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Review

Aquilaria spp. (agarwood) as source of health beneficial compounds: A review of traditional use, phytochemistry and pharmacology

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ABSTRACT

Ethnopharmacological relevance: *Aquilaria* spp. (agarwood) has been a part of Ayurvedic and Traditional Chinese Medicine for centuries. Agarwood has also been used as a traditional medicine in Southeast Asian countries, Bangladesh and Tibet. Its common uses include the treatment of joint pain, inflammatory-related ailments, and diarrhoea, as well as a stimulant, sedative and cardioprotective agent. In this paper, we aim to provide an overview of the phytochemistry, ethnomedicinal use, pharmacological activities and safety of plant materials from *Aquilaria* spp. as an evidence base to further appraise its potential use as a source of health beneficial compounds.

Materials and methods: Literature abstracts and full text articles from journals, books, reports and electronic searches (Google Scholar, Elsevier, PubMed, Read Cube, Scopus, Springer, and Web of Science), as well as from other relevant websites, are surveyed, analysed and included in this review.

Results: A literature survey of agarwood plant materials showed that they contain sesquiterpenes, 2(-2-phenylethyl)-4H-chromen-4-one derivatives, genkwanins, mangiferins, iriflophenones, cucurbitacins, terpenoids and phenolic acids. The crude extracts and some of the isolated compounds exhibit anti-allergic, anti-inflammatory, anti-diabetic, anti-cancer, anti-oxidant, anti-ischemic, anti-microbial, hepatoprotective, laxative, and mosquitocidal properties and effects on the central nervous system. Agarwood plant materials are considered to be safe based on the doses tested. However, the toxicity and safety of the materials, including the smoke from agarwood incense burning, should be further investigated. Future research should be directed towards the bio-guided isolation of bioactive compounds with proper chemical characterisation and investigations of the underlying mechanisms towards drug discovery.

Conclusions: The traditional medicinal use of agarwood plant materials has provided clues to their pharmacological properties. Indeed, agarwood contains a plethora of bioactive compounds that now

Abbreviations: CITES, the Convention on International Trade in Endangered Species of Wild Fauna and Flora; IUCN, International Union for Conservation of Nature and Natural Resources; $O_2^{\bullet-}$, superoxide anion; $HO^{\bullet}$, hydroxyl radical; ABTS, 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid; AChE, acetylcholinesterase; ALP, alkaline phosphatase; ALT, alanine transaminase; AMPK, 5′ adenosine monophosphate-activated protein kinase; AST, aspartate transaminase; cAMP, cyclic adenosine monophosphate; cm, centrimetre; CMC-Na, carboxymethylcellulose-sodium; CUPRAC, cupric reducing anti-oxidant capacity; ddH_2O, double distilled water; DCM, dichloromethane; DEET, N,N-diethyl-meta-toluamide; DPPH, 2,2-diphenyl-1-picrylhydrazylradical; EC_{50}, effective concentration to 50% test organisms; EC_{90}, effective concentration to 90% test organisms; ED_{50}, effective dose to 50% test organisms; FRAP, ferric reducing anti-oxidant power; GAE/g DW, gallic acid equivalents per gram dry weight; GC–MS, gas chromatography mass spectrometry; h, hour; HbA1c, glycosylated haemoglobin; IC_{50}, half maximal inhibitory concentration; ICR, Imprinting Control Regions mouse; LC_{50}, lethal concentration to 50% test organisms; LC_{90}, lethal concentration to 90% test organisms; LPS, lipopolysaccharide; m, metre; MBC, minimal bactericidal concentration; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NMR, nuclear magnetic resonance; NO, nitric oxide; p.o., *per os* (Latin) for oral administration; QE/g DW, quercetin equivalents per gram dry weight; RT, room temperature; SRB, sulforhodamine B; TAC, total anti-oxidant capacity; wk, week

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elegantly support their use in traditional medicine. As wild agarwood trees are critically endangered and vulnerable, sustainable agricultural and forestry practices are necessary for the further development and utilization of agarwood as a source of health beneficial compounds.

Contents

1. Introduction

Agarwood (also known as aloeswood or eaglewood) normally refers to dense, heavy and fragrant resinous wood which is formed in the trees of *Aquilaria, Gonystylus* and *Gyrinops.* According to Swee (2008), the term 'agarwood' refers to resin-impregnated pieces of wood that have been at least partially shaved from the non-impregnated woods. Throughout this review, the term 'agarwood' denotes the above definitions unless otherwise stated. The term 'heartwood' is also used interchangeably with 'agarwood' based on its occurrence in many of the literature reviewed for this work. More discussion on the accurate term to use with particular reference to pharmacological activities can be found in Section 6.1 of this review.

Agarwood is considered to be the finest natural incense and has been used in many communities to fulfil cultural, religious and medicinal purposes for centuries. It is known by many names; it is called 'gaharu' in Indonesia and Malaysia, 'jin-koh' in Japan, 'chen hsiang' or 'chenxiang' in China, 'agar' in India (from Sanskrit 'aguru'), 'chim-hyuang' in Korea, 'kritsana noi' in Thailand, 'tram huong' in Vietnam, 'bols d'agle', 'bols d'aloes', 'calambac' or 'calambour' in French and 'oud' in the Middle East (Burkill, 1935; Ng et al., 1997; Sidiyasa, 1986). Previously, at least in the Malay language, the agarwood tree was known as 'karas' or 'kekaras', whereas 'gaharu' referred to heavy fragrant wood (Burkill, 1935). However, current practice uses 'gaharu' as the generic term to refer to both the tree and its resin, similar to the term 'agarwood'.

The economic interest in agarwood has always been directed towards its pathological heavy and dense resin-impregnated wood, which is formed in the tissues of the stem in response to injury. The formation and infiltration of resin in agarwood trees is beyond the scope of this review. Briefly, the resin could develop through pathological, wounding and non-pathological mechanisms (Ng et al., 1997). These mechanisms have been the basis for inoculation or induction techniques to induce resin formation in cultivated agarwood trees, where the techniques often involve physical penetration into the trunk (wounding), insertion of a microbial (mainly fungal) concoction (pathology) and response of the tree towards the administered stress (non-pathological). A method of producing agarwood resin by creating an artificial wound in the xylem of agarwood trees have been patented (Blanchette and van Beek, 2005). Further discussions on various aspects of agarwood resin formation can be found in publications from Xu et al. (2013), Mohamad and Zali (2010) and Bhore and Kandasamy (2013).

The fragrant wood has many ties with cultures around the world, such as the Arabian, Chinese and Japanese cultures, and is also associated with religious history, rituals and ceremonies in Buddhism, Christianity, Hinduism, and Islam (Barden et al., 2000). Nevertheless, other materials from the agarwood plant have also found prominent uses in the traditional medicine practices of the Southeast Asian communities, such as Chinese, Tibetan, Unani and Ayurvedic medicines (Barden et al., 2000; Blanchette and van Beek, 2005). This ethnopharmacological evidence, together with the current trends in bioprospecting, have spurred the interest of the scientific community to investigate claims using modern tools. This is manifested in the surge of the number of scientific publications in recent years, particularly those describing the pharmacological actions of agarwood, including the anti-diabetic (Feng et al., 2011; Jiang and Tu, 2011; Pranakhon et al., 2015; Zulkiflie et al., 2013), anti-inflammatory (Chitre et al., 2007; Kumphune et al., 2011; Rahman et al., 2012; Sattayasai et al., 2012; Zhou et al., 2008), anti-cancer (Dahham et al., 2014, 2015a; Gunasekera et al., 1981; Hashim et al., 2014a), anti-depressant (Okugawa et al., 1993; Takemoto et al., 2008), and anti-oxidant (Dahham et al., 2014; Han and Li, 2012; Huda et al., 2009; Kamonwannasit et al., 2013; Miniyar et al., 2008; Moosa, 2010; Nik Wil et al., 2014; Owen and Jones, 2002; Ray et al., 2014; Sattayasai et al., 2012; Tay et al., 2014) activities of agarwood plant materials.

The diminishing number of these trees in the wild due to indiscriminate felling in search of the resin has led to conservation actions by listing the genus *Aquilaria* in Appendix II of Convention

Nomenclature

AGS	gastric epithelial cancer cells
AVRM	adult rat ventricular myocytes
GES-1	human normal gastric epithelial cells
H9c2	myoblasts
HCT116	colorectal carcinoma cells
HeLa	cervical carcinoma cells
Hep G2	human hepatocellular liver carcinoma
HT29	human colon adenocarcinoma cells
HUVEC	human umbilical vein endothelial cells
K562	human myeloid leukaemia cells
MIA PaCa-2	human pancreatic carcinoma cell
MCF-7	breast cancer cell
P388	leukaemia cells
PANC-1	pancreas cancer cells
PC3	prostate cancer cells
RPMC	rat peritoneal mast cells
SGC7901	human gastric cancer cells
SMMC7221	human hepatoma cells
T24	human bladder carcinoma cells
WRL-68	human normal hepatic cells

on International Trade in Endangered Species of Wild Fauna and Flora (CITES) (UNEP-WCMC (Comps.), 2014). The International Union for Conservation of Nature and Natural Resources (IUCN) Red List of Threatened Species has listed *Aquilaria crassna* as critically endangered, and *Aquilaria malaccensis* and *Aquilaria sinensis* are listed as vulnerable (Asian Regional Workshop (Asian Regional Workshop Conservation and Sustainable Management of Trees, 1996)). In response to this situation, sustainable agarwood planting and management with artificial induction of agarwood resin formation have been implemented. This has led to a ready supply of different parts of the agarwood plant, which provides opportunities for the development of a range of value added products.

Although earlier literature concentrated on the phytochemistry of the resinous wood, and to some extent the oil produced from the resinous wood (Ishihara et al., 1991a, 1991b; Jain, 1959; Nakanishi et al., 1981, 1983, 1984; Varma et al., 1965; Yoneda et al., 1984), the review literature on current work related to the compounds and bioactivities of the different parts of the agarwood plant is very limited, with existing publications focused on specific species, namely, *Aquilaria agallocha* (Alam et al., 2015) and *Aquilaria sinensis* (Li et al., 2014). Another review attempted to report the pharmacological properties of *Aquilaria* spp., but provided limited information (Jok and Ku Hamid, 2015).

Therefore, this paper aims to provide an overview of the phytochemistry, ethnomedicinal use, pharmacological activities, toxicity and safety of plant materials derived from *Aquilaria* spp. This review will provide a platform to appraise the potential use of agarwood plant parts as sources of health beneficial compounds towards the development of value added products, including pharmaceuticals. Literature abstracts and full text articles from journals, books, reports and electronic searches (Google Scholar, Elsevier, PubMed, Read Cube, Scopus, Springer, and Web of Science), as well as from other relevant websites, are surveyed, analysed and included in this review.

2. Taxonomy and botanical profile

Agarwood plants are classified under the family Thymelaeaceae, which has 54 genera, including *Aquilaria*, *Daphne, Gonystylus*, *Gyrinops* and *Wikstroemia* (The Plant List, 2013). This review will focus only on *Aquilaria* spp. Table 1 shows the 21 accepted species names from a total of 57 scientific plant names of species from the genus *Aquilaria* (The Plant List, 2013).

Agarwood (resin)-producing species are found from India eastwards to the island of New Guinea, including all Southeast Asian countries, and north to Hainan Island in southern China (Persoon, 2008). Nine *Aquilaria* species have been reported to produce agarwood, namely, *Aquilaria beccariana* Tiegh., *Aquilaria crassna* Pierre ex Lecomte, *Aquilaria filaria* (Oken) Merr., *Aquilaria hirta* Ridl., *Aquilaria khasiana* Hallier f., *Aquilaria malaccensis* Lamk., *Aquilaria microcarpa* Baill., *Aquilaria rostrata* Ridl., and *Aquilaria sinensis* (Lour.) Spreng. (Ding Hou, 1960; Ng et al., 1997). Accordingly, these species appear more frequently in the literature, particularly *A. crassna*, *A. malaccensis* and *A. sinensis*, with author affiliations corresponding to the geographical areas in which the species are endemic. *A. crassna* principally grows in Indochina; *A. malaccensis* is an Indomalesian type found in Malaysia, Thailand and India; and *A. sinensis* is endemic in China (Ng et al., 1997).

Although there is a substantial amount of literature pertaining to *Aquilaria agallocha* Roxb. (endemic in India), the species name is still unresolved (The Plant List, 2013). The index of CITES species listed *A. agallocha* Roxb. as a synonym of *A. malaccensis* Lamk. (UNEP-WCMC (Comps.), 2014). Further, *A. agallocha* is listed as either invalid or illegitimate in the Missouri Botanical Garden website (Missouri Botanical Garden, 2016). Meanwhile, referring to the Medicinal Plant Names Services Portal of the Kew Royal Botanic Garden; *A.malaccensis* is an accepted scientific name while *A.agallocha* is listed as synonym based on several medicinal plant references including the Ayurvedic and Unani Pharmacopoeias (Medicinal Plant Names Services Portal, 2016). Accurate scientific nomenclature is paramount to avoid ambiguities and error particularly for ethnopharmacological relevant plants (Rivera et al., 2014). In the case of *A.malaccensis* and *A. agallocha*, researchers in the field should be more aware of the issue and exercise on best practices such as depositing voucher specimens in recognized herbariums and documenting evidence for the identification of the plants (Rivera et al., 2014).

With regards to *Aquilaria malaccensis,* some literature reported it is as *Aquilaria malaccensis* Lamk. while others refer it as *Aquilaria malaccensis* Lam.; with the latter found to be more frequently used. *Aquilaria malaccensis* Lamk. is also synonym to *Aquilariella malaccensis* (Lam.) Tiegh. and *Agallochum malaccense* (Lam.) Kuntze (Missouri Botanical Garden, 2016; The Plant List, 2013; UNEP-WCMC (Comps.), 2014).

Other discrepancies in the taxonomy are also reported: (i) *A. malaccensis* Benth., a synonym for *A. malaccensis* Lam., is reported to be of illegitimate status (The Plant List, 2013), (ii) *Aquilaria banaensis* P.H. Hô, is the legitimate name as opposed to *Aquilaria banaense* P.H. Hô, where this has been ortographically corrected in 1992 (Missouri Botanical Garden, 2016); (iii) *Aquilaria crasna* Pierre is invalid (as opposed to the accepted *Aquilaria crassna* Pierre ex Lecomte) (The Plant List, 2013); (iv) *Aquilaria cumingiana* (Decne.) Hallier f. is illegitimate as opposed to *Aquilaria cumingiana* (Decne.) Ridl. (Missouri Botanical Garden, 2016) and (v) *Aquilaria chinenis* Spreng. is a spelling variant of *Aquilaria sinensis* (Lour.) Spreng. (The Plant List, 2013). However, *Aquilaria chinensis* Spreng. is listed as invalid while *Aquilaria sinensis* (Lour.) Merr. and *Aquilaria sinensis* (Lour.) Gilg, are listed as illegitimate as opposed to *Aquilaria sinensis* (Lour.) Spreng. (legitimate) (Missouri Botanical Garden, 2016). Meanwhile, work on *Aquilaria subintegra* (principally found in Thailand) (UNEP-WCMC (Comps.), 2014) is less frequently reported.

Aquilaria trees can reach 40 m in height and 60 cm in diameter (Blanchette and van Beek, 2005). They are usually found in lowland tropical forests with optimal sunlight, shade and moisture. Agarwood-producing species have a small flower similar to that of 'jasmine', and the fruit is bitter (Sitepu et al., 2011). The healthy wood is white, soft, even-grained and not scented when freshly cut compared with the dark, hard and heavy wood when it is infiltrated or saturated with resin in certain pathological conditions (Blanchette and van Beek (2005). The mechanism of agarwood (resin) formation is still not fully understood or elucidated, despite the increasing research activity in this area. A more elaborate botanical description of the 'agarwood' tree can be found in the report by Wang et al. (2007). Fig. 1 shows the different agarwood plant materials used for commercial and/or traditional purposes.

3. Agarwood use and trade

Agarwood is a valuable, non-timber forest product which has been used throughout different societies for medicinal, aromatic, cultural and religious purposes (Swee, 2008). However, classic literature pertaining to agarwood reported mainly on its local traditional medicinal uses, with very limited information on other applications (Guerrero, 1921; Lemmens and Bunyapraphatsara, 2003; Oyen and Dung, 1999; Perry and Metzger, 1980). This section describes various uses of agarwood with minimum emphasis on its medicinal importance. The ethnopharmacology aspect of agarwood is discussed in more detail in Section 4 of this review.

The majority of agarwood is traded in various forms of product derivatives, such as wood (solid pieces traded individually), wood chips, flakes, powder and oil. From a large piece of agarwood, only 10–20% can be processed into chips and flakes with the remainder sold as powder/dust or used for oil distillation (Barden et al., 2000). High quality wood is used as incense in Arabian households and for the 'koh-doh' incense ceremony in Japan (Compton and Ishihara, 2004). Wood chips are ground into a powder for the distillation of oil, making of incense, production of traditional Chinese and Korean medicines, and preparation of medicinal wine (Persoon, 2008; Sitepu et al., 2011). Waste powder, a by-product from oil distillation is also being traded in the market with much cheaper price (Barden et al., 2000).

The oil is always in high demand from Middle Eastern countries, where it is used as a customary perfume (Barden et al., 2000). Agarwood perfumes are commonly prepared in both alcoholic and non-alcoholic carriers, with the oil functioning as a fixative (Sitepu et al., 2011). 'Attar' is an example of a water-based perfume containing agarwood oil, which is traditionally used by Muslims to lace prayer clothes (Yaacob, 1999). The oil is also used as a fragrance in the production of cosmetics and personal care products, such as soaps and shampoos (Chakrabarty et al., 1994). The market value of agarwood derivative products is dependent on the classification or grading of agarwood, which is determined by a cumulative factor of the fragrance strength and longevity, resin content, geographical origin and purity (for oil) (Barden et al., 2000).

The uses of *Aquilaria* spp. are not restricted to incense and perfumery. Solid pieces of agarwood are carved into natural art sculptures, beads, bracelets and boxes (Barden et al., 2000; Persoon, 2008). The wood of *A. agallocha* is used as decorative ornaments (China), 'joss sticks' (China and India), and flea and louse repellents (India), whereas the bark has been used to manufacture paper (China) (Borris et al. (1988)). In India, the wood of *A. malaccensis* has been used as fuel for fumigation, and the bark has been used to make cloth and rope. In Taiwan, agarwood is also traded as crude and prepared medicine based on Traditional Chinese Medicine (TRAFFIC East Asia-Taipei, TRAFFIC East Southeast Asia, 2005).

More recently, a Malaysian-based agarwood entrepreneur has incorporated agarwood leaves as ingredients in biscuits, herbal soup, instant noodles and a 'miracle beauty powder' (Chen, 2013). Agarwood materials have also been formulated into a balm (muscle rub) and candle wax (http://www.agarharvest.com/, 2015).

Table 1
Species in the genus *Aquilaria* (accepted names) (The Plant List, 2013).

Species	Authorship
Aquilaria apiculata	Merr., 1922
Aquilaria baillonii	Pierre ex Lecomte, 1915
Aquilaria banaensis	P.H. Hô, 1986
Aquilaria beccariana	Tiegh., 1893
Aquilaria brachyantha	(Merr.) Hallier f., 1922
Aquilaria citrinicarpa	(Elmer) Hallier f., 1922
Aquilaria crassna	Pierre ex Lecomte, 1915
Aquilaria cumingiana	(Decne.) Ridl., 1901
Aquilaria decemcostata	Hallier f., 1922
Aquilaria filaria	(Oken) Merr., 1950
Aquilaria hirta	Ridl., 1901
Aquilaria khasiana	Hallier f., 1922
Aquilaria malaccensis	Lam., 1783
Aquilaria microcarpa	Baill., 1875
Aquilaria parvifolia	(Quisumb.) Ding Hou, 1960
Aquilaria rostrata	Ridl., 1924
Aquilaria rugosa	K. Le-Cong and Kessler, 2005
Aquilaria sinensis	(Lour.) Spreng., 1825
Aquilaria subintegra	Ding Hou, 1964
Aquilaria urdanetensis	(Elmer) Hallier f., 1922
Aquilaria yunnanensis	S.C. Huang, 1985

3.1. Adulteration and substitution

Due to its high price, agarwood industry has been tainted with adulteration, artificial and substitution products in order to meet the market demand and increase profit. Powder is the most susceptible agarwood item for adulteration, where it is mixed with healthy (un-infected) *Aquilaria* wood and sold at much cheaper price (Barden et al., 2000).

In India, agarwood chips are commonly adulterated with chips from other resin-producing species possibly from the *Symplocos racemosa* (called 'lodh') and *Mandragora officinalum* (called 'astrang') (Barden et al., 2000). Meanwhile, two types of fake agarwood have been described; (i) low quality agarwood painted with small layer of shavings mixed with wax and other material; and (ii) "Black Magic Wood" which refers to low quality agarwood impregnated with a liquid mix of agarwood oil and alcohol (Antonopoulou et al., 2010). Iron shavings and carbon powder from spent batteries have also been reported to be used to increase the weight and create resemblance to high quality agarwood (Barden et al., 2000). In Taiwan market, inferior quality of agarwood has been increasingly mis-classified and substituted as the top-grade agarwood (known as Chen Hsiang) (TRAFFIC East Asia-Taipei, TRAFFIC East Southeast Asia, 2005). Agarwood oil has also been reported to be adulterated either with 'lodh' oil, kerosene, other coloured oils, a mixture of other chemicals and or agarwood powder that gives the aroma of agarwood (Barden et al., 2000). Synthetic agarwood compounds have also been developed. However, these are used to produce poor-quality fragrances as no synthetic substitutes are available for high-grade fragrances due to its complexity of compound structure and high cost to synthesize (Barden et al., 2000).

The adulteration and substitution of agarwood (and its related materials) pose a crucial challenge to the industry. This problem could be due to the lack of concerted monitoring and law

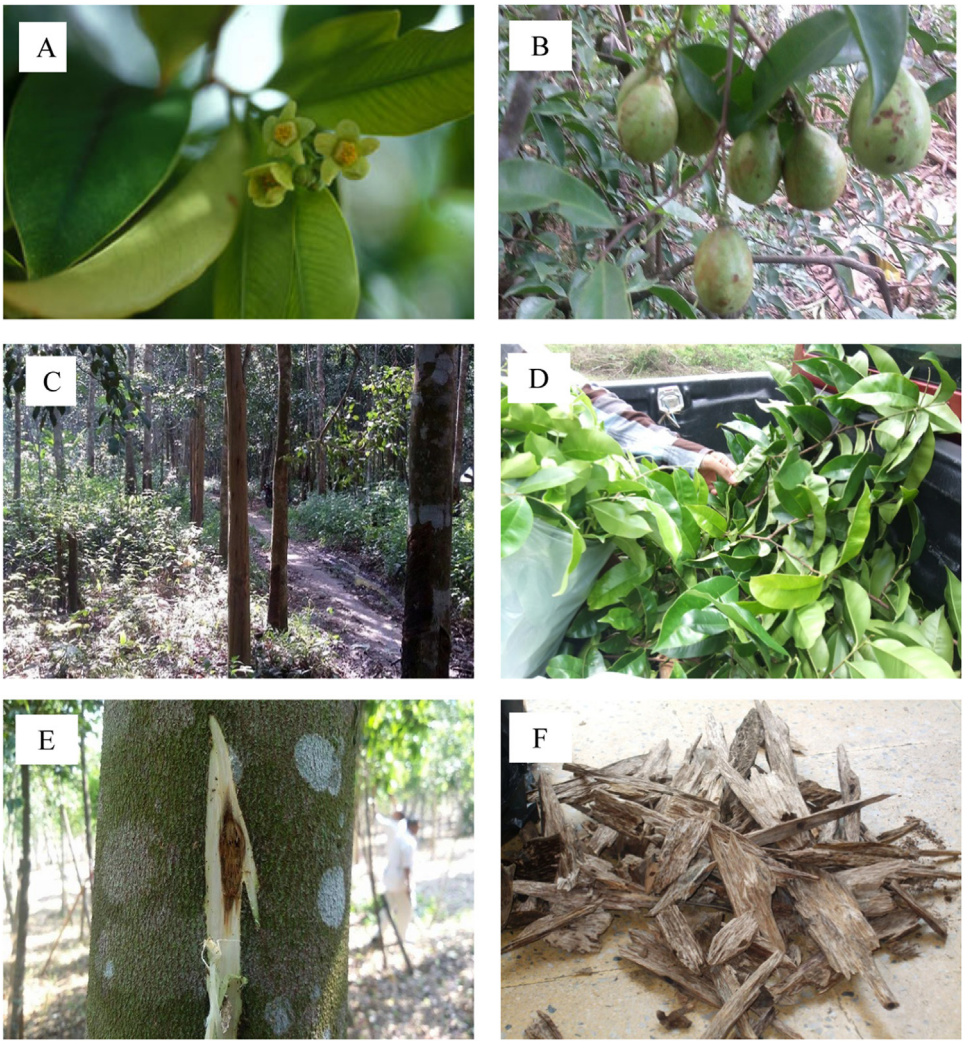


Fig. 1. *Aquilaria* spp. (A) flowers (*A. malaccensis*), (B) fruits (*A. malaccensis*), (C) trees in a plantation (*A. malaccensis*), (D) leaves (*A. subintegra*), (E) agarwood (resin) formation (*A. malaccensis*), and (F) resin-impregnated wood chips (mixture of different species of Aquilaria) (Photo: P. Abbas, 2010, Kajang, Selangor, Malaysia).

enforcement by the authorities. To date, there have been many efforts to develop scientific-based agarwood grading system (Hidayat et al., 2010; Ismail et al., 2014, 2012; Najib et al., 2012). However, the system has not been routinely used in the industry where agarwood is still being put through subjective grading. In the medicinal field, the authenticity of agarwood is particularly important as it may jeopardize the pharmaceutical effects intended. To this end, apart from monitoring and law enforcement; practice of integrity should be embraced by the agarwood industry towards eradicating the problem of adulteration and substitution.

4. Ethnopharmacology

Agarwood is used in a number of different communities, with the majority of its medicinal uses involved in anti-inflammatory and related activities. For instance, it is used to treat rheumatism, arthritis, body pain, asthma and gout. An earlier study of medicinal uses of *A. agallocha* listed the species as being a laxative, aphrodisiac, and stimulant, as well as a treatment for rheumatism, asthma and liver disease (Borris et al., 1988). Table 2 summarises the ethnomedicinal uses of agarwood in different locations. Some of these traditional uses have been corroborated by scientific investigations (Section 6).

5. Phytochemistry

The phytochemistry of agarwood resin, essential oil, fruit, hull and leaves are discussed in more detail below. Fig. 2 shows the major compounds found in agarwood plant materials.

5.1. Resin and essential oil

The phytochemical analysis of agarwood resin has been the subject of many studies and will only be briefly described here. In a review on the chemical constituents of agarwood, Chen et al. (2012c) reported that sesquiterpenes and 2-(2-phenylethyl)-4H-chromen-4-one derivatives were characteristics of the resin-infiltrated wood of the tree. Sesquiterpenes are divided into several categories, namely, agarofurans, agarospiranes, guaianes, eudesmanes, eremophilanes and prezizaanes. Aromatics (such as benzylacetone) and triterpenes were also reported to be present in the resin. Naef (2011) provided an excellent review of the constituents of agarwood resin, together with commentary on their organoleptic properties.

Earlier publications reflect the fact that agarwood resin constituents were isolated using solvent extraction, with subsequent purification via column chromatography and structural elucidation using spectroscopic techniques, including NMR (Bhandari et al., 1982; Ishihara et al., 1991a, 1991b; Jain, 1959; Nakanishi

et al., 1986, 1981, 1983, 1984; Yoneda et al., 1984). More recent articles focus on the use of the 'hyphenated' techniques to detect and identify compounds. For instance, Gao et al. (2014) used GC–MS coupled with multivariate data analysis to construct chemical profiles of chloroform extracts of natural and artificial agarwood.

The chemical constituents of agarwood essential oils are also being studied. Essential oils are produced by the hydrodistillation of resin or the newer technique of supercritical fluid extraction (SFE), which shows a similar suite of compounds. It is worth noting that in publications dealing with agarwood, the term 'agarwood oil' is used more frequently than 'essential oil'. The motivation to study the compounds in oil is often related to the development of scientific grading and quality control for commercial applications (Ismail et al., 2014, 2013; Tajuddin et al., 2013; Tajuddin and Yusoff, 2010). Variations in species and origin were also studied, as they are considered to be related to the oil quality (Hashim et al., 2014b; Nor Azah et al., 2008). Optimization of hydrodistillation and its related techniques have also been studied to improve the yield and quality of oil (Mat Yusoff et al., 2015; Yoswathana et al., 2012). Despite the considerable efforts into the identification of chemical compounds in agarwood essential oil towards grading and classification, the findings are not conclusive, with similar compounds present throughout the spectrum of investigated samples. However, the comprehensive chemical information shall contribute to future drug discovery and biotechnological exploitation, as suggested by Wong et al. (2015), who provided a metabolic profile of *A. malaccensis* essential oil from naturally infected trees using a GC x GC method coupled to time-of-flight mass spectrometry (TOFMS). Indeed, very little information from scientific studies of the biological effects of agarwood 'essential oil' and its potential applications as a drug has been noted. This information may have been overshadowed by its main use in the perfume industry.

5.2. Stem wood

The phytochemistry of agarwood healthy wood (or termed as fresh stem in some publications) has attracted less attention, despite the plethora of compounds present in this part of the tree. For instance, Chen et al. (2012a) isolated twelve flavonoids from *A. sinensis* healthy wood, as shown in Fig. 3. Several flavonoids, benzenoids, steroids and lignans in agarwood healthy wood of the same species were also reported (Chen et al., 2013a, 2013b). Peng et al. (2011) isolated aquilarin B (**25**), phorbol 13-acetate (**26**) and dihydrocucurbitacin F (**27**), and Wang et al. (2010) isolated aquilarin A (**28**), balanophonin (**29**) and (+)-lariciresinol (**30**) from the same species.

Additional classes of compounds were identified in ethanol, methanol and water extracts of branch, stem, stembark or heartwood, including amino acids, anthraquinones and terpenoids (Chitre et al., 2007; Dahham et al., 2014; Dash et al., 2008). The total phenolic content of a branch chloroform extract was 210 mg GAE/g DW (Bahrani et al., 2014).

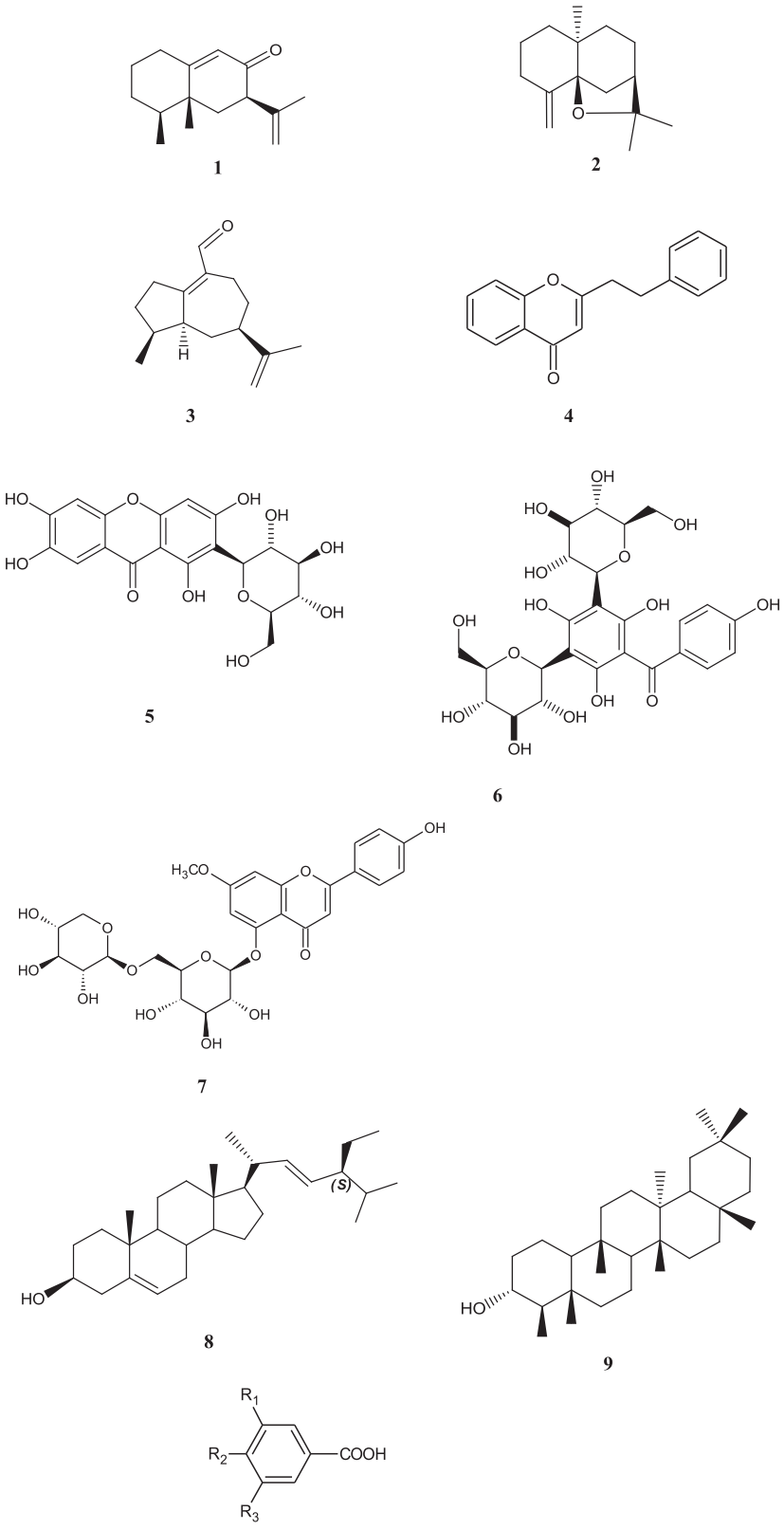
5.3. Leaves

Phytochemical screening of ethanol, methanol and water extracts of agarwood leaves across several species shows the consistent presence of flavonoids, tannins and saponins (Kamonwannasit et al., 2013; Khalil et al., 2013; Nik Wil et al., 2014; Vakati et al., 2013). Alkaloids and terpenoids were also identified

Table 2
Ethnopharmacology of *Aquilaria* spp.

Locality[a]	Ethnomedicinal uses	Preparations/route of intake	Reference
Bangladesh	Treatment of rheumatism	Agarwood taken orally	Rana et al. (2010)
China	Treatment of gastric problems, coughs, rheumatism and high fever; and used as sedative, analgesic and carminative agents	[b]Heartwood decoction	Chinese Pharmacopoeia Commission (2010)
India	Treatment of diarrhoea, dysentery, vomiting, anorexia, mouth and teeth diseases, facial paralysis, shivering, sprains, bone fracture	[b]Heartwood in Ayurvedic formulation such as Chawanprash, Arimedadi Taila and Mahanarin Taila	Anon (1978)
	Treatment of inflammation, arthritis, vomiting, cardiac disorders, cough, asthma, leprosy and anorexia	Information not available	Iyer (1994)
	Treatment of headache, inflammation, gout and arthritis	Information not available	Kirtikar and Basu (1999)
Indonesia	Treatment of joint pain	Wood burned and smoke held over the affected area	Grosvenor et al. (1995)
Japan	Stomachic and sedative agent	Information not available	Okugawa et al. (1993)
Korea	Treatment of cough, acroparalysis, croup, asthma, stomachic agent, tonic, sedative and expectorant	Information not available	Takagi et al. (1982); Yuk et al. (1981)
Malay peninsula (Malaysia)	Tonic, stimulant and carminative agent after childbirth	[b]Heartwood mixed with coconut oil (liniment)	Burkill (1935)
	Treatment of rheumatism and body pains Treatment of small pox	[b]Heartwood decoction (mixed with other types of woods) [b]Heartwood prepared into ointment	
Philippines (*A. cumingiana)* Thailand	Stop bleeding of the wounds	Bark and roots. Information on preparation is not available.	Lemmens and Bunyaprapatsara (2003)
	Treatment of malaria (substitute for quinine)	Bark, wood and fruits. Information on preparation is not available.	Kamonwannasit et al. (2013)
	Treatment for diarrhoea, dysentery and skin diseases as well as used antispasmodic and cardiovascular function enhancer in fainted patient	Various agarwood plant materials are used in traditional medicinal preparation 'Krisanaglun'	
	Treatment of fainting, nausea and vomiting	Agarwood in folk medicine 'Ya –Hom'	Suvitayavat et al. (2005)
Tibet	Treatment of nervous and emotional disorders	Information not available	Clifford (1984)
	Cardioprotective agents	Information not available	Owen and Jones (2002)

[a] No information on species reported on the ethnomedicinal uses listed unless otherwise stated. However, different species are endemic to certain regions.
[b] Heartwood is being interchangeably used with agarwood. See Sections 1 and 6.1 for more discussion.



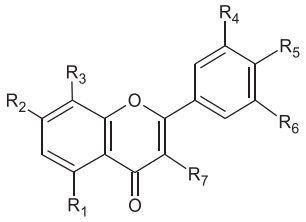
10 $R_1 = H,\ R_2 = OH,\ R_3 = H$
11 $R_1 = OCH_3,\ R_2 = OH,\ R_3 = OCH_3$
12 $R_1 = H,\ R_2 = OCH_3,\ R_3 = OH$

Fig. 2. Chemical structures of the major compounds found in agarwood plant materials: neopetasane (eremophilane) (**1**), β-agarofuran (**2**), (−)-guaia-1(10),11-dien-15-al (**3**), 2-(2-phenylethyl)chromone (**4**), mangiferin (**5**), iriflophenone 3,5-C-β-diglucoside (**6**), genkwanin. 5-O-β-primeveroside (**7**), stigmasterol (**8**), 3b-friedelanol (**9**), 4-hydroxybenzoic acid (**10**), syringic acid (**11**) and isovanillic acid (**12**).

(Dash et al., 2008; Huda et al., 2009; Khalil et al., 2013).

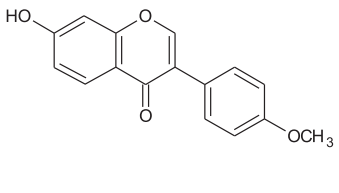
The total phenolic contents in leaves extracted with the aforementioned solvents were estimated to be between 157.41 and 183.5 mg GAE/g DW (Han and Li, 2012; Kamonwannasit et al., 2013; Tay et al., 2014). The chloroform extracts of leaves gave total phenolic contents of 164 mg GAE/g DW (Bahrani et al., 2014).

The total flavonoid content in the ethanol leaf extract was 249 mg QE/g DW (Tay et al., 2014) and 414 mg QE/g DW in the chloroform extract (Bahrani et al., 2014). Huda et al. (2009) reported the presence of flavonoids and steroids in leaves extracted



No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Compound
13	OH	OCH_3	H	H	OCH_3	H	H	5-hydroxy-4',7-dimethoxyflavone
14	OH	OCH_3	H	OCH_3	OCH_3	H	H	7,3',4'-tri-*O*-methylluteolin
15	O-Xyl(1,6)Glc	OCH_3	H	H	OCH_3	H	H	7,4'-ti-*O*-methylapigenin-5-*O*-xylosylglucoside
16	O-Glc(6,1)Xyl	OCH_3	H	H	OCH_3	OCH_3	H	lethedioside A
17	O-β-Glc	OCH_3	H	H	OCH_3	OCH_3	H	lethedoside A
18	O-β-Glc	OH	H	H	CH_3	H	H	7-hydroxyl-4′-methyl-flavone-5-*O*-glucoside
19	O-β-Glc	CH_3	H	CH_3	OH	H	H	7,3′-dimethyl-4′-hydroxyl-flavone-5-*O*-glucoside
20	O-β-Glc	CH_3	H	H	CH_3	H	H	7,4′-dimethyl-flavone-5-*O*-glucoside
1	OH	OH	H	H	OCH_3	H	H	5,7-dihydroxyl-4′-methoxyflavone
22	OH	OCH_3	H	H	OH	H	OH	hydroxylgenkwanin
23	O-Glc(6,1)Xyl	OH	H	H	OCH_3	H	H	aquilarinoside A_1

Glc = glucopyranose Pri = primeverose Xyl = xylopyranoside



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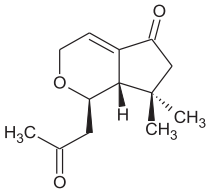

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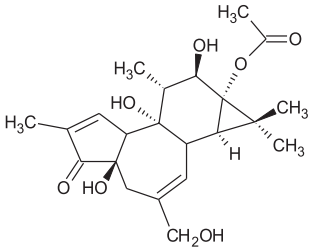

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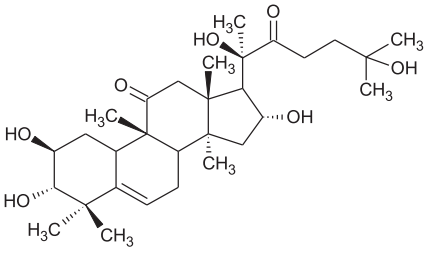

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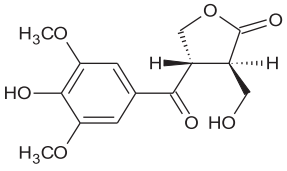

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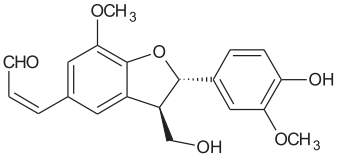

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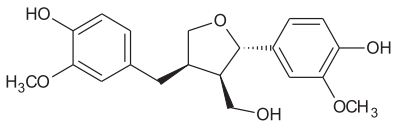

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Fig. 3. Chemical structures of the compounds found in agarwood stem wood (*i.e.*, healthy wood) of *A. sinensis*: compounds (**13** -**23**) (Chen et al., 2012a), formononetin (**24**), aquilarin B (**25**), phorbol 13-acetate (**26**), dihydrocucurbitacin F (**27**), aquilarin A (**28**), balanophonin (**29**), (+)-lariciresinol (**30**), compound (**24**) (Chen et al., 2012a), compound (**25–27**) (Peng et al., 2011), and compound (**28–30**) (Wang et al., 2010).

with hexane, dichloromethane or ethyl acetate, whereas alkaloids and saponins were identified in the ethyl acetate extract.

The constituents of agarwood leaf have only recently become a research focus. To the best of our knowledge, there is no review literature available in this area. Here, we include studies on agarwood leaf from 2008 to the present. The phytochemicals present in agarwood leaves are from a range of chemical classes, including phenolic acids, benzophenones, xanthonoids, flavonoids, terpenoids, phytosterols and fatty acids. Some of the phytochemicals showed pharmacological effects, as discussed in Section 6.3 below and, as such, could be candidates for future drug discovery. Furthermore, identification of the phytochemicals is important for the quality control and standardization of extracts, such as in the development of food supplements, herbal preparations or botanical drugs. Putalun et al. (2013) developed a polyclonal antibody against iriflophenone 3-*C*-β-D-glucoside, a major compound from agarwood leaf, that can be used as a biomarker of quality in agarwood plant samples and products. Table 3 shows the chemical constituents found in agarwood leaves.

6. Pharmacological activities

Plant materials of *Aquilaria* spp. have been reported to exert various bioactivities, including anti-allergic, anti-cancer, anti-inflammatory, anti-ischemic (cardioprotective), antimicrobial, anti-oxidant, anti-depressant (effects on the central nervous system) activities, as well as hepatoprotective, laxative and mosquitocidal effects.

Some of these biological activities are a relatively new pre-clinical practice of *Aquilaria* spp., whereas some have been practiced in traditional medicine and are now being scientifically verified. For instance, materials from agarwood plant have traditionally been used to treat inflammatory-related ailments (such as joint pain, rheumatism, arthritis and asthma). Pre-clinical studies showed that these materials possess prominent anti-inflammatory activities. As reported in this section, other traditional uses have also been scientifically proven at the pre-clinical level, namely, the sedative (effects on the central nervous system) and cardioprotective effects and treatment of gastric problems (laxative).

Although the anti-microbial, anti-oxidant, anti-cancer and anti-diabetic activities seem to be relatively new biological effects found in agarwood, they are interconnected with each other and to some extent are related to traditional use. For instance, microbial infections could be the cause of many (traditional) diseases, such as cough, diarrhoea, dysentery and leprosy (see Table 2). Therefore, the anti-microbial effects observed in the more recent pre-clinical studies supported the traditional uses. Meanwhile, oxidative stress is an underlying mechanism of many diseases, including cancer and diabetes. Therefore, the anti-oxidative properties of agarwood plant materials are useful for treating many diseases. Further, inflammation is one of the mechanisms of carcinogenesis and could be a target for prevention and or treatment using agarwood plant materials with anti-inflammatory activities.

The biological effects of the crude extract and isolated compounds of agarwood plant materials obtained from solvent extraction are discussed further below.

6.1. Crude extracts from agarwood plant material

Four species dominate the literature, namely, *A. agallocha* (despite the unresolved nomenclature), *A. crassna, A. malaccensis* and *A. sinensis.* The plant materials investigated include leaf, bark, branch, heartwood, oil, stem, stembark and woody hull. However, in the agarwood literature, these terms are often not well characterised. The age and status of the tree (infected or non-infected; wild or cultivated) are often not specified. However, it is most likely that the materials were obtained from infected trees, either artificial or wild, because the bioactive compounds are associated with the resin formed and impregnated in the plant tissue in response to injury. Therefore, bark, branch, heartwood, stem and stembark may refer to the resin-impregnated wood material, with heartwood being the most infiltrated material. Perhaps the most accurate term used is *Aquilariae Lignum Resinatum*, although it specifically refers to the resin of *A. sinensis* (chenxiang), which has been a part of Traditional Chinese Medicine for centuries (Chinese Pharmacopoeia Commission, 2010; Li et al., 2012). In a recent study, the anti-diabetic activity of green tea fermented with *Aquilariae Lignum Resinatum* was enhanced in a Type II diabetic db/db mouse compared with green tea alone (Kang et al., 2014a).

In future studies, it is important to include a detailed portfolio of the plant materials used, as it would assist in understanding the profile of infected and non-infected trees. Espinoza et al. (2014) showed that wild trees can be distinguished from cultivated trees based on certain chromone characteristics.

A uniform nomenclature should be used by the research community to ensure accurate interpretation of findings. For instance, heartwood can specifically refer to the inner, dark part of the stem, which is heavily impregnated with resin post-injury, as opposed to the soft white wood (or can be referred to as healthy wood or fresh stem; as previously discussed in Section 5.2). The latter may be sourced from either infected (from the bark of the infected tree where no resin is formed) or non-infected trees. Pictures or diagrams can be included to provide more accurate descriptions of ambiguous plant materials, such as the woody hull (exocarp and mexocarp), which is more specific than the term fruit (inclusive of hull and seed).

Detail portfolios of plant materials are also important in bioactivity studies. Some bioactivities have been exclusively observed in a certain type of plant material. For example, anti-diabetic effects were exclusively studied in leaf (Feng and Yang, 2011; Pranakhon et al., 2015, 2011; Zulkiflie et al., 2013), whereas cardioprotective effects were seen observed in heartwood (Jermsri et al., 2012; Jermsri and Kumphune, 2012; Kumphune et al., 2012; Suwannasing et al., 2012).

We have summarised the pharmacological actions of crude extracts of agarwood plant material from literature from 1997 to the present (Table 4). Meanwhile, pharmacological actions of isolated compounds are described in Sections 6.1 and 6.2. The majority of pharmacological studies on agarwood plant are being carried out on the crude extracts with very limited further work on the isolated compounds either for chemical characterisation purposes or determination of the pharmacological effects. Indeed proper chemical characterisation is of paramount importance in natural product-based drug discovery (Lombardino and Lowe, 2004). Therefore, future work in elucidating the pharmacological actions of agarwood plant should carefully include parallel work on the chemical characterisation.

6.2. Compounds isolated from resinous and healthy wood

Compounds isolated from agarwood resin and healthy wood showed acetylcholinesterase inhibition, antibacterial, anti-inflammatory, cytotoxic and analgesic actions. The majority of the reported studies focused on *A. sinensis.* Sesquiterpenoids and 2-(2-phenylethyl)chromone derivatives (tested at 50 μg/mL) inhibited 12.3–61.9% of acetylcholinesterase activity compared with tacrine (positive control), which inhibited approximately 70% of the activity at 0.08 μg/mL (Li et al., 2015b; Yang et al., 2014a, 2014b). Neopetasane (**1**), an eremophilane sesquiterpene, showed the strongest inhibition (61.9%) (Yang et al., 2014a).

Table 3
Phytochemistry of *Aquilaria* spp. leaves.

Chemical constituents	Compound number	Reference
Phenolic acids		
4-hydroxybenzoic acid	10	Nie et al. (2009); Wang et al. (2008) Kang et al. (2014b); Li et al. (2015a), Feng et al. (2011)
isovanillic acid	12	Kang et al. (2014b); Li et al. (2015a)
methylparaben	31	Kang et al. (2014b); Li et al. (2015a)
protocatechuic acid	32	Pranakhon et al. (2015)
syringic acid	33	Kang et al. (2014b); Li et al. (2015a)
vanillic acid	34	Kang et al. (2014b); Li et al. (2015a)
Benzophenones		
Aglycones		
aglycone of aquilarisinin (= iriflophenone) (=4-hydroxyphenyl)(2,4,6-trihydroxyphenyl)methanone	35	Feng et al. (2011)
Mono-glycosides		
aquilarinoside A (4-hydroxyphenyl)[3′,4,4′,6-tetrahydroxy-5′-(hydroxymethyl)-4′,5′-dihydro-3*H*,3′*H*-spiro[1-benzofuran-2,2′-furan]-7-yl] methanone	36	Qi et al. (2009); Yu et al. (2013)
iriflophenone 2-*O*-α-L-rhamnopyranoside[a]	37	Feng et al., (2011); Yu et al., (2013); Xia et al., (2013); Hara et al., (2008); Ito et al., (2012a), (2012b); Kakino et al., (2010a)
iriflophenone-3-*C*-β-D-glucoside[a]	38	Feng et al., (2011); Ito et al., (2012a); Pranakhon et al., (2015); Tay et al., (2014); Yu et al., (2013)
iriflophenone, [2-(2-*O*-acetyl-α-L-rhamnopyranosyl)oxy]	39	Yu et al. (2013)
iriflophenone, [2-(3-*O*-acetyl-α-L-rhamnopyranosyl)oxy]	40	Yu et al. (2013)
iriflophenone, [2-(4-*O*-acetyl-α-L-rhamnopyranosyl)oxy]	41	Yu et al. (2013)
Di-glycosides		
iriflophenone 2-*O*-α-L-rhamnopyranosyl-(1− > 4)-*O*-α-L-rhamnopyranoside [aquilarinenside A]	42	Sun et al. (2014)
iriflophenone 2-*O*-β-D-fucopyranosyl-(1− > 4)-*O*-α-L-rhamnopyranoside [aquilarinenside B]	43	Sun et al. (2014)
iriflophenone 2-*O*-β-D-quinovopyranosyl-(1− > 4)-*O*-α-L-rhamnopyranoside [aquilarinenside C]	44	Sun et al. (2014)
iriflophenone 2-*O*-β-D-xylopyranosyl-(1− > 4)-*O*-α-L-rhamnopyranoside [aquilarinenside D]	45	Sun et al. (2014)
iriflophenone 2-*O*-α-L-(4″-acetyl)-rhamnopyranoside [aquilarinenside E]	46	Sun et al. (2014)
iriflophenone 2-*O*-β-D-glucopyranosyl-(1− > 4)-*O*-α-L-rhamnopyranoside [aquilarisinin]	47	Feng et al. (2011)
iriflophenone 3,5-*C*-β-D-diglucopyranoside[a]	48	Feng et al., (2011); Hara et al., (2008); Ito et al., (2012a), (2012b); Yu et al., (2013)
iriflophenone 3-*C*-β-glucoside	49	Ito et al., (2012b)
Xanthonoids		
Aglycones		
1,2,3,6,7-pentahydroxy-9*H*-xanthen-9-one	50	Ito et al., (2012b)
Mono-glycosides		
aquilarixanthone	51	Yu et al. (2013)
homomangiferin	52	Yu et al. (2013)
isomangiferin	53	Yu et al. (2013)
mangiferin	54	Feng et al., (2011); Hara et al., (2008); Ito et al., (2012a), (2012b); Kakino et al., (2010a); Pranakhon et al., (2015); Qi et al., (2009); Ray et al., (2014); Yu et al., (2013)
Di-glycosides		
neomangiferin	55	Yu et al. (2013)
Flavonoids		
Aglycones		
Flavanols		
epicatechin gallate	56	Tay et al. (2014)
epigallocatechin gallate	57	Tay et al. (2014)
Tri-oxygenated flavones		
apigenin-7,4′-dimethylether (=5-hydroxy-4′,7-dimethoxyflavone)	58	Feng and Yang (2012); Kang et al. (2014b); Li et al. (2015a); Lu et al. (2008); Nie et al. (2009); Pranakhon et al. (2015); Wang et al. (2008)
7-hydroxy-5,4′-dimethoxyflavone	59	Nie et al. (2009)
genkwanin (4′,5-dihydroxy-7-methoxyflavone)	60	Feng and Yang, (2012); Hara et al., (2008); Ito et al., (2012a, 2012b); Lu et al. (2008); Nie et al. (2009); Pranakhon et al., (2015); Qi et al. (2009); Ray et al. (2014); Wang et al. (2008); Yu et al. (2013)

Table 3 (*continued*)

Chemical constituents	Compound number	Reference
Tetra-oxygenated flavones		
luteolin (3′,4′,5,7-tetrahydroxyflavone)	61	Feng and Yang (2012); Lu et al. (2008); Qi et al. (2009); Wang et al. (2008)
hydroxygenkwanin (=3′-hydroxygenkwanin) (3′,4′,5-trihydroxy-7-methoxyflavone)	62	Lu et al. (2008); Qi et al. (2009); Yu et al. (2013)
luteolin-7,4′-dimethylether (3′,5-dihydroxy-4′,7-dimethoxyflavone)	63	Kang et al. (2014b); Li et al. (2015a); Lu et al. (2008)
luteolin-7,3′,4′-trimethyl ether (=7, 3′,4′-tri-*O*-methylluteolin)	64	Kang et al. (2014b); Li et al. (2015a);Lu et al. (2008); Nie et al. (2009); Wang et al. (2008); Yu et al. (2013)
5,4′-dihydroxy-7,3′-dimethoxyflavone	65	Nie et al. (2009)
Penta-oxygenated flavones		
7,3′,5′-tri-*O*-methyltricetin	66	Xia et al. (2013)
Mono-glycosides		
delphinidin-3-glucoside[a]	67	Feng et al. (2011); Yu et al. (2013)
7-*O*-β-D-glucopyranoside of 5-*O*-methylapigenin	68	Qi et al. (2009); Xia et al. (2013)
hypolaetin 5-*O*-β-D-glucuronopyranoside	69	Feng et al. (2011); Yu et al. (2013)
genkwanin-5-*O*-β-D-glucopyranoside[a]	70	Feng and Yang (2012); Hara et al. (2008); Ito et al. (2012a)
Di-glycosides		
4′-hydroxy-5 methoxyflavone-7-*O*-glucoxyloside[a]	71	Feng and Yang (2012)
7,4′-di-*O*-methylapigenin-5-*O*-xylosylglucoside[a]	72	Yu et al. (2013)
5-*O*-xylosylglucoside of 7-*O*-methylapigenin[a]	73	Qi et al. (2009)
5-*O*-xylosylglucoside of 7,4′-di-*O*-methylapigenin[a]	74	Qi et al. (2009)
aquisiflavoside	75	Yang et al. (2012)
genkwanin-4′-methyl ether 5-*O*-β-primeveroside	76	Hara et al. (2008); Ito et al. (2012a)
genkwanin-5-*O*-β-D-primeveroside (yuankanin)	77	Feng and Yang (2012); Hara et al. (2008); Ito et al. (2012a); Ito et al. (2012b); Kakino et al. (2010a)
Terpenoids		
Diterpenoids		
cryptotanshinone	78	Feng and Yang (2011)
dihydrotanshinone I	79	Feng et al. (2011)
tanshinone I	80	Feng et al. (2011)
tanshinone IIA	81	Feng et al. (2011)
3,7,11,15-tetramethyl-2-hexadecen-1-ol (phytol)	82	Khalil et al. (2013)
Triterpenoids		
2-α-hydroxyursane	83	Feng and Yang (2011)
2-α-hydroxyursolic acid	84	Feng et al. (2011)
3-friedelanol[a]	85	Moosa (2010)
epifriedelanol	86	Nie et al. (2009)
friedelan	87	Nie et al. (2009)
friedelin	88	Nie et al. (2009)
squalene	89	Khalil et al. (2013)
Phytosterols/steroids		
stigmasterol[a]	90	Kang et al. (2014b); Li et al. (2015a);Moosa (2010)
(3β,7α)-stigmast-5-ene-3,7-diol	91	Xia et al. (2013)
stigmasta-4,22-dien-3-one	92	Kang et al. (2014b)
β-sitostenone	93	Kang et al. (2014b); Li et al. (2015a)
β-sitosterol	94	Feng and Yang (2011); Kang et al. (2014b); Li et al. (2015a); Moosa (2010)
daucosterol (glycoside of sitosterol)[a]	95	Feng and Yang (2011)
Fatty acids		
triacontenoic acid[a]	96	Nie et al. (2009)
n-hexadecanoic acid	97	Khalil et al. (2013)
hexacosanoic acid	98	Feng and Yang (2011)
1,2,3-propanetriol, monoacetate	99	Khalil et al. (2013)
9*Z*,12*Z*,15*Z*-octadecatrienoic acid	100	Khalil et al. (2013)
Fatty acid esters		
dodecyl acrylate	101	Khalil et al. (2013)
Fatty alcohol		
1-tetradecanol	102	Khalil et al. (2013)
Carbohydrate/carbohydrate conjugates		
glycerine	103	Khalil et al. (2013)
1,3-dihydroxy propanone	104	Khalil et al. (2013)
phenyl-β-D-glucopyranoside	105	Khalil et al. (2013)
2-phenylethyl-D-glucopyranoside	106	Xia et al. (2013)
benzyl alcohol-*O*-β-D-glucopyranoside	107	Xia et al. (2013)

Table 3 (*continued*)

Chemical constituents	Compound number	Reference
Phenols		
hydroquinone	108	Feng and Yang (2011)
4-hydroxyacetanilide	109	Afiffudden et al. (2015)
Phenolic glycosides		
salidroside	110	Xia et al. (2013)
vanilloloside	111	Xia et al. (2013)
Pyranones		
2,3-dihydro-3,5-dihydroxy-6-methyl-(4*H*)-pyran-4-one	112	Khalil et al. (2013)
Quinones		
6-ethyl-5-hydroxy-2,3,7-trimethoxynaphthoquinone	113	Khalil et al. (2013)
β-tocopherol	114	Xia et al. (2013)
Lignans		
(+)-syringaresinol	115	Xia et al. (2013)
Alkaloids		
isocorydine	116	Nie et al. (2009)
Alkanes		
hentriacontane	117	Nie et al. (2009)

Note: All compounds were isolated from *A.sinensis,* except for those reported by Li et al. (2015a) (*A .agallocha*), Ito et al., (2012a); Kakino et al., (2010a); Ray et al., (2014); Tay et al., (2014) (*A. crassna*); Khalil et al. (2013) and Moosa (2010) (*A. malaccensis*).

[a] Not all authors distinguish clearly all stereochemical details: of absolute configurations, location of double bonds, or attached glycosides. This is because insufficient physical properties of compounds isolated have been reported.

The sesquiterpenoid 12,15-dioxo-α-selinene (**121**) showed the largest inhibition zone(20.02 ± 0.12 mm) for *S. aureus*, and (*5S, 7S, 9S, 10S*)-(+)-9-hydroxy-selina-3,11-dien-12-al (**122**) showed the largest inhibition zone (18.02 ± 0.07 mm) for *R. solanacearum* (Li et al., 2015b). Both compounds were tested at 10 mg/mL. In comparison, kanamycin sulfate (0.5 mg/mL) showed an inhibition zone of 22.05 ± 0.28 mm for *S. aureus* and 31.95 ± 0.13 mm for *R. solanacearum* (Li et al., 2015b).

Different classes of compounds were identified in the infected and healthy wood of *A. sinensis*, with 2-(2-phenylethyl)chromone derivatives observed exclusively in the resinous wood (Chen et al., 2012b) and glycosylflavones observed in the healthy wood (Chen et al., 2012a). Aquilarone B [(*5S,6S,7S,8R*)-2-(2-phenylethyl)-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone] (**123**) from infected wood showed the greatest inhibition of nitric oxide (NO) production by activated RAW 264.7 cells, with an IC_{50} of 5.12 μM (Chen et al., 2012b). For healthy wood, the highest anti-inflammatory effect was shown by lethedioside A (**16**), with an IC_{50} of 7.91 μM (Chen et al., 2012a). The IC_{50} for the positive control, ibuprofen, was reported to be 94.12 μM (Chen et al., 2012a, 2012b).

Mixed findings were reported with regards to the cytotoxic effects of agarwood compounds against several cell lines. Dihydrocucurbitacin F (**27**) from healthy wood of *A. sinensis* gave the lowest IC_{50} of 0.5 μg/mL in SMMC7221 human hepatoma cells (Peng et al., 2011). Aquilarin A (**28**) and B (**25**) from healthy wood showed no cytotoxicity against K562 human myeloid leukaemia cells, SGC-7901 human gastric cancer cells or SMMC-7721 human hepatoma cells (Peng et al., 2011; Wang et al., 2010). Meanwhile, 8-chloro-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one (**124**) from the resin showed an IC_{50} of 14.6 mg/mL in SGC7901 cells (Liu et al., 2008); 5,6,7,8-tetra-hydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one (**125**) showed no cytotoxic effects against K562, SGC-7901, and SMMC-7721 cells (Dai et al., 2009). A classic publication on the anti-cancer/cytotoxic effects in P388 leukaemia cells showed that the agarwood compounds from *A. malaccensis* exhibited an ED_{50} of 0.0022 μg/mL and ED_{50} of 0.8 μg/mL for 12-*O*-*n*-deca-2,4,6-trienoylphorbol-13-acetate (**126**) and 1,3-dibehenyl-2-ferulyl glyceride (**127**), respectively (Gunasekera et al., 1981). Another study on compounds from *A. malaccensis* reported the sedative and analgesic effects of two sesquiterpenoids, jinkoh-eremol (**128**) and agarospirol (**129**), in mice (Okugawa et al., 1996b, 2000).

More recently, sesquiterpene β-caryophyllene (**130**) purified from *A. crassna* essential oil was shown to exhibit anti-proliferative effects against HCT116 colorectal cancer cells, with an IC_{50} of 19 μM, and potent inhibition against clonogenicity, migration, invasion and spheroid formation in colon cancer cells (Dahham et al., 2015b). The same group also demonstrated the *in vivo* inflammatory activity of β-caryophyllene, where a 200 mg/kg dose of the compound reduced 87.6% of the inflammation in the carrageenan-induced rat hind paw edema model compared with the control (distil water), whereas a standard drug, indomethacin, showed 75.5% inhibition at 10 mg/kg (Dahham et al., 2015b). β-caryophyllene also showed antibacterial activity against *S. aureus* (MIC 3 ± 1.0 μM) compared with the standard reference kanamycin (MIC 8 ± 2.3 μM), as well as anti-oxidant activities, with IC_{50} values of 1.25 ± 0.06 μM (DPPH; IC_{50} of 1.5 ± 0.03 μM for ascorbic acid) and 3.23 ± 0.07 μM (FRAP; IC_{50} of 1.5 ± 0.03 μM for ascorbic acid) (Dahham et al., 2015b). Fig. 4 shows the chemical structures of compounds with known pharmacological activities that were isolated from agarwood resin.

6.3. Compounds isolated from fruit, hull and leaf

Four compounds from the fruit of *A. sinensis*, namely,

Table 4
Pharmacological activities of crude extracts from various parts of agarwood plant

No	Pharmacological activities	Species	Part of plant	Formulation/dosage/extract	Model/cell line/organism/ microorganism	Result	Reference
1	Anti-allergic (anti-anaphylaxis)	*A. agallocha*	Stem	0.05, 0.25 and 0.50 g/kg body weight aqueous extract for passive cutaneous anaphylaxis reaction *in vivo*	*in vivo* Male Wistar rats	Inhibition of passive cutaneous anaphylaxis reaction at of 0.25 and 0.50 g/kg body weight. Positive control: Ketotifen at 0.25 g/kg body weight inhibited the reaction.	Kim et al. (1997)
				0.03 to 2.00 g/kg body weight aqueous extract for compound- 48/80 induced anaphylactic shock *in vivo*		Biphasic reduction of mortality (0-57.1% mortality) in compound 48/80-induced anaphylactic shock rats when tested between 0.06 to 2.00 g/kg body weight. Positive control: Ketotifen at 0.50 g/kg body weight resulted in 0% mortality. Biphasic inhibition of histamine release in compound 48/80-induced anaphylactic with the highest inhibition (78.08 ± 2.70 %) at 0.5 g/kg body weight. Positive control: Ketotifen at 0.50 g/kg body weight inhibited 71.90 ± 2.24 % histamine release.	
				0.05 to 1.6 mg/mL aqueous extract	*in vitro*	Dose-related inhibition of histamine release from RPMC. The highest inhibition is approximately 85%; at 1.6 mg/mL extract	
				(extraction: distilled water on water bath)	RPMC (rat peritoneal mast cells)	Positive control: Ketotifen at 1.6 mg/mL resulted in 90% inhibition. Increased of intracellular cAMP content of mast cells when treated with 10 μg/mL extract as compared to basal cells, suggesting that the degranulation of mast cells may be mediated through an increase in cAMP level.	
2	Anti-diabetic (anti-hyperglycemic)	*A. sinensis*	Leaf	1.0 g/kg body weight methanol extract	*in vivo*	1.0 g/kg of methanol reduced blood glucose levels by 40.30%.	Pranakhon et al. (2015)
					diabetic (streptozotocin; STZ-induced) ICR mice	Negative control: Distilled water. Positive control: 8 U/kg of insulin reduced blood glucose levels by 41.50%.	
		A. sinensis	Leaf	Ethanol, petroleum ether, ethyl acetate, butanol and water soluble extract	*in vitro*	Ethyl acetate fraction showed the lowest IC_{50} of 366.0 ± 45.1μg/mL, followed by butanol fraction (990.1 ± 59.1 μg/mL), water soluble fraction (993.2 ± 68.2 μg/mL), petroleum ether fraction (1046.0 ± 42.1 μg/mL) and ethanol extract (1056.0 ± 28.6 μg/mL).	Feng et al. (2011)
					α-glucosidase inhibition assay	Negative control: DMSO in phosphate buffer. Positive control: Acarbose (IC_{50} of 372.0 ± 37.8 μg/mL).	
		A. malaccensis and A. hirta	Leaf	100 to 1000 μg/mL methanol extract	*in vitro*	Extract inhibited α-glucosidase at IC_{50} of 375.50 μg/mL (*A. malaccensis*) and IC_{50} of 452.82 μg/mL (*A. hirta*)	Zulkiflie et al. (2013)
					α-glucosidase and α-amylase inhibition assay	Positive control: Acarbose (IC_{50} of 823.94 μg/mL) Extract inhibited α-amylase at IC_{50} of 397.23 μg/mL (*A .malaccensis*) and IC_{50} of 301.99 μg/mL (*A. hirta*)	

Table 4 (*continued*)

No	Pharmacological activities	Species	Part of plant	Formulation/dosage/extract	Model/cell line/organism/ microorganism	Result	Reference
						Positive control: Acarbose (IC50 of 940.11 μg/mL)	
		A. sinensis	Leaf	300 and 600 mg/kg ethanol extract	*in vivo*	600 mg/kg extract gave the largest reduction of fasting blood glucose (60 %) and HbA1c (30 %) as compared to control.	Jiang and Tu (2011)
				(extraction: 95 % ethanol (v/v), reflux twice at 3 h each time)	diabetic female db/db mice	600 mg/kg extract also improved glucose tolerance in mice without weight gain. Extract increased p-AMPK in mice liver suggesting that the hypoglemic effects seen were governed through this metabolic regulator.	
						Negative control: Water. Positive control: Rosiglitazone (5 mg/kg).	
		A. sinensis	Leaf	1.0 g/kg body weight methanol, water & hexane extract	*in vivo*	1.0 g/kg of methanol and water extracts reduced blood glucose levels by 54.29% and 40.54%, respectively.	Pranakhon et al. (2011)
					diabetic (streptozotocin; STZ-induced) Male Sprague-Dawley rats	Hexane extract showed no effects.	
						Negative control: Distilled water. Positive control: 4 U/kg of insulin reduced blood glucose levels by 73.42%.	
				1, 3, 10, 30 μg/mL methanol, water & hexane extract extract	*in vitro*	10 μg/mL water extract showed the highest glucose uptake at 176 % of negative control followed by 10 μg/mL methanol extract at 172 %.	
					white adipocytes from the epididymal fat pad of normal rats	Hexane extract showed no effects.	
						Negative control: Krebs-Ringer bicarbonate buffer (KRBB) Positive control: 1.5 nM of insulin showed glucose uptake at between 161 to 172 % of negative control.	
3	Anti-cancer	*A. crassna*	Oil	3.1 to 200 μg/mL oil for MTT assay	*in vitro* MTT assay	Anti-cancer (anti-metastatic activities). Cytotoxicity (MTT): IC_{50} of 11 ± 2.18 μg/mL (positive control; 5-FU; IC_{50} of 6.5 ± 1.4 μg/mL).	Dahham (2015a)
				5 and 10 μg/mL oil for cell migration assay	Cell migration (wound healing) assay	10 μg/mL oil significantly inhibited the migration of cells as compared to control (untreated cells) where wound closure after 24 h was 92.6 %.	
				5, 10 and 20 μg/ml oil for colony formation assay	Colony formation assay	Percentage of plating efficiency (PE) in negative control group (0.1% DMSO) was 76 ± 2%. Treatment at 5, 10 and 20 μg/ml oil significantly decreased PE to 41 ± 3%, 28.6 ± 2% and 10 ± 4% respectively. Positive control (5-FU) showed PE at approximately 20 %.	
		Aquilaria spp.	Oil	7.8125 to 1000 μg/mL essential oil in 10% (v/v) DMSO	MIA PaCa-2 cell line *in vitro* SRB assay	Anti-cancer activities with IC_{50} of 44 μg/mL. Negative control: DMSO 0.1% (v/v).	Hashim et al. (2014a)
		A. crassna	Stembark	Ethanol extract	MCF-7 cell line *in vitro*	Anti-cancer/antiproliferative activities with IC_{50} of 38 μg/mL (HCT116) , 72 μg/mL	Dahham et al. (2014)

				(extraction: 80% (v/v); maceration)	MTT assay	(PANC-1), 119 μg/mL (PC3) and 140 μg/mL (MCF-7). Positive control: IC_{50} of 12.7 μg/mL (5FU for HCT116), 19.4 μg/mL and 8.4 μg/mL (betulinic acid for PANC-1 and PC3 respectively) and 9μg/mL (tamoxifen for MCF-7).	
					HCT116, PANC-1, PC3, MCF-7 cell lines		
		A. agallocha	Woody hull of fruit	1.56 to 100 μg/mL methanol extract	*in vitro*	Anti-cancer activities with IC50 of 17.82 μg/mL (T24), 18.5 μg/mL (HT29), 35.19μg/mL (HeLa) 43.13 μg/mL (AGS) and 58.69 μg/mL (HepG2).	Wang et al. (2012)
					MTT assay T24, HT29, HeLa, AGS and Hep G2 cell lines		
				15 and 30 mg/kg/day methanol extract	*in vivo*	11.1% increase in lifespan (%ILS) as compared to control for 15mg/kg/day extract and 44.4% increase for 30mg/kg/day extract. Negative control: DMSO 0.1%.	
					CDF1 mice with P388D1 lymphocytic leukemia cells subcutaneously inoculated to abdominal cavity		
						Positive control: Daunorubin (1 mg/kg/day).	
		A. malaccensis	Stembark (clean and infected part)	2 to 25 μg/mL oleoresin	*in vitro* MTT assay	Anti-cancer activities with IC_{50} of 4 μg/mL.	Ibrahim et al. (2011)
				(extraction: supercritical CO2 (50°C, 20.7 MPa, CO2 flow rate ≤ 1 mL/min, particle size ≤ 500, fraction obtains from the first 10 min run)	HCT116 colorectal cancer cell line	Negative control: DMSO.	
						Positive control: Suramin (IC_{50} not reported).	
		A. malaccensis	Stembark	Petroleum ether, and chloroform extract	*in vitro*	ED_{50} = 0.35 μg/mL (petroleum ether), ED_{50} = 0.41 μg/mL (chloroform)	Gunasekera et al. (1981)
					P388 lymphocytic leukemia cell line		
4	Anti-inflammatory/ anti-nociceptive/analgesic/ antipyretic	*A. crassna*	Leaf	200, 400 and 800 mg/kg methanol extract	*in vivo*	Antipyretic activity (Baker's yeast-induced fever): 400 and 800 mg/kg extract showed reduction of rectal temperature (TR) between 50 to 75% at 5 and 6 hours after yeast injection in rats when compared to the control at the same time point.	Sattayasai et al. (2012)
				(extraction: maceration, 24h)	male ICR mice, male Sprague Dawley rats	Analgesic activity (Hot plate test in mice):800 mg/kg increased thermal threshold 35 to 50% as compared to control. Anti-inflammatory activity (carrageenan-induced paw edema in rats): no anti-inflammatory effects were observed. Negative control: Water Positive control: Aspirin (150 mg/kg or 300 mg/kg)	
		A. agallocha	Heartwood	100, 250 and 500 μg/mL of hexane extract for in *vitro* assay	*in vitro*	500 μg/mL showed the highest (78.50%) protection of HRBC in hypotonic solution. Negative control: Distilled water Positive control: Diclofenac at 50, 100 and 200 μg/mL (giving range of protection between 43.74 to 86.73%)	Rahman et al. (2012)
					human red blood cell (HRBC)		
				50 and 100 mg/kg hexane extract for *in vivo* study	*in vivo*	100 mg/kg extract showed the highest reduction (62.11%) in carrageenan-induced paw edema in rats	

Table 4 (*continued*)

No	Pharmacological activities	Species	Part of plant	Formulation/dosage/extract	Model/cell line/organism/ microorganism	Result	Reference
					rats	Negative control: Tween 80	
				(extraction: Soxhlet)		Positive control: Diclofenac (10 mg/kg caused reduction in paw edema by 68.94%)	
		A. crassna	Heartwood	0.5 to 3.0 mg/mL ethyl acetate	*in vitro*	Extract showed dose dependent inhibition of TNF-α production in LPS-stimulated hPBMC cells.	Kumphune et al. (2011)
				(extraction: consecutive reflux, 2 days)	Human peripheral blood mono-nuclear cells (hPBMCs)	Negative control: DMSO.	
						1.5 mg/mL extract inhibited TNF-α gene expression. Co-treatment of the extract with LPS could not block p38 MAPK activation, but pre-treatment of the extracts significantly reduced the p38 MAPK phosphorylation without affecting the ERK1/2 MAPK activation.	
		A. sinensis	Leaf	424 and 848 mg/kg ethanol extract	*in vivo*	Extract showed analgesic effects where there were (i) ~65% inhibition of writhing as compared to control, and (ii) 32 to 51% inhibition of paw edema at 848 mg/kg as compared to control.	Zhou et al. (2008)
					ICR mice	Positive control: Indomethacin (20 mg/kg)	
				50, 100 and 200 μg/mL ethanol extract in *in vitro* model	*in vitro*	Extract showed anti-inflammatory effects where there were (i) dose-dependent inhibition of CMC-NA-induced leukocyte emigration with 90.6% inhibition at 848 mg/kg, (ii) dose-dependent suppression of xylene-induced ear swelling in mice with 51.0% inhibition rate at 848 mg/kg, and (iii) dose-dependent decrease of NO release from LPS-stimulated macrophages with IC_{50} of 80.4 mg/mL	
					Thioglycollate-elicited mouse	Positive control: Hydrocortisone (10 μg/mL)	
				(extraction: reflux, 2 h, twice)			
		A. agallocha	Heartwood	50, 100 and 200 mg/kg body weight ethyl acetate extract	*in vivo*	Extract showed dose dependent analgesic effects where there were (i) inhibition of writhing, (ii) increased total time in paw licking and (iii) increased latency in tail flicking as compared to control.	Chitre et al. (2007)
					male albino mice (analgesic model)		
				(extraction: Soxhlet, 72 hr, 60-80°C)	Wistar rats (anti-inflammatory model)	Extract showed anti-inflammatory effects where there were reduced (ii) carrageenan-induced edemas, (ii) granuloma dry weight as compared to control.	
						Negative control: 10 mL/kg 2% Tween 80 in water.	
						Positive control: Diclofenac (10 mg/kg).	
5	Anti-ischemic/ cardioprotective	*A. crassna*	Heartwood	1 to 10 mg/mL ethyl acetate extract	*in vitro*	Extracts were treated prior to ischemia simulation. 5 mg/mL extract gave the highest percentage of cell viability (~80%) and reduced LDH activity.	Jermsri et al. (2012)
						Extract > 6 mg/mL reduced cell viability and but failed to reduce cell injury.	
				(extraction:consecutive reflux, 2 days)	H9c2 rat cardiac myoblast; simulated ischemia/reperfusion	5mg/mL extract inhibited p38MAPK phosphorylation when tested prior, at onset or	

					model	both conditions suggesting the ischemia induced cell injury and death is reduced through this signaling pathway. Negative control: 0.001% DMSO.	
		A. crassna	Heartwood	1 to 8 mg/mL ethyl acetate extract	*in vitro*	5 mg/mL extract gave the highest percentage of cell viability (~80%) and reduced LDH activity.	Jermsri and Kumphune (2012)
					MTT assay	Extract > 6 mg/mL reduced cell viability and gave higher LDH activity.	
				(extraction:consecutive reflux, 2 days)	H9c2 rat cardiac myoblast; simulated ischemia/reperfusion model	5 mg/mL extract preserves F-actin organization (between 35-60% as compared to control) when tested prior, at onset or both conditions. Negative control: 0.001% DMSO.	
		A. crassna	Heartwood	1 to 10 mg/mL ethyl acetate extract	Ex vivo	5 mg/mL extract gave the highest percentage of cell viability (~91%) and reduced LDH activity.	Kumphune et al. (2012)
				(extraction: consecutive reflux, 2 days)	Isolated Adult Rat Ventricular Myocytes (ARVM) ischemia/reperfusion model	Pre-treatment (prior to simulated ischemia, SI) and co-treatment (prior and during SI) reduced cell injury and death through attenuation of p38MAPK phosphorylation. Negative control: 0.001% DMSO.	
		A. crassna	Heartwood	5 mg/mL ethyl acetate extract	Ex vivo	Pre-treatment of the heart with the extract for 30 min (prior to global ischemia) reduced infarct volume by 56 % as compared to control.	Suwannasing et al. (2012)
				(extraction:consecutive reflux, 2 days)	Isolated ICR mouse heart ischemia/reperfusion model	Pre-treatment of the extract inhibited p38MAPK phosphorylation leading to reduction of infarct size. Negative control: 0.001% DMSO.	
6	Anti-microbial	*A. sinensis*	Oil	1 to 64 mg/mL of essential oil from wild tree (W), tree induced by L.theobromae (F) and health tree (H)	*in vitro*	MIC for *C.albicans, F.oxysporum,* and *L.theobromae* were 0.5, 2.0 and 4.0 mg/mL (W); 1.0, 1.0 and 2.0 mg/mL (F) and 16, 32 and 64 mg/mL (H); respectively.	Zhang (2014)
					microwell dilution method	Negative control (DMSO and water) showed no inhibition zones.	
					C.albicans, F.oxysporum and *L. theobromae*	Positive control (fluconazole) tested in the range of 0.01 to 0.64 mg/mL gave MIC of 0.04 (*C.albicans*), 0.08 (*F.oxysporum*) and 0.16 (*L.theobromae*) mg/mL.	
		A. crassna	Leaf	2, 4 and 6 mg aqueous extract	*in vitro*	MIC = 6 mg/mL; MBC = 12 mg/mL	Kamonwannasit et al. (2013)
					disc diffusion assay, MIC MBC	The extract caused swelling and distortion of bacteria cells and inhibited bacterial biofilm formation. Rupture of bacterial cell wall occurred after treated with the extract for 24 h.	
				(extraction: boiling water)	*S. epidermidis*	Positive control: Vancomycin gave MIC of 1.5 μg/mL and MBC of 3.0 μg/mL	
		A. agallohca	Heartwood	2.5, 5.0 and 10 % (v/v) oil	*in vitro*	All samples showed inhibition zone between 5.3 ± 0.14 to 9.5 ± 0.13 mm with the largest inhibition zone observed for 10 % (v/v) oil against *E. coli.*	Ghosh et al. (2013)
				(extraction: hydrodistillation to obtain oil)	agar well diffusion method	Negative control: DMSO	
					E. coli, S. aureus, P. aeruginosa and *E. Faecalis*	Positive control: Ciprofloxacin (at 100 μg/mL showed 31.6 ± 0.17 mm zone inhibition for *E. coli*)	
		A. subintegra	Leaf	200 μg/mL ethanol, acetone, hexane, diethyl, ether, ethyl, acetate extracts	*in vitro*	All extracts showed inhibition zone between 9-12 mm with the largest inhibition	Hashim et al. (2012)

Table 4 (*continued*)

No	Pharmacological activities	Species	Part of plant	Formulation/dosage/extract	Model/cell line/organism/ microorganism	Result	Reference
						zone (12 mm) observed for acetone extract against *B. subtillis* and hexane extract against *S. aureus.*	
					disc diffusion method	The smallest inhibition zone (9.3 ± 0.6 mm) was observed for hexane extract against *P. aeruginosa.*	
				(extraction: 1 to 10 solid to solvent ratio, 35°C, 150 rpm, 10h)	*E. coli, P. aeruginosa, B. subtilis* and *S. aureus*	Negative control: DMSO	
						Positive control: Tetracycline (inhibition zone between 22-24 mm)	
		A. crassna	Leaf	Aqueous and ethanol extract	*in vitro*	Both aqueous and ethanol extract showed antimicrobial activities against gram-positive and gram-negative bacteria, i.e. *B. vulgatus* (MIC = 8 mg/mL), *B. longum* (MIC = 8 mg/mL),	Kakino et al. (2012)
					MIC		
				(extraction aqueous: 95°C for 4h; ethanol: 60% ethanol (v/v), 25.0°C, 24 h)	*E. coli, B. vulgatus, B. fragilis, S. aureus, E. faecalis, C. difficile, P. anaerobius, B. longum* and *B. adolescentis*	*S. aureus* (MIC = 4), *C. difficile* (MIC = 8 and 4 mg/mL [aqueous and ethanol extract, respectively]), and *P. anaerobius* (MIC = 4 mg/mL). Neither aqueous nor ethanol showed antimicrobial activities against *E. coli, E. faecalis,* or *Bifidobacterium* spp. (MICs > 8 mg/mL).	
		A. sinensis	Stem from chemically stimulated plants (S1), wild agarwood (S2) and six-year-old healthy trees (S3)	3.9 to 50 mg/mL oil dissolved in DMSO (extraction: hydrodistillation of stem)	*in vitro*	Lowest MIC (0.195 mg/mL) was for S2 oil against *B. subtilis* and *S. aureus*. S3 oil showed higher MIC and MBC towards all bacteria tested as compared to SI and S2.	Chen et al. (2011)
					agar well diffusion method, MIC, MBC	Negative control: DMSO and ddH2O	
					E. coli, B. subtilis, S. aureus	Positive control: Gentamycin (MIC and MBC both giving 0.487 μg/mL)	
		A. crassna	Leaf and bark	4 to 10 mg hexane, dichloromethane (DCM) and methanol extract	*in vitro*	DCM leaves extract at 10 mg/mL gave the highest inhibition zone (11.33 ± 0.61 mm) when tested against *S. aureus.*	Alimon et al. (2011)
					disc diffusion method	Methanol bark extract (4 mg/mL) gave the lowest inhibition zone (6.77 ± 0.10 mm) when tested against *P. aeruginosa.*	
					P. aeruginosa, B. spizizenii, S. aureus and *S. flexneri*		
		A. crassna	Wood	1 to 5% (w/w) ethanol, hexane, ethyl acetate and butanol extract	*in vitro*	Ethyl acetate extract (4% (w/w)), showed the highest antifungal activity (AFA) of 52.5% which is categorized as strong activity level.	Novriyanti et al. (2010)
					anti-fungal bioassay	Ethanol, hexane and butanol extracts exhibited AFA between 10-18 % which correspond to low activity level.	
					F. solani		
		A. crassna	Heartwood from stem and branch	Oil and oleoresin	*in vitro*	MICs for all extracts towards *S. aureus* and *C. albicans* were in the range of 0.5 to 2.0 mg/mL. The lowest MIC was 0.5 mg/mL for WD and SFE+co respectively. MICs for all extracts towards *E. coli* were ˃2 mg/mL.	Wetwitayaklung et al. (2009)
				(extraction: water distillation producing oil, SFE and SFE with co-solvent (SFE+co)	MIC	Positive control: Doxycycline (MIC 0.0625 μg/mL for *S. aureus* and 4 μg/mL for *E. coli*)	

				producing oleoresin)		and clotrimazole (MIC 4 0μg/mL for *C. albicans*).	
		A. sinensis	Heartwood	Oil (50 mg/mL in acetone) (extraction: hydrodistillation using Clevenger-type apparatus, 4 h)	*S. aureus, E. coli, C. albicans* *in vitro* disc diffusion method MRSA strain 9551	The inhibition zone diameters were 9 mm (at 1.5 mg oil) and 12 mm (at 2.5 mg oil). Negative control: Acetone. Positive control: 4 μg kanamycin sulfate (diameter of inhibition zone was 15 mm).	Pornpunyapat et al. (2011)
		A. agallocha	Bark and leaf	50 mg/mL methanol and water extracts (extraction: Soxhlet)	*in vitro* agar well diffusion method *S. flexneri, B. brevis, P. aeruginosa, B. subtilis*	Methanol leaf extract gave the highest zone of inhibition against *B. subtilis* (19 mm). All other extracts showed moderate zones of inhibition (14 - 18 mm) against all the bacteria tested. Negative control: DMSO Positive control: Gentamycin (10 μg/disc) showed inhibition zone between 19- 23 mm for all bacteria except *P.aeruginosa* where no inhibition zone was observed.	Dash et al. (2008)
7	Anti-oxidant	*A. crassna*	Leaf	100, 200, 400, 800 and 1600 mg/L ethanol extract (extraction: 40% (v/v) ethanol, 1:60 (w/v) for 30 min)	*in vitro* DPPH	Anti-oxidant activity (DPPH) with IC_{50} of 24.6 μg/mL Positive control: Hydroxyanisole (BHA) (IC_{50} of 13.6 μg/mL) and (+)-catechin (IC_{50} of 11.7 μg/mL)	Tay et al. (2014)
		A. malaccensis	Leaf	100, 200, 400, 600, 800 and μg/mL (i) methanol and (ii) water extract of dried and fresh leaves; respectively (extraction: (i) maceration with methanol at 1:50 solid to solvent ratio, 72 h, RT; and (ii) boiling water at 1:1 solid to solvent ratio for 30 min)	*in vitro* DPPH, TAC, CUPRAC	The highest anti-oxidant activities were shown by ethanol extracts from dried leaves with IC_{50} of 1091 μg/mL, CUPRAC value of 3.32 ± 0.01 μg/mL and TAC value of 398.74 ± 0.66 μg/mL. Positive control: Ascorbic acid (IC_{50} of 219 μg/mL; CUPRAC value of 3.51 ± 0.08).	Nik Wil et al. (2014)
		A. crassna	Stembark	Ethanol extract (extraction: 80% (v/v) ethanol; maceration)	*in vitro* DPPH, ABTS, FRAP	Anti-oxidant activity with IC_{50} of 62.8 μg/mL (DPPH), 89.4 μg/mL (ABTS) and 43.1 μg/mL (FRAP) Positive control (ascorbic acid): IC_{50} of 49. 3μg/mL (DPPH), 58.4 μg/mL (ABTS) and 39.7 μg/mL (FRAP)	Dahham et al. (2014)
		A. crassna	Leaf	0-50 μg/mL aqueous extract (extraction: boiling water)	*in vitro* DPPH, ABTS, FRAP	Anti-oxidant activity with IC_{50} of 7.25 ± 29.77 μg/mL (DPPH), 218.93 ± 29.77 μg/mL (ABTS) and 1.18 ± 0.07 μmolFe2+/mg dried extract (FRAP) Positive control: IC_{50} of 1.33 ± 0.08 μg/mL (ascorbic acid, DPPH) and 83.09 ± 0.45 μg/mL (Butylated hydroxytoluene (BHT), ABTS)	Kamonwannasit et al. (2013)
		A. crassna	Leaf	Filtrate and precipitate of dried ethanol extract reconstituted in 1 mg/mL methanol as stock (extraction: 95 % (v/v) ethanol, soxhlet)	*in vitro* DPPH	The filtrate of ethanol extract showed IC_{50} of 32.25 ± 0.48 μg/mL and the precipitate gave IC50 of 15.94 ± 0.16 μg/mL. Positive control: Trolox (EC_{50} of 16.81 ± 0.58 μg/mL)	Ray et al. (2014)
		A. sinensis	Leaf	0-140 μg/mL methanol extract (extraction: methanol, soxhlet, 12 h)	*in vitro* Several types of assays	IC_{50} for DPPH: 11.63 ± 0.16 μg/mL IC_{50} for ABTS: 2.05 ± 0.06 μg/mL IC_{50} for O2•- scavenging: 30.20 ± 0.57 μg/mL IC_{50} for OH• scavenging: 7.73 ± 0. 59 μg/mL IC_{50} for reducing power Fe2+: 18.56 ± 1.60 μg/mL IC_{50} for reducing power Cu2+: 16.25 ±	Han and Li (2012)

Table 4 (*continued*)

No	Pharmacological activities	Species	Part of plant	Formulation/dosage/extract	Model/cell line/organism/ microorganism	Result	Reference
						0.10 μg/mL IC_{50} for chelating Fe2+: 94.24 ± 3.19 μg/mL IC_{50} for chelating Cu2+: 134.01 ± 7.04 μg/mL IC_{50} for lipid peroxidation: 0.49 ± 0.05 μg/mL Positive control: Trolox IC_{50} between 0.02 ± 0.01 to 540.78 ± 175.40 μg/mL BHA IC_{50} between 0.02 ± 0.00 to 407.96 ± 77.33 μg/mL	
		A. crassna	Leaf	8, 16, 31, 63, 250 and 500 g/mL methanol extract (extraction: maceration, 24 h)	*in vitro* DPPH	Anti-oxidant activity with IC_{50} of 47.18 g/mL Positive control: Ascorbic acid (IC_{50} of 2.19 g/mL)	Sattayasai et al. (2012)
		A. malaccensis	Leaf	0 – 1000 μg/mL methanol, hexane, dichloromethane, ethyl acetate, butanol extract (extraction: maceration with methanol at solid to solvent ratio of 3:10 and successive extraction using other solvents in the order as above)	*in vitro* DPPH, Xanthine oxidase assay	Methanol extract showed the highest DPPH scavenging activity (80%) at 1000 μg/mL as compared to other extracts. Positive control: Quercetin (100 μg/mL showed 80 % DPPH scavenging activity) At 250 μg/mL, butanol fraction showed the highest DPPH scavenging activity (96.2 ± 1.55 %) and superoxide scavenging activity (89.9 ± 0.35 %). The DPPH scavenging activities for other solvents were in the order of hexane (37.9 %) > ethyl acetate (37.3 %) > dichloromethane (33.8 %). Positive control: 5 μg/mL ascorbic acid The superoxide scavenging activities for other solvents were in the order of ethyl acetate (68.2 %) > hexane (64.4 %) > dichloromethane (53.0 %) Positive control: 0.006 U/mL superoxide dismutase (SOD)	Moosa (2010)
		A. malaccensis	Leaf	0.15625 to 10 mg/mL hexane, dichloromethane (DCM), ethyl acetate and methanol extract (sequential maceration extraction)	*in vitro* DPPH	Anti-oxidant activity (DPPH) with IC_{50} of 800 μg/mL, 160 μg/mL, 140 μg/mL and 30 μg/mL for hexane, DCM, ethyl acetate and methanol , respectively. Positive control (quercetine): IC_{50} of 3.33 μg/mL	
		A. agallocha	Heartwood	500-3500 μg/mL ethyl acetate extract (extraction: Soxhlet, 60-80°C, 72 hrs)	*in vitro* human blood haemolysate	Extract inhibited nitrite-induced methaemoglobin formation when tested in the range between 500 to 3000 μg/mL but exhibited pro-oxidant activities at higher concentration. Positive control: Curcumin	
		A. agallocha	Wood	Methanol, hexane, chloroform, ethyl acetate and aqueous extract	*in vitro*	Extract showed anti-oxidant activities with IC_{50} of 60.65 ± 2.77 ppm (methanol), 79.19 ± 3.04 ppm (hexane), 49.03 ± 2.60 ppm (chloroform), 58.25 ± 1.01 ppm (ethyl	Huda et al. (2009)

					DPPH	acetate) and 51.44 ± 1.51 ppm (water). Positive control: Ascorbic acid, quercetin, catechin and epicatechin (IC_{50} of ~10 ppm for each control)	
					TBARS and conjugated dienes formation analysis in human low density lipoprotein (LDL)	Chloroform extract (2.5 ppm) showed reduced TBARS as compared to control with 28 % reduction at pre-incubation and between 73 – 85% at post-incubation. Aqueous extract (2.5 ppm) showed reduced TBARS as compared to control with 17 % reduction at pre-incubation and between 42 – 51% at post-incubation. Positive control: Trolox (8.95 μM), ascorbic acid (12.71μM) and Trolox+ascorbic acid (50/50, v/v)	Miniyar et al. (2008)
						Chloroform and aqueous (1 ppm; respectively) extract showed prolonged conjugated diene formation (between 200-250 lag time (min)). Positive control: Trolox (450 lag time (min)).	Owen and Jones (2002)
8	Effect on central nervous system (CNS)	*A. subintegra*	Leaf and stem	0.000437 to 125 μg/mL chloroform extract (extraction performed in water bath at 60°C, 2 h)	*in vitro* AChE inhibitory activity assay	0.06 μg/mL stem extract gave the highest inhibition of AChE activity (90% inhibition). For leaf extract, 0.12 μg/mL leaf extract gave the highest inhibition of AChE activity (80% inhibition) Positive control: Berberine and kaempherol	Bahrani et al. (2014)
					in vivo male and female adult ICR mice (Radial Arm Maze, RAM assessment)	Stem and leaf extracts caused reduction of repeat entries to arms of the maze that were already visited (NRE) and increased number of entries to arms of maze until the first error occurs (NEF) in mice with valium-impaired memory. This suggests the extracts were able to restore and or improve the working memory. Positive control: Berberine and kaempherol	
		Aquilaria spp.	Oil from (i) Hong Kong and (ii) Vietnam	400 μL of oil dissolved in triethylcitrate	Male ddY mice Spontaneous vapor administration (inhalation) system in open field test	Agarwood oil reduced ~50% total spontaneous motor activity in mice as compared to control, indicating the sedative effects. Positive control: Lavender oil (400μL)	Takemoto et al. (2008)
		Aquilaria spp. (Vietnam)	Wood	10 to 100 μg/mL ethanol extract (extraction: successive sonication with diethyl ether, ethanol and water)	*in vitro* Primary culture of rat cortical cells from the cerebral cortexes of 17-day-old Sprague–Dawley (SD) rats	Ethanol extract at 100 μg/mL significantly induced the brain-derived neurotrophic factor (BDNF) exon III–V mRNA expression in rat cortical cells, indicating an improved brain function. Positive control: Deltamethrin	Ueda et al. (2006)
		A. malaccensis	Heartwood	1000 mg/kg p.o	*in vivo*	Benzene extract showed reduced spontaneous motility, prolonged effect on hexobarbiturate-induced sleeping time as well as reduced rectal temperature and acetic	Okugawa et al. (1993)

Table 4 (*continued*)

No	Pharmacological activities	Species	Part of plant	Formulation/dosage/extract	Model/cell line/organism/ microorganism	Result	Reference
						acid writhing. Taken together, the effects suggest the CNS-anti-depressant effects of the extract. However, there was no anti-convulsant effects observed.	
				(extraction: successive extraction with petroleum ether, benzene, chloroform, methanol and water; at 1:5 solid to solvent ratio)	male ddY mice	Negative control: 5 % Arabic gum or 15 % Tween 80	
9	Hepatoprotective	*A. agallocha*	Leaf	200 mg/kg and 400 mg/kg body weight Ethanol	*in vivo*	Extract showed decrease in hepatic enzyme (ALT, ASTand ALP) levels in carbon tetra-chloride (CCl4)-induced hepatic damage in rats.	Vakati et al. (2013)
				(extraction: 95% (v/v) ethanol, Soxhlet, 45-55°C)	rats	Histopathological study of liver tissue showed that extract exhibited normal-ization of cells and reduced sinusoidal di-lation as compared to control. Negative control: 2% Tween80 Positive control: Silymarin (100 mg/kg)	
10	Laxative effect	*A. crassna*	Leaf	100, 300, 1000 mg/kg/day aqueous and ethanol extract	*in vivo*	Single administration and multiple admin-istrations for 7 days of water extract at 1,000 mg/kg/day decreased the contents of intestinal toxins (indoles and ammonium) in fecal beads.	Kakino et al. (2012)
				(extraction aqueous: 95°C for 4h; ethanol: 60% ethanol (v/v), 25.0°C, 24 h)	Male ddY mice (fed with high protein and high fat diet)	Multiple administrations of ethanol extract decreased contents of indoles, but have no effects on ammonium. Interruption of administration abolished the effects of both water and ethanol extracts. Both extracts accelerated the carmine egestion indicating laxative effects. Positive control: 10% gum Arabic.	
		A. sinensis and A. crassna	Leaf	300, 500 and 1000 mg/kg ethanol (*A.si-nensis* and *A.crassna*) extract	*in vivo*	1000 mg/kg extracts increased frequency and weight of stools as well as gastro-intestinal transit but did not cause diarrhea in mouse model.	Kakino et al. (2010a)
					Male and female ddY mice (lo-peramide-induced constipation model)	Negative control: Distilled water Positive control: Senna extract (500 mg/kg) (gave similar or slightly superior effects as above but caused diarrhea)	
				10, 40 and 140 μg/mL ethanol (*A.sinensis*) extract	Male Hartley guinea pigs	Ethanol (*A.sinensis*) extract (but not senna) increased intestinal tension of isolated je-junum and ileum of guinea pigs. The in-crement of intestinal tension was decreased by atropine, an acetylcholine receptor an-tagonist. This suggests that the laxative ef-fects of the extract partly act via acet-ylcholine receptors.	
				(extraction: 60% (v/v) ethanol, 1 to 20 solid to solvent ratio, RT, 24 h)		Negative control : DMSO (0.001, 0.004 and 0.014% v/v) Positive control: Senna extract (10 mg/mL)	
		A. sinensis	Leaf	150, 300 and 600 mg/kg ethanol extract	*in vivo*	A single treatment of extract (600 mg/kg) significantly increased stool frequency,	Kakino et al. (2010b)

						weight, and water content and accelerated carmine egestion.	
					male SD rats (low fibre-diet induced constipation)	Multiple administrations of extracts at 300 and 600 mg/kg significantly increased the frequency and weight of stools. Multiple administrations at150-600 mg/kg significantly	
				(extraction: 60% (v/v) ethanol, 1 to 20 solid to solvent ratio, RT, 24 h)		increased stool water content and the rate of carmine egestion.	
						Negative control: Gum Arabic (5% w/w)	
						Positive control: Senna extract (150 and 300 mg/kg)	
		A. sinensis	Leaf	100, 300 or 1000 mg/kg, p.o. acetone and methanol extracts	*in vivo*	Acetone extract at 1000 mg/kg, p.o. increased stool frequency and stool weight . However, extract at 100 or 300 mg/kg, p.o. showed no significant effects.	Hara et al. (2008)
				(successive extraction of acetone followed by methanol)	Male ddY mice	Methanol extract showed no significant effects.	
						Acetone and methanol extracts (100–1000 mg/kg, p.o.) did not induce diarrhea.	
						Negative control: Distilled water	
						Positive control: Senna extract (30 to 1000 mg/kg)	
						300 mg/kg, p.o. senna extract (but not at 30 or 100 mg/kg) induced diarrhea.	
		A. sinensis	Leaf	500 and 1000 mg/kg aqueous and ethanol extract	*in vivo*	1000 mg/kg aqueous extract (extracted at 95°C) restored stool wet weight (by 67% of control) and frequency of stools (by 50% of control).	Ito et al. (2012b)
				(extraction: (i) hot water extraction (30, 50, 70, and 95°C respectively, 24h; and (ii) 60% (v/v) ethanol, 30°C, 24h)	Male ddY mice (loperamide-induced constipation model)	1000 mg/kg ethanol extract restored stool wet weight (by 57% of control) but did not significantly affect frequency of stool.	
						Negative control: Distilled water	
11	Mosquitocidal	*A. malaccensis*	Wood oil	12.5, 25, 50, 100 and 200 mg/L oil in 95% ethanol	Mosquito larvacidal, repellent and knockdown evaluation bioassay	Extract showed larvacidal LC_{50} of 20.19 mg/L and LC_{90} of 32.93 mg/L.	Zaridah et al. (2006)
						Extract showed repellent activities with EC_{50} of 0.0016 mg/L and EC_{90} of 0.0190 mg/L.	
						Positive control (repellent): Dimethyl phthalate (EC_{50} of 0.0007 mg/L; EC_{90} of 0.0026 mg/L) and deet (EC_{50} of 0.0005 mg/L and EC_{90} of 0.0015 mg/L)	
						Extract did not show knock down effects on mosquitoes.	

Note: The parts of plant recorded are based on the terms used in the original articles reviewed. The terms bark, branch, heartwood, stem and stembark may or may not refer to the same actual part of plant, rendering the need to be cautious in interpreting and comparing results of pharmacological activities. There is a need for a uniform and standard nomenclature as discussed in the text.

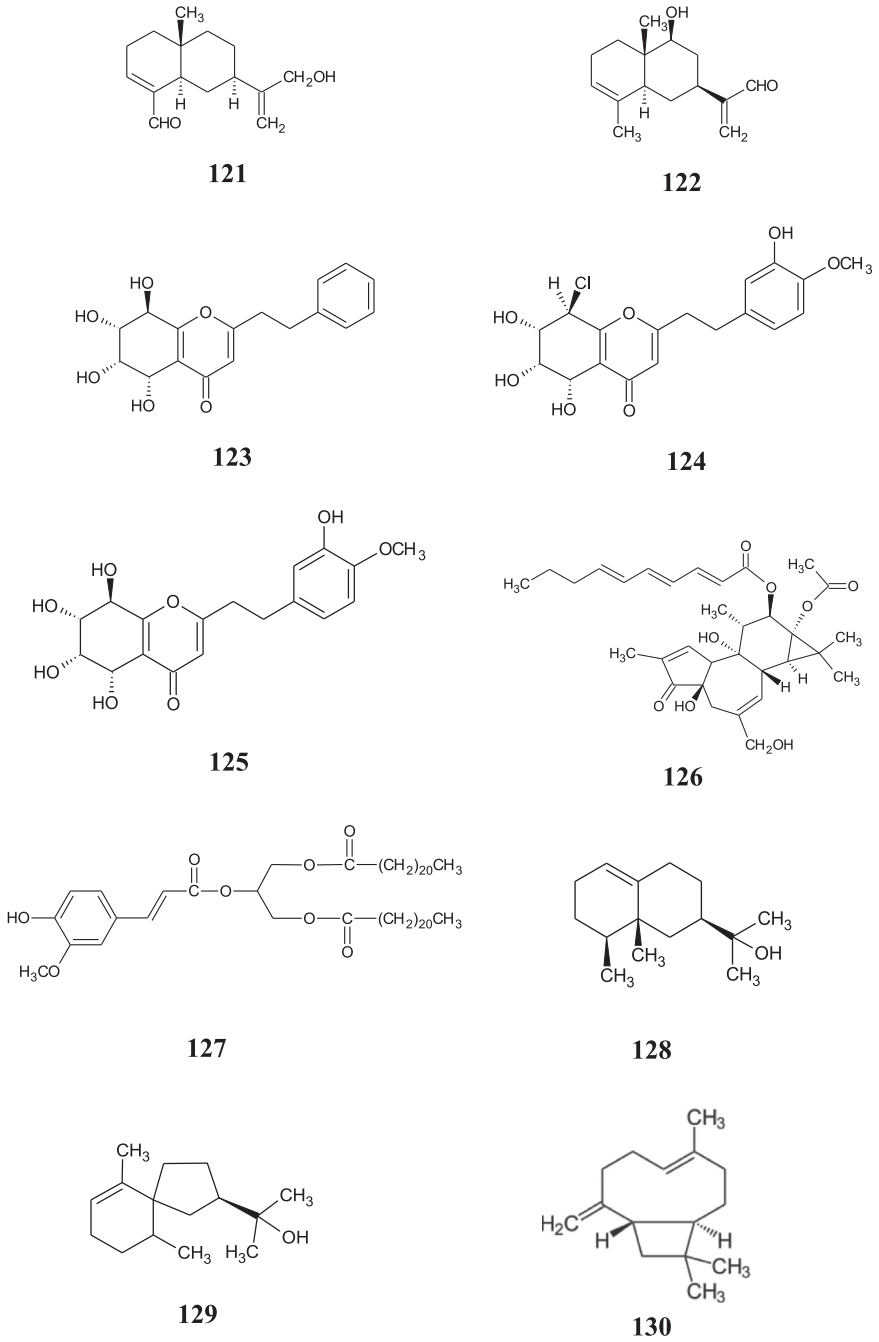

Fig. 4. Chemical structures of compounds isolated from agarwood resin with known pharmacological activities: 12,15-dioxo-α-selinene (**121**), (*5S, 7S, 9S, 10S*)-(+)-9-hydroxy-selina-3,11-dien-12-al (**122**), aquilarone B [(*5S,6S,7S,8R*)-2-(2-phenylethyl)-5,6,7,8-tetrahydroxy-5,6,7,8-tetrahydrochromone] (**123**), 8-chloro-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one (**124**), 5,6,7,8-tetra-hydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one (**125**), 12-*O*-*n*-deca-2,4,6-trienoylphorbol-13-acetate (**126**), 1,3-dibehenyl-2-ferulyl glyceride (**127**), jinkoh-eremol (**128**), agarospirol (**129**), and β-caryophyllene (**130**). Compounds (**121–125**) were isolated from *A. sinensis* (Chen et al., 2012b; Dai et al., 2009; Li et al., 2015b; Liu et al., 2008). Compounds (**126–129**) were isolated from *A. malaccensis* (Gunasekera et al., 1981; Okugawa et al., 1996a, 2000), and compound (**130**) was isolated from *A. crassna* (Dahham et al., 2015b, 2015b).

hexanorcucurbitacin I (**131**), cucurbitacin I (**132**), isocucurbitacin D (**133**), and neocucurbitacin (triterpenoid/nor-triterpenoid) B (**134**), showed cytotoxic activities against K562, SGC-7901 and SMMC-7721 cells (Mei et al., 2012). Several compounds from *A. agallocha* hulls also showed anti-cancer/cytotoxic activities. Cucurbitacin I (**131**) showed IC_{50} values of 15.8 μg/mL and 7.4 μg/mL against HT29 and P388 cells, respectively, whereas cucurbitacin E (**135**) showed IC_{50} values of 14.1 μg/mL and 6.5 μg/mL against HT29 and P388 cells, respectively (Wang et al., 2012). Fig. 5 shows the structures of compounds found in agarwood fruit and hull.

The biological activities of the compounds isolated from agarwood leaf are summarised in Table 5 below. Similar to resin and healthy wood, the majority of the studies on agarwood leaf were performed on *A. sinensis*, which may be due to the established use of agarwood in traditional Chinese medicine. The studied compounds were mangiferin, iriflophenone, genkwanin and aqualirisin, which were obtained from methanol, ethanol or water extracts. These compounds showed anti-diabetic, anti-inflammatory, anti-oxidant and laxative activities.

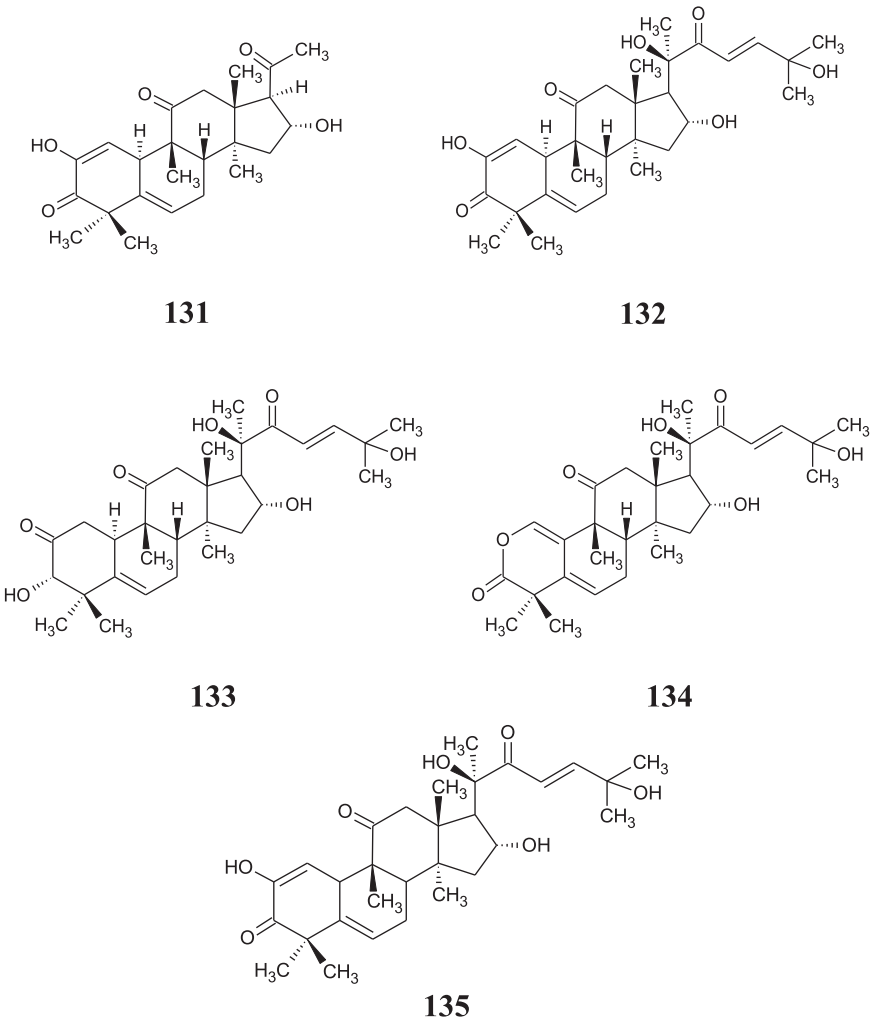

Fig. 5. Chemical structures of compounds found in agarwood fruit and hull: hexanorcucurbitacin I (**131**), cucurbitacin I (**132**), isocucurbitacin D (**133**), neocucurbitacin (triterpenoid/nor-triterpenoid) B (**134**) and cucurbitacin E (**135**). Compounds (**131–134**) were isolated from *A. sinensis* (Mei et al., 2012); compounds (**132**) and (**135**) were isolated from *A. agallocha* (Wang et al., 2012).

7. Toxicity and safety

Toxicity studies of *Aquilaria* spp. have only recently been performed, despite the known toxic effects of plants in the family Thymelaeaceae (Borris et al., 1988). Table 6 summarises the *in vitro* and *in vivo* toxicity studies of different plant parts of several *Aquilaria* species from 2011 to the present. However, no report on *A. malaccensis* was available. The cell culture work presented here is based on studies of various normal cells. Based on these findings, *Aquilaria* plant materials are found to be safe, at least at the doses tested.

In addition to the raw plant materials, agarwood smoke is also becoming a safety concern, particularly in the Arabian tradition, where agarwood incense is burned on charcoal briquettes. This creates a slow and continuous burn with incomplete combustion that emits smoke with characteristic indoor air pollution (Cohen et al., 2013). The same author reported that emissions from agarwood increased the levels of the IL-8 cytokine in A549 human lung epithelial cells, indicating that an inflammatory response was induced that is often associated with asthmatic conditions.

Studies in rats showed different results in short- (28 days) and long-term (maximum 16 weeks) exposure. According to Karimi et al. (2011) and Miraghaee et al. (2011), the serum levels of hepatic enzyme markers and lipid/lipoprotein profiles were not significantly affected by short-term exposure to agarwood smoke. However, both studies showed decreased plasma testosterone levels. In contrast, chronic exposure resulted in increased levels of oxidative stress and inflammation markers, as well as marked ultrastructural changes in the heart muscle (Al-Attas et al., 2015; Alokail et al., 2011; Hussain et al., 2014). Considering the potential health risks of the emission from agarwood smoke, more refined studies are warranted to ensure the safety of indoor agarwood burning for human health.

8. Conclusions

Agarwood plant materials have been widely used as traditional medicines in Southeast Asian communities, as well as Chinese, Tibetan, Unani and Ayurvedic medicine. They are used for the treatment of arthritis, asthma, and diarrhoea and have sedative effects. Phytochemical studies show that they contain sesquiterpenoids, 2(-2-phenylethyl)-4H-chromen-4-one derivatives, genkwanins, mangiferins, iriflophenones, cucurbitacins, other terpenoids and phenolic acids. Many pharmacological studies have been performed on crude extracts, and these extracts exhibit anti-allergic, anti-inflammatory, anti-diabetic, anti-cancer, anti-oxidant, anti-ischemic, anti-microbial, hepatoprotective, laxative, and mosquitocidal properties, as well as effects on the central nervous system. Agarwood plant materials are considered safe, based on the doses tested.

Table 5
Pharmacological activities of the compounds from agarwood leaf.

Compound	No	Species	Pharmacological activities	Details/IC_{50}	References
Aglycone of aquilarisinin	**35**	*A. sinensis*	[a]α-glucosidase inhibition	IC_{50} 131.8 ± 7.3 μg/mL	Feng et al. (2011)
Aquilarinoside A	**36**	*A. sinensis*	Anti-inflammatory	Compounds inhibit neutrophils respiratory burst stimulated by PMA (phorbol 12-myristate 13-acetate) using chemiluminescence assay with IC_{50} of 89.92 ± 1.07 μmol/L	Qi et al. (2009)
Aquilarisinin [iriflophenone 2-O-β-D-glucopyranosyl-(1→4)-O-α-L-rhamnopyranoside]	**47**	*A. sinensis*	[a]α-glucosidase inhibition	IC_{50} 151.6 ± 22.1 μg/mL	Feng et al. (2011)
Aquilarixanthone [2-C-β-D-xylopyranosyl-1,3,4,6,7-pentahydroxyxanthone]	**51**	*A. sinensis*	[a]α-glucosidase inhibition	IC_{50} 142.9 ± 13.3 μg/mL	Feng et al. (2011)
Aquisiflavoside	**75**	*A. sinensis*	Anti-inflammatory	Compound showed IC_{50} of 34.95 μM in inhibiting nitric oxide (NO) production induced by LPS macrophage RAW247 cells. L-N 6-(1-iminoethyl)lysine was used as positive control with IC_{50} of approximately 30 μM	Yang et al. (2012)
Genkwanin	**60**	*A. crassna*	Anti-oxidant	IC_{50} 70.05 ± 1.04 μg/mL IC_{50} Trolox (positive control) 16.81 ± 0.58 μg/mL. Anti-oxidant activities were determined using DPPH assay.	Ray et al. (2014)
Genkwanin 5-O-β-primeveroside	**77**	*A. crassna*	Laxative	10 mg/kg restored stool frequency and weight to 67.2 ± 9.4% and 68.1 ± 5.7% of control respectively	Kakino et al., (2010a)
		A. sinensis	Laxative	At 100–1000 mg/kg, compound increased stool frequency and weight but did not induce diarrhoea. 1 μg/mL of compound increased spontaneous motility in isolated rabbit and guinea pig ileum.	
Hypolaetin 5-O-β-D glucorunopyranoside	**69**	*A. sinensis*	[a]α-glucosidase inhibition	IC_{50} 276.7 ± 56.1 μg/mL	Feng et al. (2011)
Iriflophenone 2-O-α-L-rhamnopyranoside	**42**	*A. sinensis*	[a]α-glucosidase inhibition	IC_{50} 165.1 ± 11.3 μg/mL	Feng et al. (2011)
Iriflophenone 3-5-C-β-D- diglucopyranoside	**48**	*A. sinensis*	[a]α-glucosidase inhibition	IC_{50} 143.7 ± 10.6 μg/mL	Feng et al. (2011)
Iriflophenone 3-c-β-D-glucoside	**38**	*A. sinensis*	[a]α-glucosidase inhibition	IC_{50} 126.5 ± 17.8 μg/mL	Feng et al. (2011)
		A. sinensis	Anti-diabetic	Compound lowered blood glucose by 46.4%, and enhanced glucose uptake by 153% as compared to control.	Pranakhon et al. (2015)
Mangiferin	**54**	*A. crassna*	Anti-oxidant	IC_{50} 15.21 ± 12.0 μg/mL IC_{50} Trolox (positive control) 16.81 ± 0.58 μg/mL. Anti-oxidant activities were determined using DPPH assay.	Ray et al. (2014)
		A. sinensis	[a]α-glucosidase inhibition	IC_{50} 273.6 ± 14.5 μg/mL	Feng et al. (2011)
		A. crassna *A. sinensis*	Laxative	10 mg/kg compound restored stool frequency and weight to 95.8 ± 14.5% and 100 ± 7.6% of control respectively	Kakino et al., (2010a)

[a] Inhibitory α-glucosidase activities were determined spectrophotometrically in a 96-well microtiter plates based on *p*-nitrophenyl-α-D-glucopyranoside (PNPG) as substrate. Positive control (acarbose) showed IC_{50} of 372.0 ± 37.8 μg/mL.

Table 6
Toxicity studies on *Aquilaria* spp.

No	Assay	Species	Extract/compound	Part of plant	Result	Reference
1	Brine shrimp lethality assay	*A. subintegra*	10, 100 and 1000 μg/mL chloroform extract	Leaf Stem	LC_{50} of 531.18 ± 49.53 μg/mL LC_{50} of 407.34 ± 68.05 μg/mL	Bahrani et al. (2014)
				Fruit	LC_{50} of 683.81 ± 76.18 μg/mL Positive control: Berberine (LC_{50} of 502.82 ± 39.81 μg/mL	
2	Cell culture study	*A. sinensis*	0.1–10 mg/mL iriflophenone 3–*C*-β-glucoside (IPG)	Leaf	Based on trypan blue dye exclusion assay, compound at all concentration tested showed cell viability of > 90% on rat adipocytes.	Pranakhon et al. (2015)
		A. subintegra	0.1–1000 μg/mL chloroform extract	Leaf and stem	Based on MTT assay, IC_{50} for three cell lines tested (HUVEC, GES-1 and WRL-68) was in the range of 261.17 ± 12.41 to 346.38 ± 18.47 μg/mL with the lowest IC_{50} shown by stem extract towards HUVEC. Negative control: DMSO. Positive control: Doxorubicin (IC_{50} between 7.42 ± 0.15 to 15.73 ± 0.21 μg/mL for the three cell lines).	Bahrani et al. (2014)
		A. crassna	1–8 mg/mL ethyl acetate extract	Heartwood	Based on MTT assay, extract showed between 96.58 ± 3.129 to 100.4 ± 2.972% cell viability when tested on H9c2 cells. Negative control: 0.001% DMSO (giving cell viability of 98.28 ± 5.178%).	Jermsri and Kumphune (2012)
		A. crassna	1–10 mg/mL ethyl acetate extract	Heartwood	Based on MTT assay, all extracts showed no significant difference in cell viability when tested on AVRM. Negative control: 0.01% DMSO.	Kumphune et al. (2012)
3	Toxicity in mice (route of administration: oral gavage)	*A. subintegra*	0.1, 0.5 and 1.0 mL/g body weight chloroform extract	Leaf and stem	Extract showed no mortality or change in normal increase of body weight in mice.	Bahrani et al. (2014)
		A. crassna	2000 and 15,000 mg/kg body weight aqueous extract	Leaf	Extract showed no gross pathological lesions, deaths or change in normal increase of body weight in mice.	Kamonwannasit et al. (2013)
		A. agallocha	2000 mg/kg ethanol extract	Leaf	Based on to OECD guidelines 423, the extract found to be non-toxic *i.e.* Category 5 or Unclassified.	Vakati et al. (2013)
		A. agallocha	2000 mg/kg oil	Wood (producing oil)	The oil was safe up to a dose of 2000 mg/kg body weight.	Rahman et al. (2012)
		A. crassna	800 and 8000 mg/kg body weight methanol extract	Leaf	Extract showed no abnormal behaviour and no effect on weight or gross appearances of the heart, liver, kidney and stomach in animals treated as compared to control. However, reduction of body weight was observed.	Sattayasai et al. (2012)

However, the toxicity and safety of the materials, including the smoke from agarwood incense burning, should be investigated further. Future research should also be directed towards the bioassay-guided isolation of bioactive compounds with proper chemical characterisation and investigations of the underlying mechanisms towards drug discovery. By linking the ethnopharmacology of agarwood with the observed pharmacological properties, it appears that the anti-inflammatory properties might be the future direction of research, as inflammation underlies many disease states. It is also important that the research community reports the studies with a detailed portfolio of plant materials, as this would assist in accurate interpretations. As wild agarwood trees are critically endangered and vulnerable, sustainable agricultural and forestry practices are necessary for the further development and utilization of agarwood as a source of health beneficial compounds.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jep.2016.06.055.

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