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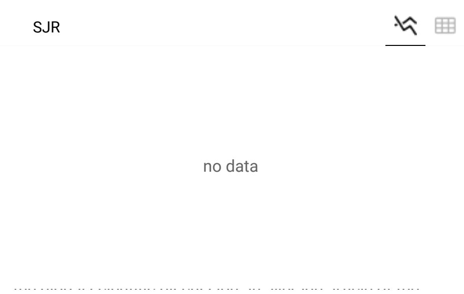

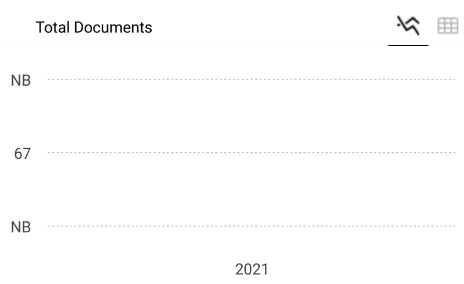

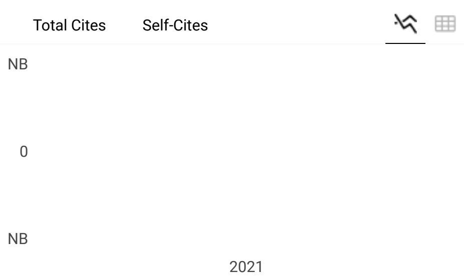

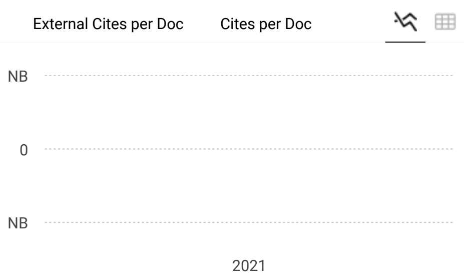

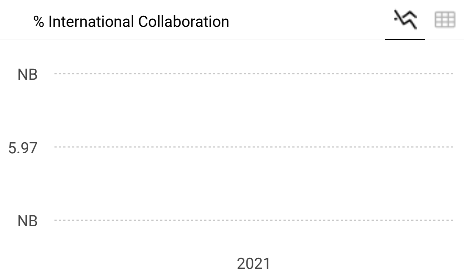

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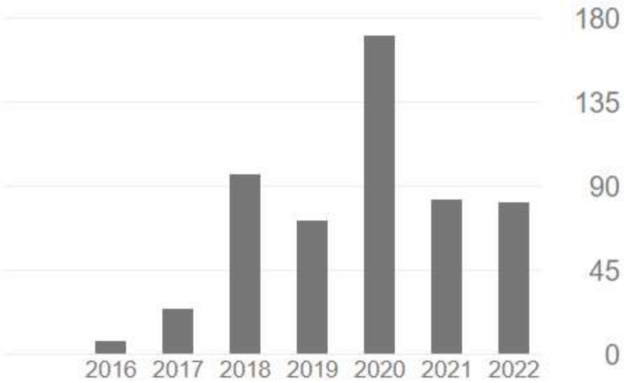

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Comparison of antifungal activity of fluconazole and clove leaf essential oil on *Candida* species isolate in HIV/AIDS patients with oral candidiasis

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***Abstract*---**Current treatment guidelines include fluconazole as the main therapeutic option for treating oral candidiasis infection in HIV/AIDS patients, but resistance increases. Several in vitro studies have shown that clove leaf essential oil with the main content of eugenol can be an alternative therapy for oral candidiasis that is resistant to fluconazole. This study was conducted to determine the zone of inhibition of clove leaf essential oil and fluconazole against *Candida* isolates species that cause oral candidiasis in HIV/AIDS patients. This study showed that the average fluconazole disk 25 μg/mL inhibition zone in 20 isolates of *Candida albicans* species was larger than *non-albicans Candida* species. The zone of inhibition of clove leaf essential oil was significantly lower than that of fluconazole ($p < 0.05$), except at a concentration of 15% against *non-albicans Candida* isolates. Clove leaf essential oil has an antifungal effect that can inhibit the growth of *Candida* species, so it can be considered an alternative antifungal therapy. Clove leaf essential oil concentration of 15% showed no significant difference in antifungal activity with the standard drug fluconazole in isolates of *non-albicans Candida* species.

***Keywords*---**oral candidiasis, fluconazole, clove leaf, antifungal, HIV/AIDS.

Introduction

Oral candidiasis is one of the most common skin and mucosal manifestations found in patients with HIV/AIDS. Nearly 90% of patients with HIV/AIDS have experienced oral candidiasis during their illness (Murtiastutik & Maharani, 2019). The average prevalence in Europe and the United States is 28% and 30%, respectively. The prevalence of oral candidiasis has also been reported in Africa at 51% and in Asia at 39% (Tappuni, 2020). Oral candidiasis can be a morbidity and can interfere in the quality of life in HIV/AIDS patients because it often lasts longer, has a high recurrence rate, and has more severe clinical symptoms (Murtiastutik et al., 2021; Sakkas et al., 2016).

Among various species, C. albicans accounts for more than 90% of cases associated with severe fungal infections and causes candidiasis in immunocompetent patients (Alshaik & Kahkashan, 2017). The proportion of Candida infections caused by C. albicans in HIV/AIDS patients has shifted to non-albicans Candida species, and it may be due to high rates of antifungal drug resistance (Berkow & Lockhart, 2017; Murtiastutik et al., 2021). Research by Moges showed that the resistance rate of several antifungal agents by disc diffusion test in HIV/AIDS patients with oral candidiasis in Ethiopia in 2013-2014 showed that all isolates of Candida spp. found that 12.3% were resistant to fluconazole, 8.4% to ketoconazole, and 1.3% to nystatin (Mulu et al., 2013). Current treatment guidelines include fluconazole as the main therapeutic option for treating oral candidiasis infection in HIV/AIDS patients (Berkow & Lockhart, 2017; Dar et al., 2015).

The existence of resistance to the main antifungal drugs urges research to find natural ingredients that can be attractive alternatives to antifungals. Most essential oils obtained from many tropical and subtropical plants contain eugenol as the main antifungal component (Schmidt et al., 2007). The concentration of eugenol in several plants is different. In the literature, it is stated that clove (Syzygium aromaticum L.) is considered the highest source of eugenol (45–90%) (Gupta & Prakash, 2021). Research conducted by Bhuiyan and colleagues compared the essential oil content of clove leaves and flowers, showing that the eugenol content was higher in clove leaves, namely 74.28%, while in flowers, as much as 49.71% (Bhuiyan et al., 2010). The most common methods for the isolation of eugenol are steam and water distillation (Khalil et al., 2017).

Research by Musta and Nurliana in 2019 regarding the effectiveness of clove leaf oil as antifungal Candida albicans showed antifungal activity for each concentration variation of 100%, 75%, 50%, and 25%, respectively, 14.2 mm, 12.2 mm, 10, 8mm and 10.4mm. The minimum concentration of clove leaf oil as antifungal Candida albicans is 17.86%. The clove leaves used were obtained from Bombana Regency, Southeast Sulawesi (Musta & Nurliana, 2019). A similar study was also conducted by Khansa (2019) who used clove flower essential oil from plantations in Yogyakarta. The diameter of the inhibition zone of clove flower essential oil at a concentration of 0.5% was 7.79 mm, a concentration of 1.0% was 12.02 mm, a concentration of 1.5% was 12.80 mm and a concentration of 2.0% was 13.96mm. This shows that the higher the clove flower essential oil concentration, the larger the resulting inhibition zone (Khansa, 2019). Variations in components and composition depend on the variety, agro-ecological conditions, pre-treatment, processing, and extraction method (Nurdjannah & N., 2012).

Clove oil has considerable antifungal activity against human fungal pathogens, including fluconazole-resistant strains. Clove essential oil can inhibit dermatophyte, Aspergillus and Candida, thus meeting the criteria for broad-spectrum agents (Alshaik & Kahkashan, 2017). Based on these data, this study aimed to compare the inhibitory of clove leaf essential oil (*Syzygium aromaticum*) and fluconazole in vitro.

Method

The research design used in this study was an experimental laboratory to compare the antifungal activity of clove leaf essential oil (Syzygium aromaticum L.) with fluconazole 25 μg/mL. There were 20 Candida albicans isolates and 20 non-albicans Candida isolates from the oral cavity of HIV/AIDS patients hospitalized at the Infectious Disease Intermediate Treatment Unit (UPIPI) RSUD Dr. Soetomo Surabaya from April – July 2019, which was reactivated. The clove leaf essential oil concentration based on the former study was 5%, 10%, and 15%. The antifungal activity was evaluated paper discs or blank discs using the disk diffusion method. These data were entered into a data collection sheet and analyzed with SPSS (Statistical Package for Social Sciences). This research has obtained ethical approval from the Ethics Committee of Dr. Soetomo General Academic Teaching Hospital Surabaya (0286/KEPK/X/2021).

Results

This study showed that the average fluconazole disk 25 μg/mL inhibition zone in 20 isolates of *Candida albicans* species was 29.31±7.847 mm, while in 20 isolates of non-*albicans Candida* species was 23.97±8.682 mm. The average inhibition zone of clove leaf essential oil concentrations of 5%, 10% and 15% in 20 isolates of *Candida albicans* species were 10.83±3.135 mm, 18.00±4.141 mm and 23.69±7.062 mm, respectively. While the 20 isolates of non-*albicans Candida* species were 9.54±6.942 mm, 17.93±5.543 mm and 21.36±6.313 mm, respectively (Table 1). Four samples (10%) of isolates showed resistance to the antifungal fluconazole 25 g/mL, one from *Candida albicans* species and three from species non-a*lbicans Candida* (one from *C. glabrata* species, two from *C. krusei* species).

Table 1
Distribution of mean diameter of the inhibition zone of fluconazole and clove leaf essential oil (*Syzygium aromaticum* L.) 5,10 and 15% in isolates *Candida* spp

Antifungal type (n=40)	Average inhibition zone (mm) ±*Standart Deviation (SD)*	
	Candida albicans (n=20)	non-*albicans Candida* (n=20)
Flukonazol 25 μg/mL	29.31 ± 7.847	23.97 ± 8.682
Clove leaf essential oil 5%	10.83 ± 3.135	9.54 ± 6.942
Clove leaf essential oil 10%	18.00 ± 4.141	17.93 ± 5.543
Clove leaf essential oil 15%	23.69 ± 7.062	21.36 ± 6.313

The comparative analysis of the average inhibition zone between fluconazole and clove leaf essential oil concentrations of 5%, 10%, and 15% on 20 isolates of Candida albicans species obtained significant differences with p-value, respectively 0.000; 0.000; 0.018. The mean diameter of the fluconazole inhibition zone was greater than that of clove leaf essential oil (Table 2).

Table 2
Comparison of the mean diameter of the inhibition zone of fluconazole with clove leaf essential oil (*Syzygium aromaticum* L.) in *Candida albicans* isolates

Antifungal type (n=20)	Average inhibition zone (mm) ±*Standart Deviation (SD)*	*p-value*
Flukonazol 25 μg/mL	29.31±7.847	-
Clove leaf essential oil 5%	10.83±3.135	0.000
Clove leaf essential oil 10%	18.00±4.141	0.000
Clove leaf essential oil 15%	23.69±7.062	0.018

The results of the comparative analysis of the average inhibition zone between fluconazole and clove leaf essential oil on non-albicans Candida isolates showed significant differences in clove leaf essential oil concentrations of 5% and 10% (p values 0.000 and 0.021), where the mean diameter of the fluconazole inhibition zone was more prominent than clove leaf essential oil. Meanwhile, clove leaf essential oil with a concentration of 15% did not show a significant difference compared to fluconazole (p=0.330), where the mean diameter of the fluconazole inhibition zone was greater (Table 3).

Table 3
Comparison of the mean diameter of the inhibition zone of fluconazole with clove leaf essential oil (*Syzygium aromaticum* L.) in non-*albicans Candida* isolates

Antifungal type (n=20)	Average inhibition zone (mm) ±*Standart Deviation (SD)*	*p-value*
Flukonazol 25 μg/mL	23.97±8.682	-
Clove leaf essential oil 5%	9.54±6.942	0.000
Clove leaf essential oil 10%	17.93±5.543	0.021
Clove leaf essential oil 15%	21.36±6.313	0.330

Discussion

Fluconazole is a systemic antifungal used in oral candidiasis in HIV/AIDS patients. Changes in species that cause oral candidiasis lead to the emergence of resistance to fluconazole (William et al., 2011). The existence of resistance to antifungal drugs, especially fluconazole, urges research to be carried out to find natural ingredients that can be an antifungal alternative. Many essential oils are obtained from several tropical and subtropical plants, containing eugenol as the main antifungal component (Schmidt et al., 2007). The concentration of eugenol in several plants is different. In the literature, it is stated that clove (Syzygium aromaticum L.) is considered the highest source of eugenol (45–90%) (Gupta & Prakash, 2021).

The average fluconazole inhibition zone in 20 isolates of Candida albicans species was 29.31±7.847 mm, while in 20 isolates of non-albicans Candida species was 23.97±8.682 mm. This indicates that fluconazole 25 μg/mL still has good antifungal activity in this study. When compared to the mean zone of inhibition between Candida albicans and non-albicans Candida species, it was found that fluconazole 25 μg/mL gave a larger zone of inhibition in Candida albicans isolates than in non-albicans Candida isolates. This is consistent with the theory which states that immunocompromised conditions, comorbidities, use of broad-spectrum antibiotics, and practical use of antimycotic drugs such as fluconazole use in HIV patients are reported to be associated with an increase in non-albicans Candida strains and an increase in fluconazole-resistant Candida albicans strains (Pudjiati et al., 2018). Combined overexpression of CDR2 and ERG11 and mutations in the ERG11 gene were the genetic mechanism of fluconazole resistance in Candida isolated from HIV patients (Rosana et al., 2015).

The fluconazole sensitivity criteria or inhibition zone category used was the size of the inhibition zone according to the Clinical and Laboratory Standards Institute

(CLSI) standards for fluconazole. Sensitive results in the sensitivity test showed that the diameter of the inhibition zone was more than and equal to 19 mm. The zone of inhibition between 14 – 18 mm indicated a susceptible-dose-dependent (SDD), and the zone of inhibition less than 14 mm indicated resistance to the growth of Candida spp. in vitro (Sumalapao et al., 2018). In the in vitro inhibition zone test of 40 isolates of research subjects, four samples (10%) of isolates showed resistance to the antifungal fluconazole 25 μg/mL because it had an inhibitory zone diameter of 14 mm. Research conducted by Murtiastik et al. (2019) in Surabaya with the number of research subjects of HIV/AIDS patients, as many as 20 patients with 37 isolates of Candida species growing in culture, in the test for resistance of Candida species to fluconazole showed that 18 (48.6%) isolates were resistant to fluconazole. The most resistant isolates were non-albicans, with as many as 13 isolates (72.2%) (Murtiastutik & Maharani, 2019).

Isolate of Candida species that showed resistance to fluconazole were derived from one sample of Candida albicans species and three samples of non-albicans Candida species (1 from C. glabrata species, two from C. krusei species). In a laboratory-based population study, the resistance to fluconazole is more excellent in isolates of non-albicans Candida species than in C. albicans. During the last ten years, there has been documentation of intrinsic resistance to azole antifungals, especially fluconazole, in several non-albicans Candida species, especially isolates of C. glabrata and C. krusei. A study conducted by Sadeghi et al. (2018) evaluated the antifungal susceptibility of non-albicans Candida species isolated from various clinical samples in vitro to fluconazole. Although C. krusei exhibits intrinsic resistance to fluconazole, it is controversial whether the increased resistance rate is related to fluconazole prophylaxis or prior treatment (Sadeghi et al., 2018). The results of the study by Houshmandzad et al. (2022), which aimed to analyze the anticandidal activity of fluconazole (FLZ) against FLZ-resistant C. krusei strains showed that 16 (76.2%) C. krusei strains were resistant to fluconazole, except for five (23, 8%) clinical isolate which showed susceptible-dose-dependent (SDD) results (Houshmandzad et al., 2022).

The average inhibition zone of clove leaf essential oil (Syzygium aromaticum L.) concentrations of 5%, 10% and 15% in 20 isolates of Candida albicans species alone were 10.83±3.135 mm, 18.00±4.141 mm and 23.69±7.062 mm. While the 20 isolates of non-albicans Candida species were 9.54±6.942 mm, 17.93±5.543 mm and 21.36±6.313 mm. The formation of inhibition zones in the study showed that clove leaf essential oil had an antifungal activity that could inhibit the growth of Candida species in both Candida albicans and non-albicans Candida. Following the research conducted by Musta and Nurliana in 2019 regarding the kinetics study of the effectiveness of clove leaf oil as an antifungal Candida albicans using clove leaves taken from Southeast Sulawesi. This study's minimum concentration of clove leaf oil as an antifungal Candida albicans was 17.86% (Musta & Nurliana, 2019). A similar study was also conducted by Khansa (2019) using clove flower essential oil from plantations in Yogyakarta. The measurement of the diameter of the inhibition zone of clove flower essential oil concentration of 0.5% is 7.79 mm, concentration of 1.0% is 12.02 mm, concentration of 1.5% is 12.80 mm and concentration of 2.0% is 13.96 mm. This shows that the higher the clove flower essential oil concentration, the larger the inhibition zone produced (Khansa, 2019).

The sensitivity values of clove leaf essential oil (Syzygium aromaticum L.) cannot be compared with fluconazole because they do not have a sensitivity standard according to CLSI, so what can be compared in this study is the average diameter of the inhibition zone between clove leaf essential oil and fluconazole 25 μg/mL as standard therapy (positive control) in mm. Fluconazole 25 μg/mL showed the largest mean diameter of the inhibition zone in all Candida spp isolates. This shows that the standard antifungal drug fluconazole 25 μg/mL still provides antifungal activity in a larger zone of inhibition compared to clove leaf essential oil concentrations of 5%, 10% and 15%. In another way, the inhibition zone formed from clove leaf essential oil in fluconazole-resistant isolates in this study gave better results.

This can be the basis that clove leaf essential oil with the main content of eugenol can be an alternative therapy for oral candidiasis that is resistant to fluconazole. These results are supported by a similar study conducted by Pinto et al. (2009) to evaluate the antifungal activity of clove essential oil and its main component, eugenol, against Candida isolates. This study stated that clove essential oil and eugenol had considerable antifungal activity against Candida, including fluconazole-resistant strains, namely C. krusei, which was intrinsically resistant to fluconazole, and C. glabrata, whose resistance was easily induced. These results strengthen further investigation of clove essential oil and eugenol for clinical application to treat fungal infections (Pinto et al., 2009).

The test results of the comparative analysis of the mean fluconazole inhibition zone to clove leaf essential oil concentrations of 5%, 10%, and 15% in 20 isolates of Candida albicans obtained a significant difference (p-value <0.05), where the diameter of the fluconazole inhibition zone bigger. There was no significant difference (p value=0.330) when an analysis of the mean inhibition zone of fluconazole was performed against clove leaf essential oil with a concentration of 15% in 20 isolates of non-albicans Candida. This shows that the inhibition zone of clove leaf essential oil concentrations of 5%, 10%, and 15% is not better than fluconazole 25 μg/mL as the standard drug. However, clove leaf essential oil has an antifungal effect that can inhibit the growth of Candida species, so it can be considered an alternative antifungal therapy, especially clove leaf essential oil concentration of 15% which shows good activity, not significantly different from the standard drug fluconazole in isolates of non-albicans Candida.

A similar study by Fristiyanti (2019) was conducted to determine whether or not the difference between two concentrations of clove leaf extract was significant. It was found that the concentration groups of 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6% had significant differences in reducing colony thickness of Candida albicans. However, the concentration of 0.6% extract and 0.6% fluconazole is not significantly different in reducing the thickness of Candida albicans colonies. This shows an inverse relationship, in which the higher the concentration of clove leaf ethanol extract given, the thinner the Candida albicans colonies that grow. In addition, it can be seen that the effective concentration that can reduce the thickness of Candida albicans colonies starts from a concentration of 0.1% in this study (Fristiyanti, 2019).

Several other factors can affect the antifungal activity, including the concentration of the extract, the content of antifungal compounds, the type of fungus inhibited, and the diffusion power. The inhibition zone formed can also be influenced by the concentration of the extract, where the higher the concentration, the larger the clear zone will be formed. The more concentrated the concentration, the more active compounds are contained, thus affecting the diameter of the inhibition zone formed on fungal growth (Andayani et al., 2014). The antifungal activity test method used can also have an effect. This study uses the diffusion method which is one method that is often used to test antifungal activity. The advantage of the diffusion method is that it is a fast and straightforward method to see the antifungal effect by looking at the diameter of the inhibition zone formed, but there are drawbacks to the disc diffusion method, namely that not all substances may be absorbed in the paper disc so that it can affect the inhibition zone formed (Jawetz & Adelberg, 2007).

Clove leaf oil has the most vigorous activity against clinical isolates of Candida albicans, which is characterized by the highest eugenol content that can inhibit pre-formed biofilm and Candida albicans biofilm formation. This compound is effective against the adaptive mechanism of Candida albicans biofilm resistance to fluconazole (Khan & Ahmad, 2012). Biofilm production was slightly higher in non-albicans Candida. Biofilm is a collection of microorganisms that adhere to the surface and are encased in an extracellular polysaccharide matrix produced by these microorganisms. Types of Candida spp. with a high ability to form biofilms are generally more virulent than others. Biofilms also play a role in resistance to antifungal drugs used, although the primary mechanism is still unknown (Williams et al., 2011).

Conclusion

Clove leaf essential oil has an antifungal effect that can inhibit the growth of Candida species. Although the mean inhibition zone formed on fluconazole was significantly more extensive than that of clove leaf essential oil, in isolates that showed resistance to fluconazole, clove leaf essential oil gave a larger diameter of the inhibition zone. In addition, clove leaf essential oil with a concentration of 15% showed no difference in antifungal activity with the standard drug fluconazole on isolates of non-albicans Candida species. It could be considered an antifungal alternative, especially for fluconazole-resistant strains.

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