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Diversity and bioactivity of endophytic fungi isolated from various fruit organs of *Physalis angulata*

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Abstract. *Wahyudi BE, Elfita, Widjajanti H, Salni, Eliza, Julinar, Musifa E. 2025. Diversity and bioactivity of endophytic fungi isolated from various fruit organs of* Physalis angulata*. Biodiversitas 26: 1485-1499. Physalis angulata* plant is known by Indonesian people for its efficacy as a traditional medicine. The fruit is traditionally known as antidiabetic, anti-inflammatory and antibacterial. The efficacy of this fruit can also be obtained through its endophytic fungi isolated from parts organ of namely peduncle, calyx and pericarp all these aspects. The objective of this study was to isolate endophytic fungi from different organs of *P. angulata* fruit, namely peduncle, calyx and pericarp and determine the diversity, bioactivity and phytochemical content while comparing all aspects with the host. Endophytic fungi were isolated from peduncle, calyx and pericarp using sterile Potato Dextrose Agar (PDA) media. The fungi were cultured on Potato Dextrose Broth (PDB) for 4 weeks, then partitioned in ethyl acetate and evaporated using rotary evaporator. The host plant organs were macerated in methanol solvent and evaporated. The antioxidant activity was tested by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) method, while the antibacterial activity tested by the Kirby-Bauer diffusion method. Potential compounds were analyzed using Thin Layer Chromatography (TLC), then Liquid Chromatography Mass Spectrometry/Mass Spectrometry (LC-MS/MS) was used to determine the compounds contained in the extract. The results showed that a total of 18 fungal isolates were obtained from the plant, including 5 isolates from the peduncle (CT1-CT5), 7 isolates from the calyx (EP1-EP7), and 6 isolates from the pericarp (BP1-BP6) which were belonged to 11 genera. *Aspergillus* was the dominant fungus as it was obtained from the peduncle, calyx and pericarp. The overall bioactivity of endophytic fungi was better than its host. Antibacterial and antioxidant activities were not comparable, some extracts had weak antibacterial but strong antioxidants. Isolate CT5-(*Diaporthe* sp.) was selected for LC-MS/MS analysis because it showed very strong activity. The results of present research provide information that endophytic fungi of *P. angulata* fruit have great potential to support medical development in the discovery of new therapeutic agents from nature.

Keywords: Antibacterial, antioxidant, *Aspergillus*, biodiversity, *Diaporthe*, endophytic fungi, *Physalis angulata*

INTRODUCTION

Medicinal plants, before the development of modern medical technology, has been used by every civilization in the world to cure diseases. Medicinal plants have also made significant contributions to the discovery of modern medicine (Ilori and Adeneye 2023; Chaachouay and Zidane 2024). In the modern era, even though the production of synthetic drugs is very high, interest in medicinal plants still exists. The main reason is the very small potential for side effects (Alzu'bi et al. 2024; Garza et al. 2024). In certain cases, resistance to synthetic drugs is also a serious problem, as is the case with antibiotics (Abdallah et al. 2023; Zouine et al. 2024). Medicinal plants provide an effective alternative treatment besides synthetic drugs that have become standard in medicine.

Physalis angulata L. (*Ciplukan*) is a traditional medicinal plant in tropical countries such as Indonesia. This plant has bioactive compounds physalin, withanolides, flavonoids, phenolics, squalen-1-ol, phytol, squalene and α-tocopherol (Okmanov et al. 2021; Odusina Onocha 2022). *P. angulata* fruit contains micronutrients, minerals, fiber, vitamin C, and several phenolic acids (ferulic and p-hydroxybenzoic) with antioxidant activity (IC_{50} 14.10 μg/mL) (de Oliveira et al. 2020). Its fruit acts as an antidiabetic, anti-inflammatory, and antibacterial (Wang et al. 2021; Silva et al. 2024). In addition to the pharmacological potential of plants, there are microorganisms that live in plant tissues, known as endophytic fungi. Endophytic fungi are microorganisms that live symbiotically in plant tissues without causing disease to the host. Endophytic fungi enter plant tissues through wounds, stomata or crack in the tissue. These fungi form colonies, create highly diverse microecosystems and obtain nutrients from the host, but not invade to cause tissue damage (Lu et al. 2021; Wen et al. 2022).

The diversity of endophytic fungi contributes to the plant microbiota ecosystem, stimulates the host to produce more effective and diverse secondary metabolites, helps the host's metabolism in environmental stress conditions, thereby increasing plant adaptability. Several studies have revealed that endophytic fungi are able to produce compounds with antioxidant and antibacterial activities that are similar to or even higher than the host (Wang et al. 2022; Jha et al. 2023). Antioxidants are very important in fighting free radicals that cause oxidative stress in cells, which trigger various chronic diseases such as cancer or cardiovascular disease (Kavyani et al. 2024). Meanwhile, the antibacterial activity of endophytic fungi has become a concern in the search for new antibacterial agents to fight pathogenic bacterial infections, especially antibiotic resistance. Studies on the diversity of endophytic fungi from medicinal plants have provided knowledge about the potential of secondary metabolites produced by endophytic fungi (Shamim et al. 2024; Tuerdibieke et al. 2024). Peduncle, calyx and pericarp of *P. angulata* fruit are plant parts that may be habitats for various species of endophytic fungi. Previous studies have revealed that fungal genera *Aspergillus, Penicillium, Fusarium*, *Colletotrichum* and *Rhizoctonia* found in *P. angulata*, are able to produce phenolic compounds with significant antioxidant activity. Several species of endophytic fungi have also been shown to have effective antibacterial activity against both Gram-positive and Gram-negative bacteria (Mahardhika et al. 2021; Palupi et al. 2021).

Each plant tissue has different microecological conditions, thus affecting the composition of endophytic fungi and the production of secondary metabolites (Wen et al. 2022). In general, isolation of endophytic fungi in fruit is taken from the most dominant part, namely the pericarp. However, the fruit of *P. angulata* is unique, its calyx grows large, covering and protecting the pericarp. The objective of this study was to isolate endophytic fungi from different organ (peduncle, calyx and pericarp) of *P. angulata* and evaluate their bioactivity as antibacterials and antioxidants. The results of this study may provide information about the potential of endophytic fungi as a source of new bioactive compounds that can be used in the development of pharmaceutical agents, especially those related to antioxidant and antibacterial therapy.

MATERIALS AND METHODS

Research plant

Samples were collected from Timbangan, North Indralaya, Ogan Ilir, South Sumatra, Indonesia (Latitude: -3.2108257; Longitude: 104.6302623). Plant identification was carried out at Andalas University Herbarium with identification number No. 401/K-ID/ANDA/VI/2024. Fresh *P. angulata* fruits were picked and then separated into peduncle, calyx and pericarp.

Isolation of endophytic fungi

The fruit samples (peduncle, calyx and pericarp) were first cleaned for ten minutes under running water. The plants were then successively submerged in ethanol (95%, 1 minute) in a laminar flow hood, followed by 2-minute treatment with sodium hypochlorite (10%) and immersion in ethanol (95%, 1 minute). The samples were rinsed three times with sterile triple-distilled water for two minutes each time and dried with sterile paper. The samples were cut to a size of 1 × 1 cm, inoculated on sterile PDA medium and incubated for seven days, at 30°C temperature. To obtain pure isolates, the fungi were sorted based on their macroscopic features and inoculated on sterile PDA medium (Rueda-Almazán et al. 2021; dos Reis et al. 2022).

Characterization and identification of endophytic fungi

Fungal characters were observed macroscopically and microscopically. Macroscopic characters consisted texture, topography, pattern, surface color, radial lines, concentric circles, and exudate drops. Microscopic characteristics included color and size of spores, spore form, conidiophore, and hyphae characteristics. Macroscopic characters were obtained by direct observation, while microscopic characters were observed under a microscope using the slide culture method (Hirox MXB-2500REZ) at a magnification of 400×. Characters were matched with references from related books to identify the genus of endophytic fungi (Watanabe 2002, 2010).

Cultivation and extraction of endophytic fungi

The culture was initiated by inoculating six inoculum plugs (6 mm) into 250 mL of sterile PDB. The culture was incubated in a dark room at 25°C for 4 weeks. Then, using filter paper, mycelium and liquid culture were separated. The mycelium was dried at 65°C and stored in a dehydrated state. For seven days, liquid culture was extracted using ethyl acetate: liquid culture (1:1) with daily stirring. The ethyl acetate extract and liquid culture were separated using a separatory funnel and then evaporated in a rotary evaporator at 50°C. The resulting concentrated extract was weighed using an analytical balance (Luo and Tian 2021; Elfita et al. 2023; Oktiansyah et al. 2024).

Extraction of host fruit parts

Fresh *P. angulata* fruit was washed thoroughly with running water. The fruit parts, such as peduncle, calyx and pericarp were cut into pieces, then dried and store in different containers. Each dried simplicia was macerated with 99.9% methanol solvent for 48 hours. The macerate was filtered and evaporated using rotary evaporator to obtain concentrated extract (Duniya et al. 2018).

Antioxidant activity test

Antioxidant test was determined by DPPH method. The endophytic fungi extract samples and positive control (ascorbic acid) were made at concentrations ranging from 1000 to 15.63 µg/mL with methanol as a solvent. One milliliter of sample and three milliliters of DPPH solution (62.5 µM in methanol) were mixed and incubated for 30 minutes in a dark room. The absorbance of the sample was measured at 517 using a spectrophotometer (Kamran et al. 2023). The absorbance value was recorded to determine the percentage of inhibition with the formula:

$$\%\text{ of inhibition activity} = \frac{(Ac - As)}{Ac} \times 100$$ (Baliyan et al. 2022)

Where:
Ac : Control reaction absorbance
As : Sample absorbance testing

The inhibition percentage data was used to find the linear regression equation: y = ax + b which was then used to determine the IC_{50} value.

Antibacterial activity test

Kirby-Bauer method was used to determine antibacterial activity of the endophytic fungi. 400 µg/disc of endophytic fungal extract in Dimethyl Sulfoxide (DMSO) was prepared. 30 µg/disc of tetracycline and pure DMSO were used as a positive control and negative control, respectively. The bacteria used were Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, and gram-negative *Escherichia coli* and *Salmonella typhi*. Each disc was immersed in 400 µg/disc of endophytic fungal extract. The test bacteria were prepared in 0.85% NaCl according to the 0.5 McFarland standard, or about $1.5x10^8$ CFU/mL of bacteria. The test bacteria were inoculated by spread plate on sterile PDA. After 1 hour, paper discs were placed on the media, then 10 µL of fungal extract and control were dropped using a micropipette and incubated at 37°C for 24 hours. Vernier calipers were used to measure the inhibition zone (Patel et al. 2021; Téllez-de-Jesús et al. 2021). Based on the tetracycline inhibition zone, the classification of the extract's inhibition zone under comparison was established using the following formula (Hapida et al. 2021; Oktiansyah et al. 2023):

Weak : $\frac{A}{B}$ x 100% < 50%
Moderate : 50% < $\frac{A}{B}$ x 100% < 70%
Strong : $\frac{A}{B}$ x 100% > 70%

Where:
A : Zone of inhibition for sample (mm)
B : Zone of inhibition for antibiotics (mm)

Antibacterial activity test was expanded to determine Minimum Inhibitory Concentration (MIC), specifically for extracts or pure compounds with the strongest antibacterial activity. The test concentration ranged from 1000 to 7.82 µg/mL. The inhibition zone >9 mm was confirmed as the MIC value while the inhibition zone less than 9 mm was not confirmed.

TLC test

Endophytic fungal extract was made at a concentration of 1% in 99.99% ethyl acetate solvent. Extracts then spotted on a TLC plate using a capillary tube and eluted with an appropriate solvent ratio. The plate was observed under Ultra-Violet (UV) lamp λ 254 to visualize spots formed from compounds in the extract. The chromatogram was sprayed 20% sulfuric acid (H_2SO_4) and heated until spots with different colors were formed which were characteristic of the compounds. Spot patterns and Retention factors (Rf) were observed as indicators of the diversity of compounds in endophytic fungal extracts (Silver 2020).

LC-MS/MS analysis

Endophytic fungal extract (code CT5) 0.5 g was added to a 10-mL volumetric flask, and then methanol was added. After sonication for 30 minutes, it was filtered with a 0.22 µm Polytetrafluoroethylene (PTFE) filter membrane. Furthermore, the filtered sample was inserted into the Ultra-High-Pressure Liquid Chromatography (UHPLC) system. The analysis was carried out using (LC-MS/MS) with a binary pump and a Quadropole Time of Flight (MS-QTOF) mass spectrometer detector with an Electro Spray Ionization (ESI) source. For sample analysis, MS-QTOF was used in positive and negative ionization modes. Samples were taken with a range of 50-1200 Da, a non-polar C18 XTerra® RP 18 column, 3.5 µm, and a column temperature of 40°C. The eluents used were 0.1% formic acid in acetonitrile (A) and 0.1% formic acid in distilled water (B), which were used in an isocratic elution system. The eluent was set at a flow rate of 0.6 mL/min and an injection volume of 10 µL. The isocratic elution system was carried out at 0-1 min 95:5 ratio, 0-1 min 95:5 linear gradient elution A from 95% to 5%, 6-7 min 95:5 ratio, 6-7 min 95:5 linear gradient elution A solvent from 0% to 100%, and 7.5-9 min 95:5 linear gradient elution A solvent from 95% to 5%. By using Unified Laboratory Intelligence (UNIFI) software, the LC-MS/MS mass spectrum data can be interpreted. The software was included the mass spectrum archive of natural product active substances from waters database (Zubair et al. 2021).

RESULTS AND DISCUSSION

Isolation and identification of endophytic fungi

A total of eighteen isolates were isolated from different parts *P. angulata* fruit. The 18 isolates consisted of 5 isolates from peduncle (CT1-CT5), 7 isolates from calyx (EP1-EP7) and 6 isolates from pericarp (BP1-BP6). Colony color and presence of fungal spores from *P. angulata* fruit parts are shown in Figures 1, 2 and 3. The color of the front of colonies were white, cream and brown. The macroscopic and microscopic characteristics of each endophytic fungus appeared to be different, showing typical characters as shown in Tables 1 and 2.

Based on observations of front and reverse side of fungi in Figures 1-3 and morphological characters, macroscopically and microscopically in Tables 1 and 2, endophytic fungi from the fruit parts of *P. angulata* were divided into several genera. Endophytic fungi from peduncle belonged to 5 genera, namely *Cylindrocarpon* sp. (CT1), *Aspergillus* sp. (CT2), *Verticillium* sp. (CT3), *Helicocephalum* sp. (CT4) and *Diaporthe* sp. (CT5). Endophytic fungi from the calyx belonged to 7 genera, namely *Penicillium* sp. (EP1), *Aspergillus* sp. (EP2), *Bispora* sp. (EP3), *Verticillium* sp. (EP4), *Periconia* sp. (EP5), *Fusarium* sp. (EP6) and *Trichoderma* sp. (EP7), whereas fungi from the pericarp belonged to 4 genera, namely *Aspergillus* sp. (BP1, BP3, BP6), *Penicillium* sp. (BP2), *Verticillium* sp. (BP4) and *Paecilomyces* sp. (BP5).

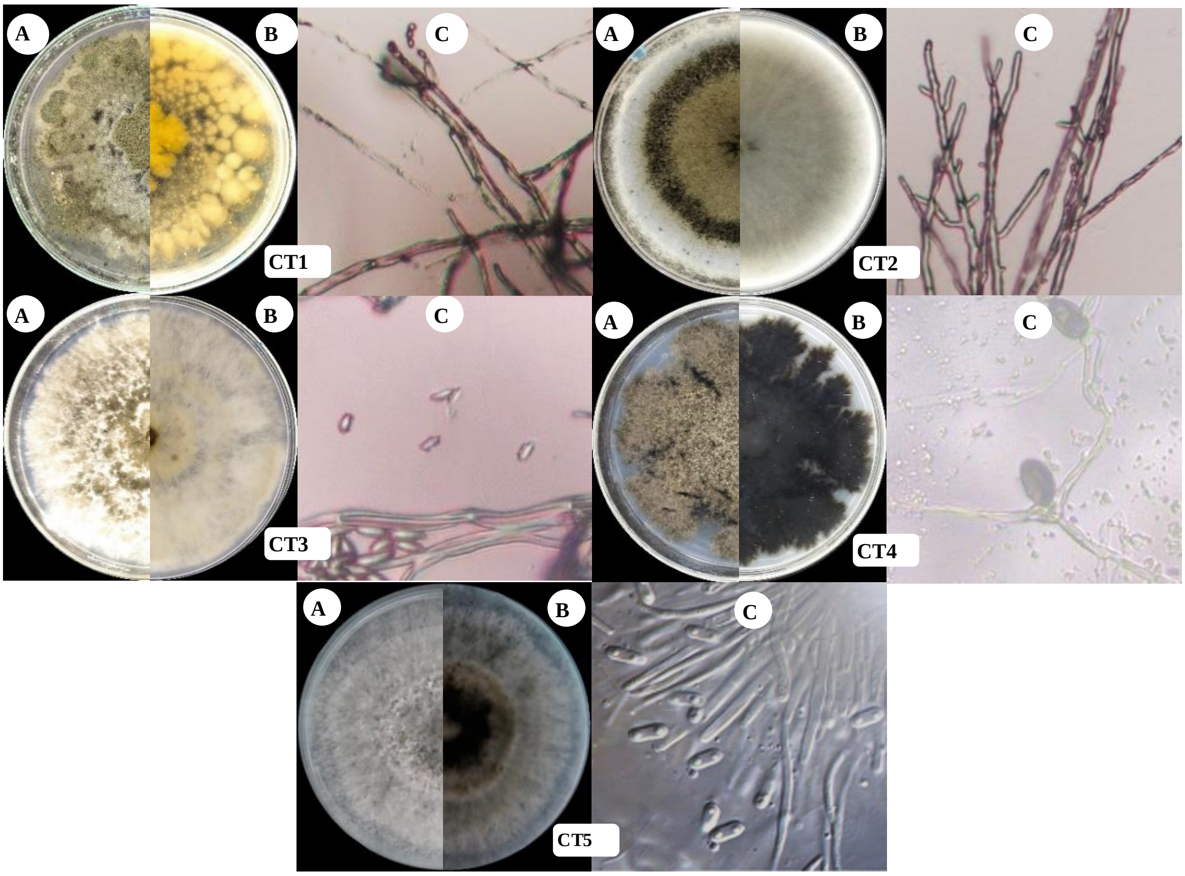

Figure 1. Characteristics of endophytic fungi from *Physalis angulata* fruit peduncle. Macroscopic view: A. Front; B. Reverse; and C. Microscopic view (Magnification 400×)

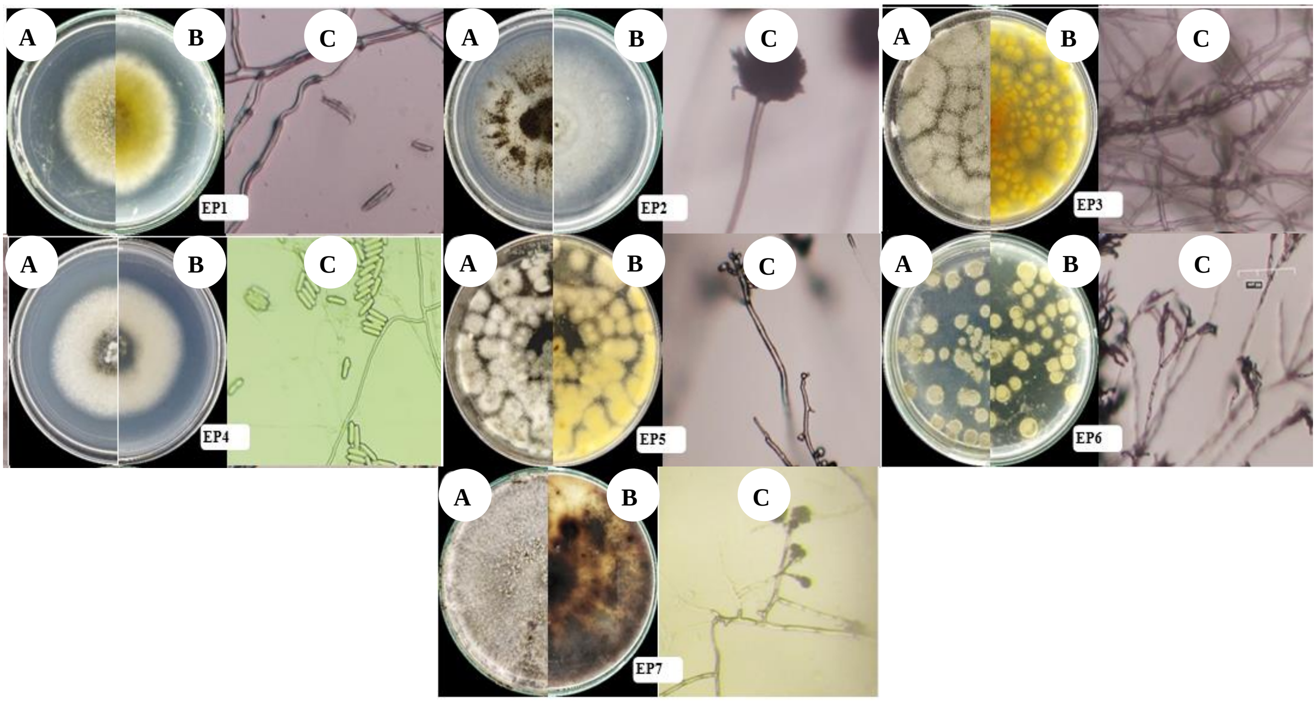

Figure 2. Characteristics of endophytic fungi from *Physalis angulata* fruit calyx. Macroscopic view: A. Front; B. Reverse; and C. Microscopic view (Magnification 400×)

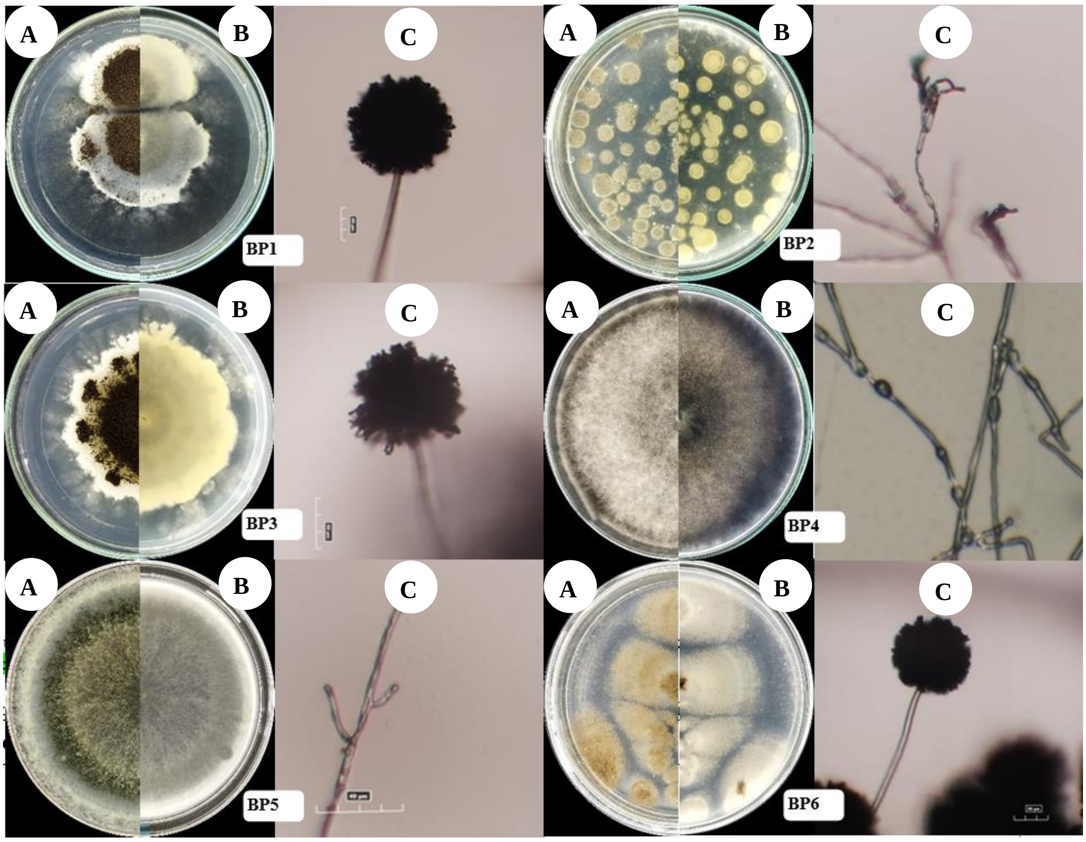

Figure 3. Characteristics of endophytic fungi from *Physalis angulata* fruit pericarp. Macroscopic view: A. Front; B. Reverse; C. Microscopic view (Magnification 400×)

Table 1. Macroscopic characteristics of endophytic fungi from peduncle, calyx and pericarp of *Physalis angulata* fruit

Codes	Surface colony	Reverse colony	Texture	Topography	Patterns	Exudate drops	Radial line	Concentric circle
CT1	Grey-green	Yellow	Cottony	Even	Spread	-	-	-
CT2	White to brown and cream	White-grey	Cottony	Raised	Zonate	-	-	●
CT3	White to grey-green	White to cream	Cottony	Even	Zonate	-	-	●
CT4	Brown	Black	Powdery	Even	Spread	-	-	-
CT5	White	White to brown	Powdery	Even	Spread	-	-	●
EP1	White to yellow-grey	White to yellow	Cottony	Raised	Spread	-	-	-
EP2	White to dark brown	White	Cottony	Raised	Zonate	-	-	●
EP3	Grey	Yellow to orange	Cottony	Even	Spread	-	-	-
EP4	White	White	Cottony	Raised	Spread	-	-	-
EP5	White-grey	Yellow-white	Cottony	Even	Spread	-	-	-
EP6	Cream	White to yellow	Cottony	Even	Spread	-	-	-
EP7	Grey	Grey to dark orange	Powdery	Even	Spread	-	-	-
BP1	White to brown	White	Cottony	Raised	Zonate	-	-	●
BP2	Cream	Cream-yellow	Cottony	Even	Spread	-	-	-
BP3	Cream to black	Cream	Cottony	Raised	Zonate	-	-	●
BP4	White-brown	Black to white-brown	Powdery	Even	Spread	-	-	●
BP5	Dark green to grey-green	White	Powdery	Even	Zonate	-	-	●
BP6	White to cream	White	Cottony	Even	Spread	-	-	-

Notes: ●: Found; -: Not found

Biodiversity of endophytic fungi from *P. angulata* fruit

A total of 18 isolates of endophytic fungi were isolated from the fruits of *P. angulata* (peduncle, calyx and pericarp), which were divided into 11 different genera (Table 3). The peduncle, calyx and pericarp parts of *P. angulata* fruit showed diverse endophytic fungi. Among the 11 genera, *Aspergillus* sp. was the most dominant fungus as it was found in all three organs (5 isolates), followed by *Verticillium* sp. which was also found in all three organs but in lesser numbers (3 isolates). Other genera, like *Paecilomyces* sp., *Trichoderma* sp., *Periconia* sp., *Cylindrocarpon* sp., *Helicocephalum* sp., *Bispora* sp., *Diaporthe* sp., *Fusarium* sp., were found in certain organs. Simpson index of diversity (1-D) showed that the peduncle and calyx had the highest diversity (1) followed by pericarp (0.80). Shannon Index of diversity (HI) showed different results where the highest diversity was in calyx (1.52) and lowest in pericarp (0.99). This shows that calyx was a good habitat for endophytic fungal colonization.

Figure 4 shows the relationship between the main and supporting components in the diversity of fungal colonies in the fruit parts of *P. angulata*. This relationship can be seen from the angle formed between the vectors. In principle, if the angle formed was <90°, the closer the relationship of the fungal colonies or positive correlation between the fruit parts. An angle of 90° indicates no correlation between parts, and an angle >90° indicates a negative correlation. The peduncle formed an angle of <90° to pericarp, but >90° to calyx. This means that fungi growing in the peduncle depend on the fungi in the pericarp, but compete with the fungi in the calyx. Furthermore, calyx made an angle of <90° to peduncle and pericarp. This means that the diversity of fungi in calyx was strongly supported or dependent on the presence of fungi in the peduncle and pericarp. Finally, calyx formed an angle of >90° to peduncle, but <90° to pericarp. This means that fungi in the calyx compete with the fungi in peduncle, but depend on the fungi in the pericarp. Furthermore, fungi that play an important role in the formation of endophytic fungal colonies in the fruit of *P. angulata* is shown in Table 4.

Table 2. Microscopic characteristics of endophytic fungi from peduncle, calyx and pericarp of *Physalis angulata* fruit

Isolates	Spore	Spore form	Hyphae	Characteristic	Species
CT1	Conidia	Cylindrical	Septate	Conidiophores were upright, uncomplex or branched. Chlamydospores were oval to elliptical, and sometimes formed chains	*Cylindrocarpon* sp.
CT2	Conidia	Globose	Septate	Conidiophores were upright, uncomplex, and rough. They bear radiating conidial heads with catenulate conidia in uniseriate	*Aspergillus* sp.
CT3	Conidia	Cylindrical	Septate	Phialides were isolated on aerial or creeping hyphae, carrying spore clusters at the apex. Conidia were single-celled	*Verticillium* sp.
CT4	Sporangia	Ellipsoidal	Septate	Sporangiophores were upright, and gradually narrow from the base to apex. Sporangia were held in clear mucilaginous droplets, and ellipsoidal	*Helicocephalum* sp.
CT5	Conidia	Cylindrical	Septate	Conidiophores were hyaline, straight to sinuous, branched. Conidiomata were pycnidial, solitary or grouped, erumpent, thin-walled	*Diaporthe* sp.
EP1	Conidia	Curved	Septate	Conidiophores resembled regular hyphae, with spore masses at their tips. Conidia were hyaline and phialosporous	*Fusarium* sp.
EP2	Conidia	Globose	Septate	Conidiophores were upright, simple, and rough. They bear radiate conidial heads with catenulate conidia in uniseriate	*Aspergillus* sp.
EP3	Conidia	Cylindrical	Septate	Conidiophores were pale brown, short. Conidia were blastosporous, brown, ellipsoidal, and 2-celled	*Bispora* sp.
EP4	Conidia	Cylindrical	Septate	Phialides were found on aerial or creeping hyphae, carrying spore clusters at the apex. Conidia were single-celled	*Verticillium* sp.
EP5	Conidia	Globose	Septate	Conidiophores were simple, with conidia aggregates at the tip. Conidia were globose and formed by budding	*Periconia* sp.
EP6	Conidia	Ellipsoidal	Septate	Conidiophores were upright, and branched. Conidia were phialidic, light green, oval or nearly spherical	*Penicillium* sp.
EP7	Conidia	Ellipsoidal	Septate	Conidiophores were erect, branched. Conidia were phialosporous, hyaline, ovate	*Trichoderma* sp.
BP1	Conidia	Globose	Septate	Conidiophores were upright, simple, and rough. They bear radiate conidial heads with catenulate conidia in uniseriate	*Aspergillus* sp.
BP2	Conidia	Ellipsoidal	Septate	Conidiophores were upright, and branched. Conidia were phialidic, light green, oval or nearly spherical	*Penicillium* sp.
BP3	Conidia	Globose	Septate	Conidiophores were upright, simple, and rough. They bear radiate conidial heads with catenulate conidia in uniseriate	*Aspergillus* sp.
BP4	Conidia	Cylindrical	Septate	Phialides were found on aerial or creeping hyphae, carrying spore clusters at the apex. Conidia were single-celled	*Verticillium* sp.
BP5	Conidia	Ovate	Septate	Conidiophores (phialides) were simple or rarely branched, erect, hyaline. Conidia were phialosporous 1-celled, slightly apiculate at one end	*Paecilomyces* sp.
BP6	Conidia	Globose	Septate	Conidiophores were upright, simple, and rough. They bear radiate conidial heads with catenulate conidia in uniseriate	*Aspergillus* sp.

The values in Table 4 were defined as significant if above >0.5 or <-0.5. There were 3 main components that determine fungal diversity in the fruit of *P. angulata*, namely peduncle, calyx and pericarp. In peduncle, diversity was influenced by increase population of *Cylindrocarpon*, *Helicocephalum*, *Diaporthe* fungi, or by decrease population of *Bispora*, *Fusarium*, *Penicillium*, *Periconia*, and *Trichoderma* fungi. In calyx, diversity was influenced by increase population of *Aspergillus* and *Verticillium*, or by decrease population of almost all fungi except *Penicillium*. In pericarp, diversity was influenced by increase population of *Verticillium* or decrease population of *Paecilomyces*, while other fungi did not affect the population of fungi in pericarp. It was found that the highest PCA score was in *Aspergillus* fungus (2.90), which means that *Aspergillus* was very dominant in influencing the growth and development of endophytic fungal colonies in *P. angulata* fruit (Table 4).

Antibacterial and antioxidant activity of host plant extracts and endophytic fungal extracts isolated from *P. angulata* fruit

The antibacterial and antioxidant activities of endophytic fungal extracts are shown in Table 5. The range of antibacterial activity was strong (***), moderate (**) and weak (*), while the range of antioxidant activity was very strong (****), strong (***), moderate (**) and weak (*). Both the host and endophytic fungi isolated from *P. angulata* fruit showed potential antibacterial and antioxidant bioactivity, as shown in Figures 5 and 6.

In this research, the strongest antibacterial activity was shown by calyx with a moderate category in bacteria (*S. aureus*, *E. coli* and *S. typhi*) but weak in *B. subtilis*. The host with the weakest activity was the peduncle with a weak category in all test bacteria. The strongest antibacterial activity of endophytic fungi isolates was shown by isolates CT5, EP6 and BP2 with strong and moderate categories in gram-positive and negative bacteria respectively, while the weakest antibacterial activity was observed in isolates CT1 and BP6 in all tested bacteria. The result of antioxidant activity showed that the strongest host was in the pericarp (IC_{50} 79.75 µg/mL), while the weakest was the peduncle (IC_{50} 827.71µg/mL). In endophytic fungi, the strongest activity was observed in isolate CT5 (IC_{50} 14.11 µg/mL) and the weakest in BP2 (IC_{50} 389.38 µg/mL). Overall, the variation of antibacterial and antioxidant activities of endophytic fungi was better than the host (Table 5; Figures 5 and 6). This variation of activity was certainly closely related to the secondary metabolite compounds produced by each endophytic fungus.

The result of TLC of host extract and endophytic fungal extract of *P. angulata* fruit is presented in Figure 7. Based on observations using UV 254 nm, each spot formed on the plate from the host extract and endophytic fungi showed different Retention factor (Rf) values, patterns, and amounts. After being sprayed with 20% sulfuric acid, the colors formed were also different. This shows that the host and endophytic fungi contain different compounds. These compounds were very likely from the phenolic group, especially flavonoids.

Based on the results, the strongest antibacterial and antioxidant activity was found in isolates EP6 and BP2 and isolate CT5, respectively. In Figure 7 isolates EP6, BP2 and CT5 showed major spots, which means that the compounds that played a role were very numerous and dominant. In isolate EP6 and BP2, the Rf value was in the range of 0 to 1, which means that the compounds in both isolates were semi-polar to non-polar. Meanwhile, in the CT5 isolate, the Rf value was 0 to 0.5, which means that the compound in this isolate was semi-polar.

Table 3. Biodiversity of endophytic fungi from *Physalis angulata* fruit

Genus	Parts of *P. angulata* fruit			Total
	Peduncle	Calyx	Pericarp	
Aspergillus	1	1	3	5
Bispora	0	1	0	1
Cylindrocarpon	1	0	0	1
Diaporthe	1	0	0	1
Fusarium	0	1	0	1
Helicocephalum	1	0	0	1
Paecilomyces	0	0	1	1
Penicillium	0	1	1	2
Periconia	0	1	0	1
Trichoderma	0	1	0	1
Verticillium	1	1	1	3
Total fungal isolates	5	7	6	18
Simpson index (D)	0	0	0.20	0.09
Simpson index of diversity (1-D)	1	1	0.80	0.91
Shannon index of diversity (H^I)	1.21	1.52	0.99	1.91

Table 4. PCA scores of endophytic fungi in the fruit of *Physalis angulata*

Genus	Parts of *P. angulata* fruit		
	Peduncle	Calyx	Pericarp
Aspergillus	0.30	2.90	-0.19
Bispora	-1.14	-0.53	0.19
Cylindrocarpon	1.61	-0.63	0.16
Diaporthe	1.61	-0.63	0.16
Fusarium	-1.14	-0.53	0.19
Helicocephalum	1.61	-0.63	0.16
Paecilomyces	0.27	-0.32	-1.56
Penicillium	-1.11	0.40	-0.33
Periconia	-1.14	-0.53	0.19
Trichoderma	-1.14	-0.53	0.19
Verticillium	0.25	1.03	0.85

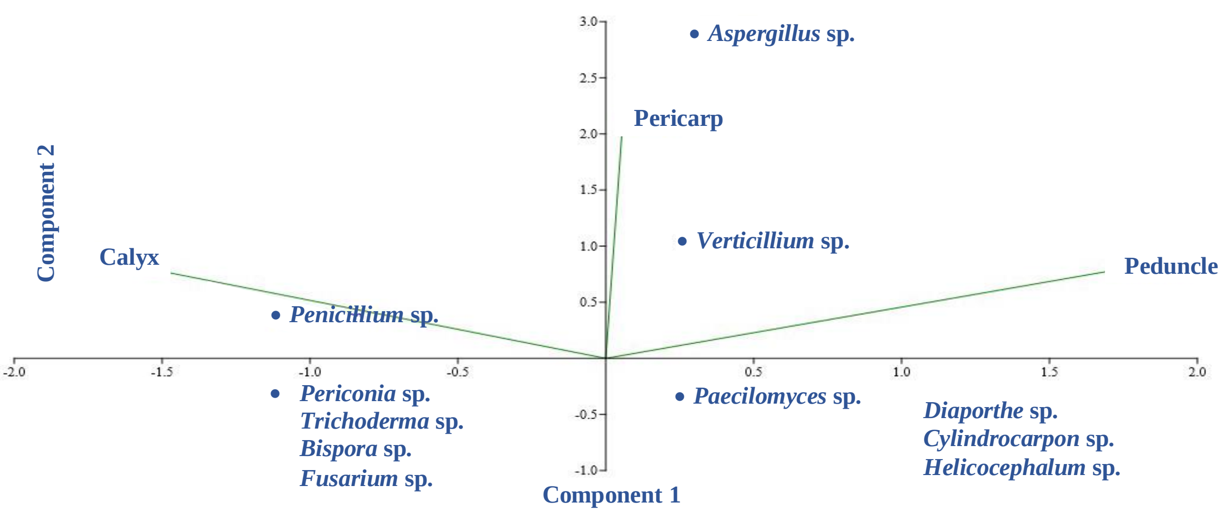

Figure 4. Principal Component Analysis (PCA) of endophytic fungi from *Physalis angulata* fruit

Table 5. Antibacterial and antioxidant activities of host and endophytic fungi isolated from *Physalis angulata* fruit

Samples	Extracts	Antibacterial activity (%)				Antioxidant activity
		S. aureus	*E. coli*	*B. subtilis*	*S. typhi*	IC_{50} (µg/mL)
Host plant	Peduncle (CT)	40.18±1.02*	38.46±0.82*	42.31±2.12*	42.19±0.14*	827.71*
	Calyx (EP)	64.21±2.04**	69.71±0.18**	38.46±0.15*	58.33±0.87**	152.35**
	Pericarp (BP)	48.20±1.43*	57.69±2.56**	54.33±0.18**	54.17±0.18**	79.75***
Endophytic fungi	CT1	40.50±0.18*	38.94±0.18*	39.42±0.18*	45.83±1.30*	108.90**
	CT2	58.25±0.71**	62.02±0.18**	73.08±0.65***	58.85±0.18**	192.02**
	CT3	64.00±2.64**	57.69±1.78**	57.69±1.83**	50.85±0.98**	242.12**
	CT4	60.25±1.26**	65.38±2.54**	69.71±0.18**	79.17±1.22***	38.89***
	CT5	72.07±1.24***	71.63±2.65***	72.12±2.09***	68.75±0.18**	14.11****
	EP1	60.28±1.50**	57.69±1.32**	57.69±2.70**	75.52±0.18***	245.63**
	EP2	44.52±0.18*	54.33±0.18**	57.69±0.87**	66.67±2.17**	242.75**
	EP3	48.55±2.04*	42.31±0.56*	58.17±0.18**	58.33±0.34**	109.70**
	EP4	52.30±1.03**	38.94±0.18*	38.94±0.18*	54.17±0.65**	303.25**
	EP5	48.00±1.43*	81.25±0.18***	57.69±0.87**	62.50±2.82**	112.09**
	EP6	72.02±1.50***	76.92±2.86***	62.02±0.18**	62.50±1.05**	195.90**
	EP7	56.60±1.07**	76.92±1.23***	50.85±1.80**	54.69±0.18**	103.67**
	BP1	48.50±0.18*	50.19±0.84**	69.23±1.23**	58.33±1.64**	205.44**
	BP2	68.23±1.21**	65.87±0.18**	77.40±0.18***	75.00±1.85***	389.38**
	BP3	48.02±0.25*	61.54±1.50**	65.38±1.60**	63.02±0.18**	147.99**
	BP4	40.50±0.18*	54.33±0.18**	38.94±0.18*	45.83±1.50*	101.72**
	BP5	52.50±2.18**	61.54±1.08**	76.92±2.27***	54.17±1.60**	70.49***
	BP6	44.20±1.23*	46.15±2.03*	50.40±1.08*	46.35±0.18*	161.51**
Positive control	Tetracycline	100±0.00***	100±0.00***	100±0.00***	100±0.00***	Ascorbic acid 12.07****

Notes: Fungal isolates CT1-CT5 were from peduncle, fungal isolates EP1-EP7 were from calyx and fungal isolates BP1-BP6 were from pericarp. Percentage of antibacterial activity: ***: Strong >70%; **: Moderate 50%-70%; *: Weak <50%. Antioxidant activity IC_{50} (µg/mL): ****: Very strong <20 µg/mL; ***: Strong 20-100 µg/mL; **: Moderate 100-500 µg/mL; *: Weak >500 µg/mL

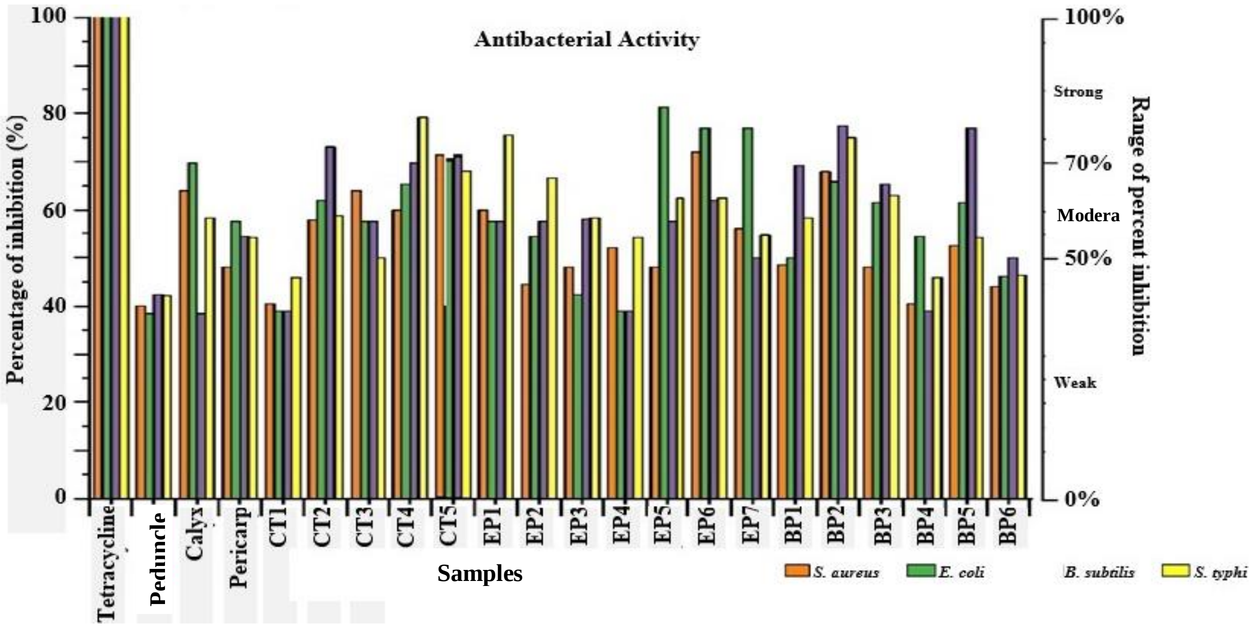

Figure 5. Comparison graph of antibacterial activity of host and endophytic fungi isolated from *Physalis angulata* fruit

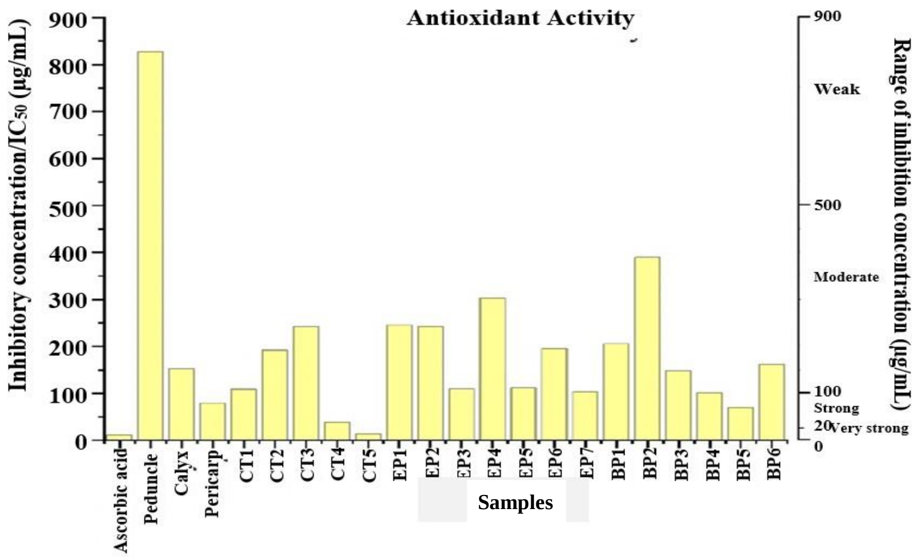

Figure 6. Comparison graph of antioxidant activity of host and endophytic fungi isolated from *Physalis angulata* fruit

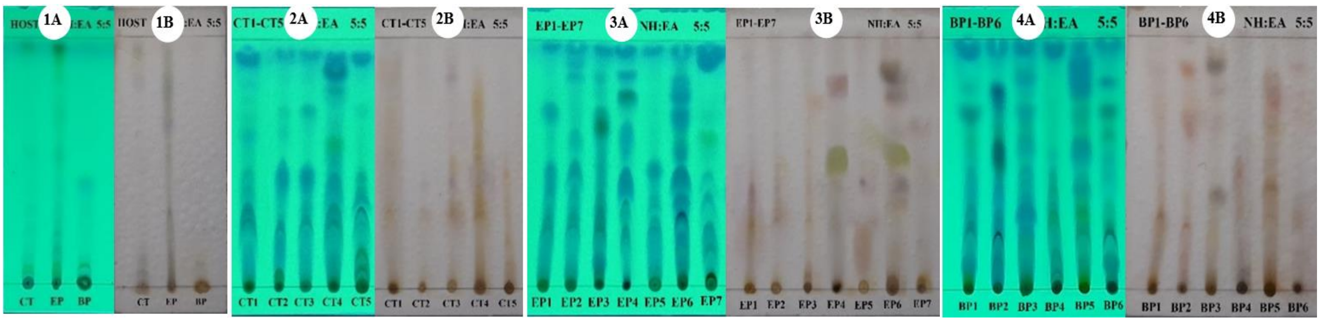

Figure 7. TLC from fruit extra cts and endophytic fungi extracts: 1. Host plant extract (CT: Peduncle, EP: Calyx, BP: Pericarp); 2. Endophytic fungal extract from the peduncle (CT1-CT5); 3. Endophytic fungal extract from the calyx (EP1-EP7); 4. Endophytic fungal extract from the pericarp (BP1-BP6). A. TLC under UV light; B. TLC after being sprayed 20% H_2SO_4

Compound analysis using LC-MS/MS

Figure 8 shows the potential peak in the LCMS/MS chromatogram of isolate CT5. The peak and retention time of the compound were detected at 2.36 to 15.72 minutes. The compound prediction from the potential peak in Table 6 shows that the compound successfully identified from isolate CT5 was 1-Salicylate glucuronide; N-(2H-Tetrazol-5-yl)hydrazinecarboxamide; Bergenin; Quercetin; 2,4,5-Triethoxybenzophenone; Dabigatran etexilate;(2Z)-7-(Octyloxy)-2,11,20,22,23,25,33,34,35,36-decaazaoctacyclo [24.6.1.1~3,10~.1~12,19 ~.1~21,24~.0~4,9~.0~13,18~.0~27,32~]hexatriaconta-1(33), 2,4,6,8,10(36),11,13,15,17,19(35),20,24(34),25,27,29,31-heptadecaene; and 3-hexanoyl-NBD Cholesterol. In addition to quercetin, the majority of these compounds were not found in their hosts and were classified as new compounds obtained from endophytic fungal extracts. Isolate CT5 was detected as *Diaporthe* sp. (Table 5). The antioxidant activity of isolate CT5 was in the very strong range (IC_{50} 14.11 µg/mL) almost approaching the activity of the positive control ascorbic acid (IC_{50} 12.07 µg/mL), while the host of CT5, peduncle, showed antibacterial activity below 50% and weak antioxidants (IC_{50} 827.72 µg/mL). This fact demonstrates that the endophytic fungus *Diaporthe* sp. has the potential to be a new very strong antioxidant agent.

Discussion

This research identified 18 isolates of endophytic fungi from the peduncle, calyx and pericarp of *P. angulata* fruit. The endophytic fungi that were successfully isolated were divided into 11 genera, namely *Aspergillus, Bispora, Cylindrocarpon, Diaporthe, Fusarium, Helicocephalum, Paecilomyces, Penicillium, Periconia, Trichoderma*, and *Verticillium*. Among the 11 genera of endophytic fungi, genera *Aspergillus* and *Verticillium* were found in all fruit organs. This provides evidence that the two genera of fungi do not require a specific habitat in a plant tissue. Specifically, the genus *Aspergillus* was found quite a lot in all three organs, which means that this fungus is very adaptive, able to grow and develop in different conditions, positions, anatomical structures, and physiology of host organs.

Table 6. Predicted compounds from major and associated peaks in the LCMS/MS chromatogram of isolate CT5

No.	Retention Time (RT)	% Area	m/z $[M + H]^+$	Formula	Identification of the compounds	Fit Conf %
3	2.36	0.82	315.0716	$C_{13}H_{14}O_9$	1-Salicylate glucuronide	35.63
4	2.99	0.56	144.0634	$C_2H_5N_7O$	N-(2H-Tetrazol-5-yl)hydrazinecarboxamide	99.62
5	4.11	4.11	329.0873	$C_{14}H_{16}O_9$	Bergenin	76.53
7	5.68	6.17	303.0505	$C_{15}H_{10}O_7$	Quercetin	89.11
10	9.30	3.63	315.1596	$C_{19}H_{22}O_4$	2,4,5-Triethoxybenzophenone	47.20
11	10.60	2.23	628.3247	$C_{34}H_{41}N_7O_5$	Dabigatran etexilate	79.40
12	11.34	2.96	595.2682	$C_{34}H_{30}N_{10}O$	(2Z)-7-(Octyloxy)-2,11,20,22,23,25,33,34,35,36-decaazaoctacyclo[24.6.1.1~3,10~ .1~12,19~.1~21,24~.0~4,9~ .0~13,18~.0~27,32~]hexatriaconta-1(33),2,4,6,8,10(36),11, 13,15,17,19(35),20,24(34),25,27,29,31-he ptadecaene	91.45
16	15.72	31.46	663.4485	$C_{39}H_{58}N_4O_5$	3-hexanoyl-NBD Cholesterol	96.95

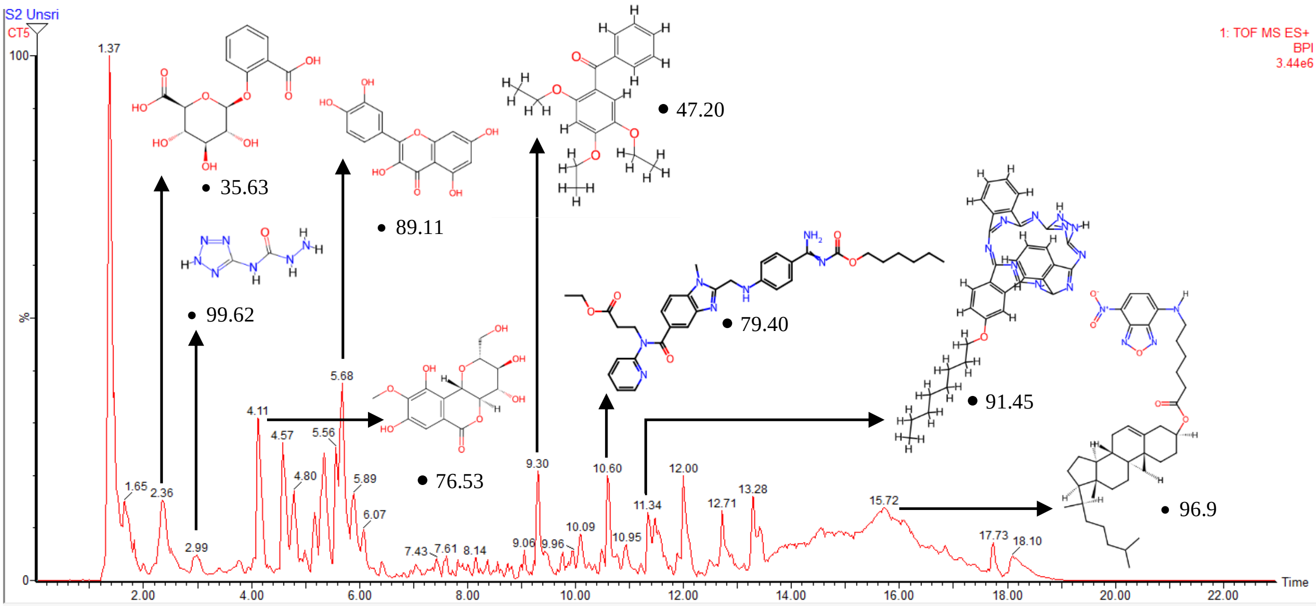

Figure 8. LC-MS/MS chromatogram of isolate CT5

Based on the analysis of endophytic fungi diversity, Simpson Diversity Index (1-D) and Shannon Diversity Index (H') provide evidence of the highest fungal diversity in the calyx, followed by the peduncle and finally the pericarp. This means that calyx was a suitable organ as a habitat for endophytic fungi to grow. Endophytic fungi obtain sufficient nutrients from the host for their survival and fungi help the host to survive and remain productive in various environmental conditions (Wu et al. 2019; Bononi et al. 2020). Endophytic fungi enhance plant growth and provide protection against pests and pathogens through various mechanisms. They produce secondary metabolites that suppress/reduce the negative effects of plant pathogens, including volatile compounds that can suppress pathogen growth (Fontana et al. 2021; Song et al. 2024). Endophytic fungi also protect their host plants by inducing plant defense mechanisms (Yan et al. 2019; Yuan et al. 2021). They are able to play a role in reducing the stress levels of abiotic and biotic environmental factors, such as drought, salinity, heavy metals carried by the environment, floods, extreme temperatures, predators and pathogens. Endophytic fungi found in the fruit of *P. angulata* also play a role in protecting organs from attacks by predatory pests or pathogenic microorganisms. Because the calyx functions to protect the pericarp that stores seeds for plant survival, it is very appropriate if the diversity of endophytic fungi is quite high in this section (Su et al. 2021; Grabka et al. 2022).

In this study, one of the dominant fungi that influences the diversity of *P. angulata* fruit was *Aspergillus*. It is a genus of fungi from the Ascomycota phylum that is quite abundant in the universe. *Aspergillus* is a genus of fungi consisting of more than 300 species, many of which have important roles in various aspects of life, both beneficial and harmful. *Aspergillus* fungi have an asexual/anamorphic reproductive stage and a sexual/teleomorphic stage. *Aspergillus* is one of the fungal genera commonly found in plant tissues, both as endophytes and pathogens (Abdel-Azeem et al. 2019; Réblová et al. 2020). In this research, *Aspergillus* was found as a endophytic fungi that lived and formed colonies in *P. angulata* fruit tissue without causing damage or disease. *Aspergillus* endophytic fungi isolated from *P. angulata* fruit had the highest number and were found in the peduncle, calyx and pericarp because they were supported by the anamorph and teleomorph properties that made this fungus easy to adapt and reproduce. *Verticillium* fungi are also found in all three organs but not as much as *Aspergillus*. In addition to being endophytic, *Aspergillus* can also be pathogenic to humans, animals and horticultural plants (Walsh et al. 2018; Vuong et al. 2024; Zakaria 2024).

The bioactivity of endophytic fungi in this study was better than the host. The antibacterial activity of endophytic fungi was strongest in isolates CT5, EP6 and BP2 with a range of moderate to strong activity in each gram of test bacteria. The antioxidant activity of endophytic fungi was very strong approaching the positive control, namely in CT5 (IC_{50} 14.11 μg/mL), followed by strong activity, namely isolates CT4 (IC_{50} 38.89 μg/mL) and BP5 (IC_{50} 70.49 μg/mL). The strong activity of isolates EP6, BP2, CT5, CT4 and BP5 was supported by active compounds in endophytic fungi. Spots on the TLC plate showed major spots and with many variations. The major spots with many variations indicate that the compounds in each endophytic fungus synergize to increase the bioactivity of the fungal extract as an antibacterial and antioxidant. The host *P. angulata* has compounds physalin, flavonoids, neochlorogenic acid, chlorogenic acid, styrene, methionine, physoperuvine, peruvianoxide, withanolide, and deoxyphysalolactone (Cuong et al. 2020; Novitasari et al. 2024). Coevolution in endophytic fungi means that they have the potential to produce the same compounds as their hosts (Alam et al. 2021). In general, the compounds contained in fungi cause balanced bioactivity between antibacterial and antioxidant. However, in this study, it was slightly different from most endophytic fungi activities as antibacterial and antioxidant. The fungal extracts with strong antibacterial had weak antioxidants, while fungi with weak antibacterial activity had strong antioxidants. This is thought to be because the compounds contained have specific compound interactions in one activity, as antibacterial only or as antioxidants.

Endophytic fungi in this study with strong antibacterial activity were *Fusarium* sp. and *Penicillium* sp., while very strong antioxidants in *Diaporthe* sp. and strong in *Helicocephalum* sp. and *Paecilomyces* sp. Fungi from the same genus in other studies showed significant activity. *Fusarium tricinctum* isolated from *Actinidia chinensis* plants were able to produce imidazole alkaloid compounds (fusaritricines). These compounds were able to inhibit the growth of *Pseudomonas syringae* pv. *actinidiae* (Psa) bacteria with MIC between 25 and 50 μg/mL (Ma et al. 2022). *Fusarium solani* DO7, was produced a type of polysaccharide compound with MIC against *E.coli*, *S. aureus*, *B. subtilis*, *Salmonella* sp., *B. cereus* and *Alcaligenes* of 20, 15, 25, 25, 35 and 30 ug/mL, respectively (Zeng et al. 2019). *Penicillium* sp. has long been known as a producer of penicillin antibiotics. One type of *Penicillium* sp. Z-16 is able to produce benzophenone derivative compounds that can inhibit the growth of *S. aureus* with an MIC of 62.5 μg/mL (Huang et al. 2024). The fungus *Penicillium sclerotiorum* isolated from the stem of *Taxus wallichiana* var. *chinensis* (Pilger) Florin, also plays a role in producing medicinal compounds. This fungus produces new chromone analog and pyrrole alkaloid compounds that are able to fight carbapenem-resistant *Pseudomonas aeruginosa* and *Enterococcus faecium* with MICs of 3.13 μg/mL each (Liao et al. 2022). The researchers proved that *Fusarium* sp. and *Penicillium* sp. fungi isolated from *P. angulata* fruit had strong antibacterial activity. Furthermore, several studies on other endophytic fungi similar to the endophytic fungi in this research, showed strong antioxidant activity.

Helicocephalum sp. is a nematophagous fungus from the Helicocephalidaceae family, Zoopagomycota division, which is parasitic mainly on nematodes and nematode eggs. *Helicocephalum* sp. with the character of hyaline sporangiophores, erect, gradually tapering from base toward apex. Sporangia borne in transparent mucilaginous water drops, ellipsoidal, yellowish brown (Watanabe 2002, 2010; Jamali 2015). *Helicocephalum* sp. is rarely reported and is a new discovery with its antibacterial and antioxidant activities.

Diaporthe fungi, for example the species *Diaporthe schini* produces compounds 1,4-diaza-2,5-dioxo-3-isobutyl bicyclo[4.3.0]nonane and benzeneethanol. Compounds from endophytic fungi *D. schini* have an inhibition rate of 96.62% against DPPH (da Rosa et al. 2020). Endophytic fungi *Diaporthe fraxini* in yeast extract sucrose broth supplemented with 5 mg/L rosmarinic acid medium, have strong antioxidant activity (IC_{50} 7.11 µg/mL) against DPPH with ascorbic acid as a comparator (IC_{50} 2.31 µg/mL) (Tan et al. 2022). The fungus *Diaporthe perseae* isolated from the *Pongamia pinnata* plant produces *isochromophilone G* compounds with an antioxidant activity of IC_{50} 7.3±0.07 µmol/mL against DPPH and its comparator ascorbic acid with IC_{50} 4.8±0.04 µmol/mL (Niaz et al. 2021).

Furthermore, fungi from the genus *Paecilomyces*, namely *Paecilomyces variotii* have a positive interaction with *Pleurotus floridanus* in the Solid State Fermentation System (SSFS) in the decomposition of difficult-to-dissolve substrates. The application of this SSFS can be in the decomposition of waste or fermentation of certain products. The advantages of *P. variotii* fungi include having better catalase (CAT) enzyme activity, having higher phenolic and flavonoid content, higher reducing power, and higher DPPH radical scavenging activity than *P. floridanus* (El-Fallal et al. 2022). *P. variotii* isolated from *P. angulata* stems produces a compound of the type 4,5,6-trihydroxy-2',3',5',6-tetramethyl-2',3'-dihydro-[3,4'-bipyranylidene]-2-one which is able to trap DPPH radicals with an IC_{50} of 23.82 µg/mL (Wahyudi et al. 2025). *Paecilomyces cicadae* fungus is able to produce polysaccharides, nucleosides, cordycepin, ergosterol, myriocin, Cordyceps acid, amino acids, terpenoids, and flavonoids. Heteropolysaccharide type polysaccharide (PCIPS3) isolated from *P. cicadae* has DPPH, Superoxide anion and hydroxyl radical scavenging activity with inhibition percentages reaching 90%, 80% and 87% respectively at a concentration of 1.2 mg/mL (Fenhui et al. 2022; Shi et al. 2022; Feiqian et al. 2023). Based on several studies by these experts, it is proven that fungi from the genus *Helicocephalum*, *Diaporthe* and *Paecilomyces* have strong antioxidant activity, related to fungi from the same genus in this research.

The results of TLC test showed that endophytic fungi from parts of *P. angulata* fruit produced very diverse secondary metabolites. Result showed that several isolates had many major and minor stains which were markers of the secondary metabolites produced by the endophytic fungi in great abundance. Of these fungi, isolate CT5 was selected for LC-MS/MS analysis because its antioxidant activity was very strong. Based on LC-MS/MS analysis, the compounds produced by isolate CT5 namely 1-Salicylate glucuronide; N-(2H-Tetrazol-5-yl)hydrazine-carboxamide; Bergenin; Quercetin; 2,4,5-Triethoxy-benzophenone; Dabigatran etexilate; (2Z)-7-(Octyloxy)-2,11,20,22,23,25,33,34,35,36 -decaazaoctacyclo[24.6.1.1~3, 10~.1~12,19~.1~21,24~.0~4, 9~.0~13,18~.0~27,32~]hexatriaconta-1(33),2,4,6,8,10(36), 11,13,15,17,19(35),20, 24(34), 25,27,29,31-heptadecaene; and 3-hexanoyl-NBD Cholesterol. Compared to the host, the compound was not found in the host fruit of *P. angulata*, from the peduncle, calyx or pericarp parts. Compounds produced by *P. angulata* fruit include lauric acid, methyl hexadecanoate, palmitic acid, linoleic acid, methyl ester, linoleic acid, diisooctyl ester, α-tocopherol, phenolic acid dan 1,2-benzenedicarboxylic acid (de Oliveira et al. 2020; Nguyen et al. 2021; Pillai et al. 2022; Zhao et al. 2024). However, quercetin, which is a type of flavonoid compound, is produced by the host.

The compounds found in the CT5 isolate had both antioxidant and antibacterial activities. The compound 1-Salicylate glucuronide is a beta-D-glucosiduronic acid which is a glucuronide conjugate of salicylic acid. This compound is functionally related to salicylic acid and is the conjugate acid of 1-salicylate O-glucuronide(1-). Salicylic acid can protect watermelon plants from oxidative stress by reducing the production of MDA and ROS, and acting directly as an antioxidant to clean up reactive oxygen species and/or indirectly modulate the redox balance through the activation of the antioxidant response (Singh 2023; Yang et al. 2024). Salicylic acid can also act as an elicitor in spinach leaves, thereby increasing the production of phenolic acids and flavonoids which function to increase the antioxidant function of spinach leaves, provide protection against environmental stress and increase nutritional content (Moustafa-Farag et al. 2020). Another role of salicylic acid is as a hand sanitizer because of its activity as an antibacterial for *S. aureus* and *E. coli* (Song et al. 2022). Bergenin is a trihydroxybenzoic acid. Bergenin compounds isolated from the *Endopleura uchi* plant are able to trap DPPH free radicals with an IC_{50} of 12.04 to 24.20 µg/mL (Muniz et al. 2020). Bergenin is also able to inhibit the development of 4 test bacterial strains as in this research and acts as a strong inhibitor of the alkaline phosphatase isoenzymes h-TNAP and h-IAP, both of which are indicative of liver damage (Nyemb et al. 2018; Oktiansyah et al. 2019). Dabigatran etexilate is the main compound used in anticoagulant drugs. Tests on mice have shown that dabigatran etexilate can inhibit Reactive Oxygen Species (ROS), a free radical in the body that is a byproduct of mitochondria (Iannucci et al. 2020; Falco et al. 2023). Dabigatran is also able to reduce the virulence of *S. aureus* which causes *Staphylococcus aureus Bacteremia* (SAB) (Butt et al. 2021). Quercetin is a pentahydroxy-flavone, one type of flavonoid that is abundant in nature, acts as an antibacterial agent, antioxidant, protein kinase inhibitor and antineoplastic agent (Qi et al. 2022; Azeem et al. 2023; Xiang et al. 2024).

In conclusion, a total of 18 isolates of endophytic fungi were found associated with parts of *P. angulata* fruit organs. The extracts of these endophytic fungi showed better antioxidant and antibacterial activity than their hosts. Based on macroscopic and microscopic, CT5 code fungal isolate was identified as *Diaporthe* sp. The CT5 code endophytic fungal extract isolate was selected for the LC-MS/MS test because its antioxidant activity was the highest compared to the others. The results of LC-MS/MS test showed the presence of quercetin compounds which are well known as strong antioxidant compounds. Based on macroscopic and microscopic, the CT5 code fungal isolate was identified as *Diaporthe* sp. The results of this study provide evidence that endophytic fungi from parts of *P. angulata* fruit organs have the potential to be new antibacterial and antioxidant therapeutic agents.

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