



**IN VITRO EVALUATION OF ANTIFUNGAL OF UNGU LEAF
(*Graptophyllum Pictum L. Griff*) EXTRACT AND ACTINOMYCETES
ISOLATES AGAINST *Candida albicans***

**EVALUASI IN VITRO ANTIJAMUR EKSTRAK DAUN UNGU (*Graptophyllum Pictum L. Griff*)
DAN ISOLAT ACTINOMYCETES TERHADAP *Candida albicans***

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Abstract

The high prevalence of infections caused by the opportunistic fungus *Candida albicans* encourages research to find alternative antifungals that are safer and more effective than synthetic drugs, which can cause side effects and resistance. This study aims to compare the antifungal potential of purple leaf extract (*Graptophyllum pictum* (L.) Griff) and *Actinomyces* isolates against the growth of *C. albicans* using the Ultrasound-Assisted Extraction (UAE) method and tested by the well diffusion method at concentrations of 30; 40; and 50%. The results showed that purple leaf extract inhibited the growth of *C. albicans* with an average inhibition zone diameter between 16.475 mm to 18.2 mm, while *Actinomyces* isolates showed a smaller inhibition zone, which was between 10.875 mm to 12.05 mm. Statistical analysis using the independent T-test and Mann-Whitney test confirmed a significant difference in inhibition between purple leaf extract and the *Actinomyces* isolate at each concentration tested. The mechanism of action of both is by binding to ergosterol in the fungal cell membrane, forming complex compounds that result in increased permeability and ultimately inhibit fungal growth. Especially at 30% concentration, purple leaf extract showed the highest effectiveness with an average inhibition zone of 18.2 mm.

Keywords: *Actinomyces*; Antifungal; *Candida albicans*; Purple leaf; Ultrasound-Assisted Extraction (UAE)

Abstrak

Tingginya prevalensi infeksi yang disebabkan oleh jamur oportunistik *Candida albicans* mendorong penelitian untuk mencari alternatif antijamur yang lebih aman dan efektif dibandingkan dengan obat sintetik yang dapat menimbulkan efek samping dan resistensi. Penelitian ini bertujuan membandingkan potensi antijamur ekstrak daun ungu (*Graptophyllum pictum* (L.) Griff.) dan isolat *Actinomyces* terhadap pertumbuhan *C. albicans* menggunakan metode Ultrasound-Assisted Extraction (UAE) dan diuji dengan metode difusi sumuran pada konsentrasi 30; 40; dan 50%. Hasil penelitian menunjukkan bahwa ekstrak daun ungu menghambat pertumbuhan *C. albicans* dengan rata-rata diameter zona hambat antara 16,475 mm hingga 18,2 mm, sedangkan isolat *Actinomyces* menunjukkan zona hambat yang lebih kecil, yaitu antara 10,875 mm hingga 12,05 mm. Analisis statistik menggunakan uji t Independen dan Mann-Whitney mengonfirmasi adanya perbedaan signifikan dalam daya hambat antara ekstrak daun ungu dan isolat *Actinomyces* pada setiap konsentrasi yang diuji. Mekanisme kerja keduanya adalah dengan berikatan pada ergosterol di membran sel jamur, membentuk senyawa kompleks yang mengakibatkan peningkatan permeabilitas dan akhirnya menghambat pertumbuhan jamur. Terutama pada konsentrasi 30%, ekstrak daun ungu menunjukkan efektivitas tertinggi dengan rata-rata zona hambat 18,2 mm.

Kata Kunci: *Actinomyces*; Antijamur; *Candida albicans*; Daun ungu; Ultrasound-Assisted Extraction (UAE)

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INTRODUCTION

In Indonesia, there are many candidiasis fungal infections with the prevalence of incidence reaching 20–25%. Candidiasis is a fungal infection caused by *Candida* species (Safitri & Qurrohman, 2022). The *Candida albicans* fungal is the most common cause of candidiasis among the *Candida* genus (Crawford et al., 2018). The use of synthetic antifungals such as fluconazole, nystatin, and amphotericin B is often relied upon in the treatment of *C. albicans* infections. However, recent studies have shown that the use of these drugs is often associated with adverse side effects and growing fungal resistance (Czajka et al., 2023).

Graptophyllum pictum (L.) Griff is one of the plants used as herbal medicine because it has pharmacological effects such as antioxidant, anti-inflammatory, anti-implantation, antidiabetic, antibacterial, antifungal, antihemorrhoidal, and has immunomodulatory properties (Dhywinanda et al., 2023). Research conducted previously suggested that *G. pictum* maceration extract can inhibit the growth of *C. albicans* with the highest antifungal power owned by 40% extract (Wahyuningtyas, 2008). In addition, *G. pictum* is known to have antifungal activity caused by various bioactive compounds in it, such as flavonoids, alkaloids, tannins, and saponins. The active compounds in *Graptophyllum pictum* are able to damage the integrity of the fungal cell membrane, causing permeability disruption. As a result, important components such as ions and essential metabolites leak out of the fungal cell (Wulandari et al., 2022).

Actinomycetes 9ISP1 is a type of Gram-positive bacterial group microorganism that can be found in soil and sea and has great potential as a producer of secondary metabolites that have biological activity as antimicrobials (Kumala et al., 2015). About 95% of *Actinomycetes* strains isolated from soil are of the genus streptomyces (Takahashi & Nakashima, 2018). Certain antifungal compounds can interact with sterols in fungal cell membranes, causing increased membrane permeability and leakage of intracellular components, which ultimately results in fungal cell death. In the research of Aminnullah et al. (2020) found that secondary metabolites produced by *Actinomycetes* can inhibit the growth of *C. albicans*.

In the present study, 32 *Actinomycetes* isolates obtained from the soil of the Arboretum of the Universitas Riau were screened for antifungal activity against *Fusarium oxysporum* f.sp. lycopersici and *Ganoderma boninense* using the agar diffusion method. A total of 31 isolates demonstrated inhibitory activity against *F. oxysporum* f.sp. lycopersici, with isolate A2.01 exhibiting the highest inhibition zone (36.10 mm). Meanwhile, 28 isolates showed activity against *G. boninense*, with the highest inhibition zone recorded for isolate D2.28 (45.71 mm) (Queendy et al., 2019)

Ultrasound Assisted Extraction (UAE) is an extraction technique that uses ultrasonics to produce rapid solvent movement, resulting in higher mass transfer rates and extraction acceleration. The device used in UAE is an ultrasonic water bath (Singla & Sit, 2021). The main mechanism involved in this process is acoustic cavitation. Acoustic cavitation is the phenomenon of the formation, growth and subsequent rupture of small bubbles in a liquid when exposed to ultrasonic waves (Carreira-Casais et al., 2021). When these bubbles burst, they damage the cell wall, allowing the solvent to penetrate into the intracellular material and increase the contact surface area between the solvent and the compound of interest, thus helping to produce increased mass transfer accompanied by good mixing (More et al., 2017). Compared to other advanced extraction techniques, UAE is more economical, environmentally friendly, efficient and practical as it can be used at room temperature (Syahir et al., 2020).

Several studies regarding the antifungal effectiveness of *G. pictum* extract and *Actinomycetes* isolates from Bogor Botanical Garden isolates showed significant results as an alternative material against the growth of *C. albicans*. Therefore, this study aims to compare the antifungal effectiveness of *G. pictum* extract (*G. Pictum* L. Griff) and *Actinomycetes* isolates using the UAE method against *C. albicans* growth.

MATERIALS AND METHODS

Materials

The samples in this study were *Actinomyces* isolates obtained from the Bogor Botanical Garden soil and *Graptophyllum pictum*. The samples were divided into eight treatment groups, namely three groups of *G. pictum* extract at concentrations of 30; 40; and 50%, three groups of *Actinomyces* isolate extracts at concentrations of 30; 40; and 50%, a positive control using fluconazole, and negative control using *dimetil sulfoksida* (DMSO), and *Candida albicans* fungal.

Methods

Isolation of *Actinomyces*

A total of 1 g of soil sample from Bogor Botanical Garden was put into a test tube, then 10 mL of distilled water was added. The mixture was homogenized until it reached a concentration of 10^{-1} . This process was repeated with the same steps until a concentration of 10^{-6} was obtained. Next, 0.1 mL of *Actinomyces* isolate that had gone through the dilution process was inoculated into the SCA media using the pouring technique. The samples were then incubated at 37 °C for two weeks. If colonies are found to form on the SCA media, it can be concluded that the soil sample contains *Actinomyces* bacteria.

The soil sample was collected using a simple random sampling approach. Soil was taken from the topsoil layer at a depth of 5–10 cm, after removing surface debris such as leaves and stones. The sampling site was selected based on criteria commonly associated with the presence of *Actinomyces*, namely well-drained soil, neutral to slightly alkaline conditions, and an area with organic matter content but without waterlogging.

According to Davis and Stout (Davis & Stout, 1971), the diameter of the inhibition zone is classified into four categories: inhibition zone diameter ≥ 20 mm is categorized as very strong inhibition, 10–20 mm is categorized as strong inhibition, 5–10 mm is categorized as moderate inhibition, and ≤ 5 mm is categorized as weak inhibition.

Extraction of Isolate *Actinomyces*

After *Actinomyces* were detected in the soil samples through the inoculation and incubation process in SCA media, the extraction step was carried out using the Ultrasound-Assisted Extraction (UAE) method with an Ultrasonic Water Bath tool. The water bath was filled with distilled water and set at 45 °C. Once the temperature reached the desired point, the mixed soil samples were placed in an iron container submerged in the ultrasonic water bath. The extraction process was run at 40 kHz for 20 minutes. After the duration is complete, the extraction results are obtained in the form of *Actinomyces* isolates with a concentration of 100%.

Extraction of *Graptophyllum pictum*

A total of 50 g of *G. pictum* powder from IP2SIP Cimanggu was weighed and put into an Erlenmeyer tube. A 70% ethanol was added in a ratio of 1:5, then extracted using an ultrasonic bath cleaner at 40 kHz for 20 minutes. The extracted filtrate was filtered with Whatman no. 1 filter paper, then evaporated using a rotary evaporator at 70 °C to obtain *G. pictum* extract.

Dilution of Extract

The results of *G. pictum* extract and *Actinomyces* isolates will be diluted with DMSO as a solvent. To achieve a concentration of 40% in the extract obtained from the UAE method with a concentration of 100%, 4 mL of isolate is dissolved with 6 mL of DMSO, to achieve a concentration of 50%, 5 mL of isolate is dissolved with 5 mL of DMSO, and for a concentration of 30%, 3 mL of isolate is dissolved with 7 mL of DMSO.

Candida albicans Fungal Suspension Manufacturing

A total of 0.5 mL BaCl₂ was mixed with 99.5 mL H₂SO₄ in a test tube and then homogenized. A suspension of 0.5 Mc. Farland suspension is a standard suspension that shows bacterial turbidity

(concentration of 10^8 CFU/mL). If the turbidity is in accordance with the standard, then the *C. albicans* suspension is taken as much as 3 mL with a syringe and then mixed into the SDA media.

Antifungal Activity Test

A total of 10 mL of SDA media was poured aseptically into a petri dish and allowed to solidify as a base layer. Next, 50 μ L of *C. albicans* suspension (10^8 CFU/mL) was poured into the petri dish and then leveled by rotating in the direction of the number 8 then allowed to solidify and become a homogeneous solution as the second layer. Next, make wells in each petri dish using a cylinder cup on top of the media. If the wells have been formed in the petri dish, remove the cylinder cup and then fill the wells with positive control solution and negative control and test solution with a volume of 50 μ L each. After that, the culture media was incubated at 37 °C for 24 hours. After the incubation process was complete, observations were made of the clear zone of the colonies in the petri dish.

RESULTS

Actinomyces identification was done macroscopically by growing samples on SCA media and microscopically using Gram stain (Figure 1). Macroscopically, bacterial colonies were found to be grayish white, slightly convex, with uneven edges. Microscopy showed filamentous rod-shaped bacteria, Gram positive, and purple in color, in accordance with the characteristics of *Actinomyces*.

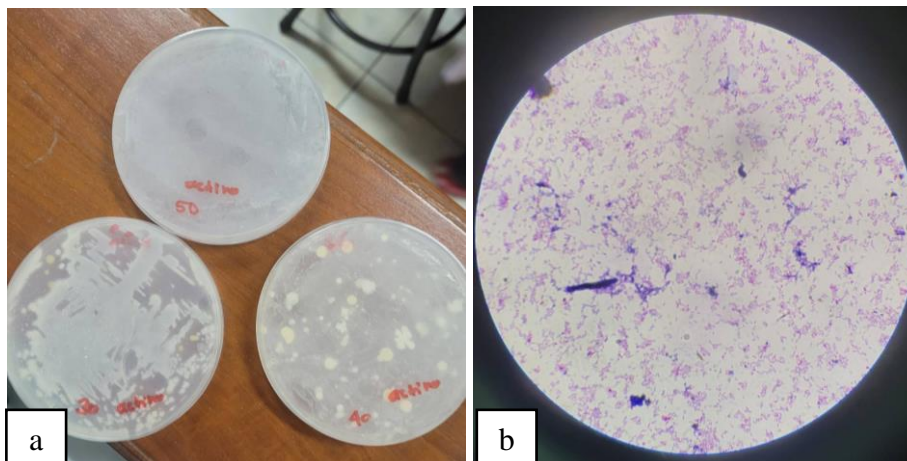


Figure 1. Identification of *Actinomyces*, macroscopic identification on Starch Casein Agar (SCA) media (a) and microscopic identification using Gram stain (b)

The identification of *C. albicans* was also done macroscopically by growing samples on Sabouraud Dextrose Agar (SDA) media and microscopically using Gram stain (Figure 2). Macroscopically, colonies of *C. albicans* fungi on SDA media looked like white and slippery cream. Microscopically, they showed blastospores, hyphae, or pseudohyphae as seen in Figure 2b, or a combination of both.

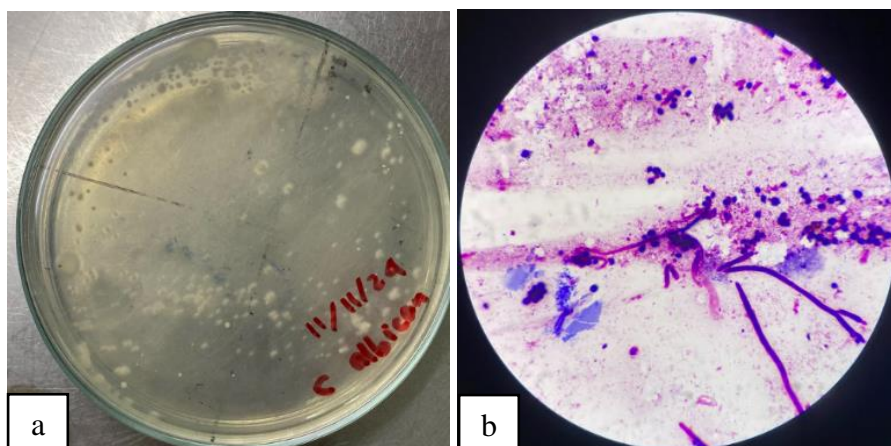


Figure 2. Identification of *Candida albicans*, macroscopic identification on Sabouraud Dextrose Agar (SDA) media (a) and microscopic identification using Gram stain (b)

Table 1. Measurement results of zone of inhibition of *Graptophyllum pictum* extract against *Candida albicans* growth

Repetition	Concentration of <i>G.pictum</i> (mm)			Positive control	Negative control
	30%	40%	50%		
1	17.7	17	17	33.5	0
2	19	17	16.2	32.2	0
3	18.6	17	16.7	31.5	0
4	17.5	18	16	32	0
Average \pm SD	18.2 \pm 0.7	17.25 \pm 0.5	16.47 \pm 0.46	32.3 \pm 0.85	0 \pm 0

The data presented in Table 1 shows the results of observations from four repetitions of *G. pictum* extract treatment with three different concentrations (30; 40; and 50%) against the growth of *C. albicans*. At 30% concentration, the observation value ranged from 17.5 mm to 19 mm, with an average of 18.2 mm and a standard deviation of 0.72 mm. The 40% concentration had observed values between 17 mm to 18 mm, with an average of 17.25 mm and a standard deviation of 0.50 mm. Meanwhile, the 50% concentration showed observation values between 16 mm to 17 mm, with an average of 16.47 mm and a standard deviation of 0.46 mm.

Table 2. Measurement results of the zone of inhibition of *Actinomyces* isolates against *Candida albicans* growth

Repetition	Concentration of <i>Actinomyces</i> isolates (mm)			Positive control	Negative control
	30%	40%	50%		
1	12.2	11.6	10.5	33.5	0
2	12.0	11.0	11.0	32.2	0
3	12.8	11.7	11.6	31.5	0
4	11.2	11.4	10.4	32	0
Average \pm SD	12.05 \pm 0.66	11.42 \pm 0.31	10.87 \pm 0.55	32.3 \pm 0.85	0 \pm 0

The data presented in Table 2 the results of observations from four repetitions of the treatment of *Actinomyces* isolates with three different concentrations (30; 40; and 50%) against the growth of *C. albicans*. At 30% concentration, the observation values ranged from 11.2 mm to 12.8 mm, with an average of 12.05 mm and a standard deviation of 0.66 mm. The 40% concentration had observation values between 11 mm to 11.7 mm, with an average of 11.425 mm and a standard deviation of 0.31 mm. Meanwhile, the 50% concentration showed observed values between 10.4 mm to 11.6 mm, with an average of 10.875 mm and a standard deviation of 0.55 mm.

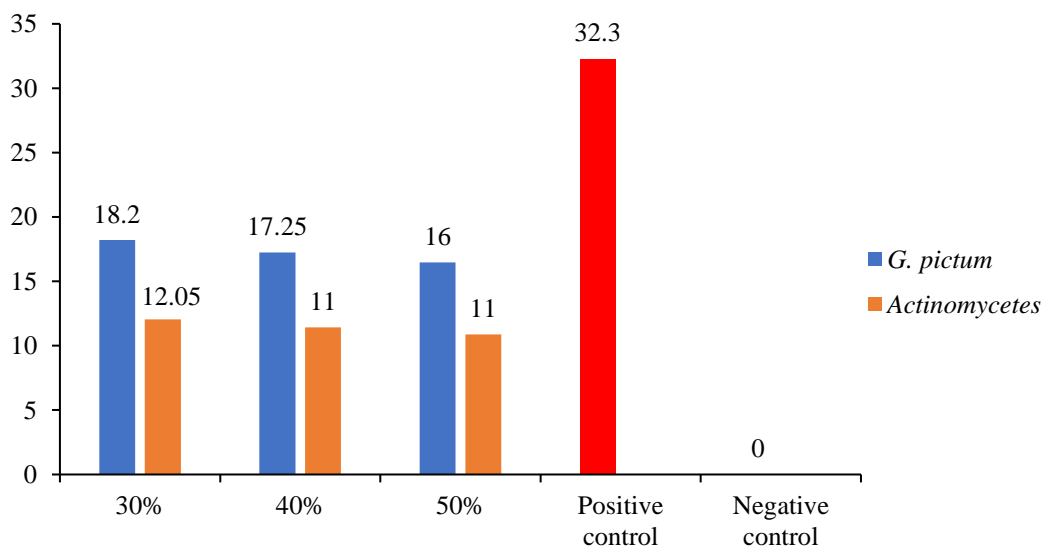
**Figure 3.** Zone of inhibition produced by *Actinomyces* isolates and *Graptophyllum pictum* extract against *Candida albicans*

Figure 3 shows the average inhibition zones of *G. pictum* extract and *Actinomyces* isolates against *C. albicans* at concentrations of 30; 40; and 50%. The results show that inhibition zone

diameters decreased as the concentration increased for both test substances. At each concentration level, *G. pictum* produced larger inhibition zones than *Actinomyces*. The positive control exhibited the highest antifungal activity, while no inhibition was observed in the negative control.

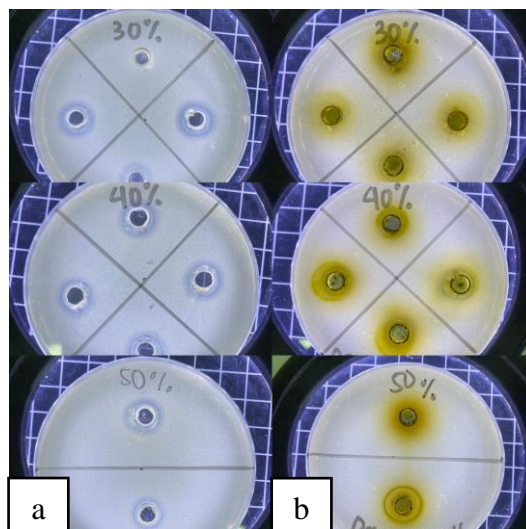


Figure 4. Zone of inhibition produced by *Actinomyces* isolates (a) and *Graptophyllum pictum* extract against *Candida albicans* (b)

Figure 4 provides a visual representation of the inhibition zones produced by *Actinomyces* isolates (a) and *G. pictum* extract (b) against *C. albicans* at concentrations of 30; 40; and 50%. The largest inhibition zones were observed at 30%, with a reduction in size at 40% and 50%. The inhibition zones produced by *G. pictum* appeared larger and more distinct compared to those formed by *Actinomyces* at corresponding concentrations. This greater inhibition is likely related to the presence of abundant bioactive secondary metabolites in *G. pictum*, such as alkaloids, flavonoids, and tannins, which exhibit strong antifungal activity. These compounds can disrupt the fungal cell wall and membrane integrity of *C. albicans*, resulting in a wider clear zone than that produced by the *Actinomyces* isolates.

Based on the results of data analysis that has been done, the significance value of the Independent T-Test test at concentrations of 30% and 50% shows a value of 0.000 ($P < 0.05$) which means that there is a significant difference between *G. pictum* extract and *Actinomyces* isolates. In the Mann-Whitney test, a significance value of 0.018 ($P < 0.05$) was obtained, indicating that the 40% concentration also had a significant difference between *G. pictum* extract and *Actinomyces* isolates.

DISCUSSION

Inhibition zone test results showed that *G. pictum* extract has antifungal activity against *C. albicans*, although its effectiveness varies depending on the concentration. Treatment of *G. pictum* extract at concentrations of 30; 40; and 50% produced inhibition zones with an average of 18.2 mm; 17.25 mm; and 16.475 mm, respectively as we can see in Table 1. Based on the category of antimicrobial activity according to Davis and Stout (Davis & Stout, 1971), the three concentrations of *G. pictum* extract produced a zone of inhibition against *C. albicans* with a strong category. *G. pictum* have various active compounds such as flavonoids, tannins, alkaloids, sitosterols, glycosides, anthraquinone, carbohydrates, coumarins, and saponins (Yasintha & Makkiyah, 2022). Several studies that conducted phytochemical tests on *G. pictum*, one of which was conducted by Wulandari et al. (2022) showed that the main compounds in *G. pictum* that play a role in antifungal activity are flavonoids, alkaloids, and tannins. These bioactive components act by increasing cell membrane permeability and inhibiting ergosterol biosynthesis, which is essential for fungal cell membrane integrity.

These findings are consistent with broader evidence from recent international studies, which highlight that phenolic compounds—including flavonoids and tannins—act as potent antifungal molecules by disrupting membrane homeostasis, inhibiting ergosterol formation, and generating

oxidative stress within fungal cells (Zhu et al., 2023). Their ability to penetrate fungal cell walls and complex with surface proteins further weakens fungal structure, contributing to the formation of clear inhibition zones observed in this study (Priyanto et al., 2024).

Flavonoids are the largest class of phenol compounds, the general nature of phenol compounds is able to increase cell permeability and precipitate proteins Wahyuningtyas (2008). The way tannin compounds work as antifungals is by inhibiting the biosynthesis of ergosterol, which is the main sterol produced by fungi as a component of the fungal cell wall (Hersila et al., 2023).

The ethanolic extract of *G. pictum* formulated into cream exhibited antifungal effects against *Tinea versicolor*, with inhibition zone diameters ranging from 10.37 to 13.57 mm at concentrations of 12.5% and 25% (Wulandari et al., 2022). In contrast, our study utilized a liquid extract obtained via Ultrasound-Assisted Extraction (UAE), targeting *C. albicans*, and demonstrated stronger antifungal activity with inhibition zones ranging from 16.475 to 18.2 mm at 30–50% concentrations. This suggests that the extraction method and formulation form (liquid and cream) may influence the efficacy of antifungal agents. Despite differences in fungal species and methodology, both studies reinforce the antifungal potential of *G. pictum*.

This study also showed that *Actinomyces* isolates have effective antifungal activity in inhibiting the growth of *C. albicans* as indicated by the formation of inhibition zones on the test media. This antifungal activity was analyzed at three different concentrations (30, 40, and 50%), and the observation results provided variations in the inhibition zone indicating the effect of concentration on the antifungal effectiveness of *Actinomyces* isolates. At a concentration of 30%, the average inhibition zone of 12.05 mm was higher than the concentration of 40% (11.425 mm) and 50% (10.875 mm) (Table 2). Based on the category of antimicrobial activity according to Davis and Stout Davis & Stout, 1971), the three concentrations of *Actinomyces* isolates produced inhibition zones against *C. albicans* with strong power. *Actinomyces* contains active compounds such as amphotericin B, actinomycins, blasticidin, and candicidin which are antifungal. This is consistent with a study by Aminnullah et al. (2020), which reported that *Actinomyces* isolates obtained from Bogor Botanical Garden soil showed antifungal activity against *C. albicans*, with clear inhibition zones formed in vitro. Their study supports the role of secondary metabolites such as amphotericin B and candicidin as key antifungal agents produced by *Actinomyces*. One of the ingredients, amphotericin B, will bind to ergosterol in the fungal cell membrane and form transmembrane channels that cause leakage of intracellular components (Gray et al., 2012).

Independent T-Test (30% and 50% concentration with p-value 0.000) and Mann-Whitney (40% concentration with p-value 0.018) tests showed significant differences in the ability to inhibit fungi between *G. pictum* extract and *Actinomyces* isolates at all concentrations tested. However, it was found that increasing the concentration of the extract decreased the antifungal activity. The decrease in inhibition zone activity may be due to complex interactions of active compounds in *G. pictum* extract and *Actinomyces* isolates that reduce the optimal ability to inhibit the growth of *C. albicans*. This is in accordance with research conducted by Camaioni et al. (2023), that some compounds show reduced activity at certain concentrations indicating antagonistic interactions between active compounds in the extract. A research by Krumina et al. (2015) showed that interactions between phytochemical compounds in a single extract or combination of extracts can produce antagonistic effects so that antimicrobial activity decreases at certain combinations/concentrations, even though each single compound is active.

Overall, the results of this study indicate that *G. pictum* extract and *Actinomyces* isolates have potential as antifungal agents against *C. albicans*, in line with research conducted by Aminnullah et al. (2020) and Wahyuningtyas (2008) although their effectiveness is lower than fluconazole as a positive control. These results also show the importance of extract concentration optimization to maximize its antifungal activity. The use of positive and negative controls in this study plays an important role in providing a comparison to evaluate the effectiveness of *G. pictum* extract treatment more comprehensively.

CONCLUSION

The results of this study indicate that *G. pictum* extracts and *Actinomyces* isolates extracted by the Ultrasound-Assisted Extraction (UAE) method have antifungal activity against *C. albicans* growth with a strong category at all concentrations (30, 40 and 50%) and show a significant difference in the activity of antifungal compounds between *G. pictum* extracts and *Actinomyces* isolates against *C. albicans* growth which can be seen from the activity of the inhibition zone formed. Greater activity is possessed by *G. pictum* extract. Future studies should control environmental conditions to reduce contamination, evaluate additional concentrations to determine the optimal level of *G. pictum* extract, and further investigate the mechanisms of *G. pictum* and *Actinomyces* at various concentrations, particularly higher ones.

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