Antioxidant and Antibacterial Activities of Ethyl Acetate Extract of Endophytic Fungi Isolated from Ciplukan (*Physalis angulata* L.) Fruit

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Abstract. *Physalis angulata* L. is known for treating various diseases caused by free radicals and bacterial infections. Endophytic fungi in *P. angulata* L. plants are of concern because they have the potential to be developed. This research identify morphological characters, macroscopic and microscopic, determine the antioxidant and antibacterial activity of the ethyl acetate extract of the fruit endophytic fungus *P. angulata* L and compare it with the host plant. Identification of fungal morphology based on macroscopic and microscopic characters. Antioxidant activity was tested using the DPPH method and antibacterial activity was tested using the Kirby-Bauer diffusion method. The results of isolating endophytic fungi from *P. angulata* L. fruit produced 2 isolates, namely CH1 and CH2. Based on macroscopic and microscopic characters, isolate CH1 was identified as *Fusarium* sp. and isolate CH2 was identified as *Aspergillus* sp. The endophytic fungal isolate was then cultivated to obtain ethyl acetate extract. The test results showed that the ethyl acetate extract of endophytic mushrooms had antioxidant and antibacterial activity. The antioxidant activity of ethyl acetate extract from endophytic fungi is weaker than that of the host plant, while the antibacterial activity is stronger than that of the host plant. It proves that endophytic fungi isolated from *P. angulata* L. fruit have the potential to be developed into medicinal ingredients to treat free radicals and bacterial infections.

Keywords: Antibacterial, Antioxidant, Endophytic fungi, *Physalis angulata* L.

1 Introduction

Antioxidants and antibiotics are common products for treating free radicals and bacterial infections. Antioxidant and antibiotic products are generally synthetic products that are standardized and effective for scavenging free radicals and curing bacterial infections from inside and outside. However, using inappropriate doses, disease targets, or undisciplined, can

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cause side effects, including DNA damage and antibiotic resistance [1,2,3]. To overcome this problem, alternative treatments were found using compounds from natural ingredients. Natural ingredients have the potential to have better interactions with disease and better pharmacokinetic effects than synthetic ingredients [4]. Natural ingredients that have the potential to be used as medicine, namely *Physalis angulata* L.

P. angulata L. plant is a traditional medicinal plant that is widely used in Central and South America as well as in Asia. *P. angulata* L. known as 'ciplukan' is a traditional medicinal plant used by Indonesian people. *P. angulata* L. is traditionally known to treat boils, ulcers, constipation, and stomach pain. [5]. *P. angulata* L. can also reduce cholesterol, cure diabetes mellitus, malaria, leishmania, asthma, tuberculosis, cancer, hepatitis and hypertension [6]. The parts of the plant used as medicine are roots, stems, leaves, flowers and fruit. The benefits of this plant are related to its bioactive compounds including flavonoids, saponins, alkaloids, terpenoids, steroids, anthraquinones, withanolides, and physalins [7,8,9]. *P. angulata* L. fruit, has antioxidant activity with IC_{50} = 63,46 µg/mL and Vitamin C with IC_{50} = 34,91 µg/mL [10]. *P. angulata* L. fruit extracted using ethanol has antibacterial activity against *S. aureus and E. coli* bacteria with MIC 10 mg/ml [11]. The strong antioxidant and antibacterial activity of *P. angulata* L fruit indicates that *P. angulata* L. fruit has the potential to be a new medicinal agent. However, *P. angulata* L. fruit depends on the reproductive phase. If the roots, stems and leaves of *P. angulata* L., can be used as medicine from young plants, the fruit of *P. angulata* L. can be used when they are mature with dark green protective calyx. The conditions of the planting media also determine the fruit of *P. angulata* L. Macronutrients such as P, Mg, and S must be added because of the limited amount in nature. These macronutrients are very necessary when entering the reproductive phase. If there is a deficiency, it will cause assimilation migration and mineral drying so that flowers and fruit can't developed [12]. Difficulties in using fruit as medicine require alternatives to obtain active compounds from the fruit of *P. angulata* L. Science in the pharmaceutical field is increasingly developing, finding alternatives to isolate active compounds from *P. angulata* L. fruit through its endophytic fungi.

Endophytic fungi are micro fungi that reside in living plant tissue [13]. Basically, endophytic fungi can be isolated from various plant tissues including roots, stems, leaves, rhizomes, flowers and seeds [14]. Endophytic fungi are involved in plant defense mechanisms and have the ability to produce active compounds similar to host compounds [15]. In addition, there are new compounds isolated from endophytic fungi with various pharmacological activities [16]. Therefore, endophytic fungi are an important source of potential bioactive compounds.

Research on endophytic fungi on *P. angulata* L. fruit is rare. Research on endophytic fungi from *P. angulata* L. fruit that has been carried out is on fruit skin with endophytic fungi that have been isolated, namely *Fusarium* sp and *Colletotrichum* sp. The antioxidant activity of both fungi was weak to moderate. Meanwhile, antibacterial activity is included in the strong category with MIC <100 µg/mL [17]. Because research on endophytic fungi on fruit is still rarely carried out, it is necessary to explore the endophytic fungi contained in *P. angulata* L. fruit. Antioxidant and antibacterial activity tests are needed to determine the content of bioactive compounds produced by endophytic fungi so that they can be further developed into new agents of antioxidant and antibacterial.

2 Material and Methods

2.1 Material Plant

Samples were taken from Timbangan Village, North Indralaya District, Ogan Ilir Regency, South Sumatra (January 17, 2023; Latitude: -3.220330; Longitude: 104.649159). Determination of plants in the Indonesian Biology Generation (Genbinesia) at determination number 08.115/Genbinesia/IX/2023. Samples were collected in August 2023. Endophytic fungi were isolated from old fruit with dark green fruit skin.

2.2 Isolation of Endophytic Fungi

Samples were thoroughly washed and surface sterilized in 3 stages. The sample was dipped in 70% alcohol for ± 2 minutes and 3% sodium hypochlorite (NaOCl) for 1 minute. The samples were rinsed with distilled water and dried on sterile filter paper [18]. The sample was split with a sterile knife and placed on Potato Dextrose Agar (PDA) which added chloramphenicol previously to prevent bacterial growth. Samples were incubated at 30^{o}C for 1-3 days. Fungal colonies that show different morphological characteristics are separated and inoculated into another PDA medium to obtain pure isolates [19].

2.3 Morphology Identification of Endophytic Fungi

Phenotypic characterization was performed macroscopically and microscopically. Macroscopic characterization is to observe colony surface color, texture, topography, pattern, exudate drops, radial line, concentric circle. Texture is the appearance of fungal hyphae. Topography is the appearance of the top surface of a fungal colony on an agar medium. Pattern is the growth pattern of the fungus. Exudate drops are liquid droplets visible on the surface of the colony. Radial line is fungal growth that forms a line with one end concentrated in the center and the other end spreading to the edge of the colony. Concentric circles are fungal growths that form small circles in the center of the colony and widen towards the edge of the colony [21,22]. Microscopic characterization using the slide culture method. Documentation using Hirox MXB-2500REZ microscope. Characterization data was matched with a fungal identification book, Larone's Medically Importan Fungi [23], Pictorial atlas of soil and seed fungi [20], Pictorial Atlas of Soil and Seed Fungi [21] and other relevant journals.

2.4 Cultivation and Extraction of Fungal Endophytes

Cultivation began with 6 agar plugs inserted into 250 ml potato dextrose broth (PDB). The culture was incubated for 3-4 weeks or until the medium changed color. After 3-4 weeks, mycelium and liquid culture were separated with filter paper. Mycelium (biomass) was dried at 60^{o}C and stored. The liquid culture was partitioned with ethyl acetate in a 1:1 ratio for 7 days. The ethyl acetate extract was separated using a separatory funnel and concentrated with a rotary evaporator. The concentrated extract was weighed (23,24).

2.5 Antibacterial Activity Test

Kirby-Bauer method was used to test the antibacterial activity with Mueller Hinton Agar (MHA) medium. The test bacteria were *Salmonella typhi* (IPBCC.11.669), *Staphylococcus aureus*

(ATCC 25923), *Escherichia coli* (ATCC 25922) and *Bacillus subtilis* (ATCC 6633). Bacteria were dissolved in distilled water or 0.85% NaCl according to McFarland Standard 0.5 with an approximate bacterial count of 1.5x108 CFU/ml. Test bacteria were inoculated onto MHA at 0.1 ml each, allowed to stand for 1 hour. Paper disks were placed into a Petri dish and dripped with 10 mL of endophytic fungal extract at a concentration of 400 µg/disk in DMSO. Negative control used 10 µL DMSO and positive control used 30 µg/disk tetracycline. Incubation at 37ºC for 24 hours. The zone of inhibition is measured with a caliper. The interpretation follows the criteria of weak, moderate and strong inhibition [26]. These criteria follow the formula in Eq. 1, 2 and 3.

Weak : $\frac{A}{B}$ x 100% < 50%.....1

Moderat : 50% < $\frac{A}{B}$ x 100% < 70%.....2

Strong : $\frac{A}{B}$ x 100% > 70%.....3

Note:
A: inhibition of sample (mm)
B: inhibition of standard antibiotic (mm)

2.6 Antioxidant Activity Test

Antioxidant activity was determined by the DPPH method. Ethyl acetate extract of endophytic fungi was dissolved in methanol. The test concentrations were 1000, 500, 250, 125, 62.5, 31.25, and 15.63 µg/mL. A total of 0.5 ml of the test solution was added with 1.5 ml of 0.06 mM DPPH. Mix until homogeneous and incubate for 30 minutes in a dark room. Absorbance was measured at a wavelength of 517 nm. Antioxidant activity was calculated based on the percentage of inhibition and IC_{50} value [27]. The percentage of inhibition follows the formula in the Eq. 4.

$$\text{Percentage inhibition (\%)} = \frac{Ac - As}{Ac} \text{ x100}\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 4$$

Note :
Ac = absorbance of control
As = absorbance of sample

3 Result and Discussion

3.1 Isolation and Identification of Endophytic Fungi

P. angulata L. fruit, which has been inoculated on PDA medium and incubated for 1-3 days. Endophytic fungi will grow near the inoculated fruit pieces (Fig. 1). The growing fungus was isolated into a different PDA medium with the same incubation time as before. The result is a pure colony of endophytic fungi on a petri disk.

Fig. 1. Endophytic fungi from *P. angulata* L. fruit (incubation day 3)

Two isolates of endophytic fungi were isolated from *P. angulata* L. fruit with codes CH1 and CH2. Endophytic fungal colonies show different macroscopic (Fig. 2) and microscopic characters (Table 1 and Table 2). Macroscopic characters are identified using the criteria of color surface colony, texture, topography, pattern, exudate drops, radial lines, concentric circles. Microscopic characters are identified using the criteria of spore type, shape of spore, hypha and specific characteristics.

The CH1 fungal isolate has the characteristics of pale cream to white and pale buff to white, cottony, raised, flowering, globose, septate, hyaline conidiophores, terminal, erect, hyaline columellae. Another macroscopic character is that the colonies are yellow in the middle and white at the edges. The surface of the edge of the colony initially appears as smooth waves, then changes to a larger wave surface [28]. Microscopic characters are elongated macroconidia with pointed tips like crescents and ovoid microconidia [29,21]. Based on these characters, the CH1 isolate was identified as *Fusarium* sp. The second fungal isolate CH2 has morphological characteristics of dark green to cream and black to dark cream, velvety, rugose, spreading, radial lines, curved shape, septate, conidia are phialosporous, hyaline, simple, have a mass of spores at the top. Another macroscopic character is that initially the mycelia are white. After three days, the isolates produced olive and dark green conidia, which then dominated the appearance of the colony. It is generally plain and flat at the edges, but bulges in the center and wrinkles in an almost cerebellar pattern. Microscopic characters are globose conidia with thin walls, but in Fig. 2, the sporangium wall is no longer present, and globose spores are faintly visible [30,31,32,21]. Based on these characters, the CH2 isolate was identified as *Aspergillus* sp.

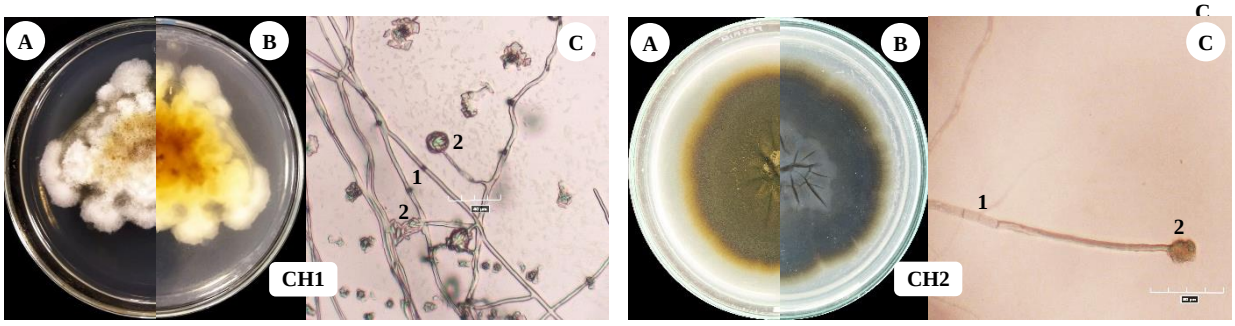

Fig. 2. Morphological characters of endophytic fungi colonies from *P. angulata* L. fruit. A. Macroscopic characters (front view; B. Reverse view); C. Microscopic characters (1: septate hypha, 2: conidia)

Table 1. The characteristics of endophytic fungi colonies isolated from *P. angulata* L. fruit

Code	Surface Colony	Reverse Colony	Texture	Topography	Pattern	Exudate drops	Radial line	Concentric circle
CH1	Pale cream to white	Pale buff to white	Cottony	Raised	Flowery	-	-	-
CH2	Dark green to cream	Black to dark cream	Velvety	Rugose	Radiate	-	√	-

Table 2. Microscopic characteristics of endophytic fungi isolated from *P. angulata* L. fruit

Code	Spore Type	Shape of spore	Hypha	Characteristic	Identification Result
CH1	Conidia	Curved	septate	Conidiophores hyaline, simple, bearing spore masses at the apexes, as tall as the length of macroconidia by a few times. Macroconidia with pointed tips like crescents and microconidia ovoid	*Fusarium* sp.
CH2	Conidia	Globose	septate	Conidia phialosporous, pale green, globose, slightly echinulate.	*Aspergillus* sp.

Tables 1 and 2 describe the morphological characters of endophytic fungal colonies from P. angulata L fruit. There were 2 genera of endophytic fungi found, namely *Fusarium* (CH1) and *Aspergillus* (CH2). The fruit of *P. angulata* L. is of the buni type, protected by protective calyx/slightly transparent fruit petals that are light green and yellowish green to brown when the fruit is ripe [33]. In this research, the endophytic fungus found in *P. angulata* L. fruit was *Fusarium* sp. and *Aspergillus* sp. The endophytic fungus *Fusarium* sp. also found on the protective calyx because the position of the protective calyx is very close to the fruit, so endophytic fungi found on the fruit are also very likely to be found on the protective calyx. But the endophytic fungus *Aspergillus* sp. not found on protective calyx [17].

Fusarium sp. can be found in other fruits. In banana *(M. acuminata)* the types *F. solani, F. oxysporum* and *F. equiseti* were found. *Fusarium* sp. found in bananas are endophytic fungi as well as primary pathogens that cause fusarium wilt disease in bananas [34]. *Fusarium* also found in tamarind fruit (*Tamarindus indica* L.) and lime fruit (*Citrus aurantifolia*). On tamarind fruit, the fungus found is *Fusarium solani* and on lime fruit is *Fusarium* sp. [30,31].

Aspergillus fungi are generally found in soil, rotting plants, and seeds where they are located develop as saprophytes. Aspergillus is divided into several different taxa, namely *Aspergillus, Fumigati, Circumdati, Terrei, Nidulantes, Ornati, Warcupi, Candidi, Restricti, Usti, Flavipedes,* and *Versicolores* [37]. *Aspergillus* represents a very diverse genus, contains approximately 180 species of substantial filamentous fungi pharmaceutical and commercial value[33,34]. *Aspergillus terreus*, one species of the genus Aspergillus has been isolated from the sea and terrestrial sources. Its secondary metabolites, known as butenolide, is a group of amino acid derivatives [40].

Many studies report that *Fusarium* sp. is a pathogenic fungus that can cause various diseases, including vascular wilt or root rot on bananas or tomatoes, stem rot, or soft rot on ginger rhizomes, so its presence on plants, especially cultivated plants, is avoided [34,35,36,37]. In

contrast to *Fusarium* sp., *Aspergillus* sp. actually has a quite good role in plant cultivation. Several types of *Aspergillus*, such as *Aspergillus alabamensis*, *Aspergillus oryzae*, and *Aspergillus tubingensis*, are able to protect pepper plants from wilt disease caused by Fusarium sp. The best activity was on *Aspergillus tubingensis* with a protection percentage reaching 83.33% [45]. However, this research provides evidence that pathogenic or not, endophytic fungi have bioactive compounds that have the potential to become medicinal ingredients.

3.2 Antibacterial and Antioxidant Activity of Endophytic Fungi Extracts

Endophytic fungi isolated from *P. angulata* L. leaves were cultivated in PDB. The fungus was then extracted with ethyl acetate solvent to determine its potential as an antioxidant and antibacterial agent (Table 3). Antioxidant activity was tested on DPPH to determine the endophytic fungal extract when scavenging 50% DPPH and was known as the IC_{50} value. The antioxidant activity of endophytic fungal extracts is moderate. The IC_{50} values of isolates CH1 and CH2 were 162.38 µg/mL and 713.79 µg/mL, respectively. This antioxidant activity is below that of ascorbic acid with an IC_{50} of 3.33 µg/mL. When compared with the host plant, the antioxidant activity of endophytic fungi is weaker. The antioxidant activity of the host plant is classified as very strong with an IC_{50} of 19.82 µg/mL.

The antibacterial activity of endophytic fungal extracts was tested on *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, and *Bacillus subtilis*. Based on Table 3, each isolate has different antioxidant and antibacterial activity. In terms of antibacterial activity, fungal isolates have weak activity on one type of bacteria, but strong activity on other bacteria. This activity is related to secondary metabolite compounds produced by fungi and their sensitivity to the test bacteria. Bacteria that are sensitive to a metabolite compound will form a large inhibition zone in a test on agar medium. Meanwhile, for bacteria that are not sensitive or resistant to a secondary metabolite, the inhibition zone formed will be small or not even formed at all. Biologically active secondary metabolites are considered natural antibiotics because they are associated with the breakdown of cell walls and cell membranes of microorganisms. Bacterial cell death occurs following release of cell contents, disruption of protein binding domains or activation of enzymes [46]. Based on the percentage of inhibition in Table 3, the antibacterial activity of CH1 is moderate on all bacteria with an inhibitory percentage of 53.85 – 65.22%. The antibacterial activity of CH2 isolate was moderate on all bacteria with an inhibitory percentage of 53.85 – 65.00%. Antibacterial activity on the host showed to be weaker for all bacteria with an inhibitory percentage of 32.20 – 34.38%.

Table 3. The percentage of antibacterial properties of endophytic fungal extract from *P. angulata* L. fruit compared to tetracycline and antioxidant activity compared to ascorbic acid as an antioxidant standard

Sample		**Ethyl acetate extract weight (g)**	**% Antibacterial activity**				**Antioxidant activity IC_{50} (µg/mL)**
			S. aureus	***E. coli***	***S. typhi***	***B. subtilis***	
Host plant		1,6	34.38±0.71*	32.20±0.71*	33.96±0.05*	32.40±0.05*	19.82****
Endophytic fungi	CH1	1,19	53,85±0,71**	55,00±0,05**	58,33±0,71**	65,22±1,05**	162.38**
	CH2	0,99	53,85±0,71**	65,00±0,05**	54,17±0,05**	60,87±1,05**	713.79*
	Control		Tetracycline 100***	Tetracycline 100***	Tetracycline 100***	Tetracycline 100***	Ascorbic acid 3,33****

Note: Antibacterial activity percentage: *** ≥ 70% (strong), **50-70% (moderate), and *< 50% (weak). Antioxidant activity IC_{50} (µg/mL): ****very strong < 20 µg/mL ***strong < 100 µg/mL; **moderat 100-500 µg/mL; * weak > 500 µg/mL

Based on the results, the antioxidant activity of endophytic fungi is weaker compared to the host. Meanwhile, the antibacterial activity is stronger than the host. *Fusarium* sp and *Aspergillus* sp. in this research, it had antioxidant and antibacterial activity, although its antioxidant activity was weaker than that of the host.

Based on this research, the antioxidant activity of *Fusarium* sp. is moderate. Similar to the antioxidant activity of the *Fusarium oxysporum* fungus isolated from *Otoba gracilipes* leaves. The free radical scavenging activity of this fungus was 51.5%, classified as moderate [47]. Another fungus, namely *Fusarium solani* isolated from *Tinospora cordifolia*, has a free radical scavenging percentage of 35.35% against DPPH [48]. Furthermore, *Fusarium* sp. isolated from the *Galium sinaicum*, has a DPPH free radical scavenging activity of 1% [49]. This research shows that the antioxidant activity of *Fusarium* sp. is in the weak to moderate range. In addition, the antioxidant activity of *Fusarium* sp. in this study was weaker than the host. In accordance with the activity of *Fusarium* sp. isolated from the leaves and stems of *Syzygium cumini*, the IC_{50} values of leaves and stems were 2.93 and 4.42 µg/mL, respectively, while Fusarium sp. IC_{50} value was 42.99 µg/mL [50]. The antioxidant activity of endophytic fungi is weaker than that of the host.

This research shows the antibacterial activity of *Fusarium* sp. is moderate, higher than the host. Indications of antibacterial activity are due to metabolite compounds, namely 3β-hydroxy-β-acorenol and fusariumins D, terpene group (fusariumins C), pyrano(2,3-g)indole moieties and amoenamide C. Other compounds are sesquiterpenoid derivatives emericellins A-B, phenolic bisabolane sesquiterpenoids, tremulane sesquiterpenes, furan derivatives, and polyketides [51]. Other research shows that *Fusarium solani* isolated from *Tinospora cordifolia* at a concentration of 100 µg/mL has an inhibitory percentage of between 45.28% – 96.71% against the bacteria *S. sureus, B. cereus, E. coli, S. typhi*, and *P. aeruginosa* [48]. Another fusarium, namely *Fusarium chlamydosporum* isolated from *Tylophora indica*, has antibacterial activity against MRSA, *E. coli*, and *S. sureus* with an inhibition zone of 11.5 – 12.5 mm. This antibacterial activity is due to the coumarin compound produced by *Fusarium chlamydosporum* [52]. Several studies have proven that *Fusarium* sp. contains bioactive compounds that are antibacterial.

Antioxidant activity of *Aspergillus* sp. in this study it was weak, but in the host *Physalis angulata* L. it showed stronger activity. This is similar to research on *Aspergillus unguis* isolated from *Sinularia* sp. The percentage of free radical scavenging from *Aspergillus unguis* ethyl acetate extract only reaches 45% [53]. Other endophytic fungi, *Aspergillus flavus* and *Aspergillus niger* isolated from the *Eugenia jambolana* plant have weak antioxidant activity. Each endophytic fungus has an inhibition percentage of 30% and 40% [54]. The endophytic fungus *Aspergillus* sp. isolated from *Fragaria x ananassa* fruit has moderate antioxidant activity. The percentage of inhibition of *Aspergillus* sp ethyl acetate extract was 52% [55].

Antibacterial activity of *Aspergillus* sp. in this research is moderate. Other studies have shown antibacterial activity similar to this study. Aspergillus flavus fungus isolated from soil has strong antibacterial activity. The percentage of inhibition was 69.57% on *Staphylococcus aureus* and 68.97% on *Escherichia coli*, with the positive control antibiotic gentamycin [56]. The endophytic fungus *Aspergillus* sp., isolated from the *Moringa oleifera* plant, has strong

antibacterial activity. The inhibitory percentage was 37.5% for *Bacillus subtilis* bacteria. The test concentration was 4 mg/ml with the positive control Ciprofloxacin [57]. The endophytic fungus *Aspergillus terreus* isolated from marine and areas terrestrial sources, have strong antimicrobial activity. Antimicrobial activity >20 ug/ml against *Staphylococcus aureus* and *Escherichia coli* [38]. Although the antioxidant activity of the *Aspergillus* sp. fungus is lower than that of the host, while its antibacterial activity is stronger than that of the host, both activities are closely related to the secondary metabolite content contained. Secondary metabolite compounds contained in *Aspergillus* sp. include phenols, amino acids, saponins, terpenes, flavonoids [54]. Several groups of metabolites influence the antioxidant and antibacterial activity of the fungus *Aspergillus* sp.

4 Conclusion

Endophytic fungi isolated from *P. angulata* L. fruit have weaker antioxidant activity and stronger antibacterial activity than their hosts. This is because the active compounds contained in endophytic fungi have an important function in antioxidant and antibacterial activity. Therefore, the isolation of active compounds is very necessary as information on the important function of a compound in scavenging free radicals or inhibiting bacterial growth. However, the differences in the antioxidant and antibacterial activities of endophytic fungi compared to their hosts in this study provide important information that endophytic fungi have diverse activities. Therefore, the endophytic fungus from the fruit of *P. angulata* L. has the potential to be developed into medicine as a solution for health practitioners, in choosing drugs for various diseases, especially diseases caused by free radicals and bacterial infections.

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