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Review

Diversity and Biosynthetic Activities of Agarwood Associated Fungi

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Abstract: Agarwood is a fragrant dark resin produced in plants belonging to the family Thymelaeaceae and which has a high economic value. The unique fragrance and medicinal applications intensify the value of agarwood. The wild populations of agarwood trees are highly threatened by high economic demand. Therefore, it is worthwhile to develop an artificial agarwood induction technology for the countries that rely on agarwood from the natural habitat of the plants. Fungal induction of agarwood has been shown to be an efficient method. Interestingly, most of the fungi known from agarwood are endophytic. In this paper, we supplement and update the bioactivity of fungi associated with agarwood and their ability to induce agarwood formation. According to the existing literature, 59 endophytic fungal strains of 16 genera induce agarwood production, most of which belong to Fusarium (28 identified strains). Hence, Fusarium is a good candidate for further studies on fungal induced agarwood production.

Keywords: antimicrobial agents; antioxidant agents; antitumor compounds; *Aquilaria*; bio-technology; Fusarium; *Gyrinops*; sustainable development; thymelaeaceae

1. Introduction

Agarwood is a highly valuable, fragrant, and dark resinous heartwood of trees in the family Thymelaeaceae [1–4]. Agarwood is also known under different names in different regions, including agar (Hindi), akil (Tamil), aloe wood (Indonesian), chen xiang (Chinese), chim-hyuang (Korean), eaglewood (Papua New Guinea), gaharu (Malaysian), jin-koh (Japanese), mai ketsana (Lao), mai kritsana (Thai), oud (Arabic), oud or agar attar (Middle Eastern), sasi or sashi (Assamese), and tramhuong (Vietnamese) [5–7]. The plants in the family Thymelaeaceae, especially the genera *Aquilaria* and *Gyrinops*, are well known for agarwood production, and these are grown in several countries in Southeast Asia (e.g., Borneo, Cambodia, China, India, Indonesia, Laos, Malaysia, New Guinea, Thailand, Philippines, and Vietnam) [2,3,8,9]. Agarwood has been referred to as the "woods of the Gods", and it has been widely used as incense, perfumes (essential oils), in medicine and religious ceremonies [2,10–15].

The price of agarwood varies with the quality of its resin [7,16]. The best agarwood ranges from $100,000 to 800,000 per kilogram, while the price of other agarwood ranges from $500 to 100,000 per kilogram according to the grade. The essential oil of agarwood in the global market is sold for $30,000 per liter (https://tmhagarwood.com/agarwood-prices-updated-in-2021, accessed on 9 March 2022). In the past decade, agarwood reached its highest commercial demand when the demand exceeded the supply mainly due to the fact that good quality agarwood is formed slowly and infrequently in old trees and the increase in consumers [17–20]. High economic value and high demand lead to overexploitation of the wild mother trees [21]. This affects mature populations of the plants and puts the future of the industry at great risk [21]. All species of *Aquilaria* and *Gyrinops* have been presented in Appendix II based on the data available at "Convention on International Trade in Endangered Species (CITES) in 2005" [6,21–23].

Under natural conditions, the formation of agarwood is rare and very slow [24,25]. Agarwood is produced when healthy white wood is damaged (lightning strike, strong wind, animal grazing and insect attack) and infected with microorganisms [7,24]. The infection stimulates the plant defense response; as a result, the dark resin is produced to suppress further infection [24,26].

For the sustainable development of the agarwood industry, many agarwood-producing countries (Cambodia, China, Indonesia, Malaysia, Thailand, and Vietnam) have been committed to developing artificial induction of agarwood resin in agarwood tree plantations [6,9]. The three common induction techniques are physical, chemical, and biological [7,9]. Among these three factors, biological (fungal inoculation) is considered to be effective, and most of the fungi used for inoculation are endophytes isolated from healthy or diseased wood of agarwood-producing trees [9,27,28]. Therefore, many scientists have been committed to isolating various endophytic fungi from different parts of agarwood-producing trees and confirming that some endophytic fungi such as *Aspergillus niger* [28], *Fusarium solani* [26], *Lasiodiplodia theobromae* [29], and *Melanotus flavolivens* [30] induce agarwood production. Moreover, the endophytic fungi associated with agarwood-producing trees contain biologically active components (e.g., *Diaporthe* sp.—antioxidant capacity [31]; *Nemania aquilariae*—antibacterial and antimicrobial properties [25]; *Xylaria mali*—antimicrobial and antitumor activity [32]).

In this paper, we review the biological activity and agarwood induction potential of endophytic fungi isolated from agarwood plants. Furthermore, we provide references for better research on the sustainable development of agarwood production through novel technologies.

1.1. Agarwood-Producing Trees and Their Geographical Distribution

Agarwood is produced in trees belonging to the family Thymelaeaceae (*Aetoxylon*, *Aquilaria*, *Gonystylus* and *Gyrinops*) [33]. Among the species in the Thymelaeaceae, *Aquilaria* and *Gyrinops* are well-known for agarwood production [21]. *Aquilaria* and *Gyrinops* belong to the same subfamily Thymelaeoideae (previously Aquilariodeae), and the two species are very similar in morphology [33]. However, the flowers in *Aquilaria* have eight to twelve stamens, while those in *Gyrinops* have five stamens [33].

Agarwood-producing trees are evergreen broadleaf trees that occur in the tropics [6,8]. They are native to Southeast Asia and are mostly distributed in the rainforests of Borneo, Cambodia, China, India, Indonesia, Laos, Malaysia, New Guinea, Philippines, Thailand, and Vietnam [2,3]. However, Indonesia has the highest diversity of natural agarwood plant species [21]. Agarwood plantations in Indonesia are relatively small (10 to 5000 trees per farmer), while in Cambodia, China, Laos, Malaysia, Thailand, and Vietnam, the plantation area is larger, ranging from 40 hectares to more than 1000 hectares [21].

1.2. Fragrant Purposes and Medicinal Uses of Agarwood

Agarwood is well known as incense because it has a pleasant fragrance when it is burned [11,14]. However, the essential oil of agarwood is the most important ingredient in high-end perfume due to its unique fragrance [11,14]. Agarwood has been widely used in Buddhist, Hindu, and Islamic ceremonies [2]. In the Middle East, agarwood is a famous incense, and the essential oil is being used as high demanding perfumes [18,34]. In addition, agarwood incense plays an important role in the Japanese "koh-doh" ceremony [19,34].

Agarwood plays an important role in both traditional and modern medicine [2,12,13]. In traditional Chinese medicine, agarwood is used as a sedative, qi-regulating drug, and carminative medicine, which can also alleviate stomach disease, cough, rheumatism, and high fever [2,12,13]. In traditional Indian medicine, agarwood is used to treat diarrhea, dysentery, vomiting, anorexia, oral and dental diseases, facial paralysis, tremor, sprain, and fracture [34,35]. In traditional Arabian medicine, agarwood essential oil is often used in aromatherapy [2]. Modern pharmacological research has shown that agarwood has the potential of inducing sedation, reducing nerve excitability as well as being antibacterial and antifungal, anti-inflammatory, having analgesic effects, gastrointestinal regulatory properties, antiasthma, anti-diabetes, and antioxidation [2,36].

1.3. Three Methods That Induce the Production of Agarwood

Agarwood is known as the most expensive natural product on the earth, but the formation of its resin is very rare and slow under natural conditions [7,16,24]. In order to meet the needs of the market, long ago, people began to explore the artificial induction methods of agarwood [20,37]. The current artificial induction methods can be summarized in the following three methods (Figure 1).

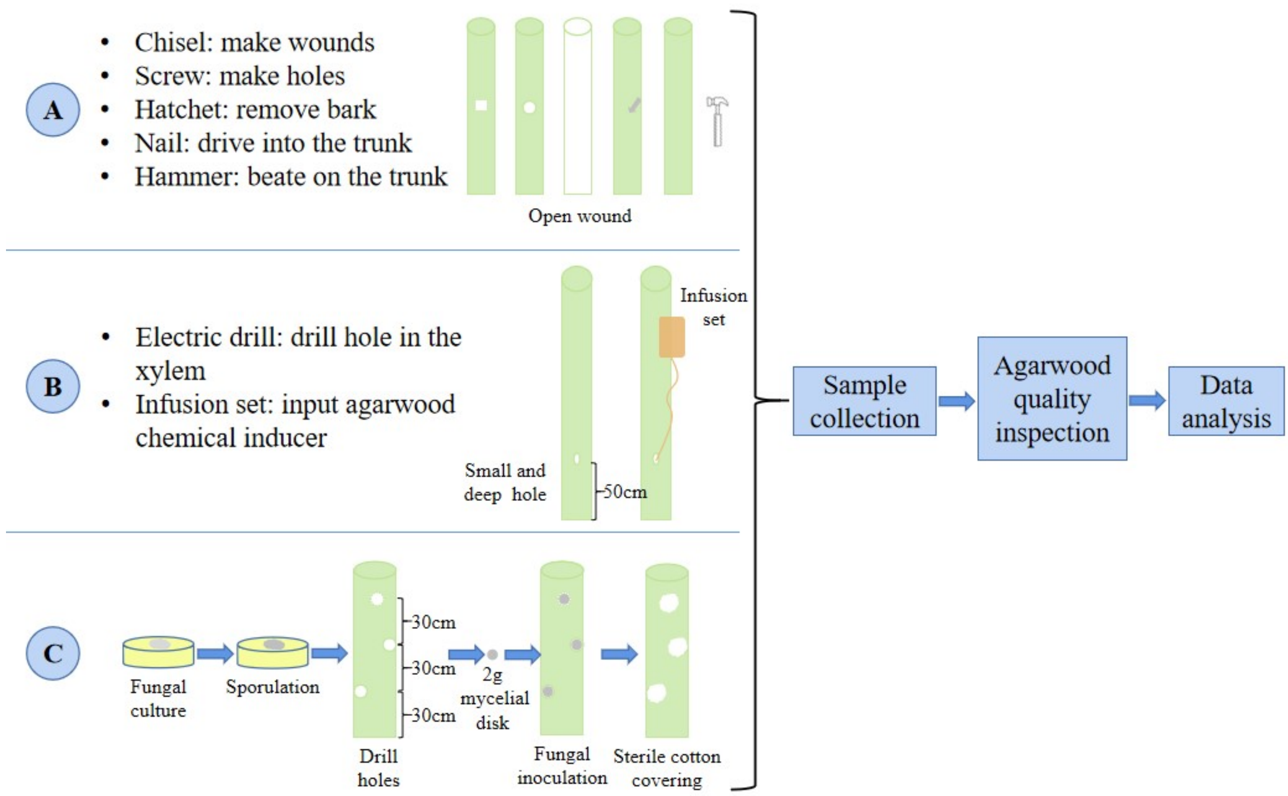

Figure 1. Methods of artificial induction of agarwood resin. A Physical injury [38], B Chemical inducer [12], C Biological inoculation (fungal inoculation) [28].

1.3.1. Physical Injury

The artificial induction technology of agarwood can be traced back to AD 300 in China [20]. Based on the literature, the color of internal tissues (branches, joints, root and stem) changed due to the formation of the resin after one year of artificial injury [20,39]. Farmers used methods such as burning, burning with a red-hot iron, cutting, drilling, holing, nailing the trees, partial pruning tree trunks, peeling and wounding trees with axes or machetes [6,9,12].

The advantage of these physical injury methods is that they are cost-effective, while the disadvantage is that it takes manpower, a few years or even one decade, and the yield is related to the number and degree of physical injury [9].

1.3.2. Chemical Inducer

Different chemicals such as brown sugar, formic acid, hydrogen peroxide, methyl jasmonate, salicylic acid, sodium chloride and soybean oil have been used to stimulate the formation of agarwood [40–43]. These chemicals are injected into the xylem of the trees in different concentrations and, as a result of being distributed throughout the plant through xylem transportation, cause damages to the whole plant [7].

The advantage of chemical induction is that it is faster, results in higher production, and furthermore, induces the whole plant to form agarwood resin [9,44]. However, the disadvantage of chemical induction is the harmful side effects of the chemicals on the environment [44].

1.3.3. Biological Inoculation (Fungal Inoculation)

The fungal inoculation of an agarwood-producing tree (*Aquilaria agallocha*) was first reported by Tunstall in 1929 [37]. Later, several studies were carried out to investigate and isolate various fungi from agarwood to induce agarwood production [26,45,46]. Such research confirmed the positive role of fungi in inducing agarwood formation [26,45,46]. At the beginning of the 21st century, there was an immense expansion of research on the role of agarwood tree endophytes on the production of agarwood (Table 1), while some fungi with inducing ability and biological activity have been studied [24,26,32,46–56].

Biological induction techniques involve the stimulation of the plant's immune response through artificial infection of "pure" or "mixed" fungal strains [9]. The majority of fungi used for the inoculation are endophytes isolated from healthy plants or the infected tissue of agarwood-producing trees [9]. The inoculation is done through open wounds [6]. The long incubation period allows microorganisms to reproduce and settle in the tree [6]. This triggers the plant defense mechanism to produce the agarwood to resist further fungal infections [6,9].

The advantage of biological agarwood induction is that it can intermittently and continuously induce the formation of agarwood [7,57]. Compared with the physical methods, biological agents are faster and more efficient, while compared to chemical methods, they are safer, healthier, and environmentally friendly [21]. In this review, we summarized the data on endophytic fungi isolated from agarwood-producing trees derived from 49 peer-reviewed publications (Table 1). Based on the literature, 171 endophytic strains in 59 genera have been isolated from agarwood plants (Figure 2, Table 1). Among these, 59 endophytic strains in 16 genera have been shown to induce agarwood production through artificial induction experiments (Table 2). In addition, 38 endophytic strains in 29 genera have been evaluated for their biological activities (such as antimicrobial, antimicrobial and antitumor) (Table 3).

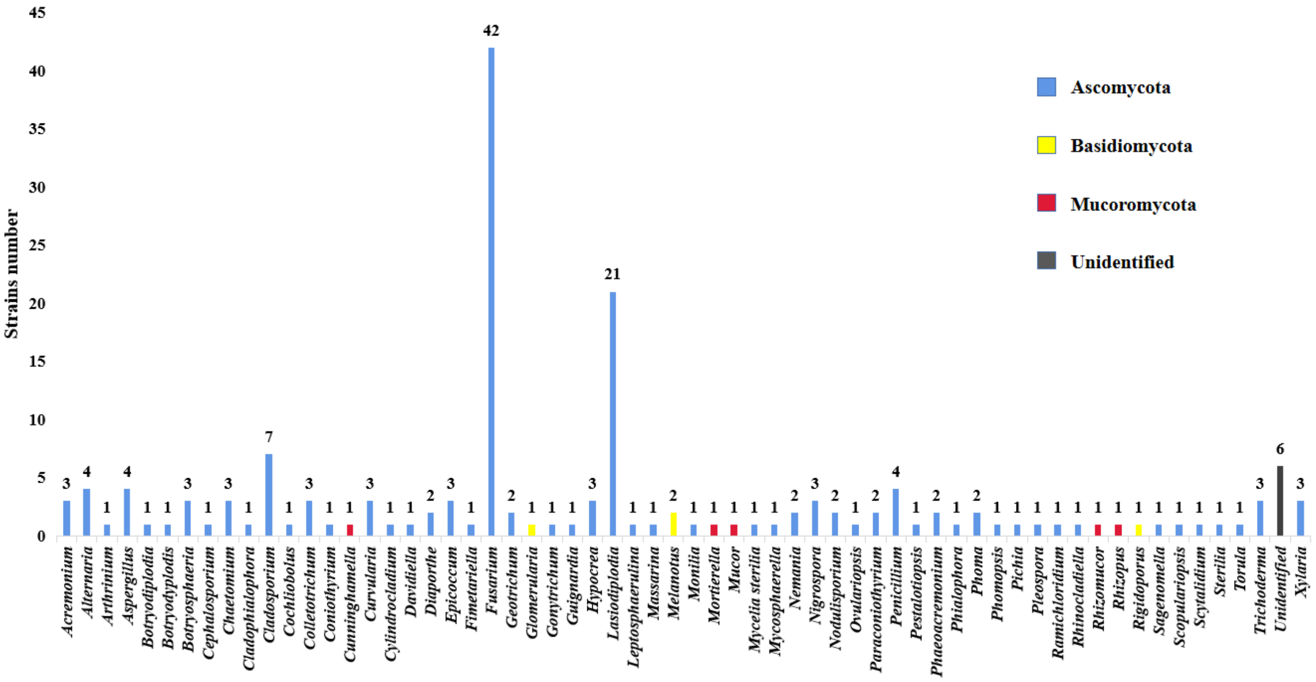

Figure 2. Endophytic fungi isolated from various parts of agarwood-producing trees.

Table 1. Endophytic fungi isolated from agarwood-producing trees. "Y" indicates an ability of this strain to induce the formation of agarwood resin, "N" indicates that this strain has not been tested to induce the formation of agarwood resin in the given study; "N/A" indicates that no information available (The table is arranged according to the time of publication).

Endophytic Fungi	Agarwood-Producing Tree Species	Isolation Source	The Ability to Induce Agarwood	Bioactivity/Important Metabolites	Country	References
Aspergillus sp.	*Aquilaria* sp.	N/A	Y	N/A	India	[58]
Botryodyplodis	*Aquilaria* sp.	N/A	Y	N/A	India	[58]
Botryosphaeria dothidea	*Aquilaria* sp.	N/A	Y	N/A	India	[58]
Diplodia sp.	*Aquilaria* sp.	N/A	Y	N/A	India	[58]
Several fungi isolated from *Aquilaria agallocha*	*Aquilaria agallocha*	N/A	N	N/A	N/A	[59]
Epicoccum granulatum	*Aquilaria agallocha*	N/A	Y	N/A	India	[60]
Cladosporium sp.	*Aquilaria agallocha*	N/A	Y	N/A	N/A	[61]
Torula sp.	*Aquilaria agallocha*	N/A	Y	N/A	N/A	[61]
Phialophora parasitica	*Aquilaria agallocha*	N/A	N	N/A	N/A	[62]
Aspergillus sp.	*Aquilaria agallocha*	infected wood	N	N/A	N/A	[37]
Aspergillus tamarii	*Aquilaria agallocha*	infected wood	N	N/A	N/A	[37]
Botryodiplodia theobromae	*Aquilaria agallocha*	infected wood	N	N/A	N/A	[37]
Fusarium solani	*Aquilaria agallocha*	infected wood	N	N/A	N/A	[37]
Penicillium citrinum	*Aquilaria agallocha*	infected wood	N	N/A	N/A	[37]
Fusarium bulbigenium	*Aquilaria* sp.	N/A	Y	N/A	N/A	[63]
Fusarium lateritium	*Aquilaria* sp.	N/A	Y	N/A	N/A	[63]
Fusarium oxysporum	*Aquilaria* sp.	N/A	Y	N/A	N/A	[63]
Melanotus flavolivens	*Aquilaria sinensis*	N/A	Y	N/A	China	[30]
Chaetomium globosum	*Aquilaria agallocha*	N/A	Y	N/A	India	[47]
Fusarium oxysporum	*Aquilaria agallocha*	N/A	Y	N/A	India	[47]
Fusarium sp.	*Aquilaria* sp.	Agarwood samples	Y	N/A	Indonesia	[48]
Fusarium sp.	*Aquilaria* sp.	N/A	Y	N/A	Sumatra island	[48]
Fusarium sp.	*Gyrinops versteegii*	Agarwood samples	Y	N/A	Indonesia	[48]
Chaetomium globosum	*Aquilaria agallocha*	N/A	Y	N/A	N/A	[49]
Fusarium oxysporum	*Aquilaria agallocha*	N/A	Y	N/A	N/A	[49]

Table 1. *Cont.*

Endophytic Fungi	Agarwood-Producing Tree Species	Isolation Source	The Ability to Induce Agarwood	Bioactivity/Important Metabolites	Country	References
Acremonium sp.	*Aquilaria microcarpa*	N/A	Y	N/A	Malaysia	[50]
Botryosphaeria rhodina	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Cephalosporium sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Cladophialophora sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Cladosporium edgeworthrae	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Colletotrichum sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Epicoccum sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Fusarium oxysporum	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Fusarium sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Geotrichum sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Glomerularia sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Gonytrichum sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Guignardia manqiferae	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Monilia sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Mortierella sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Mycelia sterilia sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Ovulariopsis sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Penicillium sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Pleospora sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Rhinocladiella sp.	*Aquilaria sinensis*	Stem, root and leaves	N	Antimicrobial activity	China	[64]
Fusarium moniliforme	*Aquilaria* sp.	N/A	Y	N/A	N/A	[51]
Fusarium sambucinum	*Aquilaria* sp.	N/A	Y	N/A	N/A	[51]
Fusarium solani	*Aquilaria* sp.	N/A	Y	N/A	N/A	[51]
Fusarium tricinctum	*Aquilaria* sp.	N/A	Y	N/A	N/A	[51]
Melanotus flavolivens	*Aquilaria sinensis*	N/A	Y	Sesquiterpenes, aromatic constituents, and fatty acids	China	[65]
Fusarium solani	*Aquilaria malaccensis*	Wood chips	N	N/A	Malaysia	[66]
Fusarium sp.	*Aquilaria malaccensis*	Wood chips	N	N/A	Malaysia	[66]
Hypocrea lixii	*Aquilaria malaccensis*	Wood chips	N	N/A	Malaysia	[66]
Lasiodiplodia theobromae	*Aquilaria malaccensis*	Wood chips	N	N/A	Malaysia	[66]
Cochliobolus lunatus	*Aquilaria malaccensis*	Wood chips	N	N/A	Malaysia	[66]
Cunninghamella bainieri	*Aquilaria malaccensis*	Wood chips	N	N/A	Malaysia	[66]
Curvularia sp.	*Aquilaria malaccensis*	Wood chips	N	N/A	Malaysia	[66]
Trichoderma sp.	*Aquilaria malaccensis*	Wood chips	N	N/A	Malaysia	[66]
Nodulisporium sp.	*Aquilaria sinensis*	Stem	N	Isofuranonaphthalenone, and benzopyran	China	[67]

Table 1. *Cont.*

Endophytic Fungi	Agarwood-Producing Tree Species	Isolation Source	The Ability to Induce Agarwood	Bioactivity/Important Metabolites	Country	References
Cladosporium tenuissimum	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Coniothyrium nitidae	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Epicoccum nigrum	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Fusarium equiseti	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Fusarium oxysporum	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Fusarium solani	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Hypocrea lixii	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Lasiodiplodia theobromae	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Leptosphaerulina chartarum	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Paraconiothyrium variabile	*Aquilaria sinensi*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Phaeoacremonium rubrigenum	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Phoma herbarum	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Rhizomucor variabilis	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[68]
Fusarium sp.	*Aquilaria microcarpa*	N/A	Y	N/A	N/A	[52]
Fimetariella rabenhorstii	*Aquilaria sinensis*	N/A	N	Frabenol (Sesquiterpene alcohol)	China	[69]
Fusarium sp.	*Aquilaria beccariana*	N/A	Y	N/A	N/A	[53]
Trichoderma spirale	*Aquilaria sinensis*	N/A	N	Trichodermic acid A, trichodermic acid B, known trichodermic acid and trichodermamide A	China	[70]
Lasiodiplodia sp.	*Aquilaria sinensis*	Natural agarwood	Y	N/A	China	[45]
Xylaria sp.	*Aquilaria sinensis*	Natural agarwood	Y	N/A	China	[45]
Paraconiothyrium variabile	*Aquilaria sinensis*	Agarwood samples	Y	N/A	China	[71]
Alternaria sp.	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]
Cladosporium cladosporoides	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]
Cladosporium sp.	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]
Curvularia sp.	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]
Davidiella tassiana	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]
Fusarium solani	*Aquilaria malaccensis*	Agarwood samples	N	N/A	India	[72]
Hypocrea fairnosa	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]
Massarina albocarnis	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]
Phaeoacremonium	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]
Pichia sp.	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]

Table 1. *Cont.*

Endophytic Fungi	Agarwood-Producing Tree Species	Isolation Source	The Ability to Induce Agarwood	Bioactivity/Important Metabolites	Country	References
Trichoderma sp.	*Aquilaria malaccensis*	Wood samples	N	N/A	India	[72]
Alternaria sp.	*Aquilaria sinensis* (nonresinous trees)	Leaves	N	N/A	China	[32]
Botryosphaeria sp.	*Aquilaria sinensis* (agarwood-producing wounded tree)	Leaves	Y	Sesquiterpenes, 2-(2-phenylethyl) chromanone, aromatics, fatty acids and esters	China	[32]
Chaetomium sp.	*Aquilaria sinensis* (agarwood-producing wounded tree)	N/A	N	N/A	China	[32]
Colletotrichum gleosporiodes	*Aquilaria sinensis* (agarwood-producing wounded tree)	Leaves	N	N/A	China	[32]
Cylindrocladium sp.	*Aquilaria sinensis* (agarwood-producing wounded tree)	Leaves	N	N/A	China	[32]
Fusarium sp.	*Aquilaria sinensis* (agarwood-producing wounded tree)	N/A	Y	Sesquiterpenes, 2-(2-phenylethyl) chromanone, aromatics, fatty acids and esters	China	[32]
Mycosphaerella sp.	*Aquilaria sinensis* (nonresinous trees)	Leaves	N	Sesquiterpenes, 2-(2-phenylethyl) chromanone, aromatics, fatty acids and esters	China	[32]
Nodulisporium sp.	*Aquilaria sinensis* (agarwood-producing wounded tree)	N/A	N	N/A	China	[32]
Penicillium sp.	*Aquilaria sinensis* (agarwood-producing wounded tree)	N/A	N	N/A	China	[32]
Pestalotiopsis sp.	*Aquilaria sinensis* (agarwood-producing wounded tree)	N/A	N	N/A	China	[32]
Phoma sp.	*Aquilaria sinensis* (nonresinous trees)	Leaves	N	N/A	China	[32]
Phomopsis sp.	*Aquilaria sinensis* (agarwood-producing wounded tree)	Leaves	N	N/A	China	[32]
Ramichloridium sp.	*Aquilaria sinensis* (nonresinous trees)	Leaves	N	N/A	China	[32]
Sagenomella sp.	*Aquilaria sinensis* (nonresinous trees)	Leaves	N	N/A	China	[32]
Xylaria mali	*Aquilaria sinensis*	Agarwood samples	N	Antimicrobial and antitumor activity	China	[32]
Xylaria sp.	*Aquilaria sinensis* (agarwood-producing wounded tree)	N/A	N	N/A	China	[32]
Lasiodiplodia theobromae	*Aquilaria sinensis*	Diseased branch	Y	Jasmonates, JAs	China	[29]

Table 1. *Cont.*

Endophytic Fungi	Agarwood-Producing Tree Species	Isolation Source	The Ability to Induce Agarwood	Bioactivity/Important Metabolites	Country	References
Nigrospora oryzae	*Aquilaria sinensis*	Stem, root and leaves	N	11-Hydroxycapitulatin B and Capitulatin B	China	[73]
Unidentified five fungi belonging to the *Deuteromycetes* and *Ascomycetes*	*Aquilaria malaccensis*	N/A	Y	Benzylacetone, anisylacetone, guaiene and palustrol	Malaysia	[54]
Fusarium oxysporum	*Aquilaria sinensis*	Agarwood samples	Y	Sesquiterpenes (agarospirol), aromatics compounds and alkanes	China	[74]
Lasiodiplodia theobromae	*Aquilaria sinensis*	Agarwood samples	Y	Sesquiterpenes (agarospirol), aromatics compounds and alkanes	China	[74]
Acremonium sp.	*Aquilaria malaccensis*	Agarwood samples pre-inoculated with *Fusarium*	N	N/A	N/A	[55]
Alternaria sp.	*Aquilaria malaccensis*	Agarwood samples pre-inoculated with *Fusarium*	N	N/A	N/A	[55]
Cladosporium sp.	*Aquilaria malaccensis*	Agarwood samples pre-inoculated with *Fusarium*	N	N/A	N/A	[55]
Fusarium sp.	*Aquilaria malaccensis*	Agarwood samples pre-inoculated with *Fusarium*	Y	N/A	N/A	[55]
Mucor sp.	*Aquilaria malaccensis*	Agarwood samples pre-inoculated with *Fusarium*	N	N/A	N/A	[55]
Nigrospora sp.	*Aquilaria malaccensis*	Agarwood samples pre-inoculated with *Fusarium*	N	N/A	N/A	[55]
Scopulariopsis sp.	*Aquilaria malaccensis*	Agarwood samples pre-inoculated with *Fusarium*	N	N/A	N/A	[55]
Scytalidium sp.	*Aquilaria malaccensis*	Agarwood samples pre-inoculated with *Fusarium*	N	N/A	N/A	[55]
Fusarium oxysporum	*Aquilaria* sp.	Agarwood samples	N	N/A	Indonesia	[75]
Fusarium solani	*Aquilaria* sp.	Agarwood samples	N	N/A	Indonesia	[75]
Fusarium sp.	*Aquilaria* sp.	Agarwood samples	N	N/A	Indonesia	[75]
Fusarium verticillioides	*Aquilaria crassna*	Agarwood samples	N	Antimicrobial activity	Vietnam	[76]
Geotrichum candium	*Aquilaria crassna*	Agarwood samples	N	Antimicrobial activity	Vietnam	[76]
Acremonium sp.	*Aquilaria crassna*	N/A	Y	N/A	N/A	[56]
Fusarium sp.	*Aquilaria crassna*	N/A	Y	N/A	N/A	[56]
Fusarium solani	*Aquilaria sinensis*	Agarwood samples	Y	N/A	China	[24]
Lasiodiplodia theobromae	*Aquilaria sinensis*	Agarwood samples	Y	N/A	China	[24]

Table 1. *Cont.*

Endophytic Fungi	Agarwood-Producing Tree Species	Isolation Source	The Ability to Induce Agarwood	Bioactivity/Important Metabolites	Country	References
Fusarium solani	*Aquilaria malaccensis*	From wild *Aquilaria malaccensis*	Y	Tridecanoic acid, a-santalol, and spathulenol	Indonesia	[44]
Fusarium sp.	*Aquilaria sinensis*	Agarwood samples	Y	N/A	China	[77]
Lasiodiplodia theobromae	*Aquilaria sinensis*		Y	N/A	China	[77]
Arthrinium sp.	*Aquilaria subintegra*	Fresh heartwood stems	N	β-agarofuran, α-agarofuran, δ-eudesmol, oxo-agarospirol, and β-dihydro agarofuran	Thailand	[31]
Colletotrichum sp.	*Aquilaria subintegra*	Fresh heartwood stems	N	β-agarofuran, α-agarofuran, δ-eudesmol, oxo-agarospirol, and β-dihydro agarofuran	Thailand	[31]
Diaporthe sp.	*Aquilaria subintegra*	Fresh heartwood stems	N	Excellent antioxidant capacity	Thailand	[31]
Fusarium sp.	*Aquilaria malaccensis*	Agarwood samples	Y	N/A	India	[78]
Rigidoporus vinctus	*Aquilaria sinensis*	Agarwood samples	Y	N/A	China	[46]
Fusarium oxysporum	*Aquilaria sinensis*	N/A	Y	N/A	China	[79]
Lasiodiplodia theobromae	*Aquilaria sinensis*	N/A	Y	N/A	China	[79]
Nigrospora oryzae	*Aquilaria sinensis*	N/A	Y	β-phenylethyl alcohol	China	[80]
Fusarium solani	*Gyrinops versteegii*	N/A	Y	Sesquiterpen, chromones, aromatic, fatty acid, triterpen	Indonesia	[81]
Fusarium solani	*Aquilaria malaccensis*	N/A	Y	Sesquiterpen, chromones, aromatic, fatty acid, triterpen	Indonesia	[81]
Aspergillus niger	*Gyrinops walla*	Agarwood samples	Y	Jinkohol, agarospirol and 2(2-phenyl) chromone derivatives, b-Seline, γ-eudesmol and valerenal, γ-Elemene	Sri Lanka	[28]
Fusarium solani	*Gyrinops walla*	Agarwood samples	Y	Jinkohol, agarospirol and 2(2-phenyl) chromone derivatives, b-Seline, γ-eudesmol and valerenal, γ-Elemene	Sri Lanka	[28]
Lasiodiplodia aquilariae	*Aquilaria crassna*	Agarwood samples	N	N/A	Laos	[3]
Lasiodiplodia brasiliensis	*Aquilaria crassna*	Agarwood samples	N	N/A	Laos	[3]
Lasiodiplodia curvata	*Aquilaria crassna*	Agarwood samples	N	N/A	Laos	[3]
Lasiodiplodia irregularis	*Aquilaria crassna*	Healthy tissue	N	N/A	Laos	[3]
Lasiodiplodia laosensis	*Aquilaria crassna*	Healthy tissue	N	N/A	Laos	[3]
Lasiodiplodia lignicola	*Aquilaria crassna*	Agarwood samples	N	N/A	Laos	[3]
Lasiodiplodia macroconidica	*Aquilaria crassna*	Agarwood samples	N	N/A	Laos	[3]
Lasiodiplodia microcondia	*Aquilaria crassna*	Healthy tissue	N	N/A	Laos	[3]
Lasiodiplodia pseudotheobromae	*Aquilaria crassna*	Healthy tissue and Agarwood samples	N	N/A	Laos	[3]
Lasiodiplodia sp.	*Aquilaria crassna*	Healthy tissue and Agarwood samples	N	N/A	Laos	[3]

Table 1. *Cont.*

Endophytic Fungi	Agarwood-Producing Tree Species	Isolation Source	The Ability to Induce Agarwood	Bioactivity/Important Metabolites	Country	References
Lasiodiplodia tenuiconidia	*Aquilaria crassna*	Agarwood samples	N	N/A	Laos	[3]
Lasiodiplodia tropica	*Aquilaria crassna*	Healthy tissue	N	N/A	Laos	[3]
Fusarium solani	*Aquilaria sinensis*	N/A	Y	N/A	China	[82]
Lasiodiplodia theobromae	*Aquilaria sinensis*	N/A	Y	N/A	China	[82]
Fusarium solani	*Gyrinops versteegii*	N/A	Y	(1) alloaromadendrene. (2) β-eudesmol. (3) β-selinene. (4) chromone derivatives 2-(2-phenylethyl) chromen-4-one. (5) 6-methoxy-2-(2-phenylethyl) chromen-4-one. (6) 6,7-dimethoxy-2-(2-phenylethyl) chromen-4-one.	Indonesia	[26]
Alternaria sp.	*Aquilaria malaccensis*	Juvenile (1-year-old) woods	N	N/A	India	[83]
Cladosporium sp.	*Aquilaria malaccensis*	Agarwood samples	N	Antibacterial effect against *Escherichia coli* and *Bacillus subtilis*	India	[83]
Curvularia sp.	*Aquilaria malaccensis*	Juvenile (1-year-old) woods	N	N/A	India	[83]
Fusarium sp.	*Aquilaria malaccensis*	Agarwood samples	N	N/A	India	[83]
Penicillium sp.	*Aquilaria malaccensis*	Agarwood samples	N	N/A	India	[83]
Rhizopus sp.	*Aquilaria malaccensis*	Juvenile (1-year-old) woods	N	N/A	India	[83]
Sterilia sp.	*Aquilaria malaccensis*	Juvenile (1-year-old) woods	N	N/A	India	[83]
Nemania aquilariae	*Aquilaria sinensis*	Agarwood samples	N	(1) Bicyclo[3.1.1]hept-3-ene-2-acetaldehyde, 4,6,6-trime-thyl-, (1R,2R,5S) rel-. (2) Naphtha-lene,1,2,3,4, 4a,5,6,7-octahydro-4a,8-dimethyl-2-(1-meth-ylethenyl)-. (3) Alloaromaden-drene. (4) Valencen. (5) α-Selinene. (Antibacterial and antimicrobial)	China	[25]
Nemania yunnanensis	*Aquilaria sinensis*	Agarwood samples	N	N/A	China	[25]

Table 2. Endophytic fungi that have been shown to induce the formation of agarwood. "N/A" indicates no information available.

Endophytic Fungi Species	Endophytic Fungi Family	Agarwood-Producing Trees	Country	References
Acremonium sp.	Incertae sedis	*Aquilaria crassna*	N/A	[56]
Acremonium sp.	Incertae sedis	*Aquilaria microcarpa*	Malaysia	[50]
Aspergillus niger	*Aspergillaceae*	*Gyrinops walla*	Sri Lanka	[28]
Aspergillus sp.	*Aspergillaceae*	*Aquilaria* sp.	India	[58]
Botryodyplodis	N/A	*Aquilaria* sp.	India	[58]
Botryosphaeria dothidea	*Botryosphaeriaceae*	*Aquilaria* sp.	India	[58]
Botryosphaeria sp.	*Botryosphaeriaceae*	*Aquilaria sinensis*	China	[32]
Chaetomium globosum	*Chaetomiaceae*	*Aquilaria agallocha*	India	[47]
Chaetomium globosum	*Chaetomiaceae*	*Aquilaria agallocha*	N/A	[49]
Cladosporium sp.	*Cladosporiaceae*	*Aquilaria agallocha*	N/A	[61]
Diplodia sp.	*Botryosphaeriaceae*	*Aquilaria* sp.	India	[58]
Epicoccum granulatum	*Didymellaceae*	*Aquilaria agallocha*	India	[60]
Fusarium bulbigenium	*Nectriaceae*	*Aquilaria* sp.	N/A	[63]
Fusarium lateritium	*Nectriaceae*	*Aquilaria* sp.	N/A	[63]
Fusarium moniliforme	*Nectriaceae*	*Aquilaria* sp.	N/A	[51]
Fusarium oxysporum	*Nectriaceae*	*Aquilaria agallocha*	India	[47]
Fusarium oxysporum	*Nectriaceae*	*Aquilaria agallocha*	N/A	[49]
Fusarium oxysporum	*Nectriaceae*	*Aquilaria sinensis*	China	[74]
Fusarium oxysporum	*Nectriaceae*	*Aquilaria sinensis*	China	[79]
Fusarium oxysporum	*Nectriaceae*	*Aquilaria* sp.	N/A	[63]
Fusarium sambucinum	*Nectriaceae*	*Aquilaria* sp.	N/A	[51]
Fusarium solani	*Nectriaceae*	*Aquilaria malaccensis*	Indonesia	[44]
Fusarium solani	*Nectriaceae*	*Aquilaria malaccensis*	Indonesia	[81]
Fusarium solani	*Nectriaceae*	*Aquilaria sinensis*	China	[24]
Fusarium solani	*Nectriaceae*	*Aquilaria sinensis*	China	[82]
Fusarium solani	*Nectriaceae*	*Aquilaria* sp.	N/A	[51]
Fusarium solani	*Nectriaceae*	*Gyrinops versteegii*	Indonesia	[81]
Fusarium solani	*Nectriaceae*	*Gyrinops versteegii*	Indonesia	[26]
Fusarium solani	*Nectriaceae*	*Gyrinops walla*	Sri Lanka	[28]
Fusarium sp.	*Nectriaceae*	*Aquilaria beccariana*	N/A	[53]
Fusarium sp.	*Nectriaceae*	*Aquilaria crassna*	N/A	[56]
Fusarium sp.	*Nectriaceae*	*Aquilaria malaccensis*	India	[78]
Fusarium sp.	*Nectriaceae*	*Aquilaria malaccensis*	N/A	[55]
Fusarium sp.	*Nectriaceae*	*Aquilaria microcarpa*	N/A	[52]
Fusarium sp.	*Nectriaceae*	*Aquilaria sinensis*	China	[32]
Fusarium sp.	*Nectriaceae*	*Aquilaria sinensis*	China	[77]
Fusarium sp.	*Nectriaceae*	*Aquilaria* sp.	Indonesia	[48]
Fusarium sp.	*Nectriaceae*	*Aquilaria* sp.	Sumatra island	[48]
Fusarium sp.	*Nectriaceae*	*Gyrinops versteegii*	Indonesia	[48]
Fusarium tricinctum	*Nectriaceae*	*Aquilaria* sp.	N/A	[51]
Lasiodiplodia sp.	*Botryosphaeriaceae*	*Aquilaria sinensis*	China	[45]
Lasiodiplodia theobromae	*Botryosphaeriaceae*	*Aquilaria sinensis*	China	[29]
Lasiodiplodia theobromae	*Botryosphaeriaceae*	*Aquilaria sinensis*	China	[74]
Lasiodiplodia theobromae	*Botryosphaeriaceae*	*Aquilaria sinensis*	China	[24]
Lasiodiplodia theobromae	*Botryosphaeriaceae*	*Aquilaria sinensis*	China	[77]
Lasiodiplodia theobromae	*Botryosphaeriaceae*	*Aquilaria sinensis*	China	[79]
Lasiodiplodia theobromae	*Botryosphaeriaceae*	*Aquilaria sinensis*	China	[82]
Melanotus flavolivens	*Strophariaceae*	*Aquilaria sinensis*	China	[30]
Melanotus flavolivens	*Strophariaceae*	*Aquilaria sinensis*	China	[65]
Nigrospora oryzae	Incertae sedis	*Aquilaria sinensis*	China	[80]
Paraconiothyrium variabile	*Didymosphaeriaceae*	*Aquilaria sinensis*	China	[71]
Rigidoporus vinctus	*Meripilaceae*	*Aquilaria sinensis*	China	[46]
Torula sp.	*Torulaceae*	*Aquilaria agallocha*	N/A	[61]
Unidentified five fungi belonging to the Deuteromycetes and Ascomycetes groups	N/A	*Aquilaria malaccensis*	Malaysia	[54]
Xylaria sp.	*Xylariaceae*	*Aquilaria sinensis*	China	[45]

Table 3. Bioactivity of endophytic fungi isolated from agarwood-producing trees. "N/A" indicates no information available.

Endophytic Fungi Species	Endophytic Fungi Family	Isolation Source	Bioactivity	References
Botryosphaeria rhodina	*Botryosphaeriaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Cephalosporium sp.	Incertae sedis	*Aquilaria sinensis*	Antimicrobial activity	[64]
Cladophialophora sp.	*Herpotrichiellaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Cladosporium edgeworthrae	*Cladosporiaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Cladosporium sp.	*Cladosporiaceae*	*Aquilaria malaccensis*	Antibacterial effect against Escherichia coli and Bacillus subtilis	[83]
Cladosporium tenuissimum	*Cladosporiaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Colletotrichum sp.	*Glomerellaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Coniothyrium nitidae	*Coniothyriaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Diaporthe sp.	*Diaporthaceae*	*Aquilaria subintegra*	Excellent antioxidant capacity	[31]
Epicoccum nigrum	*Didymellaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Epicoccum sp.	*Didymellaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Fusarium equiseti	*Nectriaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Fusarium oxysporum	*Nectriaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Fusarium oxysporum	*Nectriaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Fusarium solani	*Nectriaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Fusarium sp.	*Nectriaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Fusarium verticillioides	*Nectriaceae*	*Aquilaria crassna*	Antimicrobial activity	[76]
Geotrichum candium	*Dipodascaceae*	*Aquilaria crassna*	Antimicrobial activity	[76]
Geotrichum sp.	*Dipodascaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Glomerularia sp.	*Platygloeaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Gonytrichum sp.	*Chaetosphaeriaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Guignardia manqiferae	*Phyllostictaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Hypocrea lixii	*Hypocreaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Lasiodiplodia theobromae	*Botryosphaeriaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Leptosphaerulina chartarum	*Didymellaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Monilia sp.	*Sclerotiniaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Mortierella sp.	*Mortierellaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Mycelia sterilia sp.	N/A	*Aquilaria sinensis*	Antimicrobial activity	[64]
Nemania aquilariae	*Xylariaceae*	*Aquilaria sinensis*	Antibacterial and antimicrobial	[25]
Ovulariopsis sp.	*Erysiphaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Paraconiothyrium variabile	*Didymosphaeriaceae*	*Aquilaria sinensi*	Antimicrobial and antitumor activity	[68]
Penicillium sp.	*Aspergillaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Phaeoacremonium rubrigenum	*Togniniaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Phoma herbarum	*Didymellaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Pleospora sp.	*Pleosporaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Rhinocladiella sp.	*Herpotrichiellaceae*	*Aquilaria sinensis*	Antimicrobial activity	[64]
Rhizomucor variabilis	*Lichtheimiaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[68]
Xylaria mali	*Xylariaceae*	*Aquilaria sinensis*	Antimicrobial and antitumor activity	[32]

2. Conclusions

In this review, the potential of artificial induction of agarwood through endophytic fungi in agarwood plants is discussed. In addition, the biological activities of endophytic fungi in agarwood plants are also reviewed. The high commercial demand for agarwood, agarwood essential oil, and agarwood-based products puts the natural agarwood-producing plants under higher threat [21]. Under the sustainable utilization of natural products, the commercial cultivation of agarwood-producing plants became important. Maintenance of higher quality is important to sustain a high level of marketability of agarwood products. The artificial induction of agarwood production became a "hot topic" among natural product researchers, especially at the beginning of the 21st century (Table 1). Most of this research was focused on the biological induction of agarwood production due to the beneficial effects. As a result of the trend towards biological induction of agarwood production, many studies were carried out to understand the fungal community present in the agarwood plants and their potential for agarwood production. A majority of studies have been focused on artificial infection of endophytic fungal strains to plants. According to the literature, 171 strains have been identified from agarwood plants, of which 59 strains have been demonstrated to induce the production of agarwood, and out of 59 strains, 28 strains belong to the family Nectriaceae (47.5%). This reflects that ascomycetous fungi belonging to the Nectriaceae have the highest potential for the artificial induction of agarwood (Table 2). Studies of endophytic fungal populations in agarwood have revealed many interesting biological properties. Based on the literature, 38 strains of a total of 171 strains were investigated for their biological properties, which is 22.2% of the known assemblage of endophytic fungi associated with agarwood plants (Tables 1 and 3).

Fungal inoculation for inducing agarwood resin production has been demonstrated to be effective, and the quality of the induced agarwood and natural agarwood are highly similar. Biological induction is faster than physical induction and safer than chemical induction. Therefore, it is necessary to further study endophytic fungi. The latest research shows that saprophytic bacteria (*Bacillus*) release the effective components of agarwood by degrading cellulose, which provides more evidence for future research [84]. Currently, studies on the fungal communities of agarwood mainly focus on endophytic fungi, while only a few reports have been published on saprophytic fungi. The research of Yang et al. [84] inspired researchers to carry out studies on saprophytic fungi in the future, in addition to in-depth research on endophytic fungi. Hence, for the sustainable development of the agarwood industry, further research is necessary to identify the endophytic fungal communities of agarwood plants that can be used to induce agarwood. The inoculation potential of non-pathogenic agarwood inducers is important. Proper research studies on the natural pathogens of agarwood trees, effective endophytic strains and effective saprobic strains must be carried out. Commercial agarwood production needs more scientific attention for the sustainability of the future agarwood industry and for environmental protection.

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