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ORIGINAL ARTICLE

Gas chromatography mass spectrometry couple with quadrupole time-of-flight (GC-QTOF MS) as a powerful tool for profiling of oxygenated sesquiterpenes in agarwood oil

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Abstract Agarwood (*Aquilaria malaccensis*) is very well known as the most expensive wood in the world due to its wide applications in perfumery, cosmetic traditional medicine, and religious ceremonies. The study aimed to give an in-depth characterisation focusing on marker compounds in *A. malaccensis* from different places in Malaysia. The establishment of an oxygenated sesquiterpenes chemical profile of the fungus-infected agarwood oil was achieved by gas chromatography mass spectrometry (GC–MS) coupled with quadrupole time (QTOF) technique. Aroma compounds were identified as sesquiterpenes and oxygenated sesquiterpenes where agarospirol was found in samples of all locations (3.12%, 3.54%, 3.36% and 2.26% from Melaka, Pahang, Kelantan A and Kelantan B respectively) and also N-hexadecanoic acid as one of the major compounds. Both compounds were further isolated by Prep-GC and confirmed by NMR. This study provides a reference for agarwood oil analysis from different origins in Malaysia.

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1. Introduction

Aquilaria malaccensis is one of 15 tree species in the genus Aquilaria (family Thymelaeceae). Fungus-infected *A. Malaccensis* agarwood oil is highly sought after by the perfumery industry for its "warm, unique, balmasic notes with sandalwood-ambergris tonalities" (Naef, 2011). There is no common grading standard or method for agarwood oil at present. Several studies carried out on oil characterization and recognized a relationship between the agarwood oil of different origins

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and volatile and semi-volatile compounds namely, oxygenated sesquiterpenes (Ahmaed, 2017; Ahmaed and Kulkarni, 2017; Tajuddin et al., 2013).

The major chemical constituents of Malaysian agarwood oils were previously reported to be 4-phenyl-2butanone (**1**), α-bulnesene (**2**), α-guaiene (**3**), agarospirol (**15**), and γ-eudesmol (**18**) (Haslina et al., 2018; Ismail et al., 2016; Tajuddin et al., 2013) as shown in Fig. 1. Generally, the major components of the oils are sesquiterpenes and chromone derivatives (Yoneda et al., 1984). Other workers have reported sesquiterpenes, sesquiterpenes furanoids, tetradecanoic acid and pentadecanoic acid to be present in all species (Ishihara et al., 1991, 1993b; Ngan et al., 2020; Ueda et al., 2006; Yoneda et al., 1984). Agarospirol (**15**), jinkohol-eremol, jinkohol and kusunol are compounds contributing to its characteristic aroma (Ishihara et al., 1993b). Such compounds have specific aroma descriptors, e.g. agarospirol (**15**), which exhibit a spicy, peppery and woody aroma. While some compounds do not contribute directly to the aroma, they are reactive and can break down to give pleasant-smelling volatiles. Agarwood oil is generally obtained in 0.2–0.3% yield (dry weight basis) by steam or hydrodistillation (Tajuddin et al., 2013). Eleven compounds had been reported present in agarwood oils from peninsular Malaysia via GC-FID analysis previously (Nor Azah et al., 2008) and seventeen major compounds were identified in different agarwood oil via two-dimensional gas chromatography (Wong et al., 2015).

Despite of the great separation power of the conventional one-dimensional modern chromatographic technique, the complex nature of the sample arising from the compact oxygenated sesquiterpenes fraction requires extended GC runs. Furthermore, deep analyses of the chromatograms frequently indicate that some peaks are the result of two or more co-eluting compounds. As a consequence of co-elution, reliable MS identification is not possible. Although one-dimensional chromatographic processes often provide rewarding analytical results, the complexity of many naturally occurring matrices exceeds the capacity of any single separation system. As a result, much research has been dedicated to hyphenated techniques to strengthen resolving power (Eyres et al., 2008; Ong and Marriott, 2002; Park et al., 2012; Ryan and Marriott, 2003; Tajuddin et al., 2013).

Comprehensive two-dimensional gas chromatography (GC × GC) employing two orthogonal mechanisms to separate the constituents of the sample within a single analysis has also been used to analyse agarwood oil. The TOF-MS brings other advantages such as full mass spectra acquisition at trace level sensitivity and mass spectral continuity, which allows for deconvolution of spectra of co-eluting peaks (López-Cobo et al., 2017; Wang et al., 2014). This study aims to develop a methodology based on a novel GC-QTOF MS technique to obtain a deep qualitative and quantitative characterization of the oxygenated sesquiterpenes in the agarwood oil obtained from difference sources of origin. Considering the complexity of the data obtained, this manuscript is focused only on the oxygenated sesquiter-

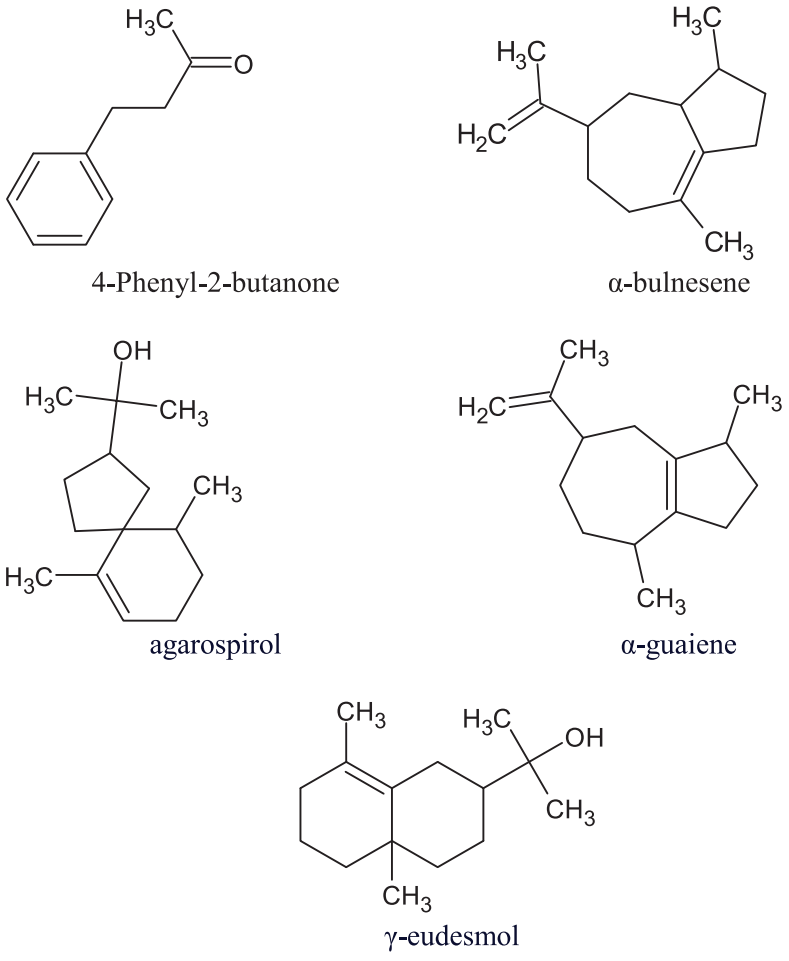

Fig. 1 Some chemical constituents of Malaysian agarwood oil.

penes as marker compound present in the samples for grading purpose by proper identification and quality analysis of commercial agarwood oil.

2. Material and method

2.1. Samples preparation

In this study, *A. malaccensis* (agarwood) oil from various places in Malaysia was analysed. The climate for Malaysia was categorised as equatorial with an average rainfall of 250 cm (98 in) a year, and an average temperature of 27 °C. The samples were collected from different origins in peninsular Malaysia; Melaka city (2.1896° N, 102.2501° E)., Rompin district, Pahang (2.7945° N, 103.4862° E) and two samples were of Kelantan, Gua Musang district and Kota Bharu (4.8843° N, 101.9682° E and 6.1248° N, 102.2544° E respectively) origin. Agarwood was subjected to hydrodistillation with 5L distilled water for 24 h, using Clavenger-type apparatus. The essential oils were isolated by extraction with hexane, distillate collected and dried over anhydrous sodium sulphate. The oils collected were stored in amber vials at 4 °C until analysis.

2.2. GC-Mass spectrometry (GC–MS)

Analysis was performed using Agilent 7890A Network System gas chromatography coupled to a mass spectrometer (Agilent 5975C) with a detector in full scan mode under electron impact ionization (EI, 70 eV) and fitted with a capillary column (DB-1 30 m × 0.25 mm, i.d.; 0.25 μm film thickness). The oven temperature was programmed at 50 °C for 0 min, then ramped at 10 °C/min to 160 °C and lastly, at 3 °C/min to 220 °C. Injector inlet and detector temperatures were set at 320 °C. Each sample was diluted in dichloromethane and then injected in 1 μL volume in the split mode (ratio 50:1) using helium as carrier gas (1 mL/min).

2.3. Comprehensive GC-QTOF

An Agilent's 7200, the world's first Q-TOF designed specifically for GC–MS were used. The non-polar column, DB-1 (30 m × 0.25 mm, i.d 0.25 μm film thickness) was purchased from J&W Scientific (Folsom, California). While handling the Q-TOF, software from Mass Hunter acquisition B.06, Mass Hunter Qualitative B.06 and NIST Mass Spectra Library 2011 were used. Helium was used as carrier gas with electronic impact (EI) ionization sources. The transfer line of the TOF was kept at 280 °C, ion source temperature at 230 °C and the mass range was around 45–500 amu. The resolution used was ~ 12,000 (FWHM), while the acquisition rate was 5 spectra per second and the acquisition time was 200 ms per spectrum. For the injection, the inlet temperature was 250 °C, using split mode with a split ratio of 150:1. The GC oven temperature was programmed with the initial temperature at 50 °C (0 min), then ramp to 160 °C (0 min) at 10 °C/min, and the final temperature was 220 °C (0 min) at 3 °C/min.

Table 1 Relative percentage area of agarwood oil (Aquilaria malaccensis) from Malaysia.

No.	Compound	Chemical Formula	Area (%)				Odor Description	Ref.
			Melaka	Pahang	Kelantan A	Kelantan B		
1	4-phenyl-2-butanone	$C_{10}H_{12}O$	1.62	2.84	1.65	–	floral, jasmine, herbal, fruity, balsam	(Buttery and Ling, 1994; Kessler and Baldwin, 2007)
2	α-bulnesene	$C_{15}H_{24}$	4.79	2.42	1.61	–	woody, warm,	(Ishihara et al., 1993a, 1993b), (Salum et al., 2009)
3	α-Guaiene	$C_{15}H_{24}$	4.33	–	0.70	–	sweet, woody, balsam, peppery	(Jirovetz et al., 2002; McGrath and Karahadian, 1994)
4	α-humulene	$C_{15}H_{24}$	0.51	–	–	–	woody	(Jirovetz et al., 2002)
5	β-humulene	$C_{15}H_{24}$	–	–	–	0.28	woody	(Jirovetz et al., 2002)
6	α-gurjunene	$C_{15}H_{24}$	0.62	2.16	1.53	–	wood, balsamic	(Jirovetz et al., 2002)
7	β-maaliene	$C_{15}H_{24}$	4.45	8.31	–	–	–	–
8	Longiflene	$C_{15}H_{24}$	9.74	–	–	–	–	–
9	Alloaromadendrene	$C_{15}H_{24}$	–	–	–	1.17	woody	(Chung et al., 1993)
10	Aromandendrene	$C_{15}H_{24}$	–	–	–	0.20	woody	(Chung et al., 1993)
11	γ-cadinene	$C_{15}H_{24}$	–	–	–	9.45	dry-woody, weak medicinal	(Jirovetz et al., 2002)
12	Eremophilene	$C_{15}H_{24}$	–	–	–	2.07	–	–
13	Farnesene	$C_{15}H_{24}$	–	2.61	–	–	citrus, green	(Choi et al., 2001)
14	Selinene	$C_{15}H_{24}$	1.27	1.46	1.08	7.59	herb	(Adedeji et al., 1991)
15	Agarospirol	$C_{15}H_{26}O$	3.12	3.54	3.36	2.30	spicy, peppery, woody	(Ishihara et al., 1993a, 1993b)
16	γ-gurjunene	$C_{15}H_{24}$	2.51	9.26	2.26	–	–	–
17	Bulnesol	$C_{15}H_{26}O$	3.23	–	–	–	weak woody, weak spicy	(Jirovetz et al., 2002)
18	γ-eudesmol	$C_{15}H_{26}O$	1.15	13.39	17.23	–	waxy, sweet	(Jirovetz et al., 2002)
19	α-elemol	$C_{15}H_{26}O$	–	10.03	–	–	green, wood	(Choi et al., 2001)
20	Myristic acid	$C_{14}H_{28}O_2$	3.11	–	–	–	–	–
21	n-Hexadecanoic acid	$C_{16}H_{32}O_2$	10.87	8.59	7.05	18.42	–	–

2.4. Preparative gas chromatography (Prep-GC)

Isolation of the compound was carried out on preparative gas chromatography Agilent 7890B model. The following conditions were applied: non– polar DB-5 ms column (30 m × 0.2 5 mm, i.d 0.53 μm film thickness), oven programmed from 80 °C to 280 °C, ramping at 5 °C/min; temperatures of injector, switching device and transfer line were set at 250 °C. High purity nitrogen (N_2) was used as carrier gas at a constant flow rate. The inlet and FID temperatures were 250 °C, respectively.

3. Results and discussion

3.1. Analysis of the chemical composition

Two methods were adopted in this study to detect and confirm the marker compounds in *A. Malaccensis* oil using GC–MS and GC-QTOF-MS. Table 1 shows the peak identification for the components. About 21 compounds have been identified whereas most of the compounds detected were either sesquiterpenes or oxygenated sesquiterpenes. This finding is also in good agreement with a previous report which found oxy-

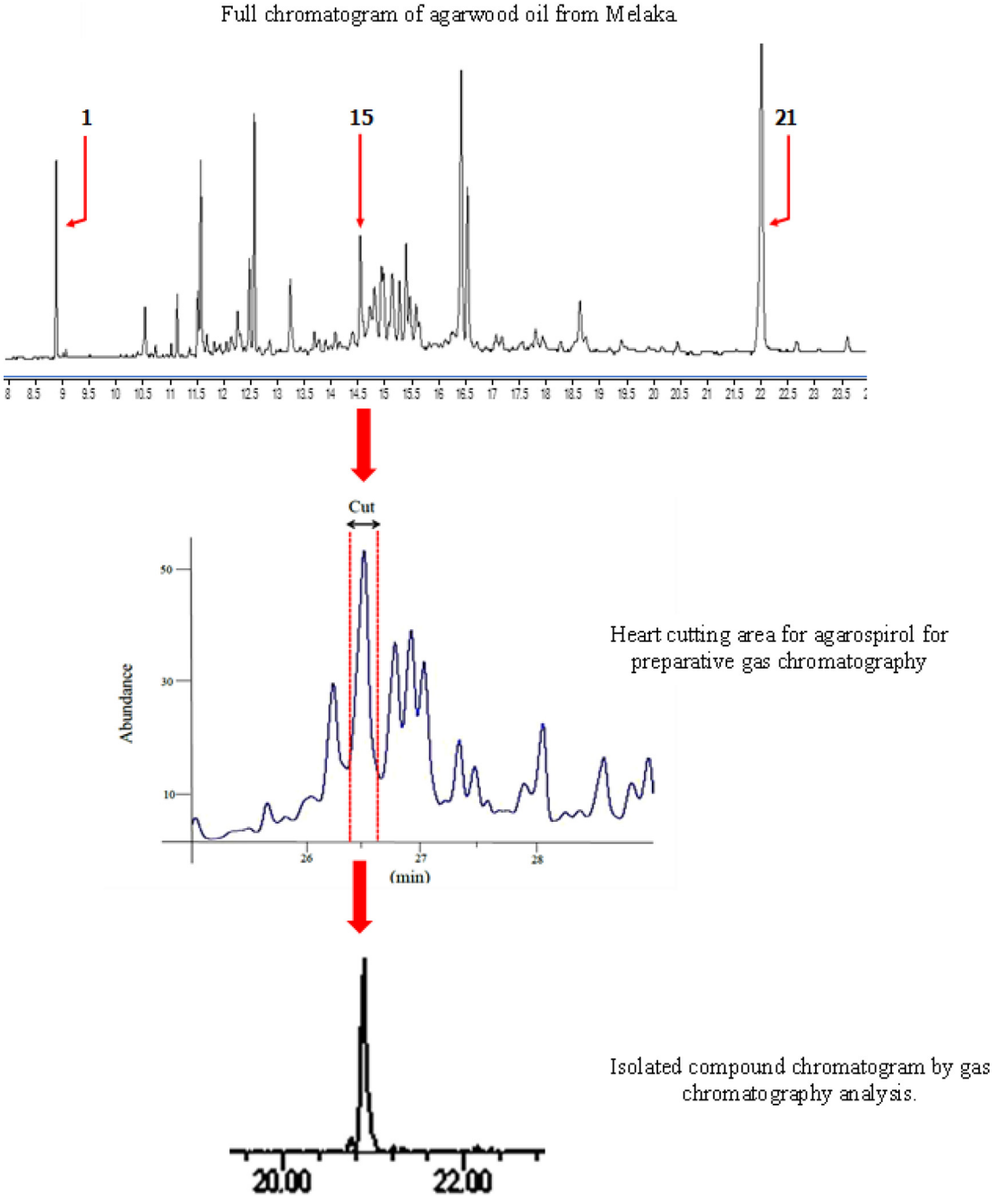

Fig. 2 Chromatogram flow of agarospirol isolation.

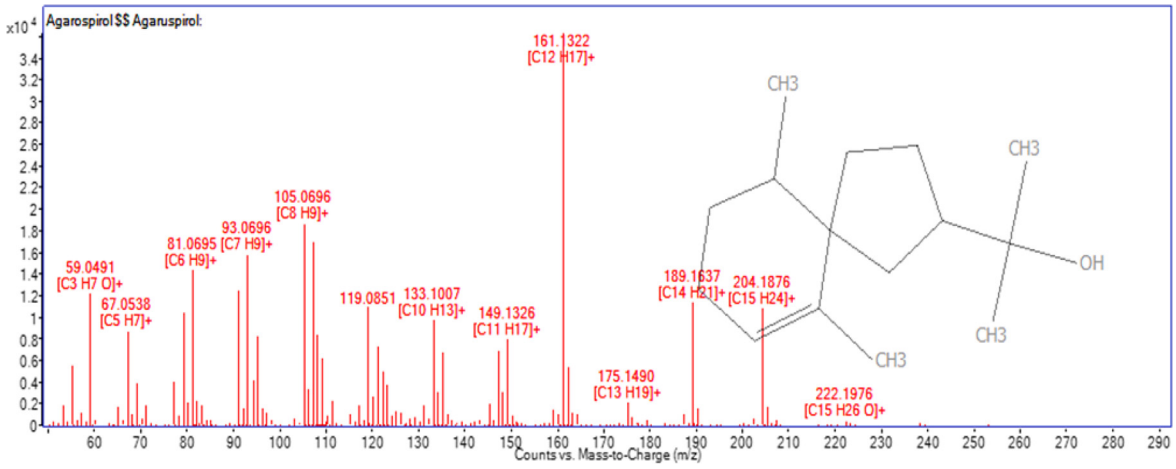

Fig. 3 EI-MS spectrum for agarospirol.

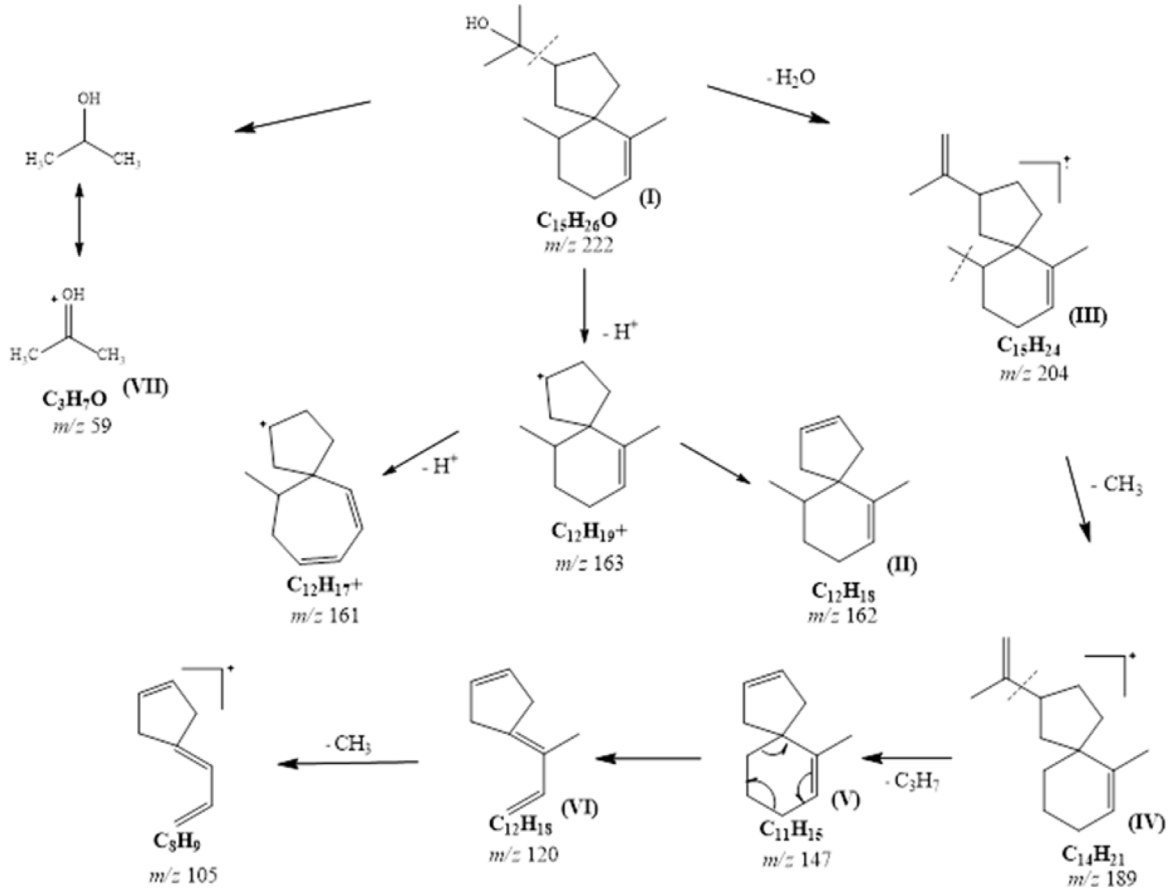

Fig. 4 Full mass fragmentation of agarospirol.

genated sesquiterpenes as the major component in agarwood oil (Atikah et al., 2015; Haslina et al., 2018). Agarwood oil from Melaka contained a greater number of compounds as compared to that of Pahang and Kelantan. The sample from Melaka appeared darker with higher viscosity compared to others. Based on the present study, selinene **(14)**, agarospirol **(15)**, and n-hexadecanoic acid **(21)** were observed to be the main components present in all agarwood oil samples as matched with the NIST library. Selinene **(14)** contributes to the herbal smell, while agarospirol **(15)** gives out the smell of spicy, peppery and woody according to literature. Thus, agarospirol can be considered to be chosen as one of the marker compounds of agarwood oil. Therefore, agarospirol in *A. malaccensis* oil was targeted for isolation in this study due to

Table 2 Accurate mass of agarospirol by GC-QTOF.

Experiment mass (Da)	Calculated mass (Da)	Mass error (ppm)	Formula
59.0594	59.0491	−4.38	C_3H_7O
105.0700	105.0699	−1.17	C_8H_9
107.0856	107.0855	−0.68	C_8H_{11}
119.0857	119.0855	−1.45	C_9H_{11}
147.1173	147.1168	−3.22	$C_{11}H_{15}$
161.1324	161.1325	0.48	$C_{12}H_{17}$
189.1648	189.1638	−5.41	$C_{14}H_{21}$
204.1882	204.1873	−4.64	$C_{15}H_{24}$
222.1989	222.1978	−4.87	$C_{15}H_{26}O$

its characteristic woody odor that may contribute to the strong smell of agarwood oil (Naef, 2011). This result also aligned with another study that identified the presence of agarospirol in agarwood oil (Nät et al., 1993; Okugawa et al., 1996; Pripdeevech et al., 2011). This compound was reported to give positive effects on the central nervous system and may decrease methamphetamine and apomorphine-induced spontaneous motility (Okugawa et al., 1996). A decade ago, previous studies have reported the isolation of this compound using column chromatography but none of these used preparative gas chromatography for isolation of agarospirol from *A. malaccensis* (agarwood) oil. The presence of agarospirol compound was proven based on further experimental analysis using GC-QTOF-MS and also spectroscopy analysis. The QTOF collects data using accurate mass in EI spectra and provides fragmentation data to identify the compound while GC–MS identified the compounds by unit mass allowing library search by NIST database. QTOF helps to confirm the compounds with mass accuracy below 5 ppm. Mass fragmentation of the main compounds was deduced based on the mass spectrum obtained.

3.2. Agarospirol

Sample with high percentage of agarospirol was selected for isolation purpose. This is important to maintain the concentration and target for high volume collection. The retention time of agarospirol was established on prep-GC for heart cutting selection and multiple injections. In this study, agarospirol was successfully isolated as colorless oil using Prep-GC, whereas the cooling trap condition was set at −20 °C. Preparative gas chromatography is a green, simple, convenient, and highly efficient method for sample collection trap (Nojima et al., 2008; Ochiai & Sasamoto, 2011; Sciarrone et al., 2015). Many researchers have proven the capability of the preparative method in isolation, including essential oil (Ball et al., 2012; Rühle et al., 2009; Sutton et al., 2005). Carotol was successively isolated from carrot seed oil using one-dimensional Prep-GC and prep-MDGC (multi-dimensional) (Sciarrone et al., 2015). In this study, the heart cutting method with multiple times injections was applied. The most crucial consideration for this isolation method is selecting the cutting time, sample concentration, and times of injection (Kim et al., 2013; Kim & Marriott, 2012). The flow of chromatogram from starting until the end product was shown in Fig. 2. Shown in Fig. 3 is the EI-MS spectrum for agarospirol. The EI-MS spectrum exhibited an [M] + m/z 222 and fragments ions appeared at m/z 204, 189, 162, 147, 120 and 105 as shown. Losing of isopropanol radical $[CH_3CH_2CH_2OH]^+$ and hydride transfer H^+ from parent ion **(I)** resulted in the formation of the base peak of ion $[C_{12}H_{18}]^+$ **(II)**, represented as m/z peak 162, with the maximum intensity (100%). Next, m/z 204 $[C_{15}H_{24}]^+$ was formed from the loss of water molecule and fragment ion of m/z 189 **(IV)** $[C_{14}H_{21}]^+$ was derived from the loss of methyl group. After the loss of propene radical **(IV)**, the ion with m/z 147, $[C_{11}H_{15}]^+$ was formed **(V)**, which underwent the Retro-Diels Alder reaction, resulting in the peak of m/z 120 **(VI)**. The ion at m/z 59 **(VII)** was produced from the loss of radical group ($\bullet C_{12}H_{19}$) to form $[C_3H_7O]^+$. Full mass frag-

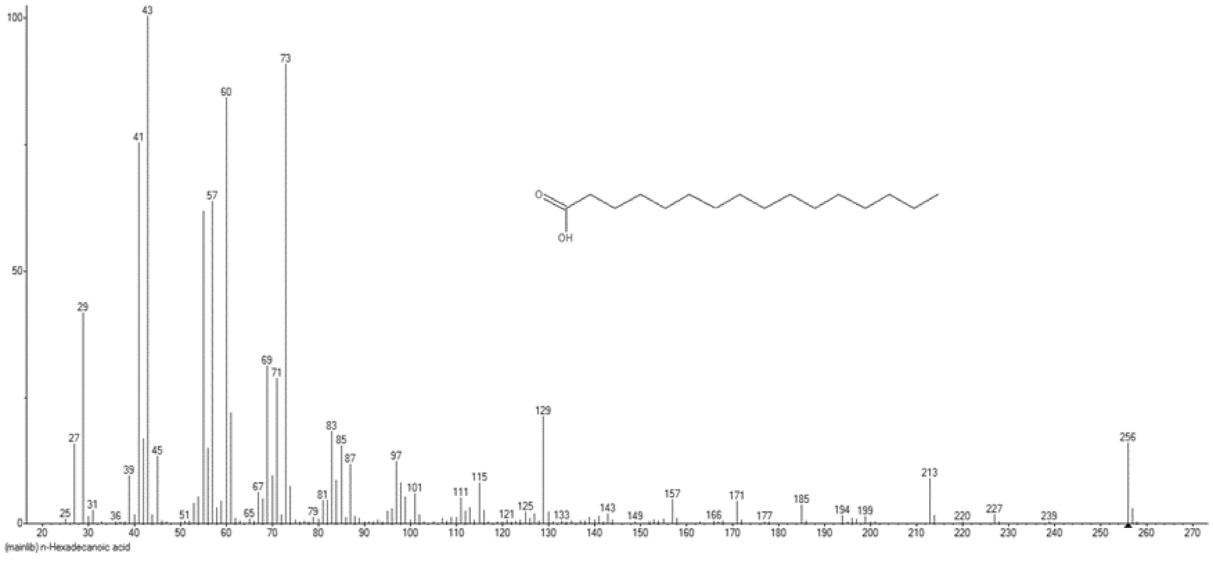

Fig. 5 Mass Spectrum of n-Hexadecanoic acid from GCQTOF-MS.

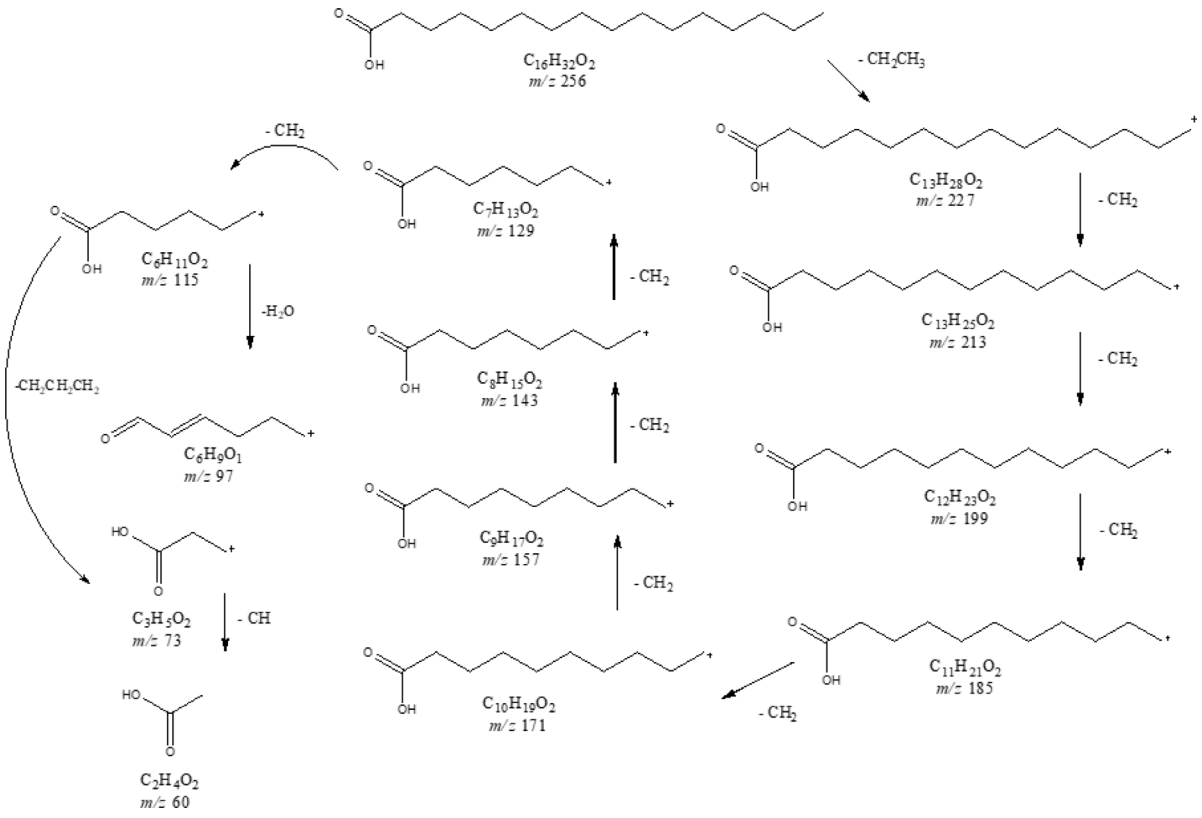

Fig. 6 Mass fragmentation of n-Hexadecanoic acid.

mentation of agarospirol is shown in Fig. 4 (Bercht et al., 1976; Rabe & Dickschat, 2016). Based on the mass fragmentation pattern, the compound can be assigned as agarospirol. The accurate mass of the agarospirol was measured using GC-QTOF MS with the mass deviation in the range −4.87 to 0.48 as shown in Table 2.

3.3. n-Hexadecanoic acid

Under the cooling trap condition setup at −20 °C by Prep-GC, this compound was obtained as a colorless oil. Further isolation method of this compound refers to the agarospirol method, except that the heart cutting method was applied at different times. Fig. 5 show the mass spectrum of n-Hexadecanoic acid from GCQTOF-MS, which exhibited a molecular ion peak at an m/z value of 256 corresponding to the molecular formula $C_{16}H_{32}O_2$. The fragmentation of n-hexadecanoic acid is shown in Fig. 6. The base peak showed a fragment at an m/z value of 60 ($C_2H_4O_2$). The fragment confirmed the presence of carboxylic acid group, while the other fragment is proven as the removal of ethyl group from the long-chain hydrocarbon. Therefore, from the spectroscopic analysis, the fragmentation pattern of MS, and the comparison of the data with the literature of the same compound isolated (Krishnan et al., 2016), this compound is assigned as n-hexadecanoic acid.

4. Conclusion

In this study, the combined use of gas chromatography spectrometry (GC–MS) and quadrupole time of flight (QTOF) was demonstrated in the successful identification of the major compounds in agarwood oil collected from different origins. GC-QTOF-MS is a highly sensitive, accurate mass detector giving high resolution mass compared to a standalone GC–MS. A number of sesquiterpens were identified and quantified successfully from different samples of agarwood oil. Three compounds agarospirol, n-hexadecanoic acid and selinene were identified in all the samples. The identification of compounds was further validated by isolating Agarospirol and n-hexadecanoic acid where agarospirol is responsible for the characteristic woody smell of Oud.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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