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ANTIFUNGAL POTENTIAL OF ENDOPHYTIC *BURKHOLDERIA* SPP., PLANT EXTRACTS, AND CURCUMIN SILVER NANOPARTICLES AGAINST *ASPERGILLUS* SPP. AND *FUSARIUM* SP.

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ABSTRACT

Numerous members of *Aspergillus* spp. and *Fusarium* spp. are pathogens possessing a broad spectrum of their host, including plants, animals, and humans. In this study, five endophytic *Burkholderia* spp., five plant extracts, and curcumin silver nanoparticles (C-AgNPs) were used to screen their antifungal activities against *Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus,* and *Fusarium* sp. ATCC 60289 (*F.* sp.). The results of dual assays showed that all five *Burkholderia* spp. strains NC119, NC148, NC160, NC166, and NC206 exhibited the antifungal activities with the percentage of inhibition (PI) ranging from 34.34% to 76.01%, in which the strain NC166 showed the strongest antifungal activity against all four studied fungi. Notably, *Burkholderia* spp. appeared to be effective against *F.* sp., with the PI greater than 50% in four out of five bacterial strains. In contrast, the results of well-diffusion assays with five plant extracts from *Perilla frutescens* L. (leaves, stems, roots), *Piper betle* L. (leaves), and *Zingiber officinale* Rosc. (rhizomes) had low probabilities of inhibiting *F.* sp. However, the bacterial strain *Burkholderia metallica* isolated from Perilla root showed the antifungal activities against *F.* sp with PI of 47.1%. In addition, the C-AgNPs performed considerable effectiveness in inhibiting the growth of all four fungi, with the highest PI of 71.17 ± 1.44% against *Aspergillus terreus.* These outcomes not only emphasize the potential of *Burkholderia* spp. and C-AgNPs as antimicrobial agents for the management of *Aspergillus* spp. and *Fusarium* spp., but also primarily rule out the antifungal possibility against *F.* sp. of some plant extracts, providing suggestions for future approaches in the research of these pathogenic fungi.

Keywords: Antifungal activity, *Aspergillus* spp., *Burkholderia* spp., curcumin silver nanoparticles, endophytic bacteria, *Fusarium* sp., plant extract.

INTRODUCTION

In recent decades, fungal infections have posed a considerable concern for public health. Opportunistic and systemic fungal pathogens such as *Aspergillus* spp. *and Fusarium* spp. not only cause diseases in plants, affecting crop yields and qualities but also induce illnesses in animals and humans,

challenging the healthcare management system.

Several members of the *Aspergillus* and *Fusarium* genera can affect humans and animals by causing serious pathogenic conditions, called aspergillosis and fusariosis, respectively. Aspergillosis, the more common disease between the two, is mostly caused by *A. fumigatus*, accounting for approximately 90% of the cases, followed by *A. flavus* and *A. terreus* (Perea & Patterson, 2002). On the other hand, despite being a rare mold infection, the incidence of fusariosis has been increasing in recent years, with *F. solani* and *F. oxysporum* causing more than 70% of the severe cases (Hoenigl *et al.*, 2021). These opportunistic fungal pathogens can penetrate and induce inflammatory reactions in humans, particularly in immunocompromised patients (Hof, 2020). The ubiquitous airborne conidia of *Aspergillus* spp. and *Fusarium* spp., after invading the body through the respiratory tract or open wounds, can cause local and systemic infections such as keratitis, onychomycosis, pneumonia, and even severe invasive fungal infections leading to mortality (Fang & Latgé, 2018; Hof, 2020). In addition, the mycotoxins produced by these fungi in contaminated food sources can lead to numerous digestive symptoms and systemic inflammation after being consumed by animals or humans. Some mycotoxins, such as aflatoxin in *Aspergillus* spp. and fumonisins in *Fusarium* spp., are even considered carcinogenic substances (Amaike & Keller, 2011; Hof, 2020).

Although the available antifungal therapies, such as azoles, echinocandins, and polyenes, are effective, numerous reports have revealed the increasing phenomenon of drug resistance and disease severity caused by *Aspergillus* spp. and *Fusarium* spp. (Al-Hatmi *et al.*, 2016; Erfandoust *et al.*, 2020; Hoenigl *et al.*, 2021; Latgé & Chamilos, 2020). As a result, new management strategies for these fungal infections are necessary. According to several international research, the utilization of microorganisms, plants, and nanoparticles for biological control is attracting increasing attention and demonstrating significant promise (Abo Elgat *et al.*, 2020; Hashem *et al.*, 2022; Muhorakeye *et al.*, 2024; Xi *et al.*, 2022). Therefore, in this study, we investigated the antifungal activity of certain endophytic *Burkholderia* strains isolated from *Oryza sativa* L., extracts from various plants, and curcumin silver nanoparticles against *A. fumigatus*, *A. flavus*, *A. terreus*, and. *F.* sp. ATCC 60289.

MATERIALS AND METHODS

Microbial strains and culture conditions

The five bacterial strains used in this study, which were obtained and isolated from roots of *Oryza sativa* L. in an upland rice paddy in Yen Bai province, were those of the *Burkholderia* genus, namely NC119, NC148, NC160, NC166, and NC206. These bacteria were cultured on Petri dishes composed of 1/6 Tryptic Soy Agar (TSA) medium (containing 5 g/L of Tryptic Soy Broth (TSB), and 16 g/L of agar) at 28 ± 2^{o}C overnight before being used for the dual culture experiment.

Fungal strains, culture conditions, and spore collection

Four fungal strains, including *A. fumigatus*, *A. flavus*, *A. terreus*, and *Fusarium* sp. ATCC 60289 (*F.* sp.) were provided by the Oxford University Clinical Research Unit

(OUCRU) in Ho Chi Minh City. Fungi were cultured on 9-cm-diameter Petri dishes containing potato dextrose agar (PDA) medium for 5 – 7 days or until they spread over more than half of the plates. Subsequently, approximately 8 - 10 mL of sterile sodium chloride solution (0.85%) was added to a culture dish, and the spores were mixed evenly into the with a sterile cotton swab. The spore suspension was collected and stored in a sterile 2 mL Eppendorf tube at 8^{o}C until being used.

Dual culture of fungi and bacteria on agar plates

Bacterial strains were cultured simultaneously with fungal strains on the 9-cm-diameter Petri dishes containing PDA medium. On each plate, one fungal strain and one bacterial strain were co-cultured. Initially, 10 µL of fungal spore suspension was introduced at the center. Then, bacteria were streaked at four positions: 0h, 3h, 6h, and 9h, about 2 cm from the fungi inoculation point. The dish was then incubated at 34 ± 2^{o}C and daily monitored for one week or until the fungus in the control dish (without bacteria) grew up to the plate's edge. The antifungal effect of each strain was expressed as the mean of the percentage of fungal growth inhibition: PI = [(C - T)/C] × 100, in which C and T were the fungus growth radius in control plates and treatment plates (mm), respectively (Dinesh *et al.,* 2015). Each experiment was run in triplicate. The effect caused by bacteria on the fungal mycelium was also studied microscopically.

Plant samples and extraction methods

Plant samples used in this study include leaves, stems, and roots of *Perilla frutescens* L. (*P. frutescens*), leaves of *Piper betle* L. (*P. betle*), and rhizomes of *Zingiber officinale* Rosc. (*Z. officinale*). All plant samples were processed within 2 hours after being harvested. Plant samples were washed with clean water, soaked in sodium chloride 0.9% for 10 minutes, then soaked in ethanol 70% for 1 minute. Cleaned samples were cut into small pieces and finely ground using a ceramic mortar and pestle with sodium chloride 0.9% in a sterile environment to obtain plant extract. This extract was subsequently ultrasound for 30 minutes at 50^{o}C and centrifuged at 10,000 rpm for 10 minutes. The experiment utilized three forms of extracts: fresh extract (used immediately after extraction), 24-hour, and 48-hour extracts (extracts were stored at 8^{o}C until use).

Agar well diffusion method

The experiment was conducted on 1/6 PTSA medium in 9 cm Petri dishes, each of which had four agar wells (6 mm in diameter) about 2 cm from the center at four positions: 0h, 3h, 6h, and 9h, respectively. Ten (10) µL of fungal spore suspension was pipetted at the center of the plate, and 30 µL of plant extract was added to each agar well (Balouiri *et al.*, 2016). The plate was incubated at 34 ± 2^{o}C and fungal growth was monitored daily, similar to a dual culture assay.

Antifungal test of curcumin silver nanoparticles

The antifungal test was modified from the poisoned food technique (Balouiri *et al.*, 2016). The experiment was carried out on 5-cm-diameter Petri dishes consisting of Potato Dextrose Agar (PDA) medium (containing 8 g glucose and 7 g agar dissolved in 115 mL of potato extract and

285 mL of water), whose pH was 5.6 ± 0.2. Subsequently, the curcumin silver nanoparticles (C-AgNPs) tube was thoroughly mixed. Next, 200 µL of nanofluid was pipetted onto the medium and spread evenly, and 15 µL of fungal spore solution was added at the center. The plate was then incubated at 34 ± 2°C until the fungus in the control dish reached the plate's edge, similar to a dual culture assay.

Data analysis

The data was analyzed using One-way ANOVA and the Tukey test on Microsoft Excel software.

RESULTS AND DISCUSSION

Fungal inhibition of five strains of endophytic bacteria in plants

Five endophytic bacterial strains were subjected to a dual culture assay with four types of pathogenic fungi: *F.* sp. ATCC 60289, *A. fumigatus*, *A. flavus*, and *A. terreus* on 1/6 PTSA medium to evaluate their antagonistic activities against those fungal pathogens. Daily observations showed that *Aspergillus* strains needed five to eight days to reach the edge of culture dishes, whereas *F.* sp. required up to 17 days to do that (Figure 1). Meanwhile, the dual culture of these fungi with all five bacterial strains led to a decrease in the growth rates of fungal colonies.

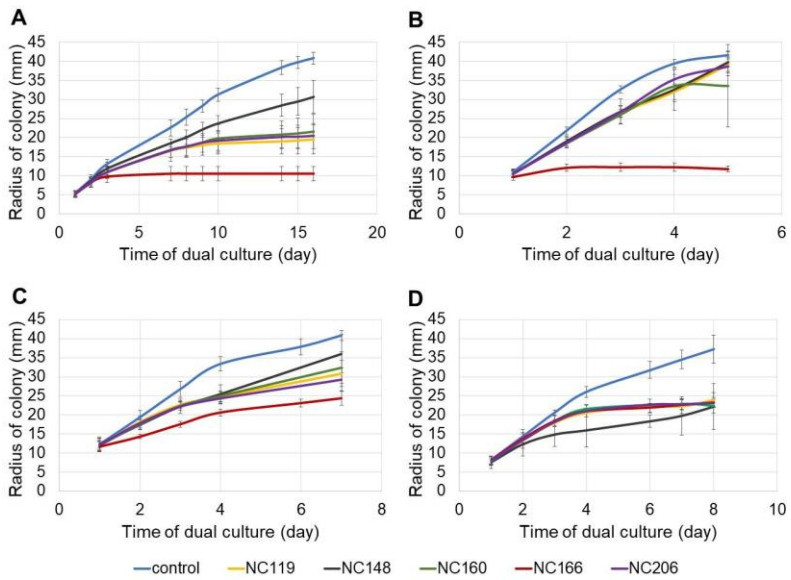

Figure 1. Growth curves of four fungi when dual cultured with endophytic bacterial strains *Burkholderia*; A – *F.* sp.; B – *A. fumigatus*; C – *A. flavus*; D – *A. terreus*

To compare the antifungal ability among these bacterial strains, their growth inhibition rates against *A. fumigatus*, two fungal strains *A. flavus*, and *A. terreus*, along with *F.* sp. were recorded on the fourth, seventh, and seventeenth days of dual culture, respectively (Table 1). Accordingly, all five bacterial strains showed inhibition against mycelial growth, with the percentage of growth inhibition (PI) ranging from 12.34

± 5.49% to 73.93 ± 4.39%. Notably, NC166 demonstrated a clear inhibitory effect on all four fungal strains, resulting in the PI of 34.34 ± 5.17% to 73.93 ± 4.39%. In particular, its inhibitory effect against two fungal strains *F.* sp. and *A. fumigatus* was the most remarkable (Figures 2A, 2B, and Table 1). In correlation with other research, the mycelial growth inhibition of these *Burkholderia* strains is not as strong as that of some *Tricoderma* and *Hypocrea* strains (Muhorakeye *et al.*, 2024b) or essential oils from *Citrus aurantium* and *C. sinensis* (Abo Elgat *et al.*, 2020). However, that inhibition is comparable with the mycelial inhibition of many antifungal bioagents, such as several yeasts (Jaibangyang *et al.*, 2020), actinomyces (Shakeel *et al.*, 2018), and mandarin (*Citrus reticulata*) peel ethanol extracts (Abo Elgat *et al.*, 2020b). Furthermore, it is even higher than that of some entomopathogenic fungi (Muhorakeye *et al.*, 2024b) and orange or lemon peel ethanol extracts (Abo Elgat *et al.*, 2020b). These results indicate that *Burkholderia* sp. NC166 is a potential antifungal bioagent.

Moreover, the strong antagonistic activity of the NC166 strain was substantiated by the mycelium morphology change when co-cultured with this strain compared to the control mycelium. Specifically, the fungal mycelia formed more septa, and the hyphae branched more and earlier. In addition, some fungal hyphae had thinner cell walls and tended to be deformed (Figure 2E, 2F, and 2G). Hence, NC166 can be a potential microbiological tool for the management and control of fungal diseases. Nevertheless, this project merely involved evaluating the percentage of mycelia growth inhibition (PI) and changes in mycelial morphology in a dual culture assay. Thus, further research is required on the antifungal mechanism, such as the biologically active substances and the aggregation site, and the optimal culture conditions to obtain the best inhibitory effect. At the same time, for biocontrol applications, the safety of this bacterial strain for the hosts needs to be thoroughly studied.

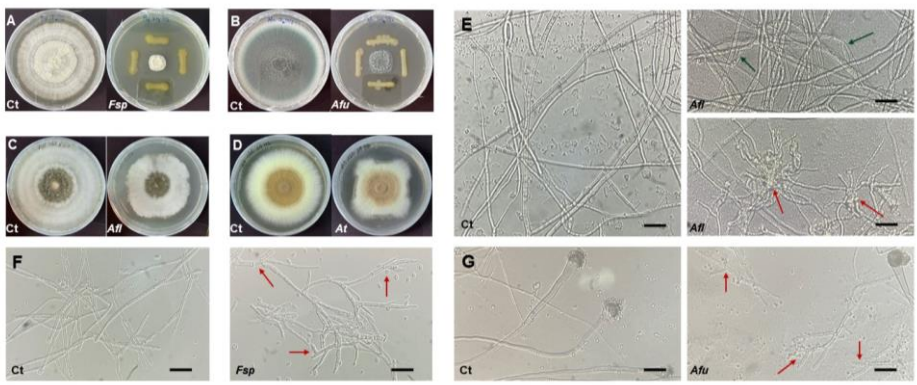

Figure 2. A - D - Dual culture assay of NC166 with four fungi: A - *F.* sp.; B - *A. fumigatus*; C - *A. flavus*; D - *A. terreus*; E - G - Fungal mycelium morphology changes when dual cultured with NC166: E - *A. flavus* which was dual-cultured with NC166 had thinner cell walls leading to abnormal hyphae form (green arrow), branched earlier and more regularly (red arrow); F - *F.* sp. mycelia formed more septa, and the hyphae branched more and earlier (red arrow); G - *A. fumigatus* when dual-cultured with NC166 had thinner cell walls, and the hyphae branched more (red arrow) (Ct - Control, *Fsp* -

NC166 dual cultured with *F.* sp., *Afu* - With *A. fumigatus*, *Afl* - With *A.flavus*, *At* - With *A. terreus*); scale bar: 20 µm.

Additionally, *F.* sp., a member of the highly drug-resistant genus *Fusarium* (Hoenigl *et al.*, 2021), could be inhibited by four bacterial strains: NC166, NC119, NC206, and NC160, with PI from nearly 50% up to 73.93 ± 4.39% (Table 1). This result is comparable with the mycelial inhibition of some previously studied potent antifungal bioagents (Muhorakeye *et al.*, 2024). This is the premise for the study of novel antifungal substances or the selection of optimal bacterial strains for biological control. It is suggested to continue testing the antagonistic activity of bacterial secretions against *F.* sp. to determine whether the biologically active substance accumulates in the cell or is secreted into the culture medium.

Table 1. The percentage of fungal growth inhibition* of endophytic strains *Burkholderia*.

Bacterial strain	Fungal growth inhibition (%)			
	Fusarium. sp.	*A. fumigatus*	*A. flavus*	*A. terreus*
	Day 16	Day 4	Day 7	Day 7
Burkholderia cenocepacia NC119	53.01 ± 8.59 b	18.38 ± 5.38 b	24.34 ± 6.06 bc	35.21 ± 5.91 a
Burkholderia cepacia NC148	24.32 ± 1.33 c	17.49 ± 1.44 b	12.34 ± 5.49 c	41.62 ± 5.91 a
Burkholderia cepacia NC160	47.63 ± 9.28 b	15.63 ± 4.66 b	21.29 ± 6.83 bc	33.54 ± 3.83 a
Burkholderia cepacia NC166	73.93 ± 4.39 a	69.67 ± 1.57 a	39.53 ± 5.01 a	34.34 ± 5.17 a
Burkholderia cepacia NC206	49.68 ± 6.7 b	11.58 ± 4.46 b	30.96 ± 0.57 b	33.68 ± 4 a

*The fungal inhibition rate is the average ± SD of three independent replicates. In each column, the mean values marked with the same letter are not statistically significantly different ($p < 0.05$).

Fungal inhibitory potential of plant extracts

With the remarkable results obtained on the *F.* sp. growth inhibition of the studied *Burkholderia* strains, the antifungal characteristics of several plant extracts were further investigated. The agar well diffusion method was applied to five types of plant extracts: leaves, stems, and roots of *P. frutescens*, leaves of *P. betle*, and rhizomes of *Z. officinale*. Overall, there was no

noteworthy difference between the growth rate of *F.* sp. in the samples with plant extracts and that of the control samples (Figure 3A). The PIs of most samples were less than 20% (Table 2), with the exceptions of bacteria-present samples, which will be discussed thereafter. Because *F.* sp. is described to be closely related to *F. solani* (*Fusarium* sp. - 60289 | ATCC, n.d.), several papers on antifungal activity against *F. solani* of plant extracts were assessed. Many plant extracts were revealed to have a mycelial growth inhibition percentage of 100% at certain concentrations, including some favorable representations like *Allium sativum*, *Capsicum annuum*, and even *Z. officinale* (Shrestha & Tiwari, 2009; Xi *et al.*, 2022). However, it is important to note that the extracting method and antifungal activity assays in those studies were designed differently from this research, which might explain the dissimilar outcomes. These results suggest that the antifungal potential against *F.* sp. of the examined plant extracts is relatively low due to the properties of the extract itself or the utilized methods being incompatible.

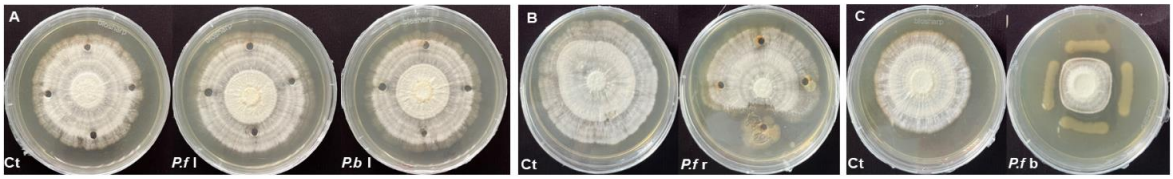

Figure 3. The growth of *F.* sp. with the presence of plant extract and/or bacteria; A – Control sample (Ct) and agar well diffusion sample with 24-hour extract *of P. frutescens* leaves *(P.f* l) and *P. betle* leaves (*P.b* l); B – The growth of *F.* sp. is restricted by bacterial strains grown from agar wells containing *P. frutescens* root extract (*P.f* r); Ct – Control sample and dual-culture sample (*P.f* b) with a bacterial strain isolated from the colony in sample 3B.

Table *2*. The percentage of *F.* sp. growth inhibition of plant extracts

Plant extracts	**The fungal resistance rate after 192-240 hours of diffusion (%)**		
	Fresh extract	24-hour extract	48-hour extract
P. frutescens leaves	12.29 ± 6.08 a	13.49 ± 4.06 bc	1.92 ± 0.75c
P. frutescens stems	1.76 ± 8.05 a	32.22 ± 8.51* a	20.44 ± 9.13* ab
P. frutescens roots	7.46 ± 10.57 a	14.61 ± 3.9* b	10.76 ± 7.53 bc
P. betle leaves	0.71 ± 5.87 a	0.37 ± 5.02 c	1.71 ± 5.25 c
Z. officinale rhizomes	2.62 ± 7.5 a	0 ± 3.24 c	28.54 ± 2.13* a

The inhibition effect of samples using fresh extract and 24-hour extract is measured after 192 hours, and that of 48-hour extract samples is measured after 240 hours. The fungal inhibition rate is the average of three intra-batch replications. The fungal strains were independently statistically recorded. In each column, the mean values marked with the same letter are not statistically significantly different ($p < 0.05$). Samples with the presence of bacteria are marked *

Bacterial strains grown from plant extracts show antifungal activity

With plant extracts, the growth of numerous bacterial strains was observed from the agar

wells of some samples. The development of *F.* sp. was restricted at the sites of agar wells containing bacteria (Figure 3B) and samples with bacteria also demonstrated a substantially higher rate of fungal growth inhibition than other samples (Table 2). A dual-culture experiment conducted with one of these strains showed limited growth of *F.* sp. (Figure 3C) and an inhibition percentage of 47.1% after 18 days. Applying the matrix-assisted laser desorption-ionization-time-of-flight mass spectrometry (MALDI-TOF MS) technique, the strain was identified as *Burkholderia metallica*. Together with the aforementioned outcomes of five bacterial strains, this result once again confirms the inhibitory activity of *Burkholderia* spp. against *F.* sp., encouraging further research on the antifungal potential of the *Burkholderia* genus against other members of *Fusarium* spp. and various pathogenic fungi groups.

Antifungal activity of curcumin silver nanoparticles

Silver nanoparticles (AgNPs or nanosilver) have been increasingly noticed thanks to their widespread use, especially their antimicrobial activities against microbe pathogens (Tran *et al.*, 2013). Recently, the results of curcumin nanosilver (C-AgNPs) antimicrobial test in our laboratory revealed that C-AgNPs 300 ppm (μg/mL) restrained the development of *Staphylococcus aureus* and *Pseudomonas aeruginosa* about 92.86% in comparison with Streptomycin 100 μg/mL and 59.57% compared with Ciprofloxacin 25 μg/mL, respectively (unpublished results of Dr. Nguyen). Therefore, in this study, the antifungal capability of C-AgNPs against the four fungal strains was examined by the poisoned food method. The results showed that C-AgNPs inhibited approximately 41.64 ± 2.98% up to 71.17 ± 1.44% mycelial growth of these fungal strains. The statistical test indicated that *A. terreus* was the most sensitive strain, followed by *A. fumigatus* (61.86 ± 1.11% of mycelial growth was inhibited by C-AgNPs). Furthermore, for *A. terreus*, this effect is maintained for up to 5 - 7 days after the control mycelium spreads out the entire Petri dish. This result suggested that curcumin silver nanoparticles can be used to control fungi, especially *A. terreus.* However, some authors are concerned that nanoparticles generally were toxic to organisms and the environment (Bartłomiejczyk *et al.*, 2013, Tortella *et al.*, 2020), the characteristics and activity mechanism of this kind of nanosilver should be investigated thoroughly before being applied.

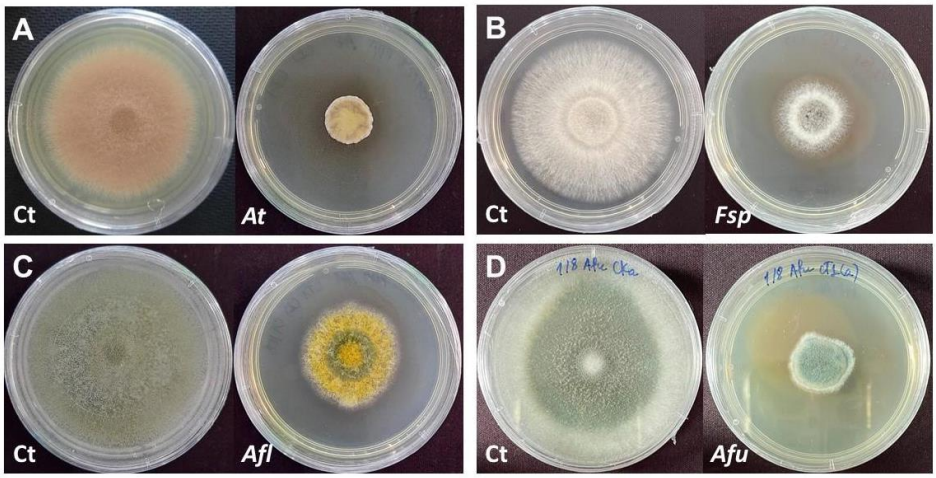

Figure 4. Mycelial growth inhibition by curcumin-silver restrained against four studied fungal strains (A-D); A - C-AgNPs restrained 71.17 ± 1.44% of mycelial growth of *A. terreus*; B – *Fusarium* sp. mycelial development was inhibited 41.64 ± 2.98% by C-AgNPs; C - C-AgNPs inhibited 42.63 ± 0.56% of mycelial growth as well as changed the mycelial color and morphology of *A. flavus;* D – The mycelial growth inhibition for *A. fumigatus* was 61.86 ± 1.11%.

CONCLUSION

This study presents preliminary results on the antifungal activity of endophytic *Burkholderia* spp. isolated from upland rice roots of *Oryza sativa* L., *B. metallica* observed in experiments with plant extracts, and curcumin silver nanoparticles against *A. fumigatus, A. flavus, A. terreus,* and *Fusarium* sp. ATCC 60289. These outcomes indicate that some endophytic *Burkholderia* spp. and curcumin silver nanoparticles are promising for the management of all four fungi as these agents performed considerable inhibitory effects on the fungal growth. To that end, the potential of *Burkholderia* strains needs to be further analyzed in terms of their secondary metabolites and metabolic mechanisms, as well as their safety for the host and environment. Additionally, the characterization and oxidation stage of nanoformulation could be investigated in greater detail for advanced applications. Furthermore, it is important to not only optimize culture conditions to obtain the maximal fungal inhibitory effect but also design a compatible extraction method of studied plants, such as maceration or essential oil, for more potential tests of antifungal activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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