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## The Inhibitory Activity of *Medinilla* Syrup Butanolic Extract against *Candida Albicans* ATCC 10231

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**Abstract:** Vulvovaginal candidiasis is a fungal infection with the leading cause being *Candida albicans*. It can interfere with women's fertility of reproductive age. Eradication of the vaginal *C. albicans* can enhance women's fertility. In this case, herbal materials that have antifungal activity may help to reduce the population of *C. albicans*. One of the prosperous plants is *Medinilla speciosa*. This plant grows in the area of Colo, Mount Muria, Kudus, Indonesia. As an ornamental plant, the local community traditionally believes that using *Medinilla speciosa* enhances female fertility. Moreover, *Medinilla* syrup is available locally. Therefore, this study aims to determine whether *Medinilla* syrup can inhibit the growth of *C. albicans*. In this experiment, *Medinilla* syrup was macerated with butanol. The inhibition zone method, the minimum inhibitory concentration (MIC) method, and the real-time planktonic growth in the personal bioreactor (RTS BioSan) were used. The MIC of the butanoic extract of *Medinilla* syrup was 8.44 mg/mL. The real-time planktonic growth showed that the extract added into the growth tubes significantly decreased the growth rate and yields of *C. albicans*. *Medinilla* syrup contains bioactive compounds that inhibit the planktonic growth but not the biofilm-growth of *C. albicans*.

**Keywords:** *Candida albicans*, *Medinilla speciosa*, parijotho, fertility.

## 梅迪尼利亞糖漿丁醇提取物對白色念珠菌美國典型培養物保藏中心 10231 的抑制活性

**摘要：**外陰陰道念珠菌病是一種真菌感染，主要原因是白色念珠菌。它會干擾育齡婦女的生育能力。根除陰道白色念珠菌可以提高女性的生育能力。在這種情況下，具有抗真菌活性的草藥材料可能有助於減少白色念珠菌的數量。繁榮的植物之一是大麥地那。這種植物生長在印度尼西亞庫杜斯的科洛、穆里亞山地區。作為一種觀賞植物，當地社區傳統上認為使用梅迪尼拉（大麥地那）可以提高女性的生育能力。此外，梅迪尼利亞糖漿在當地有售。因此，本研究旨在確定梅迪尼利亞糖漿是否可以抑制白色念珠菌的生長。在這個實驗中，梅迪尼利亞糖漿用丁醇浸漬。使用了抑菌圈法、最小抑菌濃度法和個人生物反應器（反向旋轉技術 BioSan）中的實時浮游生長。梅迪尼利亞糖漿丁醇提取物的最低抑菌濃度為 8.44 毫克/毫升。實時浮游生長表明，添加到生長管中的提取物顯著降低了白色念珠菌的生長速度和產量。梅迪尼利亞糖漿含有抑制浮游生物生長但不抑制白色念珠菌生物膜生長的生物活性化合物。

**关键词：**身体素质、职业倦怠、心理健康、体育教师。

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## 1. Introduction

Vulvovaginal candidiasis is a yeast infection caused by the *Candida albicans*. The infection rate is 15-25% for women of reproductive age from all cases of vaginitis, and the prevalence caused by *C. albicans* reaches 85-95% [1]. *C. albicans* can affect a woman's fertility because of the problems caused, such as vaginal pH becoming unbalanced, mucus that interferes with the rate of sperm, and impairs the quality of the sperm itself, which in the end, makes the sperm die. *C. albicans* can reduce the motility of sperms and agglutinate sperms. Therefore, genital tract infections by *C. albicans* may cause human infertility, particularly with a marginal state of fertility [2, 3]. As a common mucosal infection, vulvovaginal candidiasis affects many women, sometimes by recurrent, often intractable forms of the disease [4].

*C. albicans* is a typical vagina inhabitant in 20-30% healthy women. It can live under aerobic or anaerobic conditions with an acidic pH for the optimal environment [5]. *C. albicans* is a common opportunist pathogen in the skin, oral cavity, esophagus, gastrointestinal tract, vascular system. It is associated with sporadic and recurrent vulvovaginal candidiasis. When the balance between these yeasts and the host is disturbed, it leads to vagina dysbiosis. This condition causes *C. albicans* can be a primary causative agent for vulvovaginal candidiasis. Moreover, *C. albicans* also produce virulence factors, such as extracellular hydrolytic enzymes, heat shock proteins, and biofilms [6].

*Medinilla speciosa* (local name: Parijoto) is an ornamental plant found in Colo, Mount Muria, Kudus. Indonesia. The local community believes parijoto has efficacy to enhance fertility, maternal health guards, mouth ulcers, and inflammation drugs, and it is already prepared and sold as syrup. *Medinilla* contains tannins chemicals that can damage the cell walls of fungi and flavonoids that may interfere with fungal cell proliferation [7-9].

This study aimed to determine the inhibitory activity of butanol extract from *Medinilla* syrup against *C. albicans* ATCC 10231. This research is the first study in using butanol to extract *Medinilla* syrup. Butanol is the lowest polar solvent that does not mix with water.

## 2. Materials and Methods

### 2.1. Materials

*Medinilla* syrup (sirup parijoto) (Figure 2) was bought from the local shop (CV Selectin Alam Muria) in Kudus, Central Java, Indonesia, in September 2020. *C. albicans* strain ATCC10231 was obtained from the Research Laboratory of this University. *C. albicans* is grown on Sabraud Dextrose Agar (SDA)

or broth (SDB, Himedia). Before using the culture, the *C. albicans* colony and microscopic characteristics were checked. Commercial ketoconazole was used as a positive control in all experiments.

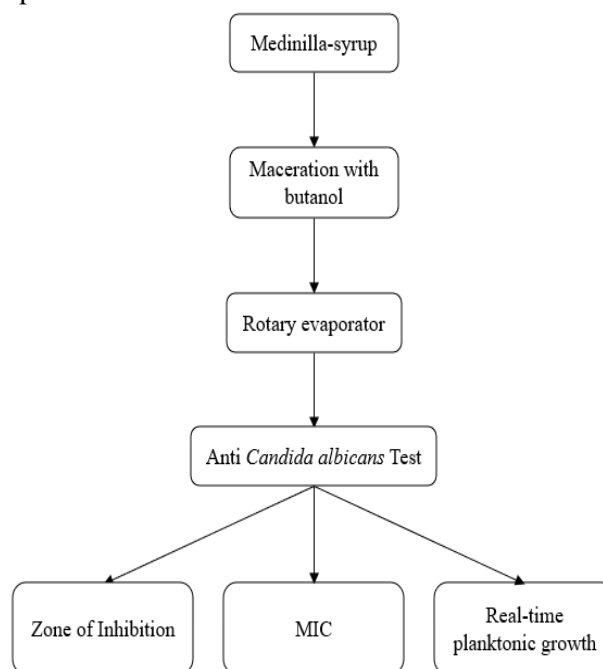


Fig. 1 Flow chart of the research procedure



Fig. 2 *Medinilla* syrup

### 2.2. Extract Preparation

*Medinilla* syrups (100 mL) (Fig. 2) were macerated with 150 mL butanol for a week. The maceration product was filtered and then concentrated with a rotary evaporator at a temperature of 70°C to obtain the *Medinilla* syrup butanoic extract.

### 2.3. Inhibition Zone Test

The agar media used for inhibition zone tests were SDA. Overnight broth cultures of *C. albicans* (0.1 mL, 1 McFarland) were used as 347 inoculums. The wells (dia: 0.6 mm) were filled either with the extract (42.21 mg) or ketoconazole (1 mg). The inoculated

plates were incubated at 37°C for 24 hours. After incubation, the inhibition zones were measured.

#### 2.4. Minimum Inhibitory Concentration (MIC) Test

The broth media used for MIC tests were SDB. A series of SDB-containing (20 mL) test tubes were prepared with gradient concentration of extract (0; 1.05; 2.11; 4.22; 8.44; 16.88 and 33.76 mg/mL) or ketoconazole (0.05 mg/mL). The MIC tubes were inoculated with an overnight liquid culture of *C. albicans* (500 µl, 1 McFarland). The MIC tubes were incubated at 37°C for 24 hours. After incubation, growth (positive or negative) was observed. The MIC was determined by observing the negative growth of the lowest concentration.

#### 2.5. Real-Time Planktonic Growth of *C. Albicans*

The real-time growth experiment was carried out with the personal bioreactor BioSan (RTS 001/001C). The working volume of the Falcon tubes was 20 mL. The growth medium was Sabouraud Dextrose Broth. The wavelength was 850 nm with a rotation speed of 1000 rpm. The personal bioreactor BioSan will calculate the growth rate and yield according to the equipment's manual. Six gradient concentrations of extract were added, i.e. 1.05; 2.11; 4.22; 8.44; 16.88; 33.76 mg/mL. Ketoconazole (0.05 mg/mL) was used as positive control.

#### 2.6. Statistic Calculation

One-way classification of ANOVA (nonparametric) was used to compare the growth rates and yields with five replications.

### 3. Results

Morphological and microscopic tests confirmed that the culture used was *C. albicans* (Fig. 3). The inhibition zone of *Medinilla* syrup butanoic extract (42.21 mg) was  $21.13 \pm 0.75$  mm weaker than ketoconazole (1 mg,  $32.04 \pm 0.41$  mm) (Fig. 4).

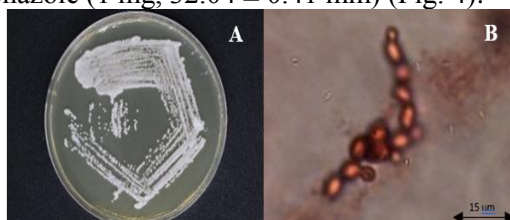


Fig. 3 Macroscopic growth (A) and microscopic (B) picture of *C. albicans*

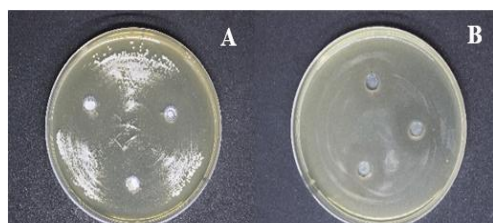


Fig. 4 Inhibition zone of 1 mg ketoconazole (A) and 42.21 mg *Medinilla* syrup Butanoic extract (B)

There were eight treatment variations in the MIC test by observing changes in turbidity color to see *C. Albicans* growth (Fig. 5). The MIC of the butanoic extract was 8.44 mg/mL. No growth was observed in the concentration above 8.44 mg/mL extracts.

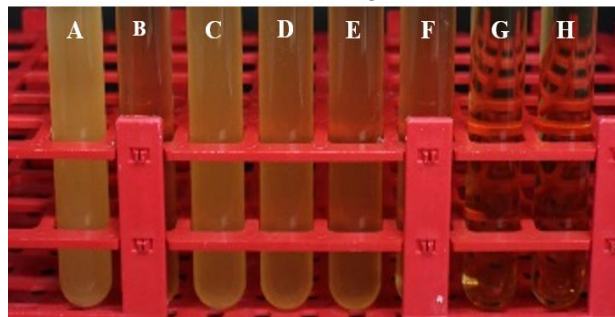


Fig. 5 MIC test results of liquid dilution in test tubes against *C. albicans*. A: control (without additional extract); B: ketoconazole (0.05 mg/mL), C: 1.05 mg/mL, D: 2.11 mg/mL, E: 4.22 mg/mL, F: 8.44 mg/mL, G: 16.88 mg/mL, H: 33.76 mg/mL

Real-time planktonic growth showed that the growth rate and yield of *C. albicans* were inhibited by the addition of *Medinilla* syrup butanoic extracts (Fig. 6). The additional extract can decrease the growth rates and yield dose-dependent (Table 1). Statistic tests for both growth parameters showed a significant difference in the influence of the extract on the growth rate and yields (Table 2 and 3), but its impact might be less or stronger than ketoconazole, depending on its concentration.

Table 1 Influence of butanoic extracts on the growth rate and yield of *C. albicans*

Treatment	Concentration (mg/mL)	Growth Rate ( $\mu\text{h}^{-1}$ )	Growth Yield (OD850)
Negative control (no extract)	0.00	$0.62 \pm 0.02$	$3.71 \pm 0.05$
Positive control (ketoconazole)	0.05	$0.23 \pm 0.02$	$1.81 \pm 0.03$
Butanoic extract of	1.05	$0.55 \pm 0.03$	$3.16 \pm 0.07$
	2.11	$0.52 \pm 0.03$	$2.88 \pm 0.03$
<i>Medinilla</i>	4.22	$0.38 \pm 0.05$	$2.37 \pm 0.03$
syrup	8.44	$0.07 \pm 0.01$	$0.75 \pm 0.01$

Table 2 ANOVA (growth rate)

sd	df	SS	MS	F (count)	F (Table)	
					0.05	0.01
Treatment	5	1.07	0.21	210.00	2.62	3.90
Error	24	0.02	0.001			
Total	29	1.09				

Table 3 ANOVA (growth yield)

sd	df	SS	MS	F (count)	F (Table)	
					0.05	0.01
Treatment	5	158.20	31.64	32.62	2.62	3.90
Error	24	23.18	0.97			
Total	29	181.3893				

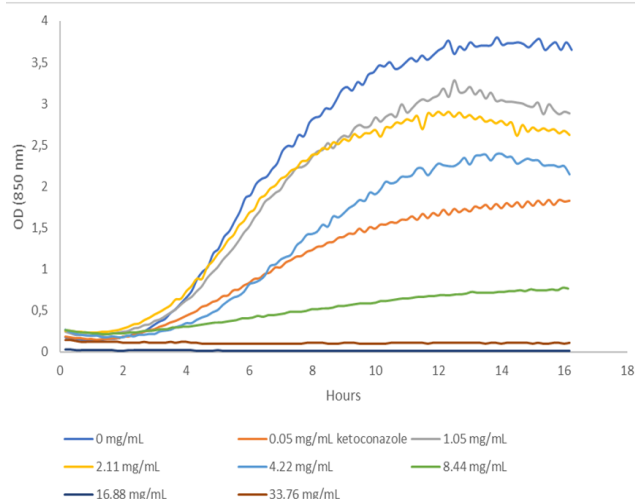


Fig. 6 Growth curve of *C. albicans* under different concentrations of extract

#### 4. Discussion

The turbidity level or optical density during the growth of *C. albicans* showed the normal growth curve that can be divided into four growth phases, namely the lag, exponential, stationary, and death phases. The lag phase is the time for microorganisms to adapt to the media environment. The exponential phase is when microorganisms can rapidly grow, mathematically described by a geometric series. The stationary phase is when the number of living microorganisms is equal to that of the dead, and the death phase is when the number of microorganisms killed exceeds the number of living ones [10]. In this study, *Medinilla* syrup butanoic extract influenced the exponential phase (growth rate) and the stationary phase (growth yield). The butanoic extract decreased the growth rate and yield significantly.

The influence of butanoic extract is different whether *C. albicans* grow on solid agar media or in rotated broth media. Butanoic extract does not effectively inhibit static growth in agar media, but it is more effective in the planktonic growth of *C. albicans* in rotated broth media. The resistance of *C. albicans* depends on their ability to form biofilm. Under stagnant growth, *C. albicans* has an opportunity to develop a biofilm to protect its cell against any external attacks. Butanoic extracts from different herbal materials showed inhibitory activity against *C. albicans* (Table 4). MIC value and inhibition zone from *Medinilla* syrup butanoic extract are in the middle compared to other plants butanoic extract [11].

The inhibition zone of the syrup butanoic extract is less than the inhibition zone of the fruit ethanolic extract of *Medinilla speciosa* [8]. This study and others indicate that butanoic extract from *Medinilla* syrup contains bioactive compounds that are not very strong to inhibit *C. albicans* growth significantly. It is possible that *Medinilla* can overcome infertility by inhibiting *C. albicans*, but it may not be effective in

syrup form. *Medinilla* syrup may effectively overcome infertility with other methods. It is also possible that the ability of *Medinilla* syrup to overcome infertility is not related to its inhibitory activity against *C. albicans*.

Table 4 Butanoic extract of other plants

Species	Part	MIC, mg/mL	IZ, mm	Ref.
<i>Cyclamen coum</i>	Tuber	0.005	Nd	[12]
<i>Cistus laurifolius</i>	Leave	0.008	Nd	[13]
<i>Sideroxylon obtusifolium</i>	Leave	0.063	Nd	[14]
<i>Euclea crispa</i>	Leave	0.63	20 ± 1	[15]
<i>Elaeagnus rhamnoides</i>	Leave	1	Nd	[16]
<i>Elaeagnus rhamnoides</i>	Twig	1	Nd	[16]
<i>Pyrostegia venusta</i>	Flower	1	Nd	[17]
<i>Medinilla speciosa</i>	Medinilla Syrup	8.44	21.13 ± 0.75	This study
<i>Equisetum hyemale</i>	Stem	13.1	Nd	[18]
<i>Euphorbia nivulia</i>	Aerial part	15.1	14.1 ± 0.52	[19]
<i>Carallume europaea</i>	Aerial part	25	Nd	[20]
<i>Ononis sessilifolia</i>	Herb	Nd	12	[21]
<i>Ononis macrosperma</i>	Herb	Nd	13	[21]
<i>Ononis basiadnata</i>	Root	Nd	14	[21]
<i>Ononis sessilifolia</i>	Root	Nd	17	[21]

Note: Nd (Not detected)

#### 5. Conclusion

Butanoic extract of *Medinilla* syrup has an inhibitory inhibition against *C. albicans*. It effectively inhibits planktonic growth, but not the biofilm growth of *C. albicans*.

As an implication, we recommend that *Medinilla* syrup may be used to eradicate *C. albicans* in combination with biofilm-disruptor.

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