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REVIEW ARTICLE

Biodiversity and application prospects of fungal endophytes in the agarwood-producing genera, *Aquilaria* and *Gyrinops* (Thymelaeaceae): A review

Tianxiao Li [a,b], Zidong Qiu [a], Shiou Yih Lee [c], Xiang Li [a], Jiaqi Gao [d], Chao Jiang [a], Luqi Huang [a,b,*], Juan Liu [a,*]

[a] *National Resource Center for Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing 100700, China*
[b] *Department of Traditional Chinese Medicine, Guangdong Pharmaceutical University, Guangzhou 510006, China*
[c] *Faculty of Health and Life Sciences, INTI International University, 71800 Nilai, Negeri Sembilan, Malaysia*
[d] *Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, 301617 Tianjin, China*

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Abstract Agarwood is originated from the resinous part of *Aquilaria* and *Gyrinops* plants and has been a precious biomaterial for applications in traditional medicine, perfumery, cosmetics, and religious purposes all over the world. In the wild, the formation of agarwood is related to the defense mechanism of the tree in response to physical damage that allows further microbial infestation into its wood, while having the whole tree covered with agarwood would take up a long time, and it rarely happens. For *Aquilaria* and *Gyrinops*, the presence of endophytes is mainly found derived from the tree. The isolated endophytes could be important sources of natural products, while some could contribute to the formation of agarwood in the tree, which is safe for the environment and human health. This review summarized the biodiversity of fungal endophytes recorded in *Aquilaria* and *Gyrinops* and their potential effects on host trees. Till now, 67 endophytic genera have been isolated from *Aquilaria* and *Gyrinops*, and 18 ones were found responsible for the promotion of agarwood formation. Additionally, 92 compounds have been reported to be produced by the agarwood endophytes, and 52 ones displayed biological activities, most of which have anti-inflammatory, anti-bacterial, and anti-cancer activities. Nevertheless, fungal endophytes are promising agents that deserved to be further studied

* Corresponding authors at: No. 16, Dongzhimen Southern Street, Beijing 100700, China.
E-mail addresses: huangluqi01@126.com (L. Huang), juanliu126@126.com (J. Liu).

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and scaled up to a commercial level for the production of agarwood oil, but the role of endophytes in the agarwood host trees needs to be furtherly investigated in future studies.

1. Introduction

Members of the agarwood-producing genera, *Aquilaria* and *Gyrinops*, are tropical evergreen trees commonly grown in the lowland forest regions, which are mainly distributed in southeast Asia. Agarwood is a highly valuable fragrance derived from the resinous wood of *Aquilaria* and *Gyrinops* trees. The intriguing aroma of agarwood makes it a valuable ingredient that has a long history record in the production of traditional medicines as well as used in religious activities, while at present, it is regarded as a luxury biomaterial in perfumery and cosmeceutical industries (Huang et al., 2013; Sun et al., 2020; Xie et al., 2020). Although all 30 species (21 *Aquilaria* species and 9 *Gyrinops* species) are believed to be able to produce agarwood, to date, evidence of agarwood formation was only reported for 14 species of *Aquilaria* and eight species of *Gyrinops* (Auri et al., 2021; Compton and Zich, 2002; Hou 1964; Kiet et al., 2005; Lee and Mohamed, 2016; Ng et al., 1997; Subasinghe et al., 2012; Turjaman et al., 2016) (Table 1). The high demand but rare occurrence of agarwood in the wild has led to the over-exploitation of these valuable species in the past, causing the decline in the population size of these agarwood-producing species in the wild. As a consequence, some of these species are classified as "Vulnerable", "Endangered", and "Critically Endangered" (IUCN 2022), as well as to aid in conserving the resources, all members of the agarwood-producing genera, *Aquilaria* and *Gyrinops*, are currently placed under strict monitoring by the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) in Appendix II (UNEP-WCMC, 2022).

Due to the conservation status and low yield of agarwood production in the wild, relying on the natural population as a source of agarwood to meet the increasing market demand is rather unviable (Deng et al., 2020; Wang et al., 2018). Therefore, the domestication of agarwood-producing trees was introduced and mass cultivation coupled with good agriculture practices was promoted (Liu et al., 2013; Persoon and Beek, 2008). In general, agarwood is naturally formed in *Aquilaria* and *Gyrinops* trees as a result of self-defense against physical damage or microbial infection on the trees (Soehartono and Newton, 2000; Xu et al., 2013). While physical damage to the tree is to introduce an opening; fungal infection has always been considered to be a key factor in agarwood formation (Rasool and Mohamed, 2016).

Endophytic fungi can live inside plant tissues without any disease symptoms. The evidence of the use of endophytic fungi to induce agarwood formation has been present for a long time, i.e. 1934 (Turjaman et al., 2016; Yoswathana, 2013), while the fungi that show promising results in the production of agarwood are developed into fungal inoculum. To mimic the mechanism of agarwood formation via microbial infestation, endophytic fungi are introduced into the cultivated stands via inoculation technique in hope that the time to form agarwood will be reduced and the yield could be increased at the same time. It is believed that the quality of the agarwood formed relies heavily on the species or strains selected among the different endophytic fungi; thus, research and exploration to discover additional useful endophytic fungi that could warrant better yield and quality of agarwood are still ongoing (Liu et al., 2022). Additionally, the secondary metabolites from endophytic fungi of agarwood lead the way as sources for various pharmacological properties.

In order to provide a comprehensive review of the information on endophytic fungi involved in the formation of agarwood, we mined various published scientific reports and summarized the distribution and biodiversity of fungal endophytes present in *Aquilaria* and *Gyrinops*. In addition, the secondary metabolites produced as well as the pharmacological values of these agarwood-related fungal endophytes in *Aquilaria* and *Gyrinops* were documented and discussed too. Finally, the effects on the host trees of *Aquilaria* and *Gyrinops* by fungal endophytes were discussed. We believe that our review could be useful for researchers to find innovative directions in the research field of agarwood endophytes.

2. Ecological distribution of *Aquilaria* and *Gyrinops* species

Aquilaria and *Gyrinops* species are widely distributed in southeast Asia, especially Indomalesia region (Lee and Mohamed, 2016). Recently, nine from the total of 21 species in the genus *Aquilaria* genus are known to grow in Malaysia (data from GBIF-Global Biodiversity Information Facility; Lee and Mohamed, 2016; Lee et al., 2018; Lee et al., 2022), including *A. beccariana*, *A. crassna*, *A. cumingiana*, *A. hirta*, *A. malaccensis*, *A. microcarpa*, *A. rostrate*, *A. sinensis*, and *A. subintegra* (Table 1), which is the country with the most species of *Aquilaria*. And five species of *Aquilaria* are naturally distributed in Malaysia, including *A. beccariana*, *A. hirta*, *A. malaccensis*, *A. microcarpa*, and *A. rostrate* (Lee et al., 2016). The other four are transplanted from China, Indonesia, Thailand, and Vietnam. Meanwhile, eight of the total of nine species in the *Gyrinops* genus are known to naturally grow in Indonesia, except for *G. vidalii* which is only distributed in Thailand and Lao People's Democratic Republic (Table 1).

At present, the wild resources of *Aquilaria* and *Gyrinops* are rather limited. Thus, the reports on agarwood production are confined to 14 species of *Aquilaria* and eight species of *Gyrinops* (Table 1). More and more plantation areas are of larger scale, and *A. sinensis* occupies more than 5245 ha in China, which has the largest plantation size of all the species reported now (Turjaman et al., 2016; Yin et al., 2016). Additionally, *A. malaccensis* is the most widespread and cultivated species, including 13 countries (Table 1). Thus, *A. malaccensis* and *A. sinensis* are the most studied species recently. However, *Gyrinops* is less planted and studied for its slow-growing features (Lee et al., 2018). Among all the *Gyrinops* species, *G. versteegii* is the most popular species in eastern Indonesia, but it is less favored compared to *A. malaccensis* when it comes to agarwood cultivation in Indonesia (Faizal et al., 2022; Nasution et al., 2020; Turjaman et al., 2016).

3. Biodiversity of fungal endophytes in *Aquilaria* and *Gyrinops*

Endophytes are microorganisms that maintain endosymbiotic relationship within plants (Turjaman et al., 2016). At present, studies on endophytic biodiversity on *Aquilaria* received more attention than that of *Gyrinops*. Eventually, species that are involved in such studies are mainly those selected as cultivation species, including *A. crassna*, *A. malaccensis*, *A. microcarpa*, *A. sinensis*, *A. subintegra*, *G. caudata*, *G. verstegii*, and *G. walla*. However, the biodiversity of fungal endophytes has not been investigated in the other species of *Aquilaria* and *Gyrinops*

Table 1 Basic information about agarwood-producing genera of *Aquilaria* and *Gyrinops*, including species name, distribution, basionyms and synonyms, and agarwood production report.

Species Name	Distribution*	Basionyms and synonyms	Agarwood production report
Aquilaria apiculata Merr.	Philippines	–	
Aquilaria baillonii Pierre ex Lecomte	Cambodia; Viet Nam; Lao People's Democratic Republic	–	Ng et al., 1997
Aquilaria banaensis P.H. Hô	Viet Nam	*Aquilaria banaensae*	
Aquilaria beccariana Tiegh.	Brunei Darussalam; Indonesia; Malaysia	*Aquilaria cumingiana var parvifolia; Aquilaria grandifolia; Gyrinops brachyantha; Gyrinopsis grandifolia*	Faridah et al., 2009Compton and Zich, 2002Turjaman et al., 2016
Aquilaria brachyantha (Merr.) Hallier f.	Phillipines	*Gyrinopsis brachyantha*	
Aquilaria citrinicarpa (Elmer) Hallier f.	Phillipines	*Gyrinopsis citrinicarpa*	
Aquilaria crassna Pierre ex Lecomte	Cambodia; Viet Nam; Thailand; China; Malaysia	–	Yoswathana, 2013Ng et al., 1997
Aquilaria cumingiana (Decne.) Ridl.	Phillipines; Indonesia; United State; Malaysia	*Aquilaria pubescens; Decaisnella cumingiana; Gyrinopsis cumingiana; Gyrinopsis cumingiana* var. *pubescens; Gyrinopsis decemcostata; Gyrinopsis pubifolia*	Turjaman et al., 2016
Aquilaria decemcostata Hallier f.	Phillippines	–	
Aquilaria filaria (Oken) Merr.	Indonesia; Phillipines; Papua New Guinea	*Aquilaria cuminate; Aquilaria tomentosa; Gyrinopsis acuminate; Pittosporum filarium*	Compton and Zich, 2002Turjaman et al., 2016
Aquilaria hirta Ridl.	Indonesia; Malaysia; Singapore; Thailand	*Aquilaria moszkowski*	Faridah et al., 2009Compton and Zich, 2002Turjaman et al., 2016
Aquilaria khasiana Hallier f.	India	–	Hallier, 1992
Aquilaria malaccensis Lam.	Bangladesh; Bhutan; China; France; India; Indonesia; Lao People's Democratic Republic; Mauritius; Malaysia; Philippines; Viet Nam; Thailand; Sri Lanka	*Agallochum malaccense; Aloexylum agallochum; Aquilaria agallocha; Aquilaria ovate; Aquilaria moluccensis; Aquilaria secundaria; Aquilariella malaccense; Aquilariella malaccensis*	Chowdhury et al., 2003Broad, 1995Rahayu and Putridan Juliarni, 2007Turjaman et al. 2016
Aquilaria microcarpa Baill.	Brunei Darussalam; Indonesia; Malaysia; Italy	*Aquilaria borneensis; Aquilariella borneensis; Aquilariella microcarpa*	Santoso et al., 2011Faridah et al., 2009Compton and Zich, 2002Turjaman et al. 2016
Aquilaria parvifolia (Quisumb.) Ding Hou	Philippines	*Gyrinopsis parvifolia*	
Aquilaria rostrata Ridl.	Malaysia; Thailand	–	Faridah et al., 2009
Aquilaria rugosa K.Le-Cong & Kessler	Thailand; Viet Nam	–	Kiet et al., 2005
Aquilaria sinensis (Lour.) Spreng.	China; Thailand; Malaysia; Viet Nam	*Agallochum grandiflorum; Agallochum sinense; Aquilaria chinensis; Aquilaria grandiflora; Aquilaria ophispermum; Ophispermum sinense*	Liu et al., 2013Liu et al., 2022Ng et al., 1997Zhang et al., 2014
Aquilaria subintegra Ding Hou	Thailand; Malaysia	–	Hou, 1964
Aquilaria urdanetensis (Elmer) Hallier f.	Philippines	*Gyrinopsis urdanetense; Gyrinopsis urdanetensis*	
Aquilaria yunnanensis S.C. Huang	China	–	Sun et al., 2019Zhang et al. 2019
Gyrinops caudata (Gilg) Domke	Indonesia; Papua New Guinea	*Aquilaria caudata; Brachythalamus caudatus; Gyrinops audate*	Auri et al., 2021
Gyrinops decipiens Ding Hou	Indonesia	–	Turjaman et al. 2016
Gyrinops ledermannii Domke	Indonesia; Papua New Guinea	–	Compton and Zich 2002Turjaman et al. 2016

(*continued on next page*)

Table 1 (*continued*)

Species Name	Distribution*	Basionyms and synonyms	Agarwood production report
Gyrinops moluccana (Miq.) Baill.	Indonesia	*Aquilaria moluccana; Lachnolepsis moluccana*	Turjaman et al. 2016
Gyrinops podocarpa (Gilg) Domke	Indonesia; Papua New Guinea	*Aquilaria podocarpus; Brachythalamus podocarpus; Gyrinops ledermannii; Gyrinops podocarpus*	Turjaman et al. 2016
Gyrinops salicifolia Ridl.	Indonesia; Papua New Guinea	*Gyrinopsis salicifolia*	Shao et al., 2016Dong et al., 2019Turjaman et al., 2016
Gyrinops versteegii (Gilg) Domke	Indonesia; Papua New Guinea	*Aquilaria versteegii; Brachythalamus versteegii*	Faizal et al., 2020Faizal et al., 2022Turjaman et al., 2016Nasution et al., 2020
Gyrinops vidalii P.H.Hô	Thailand; Lao People's Democratic Republic	–	
Gyrinops walla Gaertn.	Indonesia; Papua New Guinea; India; Sri Lanka	*Aquilaria walla*	Subasinghe et al., 2012

* The distribution data of this table were calculated out from GBIF (the Global Biodiversity Information Facility, https://www.gbif.org) database and references (Lee and Mohamed, 2016; Lee et al., 2018; Lee et al., 2022).

due to the limited plantations, slow-growing features, and difficult species-identification (Hidayat et al., 2021; Lee et al., 2018; Turjaman et al., 2016). Based on our knowledge, a total of 42 fungal families and 67 fungal genera were isolated and identified in these eight agarwood-producing taxa, and 82.8 % of fungal species belonged to Ascomycota (Table 2). Among all the above endophytic genera, *Fusarium* is the most encountered species recorded in all studied taxa, except for *A. microcarpa* and *G. caudata*.

It is worth mentioning that there is a discrepancy in the endophytic fungal diversity pattern in *Aquilaria* trees based on their growing regions, such as *A. sinensis*, an agarwood-producing species endemic to China that is naturally distributed in three provinces, including Guangdong, Guangxi, and Hainan. It was proposed that the biodiversity of fungal endophytes in *A. sinensis* might be due to the various geographical locations containing different levels of the atmosphere, light, soil moisture, and nutrient contents. To date, endophytic fungal studies on *A. sinensis* are abundant and well-documented. It was revealed that the dominant fungal genus from the population in Hainan was *Penicillium* (Zhang et al., 2009a), while the endophytic fungal diversity for *A. sinensis* growing in Guangxi was dominated by *Fusarium* (Huang et al., 2017). The fungal diversity could also be regionally specific, in which two genera, *Chaetomium* and *Pichia*, were only identified in *A. sinensis* of Hainan, but not from those in Guangdong and Guangxi (Chen et al., 2019). Also, the fungal diversity of agarwood derived from *A. sinensis* showed regional specificity. *Lignosphaeria* is the dominant fungal genus in agarwood samples produced from Haikou and Wanning in Hainan province. *Perenniporia* and *Pyrigemmula* are the dominant fungal genera in agarwood products from Danzhou and Ledong in Hainan province. *Phaeoacremonium* is the dominant fungal genus in agarwood products collected from Huazhou and Dongguan in Guangdong province.

Furtherly, the variation in microbiome composition is represented by multiple plant host organs, and tissue types (Cregger et al., 2018; Jia et al., 2016). In general, most of the fungal endophytes reside in the root, stem, and leaf at the same time; yet, the leaf tissue contains more fungal species when compared to the root and stem parts. So far, a total of 16 fungal endophytes were discovered commonly present in all three vegetative parts of *A. sinensis*, including *Botryosphaeria*, *Cephalosporium*, *Cladophialophora*, *Epicoccum*, *Fusarium*, *Geotrichum*, *Glomerularia*, *Gonytrichum*, *Guignardia*, *Monilia*, *Mortierella*, *Mycelia sterilia*, *Ovulariopsis*, *Penicillium*, *Pleospora*, and *Rhinocladiella* (Gong and Guo, 2009; Tian et al., 2013). On the other hand, four were reported specific to the leaf tissue of *A. sinensis*, including *Alternaria*, *Cylindrocladium*, *Phoma*, and *Phomopsis* (Gong and Guo, 2009; Tian et al., 2013), suggesting that these fungal endophytes are only able to survive under certain habitat, which in this event, the requirement for survival was fulfilled in the leaf tissue, but not in the root and stem parts.

At the stem and branch part, fungal endophytes not only colonize the healthy part (white wood), but also can be found in the resinous part (agarwood). Additionally, the diversity of fungal endophytes in resinous wood is much higher than that in the healthy wood of *Aquilaria* (Chen et al., 2017a); Liu et al., 2022). Based on the studies on *A. malaccensis* and *A. sinensis*, it was deduced that the resinous wood of the trees not only contained some of the fungal endophytes which were recorded to be present in both the healthy and resinous wood of the tree, such as *Alternaria* sp., *Hypocrea* sp., *Lasidiplodia* sp., and *Trichoderma* sp., but also included some of the fungal endophytes which were enriched in the resinous wood, i.e. *Cladosporium* sp., *Curvularia* sp., *Fusarium* sp., *Phaeoacremonium* sp., and *Preussia* sp. (Liu et al., 2022; Mohamed et al., 2010; Tian et al., 2013). Endophytic fungi isolated from resinous parts were proven to be good candidates in developing fungal inoculum that could promote agarwood production; however, only a few were evaluated on their efficacies. To date, 18 fungal genera were reported on their capability to promote the formation of agarwood, including *Acremonium* sp., *Aspergillus* sp., *Botryodyplodias* sp., *Botryosphaeria* sp., *Chaetomium* sp., *Cladosporium* sp., *Diplodia* sp., *Fomitopsis* sp., *Fusarium* sp.,

Table 2 Host species distribution of fungal genera isolated from *Aquilaria* and *Gyrinops*, and their agarwood-inducing effects.

Fungal taxa	Host species	Distribution percentages[a]	Agarwood-inducing methods	Inducing time	Inducing effects	References
Ascomycota						
1. Apiosporaceae						
1. *Arthrinium*	*A. subintegra*	12.5 %	—	—	—	Monggoot et al., 2017
2. *Nigrospora*	*A. sinensis*	12.5 %	—	—	—	Li et al., 2014
2. Ascomycota incertae sedis						
3. *Gonytrichum*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
3. Aspergillaceae						
4. *Aspergillus* *	*G. walla*	25.0 %	—	—	—	Vidurangi et al., 2018
	A. crassna		Solid inoculation	1 year	Tissue discoloration and resin content improved	(Subasinghe et al., 2019)
			—	—	Inducing agarwood formation	Bose, 1938
5. *Penicillium* *	*A. sinensis*	25.0 %	Solid inoculation	30 days	Promoting sesquiterpene accumulation	Liu et al., 2022
			Infusion	10 months	Promoting the accumulation of active ingredients	Wang et al., 2016
			—	—	—	Gong and Guo, 2009
	A. malaccensis		—	—	—	(Chhipa et al., 2017)
4. Botryosphaeriaceae						
6. *Endomelanconiopsis*	*A. sinensis*	12.5 %	—	—	—	Chen et al., 2018
7. *Diplodia* *	*Aquilaria* sp.	—	—	—	Inducing agar formation	Bose, 1938
8. *Lasiodiplodia* *	*A. sinensis*	37.5 %	Inoculating the fermentation broth	2 months	Promoting the agarwood formation	Chen et al., 2017a
			—	—	—	Cui et al., 2011
			Inoculation of solid strains	6 months	Promotion of 34 sesquiterpenes and 4 aromatic compounds	Zhang et al., 2014
			Infusion	10 months	Promoting the accumulation of active ingredients	Wang et al., 2016
	A. malaccensis		—	—	—	Mohamed et al., 2010
	A. crassna		—	—	—	Chi et al., 2016
			—	—	—	Wang et al., 2019
9. *Botryosphaeria* *	*A. sinensis*	37.5 %	Formic acid and pinhole-infusion	1 ~ 2 years	Producing high yield and high quality artificial agarwood in a relatively short time	Tian et al., 2013
			Infusion	10 months	Promoting the accumulation of active ingredients	Wang et al., 2016
			Liquid injection	160 days	Promote the formation of the main components of agarwood and incenses	Feng, 2008
	A. crassna		—	—	Inducing agar formation	Bose, 1938
	G. walla		—	—	—	Vidurangi et al., 2018
5. Chaetomiaceae						
10. *Chaetomium* *	*A. malaccensis*	25.0 %	Artificial boring onto the plants	30 days	It is different between the oils obtained from naturally infected and healthy plants with regards to their quality.	Tamuli et al., 2005
	A. sinensis		—	—	—	Tian et al., 2013

(*continued on next page*)

Table 2 (*continued*)

Fungal taxa	Host species	Distribution percentages[a]	Agarwood-inducing methods	Inducing time	Inducing effects	References
6. Chaetothyriales incertae sedis						
11. *Sarcinomyces*	*G. walla*	12.5 %	—	—	—	Vidurangi et al., 2018
7. Cladosporiaceae						
12. *Cladosporium* *	*A. sinensis*	37.5 %	—	—	—	Cui et al., 2011
			—	—	—	Gong and Guo, 2009
			Solid inoculation	30 days	*C. cladosporioides* promotes the accumulation of agarwood sesquiterpenes and chromones, while *C. parahalotolerans* could not promote agarwood formation.	Liu et al., 2022
	A. malaccensis		—	—	—	Premalatha and Kalra, 2013
	A. subintegra		—	—	—	Monggoot et al., 2017
8. Coniothyriaceae						
13. *Coniothyrium*	*A. sinensis*	12.5 %	—	—	—	Cui et al., 2011
9. Diaporthaceae						
14. *Diaporthe*	*A. sinensis*	50.0 %	—	—	—	Chen et al, 2018
	A. microcarpa		—	—	—	(Vidurangi et al., 2018)
	A. subintegra		—	—	—	Monggoot et al.,2017
	G. verstegii		—	—	—	Mega et al., 2016
10. Didymellaceae						
15. *Epicoccum*	*A. malaccensis*	25.0 %	—	—	—	Bhattacharyya et al, 1952
	A. sinensis		—	—	—	Gong and Guo, 2009Cui et al., 2011
16. *Leptosphaerulina*	*A. sinensis*	12.5 %	—	—	—	Cui et al., 2011
11. Didymosphaeriaceae						
17. *Paraconiothyrium*	*A. sinensis*	12.5 %	—	—	—	Cui et al., 2011
18. *Montagnulaceae*	*A. sinensis*	12.5 %	—	—	—	Wang et al., 2016
12. Dipodascaceae						
19. *Geotrichum*	*A. crassna*	25.0 %	—	—	—	Chi et al., 2016
	A. sinensis		—	—	—	Gong and Guo, 2009
20. *Galactomyces*	*A. crassna*	12.5 %	—	—	—	Chi et al., 2016
13. Dissoconiaceae						
21. *Ramichloridium*	*A. sinensis*	12.5 %	—	—	—	Tian et al., 2013
14. Erysiphaceae						
22. *Ovulariopsis*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
15. Glomerellaceae						
23. *Colletotrichum*	*A. crassna*	50.0 %	—	—	—	Chi et al, 2016
	A. sinensis		—	—	—	Tian et al. 2013
	A. subintegra		—	—	—	Monggoot et al., 2017
	G. walla		—	—	—	Vidurangi et al., 2018

Table 2 (*continued*)

Fungal taxa	Host species	Distribution percentages[a]	Agarwood-inducing methods	Inducing time	Inducing effects	References
16. Herpotrichiellaceae						
24. *Rhinocladiella*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
25. *Cladophialophora*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
17. Hypocreaceae						
26. *Trichoderma* *	*A. sinensis*	50.0 %	—	—	—	Li et al., 2012
			Infusion	10 months	Promoting the accumulation of active ingredients	Wang et al., 2016
	A. malaccensis		—	—	—	Mohamed et al.,2010
	G. versteegii		—	—	Contributing to the formation of agarwood sapwood	Mega et al., 2020
	G. walla		—	—	—	Vidurangi et al., 2018
27. *Hypocrea* *	*A. malaccensis*	25.0 %	—	—	—	Mohamed et al., 2010
	A. sinensis		—	—	—	Cui et al., 2011
			Liquid injection	160 days	Promoting the transformation of agarwood and speeding up the process of making incense	Feng, 2008
18. Hypocreales incertae sedis						
28. *Acremonium* *	*A. microcarpa*	37.5 %	—	—	The wood color and terpenoid compounds were changed.	Rahayu and Putridan Juliarni, 2007
	G. verstegii		—	—	—	Mega et al., 2016
	G. caudata		Fungal-induction with pruning	3–6 months	Showing a considerable effect in wood internal tissue and fragrance.	Auri et al., 2021
29. *Cephalosporium*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
30. *Verticillium*	*A. sinensis*	12.5 %	—	—	—	Wang et al., 2016
19. Hypocreaceae						
31. *Diplocladium*	*G. walla*	12.5 %	—	—	—	Subasinghe et al., 2019
20. Lasiosphaeriaceae						
32. *Fimetariella*	*A. sinensis*	12.5 %	—	—	—	Tao et al., 2011aTao et al., 2011b
21. Mycosphaerellaceae						
33. *Mycosphaerella* (Synonym: *Davidiella*)	*A. sinensis*	25.0 %	—	—	—	Tian et al., 2013
	A. malaccensis		—	—	—	Premalatha and Kalra, 2013
34. *Botryodyplodis* * (Synonym: *Physalospora*)	*Aquilaria* sp.	—	—	—	Inducing agar formation	Bose, 1938
22. Nectriaceae						
35. *Cylindrocladium*	*A. sinensis*	12.5 %	—	—	—	Tian et al., 2013
36. *Fusarium* *	*A. crassna*	75.0 %	—	—	—	Chi et al., 2016
			—	0.5 ~ 1.5 years	Inducing the formation of agarwood	Nobuchi and Siripatanadilok, 1991
	A. sinensis		Formic acid and pinhole-infusion	1 ~ 2 years	Producing high yield and high quality artificial agarwood in a relatively short time	Tian et al., 2013
			—	—	—	Cui et al., 2011

(*continued on next page*)

Table 2 (*continued*)

Fungal taxa	Host species	Distribution percentages[a]	Agarwood-inducing methods	Inducing time	Inducing effects	References
			Infusion	10 months	Promoting the accumulation of active ingredients	Wang et al., 2016
			Inoculating the fermentation broth	2 months	Promoting the agarwood formation at the initial stage	Chen et al., 2017a
	A. malaccensis		—	—	—	Mohamed et al., 2010
	A. subintegra		—	—	—	Monggoot et al., 2017
	G. walla		—	—	—	Vidurangi et al., 2018
			Solid inoculation method	1 year	Promoting the tissue discoloration and resin content	Subasinghe et al., 2019
	G. versteegii		—	—	Contributing to the formation of agarwood sapwood	Mega et al., 2020
			Fungal inoculant formulation	16 months	Producing the agarwood with good quality.	Mega et al., 2016
37. *Nectria*	*A. sinensis*	12.5 %	—	—	—	Wang et al., 2016
23. Phyllostictaceae						
38. *Guignardia*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
24. Pichiaceae						
39. *Pichia*	*A. malaccensis*	25.0 %	—	—	—	Premalatha and Kalra, 2013
	A. sinensis		—	—	—	Cui et al., 2011
25. Pleosporaceae						
40. *Curvularia*	*A. crassna*	37.5 %	—	—	—	Chi et al., 2016
	A. malaccensis		—	—	—	Mohamed et al., 2010
	G. verstegii		—	—	—	Mega et al., 2016
41. *Alternaria*	*A. malaccensis*	25.0 %	—	—	—	Premalatha and Kalra, 2013
	A. sinensis		—	—	—	Tian et al., 2013
42. *Pleospora*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
43. *Cochliobolus*	*A. malaccensis*	12.5 %	—	—	—	Mohamed et al., 2010
44. *Phoma*	*A. sinensis*	12.5 %	—	—	—	Cui et al., 2011Tian et al., 2013
26. Saccharomycetaceae						
45. *Lodderomycetes*	*A. malaccensis*	12.5 %	—	—	—	Premalatha and Kalra, 2013
27. Sclerotiniaceae						
46. *Monilia*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
28. Sporocadaceae						
47. *Pestalotiopsis* *	*A. sinensis*	25.0 %	Infusion method	6 months	Promoting the agarwood production	Chen et al., 2014Tian et al., 2013
	A. subintegra		—	—	—	Monggoot et al., 2017
48. *Preussia*	*A. malaccensis*	12.5 %	—	—	—	Premalatha and Kalra, 2013

Table 2 (*continued*)

Fungal taxa	Host species	Distribution percentages[a]	Agarwood-inducing methods	Inducing time	Inducing effects	References
29. Togniniaceae						
49. *Phaeoacremonium* *	*A. malaccensis*	25.0 %	—	—	—	Premalatha and Kalra, 2013
	A. sinensis		—	—	—	Cui et al., 2011
			Solid inoculation	30 days	Promoting the agarwood sesquiterpene accumulation	Liu et al., 2022
30. Trichocomaceae						
50. *Sagenomella*	*A. sinensis*	12.5 %	—	—	—	Tian et al., 2013
31. Valsaceae						
51. *Phomopsis*	*A. sinensis*	12.5 %	—	—	—	Tian et al., 2013
32. Xylariaceae						
52. *Xylaria* *	*A. sinensis*	12.5 %	—	—	—	Cui et al., 2011
			—	—	—	Tian et al., 2013
			Solid inoculation	2 ~ 8 months	Promoting agilawood accumulation	Cui et al., 2013
53. *Nemania*	*A. sinensis*	12.5 %	—	—	—	Tibpromma et al, 2021
54. *Nodulisporium*	*A. sinensis*	12.5 %	—	—	—	Tian et al., 2013Wu et al., 2010
33. Massarinaceae						
55. *Massarina*	*A. malaccensis*	12.5 %	—	—	—	Premalatha and Kalra, 2013
<u>Mucoromycota</u>						
34. Cunninghamellaceae						
56. *Cunninghamella*	*A. malaccensis*	12.5 %	—	—	—	Mohamed et al., 2010
35. Lichtheimiaceae						
57. *Rhizomucor*	*A. sinensis*	12.5 %	—	—	—	Cui et al., 2011
36. Mortierellaceae						
58. *Mortierella*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
37. Mucoraceae						
59. *Mucor*	*G. walla*	12.5 %	—	—	—	Subasinghe et al., 2019
60. *Rhizopus* *	*G. versteegii*	12.5 %	—	—	Promoting the formation of agarwood sapwood	Mega et al., 2020
			Mixture of fungal liquid with *Fusarium solani*	—	Promoting the production of agarwood with best quality	Mega et al., 2016
<u>Basidiomycota</u>						
38. Exobasidiaceae						
61. *Glomerularia*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
39. Fomitopsidaceae						
62. *Fomitopsis* *	*A. sinensis*	12.5 %	Infusion method	6 months	Promoting the agarwood production	Chen et al., 2017b
40. Meripilaceae						
63. *Rigidoporus* *	*A. sinensis*	12.5 %	Trunk surface agarwood-inducing technique	2 months	Promoting the agarwood formation	Chen et al., 2018

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Table 2 (*continued*)

Fungal taxa	Host species	Distribution percentages[a]	Agarwood-inducing methods	Inducing time	Inducing effects	References
41. Psathyrellaceae						
64. *Coprinopsis*	*A. sinensis*	12.5 %	—	—	—	Chen et al., 2018
42. Russulaceae						
65. *Russula*	*A. subintegra*	12.5 %	—	—	—	Monggoot et al., 2017
Unclassified						
66. *Mycelia sterilia*	*A. sinensis*	12.5 %	—	—	—	Gong and Guo, 2009
67. *Pleosporales*	*A. sinensis*	12.5 %	—	—	—	Chen et al., 2018

a. Distribution percentage = host species number of an isolated fungal genus × 100 % / number of all the reported host species (nine species which include *A. crassna*, *A. malaccensis*, *A. microcarpa*, *A. sinensis*, *A. subintegra*, *G. walla*, *G. caudata*, and *G. verstegii*).

* The endophytic fungi which could improve the quality and yield of agarwood.

Hypocrea sp., *Lasiodiplodia* sp., *Penicillium* sp., *Pestalotiopsis* sp., *Phaeoacremonium* sp., *Rhizopus* sp., *Rigidoporus* sp., *Trichoderma* sp., and *Xylaria* sp. (Table 2).

Given that the diversity of endophytic fungi in *Aquilaria* trees could be varied in different regions, little was reported for other agarwood-producing species, especially those from *Gyrinops*. While the diversity of endophytic fungi in different *Aquilaria* host parts might be related to the environmental filtering or biotic interaction at the species level which was similar to *Populus* trees (Cregger et al., 2018). The fungal endophytes that can be identified in the while wood and resinous wood of *Aquilaria* and *Gyrinops* could be varied largely. Therefore, it is suggested that studies on endophytic fungi in other agarwood-producing species need to be hastened to uncover the uncertainties.

4. Effects on the host trees of *Aquilaria* and *Gyrinops* by endophytes

4.1. Use of fungal endophytes in the promotion of agarwood

In nature, endophytes could maintain endosymbiotic relationship within plants without any harm. However, after the trees of *Aquilaria* and *Gyrinops* were wounded, the micro-ecosystem balance was broken, and some of the fungal endophytes might grow fast and could trigger the self-defense reaction of the tree and thus, stimulate the formation of secondary metabolites that protect the host trees against invasions and diseases (Cui et al., 2013; Faizal et al., 2020; Liu et al., 2022; Xu et al., 2013). Similarly, the inoculating the isolated endophytes with agarwood promoting ability to the holed trees could quickly induce the phosphorylation of the plant immune reaction and promote agarwood accumulation (Liu et al., 2022; Xu et al., 2013). Therefore, the agarwood produced in the tree is recognized as the product of the tree's defense response (Xu et al., 2013). Since the work to investigate the relationship between fungi and agarwood-producing trees in the process of agarwood formation started off in the early nineteenth century, for the past two decades, a considerable number of studies provided evidence on the crucial roles of fungi in enhancing agarwood formation (Huang et al., 2013; Mega et al., 2016; Zhang et al., 2014). It is believed that endophytes secrete signals that will initiate the defense mechanism of the tree; thus, endophytes promote the formation of agarwood (Chen et al., 2017; Sen et al., 2017). Chemometric analysis revealed that aroma (e.g. dodecane, 4-methyl-, tetracosane) in *Fusarium* sp. played a direct role in the activation of *A. malaccensis* tree's defense and secondary metabolism (Sen et al., 2017). Fungal infection often leads immediately to the increased formation of free fatty acids that trigger oxidative burst and fatty acid oxidation cascades leading to the production of oxylipins such as jasmonates (Sen et al., 2017). And the endophytic strains of *Lasiodiplodia theobromae* were found to produce jasmonic acid (JA) (Chen et al., 2017). JA is known to be one of the crucial signal transducers that is responsible to induce sesquiterpene and chromone derivative formation in *A. sinensis* and *A. malaccensis* (Faizal et al., 2021; Xu et al., 2016). Furthermore, agarwood sesquiterpene accumulation can also be achieved by having *Phaeoacremonium rubrigenum* to induce phosphorylation of the transcription factors (TFs)-mevalonate (MVA) network in *A. sinensis* (Liu et al., 2022). Despite studies on the molecular interaction between agarwood-producing trees and fungal endophytes have been constantly reported, the findings are still limited and in-depth research ought to be fostered.

To date, six fungal taxa, i.e. *Fusarium* sp., *Trichoderma* sp., *Acremonium* sp., *Curvularia* sp., *Cunninghamella* sp., and *Phaeoacremonium* sp., were commonly known to be potential agents in promoting agarwood formation in *Aquilaria* and *Gyrinops* trees (Blanchette 2003; Hidayat et al., 2021; Liu et al., 2022; Mohamed et al., 2010). For the endophytes, *Fusarium* was most reported when compared to other fungal taxa; while for the host plant, studies on *A. sinensis* were most abundant (Table 2). In *A. sinensis*, it is believed that agarwood formed with the aid of *Cladorrhinum bulbillosum*, *Fusarium solani*, *Gongronella butleri*, *Humicola grisea*, *Lasiodiplodia theobromae*, *Phaeoacremonium rubrigenum*, *Rigidoporus vinctus*, *Saitozyma podzolica*, and *Tetracladium marchalianum* was able to produce high-quality raw material for essential oil production (Chen et al., 2017; Chen et al., 2018; Liu et al., 2022; Ma et al., 2021; Zhang et al., 2014). So far, a total of 12 fungal taxa were identified to induce agarwood formation in *A. sinensis*, including *Botryosphaeria*, *Cladosporium*, *Fusarium*, *Fomitopsis*, *Hypocrea*, *Lasiodiplodia*, *Phaeoacremonium*, *Pestalotiopsis*, *Penicillium*, *Rigidoporus*, *Trichoderma*, and *Xylaria* (Table 2). Three fungal taxa, *Aspergillus* sp., Botryosphaeria sp., and *Fusarium* sp. were also reported useful in promoting agarwood formation in *A. crassna* (Chi et al., 2016), while a mixture of fungi *Phialophora* sp. and *Fusarium* sp. applied to *A. crassna* could result in higher sesquiterpene content compared to the chemical and mechanical treatments (Thanh et al., 2015). Similar to *Aquilaria*, endophytes in *Gyrinops* also play an active role in the agarwood development of trees. In *Gyrinops walla*, the endemic species of Sri Lanka, *Aspergillus niger* and *Fusarium solani* have been described to be contributing to agarwood formation; *Aspergillus niger* is more effective than *Fusarium solani* in the tree host tissue discoloration and resin content (Subasinghe et al., 2019). On the other hand, three fungal taxa, including *Fusarium* sp., *Rhizopus* sp., and *Trichoderma* sp., were proven effective in the promotion of agarwood in *Gyrinops versteegii*, a plantation species that is mass cultivated in the western region of Indonesia (Mega et al., 2020; (Faizal et al., 2020)).

4.2. Endophytes improve the ecological adaptability of Aquilaria and Gyrinops

Another function of fungal endophytes of *Aquilaria* and *Gyrinops* is improving the ecological adaptability of hosts. Different types of fungi strains could induce the different compounds of *Aquilaria* and *Gyrinops* (Monggoot et al., 2017; Mega et al., 2020), which could explain the diversity of agarwood components to increase the resistance to environmental stresses. Similarly, either *Aquilaria* or *Gyrinops* grows in certain places with different geographic and climate conditions with certain kinds of fungi, which could promote the ecological adaptability of the host. Consistent with the roles of fungi in the plant defense system, they may be a contributory role in increasing antimicrobial activity, because the resinous site of agarwood tree has a less fungal abundance. When *A. malaccensis* was infected by *Lasiodiplodia theobromae*, *Cunninghamella bainieri*, and *Fusarium solani*, the abundance of fungi decreased after wounding and the number of target DNA molecules also declined, especially at 6–12 months of post-injury (Mohamed et al., 2014). The lower level of fungal species may be due to the high level of terpenes which are the major components of agarwood and can prevent or control pathogen attacks (Tamuli et al., 2005; Naef, 2011; Zulak and Bohlmann, 2010). Similarly, the agarwood derived from the infected *A. sinensis* and decayed *Gyrinops* spp. could show antifungal activity against *Candida albicans*, *Fusarium oxysporum*, *Fusarium solani*, and *Lasiodiplodia theobromae* (Hidayat et al., 2021; Zhang et al. 2014). So it is believed that the fungi can trigger the plant defense system to protect plants from invasions. And the metabolites produced by fungi also can provide protection for the host, which gives plants the ability to be resistant to abiotic and biotic stresses (Chowdhary et al., 2012; Jong 2012; Kharwar et al., 2011; Kumar and Kaushik, 2013; Suryannaryanan et al., 2009). And agarwood endophytes can also produce chemical compositions such as 2-phenylethyl-1 H-indol-3-yl-acetate, (2*R*)-(3-indolyl)-propionic acid, and 9,11-dehyroergosterol peroxide, which displayed phytotoxic activity, cytotoxic activity, and anti-fungi and anti-bacterial activities, resulting in the enhancement of plant ecological adaptability. However, there are also a plenty of compounds, such as benzylacetone, benzaldehyde, palustrol, anisylacetone and chromone derivatives, the ecological functions of which have not been explored. It is possible that the fungal endophyte is one of the factors to resist the invasion of exogenous pathogens and to keep the plant growing well. Thus, we summarized the effects of fungal endophytes on the host trees of *Aquilaria* and *Gyrinops* on two sides: inducing the plant defense system and improving their ecological adaptability (Fig. 1).

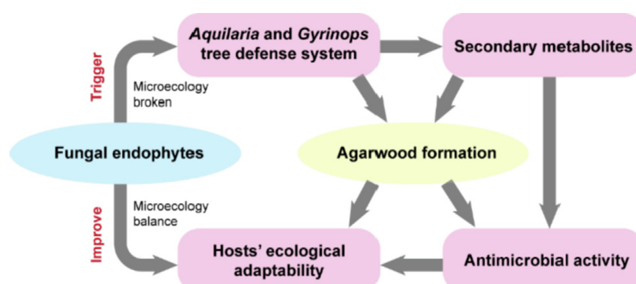

Fig. 1 Effects of endophytes on their agarwood host trees, *Aquilaria* and *Gyrinops*.

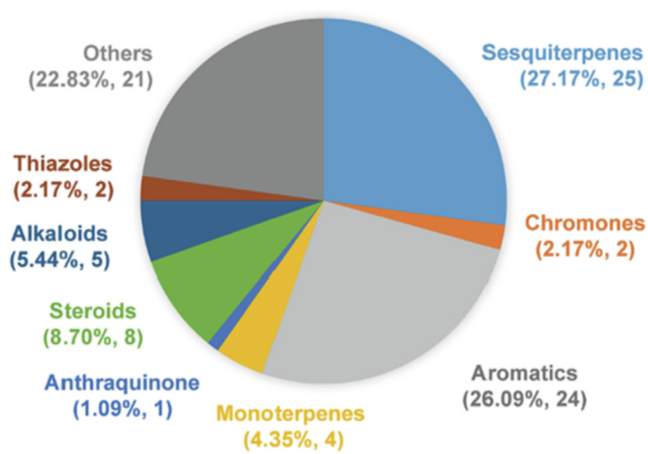

Fig. 2 The categories of 92 compounds produced by the endophytes of *Aquilaria* and *Gyrinops*.

Table 3 Metabolites produced by endophytes of *Aquilaria* and *Gyrinops* and their pharmacological values.

No.	Compounds	Molecular Formula	Pharmacological Values	Fungal Endophytes	Host Plant	References
Monoterpenes						
1	γ-Terpinene	$C_{10}H_{16}$	Trypanocidal effect Acaricidal activity	*Acremonium* sp.	*A. sinensis*	Tibpromma et al., 2021Zhang et al., 2009b
2	Terpinen-4-ol	$C_{10}H_{18}O$	—	*Arthrinium* sp. *Collectotrichum* sp.	*A. subintegra*	Monggoot et al., 2017
3	1,8-Cineole	$C_{10}H_{18}O$	Antibacterial activity	*Acremonium* sp.	*A. sinensis*	Wang et al., 2007Zhang et al., 2009b
4	Bicyclo[3.1.1]hept-3-ene-2-acetaldehyde, 4,6,6-trimethyl,	$C_{12}H_{18}O$	—	*Nemania aquilariae*	*A. sinensis*	Tibpromma et al., 2021
Sesquiterpenes						
5	β-Agarofuran	$C_{15}H_{24}O$	—	*Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Monggoot et al., 2017
6	Alloaromadendrene	$C_{15}H_{24}$	Anti-oxidant activity Cytotoxic activity Anti-feedant activity Anti-proliferative activity	*Nemania aquilariae*	*A. sinensis*	Baldissera et al.,2016Jesionek et al, 2018Sawant et al., 2007Yu et al.,2014
7	1,2,3,4,4α,5,6,7-Octahydro-4α,8-dimethyl-2-(1-methylethenyl)-naphthalene	$C_{15}H_{24}$	—	*Nemania aquilariae*	*A. sinensis*	Baldissera et al., 2016
8	*Z*-Eudesma-6,11-diene	$C_{15}H_{24}$	—	*Arthrinium* sp. *Diaporthe* sp.	*A. subintegra*	Capello et al., 2015Monggoot et al., 2017
9	α-Selinene	$C_{15}H_{24}$	Anti-cancer activity Repellent activity	*Nemania aquilariae*	*A. sinensis*	Alakanse et al., 2019Baldissera et al., 2016Mauti et al.,2019
10	α-Agarofuran	$C_{15}H_{24}O$	Antianxiety activity	*Arthrinium* sp. *Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Monggoot et al., 2017Peeraphong et al., 2021Zhang et al., 2004
11	Oxo-agarospirol	$C_{15}H_{24}O_2$	Antioxidant activity	*Arthrinium* sp. *Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Capello et al., 2015Monggoot et al., 2017
12	Ar-Curcumene	$C_{15}H_{22}$	Mosquito larvicides Anti-inflammatory activity Anti-ulcer activity	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007Podlogar et al., 2012Yamahara et al.,1992Zhang et al., 2009b
13	Zingiberene	$C_{15}H_{24}$	Anti-inflammatory activity Anti-apoptotic effect Anti-oxidant activity Anti-cancer activity Cytotoxicity, Genotoxicity	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007Li et al., 2021Togar et al., 2015Türkez et al., 2014Zhang et al., 2009b
14	10-*epi*-γ-Eudesmol	$C_{15}H_{26}O$	Prevention of mosquito-related disease	*Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Capello et al., 2015(Kracht et al., 2019)
15	*cis*-Dihydroagarofuran	$C_{15}H_{26}O$	Antimicrobial activity	*Diaporthe* sp.	*A. subintegra*	Capello et al., 2015Sadgrove et al., 2015
16	β-Dihydroagarofuran	$C_{15}H_{26}O$	—	*Arthrinium* sp. *Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Capello et al., 2015Monggoot et al., 2017
17	Valencen	$C_{15}H_{24}$	—	*Nemania aquilariae*	*A. sinensis*	Baldissera et al., 2016

Table 3 (*continued*)

No.	Compounds	Molecular Formula	Pharmacological Values	Fungal Endophytes	Host Plant	References
18	*Z*-Caryophyllene	$C_{15}H_{24}$	—	*Arthrinium* sp. *Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Capello et al., 2015Monggoot et al., 2017
19	*β*-Elemene	$C_{15}H_{24}$	High cytotoxic activity	*Diaporthe* sp.	*A. subintegra*	Capello et al., 2015Monggoot et al., 2017
20	*δ*-Elemene	$C_{15}H_{24}$	—	*Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Capello et al., 2015Monggoot et al., 2017
21	Agarospirol	$C_{15}H_{26}O$	Anti-nociceptive activitiy Anti-oxidant activity	*Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Capello et al., 2015Monggoot et al., 2017Okugawa et al., 1996
22	rel-(1*S*,4*S*,5*R*,7*R*,10*R*)-10-Desmethyl-1-methyl-11-eudesmene	$C_{15}H_{26}O$	Cytotoxic activity	*Nodulisporium* sp.	*A. sinensis*	Li et al., 2011
23	Capitulatin B	$C_{15}H_{26}O_2$	—	*Nigrospora oryzae*	*A. sinensis*	Zhang et al., 2004
24	6*α*-Hydroxycyclonerolidol	$C_{15}H_{26}O_2$	Cytotoxic activity	*Nodulisporium* sp.	*A. sinensis*	Li et al., 2011
25	Frabenol	$C_{15}H_{26}O_2$	—	*Fimetariella rabenhorstii*	*A. sinensis*	Tao et al., 2011a
26	6-Methyl-2-(5-methyl-5-vinyltetrahydrofuran-2-yl) hept-5-en-2-ol	$C_{15}H_{26}O_2$	—	*Nodulisporium* sp.	*A. sinensis*	Li et al., 2011
27	11-Hydroxycapitulation B	$C_{15}H_{26}O_3$	—	*Nigrospora oryzae*	*A. sinensis*	Zhang et al., 2004
28	*δ*-Eudesmol	$C_{15}H_{28}O$	Prevention of mosquito-related disease	*Arthrinium* sp. *Diaporthe* sp.	*A. subintegra*	Capello et al., 2015(Kracht et al., 2019)
29	(3*R*,6*E*,10*S*)-2,6,10-Trimethyl-3-hydroxydodeca-6,11-diene-	$C_{15}H_{28}O_3$	—	*Colletotrichum gloeosporioides*	*A. sinensis*	Liu et al., 2018
Chromones						
30	2,3-Dihydro-5-hydroxy-2-methylchromen-4-one	$C_{10}H_{10}O_3$	Cytotoxic activity	*Nodulisporium* sp.	*A. sinensis*	Wu et al., 2010
31	Mellein	$C_{10}H_{10}O_3$	Antibacterial activity	*Aspergillus* sp.	*A. sinensis*	Peng et al., 2011
Anthraquinones						
32	1,7-Dihydroxy-3-methoxyanthraquinone	$C_{15}H_{10}O_5$	Anti-bacterial activity	Unknown fungal strain AL-2	*A. malaccensis*	Blakeney et al., 2019Shoeb et al., 2010
Steroids						
33	Ergosterol	$C_{28}H_{44}O$	Anti-inflammatory activity	*Nodulisporium* sp.	*A. sinensis*	Kobori et al., 2007Li et al., 2011
34	Ergosterol peroxide	$C_{28}H_{44}O_3$	Induced apoptosis of cells Anti-inflammatory activity Cytotoxic activity Anti-oxidant activities Anti-complementary activity Trypanocidal activity Antibacterial activity Anti-proliferative activity	*Nodulisporium* sp.	*A. sinensis*	Li et al., 2011Takei et al.,2005Kobori et al., 2007Nam et al., 2001Kim et al., 1999Kim et al., 1997Ramos-Ligonio et al., 2012Duarte et al., 2007Nowak et al., 2016
35	5*α*,8*α*-Epidioxy-(22*E*,24*R*)-ergosta-6,22-dien-3*β*-ol	$C_{28}H_{44}O_3$	Anti-tumor activity	*Fimetariella rabenhorstii*	*A. sinensis*	Li, 2016Plotnikov et al., 2021Tanapichatsakul et al., 2020Nam et al., 2001Kim et al., 1999
36	3*β*,5*α*,9*α*-Trihydroxy-(22*E*,24*R*)-ergosta-7,22-dien-6-one	$C_{28}H_{44}O_3$	Anti-tumor activity	*Fimetariella rabenhorstii*	*A. sinensis*	Li, 2016Plotnikov et al., 2021Takei et al., 2005

(*continued on next page*)

Table 3 (*continued*)

No.	Compounds	Molecular Formula	Pharmacological Values	Fungal Endophytes	Host Plant	References
37	Cerevisterol	$C_{28}H_{46}O_3$	Anti-microbial activity Resistance modifying activity	*Nodulisporium* sp.	*A. sinensis*	Li et al., 2011Appiah et al., 2020
38	(3*β*,5*α*,6*β*,22*E*)-Ergosta-7,22-diene-3,5,6-triol	$C_{28}H_{46}O_3$	—	*Phaeoacremonium rubrigenum*	*A. sinensis*	Ribeiro et al., 2007
39	3*β*,6*β*,7*α*-Trihydroxy-(24*R*)-ergosta-8(14),22-diene	$C_{28}H_{46}O_3$	—	*Fimetariella rabenhorstii*	*A. sinensis*	Li, 2016Plotnikov et al., 2021
40	3*β*,5*α*,6*β*-Trihydroxy-(22*E*,24*R*)-ergosta-7,22-diene	$C_{28}H_{46}O_3$	Anti-tumor activity	*Fimetariella rabenhorstii*	*A. sinensis*	Li, 2016Plotnikov et al., 2021Kobori et al., 2007Kim et al.,1997
Aromatics						
41	Methylphenol	C_7H_8O	Antibacterial activity	*Fimetariella rabenhorstii* *Phaeoacremonium rubrigenum*	*A. sinensis*	Li, 2016Wei et al., 2011
42	*p*-Hydroxybenzaldehyde	$C_7H_6O_2$	Anti-oxidative activity Blood-brain barrier Toxicity	*Phaeoacremonium rubrigenum*	*A. sinensis*	Ribeiro et al., 2007Kinjo et al., 2020Borneman et al., 1986Wei et al., 2011
43	Phenylethyl alcohol	$C_8H_{10}O$	Antibacterial Sedative effects Antifungal activity	*Acremonium* sp.	*A. sinensis*	Duarte et al.,2007Lilley and Brewer, 1953Oshima and Ito, 2021Boukaew and Prasertsan, 2018Zhang et al., 2009b
44	4-Hydroxyphenyl ethyl alcohol (Tyrosol; 4-Hydroxy-benzeneethanol)	$C_8H_{10}O_2$	Nematicide Antioxidant activity Anti-inflammatory activity	*Fimetariella rabenhorstii* *Acremonium* sp. *Nodulisporium* sp.	*A. sinensis*	Tao et al., 2011bDuarte et al.,2007Li et al.,2018Zhang et al., 2009bLi et al., 2011Wei and Liu, 2007Tao et al., 2011b
45	6-Methoxy-7-*O*-(*p*-methoxyphenyl)-coumarin	$C_{17}H_{14}O_5$	—	Unkonw fungal strain AL-2	*A. malaccensis*	Blakeney et al., 2019
46	3,4-Dihydroxybenzoic acid	$C_7H_6O_4$	Antibacterial activity	*Phaeoacremonium rubrigenum*	*A. sinensis*	Ribeiro et al., 2007
47	Phthalic acid diisobutyl ester	$C_{16}H_{22}O_4$	Phytotoxicity Testicular atrophy	*Colletotrichum gloeosporioides*	*A. sinensis*	Appiah et al., 2020Huang et al.,2021Oishi et al.,1980
48	Decyl butyl phthalate	$C_{22}H_{34}O_4$	—	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007
49	1-(2,6-Dihydroxyphenyl) ethanone	$C_8H_8O_3$	Cytotoxic activity	*Nodulisporium* sp.	*A. sinensis*	Wu et al., 2010
50	8-Methoxynaphthalen-1-ol	$C_{11}H_{10}O_2$	Antifungal activity	*Nodulisporium* sp.	*A. sinensis*	Li et al, 2011;Takei et al., 2005
51	*p*-Hydroxyphenethyl alcohol	$C_8H_{10}O_2$	Antibacterial activity	*Phaeoacremonium rubrigenum*	*A. sinensis*	Wei et al., 2011
52	Ethyl benzoate	$C_9H_{10}O_2$	—	*Arthrinium* sp. *Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Monggoot et al., 2017
53	Phenyl butanone	$C_{10}H_{12}O$	—	*Collectotrichum* sp. *Diaporthe* sp.	*A. subintegra*	Monggoot et al., 2017
54	1-(2,6-Dihydroxyphenyl) butan-1-one	$C_{10}H_{12}O_3$	Cytotoxic activity	*Nodulisporium* sp.	*A. sinensis*	Wu et al., 2010
55	1-(2,6-Dihydroxyphenyl)-3-hydroxybutan-1-one	$C_{10}H_{12}O_4$	Cytotoxic activity	*Nodulisporium* sp.	*A. sinensis*	Wu et al., 2010
56	Benzeneacetic acid	C8H8O2	—	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007
57	(2*R**,4*R**)-3,4-Dihydro-4-	$C_{11}H_{14}O_3$	Cytotoxic activity	*Nodulisporium* sp.	*A. sinensis*	Wu et al., 2010

Table 3 (*continued*)

No.	Compounds	Molecular Formula	Pharmacological Values	Fungal Endophytes	Host Plant	References
	methoxy-2-methyl-2*H*-1-benzopyran-5-ol					
58	Phenethyl 2-hydroxypropanoate	$C_{11}H_{14}O_3$	—	*Colletotrichum gloeosporioides*	*A. sinensis*	Liu et al., 2018
59	Benzyl benzoate	$C_{14}H_{12}O_2$	Treatment of scabies	*Arthrinium* sp. *Diaporthe* sp.	*A. subintegra*	Monggoot et al., 2017;Li et al., 2011
60	1,8-Dimethoxynaphthalene	$C_{12}H_{12}O_2$	—	*Nodulisporium* sp.	*A. sinensis*	Li et al., 2011
61	(7*R**,8*S**)-3,6,7,8-Tetrahydro-4,7,8-trihydroxynaphtho [2,3-	$C_{12}H_{12}O_5$	Cytotoxic activity	*Nodulisporium* sp.	*A. sinensis*	Wu et al, 2010
62	Propyl *p*-methoxy phenyl ether	$C_{10}H_{14}O_2$	—	Unkonw fungal strain AL-2	*A. malaccensis*	Shoeb et al., 2010
63	*p*-Hydroxyphenylacetic acid	$C_8H_8O_3$	—	*Phaeoacremonium rubrigenum*	*A. sinensis*	Ribeiro et al., 2007
64	4-Pentylbenzoic acid	$C_{12}H_{16}O_2$	—	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007
Alkaloids						
65	Nicotinic acid	$C_6H_5NO_2$	Prevention of atherosclerosis and reduce the risk of cardiovascular events	*Fimetariella rabenhorstii*	*A. sinensis*	Okugawa et al., 1996(Gille et al., 2008)
66	Thymidine	$C_{10}H_{14}N_2O_5$	Anti-cancer activity Anti-metabolites activity	*Phaeoacremonium rubrigenum*	*A. sinensis*	Ribeiro et al., 2007Stokes and Lacey, 1978Martin et al., 1980O'Dwyer et al, 1987
67	*N*-Phenylacetamide	C_8H_9NO	Cytotoxic activity	*Fimetariella rabenhorstii*	*A. sinensis*	Okugawa et al.,1996
68	*N*-(6-Hydroxyhexyl)-acetamide	$C_8H_{17}O_2N$	Antibacterial activity	*Phaeoacremonium rubrigenum*	*A. sinensis*	Ribeiro et al., 2007
69	2-Anilino-1,4-naphthoquinone	$C_{16}H_{11}NO_2$	Anti-fungal activity	*Fimetariella rabenhorstii*	*A. sinensis*	Okugawa et al.,1996(Leyva et al., 2017)
Thiazoles						
70	Colletotricole A	$C_9H_{13}NO_3S$	—	*Colletotrichum gloeosporioides*	*A. sinensis*	Appiah et al., 2020
71	2-(4-Methylthiazol-5-yl)ethyl 2-hydroxypropanoate	$C_9H_{13}O_3NS$	—	*Colletotrichum gloeosporioides*	*A. sinensis*	Appiah et al., 2020
Others						
72	Colletotricone A	$C_{14}H_{20}O_4$	Anti-tumour activity Cytotoxic activity	*Colletotrichum gloeosporioides*	*A. sinensis*	Appiah et al., 2020Kim et al., 2019Liu et al., 2018
73	Colletotricone B	$C_{14}H_{20}O_4$	—	*Colletotrichum gloeosporioides*	*A. sinensis*	Liu et al., 2018
74	Nigrosporanene A	$C_{14}H_{20}O_4$	Cytotoxicity Radical scavenging activity	*Colletotrichum gloeosporioides*	*A. sinensis*	Appiah et al., 2020Liu et al., 2018Ma and Qi, 2019
75	Nigrosporanene B	$C_{14}H_{22}O_4$	Radical scavenging activity	*Colletotrichum gloeosporioides*	*A. sinensis*	Appiah et al., 2020Liu et al., 2018Ma and Qi, 2019
76	D-Galacitol	$C_6H_{14}O_6$	—	*Fimetariella rabenhorstii*	*A. sinensis*	Tao et al., 2011b
77	2,3-Dihydroxybutane	$C_4H_8O_3$	—	*Acremonium* sp.	*A. sinensis*	Zhang et al., 2009b
78	5-Hydroxymethylfurfural	$C_6H_6O_3$	Antibacterial activity	*Phaeoacremonium rubrigenum*	*A. sinensis*	Wei et al., 2011

(*continued on next page*)

Table 3 (*continued*)

No.	Compounds	Molecular Formula	Pharmacological Values	Fungal Endophytes	Host Plant	References
79	Cyclohexanone	$C_6H_{10}O$	—	*Acremonium* sp.	*A. sinensis*	Zhang et al., 2009b
80	4-Hydroxy-4-methyl-2-phentanone	$C_6H_{12}O_2$	—	*Acremonium* sp.	*A. sinensis*	Zhang et al., 2009b
81	3,5-Dimethyl cyclopentenolone	$C_7H_{11}O_2$	—	*Acremonium* sp.	*A. sinensis*	Zhang et al., 2009b
82	5-Methyl-2-vinyltetrahydrofuran-3-ol	$C_7H_{12}O_2$	—	*Nodulisporium* sp.	*A. sinensis*	Li et al., 2011
83	Octanoic acid	$C_8H_{16}O_2$	Toxicity Reducing the magnitude of tremor Anti-tumor activity	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007Viegas et al., 1995Lowell et al., 2019Altinoz et al., 2020
84	(*Z*)-9,17-Octadecadienal	$C_{18}H_{32}O$	—	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007
85	Sorbic acid	$C_6H_8O_2$	Anti-fungal activity Anti-microbial activity	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007Razavi-Rohani and Griffiths, 1999Eklund et al., 1983
86	Linoleic acid	$C_{18}H_{32}O_2$	Pro-inflammatory activity Anti-cancer activity Cholesterol and blood pressure lowering effects Epidermal permeability barrier Anaerobic degradability Inhibitory effects	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007Young et al., 1998Burns et al., 2018Lalman et al., 2000Elias et al., 1980
87	Acetic acid	$C_2H_4O_2$	—	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007
88	Oleic acid	$C_{18}H_{34}O_2$	Anti-tumor Anti-inflammatory Anti-bactericidal Vasculoprotective effects Pro-inflammatory	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007(Carrillo Pérez et al., 2012) Sales-Campos et al., 2013Speert et al., 1979Massaro et al., 2002Young et al., 1998
89	Isovaleric acid	$C_5H_{10}O_2$	Reduces Na^+, K^+-ATPase activity Causes colonic smooth muscle relaxation	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007Ribeiro et al., 2007Blakeney et al., 2019
90	Methyl jasmonate	$C_{12}H_{18}O_3$	Against pathogens Salt stress Drought stress Low temperature Heavy metal stress and toxicities of other elements	*Lasiodiplodia theobromae*	*A. sinensis*	Han et al., 2014Yu et al., 2018
91	Octadecanoic acid	$C_{18}H_{36}O_2$	—	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007
92	Butanoic acid	$C_{10}H_{22}O_2Si$	—	*Acremonium* sp.	*A. sinensis*	Duarte et al., 2007

Bioactivity: the effects of the fungal endophytes; **Pharmacological values:** the functions of the compounds produced by the fungi.

5. Pharmacological effects of metabolites produced by fungal endophytes derived from *Aquilaria* and *Gyrinops*

Endophytic fungi can be one of the best-known sources of natural products, while the endophytic fungi present in *Aquilaria* and *Gyrinops* tree, in the process of agarwood formation, were also recognized as the new sources of secondary metabolites, which hold pharmaceutical and ecological significance. A total of 92 compounds were recorded from the endophytes of *Aquilaria* and *Gyrinops* trees, including terpenoids (40.22 %: containing monoterpenes, sesquiterpenes, and steroids), aromatics (26.09 %), alkaloids (5.44 %), chromones (2.17 %), and others (Fig. 2, Table 3). Interestingly, some endophytes of *Aquilaria* and *Gyrinops* could produce sesquiterpenes which were the important compounds of agarwood (Fig. 3, Table 3). *Acremonium* sp., *Arthrinium* sp., *Collectotrichum* sp., *Diaporthe* sp., *Fimetariella rabenhorstii*, *Nemania* sp., *Nigrospora oryzae*, and *Nodulisporium* sp. are responsible for the production of sesquiterpenes (Li et al., 2014; Monggoot et al., 2017; Tao et al., 2011a; Tibpromma et al., 2021; Wu et al., 2010; Zhang et al., 2009b). Thus, those fungal stains were considered to

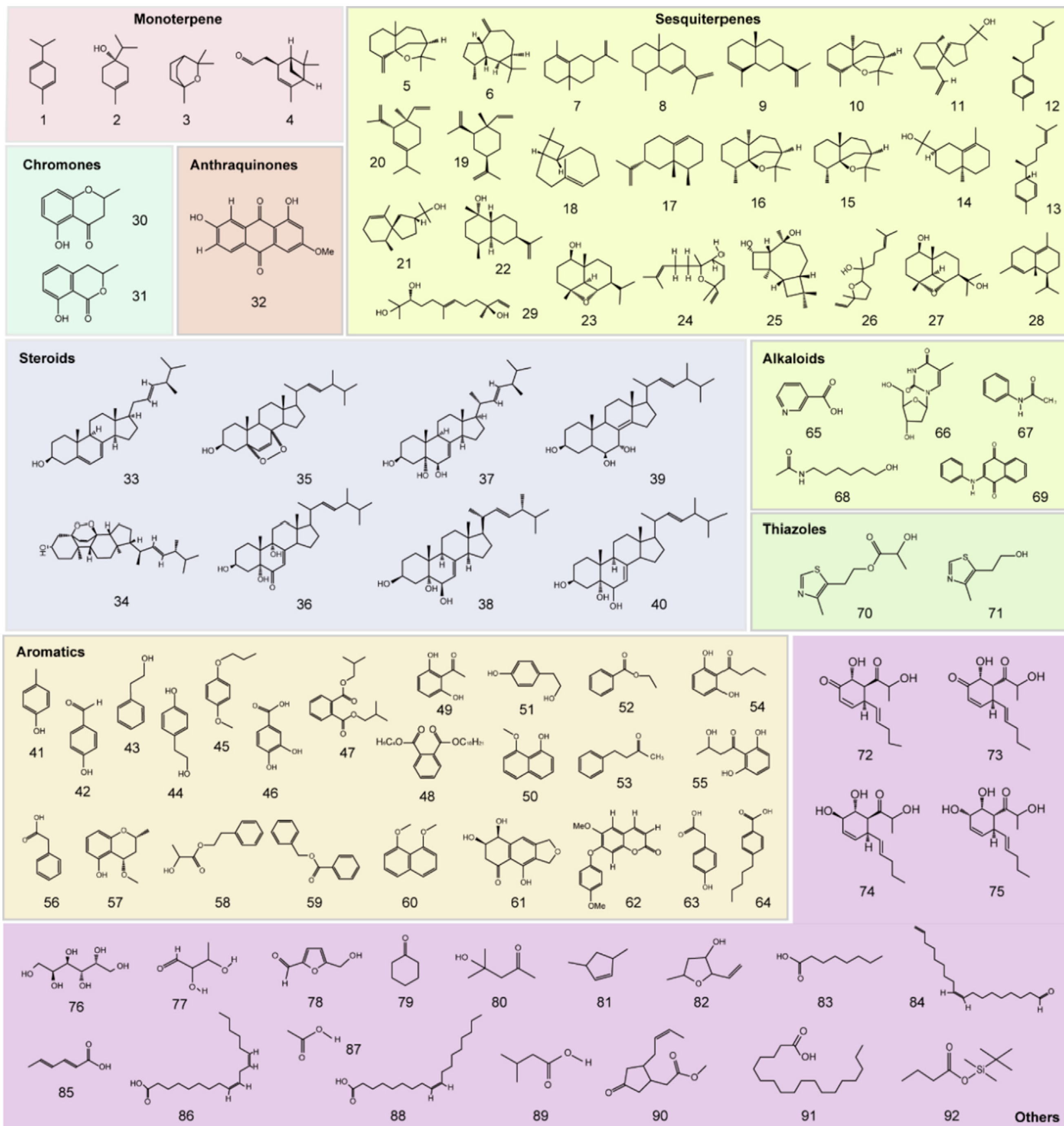

Fig. 3 The structures of 92 compounds produced by the endophytes of *Aquilaria* and *Gyrinops*.

be the potential materials for fermenting agarwood compounds.

Endophytic fungi in agarwood-producing trees can also be a rich source of medicinal agents with various pharmacological properties (Chhipa et al., 2017). The majority of endophytes derived from *Aquilaria* showed both antimicrobial and antitumor activities simultaneously, including *Cladosporium tenuissimum*, *Coniothyrium nitidae*, *Epicoccum nigrum*, *Fusarium equiseti*, *Fusarium oxysporum*, *Fusarium solani*, *Hypocrea lixii*, *Lasiodiplodia theobromae*, *Leptosphaerulina chartarum*, *Paraconiothyrium variabile*, *Phaeoacremonium rubrigenum*, *Rhizomucor variabilis*, and *Xylaria mali* (Cui et al., 2011). However, few of them were reported to display only antimicrobial activities, i.e. *Phoma herbarum*, *Geotrichum candium*, and *Fusarium verticillioides* (Chi et al., 2016; Cui et al., 2011). The endophytic fungi, *Diaporthe* sp. and *Colletotrichum* sp., which were believed to be responsible for the production of sesquiterpene compounds in *Aquilaria* trees, were claimed to have antioxidant properties; while the latter taxa also came with anti-inflammatory activities (Monggoot et al., 2017; Wang et al., 2016). Although a total of 92 compounds produced by fungal endophytes in *Aquilaria* were identified so far (Fig. 3), only 52 of them were proven to come with their related biological properties; in general, most of the identified compounds contained anti-inflammatory, anti-bacterial, and anti-cancer properties (Table 3). Compounds produced by all the isolated endophytes from *Aquilaria* and *Gyrinops* and their pharmacological values have been shown in Table 3.

6. Conclusion

Endophytes could maintain endosymbiotic relationship within plants at least in one stage of their life cycle (Turjaman et al., 2016). Compared with physical and chemical methods, the use of endophytic fungi has been recognized as a safe method to promote agarwood production for the environment and human health (Tan et al., 2019). Additionally, the endophyte inducing method could be seemed as a prioritized approach to enhance agarwood formation due to its ability to produce the signals associated with continuous agarwood formation and compounds with bioactivity. And the advantages of induced agarwood by endophytes are more pharmaceutical values, higher environmental adaptability, and faster speed of agarwood formation.

To our knowledge, 14 species of *Aquilaria* and eight of *Gyrinops* were known to produce agarwood, and different fungal species and abundances were detected because of different planting regions and various species. *Fusarium* sp. accounted for the largest proportion of *Aquilaria* and *Gyrinops*, followed by *Colletotrichum* sp., *Diaporthe* sp., and *Trichoderma* sp. The endophytic fungi spread over various host species with high biodiversity, however, the biodiversity of fungal endophytes distributed in various planting areas is seldom reported, which needs more detailed research. Furtherly, the variation in microbiome composition is represented by multiple *A. sinensis* tree host organs, and tissue types. The high diversity of fungal endophytes in resinous wood could give some good candidates for developing fungal inoculum that could promote agarwood production.

Various endophytic fungi have been reported to produce metabolites containing sesquiterpenoids and aromatic groups, which are a rich source of medicinal agents to improve the quality and quantity of agarwood. Most of the endophytes from *Aquilaria* and *Gyrinops* showed antimicrobial and antitumor activities, and a few fungi that have special abilities, such as the antioxidant activity of *Diaporthe* sp., and anti-inflammatory activities of *Colletotrichum* sp. Besides that, some of the secondary metabolites are formed when the fungal endophytes trigger the self-defense reaction of *Aquilaria* and *Gyrinops*. In this way, the agarwood fungal endophytes not only protect host trees from microbe invasions and diseases but also activate the accumulation of agarwood. And these compounds produced by the fungal strains are various due to the different species or strains, which might enhance the resistance abilities to various environmental stresses. Conversely, both *Aquilaria* and *Gyrinops* trees grow in different places with various geographic and climate conditions and need different sorts of fungi, which could promote the host's ecological adaptability. In summary, the fungal endophytes on the host trees of *Aquilaria* and *Gyrinops* are responsible for activating the plant defense system, strengthening the hosts' ecological adaptability, and enhancing agarwood production, which may be the reasons why agarwood artificial induction by endophytes has become popular. The mechanism of aroma accumulation and the crucial role of endophytes in the agarwood host trees need to be furtherly explored in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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