

## Overview of Medicinal Properties and Toxicities of Agarwood Species

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### ABSTRACT

Agarwood is a type of wood that originated from an *Aquilaria* tree. It is considered to be a highly valuable resin that formed inside the main stem. The tree belongs in the Thymelaeaceae family and there are numerous types of *Aquilaria* tree available. The common ones are *Aquilaria malaccensis*, *Aquilaria sinensis*, *Aquilaria crassna*, and *Aquilaria subintegra* due to its being favoured among planters. In order to avoid any wastage, planters used various parts of the *Aquilaria* tree such as the leaves, stem, bark and root to produce various types of agarwood products (i.e.oud oil, agarwood tea, and incense). Based on the extensive researches that had been carried out, it was discovered that the agarwood or *Aquilaria* tree possess various medicinal properties, such as anticancer, anti-inflammatory, analgesics, antidiabetic, antihistaminic, antianxiety, antibacterial, hepatoprotective, laxative, and improved neural activity. Although agarwood contained various medicinal properties, there are still insufficient information regarding its toxicity, resulted in the halt on the production of agarwood medicine. Therefore, this article summarized the various pharmacological properties of agarwood and its known toxicity, that will be used for future studies.

**Keywords:** Agarwood, *Aquilaria*, Medicinal plants, Medicinal properties, Toxicity

### INTRODUCTION

Previous studies had estimated that there are roughly between 374, 262 to 450,000 species of plants existed throughout the world [1] The majority of the plants possess several chemical constituents that can be useful for human purposes and play a crucial role in the development of public healthcare. These medicinal plants can be developed into drugs or medicine that can cure different ailments. It is expected that future drugs and medicines will rely heavily on medicinal plants due to their promising pharmacological effects in health care [2]. World Health Organization (WHO) has stated that 80% of the world's population depended on medicinal plants as their source of medicine and their usage is exponentially high in rural areas [3]. Nonetheless, numerous researchers have claimed that medicinal plants may be the key to cure chronic diseases, such as Alzheimer, diabetes, and cancer [4].

One example of medicinal plant is the *Aquilaria* species plant or also known as agarwood plant. This plant reputation has increased significantly in recent years due to its many medicinal properties. Such medicinal properties are anticancer which can help in fighting cancer [5-9] antihistaminic which can prevent allergic reaction [10-11], laxative which can aid the digestive process [12-13] and many more. Even though this plant has various beneficial prospect, improper usage can also lead to numerous complications. This situation can be seen in other plants that has been considered as medicinally proven. For example, one report stated that a patient suffered from lupus-like syndrome and renal failure due to uncontrolled medicinal plant

consumption. The patient took 5.4 mg of yohimbine three times daily for four days straight thinking it will cure his erectile dysfunction [14].-Because of this, various researchers have given their time in finding the pros and cons of the *Aquilaria* plant. This is to ensure that proper usage of the plant can be conducted and further preventing any harmful side effects that can cause serious diseases or even mortality.

The purpose of this review article is to lay out all the known information regarding the beneficial and harmful aspect of the *Aquilaria* plant. As mentioned before, even medicinal plants are considered to be dangerous if consume without consideration and this include the *Aquilaria* plant. Countless researchers have conducted various studies on the medicinal and toxicological properties of the plant. This is to make sure whether or not the *Aquilaria* plant is safe to use for medicinal practice. Therefore, this review article can aid future researchers in knowing the crucial information concerning the plant medicinal and toxicological properties. This will eventually help future product developers to produce suitable products that can be use properly without causing any major adverse side effects.

### Agarwood Past and Present

Agarwood is a well-known material that originated from a medicinal plant called *Aquilaria* tree. The plant belongs to the Thymelaeaceae family of angiosperms and is endemic in the Indomalayan region that contains various types of medicinal properties. It is reported that a total of 21 *Aquilaria* species have been confirmed and documented, but only 13 of them can produce agarwood [15]. The agarwood derives from the resinous part of the *Aquilaria* tree and it is a highly valuable material for fragrance and medicine development [16]. Some examples of *Aquilaria* plants are *Aquilaria malaccensis*, *Aquilaria hirta*, *Aquilaria beccariana*, *Aquilaria rostrata* and *Aquilaria microcarpa* and this are commonly found throughout Malaysia [23]. In 2014, various companies in Malaysia have identified a total of 1,571,100 *Aquilaria* trees with ratio to 19 ha (2763.9 acres) totalling its worth to approximately RM 785,550,000 [24]. Besides Malaysia, other countries have also used *Aquilaria* plant as their agarwood source (i.e. *Aquilaria malaccensis*, *Aquilaria subintegra*, *Aquilaria crassna* and *Aquilaria sinensis*). The four species mentioned are considered to be the major *Aquilaria* types due to their ability in producing agarwood [25].

Moreover, agarwood formation usually occurred when the *Aquilaria* tree is wounded and infected with fungal [17]. As an act of self-defense, the tree will secrete a dark resinous substance that will eventually cover the wound to protect itself from further infection. After several years, the volatile compounds accumulate and form agarwood [18]. This shows how difficult it is to produce agarwood because of the condition and requirement it required. But due to its high demand, humans have come up with a way to ease the production process so that it can be produced regularly. One the common method is by intentionally injure the tree and within a year, the agarwood will be formed. Past research has stated that this method was firstly introduced by the Chinese civilization [19]. Nowadays, chemical usage, insects and pathogen-inducing methods are more preferred, due to its high production rate [17].

As aforementioned, the usage of agarwood back in the early Jin dynasty where it was being used to treat malaria [28]. After it was first discovered, agarwood's popularity has risen and other civilization started to use it as well. It was documented in *Materia Medica* by Dioscorides (a Greek physician) that root extracts from agarwood tree able to treat stomach disorders, dysentery and pains in the lungs and liver [20]. Besides the Greek civilization, Islamic practices also mentioned the medicinal value of agarwood. Prophet Muhammad has stated that agarwood can be used to treat pleurisy and swollen uvula [19]. Besides medicinal values, agarwood also possesses other attributes that has further popularize its status, for example, agarwood aromatic properties that led to the production of incense. Incense produced from agarwood has been used for many occasions such as house decorations, religious ceremonies, meditation and ritual. Because of this, agarwood incense has been considered to be valuable to many European's perfumers' enthusiast in the mid-90s. [21]. This explains why to this day the production of incense from agarwood is still widely praised. Its versatility has further popularized its value ever more than before.

With roughly half a million medicinal plants discovered around the globe, it holds a promising future for mankind's health treatment and medicine development [22]. But due to its high number, providing information about its toxicity will require a lot of work. Usually, researchers will focus on a specific species

of medicinal plants to help them to fully immerse themselves in the knowledge they obtained. This study will follow a similar path by providing toxicity information of different agarwood to ensure a better understanding of the plant's medicinal properties.

### Agarwood Medicinal Properties

Agarwood possesses various medicinal properties that have been confirmed by multiple researches, as to ensure the safety of the users. An earlier study had stated that agarwood obtained from the *Aquilaria sinensis* tree can assist diabetic patients. Hypoglycemic properties of an ethanolic extract from the *Aquilaria sinensis* leaves were used to treat diabetic mice/rats [26]. In addition, agarwood extracted from the *Aquilaria crassna*, *Aquilaria malaccensis* and *Aquilaria sinensis* have the ability to fight cancer. Cucurbitacin I has shown to be a strong anticancer property [27], in line with a previous work that revealed cucurbitacin I found in its shoot and callus, can inhibit cancer cells activity [5]. Aside from the aforementioned compounds, isocorydine present in the *Aquilaria sinensis* leaves [6] also contained anticancer property [7]. In order to treat complicated symptoms, sometimes agarwood required other chemicals in order to increase the effectiveness of the medicine.

Nonetheless, there are plenty of medicinal and pharmacological properties contained within the agarwood plant. Those properties have popularized agarwood plants, hence, making it well-known amongst the society and scientific counterparts. Countless researches has been conducted to determine the validity of the medicinal and pharmacological properties that resides within the *Aquilaria* plant, as further described in Table 1.

**Table 1:** Medicinal properties of *Aquilaria* species

<i>Aquilaria</i> species	Medicinal properties	Tree part	Description	Reference
<i>Aquilaria malaccensis</i>	Anticancer	Callus and shoot	Cucurbitacin I contained in callus and shoot, showed cytotoxic activity towards human breast cancer cells.	5, 7
	Anti-arthritis	Heartwood	Chemical constituents present inside oud oil exhibited anti-arthritis property due to the prevention of protein denaturation caused by the constituents.	31
	Antidiabetic	Leaves	An active fraction from leaves increased the level of GLUT4 in diabetic Wistar rats' skeletal muscle.	35
	Antioxidant	Leaves	Its antioxidant properties contained in the ethanolic extract acquired from coarse agarwood tea have been confirmed.	41

		Leaves	Chemical constituents present inside the leaves showed antioxidant activity when tested against a DPPH assay.	43
	Antibacterial	Leaves	Methanolic extract from leaves contained hexadecanoic acid, which exhibited antibacterial activity.	45, 46
		Callus and shoot	Cucurbitacin I contained in callus and shoot revealed antibacterial activity against bacterial pathogens.	8
	Antifungal	Callus and shoot	Cucurbitacin I contained in callus and shoot showed antifungal activity	8
	Hepatoprotective	Leaves	Rats induced with paracetamol hepatotoxicity have shown hepatoprotective properties when treated with an ethanolic extract from leaves.	50
	Improve neural activity	Heartwood	Agarofuran found inside the essential oil contained an anxiolytic agent that can be used for anxiety and depression treatment.	53
		Wood	Benzene extract from crushed wood possessed strong central nervous system depressant activities.	54
	Improve sperm characteristics	Leaves	Aqueous extract from leaves showed increased sperm quality when treated on mice.	58
<i>Aquilaria sinensis</i>	Anticancer	Leaves	Isocorydine presents in leaves can inhibit the growth of tumour in the human's lungs, gastric, and liver.	6, 7

		Peel	The extracted peel showed antitumor activity.	29
	Anti-inflammatory	Leaves	Ethanol extract from leaves revealed swelling on mice ear and paw.	30
	Anti-hyperglycemic	Leaves	Methanol and water extract from leaves enhanced the glucose uptake activity on diabetic rats' adipocytes.	36
		Leaves	2 $\alpha$ -hydroxy ursolic acid contained within ethanolic extract from the leaves has showed hypoglycemic properties when treated on mice and rats.	37
		Leaves	Multiple constituents present inside the ethanol extract from leaves have the potential to be an antidiabetic agent, due to its capabilities in inhibiting $\alpha$ -glucosidase activity.	38
	Antioxidant	Leaves	Flavonoids contained inside the leaves showed antioxidant activity .	39, 40
	Antihistaminic	Leaves	Ethanol extract from leaves delayed asthma attack.	10
		Leaves	Luteolin and genkwanin found inside the leaves can soothe coughs and asthma.	11
	Anti-depressive and antianxiety	Leaves	Mangiferin contained inside the leaves can lower the interleukin-1 beta levels, which can be a suitable source for anti-depressive and antianxiety agents.	44
	AMPK-activating	Leaves	Ethanol extract from leaves can activate AMPK that resulted in a decrease in mice fasting blood	48

			glucose and glycosylated hemoglobin levels which can reduce the insulin opposition.	
		Leaves	The activation of AMPK was identified in L6 myotubes, due to the presence of mangiferin contained within the leaves extract.	38, 49
	Laxative	Leaves	Ethanol extract from leaves increased contractions tension of ileum and jejunum.	12
		Leaves	Aqueous extract from leaves lowers cholesterol and triglyceride levels.	12, 51
	Potential to cure cardiovascular disease	Leaves	Flavonoids contained in the leaves can cure cardiovascular diseases by hindering the oxidation process of low-density lipoprotein.	39, 40, 57
	Improve animal digestion	Leaves	Active nutritional compounds extracted from the leaves can enhance the growth and digestion of farm animals.	58
<i>Aquilaria crassna</i>	Anticancer	Bark	$\beta$ -caryophyllene found inside the essential oil inhibits clonogenicity of colon cancer cells.	9
	Anti-inflammatory	Heartwood	Ethyl acetate extract from heartwood showed anti-inflammatory on human peripheral blood mononuclear cells.	34
	Analgesic	Leaves	Due to an increase in thermal threshold within the mice, mice treated with the leaves extract had a similar analgesic effect with	33

			mice treated with aspirin when tested using the hot-plate method.	
Antipyretic	Leaves		Rats undergone Baker's yeast-induced fever showed decrease in rectal temperature when treated with the leaves extract.	33
Antioxidant	Bark		$\beta$ -caryophyllene contained inside the essential oil exhibits antioxidant activity when tested with a DPPH assay.	9
	Leaves		Leaves extract tested with DPPH antioxidant assay showed an anti-oxidative effect, similar to ascorbic acid.	33
Antibacterial	Bark		$\beta$ -caryophyllene contained inside the essential oil exhibits antibacterial activity when tested against <i>S. aureus</i> .	9
	Callus and shoot		Cucurbitacin I contained in callus and shoot showed antibacterial activity	8
	Leaves		Aqueous extract from leaves had ruptured the <i>Staphylococcus epidermidis</i> cell wall, which indicates antibacterial response.	47
Antifungal	Bark		$\beta$ -caryophyllene contained inside the essential oil showed antifungal activity when tested against fungal strains.	9
	Callus and shoot		Cucurbitacin I contained in callus and shoot showed antifungal activity	8
Laxative	Leaves		Ethanol extract from leaves able to increase contractions tension of intestines.	12, 13

	Anti-ischemic	Heartwood	Ethyl acetate extract from heartwood showed anti-ischemic activity that reduced the activation of P38-MAPK on ischemic mice heart.	56
<i>Aquilaria subintegra</i>	acetylcholinesterase (AChE) inhibitor	Stem and leaves	Kaempferol 3,4,7-trimethyl ether obtained from chloroform extraction of the leaves stem exhibits AChE inhibitor, which can assist in treating Alzheimer's disease.	42
	Improved neural activity	Stem and leaves	Phytol contained inside the stem and leaves showed anticonvulsant activity by controlling the neurotransmitter system in mice.	42, 52

#### Anticancer and antitumor properties

Cucurbitacin has the potential as an antitumor and anticancer agent that can treat cancers [8]. Previous studies have shown that cucurbitacin can be found in the *Aquilaria* leaves whilst the cucurbitacin I present in the callus and shoot of *Aquilaria malaccensis* can inhibit cancer activity in cells and demonstrate cytotoxic activity against human breast cancer cells [5]. Besides cucurbitacin, isocorydine also possessed anticancer and antitumor properties. A research by Zhong [7] proved this theory by conducting an experiment that focussed on the prevention of cancer cell growth in human liver, lung and gastric as well as tumour inhibition in sarcoma and hepatoma using only isocorydine [7]. These compounds can be found in *Aquilaria sinensis* as stated by Nie C [6]. Other than that, the peel extract from *Aquilaria sinensis* has also shown antitumor activity [29]. Similarly, *Aquilaria crassna* also showed anticancer properties when it was treated with human colon cancer cell lines [9].

#### Anti-inflammatory, anti-arthritis and analgesics properties

*Aquilaria sinensis* has shown its characteristics as an anti-inflammatory agent due to the presence of flavonoid compounds found inside the plant [30]. *Aquilaria malaccensis* has the potential to be an anti-arthritis agent due to the presence of glycosides, oleic acids, phenolic compounds, tannins, terpenes and terpenoids. These chemical constituents are known to be an excellent source for preventing protein denaturation which can cause rheumatoid arthritis due to autoantigen productions [31]. Past research mentioned that *Aquilaria* leaves does contained alkaloids that can treat colic, rheumatism, toothache, severe headache and pregnancy pains [32]. It showed analgesic activity which is the ability to relieve pain. In addition, *Aquilaria crassna* leaves possessed these same properties, as shown in the ability of the aqueous extract in treating mice [33]. Moreover, *Aquilaria crassna* can also be an anti-inflammatory agent [34].

#### Antidiabetic and hypoglycemic properties

Hypoglycemic properties can help to decrease blood sugar in one's body level, making it useful for diabetic treatments. An earlier study noted that active fraction *Aquilaria malaccensis* leaves (fraction of ethanol water and fractions of ethyl acetate) have the ability to amplify glucose uptake in diabetic Wistar rats by controlling their glucose transporter type 4 (GLUT4) levels. Results showed and an increase of 20% glucose



uptake making it more useful than pioglitazone which is a type of drug that help diabetic patients [35]. Meanwhile, methanol and water extracted from *Aquilaria sinensis* leaves have shown to be an excellent substitute for insulin due to their anti-hyperglycemic properties [36]. This characteristic can also be observed from the ethanolic extracts of *Aquilaria sinensis* leaves. 2 $\alpha$ -hydroxy ursolic acid contained inside it has shown hypoglycemic effects when treated to diabetic mice/rats [37]. In addition, iriflophenone 2-O- $\alpha$ -L-rhamnopyranoside, iriflophenone 3-C- $\beta$ -D-glucoside iriflophenone 3,5-C- $\beta$ -D-diglucoopyranoside, and mangiferin contained in the ethanol extracts of *Aquilaria sinensis* leaves that possessed the ability to inhibit  $\alpha$ -glucosidase activity, hence, making it a potential antidiabetic agent. These compounds can control the absorption of carbohydrates in the intestines that will eventually lower the blood glucose level [38].

### **Antioxidant and acetylcholinesterase (AChE) inhibitory properties**

A previous work carried out by Duan [39] documented the vigorous antioxidant activity contained within *Aquilaria sinensis* in its flavonoid's compounds. At a particular dose (i.e. genkwanin and luteolin) which can protect damaged hydroxyl-induced DNA [39-40]. Moreover, the ethanolic extract acquired from coarse agarwood tea has demonstrated exceptional antioxidant activity when administered *in vitro* [41]. It also contained acetylcholinesterase (AChE) inhibitory property which is suitable for Alzheimer's treatment. Meanwhile, kaempferol 3,4,7-trimethylether found in the crude extract of *Aquilaria subintegra* possessed the aforementioned ability and considered a substitute for berberine when treating Alzheimer's disease [42]. Likewise, *Aquilaria malaccensis* [43] *Aquilaria crassna* [9] were also known to possess antioxidant properties.

### **Antihistaminic, anti-depressive and antianxiety properties**

Ethanol extracts from *Aquilaria sinensis* also possessed antihistaminic properties that will lengthen asthma latency, hence, preventing patients from experiencing asthma attacks [10]. Luteolin and genkwanin contained within *Aquilaria* leaves can also relieve asthma and coughs [11]. In addition, mangiferin also played an important role in treating depression and anxiety due to a report indicating that it has the potential as an antidepressant and antianxiety agent by reducing interleukin-1 beta levels [44].

### **Antifungal and antibacterial properties**

Hexadecanoic acid is a common saturated fatty acid. It has been stated that this compound has the capability of fighting bacterial infections due to its antibacterial properties. This statement has been confirmed by Saidana [45] which showed hexadecanoic acid antibacterial activity on Gram-positive and Gram-negative bacteria [45]. The compound is said to be present inside methanolic extracts of *Aquilaria* leaves [46]. Previously mentioned cucurbitacin, which can be found in *Aquilaria malaccensis* and *Aquilaria crassna*, also possessed antibacterial and antifungal properties. It has been said that cucurbitacin located inside both *Aquilaria malaccensis* and *Aquilaria crassna* extract can combat bacterial and fungal pathogen [8]. Meanwhile, aqueous extract from *Aquilaria crassna* showed antibacterial activity when treated against *Staphylococcus epidermidis* which caused the bacteria cell wall to rupture [47].

### **AMP-activated protein kinase (AMPK) activating and hepatoprotective properties**

*Aquilaria sinensis* is accounted for the activation of AMPK so that it can decrease the fasting blood glucose and glycosylated hemoglobin levels in mice, and subsequently bringing about a reduction on insulin opposition [48]. Other than that, *in vitro* activation of AMPK in L6 myotubes occurred because of the mangiferin compound [49]. Meanwhile, ethanolic concentrates of *Aquilaria agallocha* also known as *Aquilaria malaccensis* leaves have hepatoprotective properties, in which counteracts harm against paracetamol (PCM) induced hepatotoxicity in Sprague Dawley rat's liver. The hepatoprotective effects probably due to antioxidant agent in the ethanolic extracts of *Aquilaria agallocha* leaves, which decreases the oxidative pressure upheld by PCM avoiding the fiery hepatic harm [50].

### **Laxative and lipid-lowering properties**

Ethanol extracts from *Aquilaria sinensis* and *Aquilaria crassna* can cause contraction in rats' small intestine that resulted in high production of faeces [12]. For *Aquilaria crassna*, the leaves have the capabilities to enhance intestinal movements due to the presence of chemicals, such as genkwanin and mangiferin [13]. Meanwhile, for *Aquilaria sinensis*, mangiferin has been identified as a lipid-lowering agent. Results from an experiment conducted by Wu [51] showed reduced triglyceride and cholesterol when used as an aqueous extract of *Aquilaria sinensis* [51]. The polyphenol compound can be used for hyperlipidemia treatment which is a genetic disorder that produces a high level of lipids inside a person's body.

### **Improved neural activity**

Another beneficial property of this plant is the improvement of neuronal activity. The first one is related to phytol where recent studies have shown that it is present inside the *Aquilaria* plant [42]. Phytol has the ability to control neuronal functions, more specifically influencing neurotransmitter systems and inhibiting the release and synthesis of inhibitory neurotransmitters. These neuronal functions are mainly associated with seizures [52]. Agarofuran contained inside agarwood (*Aquilaria malaccensis*) essential oil is another example of a compound that possesses the ability to manipulate the functions of the nervous systems. It can be used as an anxiolytic agent where it can be used for depression and anxiety treatment [53]. Benzene present within *Aquilaria malaccensis* can reduce spontaneous motility [54]. Moreover, benzylacetone detected in the agarwood's essential oil also contained sedative effect [55].

### **Other medicinal properties**

Ethyl acetate extract acquired from *Aquilaria crassna* has said to be an excellent source for anti-ischemic agent due to its ability in attenuating P38-MAPK activation [56]. Moreover, cardiovascular disease can be reduced when flavonoids are used as a treatment drug. It is reported that this compound can be found inside *Aquilaria* leaves and the compound can hinder the oxidation process of low-density lipoprotein, hence, proving its ability in curing cardiovascular diseases [57]. Besides that, aqueous extracts obtained from *Aquilaria crassna* also possessed antipyretic effect when used to treat mice [33]. The leaves can also be used as a feeding material for farm animals. It is also mentioned by Huang [58] that it can enhance their digestion system as well as their growth production [58]. A previous study had documented the effects of *Aquilaria malaccensis* leaves aqueous extract on ICR mice sperm. A decrease in abnormal sperm count and increase in sperm motility were observed in the mice, after sub-acute treatment were conducted. The findings showed that the extract can significantly enhance the fertility rate of mice, resulted in a healthier sperm production [67].

### **Agarwood Toxicities**

Nowadays, plenty of agarwood products had been introduced. In 2013, global market estimation for oud oil and other related agarwood products is at 6 billion US\$ (RM 25 billion) to 8 billion US\$ (RM 33 billion) [60-61]. Some of the examples of agarwood products are oud oils, fragrant incense, agarwood tea, and powder. Even with its increasing popularity, people still do not fully grasp the information regarding the dangers and toxicity of agarwood. Table 2 further describes the known and unknown toxicities that have been reported from agarwood.

**Table 2:** *Aquilaria* species known and unknown toxicities

<i>Aquilaria</i> species	Tree part	Tested subject	Toxicity status	Reference
<i>Aquilaria malaccensis</i>	Leaves	Various human cells	Showed cytotoxic activity towards human's peripheral blood mononuclear cells and caused DNA fragmentation, when 4537 mg/kg of hydrodistilled solvent-extract.	26
	Heartwood	Salmonella reversion test	Smoke from incense stick showed cytotoxic and mutagenic properties when tested on salmonella reversion.	62
<i>Aquilaria sinensis</i>	Leaves	Mice and salmonella reversion test	No signs of toxicity towards mice sperm and bone marrow after oral fed with extract as well as no signs of toxicity when tested with salmonella reversion test.	65
<i>Aquilaria crassna</i>	Leaves	Mice	Showed no signs of toxicity when aqueous extract of leaves was used, even at a high dosage of 2000 mg/kg and 15000 mg/kg in acute toxicity study.	47, 64
<i>Aquilaria subintegra</i>	Leaves	Rats	Showed signs of toxicity on liver and kidney of rats when used 2000 mg/kg concentration of aqueous extract in sub-acute toxicity study.	63
	Leaves and stem	Human cells	No cytotoxic activity towards various human cell lines.	42

### Known agarwood toxicity

There has not been much research that focused on agarwood toxicity, resulted in the difficulties to obtain the information needed to further analyse agarwood capabilities. The agarwood potential as a medicinal plant is still questionable due to the insufficient data regarding its toxicity. Research findings conducted by Aimi Zafirah [26] documented on *Aquilaria malaccensis* cytotoxic properties towards human's peripheral blood mononuclear cells. Fragmentation inside the cell's DNA has marked *Aquilaria malaccensis* as a candidate for genotoxicity initiator [26]. The toxic dose mentioned in that research were 4537 mg/kg of *Aquilaria malaccensis* methanol extract and the toxicity test used were acute toxicity test. Besides that, another study also mentioned *Aquilaria malaccensis* cytotoxicity and mutagenic properties in incense

smoke from natural and cultivated agarwood [62]. This does not conclude that *Aquilaria malaccensis* toxicity status as it does not provide sufficient data to ensure it is safe for human consumption. Aside from *Aquilaria malaccensis*, there is also other research reported on the *Aquilaria subintegra* toxicity. It is stated that at 2000 mg/kg of *Aquilaria subintegra* aqueous extract, abnormalities started to occur inside mice liver and kidney tissues after they have been treated orally with the extract. This indicates that *Aquilaria subintegra* might have caused some toxic reaction towards their tissues. Apart from that, the data from this research does not conclude *Aquilaria subintegra* overall toxicity due to the reaction occurred only at sub-acute method and not at acute method [63]. These are the only information acquired regarding agarwood toxicity and there are still many types of agarwood toxicity that needed to be discovered.

### Unknown toxicities of agarwood

Besides *Aquilaria malaccensis* and *Aquilaria subintegra*, other researchers have also provided findings that focused on the toxicity of agarwood. However, these researches does not provide an accurate information for agarwood toxicity due to the lack of adverse reactions and mortality among its treated subjects after the extracts were administered. In 2013, Kamonwannasit [47] stated that aqueous extracts acquired from *Aquilaria crassna* showed no toxicity effect when mice are fed with the extract at a high dosage of 15000 mg/kg [47]. A previous study carried out in 2016 claimed that the toxicity of aqueous extract of *Aquilaria crassna* is higher than 2000 mg/kg [64]. In contrast, a research conducted by Kamonwannasit in 2013 have proven that even an ethanol extract at a high dose showed no signs of toxicities. Even though is the study used only the ethanol extract, it is still valid to predict its toxicity due to no reaction occurred on the subjects. Furthermore, there were also no signs of oral toxicity, genotoxicity and mutation reaction mice's sperm and micronucleus after being treated with *Aquilaria sinensis* leaves extract [65]. Although *Aquilaria subintegra* toxicity occurred in mice liver and kidney, kaempferol extracts from *Aquilaria subintegra* showed no cytotoxicity towards various human cell lines [42]. This further proves that *Aquilaria subintegra* toxicity is still inaccurate due to the mixed results obtained from multiple researches. Therefore, information regarding agarwood toxicity is still considered incomplete due to the insufficient and mixed data acquired from past studies.

## CONCLUSION

Even though agarwood production from *Aquilaria* tree can be tedious due to its complicated technique, its potential as a medicine still holds up to this day. We can see that agarwood usage has increase significantly in the last few years. This is due to the medicinal content present inside agarwood. This has also lead to an increasing of its popularity among researchers and agarwood planters. Many researchers tend to conduct pharmacological researches on agarwood in order to understand and analyse the potential medicinal properties hidden inside them. As mentioned before, most of those medicinal properties such as anticancer, anti-inflammatory, anti-arthritic, antidiabetic, antioxidant, anti-bacterial, laxative and improved neural activity has been identified. Apart from that, accurate information on its medicinal properties are still vague. Not to mentioned that details regarding agarwood side effects are still unknown due to the insufficient amount of data collected. That is one of the reasons why researchers are now focussed on finding the toxicity as well as the harmful side effects of agarwood. This is to ensure that any incidents regarding agarwood usage can be avoided in the future. Before any medicinal development begins, all information regarding agarwood medicinal properties, toxicity and safety regulation should be prepared. This is to guarantee that the medicine developed is safe to the users. To achieve that, research regarding agarwood medicinal properties and toxicity should be conducted at all cost so that all information regarding agarwood can be collected properly. Future researchers should come up a way to deduce agarwood medicinal property and toxicity simultaneously. They should also identify the suitable dosage for consumption so that agarwood can be use in everyday life. If they can achieve this, an appropriate medicine can be created. This will eventually help in improving society's health and everyday life. That is why it is important to conduct research regarding agarwood medicinal properties and its toxicities.

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