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Isolation and screening of lovastatin-producing endophytic fungi from lemongrass (*Cymbopogon nardus*)

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Abstract. *Rahmi Z, Yurnaliza Y, Hastuti LDS. 2022. Isolation and screening of lovastatin-producing endophytic fungi from lemongrass (*Cymbopogon nardus *L.). Biodiversitas 23: 4189-4194.* Fungi have long been studied for their cholesterol-lowering compounds, known as statins and the derivatives through fermentation in laboratory investigations. Therefore, this study aimed to isolate and screen endophytic fungal strains from lemongrass capable of producing lovastatin. Endophytic fungi were isolated from the stems and leaves of lemongrass (*Cymbopogon nardus*) and the selection of their ability to produce lovastatin was assayed using three approaches, namely negative test against *Candida albicans*, measurement based on absorbance at a wavelength (λ) of 230 nm or colorimetric assay, and observation using thin layer chromatography (TLC). A total of 22 endophytic fungi, 15 from the leaves and 7 from the stems were isolated from lemongrass. The capability to produce lovastatin was confirmed using three approaches, resulting in three potential fungal strains, namely *Trichoderma* sp. CNB 2.5.3, unidentified fungus CND 2.5.4, and *Nigrospora* sp. CND 2.1.1. Based on the colorimetric assay, the potential strains produced a significant zone of inhibition against *C. albicans*, with greater lovastatin levels than the other isolates. The TLC analysis showed that the fungal ethanolic extracts contained crude lovastatin as indicated from the same retention factor (*Rf*) value as standard lovastatin. The presence of lovastatin-producing endophytic fungi can be investigated progressively for optimum production through fermentation and evaluation of its cholesterol-lowering activity in the future.

Keywords: *Cymbopogon nardus*, endophytic fungi, lovastatin, lemongrass

INTRODUCTION

Cholesterol is a form of lipid referred to as steroids or sterol fats. Lowering cholesterol levels in the blood can prevent stroke and mortality from cardiovascular disease. Practically, the reduction can be achieved by taking medicine, ezetimibe or using statin inhibitors for medical treatment (Alenghat and Davis 2019). Statins and their derivatives are the most extensively used drugs for reducing blood cholesterol levels. Microorganisms that produce statin-type compounds such as *Aspergillus terreus* can synthesize lovastatin compounds. The synthesized lovastatin compound can be purified and produced on large scales (Azeem et al. 2020). It is the most effective drug for lowering cholesterol levels in the blood, therefore, it can help individuals with cardiovascular disease (Pandey et al. 2019).

Lovastatin is a secondary metabolite of fungi produced through the polyketide pathway by certain fungi in their metabolic processes. It is referred to as an inhibitor of the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase or HMG-CoA reductase (EC 1.1.1.88) involved in synthesizing cholesterol in the liver. Lovastatin present in the hydroxy acid form will compete competitively with the HMG-CoA substrate for binding to HMG-CoA reductase. A high level of the compound can bind to HMG-CoA reductase, inhibiting the conversion to mevalonate and cholesterol production, with a final effect of lowering the mortality risk in cardiovascular disease patients (Zhang et al. 2020; Thurman et al. 2020).

Several notable lovastatin producers have been documented, including the primary agents, such as *Aspergillus terreus* (Ascomycetes) and *Pleurotus ostreatus* (Basidiomycetes) (Alarcón and Águila 2006). It has been reported that some strains of endophytic fungi originating from bryophytes, ferns, gymnosperms and angiosperms also produced a significant level of this compound under optimum fermentation conditions (Hipol et al. 2020). In addition, it exhibits antifungal activities, particularly against human pathogenic yeasts such as *Candida albicans*, *C. glabrata, C. krusei, C. parapsilosis, C. tropicalis*, and *Cryptococcus neoformans* (Tavakkoli et al. 2020).

The lemongrass (*Cymbopogon nardus* L.) plant has been utilized as a traditional medicine with anti-inflammatory, antioxidant, and antimicrobial properties (Bayala et al. 2020). The essential oil has been proven to treat hyperlipidemia in rats (Kumar et al. 2011). This study isolated and selected the potential of endophytic fungus from lemongrass as a producer of lovastatin compounds. However, there is limited information on the assemblage of endophytic fungi in lemongrass and their propensity to produce anticholesterol compounds. This study aims to designate the potential endophytic fungal strains in sustainably producing lovastatin through fermentation.

MATERIALS AND METHODS

Isolation of endophytic fungi from lemongrass

The procedure for isolating endophytic fungi from lemongrass followed the preparatory stage and surface sterilization protocol as described earlier by Yurnaliza and Jamilah (2018). The leaves and stems were cleaned with running tap water for 20 min, and the plant samples were sterilized in the following disinfectants: 96% (v/v) ethanol for 2 min, 3% (v/v) NaOCl for 5 min, and 96% (v/v) ethanol for 30 sec. Subsequently, the samples were rinsed with sterile distilled water twice and dried with a filter paper. The samples were inolculated onto potato dextrose agar (PDA) medium supplemented with 0.1% (w/v) of chloramphenicol and incubated in the dark at room temperature for 7 days. The plates were checked daily for visible fungal growth and purified into a single culture in a new PDA plates. Meanwhile, the collection of endophytic fungi was characterized and grouped based on their colony characteristics to obtain several isolates for further experimentation.

Fermentation and extraction of extracellular metabolites

Each endophytic fungal isolate was grown in a fresh potato dextrose broth (PDB) medium at room temperature and agitated at 180 rpm for 10 days, and the filtrates were removed from the mycelial mass through filtration. Furthermore, they were extracted with ethyl acetate and concentrated *in vacuo* using a rotary evaporator to yield a 20 mL solution (Dhar et al. 2015), and the crude extracts were stored at a cool temperature before further analysis.

Determination of lovastatin concentration in the crude extract

The determination of lovastatin in the crude ethyl acetate extract was assayed with a colorimetric method. A standard curve was prepared in concentrations of 3.2, 12.8, 19.2, 25.6, 32.0, and 38.4 mg/L by dissolving 3.2 mg of lovastatin into 50 mL of 75% (v/v) ethanol and the absorbances were read at 230 nm. The concentration in crude extracts was estimated using the linear regression equation by plotting the standard and the absorbance readings.

Antifungal activity of endophytic fungi and crude extracts against *Candida albicans*

Candida albicans inoculum was prepared in a sterile physiological saline solution containing 10^8 CFU/mL with an immediate suspension. In addition, the suspension of *C. albicans* was swabbed entirely on a PDA plate and allowed to dry at room temperature. Agar plugs of active-growing endophytic fungal colonies (Ø 5 mm) were placed on top of inoculated PDA plate and incubated at room temperature for 24 hr. In a separate experiment, blank disks impregnated with crude ethyl acetate extract were placed on the inoculated PDA plate. The clear zone around agar plugs and disks indicated the antifungal activity against *C. albicans* and was measured with a digital calliper (mm).

Detection of lovastatin using thin-layer chromatography

Approximately 0.5 mL of crude fungal extracts were dried and concentrated into a 50µL solution for thin-layer chromatography (TLC) analysis. The solution was spotted on a TLC plate impregnated with silica gel 60F254 (Merck® 20×20 cm) with mobile phase using dichloromethane and ethyl acetate (70:30, v/v). Subsequently, the TLC plate was observed after exposure to iodine vapors under UV exposure at 254 nm. The retention factor (*Rf*) of both lovastatin standard and fungal extracts was calculated and compared.

RESULTS AND DISCUSSION

Endophytic fungi isolated from lemongrass

A total of 22 endophytic fungi, 7 from stems (Code: CNB) and 15 from leaves (Code: CND) were isolated from lemongrass. Total sampling units were 25 for each leaf and stem part. The assemblage of culturable endophytic fungi was higher in leaves than in stems. Gazis and Chaverri (2010) stated that more endophytic fungi could be found on the leaves because they do not have a complex protective system, supporting the initiation of infection and colonization. Microbes' infection process is influenced by the mechanism of the spread of fungi on the ground through the air, raindrops or insect vectors. Endophytic fungal hosts are invaded using wounds or natural openings (stomata or lenticels).

Once inoculated on a PDA plates, not all plant portions were colonized by fungal endophytes. The endophytic fungus can be one or multiple species growing on lemongrass pieces. Fast-growing species dominated the endophytic fungi that grow on lemongrass, and they may exist in various population densities depending on the site or tissue suitability. In addition, they are mostly saprophytes which can be altered following the fluctuation of the host environment and abiotic factors (Zhou et al. 2018). The results of macroscopic observations can be seen that there are morphological features in the shape of the colonies (irregular, round and filamentous). Meanwhile, the color is dominated by white, and the surface is fibrous (Figure 1). Green, white and black colonies were obtained with about 3, 7 and 9 isolates, respectively.

Lovastatin yield in the crude fungal extracts

The results of screening through absorbance reading at 230 nm from crude ethyl acetate extracts showed that all fungal isolates could synthesize lovastatin in varying concentrations, from 0.54 to 40.67 mg/L (Table 1). The sensitivity of lovastatin detection was confirmed using the appropriate wavelength for detection (Li et al. 2014). Furthermore, the highest producers were CNB 2.5.3, CND 2.1.1, and CND 2.5.4 and were subjected to further tests. Azeem et al. (2020) reported that the highest strain in producing lovastatin based on fermentation technique was *Aspergillus terreus* with 74.76 mg/L compared to others. CNB 2.5.3 fungal isolate that generated hyaline conidiophores is mainly branched, with greenish conidia/ phialospores, and oval-shaped, resembling a member of

Trichoderma. In addition, CND 2.1.1 is characterized by having a dull, blackish-to-brownish colony, rough texture with black color on the lower colony, hyaline hypha, black conidia, unicellular and septate, resembling *Nigrospora*. The isolate CND 2.5.4, was still unidentified, showing only a typical whitish colony, cottony texture, and absence of conidia and hyphal anastomoses during a microscopical examination (Figure 2).

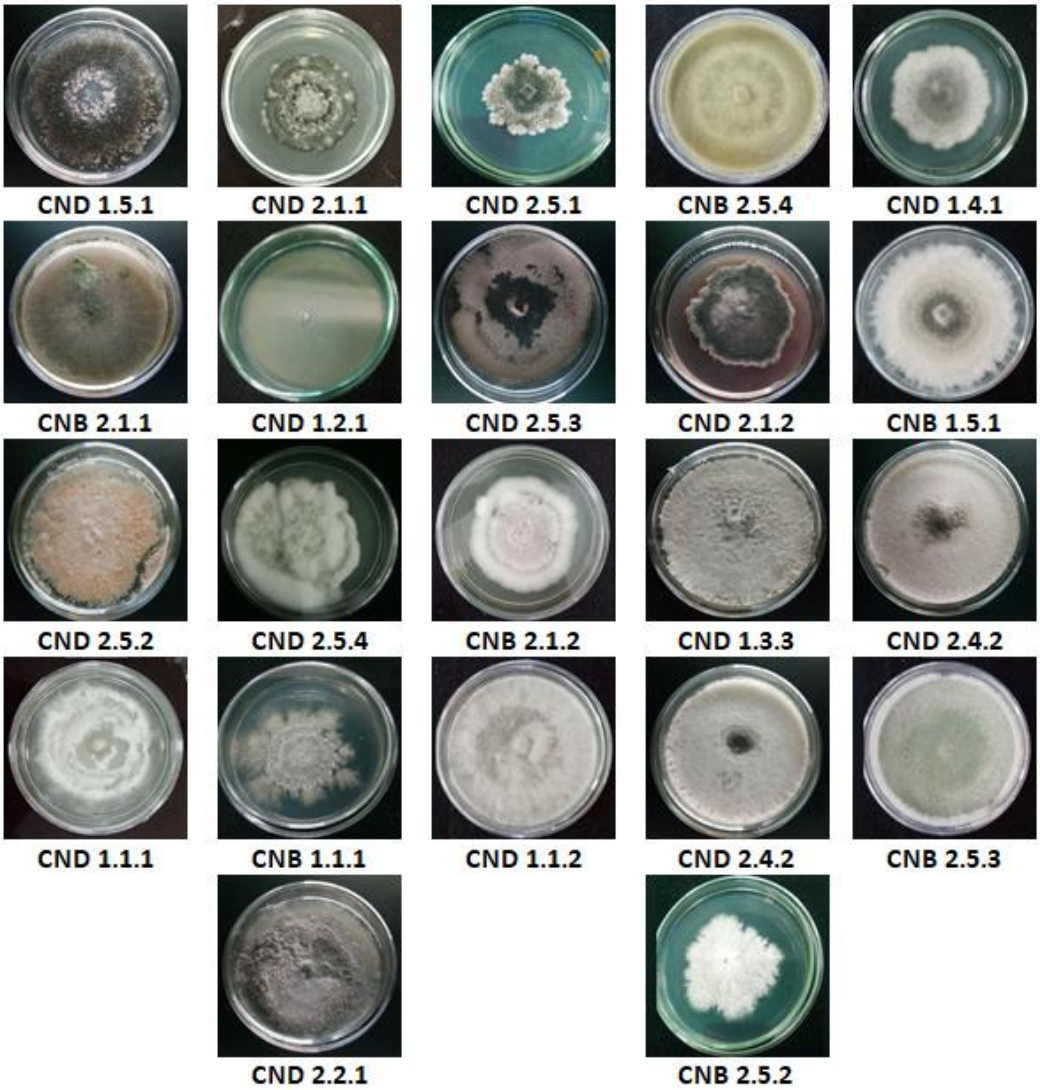

Figure 1. Colony appearance of endophytic fungi of lemongrass (*Cymbopogon nardus* L.) isolated from leaves (Code: CND) and stems (Code: CNB).

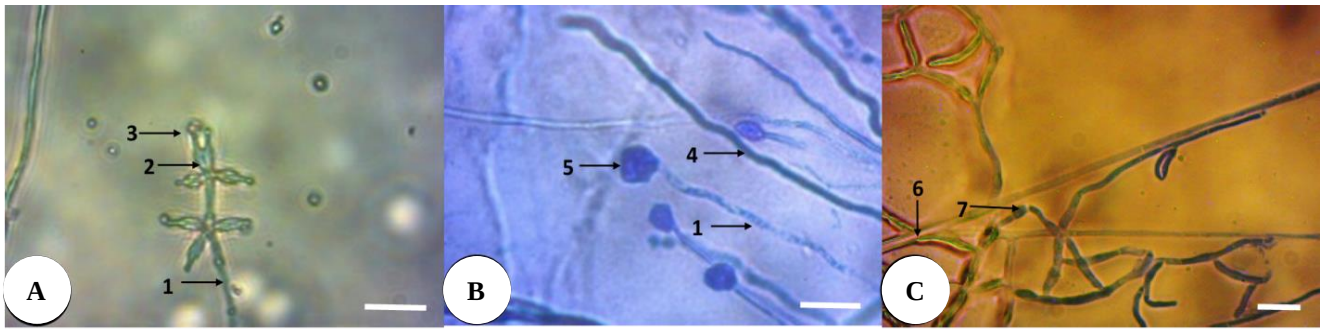

Figure 2. Microscopical feature of potential lovastatin-producing fungal isolates: (A) Isolate CND 2.5.3 showing (1) Conidiophore, (2) Phialide, (3) Phialospore; (B) Isolate CND 2.1.1 showing (1) Conidiophore, (4) Hyphae, (5) Conidium; (C) Isolate CND 2.5.4 showing (6) Septum, (7) Hyphal anastomoses

Table 1. Absorbance reading of crude ethyl acetate extract of lemongrass endophytic fungi and its lovastatin yields

Isolates	Absorbance at 230 nm	Yield (mg/L)
CND 1.5.1	1.106	13.29
CND 2.1.1	3.436	40.67
CND 2.5.1	2.311	27.45
CNB 2.5.4	2.451	29.09
CND 1.4.1	1.183	14.19
CNB 2.1.1	1.583	18.89
CND 1.2.1	1.182	14.18
CND 2.5.3	0.57	6.99
CND 2.1.2	3.311	39.20
CNB 1.5.1	0.231	3.01
CNB 2.5.4	2.311	27.45
CND 2.5.4	3.436	40.67
CNB 2.1.2	0.502	6.19
CND 1.3.3	3.331	39.20
CND 1.3.4	0.377	4.72
CND 1.1.1	3.311	39.20
CNB 1.1.1	0.377	4.72
CND 1.1.2	3.311	39.2
CND 2.4.2	0.303	38.02
CND 2.2.1	0.021	3.85
CND 2.5.2	0.123	0.54
CNB 2.5.3	3.436	40.67

Antifungal activity of endophytic fungi against *Candida albicans*

The results showed that three potential fungal strains produced clear zones on agar plugs and ethyl acetate extracts of *C. albicans* (Table 2, Figure 3). The antagonistic activity of fungal strains against *C. albicans* is considered a new method for rapidly screening lovastatin-producing fungi. The inhibition zone formed was correlated with the level of lovastatin produced by the fungus. The minimum period of detection for the antagonism result may be observed after 6 hr of incubation (Ferron et al. 2005), and the inhibitory mechanism of lovastatin against *C. albicans* is highly selective. Lima et al. (2019) stated that statin produced a selective inhibition towards *C. albicans*, but not against Gram-positive and Gram-negative bacteria. The mechanism involved the reduction of ergosterol synthesis through inhibition of HMG-CoA reductase, similar to azole compounds in inhibiting lanosterol-14-α-demethylase.

Statins prevent isoprenylation, a post-translational modification of several proteins involved in controlling cell proliferation, differentiation, apoptosis, and content in the cytoskeleton, by blocking the mevalonate pathway. Atorvastatin has been shown to interfere with protein isoprenylation in *Saccharomyces cerevisiae* (Callegari et al. 2010), similar to lovastatin affecting heme synthesis. Meanwhile, farnesyl pyrophosphate (FPP) is involved in the biosynthesis of heme A (Bhattacharya et al. 2018), which is part of cytochrome C. This indicates the statins can interfere with the normal function of cytochrome C and respiration (Tavakkoli et al. 2020).

The inhibition of the growth of *C. albicans* by lovastatin was due to the formation of hydroxy acid, which is known as an effective antifungal compound. *C. albicans* has a lipid bilayer on its cell membrane and the cell wall is composed of sterols, which are primary targets of antifungal agents. The mechanism of fungal inhibition may occur due to the interaction between lovastatin and the cell membrane's electronegative charge, leading to changes in membrane permeability and consequent leakage of proteins and other intracellular electrolytes (Khalil and Yousef 2020). The presence of lovastatin and other physiologically active secondary metabolites may explain the substantially stronger inhibition (Mahmoud and Abdel-Hadi 2022).

Biosynthesis is the method through which fungi produce lovastatin from their surroundings. This study found that the antifungal activity of lovastatin extracted using ethyl acetate was considered low. Lactose, ethanol, and glycerol are not carbon sources that may activate CreAp. Biosynthesis of lovastatin begins after the depletion of lactose supply in the fermentation medium. This shows that the synthesis has reached the end of the fungal growth limit, indicating substrate insufficiency. The ech42 kinase gene is only expressed in secondary metabolism when there is a lack of glucose or glycerol substrates (Hajjaj et al. 2001).

Table 1. Diameter zone of inhibition of lemongrass endophytic fungi and its crude extracts against *C. albicans*

Isolate Code	Diameter zone of inhibition (mm)	
	Agar plugs	Crude extracts
CNB 2.5.3	29	22
CND 2.5.4	25	20
CND 2.1.1	20	15

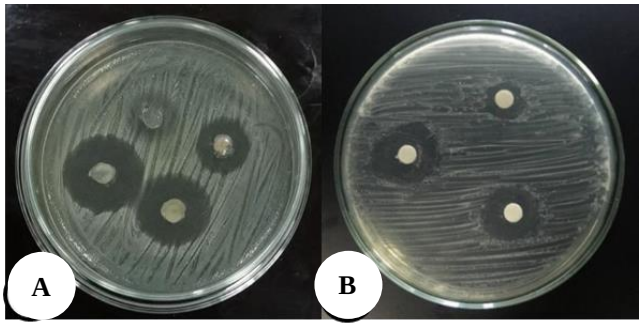

Figure 2. Clear zones result from the antagonistic and antifungal activity of endophytic fungi. (A) agar plugs, (B) ethyl acetate extracts

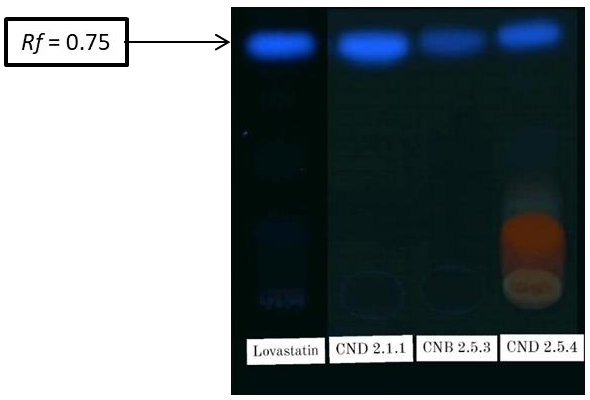

Figure 3. The visual appearance of lovastatin band after UV exposure on a TLC plate from standard solution and crude fungal extracts of lemongrass endophytic fungi

Detection of lovastatin using TLC analysis

The presence of lovastatin was confirmed through visual observation under UV exposure on the TLC apparatus. The results showed that the *Rf* of standard lovastatin was 0.75, similar to the *Rf* of any metabolite detected from all fungal extracts. The results confirmed that this endophytic fungi could secrete lovastatin in the fermentation broth (Figure 3). The principle of TLC in separating a compound's mixture relies heavily on the polarity of the solvent and a ratio of combined solvents used as the mobile phases (Praveen et al. 2014).

The utilization of the TLC technique to detect lovastatin from Ascomycetous and Basidiomycetous fungi has been reported in several studies. Dikshit and Tallapragada (2015) compared the lovastatin quantity produced by *Monascus purpureus* and *M. sanguineus.* The *Rf* value detected using TLC analysis was 0.63–0.65. Meanwhile, Balraj et al. (2018) screened 36 filamentous fungi from soil samples to produce lovastatin through fermentation. Strain C9, *Cunninghamella blakesleeana* produced a considerable quantity as confirmed through TLC analysis with an *Rf* value of 0.52–0.53. Mahmoud and Abdel-Hadi (2022) also detected lovastatin from *Laetiporus sulphureus,* producing a conserved *Rf* value at 0.55. The difference in *Rf* value for lovastatin from other studies may be due to the different non-polar and polar solvents employed as mobile phases to facilitate compound separation on the TLC plate. In addition, the quantity obtained from the potential strains may be analyzed using HPLC to validate its presence and concentration. The content of lovastatin produced by a collection of local *Monascus purpureus* strains from Indonesia through solid state fermentation yielded 0.05–0.92% of lovastatin using HPLC analysis (Kasim et al. 2005). The lovastatin content may also be influenced by the type of substrate for fermentation for example rice using *M. purpureus* (Kasim et al. 2006), wheat bran using *Aspergillus terreus* (Kamath et al. 2015), fruits waste using *Aspergillus flavipes* (Valera et al. 2005), etc. Further investigation is needed to maximize the production of lovastatin by lemongrass endophytes through modification of substrate and culture conditions in the laboratory.

In conclusion, a total of 22 endophytic fungal isolates were obtained from the leaves and the stems of lemongrass. The three screening procedures utilized to select lovastatin-producing endophytic fungus produced consistent results. Potential isolates were CNB 2.5.3, CND 2.1.1 and CND 2.5.4. These isolates produced the largest zone of inhibition against *C. albicans*, and the highest lovastatin levels in crude extracts. They produced the same *Rf* values from TLC results similar to the standard lovastatin.

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