulated ischemia [182]. Phosphodiesterases (PDEs) are enzymes that regulate cellular signaling by hydrolysis of intracellular second messengers, cyclic adenosine monophosphate (cAMP), and cyclic guanosine monophosphate (cGMP) [183]. In cardiovascular tissues, PDE 3A is one of the dominant cAMP-hydrolyzing isozymes, and PDE 3 inhibitors may be used in congestive heart failure [183]. On the other hand, PDE 5 is the major GMP hydrolyzing enzyme in human corpus carvernosal tissue, and PDE 5 inhibitors such as sildenafil have been used to treat erectile dysfunction [183]. A recent study reported

that the new FPEC (**85a**, Fig. 14) and DIPECs **198a–198d** (Figure 18), have considerable activity against PDE (Table 25).[79] Additionally, the PECs compounds **19, 20, 47, 48, 56, 60** and **81** (Figure 14), are also reported to have PDE 3A inhibitory activity [104].

No.[a]	PDE	IC_{50}	Ref.
19	PDE 3A	89.3 μM	79
	PDE 5A1	19.4 μM	79
48	PDE 3A	4.83 μM	104
85a	PDE 3A	44.2 μM	79
	PDE 5A1	20.7 μM	79
198a	PDE 3A	> 100 μM	79
	PDE 5A1	4.2 μM	79
198b	PDE 3A	> 100 μM	79
	PDE 5A1	7.9 μM	79
198c	PDE 3A	42.6 μM	79
	PDE 5A1	15.1 μM	79
198d	PDE 3A	> 100 μM	79
	PDE 5A1	4.3 μM	79

[a]Compound number

Table 25: Effect of agarwood compounds against PDE activity.

3.7. Other activities

The sesquiterpenoid **D8** (Figure 6) reported as inhibitor of innate and adaptive immunity through suppressing the STAT signaling pathway [184]. The PECs **18, 65, 75** (Figure 14), and **158** (Fig. 17), showed $ABTS^{+}$ radical scavenging activity, with IC_{50} values of 34.7, 16.5, 12.1 and 12.3 μM, respectively [92]. The *A. sinensis* PEC compound **136** (Figure 16), suppressed the survival, activation, proliferation, and differentiation of B cells through reduced B-cell activating factor from the tumor necrosis factor family (BAFF) signaling [185]. The PEC compounds **16, 44** and **82** (Fig. 14), showed the tyrosinase inhibitory activity [75,103]. The ethanolic extract of agarwood produced by the whole-tree agarwood-inducing technique, improved the intestinal peristalsis, enhanced gastric emptying, and inhibited gastric ulcer [175]. Additionally, agarwood ethanol extract showed protective effect of intestinal injury induced by fluorouracil (5-FU) through reduced inflammation and, enhanced antioxidant enzymes and Nrf2 signalling [186]. The alcoholic extract of Agar-Wit agarwood alleviate the inflammation and asthma in the asthma mouse model induced by intraperitoneal injection of ovalbumin+$Al(OH)_3$ [187]. The agar wood decotions/infusions traditionally used for alleviating abdominal discomfort, however the gastrointestinal effect on a specific disease is not completely explored yet.

3.8. Biological activities of *Excoecaria formosana* compounds

Formosins F (**N6**, Figure 24) showed moderate anti-microbial activity against two strains of *Helicobacter pylori* (Hp-SS1 and ATCC 43504) with MIC values of 50 and 50 μg/mL, respectively [157]. Compounds **N44**, and **N46**–**N48** (Figure 24), at a 100 μM concentration showed a 2.97-, 3.17-, 2.73-, 2.63-, 6.57, and 2.62-fold increase in glycine N-methyltransferase (GNMT)-promoter activity, respectively [158].

3.9. Clinical Application of agarwood

The clinical studies indicating that agarwood has therapeutic effect in various diseases, including cardio-cerebrovascular system, urinary system, and respiratory system. The agarwood

product Bawei Chenxiang powder (agarwood, nutmeg, jujube, travertine, frankincense, radix aucklandiae, chebula, kapok), showed therapeutic effect in patients with bronchial asthma [188]. Additionally, the Bawei Chenxiang powder showed superior protective effect in the patients with angina pectoris (a coronary heart disease), after continuous administration for four weeks, as compared with the conventional medicine treated patients [189]. In an another study 30 constipation patients are treated with Chenxiang Tongbian powder. The results showed that the total effective rate of Chenxiang Tongbian powder is higher (13.33%) than that of patients treated with polyethylene glycol electrolyte orally, and the symptoms of the patients were significantly relieved after two weeks of treatment [190].

4. EXTRACTION AND ANALYSES OF AGARWOOD

4.1. Extraction of agarwood

In general, the agarwood extraction method depends on the purpose of the extract [191]. The agarwood essential oils are obtained through hydrodistillation, or steam distillation [191]. The chemical constituents of agarwood usually obtained from the solvent extraction, such as acetone, methanol, ethanol and water or supercritical fluid extraction [191]. Various extraction process such as maceration, soxhlet, supercritical fluid, ultrasonic-assisted, microwave-assisted, and high-pressure processing extractions are used to get the desired extract/compounds [191]. Each solvent and/or extraction process produces different extracts in terms of quantity and quality of the constituents [191]. Although water is a cheap solvent and relatively safe, however, aqueous extracts resulted the impurities that makes difficult to isolate the desired compound. Therefore, after the aqueous extraction process, the crude extract was fractionated with hydroalcohol into the desired compounds [191]. This technique is widely applied, especially in the whole process of extraction of the agarwood [191]. Methanol also suitable as an extraction solvent since aqueous methanol was more effective in extracting total sesquiterpenes, 2-(2-phenylethyl)-4H-chromen-4-one derivatives (PECs), and aromatic compounds as compared with water [191]. Alternatively, ethanol is also a suitable solvent for agarwood extraction. It is a non-toxic for human consumption, and widely used for natural products extraction [191]. Most secondary metabolities are dissolved in ethanol except protein, phlegm, pectin, starch and polysaccharide [191].

4.2. Analyses of agarwood

It is difficult to distinguish agarwood quality by observing its morphological characteristics, and the handicrafts of incense are more complicate to identify. Recently, the chemical constituents of agarwood has gained increasing attention due to the agarwood quality is correlate its resin yield and metabolites [72,192]. At present, various methods are established to control the quality of agarwood, including the coloration of chemical reagents, the content of alcohol extracts, the content of agarwood agarotetrol (**98**, Figure 15), the content of chromone, the HPLC fingerprint of alcohol extract, etc. Using these methods, it is conceivable to clarify the agarwood obtained either from wild or artificial induction methods [193,194]. The Chinese Pharmacopoeia (2020 edition) indicates that the content of the ethanol extract of agarwood resin needs to be more than 10% (w/w, dry weight), and the content of the marker compound, agarotetrol (**98**, Figure 15) needs to be more than 0.1% [10].

4.2.1. Analyses of agarwood sesquiterpenoids

Several analytical techniques are applied to analyze the agar wood chemical compounds of essential oils, such as electronic nose (Enose), gas chromatography (GC), GC/mass spectrometry (GC/MS), solid phase micro extraction (SPME), GC–flame ionization detector (GC-FID), GC-olfactometry (GC-O), and comprehensive two dimensional GC [191]. Among these, GC/MS, followed by SPME techniques are preferential, which showed promising result in analysing the chemical compounds of agarwood oil [191]. The sesquiterpenoids from the agarwood of A. agallocha and A. malaccensis are identified using the combination of GLC and GC/MS [191]. It is reported that the abundances (percentage of relative peak area measured by GC-MS) of the same compound in high quality oil is more than that of low quality agarwood oil [196]. Further, Ishihara et al., (1993), classified the quality of agarwood oil based on peak area percentage (or abundances) of α-guaiene (**F8**, Figure 8) with the peak area <0.05% classified as a high quality oil, however the wood oil which is not containing α-guaiene (**F8**) classified as low quality [65]. Moreover, lower quantity of benzaldehyde (**P9**, Figure 22) and anisaldehyde (**P10**, Figure 22) are present in high grade agarwood oil (i.e. Kanankoh), as compared with the low grade (i.e. Jinkoh), agarwood oil [65]. Additionally, the same authors also reported that the quantity of agarwood resin and content of oxygenated sesquiterpenes are comparatively higher in high grade agarwood oil [42]. Table 26 summarizes the component based characteristic of agarwood oil. It is reported that the GC-MS analysis of aromadendrene (**F42**, Figure 8), showed a

positive linier relationship with the agarwood resin yield and quality, and therefore suggests as a marker compound for agarwood grading [72]. The eremophilane-type sesquiterpene, valencene (**E39**, Figure 7) from *A. malaccensis* is reported as a marker compound in the grading of agarwood oil [64].

Component	*High Quality*	*Low Quality*	Ref.
α-guaiene (**F8**)	<0.05%	Not available	19,65
Resin content	high	low	197
Benzaldehyde (**P9**), anisaldehyde (**P10**)	Less amount	More amount	65,198
10-epi-γ-eudesmol (**D21**), β-agarofuran (**D44**), α-agarofuran (**D49**)	Presence	Not mentioned	154
β-agarofuran (**D44**)	Marker compound	Not mentioned	199

Table 26: Component based characteristic of agarwood oil.

4.2.2. Analyses of agarwood 2-(2-phenylethyl)chromens (PECs)

On the other hand, the PECs compounds are the major fragrance constituents of agarwood, which contributors to the sweet, fruity and long lasting scent of agarwood when it is burn [3,6,12]. The content of agarwood PECs are used to evaluate the grading of agarwood products [86]. Various types of agarwood specific PECs are identified as potential marker for its authentication [25]. These PEC compounds are obtained through solvent extraction methods, but are not extractable using hydrodistillation [200,201]. Structural studies revealed that most of the reported agarwood PEC compounds has the same basic skeleton (MW: 250) and similar substituents, i.e., hydroxy or methoxy or both groups [202]. The determination of PECs in agarwood using GC-MS are relatively limited, as compared with the sesquiterpene constituents. It is reported that agarwood "Kanankoh" oil as a high-grade one, while the "Jinkoh" agarwood is the low quality [42,65,197]. The "Kanankoh" oil contains 66.47 % of PECs and 2-(2-4-methoxy-phenylethyl) chromone, which is higher than the "jinkoh" (1.5%) [196]. The contents of PECs, agarotetrol (**98**, Figure 15) and isoagarotetrol (**103**, Figure 15), have positive correlation with the quality of commercial agarwood [203]. An integrated strategy using SHS-GC-MS and UPLC-Q/Tof-MS is used to discriminate the high grade wild Chi-Nan agarwood from *A. sinensis*, and ordinary agarwood. The results revealed that average contents of 2-(2-phenylethyl) chromones and sesquiterpenes in Chi-Nan agarwood is higher as compared with ordinary agarwood [204]. A recent study reported that the pharmacokinetic results of major PECs in rat plasma using UHPLC with tandem mass spectrometry after oral administration of agarwood ethanol extract [205]. It is interesting to note that HPLC is a superior analytical technique to analyze the agarwood PECs. The details are presented in Table 27.

Species	**Sample**	**Extraction method**	**Column / Temerature**	**IV[a]/DW[b]**	**Mobile phase/ runtime (min)**	**FL[c] (ml/min) / Compounds**	**Ref.**
Agarwood spp.	AW	EtOAc fract. of 95%EtOH	Gemini RP-C18 (250 × 10, 5 µm)	5/254	CH_3OH–H_2O (70:30) / 25	PECs	162
Agarwood spp.	AW	alcohol	Diamonsil C18 (250 × 4.6, 5 µm)/ 32°C	10 /252	0.7 /	PECs	206
Agarwood spp	Wild, cultivar		Phenomenex Luna C18 150×4.6,5mm/31°C	10 / 252	CH_3CN - 0.1% HCOOH / 60	0.7/ PECs	207
Agarwood spp	AW	95%ethanol	Diamonsil C18 (4.6 ×250, 5 µm) / 30°C	5 / 252	CH_3CN, 0.1% HCOOH	0.7 /	208

A. crassna	Trunk	Et_2O	Dionex-Acclaim 120 C18 (250× 4.6, 5 µm)/ 26°C	20 /254	CH_3CN, CH_3OOH (99.5:0.5)/ 95	0.4 / PECs	209
A. sinensis	AW	Ultrasonic ext. with Et_2O	Dionex-Acclaim 120 C18(250 ×4.6,5 µm)/ 26°C	20 / 254	CH_3CN, HCOOH (99.5:0.5, / 95	0.4 mL/min/ PECs	210
A. sinensis	AW	MeOH ext	HPLC, QAMS, and UPLC-MS			PECs	211
Agarwood spp	HPLC- L-7100 pump, L-7300 column oven (Hitachi, Ltd.). 5C18MS-II (Cosmosil) column, 4.6 mm × 250 mm; solvent, MeOH–water; FW-1 ml/min, IV-olume, 10 µl; DW-254 nm.					Agarotetrol	212

AW- agarwood; [a]IV- Injection volume (in µL); [b]DW- Detection wavelength (nm); [c]FL- flow rate; PECs- 2-(2-phenylethyl)chromones

Table 27: HPLC analyses of agarwood samples.

4.2.3. Identification of agarwood adulteration

Due to its high demand and high price, agarwood commercial products are tainted with adulteration and substitution products in order to meet the market demand. Agarwood adulteration happened in different forms, such as painting and covering with oil or making the wood heavier, etc. In general, the impregnation of agarwood with abietic acid or wax to create a resemblance to high-grade agarwood [213]. Powder is the most susceptible agarwood item for adulteration, where it is mixed with healthy (uninfected), wood. Two types of fake agarwood have been described; (i) low quality agarwood painted with small layer of shavings mixed with wax and other material; and (ii) "Black Magic Wood" which refers to low quality agarwood impregnated with agarwood oil and alcohol [214]. Iron shavings and carbon powder from spent batteries are also used to increase the weight and create resemblance to high grade agarwood [51]. In Taiwan market, inferior quality of agarwood has been increasingly mis-classified and substituted as the top-grade agarwood. On the other hand, agarwood oil is adulterated either with 'lodh' oil, kerosene, other coloured oils, a mixture of other chemicals that gives the aroma of agarwood [51]. In this connection, various synthetic agarwood compounds are developed [118,212]. However, these are used to produce poor-quality fragrances as no synthetic substitutes are available for high-grade fragrances due to the complexity of natural agarwood composition [51].

Various PECs are specific in agarwood. The DART-TOFMS characteristic fragmentation behavior of PECs is applied for their accurate identification in agarwood [215]. The presence of the diagnostic TPEC ions at *m/z* 349.129 or at *m/z* 319.118, are characteristic of the PECs [215]. Interestingly, cultivated agarwood and wild agarwood samples showed differences in PECs, which helped to distinguish the wild agarwood from cultivated one [216]. The characteristic fragmentation behaviors of FPECs, and cleavage of the CH_2–CH_2 bond between the chromone moiety and phenyl moiety are used to calculate the number of methoxy or hydroxy groups, which enabled the identification of FPECs [202]. Further, the characteristic fragmentation behaviors of DPECs, EPECs and TPECs are analyzed using LC-MS without databases or reference standards [209]. A recednt study reported an integrated method of FT-NIR, GC-MS and UHPLC-Q-Exactive Orbitrap/MS, to identify the chemical variation between wild and cultivated agarwood. This novel method identified eight key marker compounds, including *flidersia* type (FPECs)-sesquiterpenes and TPECs, which are putatively distinguish between wild and cultivated agarwood [217]. Tian et al., developed an UHPLC-TOF-MS method to compare the chemical composition and the bioactivities of wild and artificial agarwood [218]. The Liquid extraction surface analysis mass spectrometry (LESA-MS) is applied in the direct qualitative analysis of agarwood from different sources [219]. During this study, a characteristic 2-(2-phenylethyl)chromone compound (*m/z* 319.1) is treated as a marker to identify agarwood and its counterfeits [219]. The headspace GC-MS is used to to distinguish the sesquiterpenes compounds between the high-quality agarwood *Kynam*, and cultivated grafting *Kynam* [220].

CONCLUSIONS / FUTURE PROSPECTS

The major compounds of agarwood apecies are sesquiterpenoids, and 2-(2-phenylethyl)chromone. These are diverse and complex, and are influenced by agarwood plant species, formation process, collection time, extraction process, and analytical approach etc. Further studies are required to understand the agarwood resin composition, and to identify

specific marker compounds of different agarwood plant species through metabolomics approach. The agarwood formation mechanism is not completely revealed; therefore, studies are required to understand the essential compounds biosynthesis mechanism of agarwood resin. Although, various pharmalogical activities are reported for the pure compounds/extracts, however, the specific active substances and pharmacological action mechanisms are not been confirmed. Therefore, systematic *in vitro* and *in vivo* studies are required for the identification of effective components of agarwood and explore their action mechanism. The active compounds can be used as a template to develop novel therapeutic agents. The relationship between the active compounds and their pharmacokinetics need to be identified to develop their clinical use. Further systematic analytical methods are required to chemically distinguish the different kinds of agarwood. Studies are required to establish an accurate and rapid identification of fake and shoddy products in commercial products.

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