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REVIEW ARTICLE

Essential oil from *Aquilaria* spp. (agarwood): a comprehensive review on the impact of extraction methods on yield, chemical composition, and biological activities

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ABSTRACT

Agarwood essential oil (AEO), a highly prized medicinal substance, holds multifaceted applications across chemistry, traditional medicine, religion, and other domains. However, its limited yield poses a significant challenge to its widespread utilization. Conventional methods such as hydro-distillation (HD) and steam distillation (SD) do not ensure optimal extraction rates. Solvent extraction (SE) offers the potential for higher yields, albeit with the need for caution due to potential solvent residue hazards. Ultrasonic-assisted extraction (UAE) uses mechanical vibrations and cavitation to speed up extraction and increase yield, however it may damage bioactive chemicals over time. Microwave-assisted extraction (MAE), with its capacity to modify treatment conditions, presents an avenue to tailor functional components. Supercritical fluid extraction (SFE), while time-efficient, faces limitations due to its high cost. Enzyme pretreatment, despite its effectiveness, is not economically viable. Optimizing HD, UAE, and MAE concurrently can substantially reduce the duration and expense of AEO production, leading to higher yields. In addition, by adapting the composition to the unique characteristics of various extraction methods, AEO production can be enhanced, and a broader spectrum of functionalities can be explored. This article comprehensively reviews the impact of HD, SD, SE, UAE, MAE, SFE, and enzyme pretreatment on AEO yield, chemical composition, and biological functionality. It aims to furnish valuable insights into diverse extraction methods and component variations, thereby serving as a seminal reference for enhancing AEO yield and fostering extensive functional research.

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KEYWORDS
Aquilaria spp; agarwood essential oil (AEO); extraction; yield; chemical composition

1. Introduction

The term 'essential oil' originated from the 16th century designation coined by Paracelsus for a substance known as *quinta essentia* (1). These aromatic, oily liquids are extracted from various plant materials, including flowers, buds, seeds, leaves, twigs, bark, herbs, timber, fruits, and roots using the essential oil extraction technique (2,3). Due to their abundant functional properties, high potency, and plant-based origin, essential oils have come into widespread use globally (4). Simultaneously, their multifaceted functions and potential applications, including scents, flavoring, and pharmaceutical properties, play a significant role in various industries such as health care, cosmetics, aromatherapy, and household nursing (5). Notably, there is a growing demand for essential oils, particularly from the cosmetics and healthcare products industries, contributing to rapid industrial growth (6). Between 2022 and 2027, the agarwood essential oil market is projected to grow at a CAGR of 6.86%. Simultaneously, the agarwood essential oil market share is anticipated to rise at a CAGR of 6.35%, aiming to achieve a target of USD 345.5 million by the conclusion of 2030 (7). Chemically, essential oils comprise various fractions, representing secondary metabolites and plant-defense phytochemicals (3). These oils are complex composites of molecules with diverse structures and functional groups, primarily derived from mevalonate, methylerythritol, and shikimic acid biosynthesis routes (8). Variability in functional activities arises from differences in the chemical composition and content of essential oils. The distinct chemical profiles of essential oils are influenced by factors such as the tree species, planting locations, and extraction methods employed. These variations lead to unique application directions in cosmetics, medicines, aromatherapy, and other applications (2,9).

Insufficient extraction capacity stands as a significant hurdle in the accelerated growth of essential oils, particularly given the global demand for increased production capacity (10,11). Traditional essential oil production industries predominantly rely on the conventional hydro-distillation (HD) extraction method.

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However, this approach suffers from several drawbacks, including inadequate yields, high electricity consumption, and prolonged extraction duration (12–14). Despite these limitations, the HD method remains the prevailing extraction technique, primarily due to its cost-effectiveness and minimal investment requirements when compared to alternative technologies such as subcritical carbon dioxide, microwaves, ultrasound, and nonpolar solvents (6,15,16).

Agarwood essential oil (AEO) is a highly prized product within the realm of essential oils, renowned for its exceptional value. It ranks as one of the most expensive options in the spectrum of essential oil offerings, subjecting it to a rigorous process of quality assessment and grading. The variations in the morphology, sizes, pigmentation, and smell characteristics of the agarwood tree significantly influence the extraction of AEO (17). In Malaysia, the superior-grade essential oil is commonly referred to as Kalambak, while the inferior-quality counterpart is known as Gaharu (18,19). In India, quality distinctions are primarily categorized into four grades: A represents black or genuine agar, B represents brown bantang wood, C represents Butha, and D represents Dhum. These grades play a crucial role in the commercial production of agarwood, encompassing most of the essential oil varieties (20).

The AEO market demonstrated a value of $250 million in 2022 and is anticipated to experience substantial growth reaching US$ 265 million in 2023 and soaring to US$ 435 million in 2032 (21). The outlook for the AEO market is highly positive, propelled by persistent global demand in the cosmetics and personal care industries. AEO has garnered increasing popularity and recognition for its numerous potential advantages.

This review aims to explore in detail the effects of different essential oil extraction methods on the yield, chemical composition, and biological activity of different varieties of agarwood. It not only provides a basis for an in-depth understanding of the chemical diversity and biological activity of essential oils, but also provides a basis for optimizing the extraction process and improving the essential oils. Yield and quality, as well as promoting innovation and sustainable development of essential oil applications provide important guidance. In addition, the special focus on AEO highlights the importance and challenges of quality control of high-value essential oils, contributing valuable insights to the advancement of the essential oil industry and the development of high-quality essential oils.

2. Agarwood essential oil (AEO)

Agarwood, recognized by various names such as aloeswood, eaglewood, gaharu, oud, oudh, kanankoh, kyara, jinkoh, Chen Xiang, and kalambak, holds significant economic value (22–25). Throughout history, AEO has been utilized as incense in various religious ceremonies, including those practiced in Buddhist, Indian, and Islamic traditions (20). Agarwood cultivation is widespread across countries such as Indonesia, Malaysia, China, India, the Philippines, Cambodia, Vietnam, Laos, Thailand, Papua New Guinea, Singapore, and others. Among the 31 varieties of *Aquilaria* trees, 19 are known to produce AEO (26,27). Table 1 presents the 19 *Aquilaria* spp. species capable of producing AEO. Various techniques for inducing agarwood formation exist, categorized as natural formation, standard induction, biological induction, and chemical induction methods (22–25,27–29). These inductions are typically initiated by methods such as drilling, insect infestations, and bacterial and fungal interactions (30), triggering a defensive reaction in agarwood trees. This reaction may result in the secretion of resin and the synthesis of diverse secondary metabolites. Over time, resin gradually accumulates around injured or decaying portions of the tree's main stem, ultimately leading to the formation of AEO due to the presence of volatile chemicals (30).

Table 1. Nineteen *Aquilaria* Spp. Capable of Producing AEO (27).

No	Species of *Aquilaria*	Origin
1	*Aquilaria apiculata* Merr	Philippines
2	*A. baillonii* Pierre ex Lecomte	Cambodia
3	*A. banaensis* P. H. Hô	Vietnam
4	*A. Beccariana* Tiegh	Borneo, Brunei, Sarawak, and Sumatra
5	*A.* citrinicarpa Hallier f	Philippines
6	*A. crassna* Pierre ex Lecomte	Cambodia, Laos, Thailand, and Vietnam
7	*A. cumingiana* Ridl	Philippines
8	*A. filaria* Merr	Philippines
9	*A. hirta* Riedl	Malaysia
10	*A. khasiana* Hallier f.	India
11	*A. malaccensis* Lam (Synonym: *A. agallocha*)	Northeastern India, Burma, Malaysia, Sumatra, Borneo, and Philippines
12	*A. microcarpa* Baill	Borneo, Sarawak, and Sumatra
13	*A. parvifolia* Ding Hon	Philippines
14	*A. rostrata* Ridl	Malaysia
15	*A. rugosa* Kiet & Kessler	Vietnam
16	*A. sinensis*	China
17	*A. subintegra*	Thailand
18	*A. urdanetensis*	Philippines
19	*A. yunnanensis* S.C. Huang	China

AEO is currently employed in the fields of medicine, perfumery, and aromatherapy. Notably, it plays a significant role in traditional Chinese medicine, where it is frequently employed in aromatherapy to address psychological disorders such as anxiety, depression, and insomnia (31–33). Additionally, there are reports suggesting that AEO may have the potential to enhance cardiac function, alleviate pain, and serve as a therapeutic option for various ailments, including gastrointestinal issues, cough, rheumatism, and hyperthermia (20,34,35). The widespread use of AEO in various aspects of daily life and medicinal interventions underscores its scientific significance in the field of essential oil extraction studies.

AEO extraction techniques have undergone extensive historical evolution and have currently reached a state of maturity following significant advancements. The quantity and quality of AEO are influenced by various factors, including the species of agarwood, geographical locations of production, induction procedures, extraction conditions, and additional contributing factors (14,36,37). Tables 2–8 present a detailed overview of primary extraction techniques, the associated parameters, and documented AEO yields to date. Figure 1 summarizes the flow of different extraction methods. The extraction yield of AEO during the process is significantly influenced by the distinct principles employed in various extraction procedures. While the HD method is popular, its popularity does not necessarily align with achieving the maximum extraction yield. SFE, despite offering a time-saving method, may not be frequently utilized. To optimize economic benefits, individuals often combine multiple extraction methods, resorting to compound extraction (13,25,37,38,47–52). Table 9 provides a comprehensive summary of extraction yields, along with the merits and drawbacks associated with various AEO extraction techniques. This resource serves as a significant reference point for selecting a suitable extraction process tailored to specific production objectives.

Table 2. AEO HD Yields and Parameters.

No.	Species	Country	Sieve (mesh)	Solid-to-liquid ratio	Soaking	Heating time	Heating temperature (℃)	Yields (%)	Components	References
1	*A. malaccensis*	India	NA	NA	NA	NA	NA	0.14	9	(38)
2	*A. sinensis* (Induced)	China	20	NA	8 hours	12 hours	NA	0.042	42	(39)
3	*A. sinensis* (Wild)	China	20	NA	8 hours	12 hours	NA	0.320	36	(39)
4	*A.sinensis* (Healthy)	China	20	NA	8 hours	12 hours	NA	0.012	30	(39)
5	*A. malaccensis*	Thailand	NA	NA	NA	48 hours	NA	0.3	18	(40)
6	*A. subintegra*	Thailand	NA	NA	NA	48 hours	NA	0.7	28	(40)
7	*A. crassna*	Thailand	NA	NA	NA	48 hours	NA	0.8	30	(40)
8	*A. crassna*	Thailand	7	1:5	5 days	30 hours	100	0.075	13	(37)
9	*A. malaccensis*	Malaysia	NA	NA	NA	12 hours	NA	0.20	49	(41)
10	*A. sinensis* (Wild)	China	20	NA	≈8 hours	12 hours	100	0.1158	42	(42)
11	*A. sinensis* (Induced)	China	20	NA	≈8 hours	12 hours	100	0.0740	45	(42)
12	*A. sinensis* (Healthy)	China	20	NA	≈8 hours	12 hours	100	0.0079	15	(42)
13	*A. crassna*	Vietnam	NA	NA	3 weeks	72 hours	NA	0.25	30	(43)
14	*Aquilaria* spp.	Malaysia	NA	1:10	14 days	72 hours	NA	0.13	NA	(44)
15	*Aquilaria* spp.	Malaysia	NA	1:10	6 days	72 hours	NA	0.06	NA	(44)
16	*A. crassna*	Vietnam	NA	1:4	3 weeks	72 hours	NA	0.32	41	(36)
17	*A. crassna*	Vietnam	NA	1:4	3 weeks	72 hours	NA	0.27	41	(36)
18	*A. crassna*	Vietnam	NA	NA	3 weeks	72 hours	NA	0.25	39	(36)
19	*A. malaccensis*	Malaysia	NA	1:4.5	7 days	30 hours	NA	0.03	21	(13)
20	*A. subintegra*	Malaysia	NA	1:10	14 days	7 hours	100	0.13	48	(45)
21	*A. subintegra*	Malaysia	NA	1:10	6 days	7 hours	100	0.06	NA	(45)
22	*A. malaccensis*	India	NA	NA	10 days (5%salt water)	7 days	NA	0.56	23	(7)
23	*G. bancanus*	Indonesia	NA	1:7	NA	6 hours	NA	0.9	20	(46)

NA: Not Available.

Table 3. AEO SD Yields and Parameters.

No.	Species	Country	Sieve (mesh)	Solid-to-liquid ratio	Soaking	Heating time	Heating temperature (℃)	Yields (%)	Components	References
1	*A. malaccensis*	China	24	1:10	12 hours	4 hours	NA	0.14 ± 0.03	32	(53)
2	*Aquilaria* spp.	Malaysia	NA	NA	7 days		NA	NA	NA	(12)

NA: Not Available.

Table 4. AEO SE Yields and Parameters.

No.	Species	Country	Solvent	Solid-to-liquid ratio	Processing conditions	Yields (%)	Components	References
1	*A. crassna*	Thailand	50% Ether	1:5	Soaked for 5 days followed by HD	0.20	9	(14)
2	*A. crassna*	Thailand	80% Ether	1:5	Soaked for 5 days followed by HD	0.21	13	(14)
3	*A. crassna*	Thailand	Sulphuric acid (pH = 2)	1:9	Soaked for 5 days followed by HD	0.20	15	(14)
4	*A. crassna*	Thailand	Sulphuric acid (pH = 4)	1:9	Soaked for 5 days followed by HD	0.21	11	(14)
5	*A. crassna*	Vietnam	Chloroform	NA	3 weeks	0.15	37	(43)
6	*A. sinensis*	China	Ether	1:60	Ultrasound 60 min,1 ml alcohol dissolve	6.65 ± 0.22	41	(54)
7	*A. crassna* (Induced-18 months)	China	Ether	1:30	Mixed liquid in ultrasound for 30 min	2.19 ± 0.53	70	(55)
8	*A. sinensis* (Induced-12 months)					6.07 ± 0.47		
9	*A. sinensis*	China	95% Ethanol	1:10	The yields is extract, not pure essential oil	20.98	NA	(70)
10	A. *sinensis* (Wild)	China	Alcohol	1:50	Refluxed in a condenser for 1 h	0.17	54	(56)
11	*A. sinensis* (Brown Zone)					0.31	52	
12	*A. sinensis* (Healthy)					0.03	23	
13	*A. sinensis* (Healthy)	China	Ether	1:30	Soaked in 100 ml of 95/5 (v/v) ethanol/water for extraction followed by thermal reflux at 90 °C for 1 h	0.45 ± 0.08	15	(57)
14	*A. sinensis* (Induced)					7.57 ± 1.76	34	(57)
15	*A. sinensis* (Wild)					7.21 ± 0.38	66	(57)
16	*G. bancanus*	Indonesia	n-hexane	1:5	NA	0.54 ± 0.11	36	(46)
17	*G. bancanus*	Indonesia	Dichloromethane	1:5		3.04 ± 0.20	33	
18	*G. bancanus*	Indonesia	Ethyl acetate	1:5		19.01 ± 1.89	28	
19	*G. bancanus*	Indonesia	Methanol	1:5		53.71 ± 0.00	24	
20	*A. sinensis* (No. CQN20220603–1)	China	Ether	1:5	Pretreatment use HD for 4 hours	1.479	49	(58)
21	*A. sinensis* (No. CQN20220603–2)	China	Ether	1:5		2.131	49	(58)
22	*A. sinensis* (No. CQN20220603–3)	China	Ether	1:5		2.615	43	(58)

NA: Not Available.

Table 5. AEO UAE Yields and Parameters.

No.	Species	Country	Solid-to-liquid ratio	Soaking	Ultrasound frequency	Ultrasound power	Ultrasound time	Heating time	Yields (%)	Components	References
1	*A. crassna*	Malaysia	NA	NA	NA	NA	NA	9 hours	0.17	NA	(59)
2	*A. crassna*	Malaysia	1:20	NA	NA	NA	NA	NA	0.14	NA	(59)
3	*A. crassna*	Malaysia	1:16	NA	NA	NA	NA	9 hours	0.11	NA	(60)
4	*A. crassna*	Thailand	1:9	NA	44–48 kHz	NA	30 hours	30 hours	0.20	9	(14)

NA: Not Available.

3. Extraction of AEO

3.1. Hydro-distillation (HD)

The hydro-distillation (HD) method involves soaking raw agarwood material, inducing water hydration. This process increases the swelling pressure of oil glands, leading to plant cell destruction and subsequent release of intracellular compounds (12,14,50,65). Figure 1(a) illustrates the design of the HD operation. Table 2 displays the most recent findings, indicating that the extraction yield of HD typically ranges between 0.0079% and 0.90% (7,13,36–39,41–46). Key factors influencing yield include origin, soaking time (44,66), solid-to-liquid ratio (43,50), and extraction time (12). A comparative analysis of studies boiling agarwood for 7 hours (0.13%) (45), 72 hours (0.25–0.27%) (36), and 7 days (0.56%) (7) reveals a proportional relationship between extraction time and yield. The origin of agarwood material and the growth environment are also key factors affecting the extraction yield. For instance, under identical extraction temperature (100 ℃) and extraction time (72 hours), AEO yield from Bac Giang Province (0.32%) exceeds that of Phu Quoc Island (0.25%) by 0.07% (36). The solid-to-liquid ratio is another critical factor impacting extraction efficiency. Under constant conditions (temperature 100 °C, soaking time 3 weeks, boiling time 72 h), ratios of 1:10 and 1:4 yield 0.25–0.32% (50) and 0.25% (43), respectively. The direct proportionality between solid-to-liquid ratio

Table 6. AEO MAE Yields and Parameters.

No.	Species	Country	Solid-to-liquid ratio	Soaking	Microwave Power	Microwave Time	Heating Time	Yields (%)	Components	References
1	*A. malaccencis*	Malaysia	NA	NA	500 W	NA	5 hours (Combined with HD)	0.22	57	(41)
2	*A. crassna*	Vietnam	NA	3 weeks	650 W	NA	6 hours (Combined with HD)	0.20	26	(43)
3	*A. malaccencis*	Malaysia	1:4.5	72 hours	800 W	1 min	30 hours	0.03	NA	(13)
4	*A. malaccencis*	Malaysia	1:4.5	72 hours	800 W	2 mins	30 hours	0.07	NA	(13)
5	*A. malaccencis*	Malaysia	1:4.5	72 hours	800 W	3 mins	30 hours	0.08	20	(13)
6	*A. subintegra*	Malaysia	1:10	14 days	300 W	NA	5 hours (Combined with HD)	0.11	48	(45)
7	*A. subintegra*	Malaysia	1:10	14 days	400 W	NA	5 hours (Combined with HD)	0.10	47	(45)
8	*A. subintegra*	Malaysia	1:10	14 days	600 W	NA	5 hours (Combined with HD)	0.13	49	(45)
9	*A. subintegra*	Malaysia	1:10	14 days	800 W	NA	5 hours (Combined with HD)	0.11	49	(45)
10	*A. subintegra*	Malaysia	1:10	6 days	600 W	NA	5 hours (Combined with HD)	0.09	41	(45)

NA: Not Available.

Table 7. AEO SFE Yields and Parameters.

No.	Species	Country	Mesh	Extraction Pressure	Extraction temperature (℃)	CO_2 extraction time	CO_2 flow rate	Yields (%)	Components	References
1	*A. crassna*	Thailand	NA	600 bar	85	3 hours	0.5 kg/h	0.47	14	(37)
2	*A. sinensis*	China	NA	25 MPa	40	2 hours	20 l/h	1.05	35	(61)
3	*A. crassna*	Vietnam	NA	NA	NA	NA	NA	0.20	21	(43)
4	*A. sinensis*	China	60	24 MPa	35	2 hours	33 l/h	2.41	100	(62)
5	*A. crassna*	NA	NA	22 MPa	47	2 hours	2 l/h	0.005–0.006	18	(63)
6	*Aquilaria* spp.	Malaysia	NA	20 MPa	65	2 hours	3.0 mL/min	0.2	70	(52)
7	*Aquilaria* spp.	Malaysia	NA	30 MPa	65	2 hours	3.0 mL/min	0.1	70	(52)
8	*Aquilaria* spp.	Malaysia	NA	40 MPa	65	2 hours	3.0 mL/min	0.3	36	(52)

NA: Not Available.

Table 8. AEO Enzyme Pretreatment Yields and Parameters.

No.	Species	Country	Solid-to-liquid ratio	Enzyme	Enzyme Time	Enzymatic hydrolysis temperature (℃)	Yields (%)	Components	Processing conditions	References
1	*A. crassna*	Thailand	1:9	Cellulase; xylase; alcalase; rohalase	3 days	55 ℃	0.21	17	Incubated for 3 days at 55 ℃	(37)
2	*A. crassna*	Vietnam	NA	Laccase 1.0 ml/g Htec-2 1.5%	10 hours	40 ℃	0.32	26	Soaked for 24 hours followed by HD for 72 hours	(43)
3	*Aquilaria* spp.	Malaysia	1:10	Cellulase 1%	6 days	55 ℃	0.10	NA	HD for 7 hours	(44)
4	*Aquilaria* spp.	Malaysia	1:10	Cellulase 3%	6 days	55 ℃	0.13	NA	HD for 7 hours	(44)
5	*Aquilaria* spp.	Malaysia	1:10	Cellulase 5%	6 days	55 ℃	0.11	NA	HD for 7 hours	(44)

NA: Not Available.

and extraction yield is evident. Under constant conditions (solid-liquid ratio 1:10, boiling time 72 h), soaking of 6 days and 14 days produced 0.06% and 0.13%, respectively (44). Jok *et al.* (2016) found that longer soaking times may increase yield, but they also increase the acidity of the culture medium, which corrodes the cell walls of agarwood, causing excessive breakage and releasing compounds into the soaking medium, resulting in lower yields (66). Under the same extraction conditions, soaking agarwood for 6 days yielded more chemical components (41 components) compared to direct extraction without soaking (18 components) (67). Based on the data, the optimal HD settings consist of soaking the material for 14 days, using a mesh size of 20, maintaining a material-to-liquid ratio of 1:10, and boiling the mixture in water for 7 days. These parameters are considered the most superior for AEO HD.

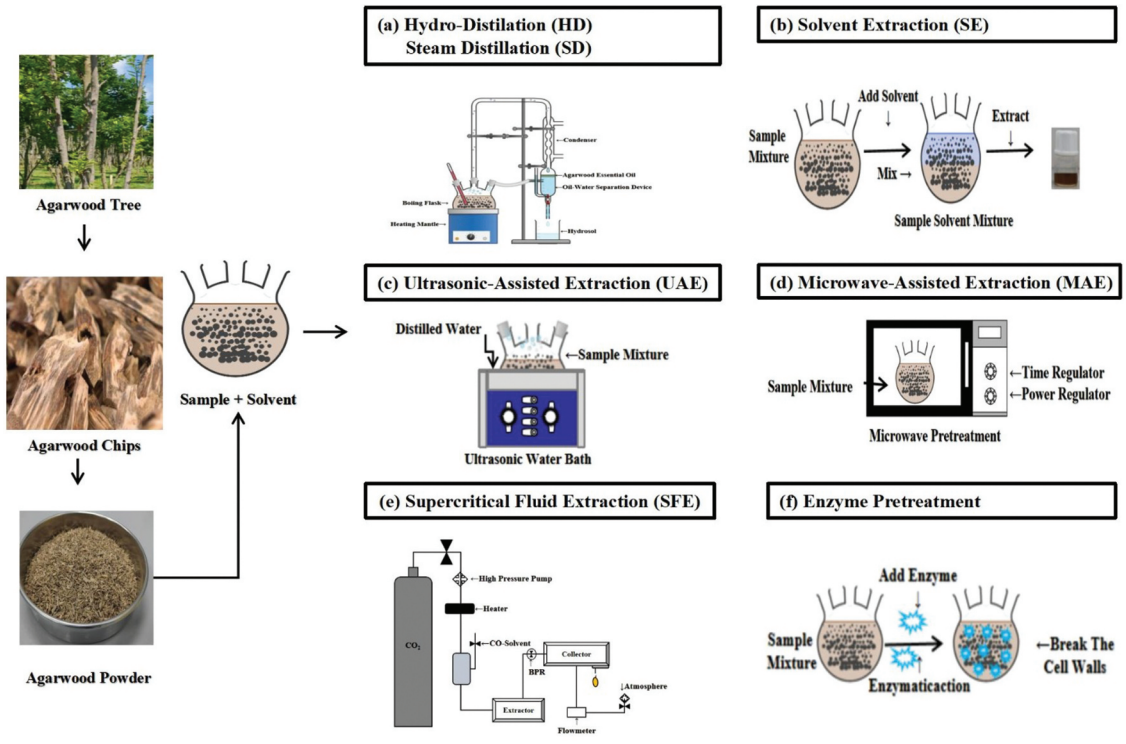

Figure 1. Different AEO Extraction Methods: (a) Hydro-Distillation (HD) and Steam Distillation (SD), (b) Solvent Extraction (SE), (c) Ultrasonic-Assisted Extraction (UAE), (d) Microwave-Assisted Extraction (MAE), (e) Supercritical Fluid Extraction (SFE), and (f) Enzyme Pretreatment.

Table 9. Comparison of Advantages and Disadvantages of Different AEO Extraction Methods.

No	Extraction method	Advantages	Disadvantages	Yield (%)	References
1	HD	1. Most widely used. 2. Equipment is cheap and easy to operate.	1. Extraction time-consuming (8 h-3 weeks). 2. High temperature causes ingredients to easily degrade.	0.0079–0.90	(7,13,36–39,41–46)
2	SD	1. Device cheap.	1. Insufficient reaction 2. Low yield.	0.14–0.33	(12,53)
3	SE	1. Highest extraction yield.	1. The use range limited by solvent residues.	0.03–53.71	(14,43,46,54–58)
4	UAE	1. Low equipment requirement. 2. Short processing time. 3. No high temperature.	1. Yield enhancement not as effective as SE and SFE.	0.11–0.20	(14,52,59,60)
5	MAE	1. Short time (1–3 min).	1. Excessive power causes ingredient degradation.	0.03–0.22	(13,41,43,45)
6	SFE	1. Low temperature. 2. Varied components.	1. The most expensive. 2. Produce greenhouse gases. 3. Difficulty in widespread industry use.	0.005–2.41	(37,43,52,61–64)
7	Enzyme pretreatment	1. Mild process (55 ℃).	1. Not suitable for industrial production.	0.10–0.32	(14,37,43,44,60)

3.2. *Steam distillation (SD)*

The steam distillation (SD) extraction procedure involves placing raw agarwood material within a still. During the process, steam permeates the raw materials on the sieve bed, causing gradual rupture of the agarwood cell walls. This rupture facilitates the transportation of essential oil by steam, achieving the intended extraction objective (12,53,68). Currently, SD utilizes either a gas furnace or an electric stove, ensuring precise temperature control to minimize the risk of AEO loss due to excessive heat during extraction (53,69). Figure 1(b) illustrates the functional layout of the SD extraction system. The sole distinction from HD is in the necessity of material-liquid separation during the extraction phase of this approach. Given that the process remains consistent, the identical graph is employed to elucidate them. According to statistical data (Table 3), the extraction yield of SD was reported as 0.14% (12,53). Key factors significantly influencing yield include the source or origin of the substance being extracted, the duration of the soaking process, the solid-to-liquid ratio, and the extraction process duration (11,12,53). Compared to

alternative extraction techniques, SD exhibits reduced efficiency due to limited contact between the raw material and water. Consequently, the HD method has gradually replaced SD due to its higher efficiency.

3.3. Solvent extraction (SE)

The solvent extraction (SE) method utilizes organic solvents with low boiling points, employing techniques such as cold soaking, hot extraction, or continuous reflux extraction. These approaches effectively reduce cell wall integrity and disrupt oil glands. Commonly used solvents include ether, water, chloroform, alcohol, n-hexane, and methanol (14,43,68). The solvent approach allows for the dissolution of a broader range of aromatic chemicals, encompassing both volatile and non-volatile compounds, resulting in an enhanced extraction yield. However, the application of this method is constrained by the challenges associated with solvent removal. According to Table 4, the extraction yield of SE varies significantly, ranging from 0.03% to 53.71%, depending on the type of solvent and the amount added (14,43,46,54–58). In a study by Yoswathana *et al* (14), an increase in the volume-to-volume ratio of the solvent from 50% to 80% resulted in a negligible increase in the extraction yield from 0.20% to 0.21%. Once the saturation point is reached, adding more solvents does not lead to an increase in the yield of AEO under the same extraction time and solvent conditions. Furthermore, the selection of the suitable solvent type is a crucial determinant of the AEO yields. Oktavianawati, Santoso, & Fatmawati (2023) conducted a comparison of the extraction of AEO using different solvents: n-hexane ($0.54 \pm 0.11\%$), dichloromethane ($3.04 \pm 0.20\%$), ethyl acetate ($19.01 \pm 1.89\%$), and methanol ($53.71 \pm 0.00\%$). The utilization of various solvents in the extraction process of AEO has a notable influence. Nevertheless, a significant issue in solvent extraction is the presence of residual solvent, which serves as the primary constraint on the potential applications of AEO. Figure 1(b) provides an example of the SE extraction system.

3.4. Ultrasonic-assisted extraction (UAE)

Ultrasonic-assisted extraction (UAE) enhances molecular motion by utilizing mechanical vibration, diffusion, and stirring induced by the ultrasonic extractor. It simultaneously induces cell wall permeation by cavitation and enhances solvent infiltration (71,72). The UAE process involves the use of ultrasonic waves to induce damage to the cellulose framework, caused by the generation of oxidative free radicals, leading to alterations in the external structure of the sample (73). Comparing UAE with traditional procedures reveals its significant ability to reduce extraction time. The extraction yield of the UAE method, as indicated in Table 5, ranges from 0.11% to 0.20% (14,59,60). However, in practical production, UAE is seldom employed as the primary extraction method for AEO. Instead, it is commonly used as a supplementary extraction technique in conjunction with other methods (14,59,60). The main factors affecting the extraction yield of UAE are extraction time and the solid-to-liquid ratio. Overall, the extraction time, ranging from 9 hours (0.11%-0.17%) (59,60) to 30 h (0.20%) (14), is directly proportional to the extraction yield of essential oil. The increased UAE yield can be attributed to the cavitation effect induced by UAE, resulting in cell disintegration and rapid rupture of interparticle collisions. The degradation of the cell wall facilitates the entry of the extraction solvent into the cellular tissue and the dispersion of metabolites from the plant matrix into the solvent (74). However, for ultrasonic treatment, a longer time does not necessarily imply better treatment. For instance, prolonged ultrasonic irradiation can lead to the degradation of polar bioactives, as observed during the treatment of ginger using ultrasound by Binello *et al*. (2020) (74). Similar degradation of phenolic compounds, such as in ginger, occurred when the irradiation time was increased from 5 to 30 minutes (75). Therefore, the UAE process is likely to have potential degradation effects on the stability of bioactive during the extraction process, reflecting the bioactivity of the spice extracts, which is highly dependent on their chemical structure (76). Figure 1(c) provides an example of the UAE extraction system.

3.5. Microwave-assisted extraction (MAE)

Microwave-assisted extraction (MAE) involves submerging samples in a solvent characterized by a low dielectric constant and high transparency to microwaves. The rapid generation of heat is facilitated by quick transitions between positive and negative poles in dipole molecules, the presence of dipole eddy currents, ion conduction, and high-frequency friction. This technique enables the enlargement and disruption of oil glands and cellular membranes within sample cells (13,72). Manipulating the microwave extraction time revealed significant differences in the primary components and content of different groups of chemical compounds. The extraction yield of the MAE method, as indicated in Table 6. In Sarih's study, hydrocarbons (12.10%) and sesquiterpene hydrocarbons (2.60%) exhibited the

highest concentration as individual components after 5 hours, while oxygenated sesquiterpenes (60.70%) achieved the highest concentration within a four-hour time frame (77). This finding suggests that varying processing time offers opportunities for isolating specific components. Previous studies indicate that the extraction yield of MAE ranged between 0.03% to 0.22%, with differences primarily attributed to microwave power and extraction time (13,41,43,45). The extraction yield can be effectively improved under the same conditions by prolonging ultrasonic treatment time by 1 min (0.03%), 2 min (0.07%), 3 min (0.08%), 5 hours (0.08% – 0.13%), and 6 hours (0.20%) (13,45). Similar improvements are observed with the extension of soaking time: 6 days (0.08%), 14 days (0.13%), and 3 weeks (0.20%) (43). However, excessive microwave power can negatively impact the extraction effect, potentially leading to the degradation or evaporation of active compounds in AEO. Therefore, careful consideration of microwave power is essential to maintain optimal extraction efficiency. The reported best extraction power in studies was 500-650W (41,43,45). Figure 1 (d) illustrates an example of the MAE extraction system.

3.6. Supercritical fluid extraction (SFE)

Supercritical fluid extraction (SFE) technology demands the most sophisticated equipment. It leverages the unique properties of a substance in its supercritical state to extract and isolate desired components from experimental materials. Following extraction, the resulting product may contain impurities, specifically oil wax, necessitating subsequent refinement (37,52). Studies indicate that an increase in pressure during the extraction process increases the density of the CO_2 solvent (52). This heightened density strengthens the interaction between the solute and the solvent, further augmenting the solubility of oil and solvent (52). As shown in Table 7, the extraction yield of SFE technology varies between 0.005% to 2.41% (37,43,52,61–63), with pressure and temperature being the primary determinants for the disparity. This method is considered safe, nontoxic, and provides a greater extraction output. However, the high operational and capital costs associated with it discourage widespread adoption in industry. The pressure range for SFE is typically between 600 Bar and 40 Mpa. Increasing pressure within this specified range has the advantageous effect of augmenting solvent density, intensifying intermolecular contact between solute particles, and enhancing the dissolution of oil in the solvent (52,78). Consequently, the extraction efficiency of essential oil is improved. Under the same conditions, the addition of an ethanol modifier significantly increases the extraction yield (1.73%) compared to the modifier-free control (0.65%) (78). Figure 1 (e) illustrates an example of the SFE extraction system.

3.7. Enzyme pretreatment

The enzyme pretreatment technique involves the use of enzymes, such as cellulase, to enzymatically degrade the cellulose framework, breach the cellular wall, and enhance the solubilization of bioactive compounds within the cell. In agarwood, the primary constituents of the cell wall are cellulose, hemicellulose, and lignin, and these components can be effectively degraded through pretreatment with cellulase (44). This enzymatic treatment approach exhibits a gentle reaction process, and when combined with other extraction methods, it significantly enhances the extraction yield of AEO. The extraction yield obtained using the enzyme pretreatment approach ranges from 0.10% to 0.32% (37,43,44). The variation in extraction yield primarily stems from the specific enzyme type and quantity used, as outlined in Table 8 (37,43,44,79). When considering enzyme types, the effect of mixed enzymes (Laccase and Htec-2) and (Cellulase, xylase, alcalase, and rohalase) in synergistically assisted extraction (0.21%-0.32%) is notably superior to that of a single enzyme (cellulase) (0.10%-0.13%) (37,43,44). This enhancement can be primarily attributed to the varied substrate specificities exhibited by different enzymes. These enzymes operate synergistically, effectively targeting a more extensive array of sites, resulting in the enhanced and expedited release of a diverse range of components from biomaterials. Under the same conditions, an increase in the amount of cellulase added by 1% (yield: 0.09%), 3% (yield: 0.12%), and 5% (yield: 0.10%), does not lead to a linear increase in extraction yield during the extraction process (44). The optimal amount of added enzyme is obtained at 3%, where the extraction yield reaches its peak (44). This optimal amount might be attributed to the limited availability of the specific substrate for the enzyme. Once saturation is reached, the extraction yield may no longer exhibit further improvements. Additionally, excessive inclusion of enzymes can result in enzyme inhibition, reducing their efficacy. Figure 1(f) illustrates an example of enzyme pretreatment extraction technology.

In conclusion, the choice of extraction process requires carefully evaluating various criteria, including product requirements, economic considerations, and safety issues. When the primary goal is maximizing yield for a specific application without considering safety hazards, SE (0.03%-53.71%) offers the highest potential yields (14,43,46,54–58). For separating specific

functional components, MAE (0.03%-0.22%) enables targeting compounds by controlling processing time (13,41,43,45). For faster extraction, SFE (0.005% to 2.41%) is the best option (37,43,52,61–63). The UAE (0.11–0.20) emerges as a viable choice for enhancing production and facilitating industrialization in the extraction of AEO, owing to its cost-effective equipment and user-friendly operation. However, enzyme pretreatment (0.10%-0.32%) can substantially increase production costs due to high enzyme prices and lower yields compared to other extraction methods (37,43,44,79). Manufacturers often favor HD (0.0079% to 0.90%) for its moderate yields, cost-effectiveness, and minimal equipment requirements (7,13,36–39,41–46). Integrating HD, UAE, and MAE may significantly reduce time and costs, which improves the overall productivity. In summary, selecting the most appropriate extraction method based on target compounds, desired yields, and economic factors enables an efficient manufacturing process.

4. Chemical composition of AEO

The main components of AEO mainly include sesquiterpenoids (182), 2-(2-phenethyl)chromones (240), simple phenolic compounds, and miscellaneous compounds (1935–2019) (20,80). Key components influencing AEO efficacy include sesquiterpenoids, chromones, volatile and semi-volatile chemicals, and fatty acids (68,72). The specific agarwood type, geographical origin, extraction method, and extraction conditions impact component content and concentrations (7,31,36–40,46,53–58,61,63,81–86). Table 10 outlines key constituents and content variations among AEO extracted using different methods. Existing literature reports significant variations in the number of essential oil components obtained through different extraction methods. The SE method (9–70 compounds) (14,43,46,54–58,70,82) and SFE (14–100 compounds) (37,43,52,54,61–63,85,86) detected a more diverse array of components. Conversely, HD (9–55 compounds) yields a relatively lower number of ingredients, with most falling within the range of 20–40 compounds (7,13,31,36–46,81,83,85,86). MAHD (20–57 compounds) enhances the richness of AEO components compared to HD (13,41,43,45). Sarih's study provides more evidence that MAE (59 compounds) is more effective than HD (49 compounds) in increasing component diversity (41). UAHD (9 compounds) has been less extensively researched in AEO extraction, but findings suggest an impact on the composition of extracted components (14). EA (17–26 compounds) does not markedly increase the composition diversity of AEO (37,43).

The lower number of components in HD compared to SE and SFE may be attributed to several factors. Firstly, thermal stability exerts influence: HD necessitates a prolonged duration for azeotroping, limiting the extraction to low-boiling-point components while potentially losing characteristic compounds such as chromones (85). Moreover, extended heating may lead to the degradation of heat-sensitive ingredients. Secondly, the extraction principle differs. In the SFE process, when temperature and pressure surpass the critical point, the fluids exhibit a dual nature of gas and liquid, enabling deeper penetration into aromatic medicinal materials, thus facilitating the extraction of volatile components with high boiling points and molecular weights (86,87). Various solvents used in SE possess different polarities, enabling the dissolution of diverse compound types, whereas HD primarily extracts polar compounds due to water's polarity, limiting its efficacy in dissolving non-polar or weakly polar components (14,54,56,58,70). However, it is noteworthy that solvent methods significantly restrict usage due to residue issues.

Sesquiterpenes, comprising three isoprene units, are commonly encountered in plants as volatile constituents in essential oils, significantly contributing to the aroma profile of agarwood (80). Notable variations in sesquiterpene composition among different extraction methods are evident from Table 10. The HD method exhibits the highest relative content of sesquiterpenes (1.99–-96.24%), whereas SFE and SE yield a higher overall number of components but with lower relative content of sesquiterpenes (74.838–75.62% for SD, 1.46–91.76% for SE, and 7.39–63.83% for SFE, and 73.28% for EA). This outcome can be attributed to several factors. Firstly, the influence of relative proportion: solvents commonly employed in SE and SFE extraction, such as ethanol, hexane, and carbon dioxide, typically possess high solubility and the capability to dissolve a broader spectrum of non-polar and low molecular weight components. Consequently, a wider variety of compounds, including lighter monoterpenes and oxides, can be extracted from agarwood, resulting in a higher overall composition, which in turn may lead to a relatively lower proportion of sesquiterpenes in the AEO. This is corroborated by the observation that the overall quantities in SE and SFE are generally larger than in HD. Secondly, heat sensitivity plays a role: sesquiterpenes generally exhibit greater heat resistance compared to monoterpenes, indicating that high temperatures during steam distillation have a lesser impact on sesquiterpenes. However, in solvent-based methods or

Table 10. The Main Chemical Components of AEO Obtained Using Different Extraction Methods.

					Relative peak area of components (%)				
No.	Species	Nation	Method	Yield (%)	Total quantity	Sesquiterpenoids	Chromone	Others	References
1	*A. sinensis*	China	HD	0.042	42	Guaia-1 (10), 11-dien-9-one (10.89); Guaiol (9.34); Hinesol (6.34); Diepi-α-cedrene epoxide (6); Selina-3,11-dien-14-al (5.5); .... Total = 72.16%	NA	Total = 27.84%	(39)
2		China	HD	0.320	36	Baimuxinal (14.78); Guaiol (10.67); α-Copaen-11-ol (10.22); 1,2,5,5,8a-Pentamethyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-1-ol (5.82); Eremophila-7 (11), 9-dien-8-one (5.42); .... Total = 85.66%	NA	Total = 14.34%	(39)
3		China	HD (Sample: Wild)	0.1158	42	Baimuxinal (15.40); α-Copaen-11-ol (10.84); (4ar-cis)-4,4α,5,6,7,8-Hexahydro-4α,5-dimethyl-3-(1-methylethylidene)-2 (3 h)naphthalenone (6.36); Guai-1 (10)-en-11-ol (6.35); α-Selinene (4.08); .... Total = 63.38%	NA	Total = 36.62%	(42)
4		China	HD (Sample: Induced)	0.0740	45	α-Copaen-11-ol (6.24); cis-Z-α-Bisabolene epoxide (4.68); Aristolone (4.06); α-Selinene (3.49); Caryophyllene oxide (3.39); .... Total = 58%	NA	Total = 42%	(42)
5		China	HD (Sample: *Healthy)*	0.0079	15	Corymbolone (1.99) .... Total = 1.99%	NA	Total = 98.01%	(42)
6		China	HD	NA	54	Guaiol (23.17); Methyl ionone (5.92); γ-eudesmol(5.63); Agarospirol(5.29); Valerianol(4.99); ... Total = 68.68%	NA	Total = 31.32%	(85)
7		China	HD (Sample: BT20210421)	NA	48	Sesquiterpenoids Total = 77.3%	NA	Total = 22.7%	(86)
8		China	HD (Sample: CXT20161009–1)	NA	55	Sesquiterpenoids Total = 83.83%	NA	Total = 16.17%	(86)
9		China	HD (Sample: QN20210421)	NA	59	Sesquiterpenoids Total = 88.07%	NA	Total = 11.93%	(86)

(*Continued*)

Table 10. (Continued).

No.	Species	Nation	Method	Yield (%)	Relative peak area of components (%)				References
					Total quantity	Sesquiterpenoids	Chromone	Others	
10		China	HD	NA	40	(+)-α-Santalol (10.13); γ-selinene (8.39); carvacrol (7.20); Dispiro[cyclohexane-1,2′-bicyclo (1.1.0)butane-4′,1″-cyclohexane] (6.04); 2,3,4,5-tetramethyl-tricyclo[3.2.1.$0^{2,7}$] oct-3-ene (4.96); ... Total = 65.6%	NA	Total = 34.4%	(83)
11		China	SE (Sample: Induced-16 Months)	NA	NA	[3S-(3.alpha.,4a.alpha.,5.alpha.)]-3,4,4a,5,6,7-hexahydro-4a,5-dimethyl-3-(1-methylethenyl)-1(2 h)-naphthalenone (2.86); Agarospirol (1.28); 4a,5-dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-ol (0.26); α-santalol (0.16); .... Total = 12.19%	6-methoxy-2-(2-phenylethyl) chromone (9.12); 6-methoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (7.29); 6,7-dimethoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (2.33); 6-hydroxy-2-(2-phenylethyl) chromone (6.16); 6-hydroxy-2-(4-methoxyphenethyl) chromone (0.72); .... Total = 82.19%	Total = 5.62%	(55)
12		China	SE (Sample: Induced-12 Months)	NA	NA	[3S-(3.alpha.,4a.alpha.,5.alpha.)]-3,4,4a,5,6,7-hexahydro-4a,5-dimethyl-3-(1-methylethenyl)-1(2 h)-naphthalenone (2.75); Agarospirol (0.44); 4a,5-dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-ol (0.34); Alpha-santalol (0.08); .... Total = 17.46%	6-hydroxy-2-(2-phenylethyl) chromone (11.58); 6-methoxy-2-(2-phenylethyl) chromone (7.17); 6-methoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (5.37); 6-hydroxy-2-(4-methoxyphenethyl) chromone (2.77); 6,7-dimethoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (2.58); .... Total = 80.13%	Total = 2.41%	(55)

(*Continued*)

Table 10. (Continued).

No.	Species	Nation	Method	Yield (%)	Relative peak area of components (%)				References
					Total quantity	Sesquiterpenoids	Chromone	Others	
13		China	SE (Sample: Induced-18 Months)	NA	NA	[3S-(3.alpha.,4a.alpha.,5.alpha.)]-3,4,4a,5,6,7-hexahydro-4a,5-dimethyl-3-(1-methylethenyl)-1(2 h)-naphthalenone (2.84); Agarospirol (0.62); Alpha-santalol (0.24); 4a,5-dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-ol (0.34); .... Total = 19.97%	6-hydroxy-2-(2-phenylethyl) chromone (14.79); 6-methoxy-2-(2-phenylethyl) chromone (6.96); 6-hydroxy-2-(4-methoxyphenethyl) chromone (4.30); 6,7-dimethoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (2.39); 6-methoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (1.97); .... Total = 79.02%	Total = 1.01%	(55)
14		China	SE (Sample: Wild)	0.17	54	cis-Z-α-Bisabolene epoxide (9.07); α-Eudesmol (8.24); Guai-1 (10)-en-11-ol (7.09); (-)-Aristolene (4.10); Aristolone (4.05); .... Total = 75.98%	NA	Total = 24.02%	(56)
15		China	SE (Sample: Brown zone)	0.31	52	α-Eudesmol (8.37); Aristolone (8.14); cis-Z-α-Bisabolene epoxide (7.68); 2,2,6-Trimethyl-1-[(1E)-3-methyl-1,3-butadienyl]-5-methylene-7-oxabicyclo[4.1.0]heptane(5.21); Cedrenol (3.88); .... Total = 76.77%	NA	Total = 23.23%	(56)
16		China	SE (Sample: Healthy)	0.03	23	2,6-Dimethyl-10-methylene-12-oxatricyclo [.0 (1,6)]tridec-2-ene (2.73); α-Eudesmol (1.10); 1,5-Dimethyl-3-hydroxy-8-(1-methylene-2-hydroxyethyl-1)-bicyclo[]dec-5-ene (0.51); (-)-Isolongifolol (0.29); α-Selinene (0.20); .... Total = 8.14%	NA	Total = 91.86%	(56)

(*Continued*)

Table 10. (Continued).

No.	Species	Nation	Method	Yield (%)	Relative peak area of components (%)				References
					Total quantity	Sesquiterpenoids	Chromone	Others	
17		China	SE	NA	14	Isoalantolactone (3.57 ± 0.43); Cyperenone (1.40 ± 0.32); .... Total = 4.97%	2-(2-phenylethyl)chromone (33.00 ± 1.53); 2-[2-(4-methxyphenyl)ethyl] chromone (30.27 ± 0.95); 2-[2-(3-hydroxy-4-methxyphenyl)ethyl] chromone (10 ± 0.35); 6-Hydroxy-2-[2-(4-methxyphenylyethyl] chromone (4 ± 0.35); .... Total = 87.23%	Total = 7.8%	(82)
18		China	SE (Sample: Hurt Induced)	NA	27	Isoalantolactone (1.46 ± 0.37) Total = 1.46%	Oxidoagaochromone C (35.48 ± 1.71); 5,8-Dihydroxy-2-[2-(4 methxyphenylyethyl] chromone (12.06 ± 8.56); 6-hydroxy-2-[2-(3-methxy-4-hydroxyphenyl)ethy] chromone (6.29 ± 8.45); 5,6-Epoxy-7,8-dihydroxy-2-[2-(3-hydroxy-4-methxyphenyl)ethyl] chromone (5.63 ± 0.24); ... Total = 87.73%	Total = 10.81%	(82)
19		China	SE (Sample: CQN20220603–1)	1.479	49	β-Agarofuran (12.41); (1β,4aβ,7β,8aβ)-Octahydro-7-[1-(hydroxymethyl)ethenyl]-1,8α-dimethylnaphthalen-4α(2 h)-ol (11.32); α-Curcumene (9.28); 4β,7α,8α-H-eremophil-9 (10)-ene-8,12-epoxy-11α,13-diol (7.8); 9-Hydroxy-selina-3,11-dien-14-al (6.95); ... Total = 87.13%	2-[2-(4-Methoxyphenyl)ethyl] chromone (0.82); 2-[2-(3-Hydroxy-4-methoxyphenyl)ethyl] chromone (0.79); 2-[2-(3-Methoxy-4-hydroxyphenyl)ethyl] chromone (0.45); 2-(2-Phenylethyl)chromone (0.12); ... Total = 2.18%	Total = 10.69%	(58)
20		China	SE (Sample: CQN20220603–2)	2.131	49	Selina-3,11-dien-9-one (6.91); 10-Epi-γ-eudesmol (6.61); 9-Hydroxy-selina-3,11-dien-14-al (6.51); 9-Hydroxy-selina-4,11-dien-14-al (4.64); β-Elemol (3.94); ... Total = 91.76%	2-[2-(3-Hydroxy-4-methoxyphenyl)ethyl] chromone (3.43); 2-[2-(4-Methoxyphenyl) ethyl]chromone (1.29); 2-(2-Phenylethyl)chromone (1.23); ... Total = 5.95%	Total = 2.29%	(58)

(*Continued*)

Table 10. (Continued).

No.	Species	Nation	Method	Yield (%)	Relative peak area of components (%)				References
					Total quantity	Sesquiterpenoids	Chromone	Others	
21		China	SE (Sample: CQN20220603–3)	2.615	43	9-Hydroxy-selina-3,11-dien-14-al (13.71); Caryophyllenol-II (10.22); Baimuxinal (6.08); Selina-3,11-dien-9-one (3.84); Agarospirol (3.1); ... Total = 73.20%	2-[2-(4-Methoxyphenyl)ethyl] chromone (10.73); 2-(2-Phenylethyl)chromone (10.53); 2-[2-(3-Methoxy-4-hydroxyphenyl)ethyl] chromone (2.42); 2-[2-(3-Hydroxy-4-methoxyphenyl)ethyl] chromone (1.38); ... Total = 25.06%	Total = 1.74%	(58)
22		China	SFE	NA	83	Velleral(8.65); Aromadendrane-4,10-diol (4.58); Guaiol(1.87); 7-isopropenyl-1,4a-dimethyl-4,4a,5,6,7,8-hexahydro-3 h-naphthalen-2-one(1.28); ... Total = 23.78%	2-phenethyl-4 h-chromen-4-one (9.5); 6-methoxy-2-phenethyl-4 h-chromen-4-one (12.91); 6,7-dimethoxy-2-phenethylchromone (6.85); 6,7-dimethoxy-2-(4-methoxyphenethyl)-4 h-chromen-4-one (0.16); ... Total = 29.42%	Total = 46.8%	(85)
23		China	SFE	6.65 ± 0.22	41	Longifolene (4.14); Calarene (2.94); Squalene(2.31); ... Total = 25.78%	6,7-dimethoxy-2-(2-phenylethyl)chromen-4-one (14.74); 2-(2-phenylethyl)chromone (8.61); 6-methoxy-2-phenethyl-4 h-chromen-4-one (8.69); ... Total = 32.83%	Total = 41.39%	(54)
24		China	SFE (Sample: BT20210421)	NA	71	Sesquiterpenoids and Others Total = 62.05%	Total = 22.42%	Total = 15.53%	(86)
25		China	SFE (Sample: CXT20161009–1)	NA	72	Sesquiterpenoids and Others Total = 63.83%	Total = 17.48%	Total = 18.69%	(86)
26		China	SFE (Sample: QN20210421)	NA	35	Sesquiterpenoids and Others Total = 28.36%	Total = 60.42%	Total = 11.22%	(86)
27	*A. malaccensis*	China	SD	0.14 ± 0.03	32	Guaiol (21.353); β-Eudesmol (7.843); Agarospirol (7.338); 10-epi-γ-Eudesmol (5.723); Caryophyllene oxide (5.086); ... Total = 75.62%	NA	Total = 24.38%	(53)

(*Continued*)

Table 10. (Continued).

No.	Species	Nation	Method	Yield (%)	Relative peak area of components (%)				References
					Total quantity	Sesquiterpenoids	Chromone	Others	
28		China	SD	0.14 ± 0.03	32	Guaiol (21.204); β-Eudesmol (7.77); Agarospirol (7.326); Caryophyllene oxide (5.197); 10-epi-γ-Eudesmol (5.091); ... Total = 74.838%	NA	Total = 25.162%	(53)
29		China	SD	0.14 ± 0.03	32	Guaiol (21.574); β-Eudesmol (8.236); Agarospirol (7.407); 10-epi-γ-Eudesmol (5.736); (-)-Aristolene (5.069); ... Total = 75.537%	NA	Total = 24.463%	(53)
30		India	HD	0.14	9	Agarospirol (12.8); Jinkoh-eremol (11.5); Valerianol (8.9); epi-γ-eudesmol (5.5); β-agarofuran (3.9); .... Total = 48.2%	NA	Total = 51.8%	(38)
31		Thailand	HD	0.3	18	Isoamyl dodecanoate (55.6); Guaia-1 (10), 11-dien-15-ol (6.5); Karanone (4.9); Cyclocolorenone (4.7); Kusunol (3.9); .... Total = 82.9%	NA	Total = 17.1%	(40)
32		India	HD	0.56	23	Cubeno (22.26); Agarospiro (14.35); Aristolene (13.22); Epi-γ-eudesmo (6.12); Isovalenceno (4.62); ... Total = 80.89%	NA	Total = 19.11%	(7)

(*Continued*)

Table 10. (Continued).

No.	Species	Nation	Method	Yield (%)	Relative peak area of components (%)				References
					Total quantity	Sesquiterpenoids	Chromone	Others	
33	*A. crassna*	China	SE (Sample: Induced-12 Months)	NA	NA	4a,5-dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-ol (0.70); [3S-(3.alpha.,4a.alpha.,5.alpha.)]-3,4,4a,5,6,7-hexahydro-4a,5-dimethyl-3-(1-methylethenyl)-1(2 h)-naphthalenone (0.62); Agarospirol (0.37); α-santalol (0.15); .... Total = 6.51%	6-methoxy-2-(2-phenylethyl) chromone (9.43); 6-hydroxy-2-(2-phenylethyl) chromone (7.55); 6-methoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (3.15); 6-hydroxy-2-(4-methoxyphenethyl) chromone (2.75); 6,7-dimethoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (2.74); .... Total = 84.04%	Total = 9.45%	(55)
34		China	SE (Sample: Induced-18 Months)	NA	NA	4a,5-dimethyl-3-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-ol (0.36); [3S-(3.alpha.,4a.alpha.,5.alpha.)]-3,4,4a,5,6,7-hexahydro-4a,5-dimethyl-3-(1-methylethenyl)-1(2 h)-naphthalenone (0.41); Agarospirol (0.22); α-santalol (0.11); .... Total = 7.24%	6-hydroxy-2-(2-phenylethyl) chromone (11.25); 6-methoxy-2-(2-phenylethyl) chromone (5.51); 6-hydroxy-2-(4-methoxyphenethyl) chromone (4.20); 6,7-dimethoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (2.32); 6-methoxy-2-[2-(4-methoxyphenyl) ethyl]chromone (1.62); .... Total = 84%	Total = 8.76%	(55)
35		Thailand	HD	0.8	30	Isoamyl dodecanoate (13.4); Kusunol (8.2); Dehydrojinkoh-eremol (7.3); 9,11-eremophiladien-8-one (6.3); Agarospirol (5.8); .... Total = 60.4%	NA	Total = 39.6%	(40)
36		Thailand	HD	0.075	13	Selina-3,7 (11)-diene (17.21); δ-Selinene (12.36); 1,3,5-trimethyl-6-methyldiene-tricyclo ($3.2.1.0^{2,7}$)oct6–3-en-8exo-ol (10.26); 4a,5-Dimethyl-3-(1-methyldiene)-4,4a,5,6,7,8-hexahydro-2(3 h)-napthalene (9.6); .... Total = 74.24%	NA	Total = 25.76%	(37)

(*Continued*)

Table 10. (Continued).

No.	Species	Nation	Method	Yield (%)	Relative peak area of components (%)				References
					Total quantity	Sesquiterpenoids	Chromone	Others	
37		Thailand	SFE	0.47	14	Furoscrobiculin B (27.98); Bicyclo[4.4.0]dec-5-ene,1,5-dimethyl-3-hydroxy-8-(1-methylene-2-hydroxyethyl-1) (18.68); (3,8,8-Trimethyl-1,2,3,4,5,6,7,8-octanhydro-2-naphthalenyl)methyl Acetate (5.39); Agarospirol (4.71); .... Total = 62.62%	NA	Total = 37.38%	(37)
38		Thailand	EA	0.21	17	Aristol-9-en-8-one (28.77); β-guaiene (14.94); Guaia-3,9-diene (14.32); 7,7-dichlorobicycl0[3.2.0]hept-2-en-6-one (7.58); .... Total = 73.28%	NA	Total = 26.72%	(37)
39		Vietnam	HD	0.32	41	Neopetasane (7.96); β-Agarofuran (4.86); (1S,2S,6S,9 R)-6,10,10-Trimethyl-11-oxatricyclo[7.2.1.$0^{1,6}$]dodecane-2-carbaldehyde (4.67); Valerianol (3.91); Dihydrokaranone (3.59); .... Total = 56.66%	NA	Total = 43.34%	(36)
40		Vietnam	HD	0.27	41	Neopetasane (8.29); Valenca-1 (10), 8-dien-11-ol (6.05); Valerianol (5.37); (1S,2S,6S,9 R)-6,10,10-Trimethyl-11-oxatricyclo[7.2.1.$0^{1,6}$]dodecane-2-carbaldehyde (4.73); β-Eudesmol (4.38); .... Total = 66.09%	NA	Total = 33.91%	(36)
41		Vietnam	HD	0.25	39	Neopetasane (7.47); β-Agarofuran (6.18); Valerianol (4.56); Jinko-eremol (4.51); β-Eudesmol (4.18); .... Total = 58.7%	NA	Total = 41.3%	(36)

(*Continued*)

Table 10. (Continued).

No.	Species	Nation	Method	Yield (%)	Relative peak area of components (%)				References
					Total quantity	Sesquiterpenoids	Chromone	Others	
42		NA	SFE	0.005–0.006	18	Valerianol (12.31); γ-Eudesmol (8.03); epi-Cyclocolorenone (3.71); Nootkatone (3.71); beta-Eudesmol (3.69); ... Total = 39.61%	NA	Total = 60.39%	(63)
43	*G. bancanus*	Indonesia	HD	0.9	20	10-epi-γ-eudesmol (60.48); β-Eudesmol (28.04); Dihydrocarvyl acetate (3.13); 6-Methyl-5-heptene-2-one (2.05); α-terpineol (1.38); ... Total = 96.24%	NA	Total = 3.76%	(46)
44		Indonesia	SE	53.71 ± 0.00	24	10-epi-γ-eudesmol (36.21); β-Eudesmol (31.41); 1-Methyl-4-(2-methyloxiranyl)-7-oxabicyclo[4.1.0]heptane (7.82); 6-Methyl-5-heptene-2-one (5.08); Limonene dioxide 1 (3.86); ... Total = 88.65%	NA	Total = 11.35%	(46)
45		Indonesia	SE	19.01 ± 1.89	28	10-epi-γ-eudesmol (26.54); β-Eudesmol (22.47); 1-Methyl-4-(2-methyloxiranyl)-7-oxabicyclo[4.1.0]heptane (5.02); 3,3,6,6,9,9-Hexamethyl-tetracyclo [6.1.0.0^{2,4}.0^{5,7}]nonane (4.59); Oleic acid (4.43); ... Total = 85.4%	NA	Total = 14.6%	(46)
46		Indonesia	SE	3.04 ± 0.20	33	10-epi-γ-eudesmol (27.28); b-Eudesmol (19.17); 1-Methyl-4-(2-methyloxiranyl)-7-oxabicyclo[4.1.0]heptane (7.56); Oleic acid (4.37); α-Copaene-11-ol (3.56); ... Total = 85.17%	NA	Total = 14.83%	(46)
47		Indonesia	SE	0.54 ± 0.11	36	10-epi-γ-eudesmol (26.95); β-Eudesmol (19.25); Oleic acid (13.35); Squalene (7.17); Dihydrocarvyl acetate (4.13); ... Total = 77.7%	NA	Total = 22.3%	(46)

(*Continued*)

Table 10. (Continued).

					Relative peak area of components (%)				
No.	Species	Nation	Method	Yield (%)	Total quantity	Sesquiterpenoids	Chromone	Others	References
48	*A. subintegra*	Thailand	HD	0.7	28	Isoamyl dodecanoate (38.0); Kusunol (6.4); Epoxybulnesene (4.9); Karanone (3.6); Cyclocolorenone (3.4); .... Total = 71.5%	NA	Total = 28.5%	(40)
49	*A. hirta*	Malaysia	HD	NA	35	γ-Cadinene (11.19); Epoxybulnesene (9.40); Allocaromadendrene (4.34); γ-Gurjunene (3.42); β-Caryophyllene (1.93); .... Total = 48.56%	4-phenyl-2-butanone (3.75) Total = 3.75%	Total = 47.69%	(81)
50	*Aquilaria* spp.	China	HD	NA	NA	Gualol (14.089); Dehydrofukinone (4.096); 6-isopropyl-4,8-α- dimethyl-1,2,3,7,8,8-hexahydronaphtHalene (3.481); Germacrene B (3.121); Sandal (2.996); .... Total = 51.132%	NA	Total = 48.868%	(31)

NA: Not Available.

supercritical extractions, the polarity of the solvent and the extraction conditions may affect the heat-sensitive components more.

Chromone compounds constitute the principal active ingredients of agarwood and AEO, serving as crucial indicators for quality assessment. Upon heating and cracking, chromone compounds yield benzaldehyde and p-methoxybenzaldehyde, contributing to a persistent fragrance (54). Comparative analysis of AEO composition obtained by HD reveals that only Mohd-Syafik reported the extraction of 4-phenyl-2-butanone from *A. hirta*, with no reports of chromone detection in AEO from other agarwood tree species using HD (81). Studies by Ma, Fu, Li, Wei, & Liu (2021), Zhang, Li, Cui, & Xu (2022), and Yu *et al.* (2023) detected chromones (2.18–84.04%) during AEO extraction via SE, with varied relative content (55,58,82). Conversely, Oktavianawati, Santoso, & Fatmawati (2023), and Z. Zhang *et al.* (2022) did not detect chromones (46,56), which may be influenced by the choice of solvent and species. The boiling point of 2-(2-phenylethyl)chromone typically exceeds that of sesquiterpenes, rendering it more accessible for SFE to extract volatile components with high boiling points, possibly accounting for the lower chromone content in AEO samples extracted by HD (86,87). Agarwood essential oil extracted by SD and EA methods reportedly contained no chromone. In summary, SFE (17.48–-60.42%) exhibits greater component diversity and preserves AEO component diversity to the fullest extent. Supercritical CO_2 fluid extraction proves effective in extracting chromones (53).

Existing reports indicate significant variations in the quantities of simple phenolic compounds and miscellaneous chemical substances across various methods: HD (3.76–51.8%); SD (24.38–25.16%); SE (2.41–91.86%); SFE (37.38–69.94%); and EA (26.72%). However, the abundance of aliphatic components in AEO is negatively correlated with its quality. Elevated levels of aliphatic components can induce rancidity during prolonged storage, leading to the development of a distinct and strong odor that adversely affects AEO quality (54).

In conclusion, SFE extraction can more accurately and comprehensively reflect the chemical components of medicinal materials, offering effects that are challenging to achieve with traditional methods (85). Microwave and ultrasonic pretreatment also emerge as economical and popular methods suitable for AEO extraction. The integration of microwave, ultrasonic, and HD may represent an ideal choice for industrial production, characterized by low cost and high efficiency.

5. Biological activity of agarwood essential oil

Studies demonstrate that AEO contains various bioactive that exhibit anti-bacterial, anti-tumor, anxiolytic, depressive, sedative, sleep-inducing, acetylcholinesterase inhibitory, neuroprotective, antioxidant, and anti-aging properties (10,11,20,24,31–33,35,88–93). For example, chromones exhibit anti-allergic, anti-inflammatory, neuroprotective, and enzyme inhibitory activities (80,94,95). These functional components substantially contribute AEO's commercial value and global market demand. Table 11 presents a comprehensive overview of key biological activities and their associated active substances in AEO.

Research indicates that AEO exerts antibacterial effects by inducing apoptosis and nuclear condensation/fission while altering mitochondrial membrane potential (88). AEO shows efficacy against *Staphylococcus aureus* and *Candida albicans*, with HD extraction demonstrating higher potency than SFE based on minimum inhibitory concentrations (MICs) of 0.5 mg/mL and 1 mg/mL for SD versus 1 mg/mL and 2 mg/mL for SFE, respectively (11). Compound 2-(2-phenylethyl)chromone derivatives, namely 5-hydroxy-6-methoxy-2-[2-(4-methoxyphenyl)ethyl] chromone, Oxidoagaro-chromone A, 6-Methoxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chromone, and Oxidoagaro-chromone B, have demonstrated inhibitory effects on *Staphylococcus aureus* (24). Furthermore, these compounds, specifically Oxidoagaro-chromone A and Oxidoagaro-chromone B, exhibit inhibitory effects on *Ralstonia solanacearum* (24). Sesquiterpene (β-caryophyllene) extracted by HD from *A. crassna* demonstrates specific anti-bacterial activity against *Staphylococcus aureus*, with a MIC of 3 ± 1.0 μM, surpassing the antibacterial efficacy of kanamycin (88). Moreover, 5-desoxylongilobol displays antibacterial activities against both *Staphylococcus aureus* and *Ralstonia solanacearum* (89). The four sesquiterpenoid compounds derived from *A. sinensis* AEO, specifically (5S,7S,9S,10S)-(+)-9-hydroxy-selina-3,11-dien-12-al; (5S,7S,9S,10S)-(+)-9-hydroxy-eudesma-3,11 (13)-dien-12-methyl ester; (4αβ,7β,8αβ)-3,4,4α,5,6,7,8,8α-octahydro-7-[1-(hydroxymethyl)ethenyl]-4α-methylnaphthalene-1-carboxaldehyde, and 12,15-dioxo-α-selinen display significant antibacterial activity against *S. aureus* and *Ralstonia solanacearum*. Additionally, (7S,8 R,10S)-(+)-8,12-dihydroxy-selina-4,11-dien-14-al exhibits antibacterial activity against *Staphylococcus aureus* (90). Exploring antimicrobial properties, isolates from agarwood (*Aquilaria crassna*) were investigated using various methods, including water distillation, supercritical fluid carbon dioxide

Table 11. Biological Activities of AEO.

No	Biological activity	Function	Method	Species	Active substances	Active effect	References
1	Anti-microbial	Inhibits *S. aurues*	HD	*Aquilaria* spp.	AEO	AEO MIC = 0.5 mg/mL	(11)
			HD	*A. malaccensis*	AEO	AEO to stop the growth: DD[a] = 50–500 μg/mL	(7)
			HD	*A. crassna*	Sesquiterpene: β-caryophyllene	MIC = 3 ± 0.4 μM	(88)
			SE	*A. sinensis*	6-Methoxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chromone	Inhibition zones = 10.01 ± 0.08 mm	(24)
			SE	*A. sinensis*	5-hydroxy-6-methoxy-2-[2-(4-methoxyphenyl)ethyl]chromone	Inhibition zones = 9.10 ± 0.06 mm	(24)
			SE	*A. sinensis*	Oxidoagarochromone A	Inhibition zones = 12.75 ± 0.09 mm	(24)
			SE	*A. sinensis*	Oxidoagarochromone B	Inhibition zones = 14.95 ± 0.05 mm	(24)
			SE	*A. sinensis*	Sesquiterpenoids:(5S,7S,9S,10S)-(+)-9-hydroxy-selina-3,11-dien-12-al	Inhibition zones = 12.90 ± 0.26 mm	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (5S,7S,9S,10S)-(+)-9-hydroxy-eudesma-3,11 (13)-dien-12-methyl ester	Inhibition zones = 14.20 ± 0.10 mm	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (7S,8 R,10S)-(+)-8,12-dihydroxy-selina-4,11-dien-14-al	Inhibition zones = 8.10 ± 0.15 mm	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (4αβ,7β,8αβ)-3,4,4α,5,6,7,8,8α-octahydro-7-[1-(hydroxymethyl)ethenyl]-4α-methylnaphthalene-1-carboxaldehyde	Inhibition zones = 9.12 ± 0.06 mm	(90)
			SE	*A. sinensis*	Sesquiterpenoids: 12,15-dioxo-α-selinen	Inhibition zones = 20.02 ± 0.12 mm	(90)
			SE	*A. crassna*	5-desoxylongilobol	Inhibition zones = 12.35 ± 0.11 mm	(89)
			SFE	*Aquilaria* spp.	AEO	AEO MIC = 1 mg/mL	(11)
		Inhibits *B. subtilis*	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	MIC = 8 ± 2.1 μM	(88)
			HD	*A. malaccensis*	AEO	AEO to stop the growth: DD[a] = 50–500 μg/mL	(7)
		Inhibits *E. coli*	HD	*Aquilaria* spp.	AEO	AEO MIC > 2 mg/mL	(11)
			HD	*A. crassna*	Sesquiterpene: β-caryophyllene	AEO MIC = 9 ± 2.2 μM	(88)
			SFE	*Aquilaria* spp.	AEO	AEO MIC > 2 mg/mL	(11)
		Inhibits *C. albicans*	HD	*Aquilaria* spp.	AEO	AEO MIC = 1 mg/mL	(11)
			SFE	*Aquilaria* spp.	AEO	AEO MIC = 2 mg/mL	(11)
		Inhibits *B. cereus*	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	MIC = 9 ± 1.1 μM	(88)
		Inhibits *K. pneumonia*	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	MIC = 14 ± 2.7 μM	(88)
		Inhibits *P. aeruginosa*	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	MIC = 7 ± 1.2 μM	(88)
		Inhibits *Rhizopus oryzae*	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	MIC = 6 ± 0.5 μM	(88)
		Inhibits *Tricho dermareesei*	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	MIC = 4 ± 0.7 μM	(88)
		Inhibits *Salmonella typhimurium*	HD	*A. malaccensis*	AEO	AEO to stop the growth: DD[a] = 50–500 μg/mL	(7)
		Inhibits *B. cereus*	HD	*A. malaccensis*	AEO	AEO to stop the growth: DD[a] = 50–500 μg/mL	(7)
		Inhibits *Aspergillus fumigatus*	HD	*A. malaccensis*	AEO	AEO to stop the growth: DD[a] = 50–500 μg/mL	(7)
		Inhibits *A. niger*	HD	*A. malaccensis*	AEO	AEO to stop the growth: DD[a] = 50–500 μg/mL	(7)
		Inhibits *S. cerevisiae*	HD	*A. malaccensis*	AEO	AEO to stop the growth: AEO DD[a] = 50–500 μg/mL	(7)
		Inhibits *C. albicans*	HD	*A. malaccensis*	AEO	AEO to stop the growth: DD[a] = 50–500 μg/mL	(7)

(*Continued*)

Table 11. (Continued).

No	Biological activity	Function	Method	Species	Active substances	Active effect	References
		Inhibits *S. mutans*	HD	*A. malaccensis*	AEO	AEO to stop the growth: DD[a] = 50–500 μg/mL	(7)
		R. solanacearum	SE	*A. sinensis*	Oxidoagarochromone A	Inhibition zones = 15.40 ± 0.10 mm	(24)
			SE	*A. sinensis*	Oxidoagarochromone B	Inhibition zones = 12.09 ± 0.06 mm	(24)
			SE	*A. sinensis*	Sesquiterpenoids: (5S,7S,9S,10S)-(+)-9-hydroxy-selina-3,11-dien-12-al	Inhibition zones = 18.20 ± 0.07 mm	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (5S,7S,9S,10S)-(+)-9-hydroxy-eudesma-3,11 (13)-dien-12-methyl ester	Inhibition zones = 10.15 ± 0.25 mm	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (4αβ,7β,8αβ)-3,4,4α,5,6,7,8,8α-octahydro-7-[1-(hydroxymethyl)ethenyl]-4α-methylnaphthalene-1-carboxaldehyde	Inhibition zones = 8.98 ± 0.11 mm	(90)
			SE	*A. sinensis*	Sesquiterpenoids: 12,15-dioxo-α-selinen	Inhibition zones = 11.02 ± 0.08 mm	(90)
			SE	*A. crassna*	5-desoxylongilobol	Inhibition zones = 16.90 ± 0.09 mm	(89)
2	Anxiolytic and Antidepression	Inhibits norepinephrine reuptake in rat brain synaptosomes	SE	*Aquilaria* spp.	Abietane diterpenoids: Aquilarabietic acid A	Norepinephrine reuptake inhibition: 10 μM = 81.4%, $IC_{50} = 9.1 \times 10^{-7}$ M;	(92)
		The AF-5 effect was caused by reducing central nervous system 5-HT, dopamine, and epinephrine levels	NA	*Aquilaria* spp.	4-Butyl-α-agarofuran	Serotonin reduce: 5.0 mg/kg = Striatum (26.3%), 5.0 mg/kg = Cortex (30.4%), 5.0 mg/kg = Midbrain (17.4%); Dopamine reduce: 5.0 mg/kg = Striatum (34.7%), 5.0 mg/kg = Cortex (19.0%); Dopamine increase: 5.0 mg/kg = hypothalamus (56.6%); Epinephrine reduce: 5.0 mg/kg = Cortex (19.0%);	(96)
		Inhibits a range of animal behaviors in stressed model mice	HD	*Aquilaria* spp.	AEO	1. AEO treatment dose-dependent to reduce the IL-1α, IL-1β, IL-6; 2. AEO reduced ACTH and CORT in stress-induced mice	(32)
3	Sedation and sleep aid	Inhibits central nervous system activity	SE	*Aquilaria* spp.	Benzene extract of agarwood	Taken orally, it reduces mice's spontaneous motility, prolongs hexobarbiturate-induced sleep, lowers rectal temperature, and decreases acetic acid-writhing.	(97)
		Collaborative pentobarbital sodium hypnosis experiment in mice.	SE	*Aquilaria* spp.	AEO	Reduced mouse locomotor activity, including total distance, movement, move time, and average velocity.	(98)
		locomotor activity and pentobarbital-induced sleeping assays in mice	HD	*Aquilaria* spp.	AEO	Elevated the expression of $GABA_A$ receptor subunits and subtypes in the cerebral cortex and increased chlorine ion (Cl^-) influx through $GABA_A$ receptors in human neuroblastoma cells.	(31)
4	Inhibits enzyme activity	Acetylcholinesterase inhibitory activity (AChE)	HD	*A. malaccensis*	AEO	AEO percentage of inhibition: 60 μL/mL = 81.66 ± 0.0050%	(7)
			SE	*A. sinensis*	6-Methoxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chromone	Percentage of inhibition: 50 μg/mL = 32.4 ± 0.6%	(24)
			SE	*A. sinensis*	5-Hydroxy-6-methoxy-2-[2-(3-hydroxy-4-methoxyphenyl)ethyl]chromone	Percentage of inhibition: 50 μg/mL = 33.6 ± 0.6%	(24)
			SE	*A. sinensis*	5,6-Epoxy-7β-hydroxy-8β-methoxy-2-(2-phenylethyl)chromone	Percentage of inhibition: 50 μg/mL = 31.5 ± 0.9%	(24)

(*Continued*)

Table 11. (Continued).

No	Biological activity	Function	Method	Species	Active substances	Active effect	References
			SE	*A. sinensis*	6-methoxy-2-[2-(3-methoxyphenyl)ethyl] chromone	Percentage of inhibition: 50 μg/mL = 10.1 ± 0.9%	(24)
			SE	*A. sinensis*	6-methoxy-2-[2-(4-hydroxyphenyl)ethyl] chromone	Percentage of inhibition: 50 μg/mL = 23.5 ± 0.8%	(24)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-phenylethyl] chromone	Percentage of inhibition: 50 μg/mL = 10.8 ± 0.9%	(24)
			SE	*A. sinensis*	6-hydroxy-2-(2-phenylethyl)chromone	Percentage of inhibition: 50 μg/mL = 19.3 ± 0.8%	(24)
			SE	*A. sinensis*	Oxidoagarochromone A	Percentage of inhibition: 50 μg/mL = 40.7 ± 0.6%	(24)
			SE	*A. sinensis*	Oxidoagarochromone B	Percentage of inhibition: 50 μg/mL = 46.1 ± 0.9%	(24)
			SE	*A. crassna*	(4S,5 R,7 R)-11,12-dihydroxy-eremophila-1 (10)-ene-2-oxo-11-methyl ester	Percentage of inhibition: 50 μL/mL = 42.9 ± 0.6%	(89)
			SE	*A. sinensis*	AEO (Wild agarwood)	AEO percentage of inhibition: 0.025 mg/mL = 45.57 ± 3.80%	(99)
			SE	*A. sinensis*	AEO (Induced agarwood)	AEO percentage of inhibition: 0.025 mg/mL = 42.02 ± 1.72%	(99)
			SE	*A. sinensis*	Sesquiterpenoids: (5S,7S,9S,10S)-(+)-9-hydroxy-selina-3,11-dien-12-al	Percentage of inhibition: 50 μg/mL = 14.7 ± 0.6%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (5S,7S,9S,10S)-(-)-9-hydroxy-selina-3,11-dien-14-al	Percentage of inhibition: 50 μg/mL < 10%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (5S,7S,9S,10S)-(+)-9-hydroxy-eudesma-3,11 (13)-dien-12-methyl ester	Percentage of inhibition: 50 μg/mL < 10%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (7S,9S,10S)-(+)-9-hydroxy-selina-4,11-dien-14-al	Percentage of inhibition: 50 μg/mL < 10%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (7S,8 R,10S)-(+)-8,12-dihydroxy-selina-4,11-dien-14-al	Percentage of inhibition: 50 μg/mL < 10%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (4αβ,7β,8αβ)-3,4,4α,5,6,7,8,8α-octahydro-7-[1-(hydroxymethyl)ethenyl]-4α-methylnaphthalene-1-carboxaldehyde	Percentage of inhibition: 50 μg/mL = 10.3 ± 0.9%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: 12,15-dioxo-α-selinen	Percentage of inhibition: 50 μg/mL = 20.8 ± 0.9%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: 15-hydroxyl-12-oxo-α-selinen	Percentage of inhibition: 50 μg/mL < 10%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: eudesmane-1β,5α,11-triol	Percentage of inhibition: 50 μg/mL < 10%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: (-)-7βH-eudesmane-4α,11-diol	Percentage of inhibition: 50 μg/mL 12.3 ± 0.6%	(90)
			SE	*A. sinensis*	Sesquiterpenoids: ent-4 (15)-eudesmen-1α,11-diol	Percentage of inhibition: 50 μg/mL < 10%	(90)
			SE	*A. crassna*	AEO (Inoculation 12 months)	AEO percentage of inhibition: 4 mg/mL = 93.44 ± 1.28%	(100)
			SE	*A. crassna*	AEO (Inoculation 18 months)	AEO percentage of inhibition: 4 mg/mL = 89.34 ± 1.61%	(100)
			SE	*A. sinensis*	AEO (Inoculation 6 months)	AEO percentage of inhibition: 4 mg/mL = 96.95 ± 0.76%	(100)

(*Continued*)

Table 11. (Continued).

No	Biological activity	Function	Method	Species	Active substances	Active effect	References
			SE	*A. sinensis*	AEO (Inoculation 12 months)	AEO percentage of inhibition: 4 mg/mL = 90.44 ± 3.06%	(100)
			SE	*A. sinensis*	AEO (Inoculation 18 months)	AEO percentage of inhibition: 4 mg/mL = 95.09 ± 1.95%	(100)
		α-Glucosidase	SE	*G. versteegii*	AEO	AEO percentage of inhibition: 100 μg/mL = 53.46%	(91)
			SE	*A. sinensis*	AEO (Wild agarwood)	AEO percentage of inhibition: 25 μg/mL = 18.51 ± 2.90%–77.25 ± 2.06%	(99)
			SE	*A. sinensis*	AEO (Induced agarwood)	AEO percentage of inhibition: 25–400 μg/mL = 11.50 ± 2.69%-72.56 ± 0.89%	(99)
			SE	*A. crassna*	AEO (Inoculation 12 months)	AEO percentage of inhibition: 1 mg/mL = 79.60 ± 1.07%	(100)
			SE	*A. crassna*	AEO (Inoculation 18 months)	AEO percentage of inhibition: 1 mg/mL = 79.42 ± 3.05%	(100)
			SE	*A. sinensis*	AEO (Inoculation 6 months)	AEO percentage of inhibition: 1 mg/mL = 65.50 ± 2.00%	(100)
			SE	*A. sinensis*	AEO (Inoculation 12 months)	AEO percentage of inhibition: 1 mg/mL = 96.24 ± 0.89%	(100)
			SE	*A. sinensis*	AEO (Inoculation 18 months)	AEO percentage of inhibition: 1 mg/mL = 89.12 ± 2.62%	(100)
5	Anti-cancer	Pancreatic (PANC-1)	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	IC_{50} = 27 μM	(88)
			HD	*A. crassna*	AEO	AEO IC_{50} = 32 μg/mL	(88)
		Colorectal (HCT-116)	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	IC_{50} = 19 μM	(88)
			HD	*A. crassna*	AEO	AEO IC_{50} = 28 μg/mL	(88)
		Colorectal (HT-29)	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	IC_{50} = 63 μM	(88)
			HD	*A. crassna*	AEO	AEO IC_{50} = 82 μg/mL	(88)
		Invasive squamous cell carcinoma (ME-180)	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	IC_{50} = 95 μM	(88)
			HD	*A. crassna*	AEO	AEO IC_{50} = 98 μg/mL	(88)
		Leukemia (K562)	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	IC_{50} = 105 μM	(88)
			HD	*A. crassna*	AEO	AEO IC_{50} = 142 μg/mL	(88)
		Hormone sensitive and invasive breast cancer cell line (MCF-7)	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	IC_{50} = 285 μM	(88)
			HD	*A. crassna*	AEO	AEO IC_{50} = 110 μg/mL	(88)
		Prostatic adenocarcinoma(PC3)	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	IC_{50} = 104 μM	(88)
			HD	*A. crassna*	AEO	AEO IC_{50} = 79 μg/mL	(88)
		Human hepatoma carcinoma cell lines (SMMC-7721)	SE	*A. sinensis*	7-hydroxy-2-[2-(3′-methoxy-4′–hydroxyphenyl)-ethyl]chromone	IC_{50} = 18.82 μg/mL	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(3′–hydroxyphenyl)-ethyl]chromone	IC_{50} = 30.01 μg/mL	(93)
			SE	*A. sinensis*	6-hydroxy-2-[2-(4′–hydroxyphenyl)ethyl] chromone	IC_{50} = 37.95 μg/mL	(93)
			SE	*A. sinensis*	2-[2-(3′-methoxy-4′–hydroxyphenyl)ethyl] chromone	IC_{50} = 31.59 μg/mL	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(4′–hydroxyphenyl) ethyl]chromone	IC_{50} = 20.01 μg/mL	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(3′-methoxy-4′–hydroxyphenyl)ethyl]chromone	IC_{50} = 24.85 μg/mL	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(3′-hydroxy-4′–methoxyphenyl)ethyl]chromone	IC_{50} = 31.06 μg/mL	(93)

(*Continued*)

Table 11. (Continued).

No	Biological activity	Function	Method	Species	Active substances	Active effect	References
			SE	*A. sinensis*	6-methoxy-7-hydroxy-2-[2-(4′–methoxyphenyl)ethyl] chromone	IC_{50} = 27.08 μg/mL	(93)
			SE	*A. sinensis*	6-hydroxy-2-[2-(3′,4′-dimethoxyphenyl) ethyl]chromone	IC_{50} = 21.40 μg/mL	(93)
		Human gastric cancer cell lines (MGC-803)	SE	*A. sinensis*	7-hydroxy-2-[2-(3′-methoxy-4′–hydroxyphenyl)-ethyl]chromone	IC_{50} = 25.35 μg/ml	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(3-hydroxyphenyl)-ethyl]chromone	IC_{50} = 35.25 μg/ml	(93)
			SE	*A. sinensis*	6-hydroxy-2-[2-(4′–hydroxyphenyl)ethyl] chromone	IC_{50} = 23.92 μg/ml	(93)
			SE	*A. sinensis*	2-[2-(3′-methoxy-4′–hydroxyphenyl)ethyl] chromone	IC_{50} = 33.12 μg/ml	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(4′–hydroxyphenyl) ethyl]chromone	IC_{50} = 31.34 μg/ml	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(3′-methoxy-4′–hydroxyphenyl)ethyl]chromone	IC_{50} = 28.60 μg/ml	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(3′-hydroxy-4′–methoxyphenyl)ethyl]chromone	IC_{50} = 28.24 μg/ml	(93)
			SE	*A. sinensis*	6-methoxy-7-hydroxy-2-[2-(4′–methoxyphenyl)ethyl] chromone	IC_{50} = 31.17 μg/ml	(93)
			SE	*A. sinensis*	6-hydroxy-2-[2-(3′,4′-dimethoxyphenyl) ethyl]chromone	IC_{50} = 36.42 μg/ml	(93)
		Human ovarian cancer cell lines (OV-90)	SE	*A. sinensis*	7-hydroxy-2-[2-(3′-methoxy-4′–hydroxyphenyl)-ethyl]chromone	IC_{50} = 31.60 μg/ml	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(3′–hydroxyphenyl)-ethyl]chromone	IC_{50} = 26.98 μg/ml	(93)
			SE	*A. sinensis*	6-hydroxy-2-[2-(4′–hydroxyphenyl)ethyl] chromone	IC_{50} = 34.83 μg/ml	(93)
			SE	*A. sinensis*	2-[2-(3′-methoxy-4′–hydroxyphenyl)ethyl] chromone	IC_{50} = 30.77 μg/ml	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(4′–hydroxyphenyl) ethyl]chromone	IC_{50} = 36.64 μg/ml	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(3′-methoxy-4′–hydroxyphenyl)ethyl]chromone	IC_{50} = 30.40 μg/ml	(93)
			SE	*A. sinensis*	6,7-dimethoxy-2-[2-(3′-hydroxy-4′–methoxyphenyl)ethyl]chromone	IC_{50} = 22.54 μg/ml	(93)
			SE	*A. sinensis*	6-methoxy-7-hydroxy-2-[2-(4′–methoxyphenyl)ethyl] chromone	IC_{50} = 33.51 μg/ml	(93)
			SE	*A. sinensis*	6-hydroxy-2-[2-(3′,4′-dimethoxyphenyl) ethyl]chromone	IC_{50} = 35.38 μg/ml	(93)
		Breast adenocarcinoma	/	*Aquilaria* spp.	AEO	AEO IC_{50} = 900 μg/mL	(101)
		Pancreatic cell line	HD	*A. crassna*	AEO	AEO cell migration inhibition = 10 μg/ml AEO colony formation obstruction = 5 μg/ml	(102)
		Colorectal carcinoma cells	HD	*A. crassna*	AEO	AEO caused growth inhibition = 200 mg/kg	(103)
		Epidermoid carcinoma of the nasopharynx	SE	*A. filaria*	4′,7-dimethoxy-6-hydroxy chromone	IC_{50} = 26.1 ± 0.7 μM	(104)
		Lung carcinoma	SE	*A. filaria*	4′,7-dimethoxy-6-hydroxy chromone	IC_{50} = 25.8 ± 0.7 μM	(104)

(*Continued*)

Table 11. (Continued).

No	Biological activity	Function	Method	Species	Active substances	Active effect	References
		Estrogen receptor-positive and HER2-negative breast cancer	SE	*A. filaria*	4′,7-dimethoxy-6-hydroxy chromone	$IC_{50} = 28.7 \pm 0.2$ μM	(104)
		Triple-negative breast cancer	SE	*A. filaria*	4′,7-dimethoxy-6-hydroxy chromone	$IC_{50} = 38.1 \pm 0.7$ μM	(104)
		Human breast adenocarcinoma (MDA-MB-231)	HD	*A. sinensis*	AEO	AEO $IC_{50} = 61.3 \pm 3.2$ μg/mL	(105)
		Murine melanoma (B16F10)	HD	*A. sinensis*	AEO	AEO $IC_{50} = 48.9 \pm 3.1$ μg/mL	(105)
		Hepatocellular (HepG2)	HD	*A. sinensis*	AEO	AEO $IC_{50} = 56.2 \pm 3.9$ μg/mL	(105)
6	Anti-inflammatory	Albumin denaturation	HD	*A. malaccensis*	AEO	AEO $IC_{50} = 22.42 \pm 0.0560$ μL/mL	(7)
		Carrageenan-induced rat paw oedema in vivo model	HD	*A. agallocha*	AEO	Reduction in paw volume AEO = 50 mg/kg (58.59%) AEO = 100 mg/kg (62.11%)	(106)
		Stabilising human red blood cell membranes in vitro	HD	*A. agallocha*	AEO	AEO = 100 μg/ml (39.66%) AEO = 250 μg/ml (62.94%) AEO = 500 μg/ml (78.50%)	(106)
		Decrease in edema induced by carrageenan in the third hour	SE	*A. agallocha*	AEO	Reduction in paw volume: AEO = 50 mg/kg (51.38%) AEO = 100 mg/kg (55.09%) AEO = 200 mg/kg (56.25%)	(107)
		Cotton pellet granuloma formation	SE	*A. agallocha*	AEO	Granuloma weight reduction: AEO = 50 mg/kg (43.46%) AEO = 100 mg/kg (68.24%)) AEO = 200 mg/kg (77.18%	(107)
		Inhibits the p38 MAPK activation.	SE	*A. crassna*	AEO	AEO inhibited the production of TNF-α	(108)
		In vivo study on mice with intestinal injury induced by 5-flurouracil	SE	*A. agallocha*	AEO	AEO promoted enterocyte proliferation, maintained tight junction integrity, inhibited oxidative stress, and reduced inflammation.	(109)
		Mitigated 5-FU-induced colon mucosa oxidative damage and inflammation.	SE	*Aquilaria* spp.	AEO	AEO significantly decreased TNF-R, TRAF6, MyD88, IKKβ, IκB-β, and NF-κB mRNA by inhibiting the NF-κB pathway.	(110)
		Protein denaturation inhibition	HD	*A. agallocha*	AEO	Protein denaturation inhibition: AEO = 100 μg/ml (23.68%) AEO = 250 μg/ml = 48.21% AEO = 500 μg/ml = 56.71% Paw volume reduction in FA model: AEO = 125 mg/kg (19.78%) AEO = 250 mg/kg (27.88%)	(111)
7	Neuroprotective	Induces brain-derived neurotrophic factor expression	SE	*Aquilaria* spp.	Sesquiterpenoid: (4 R,5 R,7 R)-1 (10)-spirovetiven-11-ol-2-one	100 μg/ml = improve BDNF exon III – V mRNA expression	(112)
		Showed comparable activity with fluoxetine	SE	*Aquilaria* spp.	6,8-dihydroxy-2-[2-(3′-hydroxy-4′-methoxyphenyl)ethyl]chromone	Human U251 cell: 10 μM = 82.2% Pheochromocytoma P12 cell: 10 μM = 86.9%	(113)
		Corticosterone-induced PC12 cell injury	SE	*A. sinensis*	Triepoxyhexahydrochromone A	Protective effects at 1, 2, 5 μM	(114)
			SE	*A. sinensis*	(+)-(7 R,10 R)-selina-4,11 (13)-diene-12,15-dial	Protective effects at 1, 2, 5 μM	(114)
			SE	*A. sinensis*	(-)-(5 R,7 R,10 R)-12,15-dioxo-α-selinene	Protective effects at 1, 2, 5 μM	(114)
			SE	*A. sinensis*	(+)-(1 R,4S,5 R)-1β-hydroxyeremophila-7 (11), 9-dien-8-one	Protective effects at 1, 2, 5 μM	(114)
		MPP±induced PC12 cell injury	SE	*A. sinensis*	Triepoxyhexahydrochromone A	Protective effects at 1, 2, 5 μM	(114)

(*Continued*)

Table 11. (Continued).

No	Biological activity	Function	Method	Species	Active substances	Active effect	References
			SE	*A. sinensis*	(-)-(5 R,7 R,10 R)-12,15-dioxo-α-selinene	Protective effects at 1, 2, 5 μM	(114)
8	Anti-oxidant	DPPH	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	IC_{50} = 1.25 ± 0.06 μM	(88)
			HD	*A. malaccensis*	AEO	AEO IC_{50} = 40.14 ± 0.0192 μL/mL	(7)
			SE	*A. sinensis*	AEO (Wild agarwood)	AEO scavenging capacity: 0.8 mg/mL = 91.59 ± 0.22%	(99)
			SE	*A. sinensis*	AEO (Induced agarwood)	AEO scavenging capacity: 0.8 mg/mL = 91.26 ± 0.60%	(99)
			SE	*G. versteegii*	AEO	AEO IC_{50} = 65.62 μg/ml	(91)
			SE	*A. crassna*	AEO (Inoculation 12 months)	AEO scavenging capacity: 2 mg/mL = 88.92 ± 1.15%	(100)
			SE	*A. crassna*	AEO (Inoculation 18 months)	AEO scavenging capacity: 2 mg/mL = 89.88 ± 1.07%	(100)
			SE	*A. sinensis*	AEO (Inoculation 6 months)	AEO scavenging capacity: 2 mg/mL = 87.20 ± 1.03%	(100)
			SE	*A. sinensis*	AEO (Inoculation 12 months)	AEO scavenging capacity: 2 mg/mL = 85.62 ± 1.76%	(100)
			SE	*A. sinensis*	AEO (Inoculation 18 months)	AEO scavenging capacity: 2 mg/mL = 93.45 ± 0.98%	(100)
		ABTS	SE	*A. sinensis*	AEO (Wild agarwood)	AEO scavenging capacity: 0.2 mg/mL = 94.80 ± 0.85%	(99)
			SE	*A. sinensis*	AEO (Induced agarwood)	AEO scavenging capacity: 0.2 mg/mL = 91.93 ± 1.01%	(99)
			SE	*A. crassna*	AEO (Inoculation 12 months)	AEO scavenging capacity: 2 mg/mL = 78.59 ± 2%	(100)
			SE	*A. crassna*	AEO (Inoculation 18 months)	AEO scavenging capacity: 2 mg/mL = 86.06 ± 1.47%	(100)
			SE	*A. sinensis*	AEO (Inoculation 6 months)	AEO scavenging capacity: 2 mg/mL = 74.53 ± 2.31%	(100)
			SE	*A. sinensis*	AEO (Inoculation 12 months)	AEO scavenging capacity: 2 mg/mL = 75.62 ± 1.25%	(100)
			SE	*A. sinensis*	AEO (Inoculation 18 months)	AEO scavenging capacity: 2 mg/mL = 94.44 ± 0.94%	(100)
		Total reducing power	SE	*A. crassna*	AEO (Inoculation 12 months)	AEO total reducing power: 3.5 mg/mL = 0.1657 ± 0.0115%	(100)
			SE	*A. crassna*	AEO (Inoculation 18 months)	AEO total reducing power: 3.5 mg/mL = 0.1830 ± 0.0230%	(100)
			SE	*A. sinensis*	AEO (Inoculation 6 months)	AEO total reducing power: 3.5 mg/mL = 0.1613 ± 0.0121%	(100)
			SE	*A. sinensis*	AEO (Inoculation 12 months)	AEO total reducing power: 3.5 mg/mL = 0.1600 ± 0.0085%	(100)
			SE	*A. sinensis*	AEO (Inoculation 18 months)	AEO total reducing power: 3.5 mg/mL = 0.2037 ± 0.0140%	(100)
		FRAP	HD	*A. crassna*	Sesquiterpene: β-caryophyllene	IC_{50} = 3.23 ± 0.07 μM	(88)
		ABTS	HD	*A. malaccensis*	AEO	AEO IC_{50} = 76.95 ± 0.009 μL/mL	(7)

NA: Not Available.

extraction, and supercritical fluid carbon dioxide extraction in combination with ethanol as a co-solvent. These isolates demonstrated significant antimicrobial activity against *Staphylococcus aureus* and *Candida albicans*. However, no discernible effect was observed against *Escherichia coli* (11).

The anxiolytic and antidepressant properties of AEO components involve modulating corticotropin-releasing hormonal pathways, attenuating serum inflammatory cytokines such as IL-α, IL-1β, and IL-6, regulating nNOS and CRFR gene transcription and protein expression in the cerebral cortex and hippocampus, and reducing ACTH and CORT downstream of the HPA axis (32). At a concentration of 10 μM, the chromone derivative Aquilarabietic acid A exhibits significant *in vitro* antidepressant efficacy by potently reducing norepinephrine reuptake in rat brain synaptosomes by 81.40 % (92). Animal behavioral studies have provided compelling evidence of the antidepressant and anxiolytic effects of AEO in stress-induced model mice (32). The sesquiterpene α-agarofuran (4-Butyl-α-agarofuran) can regulate central serotonin and dopamine levels in serotonin-injected anxiety rat models to deliver an anxiolytic effect (96).

According to a study by Wei *et al*. (2017), AEO elicits sedative effects by modulating GABA receptor gene expression and enhancing GABA receptor activity, thereby promoting calming and sleep-inducing pharmacological actions (31). The Agar-Wit (agarwood-inducing technique) agarwood ethanol extract and AEO have demonstrated a significant increase in sleep rate and prolonged sleep time (98). Compounds extracted from AEO using benzene exhibit potent central nervous system depressant activity (97). Notably, AEO itself exhibited notable sedative properties by suppressing locomotor activity and inducing a hypnotic effect in mice treated with pentobarbital, leading to increased sleep duration (31). Furthermore, when administered through a spontaneous vapor delivery system, the inhalation of agarwood oil vapor has demonstrated a sedative effect in mice (33). The sedative efficacy of benzylacetone derived from AEO is subject to variation. The sedative efficacy of benzylacetone is influenced by factors such as the functional group position along the carbon chain, the substituent on the benzene ring, and their potential combinations (115).

Functional components within AEO have demonstrated significant inhibitory activity against key enzymes. Acetylcholinesterase is inhibited by compound 2-(2-phenylethyl)chromone derivatives; 6-methoxy-2-[2-(3-methoxyphenyl)ethyl] chromone; 6-methoxy-2-[2-(4-hydroxyphenyl)ethyl]chromone; 6,7-dimethoxy-2-[2-phenylethyl]chromone; 6-hydroxy-2-(2-phenylethyl) chromone; Oxidoagaro-chromone A, Oxidoagaro-chromone B (24), and (4S,5 R,7 R)-11,12-dihydroxy-eremophila-1-ene-2-oxo-11-methyl ester (IR 42.90 ± 0.60 %) (89). The acetone extract derived from *Gyrinops versteegii*, an endemic plant in Lombok, exhibits significant inhibitory activity against α-glucosidase (53.46 μg/mL) (91). Two additional studies have shown that *Aquilaria sinensis* EO and specific components derived from SE have significant anti-acetylcholinesterase and anti-α-glucosidase properties (99,100). These findings suggest that these natural products have the potential to be used in the development of drugs for Alzheimer's disease and diabetes treatment while also offering the advantage of reducing the typical side effects associated with their use.

AEO demonstrates anti-tumor effects attributed to its diverse anti-cancer components. Sesquiterpene (β-caryophyllene), for instance, exhibits a notable reduction in colorectal cancer cell proliferation, with a half-inhibitory concentration of 19 μM. Moreover, it effectively inhibits colon cancer cell clonality, migration, invasion, and spheroid formation (88). In another study, researchers isolated two new chromones, namely 2-(2-hydroxy-2-phenylethyl)chromone, along with ten recognized chromones from MeOH extracts of agarwood (*Aquilaria filaria*). These compounds demonstrated the ability to inhibit tumor development at non-cytotoxic concentrations, displaying half-inhibitory values ranging from 25 to 38 μM against different tumor cell lines (104). Furthermore, AEO (extracted by HD from *A. crassna*) exhibited significant inhibition of HCT 116 colorectal cancer cell-induced subcutaneous tumors in nude mice (103). In MIA PaCa-2 pancreatic cells, AEO (extracted by HD from *A. crassna*) exhibited potent cytotoxic activity with a half-inhibitory concentration of 11 ± 2.18 μg/mL and inhibited cell migration at 10 μg/mL (102). AEO also displayed anticancer effects on MCF-7 breast cancer cells (101). Two novel chromone derivatives, namely 7-hydroxy-2-[2-(3'-methoxy-4'–hydroxyphenyl)-ethyl] chromone and 6,7-dimethoxy-2-[2-(3'–hydroxyphenyl)-ethyl]chromone isolated from *A. sinensis* ethanol extract, exhibited weak cytotoxic activities (IC50: 18.82–37.95 mg/mL) against SMMC-7721, MGC-803, and OV-90 cell lines (93). The exploration of innovative extraction methods and procedures offers the possibility of discovering additional bioactive chemicals, improving the effectiveness of current components, as well as creating new therapeutic agents. This has the potential to greatly broaden the range and influence of AEO in cancer treatment and other medicinal applications.

AEO exhibits anti-inflammatory effects through various mechanisms. It suppresses granulocyte respiratory

burst, inhibits the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, and reduces lipid peroxidation measured by MDA levels (116). In a study utilizing TPA-induced mouse ear inflammation, AEO significantly decreased the levels of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α (117). A study was conducted using mice intestinal mucosal inflammation generated by 5-fluorouracil, *A. agallocha* AEO extracted by SE was found to dramatically increase the expression of PCNA in the ileum, while also lowering the levels of COX-2 and TNF-α (109). In a study involving carrageenan-induced paw edema in mice and the stabilization of human red blood cell membranes, *A. agallocha* AEO obtained through the HD demonstrated significant anti-inflammatory activity in reducing edema in a dose-dependent manner, its mechanism of action being similar to diclofenac through the inhibition of COX enzyme and hence, additionally, in terms of stabilizing the human red blood cell membrane, it was comparable to standard diclofenac (106). An investigation into the anti-inflammatory properties of the ethyl acetate extract obtained from *A. agallocha* demonstrated significant efficacy in lowering carrageenan-induced oedema and suppressing the formation of cotton pellet granuloma (107). Another study also confirmed the anti-inflammatory effect of AEO obtained from SE extraction of A. *crassna*, demonstrating its ability to inhibit LPS-induced tumor necrosis factor-α production by attenuating P38 MAPK activation (108). A study showed that AEO extracted by SE from *Aquilaria* spp. enhanced the intestinal advancing rate, reduced IL-17 and IL-33 levels, elevated IL-10, upregulated Nrf2–ARE mRNA expression, and downregulated NF-κB mRNA levels, indicating its potential as an adjuvant for treating intestinal inflammation (110). Notably, both linalool and its corresponding acetate derivative contribute significantly to the anti-inflammatory activity of AEO (118). Further research has identified specific compounds within AEO, including 10-epi-γ-eudesmol, jinkoh-eremol, and agarospirol, which exhibit higher anti-inflammatory activity compared to other compounds (117).

Specific components found in AEO demonstrate neuroprotective effects. Isolates such as 3-(2-Phenylethyl) chromones and a 2- (2-phenylethenyl) chromone derived from AEO extracted by SE have exhibited significant neuroprotective activity against neurotoxicity (113). Brain-derived neurotrophic factor (BDNF) is critical for neuron survival, differentiation, and synapse creation, and plays a pivotal role in the development of the mammalian central nervous system. Particularly noteworthy is the ability of 2-(2-phenylethyl) chromone to induce BDNF expression (112). AEO components isolated from SE-extracted *A. sinensis*, namely Triepoxyhexahydrochromone A; (+)-(7 R,10 R)-selina-4,11 (13)-diene-12,15-dial; (-)-(5 R,7 R,10 R)-12,15-dioxo-α-selinene, and (+)-(1 R,4S,5 R)-1β-hydroxyeremophila-7 (11), 9-dien-8-one demonstrated significant protective effects ($p < 0.01$) on corticosterone-induced PC12 cell injury at concentrations of 1, 2, and 5 μM, also indicating the potential of AEO as a candidate for the development of antidepressant therapies by inhibiting CORT-induced neuronal damage; additionally, Triepoxyhexahydrochromone A and (-)-12,15-dioxo-α-selinene showed significant protective effects ($p < 0.01$) on MPP±induced cell injury at the same concentrations, indicating potential for use in treatments for neurodegenerative diseases such as Alzheimer's disease disease. Recent studies indicate that AEO or its constituents possess substantial neuroprotective properties, underscoring the importance of additional investigation to comprehend its mechanisms of action.

AEO has been reported to possess antioxidant properties, including the presence of β-Caryophyllene, as demonstrated in DPPH and FRAP scavenging experiments (88). In a study conducted by Roktim, AEO exhibited significant ABTS scavenging activity of 76.95 ± 0.009 % at a concentration of 100 μL/mL (7). In a study by Ma *et al.* (2023), essential oils extracted from *Aquilaria sinensis* using the SE method demonstrated similar antioxidant effects for fungal-induced (IA) and wild (WA) agarwood with DPPH radical scavenging rates of 91.26 ± 0.60% and 91.59 ± 0.22% at 0.8 mg/mL, respectively, and ABTS radical scavenging rates of 91.03 ± 1.01% and 94.80 ± 0.85% at 0.2 mg/mL, respectively (99). Ma *et al.* (2021) employed the SE method to extract essential oils from *A. sinensis* and *A. crassna* at various induction times, revealing that extended inoculation periods improved their ABTS and DPPH radical scavenging effects with 18-month *A. sinensis* demonstrating superior scavenging capacities (AEO = 2 mg/mL; DPPH radical scavenging activity = 93.45 ± 0.98%; ABTS radical scavenging activity = 94.44 ± 0.94%) compared to *A. crassna* (AEO = 2 mg/mL, DPPH radical scavenging activity = 89.88 ± 1.07%; ABTS radical scavenging activity = 86.06 ± 1.47%) (100). The current research primarily concentrates on investigating the antioxidant properties of AEO extracted using SE and HD processes. Nevertheless, the untapped potential of alternative extraction methods, such as SFE, UAE, or MAE, has not been fully explored. Such methods might potentially alter the composition of the extracts, leading to varied antioxidant

qualities. A systematic comparison is vital for comprehending and utilizing the antioxidant characteristics of AEO.

In summary, the diverse range of bioactive compounds present in AEO extracts holds promise for the treatment of various diseases and has potential applications in numerous industries. The functionality of essential oils is intricately linked to the content and composition of their components, resulting in a wide spectrum of functional qualities. Variations in the chemical composition of agarwood essential oil can be attributed to the diversity among agarwood varieties and the distinct extraction methods employed (119). The diverse natural functional capabilities demonstrated by the various constituents of AEO, as highlighted earlier, underscore a significant potential for the development of products utilizing AEO as the primary functional components. It is important to recognize that plant extracts, such AEO, present a comparatively safer alternative to synthetic medications, offering a potential avenue for health maintenance and disease mitigation. Nevertheless, the complex chemical composition of natural products necessitates further safety evaluations and toxicological inquiries to eliminate any potential risks to human health.

6. Future prospects

The limited yield of AEO extraction results in substantial agarwood waste production, mainly in the form of agarwood powder. This waste material can be repurposed as a filler in polymer blends, contributing to the creation of biodegradable products. This innovative application serves to minimize natural resource depletion, reduce pollution, and optimize the value of agarwood (120). Additionally, byproducts from agarwood extraction can be transformed into activated carbon. This approach not only enhances agarwood utilization but also mitigates environmental pollution. Repurposing agarwood waste into activated carbon renders it valuable for both water and air purification. This eco-friendly and sustainable process highlights the potential for a circular economy centered around agarwood extraction, promoting a more conscientious and environmentally aware utilization of this precious resource (121).

7. Conclusion

Agarwood, revered as a precious aromatic plant, holds significant development potential due to its unique fragrance and diverse functional substances. The quality and composition of AEO are notably influenced by factors such as agarwood species, geographical origins, extraction methods, and extraction conditions. The abundant and varied components in AEO, with their wide range of biological activities, have spurred substantial demand for its application across various industries, including cosmetics, medicines, condiments, and household products. The functional substances present in essential oils, particularly those in AEO, have emerged as focal points of current research due to their impressive array of anti-bacterial, anti-tumor, anxiolytic, antidepressant, sedative, sleep aid, acetylcholinesterase inhibitory, neuroprotective, antioxidant, and antiaging properties. The composition and content of AEO components are intricately linked to the extraction methods employed in its production. Careful selection of an appropriate extraction method can significantly enhance the yield of AEO, facilitating the extraction of desired natural functional active substances and enabling a comprehensive exploration of the potential value that AEO offers.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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