

A REVIEW: AQUILARIA SPECIES AS POTENTIAL OF PHARMACOLOGICAL

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ABSTRACT

One of the plants that is rich in benefits is from the genus *Aquilaria* spp. which is known to be able to produce agarwood resin. This genus includes 47 species, of which the four main species are *Aquilaria malaccensis*, *Aquilaria subintegra*, *Aquilaria crassna* and *Aquilaria sinensis*. *Aquilaria* species are known to have a wide spectrum of pharmacological activity and have been reported in many studies, including activity, anticancer, anti-inflammatory, AChE inhibitor (Acetylcholinesterase), anti-proliferative, and antidiabetic. The aim of this review is to expand information on the pharmacological activity of various *Aquilaria* species that can support future studies in the medical field of medicine.

Keywords: *Aquilaria*, pharmacological, natural.

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INTRODUCTION

Aquilaria is a tree native to the rainforests of Southeast Asia and belongs to the Thymelaeaceae family [4], of which the genus *Aquilaria* spp. this includes 47 species, and 22 of them are included in the plant list. Some of the known species including *Aquilaria malaccensis*, *Aquilaria subintegra*, *Aquilaria crassna*, and *Aquilaria sinensis* [4] are used for therapeutic purposes as a traditional medical treatment of gout, headache, arthritis, cough, vomiting, asthma, leprosy and anorexia [10]. The *aquilaria* tree is known to produce a fragrant agarwood resin and is used in perfumes. This type of tree is found in many countries in the oriental region such as Indonesia, Malaysia, Thailand, India, Laos, and China [8]. In addition, *Aquilaria* extract has also been reported to have anticancer activity [9,11,14], anti-inflammatory [1], antioxidant [3,9,14], and antidiabetic [14] which have been demonstrated in many in vivo and in vitro models. Therefore, the pharmacological effects of *Aquilaria* with different species and tree parts have different and similar pharmacological properties. This review will focus on the pharmacological effects for the 4 main species mentioned, a brief overview of the preparation methods and a discussion on the evaluation of their pharmacological properties.

Aquilaria malaccensis

Aquilaria malaccensis is one of the species of *Aquilaria* [7]. The leaves are known to have antioxidant activity. In the research of Batubara *et al.*, (2020) [3] concerning the antioxidant activity of *Aquilaria malaccensis* leaves. Extraction of sample using maceration method, leaf ethanol extract followed by phytochemical tests to determine the content of secondary metabolites compounds. The antioxidant test was determined by the activity of free radical scavenging against 1,1-diphenyl-2-picrylhydrazyl (DPPH) with the percentage of free radical reduction parameters at different concentrations (40, 60, 80, and 100 ppm) and inhibitory concentration values (IC₅₀). Based on these studies, the results indicated the presence of

secondary metabolites of alkaloids, steroids, triterpenoid, saponins, flavonoids, and tannins. The highest antioxidant activity of the ethanol extract of *Aquilaria malaccensis* leaves was 27.807 ± 4.630 ppm [3].

On the other hand, Apridamayanti *et al.*, (2018) [1] reported that *Aquilaria malaccensis* has core-inflammatory activity. Leaf powder extraction by maceration method using ethanol solvent and concentration using a rotary evaporator. The anti-inflammatory potential of the ethanol extract of *Aquilaria malaccensis* leaves was evaluated using an in vivo model, using the carrageenan-induced leg edema method of rats. Measurement of the volume of the test animal's feet using a plestimometer containing mercury. The ethanol extract of *Aquilaria malaccensis* L. showed statistically significant inflammatory activity at a dose of 180 mg/kg of 37.9% [8]. Another in vitro study showed that the extract from *Aquilaria malaccensis* leaves had the highest anti-inflammatory activity which inhibited more than 50% of heat-induced protein denaturation with Soxhlet ethanol extract (ALEXB) [5].

Aquilaria sinensis

Aquilaria sinensis is best known for its wood resin or gaharu. Gaharu as an incense is widely used in oriental areas such as Thailand and Taiwan. This plant has various pharmacological activities. One of them was reported by Liu *et al.*, (2018) [9] which evaluated the antioxidant activity and cytotoxicity of *Aquilaria sinensis*. *Aquilaria sinensis* stem samples were repeatedly extracted with MeOH. Phytochemical compounds were isolated and analyzed by IR, UV, ESI-MS, ¹HNMR, AND ¹³C NMR, then tested for their anti-proliferative and antioxidant activity based on the DPPH test (2,2-diphenyl-1-picrylhydrazyl) and the MTT test to determine the antiproliferative activity. The content of flavonoids 5-hydroxy-7,3', 4'-trimethoxyflavones was effective against DPPH radicals at a concentration of 10 mM with activity of $20.68 \pm 5.50\%$. In the anti-proliferative activity of the compounds tested in A375 cells after 24 hours treatment, cells were treated with 5-hydroxy-7,3', 4'-trimethoxyflavone at concentrations of 10, 50, and 100 μ M. These compounds showed significant inhibitory power at a concentration of 100 μ M in A375 cells, namely $68.00 \pm 1.33\%$ of the cell survival rate.

Aquilaria subintegra

The leaves of the *Aquilaria subintegra* plant are claimed to be effective in the treatment of Alzheimer's disease by traditional Malaysian Malay practitioners [2]. In the study of Bahrani *et al.*, (2014) [2] reported that extracts from the leaves and stems of *Aquilaria subintegra* can be used as a natural acetylcholinesterase (AChE) inhibitor as an alternative treatment for Alzheimer's Disease (AD). Extraction and analysis of compounds from the leaves and stems of *Aquilaria subintegra* with Thin Layer Chromatography (TLC) and LCMS-MS methods, where TLC results showed alkaloids and phenols, while LCMS-MS analysis showed that the stem extract contained kaempferol. The effect of chloroform extracts of leaves and stems and kaempferol was determined in Radial Arm Maze (RAM) after oral administration in ICR of male and female mice with valium memory impairment. Administration of kaempferol in mice significantly reduced the number of repeated entries into the labyrinth arm in males and females. Kaempferol is one of the flavonoids with high AChE inhibitory activity. The AChE inhibitory activities of chloroform extracts of leaves and stems and kaempferol were 80%, 93%, and 85.8%, respectively. The inhibition of AChE by extracts from *Aquilaria subintegra* can be caused by the presence of kaempferol, so this extract is safe to use as a natural AChE inhibitor in an alternative treatment for AD.

Another study shows the potential of *Aquilaria subintegra* fruit extract as an anticancer drug. *Aquilaria subintegra* fruit and seed extraction using methanol, ethanol and n-hexane as solvents. The extracts were individually treated against avorium, breast and colorectal cancer cells for 72 hours. The cell percentage and maximum inhibitory concentration (IC₅₀ value) used the sulforhodamine B-test. Fruit ethanol extract had the highest anticancer activity, namely IC₅₀ $<0.1 \mu\text{g mL}^{-1}$ while the other extracts were inactive (IC₅₀ $> 100 \mu\text{g mL}^{-1}$). Based

on the results of chemical profile analysis using HPLC showed the presence of mangiferin in fruit extracts which was active when tested in each cancer cell line [11]. Table 1 summarizes the pharmacological effects of the four species of *Aquilaria* spp.

Table 1. Effects of pharmacological activity of *Aquilaria* spp.

Species	Extracts	Plant Section	Pharmacological Effects	Extraction Methods	References
<i>Aquilaria malaccensis</i>	Ethanol extract	Leaves	Antioxidant	Maceration with ethanol solvents	[3]
	Ethanol extract	Leavers	Anti-inflammatory	Maceration of leaf powder with ethanol solvent and concentration using a rotary evaporator	[1]
<i>Aquilaria sinensis</i>	Flavonoids (5-hydroxy-7,3',4'-tri-methoxiflavone)	Stem	Antioxidant and anti-proliverative	Repeated extraction with MeOH and column chromatographic separation	[9]
<i>Aquilaria subintegra</i>	Chloroform extract	Leaves and stem	Acetylcholinesterase (AChE) inhibitor	Extraction with chloroform solvent	[2]
	Ethanol, methanol, and n-hexane extracts	Fruit	Anticancer	Extraction with methanol, ethanol, and n-hexane	[11]
<i>Aquilaria crassna</i>	Leaf ethanol extract and mangiferin	Leaves	Antioxidant, antidiabetic, and anticancer	Soxhlet extraction using ethanol and identification of compounds based on TLC-densitometric	[14]

Aquilaria crassna

Aquilaria crassna or agarwood belongs to the flowering plant family Thymelaeaceae. According to Ray *et al.*, (2014) [12] that this plant is well-known for its aromatherapy purposes and as a medicinal plant to cure some symptoms of inflammation, pain, fever, and constipation. Mangiferin is a xanthone derivative which is reported as one of the compounds isolated from *Aquilaria crassna* which has activities as a super antioxidant, anti-allergic, antidiabetic, anti-inflammatory and antibacterial [6]. In a study by Thitikompong *et al.*, 2019 [14] which investigated the antidiabetic activity, antioxidant and cytotoxicity of the ethanol extract of *Aquilaria crassna*. The leaves of *Aquilaria crassna* were extracted with ethanol using a Soxhlet kit and identified the mangiferin content in the extract using the TLC-densitometric method.

In antidiabetic testing using alpha-glucosidase activity inhibition test with p-nitrophenyl- β -D-glucopyranoside (PNPG) as a substrate. Mangiferin and leaf ethanol extract showed a stronger inhibitory effect of alpha-glucosidase activity than acarbose (control with activity and 17.3947 ± 0.0189 mg/mL) by means of a concentration response with each IC₅₀ value of 0.5714 ± 0.0044 mg/mL and 0.1840 ± 0.0032 mg/mL [14].

The antioxidant activity was carried out based on the 2,2-diphenyl-1-picrihydrazyl (DPPH) test and the FRAP test, the reducing power was expressed in μ M of iron sulfate which was equivalent in milligrams per dry weight of the sample. The results of the DPPH mangiferin test and the ethanol extract of *Aquilaria crassna* leaves, respectively, IC₅₀ values were 0.64 ± 0.005 mg / mL and 21.54 ± 0.17 mg / mL. This study implies that mangiferin and ethanol extract of leaves have potential as natural antioxidants through their phenolic properties in inhibiting RNS and ROS. Meanwhile, in the antioxidant test based on iron ion reduction (FRAP), where the antioxidant power of the ethanol extract of leaves and mangiferin is based on the reduction power of TPTZ-Fe³⁺ to TPTZ-Fe²⁺ and the FRAP value

obtained from the calculation of the ferrous sulfate calibration curve, respectively, is 11, 82 $\mu\text{M Fe (II)}/\text{mg}$ and 2.52 $\mu\text{M Fe (II) mg}$ [14].

On the other hand, *Aquilaria crassna* was also reported by Thitikompong *et al.*, 2019 [14] to have anticancer properties. Tests were carried out based on their cytotoxicity properties with the MTT test method and the relative number of cells was assessed by measuring the absorbance of the product at 570 nm with a micro plate reader. The test medium used human breast cancer cells (MDA-MB-231), human colorectal adenocarcinoma (HT-29), and human hepatocellular carcinoma (HepG2) from the American Type Culture Collection. In the study, the ethanolic extract of the leaves showed significant toxicity in all the cancer cell test samples. While mangiferin as a cytotoxic potential with cell viability of 100 $\mu\text{g}/\text{mL}$ was 62.93% (MDA-231), 63.52% (HT-29) and 67.85% (HepG2).

CONCLUSION

The above mentioned review provides evidence that *Aquilaria* spp. many have interesting and useful potential in various applications in the medical field in improving human health. The review can also be useful for future studies and exploitation of various parts of the *Aquilaria* spp. potential as a treatment and prevention related to pharmacological fields.

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