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A Review on Medicinal and Pharmacological Potential of Agaru (*Aquilaria malaccensis* Lamk.), it's Chemical Constituents and Oil Quality

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ABSTRACT: The present paper is an overview of *Aquilaria malaccensis* phytochemistry, its medicinal and pharmacological properties and its utilization in traditional medicine and drug industry. The plant is used in treatment against variety of diseases due to the presence of chromone derivatives, sesquiterpenes, terpenoids, flavonoids and phenolic compounds. This review also describes the chemical standards formulated by API (Ayurvedic Pharmacopoeia of India) such as permissible limit of foreign matter, purity, strength, macroscopic and microscopic characters for drug preparation from agarwood. So far, no scientific and common grading system has been developed to grade agar oil based on its chemical composition which leads to the lack of coordination and regulation at international level. GC-MS analysis of agar oil reveals that oxygenated sesquiterpenes responsible for it's unique aroma and quality are present in high grade agar oil. Some of the constituents such as α-guaiene, α-agarofuran, β-eudesmol, agarospirol, 10-epi-γ-eudesmol, etc are only found in high grade agar oil. In conclusion, these chemical compounds present in high grade agar oil can be used as standards for determining the best quality oil which can be followed by all traders and buyers in the international market.

Keywords: Agarwood high grade oil, sesquiterpenes, chromone derivatives, medicinal properties, GC-MS analysis.

INTRODUCTION

Aquilaria malaccensis (Thymelaeaceae) or agarwood also popularly known as "Wood of Gods" is one of the critically endangered species found extensively cultivated in Assam and other North-Eastern states of India, which have been in practice as traditional medicine. There are plenty of medicinal and pharmacological properties contained within the agarwood plant. It was reported that out of 21 species of *Aquilaria* four species are assessed as Critically Endangered (*A. crassna, A. khasiana, A. malaccensis and A. rostrata*), one species as Endangered (*A. microcarpa*) and eight species as Vulnerable (*A. banaensis, A. beccariana, A. cumingiana, A. hirta, A. filaria, A. rugosa, A. sinensis* and *A. yunnanensis*) (CITES, 2022). While, the remaining seven species are assessed as Data Deficient due to a lack of recent data on distribution, population and threat information.

(a) Scientific name: *Aquilaria malaccensis* Lamk.
(b) Pharmacopoeial name of the medicinal plant: Agaru
(c) Local name (Specify language):
Assamese: Xasi, Sashi
Bengali: Agar Chandan, Agor
English: Eagle Wood
Hindi: Agar
Kannada: Krishna Agaru
Malayalam: Akil
Punjabi: Ooda
Sanskrit: Aguru
Tamil: Aghil
Telegu: Agaru

It is a medium to large sized tree of height ranging from 20-40 meters. Agar tree grows well in high humid, tropical to sub-tropical climate with annual rainfall of about 1500 to 6500 mm and a mean annual maximum temperature of 22-28°C and minimum temperature of 14-21°C. The tree requires a lot of sunshine (70% sunlight) and is found in natural forest, at an altitude of a few meters to about 1000 meters above msl, while it grows best around 500 meters above msl. *Aquilaria* species occurs naturally in all ecological zones and in a wide variety of soils ranging from clay loam to sandy loam soil except heavy clay soil. The species prefers soft and sandy clay soil with pH ranging from 6.4-7 (Harvey-Brown, 2018). It naturally grows on good forest soil of slightly acidic reaction, with a light to medium soil texture and well drained with high organic matter content. It can also be grown in marginal soils and in shallow soil over rocky beds in hilly slopes.

The heartwood of the plant is rich in secondary metabolites such as alkaloids (Liriodenine), saponins, steroids, terpenoids, tannins, flavonoids, phenolic compounds, essential oil and resins which are

responsible for it's drug value (Satapathy *et al.*, 2009). Numerous medical conditions, including inflammation, cancer, and oxidative stress have been traditionally treated using Aquilaria malaccensis (Nahar *et al*., 2023). The wood of the plant predominantly contains 2-(2-phenylethyl)-4H-chromone derivatives and sesquiterpenes (Wang *et al*., 2016), which are primarily responsible for it's immense value in perfumery and pharamaceutical industry. The plant essential oil also contains compunds such as selinene, dihydroselinene, agarol, b-agarofuran, vetispira-2(11), valerianol, dihydrokaranone and tetradecanoic acid (Naf *et al*., 1992, 1995).

PHARMACOLOGICAL POTENTIAL OF *AQUILARIA MALACCENSIS*

(a) Anti-cancer activity. The leaves of *Aquilaria malaccensis* is known to contain antioxidant and cytotoxic activity against several cancer cells. In a study conducted by Millaty *et al.* (2020), the metabolites of chloroform and ethanol extracts of *A. malaccensis* leaves was screened using Gas Chromatography–Mass Spectrometry (GC–MS). Results revealed that metabolites such as 9–Hexadecanoic acid and Tetracosanoic acid, derived from chloroform extracts have potential as anticancer activity. Nahar *et al.* (2023) in their study revealed that A. malaccensis showed significant cytotoxicity against A549 lung cancer cells at 1000 µg/mL. Their study revealed that the plant extracts from A. malaccensis could exert a cytotoxic effect on lung adeno-carcinoma cells through the activation of an intrinsic signaling pathway. Zaid *et al*. (2022) in a study proved that ethanolic extract of A. malaccensis leaves has the potential as anti-cancer agent for curing chronic myeloid leukemia K-562 cell line. The ethanolic leaf extract obtained from *Aquilaria malaccensis* leaves is cytotoxic on MCF-7 cells, resulting to apoptotic cell death, thus helping in reducing the abnormal growth of cancer cells (Aziz *et al*., 2023).

(b) Anti-inflammatory activity. A recent study conducted by Eissa *et al*. (2022) investigates the anti-inflammatory activity of both ethanolic extract and isolated compounds from *A. malaccensis* leaves. The anti-inflammatory activity of the extract and eight compounds was evaluated, and they demonstrated the ability to suppress NO levels in RAW 264.7 cells induced by LPS/IFN-γ. The essential oil from agarwood also has a potential to cure many chronic inflammatory diseases by blocking some of the major pathways causing inflammation (Alamil *et al*., 2022).

(c) Anti-diabetic activity. The leaf extract of *A. malaccensis* proved to be effective against Type 2 diabetes mellitus which affects the glucose metabolism resulting in hyperglycemia. The experiment findings by Bahtiarsyah *et al*. (2023) suggested that the presence of compound palustrol in leaf extract of *A. malaccensis* reduce the glucose level. Sukito *et al.* (2020) also found the highest anti-diabetic activity in the methanol extract of leaves from infected species. Moreover, the methanolic extract of *A. malaccensis* possesses the ability to control the lipid peroxidation and biochemical disruption associated with insulin resistance (Derouiche *et al*., 2019). The methanolic and aqueous leaf extract of *A. malaccensis* showed dose dependant inhibitory effects against alpha-glucosidase activity with (Inhibitory Concentration) IC50 values of 428.92 and 425.09 µg/mL repectively, which potentially lower the blood glucose level in diabetic patients without inflicting harmful side effects (Zulkifle, 2018).

(d) Anti-oxidant activity. The experimental findings by Halim *et al.* (2022) proves that the ethanol, ethyl acaetate and n-hexane extracts of *A. malaccensis* leaves showed an anti-oxidant activity when evaluated by three different type assays. Out of all, the ethanol extract had the highest anti-oxidant activity for all assays. The result of another anti-oxidant activity test showed that agarwood leaf extract has IC50 (Inhibitory Concentration) value of 56,985 dan 44,382 µg/mL, which meant very strong anti-oxidant activity category (Surjanto *et al*., 2019). Batubara *et al*. (2020) also proved that the ethanol extract of *A. malaccensis* leaves had a very strong antioxidant activity which can reduce free radicals in our body.

(e)Anti-microbial activity. *In many experiments, leaf extracts of A. malaccensis* showed significant anti-microbial activity against the gram-positive and negative bacteria. In a study by Afendi *et al.* (2019) the antibacterial activities of *Aquilaria malaccensis, Aquilaria sinensis* and *Aquilaria subintegra* leaf extracts against *Staphylococcus aureus* and *Escherichia coli* were evaluated. Results showed that among the three species of Aquilaria, *A. malaccensis* possess the best antibacterial activity at zone of inhibition even tested at the smallest concentration of 75 mg/mL. In an experiment conducted by Batubara *et al*. (2020), the antibacterial and antifungal activities of agarwoood leaf extract was tested against three species of bacteria (*Staphylococcus epidermis, Staphylococcus aureus* and *Propionibacterium acnes*) and two fungi species (*Candida albicans* and *Trichophyton* sp.) known for commonly causing skin infection in human. The results revealed that, 5% concentration of ethanol leaf extract inhibited the bacterial and fungal growth zone diameter. The antimicrobial activity was attributed to the bioactive compounds such as flavonoids and tannins present in the extract. Crude leaf extract of *A. malaccensis* was tested for antibacterial activity against Gram-negative bacteria *i.e., Acinetobacter baumannii, Klebsiella pneumonia* and *Escherichia coli* (Jihadi *et al*., 2020). The outcome of the experiment showed significant antibacterial activity against these bacteria spp. and to develop potential treatment against bacteria. Mei *et al.* (2014) revealed that volatile oil had antibacterial activity against methicillin-resistant Staphylococcus aureus.

(f) Immunological activity. A study by Yana *et al.* (2022) indicated that *A. malaccensis* leaf extract showed a promising immunomodulatory activity against pathogenic bacteria *Staphylococcus aureus,* infected macrophages in vitro. Cholroform and ethanol extracts at a 50 µg/mL concentration showed the best results with the phagocytic activity. Hegde *et al*. (2019)

in their study showed that ethanolic extract of leaves of *Aquilaria malaccensis* was able to exhibit significant immunomodulatory effect against cyclophosphamide and sheep RBC induced immune response. Thus, the phytoconstituents present in extract might be beneficial in the treatment of immune suppression related disorders. A study conducted by Pang *et al*. (2023) revealed that agarwood leaf extract showed enhance immune-stimulatory effects using RAW264.7 murine macrophages.

PLANT PARTS USED FOR MEDICINAL PURPOSES

The plant parts known to possess medicinal properties are leaf, stem, essential oil and fungus infected heart wood. From the leaves of *A. malaccensis*: antidiabetic (Said and Kamaluddin 2016), antioxidant (Simatupang *et al.,* 2015), antibacterial (Khalil *et al.,* 2013) and hepatoprotective properties (Alam *et al.,* 2017) have been reported. Also the leaves of *Aquilaria* are found to be useful in throat itching (Kumar *et al*., 1980). The young shoots, the first and second leaflets are selected for making agar tea. Pharmacological properties of agar tea include anti analgesic, anti-arthritic, anti-inflammatory, anti-cancer, anti-tumor, anti-oxidant, anti- bacterial, anti-fungal, anti-diabetic etc. Moreover, anticancer (Knecht *et al*., 2010), antibacterial and antifungal (Chen *et al*., 2014) activities have been reported from callus and shoot of *A. malaccensis.* Aqueous extract of stem shows activity against immediate hypersensitivity by inhibiting the histamine secretion from mast cell. In ayurvedic medicinal practices, topical application of *Aquilaria malaccensis* stem paste is useful in skin disorders while leaf paste is useful in leprosy and pruritus.

The wood of the plant has also been used as antidepressant (Kakino *et al*., 2010) thus aiding to improve the neural activity. Benzene extract of the wood showed CNS depressant activity. Woodfumes of infected agarwood possesses antiseptic, antioxidant and insecticidal activities. Heartwood of *A. malaccensis* is found to show anti- arthritic (Rahman *et al.,* 2016) along with improving neural activity. The agarwood with a resin content exceeding 25% can be used for medicinal purposes (Peng *et al.,* 2020). The agarwood powder is mainly used in the manufacture of fumigators, pastilles and agarbatties. The essential oil is known for stimulant, cardiotonic and carminative properties. The chemical constituents present in the essential oil prevent denaturation of protein accounting to antiarthritics property and can also be used for anxiety and depression treatment accounting to anxiolytic property. The essential oil of infected agarwood is one of the highly priced essential oils used in perfumery industry across the world. The volatile oil of agarwood also contains a variety of anti-tumor components, which have inhibitory effects on many kinds of cancer cells (Dahham *et al.,* 2016).

MAJOR CHEMICAL COMPOUNDS RESPONSIBLE FOR DRUG VALUE

The whole plant contains various chemical constituents: sesquiterpenes, chromones, phenolics, steroids, benzophenones, flavonoids, terpenoids, lignans and other compounds naturally found in all trees. Among all these bioactive compounds, chromones and terpenoids (sesquiterpenoids) are the major compounds that are potentially known for their pharmaceutical value, bioactivity and medicinal properties.

(a) Sesquiterpenes: Most of the sesquiterpenes obtained from genus *Aquilaria* are oxygenated. Dahham *et al.* (2016) found that the sesquiterpene component (β-caryophyllene) was found to possess antibacterial activity against six kinds of human pathogenic bacteria and two kinds of fungi. Wang *et al.* (2016) revealed that the compound 5-deoxylongiferol isolated from agarwood showed antibacterial effect on Staphylococcus aureus and Ralstonia solanacearum. Prezizaanes are the tricyclic sesquiterpenes found in A. malaccensis with a special fragrance (Nakanishi *et al*., 1984), which possess antidiabetic activity. Similarly, agarol obtained from *A. malaccensis*, an eudesmane sesquiterpene, and 8bH-Dihydrogmelofuran and gmelofuran, a cadinene sesquiterpenes isolated from A. malaccensis were reported to have anticancer, antioxidant and antimicrobial properties (Dahham *et al.,* 2016). A study conducted by Nakanishi *et al.* (1984), revealed three sesquiterpenes as alpha-agarofuran, -10-epi-gamma-eudesmol and oxo-agarospirol as major contributors to the fragrant nature of agarwood.

(b) Chromones: 2-(2-phenylethyl) chromone compounds isolated from agarwood have inhibitory action on five kinds of human tumor cells (Suzuki *et al*., 2017). Sugiyama *et al.* (2018) found that several 2-(2-phenylethyl) chromones isolated from agar incense could inhibit PED 3A in phosphodiesterase (PDEs). Chromone derivatives like epifriedelanol, 5-hydroxy-7,4′-dimethoxyflavone, luteolin-7,3′,4′-trimethyl ether, luteolin 7,4′- dimethyl ether, acacetin, aquilarinenside E and 3-C-β-glucoside isolated from the leaves of *A. malaccensis* are used in the treatment of inflammatory disorder.

(c) Alkaloids: The alkaloid Liriodenine from wood was reported to have significant in vitro inhibitory activity against the 9 KB tumour test system (Sarma *et al.,* 2015) and was also reported to act *in vitro* upon the cells of human nasopharyngeal carcinoma (Shamma and Castenson 1973).

NATIONAL QUALITY EVALUATION OF THE MEDICINAL PLANT MATERIAL

The Ayurvedic Pharmacopoeia of India (**API**) is a legal document of standards compiled by Government of India. It is the SOP for the quality of Ayurvedic drugs and substances included therein (under Drugs and Cosmetics Act, 1940). API describes macroscopic and microscopic characters of different parts of Ayurvedic drugs along with their chemical standards of identity, permissible limit of foreign matter, purity and strength. Their protocol has been approved by the Ayurvedic Pharmacopoeia Committee, Ministry of Ayush (Govt. of India).

According to API, Agaru consists of dried heart wood of *Aquilaria malaccensis* Lamk. (Fam. Thymelacaceae), whose heartwood and essential oil are used in pharmacological industries for ayurvedic drug preparation. In ayurveda, for therapeutic purposes essential oil (dose 1-3 g) is generally used.

Quality parameters of Agaru determined by Ayurvedic Pharmacopoeia of India (API):

(i) Macroscopic characters: Drug available in cut pieces, dark brown to nearly black; fracture, hard; no characteristic smell and taste.

(ii) Microscopic characters: Shows mostly uniseriate sometimes biseriate xylem rays; vessels isolated having simple pitted thickening and filled with dark brown contents; xylem fibres short having narrow lumen occupying a major portion of wood; xylem parenchyma less in number and simple pitted; included phloem tissues in pockets partially dis-organised, leaving large circular or oval holes, containing collapsed and broken tissues.

(iii) Powder: Dark brown; showing numerous aseptate fibres, simple pitted vessels with dark brown contents.

(iv) Identity, Purity and Strength of Drug: Quantitative parameters such as Foreign matter (Not more than 1 %), Total Ash (Not more than 13 %), Acid-insoluble ash (Not more than 0.5 %), Alcohol-soluble extractive(Not more than 1 %) and Water-soluble extractive (Not more than 2 %) (Appendix 2, The Ayurvedic Pharamacopoeia of India, 2004).

(v) Thin Layer Chromatography (T.L.C): TLC technique is used to isolate non-volatile mixtures for extracting active ingredient for drug preparation from agarwood. All the agarwood chips and wood are powdered and filtered (26 meshes). Then, the powder (1 g) was extracted in methanol (25 ml) for 30 min. T.L.C. of the alcoholic extract of agaruon Silica gel 'G' plate is performed using Toluene: Ethylacetate (9:1) shows in visible light two spots at Rf. 0.17 and 0.27 (both light brown). Under U.V. (366 nm) five fluorescent zones appear at Rf. 0.17, 0.27, 0.36, 0.57 and 0.80 (all blue). On exposure to Iodine vapour eight spots appear at Rf. 0.05, 0.11, 0.15, 0.24, 0.33, 0.57, 0.73 and 0.80 (all yellow). On spraying with Vanillin-Sulphuric acid reagent and after heating the plate for ten minutes at 105°C five spots appear at Rf. 0.13, 0.18, 0.25, 0.37 and 0.59 (all violet) (The Ayurvedic Pharamacopoeia of India, 2004).

vi) Heavy metal content: The permissible limits of heavy metal contents in drug are given as: Lead (10 ppm), Arsenic (3 ppm), Cadmium (0.3 ppm) and Mercury (1 ppm) (The Ayurvedic Pharamacopoeia of India, 2016).

MAJOR CHEMICAL CONSTITUENTS PRESENT IN AGARU

The major chemical compounds extracted from Aquilaria *malaccensis* are sesquiterpenoids and chromones. From the analysis of essential oil, 182 sesquiterpenes and 240 2-(2-phenylethyl) chromones, 17 phenylpropanoids and 36 flavonoids have been isolated and identified from agarwood produced by *Aquilaria* plants including *A. sinensis*, *A. malaccensis*, *A. crassna*, *A. filaria* and *Gyrinops salicifolia*.

The chemical compounds are divided into two categories:

(A) Volatile compounds of agarwood

(B) Non-volatile compounds of agarwood (Fatty acids, chromones, terpenoids, steroids, flavonoids, alkaloids)

Table 1: Chemical constituents in agarwood and essential oil.

Chromones	Sesquiterpenes	Phenyl-propanoids	Phenyl-chromones	Flavonoids	Volatile Compounds
Agarotetrol	Eudesmane	Anisic acid	FTPECs	Flavone	Benzylacetone
Oxidoagar-chromones A	Agarospirane	Cinnamaldehyde	DEPECs	Isoflavone	3,5-Di-tert-butylphenol
Isoagarotetrol	Cadinene	Syringin	THPECs	Flavanol	4-Methoxyphenyl acetone
2-(2-phenylethyl) chromone	Guainene	Anisaldehyde	EPECs	Benzophenone	2,4-Di-tert-butylphenol
2-[2-(4-Hydroxyphenyl) ethyl] chromone	Preazines	Benzaldehyde	-	Xanthones	-

QUALITY EVALUATION OF AGARWOOD OIL

There are various grading methods for determining the quality of agarwood oil. Different countries have various methods to grade/classify the agarwood oil. Till date there is no international common system or scientific protocol for determining the grades on qualitative basis, each sourcing country may have their own grading system or none at all. The market grades are predetermined by sellers and buyers based on experiences and these grades are not necessarily accurate. Conventionally, the agarwood oil was graded according to its colour, aroma and fixative based on human's sense. However, it was difficult to standardize the quality from the aroma due to human nose cannot smell many samples continuously. In Malaysia, agarwood oil is classified according to the grade of A, B, C and (Sidik, 2008). In India, they use grades too; A, B, C and D but were based on the color of agarwood oil (Naef, 2011). Color black, all resin with no white wood is considered as first grade while heavyweight, multi resin with white wood is the second or inferior grade.

Jayachandran *et al.* (2014) classified 4 grades of agarwood oil (Grade-1,2,3,4) based on the chemical composition present in each grade to determine the quality of oil by using GC-MS (gas chromatography mass spectrometry) analysis. Agar oil obtained from

highly infected tree is specified as Grade 1, moderately infected as Grade 2, less infected as Grade 3 and healthy wood as Grade 4. GC-MS analysis reveals that the highly infected wood oil (G1) contains aromadendrene-2, valencene-2, calarene, 1(5), 6-Guaiadiene, etc. The presence of chemical compounds like aromadendrene and valencene plays an important role in grading of agar oil was also stated by Jayachandran *et al.* (2014). The quantity of these two compounds in the four grades of wood are found in the following order G1>G2>G3 and absent in G4 grade wood oil.

GC-MS analysis identifies the significant existence of common compositions in agar oil and it is considered as the best method for qualitative analysis. The major compounds present in the *Aquilaria malaccensis* oil after GC-MS analysis were 4-phenyl-2-butanone (32.1%), jinkoh-eremol (6.5%) and α-guaiene (5.8%), while the major compounds present in the commercial oil were α-guaiene (10.3%), caryophellene oxide (8.6%), and eudesmol (3.2%). After GC-MS analaysis of high grade agarwood oil, it was found that the sesquiterpenes are found to exist in oxygenated form. Other studies revealed that for instance:7-epi-α-Cadinene, beta-guanine, caryophyllene-11, alpha-guaiene, beta-agarofuran, jinkoh-eremol, kusunol, selina-3,11-dien-9-one and oxo-agarospirol are some of the chemical compounds found in high grade oil irrespective of the *Aquilaria* species. These oxygenated sesquiterpenes present in agarwood provides it's unique aroma and quality and extracted from highly infected plants. Therefore, these chemical compounds present in high grade agar oil can be used as standards for determining good quality oil.

Globally accepted chemical profile of high grade agaru oil (Islam *et al.*, 2022)

Table 2: Compounds in superior grade oil.

Compounds in superior grade oil	
Agarospirol	3-phenyl-2-butanone
β-eudesmol	α-guaiene
Jinkoh-eremol	α-agarofuran
Kusunol	β-agarofuran
Jinkohol II	Nor-ketoagarofuran
10-epi-γ-eudesmol	

Some essential characteristics of superior grade agarwood oil (Islam *et al.*, 2022)

(a) The superior grade oil does not lose its mobility even when cooled at 4°C for 5 min.

(b) Pure agarwood oil samples reveal single-stage volatilization at 110-260°C.

(c) The average grade sample is free moving till 12°C, whereas the poor grade samples lost their mobility even at 22°C.

(d) The mobility of low quality agarwood oil generally decreases (viscosity increases) with lowering temperature due to the fatty contaminants or due to their richness in fatty constituents.

(e) 2-(2-phenylethyl) chromone was present in natural agarwood and agarwood formed by physical injury, but not in agarwood formed by chemical stimulation without and with fungal infection

CONCLUSIONS

This paper critically reviews published research studies on medicinal and pharmacological properties of agarwood along with the chemical constituents responsible for it's fragrance and drug value. It also covers topics related to it's essential oil quality and grading as agarwood trade is highly dependent on it's quality. Currently various countries follows different grading methods for determining it's quality as till date no international common system or scientific protocol has been established. Conventionally, the agarwood oil is graded according to its physical appearance, colour and aroma. However, recent studies mentioned techniques like GC-MS analysis, which is considered as the best method for qualitative analysis and scientific grading. The review found that certain chemical compounds present in oil can be used to decide the quality, since high grade agar oil consists of a complex mixture of sesquiterpenes, oxygenated sesquiterpenes and chromone derivatives responsible for it's unique aroma and quality.

FUTURE SCOPE

Further research needs to be conducted to prepare more effective drug from agarwood to cure human ailments and also to find the most suitable method for qualitative analysis of agar oil.

Conflict of Interest. None.

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