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Effectiveness of Cardamom Ethanol Extract (*Amomum compactum* Soland Ex Maton) in Inhibiting the Growth of *Candida albicans* Biofilm

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ABSTRACT

Cardamom (Amomum compactum Soland Ex Maton) is a spice known for its pharmacological properties. It contains bioactive compounds such as flavonoids, alkaloids, saponins, terpenoids, and tannins, which have the potential antibiofilms activity. This study aims to evaluate the effectiveness of cardamom ethanol extract in inhibiting the growth of *Candida albicans* biofilm. A true experimental design with a post-test only control group design approach was employed. The extraction method used is the maceration method, and biofilm inhibition was assessed using the microtiter plate biofilm assay method. The Optical Density (OD) value was measured at 595 nm using a microplate reader . The results indicate that cardamom ethanol extract significantly inhibited *C. albicans* biofilm growth ($p<0.05$). The highestinhibition was observed at a 50% concentration of Cardamom extract. Probits analysis revealed the minimum biofilm inhibitory concentration ($MBIC_{50}$) of cardamom extract to be 21.768%. In conclusion, cardamom ethanol extract is effective in inhibiting *C. albicans* biofilm formation with significant activity observed at concentration as low as 3.175, with the highest efficacy at 50%. Thus, cardamom ethanol extract can be used as an antibiofilm for the treatment of various infectious diseases caused by *C. albicans* biofilm. The findings suggest that cardamom ethanol extract could serve as a promising candidate for the development of novel antibiofilm agents targeting *C. albicans* infections. Further research, particularly in vivo studies, is necessary to validate its therapeutic potential and explore its mechanism of action in clinical settings.

Keywords: Biofilm, *Candida albicans,* Cardamom

INTRODUCTION

Candidiasis is a common fungal infection caused by the species *Candida* (Bilal *et al*., 2023). The prevalence rate of candidiasis in Indonesia is around 20-25% which can attack hair, nails, skin, oral mucosa, and genitals (Puspitasari *et al*., 2019). The incidence rate varies depending on age and risk factors. Risk factors that can cause candidiasis are, impaired salivary gland function, dentures, smoking, diabetes mellitus, malignancy, immunosuppressive conditions, and many others (Hellstein & Marek, 2019).

A weakened immune system such as in people with HIV or someone undergoing immunosuppressive therapy, and the use of pacemakers can result in *C. albicans* to overgrow and cause infection (Nobile & Johnson, 2015). In addition, the acidic pH condition in the oral cavity is good for the attachment stage of *C. albicans* and good for enzymatic and proteinase. Therefore, too acidic pH conditions in the oral cavity can cause *C. albicans* to grow excessively (Klis & Brul, 2015). Chronic antibiotic use also causes many bacteria that are normally in the body to die so that *C. albicans* can overgrow and cause infection (Jawhara, 2023).

One of the virulence factors of *C. albicans* is the ability of *C. albicans* in the formation of biofilms. Biofilm is a collection of microorganisms surrounded by an exopolymer matrix as a defense against antifungals (Tsui *et al*., 2016). Biofilms have a structure that varies depending on their constituents. Its structure consists of DNA, proteins, as well as one or more extracellular polysaccharides. The biofilm formation stage starts from planktonic cells that carry out the adhesion stage. After that, microcolonies will be formed and exopolysaccharide matrix will be formed. Furthermore, microcolonies will

form mature biofilms (Rabin *et al*., 2015). An important clinical impact due to the formation of *C. albicans* biofilm is an increase in resistance to antifungal and protection against host cell attack (Wall *et al*., 2019). The formation of biofilms at the end of this period has been found to be given amphotericin B at high doses so that it causes resistance to increase. In addition, the administration of amphotericin B at high doses also has adverse effects on the body such as nephrotoxicity (Wang *et al*., 2021). Therefore, the formation of biofilms is a virulence factor of *C. albicans* that causes candidiasis therapy to be less than optimal (Galdiero *et al*., 2020).

The therapy given for candidiasis is antifungal. Antifungal drugs have side effects due to the presence of biofilms, namely the emergence of resistant fungi. Examples of resistant antifungals such as fluconazole, itraconazole, and triazole (Lyu *et al*., 2016). It is necessary to highlight the need for alternatives that have compounds to degrade *C. albicans* biofilms. Several antibiofilm studies using plant extracts include Rahmadianti (2015) research using eucalyptus leaf extract as an antibiofilm for *Staphylococcus aureus* isolate blood and urine. The results showed that tannins, flavonoids, and terpenoids contained in eucalyptus leaf extract had the effect of inhibiting adhesin molecules that are important for the formation of biofilms. In addition, terpenoid compounds and saponins can also degrade biofilms and kill bacteria in biofilms. Another study by Putri (2016) showed that cardamom seed extract (*Amomum compactum* Soland Ex Maton) had antimicrobial activity against *Aeromonas hydrophila* with a MIC of 2.70%. Active compounds of tannins, flavonoids, terpenoids, alkaloids, and saponins that have activity as antibiofilms can also be found in cardamom (*Amomum compactum* Soland Ex Maton) (Komala & Maulana, 2020).

Due to the presence of active compounds in cardamom, researchers want to conduct research to prove the effectiveness of cardamom ethanol extract in inhibiting the growth of *C. albicans* biofilm that causes candidiasis.

METHODS

Research design

The research on "The Effectiveness of Cardamom Ethanol Extract (*Amomum compactum* Soland Ex Maton) in Inhibiting the Growth of *Candida albicans* Biofilm Causing Candidiasis" includes *a true experimental* research with a post-test only control group design approach using the microtiter plate biofilm assay method.

Location and Time

The cardamom extraction process is carried out in the Biochemistry laboratory of the Faculty of Medicine, Wijaya Kusuma University, Surabaya. The antibiofilm test research was carried out in the Microbiology laboratory of the Special Hospital for Infections, Universitas Airlangga in January – May 2024.

Population and Sample

The population used in this study was *C. albicans* ATCC 14053 culture obtained from the Surabaya Public Health Laboratory Center. The sample used was *C. albicans* isolated from candidiasis patients. In this study, there were 8 treatment groups, namely 6 test groups, positive control, and negative control. Based on the calculation results using the Fereder Formula, the number of repetitions of each treatment group was 4 times so that the total sample used was 32.

Tools and Materials

The instruments used are microplate well 96, microplate reader, microscope, micropipette, preparation glass, object glass, Laminar Air Flow (LAF), autoclave, rotary vacuum evaporator, water bath, analytical scale, rack and test tube, petri dish, incubator, measuring cup, ose, glass stirrer, erlemeyer, bunsen, spiritus burner, shaker, spectrophotometer, timer, black cloth, blender and droppipette.

The materials used are C. albicans cultures from candidiasis patients, Sabouraud Dextrose Agar (SDA) media, Sabouraud Dextrose Broth (SDB) media, alcohol, fluconazole, sterile aquatics, spirtus, aluminum foil, ethanol, cotton, Phosphate Buffered Saline (PBS), RPMI 1640 (Roswell Park Memorial Institute 1640) media, magnesium powder, crystal violet, DMSO and cardamom obtained from Hargomulyo Village, Ngawi.

Making Cardamom Extract

Cardamom Plant Determination

Cardamom determination was carried out at the Materia Medica Batu Herbal Laboratory UPT which aims to ensure that the species used is *Amomum compactum* Soland Ex Maton. The determined part of the plant is the cardamom fruit.

Cardamom Preparation

Cardamom is obtained from Hargomulyo Village, Ngrambe District, Ngawi Regency. Cardamom fruits have been picked from the stem directly by hand to avoid damaging the sample, and then washed to clean the mixed foreign objects. Drying cardamom fruits with the sun drying method is directly covered with a black cloth. After drying in dry sorting, it is mashed with a blender until it becomes powder or simplicia (Nofriyaldi *et al*., 2023).

Cardamom Extraction

Cardamom simplicia is weighed as much as 900 grams, then soaked with ethanol solvent in a ratio of 1 : 4. The mixture is then left for 3 x 24 hours and stirred every 6 hours. Every 24 hours, the results of immersion (maceration) are filtered using coarse filter paper followed by whatman paper No. 1. The results of the filtration are then added 96% ethanol in the resulting residue. The resulting filtrate is concentrated using a rotary vacuum evaporator. The solvent that is still in the extract is then vaporized on a water bath until a thick extract of cardamom is obtained (Novelni *et al*., 2019).

C. albicans Suspension Manufacturing

One single colony of *C. albicans* was taken from SDA media and inserted into an Erlenmeyer tube that already contained 10 mL of SDB. Erlenmeyer is agitated for 18-24 hours at a speed of 150 rpm at room temperature so that the inoculum of *C. albicans* is produced (Kining *et al*., 2015). The *C. albicans* inoculum is centrifuged at 3000 rpm for 15 minutes. The formed

pellets will be separated from the supernatant and then suspended with 10 mL of PBS buffer and divortex. This same process is repeated twice. The last centrifugal pellet is suspended with 10 mL of PBS and then divortex. The suspension of *C. albicans* was measured in Optical Density (OD) using an ELISA reader. *C. albicans* suspension with OD 0.5 is ready to be performed for antibiofilm testing (Kining *et al*., 2015).

Antibiotic Film Activity Test at the Formation Stage

The formation of *C. albicans* biofilms begins with the cell attachment stage. A total of 100 µL of suspension of *C. albicans* albicans with OD 0.5 was inserted into the microplate well 96 columns 1 – 6, 9, and 10 in rows A – D. Furthermore, the microplate was incubated at 37ºC for 2 hours for the cell attachment stage. After incubation, the microplate is washed using PBS. Furthermore, in columns 1 – 6 rows A – D, 100 µL of cardamom extract was added with concentration variations of 1.5625%, 3.125%, 6.25%, 12.5%, 25%, and 50%. In columns 9 and 10 of rows A – D, 100 µL of fluconazole (0.1 mgmL) as a positive control and 100 µL of RPMI 1640 media were added as a negative control, respectively. The selection of fluconazole concentration for positive control in this study was Fluconazole is a first-line treatment for **vulvovaginal candidiasis** and other systemic fungal infections, making it a **clinically meaningful benchmark** in evaluating new antibiofilm agents. Meanwhile, column 12 rows A – D are filled with 100 µL of RPMI 1640 media as blanks. Next, the microplate is incubated at 37ºC for 48 hours.

After incubation, washing is carried out using PBS. Each microplate well is added 100 mL of 100% methanol. The next stage is the addition of 0.1% crystal violet to give coloring and leave at room temperature for 30 minutes. Next, the microplate is washed using PBS three times. Then measure the OD value of biofilm growth using an ELISA – reader at a wave of 595 nm (Zhu *et al*., 2023).

MBIC5₀ Value Determination

The $MBIC_{50}$ value was determined using the data on the percentage of inhibition of biofilm formation obtained through the following formula:

$$\%\ inhibitor = \left(\frac{OD_{negative\ control} - OD_{sample}}{OD_{negative\ control}}\right) \times 100\%$$

The data was analyzed using SPSS probit to determine the MBIC value of 50%. The MBIC50 value is the minimum concentration of cardamom extract which inhibits 50% of the growth of *C. albicans* biofilm.

Data Analysis Techniques

The study compared several treatments and used a sample number of more than 2 groups so that the test used was the One Way ANOVA test on the condition that the data obtained were normally distributed and homogeneous. If the conditions are not met, continue with the Kruskal Wallis test and continue with the Post Hoc test.

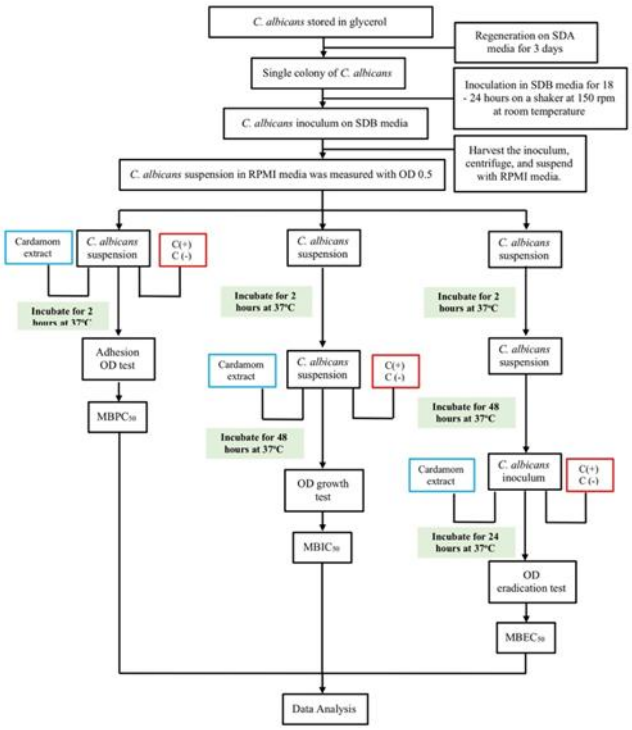

Figure 1. Research Procedure Flow Treatment Stage

RESULTS AND DISCUSSION

This study was conducted to determine the effectiveness of cardamom extract against C. albicans biofilms that cause candidiasis. This cardamom was obtained from Hargomulyo Village, Ngrambe District, Ngawi Regency. This cardamom has undergone a determination test at the UPT Laboratorium Medica Batu, where the results showed that the cardamom used was indeed the Javanese cardamom species (*Amomum compactum* Soland ex Maton). The result of this cardamom thick extract is reddish-brown. In this study, a thick extract of cardamom was produced as much as 84.5 grams with a yield value of 9.38%. The yield value of this study is higher than that of Nofriyaldi's (2023) research which produced a yield value of cardamom extract of 6.84%. The manufacture of extracts in Nofriyaldi's research (2023) uses 70% ethanol solvent, while in this study 96% ethanol solvent is used. The difference in solvent can have a significant influence on the yield value of the extract (Pujiastuti & Zeba, 2021). The water content in ethanol is 70% more compared to ethanol 96%. The water content in ethanol can reduce the extraction efficiency of bioactive compounds and can cause the deposition of some compounds that should be extracted properly (Supriningrum *et al*., 2019).

The antibiotic film activity test of cardamom extract against *C. albicans* biofilm at the stage of *C. albicans* biofilm formation was carried out using the microtiter plate assay method. This method uses a U bottom microplate as a treatment site and uses a microplate reader to read the OD value. The results of the observation of the test of inhibition of biofilm formation by cardamom extract with crystal violet staining can be seen in Figure 1.

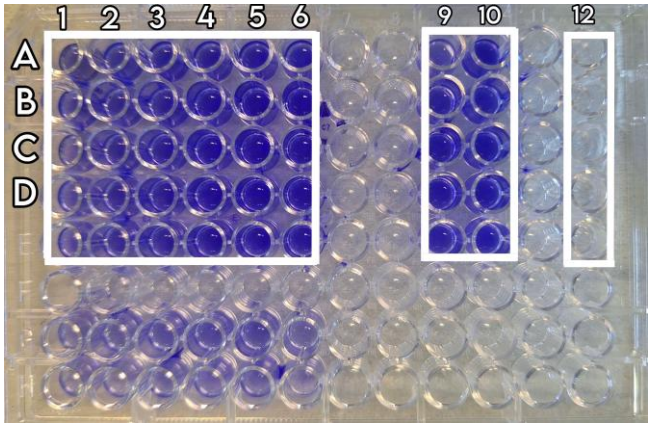

Figure 2. Results of Observation of Growth Inhibition Test of *C. albicans* Biofilm with Crystal Violet Staining

Information :
Column 1_{A-D} = 50% concentration
Column 9_{A-D} = Positive control
Column $2_{A-D.}$ = 25% concentration
Column 10_{A-D} = Negative control
Column 3_{A-D} = 12.5% concentration
Column 12_{A-D} = Blank
Column 4_{A-D} = 6.25% concentration
Column 5_{A-D} = 3.125% concentration
Column 6_{A-D} = 1.525% concentration

Based on Figure 1. It can be seen that in the treatment group, the greater the concentration, the fading purple color produced. This shows that the more biomass the biofilm, the more intense the color intensity produced. This crystal violet reagent will give color to the polysaccharide matrix of *C. albicans* cells adhering to the base of the microplate or measuring biomass of the biofilm (Haney *et al.*, 2015).. The results of measuring OD values through ELISA Reader can be seen in Table 1.

Based on Table 1. The results of the *C. albicans* biofilm growth inhibition test with an OD value that is getting higher from 50% concentration to 1.5625% were obtained. In the treatment group, the lowest OD value was found in a concentration of 50%, which was 0.753 and the highest OD value was found in a concentration of 1.5625%, which was 1.414. This shows that the concentration of 50% has the highest inhibition of biofilm growth so that *C. albicans* biofilm grows the lowest.

Table 1.
Results of OD Value of Antibiofilm Activity Test

Replication	Optical Density Value							
	Cardamom Extract Group						Control Group	
	50%	25%	12.5%	6.25%	3.125%	1.5625%	C(+)	C(-)
1	0.644	0.887	1.932	1.911	0.407	0.98	1.262	2.178
2	0.676	0.977	1.325	1.048	1.092	1.112	1.277	2.032
3	0.824	1.016	1.379	1.231	1.151	2.023	1.251	2.155
4	0.867	1.047	0.592	1.077	2.618	1.543	1.264	2.086
Mean	0.753	0.982	1.307	1.317	1.317	1.414	1.263	2.112
Standard Deviation	0.096	0.060	0.476	0.350	0.806	0.408	0.009	0.057

Based on normality and homogeneity tests, the data from the test results of the antibiofilm activity of cardamom extract on the formation of *C. albicans* biofilm was normally distributed ($p>0.05$), but not homogeneous ($p<0.05$). Thus, to determine the effectiveness of cardamom extract on *C. albicans* biofilm, the data were analyzed using non-parametric statistics, namely the Kruskal-Wallis test. Based on the results of statistical analysis of the Kruskal-Wallis test, a significance value of 0.014 ($P<0.05$) was obtained, so it can be concluded that cardamom extract has a significant effect on the formation of *C. albicans* biofilm. Next, the data was analyzed with the Post Hoc Games-Howell test to find out which groups differed significantly. The results of the Post Hoc analysis can be seen in Figure 3.

Based on the results of the Post Hoc Games-Howell test in Figure 2. showed that the 50% concentration of cardamom extract was significantly different from other concentrations, positive controls, and negative controls. In addition, negative control also differs significantly from other concentrations and positive controls. Thus, the most effective concentration of cardamom extract is 50%.

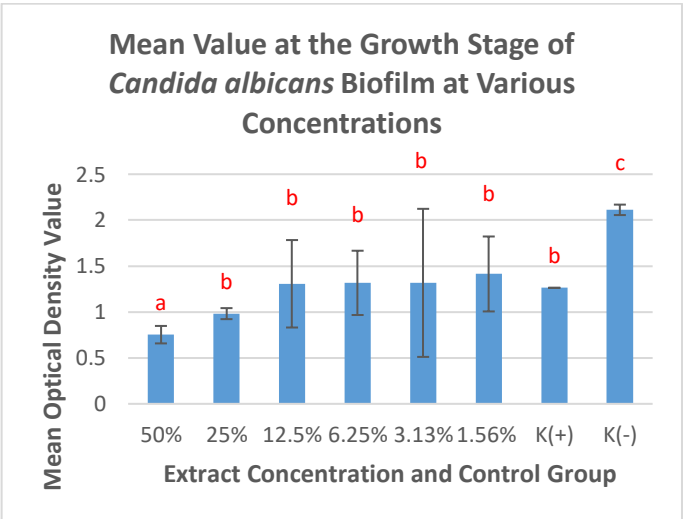

Figure 2. Chart of Post Hoc Test of Growth Stage of C. albicans Biofilm

Information:
If the superscript abc graph contains the same letters, it means that there is no significant difference, if it contains

different letters, it means that there is a significant difference between the treatment groups based on the Post Hoc test.

The process of inhibiting the formation of *C. albicans* biofilms can occur due to several factors such as the presence of farnesol or small molecules that interfere with quorum sensing in *C. albicans*, thus inhibiting the planktonic form to the biofilm. Then, inhibition of gene expression can also lead to inhibition of cell growth. In addition, UV exposure also plays a role in inhibiting the growth of biofilms by damaging fungal DNA and biofilm structures (Atriwal *et al*., 2021).

Cardamom extract contains bioactive compounds such as tannins, alkaloids, terpenoids, and alkaloids. Tannins can inhibit biofilm formation by reducing the surface area of the peptidoglycan layer. Alkaloids work by interfering with genes and QS. Flavonoids work by damaging the cytoplasmic membrane, inhibiting the synthesis of nucleic acids, and cell walls. As well as terpenoids inhibit nucleic acids and QS which play an important role in the formation of biofilms (Rosyada *et al*., 2023).

OD values in Table 1. used to determine the percentage of resistance that can be seen in Table 2.

Table 2.
Results of *C. albicans* Biofilm Growth Inhibition Percentage Results

Replication	Cardamom Extract Concentration					
	50%	25%	12.5%	6.25%	3.125%	1.5625%
% Growth Inhibition	64.409	53.520	38.125	37.664	37.628	33.049

The difference occurred because in the Sari (2014) study used cardamom fraction against E. coli biofilm, while this study used cardamom extract against *C. albicans* biofilm. This is supported by Putri's (2022) research on the potential of tamarind leaf extracts and fractions which shows that extracts have a higher inhibitory power compared to fractions because more complex compounds are found in extracts compared to fractions.

Importantly, this study extends the relevance of cardamom extract specifically to *C. albicans*, a pathogenic yeast with robust biofilm-forming capabilities that complicate antifungal treatment. Unlike previous research focused on bacterial biofilms or fractionated plant components, this investigation used crude ethanol extract and *Candida albicans* as the test organism, thereby reflecting more closely the complexity of phytochemical interactions and the clinical challenge of fungal biofilms. This aligns with findings by Tsopmene et al. (2024), who reported potent antibiofilm activity of a curcumin–piperine combination against *C. albicans*, albeit with a much lower $MBIC_{50}$. The difference in efficacy may be attributed to synergistic effects from the combination therapy, while the present study involved a single plant extract. This can cause this combination of extracts to have a large biofilm inhibition (Octora *et al*., 2023).

Thus, while the data substantiate the potential of cardamom extract as an antibiofilm agent, its use in clinical settings requires further validation. Future investigations, including *in vivo studies*, mechanistic analyses, and formulation development, are essential before any therapeutic application can be proposed. These findings contribute valuable baseline data and encourage continued exploration of plant-derived compounds for antifungal biofilm control.

CONCLUSIONS

Based on the results of the study, cardamom extract has an effect in inhibiting the growth of *C. albicans biofilm* with the lowest concentration at 3.175% concentration and the highest at 50% concentration Cardamom extract has an $MBIC_{50}$ value of 21.768%. This study was limited to in vitro testing using a single strain of *Candida albicans* under controlled conditions. The results may not fully represent the complexity of biofilm behavior in vivo or across different clinical isolates. Further studies are needed to investigate the extract's mechanism of action, test multiple *C. albicans* strains, and validate the findings in in vivo models. Exploring potential synergistic effects with standard antifungals is also recommended.

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