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Antifungal Activity of Endophytic Bacteria Isolated from Dayak Onion (*Eleutherine bulbosa*) Against *Candida albicans*

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Candidiasis is a fungal infection due to a decrease in the immune system caused by *Candida* spp. In general, candidiasis is treated with antifungal drugs, but uncontrolled use can result in the emergence of drug resistance and toxicity. Endophytic bacteria have the potential to be biological control agents against various fungal infections including candidiasis. This study aims to determine the antagonistic activity of endophytic bacteria isolated from Dayak onions and the antifungal activity of its cell-free supernatant (CFS) against *Candida albicans*. Thirteen isolate strains of endophytic bacteria were used in this study. Antagonistic activity was tested using the agar plug diffusion method. Endophytic bacteria that showed antagonistic activity against *C. albicans* were cultivated in Nutrient Broth media to produce CFS. The antifungal activity of CFS was tested using the Kirby–Bauer disk diffusion method. The results indicated that six isolates of endophytic bacteria from dayak onions have antagonistic activity against *C. albicans*. CFS from strain CED4 has a strong antifungal activity against *C. albicans* with a clear zone diameter of 18.5 mm. Further studies are needed to determine the antifungal compounds produced by CED4 isolates for the development of anticandidal.

Key words: Anticandidal, Antagonistic, CFS, Endophyte

INTRODUCTION

Fungal infections occur in 20-25% of the world's population and are a common infectious problem in tropical and humid countries including Indonesia. Fungal infections can occur on the skin, hair, and nails. One fungal infection known as Candidiasis is generally caused by *Candida* spp.. Candidiasis is an infection that occurs due to a decrease in the immune system caused by *Candida*. It is infectious and can attack all age (Soetojo & Astari 2016).

About 90% of candidiasis is caused by *C. albicans* which is a commensal pathogen and can be an opportunistic organism in the gastrointestinal, oropharyngeal, and vaginal tracts. *C. albicans* can also be invasive through blood circulation. This fungus can infect the kidneys and attach to prosthetic heart valves. Invasive candidiasis (IC) includes several severe complications such as endophthalmitis, meningitis, peritonitis, pancreatitis, endocarditis, arthritis, central nervous system infection, and osteomyelitis (Uppuluri *et al.* 2017).

In general, treatment of candidiasis is carried out using antifungal drugs, but uncontrolled use is thought to lead to the emergence of drug resistance and toxicity. Continuous consumption of antifungal drugs results in suppression of the immune system for patients who use antifungal drugs as prophylaxis. The toxicity effects caused by the use of several antifungal drugs include hemolytic anemia, digestive dysfunction, and kidney and liver damage (Novilla *et al.* 2017).

Cases of *Candida albicans* resistance to several antifungal drugs (multidrug resistance) continue to increase (Murray *et al.* 2015). A recent study showed an increase in infections caused by resistant fungal species, especially *C. albicans* that are resistant to several antifungal drugs such as azoles, echinocandins (Pristov & Ghannoum 2019), polyenes, and flucytosine (Bhattacharya *et al.* 2020). Therefore, it is necessary to find new anticandidal drugs as an alternative for the prevention and treatment of candidiasis which is relatively safer. One of the efforts that can be made is to use bioactive compounds produced by endophytic bacteria isolated from medicinal plants.

Endophytic bacteria have the potential to be biocontrol agents against various fungal infections. Several previous studies reported that endophytic bacteria isolated from various plant species have antimicrobial activity (Beiranvand *et al.* 2017;

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Sharma & Mallubhotla 2022; Boonman *et al.* 2023). Endophytic bacteria isolated from the medicinal plant, *Phyllanthus niruri*, have anticandida activity (Chellaram 2015). In addition, *Equisetum arvense* L. also has anticandida effects against *C. albicans* and *C. glabrata* (Das *et al.* 2017). The anticandidal potential of endophytic bacteria depends largely on the type of plant and its chemical composition.

Dayak onion (*Eleutherine bulbosa*) is a medicinal plant that has potential as antimicrobial, anti-inflammatory, antioxidant (Shi *et al.* 2019), and antiobesity (Fauzi *et al.* 2019). Endophytic bacteria isolated from Dayak onions have been reported to have several pharmacological effects including antioxidants (Shabira *et al.* 2022) and antibacterial (Naibaho *et al.* 2023a). The utilization of endophytic bacteria of dayak onion is expected to produce the same bioactive compounds as their host plants (Rahayu *et al.* 2019). Until now, there is no information on the antifungal effect of Dayak onion endophytic bacteria against *C. albicans*. Thus, this study aims to determine the antagonistic activity of endophytic bacteria isolated from dayak onion against *C. albicans* and to determine the antifungal activity of cell-free supernatants (CFS) of endophytic bacteria from dayak onion against *C. albicans*.

MATERIALS AND METHODS

Material. The research was conducted at the Laboratory of Microbiology, Pusat Pengembangan Iptek dan Inovasi Gambut (PPIIG) Universitas Palangka Raya. There were thirteen bacteria isolates of dayak onion (*Eleutherine bulbosa*) used in this study, namely CED1, CED2, CED3, CED4, CED9, CED13, CEA1, CEA2, CEA3, CEU4, CEU5, CEU6 and CEU7. The thirteen isolates were isolated from the dayak onion plant in a previous study (Naibaho *et al.* 2023a).

Subcultures of Endophytic Bacteria and *Candida albicans*. All endophytic bacteria isolates were subcultured on Nutrient Agar (NA) media and incubated at 30°C for 24-48 hours while *C. albicans* was subcultured on Potato Dextrose Agar (PDA) media and incubated at 25°C for 48 hours (Naibaho *et al.* 2023a).

Antagonism Test of Endophytic Bacteria against *Candida albicans*. The antagonistic test was carried out using the agar plug diffusion method. Each endophytic bacterial was suspended in 5 ml of 0.9% NaCl solution. The suspension was equaled to standard McFarland 0.5 (1.5×10^8 CFU/ml). Then the endophytic bacterial suspension was streaked tightly on the NA plate surface with a sterile cotton swab and incubated at 30°C for 48 hours. *C. albicans* isolate was suspended in a tube containing 5 ml of 0.9% NaCl and then spread tightly using a sterile cotton swab over the surface of the PDA media. After incubation, the NA medium which has been grown by endophytic bacteria was cut aseptically with a sterile cork borer and then deposited on the surface of the PDA plate previously inoculated by *C. albicans.* Pieces of NA containing nystatin 60µg/ml were used as positive controls while pieces of sterile NA were used as negative controls. Then, all petri dishes were incubated at 30°C for 24-48 hours. The antagonistic activity of the endophytic bacteria was detected by the appearance of the clear zone formed around the agar plug (Balouiri *et al.* 2016; Naibaho *et al.* 2023a).

Cell-Free Supernatant Produced by Endophytic Bacteria. Endophytic bacteria isolates that showed antagonistic activity against *C. albicans* were cultivated in Nutrient Broth (NB) media. One loop of endophytic bacteria isolates was inoculated into an Erlenmeyer flask containing 100 ml NB then incubated on an incubator shaker at 30°C for 5 days. The bacterial culture was centrifuged at 6,000 rpm for 20 minutes to separate the supernatant from the cells. Then, the supernatant is sterilized with a syringe filter (Sulistiyani *et al.* 2016).

Antifungal Activity Test of Cell-Free Supernatant Against *Candida albicans*. The antifungal activity assay of cell-free supernatant (CFS) was carried out using the Kirby–Bauer disk diffusion method. Disc paper was soaked in the cell-free supernatant of bacterial isolate, then placed on the surface of PDA media which had been inoculated with *C. albicans* suspension. Nystatin was used as a positive control while distilled water was used as a negative control. Then, all petri dishes were incubated at 28°C for 48 hours. The antifungal activity of cell-free supernatant was detected by the appearance of the clear zone formed around the paper disc (Naibaho *et al.* 2023b).

RESULTS

Antagonistic Activity of Endophytic Bacteria Against *Candida albicans*. Endophytic bacteria have different responses against *C. albicans*. Based on the agar plug diffusion method, 6 out of 13 isolate strains showed antagonistic activity against *C. albicans*. They were CEA1, CED3, CED4, CED9, CEU6, and CEU7. Antagonistic activity is characterized by the formation of a clear zone around the agar plug (Figure 1). The wider the diameter of the clear zone formed, the higher the antagonistic activity. Strain CEU6 produced the widest clear zone (19.6 mm). The results of the antagonistic test are shown in Table 1.

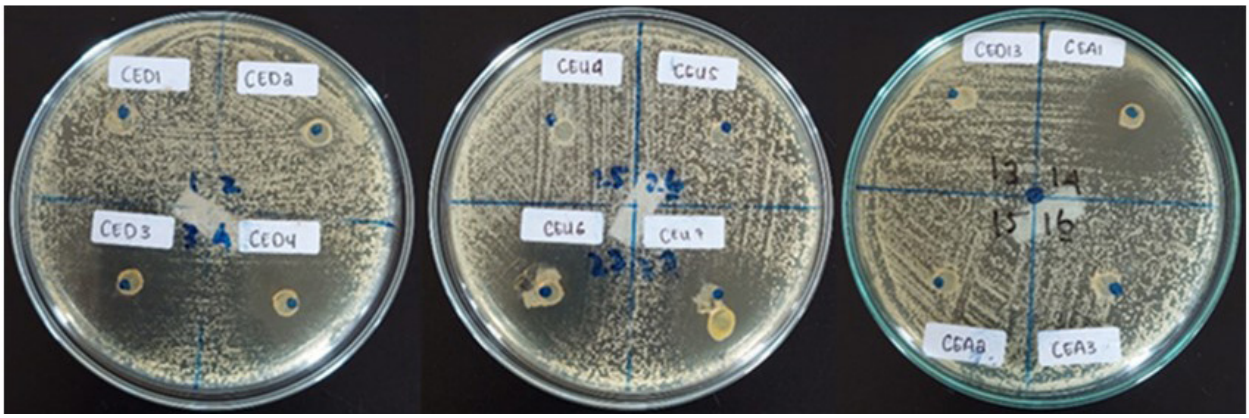

Figure 1. Inhibition zone formed from the antagonistic activity of endophytic bacteria isolates against *Candida albicans*

Table 1. Results of diameter measurements of the clear zone formed in the antagonistic activity test against *Candida albicans*

Isolate	Diameter of clear zone (mm)			Average diameter of the inhibition zone (mm)
	I	II	III	
CED1	-	-	-	-
CED2	-	-	-	-
CED3	17.2	17.5	16.5	17.1±0.51
CED4	17.1	16.6	16.0	16.6±0.55
CED9	11.9	11.5	11.5	11.6±0.23
CED13	-	-	-	-
CEU4	-	-	-	-
CEU5	-	-	-	-
CEU6	19.6	19.5	19.2	19.4±0.21
CEU7	16.2	16.0	16.5	16.2±0.25
CEA1	16.7	16.7	16.5	16.6±0.12
CEA2	-	-	-	-
CEA3	-	-	-	-
K(+)	11.0	11.0	11.5	11.2±0.29
K(-)	-	-	-	-

(-) indicates no visible of clear zone, K (+): positive control (Nystatin 60 µg/ml) K(-): negative control (sterile NA)

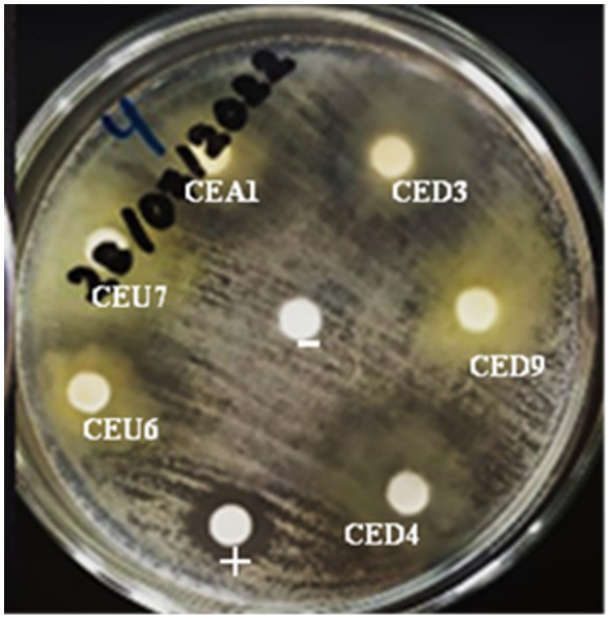

Figure 2. Antifungal activity assay of cell-free supernatant (CFS) using the Kirby–Bauer disk diffusion method

Antifungal Activity of Cell-Free Supernatant (CFS) Against *Candida albicans*. Based on the antifungal activity test of cell-free supernatant (CFS) from endophytic bacteria of Dayak onion, it was revealed that only 4 out 6 isolates could inhibit *C. albicans*, namely isolates CEA1, CED3, CED4, and CEU6. Isolate CED4 had the highest antifungal activity because of the widest clear zone formed (18.5±0.50 mm) (Figure 2). Results of Antifungal Activity of Cell-Free Supernatant (CFS) against *C. albicans* are shown in Table 2.

Table 2. Results of antifungal activity of cell-free supernatant (CFS) against *Candida albicans*

Isolate	Diameter of clear zone (mm)			Average of clear zone diameter ±SD (mm)	Level
	I	II	III		
CEA1	10.6	10.8	10.5	10.6±0.15	Moderate
CED3	10.4	10.2	10.0	10.2±0.20	Moderate
CED4	18.0	18.4	19.0	18.5±0.50	Strong
CED9	-	-	-	-	-
CEU7	-	-	-	-	-
CEU6	10.8	10.7	10.9	10.8±0.10	Moderate
K(+)	8.2	8.5	8.4	8.4±0.15	Moderate
K(-)	-	-	-	-	-

(-) indicates no activity, K (+): control positive (Nystatin), K (-): control negative (Aquadest)

DISCUSSION

The agar plug diffusion method is often used to determine the effects of antagonism between microorganisms. It involves making a culture of the desired isolate strain by tightly streaking it on the surface of the agar plate. During growth, microbial cells release compounds that diffuse in the agar medium. Then, the compound diffuses from the agar plug to the test medium. Antifungal activity of molecules secreted by microbes was detected by the formation of an inhibition zone around the agar plug (Balouiri *et al.* 2016).

Various microorganism including bacteria are known as potential antagonistic organisms to control *C. albicans*. Bacteria from the genera *Bacillus, Bifidobacterium, Lactobacillus, Pseudomonas*, and *Enterococcus* were reported to have antagonistic activity against *C. albicans* (Li *et al.* 2022). Antagonism is an activity carried out by a microbial population to suppress the growth of other microbial communities so that microbes that have an antagonistic effect can survive. Generally, antagonistic activity is caused by the effects of chemical compounds from microbes known as antibiosis (Narayanan *et al.* 2022). Apart from antibiotic production, mechanisms of bacterial antagonism against fungi include the secretion of lytic exoenzymes and competition for space and nutrients (Zhou *et al.* 2014).

Several antifungal compounds derived from bacterial secondary metabolites have strong inhibitory power against *C. albicans*. From several previous studies, it is known that *Bacillus subtilis* produces 5-hydroxymethyl-2-furaldehyde which can inhibit morphological transitions, biofilm formation, and virulence of *C. albicans* (Subramenium *et al.* 2018). In addition, *Pantoea agglomerans* strain C9-1 produced 2-amino-3-(oxane-2,3- dicarboxamido) propanoyl-valine and *Tenacibaculum discolor* sv11 produced Dipyrrolepyridines A and B which also inhibited *C. albicans* (Sammer *et al.* 2009; Wang *et al.* 2022).

The result of antifungal activity of Cell-Free Supernatant (CFS) indicated that it has strong inhibition against *C. albicans*. According to Davis & Stout (1971), based on the clear zone formed in antimicrobial testing, there are four categories of inhibitory levels namely very strong >20 mm, strong 11-20 mm, moderate 6-10 mm, and weak inhibitory power is divided into four categories, namely: very strong>20 mm; strong 11-20 mm; moderato 6-10 mm and weak ≤5 mm). Cell-free supernatant (CFS) is liquid containing metabolites resulting from microbial growth and remaining nutrients from the media used. It contains various compounds such as enzymes, proteins, and secondary metabolites such as antimicrobials (Mao *et al.* 2023). Several studies have been carried out to investigate the potential application of CFS from endophytic bacteria. Al-Nadabi *et al.* (2021) found that CFS of endophytic bacteria isolated from date palm leaves showed antifungal activity against pathogenic fungi that cause leaf spots on date palms. It inhibits mycelial growth and causes cell leakage in the mycelia of pathogenic fungi. Other research also revealed that CFS of *Lactobacillus plantarum* showed anticandidal activity (Mondal *et al.* 2020).

The antifungal activity of CFS is influenced by the culture medium, pH, and incubation temperature (Liu *et al.* 2023). Gould (2000) also stated that the ability of antifungal compounds produced by bacteria is influenced by the bacterial species and the type of antifungal compound produced (Yunita *et al.* 2022). Several previous studies reported that endophytic bacteria isolated from several medicinal plants have an anticandidal activity such as *Dryopteris uniformis* (Das *et al.* 2019), *Urena lobata* (Fokou *et al.* 2023), and *Annona muricata* (Aisyah *et al.* 2023). Endophytic bacteria can produce metabolite compounds such as antibiotics, bacteriocins, metabolic by-products, lytic enzymes exotoxins, and short-chain fatty acids as a defense system against pathogens (Sulistiyani *et al.* 2016).

The inhibition mechanism of *C. albicans* by antifungal compounds can inhibit the growth and virulence factors of the pathogen. Inhibition of pathogen growth includes damaging cell walls and cell membranes, inhibiting cell respiration, and protein synthesis (Jakab *et al.* 2022). Meanwhile, Virulence factor inhibition includes inhibition of the yeast phase transition to the biphasic hyphal phase, inhibition of adhesion, secretion of hydrolase enzymes, pathogen invasion, and biofilm formation (Mayer & Kronstad 2017). Systematic study of these mechanisms may encourage the exploration of safer and more effective antifungal drugs, thereby providing a more substantial basis for the selection of anticandidal strategies (Wang *et al.* 2022).

Six isolates of endophytic bacteria from Dayak onions (*Eleuthetine bulbosa*) have antagonistic activity against *Candida albicans*. Cell-free supernatant (CFS) from strain CED4 have the highest antifungal activity in inhibiting *Candida albicans* growth. Further studies are needed to determine the antifungal compounds produced by CED4 isolates for the development of anticandidal.

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