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ISOLATION OF *Penicillium* STRAINS FROM THE MANGROVE FORESTS OF THE NORTHERN COASTAL REGION WITH HIGH POTENTIAL FOR MYCOPHENOLIC ACID PRODUCTION FOR PHARMACEUTICAL APPLICATIONS

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ABSTRACT

Penicillium is known as a genus of fungi that is widely distributed throughout the environment and found all over the world. The *Penicillium* genus is found both on land and in coastal mangrove areas, where it exists on various parts of plants and animals, playing roles in symbiosis and the decomposition of organic matter. Coastal mangrove forests are highly regarded for the diversity of their microbial populations, especially fungal species. Previous studies have shown that marine fungal strains contain many potential bioactive compounds that may be utilized in the pharmaceutical, cosmetic, and food industries. Compounds derived from fungal strains originating in coastal mangrove areas have commercial value and demonstrate greater potential for research and the production of new drugs compared to those isolated from terrestrial environments. Among them, marine fungal strains of the genus *Penicillium* have been shown to exhibit novel biological activities, particularly those with significant medical applications, such as antibiotics, antifungal, anti-inflammatory, anticancer agents, and immunosuppressants for preventing organ transplant rejection. In the context of the developing healthcare sector and the growing demand for organ transplants in the country, there is a priority to actively produce mycophenolic acid (MPA) from domestic sources. Therefore, this study reports the isolation of 24 *Penicillium* strains from the Northern coastal region, which exhibit high potential for mycophenolic acid biosynthesis, with a focus on production for pharmaceutical applications in Vietnam.

Keywords: Mangrove, marine fungus, MPA, mycophenolic acid, *Penicillium*.

INTRODUCTION

Penicillium is a large genus of fungi, also known as green mold, with approximately 483 species isolated from various regions around the world (Ferreira *et al*., 2020). *Penicillium* fungi are widely distributed globally and can be found in soil, water, on living and dead animals and plants, in freshwater, marine, and estuarine

environments, and even in the air. The role of this genus is to help decompose organic matter, and therefore, it is also considered a group that poses a risk of causing diseases in agricultural crops (Vinokurova *et al*., 2005). Studies have shown that the ideal temperature for the growth of *Penicillium* strains is between 20°C and 25°C, and above 37°C (Dang, 2015). However, some strains can also grow at lower temperatures (Kozlovskii *et al.,* 2013; Hong *et al.,* 2022). Under various environmental conditions, such as salinity, pH, water pressure, or extreme cold or heat, this results in the diversity and special bioactivity of secondary metabolites produced by the *Penicillium* genus (Anand & Srivastava, 2020).

Coastal mangrove forests are known for their high biodiversity and provide habitats for various microorganisms, including fungi, bacteria and actionmycetes, which are of significant ecological and economic value. The fungi in these ecosystems perform various functions, primarily decomposing organic matter from sediments, leaves, roots, and dead plant and animal material in the mangrove forest (Veettil *et al.,* 2018; Yang *et al*., 2021). According to statistics, there are approximately 850 different fungal species isolated from coastal mangrove areas, belonging to genera such as *Aspergillus*, *Fusarium*, *Penicillium*, and *Trichoderma*… exhibiting promising biological activities like antibacterial, antifungal, antioxidant, and antitumor properties (Devadatha *et al*., 2021). Therefore, these fungi represent a valuable source for the discovery of new bioactive compounds with potential uses in the food, cosmetics, and pharmaceutical industries (Ferreira *et al*., 2020).

The *Penicillium* genus is also a large genus of fungi that has been extensively studied and isolated in mangrove areas along the coast, with the potential to discover a wide range of novel bioactive compounds each year. Between 1990 and 2014, 390 new secondary metabolites were identified from *Penicillium* strains, and an additional 188 new bioactive compounds were discovered between 2015 and 2020 (Fang & Zeng, 2024). As much as 56% of the newly discovered bioactive compounds from the *Penicillium* genus were isolated from mangrove regions and marine sediments, exhibiting a variety of bioactivities with potential applications in medicine (Carroll *et al*., 2023; Hong *et al*., 2022).

Mycophenolic acid (MPA) is a secondary product of the mevalonate metabolic pathway in fungi from the *Penicillium* genus, such as *P. brevicompactum*, *P. roqueforti*, *P. puberulum*, *P. stoloniferum*, as well as the species *Byssochlamys nivea* and some species from the *Aspergillus* genus (Dasgupta, 2016). Based on the significant medical applications of MPA and its derivatives, previous studies have focused on optimizing conditions for high-yield fermentation of MPA from strains of *P. brevicompactum* and *P. roqueforti* (Vinokurova *et al*., 2005).

In this study, we present the results of isolating several *Penicillium* fungal strains with the ability to produce MPA from the Northern coastal mangrove regions. This ecosystem is one of the most biodiverse in the world, with a tropical monsoon climate that provides an ideal environment for discovering microorganisms with special bioactive properties. The goal is to screen marine fungi from Vietnam with the potential for MPA production, aiming for industrial-scale production to help meet part of the current demand and gradually supply sufficient drugs for the domestic organ transplantation sector.

MATERIALS AND METHODS

Collection and isolation of samples

A total of thirty sediment samples from the coastal mangrove forests of Ninh Binh, Hai Phong and Quang Ninh were used to isolate marine fungal strains. The samples were collected and stored at 4°C before the experiments were conducted. For each mud and water sample, 10 g of the sample was placed into a flask containing 90 mL of sterilized distilled water, then shaken at 200 rpm for 30 minutes. The resulting mixture was used for serial dilution (10^{-1} to 10^{-4}), followed by plating on Potato Dextrose Agar (PDA), Czapek's (Cz), and Czapek Yeast Autolysate Agar (CYA). The agar plates were then incubated for 4 days at 25°C to isolate the fungal strains. The experiments were conducted at the Department of Bioactive compounds from Microorganisms, Institute of Biology, Vietnam Academy of Science and Technology.

Media

Potato Dextrose Agar (g/L)**:** dextrose 20, potato extract (boil 200 g of fresh potatoes with distilled water, extract the liquid, and discard the residue) up to 1000 mL, agar 20, pH 6.5 ± 0.2. Czapek's Agar (Cz) (g/L)**:** Czapek concentrate 10 mL, sucrose 30, trace salts 1.0 mL, agar 20. Czapek Yeast Autolysate Agar (CYA) (g/L)**:** Czapek concentrate 10 mL, sucrose 30, yeast extract 5, K_2HPO_4 1.0, trace salts 1.0 mL, agar 20, pH 6.2 ± 0.2. Czapek Yeast Autolysate Agar with 5% NaCl (CYAS) (g/L)**:** Czapek concentrate 10 mL, sucrose 30, yeast extract 5, K_2HPO_4 1, NaCl 50, pH 6.2 ± 0.2. Malt Extract Agar (MEA) (g/L)**:** malt extract 50, trace salts 1.0 mL, agar 20, pH 5.4 ± 0.2. The trace element solution consisted of (g/L): $FeSO_4 \cdot 7H_2O$ 2.2; $CuSO_4 \cdot 5H_2O$ 0.3; $ZnSO_4 \cdot 7H_2O$ 2.4; $MnSO_4 \cdot 4H_2O$ 0.16 and $KMnO_4$ 0.2 (Dang, 2015; Mohamed *et al.*, 2015).

Morphological identification of *Penicillium*

The isolated *Penicillium* strains will be purified and inoculated on PDA medium for 5 to 7 days at 25°C. Afterward, spores will be collected, and morphological studies of the strains will be conducted based on colony development on Cz, CYA, CYAS, and MEA media (Dang, 2015; Frisvad, 1981; Mohamed *et al.*, 2015).

The morphological characteristics will be compared with the fungal identification keys of Dang (2015) and Mohamed *et al*. (2015). The morphological characteristics of the *Penicillium* sp. strain were observed based on the colony morphology, colony color on different culture media, and the examination of the hyphal and spore structures using an optical microscope (LAICA, DME). The morphological features were evaluated based on the following criteria: growth rate, shape, color, surface and margin of the colony, pigment production in the medium, hyphal morphology, conidiophore structure, spore shape and color, and the presence of aerial and substrate mycelium.

Mycophenolic acid analysis

The fungal fermentation broth obtained after 4 days of incubation at 25°C was diluted with methanol at a ratio of 1:25 (v/v) and passed through a 0.45 µm Millex-HV filter (Merck Millipore) before being analyzed by high-performance liquid chromatography (HPLC) (LaChrom Elite - Hitachi). A C18 column (Symmetry® C18, 5 µm, 4.6 x 250 mm) was used at a temperature of 40°C. The mobile phase, consisting of double-distilled water and acetonitrile in a 50:50 (v/v) ratio,

was adjusted to pH 3.0 and pumped at a flow rate of 0.5 mL/min. A 10 µL injection volume was applied, and detection was carried out with a photodiode array detector at 220 nm (Elbarbry *et al*., 2007).

A standard solution was prepared using pure MPA (HPLC grade) as a control. The stock solution of MPA (1 mg/mL) was made in methanol and kept at -20°C. As needed, it was serially diluted with methanol to prepare MPA concentrations between 2.5 and 125 µg/mL. All measurements of MPA were performed in triplicate.

The formula used to calculate the MPA concentration is:

$$X = \frac{Y - 5245911.81}{1186680.641}$$

Whereas X: MPA concentration (mg/mL); Y: Absorbance area at the wavelengths

RESULTS AND DISCUSSION

Screening fungal strains with the ability to produce MPA

From the samples collected in the mangrove forest region along the northern coast of Vietnam, over 100 strains of various molds were isolated (Figure 1). The isolation results showed that the marine sediment samples had high diversity; the colonies of these fungal strains exhibited various colors, such as white, gray, yellow, green, black, pink, etc. Preliminary descriptions showed that the colony surfaces of the strains were highly diverse, ranging from smooth to velvety or wrinkled, with colony edges being either cotton-like or frayed. Many strains were capable of producing pigments in the culture medium (details not presented in this report). The mold strains were then cultured for biological characterization and preliminary classification, based on the descriptions in the taxonomy guide by Dang (2015) and Mohamed *et al.* (2015). The results identified 34 strains that resembled species within the genus *Penicillium*. The strains were then cultured in liquid medium under shaking conditions at 200 rpm at 25°C. After 5 days of cultivation, the fermentation broth obtained from the strains was analyzed for MPA production using the HPLC method (Elbarbry *et al*., 2007).

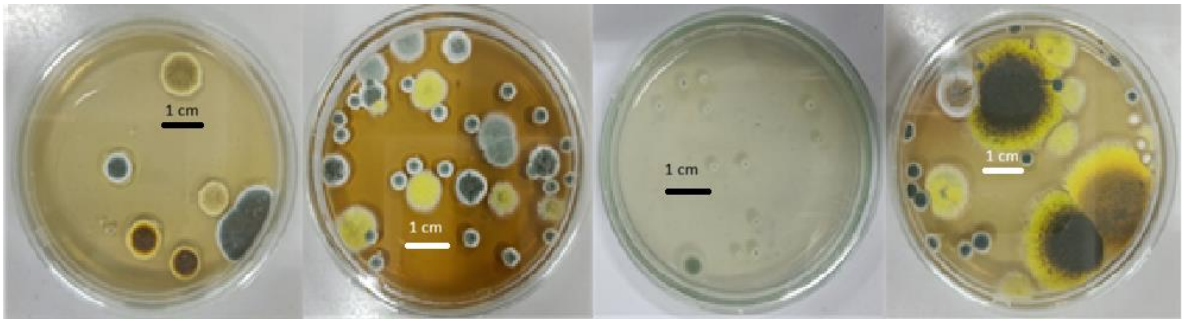


Figure 1. Some fungal isolation plates from samples of the mangrove forest region on the northern coast of Vietnam.

Table 1. Source of isolation and MPA content of marine fungal strains.

No.	Strains	Isolation sources	MPA concentration (µg/mL)	No.	Strains	Isolation sources	MPA concentration (µg/mL)
1	N22	Hai Thinh, Ninh Binh	311 ± 9	18	BV212	Cat Ba, Hai Phong	0
2	N29	Hai Thinh, Ninh Binh	325 ± 15	19	BV216	Cat Ba, Hai Phong	0
3	BD103	Hai Thinh, Ninh Binh	43 ± 3	20	BV228	Cat Ba, Hai Phong	0
4	BD113	Hai Thinh, Ninh Binh	47 ± 3	21	BV229	Cat Ba, Hai Phong	132 ± 10
5	BD231	Hai Thinh, Ninh Binh	130 ± 8	22	BV312	Cat Ba, Hai Phong	0
6	BD304	Hai Thinh, Ninh Binh	0	23	BV315	Cat Ba, Hai Phong	135 ± 9
7	BD317	Hai Thinh, Ninh Binh	68 ± 4	24	BV318	Cat Ba, Hai Phong	0
8	CP2	Cat Hai, Hai Phong	275 ± 16	25	BV507	Cat Ba, Hai Phong	0
9	BT111	Cat Hai, Hai Phong	0	26	BV825	Cat Ba, Hai Phong	173 ± 12
10	BT157	Cat Hai, Hai Phong	0	27	BB21	Bai Tu Long Bay, Quang Ninh	435 ± 9
11	BT218	Cat Hai, Hai Phong	67 ± 3	28	BB24	Bai Tu Long Bay, Quang Ninh	377 ± 12
12	BT251	Cat Hai, Hai Phong	85 ± 5	29	BB32	Bai Tu Long Bay, Quang Ninh	180 ± 8
13	BT425	Cat Hai, Hai Phong	0	30	BB114	Bai Tu Long Bay, Quang Ninh	135 ± 5
14	BV103	Kien An, Hai Phong	35 ± 3	31	BB122	Bai Tu Long Bay, Quang Ninh	367 ± 13
15	BV108	Cat Ba, Hai Phong	0	32	BB242	Bai Tu Long Bay, Quang Ninh	350 ± 21
16	BV109	Cat Ba, Hai Phong	167 ± 11	33	BB425	Bai Tu Long Bay, Quang Ninh	435 ± 9
17	BV119	Cat Ba, Hai Phong	165 ± 13	34	CH155	Cat Ba, Hai Phong	211 ± 19

A total of 124 fungal strains isolated from coastal sediment samples were morphologically identified based on colony color, spore shape, conidiophore structure, and growth ability on basic media of the genus *Penicillium*, according to the identification key of Dang (2015) and Mohamed *et al.* (2015). Thirty-four strains with characteristics similar to species of the *Penicillium* genus were identified (Table 1). Among these, 7 strains were isolated from Ninh Binh Province, 7 strains from the

coastal region of Quang Ninh Province, and the remaining 20 strains were isolated from Hai Phong's coastal area. These strains were cultured on appropriate liquid media for 4 days to determine the MPA content produced (Table 1). Out of 34 fungal strains with characteristics similar to those of *Penicillium* species, 24 strains were found to have MPA activity, accounting for 67.65%. Among these, 6 strains produced MPA levels under 100 µg/mL, accounting for 26.08%; 8 strains produced MPA levels ranging from 101 to 200 µg/mL, accounting for 34.78%; 2 strains produced MPA levels > 200 µg/mL, accounting for 8.69%; and 8 strains showed high MPA activity > 300 µg/mL, including strains N22, N29, CP2, BB21, BB24, BB122, BB242, and BB425. Therefore, this study indicates that fungal strains of the genus *Penicillium* isolated from the coastal region of Bai Tu Long Bay exhibit higher MPA production compared to those from other marine areas. These strains will be used for further research in subsequent studies.

Some samples collected from coastal sediment areas have demonstrated the richness and diversity of fungal strains. Since the objective of this study was to collect strains of the *Penicillium* genus, we did not proceed with the isolation of other fungal strains. However, many previous studies have assessed the coastal sediment regions of Vietnam as having high ecological diversity in terms of flora, fauna, and microorganisms (Veettil *et al*., 2018). These areas represent a potential source for discovering new bioactive compounds. The collected samples were from the shorelines, where the vegetation cover provides a diverse source for fungal isolation (Yang *et al*., 2021).

Morphological identification of *Penicillium* strains

Besides the colony color characteristics on culture media, the characteristics of reproductive organs are also important for the classification of *Penicillium* strains. The *Penicillium* species have branched hyphae, which often appear with a very fine structure, forming a network of hyphal threads. These hyphae can be septate, dividing into separate cells.

The reproductive structure of *Penicillium*: conidia (asexual spores) are the main reproductive product of *Penicillium* species. Conidia are formed on structures called phialides, which are often arranged in clusters resembling a brush. This is a distinctive feature of *Penicillium*. The phialides arise from the main hyphae and produce conidia (spores) that are typically round or elliptical in shape. Conidia are usually green, yellow, or blue in color. This creates a distinctive structure called "penicillus," from which the spores are released into the air. This characteristic is commonly used for the species classification of fungal strains. Conidiophores are the conidial chains of the fungus, which can be single or multiple, clustered together in a bundle, and either straight or tangled. Based on their length and branching patterns, the conidiophores are also used as distinguishing characteristics for classification. The reproductive structures of species may branch (branches-rami) into biverticylates (two branches), triverticylates (three branches), or quaterverticylates (four branches) (Dang, 2015).

The *Penicillium* strains with high MPA activity were studied for their biological characteristics, showing morphological diversity in colony appearance, color, and optical microscope images (Figure 2). The

colors of the strains were primarily green, gray-green, and light gray-green. Compared with the classification of Dang (2015) and Mohamed *et al*. (2015), the strains showed similarities to species of the genus *Penicillium*.

The colonies of strain N22 have a dark green color, with white colony edges and a serrated margin on Cz medium. The hyphae are branched, and the conidiophore stalk divides into two branches (biverticillates), with each penicillus branch containing 2 to 3 chains of conidia, which are straight and contain 30 to 50 conidia. The colonies of strain N29 have a grey-green color, with light grey edges and center, while the middle layer is dark greyish-green. The colony margin is serrated. The hyphae are branched, and the conidiophore stalk divides into 3 to 4 branches, with each penicillus branch containing 2 to 3 short chains of conidia, closely packed together, forming a brush-like structure, with 7 to 20 conidia.

Strain CP2 has green-colored colonies with white edges and a slightly fluffy margin on MEA medium. The colony growth is poor on Cz medium. The hyphae are branched, and the conidiophore stalk divides into 4 to 5 branches. Each penicillus branch contains one long, slightly wavy chain of conidia with 30 to 50 conidia.

Strain BB122 has a greyish-green color, with grey edges that turn green after 2-3 days of cultivation on MEA medium. The strain shows poor growth on Cz and CYA medium. The hyphae are branched, and the conidiophore stalk divides into two branches. Each penicillus branch contains 2 to 3 short chains of conidia, with 2 to 5 conidia per chain. The conidial cells are clearly visible under the microscope.

The colonies of strain BB21 have a light grey-green color, with white edges and centers when cultured on CYA medium. It shows poor growth on CYAS, Cz, and MEA media. The hyphae are branched, and the conidiophore stalk divides into 2 to 3 branches. Each branch contains 10-30 conidia.

Strain BB24 grows well on CYAS and MEA media. The colonies are dark green on Cz medium, with grey edges. The hyphae have septa and are branched. The conidiophore stalk divides into 2 to 3 branches, with each branch containing 2 short chains of conidia, with 7 to 15 conidia per chain.

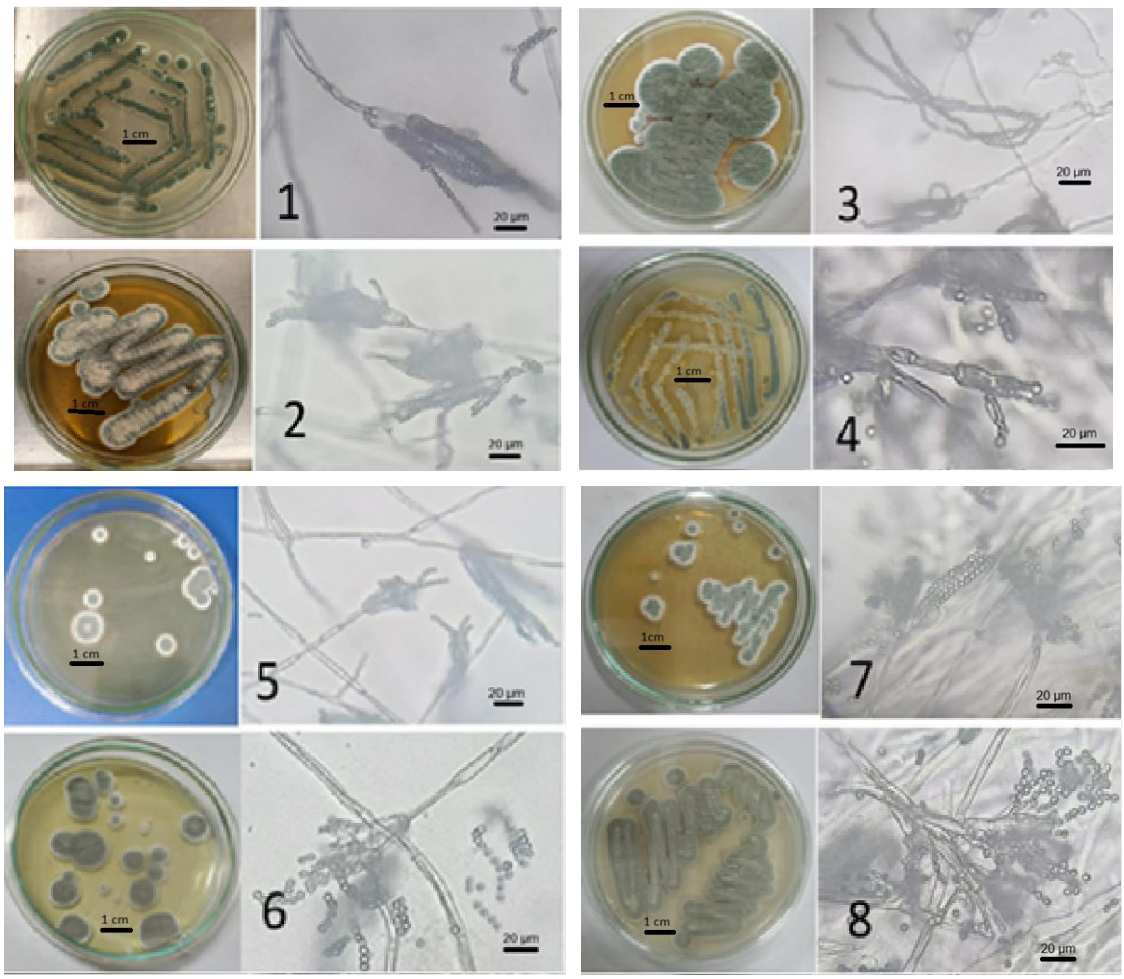
Strain BB242 shows poor growth on CYAS but grows well on MEA, Cz, and CYA media. The colonies have a grey-green color, with slightly fluffy edges that are white. The conidiophore stalk divides into 2 to 3 branches, with each branch containing long, straight chains of conidia, with 10 to 20 conidia per chain.

The colonies of strain BB425 do not grow on CYA medium, but grow well on YES medium, and have limited growth on MEA and Cz media. The colony has a dark grey-green color, fading towards the center. The hyphae are branched, and the conidiophore stalk divides into 3 branches, with each branch containing 2 to 3 separate chains of conidia, each chain consisting of 5 to 10 conidia.

Based on the research results above, we have described and confirmed that all 8 screened fungal strains exhibit the typical characteristics of species belonging to the genus *Penicillium*. However, to identify the strains at the species level, further ITS gene sequencing analysis is required, which could be published in future studies. In this paper, we focused on screening marine *Penicillium*

strains with high MPA production potential, aiming to explore additional distinctive characteristics from coastal regions for the development of materials for domestic pharmaceutical production.

This study reports the potential for screening *Penicillium* strains producing MPA, isolated from mangrove forests in three provinces: Ninh Binh, Hai Phong, and Quang Ninh. Among the 124 fungal strains isolated, 24 out of 34 strains were found to have MPA production activity. Of these, eight strains were capable of producing MPA at concentrations greater than 300 µg/mL. Additionally, the biological characteristics of the eight strains were identified as belonging to the genus *Penicillium*. The focus is on identifying and developing high MPA-producing strains for application in the production of materials for the domestic pharmaceutical industry. Additionally, it provides a valuable opportunity to explore and screen new bioactive compounds from marine fungal strains found in Vietnam.



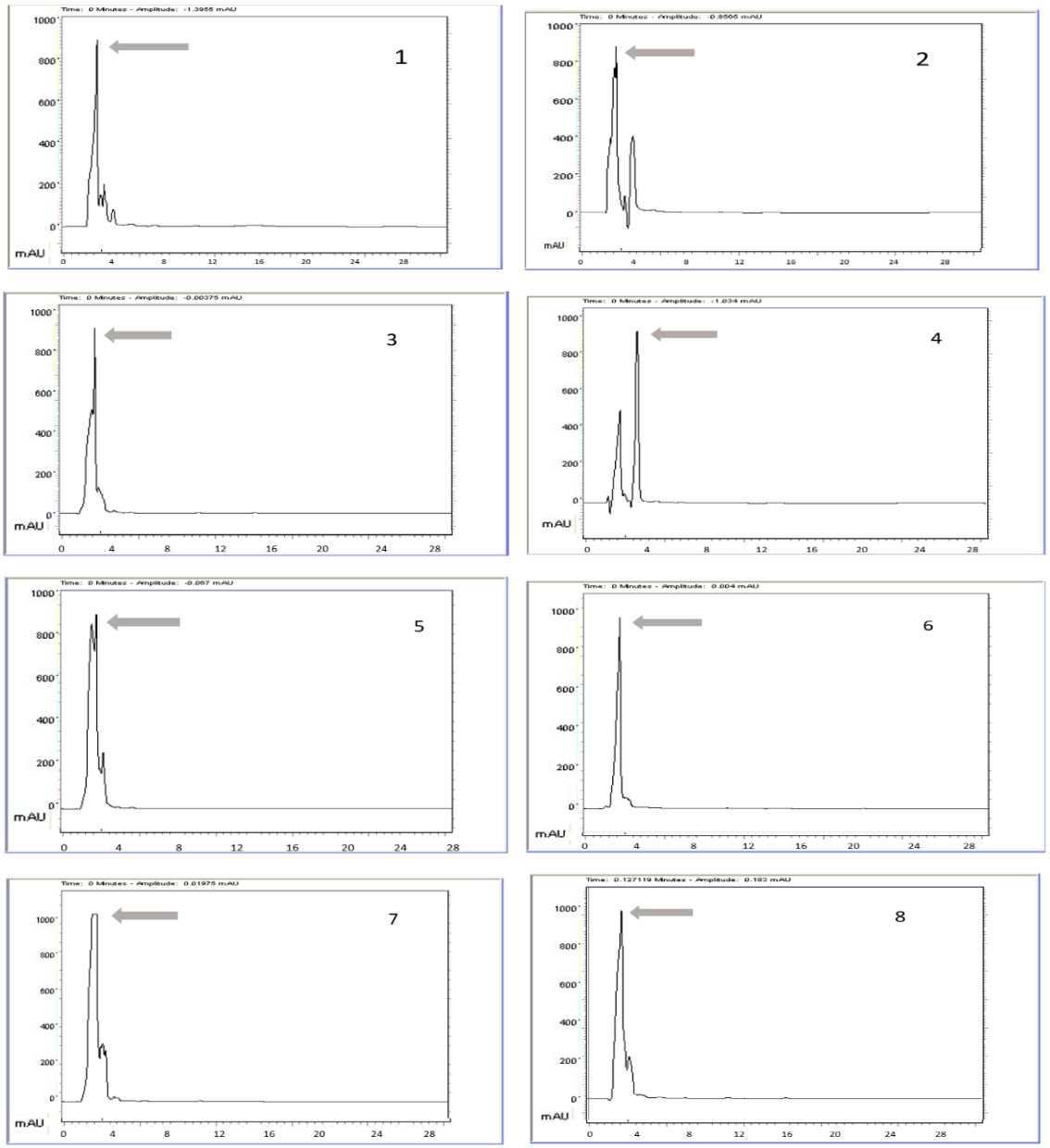


Figure 2. Photographs of colonies, electron microscopy images (x400) (A) and HPLC chromatograms (B) of fungal strains with MPA biosynthesis activity isolated from the northern coastal region of Vietnam. Specifically, the strains are as follows: 1. Strain N22; 2. Strain N29; 3. Strain CP2; 4. Strain BB122; 5. Strain BB21; 6. Strain BB24; 7. Strain BB242; 8. Strain BB425.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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