Review

The Therapeutic Potential of Agarwood as an Antimicrobial and Anti-inflammatory Agent: A Scoping Review

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The Therapeutic Potential of Agarwood as an Antimicrobial and Anti-inflammatory Agent: A Scoping Review

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Abstract: Microorganisms such as bacteria, viruses and fungi are frequently the cause of infections. Antimicrobial agents, such as antibiotics, antivirals, and antifungals, are used to target and eliminate these infectious agents. On the other hand, inflammation is a natural response of the immune system to injury, infection, or irritation. Although herbal remedies have been used for centuries and can be effective in certain situations, it is crucial to use them with caution. Not all herbal remedies are supported by scientific evidence, and their safety and efficacy can vary. Thus, we conducted this review to determine the potential health benefits of agarwood as an antimicrobial and anti-inflammatory agent. Original articles were searched in three databases (PubMed, Scopus and Google Scholar) from the year 2013 to 2023 using the Medical subject heading (MeSH) terms "antimicrobial" and/or "anti-inflammatory", crossed with the term "agarwood". Synonyms and relevant search terms were also searched. The most studied agarwood for antimicrobial and anti-inflammatory agents is *Aquilaria sinensis*. Some studies have shown its potential application as a potent inhibitor for fungi, including *Lasiodiplodia theobromae*, *Fusarium oxysporum*, and *Candida albicans*. Moreover, it is capable of inhibiting *Bacillus subtilis* and *Staphylococcus aureus* activities. Several chromones detected in agarwood have been revealed to inhibit NF-κB activation, LPS-induced NO production and superoxide anion generation. In conclusion, agarwood and its isolates are worthy of further biomedical investigation and could be developed as potential candidates for the treatment or prevention of various microbial and inflammatory diseases. This review reveals that despite the absence of clinical trials, agarwood exhibits antimicrobial and anti-inflammatory properties.

Keywords: *Aquilaria* spp.; antimicrobial; anti-inflammatory

1. Introduction

The primary source of agarwood, also known as oud, is Aquilaria trees. These trees are native to several Asian nations, mainly in Southeast Asia. In some countries, Aquilaria trees grow in natural forests and in plantations [1]. In natural forests, Aquilaria trees that produce agarwood are often found in countries such as Thailand, Cambodia, Vietnam, Malaysia, Indonesia, Laos, India, Bangladesh, and parts of China [2]. Specific locations where agarwood is found within these countries can vary due to climate and soil conditions [3]. Certain ecological circumstances, such as hilly or mountainous regions with particular soil types and sufficient rainfall, are more conducive to the growth of these plants. In recent years, some countries have tried cultivating Aquilaria trees in plantations. These plantations aim to sustainably produce agarwood by stimulating the resinous formation in the trees. Plantations can be found in Southeast Asia, such as Malaysia and Indonesia [4].

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While some preliminary research has suggested antimicrobial properties in agarwood, concrete scientific evidence supporting this claim was limited, and most studies were in the early stages. The ethanol extract of agarwood leaves has been shown to have antimicrobial activity against bacteria and fungi. The extract contains bioactive compounds like flavonoids and tannins, contributing to this antimicrobial activity [5]. Agarwood produces oud oil, which is rich in a variety of volatile compounds that include sesquiterpenes such as α- and β-guaiene, agarospirol, agarol, and various other sesquiterpenoids and phenylethyl chromones [6]. These bioactive substances found in agarwood have been shown to possess antimicrobial properties. The general potential mechanisms through which agarwood might exert antimicrobial effects could include (a) disruption of cell membranes by which agarwood's compounds have the potential to cause microorganisms' cell membranes to rupture, allowing internal organelles to seep out and the cell to eventually die [7], (b) interference with microbial enzymes, where the components of agarwood may block or obstruct vital microbial enzymes, impairing the metabolic activities that are necessary for microbial viability [8], (c) antioxidant effects that may help fight microbial infections by modifying microbial viability and lowering oxidative stress [9], (d) modulation of gene expression by compounds found in agarwood that may affect the pathogenicity, survival, or replication of the microbes [10] and (e) impact on biofilm formation of bacteria colonies that are frequently resistant to antimicrobial treatments [11].

Agarwood has also been studied for its potential anti-inflammatory properties. Agarwood extracts have shown potential in inhibiting various inflammatory mediators such as cytokines, prostaglandins, and leukotrienes [12]. These mediators play critical roles in the inflammatory response, and the ability of agarwood to inhibit their release or activity suggests anti-inflammatory potential. Some studies indicate that agarwood extracts may inhibit enzymes like cyclooxygenase (COX) and lipoxygenase (LOX) involved in the production of inflammatory mediators, such as prostaglandins and leukotrienes [7]. By inhibiting these enzymes, agarwood could potentially suppress the inflammatory cascade. Moreover, agarwood may modulate the immune response, potentially influencing the activities of immune cells involved in inflammation. Its immunomodulatory effects could help regulate inflammatory responses. Other than that, agarwood might interfere with specific cellular signalling pathways involved in inflammation, such as NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and MAPKs (mitogen-activated protein kinases), which are associated with the regulation of inflammatory responses. Inflammation often involves oxidative stress, and the antioxidant activity of agarwood may help neutralize free radicals and reduce inflammation induced by oxidative stress. Thus, this scoping review was conducted to determine the effect of agarwood as a potential antimicrobial and anti-inflammatory agent.

2. Results

We have examined 321 publications in the initial stage before screening. Following screening, 282 out of 313 articles were excluded according to established inclusion and exclusion criteria. Articles that have met the requirements of being in English or Malay, having available full text, and being peer-reviewed were included, ensuring the selection of high-quality and relevant research. In contrast, articles were excluded when they were review papers, letters to the editor, or duplicates, as these did not contribute original research data or were redundant. We also limit publication for a period of 10 years for several reasons:

a) Relevance and recent publications are required to ensure the review reflects the most current research and knowledge.
b) Focus and scope of the study: Limiting the timeframe helps maintain focus on recent developments and trends within a manageable scope.
c) Manageability of the reviewing process to make the task more feasible in terms of time and effort.

The search resulted in a total of 29 articles produced with a refined search based on the availability of full text, peer-reviewed articles and library collection access (Figure 1). Upon further assessment, only 27 full-text articles were found to be relevant and included for final review (Table

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1). All the related articles were printed out for further assessment of evidence-based to explore the effectiveness of agarwood as a potential antimicrobial and anti-inflammatory agents. While the ten-year limit is standard, it can vary depending on the field, topic, and specific requirements of the review paper. Ultimately, the timeframe chosen should balance comprehensiveness with relevance to provide the most insightful and valuable literature synthesis.

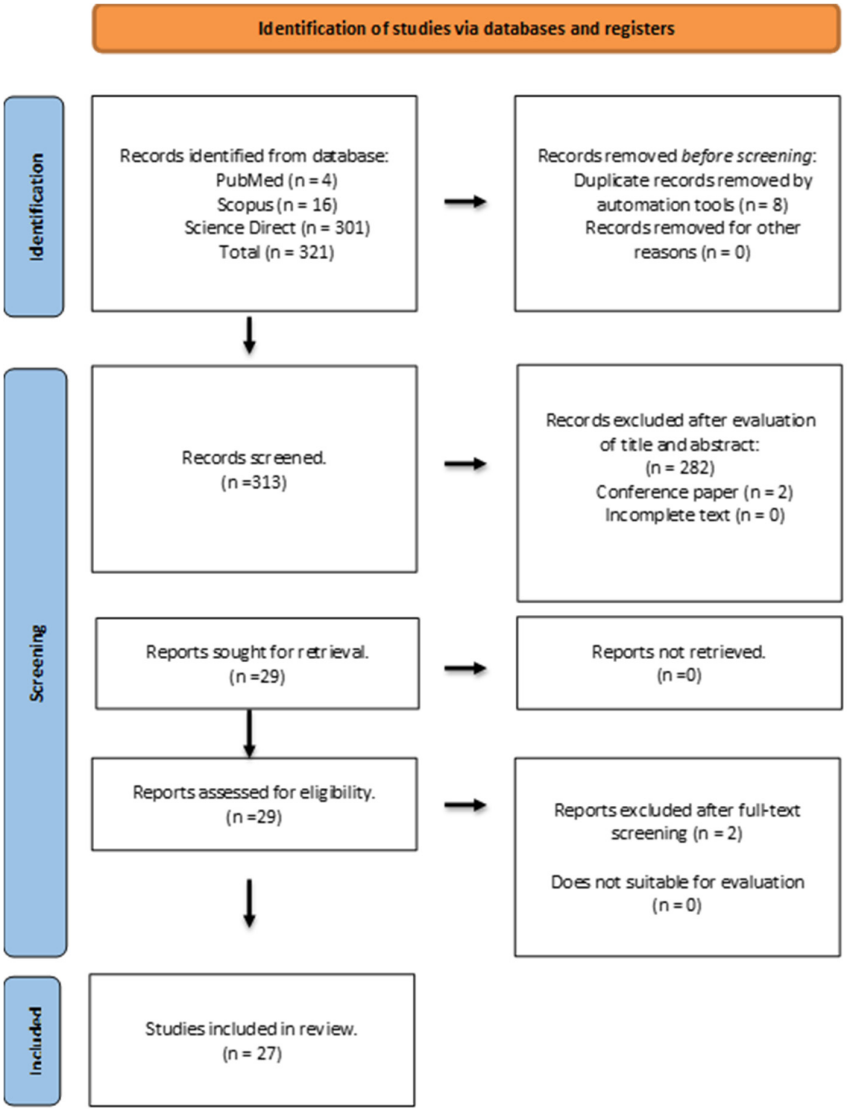

Figure 1. Flowchart of the Search Strategy.

Table 1. Tabulated summary of articles that was included in this review.

No	Reference	Objective	Method	Findings	Conclusion/Recommendation
1	[13]	• To investigate the chemical composition of volatile components and alcohol extracts from different agarwoods • To investigate the role of chromone compound 2-phenylethyl-benzopyran and the mechanism of agarwood formation	• Chemical composition using GC-MS. • Antibacterial properties	• The volatile components of A. sinensis included 3-ethyl-5-(2-ethylbutyl)-octadecane, oleic acid 3-(octadecyloxy) propyl ester, and docosanoic acid 1,2,3-propanetriyl ester, while the alcohol extracts of A. sinensis contained benzoic acid ethyl ester, hexadecanoic acid ethyl ester, oleic acid, and n-hexadecanoic acid • The main active ingredients were sesquiterpenoids, aromatic species, and chromone compounds. • An antibacterial activity test showed that the inhibition effect of the essential oil was better against Gram-positive bacteria than against Gram-negative	• The present study identified the chemical compositions of agarwood and provides a basis for selecting the best quality agarwood from different origins. Also, this study provides a new approach to the identification of agarwood from domestic and exotic species
2	[14]	• To identify the in vitro antimicrobial activity of ethanol extract of *A. agallocha* roots	• Disk diffusion method on 17 bacteria and 1 fungus (*Bacillus*, *Candida*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Klebsiella*, *Listeria*, *Pseudomonas*, *Salmonella* and *Staphylococcus* genera)	• The ethanol extracts have a clear antimicrobial activity against all microorganism except *Escherichia coli* ATCC 25922 and *S. typhimurium* SL 1344 • The volatile components of A. sinensis included 3-ethyl-5-(2-ethylbutyl)-octadecane, oleic acid 3-(octadecyloxy) propyl ester, and docosanoic acid 1,2,3-propanetriyl ester, while the alcohol extracts of A. sinensis contained benzoic acid ethyl ester, hexadecanoic acid ethyl ester, oleic acid, and n-hexadecanoic acid • The main active ingredients were sesquiterpenoids, aromatic species, and chromone compounds	• *A. agallocha* roots have a medicinal use especially against *E. faecium*, *L. monocytogenes* ATCC 7644, *B. subtilis* DSMZ 1971, *C. albicans* DSMZ 1386, *S. epidermidis* DSMZ 20044 and *S. aureus* ATCC 25923

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					• An antibacterial activity test showed that the inhibition effect of the essential oil was better against Gram-positive bacteria than against Gram-negative	
3	[15]	• To determine the content type of secondary metabolites and antibacterial activity against *S. aureus* and *Proteus mirabilis* by the method of Kirby-Bauer disc diffusion	• Phytochemical screening • Thin layer chromatography • Kirby-Bauer disc diffusion	• The average diameter zone obstruent extract ethanol leaves agarwood in *S. aureus* by concentration of the 300 mg / ml, 400 mg / ml, 500 mg / ml is 12.50 mm, 13.51 mm, 15.80 mm. While in *P. mirabilis* by concentration of the 300 mg / ml, 400 mg / ml, 500 mg / ml is 12.10 mm, 13.26 mm, and 15.19 mm	• Ethanol extracts from agarwood leaves exhibited activity on Gram positive and Gram negative
4	[16]	• To determine bioactive compounds of agarwood (*A. malaccensis*) ethanol extract and its antibacterial and antifungal activities against bacteria (*Staphylococcus epidermidis* ATCC 12228, *S. aureus* ATCC 25923, and *Propionibacterium acnes* ATCC 6919)/fungi (*C. albicans* ATCC 10231 and *Trichophyton* sp. ATCC 18748) species that commonly caused skin infection	• Ethanol extracts of agarwood leaves. • Disc diffusion method (Kirby-Bauer Test) • Antifungal activity using Müeller-Hinton and nutrient agar media on petri dishes for fungi growth • Positive control using amoxicillin and negative control using ketoconazole	• Antimicrobial activity: The maximum inhibitory zone of extracts toward *S. epidermis* and *P. acnes* was on 20% concentration whereas *S. aureus* was on 5% concentration • Based of Clinical Laboratory Standard Institute (CLSI), *S. aureus* was classified as susceptible (at 5.00% concentration) and intermediate (at 2.5% concentration), other concentration at 1.25%, 10% and 20% and all concentration for *S. epidermis* and *P. acnes* classified as resistant • Antifungal activity: Inhibitory zone of *C. albicans* was classified intermediate (at 20.00% concentrations) and the rest concentration was classified as resistant. The inhibitory zone of *Trichopyiton* sp. for all concentrations was classified as resistant • The ethanol extracts from agarwood leaves had nine biologically active compounds	• The ethanol extract from agarwood leaves (*A. malaccensis*) had antibacterial and antifungal activities. The chemical compounds contained in the extract were flavonoids, tannins, and triterpenoids

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5	[17]	• To examine antibacterial activity of the *A. crassna* leaf extract against *S. epidermidis* and its underlying mechanism. • The antioxidant activity and acute toxicity were studied as well	• FRAP, ABTS and DPPH scavenging methods • Disc diffusion assay and the minimum inhibitory concentration (MIC)	• *S. epidermidis* was susceptible to the extract with the MIC and MBC of 6 and 12 mg/ml, respectively • The extract caused swelling and distortion of bacterial cells and inhibited bacterial biofilm formation. Rupture of the bacterial cell wall occurred after being treated with the extract for 24 h • Acute toxicity tests in mice showed no sign of toxicity or death at the doses of 2,000 and 15,000 mg/kg body weight	• The aqueous extract of *A. crassna* leaves possesses an in vitro antibacterial activity against *S. epidermidis*, with no sign of acute oral toxicity in mice, probably by interfering with bacterial cell wall synthesis and inhibiting biofilm formation
6	[18]	• To evaluate the combination effects of *A. malaccensis* extract with polymyxins against *Acinetobacter baumannii* and *Klebsiella pneumoniae*	• In vitro time-kill studies. • GC-MS analysis	• The crude extract alone and its combination with polymyxin B minimized and inhibited the bacteria growth over the 24 h • More than sixty constituents with major component of phytol and 9,12-octadecadienal	• Further study is warranted to investigate pure bioactive compounds from the extract of *A. malaccensis* leaves although no synergy effect was observed • The combination of polymyxin B and *A. malaccensis* extract enhanced the bacterial killing compared to polymyxin B alone • The compounds that likely to contribute to the antibacterial activity of the extract including phytol, 9,12-octadecadienal, oleic acid, n-decanoic acid, n-hexadecanoic acid and squalene • *A. malaccensis* leaf extract is a promising candidate of antibacterial agent either to be used alone or in combination with polymyxins for the treatment against MDR Gram-negative bacterial infections particularly *A. baumannii* and *K. pneumoniae*

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7	[19]	• To evaluate the potential of using *A. malaccensis* leaf extract as a biogenic medium to generate CuO NPs with antimicrobial potential	• The procedure employed was to add 5 mM copper sulfate ($CuSO_4.5H_2O$) as the precursor to *A. malaccensis* leaf extract to study the generation of CuO NPs under different incubation conditions such as methods of crude extract preparation, precursor concentration and incubation temperature	• The boiled leaf extract reacted with 5 mM CuSO4.5H2O at pH 6 and incubated under non-shaking conditions at 70 °C, resulting in a high rate of CuO NPs formation and depicting a UV absorbance peak of 430 nm. Green synthesized CuO NPs were characterized using field emission scanning electron microscopy (FESEM) and energy-dispersive X-ray spectroscopy (EDX), Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), and transmission electron microscopy (TEM). FESEM and TEM revealed that the nanoparticles are mainly spherical, ranging from 6 to 32 nm. Antimicrobial studies showed that 20 µL and 40 µL of 70 µg/µL CuO NPs displayed potent inhibition towards Gram-positive bacteria B. subtilis, with the average zone of inhibition measuring 24.43 ± 0.10 mm and 27.31 ± 0.13 mm, respectively	• A facile, cost-effective, and sustainable synthesis of CuO NPs was achieved using the leaf extract of *A. malaccensis* as a reducing agent • Further studies should be conducted to determine the antimicrobial potential of these nanoparticles in a broader range of microbial pathogens
8	[20]	• To report the chemical constituents and antimicrobial activity of essential hydrodistilled from the leaves and trunk of *A. banaensis P.H.Hô* (*Thymelaeceae*) from Vietnam	• Uses leaves and trunk of *A. banaensis* for hydrodistillation of the essential oils using Clevenger-type apparatus—3H normal pressure distillation • Three Gram positive bacteria *B. subtilis* (ATCC 6633), *S.*	• Antimicrobial activity of Trunk essential oil—against *S. aureus* with the minimum inhibitory concentration (MIC) value of about 256.0 µg/mL and IC50 value of 153.7 µg/mL. Also, exhibited moderate action against, *B. subtilis*, *Lactobacillus fermentum*, *E. coli*, *Salmonella enteric*, *Pseudomonas aeruginosa* and *C. albicans*,	• The trunk essential oil also exhibits potential antimicrobial activity against *S. aureus* with MIC value of 256.0 µg/mL. Therefore, the present result opens up a possibility for further exploitation of *A. banaensis* essential oil

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				aureus (ATCC 13709), *Lactobacillus fermentum* (N4) and three-Gram negative bacteria *E. coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 15442), *Salmonella enterica* and the yeast *C. albicans* (ATCC 10231) were used in this study • Agar well diffusion and broth microdilution methods • To report the chemical constituents and antimicrobial activity of essential hydrodistilled from the leaves and trunk of *A. banaensis P.H.Hô* (*Thymelaeceae*) from Vietnam	with MIC value in the range > 256.0 µg/mL • Antimicrobial activity of the leaf essential oil did not show meaningful and considerable activity towards the tested microorganisms	
9	[21]	• This research aimed to determine the potential of oleanane triterpenoids (1-oxo- β -amyrin, hederagenin-an, 3β-acetoxyfriedelane and ursolic acid) from agarwood as a covid-19 antiviral by in-silico study	• The research methods were molecular docking, prediction of Lipinski rules of five, and prediction of ADME. Main protease (Mpro) Covid-19 was used as a receptor	• The affinity of the tested ligand is better to the main protease (Mpro) receptor than remdesivir and lopinavir	• According to Lipinski's rule of five, hederagenin-an is potential for development as oral medicine of covid-19 antiviral	
10	[22]	• To investigate the secondary metabolites class of agarwood (*A. malaccensis* Lamk) parts (leaf, trunk, skinned stems and bark) of distilled extracts in phytochemical screening and the antimicrobial activity	• Agarwood (*A. malaccensis* Lamk) leaves, stems (agarwood stems formed by inoculation), barkless stems (agarwood stems formed by barking the stems), and bark • Dried for ± 4 hours in the sun and then dried indoors	• *Streptococcus* mutants bacteria to distilled water from parts (leaf, trunk, bark and TK rod) of the agarwood plant (*A. malaccensis* Lamk) can all be categorized as resistant	• Glycosides was found in leaf, trunk, skinned stems and bark. Distilled water from parts of the agarwood plant (*A. malaccensis* Lamk) has antibacterial activity against *Streptococcus* mutants bacteria	

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				for several days, cut into pieces and blended • Hydrodistillation method 100g in 1L heated at 100°C • Disc Diffusion method (Kirby-Bauer test) using gram-positive bacteria *Streptococcus* mutants incubation for 37 °C for 24H with 50% and 100% distilled extracts		
11	[23]	• To determine anticancer, antioxidant and antimicrobial properties of the sesquiterpene β-caryophyllene from *A. crassna*	• Structure confirmation using FT-IR, NMR and MS. • The antimicrobial effect study using human pathogenic bacterial and fungal strains	• β-caryophyllene demonstrated selective antibacterial activity against *S. aureus* (MIC 3 ± 1.0 μM) and more pronounced anti-fungal activity than kanamycin • β-caryophyllene also demonstrated potent inhibition against clonogenicity, migration, invasion and spheroid formation in colon cancer cells	• β-caryophyllene is the active principle responsible for the selective anticancer and antimicrobial activities of *A. crassna* • β-Caryophyllene has great potential to be further developed as a promising chemotherapeutic agent against colorectal malignancies
12	[24]	• To determine the antibacterial activity of agarwood bouya (*Aquilaria agallocha*) oil nanoemulsion against multidrug-resistant bacteria (MDR) and nonresistant antibiotics bacteria	• The antibacterial activity of the agarwood bouya oil nanoemulsion was carried out by the disk diffusion method against: • *E. coli* ATCC 35218, • *S. aureus* ATCC 43300, • *K. pneumoniae* ATCC 700603, • *E. coli* ATCC 25922, • *S. aureus* ATCC 25923 • *K. pneuomoniae* ATCC 8724	• Agarwood bouya oil nanoemulsion with a concentration of 1% had the smallest size around 17.7 nm with a percent transmittance of 99.35%. The agarwood bouya oil nanoemulsion 20% was only able to inhibit ESBLs-producing *E. coli* ATCC 43300 by 3.3 mm. The non-resistant *E. coli* ATCC 25922 bacteria were able to inhibit with the inhibition zone at 13.3 mm actively, while the bacteria *S. aureus* ATCC 25923 and *K. pneumoniae* ATCC 8724 have inhibition zones of 2.6 mm and 3.3 mm, respectively	• A higher concentracion of oil nanoemulsion will increase its inhibitory activity on multidrug resistant bacteria (MDR)

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13	[25]	• To confirm the silver nanopartilces (AgNPs) formation and their biophysical characterization • To evaluate the larvicidal and pupicidal toxicity of *A. sinensis* essential oil (AsEO), *P. cablin* essential oil (PcEO) and biosynthesized AgNPs against larvae and pupae of the dengue and zika virus vector *Aedes albopictus*	• Synthesis and confirmation of AgNPs formation • Larvicidal and pupicidal bioassays • Histological analysis	• Compared to the tested essential oils, the biofabricated AgNPs showed the highest toxicity against larvae and pupae of Ae.albopictus. In particular, the LC50 values of AsEO ranged from 44.23 (I) to 166 (pupae), LC50 values of PcEO ranged from 32.49 (I) to 90.05(IV), LC50 values of AsEO-AgNPs from 0.81 (I) to 1.12 (IV) and LC50 values of PcEO-AgPNs from 0.85 (I) to 1.19 (IV) • Histological analysis of the midgut cells of the control and treated larvae exhibited that the epithelial cells and brush border were highly affected by the fabricated AgNPs compared to the essential oils (AsEO and PcEO)	• *A. sinensis* and *P. cablin* essential oils fabricated AgNPs have a potential of application as a biopesticide for mosquito control through safer and cost-effective approach. • Further studies are needed to clarify the exact mechanism of action of Ag nanoparticles against mosquito vectors regarding skin impact and mineral balances and transportation within the cells of insect body
14	[26]	• To test the quality of the agarwood originated from *A. sinensis* stimulated by the chemical method (S1), compared with the wild agarwood (S2) and healthy trees (S3) as controls • To determine antimicrobial activities of essential oils of the agarwood originating from *A. sinensis*	• The chemical composition of S1 using gas chromatography-mass spectrometry (GC-MS) *S. aureus* ATCC 25923, *B. subtilis* ACCC11060 and *E. coli* ATCC25922, were used as test organisms in the screening • Agar well diffusion method for susceptibility screening • MIC and Minimum Bactericidal Concentration (MBC) assay	• The essential oil of S1 showed a similar composition to that of S2, being rich in sesquiterpenes and aromatic constituents. However, the essential oil of S3 was abundant in fatty acids and alkanes • Essential oils of S1 and S2 had better inhibition activities towards *B. subtilis* and *S. aureus*, compared with essential oil of S3. *E. coli* was not sensitive to any of them	• The characterization of the essential oil obtained from the agarwood originated from *A. sinensis* stimulated by the chemical method has very high similarity with that of the essential oil of wild agar wood, both in chemical composition and antimicrobial activity • This suggests that agarwood could be produced by the artificially chemically stimulation method • Further studies are required to determine the type of chemical agents and suitable duration for inducing better agarwood formation

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15	[27]	• To characterize and compare the composition and antimicrobial activity of essential oils obtained from agarwood originating from *A. sinensis* (Lour.) Gilg induced by a biological agent of agarwood, *Lasiodiplodia theobromae* (F), to those from wild agarwood (W) and uninoculated healthy trees (H)	• Chemical composition determination using GC-MS • Two phytopathogenic fungi (*Lasiodiplodia theobromae* and *F. oxysporum*) and one clinical fungus (*C. albicans* ATCC10231) were used as test organisms in the screening • Agar well diffusion method • Antifungal activity using MIC and MFC values of essential oil against *L. theobromae*, *F. oxysporum*, and *C. albicans*	• The essential oil of F showed a similar composition to that of W, being rich in sesquiterpenes and aromatic constituents • The essential oil of H was abundant in alkanes • Essential oils of F and W were more potent inhibitors of *L. theobromae*, *F. oxysporum*, and *C. albicans* than the essential oil of H. • The essential oil obtained from the agarwood originating from *A. sinensis* induced by *L. theobromae* had a high similarity to that of the essential oil of wild agarwood, both in chemical composition and in antimicrobial activity	• The strategy of agarwood induced by fungi could be potentially applied in agarwood and essential oil production in *Aquilaria* trees
16	[28]	• To analyse the ability of *G. versteegii* fruit extract as an antibacterial agent against *E. coli* and *S. aureus* • To identify the chemical compounds of the fruit	• Extraction by n-hexane, dichloromethane and methanol • Antibacterial assay using agar well diffusion method on *E. coli* (ATCC 25922) and *S. aureus* (ATCC 29213) • Chemical composition analysis using GC-MS	• The dichloromethane extract showed the most effective antibacterial activity against *S. aureus* at a concentration of 40%, with a zone of inhibition of 13.17 mm compared to *E. coli*, for which it was 7 mm • Total and partial inhibition was shown by the *G. versteegii* fruit extracts against *S. aureus* and *E. coli*, respectively • GC-MS identified the following compounds in *G. versteegii* fruit extract: palmitic, oleic, and stearic acid, as well as bis-(2-ethylhexyl) phthalate, 2,3-dihydro-3,5dihydroxy-6-methyl-4H-pyran-4-one, methyl octadec-9-enoate, squalene, and 2monopalmitin derivates	• The antibacterial activity of the extract was stronger against *S. aureus* compared to *E. coli* • The dichloromethane extract at 40% concentration was the most effective in inhibiting the growth of *S. aureus*, with an inhibition zone of 13.17 mm • GC-MS analyses of various compound in *G. versteegii* fruit extracts were identified
17	[29]	• To isolate, identify and report on the biological activities of four	• Spectroscopic methods for structure elucidation.	• Four new 5,6,7,8-tetrahydro-2-(2-phenylethyl) chromones were isolated	• Eleven 2-(2-phenylethyl)chromones (1–11), including four undescribed

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			new chromones derivatives and seven known analogues	• Evaluation for anti-inflammatory activities by inhibiting the lipopolysaccharide (LPS)-induced nitric oxide (NO) release in RAW264.7 cells	• Compound 1 features a (5,5″)-carbon-carbon bond linkage connecting two chromone monomeric units • Significant anti-inflammatory effects, compound 2 with an IC50 value of 3.46 μM	ones were isolated and identified from the agarwood produced via Agar-Wit of *A. sinensis* • *All the new compounds showed significant anti-inflammatory effects by inhibiting LPS-induced NO release in RAW264.7 cells*
18	[30]	•	To investigate the chemical constituents and anti-inflammation of agarwood produced via whole-tree agarwood-inducing technique (Agar-Wit) from *A. sinensis*	• Chemical constituents and anti-inflammation by column chromatographic technique and semi-preparation HPLC • Evaluation of the anti-inflammatory activity of RAW264. 7 cells with LPS-induced	• Eleven sesquiterpenes were identified • Compound baimuxinol (1) was a new natural product, and this is the first time to report its ^{13}C NMR spectroscopic data • Compounds [petafolia A (4), (4αβ,7β, 8αβ)-3,4,4α,5,6,7,8,8α-octahydro-7-[1-(hydroxymethyl) ethenyl]-4α-methylnaphthalene-1-carboxaldehyde (9) and 12-hydroxy-4(5),11(13)-eudesmadien-15-al(10) were reported from Aquilaria for the first time, and all the compounds are firstly isolated by Agar-Wit from *A. sinensis* • Compound 1,4 and 9 showed potential anti-inflammatory activities with IC50 values (2.5 ± 0. 35), (3.2 ± 0.2), (4.3 ± 0.56) μmol·L-1, respectively	• Eleven sesquiterpenes were isolated and identified and showed significant anti-inflammatory effects by inhibiting LPS-induced NO release in RAW264.7 cells
19	[31]	•	To isolate a flavonoid compound, pilloin, from *A. sinensis* and investigated its anti-inflammatory activity in bacterial LPS-induced RAW 264.7 macrophages and septic mice	• Anti-inflammatory activity in bacterial LPS-induced RAW 264.7 macrophages and septic mice	• Pilloin inhibited NF-κB and MAPK signalling pathways in LPS-activated macrophages • Pro-inflammatory cytokines (e.g., TNF-α and IL-6), as well as enzymes (e.g., iNOS and COX-2) were also downregulated by pillion • The phenotypes and functions of activated macrophages (i.e., ROS	• Pilloin is a potential anti-inflammatory compound

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					production and phagocytic activity) were also suppressed by pillion • Pilloin attenuated the LPS-stimulated production of cytokines (i.e., TNF-α and IL-6) in serum and in tissues in vivo	
20	[32]	• To isolate and structural elucidation of the compounds as well as their inhibitory effects on NO production in LPS-stimulated RAW264.7 cells are discussed	• Extraction and isolation with ethanol. • Cell culture, viability assay, and measurement of NO production • Structural elucidation using LCMS-guided isolation of bioactive EtOAc soluble extracts	• Fifteen previously undescribed 2-(2-phenylethyl)chromone dimers, along with two known analogues were isolated from Chinese agarwood (*A. sinensis*) • The isolated compounds exhibited significant inhibition of NO production in LPS-stimulated RAW264.7 cells with IC50 values in the range 0.6–37.1 μM	• All the tested 2-(2-phenylethyl)chromone dimers showed significant inhibition of NO production which implied their potential leads for the development of anti-inflammatory agents
21	[33]	• To describe the structural elucidation of the compounds and the inhibitory activities of all isolates from *A. sinensis*	• Determination of four new 2-(2-phenylethyl)-4H-chromen-4-one derivatives and nine known compounds through spectroscopic and MS analyses • Inhibitory activities on LPS-induced NF-κB activation of macrophages	• Neopetasan, 7-methoxy-2-(2-phenylethyl)- chromone, 6,7-dimethoxy-2-(2-phenylethyl)chromone, and 6,7-dimethoxy-2-[2-(40 -methoxyphenyl)ethyl]chromone inhibited NF-κB activation in LPS-stimulated RAW 264.7 macrophages with relative luciferase activity values of 0.55 ± 0.09, 0.54 ± 0.03, 0.31 ± 0.05, and 0.38 ± 0.14, respectively, versus that of vehicle control (1.03 ± 0.02) • 5,6-dihydroxy-2-[2-(30 -hydroxy 4 0 -methoxyphenyl)ethyl]chromone, 7-methoxy-2-(2-phenylethyl)chromone, 7-dimethoxy-2-(2- phenylethyl)chromone, and 6,7-dimethoxy-2-[2-(40 -methoxyphenyl)ethyl]chromone could suppress LPS-induced NO production in RAW 264.7 cells and did not induce	• Agarwood and its isolates (especially compound 11) are worthy of further biomedical investigation and could be developed as potential candidates for the treatment or prevention of various inflammatory diseases • The structure-and-activity relationship (SAR) of these isolated compounds in term of anti-inflammatory activity certainly merits further investigation

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					cytotoxicity against RAW 264.7 cells after 24-h treatment	
22	[34]	• To isolate 16 new 2-(2-phenylethyl)chromone dimers, including four pairs of enantiomers (1a/1b, 3a/3b, 6a/6b, and 8a/8b), along with eight optically pure analogues (2, 4, 5, 7, and 9–12) from *A. sinensis*	• Their structures determination using spectroscopic analysis (1D and 2D NMR, UV, IR, and HRMS) and experimental and computed ECD data	• Compounds 1–10 feature an unusual 3,4-dihydro-2H-pyran ring linkage connecting two 2-(2-phenylethyl)chromone monomeric units, while compounds 11 and 12 possess an unprecedented 6,7-dihydro-5H-1,4-dioxepine moiety in their structures • A putative biosynthetic pathway of the representative structures via a diepoxy derivative of a chromone with a nonoxygenated A-ring is also proposed	• Compounds 1a/1b, 2, 3a/3b, 5, 7, 8a/8b, and 10–12 exhibited significant inhibition of nitric oxide production in lipopolysaccharide-stimulated RAW264.7 cells with IC50 values in the range 7.0–12.0 μM
23	[35]	• To report the isolation, structure elucidation, and anti-inflammatory activity of these compounds	• Extraction and isolation of compounds • Establishment structures by spectroscopic analyses (1D and 2D NMR, HR- ESI-MS, IR • Measurement of O_2 generation	• Nine compounds, including 1 showed more than 80% inhibition of superoxide anion generation by human neutrophils in response to formyl-L-methionyl-L-leucyl-L-phenylalanine at 50 μM	• Resinous wood of *A. sinensis* and its constituents (especially 8 and 18) may deserve further investigation as potential candidates for the treatment or prevention of various inflammatory diseases
24	[36]	• To describe the structural elucidation of the compounds numbered 1 through 3, and the inhibitory activities of all isolates on superoxide generation and elastase release by neutrophils	• Extraction and isolation with methanol • Biological assay (inhibition of superoxide anion generation and elastase release in fMLP/CB-activated human neutrophils), and purity test using NMR and MS	• Compounds 2, 3, 5, 6, and 8–10 exhibited inhibition ($IC_{50} \leq 12.51$ μM) of superoxide anion generation by human neutrophils in response to formyl-l-methionyl-l-leucyl-l-phenylalanine/cytochalasin B (fMLP/CB) Compounds 3, 6, 8, 10, and 19 inhibited fMLP/CB-induced elastase release with IC_{50} values ≤ 15.25 μM	• This investigation reveals bioactive isolates (especially 2, 3, 5, 6, 8, 9, 10, and 19) could be further developed as potential candidates for the treatment or prevention of various inflammatory diseases
25	[37]	• To isolate and elucidate the structural of five new 2-(2-phenylethyl)chromones (1–5)	• Elucidation of structures by spectroscopic data (NMR, UV, IR, and MS) analyses	• Five new 2-(2-phenylethyl)chromone derivatives (1–5), along with eleven	• Preliminary structure-activity relationship analysis showed that chlorine substituent and epoxy

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		• To describe their inhibitory effects on nitric oxide (NO) production in LPS-stimulated RAW264.7 cells	• Determination of the absolute configurations of compounds 2–4 by electronic circular dichroism (ECD) calculations • Cell viability assay, and measurement of NO production using Griess assay	known compounds (6–16) were isolated from Chinese agarwood • Compounds 2–4, 11, 12, and 15 exhibited significant inhibition of nitric oxide production in lipopolysaccharide-stimulated RAW264.7 cells with IC50 values in the range 1.6–7.3 μM • Compounds 7–9, 13, 14, and 16 were inactive • Due to the decrease of cell number (cytotoxicity), the effects of compounds 2–4, 11, 12, and 15 on cell proliferation/viability were measured using the MTT method. • These six compounds (up to 100 μM) did not show any significant cytotoxicity with LPS treatment for 24 h • The bioassay data of other compounds were not reached due to quantity limitation	group on the A-ring could be related to the anti-inflammatory activity of 5,6,7,8-tetrahydro-2-(2-phenylethyl)-chromones
26	[38]	• To investigate the antipyretic, analgesic, anti-inflammatory and anti-oxidative properties of *A. crassna* leaves extract at a wide dose range in rodents	• Experimental animals were treated orally • with an aqueous extract of A. crassna leaves (ACE) • Antipyretic assay (Baker's yeast-induced fever in rats), analgesic (hot plate test in mice) and anti-inflammatory (carrageenan-induced paw edema in rats) activities • An anti-oxidative effect of ACE using the DPPH assay	• 5 hours of yeast injection, 400 and 800 mg/kg ACE significantly reduced the rectal temperature of rats • Mice were found significantly less sensitive to heat at an oral dose of 800 mg/kg ACE, after 60 and 90 min • No anti-inflammatory activity of ACE at an 800 mg/kg dose could be observed in the rat paw assay • An anti-oxidative activity of ACE was observed with an IC50 value of 47.18 μg/ml	• No toxicity was identified • *A. crassna* leaves extracts possess antipyretic, analgesic and anti-oxidative properties without anti-inflammatory activity	

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				• No behavioral or movement change could be observed in mice after oral administration of ACE (800 or 8,000 mg/kg) for seven consecutive days • From the second day of treatment, animals had a significant lower body weight at the 8,000 mg/kg dose of ACE compared to the control	
27	[39]	• To analyse the chemical constituents of incense smoke generated from whole-tree agarwood-inducing technique (AWIT), agarwood induced by axe wounds (AAW), burning-chisel drilling agarwood (BCDA), and wood of *A. sinensis* trees (AS) • To investigate the effect of chemical constituents on TNF-α and IL-1α release in LPS-stimulated RAW264.7 cells	• Sample analysis using chromatographic separation of the resulting mixture (1.0 μL) was undertaken on an Agilent 7890 A GC coupled to a 5975C quadrupole mass spectrometer • Measurement of TNF-α and IL-1α production using ELISA kits	• 484 compounds were identified • The experimental data showed that aromatic compounds were the main chemical constituents in agarwood smoke and that some chromone derivatives could be cracked into low-molecular-weight aromatic compounds (LACs) at high temperature • A total of 61 aromatic compounds • from AWIT, representing 54.837%, were also found in AAW and BCDA • The anti-inflammatory activities of AAW, AWIT, and indomethacin were comparable and superior to that of BCDA	• Agarwood incense smoke showed anti-inflammatory activities by inhibiting lipopolysaccharide-(LPS-) induced TNF-α and IL-1α release in RAW264.7 cells

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3. Discussion

Most studies on agarwood have been related to its aromatic properties, traditional applications in perfumes, and potential medicinal benefits when used topically or inhaled through aromatherapy. While agarwood is not commonly consumed as a food or part of a regular diet, it has been utilized in some cultures for its purported medicinal properties. In certain traditional practices, agarwood has been used in minimal quantities or as an ingredient in herbal remedies for various health conditions such as digestive issues, asthma, pain relief, and even as an aphrodisiac [7]. Agarwood may also be found in traditional medicines such as tea or extract. As with any herbal or natural remedy, it is essential to be aware of potential allergic reactions, interactions with medications, and the lack of scientific evidence supporting its effectiveness and safety for consumption. However, the safety and efficacy of consuming agarwood for these purposes must be extensively studied in clinical trials. It is important to note that the consumption of agarwood or its derivatives should be approached cautiously and under the guidance of a healthcare professional due to limited scientific evidence regarding its safety and potential side effects. As of our knowledge cutoff in January 2023, more scientific research explicitly focusing on agarwood consumption is needed.

At the initial stage, we tried to separate antimicrobial and anti-inflammatory activities. However, during the write-up process, we found that combining antimicrobial and anti-inflammatory activities offers several advantages and synergistic effects. Thus, it is suitable to combine them because many infections are accompanied by inflammation, and vice versa. Treatment can provide a more comprehensive therapeutic approach by targeting antimicrobial activities to combat the disease and anti-inflammatory activity to reduce inflammation and associated symptoms. Moreover, research into compounds or formulations that exhibit both antimicrobial and anti-inflammatory properties can develop novel therapeutic agents with unique mechanisms of action and improved therapeutic profiles. Overall, combining antimicrobial and anti-inflammatory activities represents a promising medical and pharmaceutical research approach, aiming to provide more effective, targeted, and holistic treatments for infectious and inflammatory diseases.

In this scoping review, we found that a group of researchers investigated the chemical composition of agarwood from different Asian countries where they discovered that the main volatile components were 3-ethyl-5-(2-ethylbutyl)-octadecane, oleic acid 3-(octadecyloxy) propyl ester, and docosanoic acid 1,2,3-propanetriyl ester [13]. Interestingly, the main active ingredients of *A. sinensis* were sesquiterpenoids, aromatic species, and chromone compounds. They also recorded that agarwood had more significant antibacterial effects against Gram-positive bacteria than against Gram-negative. This effect may be due to the LPS layer on the Gram-negative bacteria cell wall, which prevents hydrophobic compounds from entering the cells and reduces the bacteriostatic impact [40]. The inhibition rates they obtained were in the following order: *S. aureus* > *B. subtilis* > *E. coli* [13].

Canli and his colleague conducted the first study to screen the antimicrobial properties of *A. agallocha* roots ethanolic extraction in vitro [14]. *A. agallocha* is considered a synonym of *A. malaccensis*. By performing a disk diffusion method on 17 bacteria and one fungus (*Bacillus*, *Candida*, *Enterobacter*, *Enterococcus*, *Escherichia*, *Klebsiella*, *Listeria*, *Pseudomonas*, *Salmonella* and *Staphylococcus* genera), they found that ethanol extracts were active against most of the strains especially against *E. faecium*, *L. monocytogenes* ATCC 7644, *B. subtilis* DSMZ 1971, *C. albicans* DSMZ 1386, *S. epidermidis* DSMZ 20044 and *S. aureus* ATCC 25923. Unfortunately, they did not perform the identification of active substances to elucidate the mechanism of action involved in this antimicrobial activity.

Another group of researchers also reported the antimicrobial effect of agarwood on *S. aureus* and *Proteus mirabilis* [15]. By using Kirby-Bauer disc diffusion assay, they found that the average diameter zone obstruent extract ethanol leaves agarwood in *S. aureus* was 12.50 mm (300 mg/mL), 13,51 mm (400 mg/mL), 15,80 mm (500 mg/mL) respectively. The study also reported that the average diameter zone obstruent extract ethanol leaves agarwood in *P. mirabilis* by concentrations of 300 mg/mL, 400 mg/mL, and 500 mg/mL were 12.10 mm, 13.26 mm and 15.19 mm, respectively. As previously reported by Wang, et al. [13], this study also confirmed that extracts of ethanol leaves agarwood have antimicrobial properties against selected Gram-positive and Gram-negative bacteria.

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In another study, an ethanol extract of *A. malaccensis* leaf was also tested for its antimicrobial activity against selected bacteria and fungi responsible for growing on the skin [16]. It was found that the antibacterial activity of the extract (1.25%–20% concentration) showed an auspicious result against *S. aureus*, where it was categorized as susceptible at 5% concentration. However, *S. epidermis* and *Propionibacterium acnes* at 20% concentration are categorized as intermediate, whereas all other tested concentrations are categorized as resistant. The study also reported the anti-fungal activity of *C. albicans*, which was classified as intermediate at 20%, whereas the other tested concentrations were classified as resistant; however, other fungi of *Trichophyton* sp. showed the inhibitory zone as resistant for all concentrations. They suggested that flavonoids, tannins, and triterpenoids are the active compound groups that contributed to its antimicrobial activity. The antimicrobial activity of *A. crassna* leaf aqueous extract against *S. epidermidis* was also reported by [17]. By disc diffusion assay, it was found that the extract inhibited the growth of *S. epidermidis* at 2 mg (12.0 ±1.0 mm), 4 mg (15.0 ± 0.4 mm) and 6 mg (18.0 ± 1.0 mm). *S. epidermidis* was disposed to the extract with the MIC and MBC of 6 and 12 mg/mL, respectively. This action is due to the disruption of biofilm and ruptured cell wall, which ultimately changed the shape of the bacteria.

Sometimes, an ingredient gives a better effect in a mixture with other active ingredients. Jihadi, et al. [18] reported the first work done on a combination of polymyxin B and *A. malacensis* extract by in vitro study targeting *Acinetobacter baumannii* and *Klebsiella pneumonia*. Polymyxin B is an antibiotic that belongs to the polymyxin group of antibiotics. The concentration of polymyxin B used in this study was at a clinically relevant dose of 1 μg/mL based on its susceptibility breakpoints at MIC of ≤2 μg/mL [41]. It is primarily used to treat bacterial infections, particularly those caused by Gram-negative bacteria. The performance of this combination extract was evaluated based on in vitro time-kill studies and GC-MS analysis at 4 h and 24 h. The researchers recorded that crude extract alone and its combination with polymyxin B was able to minimize and inhibit the bacteria growth over 24 h. However, the combination provides a much stronger bactericidal effect exceeding ≥3 log10 CFU/mL until the end of the 24-hour study period, especially for the extract at a concentration of 64 mg/mL compared to polymyxin B. alone, which was around ≥1 log10 CFU/mL only. From GC-MS analysis of *A. malaccensis* ethanolic crude leaf extract identified more than sixty constituents with significant components of phytol and 9,12-octadecadienal. Furthermore, compounds likely to contribute to the antimicrobial activity of the extract include phytol, 9,12-octadecadienal, oleic acid, n-decanoic acid, n-hexadecanoic acid and squalene.

In another intriguing study, *A. malaccensis* has been used as a biogenic medium to generate CuO NPs with antimicrobial potential [19]. The boiled leaf extract reacted with 5 mM $CuSO_4.5H_2O$ at pH 6 and incubated under non-shaking conditions at 70°C, resulting in a high rate of CuO NPs formation and depicting a UV absorbance peak of 430 nm. Field emission scanning electron microscopy (FESEM) and transmission electron microscopy (TEM) revealed that the nanoparticles are mainly spherical, ranging from 6 to 32 nm. Antimicrobial studies showed that 20 μL and 40 μL of 70 μg/μL CuO NPs displayed potent inhibition towards Gram-positive bacteria *B. subtilis*, with the average zone of inhibition measuring 24.43 ± 0.10 mm and 27.31 ± 0.13 mm, respectively.

In Vietnam, essential oils derived from the trunk of Vietnam-originated agarwood of *A. banaensis P.H.Hô* were explored against *S. aureus*, *B. subtilis*, *L. fermentum*, *E. coli*, *S. enteric*, *P. aeruginosa* and *C. albicans*. The researchers found a promising antimicrobial effect of the essential oil from the trunk compared to the leaf extract [20]. The study also explored the chemical composition of the leaf extract contains β-caryophyllene, α-selinene, α-humulene, β-selinene, β-guaiol and β-elemene. In contrast, the trunk contains hexadecanoic acid, oleic acid and tetradecanoic acid, which might be the reason for the differences in the outcomes from these two extracts as the potential antimicrobial agent.

During the COVID-19 pandemic, agarwood was also explored for its effectiveness using an in-silico approach. The potential antiviral activity of oleanin triperpenoids in agarwood towards coronavirus 2 (SARS-CoV-2) has been investigated based on Lipinski's rule of five and the prediction of Absorption, Distribution, Metabolism, and Excretion (ADME) [21]. The study found four oleanin triperpenoid's of 11-oxo- β-amyrin (ΔG = -9.8 kcal/mol), hederagenin-an (ΔG = -9.6 kcal/mol), 3β-acetoxyfriedelane (ΔG = -9.4 kcal/mol), and ursolic acid (ΔG = -9.5 kcal/mol) resulted in higher affinity

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compared to the treatment of lopinavir (ΔG = -6.2 kcal/mol) and remdesivir (ΔG = -7.2 kcal/mol) when molecularly docked in the main protease (Mpro) receptor. The prediction of ADME contributed to a potential oral medication of hederagenin, in which several primary amino acids were involved in the interactions, including methionine 49 and 165, proline 168, glutamine 189, arginine 188, and threonine 25.

Based on the study of the phytochemical screening of distilled water and parts of the agarwood plant (*A. malaccensis* Lamk), the secondary metabolites of glycosides were found to be responsible for the antimicrobial activity derived from several parts of agarwood including leaf, trunk, skinned stem and bark [22]. The distilled water from parts of *A. malaccensis* Lamk has antibacterial activity against *Streptococcus* mutants and can resist the bacteria's activity.

Conversely, Dahham, et al. [23] isolated β-caryophyllene from the essential oil *of A. crassna*, which belongs to the class of compounds known as terpenes. β-caryophyllene was recorded as the highest component at 8.1%, followed by 1-phenanthrenecarboxylic acid (7.1%) and 2-naphthalene-methanol (6.2%). The antimicrobial effect of β-caryophyllene was examined using human pathogenic bacterial and fungal strains. β-caryophyllene exhibited a strong antibacterial effect against all the tested microbial strains (*B. cereus*, *B. subtilis*, *S. aureus*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. niger*, *P. citrinum*, *R. oryzae*, *T. reesei*) and pronounced anti-fungal activity than kanamycin.

In recent years, the synthesis of nanoparticles using plant extracts as biopesticides has gained attention due to its low cost, eco-friendliness, and single method for the biosynthesis process. In Indonesia, Prasetya [24] explored the antibacterial activity of *A. agallocha* oil nanoemulsion against multidrug-resistant bacteria (MDR) and non-resistant antibiotics bacteria which include *E. coli* (ATCC 35218), *S. aureus* (ATCC 43300), *K. pneumoniae* (ATCC 700603), *E. coli* (ATCC 25922), *S. aureus* (ATCC 25923), and *K. pneuomoniae* (ATCC 8724. T). The study reported that with a 99.35% transmittance, the 1% agarwood oil nanoemulsion concentration had the lowest size, measuring 17.7 nm. The bacteria *S. aureus* ATCC 25923 and *K. pneumoniae* ATCC 8724 have inhibition zones of 2.6 mm and 3.3 mm, respectively. In comparison, the non-resistant *E. coli* ATCC 25922 was inhibited with an inhibition zone of 13.3 mm. Based on their findings, the researchers suggested that a higher concentration of the oil nanoemulsion may be required to boost its inhibitory action against MDR than non-resistant antibiotic bacteria. In another study on nanoparticles, Ga'al, et al. [25] investigated *Pogostemon cablin* essential oil (PcEO) and biosynthesized the silver nanoparticles (AgNPs) against larvae and pupae of the dengue and zika virus vector Aedes (Ae) albopictus including the AgNPs formation and their biophysical characterization. When compared to the tested essential oils, the biofabricated AgNPs showed the highest toxicity against larvae and pupae of Ae. albopictus. In particular, the LC50 values of AsEO ranged from 44.23 (I) to 166 (pupae), LC50 values of PcEO ranged from 32.49 (I) to 90.05 (IV), LC50 values of AsEO-AgNPs from 0.81 (I) to 1.12 (IV) and LC50 values of PcEO-AgPNs from 0.85 (I) to 1.19 (IV). Their study showed that control and treated larvae exhibited epithelial cells and brush borders that were highly affected by the fabricated AgNPs compared to the essential oils (AsEO and PcEO).

Meanwhile, Chen, et al. [26] reported that the quality of the agarwood originated from *A. sinensis* stimulated by the chemical method (S1), compared with the wild agarwood (S2) and healthy trees (S3). He and his friends also performed antimicrobial activities of that particular essential oil. From GC-MS chromatograms, they found that the essential oils of S1 and S2 were similar, with an abundance of constituents in sesquiterpenes and aromatic. However, the essential oil of S3 was high in fatty acids and alkanes. Essential oils of S1 and S2 had better inhibition activities towards B. subtilis and *S. aureus*. The three extracts were not active against *E. coli* even at a maximum study concentration of 2 mg/mL.

Lasiodiplodia theobromae (F) was utilised in a work by another researcher to stimulate *A. sinensis* (Lour.) Gilg to produce agarwood [27]. The chemical composition of F was investigated using GC-MS. Their findings demonstrated that essential oils obtained from the agarwood originating from *A. sinensis* induced by *L. theobromae* were highly similar to that wild agarwood (W), both in chemical composition and antimicrobial activity. The essential oil of F showed a similar composition to that of W, rich in sesquiterpenes and aromatic constituents. However, the essential oil of uninoculated

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healthy trees (H) was abundant in alkanes. Regarding its anti-fungal activity, essential oils of F and W were more potent inhibitors of *L. theobromae*, *F. oxysporum*, and *C. albicans* than the essential oil of H.

Being in the same family as *Aquilaria*, *G. versteegii* fruit extract was assessed for its antibacterial efficacy against *E. coli* and *S. aureus* Hidayati, et al. [28]. *G. versteegii* is a tree from the *Thymelaeaceae* family known to produce agarwood. The researcher used n-hexane, dichloromethane, and methanol for the extraction process and employed agar well diffusion and GC-MS methods for analysis. The dichloromethane extract, particularly at a 40% concentration, exhibited the most potent antibacterial activity, with a 13.17 mm inhibition zone against *S. aureus*, compared to 7 mm for *E. coli*. The extracts demonstrated total and partial inhibition against *S. aureus* and *E. coli*. GC-MS analysis identified compounds including palmitic, oleic, and stearic acid, bis-(2-ethylhexyl) phthalate, 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one, methyl octadec-9-enoate, squalene, and 2-monopalmitin derivatives. The study revealed a more potent antibacterial effect against *S. aureus*, particularly with the 40% concentration of dichloromethane extract, and identified various compounds in *G. versteegii* fruit extracts.

For studies that look at the ability of agarwood as an anti-inflammatory agent, 5,6,7,8-tetrahydro-2-(2-phenylethyl) chromones derived from agarwood of *A. sinensis* have been studied by Yu, et al. [29]. The anti-inflammatory activity was conducted in RAW264.7 cells by inhibiting the lipopolysaccharide (LPS)-induced nitric oxide (NO) release. All the new compounds showed significant anti-inflammatory effects, and compound 2 [(5S,6R,7S,8S)-8-chloro-5,6,7-trihydroxy-2-(2-phenylethyl)-5,6,7,8-tetrahydrochromone) recorded the strongest IC50 value of 3.46 μM.

Like so many other terpenes and natural products, sesquiterpenes have attracted significant interest because of their roles in biological systems and their utility for human use. In 2019, Yu, et al. [30] recorded the existence of eleven sesquiterpenes in *A. sinensis*. Among them, compound baimuxinol (1) was a new natural product, and this is the first time to report its ^{13}C NMR spectroscopic data. They recorded that compound 1,4 and 9 showed potential anti-inflammatory activities with IC50 values (2.5 ± 0. 35), (3.2 ± 0.2), (4.3 ± 0.56) μmol/L, respectively.

Flavonoids, widely present in medicinal plants and fruits, exhibit multiple pharmacological activities. A flavonoid compound, pillion, has been isolated from *A. sinensis* and investigated for its anti-inflammatory activity using in vitro and in vivo studies [31]. This compound was found to inhibit NF-κB and MAPK signalling pathways in LPS-activated macrophages, downregulated pro-inflammatory cytokines (e.g., TNF-α and IL-6), as well as enzymes (e.g., iNOS and COX-2) and suppressed the phenotypes and functions of activated macrophages (i.e., ROS production and phagocytic activity). Furthermore, pilloin attenuated the LPS-stimulated production of cytokines (i.e., TNF-α and IL-6) in serum and tissues of septic mice.

Wang, et al. [33] have done an extensive study on the anti-inflammatory effects of various compounds of *A. sinensis*. The methanolic extract of resinous *A. sinensis* revealed several chromones inhibited NF-κB activation in LPS-stimulated RAW 264.7 macrophages with relative luciferase activity values ranging from 0.31 ± 0.05 to 0.55 ± 0.09 compared to vehicle control of 1.03 ± 0.02. Moreover, some compounds could suppress LPS-induced NO production in RAW 264.7 cells with no cytotoxicity effect after 24 hours of treatment [33]. In addition, several chromone-related compounds exhibited more than 80% inhibition towards superoxide anion generation by human neutrophils in response to formyl-l-methionyl-l-leucyl-l-phenylalanine (fMLP) at 50 μM [35]. Moreover, methanolic extract of several compounds of *A. sinensis*' stem barks inhibited (IC50 ≤ 12.51 μM) superoxide anion generation in response to fMLP/cytochalasin B in human neutrophils. In addition, 7-Hydroxy-6-methoxy-2-(2-phenylethyl)chromone, velutin, 3'-hydroxygenkwanin, 6,7-di-methoxy-2-(2-phenylethyl)chromone, and ergosta-4,6,8(14),22-tetraen-3-one exhibited the most effective between the isolates (IC_{50} values ≤ 15.25 μM) through fMLP/CB-induced elastase release inhibition [36].

Anti-inflammatory effects of 2-(2-phenylethyl) chromone derivatives have also been reported by Huo, et al. [37] using ethanolic extract of resinous *A. sinensis*. Their preliminary analysis of the structure-activity relationship revealed that chlorine substituent and epoxy group on the A-ring

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could be correlated with the anti-inflammatory activity of 5,6,7,8-tetrahydro-2-(2-phenylethyl)-chromones. Compounds 2–4, 11, 12, and 15 exhibited significant inhibition of NO production in LPS-stimulated RAW264.7 cells with IC50 values of 1.6–7.3 μM. Additionally, these compounds showed no significant cytotoxicity (up to 100 μM) after 24 hours of LPS treatment, as assessed using the MTT method. In another study utilizing the same ethanolic extraction method, several compounds also exhibited significant inhibition of NO production in LPS-stimulated RAW264.7 cells with IC_{50} values ranging from 7.0 to 12.0 μM and no cytotoxicity effect (up to 80 μM) after 24 hours of LPS treatment [34]. Huo, et al. [32] have isolated fifteen previously undescribed 2-(2-phenylmethyl)chromone dimers, along with two known analogues from *A. sinensis* using an LC-MS-guided fractionation procedure. As one might have expected, these isolated compounds exhibited significant inhibition of NO production in LPS-stimulated RAW264.7 cells with IC_{50} values in the range 0.6–37.1 μM, which implied their potential leads for the development of anti-inflammatory agents. These findings suggest the potential anti-inflammatory properties of these chromone derivatives, emphasizing their therapeutic potential without inducing cytotoxic effects at relevant concentrations.

The leaves of *A. sinensis* were previously reported to have analgesic and anti-inflammatory activities [42]. Leaves of *A. sinensis* also contain eight α-glucosidase inhibitors [43], which might be used as traditional medicine to treat diabetes. However, based on an in vivo study by Sattayasai, et al. [38] using the rat paw assay at 800 mg/kg, methanolic *A. crassna* leaves extract had no anti-inflammatory activity. Nevertheless, the extract possesses antipyretic, analgesic and anti-oxidative properties.

A study published by Peng, et al. [39] on incense smoke from agarwood exhibited low amounts of TNF-α and IL-1α by normal inactivated RAW264.7 cells; however, with LPS exposure, higher amounts were obtained after 24 hours of incubation. Treatment with indomethacin showed AAW, BCDA, and AWIT produced a concentration-dependent decrease at concentrations of 20, 40, and 80 μg/mL. Compared to the normal group, TNF-α and IL-1α levels were significantly higher ($P < 0.05$ or $P < 0.01$), exhibiting better anti-inflammatory effects.

4. Materials and Methods

Original articles were searched in three databases (PubMed, Scopus and Google Scholar) from the year 2013 to 2023 using the Medical subject heading (MeSH) terms “agarwood”, crossed with the term “antimicrobial” and/or “anti-inflammatory”. Publications with available full paper were reviewed and only studies published in English and Malay were considered for assessment. Papers on human and clinical trials related to agarwood were included. Letters to the editor and reviews, however, were not included. Duplicate articles were eliminated.

5. Limitations of The Study

This review paper has several limitations because some information cannot be fully obtained from the original article. The use of various tested materials, such as the type of solvent used in the extraction of either ethanol or methanol, essential oil, and nanoemulsion, also makes more accurate conclusions difficult to make. The small number of studies also limits the ability to identify the effectiveness of agarwood.

6. Conclusions

We have found twenty-seven relevant studies worldwide related to agarwood as a potential anti-inflammatory and antimicrobial consisting of chemical composition, in silico, in vitro, in vivo, and combined in vitro and in vivo. We found that active compounds in agarwood positively affect its effectiveness. However, more studies and evidence need to be done with a particular emphasis on intervention studies performed in the future to improve knowledge and understanding of agarwood and its isolates, which are worthy of further biomedical investigation and could be developed as potential candidates for the treatment or prevention of various microbial and inflammatory diseases.

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7. Future Perspective

The future perspective of agarwood as an antimicrobial and anti-inflammatory agent is promising, based on findings driven by ongoing research. In addition to being applicable and potential applications in various fields, agarwood could potentially **be** used in pharmaceuticals, cosmetics, and food preservation due to its antimicrobial effects. It can also potentially be used as an alternative to synthetic agents. With increasing concerns over antibiotic resistance, natural products like agarwood could serve as alternatives to synthetic antimicrobial agents. Agarwood has also been traditionally used in various cultures for its anti-inflammatory properties; hence, it has the potential to treat inflammatory conditions such as arthritis, skin inflammation, and gastrointestinal disorders.

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