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Research Article

The preliminary study on the antifungal effect of Kaffir lime (*Citrus hystrix* DC) peel extract against *Malassezia furfur*

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Abstract: *Pityriasis versicolor* is one of the most common fungal infections on the skin caused by *Malassezia furfur*. Kaffir lime fruit (*Citrus hystrix* DC), especially its peels' contents in secondary metabolite, may play a healing role against such infections. Therefore, the aim of this study was to determine the antifungal potential of Kaffir lime peel extract against *Malassezia furfur*. Ethanol extracts of the peels of Kaffir lime were tested for its antifungal properties against *Malassezia furfur* at different tested concentrations, namely 25%, 50%, 75%, and 100%. Every treatment was performed with 4 replications. Inhibition zone formed surrounding the paper disc measured after 24 hours of incubation using the caliper method. Data were subjected to the Kruskal-Wallis test and the Mann-Whitney Post hoc test. The study revealed that the kaffir lime fruit extract gave a significant effect on the inhibition zone ($p< 0.05$). The results showed that the higher inhibition zone was found at control group and it was different significantly from other treatments. However, among the tested concentrations, the best treatment was detected at a concentration of 100%, which was significantly different from other concentrations. Kaffir lime peel has an antifungal effect against *Malassezia furfur* and the best tested concentration was 100%.

1. INTRODUCTION

Skin infection is a common disease in tropical countries, including Indonesia, where fungi are the most frequent pathogens that cause such diseases. Fungal skin diseases were the most common skin diseases worldwide in 2017 (10.09%). In addition, skin fungus was the fourth most common disease (2.1 billion cases) compared to 328 diseases and injuries worldwide (Alastruey-Izquierdo *et al*., 2015; Celis *et al*., 2017; Ariana, 2018). *Malassezia* is a lipophilic fungus which commonly finds normal flora on human skin. *Malassezia furfur* is one of the species of fungus that causes *pityriasis versicolor*. *Malassezia furfur* is a yeast that leads to skin lesions when it transforms into a pathogenic filament (Georgios Gaitanis *et al*., 2012; Agusrimansyah *et al*., 2019).

Currently, the treatment for *P. versicolor* is by administering topical drugs as the first line therapy and systemic antifungal drugs as the second line. Ketoconazole is one of the common

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topical treatments in cream or shampoo preparations for this infection. However, antifungal drugs have some limitations, such as severe side effects, narrow spectrum, minimal penetration of some tissues, and potential of resistance (Gupta & Foley, 2015; Pusung *et al*., 2021; *Lee et al*., 2023). The resistance of anti-fungal drugs has been reported by several researchers; for instance, the incidence of *Candida albicans* resistance to the antifungal fluconazole was 34.07%, and resistance to ketoconazole was 7.69% (Apsari & Adiguna, 2013). Helou *et al* (2014) reported that there was a case related to a 52-year-old man who had *P. versicolor* and developed resistance to fluconazole, ketoconazole, itraconazole, and fenticonazole cream as a result of repeated cases and ongoing usage of these medications without doctor's advice (Helou *et al*., 2014).

Thus, it is essential to investigate various alternative materials as antifungal agents to avoid the resistance case. The contents of secondary metabolite from plants may potentially be used as substances in phytotherapeutic approaches. According to Masloman *et al* (2016), the active materials compound from plants has low side effects, does not cause resistance, and is easy to obtain and relatively inexpensive (Masloman *et al*., 2016). Kaffir lime (*Citrus hystrix* DC), especially the peel of the fruit, has active metabolites compound such as saponins, tannins, flavonoids and steroids which have potential as antifungals (Rachmatiah & Octaviani, 2022).

The previous report by Halawa *et al* (2019) shows that kaffir lime peel extract has a potential inhibition effect on the growth of *Aspergillus niger* and *Candida albicans* (Halawa *et al*., 2019). Another study also reported that kaffir lime leaf extract with concentrations of 25%, 50% and 75% could inhibit the growth of *Pityrosporum ova*l (Ramadhani *et al*., 2021). In addition, Khafidhoh *et al*. (2015) reported that the kaffir lime peel infusion with concentrations of 10%, 15% and 20% gave an antifungal effect on the growth of *Candida albicans* in vitro (Khafidhoh *et al*., 2015). To date, there has been no study on the potency of kaffir lime peel as antifungal for *Malassezia furfur*. Therefore, the objective of this study was to investigate the antifungal activity of Kaffir lime peel extract against *M. furfur* and established the optimal concentration.

2. MATERIAL and METHODS

2.1. Experimental Design

The research, a non-factorial experiment, used a completely randomized design. The treatment was based on differences in kaffir lime peel extract at four tested concentration, namely 25%, 50%, 75% and 100%. The sample of *M. furfur* ATCC. 14521 consists of five groups, namely control group, group 1 for 25% concentration, group 2 for 50% concentration, group 3 for 75% concentration, and group 4 for 100% concentration of the kaffir lime peel extracts. The diameter of the *M.furfur* growth inhibition zone was the assessed variable.

2.2. *Malassezia furfur* Colonies Preparation

The *Malassezia furfur* fungal was cultured using sterile ose and strake on Sabouroud Dextrose Agar (SDA) + olive oil medium which had solidified (Purwanti & Susanti, 2016). Then, the media were incubated at 37^{o}C for 18-24 h until *M. furfur* colony growth (Silvia *et al*., 2015). *Malassezia furfur* colonies were then separated into five test groups. Ketoconazole was used as a control. The solution ketoconazole was made by mixing 200 mg ketoconazole tablets which were crushed and diluted in 10 mL of sterile distilled water (Maulana *et al*., 2020). The treatment group was given extracts with respective tested concentrations (25%, 50%, 75% and 100%). A previous study reported that the antifungal effect of kaffir lime peel extract had the Minimum Inhibitory Concentration (MIC) at a concentration of 25% (Halawa *et al*., 2019).

2.3. Kaffir Lime Peels Extract Preparation

Kaffir lime extracts were prepared by taking peels parts, macerated in ethanol 96%, and then stored for 5 days. The extraction solution was filtered using a filter paper and a glass funnel. The filtrated biomass was collected in a sealed beaker glass. The maceration process was repeated using the medicinal residue once by using the same extraction solvent. The two

filtrates were pooled together and then drained using a rotary evaporator at 60°C with a pressure of 60 rpm for 8 hours (Halawa *et al*., 2019). Phytochemical test on Kaffir lime peels extracts was examined to define secondary metabolites including saponins, tannins, alkaloids, flavonoids, steroid, and terpenoid. The qualitative test identifies the presence of certain secondary metabolites by a color reaction or precipitate as a positive result using Mayer's reagent, Libermann-Burchard reagent, and FeCl 5% (Julianto, 2019).

2.4. Antifungal Activity Test

The difference in extract concentration can be prepared by diluting the kaffir lime peel extract with DMSO**.** 25% extract concentration can be prepared by diluting 2.5 ml of kaffir lime peels extract with 7,5 ml of DMSO, 50% concentration by diluting 50 ml of kaffir lime peel extract, and 50 ml of DMSO, and 75% concentration (4:1) with 7,5 ml of kaffir lime peel extract and 2,5 ml of DMSO. A positive control can be prepared by diluting 200 mg ketokonazol with 10 ml sterile distilled water. A negative control uses DMSO 100% (Maulana *et al*., 2020). In our study a blank disc paper with a 6 mm diameter was tested for antifungal activity. One milliliter of extract from kaffir lime peels was added to the disc sheets. The plates were allowed to incubate at 32°C during 48 hours. The presence of a clear zone indicated that fungus growth was inhibited, and the diameter was calculated in millimeters using a caliper. The inhibition zone was determined based on the diameter of the filter paper disc minus the diameter of the disc paper employed (Mulyadi *et al*., 2017). The inhibitory response of fungal growth according was determined according to Davis and Stout (1971), namely diameters: >20 mm, very strong; 10-20 mm, strong, 5-10 mm, medium; and <5 mm, no response.

2.5. Data Analysis

The data were subjected to Kruskal-Wallis test to examine the effect of kaffir lime peels extract on the growth of *M. furfur* at different concentrations. A Mann- Whitney Post hoc test was conducted to identify the optimal concentration of kaffir lime peel extract on the *M. furfur* growth inhibition.

3. RESULTS

3.1. Antifungal Effect of Kaffir Lime

The antifungal activity test showed that the inhibition zone was formed at the control group, and all tested concentrations. Among the tested concentrations, a concentration of 25% formed the smallest diameter of inhibition (9.7 mm), while the largest inhibition diameter was formed at a concentration of 100% (24.5 mm). Figure 1 shows the inhibition diameter formed at respective tested concentrations. The zone of inhibition was a circular area around the discs of the Ketoconazole and kaffir lime peels extract in which the *M. furfur* colonies did not grow.

Our study revealed that the inhibition zone at a concentration of 25% had a moderate category and had strong category at a concentration of 50% and 75% while it had strongest category at a concentration of 100%. Kruskal-Wallis test revealed that concentration of kaffir lime peel extracts gave a significant effect on the inhibition zone of *M. furfur* ($p< 0.05$). The higher inhibition zone was found at a concentration of 100% (24.5 mm). This value was significantly different for all groups except the control group according to the Mann Whitney post hoc test. Therefore, the concentration of 100% of kaffir lime peels extract showed the most effective antifungal effect against *M. furfur* among the other tested concentrations (Table 1).

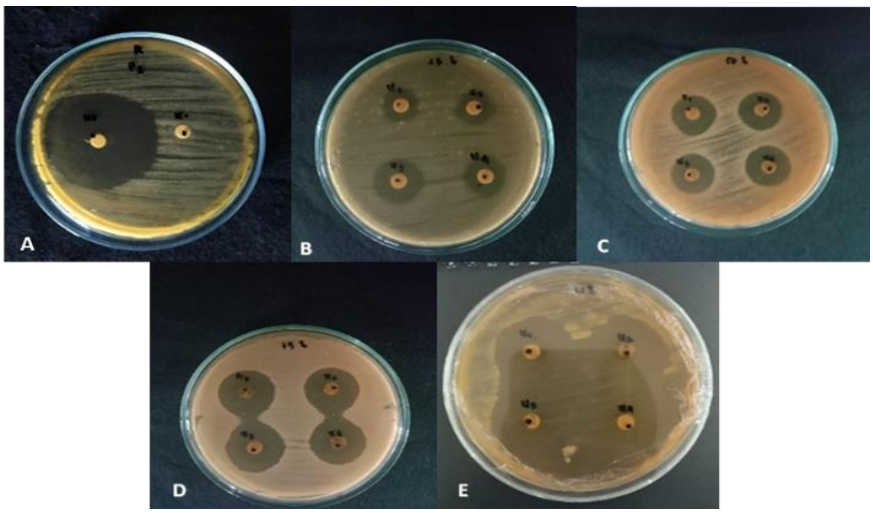

Figure 1. Streaking results of Ketoconazole (A); Kaffir lime peel extract on Group 1 (25%) (B), Group 2 (50%) (C), Group 3 (75%) (D), Group 4 (100%) (E).

Tabel 1. The inhibition zone of the growth *Malassezia furfur* between groups.

Parameters	Control	Group 1 (25%)	Group 2 (50%)	Group 3 (75%)	Group 4 (100%)
Inhibition zone	46.5 ± 4.0^{a}	9.7 ± 1.7^{e}	14.1 ± 0.8^{d}	18.2 ± 0.3^{c}	24.5 ± 3.3^{b}

Notes: Values are mean zone of inhibition diameter ± Standard Deviation. Different superscripts within the same row mean statistical difference at ($p < 0.05$).

3.2. Result of Identification Secondary Metabolite

Based on phytochemical essay kaffir lime peels extract contained secondary metabolites such as alkaloids, saponins, tannins, flavonoids, steroids, and terpenoid as observed in this study (Table 2).

Table 2. The phytochemical essay of secondary metabolites**.**

Secondary metabolites	Reagent	Result
Alkaloid	Bouchardart	+
	Maeyer	+
Saponin	Aquadest + Alkohol 96% +HCl 2N	+
Tannin	$FeCl_3$ 5%	+
Flavonoid	$FeCl_3$ 5%	+
Steroid	Salkowsky	+
	Liebermann-Bouchard	+
Terpenoid	Salkowsky	+
	Liebermann-Bouchard	+

The positive results of alkaloid test in Wagner test were confirmed by the presence of brownish to yellowish precipitate as Bouchardart test identified brownish precipitate as well. The foam formation in sapponin test provided the presence of glycosides that have an ability to produce foam in water hydrolyzed in glucose and other compounds. The positive results of alkaloid test in $FeCl_3$ 5% test were confirmed by the presence of blackish green precipitate. The extract samples that contained flavonoid compounds form the black flavium salt after addition of FeCl3 5%. Steroid/terpenoid screening is based on Salkowsky test, a positive result with a marked reddish color change indicating triterpenoid content and golden yellow steroid. The addition of Liebermann-Bouchard was confirmed by the presence of brown ring indicating triterpenoid content and greenish blue color change for steroid.

4. DISCUSSION

This study has shown that Kaffir lime peels extract at all tested concentrations inhibits the growth of the *M. furfur* in vitro. The formation of an inhibition zone indicated by the clear zone around the disc resulted in the moderate category at a concentration of 25%, and at 50% and 75% concentrations gave strong category, while at 100% concentration resulted in a very strong category. Thus, the results of this study showed the kaffir lime peels extract had potential as an antifungal effect. The study revealed that the diameter inhibitor zone increased proportionally with the increasing Kaffir lime extract concentration. The study conducted by Choirunnisa *et al.* (2022) reported that the ability of an antimicrobial depends on the concentration and the type of antimicrobial produced (Choirunnisa *et al*., 2022). The diameter of the inhibition zone increases with increasing extract concentration as recorded in this study. This is due to a higher concentration, ingredients of antimicrobials are also increasing. Besides inhibit the M. furfur, the kaffir lime peel extract also inhibited the growth of Staphylococcus aureus where the inhibition zone was increased as increases of kaffir lime peel extracts concentration (Madduluri *et al*., 2013).

The results of phytochemical essay kaffir lime peel extracts contained secondary metabolites as essentials materials that play antimicrobials and antifungal activities. For instance, flavonoids inhibit the growth of fungi by damaging the permeability of the plasma membrane, disrupt the mitochondria, disrupt the fungal cell wall synthesis, and inhibit RNA and protein synthesis resulting in disrupted reproduction and metabolism fungi (Serpa *et al*., 2012; Sari DP *et al*., 2017; Al Aboody & Mickymaray, 2020; Susilawati *et al*., 2023). Alkaloids have antifungal activities that result in disruption of the cell respiration system and protein synthesis, can trigger the loss of nutrients in fungal cells, slow reproduction of fungi, and even cell death *(Dhamgaye et al*., 2014; Swandiyasa *et al*., 2019). Alkaloids as an antifungal can destroy peptidoglycan in the fungal cell wall and trigger disruption of the permeability of the fungal cell wall. The decrease in the proliferation of fungal is due to the presence of saponin activity that damages the permeability of the fungal membrane that results in the leakage of cellular materials including nucleic acids and proteins (Lely & Rahmanisah, 2017; Porsche *et al*., 2018; *Dong et al.*, 2020).

Tannin can inhibit the ergosterol formed as the protein structure and regulatory components of the fungal cell membrane. Steroids can destroy the lipid membranes, which leads to the leakage of liposomes (Ernawati & Sari, 2015; Arifin *et al*., 2018). Additionally, it is known that steroids can penetrate lipophilic substances to interact with phospholipid membranes and thus can impair the cell membrane's integrity, resulting in cell lysis (Madduluri *et al*., 2013; Anggraini *et al*., 2019; Subaryanti *et al*., 2022). Terpenoids have the potential to interact with porins, which are transmembrane proteins in the outer membrane of the fungal cell wall. Terpenoids have the potential to interact with porins, which are transmembrane proteins in the outer membrane of the fungal cell wall. Terpenoids and porin create polymer bonds that can destroy the protein structure, lead to decrease in permeability, and therefore trigger bacterial cells to lose nutrients and even die (Ernawati & Sari, 2015; Amalia *et al*., 2017). There are several uses of kaffir lime peels, namely it has potential as a herbal shampoo for dandruff treatment because it is effective against dandruff microbial and also kaffir lime peel can potentially be a disinfectant solution on cutlery to reduce germ numbers (Tanzil *et al*., 2017; Rusmiati *et al*., 2023).

5. CONCLUSION

In conclusion, this study shows that the Kaffir lime peels extract has a potential antifungal activity against M. furfur while its concentration of 100% is the best concentration to inhibit the growth of this fungal, possibly due to its secondary metabolite content. The findings obtained in the current study therefore lead us to believe that Kaffir lime peels extract has potential as antifungal against M. furfur.

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Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the author(s). This research was approved by the Research Ethics Committee Malikussaleh University Faculty of Medicine. **Ethics Committee Number**: 10/KEPK/FKUNIMAL-RSUCM/2023.

Authorship Contribution Statement

Mulyati Sri Rahayu and **Wizar Putri Mellaratna:** Investigation, Methodology, Validation Resources, Formal Analysis, and Writing - original draft. **Nailah Najah:** Investigation, Visualization, Software, and Writing.

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