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Review Article

An Updated Review of *Aquilaria* Species: Distribution, Chemical Constituents and Authentication Methods

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Abstract

The genus *Aquilaria* Lam. (Thymelaeaceae) encompasses species famous for their invaluable resinous heartwood known as agarwood. Unfortunately, the increased use of their agarwood, due to the significant demand in industries such as perfumery, incense and traditional medicine, poses a severe threat to the existence of these species in nature. This comprehensive review delves into the issues of *Aquilaria* species, with a primary focus on their geographical distribution, chemical constituents and authentication methods. The *Aquilaria* genus is native to tropical and subtropical regions of South and Southeast Asia. Alarmingly, twenty-one *Aquilaria* species have been classified on the Red List of Threatened Species, from critically endangered to vulnerable. Besides this, some species do not have enough data to classify in conservation status. In the review, first, a listing of 21 distinct *Aquilaria* species with their regional distribution and conservation status is provided. This enumeration could give further information for the evolutionary trajectory and diversification. Next are the types and derivatives of the principal chemical constituents in *Aquilaria* trees. Among these, sesquiterpenes and chromones emerged as the main aromatic compounds in *Aquilaria* species, responsible for agarwood's distinct scent and medicinal effects. Of particular interest, all reliable verification methods, including morphology-based and genome-based approaches, were given to highlight their advantages and limitations. Finally, several potential techniques have been indicated to steer *Aquilaria* species toward a sustainable equilibrium in usage and conservation.

Key words: *Aquilaria*, agarwood, identification, descriptor, phytochemicals

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INTRODUCTION

Aquilaria, a genus of about 21 species from the Thymelaeaceae family of the order Malvales that originated in Southeast Asian rainforests, is well-known for distinctively producing fragrant heartwood[1,2]. This aromatic heartwood creates as a result of injury or artificial induction[3], including lightning, chopping, burning, moth-eating and bacterial or fungal diseases[4-9] and it is a rare and desirable by-product[10-12]. Despite being rare, the heartwood's characteristic scent has a variety of applications in the creation of incense, fragrances[13,14] and conventional medicines related to ailments requiring sedative, carminative and antiemetic treatment[4,15]. *Aquilaria* trees are characterized by their remarkable heights of 20-40 m, broad crowns, smooth grey bark, evergreen leaves and small, yellowish-white flowers year-round. More interestingly, major bioactive compounds of agarwood extracts, like sesquiterpenoids and chromones, exhibited numerous bioactivities, such as gastrointestinal modulation, neuroactive, antibacterial and antifungal, cytotoxicity, acetylcholinesterase inhibition, antidiabetic and antioxidant activities. Unfortunately, due to severe over-exploitation brought on by the demand for agarwood, all *Aquilaria* species were added to the Red List of Threatened Species by the International Union for Conservation of Nature (IUCN) in 2018[16,17]. The continued exploitation imperils biodiversity and the future accessibility of this priceless resource, stressing the urgent need for quick, long-term conservation measures.

Several Asian countries have recently begun mass plantings of *Aquilaria* trees to safeguard endangered wild species and produce enough agarwood supplies to meet global demand[5,18,19]. This selection process is crucial to ensure the success and sustainability of agarwood production. Another vital step is regulated agarwood production through artificial injury[3,6,20,21], which could be induced using various chemical and biological methods[22]. This controlled approach helps alleviate pressure on wild populations while meeting the demand for agarwood. Considering the resource's high demand and price[11], confirming the validity of *Aquilaria* species and the agarwood it generates is a crucial task[23-25]. A wide range of approaches, including morphological examination[26], chemical profiling[22,27,28] and genetic identification[17,25,29,30], have been used to achieve this goal. Previous phenomic-based identification methods rely solely on classifications of the diverse morphological traits of flower, seed and fruit samples due to the high level of similarity in morphological descriptors of *Aquilaria* species[26], making it difficult to authenticate *Aquilaria* species only via field sampling of their fruits and blooms. Recently, DNA barcoding has been considered a quick and accurate approach to categorising different species based on a selection of standard DNA segments. As a result, authentication plays a crucial role in detecting and preventing illegal trafficking while supporting conservation initiatives[23,25]. Despite the significance of this coveted genus, comprehensive information on *Aquilaria* species is still lacking. Thus, systematic data collection and updated information are imperative to enhance our understanding of these valuable trees.

The current review aims to give a thorough history of the *Aquilaria* species. Firstly, the origin and global distribution of the *Aquilaria* species were summarized to get insight into the evolution and expansion of these *Aquilaria* species. We then discussed the chemical components of the *Aquilaria* species to provide their corresponding bioactivities of particular interest, all reliable authentication methods using morphological descriptors and molecular markers were provided to bring their advantages and limitations. Finally, various prospective methods have been employed to create a trajectory toward a sustainable equilibrium of usage and conservation of *Aquilaria* species, thereby ensuring their resilience for forthcoming generations while maintaining the ongoing production of agarwood.

ORIGIN AND DISTRIBUTION OF THE *AQUILARIA* SPECIES

The *Aquilaria* genus is believed to originate from the rainforest of South and Southeast Asia[1,25,31]. This genus composes of 21 accepted species and has geographic distribution throughout India, the Philippines, Malaysia, Southern China[11,29,32,33], Indonesia[2,34-37], Vietnam[19,38-41], Cambodia, Laos and Thailand[42-45]. Some species have a narrow range, while others were found in multiple countries and regions. It is noted that these species have become highly dispersed and adapted to a variety of climate scenarios and environmental conditions across these regions over thousands of years[45,46]. All *Aquilaria* species have been found in the tropical and subtropical parts of these locations[24,25], which can range from the lowland forests to the mountainous rainforest forests in an elevation of 1,000 m above sea level (asl)[46,47]. Interestingly, the genus *Aquilaria* has been demonstrated to grow in various soil types, even in sandy soils[25,42,48]. Such adaptability demonstrates their ecological diversity and adaptability to different environmental conditions.

In 2010, the IUCN added nine *Aquilaria* species to the Red List of Threatened Species[49]. However, the updated information shows that at least 21 species must be added to this list[17,45,49-51]. The most recent IUCN publication classifies the following *Aquilaria* species under various conservation status, including "Critically Endangered" (CR) for *A. crassna*, *A. khasiana, A. malaccensis* and *A. rostrata*; "Endangered" (EN) for *A. microcarpa;* "Vulnerable" (VU) for *A. banaensis*, *A. beccariana*, *A. cumingiana*, *A. decemcostata*, *A. filaria*, *A. hirta, A. rugosa*, *A. sinensis* and *A. yunnanensis* and "data deficient" (DD) for *A. apiculata*, *A. baillonii*, *A. brachyantha*, *A. citrinicarpa*, *A. parvifolia*, *A. subintegra* and *A. urdanetensis* (Table 1). Almost all *Aquilaria* species face severe threats, which raises a warning signal about the risk of biodiversity loss. Besides, some species are marked as DD, indicating that information about them is still lacking and makes their conservation challenging. Among the twenty-one *Aquilaria* species, 14 species are reported to produce agarwood, while others have no reports and mainly belong to the DD group. Fourteen *Aquilaria* species have been identified as agarwood producers, including *A. baillonii*, *A. beccariana*, *A. crassna*, *A. cumingiana*, *A. filaria*, *A. hirta*, *A. khasiana*, *A. malaccensis*, *A. microcarpa*, *A. rostrata*, *A. rugosa*, *A. sinensis*, *A. subintegra* and *A. yunnanensis*[2,5,52-54]. However, only the agarwood of *Aquilaria crassna*, *Aquilaria malaccensis*, *A. sinensis* and recently, *A. filarial* is used for trade.

The geographical distribution of 21 *Aquilaria* species was given in Fig. 1. Although, widespread, almost all species occurred at low density[1]. Particularly, two *Aquilaria* species, including *A. sinensis* (Lour.) Gilg and *A. yunnanensis* S.C. Huang are the only two species discovered in China. Among them, the wild *A. sinensis* exists in Hainan, Guangdong, Guangxi and Yunnan Provinces[29,50,55,56], while *A. yunnanensis* is located on the Yunnan Province boundary[29,50]. As the wild population of *A. sinensis* diminishes, it is being cultivated on a huge scale in Hainan, Guangdong, Guangxi, Yunnan and Fujian Provinces. Meanwhile, nine *Aquilaria* species were found in the Philippines, namely *A. apiculata* Merr., *A. brachyantha* (Merr) Hallier f., *A. citrinicarpa* (Elmer) Hallier f., *A. cumingiana* (Decne.) Ridl., *A. decemcostata* Hallier f., *A. filaria* (Oken) Merr., *A. malaccensis* Lam., *A. parvifolia* (Quisumb.) DingHou and *A. urdanetensis* (Elmer) Hallier f. According to recent report, nine *Aquilaria* species are known in Malaysia[57]. However, five species, including *A. beccariana*, *A. hirta*, *A. malaccensis*, *A. microcarpa* and *A. rostrate* are naturally distributed[26,34,57].Vietnam is home to 5 *Aquilaria* species, namely *A. baillonii*, *A. banaensis*, *A. crassna*, *A. rugosa* and *A. yunnanensis*[19,38-40].

Aquilaria crassna appears in Vietnam, Cambodia, Lao PDR and Thailand at approximately 300-900 m.a.s.l altitudes[24,31,58-60].

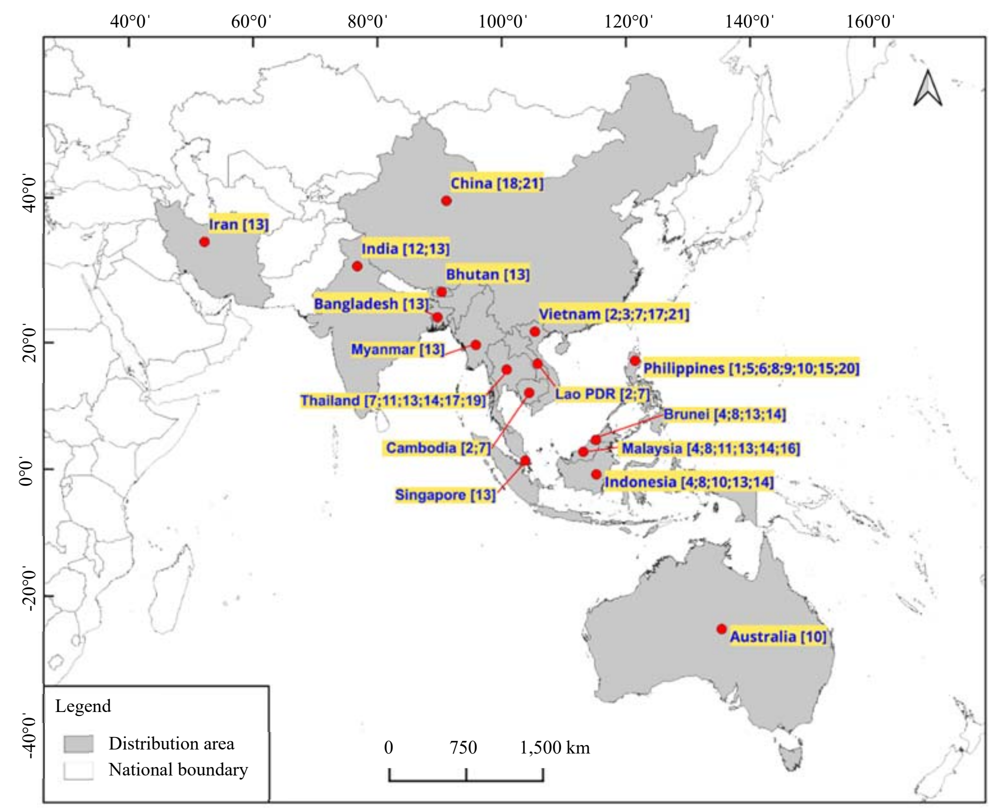

Fig. 1: Distribution map of *Aquilaria* species, numbers in parentheses indicated species names corresponding to Table 1

Table 1: Ecological distribution, agarwood report and conservation status of *Aquilaria* species

Species	Year (first reported)	Origin	Elevation (m.a.s.l)	Ecological distribution	Agarwood (reports)	Conservation status
Aquilaria apiculata Merr.	1922	Philippines	1,000-1,800	Dry and mossy forests	-	DD
Aquilaria baillonii Pierre ex Lecomte	1915	Cambodia, Lao PDR, Vietnam	200-900	Natural forest	+	DD
Aquilaria banaensis P.H.Hô	1986	Vietnam	750-1,050	Natural forest	-	VU
Aquilaria beccariana Tiegh.	1893	Brunei, Indonesia and Malaysia	850	Primary and secondary forest	+	VU
Aquilaria brachyantha (Merr.) Hallier f.	1922	Philippines	Low elevation	Dense primary forest	-	DD
Aquilaria citrinicarpa (Elmer) Hallier f.	1922	Philippines	1,300	Moist, compact soil of forested ridges	-	DD
Aquilaria crassna Pierre ex Lecomte	1914	Vietnam, Cambodia, Lao PDR and Thailand	300-900	Natural forest, planted forest, evergreen forest	+	CR
Aquilaria cumingiana (Decne.) Ridl.	1922	Borneo Island, Indonesia and Philippines	Low-medium elevation	Primary forest	+	VU
Aquilaria decemcostata Hallier f.	1922	Philippines	-	-	-	VU
Aquilaria filaria (Oken) Merr.	1950	Indonesia, Australia and Philippines	130	Lowland forests, occasionally in open swamp forest	+	VU
Aquilaria hirta Ridl.	1901	Malaysia and Thailand	300	Hill cliff areas up to the mountains	+	VU
Aquilaria khasiana Hallier f.	1922	India	1,100	Subtropical broad-leaved dense evergreen forest	+	CR
Aquilaria malaccensis Lam.	1783	Bangladesh, Bhutan, India, Iran, Indonesia, Malaysia, Myanmar, Borneo Island, Singapore, Thailand and Philippines	750	Evergreen forest	+	CR
Aquilaria microcarpa Baill.	1875	Indonesia, Malaysia and Brunei	200	Lowland forests	+	EN
Aquilaria parvifolia (Quisumb.) Ding Hou	1960	Philippines	1,000	Forested slopes	-	DD
Aquilaria rostrata Ridl.	1924	Malaysia	700-750	Subtropical/tropical lowland dipterocarp forest	+	CR
Aquilaria rugosa K. Le-Cong, Kessler	2005	Thailand, Vietnam	500	Plantation in Vietnam Natural forest in Thailand	+	VU
Aquilaria sinensis (Lour.) Spreng.	1825	China	200-700	Lowland forests, sunny places on slopes or along roadsides	+	VU
Aquilaria subintegra Ding Hou	1964	Thailand	-	Dry tropical forests	+	DD
Aquilaria urdanetensis (Elmer) Hallier f.	1922	Philippines	1700	Mossy forests, growing on exposed ridges	-	DD
Aquilaria yunnanensis S.C. Huang	1985	China, Vietnam	1,200 (China) 400-480 (Vietnam)	Natural forest	+	VU

CR: Critically endangered, DD: Data deficient, EN: Endangered, VU: Vulnerable and-: No data available

It is widely discovered in Vietnam from Central Vietnam to Phu Quoc Island in the province of Kien Giang[44,58,61,62]. *Aquilaria crassna* is only found in scattered stands along streams with low numbers of mature individuals and low natural regeneration[24,31,50,59-61]. Moreover, the population of this species has been decreasing in natural forests, which is challenged to seek trees with a diameter at breast height over 15 cm[41]. Similarly, *A. crassna* is described as rare and remains in protected natural forests in Cambodia, Lao PDR and Thailand[44,63]. Besides, *A. crassna* is also cultivated in several countries[24,31,58-60]. A large plantation size in Vietnam with more than 10,000 ha of *A. crassna* has been established in Phu Quoc Island and Khanh Hoa Province[41,58,64].

Aquilaria malaccensis is the most dominant species throughout many countries, from the Indian subcontinent, Myanmar, the Malay Peninsula and Borneo Island to the Philippines[1,31,35,65-68]. Previously, *A. agallocha* Roxb. was listed as a synonym of *A. malaccensis* Lam.[31,48,69]. Therefore, this current work combines all aspects reviewed in *A. agallocha* into *A. malaccensis*. *Aquilaria malaccensis* is found at elevation from 0 to 1,000 m.a.s.l[58]. In Indonesia, this species was evaluated to be only a few individuals per hectare[31,35,41,67]. Only a few mature trees of this species remained in India and it was almost extinct in 2003[45,70]. The exploitation of agarwood from *A. malaccensis* has declined by 80% over the last three generations in several countries[16,17]. A similar trend was observed in *A. crassna*; both species are categorised as CR[58]. Because of the quality of agarwood and its ability to survive in different habitat conditions such as rocky, sandy slopes, ridges and areas near swamps, *A. malaccensis* becomes the most popular species selected in cultivation in thirteen countries[65-67,71,72]. For example, *A. malaccensis* is cultivated by the Building Resources Across Communities (India) with 68.8 ha plantation and 84,400 saplings[13,22].

Aquilaria khasiana is a shrub or small endemic tree in the hills of Khasi, Meghalaya, in India. This plant species was first recorded by Mir *et al.*[73] and rediscovered in 2016 after 74 years of absence[58,74]. Recently, *A. khasiana* was confirmed by only nine individuals (one mature and eight saplings)[73]. Although, this species is reported to produce agarwood, information for plantation or *ex situ* collections has been mentioned yet[75]. Similarly, *A. rostrata* is a small endemic tree in Peninsular Malaysia[17,26,31]. *Aquilaria rostrata* only occurs at particular altitudes of 700-750 m.a.s.l and is threatened by the over-exploitation of agarwood. Before 2015, *A. rostrata* was extinguished based on the documentation of 100-year-old British research. It was discovered again by a group from the University of Putra Malaysia in June 2015 in Gunung Tebu in Besut, Terengganu (Malaysia), thus giving great hope for the survivability of indigenous species[26,31]. Therefore, both *A. khasiana* and *A. rostrata* are listed as CR.

Aquilaria microcarpa is a large tree in Eastern Malaysia, Brunei, Singapore and Indonesia[76,77]. The population density has been decreasing due to anthropogenic pressure for agarwood demand. There has been a decline in habitat by over 50% for the past three generations. Thus, *A. microcarpa* is assessed as an EN level. In Malaysia, it occurs at altitudes around 250 m.a.s.l, which can thrive even in acidic soil sites with 4.0 pH. In Indonesia, this species is distributed in the coastal hill forests with low natural regeneration[37,58,78]. *Aquilaria microcarpa* is successfully cultivated as plantations by farmers in Sumatra and Kalimantan in Indonesia, Borneo Region[1,31,34,76,79].

Nine species were reported as VU, including *A. banaensis*, *A. beccariana*, *A. hirta, A. rugosa, A. sinensis, A. yunnanensis, A. cumingiana, A. decemcostata* and *A. filaria.* Populations of these species are declining in habitat (30%) due to anthropogenic pressure on natural forests[58]. Some of the species are confined to some geographical regions. *Aquilaria banaensis* (synonym *A. banaensae*) was first described by Pham Hoang Ho in 1986[22,38]. It is a native species specifically localized to Ba Na mountain in Da Nang City, Vietnam, resulting in the prefix "bana" of its scientific name[38]. However, recent study noticed that *A. banaensis* was also recorded in the Sao La Nature Reserve of Thua Thien Hue Province adjacent to Ba Na mountain, in the Truong Son range[38]. This finding extends the known distribution of *A. banaensis* and emphasizes the significance of the Sao La Nature Reserve in conserving this unique species and its habitat.

Aquilaria beccariana has a broader distribution than *A. banaensis* and occurs in Eastern Malaysia, Brunei and Indonesia[22,31,37,78]. *Aquilaria beccariana* is a medium and large tree which has been found at the elevation of 850 m.a.s.l in lowland forest areas[1,22]. *Aquilaria hirta* is a small tree which appears in lowland tropical forests in Terengganu, Pahang and portions of the Eastern Coast of Johore, as well as in hill cliff areas to an altitude of 300 m.a.s.l, primarily on the West Coast of Peninsular Malaysia and in the South of Thailand[31,58]. This species is cultivated in home gardens in Malaysia and Indonesia[1]. *Aquilaria rugosa* is a tree which was first found in Kontum, Vietnam (only in plantation forests) and North of Thailand from 2005, at altitudes between 700 and 1,400 m.a.s.l[22,31,58].

Preliminary reports indicate that more than 50 million *A. sinensis* trees are suitable for producing incense[80]. This species occupies more than 5,245 ha in China, the largest plantation size of all reported species[50,80,81]. *Aquilaria yunnanensis* was first described by Huang S.C. in 1985 at around 1,200 m.a.s.l, which has been proposed to be endemic species in the Yunnan Province, China[50,82,83]. Between 2017 and 2018, van Sam *et al.*[84] confirmed this species in Quang Ninh, Vietnam. In Vietnam, *A. yunnanensis* appears in natural forests in the Nature Reserve of Dong So Ky at an altitude of 400-480 m.a.s.l[50,84]. However, the number of mature trees is only nine in Quang Ninh Province, so van Sam *et al.*[84] proposed that this species should be considered EN on the IUCN Red List[84]. *Aquilaria cumingiana* appeared in Borneo Island, Indonesia (Maluku Islands) and the Philippines, while *A. filaria* occurs in Maluku (Indonesia), New Guinea (Australia) and the Philippines. Surprisingly, the Philippines, located in Northeast Asia, is the only nation in that region to have six endemic species, including *A. brachyantha* in Cagayan, *A. decemcostata* in Luzon Island, *A. parvifolia* in Camarines. *Aquilaria apiculata* in Bukidnon and *A. citrinicarpa* and *A. urdanetensis* in Mount Urdaneta.

CHEMICAL CONSTITUENTS FROM THE *AQUILARIA* SPECIES

The primary chemical constituents originating from *Aquilaria* plants consist of sesquiterpenoids and chromones primarily sourced from agarwood[32,52,85], in addition to flavonoids, glycosides, tannins and triterpenoids derived from the leaves[22,78,86,87]. *Aquilaria* leaves have been utilized in traditional medicine for various purposes, including treating bone fractures and bruises as a supplement for addressing high blood pressure, constipation, headaches and diabetes for managing digestive ailments and providing mild sedation[12,38,58]. Furthermore, in recent years, *Aquilaria* leaves have found their way into culinary applications, such as being used in packaged tea or mixed with coffee, cookies and tea cream[12,38,58,88,89]. Agarwood is widely used and often referred to as "liquid gold". It holds significant economic value due to its rarity and high demand in traditional medicinal practices[63,81,90] and its indispensable role in religious rituals. The seductive scent of the resin has been loved and used for centuries by Buddhists, Hindus and Muslims as incense for sacred religious ceremonies[49]. As of 2021, the value of agarwood oil has been known to eclipse gold, with prices reaching tens of thousands of dollars per kilogram. Besides its market valuation, agarwood plays a crucial role in bolstering the economies of major producing nations like India, Malaysia, Thailand, Indonesia and Vietnam by giving employment opportunities and revenue streams for harvesters, processors and dealers[13,32,49]. Agarwood is a fragrant, dark, resinous wood produced by various plants belonging to two genera, namely *Aquilaria* spp. and *Gyrinops* spp.[57,91]. These trees generate resinous wood in response to external stimuli, such as physical damage[22,92], insect infestations and bacterial or fungal infections[14,66,82,93,94], as a natural mechanism to aid in their self-healing processes. Nonetheless, all agarwood-producing plants are characterized by a significantly lengthy growth period. The resinous component develops within the wood and agarwood produced in only a limited number of *Aquilaria* trees[33]. The best agarwood aroma is sweet and mellow, with plenty of penetration and persistence[2,57,70,95]. The powdery, waxy material on the surface can be scraped off and kneaded into a ball. Thus, its scent is recognized as a quality indicator[6,96]. There are different types of volatile components, each with its scent.

The phytochemicals from *Aquilaria* agarwood were well-characterized as sesquiterpenoids and chromones, which account for 35 and 57%, respectively[52,97-99]. These constituents could be categorized into two groups, like volatile compounds and nonvolatile compounds of agarwood. The distinctive and fragrant-smelling qualities of agarwood are formed by combining these essential chemicals and a few low abundance volatile aromatic metabolites[32,33,82]. Species known to contain these compounds include *A. sinensis*, *A. malaccensis* and *A. crassna,* making them the most significant agarwood species[6,33,66]. The quality of agarwood can only be defined after oil extraction by measuring several chemical constituents[6,70,96,99,100]. Thus, *Aquilaria* species are recognized for their essential oils, which are extracted from the resinous wood using hydrodistillation or steam distillation. These essential oils contain a complex mixture of volatile compounds, including sesquiterpenes, oxygenated sesquiterpenes and aromatic compounds[97,101,102]. The composition of essential oils can vary depending on the species, geographic origin and extraction technique[70,103,104].

Aquilaria species are rich sources of sesquiterpenes, responsible for agarwood's unique aroma and therapeutic properties[12,32,72,90]. The main sesquiterpenes found in *Aquilaria* species include (A) agarospiranes, (B) eudesmanes, (C) eremophilanes, (D) guaianes, (E) humulenes and (F) other sesquiterpenoids (Table 2). These compounds have been identified in six *Aquilaria* species, namely *A. sinensis, A. malaccensis, A. crassna, A. filaria, A. subintegra* and an unidentified *Aquilaria* spp.[32,52,102,105]. Among them, *A. crassna* and *A. malaccensis* are CE species, which were mentioned above. However, only some chemical compound studies concentrate on *A. crassna* compared to *A. malaccensis*[13], whereas most research has been focused on *A. sinensis* and *A. malaccensis*[32,52,102,105]*.* Sesquiterpenoids and chromones are the majority of phytochemicals from the *Aquilaria* genus, which have been widely utilized in the pharmacological field. Several pharmacological uses of these compounds, such as anti-bacterial, anti-tumour, anti-inflammation, anti-oxidation, cytotoxicity, anti-anxiety and anti-cancer, were mentioned in Table 2.

Agarospiranes: The agarospirane sesquiterpenes were reported in agarwood from *A. sinensis*, *A. malaccensis*, *A. crassna* and *A. subintegra*[32]. Agarospirol (A1) is the first agarospirane sesquiterpene from the agarwood of *A. malaccensis*. The agarospirol (A1), Oxo-isoagarospirol (A3), β-agarofuran (A10) and β-dihydroagarofuran (A11) were shown in the four of these species. Most of agarospiranes' constituents were mainly discovered in the agarwood species of *A. sinensis,* excepted agarospirane A2, A9, A12 and A13. The sesquiterpenes from A4 to A8 were obtained from the volatile oil of *A. sinensis*. In general, the agarospirane group from agarwood of *Aquilaria* species has several properties, including anti-oxidant (A1, A3 and A9-A13), anti-inflammatory (A4-A6 and A8), antimicrobial (A2), anti-nociceptive (A1) and anti-neuroinflammatory (A7).

Eudesmanes: The main compounds of sesquiterpene found in *Aquilaria* species were eudesmane-type sesquiterpenes. These constituents are also distributed in *A. sinensis*, *A. malaccensis*, *A. crassna* and *A. subintegra.* Only 10-epi-eudesmol (B1) was reported in four of these

Table 2: Main chemical constituents of *Aquilaria* genus

	Sesquiterpenes		
Compounds	*Aquilaria* species	Pharmacological effects	References
(A) Agarospiranes			
A1. *Agarospirol*	*Aquilaria subintegra* *Aquilaria malaccensis* *Angelica sinensis* *Aquilaria crassna*	Anti-nociceptive activity; Anti-oxidant activity	Monggoot *et al.*[14] and Pripdeevech *et al.*[127]
A2. Isoagarospirol	*Aquilaria malaccensis*	-	Gao *et al.*[99]
A3. Oxo-isoagarospirol	*Aquilaria subintegra* *Aquilaria malaccensis* *Angelica sinensis* *Aquilaria crassna*	Anti-oxidant activity	Monggoot *et al.*[14] and Pripdeevech *et al.*[127]
A4. Baimuxinol	*Angelica sinensis*	Anti-inflammatory	Yu *et al.*[128]
A5. 4-hydroxyl-baimuxinol	*Angelica sinensis*	Anti-inflammatory	Yang *et al.*[129]
A6. Baimuxinic acid	*Angelica sinensis*	Anti-inflammatory	Yu *et al.*[128]
A7. Baimuxifuranic acid	*Angelica sinensis*	Anti-neuroinflammatory	Huo *et al.*[130]
A8. Iso/Dehydro-baimuxinol	*Angelica sinensis*	Anti-inflammatory	Gao *et al.*[99]
A9. α-Agarofuran	*Aquilaria subintegra* *Aquilaria malaccensis* *Aquilaria crassna*	Antianxiety activity, Antioxidant activity	Monggoot *et al.*[14] and Pattarachotanant *et al.*[63]
A10. β-Agarofuran	*Aquilaria subintegra*	Antioxidant activity	Monggoot *et al.*[14]
A11. β-Dihydroagarofuran	*Aquilaria malaccensis* *Aquilaria crassna,* *Angelica sinensis*		Monggoot *et al.*[14] and Gao *et al.*[99]
A12. *cis*-Dihydroagarofuran	*Aquilaria subintegra*	Antioxidant activity Antimicrobial activity	Monggoot *et al.*[14]
A13. Epoxy-β-Agarofuran	*Aquilaria malaccensis*	Antioxidant activity	Gao *et al.*[99]
(B) Eudesmanes			
B1. 10-epi-Eudesmol	*Aquilaria malaccensis* *Aquilaria subintegra* *Aquilaria crassna* *Angelica sinensis*	Antioxidant activity Prevention of mosquito-related disease	Pripdeevech *et al.*[127] Monggoot *et al.*[14]
B2. (5S,7S,10S)-(-)-Selina-3,11-dien-9-one	*Aquilaria subintegra* *Aquilaria malaccensis* *Aquilaria crassna*	Anti-neuroinflammatory	Li *et al.*[3] and Huo *et al.*[130]
B3. (5S,7S,9S,10S)-(+)-Selina-3,11-dien-9-ol	*Aquilaria subintegra* *Aquilaria malaccensis* *Aquilaria crassna*	-	
B4. (5S,7S,9S,10S)-(+)-Selina-3,11-dien-12-al	*Angelica sinensis*	Anti-bacterial activity	Li *et al.*[3]
B5. (5S,7S,9S,10S)-(+)-Selina-3,11-dien-14-al	*Angelica sinensis*		
B6. (5S, 7S, 9S, 10S)-(+)-9-hydroxy-eudesma-3,11 (13)-dien-12-methyl ester	*Angelica sinensis*		
B7. (7S, 9S, 10S)-(+)-9-hydroxy-selina-4,11-dien-14-al	*Angelica sinensis*		
B8. (7S, 9S, 10S)-(+)-8,12-hydroxy-selina-4,11-dien-14-al	*Angelica sinensis*	Anti-bacterial activity Acetylcholinesterase inhibitory activity	Pripdeevech *et al.*[127] and
B9. Selina-3,11-dien-14-al	*Aquilaria subintegra* *Aquilaria malaccensis* *Aquilaria crassna*	Anti-oxidant activity	Ishihara *et al.*[131]
B10. Selina-3,11-dien-14-oic acid	*Aquilaria malaccensis*	Anti-oxidant activity	Ishihara *et al.*[131]
B11. Selina-4,11-dien-14-al	*Aquilaria subintegra* *Aquilaria malaccensis* *Aquilaria crassna*	Anti-oxidant activity	Pripdeevech *et al.*[127]
B12. Selina-4,11-dien-14-oic acid	*Aquilaria malaccensis*	Anti-oxidant activity	Ishihara *et al.*[131]
B13. 9-Hydroxy-selina-4,11-dien-14-oic acid	*Aquilaria malaccensis*		
B14. Z-Eudesma-6,11-diene	*Aquilaria subintegra*	Anti-oxidant activity	Monggoot *et al.*[14]
B15. β-Eudesmol	*Aquilaria crassna* *Aquilaria subintegra*	Anti-oxidant activity	Hashim *et al.*[13] and Gao *et al.*[99]
B16. α-Selinene	*Angelica sinensis* *Aquilaria crassna*	Anti-cancer activity Repellent activity	Hashim *et al.*[13] and Gao *et al.*[99]

Table 2: Continued

	Sesquiterpenes		
Compounds	*Aquilaria* species	Pharmacological effects	References
B17. δ-Selinene	*Angelica sinensis*	-	
B18.-Selinene	*Angelica sinensis*	-	
B19. Aquisinenoid A	*Angelica sinensis*	Anti-cancer activity	Zhou *et al.*[52] and Chen *et al.*[54]
B20. Aquisinenoid B	*Angelica sinensis*		
B21. Aquisinenoid C	*Angelica sinensis*		
B22. Aquisinenoid D	*Angelica sinensis*		
B23. Aquisinenoid E	*Angelica sinensis*		
B24. Aquisinenoid F	*Angelica sinensis*	Anti-cancer activity Anti-inflammatory	Zhou *et al.*[52] and Chen *et al.*[54]
B25. Aquisinenoid G	*Angelica sinensis*		
B26. Aquisinenoid H	*Angelica sinensis*		
B27. Aquisinenoid I	*Angelica sinensis*		
B28. Aquisinenoid J	*Angelica sinensis*		
(C) Eremophilanes			
C1. Eremophila-9,11(13)-dien-12-ol	*Aquilaria malaccensis*	-	Gao *et al.*[99]
C2. Valence-or eremophila-9-en-12-al (tentative)	*Aquilaria malaccensis*	-	
C3. (+)-9β,10β-epoxy eremophila-11(13)-en	*Angelica sinensis*	Anti-neuroinflammatory	Huo *et al.*[130]
C4. (1β,4aβ,7β,8aβ)-octahydro-7-[1-(hydroxymethyl) ethenyl]-1,8a-dimethylnaphthalene-4a(2H)-ol	*Angelica sinensis* *Aquilaria malaccensis*	-	Ishihara *et al.*[131]
C5. 2-[(2β,4aβ,8β,8aβ)-decahydro-4α-hydroxy-8,8 a-dimethylnaphthalene-2-yl]prop-2-enal	*Angelica sinensis* *Aquilaria malaccensis*	Anti-neuroinflammatory	Huo *et al.*[130]
C6. 11,13-dihydroxy-9(10)-ene-8β,12-epoxyemophilane	*Aquilaria crassna* *Anti-bacterial activity*	Anti-bacterial activity	Wang *et al.*[132]
C7. 8,12-epoxy-eremophila-9,11 (13)-diene	*Aquilaria malaccensis*	-	Gao *et al.*[99]
C8. 7β-H-9 (10)-ene-11,12-epoxy-8-oxoeremophilane	*Angelica sinensis*	Acetylcholinesterase inhibitory activity	Yang *et al.*[129]
C9. (+)-(4S,5R)-Karanon	*Aquilaria malaccensis*	Anti-inflammatory	Ishihara *et al.*[131]
C10. (+)-(4S,5R)-dihydrokaranone-[7 (11)-eremophilen-8-one]	*Aquilaria malaccensis* *Angelica sinensis*	Anti-inflammatory	Yu *et al.*[128]
C11. 7α-H-9(10)-ene-11,12-epoxy-8-oxoeremophilane	*Angelica sinensis* *Aquilaria crassna*	Acetylcholinesterase inhibitory activity	Yang *et al.*[129]
C12. Valenca-1(10),8-dien-11-ol	*Aquilaria malaccensis*	-	Gao *et al.*[99]
(D) Guaianes			
D1. (+)-Guaia-1 (10),11-dien-9-one	*Aquilaria malaccensis*	Anti-cancer activity	Ito and Ito[58]
D2. (-)-1,10-epoxyguai-11-ene	*Aquilaria malaccensis*	Anti-oxidation activity	
D3. Methyl guaia-1 (10),11-diene-15-carboxylate	*Aquilaria malaccensis*		Ishihara *et al.*[131]
D4. (-)-Guaia-1 (10),11-diene-15-carboxylic acid	*Aquilaria malaccensis*		Ito and Ito[58]
D5. α-Bulnesene	*Aquilaria malaccensis* *Aquilaria crassna* *Aquilaria subintegra*		Pripdeevech *et al.*[127] and Ishihara *et al.*[131]
D6. (-)-Guaia-1 (10), 11-dien-15-ol	*Aquilaria malaccensis* *Aquilaria crassna* *Aquilaria subintegra*		Ito and Ito[58]
D7. (-)-Guaia-1(10), 11-dien-15-al	*Aquilaria malaccensis* *Aquilaria crassna* *Aquilaria subintegra*		Pripdeevech *et al.*[127] and Ishihara *et al.*[131]
D8. α-Guaiene	*Aquilaria malaccensis* *Aquilaria crassna* *Aquilaria subintegra*		Pripdeevech *et al.*[127] and Ishihara *et al.*[131]
D9. (-)-Rotundone	*Aquilaria malaccensis*		Ito and Ito[58]
D10. (-)-Guaia-1(10),11-dien-15,2-olide	*Aquilaria malaccensis*		
D11. (4R)-2-oxo-gweicurculactone	*Lymphatic filariasis*	Cytotoxic, anti-cancer,	Mi *et al.*[110]
D12. 1(5)-ene-7,10-epoxy-guaia-12one	*Lymphatic filariasis*	α-glucosidase inhibitory activities	
D13. (4R,5S)-2-oxo-5,6-dihydro-gweicurculactone	*Lymphatic filariasis*		
D14. 1,8-epoxy-5H-guaia-9-en-12,8-olide	*Lymphatic filariasis*		
(E) Humulenes			
E1. Aquilanol A	*Aquilaria malaccensis* *Angelica sinensis*	Anti-neuroinflammatory	Huo *et al.*[130] and Ma *et al.*[133]

Table 2: Continued

Compounds	Sesquiterpenes		
	Aquilaria species	Pharmacological effects	References
E2. Aquilanol B	*Aquilaria malaccensis* *Angelica sinensis*		
E3. 12-Hydroxyhumula-2Z,6E,9E-triene	*Aquilaria malaccensis* *Angelica sinensis*		
E4. 14-Hydroxy-α-humulene	*Aquilaria malaccensis* *Angelica sinensis*		
E5. β-caryophyllene	*Aquilaria crassna* *A. banaensis*	Anticancer, antioxidant, antimicrobial properties	Dahham *et al.*[10] and Dahham *et al.*[134]
E6. 2,3,6,7-Diepoxy-9E-umulen-12-ol	*Aquilaria malaccensis*	Anti-inflammatory	Ma *et al.*[133]
E7. (6R)-6-hydroxy-humula-2E,9E, 7(13)-trien-12-ol	*Aquilaria malaccensis*		
E8. Hydroperoxyl-humula-2E,9E, 7(13)-trien-12-ol	*Aquilaria malaccensis*		
E9. (7R)-12-formyl-7B-hydroxy-humula-2Z,9E-dien-5-one	*Aquilaria malaccensis*		
Chromones			
2,3-Dihydro-5-hydroxy-2-methylchromen-4-one	*Angelica sinensis* *Aquilaria malaccensis*	Cytotoxic activity cardiovascular system	Gao *et al.*[99]
Mellein	*Angelica sinensis*	Antibacterial activity Cardiovascular system	Gao *et al.*[99]
7-(Benzyloxy)-5-hydroxy-2-methylchromone	*Aquilaria malaccensis*	Relieving cough and asthma	Nasution *et al.*[135]
7-methoxy-2-[2-(4'-hydroxyphenyl)ethyl]chromone	*Angelica sinensis*	Anti-inflammatory	Wang *et al.*[132]
7-hydroxy-2-[2-(4'-methoxyphenyl)ethyl]chromone	*Angelica sinensis*	Anti-inflammatory	
5,6-dihydroxy-2-[2-(3°-hydroxy-4° -methoxyphenyl)ethyl]chromone	*Angelica sinensis*	Anti-inflammatory	
5,6,7,8-tetrahydro-2-(2-phenylethyl)chromones	*Aquilaria crassna*	Cytotoxic activity	Nguyen *et al.*[61] and Yang *et al.*[136]
Dimeric 2-(2-phenylethyl)chromone	*Aquilaria crassna* *Lymphatic filariasis*	Cytotoxic activity	
2-(2-phenylethyl)-4H-chromen-4-one	*Angelica sinensis*	Anti-inflammatory	Wang *et al.*[132]
Diepoxy-tetrahydro-2-(2-phenylethyl) chromones 110-112 Crassin A Crassin B Crassin C Crassin D Aquilacrassnin A Aquilacrassnin B Aquilacrassnin C Aquilacrassnin D Aquilacrassnin E Aquilacrassnin F	*Aquilaria crassna*	Anti-microbial and anti-cancer properties	Gao *et al.*[99] and Yang *et al.*[129]

species[14,32]. Most eudesmane-type sesquiterpenes contain an isopropenyl or 2-hydroxy isopropyl group at the C-7 position and the oxidized methyl groups at C-4/C-11. The eudesmanes (B2, B9-B13) show the oxidation at C-9/C-15 and the isopropenyl group at the C-7 position. Although many eudesmane-type sesquiterpenes were isolated from *A. sinensis* (B1, B4-B8 and B16-B28), several eudesmanes (B2, B3 and B9-B15) were only reported in other species. Remarkably, the eudesmanes (B10, B12, B13) were only presented from the agarwood of *A. malaccensis* and the Z-eudesma-6,11-diene (B14) from *A. subintegra.* Regarding the pharmacological effects, eudesmane sesquiterpene can also be used for anti-oxidant (B1 and B9-B15), anti-inflammatory (B24-B28), anti-neuroinflammatory (B2, B3) and anti-bacterial (B4-B8) activities[52,54,102,105]. Besides, other effects of eudesmane group can be mentioned such as preventing the mosquito-related disease of the 10-epi-eudesmol (B1), inhibitory activity against acetylcholinesterase (AChE) of the 7S, 9S, 10S)-(+)-8,12-hydroxy-selina-4,11-dien-14-al (B8) or anti-cancer activity (B19-B28).

Eremophilanes: The eremophilane-type sesquiterpene consists of two six-membered ring structures, which were found in agarwood of *A. malaccensis*, *A. sinensis* and *A. crassna*[14,102,106,107]. The (+)-(4S,5R)-Karanon (C9) and (+)-(4S,5R)-dihydrokaranone-[7(11)-eremophilen-8-one] (C10) are two significant eremophilanes of agarwood compounds, which are unsaturated and conjugated ketones. The eremophilane sesquiterpenes have some properties such as anti-inflammatory (C9, C10), anti-neuroinflammatory (C3, C5), anti-bacterial (C6) and AChE inhibitory (C8, C11)[10,13,54,108,109].

Guaianes: The guaiane-type sesquiterpenes D1-D10 were isolated from the agarwood of *A. malaccensis*. In contrast, guaianes D5-D8 were also identified from *A. crassna* and *A. subingtegra*[102,110-112]. Mi *et al.*[110] discovered four new guaiane sesquiterpenoids (D11-D14) from *A. filaria.* The guaianes are coupled with 5 and 7-membered rings, including 4, 10-dimethyl-7-isopropenyl moiety. The guaiane compounds (D11-D14) were assessed for inhibitory activity against α-glucosidase, cytotoxic activity and healing human cancer cell lines[54]. Moreover, other constituents of guaianes can also be utilized for anti-cancer activities[54,109,110,112,113].

Humulenes: Nine humulene-type sesquiterpenes E1-E9 were mainly described from *A. malaccensis* agarwood, except for β-caryophyllene (E5). Four humulenes (E1-E4) were reported in the agarwood of both *A. malaccensis* and *A. sinensis*. The aquilanol A and B (E1, E2) contain the structure of an unprecedented macrocyclic humulene with bicyclic 7/10-membered rings[32]. The β-caryophyllene sesquiterpene was indicated from the essential oils of *A. crassna*[10] and *A. banaensis*[38]. The β-caryophyllene was isolated from *A. crassna* possess cytotoxicity against seven human cancer cell lines, anti-proliferative effects against colorectal cancer cells, antibacterial activity against *Staphylococcus aureus*, anti-oxidant solid effects, inhibition against clonogenicity, migration, invasion and spheroid formation in colon cancer cells. Thus, β-caryophyllene is one of the sesquiterpenes with great potential pharmacological activities from agarwood of *Aquilaria* species.

Other sesquiterpenoids: Regarding the above-mentioned sesquiterpenoids, the sesquiterpenes of prezizaanes and zizaanes are also reported from agarwood of other *Aquilaria* spp. For example, tricyclic prezizaane-type sesquiterpenes aquilarene A-J, agarozizanol A-C, jinkoholic acid, jinkohol, jinkohol II are presented from the agarwood of *Aquilaria* spp., whereas, jinkohol II and jinkohol are reported from *A. malaccensis*. Besides, the species of agarwood also resulted in the isolation and structure determination different minor sesquiterpenes[32].

Chromones are a large group of secondary metabolites with broad therapeutic potential for immunomodulation, inflammation, cancer, diabetes, neurological conditions and infections caused by bacteria and viruses[4,39,86,114]. Chromones are unique compounds found predominantly in agarwood of three main species (*A. sinensis, A. malaccensis* and *A. crassna*). *Aquilaria* species produce several chromones, including 2-(2-phenylethyl) chromone), 2-(2-phenylethyl)-4H-chromen-4-one derivatives) and 2-(2-phenylethyl) chromone derivatives[53,85,102,115-118]. Particularly, 2-(2-phenylethyl) chromone is a member of the chrome class, which is substituted by a 2-phenylethyl group at the C2 position[115]. Meanwhile, the derivatives of 2-(2-phenylethyl) chromone are the other main group of compositions in the agarwood species[115,116]. Based on the molecular skeleton, 2-(2-phenylethyl) chromones are divided into monomeric 2-(2-phenylethyl) chromone, dimeric 2-(2-phenylethyl) chromones and sesquiterpenoid-4H-chromones, trimeric chromones[32].

Recently, Yang *et al.*[53] found four new 2-(2-phenylethyl) chromone dimers from the agarwood phytochemistry of *A. filaria* obtained in Philippines. These four compounds can exhibit inhibition of nitric oxide production in lipopolysaccharide-stimulated RAW264.7 cells of *A. filaria*. These compounds contribute to the characteristic fragrance of agarwood and possess various biological activities, such as antimicrobial and anticancer properties. Among them, 2-(2-phenylethyl) chromones exhibited various kinds in agarwood[86,117]. For example, using the gas chromatography-mass spectrometry approach, the relative level of 2-(2-phenylethyl) chromone compounds was approximately 60% in agarwood samples[119]. Two Chinese groups also estimated agarwood's quality and determined the absorbance score of these chromones at 230 and 250 nm wavelengths using a spectrophotometer[27,120]. Endophytic strains were co-fermented with agarwood to produce a variety of 2-(2-phenylethyl) chromone derivatives[14,121]. Some of the thirteen 2-(2-phenylethyl) chromone derivatives obtained by ethanol extraction have been demonstrated to exhibit inhibitory effects on *Staphylococcus aureus*. Xia *et al.*[27] and Yang *et al.*[122] reported that Aquilacrassin A-F and Crassin A-C of chromones are also very rare from *A. crassna* agarwood.

Besides, *Aquilaria* species also contain various phenolic substances, including flavonoids, tannins and lignans[58,86,123]. These compounds contribute to agarwood's antioxidant and free radical scavenging properties[13,86]. Some significant phenolic compounds identified in the *Aquilaria* species are quercetin, kaempferol, catechins, epicatechins and lignan glycosides[124]. Additionally, certain *Aquilaria* species contain triterpenes, such as lupeol, β-sitosterol and α-amyrin, which exhibit various pharmacological characteristics, including anti-inflammatory, anti-diabetic and anti-cancer activities[13]. In plants, the isoprenoid precursors for synthesizing sesquiterpenes, triterpenes and sterols, which are therapeutic compounds with antimicrobial and anti-inflammatory effects, are commonly believed to be provided by the mevalonic acid pathway in the cytosol[8]. For example, several important herbicidal species belonging to *Amomum* and *Zingiber* genera also play a vital role in anti-bacteria and anti-inflammatory like *Aquilaria* species, such as *Leoheo domatiophorus*, *Amomum unifolium*[125], *Newmania sontraensis*[126] and *Zanthoxylum monophyllum*[125].

AUTHENTICATION OF THE *AQUILARIA* SPECIES

The identification of *Aquilaria* species is crucial due to the valuable market of their agarwood, which makes adulterated to meet the increase in demand[1]. Numerous attempts have been made to identify the species of *Aquilaria* using several methods[1,137]. Traditionally, authentication based on morphological descriptors has been extensively employed; however, the categorization procedure is challenging due to the significant similarity among these species and the instability of morphology characteristics[2]. Recently, DNA barcoding has emerged as a prominent tool for authentic *Aquilaria* species. Nevertheless, the invention and selection of appropriate DNA barcodes may differ depending on the particular materials under research[29]. In this section, we will review and summarize the obtained results and the limitations associated with commonly used techniques for *Aquilaria* species authentication.

Using morphological features for *Aquilaria* identification is simple and cost-effective[2,26]. Within the tribe Aquilarieae, two sister agarwood-producing genera, *Aquilaria* and *Gyrinops*, have been traditionally distinguished based on the number of stamens in the flower: *Gyrinops* has five stamens, whereas *Aquilaria*'s stamens are twice the number of the calyx lobes[22]. Nevertheless, following this criterion, *A. cumingiana* may pose classification challenges[17,25,29]. Additional morphological characteristics, such as the shape of the calyx tube, fruit features, the presence or absence of leaf indument and the chemotaxonomic and anatomical markers, have been proposed for taxonomic identification. However, these features still do not serve as strong discriminators for both genera yet[23-25]. In general, *Aquilaria* can be distinguished from other genera in the Thymelaeaceae family based on its distinctive traits, which include a calyx tube with various shapes (campanulate, tubular, cupular, or infundibular), 8-12 stamens that emerge from the calyx tube, fruits characterised by a leathery capsule and consisting of 2 carpels (occasionally three), petaloid appendages that are typically distinct and densely pubescent or puberulous and the presence of intercalary phloem[30,138]. Within the *Aquilaria* genus, several species could be distinguished by observing leaf features, flower and fruit structure (Table 3). For example, when observing leaf shape and texture, *A. hirta* stands out from other cultivated agarwood tree species (*Aquilaria crassna*, *Aquilaria subintegra*, *Aquilaria malaccensis* and *Angelica sinensis*) due to its distinctive characteristics, including the presence of puberulous leaf abaxial and leaf petiole. However, it is important to note that leaf features have the potential to vary due to environmental adaptations[1]. Recently, five cultivated *Aquilaria* species in Peninsular Malaysia were successfully distinguished based on the fruit and the calyx lobes: *Aquilaria crassna* is characterised by huge and wrinkly fruit; *A. hirta* is distinguished by velvety fruit with acute tip; *Aquilaria malaccensis* exhibited triangular-shaped fruit; *Angelica sinensis* featured with diamond-shaped and oblong fruit and *Aquilaria subintegra* identified by rounded calyx lobes with fine hairs. Moreover, *Angelica sinensis* can be recognised by its smooth fruit surface, sometimes with scant hair and lengthy appendages on its seeds. In contrast, the seeds of *A. yunnanensis* have extensive golden pubescence and short appendages[29]. More specifically, *Angelica sinensis*' capsule possesses a relatively thin texture, its outer layer remains intact when dry, the seeds are silky, white and glabrous, the apex features an extended beak and the base appendage is approximately 1.5 cm longer than the seed. Meanwhile, *A. yunnanensis* has thick capsules, small florals on top, yellow pubescence and shriveled dry pericarps on the seeds and short base appendages that are nearly as long as the seeds, measuring 0.8-1.0 cm in length[29]. These seed and fruit characters could be key identifying traits for Chinese *Aquilaria*. Flower, seed and fruit characters are key features for authenticating *Aquilaria* species[26]. However, these traits could only be observed during the flowering and fruit seasons[26]. The restricted distribution of some species and the limited availability of wild resources also complicate field sampling for fruits and flower surveys more complicated[2]. Conversely, wood samples from mature trees are consistently accessible, making them a valuable resource for species identification. The fibre morphology and extractive content of *Aquilaria* species are critical for determining agarwood quality. Traditionally, agarwood has been graded based on sensory attributes such as aroma and colour. However, this approach is subjective, time-consuming, inconsistent and involves high labour costs[22,27,28]. Andary *et al.*[139] analysed chemotaxonomics to differentiate *Aquilaria* species by identifying polyphenolic

Table 3: Descriptors of 11 common *Aquilaria* species, Data was collected from previous studies[17,25,45,47,48,149-153]

Species	Morphological descriptors			Molecular descriptors	
	Tree	Leaf	Fruit/Capsule/Calyx	DNA barcode (Genbank accession number)	Chloroplast sequence in NCBi/genome size
Aquilaria beccariana	Medium to large tree/20 m	Leaves papery, usually glabrous on both surfaces, second vein leaf visible, greyish green, not shiny	Fruit obovoid, laterally compressed, slightly contracted in the middle, the base abruptly narrowed to the elongate stipe	*matK* (LC737218) *rbcL* (LC736084) *trnL-trnF* (KT364470) *ITS* (KT364477)	NC-052855 174831 bp
Aquilaria crassna	Large tree	Elliptic, leathery, smooth	Pear-shaped fruit obovoid, huge (3-4 cm) and wrinkled capsule calyx lobes are rounded and persistent tube	*matK* (LC383997) *rbcL* LC383710) *trnL-trnF* (KT364471) *ITS* (KT364478)	NC-043844 174830 bp
Aquilaria cumingiana	Shrub/ small tree 5 m	Long petiole with no stipples	Globose to an ellipsoid fruit loculicidal capsule and protruding laterally	*matK* (MF443400) *rbcL* (MF443407) *trnL-trnF* (KT726320) *ITS* (MH134140)	NC-065041 174834 bp
Aquilaria hirta	Small tree 2-10 m tall, to 15 cm diam	Furry leaf underside	Thin pear-shaped fruit The capsule has wrinkled and velvety surface Obtuse calyx lobes	*matK* (KU244190) *rbcL* (KU244216) *trnL-trnF* (KT364472) *ITS* (KT364479)	NC-052856 174761 bp
Aquilaria malaccensis	Medium to large tree/20-40	Elliptic, smooth, papery	Pear-shaped fruit The capsule has a blunt apex, a rounded base, wrinkled and velvety surface	*rbcL* (LC383712) *matK* (LC383998) *trnL-trnF* (KT364473) *ITS* (KT364480)	NC-041117 174832 bp
Aquilaria microcarpa	Large tree	Small heart-shaped leave	Fruit sub-cordiform, slightly compressed	*rbcL* (KU244196) *matK* (KU244222) *trnL-trnF* (KT364474) *ITS* (KT364481)	NC-052857 174819 bp
Aquilaria rostrata	Small tree 2-5 m high, 3-4 cm diam	Leaves lanceolate, ovate-oblong, glabrous, shining on both surfaces, base obtuse, cuneate to attenuate; apex acuminate	Ovate-oblong or oblanceolate fruit, including stipe Long-beaked capsules Calyx puberulous on both surfaces	*matK* ((MF443401) *rbcL* (MF443408) *trnL-trnF* (KT364475) *ITS* (KT364482)	NC-052858 174693 bp
Aquilaria rugosa	Small tree/4-5 m	Ovate to obovate; both surfaces are mostly glabrous	Capsules globose, exocarp heavily rugose	*matK* (MF443402) *rbcL* (MF443409) *trnL-trnF* (MF443430) *ITS* (MH134145)	NC-065042 174893 bp
Aquilaria sinensis	Medium tree/15 m	Elliptic-oblong, puberulous leaf abaxial and leaf petiole	Diamond-shape fruit The capsule has a blunt apex, a pointed base, wrinkled surface covered with fine hair Oblong calyx lobes, persistent calyx tube	*matK* (KU244202) *rbcL* (KU244228) *trnL-trnF* (KU244046) *ITS* (MH134146)	MN720647 174914 bp
Aquilaria subintegra	Shrub	Elliptic-oblong or slightly obovate-oblong, papery	Pear-shape fruit Capsule is blunt at the apex and pointed at the base, attached to a persistent calyx tube; the surface of the capsule is wrinkled and covered with fine hair	*rbcL* (LC383711) *matK* (LC383999) *trnL-trnF* (KT364476) *ITS* (KT364483) *matK* (KU244207)	NC-052859 174828 bp
Aquilaria yunnanensis	Medium tree/15 m	Elliptic-oblong	Obovoid, slightly compressed valves thin, stretched at acute angle; Slightly rugose	*rbcL* (KU244233) *trnL-trnF* (KU244051) *ITS* (MH134148)	NC-036940 174885 bp

molecules as taxonomic markers. This method provides a straightforward and effective means of distinguishing between species, thereby improving the accuracy of identifying agarwood-producing trees. A study by Villareal *et al.*[140] further explored the potential of wood characteristics and extractive content for identifying *Aquilaria* species. This research revealed variations in fibre morphology and extractive content in *A. cumingiana* wood samples from the Philippines correlated with distinct sample classifications. It is worth noting that different solvents used for extraction produced varying results, underscoring the intricacies of chemical analysis in accurately characterising species. However, it is crucial to recognise the inherent limitations of the chemical approach. Various external factors, including environmental conditions, soil composition and geographical location, can influence the presence and concentration of chemical compounds. As a result, the chemical profile of a species may differ across different regions, potentially leading to misclassifications based solely on chemical markers.

Molecular techniques have accumulated widespread recognition in identifying the *Aquilaria* species to overcome the limitations of morphological and chemical-based authentication[137]. As molecular approaches progress, new molecular techniques have emerged, especially those employing next-generation sequencing technologies, thanks to the reduction of sequencing costs in recent years[141,142] DNA barcoding is centred on species-level recognition by molecular methods. For the authentication of *Aquilaria* species, several barcode markers have been widely employed, including ribulose 1,5-biphosphate carboxylase large subunit (*rbcL*), megakaryocyte-associated tyrosine kinase gene (*matK*), the intergenic region between chloroplast genes *trnL* and *trnF* (*trnL-trnF*) and internal transcribed spacer (*ITS*)[143,144]. The plastid protein-coding gene, *rbcL* and the noncoding intergenic spacer region, *trnL-trnF*, were first employed in 2002 to investigate as a potential barcode for Thymelaeaceae. The combination of these two regions is well-supported in distinguishing four subfamilies in the Thymelaeaceae genera: Thymelaeoideae, Aquilarioideae, Gonystyloideae and Gilgiodaphnoideae[145]. However, at a lower level, using *trnL-trnF* sequences is insufficient to differentiate between *A. beccariana* and *Aquilaria malaccensis*. Subsequent study has shown that relying on a single DNA barcode or a single gene does not provide enough resolution at the species level. As a result, a combination of multiple DNA regions, including *trnL-trnF+ITS1*, *trnL-trnF+ITS2*, *matK+ITS*, *rbcL+ITS, matK+trnH-psbA+ycf1* and *psbJ-petA+trnT-trnL*, has been employed as DNA barcodes to differentiate *Aquilaria* species[16,23,24,29,50,146]. Particularly, Jiao *et al.*[147] realized that the considerable clustering effect of *Angelica sinensis* phylogenetic tree construction by *trnL-trnF* and *ITS1*[147], while the ITS2 and *matK* barcode combination has the highest species identification success rate (approximately 96%), which might be used for *Angelica sinensis* and *A. yunnanensis* authentication[29]. Li *et al.*[24] discovered that the phylogenetic tree generated by *ITS+matK and ITS+trnL-trnF* is useful for identifying three *Aquilaria* species[24]. Lee *et al.*[25] used the combination of *trnL-trnF+ITS* as a potential DNA barcode for discriminating eight *Aquilaria* species including *A. beccariana*, *A. crassna, A. filariasis*, *A. hirta*, *Aquilaria malaccensis*, *A. microcarpa*, *Angelica sinensis* and *Aquilaria subintegra*, however, *A. crassna* and *Aquilaria subintegra* lacked unique polymorphisms and could not be effectively distinguished. The choice of DNA barcode combination may vary depending on the samples[29]; for example, for the verification of six species *(A. crassna*, *A. hirta*, *Aquilaria malaccensis*, *A. microcarpa*, *Angelica sinensis* and *A. yunnanensis*), the combination of *ITS+matK* proved to be more effective[24]. Another drawback is the availability of *Aquilaria* samples employed in these investigations. Despite the IUCN Red List of Threatened Species listing 21 species of *Aquilaria*, only a few species have been focused on authenticating research. Consequently, the current DNA barcodes have not yet demonstrated sufficient accuracy in identifying all *Aquilaria* species[24] and further studies with a broader representation of species are needed. Recently, scientists have expressed an interest in using the next-generation sequencing technology to collect the complete plastid genome sequences. Plastids are unique organelles in organism cells and contain small DNA. The plastid genome offers several advantages for species identification, including its smaller size than the nuclear genome, uniparental inheritance pattern and low nucleotide substitution rate. These characteristics make the plastid genome a reliable molecular marker for phylogenetic research and species identification in plants and animals. However, fewer plant mitochondrial genomes have been constructed and reported than chloroplast ones because they differ significantly in size and structure. To date, whole chloroplast genome sequence data of more than 11 species of *Aquilaria* were public on the National Center for Biotechnology Information. The DNA barcoding and the whole chloroplast genome are used for taxonomic distinctions among closely related species and reveal a rich array of informative genetic traits, providing valuable insights into the evolutionary relationships[24,50,148]. For example, *A. agallocha* is traditionally synonymous with *Aquilaria malaccensis*[1]. However, a phylogenetic tree constructed using combined sequences from five chloroplast loci and the nrDNA ITS region showed that *A. agallocha* and *Aquilaria malaccensis* formed two separate clusters. *Aquilaria agallocha* grouped with *A. crassna, A. rugosa, Angelica sinensis, Aquilaria subintegra* and *A. yunnanensis*, originating from the Indochina region, while *Aquilaria malaccensis* is clustered with *A. beccariana*, *A. hirta*, *A. microcarpa* and *A. rostrata*, primarily found in the Malesian region[17,23,31]. The evidence from the chloroplast genome also demonstrated that *A. agallocha* is more closely genetically related to *Aquilaria* from Indo, Indo-China and Southeast Asia than *Aquilaria malaccensis* from Malesia[48]. Therefore, the availability of whole chloroplast genome sequence data for *Aquilaria* species marks a significant milestone in molecular research and conservation efforts. By harnessing the power of molecular markers and next-generation sequencing technologies, we can gain valuable insights into the genetic diversity and evolutionary history of *Aquilaria*, contributing to the protection and sustainable management of these valuable tree species.

FUTURE STRATEGIES FOR THE CONSERVATION AND SUSTAINABLE DEVELOPMENT OF THE *AQUILARIA* SPECIES

The heightened global demand for *Aquilaria* species in response to infections has led to an alarming over-exploitation of these trees[11,15,17,21,22]. Prized for its rarity and versatility in uses including perfumery, incense production and traditional medicinal applications[22,154], agarwood's appeal has unfortunately sparked unsustainable harvesting methods, posing a severe threat to these species' existence. *Aquilaria* was further categorized in Appendix II of the Convention on International Trade in Endangered Species (CITES) of Fauna and Flora as EN[31]. Therefore, all species in the entire *Aquilaria* genus are under CITES protection, which, among others, mandates trading permits for export purposes. Thus, it is significant to generate a sustainable strategy for conserving and developing the *Aquilaria* species.

The primary distribution of *Aquilaria* species in Southeast Asia's tropical or subtropical regions introduces significant hurdles for taxonomic research[29]. However, with the introduction of DNA barcoding technology, the reliability of taxonomic authentication can be significantly bolstered, provided that the sampling is conducted meticulously and covers a wide geographical span. The DNA barcoding has been shown to offer a clear advantage in navigating the taxonomic complexities associated with visually similar species, a challenge seen in the *Aquilaria* genus[24,25,29,143,144]. Furthermore, while Indonesia and Malaysia serve as the biodiversity centres for *Aquilaria* species, native species are also found in neighbouring countries such as Vietnam, China and the Philippines. By combining pan-collection approaches with DNA barcoding[155], researchers and conservationists can unravel the evolutionary history and geographical patterns of *Aquilaria* species. This knowledge is essential for making informed conservation decisions and implementing effective management strategies for these valuable trees in Southeast Asia. Moreover, the insights gained from such comprehensive studies contribute to the overall understanding of the region's biodiversity conservation and sustainable development[29].

Another strategy is to improve the efficiency of agarwood induction. Agarwood formation is often linked to the physical wounding or damage of *Aquilaria* trees caused by natural factors, such as animal grazing, thunder strikes, disease and pest infestations[67]. These occurrences exposed the inner parts of the *Aquilaria* trees to these factors, triggering *Aquilaria*'s defence mechanism and initiating resin production. However, the main weaknesses of the agarwood formation by natural factors could be unsustainable, undetermined and extremely low yield, while this process required indiscriminately harvesting wild trees. Argarwood formation is also triggered by other physical wounds of the tree, like wounding using an axe or machete, bark removal, cutting, holding and nailing. This conventional approach was reported to be laborious and time-consuming in order to obtain the agarwood with uncertain quality. Meanwhile, localized agarwood formation mainly occurred at the wounded locations[5,67,95]. Genome editing technologies like CRISPR/Cas9[156] can be employed to target and modify specific genes responsible for agarwood production, thereby enhancing both the quantity and quality of agarwood resin.

At least 14 (out of 21) *Aquilaria* species are thought to be agarwood-producing plants[32,52,102,105]. The initiation of large-scale cultivation and expansive plantations of *Aquilaria* trees introduces a sustainable avenue for sourcing agarwood. Previously, the development of susceptible *Aquilaria* lines was mostly through tissue culture[69], seed propagation and cutting and grafting propagation[80,157]. However, the restricted longevity of *Aquilaria* species' seeds presents a considerable impediment to agarwood production[50], whereas the development of roots presents a significant limiting factor for successful reproduction during the micropropagation of *Aquilaria* species. Cultivating new *Aquilaria* lines showcasing desirable traits has relied on selective breeding based on phenotypic selection[21,158]. Modern technical developments like marker-assisted selection offered substantial potential for creating promising *Aquilaria* lines[159]. The primary benefit of this approach lies in the use of a collection of molecular markers and biochemical markers to anticipate phenotypic traits before they fully manifest, allowing for the early identification and selection of *Aquilaria* plants with beneficial traits[29]. Utilizing such innovative methods could be instrumental in improving the quality and yield of agarwood production.

CONCLUSION

This review has aimed to provide a comprehensive overview of *Aquilaria* species. Twenty-one distinct *Aquilaria* species have been extensively documented, emphasising their origins and geographical distributions. Most of these species are concentrated in regions spanning India, China and various Southeast Asian countries. Furthermore, we delved into the significant chemical constituents found within *Aquilaria* species by drawing upon previous research. Numerous phytochemicals, including sesquiterpenes, triterpenes, chromones and various phenolic compounds, have been identified, each with well-documented pharmacological uses. Of particular importance, we explored the methods employed for authenticating *Aquilaria* species, including both traditional morphological descriptors and cutting-edge DNA barcoding approaches. These techniques play a pivotal role in ensuring the accurate classification of these species. Lastly, we discussed strategies for preserving and cultivating *Aquilaria* species to support sustainable agarwood production. These measures entail recognizing the ecological importance of these trees and implementing measures to safeguard their populations. In light of the significant economic value and ecological significance of *Aquilaria* species, continued research and conservation efforts are essential to ensure their long-term survival and sustainable agarwood production.

SIGNIFICANCE STATEMENT

This review endeavors to furnish an exhaustive survey of *Aquilaria* species. It documents 21 distinct species, highlighting their origins, primarily across India, China and Southeast Asian nations. We next summarize key chemical constituents in these species, including sesquiterpenes, triterpenes, chromones and phenolic compounds. Significantly, this review scrutinizes the methodologies for authenticating *Aquilaria* species. This includes traditional morphological descriptors alongside DNA barcoding techniques. Furthermore, it addresses conservation and cultivation strategies for *Aquilaria* species, essential for sustainable agarwood production. These strategies involve recognizing their ecological value and implementing protective measures for their populations. Given the *Aquilaria* species' considerable economic importance, this review underscores the necessity for ongoing research and conservation initiatives to guarantee their enduring viability and sustainable exploitation of agarwood.

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