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Research Paper

Bioactivity of Endophytic Fungi Isolates from *Syzygium malaccense* Twigs

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Abstract
Searching for medicinal raw materials derived from the isolation of secondary metabolite compounds is still being carried out to cure a range of illnesses, including infections and degenerative diseases caused by bacteria and free radicals. This research used endophytic fungi extract from the twig of *Syzygium malaccense*. The diffusion method was used for antibacterial activity and 2,2-diphenyl-1-picrylhydrazyl (DPPH) was used for antioxidant activity. Chemical compound was identified by using NMR spectroscopic method. This research found 5 isolate of endophytic fungi from twig of *S. malaccense* (YR1 – YR5). Strong antibacterial and antioxidant activity were showed by YR5. Based on molecular identification, YR5 was *Fusarium verticillioides*. Pure compound prodeced by endophytic fungi *F. verticilloides* was naphthalene (3-methoxy-7-methylnaphthalene-1,6-diol). This finding can be used as a basis for drug development.

Keywords
Antibacterial, Antioxidant, Endophytic Fungi, *Syzygium malaccense*

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1. INTRODUCTION

Endophyte microorganisms live in plant tissues without causing the disease (Alam et al., 2021). The majority of common endophytes are bacteria and fungi. The most common endophytic fungal species were isolated in vitro in various experiments (White et al., 2019). Endophytic fungi that have symbiosis in the endodermis of plants can produce the same secondary metabolites with their hosts and have a lot of potential for use in the pharmaceutical industry, in making raw materials for traditional medicine, as well as in agriculture using contemporary biotechnology (Slama et al., 2021; Habisukan et al., 2022; Tiwari and Bae, 2022).

Symbiosis in other endophytic fungi forms antagonism, mycoparasitism, antibiosis, and competition to protect the host (Herlinda et al., 2020; White et al., 2019). Other research has discovered that endophytic fungus can protect plants from stress due to the environment (Kushwaha et al., 2020; Khan et al., 2019). Many secondary metabolites and various bioactivities, including antibacterial and antioxidant properties, can be produced by endophytic fungi (Oktiansyah et al., 2024). These findings demonstrate that research on endophytic fungus continues to be substantial, particularly in the health sector and the development of alternative medicine.

One member of the Myrtaceae family, *S. malaccense*, which in Indonesia is known as Jambu Bol, has been proven to have antioxidant, anti-inflammatory, cytotoxic, antihyperglycemic, antimicrobial, and anticancer potential (Mustaqim, 2021; Savi et al., 2020). Studies uon endophytic fungi revealed several fungi that have antibacterial properties on *S. malaccense* plants (Hapida and Widjajanti, 2022). Endophytic fungi associated with medicinal plants produce future natural biotechnology which has great opportunities for development because it is estimated that it can produce the same active compounds in a short period (Rodrigo et al., 2021).

The focus of this study is to find opportunities to obtain antioxidant and antibacterial bioactive compounds from various endophytic fungi isolated from *S. malaccense* twigs and determine the chemical structure of compounds from potential endophytic fungi to open development opportunities for providing immunomodulatory medicinal ingredients in the future.

2. EXPERIMENTAL SECTION

2.1 Materials

The materials of this study were Potato Dextrose Agar (PDA), Potato Dextrose Broth (PDB) from Oxoid, alcohol 70%, NaOCl solution from Onemed, TLC Si Gel plates (Merckkieselgel 60 GF254, 0.25 mm, 20 × 20 cm, column chromatography using Merck SiGel 60 (70–230 mesh). The solvents used were n-hexane, ethyllacetate, methanol, aquabidest, DPPH (D9132 Sigma-Aldrich). The twig of *S. malaccense* were collected from Sako, Palembang, in March and it was identified in the Biosystematics Laboratory, Sriwijaya University with number 233/UN9.1.7/4/EP/2021. The spectrophotometer UV-Vis (Shimadzu UV-1900) used to check the absorption of DPPH for determining antioxidant while the antibacterial activity test used Laminar Air Flow (LVG-4AG-F8) to avoid contamination. The characterization of chemical compounds using an NMR spectrum on JEOL JNM-ECZ500R/ S1 500 MHz (1H); 125 MHz (13C).

2.2 Methods

2.2.1 Isolation and Morphological Identificationn

The surface of sample was sterilized by rinsing with sterile Aqua DM and 70% ethanol and 30% sodium hypochlorite (NaOCl) for 180 and 300 seconds. It was inoculated on potato dextrose agar (PDA) media after being cut measuring 1×3 cm. After six days of growth on PDA media, isolates of endophytic fungi were identified morphologically based on macroscopic and microscopic characteristics (Manias et al., 2020). Apart from paying attention to the character of the fungal colony, macromorphological observations were also carried out as well as the morphology of the surface. The physical characteristics of endophytic fungi are identified using fungal identification guidelines (Walsh et al., 2018; Watanabe, 2010).

2.2.2 Molecular Identification

The endophytic fungal isolates with the greatest bioactivity were chosen for molecular identification. The ITS DNA (rDNA) region was used for identification. ITS1 and ITS4 primers were employed throughout the amplification procedure and then BLAST (http://blast.ncbi.nlm.nih.gov/Blast.cgi) included the sequences. Furthermore, the sequences were aligned using the MEGA11 and a phylogenetic tree was generated using the neighbour-joining tree method with a bootstrap ovalue of 1000 (Tamura et al., 2021).

2.2.3 Cultivation and Extraction

To grow spores in PDB liquid media, isolated culture plates were utilized in six bottles containing 300 milliliters of potato dextrose broth (PDB) with fresh cultivation isolates of endophytic fungi (Gustianingtyas et al., 2020). Spore culture was then left at room temperature for about 28 days under static conditions. The liquiddculture is then isolated from the mycelial biomass. The liquid culture mixture is then combined with ethyl acetate solvent at a 1:1 ratio. The extraction is then performed in partitions (three times) to yield a thicke xtract. An ethyl acetate extract was evaporated using a rotary evaporator (Aini et al., 2023; Nagarajan, 2019).

2.2.4 Antibacterial Activity

The acquired endophyte isolates were subjected to the cakram diffusion method to test for antibacterial activity. Ethyl acetate extract was utilized at a dose of 400 g/mL and tetracycline was used as an antibiotic at a dose of 30 g/mL. As test bacteria, *Salmonella typhi*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli* were employed. Antibacterial activity levels of weak 50%, medium 50%, and strong 70% were established by comparing the clear zone of antibiotics (B) with endophytic fungal extracts (A) (Hapida and Widjajanti, 2022).

$$\text{Antibacterial Activity (\%)} = \frac{A}{B} \times 100\% \quad (1)$$

2.2.5 Antioxidant Activity

Following dissolution, quantities of 1000, 500, 250, 125, 62.5, 31.25, and 15.625 g/mL were obtained from endophytic fungal extracts. 0.2 mL of each concentration was combined with 3.8 mL of DPPH 0.5 mM. Once the mixture is well combined, let it sit in a dark test tube for half an hour. A UV-Vis spectrophotometer was used to determine the maximum absorption of 517 nm. Methanol serves as a solvent standard in this study, whereas ascorbic acid serves as thepositive control. The DPPH absorption retention value, which can be used to assess antioxidant activity, is computed using the IC50 value and the percentage of DPPH absorption inhibition (Syarifah et al., 2021).

$$\text{Inhibition (\%)} = \frac{\text{Control Abs} - \text{Sample Abs}}{\text{Control Abs}} \times 100\% \quad (2)$$

2.2.6 Isolation of Chemical Compound

Pre-absorption is used to prepare the chosen sample extract, which is then uniformly put into the chromatography column and eluted with an eluent of increasing polarity. Each of the 10 mL bottles containing the eluates was collected, and thin layer chromatography was used to separate each one into column fractions. Until a pure product is attained, each column fraction is evaporated, separated, and purified using chromatographic procedures. Through the use of specthroscopic techniques, such as ^{1}H-NMR, ^{13}C-NMR, HMQC, and HMBC, the chemical structure was determined (Oktiansyah et al., 2024).

3. RESULTS AND DISCUSSION

Results of the isolation of pendophytic fungi from the *S. malaccense* twig obtained five isolates, YR1-YR5, found four (4) genera: *Madurella*, *Trichoderma*, *Pythium*, and *Fusarium*. The YR1 has septate hyphae, have globase and conidia type form spore, have velvety texture and rugose topography identified in *Madurella sp*. YR2 has septate hyphae, have globase and conidia type form spore, have cottony texture and umbonate topography identified in *Trichoderma sp*. YR3 has septate hyphae, have ellipsoidal and sporangiofor type form spore, have cottony texture and rugose topography identified in *Pythium sp*.

YR4 has similiar like *Pythium sp.* With non septate hyphae, have ovate form spore and flowery topography. YR5 has non septate hyphae, have macroconidia and conidia type form spore, have cottony texture and Umbonate topography identified in *Fusarium sp.* in Figure 1.

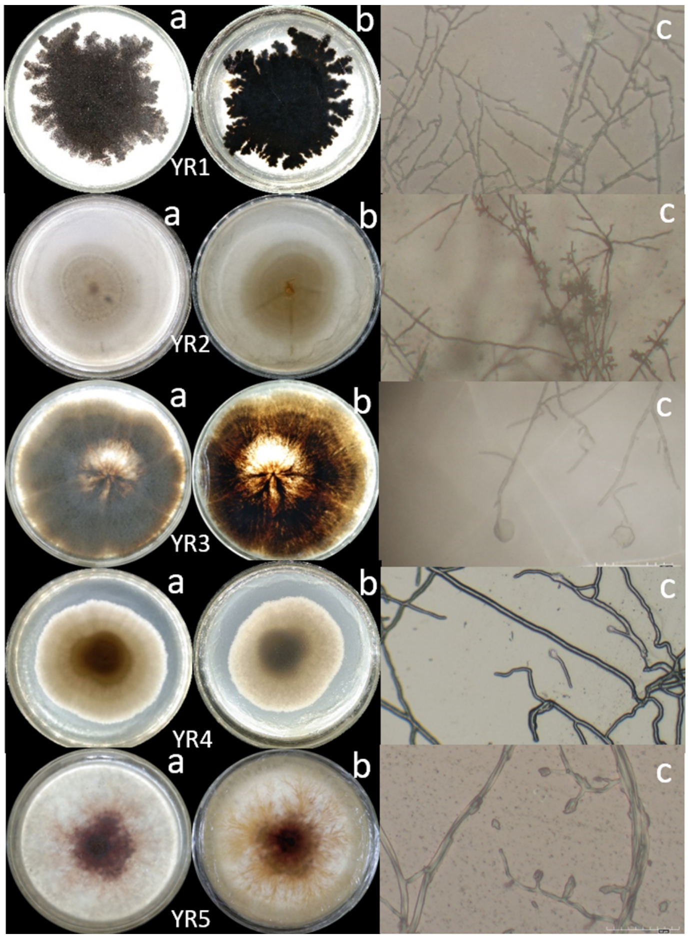

Figure 1. Characteristics of Endophytic Fungus from Twig of *S. malaccense* (a: Front; b: Reverse; c: Micoscopic)

The four genera of endophytic fungi found as a result of isolation and identification on *S. malaccense* twigs (Table 1) are often found on the rhizomes and roots of other medicinal plants, especially the *Fusarium* genus (Jigjiddorj et al., 2024), but are also found in *S. aqueum, S. zeylanicum, S. jambos* (Aini et al., 2023; Habisukan et al., 2021; Syarifah et al., 2021), these findings indicate that there are certain types of endophytic plant fungi that can struggle in different anatomical structures and conditions of host plant (Alam et al., 2021).

3.1 Antibacterial and Antioxidant of Endophytic Fungi

To assess the disc paper's capacity to destroy bacteria, examine the clear region that the ethyl acetate extract of YR1–YR5 fungal isolates created around it. These results led to the discovery that YR1–YR5 exhibited antibacterial action (Table 2). While YR2 *Trichoderma sp.* shown significant activity against

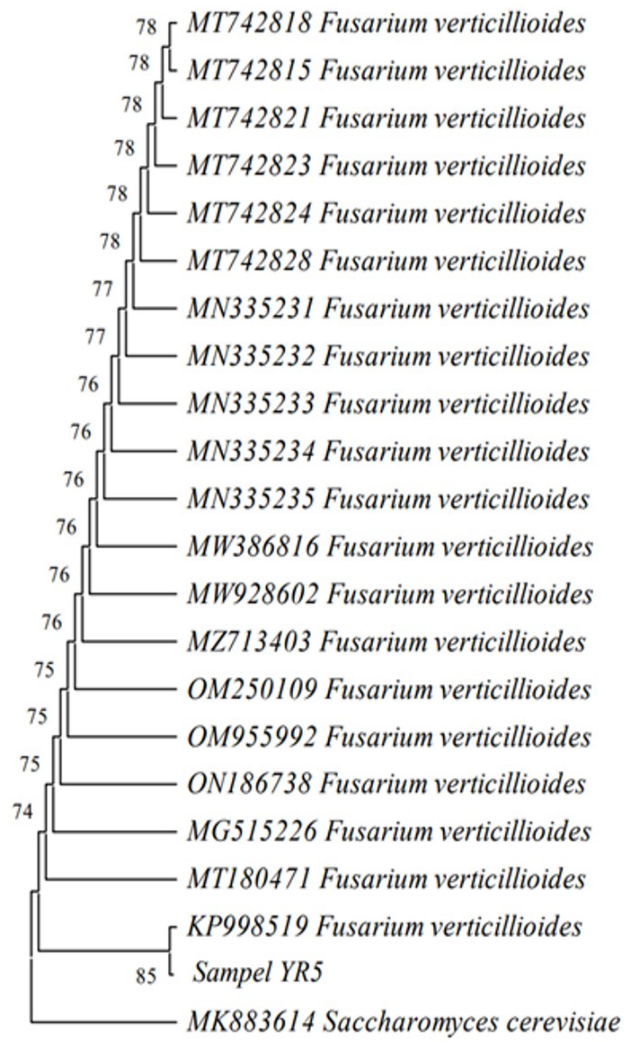

Figure 2. Species *Fusarium verticillioides* (YR5)

S. aureus and *B. subtilis*, YR1 *Madurella sp.*, an endophytic fungal isolate, demonstrated modest activity against *E. coli* and *S. typhi* bacteria. Although their efficacy was lower against *E. coli*, isolated endophytic fungi YR3 and YR4 as *Pythium sp*. demonstrated good activity against the test bacteria *S. aureus*, while YR5 shown great activity against all test bacteria. For YR1–YR5, antioxidant activity was assessed using the DPPH technique, as indicated in Table 2. The fungal endophyte that was isolated from *S. malaccense*.

3.2 Molecular Identification

Isolate YR5 was selected for DNA identification according to the results of the PCR analysis because it exhibited the highest level of bioactivity among the five other isolates. The phylogenetic tree was presented in Figure 2, along with the results of the molecular testing of the endophytic fungi. sample YR5, which includes the nitrogen base composition and configuration: TGAACCTGCGGAGGGATCATTACCGAGTTTACAACT

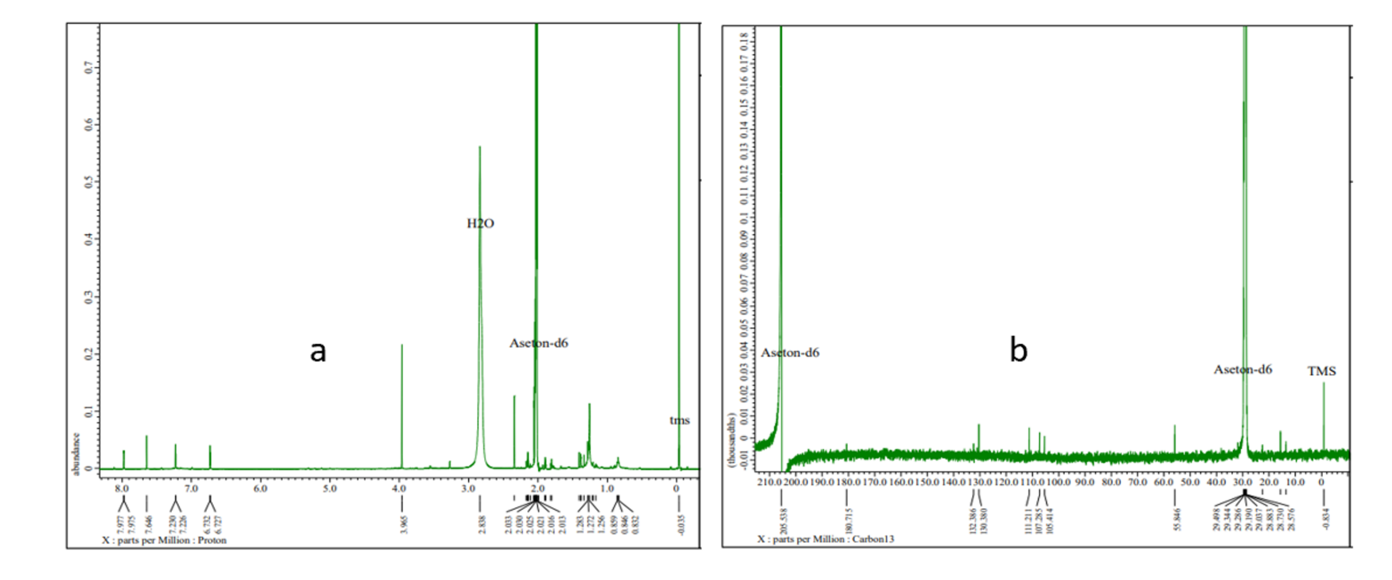

Figure 3. The ^{1}H-NMR (a) and ^{13}C-NMR (b) Spectra of Compound ^{1}H-500 MHz; ^{13}C-125 MHz in Aceton

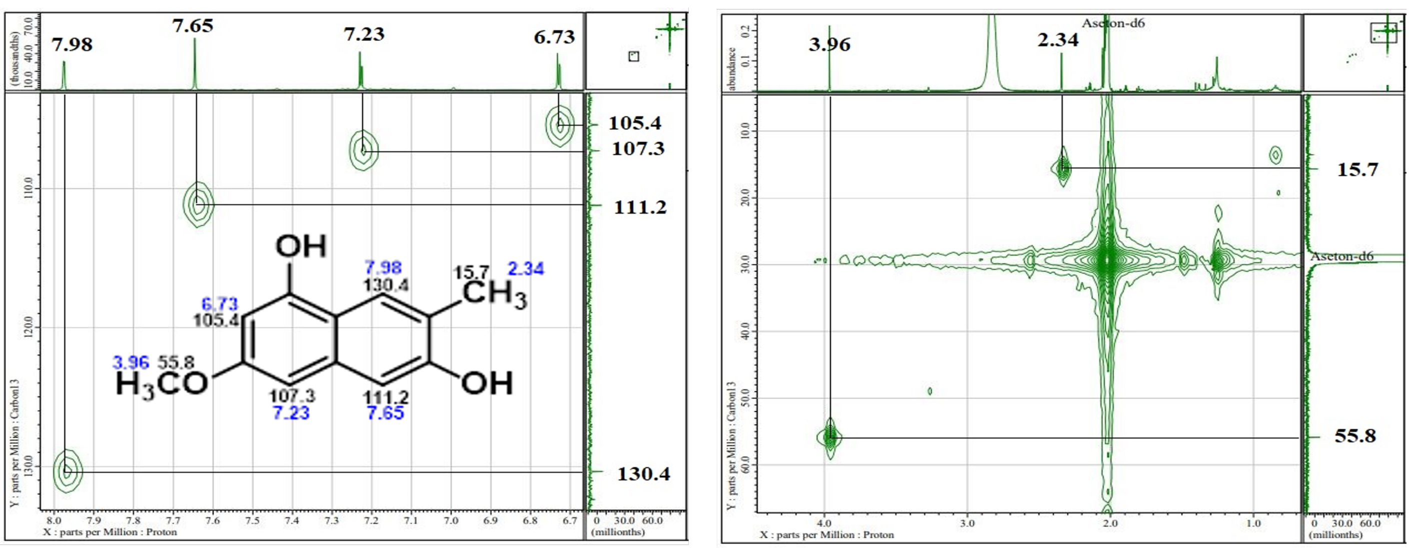

Figure 4. The HSQC Spectra of Compound

CCCAAACCCCTGTGAACATACCAATTGTTGCCTCGG
CGGATCAGCCCGCTCCCGGTAAAACGGGACGGCCCG
CCAGAGGACCCCCAAACTCTGTTTCTATATGTAACT
TCTGAGTAAAACCATAAATAAATCAAAACTTTCAAC
AACGGATCTCTTGGTTCTGGCATCGATGAAGAACGC
AGCAAAATGCGATAAGTAATGTGAATTGCAGAATTC
AGTGAATCATCGAATCTTTGAACGCACATTGCGCCC
GCCAGTATTCTGGCGGGGCATGCCTGTTCGAGCGTC
ATTTCAACCCTCAAGCCCGGCTTGGTGTTGGGACTC
GCGAGCAAATCGCGTTCCCCAAATTGATTGGCGGTC
ACGTCGAGCTTCCATAGCGTAGTAGTAAAACCCTCG
TTACTGGTAATCGTCGCGGCCACGCCGTAAACCCCA
ACTTCTGAAATGTTGACCTCGGATCAGTAGGAATAC
CCGCTGAACTTAAGCATATCAATAAGCG. Based on molecular identification, isolate YR5 showed 1 clade with *Fusarium verticillioides*.

3.3 Isolation Secondary Metabolite Compound

Based on antibacterial and antioxidant test data, the YR5 fungal isolate has the potential to continue with the separation and purification of its secondary metabolites. Pure compounds of secondary metabolites from YR5 extract (5.7 mg) were isolated using multiple-column chromatography and identified via ^{1}H-NMR, ^{13}C-NMR, HMQC, and HMBC structures. The ^{1}H-NMR spectrum of the compound (Figure 3a) shows the presence of six proton signals, of which four are signals on the

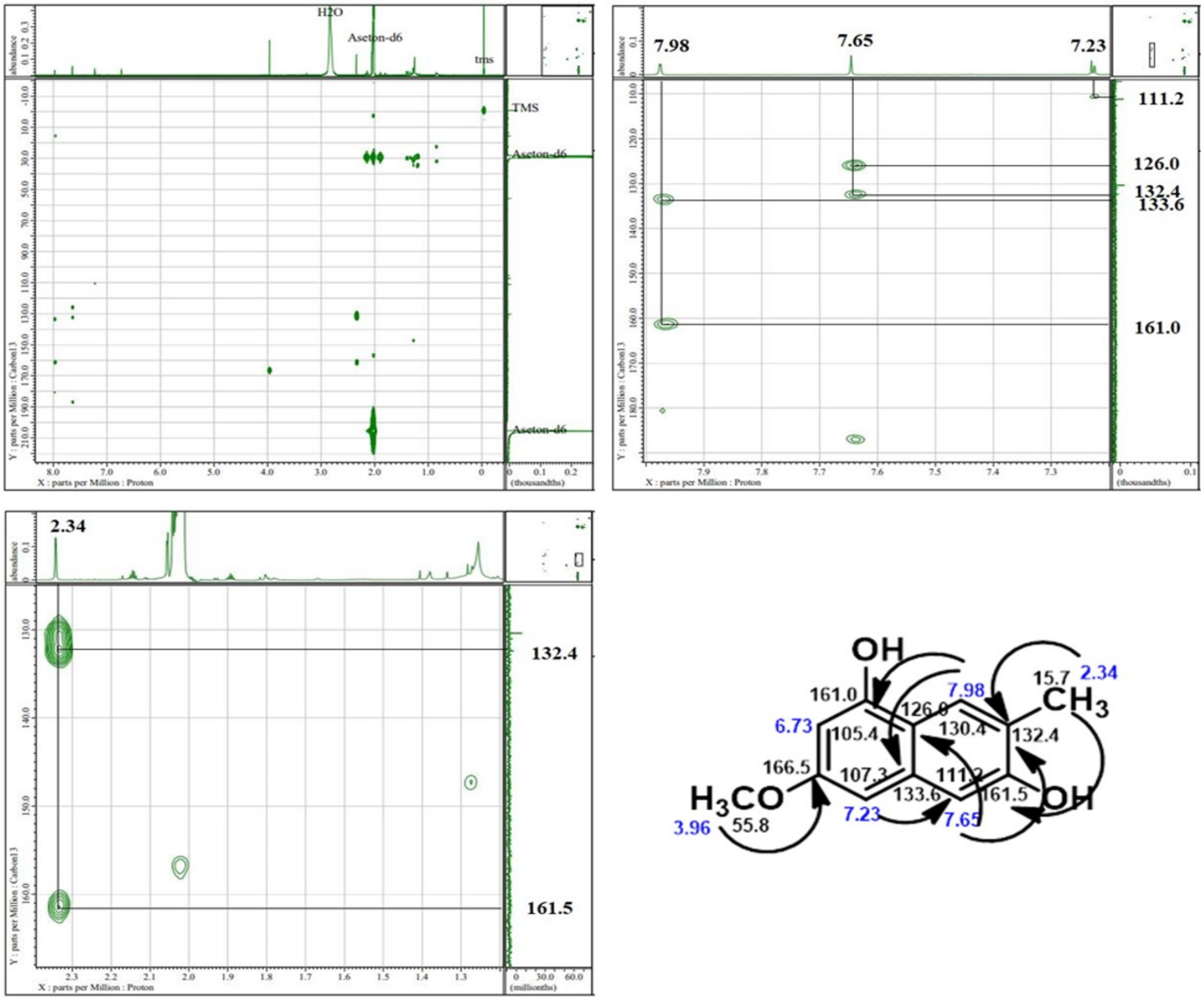

Figure 5. The HMBC Spectrum of Compound

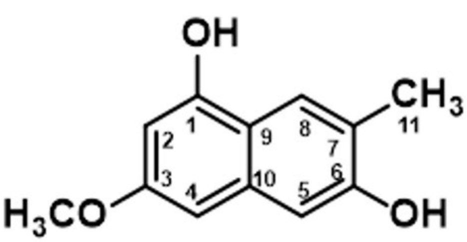

Figure 6. Chemical Structure of ('3-methoxy-7-methyl naphthalene-1,6-diol')

aromatic chemical shift, each at δ_H 6.730 (1H, d, J= 2.50Hz); 7.230(1H, d, J= 2.50Hz); 7.650(1H, s); and 7.980 ppm (1H, d, J= 1.0Hz). Protons at δ_H 6.730 and 7.230 ppm with coupling constant (J=2.50Hz) indicate that the two aromatic protons are in the meta position. Furthermore, a proton at δ_H 7.980 ppm with a coupling constant (J=1.00Hz) and a singlet proton at δ_H 7.650 ppm indicate that the two aromatic protons are in the para position. There is also a methyl proton signal and a methoxy proton. These proton signals indicate that compound 1 has a naphthalene skeleton with four aromatic protons bound to the methyl and methoxy groups.

The ^{13}C-NMR spectrum of compound (Figure 3b), supported by the spectra of HSQC (Figure 4) and HMBC (Figure 5), shows that compound 1 has 12 carbon atoms, namely at δC 166.50 ppm; 161.50 ppm; 161.0 ppm; 133.60 ppm; 132.40 ppm; 130.4 ppm; 126.0 ppm; 111.2 ppm; 107.3 ppm; 105.4 ppm; 55.8 ppm; and 15.70 ppm. However, in the ^{13}C-NMR spectrum, the carbon signal has a low intensity so not all carbon is observed. The HSQC spectra show six ^{1}H-^{13}C correlations through one bond: four aromatic ^{1}H-^{13}C correlations, a methyl ^{1}H-^{13}C correlation, and a methoxy ^{1}H-^{13}C correlation. There are three carbon signals in the low field indicating the presence of three oxyaryl carbons. It is thus known that compound 1 has a naphthalene framework attached to it a methyl group, a

Table 1. Characteristics Isolate YR1-YR5 Microscopically

Isolate	Specific Characteristic	Genus/Species
YR1	Microscopically less characteristic conidia	*Madurella sp.*
YR2	Arising singly phialides along the main axis of the conidiophores and along branches from the main axis	*Trichoderma sp.*
YR3	Swelling hypha in terminal and intercalary	*Pythium sp.*
YR4	Swelling hypha in terminal and intercalary	*Pythium sp.*
YR5	Long and slender phialides and macroconidia, almost straight, thini-walled, with foot-shaped in basal cells.	*Fusarium sp.*

Table 2. Antibacterial and Antioxidant Activity of Endophytic Fungi Extract

Sample	Genus/Species	Antibacterial Activity (%)				Antioxidant Activity (IC_{50})
		a	b	c	d	
Positive Control	-	100 ***	100 ***	100 ***	100 ***	6.12 ± 0.023 ++++
YR1 (4%)	*Madurella sp.*	37.67±0.8 *	17.79±1.01 *	58.93±1.0 **	51.4±0.1 **	379.71± 50.4 +
YR2 (4%)	*Trichoderma sp.*	53.5±0.84 **	62.5±0.77 **	75.3±1.27 ***	74.9±0.2 ***	65.21±0.6 ++
YR3 (4%)	*Pythium sp.*	38.5±0.32 *	68.1±0.53 **	72.04±0.8 ***	66.7±1.9 **	54.32±0.08 ++
YR4 (4%)	*Pythium sp.*	51.4±0.69 **	66.5±0.35 **	70.7±0.83 ***	65.2±1.2 **	95.45±0.57 ++
YR5 (4%)	*Fusarium sp.*	45.8±0.26 *	78.9±0.59 ***	81.5±0.24 ***	70.5±0.5 ***	53.02±0.23 ++

Note: *) weak; **) moderate; **) strong;***) for antibacterial activity, -) very weak; +) weak; ++) moderate; +++) strong; ++++) very strong for antioxidant activity, the control positive of the antibacterial test used tetracycline 4% whereas the antioxidant test used ascorbic acid. a. *E.coli*, b. *S. typhi*, c. *S. aureus*, d. *B. subtilis*

methoxyl group, and two hydroxyl groups.

The HMBC spectrum (Figure 5) showed the ^{1}H-^{13}C correlation through two or three bonds. The aromatic proton signal at δ_H 7.980 ppm correlates through three bonds with quaternary aromatic carbon at δ_C 133.60 ppm and oxyaryl carbon at δ_C 161.00 ppm. The aromatic proton at δ_H 7.65 ppm is correlated through three bonds with two quaternary aromatic carbons at δ_C 126.00 and 132.40 ppm. Aromatic protons at δ_H 7.230 ppm have a three-bond correlation with tertiary aromatic carbon at δ_C 111.20 ppm. Another correlation shows the methoxy proton at δ_H 3.96 ppm through three bonds to the oxyaryl carbon at δ_C 166.50 ppm. In addition, the correlation of the methyl proton at δ_H 2.34 ppm through two bonds with tertiary aromatic carbon at δ_C 132.40 ppm and three bonds with oxyaryl carbon at δ_C 161.50 ppm. The 1D and 2D NMR spectral data for compound 1 are shown in Table 3.

Based on spectral analysis of ^{1}H-NMR, ^{13}C-NMR, HMQC, and HMBC, compound 1 has a naphthalene skeleton with four aromatic protons: two aromatic protons in the meta position and two other aromatic protons in the para position. In the framework of naphthalene, there is a bonded methyl group, a methoxyl group, and two hydroxyl groups. Thus, the proposed chemical structure of compound 1 is 3-methoxy-7-methylnaphthalene-1,6-diol as shown in Figure 6.

Numerous secondary metabolites produced by *Fusarium* species have been found to be useful in bioactivity tests (Pessôa et al., 2017). These include bikaverine, which has been shown to have antibacterial and antimicrobial properties (Deshmukh et al., 2014), isoquinoline, which has been shown to be an antilarvacidal agent (Pradeep et al., 2015), fusarielin, which has been shown to be effective against human breast cancer (Sondergaard et al., 2012), fugerin, which has been shown to be an antifungal (Trisuwan et al., 2010), fusarithioamide, which has been shown to be an inhibitor of cell proliferation (Ibrahim et al., 2016), and enniatin, which has been shown to have antileishmanial activity (Zaher et al., 2015).

The antibacterial and antioxidant properties of the separated compounds were further examined. According to Azam et al. (2007), the isolated chemical compound contains a naph-

Table 3. The NMR Data of Compound 1, Recorded at ^{1}H-500 MHz; ^{13}C-125 MHz in Acetone

No. C	δ_C ppm	Type of C	δ_H ppm (ΣH. Multiplicity. *J* (Hz))	HMBC
1	161.00	C	-	-
2	105.40	CH	6.730(1H, d, J= 2.50Hz)	-
3	166.50	C	-	-
4	107.30	CH	7.230(1H, d, J= 2.50Hz)	111.2
5	111.20	CH	7.650(1H, s)	126.0; 132.4
6	161.50	C	-	-
7	132.40	C	-	-
8	130.40	CH	7.980(1H, d, J= 1 Hz)	133.6; 161.0
9	126.00	C	-	-
10	133.60	C	-	-
11	15.70	CH_3	2.340	132.4; 161.50
3-OCH_3	55.80	CH_3	3.960	166.50

Table 4. Antibacterial and Antioxidant Activity Isolated Compound from YR5

Sample	Concentration	Antibacterial Activity (mm)				Antioxidant Activity (IC_{50})
		a	b	c	d	
Isolated Compound	500	18.20±0.92	19.10±1.23	19.90±0.78	19.47±1.87	71.34 ± 0.414 ++
	250	13.43±0.56	14.13±0.67	16.40±0.63	15.07±1.02	
	125	13.21±0.87	14.20±1.53	14.62±0.43	12.87±0.13	
	62.5	8.52±1.23	10.15±0.13	9.81±0.23	11.32±0.19	
	31.25	8.00±0.04	8.07±0.11	8.27±0.11	8.36±0.02	
Positive Control	Tetracycline	22.4 ± 0.32	23.1 ± 0.59	21.5 ± 0.73	22.7 ± 0.29	-
	Ascorbic Acid	-				6.12 ± 0.023 ++++

Note: -) very weak; +) weak; ++) moderate; +++) strong; ++++) very strong for antioxidant activity.
a. *E. coli*, b. *S. typhi*, c. *S. aureus*, d. *B. subtilis*

thalene ring group, which exhibits strong biological activity of the active component against various microorganisms. Patel and Patel (2019) synthesized seven naphthalene ring compounds that can inhibit with the highest minimum inhibitory concentration (MIC) as antibacterial. The naphthalene derivative compound is known as chrome-6-one, 7-hydroxy-4-metho xy-9-(naphthalene-2-yl)-6H-benzo(c). The isolated compound was then tested for antibacterial and antioxidant activity with results shown in Table 4.

Another finding from Salae et al. (2010) showed that isolating 3 naphthalene derivatives from *Diospyros wallichii* with the compound names 2-hydroxymethyl-1,5-dimethoxynaphthale ne-4-ol; 2,2'-bis-hydroxymethyl-1,1',5,5'-tetramethoxy-3,3'-biinaphthalene-4,4'-diol; and 5,5'-dihydroxy-2,2'-dimethyl-7,7'-binaphthalene-1,1',4,4'-tetraone which shows moderate activity against several bacteria (gram-positive bacteria *S. aureus*, *B. subtilis*, *E. faecalis*; gram-negative bacteria *S. typhi*, *S. sonnei*, and *P. aeruginosa*). With substitutions 4 and 5, Kelley et al. (2013) were able to find the compound 1-phenyl naphthalene. They next assessed the changed compounds' antibacterial capabilities, finding that the MIC values for *S. aureus* and *E. faecalis* varied only slightly.

The active compound of tetracyclic conjugates, namely juglone (5-hydroxy-1,4-naphthoquinone), can selectively target cancer cells and exhibit potent antimicrobial properties (Sabutski et al., 2020. Naphthalene rings have been consistently shown in all the publications to serve as effective substitutes for antibacterial and antioxidant agents, with varying degrees of bioactivity depending on the substituted groups.

4. CONCLUSIONS

Four types of endophytic fungi were found on *Syzygium malaccense* twigs: *Madurella* (YR1), *Trichoderma* (YR2), two *Pythium* (YR3–YR4), and *Fusarium* (YR5). Tests for antioxidant and antibacterial qualities revealed that all four species possess these qualities. Molecular studies indicate that *Fusarium sp*. belongs to the species *Fusarium verticillioides*. The chemical substance extracted from the secondary metabolite chemicals in isolate YR5 was named 3-methoxy-7-methylnaphthalene-1,6-diol.

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