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Review Article

Review of Potential Pharmacological Activities of Agarwood Plants (Aquilaria Sp.) as Herbal Medicine and Development as Potential Herbal Preparations

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ABSTRACT

Aquilaria spp is a tropical plant known for producing valuable aromatic resin. Although the resin has been widely used, the leaves of Aquilaria, especially Aquilaria sinensis, Aquilaria malaccensis, and Aquilaria crassna, are often considered waste. However, recent studies have shifted the focus to the pharmacological potential of these leaves, highlighting their use in traditional medicine and their potential as active ingredients in herbal medicine development. These Aquilaria species have demonstrated a broad spectrum of bioactivity and are currently being explored for inclusion in modern drug delivery systems, including nanoemulsions and nanoencapsulation techniques. Therefore, this review aims to systematically investigate the pharmacological potential of Aquilaria leaves and contribute to the scientific foundation for future efforts in herbal medicine development and drug formulation. To collect relevant scientific information, a comprehensive search was conducted using major academic databases, including ScienceDirect, Google Scholar, Scopus, and PubMed, with a focus on leaf extracts from the three species mentioned above. The results indicate that Aquilaria malaccensis, Aquilaria sinensis, and Aquilaria crassna possess various pharmacological actions, including antioxidant, cytotoxic, anti-inflammatory, antibacterial, and antidiabetic properties. These pharmacological benefits can be attributed to bioactive secondary metabolites, including flavonoids such as apigenin, quercetin, and kaempferol. In conclusion, Aquilaria leaves have significant potential as a source of therapeutic agents for the development of herbal medicines. Further multidisciplinary studies are recommended, including biochemical characterisation, bioavailability studies, clinical investigations, and the development of modern drug delivery technologies, such as nanoparticle-based systems, which can enhance the absorption and therapeutic efficacy of active compounds.

Keywords: *Aquilaria malaccensis, Aquilaria sinensis, Aquilaria crassna,* pharmacological activity, secondary metabolite

Introduction

Aquilaria species, belonging to the family Thymelaeaceae, play an important ethnomedicinal role in various traditional healing systems across Asia. Presently, 21 species have been documented within this genus, several of which are used by indigenous communities due to the therapeutic properties. In general, taxonomic studies are essential for understanding genetic diversity and determining the origin of agarwood-producing species, thereby supporting *Aquilaria* conservation efforts. Among the various species, *Aquilaria malaccensis*, *Aquilaria crassna*, and *Aquilaria sinensis* are the most extensively studied. In the Indonesian flora, agarwood-producing plantsare primarily distributed among three dominant families, namely Thymelaeaceae, Euphorbiaceae, and Fabaceae, reflecting both taxonomic diversity and ecological adaptation.

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A total of 33 agarwood species are found across Asia, with 27 being endemic to Indonesia[2]. The high economic value of agarwood primarily due to the aromatic resin has led to overexploitation, bringing several species to the brink of extinction, while the leaves are often discarded. Historically, agarwood leaves have been used in traditional medicine as an ingredient in herbal tea due to the elevated antioxidant content[3]. The three most common Aquilaria species are *Aquilaria sinensis, Aquilaria malaccensis*, and *Aquilaria crassna*, which are mostly used in herbal medicine. The secondary metabolite compounds present in these three species show potential pharmacological activity. In general, the extraction method used plays an important role in obtaining secondary metabolite compounds from medicinal plants. Based on the description above, this review aimed to examine pharmacological properties attributed to *Aquilaria* species, particularly the three most prominent sources of agarwood namely *Aquilaria sinensis, Aquilaria malaccensis*, and *Aquilaria crassna*. It also evaluates the bioactive compounds identified in these species. A unique aspect of this review is the focus on pharmacological potential of *Aquilaria* leaves, an area that has received limited attention in previous studies. The results will provide a foundational reference for subsequent studies on agarwood and facilitate the advancement of *Aquilaria*-based drug delivery systems, such as phytosome, microparticulate, and nanoparticulate formulations.

Materials and Methods

The review methodology was designed to comprehensively evaluate and integrate existing knowledge on the pharmacological potential of agarwood plants. By adopting this approach, the study secures an in-depth and consistent examination of the issue. The assessment of the methodology comprises careful consideration of various important criteria to ensure reliable and valid results.

Strategy for literature search

Major scientific databases were used to undertake a thorough and methodical evaluation of the literature, including *PubMed*, *ScienceDirect*, *Scopus*, and *Google Scholar*[4]. The search strategy carried out includes the use of specific keywords such as *"pharmacological activity of Aquilaria"*, *"pharmacological activity of Aquilaria malaccensis"*, *"pharmacological activity of Aquilaria sinensis"*, and *"pharmacological activity of Aquilaria crassna"*. To ensure the relevance and timeliness of the data, only articles published within a 10-year range (2015–2025) were included in the review. Predefined inclusion and exclusion criteria were rigorously applied to identify studies that were methodologically sound and consistent with the objectives of the review. Inclusion criteria consisted of Original articles focused on *Aquilaria* species, studies that reported pharmacological or bioactivity data, articles published in peer-reviewed journals within the 2015–2025 range, and full-text availability in English or Indonesian. A totals 75 articles were selected by the author for review based on a set of inclusion and exclusion criteria. Exclusion criteria included reviews, editorials, or opinion pieces, studies lacking clear data on pharmacological activity, duplicates, and non-peer-reviewed sources[5].

Extraction and synthesis of data

A comprehensive data extraction procedure was applied to the selected journal articles to collect information on pharmacological potential and secondary metabolite content of *Aquilaria* species, particularly *Aquilaria malaccensis*, *Aquilaria sinensis*, and *Aquilaria crassna*. Data synthesis was carried out by the classification and integration of relevant results, followed by the construction of a coherent and logical narrative. This approach ensured the generation of clear, structured, and meaningful insights from the reviewed literature[5].

Evaluation of the quality of the included reviews

An in-depth evaluation on the quality of each selected study was conducted based on predefined criteria. The reliability of the data extracted from each study was assessed by examining methodological rigor, transparency of reporting, and the robustness of the experimental design. This evaluation was essential to ensure the validity and credibility of the result synthesized[5].

Diversity analysis of potential pharmacological activity

A comprehensive investigation into potential pharmacological activity was conducted to examine the diversity of *Aquilaria* species with therapeutic value. Accordingly, it is essential to classify the three most frequently studied species, namely *Aquilaria malaccensis*, *Aquilaria sinensis*, and *Aquilaria crassna*. This approach enhanced the understanding of individual pharmacological potentials[5].

Evaluation of secondary metabolite compounds for potential pharmacological activity

This review methodology comprised a critical evaluation of the secondary metabolite content in *Aquilaria malaccensis*, *Aquilaria sinensis*, and *Aquilaria crassna*, responsible for potential pharmacological activity. The focus of the review is on the underlying biological processes associated with the formation of these secondary metabolites and pharmacological potential for development into conventional pharmaceutical formulations[5].

Ethnomedicinal investigations and pharmaceutical development

To develop both ethnomedicinal applications and pharmaceutical formulations, the secondary metabolite content of gaharu (*Aquilaria*) serves as a foundational knowledge base for both traditional and modern uses. An extensive evaluation was conducted on relevant studies, emphasizing pharmacological potential and bioactive compounds that can be further developed into comprehensive pharmaceutical preparations with high commercial value[5].

Determination of existing study gaps

This review used a structured methodology to identify gaps in the existing literature, thereby providing a solid foundation for future studies. Accordingly, this review actively contributes to the ongoing development of knowledge and understanding of potential pharmacological activity of *Aquilaria* species[5].By adhering strictly to predefined criteria, the methodology ensures a thorough, transparent, and comprehensive evaluation of potential pharmacological activity. This methodological approach enhances the reliability of the synthesized data, making it a valuable resource for students, academics, and professionals interested in pharmacological potential of *Aquilaria malaccensis*, *Aquilaria sinensis*, and *Aquilaria crassna*. The results are expected to support the development of modern pharmaceutical formulations derived from gaharu, with high therapeutic and commercial value[5].

Results and Discussion

This review intends to furnish readers with an extensive summary of the varied pharmacological activity of different Aquilaria species, focusing specifically on Aquilaria malaccensis, Aquilaria sinensis, and Aquilaria crassna. These species are known for rich content of bioactive compounds, which may offer significant health benefits. The following section presents a summary of pharmacological potentials identified in previous scientific studies.

Antioxidant activity

A study explored the possible pharmacological activity specifically antioxidant properties of Aquilaria malaccensis leaves using several extraction procedures and solvents of differing polarity, including distilled water, ethanol, methanol, chloroform, and n-hexane. The methanol extract, produced by solvent polarity separation and freeze-drying, showed the best antioxidant activity, according to the assays. Compared to ethanol and aqueous extracts (AE), the methanol showed significantly stronger free radical scavenging capacity, while the chloroform and n-hexane showed comparatively lower activity. A detailed comparison of the antioxidant activity of each extract is presented in Table 1[6]. Another study investigating a combination of black tea, green tea, and *Aquilaria malaccensis* leaves showed significant antioxidant activity, with ascorbic acid used as the control. The IC_{50} value of standard ascorbic acid was reported as 4.366 mg/mL. The results showed that the IC_{50} values of green tea, *Aquilaria* leave, and black tea extract were all lower compared to ascorbic acid, indicating stronger antioxidant potential compared to the standard control[7].

In a study of *Aquilaria crassna*, the antioxidant activity of leaves at different stages of maturity was compared. Extraction was performed using Soxhlet apparatus with chloroform and methanol as solvents. The results showed that methanol extract from mature leaves had the highest antioxidant activity, with an IC_{50} value of 17.39 ± 1.43 µg/mL. Compared to methanol extracts from younger leaves and all chloroform extracts regardless of maturity stage, the mature extract showed significantly greater antioxidant potential, underscoring the influence of leave maturity and solvent type on antioxidant efficacy[8]. In a different investigation, n-hexane was used for extraction by maceration, and then a solvent mixture with ethyl acetate (90:10) was used for isolation. Two distinct assays, DPPH and ABTS, were used to evaluate the samples antioxidant activity. The results showed that the sample had IC_{50} values of 3.55 ± 1.64% in the DPPH assay and 5.07 ± 1.00% in the ABTS assay.

Table 1: DPPH radical scavenging activity of *Aquilaria malaccensis* in different solvent polarities and drying methods[6]

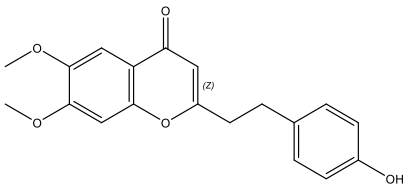
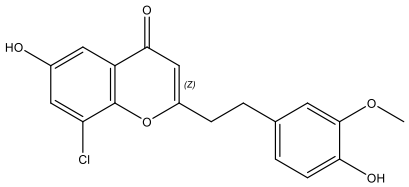
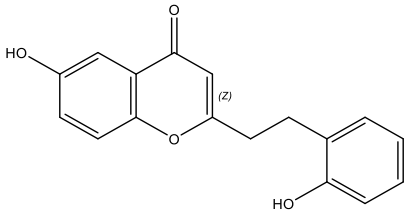
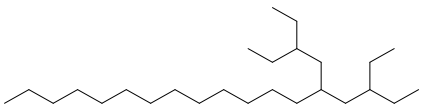
Sample	DPPH radical scavenging activity			
	Air Dry (AD)		Oven Dry (OD)	
	IC_{50} (µg/ml)	Inhibition (%) (0.5 mg/ml)	IC_{50} (µg/ml)	Inhibition (%) (0.5 mg/ml)
DW	303.57 ± 3.11[a]	72.87 ± 4.75[a]	nd	38.06 ± 1.34[c]
ETOH	201.09 ± 4.54[b]	90.56 ± 1.51[b]	152,17 ± 3,55[d]	84.29 ± 0.44[a]
MEOH	84.55 ± 2.93[c]	92.20 ± 1.55[b]	77,21 ± 4,88[c]	91.27 ± 0.42[c]
CHL	nd	32.59 ± 4.37[c]	nd	47.81 ± 0.42[c]
HEX	nd	34.76 ± 1.07[c]	nd	32.83 ± 0.49[c]
Positive control	IC_{50} (µg/ml)		Inhibition (%) (0,5 mg/ml)	
Quercetin	10.65 ± 0.25[f]		94.15 ± 1.21[b]	

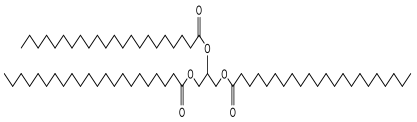
Values are expressed as mean ± standard deviation (n=3), nd means not detected

This difference in IC_{50} values suggests varying sensitivities between the two assays in evaluating the antioxidant capacity of the sample[9]. Another study on *Aquilaria crassna* investigated antioxidant activity of leave extracts prepared by boiling 400 ml of water for 30 minutes. Three distinct assays, namely DPPH, ABTS, and FRAP were used to evaluate the antioxidant activity. The DPPH assay yielded an IC_{50} value of 7.25 ± 29.77 µg/mL, while the ABTS assay produced a significantly higher value of 218.93 ± 29.77 µg/mL. The FRAP assay also yielded a value of 1.18 ± 0.07 µmol Fe^{2+}/mg of dry extract. These differences underscore the varying sensitivities and mechanisms of each assay in measuring the antioxidant capacity of *Aquilaria crassna* leave extract[10].

The compounds isolated from *Aquilaria sinensis* were identified using FTIR, MS, and NMR methods, with the antioxidant activity evaluated using the ABTS assay [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)]. Among the twelve compounds analyzed, three compounds showed significantly exhibited significantly stronger antioxidant activity than the others, as shown in table 2

Table 2: Compounds identity with antioxidant activity

No	Antioxidant activity compounds	Structure
Page 7		
1	2-(4-hydroxyphenethyl)-6,7-dimethoxy-4H-chromen-4-one	
2	8-chloro-6-hydroxy-2-(4-hydroxy-3-methoxyphenethyl)-4H-chromen-4-one	
3	6-hydroxy-2-[2-(2-hydroxyphenyl)ethyl]chromone	
Page 8		
1	3-ethyl-5-(2-ethylbutyl) octadecane	

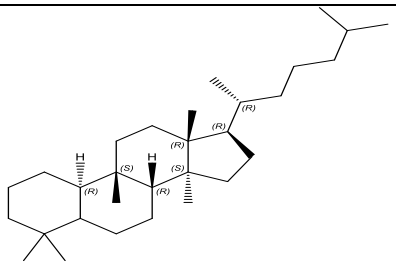
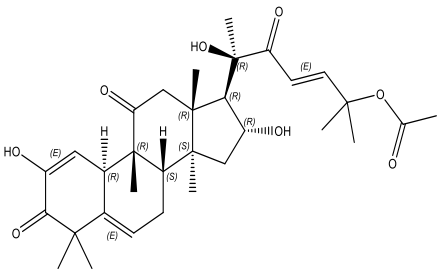
2	oleic acid 3-(octadecyloxy) propyl ester	
3	docosanoic acid 1,2,3-propanetriyl ester	

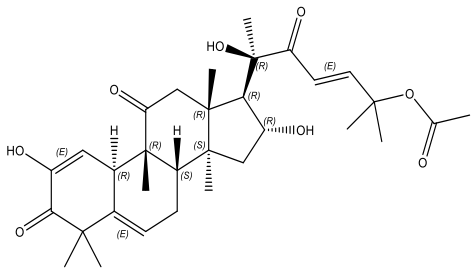
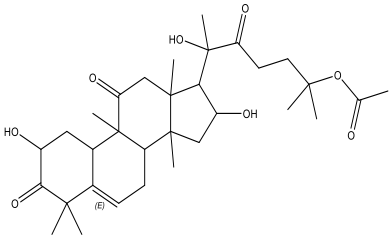
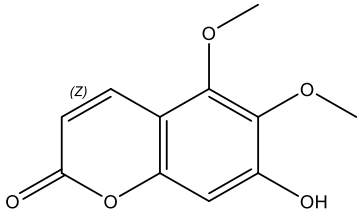
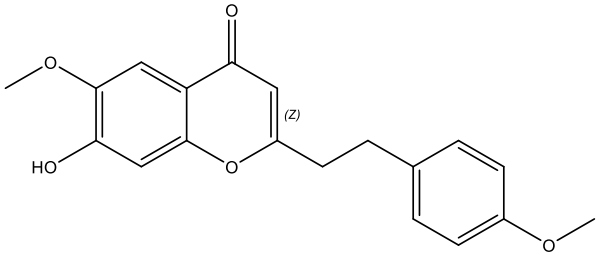
This variation in activity underscores potential of these specific compounds as promising candidates for developing antioxidant agents derived from *Aquilaria sinensis*[11]. Another study on *Aquilaria sinensis* leaves, also known as 'Qi-Nan,' evaluated antioxidant activity using both DPPH and ABTS radical scavenging assays. With a DPPH assay IC_{50} value of 12.64 µg/mL, the extract showed a far better antioxidant action than the ABTS assay, which had a higher IC_{50} value of 66.58 µg/mL. This difference suggests that the extract has greater potency against DPPH radicals than ABTS radicals, showcasing variability in antioxidant capacity depending on the assay method used. Through studies on the leave extracts of *Aquilaria crassna*, *Aquilaria microcarpa*, and *Gyrinops versteegii*, a variety of secondary metabolites have been found, including alkaloids, flavonoids, tannins, saponins, glycosides, and steroid/triterpenoid glycosides. Potential antioxidant properties of each of these substances were evaluated. With IC_{50} values of 30.01 µg/mL and 29.33 µg/mL, respectively, the ethanol extracts of *Aquilaria crassna* and *Aquilaria microcarpa* showed similar antioxidant efficacy, although *Gyrinops versteegii* demonstrated a marginally higher IC_{50} value of 31.63 µg/mL. Despite the slight variations, these results show that *Aquilaria microcarpa* has the highest antioxidant activity among the three species[13]. The volatile components of *Aquilaria sinensis* identified by GC-MS are shown in table 2, while the alcohol extract contains ethyl benzoate ester, ethyl hexadecanoate ester, oleic acid, and n-hexadecane. Antioxidant activity assays showed that the volatile components of *Aquilaria sinensis* have significantly higher antioxidant activity compared to the non-volatile alcohol extract, underscoring the superior potential of the volatile fraction in scavenging free radicals[14]. The antioxidant activity of *Dennettia tripetala* root extract extracted with ethanol was assessed in a different investigation. The extract capacity to scavenge hydrogen peroxide (H_2O_2) radicals was used to evaluate the antioxidant potential, with ascorbic acid acting as the reference standard. The extract contains a variety of secondary metabolites, including alkaloids, flavonoids, tannins, and saponins, according to phytochemical screening. Additionally, it was found to be rich in polyphenols and vitamin E, both of which are known for antioxidant properties. The H_2O_2 scavenging assay showed that the extract had antioxidant activity with an IC_{50} value of 86.79 µg/mL. In contrast to the typical antioxidant molecule, this suggests a moderate antioxidant potential. The results offer experimental proof of *Dennettia tripetala* root extract capability, showing that it may be used as a natural antioxidant source in pharmaceutical or nutraceutical applications[15].

Cytotoxic activity

Soxhlet extraction with solvents of different polarity, specifically ethanol, ethyl acetate, and chloroform, has been used in studies on Aquilaria malaccensis. The MTT test was used to assess each extract cytotoxicity. With the lowest IC_{50} value of 111.4 µg/mL, the chloroform extract showed the most potent cytotoxic impact. In contrast, the aqueous leave extract showed comparatively lower cytotoxic activity. These results suggest that the chloroform extract of *Aquilaria malaccensis* leaves has a higher cytotoxic potential than those obtained using other solvents[16]. A study on the flowers of *Aquilaria sinensis* was conducted using both aqueous and ethanolic extraction methods. The extracts were subsequently partitioned with solvents of varying polarity and subjected to column chromatography for the isolation of active compounds. Cytotoxic evaluations of the isolated fractions were conducted using multiple human lung cancer cell lines to determine potential anticancer effects, including SPC-A-1, NCL-H520, and A549. This study identified several bioactive compounds, which can be seen in Table 3.

Table 3: Compounds identity with cytotoxic activity

No	Cytotoxic activity compounds	Structure
1	Cucurbitane (8R,9S,10R,13R,14S,17R)-4,4,9,13,14-pentamethyl-17-[(2R)-6-methylheptan-2-yl]-2,3,5,6,7,8,10,11,12,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthrene	
2	23,24-dihydrocucurbitacin E [(6R)-6-[(8S,9R,10R,13R,14S,16R,17R)-2,16-dihydroxy-4,4,9,13,14-pentamethyl-3,11-dioxo-8,10,12,15,16,17-hexahydro-7H-cyclopenta[a]phenanthren-17-yl]-6-hydroxy-2-methyl-5-oxoheptan-2-yl] acetate	

3	Cucurbitacin E [(E,6R)-6-[(8S,9R,10R,13R,14S,16R,17R)-2,16-dihydroxy-4,4,9,13,14-pentamethyl-3,11-dioxo-8,10,12,15,16,17-hexahydro-7H-cyclopenta[a]phenanthren-17-yl]-6-hydroxy-2-methyl-5-oxohept-3-en-2-yl] acetate	
4	Cucurbitacin B [6-(2,16-dihydroxy-4,4,9,13,14-pentamethyl-3,11-dioxo-2,7,8,10,12,15,16,17-octahydro-1H-cyclopenta[a]phenanthren-17-yl)-6-hydroxy-2-methyl-5-oxoheptan-2-yl] acetate	
5	7-hydroxy-5,6-dimethoxychromen-2-one	
6	7-hydroxy-6-methoxy-2-{2-(4-methoxyphenyl)ethyl}-4H-1-benzopyran-4-one	

Among these compounds, cucurbitacin B and E showed the most potent cytotoxic effects, significantly inhibiting cell viability across all tested cancer cell lines. In contrast, the other isolated compounds showed moderate to low cytotoxic activity. These results suggest that specific cucurbitacins from *A. sinensis* flowers hold stronger therapeutic potential and merit further investigation as lead compounds for lung cancer treatment[17]. Furthermore, the study showed that four bioactive flavonoids apigenin-7,4′-dimethyl ether, genkwanin, quercetin, and kaempferol have significant cytotoxic activity against hepatocellular carcinoma cells. Among these compounds, quercetin and kaempferol showed comparatively stronger cytotoxic effects, suggesting potential for anticancer therapy. In addition to the cytotoxic properties, *Aquilaria sinensis* extracts from both the leaves and stems also contain diverse phytochemical constituents with promising pharmacological potential, particularly as anti-inflammatory agents, showcasing the plant multifaceted therapeutic value[18,19]. To assess selectivity and therapeutic relevance, the cytotoxic activity of extracts, fractions, and isolates derived from *Aquilaria sinensis* were investigated in a different study using different lung cancer cell lines, such as A-549, NCI-H520, SPC-A-1, and A549/Taxol (a drug-resistant variant), in comparison with the normal human bronchial epithelial cell line BEAS-2B. The results showed that several fractions and isolates had stronger cytotoxic potential against the drug-resistant A549/Taxol cells compared to other cancer cell lines. In contrast, the effects on BEAS-2B cells were relatively lower, showing a promising degree of selectivity for the bioactive compounds present in *Aquilaria sinensis*[20]. A study compared leave extracts from three *Aquilaria* species obtained through hydrodistillation and solvent extraction. The biological activity of the tested extracts was assessed on human peripheral blood mononuclear cells (PBMCs) through cytotoxicity and genotoxicity evaluations using the MTT and comet assays, respectively. Among the evaluated species, the methanolic extract of *Aquilaria malaccensis* showed the most potent cytotoxic effect, with an IC_{50} value of 24.5 mg/mL and an LD_{50} of 4.537 mg/kg. These results suggest that *A. malaccensis* has a higher toxic potential compared to other *Aquilaria* species evaluated, showing the presence of more potent bioactive compounds in the extract[21]. A study on the leaves of *Aquilaria sinensis* resulted in the isolation of 28 compounds, including terpenoids, phenolics, lipids, chromones, flavonoids, glycosides, and phenophors. Among these compounds, Pheophorbide A (PA) showed a prominent activity in modulating the expression of MMP-2 and MMP-9. The upregulation of these proteins is associated with tumor angiogenesis, inflammation, cancer metastasis, as well as tissue regeneration processes including wound healing. Compared to other isolated compounds, PA significantly underscores the critical role of the C-17 position in determining bioactivity. The significant modulation of MMP-2 and pro-MMP-9 by PA suggests potential to inhibit scar formation, thereby underscoring therapeutic value for development in topical pharmaceutical formulations[22]. Another study on the insecticidal toxicity of essential oil from *Pyrenacantha staudtii* Hutch. & Dalz (Icacinaceae) aimed to assess the effectiveness and safety of the chemical constituents against insect pests. The essential oil was extracted through hydrodistillation using a Clevenger apparatus and subsequently analyzed by gas chromatography-mass spectrometry (GC-MS). The analysis showed that the oil comprises monoterpenoids, sesquiterpenoids, and fatty acids, with hexadecanoic acid (30%) and tetradecanoic acid (22%) identified as the major components. Insecticidal activity assays showed that the essential oil had 80% mortality against *Rhyzopertha dominica* and 60% against *Tribolium castaneum*. The observed insecticidal effect is presumed to be associated with the presence of active chemical

constituents and the susceptibility of the target insect species. The presence of limonene, known for toxicity to Coleopteran insects, along with the high concentration of fatty acids, is likely to contribute toward the oil toxic effects against *R. dominica*[23].

Antibacterial activity

The antibacterial properties of *Aquilaria malaccensis* leaves were investigated across different maturity stages to determine variations in bioactivity. Leave extracts were obtained using chloroform and methanol solvents through Soxhlet extraction and subsequently tested against *Escherichia coli* and *Staphylococcus aureus*. Among the tested extracts, the chloroform fraction showed the most pronounced antibacterial effect, as evidenced by inhibition zone diameters of 10.83 mm against *S. aureus* and 9.92 mm against *E. coli*. This antibacterial efficacy was attributed to the presence of bioactive compounds, specifically alkaloids and terpenoids. Compared to the methanol extract, the chloroform extract showed superior potency, underscoring the influence of solvent polarity and leave maturity on bioactive compound extraction and antibacterial effects[8]. In another investigation, *Aquilaria malaccensis* leave material was extracted using 96% ethanol through maceration, and the resulting extract was evaluated for antibacterial efficacy against *S. epidermidis*, *S. aureus*, and *P. acnes*. The results showed that extracts at concentrations of 5% and 2.5% produced the largest inhibition zones against *Staphylococcus aureus*, measuring 19.90 ± 2.08 mm and 16.40 ± 3.11 mm, respectively. Compared to the antibacterial effects on *S. epidermidis* and *P. acnes*, the extract showed significantly higher potency against *S. aureus*, showing selective antibacterial activity and a concentration-dependent effect of the extract[24]. The essential Oil of *Aquilaria crassna* has pharmacological activity as antimicrobial[25] This study investigated the antimicrobial efficacy of combined extracts from tea leaves (both green and black varieties) and agarwood (*Aquilaria*) leaves against multidrug-resistant pathogens. Phytochemical screening of the extracts identified a variety of secondary metabolite classes, including alkaloids, tannins, flavonoids, glycosides, and saponins. Comparative antimicrobial assays demonstrated that the combined extracts showed significant inhibitory effects against multidrug-resistant (MDR) pathogens, including both Gram-negative and Gram-positive bacteria, as well as pathogenic fungi. The results suggest that the combination of tea and agarwood leave extracts may exert a synergistic effect on drug-resistant pathogens, underscoring potential as alternative or adjunct therapeutic agents for infections caused by these resistant microorganisms[7]. The antibacterial evaluation of *Aquilaria sinensis* essential oil showed a stronger inhibitory effect against Gram-positive bacteria relative to Gram-negative bacteria. This differential activity is likely associated with the volatile constituents of the essential oil, including 3-ethyl-5-(2-ethylbutyl)-octadecane, 3-(octadecoxy) propyl oleate ester, and 1,2,3-propane-triyl decanoate ester, which are presumed to exert a more effective mechanism of action on the cell wall structure of Gram-positive bacteria[14].

The inhibitory activity of the α-glucosidase enzyme

The antidiabetic effects of *Aquilaria crassna* leave AE were investigated through in vitro and in vivo experiments. The in vitro α-glucosidase inhibition assay indicated significant activity with an IC_{50} of 36.3 µg/mL, showing competitive potential compared to standard enzyme inhibitors. Subsequently, the in vivo study on streptozotocin-nicotinamide (STZ-NA) induced rats administered doses of 500 and 1000 mg/kg showed a more pronounced blood glucose reduction at the 1000 mg/kg dose. At this dose, blood glucose levels decreased by approximately 66% and 86% after oral administration of 2 g/kg glucose at 30 and 60 minutes, respectively. These results confirm that *Aquilaria crassna* leave extract has superior therapeutic potential as an antidiabetic agent compared to the lower dose, showing promising effects for pharmaceutical development[26]. Phytochemical investigation of the ethyl ether extract from *Aquilaria* plants resulted in the identification of six sesquiterpenoids reported for the first time, in addition to four known sesquiterpenoids and six established 2-(2-phenylethyl) chromones. Among these compounds, numbers 2, 4, 5, and 7 through 10 showed significantly stronger inhibitory activity against α-glucosidase compared to the others. The combination of enzyme kinetic assays and molecular docking studies showed that compound 5a, identified as a novel zizaane-type sesquiterpenoid, inhibits α-glucosidase through a non-competitive mechanism. This compound suppresses enzymatic activity by blocking the entrance to the active site through specific interactions, thereby providing a distinct and more targeted inhibitory mechanism than the other compounds in the extract[27]. The investigation evaluated the antidiabetic activity of methanol extracts from *Aquilaria malaccensis* leaves, with particular attention to how variations in extraction techniques affect the composition of bioactive constituents. The results showed that the methanol extract obtained through air-drying had the most significant α-glucosidase inhibitory activity compared to those obtained through other methods. This observation was further supported by the IC_{50} value for α-glucosidase inhibition, determined to be 196.31 ± 4.11 µg/mL, underscoring the superiority of the air-drying method in producing extracts with enhanced antidiabetic potential[6]. The inhibitory effects of AE and polysaccharides (PS) from leaves of multiple *Aquilaria* species on α-glucosidase enzyme activity were evaluated, and the corresponding IC_{50} values were calculated to measure the degree of inhibition. The results showed that extracts from *Aquilaria malaccensis* and *Aquilaria sinensis* had significantly higher inhibitory activity compared to *Aquilaria subintegra*, with IC_{50} values ranging from 0.014 to 0.78 mg/mL. Among all AE tested, *Aquilaria malaccensis* showed the most potent inhibition, while *Aquilaria subintegra* had the least. Similarly, PS from *Aquilaria malaccensis* showed the strongest α-glucosidase inhibitory effect, while those from *Aquilaria subintegra* had the weakest activity. These results underscore the variation in inhibitory potential among different *Aquilaria* species and potential as natural α-glucosidase inhibitors[28].

Leave tea from *Aquilaria sinensis* (ALTE) has been showed as an effective tea substitute, based on studies conducted with 70% ethanol extracts of ALTE. These studies showed that the extract has superior anti-α-glucosidase activity and significantly enhances glucose uptake in T3-L1 preadipocyte cells. The biological activity is attributed to the phenolic profile of ALTE, which consists of compounds as shown in table 4. Compared to other tea sources, ALTE has competitive bioactive potential as a natural anti-diabetic agent[29]. The flavonoid extract from *Aquilaria sinensis* 'Qi-Nan' leaves has been showed to possess significant potential in regulating blood glucose levels and treating diabetes mellitus, with an IC_{50} value of 38.76 µg/mL. Compared to flavonoid extracts from other sources, this extract has promising inhibitory activity against enzymes associated with glucose regulation, underscoring potential as an effective natural antidiabetic agent[12]. This study explored the antidiabetic potential of leave extracts from various *Aquilaria* species, with particular emphasis on the phenolic constituents, including iriflophenone glycosides, mangiferin, and genkwanin. The analysis and identification of these compounds were performed using HPLC and LC/MS techniques. Comparative results of the chemical composition and α-glucosidase inhibitory activity showed that *A. rugosa* had a higher content of iriflophenone glycosides compared to *A. sinensis* and *A. crassna*, suggesting a stronger potential for antidiabetic effects in *A. rugosa*[30].

Anti-inflammatory activity Immunomodulatory assays were conducted on murine macrophage RAW 264.7 cells using leave extracts obtained through supercritical carbon dioxide extraction. The objective of this study was to assess cytokine and nitrite production, particularly TNF-*α*, and to examine the expression of IL-1*β*, IL-6, IL-10, iNOS, along with COX-2 as key inflammatory mediators. The observed effects can be attributed to the chemical composition of the extract, which primarily includes benzoic acetic acid (11.91%), benzoic acid (10.02%), squalene (8.75%), patchouli alcohol (3.32%), phenolic acid (2.49%), galactitol (2.29%), aspidinol (1.84%), and geranylisovalerate (1.13%)[31].

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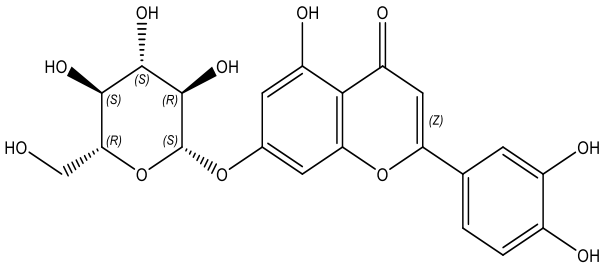
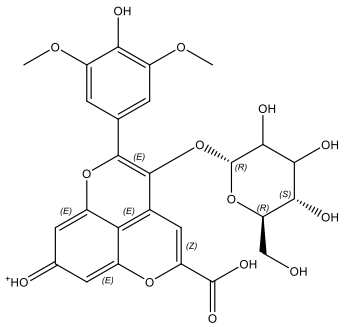
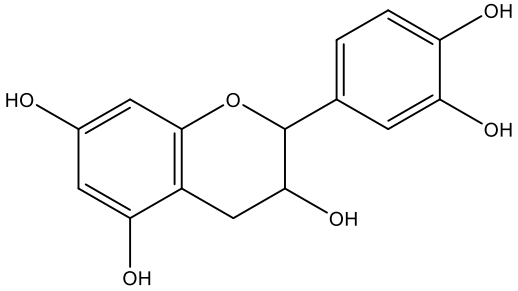
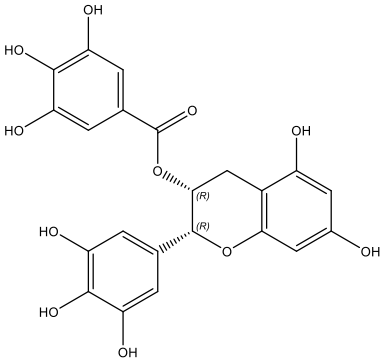
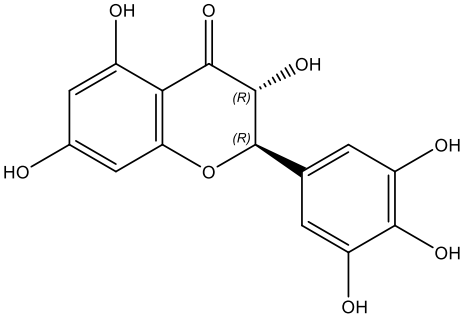
Table 4: Compounds Identity with inhibitory activity

No	Inhibitory activity compounds	Structure
1	Cynaroside-3,5-diglucose 2-(3,4-dihydroxyphenyl)-5-hydroxy-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	
2	Malvidin 3-glucoside [7-carboxy-3-(4-hydroxy-3,5-dimethoxyphenyl)-4-[(2R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2,8-dioxatricyclo[7.3.1.05,13]trideca-1(12),3,5(13),6,9-pentaen-11-ylidene]oxidanium	
3	Epicatechin	
4	Epigallocatechin gallate [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate	
5	Dihydromyricetin (2R,3R)-3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-2,3-dihydrochromen-4-one	

Aquilaria malaccensis has a long-standing history of traditional use, particularly during pregnancy and the postpartum period. Ethnopharmacological evidence suggests that this plant possesses broad therapeutic potential, traditionally used in the treatment of various ailments such as weight loss, heart palpitations, jaundice, ulcers, edema, skin disorders, fever, and general body pain. The use in fumigation practices has been associated with the management of central nervous system disorders, including epilepsy and schizophrenia[22]. In addition, pharmacological activity, such as anti-cancer and antibacterial[32], antioxidant[8], anti-inflammatory[6], immune modulator, antidiabetic[33], embryogenesis[34] and anti-trypanosomal have been reported[35,36,37]; A previous study used 95% ethyl acetate to extract *Aquilaria malaccensis* leaves, followed by sequential fractionation using n-hexane, dichloromethane, ethyl acetate, and n-butanol to obtain distinct solvent fractions. Purification of the dichloromethane fraction was carried out through an elution process using a solvent mixture of *n*-hexane:ethyl acetate:methanol, followed by gradient-based column chromatography with *n*-hexane and ethyl acetate as the mobile phases. Through this procedure, one terpenoid, four flavonoids, and three benzophenones were isolated. Anti-inflammatory assays showed that both the extract and the constituents from *Aquilaria malaccensis* effectively inhibited NO production in RAW 264.7 cells activated with LPS and IFN-γ, suggesting promising anti-inflammatory properties[37].

Aquilaria malaccensis, a plant traditionally used in ethnomedicine, was extracted using 70% methanol and subsequently fractionated with solvents of increasing polarity. Subsequent purification of the diethyl ether fraction using column chromatography yielded sesquiterpenoid compounds belonging to the guaiane and humulene skeleton types. The chemical structures of the isolated compounds were elucidated through integrated spectroscopic techniques, including UV, MS, and NMR analyses. The isolated compounds were found to suppress LPS-induced nitric oxide (NO) production in RAW 264.7 macrophage cells, suggesting relevance as candidates for anti-inflammatory drug development[38,39]. The results of the identification and activity testing are presented in Table 6.

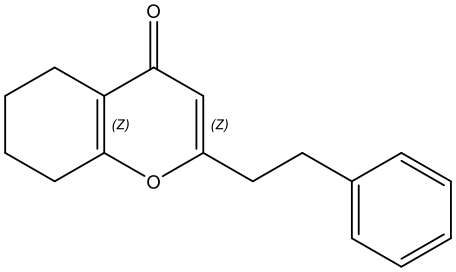
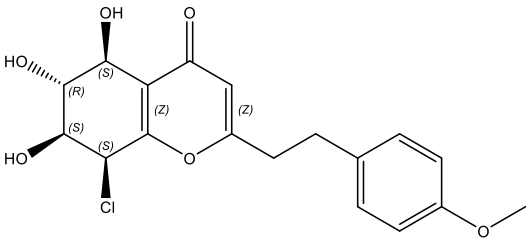
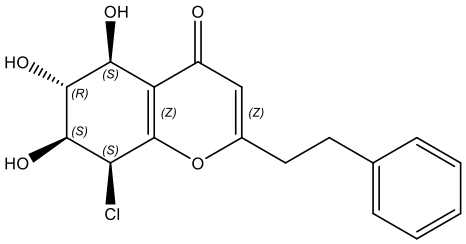
Table 6: Anti-inflammatory effects of compounds 1–9 on NO production in LPS stimulated RAW 264.7 cells (n=3)[39]

Compound	IC_{50} ± SD (µM)	CC_{50} (µM)
1	66.0 ± 3.5	>100
2	76.8 ± 6.0	>100
3	62.7 ± 4.4	>100
4	18.8 ± 3.9	>100
5	72.8 ± 4.2	>100
6	89.5 ± 1.7	>100
7	68.5 ± 1.9	>100
8	74.8 ± 1.1	>100
9	84.3 ± 2.3	>100

The anti-inflammatory potential of nanoencapsulated *Aquilaria malaccensis* extract was evaluated using a dual approach namely in vitro assays on macrophage cells and in vivo analysis in zebrafish (*Danio rerio*) embryos. In vitro results showed that the nanoencapsulated extract significantly enhanced macrophage cell viability compared to the non-encapsulated. Moreover, the in vivo study showed that the nanoformulation effectively reduced NO levels across different concentrations. These results suggest that nanoencapsulation improves cellular uptake and permeability, thereby enhancing pharmacological efficacy of the extract[40,41].

In a separate study, *Aquilaria sinensis* leaves were extracted with 75% ethanol, followed by sequential fractionation using petroleum ether (PE), dichloromethane, and ethyl acetate as solvents. The ethyl acetate fraction was then purified by column chromatography, resulting in the isolation of three different chromone derivatives, as shown in Table 7.

Table 7: Compounds identity with anti-inflammatory activity

No	Anti inflammatory activity compounds	Structure
1	2-(2-phenylethyl)-5,6,7,8-tetrahydrochromen-4-one	
2	(5S, 6R, 7S, 8S)-8-chloro-5,6,7-trihydroxy-2-{2-(4'-methoxyphenyl)ethyl}-5,6,7,8-tetrahydrochromone	
3	(5S, 6R, 7S, 8S)-8-chloro-5,6,7-trihydroxy-2-(2-phenylethyl)-5,6,7,8-tetrahydrochromone	

The anti-inflammatory potential of the isolated compounds was evaluated by measuring the inhibition of LPS-induced NO production in RAW 264.7 macrophages. Compound 2 showed the strongest activity, with an IC_{50} of 3.46 μM, surpassing the inhibitory effects of the other tested compounds. Four chromone derivatives were isolated and structurally characterized from the ethyl acetate fraction of *Aquilaria sinensis*, showing that variations in molecular structures significantly influenced anti-inflammatory properties. Compound 2, possessing a 4′-methoxyphenyl group along with multiple hydroxyl groups, was identified through bioassay-guided screening as the most potent inhibitor of NO production in LPS-activated RAW 264.7 cells. The superior IC_{50} value (3.46 μM) compared to the other compounds suggests that the presence of both hydroxyl and aromatic methoxy groups enhances bioactivity. These results support the hypothesis that substitution patterns, particularly hydroxylation and aromatic modifications, play a critical role in modulating the biological effects of chromone-based compounds. Chomones from *A. sinensis* may also serve as promising candidates for the development of natural anti-inflammatory agents[42].

The extraction of agarwood (*Aquilaria* spp.) leaves was carried out using 95% ethanol, followed by suspension in 80% methanol for subsequent fractionation with PE and ethyl acetate. The ethyl acetate fraction was further purified through vacuum liquid chromatography (VLC), using a PE:ethyl acetate gradient as the elution system. The separation and purification processes were facilitated by Liquid Chromatography–Mass Spectrometry (LC-MS), which offers higher sensitivity and precision compared to conventional analytical techniques. The results of compound isolation and characterization are summarized in Table 5.[43]

Table 5: Inhibitory activity of isolates against LPS-induced NO Production in RAW 264.7 cells[43]

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
1	4.3 ± 0.3	11	8.0 ± 0.3
3	1.9 ± 0.2	12	37.1 ± 0.5
4	1.6 ± 0.1	14	7.6 ± 0.2
5	5.8 ± 0.3	15	2.3 ± 0.4
9	0.7 ± 0.1	17	7.4 ± 0.1
10	0.6 ± 0.1	Indomethacin	45.6 ± 0.4

The ethyl ether extract of *Aquilaria* sp. yielded three previously unreported zizaane derivatives (1–3) and six known zizaane-type sesquiterpenoids (4–9), which were successfully isolated and structurally characterized. These compounds are proposed to represent characteristic chemical markers. The molecular structures of the isolated compounds were comprehensively elucidated using high-resolution electrospray ionization mass spectrometry (HRESIMS), one-dimensional (1D) and two-dimensional (2D) nuclear magnetic resonance (NMR) spectroscopy, as well as comparative analysis of experimental and calculated electronic circular dichroism (ECD) spectra. In vitro evaluation of anti-inflammatory activity showed that only compound nine had detectable inhibitory effects, but with low potency, as evidenced by an IC_{50} value of 62.22 ± 1.27 μM, substantially weaker compared to standard anti-inflammatory reference compounds[44].

The phytochemical investigation of *Aquilaria sinensis* resulted in the isolation of two novel 2-(2-phenylethyl) chromones (compounds 1–2), two previously undescribed sesquiterpenoids (compounds 12–13), and twelve known compounds (compounds 3–11 and 14–16). The structures of all isolated constituents were unambiguously elucidated through HRESIMS combined with detailed one-dimensional (1D) and two-dimensional (2D) NMR spectroscopy. The anti-inflammatory potential was assessed by evaluating inhibitory effects on lipopolysaccharide (LPS)-induced NO production in RAW 264.7 macrophage cells. Compounds 2–5, 7, 9–10, and 13–14 showed significant NO inhibition, with IC_{50} values ranging from 4.0 to 13.0 μM, suggesting superior activity compared to the other constituents isolated[45]. A phytochemical investigation was carried out to isolate and characterize secondary metabolites from *Aquilaria sinensis* agarwood, using 95% ethanol as the extraction solvent. Eight derivatives of 2-(2-phenylethyl) chromone were successfully isolated, and the bioactivity evaluations showed significant potential in modulating inflammatory responses and attenuating renal fibrosis. These results suggest that the chromone derivatives have enhanced bioactivity compared to previously reported compounds, underscoring potential as lead candidates for therapeutic development[46].

A study investigated the bioactive components of *Aquilaria crassna* leave extracts through a comparative analysis of young and mature leave extracts obtained by maceration using water and 70% ethanol as solvents. Comparative analysis demonstrated that the AE of young *A. crassna* leaves showed superior anti-inflammatory efficacy, marked by a more pronounced inhibition of IL-1α and IL-8 expression relative to the 70% ethanolic extract. These results show significant potential as a bioactive ingredient in cosmetic formulations aimed at mitigating inflammatory responses[47]. Accumulating evidence from previous studies underscores the potent anti-inflammatory activity of *Aquilaria sinensis* oil formulated as nanoemulsions, primarily through a more effective attenuation of ROS and NO secretion in inflammatory models. Moreover, these nanoemulsion formulations consistently showed greater inhibitory effects on LPS-induced expression of inducible nitric oxide synthase (iNOS), pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β), as well as the antioxidant enzyme heme oxygenase-1 (HO-1), compared to conventional counterparts[48].

Aquilaria species have diverse and significant pharmacological activity, leading to the use as raw materials for pharmaceutical formulations. This pharmacological advantage is largely ascribed to the complex and diverse array of secondary metabolites, which are believed to play a crucial role in mediating the observed bioactivity. Additional pharmacological potentials of various *Aquilaria* species, along with comparative profiles, are detailed in Table 8.

Table 8: Other potential pharmacological activity and other Aquilaria species

No	Potential pharmacological activity	Aquilaria species	References
1	Inhibitory activity against acetylcholinesterase, Antitumor and antimalarial, Efficacy of Metabolic Syndrome and Obesity, A protective effect on the gastric tissue, AChE inhibitory activity, Anti-neuroinflammatory activity, Antioxidant activity, α-glucosidase inhibitory activity, inhibitory effects on tumor cells, α-glucosidase inhibitors	*Aquilaria sinensis*	[12,49,50,51,52,53,54,55,56,57,58]

2	Neuroprotective Effects, Improvement in Lifespan and Health Span, Reduction of Gene Expression, Antidiabetic activity	*Aquilaria crassna*	[9,59,60]
3	Antimicrobial activity	*Aquilaria banaensis P.H.Ho*	[61]
4	Cytochrome P450 enzyme activity, Potent targets related to cancer through network pharmacology analysis	*Aquilaria malaccensis*	[62,63]
5	Anti-Inflammatory effect	*Aquilaria yunnanensis*	[64]
6	Tyrosinase inhibitory and anti-inflammatory activity, α-Glucosidase inhibitory activity, Cytotoxicity against K562 tumor cell lines, Anti-inflammatory activity.	*Aquilaria filaria*	[65,66,67,68]
7	anti-inflammatory activity, Antioxidant and Antibacterial Activity.	*Aquilaria agallocha*	[69,70]
8	The protective effects intestinal mucositis	*Aquilariae Lignum Resinatum*	[71]
9	Anti-neuroinflammatory effects	*Aquilariae Lignum*	[72]
10	Tyrosinase inhibition; α-glucosidase inhibition.	*Aquilaria plant*	[27]
11	Cytotoxic activity	*Aquilaria walla*	[68,73]
12	A potential therapeutic for Alzheimer's disease	Agarwood	[74]
13	Anti-inflammatory, antibacterial, hypoglycemic, and lipid-lowering effects	*Agarwood Leave*	[75]

Conclusion

In conclusion, Aquilaria, commonly known as agarwood, is a traditional medicinal plant with broad and diverse pharmacological potential. This study confirms that the three primary species *Aquilaria malaccensis*, *Aquilaria sinensis*, and *Aquilaria crassna* have significant antioxidant, cytotoxic, antibacterial, α-glucosidase inhibitory, and anti-inflammatory activity. Moreover, other *Aquilaria* species show important pharmacological effects, particularly as anti-hyperuricemic agents. The development of innovative pharmaceutical formulations such as phytosomes, nanoparticles, and microparticles presents promising opportunities to enhance the bioavailability and therapeutic efficacy of *Aquilaria* extracts. In general, these results underscore *Aquilaria* as a valuable source of natural bioactive compounds. Further studies are needed to explore additional pharmacological activity and to develop advanced herbal drug delivery systems that support clinical applications and improve therapeutic outcomes.

Conflict of interest

The author declares no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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