Borneo Journal of Resource Science and Technology (2025), 15(1): 81-96
DOI: https:doi.org/10.33736/bjrst.6088.2025

Pharmacological Properties and Health Benefits of *Aquilaria* Leaf Extract: A Review of its Antioxidant, Antidiabetic, Antimicrobial, Anti-Inflammatory, and Gastrointestinal Regulation Effect

NADIA NABILA MOHD KODEEM[1], BALKIS A TALIP*[1], KHAIRUNNISA ABDHUL MUTHALIB[1], MOHAMAD IKHWAN JAMALUDIN[2], ABD FATHUL HAKIM ZULKIFLI[3], NORHAYATI MUHAMMAD[1], HATIJAH BASRI[1], NUR HAFIZAH MALIK[1] & HAZIAN SALLEH[4]

[1]Department of Technology and Natural Resources, Faculty of Applied Sciences and Technology, Universiti Tun Hussein Onn Malaysia, Pagoh Higher Education Hub, KM1 Jalan Panchor, 84600, Panchor, Johor, Malaysia; [2]BioInspired Device and Tissue Engineering Research Group, School of Biomedical Engineering and Health Sciences, Faculty of Engineering, Universiti Teknologi Malaysia, Skudai 81300, Johor, Malaysia; [3]Centre of Automotive and Powertrain Technology, Faculty of Engineering Technology, Universiti Tun Hussein Onn Malaysia, Pagoh Higher Education Hub, KM1 Jalan Panchor, 84600, Panchor, Johor, Malaysia; [4] Synergy One Holding Sdn Bhd., Blok 3A, MTDC-UTM Technology Centre, Technology Park, 81300, Skudai, Johor.
*Corresponding email: balkis@uthm.edu.my
Received: 18 September 2023 Accepted: 10 February 2025 Published: 30 June 2025

ABSTRACT

Aquilaria or Karas tree belongs to the *Thymelaeaceae* family, a famous agarwood producer. This plant is widely distributed in the Indomalesia region, including Malaysia. Recently, these plants have attracted the attention of researchers. Infected wood resin from *Aquilaria* plants, also known as agarwood, is widely used for perfume production, religious and medicinal purposes. Due to the long development time of the plants and the need to inoculate them to initiate agarwood resin production, farmers have sought an alternative source of income by marketing the leaves of the *Aquilaria* tree. *Aquilaria* leaves are also known to have antioxidant, antidiabetic, antimicrobial, and anti-inflammatory properties and are commonly used to regulate the gastrointestinal tract. In contrast to the abundant benefits of the *Aquilaria* leaves, there were lacking reports on the cytotoxicity of the leaves and their extract. Therefore, this review investigates and points out the pharmacological properties of Aquilaria leaves, their human health benefits, and toxicity of the leaves based on the in-vitro and in-vivo studies as it is crucial for safety consumption and downstream applications, including food and beverages, pharmaceutical and cosmeceutical industry.

Keywords: *Aquilaria* leaves, pharmacological properties, toxicity effect

Copyright: This is an open access article distributed under the terms of the CC-BY-NC-SA (Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License) which permits unrestricted use, distribution, and reproduction in any medium, for non-commercial purposes, provided the original work of the author(s) is properly cited.

INTRODUCTION

Aquilaria spp., also commonly acknowledged as agarwood, karas, or oudh (Maharani *et al*., 2016; Surjanto *et al*., 2019), is a member of the Thymelaeaceae that is extensively dispersed in Southern Asia and is readily available in Malaysia (Kenzo *et al*., 2019; Razak *et al*., 2019; Surjanto *et al*., 2019). *Aquilaria* trees are massive, rapid-growing, and can reach heights of 30 meters and diameters of 2.5 meters (Razak *et al*., 2019; Zainurin *et al*., 2020).

This genus contains 21 species, 13 of which are agarwood producers. *Aquilaria malaccensis, Aquilaria rostrata, Aquilaria microcarpa, Aquilaria beccariana,* and *Aquilaria hirta* are the most common species in Malaysia. On the other hand, the species of *Aquilaria subintegra* and *Aquilaria sinensis* are native to southern Thailand and China, respectively. In addition, *Aquilaria crassna* is widely distributed in Cambodia, Laos, Vietnam, and northern Thailand (Lee & Mohamed, 2016; Adhikari *et al*., 2021).

Historically, each part of the Aquilaria tree has been beneficial for its use in food and beverages and its medicinal and cosmetic applications (Zakaria *et al*., 2020). Agarwood or a dark resinous stem part cannot be produced by *Aquilaria* trees, whether wild or cultivated, unless they have been externally injured by physical damage, insect feeding, or microbial infection (Zhang *et al*., 2012). Agarwood resin is one of the costliest natural products in the world (Zakaria *et al*., 2020).

However, the difficulty of resin formation leads to unlawful deforestation and a reduction of the *Aquilaria* plant population (Desa *et al*., 2021). In addition, agarwood production has been inconsistent and rampant illegal logging, which poses a threat to agarwood propagation is leading to an increase in the planting of agarwood trees to compensate for insufficient supply (Desa *et al*., 2021; Lee & Mohamed, 2016). Besides the agarwood resin, the hydrosol from the agarwood essential oil hydro distillation is the secondary product, which consists of the water-soluble compound. Globally, it has been diluted for human consumption (Kahar *et al*., 2021).

Due to the plant's long growing season and the need for induction to produce dark resinous stem or agarwood, farmers have sought profitable alternatives (Adam *et al*., 2017). While *Aquilaria* leaves are usually considered waste during pruning, they can be used as income substitutes while awaiting agarwood formation (Wangiyana *et al*., 2022). According to Zakaria *et al.* (2020), *Aquilaria* leaves have a tremendous potential for therapeutic use. In ancient times, *Aquilaria* leaves were traditionally used to treat trauma, hypertension, constipation, diabetes, headaches and digestive ailments (Zhou *et al.*, 2008; Kakino *et al*., 2010[a]; Prakhanon *et al*., 2011).

Rashid *et al*. (2020) reported that dried *Aquilaria* leaves contain crude fibre, protein and carbohydrates suitable for usage in the food and beverages industries. These include tea in bags or with other foods such as ice cream, cookies, or coffee (Adam *et al*., 2017). According to Hsiao *et al.* (2021), *Aquilaria* leaves are used to make a nourishing herbal tea, and consumption steadily rises over time (Adam *et al*., 2017). In Malaysia, *Aquilaria* leaves are used as an ingredient in tea and coffee. The cultivation area in Malaysia has become a tourist attraction that allows visitors to admire the landscape while drinking tea made from *Aquilaria* leaves, such as in Hoga Gaharu Tea Valley, Gopeng, Perak. *Aquilaria* leaf extract is also an active ingredient in coffee formulation to enhance the health benefits of coffee products such as HOGA coffee and Black Gaharu, which have several flavours, including mocha latte, matcha, and classic black.

Furthermore, *Aquilaria* leaves have also been utilised to manufacture tea in Indonesia, which is one of the potential herbal product advancements (Wangiyana *et al*., 2022). Research and development of *Aquilaria* leaf tea in Indonesia has thoroughly addressed the finished product selection of raw materials, processing, safety, and marketing. To date, there are seven brands of *Aquilaria* leaf teas in Indonesia (Wangiyana *et al*., 2022).

The consumption of *Aquilaria* can bring health benefits to humans. *Aquilaria* leaves are highly abundant and available, allowing their use for commercial purposes and capable of becoming new prospects for product development. The excellent pharmacological properties of *Aquilaria* leaves can be utilised as an ingredient for downstream applications, including in the food and beverage, pharmaceutical and cosmeceutical industries.

On the other hand, consuming plant leaves-based products and herbs might have side effects and toxicity concerns towards human health. This issue leads to the in-vitro and in-vivo toxicity tests, which can help determine the toxicity level of the product. In this case, many toxicity studies of *Aquilaria* leaves and their extract have been conducted by the researcher. However, the study of the cytotoxicity of *Aquilaria* leaves is too scattered. Therefore, in this review, the pharmacological effects and toxicity of the *Aquilaria* leaves are discussed and organised.

Materials and Methods

This review article searched all literature using six databases: Google Scholar, Elsevier, PubMed, Web of Science, local books, and thesis dissertation. The keywords used for identification of the sources were "*Aquilaria* leaves", or "agarwood leaves", "antioxidant activity of *Aquilaria* leaves", "antidiabetic properties of *Aquilaria* leaves", or "antibacterial properties of *Aquilaria* leaves" or "anti-inflammatory properties of *Aquilaria* leaves" or "laxative properties of *Aquilaria* leaves" or "cytotoxicity of *Aquilaria* leaves". All articles or books regarding *Aquilaria* leaves were taken from 2008 until 2023.

This article delves deeper into the pharmacological properties and cytotoxicity of *Aquilaria* leaves and their extract. Moreover, in order to improve the sensitivity of searched data, the top 250 from searched databases, ordered by relevance, including journal articles, proceedings, books, and dissertations, were included in the study. Non-English periodicals were omitted, and the review focused solely on English content to ensure clear interpretation.

Pharmacological properties of *Aquilaria* leaves

Natural bioactive substances found in plants are known as phytochemicals and are divided into two categories according to function in plant metabolism: primary and secondary metabolites. Amino acids, chlorophyll, proteins, and carbohydrates are primary metabolites, while alkaloids, phenolic compounds, and terpenoids are secondary metabolites (Krishnaiah *et al*., 2009).

While the bioactivity of *Aquilaria* has been highly appreciated and has recently piqued the curiosity of researchers in recent years, it has not yet been adequately explored (Hsiao *et al.*, 2021). Various phytochemical compounds are found in *Aquilaria* leaves, and all of these compounds are related to pharmacological properties (Ridwanti *et al*., 2020). Studies have shown that flavonoid and 2-(2-phenylethyl) chromone are the predominant constituents in *Aquilaria* leaves (Wang *et al*., 2018).

Aquilaria leaves consist of many chemical constituents, including chromones, phenolic acids, steroids, fatty acids, benzophenones, xanthonoids, flavonoids, terpenoids, and alkanes that provide various benefits towards human health (Adam *et al*., 2017; Razak *et al*., 2019). Mangiferin, genkwanin, genkwanin-5-O-β-primeveroside, iriflophenone 2-O-α-L-rhamnopyranoside, iriflophenone 3-C-β-D-glucoside, and iriflophenone 3,5-C-β-D-diglucopyranoside have been recognised as potent phenolic compounds in the *Aquilaria* leaves (Hashim *et al*, 2016; Ibrahim, 2016). This review focuses on the potential of antioxidant, antidiabetic, antibacterial, anti-inflammatory and laxative effects in *Aquilaria* leaves.

Antioxidant Properties

The production of reactive oxygen species (ROS), which are necessary for tissue homeostasis and cell communication, occurs due to regular physiological activities. Unfortunately, too many radical species negatively affect cells and promote various diseases, including damage to DNA, lipids, and proteins (Su *et al*., 2019). Antioxidants can break down ROS and neutralise metabolically active products to protect cells from oxidative damage associated with illnesses such as ageing, cancer, and diabetes (Wil et *al*., 2014). The antioxidant and phenolic compounds, which comprise phenolic acids, tannins, and flavonoids, are plentiful in plants, especially in the leaves (Batubara *et al*., 2018; Surjanto *et al*., 2019). According to Batubara *et al*. (2018), *Aquilaria* leaves have high antioxidant activity.

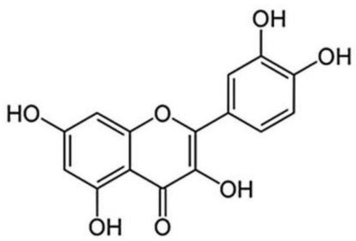
The study by Surjanto *et al*., (2019) reported in North Sumatera, Indonesia, showed that *A. malaccensis* leaves collected in the Sigiring-giring village contain terpenoids and saponins. The leaves of *A. malaccensis* from S. Kalangan II have tannins and saponins. The 50 % inhibition concentration (IC50) of 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay showed that the leaf extract from S. Kalangan II was higher than that from Sigiring-giring village (Surjanto *et al*., 2019). The secondary metabolites component is influenced by extrinsic factors, which include humidity, temperature, precipitation and solar radiation, which are usually related to the geographical location, climate and soil composition (Xu *et al*., 2022; Ciocan *et al*., 2023)

In addition, Hendra *et al*. (2016) examined the antioxidant activity of *A. malaccensis* leaves regarding the effects of different stages of leaf maturity with different solvents as extraction mediums on antioxidant activity. The free radical scavenging inhibition (IC50) indicates that the old, matured leaves with methanol extraction had the highest antioxidant compared to young leaves, which are 19.62 ± 1.49 μg/ml and 68.52 ± 2.12 μg/ml, respectively. The growth-differentiation balance theory proposes that longer-growing plant parts have more defensive resources, enhancing antioxidant activity in old leaf extract due to more secondary metabolites (Hendra *et al*., 2016). Moreover, the development process of the leaf leads to an increase in photosynthesis capability and antioxidant activity (Nadeem & Zeb, 2018).

In contrast, a study by Wongwad *et al*. (2019) reported that the DPPH scavenging assay revealed that extracts from young leaves demonstrate significantly higher antioxidant activity compared to those from mature leaves. The IC50 values for young leaf extracts ranged from 13.3 to 26.5 μg/mL, whereas for mature leaf extracts, the IC50 values were between 37.5 and 71.4 μg/mL. This finding aligns with recent studies by Kuntorini *et al*. (2022), which discovered that ethanol extracts from green fruits and young leaves have more antioxidant activity than older leaves. The younger leaves had a higher flavonoid content, which contributed to their increased antioxidant activity.

Regarding their phytochemical properties, Huda *et al*. (2009) reported that *A. malaccensis* leaves contain antioxidants. In this regard, phytochemical screening shows the presence of alkaloids, steroids, saponins, and flavonoids in *A. malaccensis* leaf extract. As a result, all crude extract of *A. malaccensis* has a high potential as an antioxidant source, especially methanol crude (Huda *et al*., 2009).

Based on the DPPH assay and 2,2'-azino-bis (3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radical assay, flavonoids isolated from ethanolic extract of *A. sinensis* leaves have potential antioxidant activity (Duan *et al*., 2015). In addition, Yang *et al.* (2018) isolated flavonoids from wild *A. sinensis* leaves using sophisticated high-speed counter-current chromatography and a multilayer spiral separation column. The four isolated flavonoids showed nitrite scavenging behaviours, namely apigenin-7,4′-diethyl ether, genkwanin, quercetin, and kaempferol. Figure 1 shows quercetin is the most effective nitrite scavenging, while kaempferol exhibited the least nitrite scavenging properties (Yang *et al*., 2018). Hence, *Aquilaria* leaves can be incorporated into food and beverage products or utilised in pharmaceutical and cosmetic products as they can reduce free radicals and disease occurrence.



Quercetin

Figure 1. Quercetin chemical compound

Anti-diabetic Properties

Diabetes is a growing non-communicable disease affecting up to 693 million adults (Saeedi *et al.*, 2019), increasing the risk of mortality, blindness, and kidney failure (Cole & Florez, 2020). According to the American Diabetes Association (2021), there are four types of diabetes: Type I, Type II, specialised types, and gestational diabetes mellitus. In 2019, over 463 million adults had type 2 diabetes due to obesity, inactivity, and unhealthy dietary habits (Tsunoda *et al*., 2022). Diabetes can be treated by decreasing glucose absorption in the intestine, using α-glucosidase inhibitors to slow glucose uptake (He *et al.*, 2014; Ezzat *et al*., 2017; Tsunoda *et al*., 2022).

Acarbose, the first microorganism-derived drug approved in Europe and the United States, has been found to lower HbA1c and lipid profile better than metformin (He *et al.*, 2014; Tsunoda *et al*., 2022). However, prolonged use can lead to gastrointestinal problems (He *et al*., 2014). Lifestyle changes and pharmacological treatment using drugs can help minimise diabetes-related mortality and morbidity (Marín-Peñalver *et al*., 2016; Blaslov *et al*., 2018), but they may also result in autoimmune assaults, β-cell dysfunction, and insulin resistance in people with diabetes mellitus (Manukumar *et al*., 2017).

Formulations from herbal sources are favoured because they are cost-effective and can prevent secondary complications while posing a minimal risk of complication (Manukumar *et al.*, 2017). Yin *et al*. (2014) and Elbashir *et al*. (2018) discovered that several medicinal plants have significant potential as natural antidiabetic medicines due to their high antioxidant and antidiabetic potential. Thitikornpong *et al*. (2019) reported that the *A. crassna* leaves and isolated mangiferin have a higher α-glucosidase inhibitory effect than acarbose, which is 0.1840 ± 0.0032, 0.5714 ± 0.0044, and 17.3947 ± 0.0189 mg/mL respectively. In this light, mangiferin, as shown in Figure 2, is a vital compound attributed to the antidiabetic properties of *Aquilaria* leaves.

Zulkiflie *et al*. (2013) reported the potential of local *Aquilaria spp.* leaves can be used as antidiabetic drugs. Methanolic extract of *A. malaccensis* and *A. hirta* inhibited α-amylase and α-glucosidase enzymes more effectively than acarbose. The inhibition percentages for α-glucosidase for *A. malaccensis* and *A. hirta* at 1000 µg/ml are higher than acarbose, about 35.14% and 36.42%, respectively. The inhibition percentages for α-amylase for *A. malaccensis* and *A. hirta* at 1000 µg/ml are higher than acarbose, about 23.04% and 18.23%, respectively. The phenolic compounds responsible for the α-glucosidase inhibitory properties of the 70% aqueous ethanolic extract of the leaves of A. sinensis are mangiferin, iriflophenone 3,5-C-β-D-glucopyranoside, iriflophenone 3-C-β-D-glucoside and iriflophenone 2-O-α-L-rhamnopyranoside in which the mangiferin has the highest potency of α-glucosidase inhibitor (Feng *et al.*, 2011).

In addition, iriflophenone 3-C-glucoside (IPG), a compound isolated from *A. sinensis*, was shown in in vitro and in vivo experiments to have a high potential to lower fasting blood glucose levels in mice with streptozotocin (STZ)-induced diabetes and to increase glucose uptake in adipocytes. In this research, IPG was isolated from the leaf extract of *A. sinensis* leaf extract using column chromatography before it was induced in fasting STZ mice. IPG can reduce blood glucose levels by 46.4% and increase glucose uptake by 53% in rats (Pranakhon *et al.*, 2015).

Air-dried *A. malaccensis* leaves extracted with methanol showed the highest α-glucosidase enzyme inhibitory activity, whereas ethanol, chloroform, water, and hexane extract showed shallow values. Methanol appears to be the most effective solvent for *Aquilaria* leaf extraction compared to water and chloroform. Air-dried samples exhibited better α-glucosidase inhibition activity than oven-dried samples. This might be because the oven's high drying temperature destroys some compounds involved in the antidiabetic activity (Ahmad *et al*., 2019).

Both the aqueous and methanol extracts of *A. malaccensis* leaves efficiently reduced normal glucose levels of male ICR mice with streptozotocin diabetes at 50 mg /kg body weight (Fayyadh *et al*., 2020). Furthermore, Said *et al.* (2016) stated that the ethanol and ethyl acetate extract of *A. malaccensis* leaves increased glucose transporter 4 (GLUT4) in the skeletal muscle of diabetic Wistar rats when induced by 0.01 g/kg body weight of *A. malaccensis* leaf extract (Said *et al.*, 2016). Therefore, this shows that *Aquilaria* leaves can be used as green sources of diabetic medication treatment with lower side effects on human health. Table 1 illustrates the antidiabetic activity of *Aquilaria* leaves.

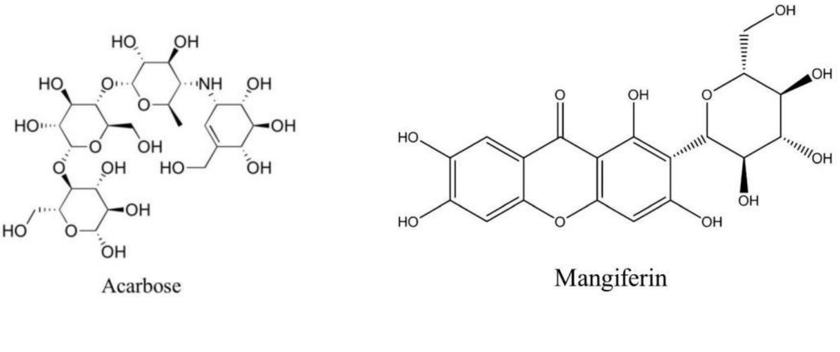


Figure 2. Chemical structure of the acarbose, a drug for Type II diabetes mellitus and mangiferin, an antidiabetic bioactive compound found in *Aquilaria* leaves

Table 1. Antidiabetic activity of the *Aquilaria* leaves

Species	Experiment	Sample tested	Results	References
Aquilaria crassna	α-glucosidase inhibition (IC50)	Leaves extract	0.1840 ± 0.0032 mg/mL	Thitikornpong *et al*. (2019)
		Isolated mangiferin	0.5714 ± 0.0044 mg/mL	
Aquilaria hirta	α-glucosidase inhibition (IC50)	Methanol extract	452.82 µg/mL	Zulkiflie *et al.* (2013)
	α-amylase inhibition (IC50)	Methanol extract	301.99 µg/mL	Zulkiflie *et al.* (2013)
Aquilaria malaccensis	α-glucosidase inhibition (IC50)	Air dried (leaves) ethanolic extract	396.12 ± 6.42 µg/mL	Ahmad *et al.* (2019)
		Air dried (leaves) methanolic extract	196.31 ± 4.11 µg/mL	
		Oven-dried (leaves) ethanolic extract	295.37 ± 5.42 µg/mL	
		Oven-dried (leaves) methanolic extract	598.22 ± 418 µg/mL	
	α-glucosidase inhibition (IC50)	Methanol extract	375.50 µg/mL	Zulkiflie *et al.* (2013)
	α-amylase inhibition (IC50)	Methanol extract	397.23 µg/mL	Zulkiflie *et al,* (2013)
	Glucose uptake in skeletal muscle on rats	Ethanol fraction	Increase the level of GLUT4 by 24.5%	Said *et al*. (2016)
		Ethyl acetate fraction	Increase level of GLUT4 by 20.6%	
Aquilaria sinensis	α-glucosidase inhibition (IC50)	Mangiferin	126.5 ± 14.5 µg/mL	Feng *et al*. (2011)
		Iriflophenone 2-O-a-L-rhamnopyranoside	143.7 ± 10.6 µg/mL	
		Iriflophenone 3-C-b-D-glucoside	165.1 ±11.3 µg/mL	
		Iriflophenone	138.3 ±7.3 µg/mL	
	Test of glucose uptake on rats	Iriflophenone 3-C-β-glucoside	Increase glucose uptake 53% and reduce blood glucose by 46%	Pranakhon *et al*. (2015)

Antibacterial Properties

There are many types of antibiotics widely used in the world. Antibiotics interfere with bacterial cells, including attacking cell walls, inhibiting protein biosynthesis, inhibiting the DNA replication process, and inhibiting folic acid metabolism (Kapoor *et al*., 2017). *Aquilaria* leaves have been reported to have antibacterial properties against various microorganisms. Microorganisms were treated with or exposed to *Aquilaria* leaf extract to observe the effect on the cell. Kammonwannasit *et al.* (2013) reported that cells of the *Staphylococcus epidermidis* treated with extracts swelled and the cell wall ruptured.

The ethanol extract of *A. macrocarpa Baill* also had a minimum inhibitory concentration (MIC) of 1.0 mg/ml against *Staphylococcus aureus* and *Bacillus cereus*, 1.25 mg/mL against *Staphylococcus epidermidis, Pseudomonas aeruginosa, Bacillus subtilis,* and *Escherichia coli*, and 10 mg/mL against *Salmonella typhi* and *Proteus mirabilis* (Sari *et al.,* 2019).

According to Jihadi (2020), an ethanolic leaf extract of *A. malaccensis* proved efficient against multidrug-resistant Gram-negative bacteria. The minimal inhibitory concentrations for *Acinetobacter baumannii* and *Klebsella pneumonia* (ATCC 10031) were 32 mg/mL and 64 mg/mL for *Escherichia coli* and *Klebsella pneumonia* (ATCC 700603), respectively. Furthermore, Sari *et al.* (2019) discovered that the ethanolic extract of *A. malaccensis* had a MIC of 1.25 mg/ml against *Staphylococcus aureus, Bacillus cereus, Staphylococcus epidermidis, Pseudomonas aeruginosa, Bacillus subtilis, Escherichia coli, Salmonella typhi,* and *Proteus mirabilis.*

Furthermore, significant antibacterial activity against *Salmonella enterica and Staphylococcus aureus* has been determined in oven-dried leaves of *A. malaccensis* hexane extract at 150 and 300 mg/ml, respectively (Ahmad *et al.,* 2019). The chloroform extract from *A. malaccensis* also inhibited the culture of gram-positive and gram-negative bacteria, including *Shigella boydii* and *Escherichia coli* (Begum, 2016).

Freeze-dried aqueous extract of A. crassna leaves also showed inhibition against *Staphylococcus epidermidi*s at a 6 mg/ml concentration. The bacterial cells were swollen and disrupted by the extract, and bacterial biofilm development was suppressed. The bacterial cell wall broke down after 24 hours of treatment with the extract (Kamonwannasit *et al.*, 2013).

Dash *et al.* (2008) performed antimicrobial determination of an aqueous extract of *A. malaccensis* leaves at a concentration of 50 mg/ml and showed zonation inhibition in *Shigella flexneri* and *Pseudomonas aeruginosa* at 18 mm and 15 mm, respectively. In addition, the methanolic extract of *A. malaccensis* at a concentration of 50 mg/ml showed inhibition of *Shigella flexneri*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* with 15 mm, 14 mm and 15 mm, respectively (Dash *et al.*, 2008). Thus, the antibacterial properties of *Aquilaria* leaves can be used to develop pharmaceutical and cosmetic products such as anti-acne products and wound treatment. The antibacterial activity of *Aquilaria* leaf is shown in Table 2.

Table 2. Antimicrobial activity of the *Aquilaria* leaves

Species	Extraction	Assay	Microogranism	Result	Reference
Aquilaria microcarpa	Ethanolic extract	Disc diffusion method	*Escherichia coli*	6.11 ± 0.02 mm	Sari *et al.* (2019)
			Staphylococcus aureus	6.12 ± 0.02 mm	
			Bacillus cereus	6.07 ± 0.02 mm	
	Ethanolic extract	MIC	*Escherichia coli*	1.25 mg/mL	
			Staphylococcus aureus, Bacillus cereus	1.25 mg/mL	
Aquilaria crassna	Aqueous extract	MIC	*Staphylococcus epidermidis*	6.00 mg/mL	Kammonwannasit *et al.* (2013)
		Determination of minimum bactericidal concentration	*Staphylococcus epidermidis*	12 mg/mL	
Aquilaria malaccensis	Ethanolic extract	Disc diffusion method	*Escherichia coli*	6.39 ± 0.02 mm	Sari *et al.* (2019)
			Staphylococcus aureus	6.73 ± 0.02 mm	
			Bacillus cereus	6.81 ± 0.02 mm	
	Ethanolic extract	MIC	*Escherichia coli, Staphyococcus aureus, Bacillus cereus*	1.25 mg/ml	
	Aqueous extract	Disc diffusion method	*Escherichia coli, Staphyococcus aureus*	6.67 mm	Hendra *et al.* (2016)
	Methanolic extract			6.83 mm	
Aquilaria agallocha	Methanolic extract	Agar cup plate method	*Bacillus subtillis*	19.00 mm	Dash *et al.* (2008)

Anti-inflammatory Properties

Inflammation occurs in response to the invasion of foreign organisms, such as pathogenic microorganisms and dust particles, that begin to disrupt the process of tissue repair and restoration of normal body homeostasis to protect the body (Arulselvan *et al.*, 2016; Azab *et al*., 2016; Eissa *et al.*, 2020). Inflammation is classified into two groups: acute inflammation, which is a simple process that can continue for a few minutes or up to a few days, and whose main characteristic is the leakage of plasma proteins or fluid and the movement of leukocytes to extravascular areas, and chronic inflammation, an essential response of the body's immune system (Arulselvan *et al.*, 2016). Several studies have reported that inflammation causes chronic and degenerative diseases (Arulselvan *et al.*, 2016; Eissa *et al*., 2020).

In the meantime, synthetic anti-inflammatory drugs can have intolerable side effects on human health, such as organ damage, developmental disorders, and gastrointestinal bleeding (Eissa *et al*., 2020; Wojcieszyska *et al*., 2022). Thus, herbal drinks are recognised globally as a traditional medicine capable of reducing inflammation. Researchers are interested in developing efficient and safe bio-based alternative chemicals for treating and preventing inflammation to avoid the adverse effects of synthetic drugs (Eissa *et al*., 2020). Polyphenolic compounds can be anti-inflammatory agents by lowering the release of inflammatory mediators and stabilising cell membranes (Adam *et al*., 2017).

Aquilarinoside A, iriflophenone, 7-b–D-glucoside of 5-O-methyl apigenin, 5-O-xylosylglycoside of 7-O-methyl apigenin, luteolin, genkwanin, hydroxygenkwanin, aquisiflavoside, iriflophenone 3,5-C-β-D-diglucoside, iriflophenone 3-C-β-D-glucoside, mangiferin, and genkwanin 5-O-β-primevoside have been attributed anti-inflammatory properties in *Aquilaria* leaves (Eissa *et al*., 2020). Qi *et al.* (2009) found that hydroxygenkwanin and luteolin (Figure 3) were compounds with IC50 of 0.80 ± 0.13 μmol/L and 2.03 ± 0.24 μmol/L respectively, that had the highest inhibitory activity against neutrophil respiratory burst.

Eissa *et al.* (2018) showed that the in-vitro study of leaf extract of *A. malaccensis* inhibited protein (albumin) denaturation in a dose-dependent manner in the studied concentration range of 400-16000 g/mL. In addition, the aqueous extract of *A. crassna* was reported to have potent inhibition of interleukin-1α (IL-1α) and interleukin-8 (IL-8), while 70% of the ethanol extract displayed inhibition of IL-1α only (Wongwad *et al.*, 2019). Besides, a single oral administration with *A. sinensis* leaf extract at a dose of 848 mg/kg can minimise the inflammation generated by xylene or carrageenan injection into the paw of mice (Zhou *et al.*, 2008, as referenced in Chiangsaen *et al.*, 2016).

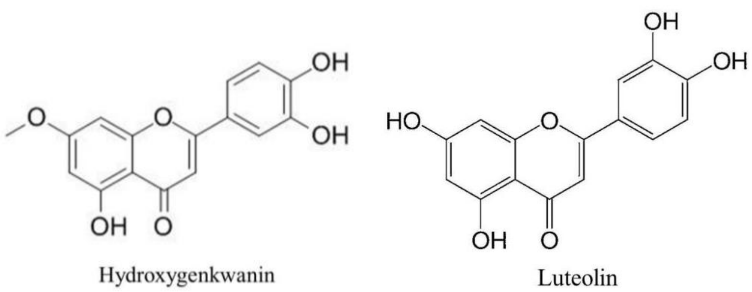


Figure 3. Chemical compounds found in *A. malaccensis* leaf that have a significant anti-inflammatory effect

Gastrointestinal Regulation (Laxative Effect)

Constipation could lead to intestinal obstruction in the human gastrointestinal tract due to the difficulty and pain in the movement of stiff stools. This issue should be treated promptly, as severe constipation might require surgery (Forootan *et al.*, 2018). There are two significant causes of constipation. First, the main reason is the slow movement of stool or constipation of the bowel outlet. The second reason is inadequate water intake, metabolic disorders, medication use, neurological disorders, myopathic disorders, and structural abnormalities (Jani & Marsicano, 2018).

Jani and Marsicano (2018) reported that patients suffering from constipation should increase their fibre and water intake, exercise healthily, and regularly perform toilet training. Apart from this practice, patients are also advised to take medications with laxative effects, such as lubiprostone, linaclotide, magnesium oxide, and sennoside (Figure 4) (Kakino *et al.*, 2010[a]; Kakino *et al.*, 2010[b]; Forootan *et al.*, 2018). When the laxative agent is ingested, the laxative helps retain fluid or water in the stool to soften the consistency, increase secretion in the bowel, lubricate the stool movement and decrease the surface tension (Portalatin & Winstead, 2012; Bashir & Sizar, 2019)

However, ingestion of linaclotide affects visceral afferent neurons and reduces nociception, whereas ingestion of lubiprostone causes mild to moderate nausea and diarrhoea (Wilson & Schey, 2015). Furthermore, medications commonly used for constipation treatment, such as magnesium oxide or sennoside, the primary component of senna, lead to severe diarrhoea (Kakino *et al.*, 2010[a]). This could be due to genkwanin 5-O-β-primeveroside (Figure 4) and mangiferin, which exhibit laxative properties (Kakino *et al*., 2010[b]). Hence, this shows that the *Aquilaria* leaves can be used to develop medication for constipation and bowel movement problems as the leaves can exhibit laxative properties. Several studies have reported that *Aquilaria* leaves have a laxative effect on constipation (Table 3) (Hara *et al*., 2008; Kakino *et al*., 2010[a]; Kakino *et al*., 2010[b]; Ito *et al*., 2012).

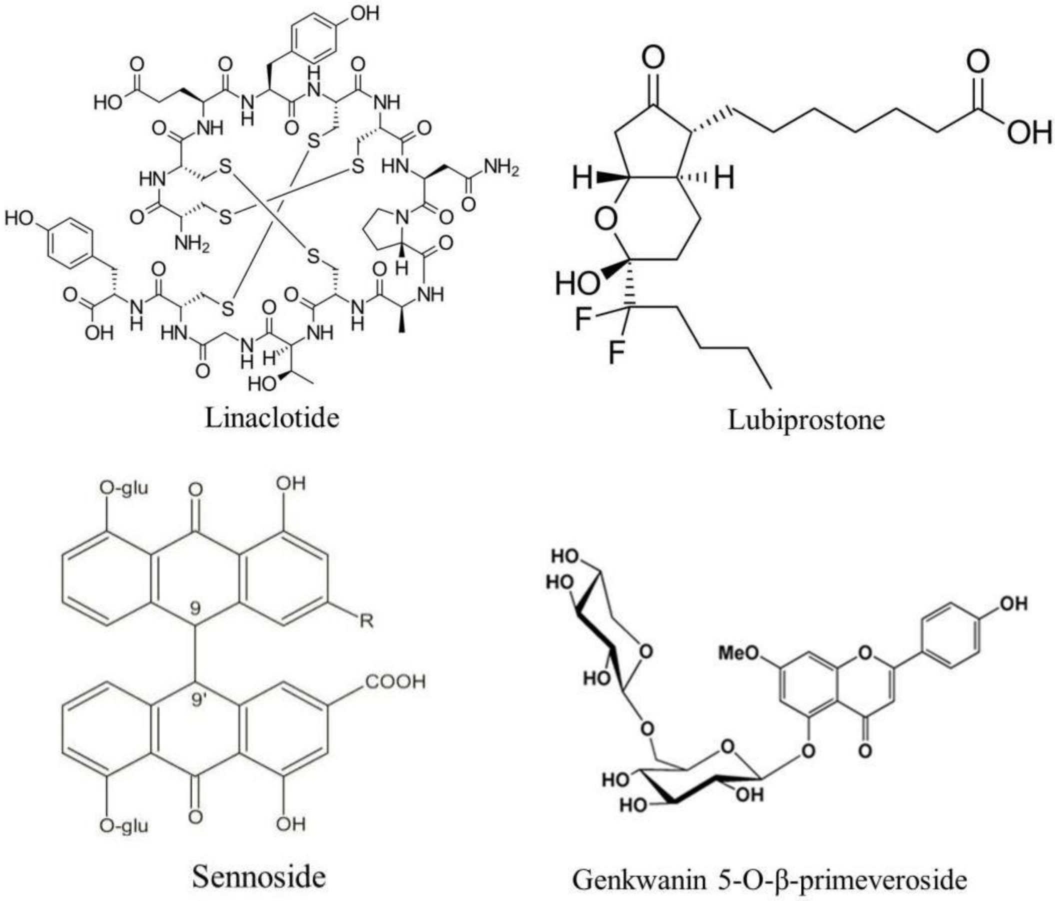


Figure 4. The chemical compound of the drugs for gastrointestinal disease, linaclotide lubiprostone, sennoside, and genkwanin 5-O-β-primeveroside

Table 3. Laxative effect of *Aquilaria* leaves

Species	Test conducted	Sample tested	Results	References
A. sinensis	In vivo test on rat / mice	Ethanol extract	Restored the stool frequency and weight to about 91 to 99 %	Kakino *et al*., (2010[b])
		Acetone–methanol extract	Reduced the diarrhea frequency in mice	Hara *et al.*, (2008)
A. crassna		Ethanol extract	Restored the stool frequency and weight to about 111 to 116 %	Kakino *et al*., (2010[b])
		Ethanol extract	Several compounds isolated from the extract are capable of increasing the stool frequency	Ito *et al*., (2012)

Table 4. Toxicity of *Aquilaria* leaves

Aquilaria species	Sample	Testing subject	Leaves toxicity	Dosage of toxicity	Reference
A. malaccensis	Methanolic extract	Human cells	Cytotoxic activity on peripheral blood mononuclear cells and results in DNA fragmentation	IC50 = 24.5 mg /mL LD50 = 4537 mg/kg	Adam *et al*. (2018)
	Aqueous extract	Rats	Shows toxicity towards liver and kidney of rats	2000 mg/kg	Razak *et al*. (2018)
A. sinensis	Extract	Mice	No symptom of toxicity on mice sperm and bone marrow after oral fed	Not detected	Li *et al.* (2015)
	Extract	*Salmonella* cell	No signs of toxicity with salmonella reversion test	Not detected	Li *et al.* (2015)
A. crassna	Ethanolic extract	Mice	No signs of toxicity	Higher than 2000 mg/kg	Ghan *et al.* (2016)
	Aqueous extract		No sign of abnormalities or death	Higher than 15,000 mg/kg	Kamonwannasit *et al*. (2013)
	Hydro distilled essential oils		No signs of toxicity	LD50 = 2000 mg/kg	Dahham *et al.* (2016).
A. subintegra	Chloroform extract	Brine shrimp	Low to moderate toxicity	LC50=531.18 ± 49.53 µg/mL	Bahrani *et al.* (2014)
		Human cells	No cytotoxic activity	Not detected	Bahrani *et al.* (2014)

Cytotoxicity of *Aquilaria* leaves

Natural product demand has sparked scientific curiosity about their biological impacts. As a result, additional research is required to evaluate their harmful effects and to define acceptable intake thresholds for safe use. This is because some extremely toxic active compounds found in plant extracts or natural goods might harm people (Adam *et al*., 2018).

Inoculation of *Aquilaria* trees using fungi is safe to handle and does not significantly impact the environment (Kahar *et al.,* 2021). Inoculation can be done by physical or mechanical methods, chemistry, and microorganisms (Tan *et al.,* 2019). Chemical induction can have questionable effects on the result of agarwood trees directly or indirectly to humans. However, Tan *et al*. (2019) concluded that the induction mechanism of *Aquilaria* trees only affects the stem part, which leads to the formation of agarwood, while the effect on the leaves and roots is small.

Adam *et al.* (2018) stated that the methanolic extract of *A. malaccensis* had a cytotoxic effect and can be classified as mildly hazardous Class III. *A. malaccensis* leaves methanol extract also causes DNA fragmentation with a comet-like appearance in human peripheral blood mononuclear cells (PBMCs), indicating that it is genotoxic (Adam *et al.*, 2018). Furthermore, *A. malaccensis* was found to be toxic to the liver and kidneys of rats in a sub-acute toxicity study at a concentration of 2000 mg/kg aqueous extract (Razak *et al.*, 2018).

According to Bahrani *et al.* (2014), the chloroform extract from *A. subintegra* leaf extract displayed minimal toxicity in the brine shrimp fatality experiment at a concentration of LC50 = 531.18 ± 49.53 g/mL. *A. sinensis (Lour.) Gilg*. leaves had an acute oral LD50 of more than 21.5 g/kg in mice. Each dosing group's micronucleus rate, sperm shape abnormalities, and frequency of reverse mutations were not substantially different from the negative control (Li *et al*., 2015).

Next, the suggested oral LD50 in female mice of crude ethanol extract of *A. crassna* (CE), young leaves containing a mixture of α-tocopherol (α-TOH) and CE/α-TOH is estimated to be more than 2000 mg/kg (Ghan *et al*., 2016). After administering a high dose of 15,000 mg/kg aqueous extract of *A. crassna* leaves, the mice showed no aberrant toxicity or death (Kamonwannasit *et al.*, 2013). Furthermore, the LD50 of *A. crassna* hydro distilled essential oils in female Swiss mice was more significant than 2000 mg/kg (Dahham *et al.*, 2016). The cytoxicity of *Aquilaria* leaves is shown in Table 4.

CONCLUSION

Aquilaria leaf extract has potent antioxidants and antidiabetic, antibacterial, anti-inflammatory, and laxative effects. The leaves of the species *A. malaccensis, A. sinensis* and *A. crassna* have been shown to have antioxidant properties that inhibit free radical scavenging activity. These leaves have antioxidants which capable of inhibiting free radical scavenging activity. The content of antioxidant-active leaves is influenced by the locations of the cultivated plant, the maturity of the leaves, the type of species, and the method of leaf extraction.

In addition, several bioactive compounds in the *Aquilaria* leaves, including mangiferin, iriflophenone 3,5-C-β-D-glucopyranoside, iriflophenone 3-C-β-D-glucoside, and iriflophenone 2-O-α-L-rhamnopyranoside have potential as an antidiabetic agent. Mangiferin in the leaf extract of *A. sinensis* and *A. malaccensis* has shown the ability to increase glucose transport and decrease blood glucose. In addition, most *Aquilaria* leaves have antibacterial properties against gram-positive and gram-negative bacteria.

Furthermore, *Aquilaria* leaves contain hydroxygenkwanin and luteolin, which have anti-inflammatory properties, while genkwanin 5-O-β-primeveroside has a beneficial laxative effect. Although the extract from *Aquilaria* leaves is generally safe, the extract from the leaves of the species *A. malaccensis* is slightly harmful to the DNA of humans and rats. Therefore, it should be taken only in small amounts.

In conclusion, *Aquilaria* leaves have great potential and are suitable for use in the food and beverages, pharmaceutical and cosmeceutical industries, as they can also benefit human health. *Aquilaria* leaves can be incorporated into food and beverage products and utilised as functional food. Besides, it can be used for medication for diabetics and constipation, as well as a good source of antioxidants. In addition, *Aquilaria* leaves also have good antibacterial and anti-inflammatory properties, which can be used to develop pharmaceutical and cosmetic products. However, further study on the in-vivo cytotoxicity is essential for the safety of the consumer.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

FUNDING

This research was supported by Ministry of Higher Education (MOHE) through Prototype Development Research Grant Scheme (PRGS), PRGS/1/2024/SKK01/UTHM/02/1 for a study framework and Universiti Tun Hussien Onn Malaysia (UTHM) through a Research Enhancement Graduate Grant, RE-GG (vot Q057) for a graduate research assistant.

ACKNOWLEDGMENTS

This research was supported by Ministry of Higher Education (MOHE) through Prototype Development Research Grant Scheme (PRGS), PRGS/1/2024/SKK01/UTHM/02/1 and Universiti Tun Hussien Onn Malaysia (UTHM) through a Research Enhancement Graduate Grant, RE-GG (vot Q057). This research was also conducted in collaboration with Synergy One Holding Sdn. Bhd. as an industry partner.

REFERENCES

Adam, A.Z., Lee, S.Y. & Mohamed, R. (2017). Pharmacological properties of agarwood tea derived from *Aquilaria (Thymelaeaceae)* leaves: An emerging contemporary herbal drink. *Journal of Herbal Medicine*, 10: 37-44. DOI:10.1016/j.hermed.2017.06.002

Adam, A.Z., Tajuddin, S.N., Sudmoon, R., Chaveerach, A., Abdullah, U.H., Mahat, M.N. & Mohamed, R. (2018). Chemical constituents and toxicity effects of leaves from several agarwood tree species (*Aquilaria*). *Journal of Tropical Forest Science*, 30(3): 342-353. DOI:10.26525/jtfs2018.30.3.342353

Adhikari, S.R., Pokhrel, K. & Baral, S.D. (2021). Economic value of agarwood and its prospects of cultivation. *International Journal of Applied Sciences and Biotechnology*, 9(1): 23-31. DOI: 10.3126/ijasbt.v9i1.35984

Ahmad, W.N.A.W., Ali, A.M., Wan Mamat, W.N.A. & Mahmod, N.H. (2019). Evaluation of DPPH free radical scavenging, α-glucosidase inhibitory, and antimicrobial activities of *Aquilaria malaccensis* leaf extracts. *Journal of Agrobiotechnology*, 10(1): 36-45. DOI: 10.13140/RG.2.2.25987.35368

American Diabetes Association. (2021). 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021. *Diabetes care*, 44(Supplement_1): S15-S33. DOI:10.2337/dc21-S002.

Arulselvan, P., Fard, M.T., Tan, W.S., Gothai, S., Fakurazi, S., Norhaizan, M.E. & Kumar, S.S. (2016). Role of antioxidants and natural products in inflammation. *Oxidative Medicine and Cellular Longevity*, 2016(1): p.5276130. DOI:10.1155/2016/5276130

Azab, A., Nassar, A. & Azab, A.N. (2016). Anti-inflammatory activity of natural products. *Molecules*, 21(10): 1321. DOI:10.3390/molecules21101321

Bahrani, J.M., Paydar, M. & Rothan, H.A. (2014). Isolation and characterisation of acetylcholinesterase inhibitors from *Aquilaria subintegra* for the treatment of Alzheimer's disease (AD). *Current Alzheimer Research*, 11(2): 1-9. DOI:10.2174/1567205011666140130151344

Bashir, A. & Sizar, O. (2019). *Laxatives.* StatPearls Publishing LLC.

Batubara, R., Hanum, T.I., Risnasari, I., Ginting, H. & Lubis, L.A. (2018). Antioxidant activity and preferences test of agarwood leaves tea (*Aquilaria malaccensis lamk*) based on leaves drying methods. *Proceedings of BROMO Conference, Indonesia*, 2018: 159-163. DOI:10.5220/0008359101590163.

Begum, Y. (2016). Study on agarwood (*Aquilaria malaccensis*) to evaluate antibacterial and antioxidant activities of n-hexane, chloroform and ethyl acetate extracts. *PharmaTutor*, 4(2): 47-50. https://www.pharmatutor.org/magazines/articles/february-2016/study-agarwood-aquilaria-malaccensis-evaluate-antibacterial-antioxidant-activities

Blaslov, K., Naranđa, F.S., Kruljac, I. & Renar, I.P. (2018). Treatment approach to type 2 diabetes: Past, present and future. *World Journal of Diabetes*, 9(12): 209. DOI: 10.4239/wjd.v9.i12.209

Chiangsaen, P., Taepavarapruk, P., Wongwad, E., Ingkaninan, K. & Taepavapruk, N. (2016). Screening of the central nervous system action of agarwood leaves extract in female ovariectomized rats. *Proceedings of the Mae Fah Luang University International Conference 2016, Chiang Rai, Thailand* (21-30).

Ciocan, A.G., Tecuceanu, V., Enache-Preoteasa, C., Mitoi, E.M., Helepciuc, F.E., Dimov, T.V., Simon-Gruita, A. & Cogălniceanu, G.C. (2023). Phenological and Environmental Factors' Impact on Secondary Metabolites in Medicinal Plant Cotinus coggygria Scop. *Plants*, 12(9): 1762. DOI:10.3390/plants12091762

Cole, J.B. & Florez, J.C. (2020). Genetics of diabetes mellitus and diabetes complications. *Nature Reviews Nephrology*, 16(7): 377-390. DOI:10.1038/s41581-020-0278-5

Dahham, S.S., Hassan, L.E.A., Ahamed, M.B.K., Majid, A.S.A., Majid, A.M.S.A. & Zulkepli, N.N. (2016). In vivo toxicity and antitumor activity of essential oils extract from agarwood (*Aquilaria crassna*). *BMC Complementary and Alternative Medicine*, 16(1): 1-11. DOI:10.1186/s12906-016-1210-1

Dash, M., Patra, J.K. & Panda, P.P. (2008). Phytochemical and antimicrobial screening of extracts of *Aquilaria agallocha Roxb*. *African Journal of Biotechnology,* 7(20): 3531-3534. DOI: 10.5897/AJB08.623

Desa, A.P., Lee, S.Y., Mustapa, M.Z., Mohamed, R. & Emang, D. (2021). Trends in the agarwood industry of Peninsular Malaysia. *The Malaysian Forester*, 84(1): 152-168. https://malaysianforester.my/forestry/archives_journal_volume.php?volume=84&nombor=1

Duan, Z.W., Li, W.G., Dou, Z.H., Xie, H., He, A. & Shi, M., (2015). Extraction and antioxidant activity of flavonoids from *Aquilaria sinensis (Lour.) Gilg* leaves. *Journal of Food Science.,* 36, 45-50. DOI: 10.7506/spkx1002-6630-201506009.

Eissa, M.A., Hashim, Y.Z.H.Y., Salleh, H.M., Abd-Azziz, S.S., Isa, M.L.M., Warif, N.M.A., Nor, Y.A., El-Kersh D.M. & Sani, M.S.A. (2020). *Aquilaria* species as potential anti-inflammatory agents–A review on in vitro and in vivo studies. *Indian Journal of Natural Products and Resources,* 11(3): 141-154.

Elbashir, S.M.I., Devkota, H.P., Wada, M., Kishimoto, N., Moriuchi, M., Shuto, T., Misumi, S., Kai H. & Watanabe, T. (2018). Free radical scavenging, α-glucosidase inhibitory and lipase inhibitory activities of eighteen Sudanese medicinal plants. *BMC Complementary and Alternative Medicine*, 18: 1-12. DOI:10.1186/s12906-018-2346-y

Ezzat, S.M., Motaal, A.A. & El Awdan, S.A.W. (2017). In vitro and in vivo antidiabetic potential of extracts and a furostanol saponin from *Balanites aegyptiaca*. *Pharmaceutical Biology*, 55(1): 1931-1936. DOI:10.1080/13880209.2017.1 343358

Fayyadh, A.A., Ibrahim, H., Zain, H.H.M. & Al-Qubaisi, M.S. (2020). The effect of agarwood leaf extracts on blood glucose level of type II diabetes mellitus in ICR male mice. *Research Journal of Pharmacy and Technology*, 13(1): 237-242. DOI : 10.5958/0974-360X.2020.00048.7

Feng, J., Yang, X. W. & Wang, R. F. (2011). Bio-assay guided isolation and identification of α-glucosidase inhibitors from the leaves of *Aquilaria sinensis*. *Phytochemistry*, 72(2-3): 242-247. DOI:10.1016/j.phytochem.2010.11.025

Forootan, M., Bagheri, N. & Darvishi, M. (2018). Chronic constipation: A review of literature. *Medicine*, 97(20). DOI: 10.1097/MD.0000000000010631

Ghan, S.Y., Chin, J.H., Thoo, Y.Y., Yim, H.S. & Ho, C.W. (2016). Acute oral toxicity study of *Aquilaria crassna* and [alpha]-tocopherol in mice. *International Journal of Pharmaceutical Sciences and Research*, 7(4): 1456-1461. DOI: 10.13040/IJPSR.0975-8232.7(4).1456-61

Hashim, Y.Z.H.Y., Kerr, P.G., Abbas, P. & Salleh, H.M. (2016). Aquilaria spp.(agarwood) as source of health beneficial compounds: A review of traditional use, phytochemistry and pharmacology. *Journal of Ethnopharmacology*, 189: 331-360. DOI:10.1016/j.jep.2016.06.055

Hara, H., Ise, Y., Morimoto, N., Shimazawa, M., Ichihashi, K., Ohyama, M. & Iinuma, M. (2008). Laxative effect of agarwood leaves and its mechanism. *Bioscience, Biotechnology, and Biochemistry*, 72(2): 335-345. DOI:10.1271/bbb.70361

He, K., Shi, J.C. & Mao, X.M. (2014). Safety and efficacy of acarbose in the treatment of diabetes in Chinese patients. *Therapeutics and Clinical Risk Management*, 505-511. DOI: 10.2147/TCRM.S50362

Hendra, H., Moeljopawiro, S. & Nuringtyas, T. R. (2016). *Antioxidant and antibacterial activities of agarwood (Aquilaria malaccensis Lamk.) leaves.* Advances of Science and Technology for Society: Proceedings of the 1st International Conference on Science and Technology 2015. Yogyakarta, Indonesia. DOI:10.1063/1.4958565

Hsiao, S.W., Wu, Y.C., Mei, H.C., Chen, Y.H., Hsiao, G. & Lee, C.K. (2021). Constituents of *Aquilaria sinensis* leaves upregulate the expression of matrix metalloproteases 2 and 9. *Molecules*, 26(9): 2537. DOI:10.3390/molecules26092537

Huda, A.W.N., Munira, M.A.S., Fitrya, S.D. & Salmah, M. (2009). Antioxidant activity of *Aquilaria malaccensis (Thymelaeaceae)* leaves. *Pharmacognosy Research*, 1(5): 270-273. https://www.phcogres.com/article/2009/1/5/nil-4

Ibrahim, A. (2016). *Comparative analysis of in vitro bioactivities and phenolic content of leaf extracts from six species of Aquilaria* (Doctoral dissertation, Universiti Sains Malaysia).

Ito, T., Kakino, M., Tazawa, S., Watarai, T., Oyama, M., Maruyama, H., Araki, Y., Hara, H. & Iinuma, M. (2012). Quantification of polyphenols and pharmacological analysis of water and ethanol-based extracts of cultivated agarwood leaves. *Journal of Nutritional Science and Vitaminology*, 58(2): 136-142. DOI:10.3177/jnsv.58.136

Jani, B. & Marsicano, E. (2018). Constipation: evaluation and management. *Missouri Medicine*, 115(3): 236-240. https://www.msma.org/Missouri-Medicine-Library

Kahar, E.E.M., Talip, B.A., Mohd Fauzi, N.A., Kamarulzaman, S.N., Zakaria, F., Muhammad, N., Mamat T.N.A.R. & Basri, H. (2021). Properties and potential of agarwood hydrosol as a drink: A review. *Food Research*, 5(3): 29-35. DOI:10.26656/fr.2017.5(3).382

Kakino, M., Tazawa, S., Maruyama, H., Tsuruma, K., Araki, Y., Shimazawa, M. & Hara, H. (2010[a]). Laxative effects of agarwood on low-fiber diet-induced constipation in rats. *BMC Complementary and Alternative Medicine*, 10(68): 1-8. DOI:10.1186/1472-6882-10-68

Kakino, M., Izuta, H., Ito, T., Tsuruma, K., Araki, Y., Shimazawa, M., Oyama, M., Iinuma, M. & Hara, H. (2010[b]). Agarwood induced laxative effects via acetylcholine receptors on loperamide-induced constipation in mice. *Bioscience, Biotechnology, and Biochemistry*, 74(8): 1550-1555. DOI:10.1271/bbb.100122

Kamonwannasit, S., Nantapong, N., Kumkrai, P., Luecha, P., Kupittayanant, S. & Chudapongse, N. (2013). Antibacterial activity of *Aquilaria crassna* leaf extract against *Staphylococcus epidermidis* by disruption of cell wall. *Annals of Clinical Microbiology and Antimicrobials*, 12(20): 1-7. DOI:10.1186/1476-0711-12-20

Kapoor, G., Saigal, S. & Elongavan, A. (2017). Action and resistance mechanisms of antibiotics: A guide for clinicians. *Journal of Anaesthesiology Clinical Pharmacology*, 33(3): 300. DOI: 10.4103/joacp.JOACP_349_15

Kenzo, T., Yoneda, R., Tanaka-Oda, A. & Azani, M.A. (2019). Growth performance and leaf ecophysiological traits in three *Aquilaria* species in Malaysia. *New Forests*, 50: 699-715. DOI:10.1007/s11056-018-09693-7

Krishnaiah, D., Bono, A., Sarbatly, R., Nithyanandam, R. & Anisuzzaman, S.M. (2015). Optimisation of spray drying operating conditions of *Morinda citrifolia L*. fruit extract using response surface methodology. *Journal of King Saud University-Engineering Sciences*, 27(1): 26-36. DOI:10.1016/j.jksues.2012.10.004

Kuntorini, E.M., Nugroho, L.H. & Nuringtyas, T.R. (2022). Maturity effect on the antioxidant activity of leaves and fruits of *Rhodomyrtus tomentosa* (Aiton.) Hassk. *AIMS Agriculture and Food*, 7(2): 282-296. DOI: 10.3934/agrfood.2022018

Lee, S.Y. & Mohamed, R. (2016). The origin and domestication of *Aquilaria*, an important agarwood-producing genus. *Agarwood: Science Behind the Fragrance*, 1-20. Springer, Singapore. DOI:10.1007/978-981-10-0833-7_1

Li, Q., Huang, J., Yang, Y., Chen, M., Liang, Y. & Chen, X. (2015). Research on the acute toxicity and genetic toxicity of *Aquilaria sinensis (Lour.) Gilg: leaf*. *China Journal of Health Laboratory Technology*, 25: 1518-1521.

Maharani, R., Fernandes, A., Turjaman, M., Lukmandaru, G. & Kuspradini, H. (2016). The characterization of Phytochemical and GC-MS analysis on Borneo agarwood (*Aquilaria malaccensis* Lamk) leaves and its utilization as an anti-browning in apple juice. *International Journal of Pharmacognosy and Phytochemical Research*, 8(10): 1576-1582. https://ijppr.com/volume8issue10/

Manukumar, H.M., Shiva Kumar, J., Chandrasekhar, B., Raghava, S. & Umesha, S. (2017). Evidence for diabetes and insulin mimetic activity of medicinal plants: present status and future prospects. *Critical Reviews in Food Science and Nutrition*, 57(12): 2712-2729. DOI:10.1080/10408398.2016.1143446

Marín-Peñalver, J.J., Martín-Timón, I., Sevillano-Collantes, C. & del Cañizo-Gómez, F.J. (2016). Update on the treatment of type 2 diabetes mellitus. *World Journal of Diabetes*, 7(17): 354-395. DOI: 10.4239/wjd.v7.i17.354

Nadeem, M. & Zeb, A. (2018). Impact of maturity on phenolic composition and antioxidant activity of medicinally important leaves of Ficus carica L. *Physiology and molecular biology of plants*, 24: 881-887. DOI: 10.1007/s12298-018-0550-3

Pranakhon, R., Aromdee, C. & Pannangpetch, P. (2015). Effects of iriflophenone 3-C-β-glucoside on fasting blood glucose level and glucose uptake. *Pharmacognosy magazine*, 11(41): 82-89. DOI: 10.4103/0973-1296.149711

Pranakhon, R., Pannangpetch, P. & Aromdee, C. (2011). Antihyperglycemic activity of agarwood leaf extracts in STZ-induced diabetic rats and glucose uptake enhancement activity in rat adipocytes. *Songklanakarin Journal of Science & Technology*, 33(4): 405-410. https://sjst.psu.ac.th/search.php

Portalatin, M. & Winstead, N. (2012). Medical management of constipation. *Clinics in colon and rectal surgery*, 25(01): 012-019. DOI: 10.1055/s-0032-1301754

Qi, J., Lu, J.J., Liu, J.H. & Yu, B.Y. (2009). Flavonoid and a rare benzophenone glycoside from the leaves of *Aquilaria sinensis*. *Chemical and Pharmaceutical Bulletin*, 57(2): 134-137. DOI:10.1248/cpb.57.134

Rashid, Z.M., Nasir, N.N.M., Ahmad, W.N.W. & Mahmod, N.H. (2020). α-glucosidase inhibition, DPPH scavenging and chemical analysis of polysaccharide extracts of *Aquilaria* sp. leaves. *Journal of Agrobiotechnology*, 11(2): 59-69. DOI:10.37231/jab.2020.11.2.225

Razak, R.N.H.A., Ismail, F., Isa, M.L.M., Wahab, A.Y.A., Muhammad, H., Ramli, R. & Ismail, R.A.S.R. (2019). Ameliorative effects of *Aquilaria malaccensis* leaves aqueous extract on reproductive toxicity induced by cyclophosphamide in male rats. *The Malaysian journal of medical sciences: MJMS*, 26(1): 44. DOI: 10.21315/mjms2019.26.1.4

Said, F., Kamaluddin, M.T. & Theodorus, (2016). Efficacy of the *Aquilaria malaccensis* leaves active fraction in glucose uptake in skeletal muscle on diabetic wistar rats. *International Journal of Health Sciences & Research.* 6(7): 162-167. https://www.ijhsr.org/archive_ijhsr_vol.6_issue7.html

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A.A., Ogurtsova, K., Shaw, J.E., Dominic B. & Williams R. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice*, 157: 107843. DOI:10.1016/j.diabres.2019.107843

Sari, R., Kartika, E. & Apridamayanti, P. (2019). Antibacterial activity from ethanolic extract karas (*Aquilaria* sp.) leaves against pathogenic bacteria. *European Journal of Biomedical and Pharmaceutical Sciences,* 6(2): 80-82. https://www.ejbps.com/ejbps/abstract_id/5413

Su, L.J., Zhang, J.H., Gomez, H., Murugan, R., Hong, X., Xu, D., Jiang, F. & Peng, Z.Y. (2019). Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis. *Oxidative medicine and cellular longevity*, 2019. DOI:10.1155/2019/5080843

Surjanto, Batubara, R., Hanum, T.I. & Pulungan, W. (2019 May). Phytochemical and antioxidant activity of gaharu leaf tea (*Aquilaria malaccensis* Lamk) as raw material of tea from middle Tapanuli Regency, North Sumatera Province. In *IOP Conference Series: Earth and Environmental Science*. 260(1): 012101. IOP Publishing. DOI:10.1088/1755-1315/260/1/012101

Tan, C.S., Isa, N.M., Ismail, I. & Zainal, Z. (2019). Agarwood induction: current developments and future perspectives. *Frontiers in Plant Science,* 10: 122. DOI:10.3389/fpls.2019.00122

Thitikornpong, W., Palanuvej, C. & Ruangrungsi, N. (2019). In vitro antidiabetic, antioxidation and cytotoxicity activities of ethanolic extract of *Aquilaria crassna* leaves and its active compound; mangiferin. *Indian Journal of Traditional. Knowledge*, 18(1): 144-150. https://www.researchgate.net/publication/330668706_In_vitro_antidiabetic_antioxidation_and_cytotoxicity_activities_of_ethanolic_extract_of_aquilaria_crassna_leaves_and_its_active_compound_mangiferin

Tsunoda, T., Samadi, A., Burade, S. & Mahmud, T. (2022). Complete biosynthetic pathway to the antidiabetic drug acarbose. *Nature Communications,* 13(3455): 1-12. DOI:10.1038/s41467-022-31232-4

Wang, S., Yu, Z.X., Wang, C.H., Wu, C.M., Guo, P. & Wei, J.H., (2018). Chemical constituents and pharmacological activity of agarwood and Aquilaria plants. *Molecules*, 23(2): 342–363. DOI:10.3390/molecules23020342

Wangiyana, I.G.A.S., Supriadi, Nikmatullah, A. & Sunarpi., (2022). A mini review on agarwood tea development towards alternative utilization of agarwood commodity in Indonesia: mini review: Agarwood tea development. *Biological Sciences*, 65(2): 189-196. DOI:10.52763/PJSIR.BIOL.SCI.65.2.2022.189.196

Wongwad, E., Pingyod, C., Saesong, T., Waranuch, N., Wisuitiprot, W., Sritularak, B., Temkitthawon, P. & Ingkaninan, K. (2019). Assessment of the bioactive components, antioxidant, antiglycation and anti-inflammatory properties of *Aquilaria crassna* Pierre ex Lecomte leaves. *Industrial crops and products*, 138: 111448. DOI: 10.1016/j.indcrop.2019.06.011

Xu, W., Cheng, Y., Guo, Y., Yao, W. & Qian, H. (2022). Effects of geographical location and environmental factors on metabolite content and immune activity of Echinacea purpurea in China based on metabolomics analysis. *Industrial Crops and Products*, 189: 115782. DOI: 10.1016/j.indcrop.2022.115782

Zainurin, N.A.A., Samsudin, N., Hashim, Y.Z.H.Y., Al-Khatib, M.F.R., Azmin, N.F.M. & Maifiah, M.H.M. (2020). Response surface optimization of the yield of agarwood (*Aquilaria malaccensis*) leaf extract using soxhlet extraction. *International Journal of Recent Technology and Engineering*, 8(6): 1926-1934. DOI: 10.35940/ijrte.F8013.038620

Zakaria, F., Talip, B.A., Kahar, E.E.M., Muhammad, N., Abdullah, N. & Basri, H. (2020). Solvent used in extraction process of agarwood: A systematic review. *Food Research*, 4(3): 731-737. DOI:10.26656/fr.2017.4(3).333

Zhou, M., Wang, H., Kou, J. & Yu, B. (2008). Antinociceptive and anti-inflammatory activities of *Aquilaria sinensis* (Lour.) Gilg. Leaves extract. *Journal of ethnopharmacology*, 117(2): 345-350. DOI:10.1016/j.jep.2008.02.005

Zulkiflie N.L., Omar N.A.M., Tajudin S.N. & Shaari, M.R. (2013, December). Antidiabetic activities of Malaysian agarwood (*Aquilaria* spp.) leaves extract. In *Conference on Industry-Academia Joint Initiatives in Biotechnology CIA: Biotech* (Vol. 13, pp. 5-7).