PHYSICAL QUALITY AND ANTIFUNGAL ACTIVITY OF KALANCHOE PINNATA LEAF EXTRACT OINTMENT AGAINST CANDIDA ALBICANS

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Abstract. Candidiasis is still a problem and the increasing resistance of microbes to drugs has encouraged the search for sources of antimicrobial drugs from natural ingredients. The Kalanchoe pinnata plant contains active compounds such as flavonoids, tannins, and saponins which have the potential to act as antifungals. This research aimed to determine the physical quality and antifungal activity of Kalanchoe pinnata leaf extract ointment against Candida albicans. The method used was experimental and four formulas were made with varying concentrations of added Kalanchoe pinnata leaf extract, namely F0 (0%), F1 (5%), F2 (10%), and F3 (15%). The results of the F0 organoleptic test are yellow, semisolid, and have a characteristic ointment odor. Meanwhile, F1, F2, and F3 are brown to dark brown, semisolid, and have a distinctive smell of Kalanchoe pinnata leaf extract. The homogeneity test results show that each formula has homogeneous properties. The pH test results on F0, F1, F2, and F3 were 5.90 respectively; 5.63; 5.54; and 5.37. The spreadability test results at F0, F1, F2, and F3 were 5.77 cm, 5.61 cm, 5.39 cm, and 5.22 cm, respectively. The antifungal activity test results at F0, F1, F2, and F3 were 0 mm, 4.31 mm, 8.04 mm, and 11.50 mm, respectively. The results obtained show that Kalanchoe pinnata leaf extract can be formulated in ointment preparations and has antifungal activity, the best seen from the inhibition test is in F3 with an extract concentration of 15%.
Keywords: *antifungal, ointment, kalanchoe pinnata, candida albicans*

Introduction

Fungi are one of the causes of infection, especially in tropical countries. Infection caused by Candida is known as Candidiasis. Candidiasis is opportunistic, namely infection due to a decrease in the body's immune system. Candidiasis occurs due to excessive growth of fungi, which can be caused by human life factors (Sophia, 2024). Climatic conditions in Indonesia, as well as humidity, poor sanitation, and unhealthy lifestyles, can trigger the growth of fungi (Soetojo and Astari, 2016). In cases in Indonesia, the prevalence of candidiasis is 20-25%, predominantly affecting hair, skin, nails, mucous membranes, mouth, and throat (Sophia, 2024). Candida is a commensal fungus that lives in the digestive, respiratory, skin and vaginal tracts. If the balance of normal flora or a person's immune defense decreases, the commensal nature of candida can turn into a pathogen (Soetojo and Astari, 2016). The most common cause of skin and mucosal diseases is Candida albicans. Cutaneous candidiasis cases are the third highest incidence among dermatomycosis cases (Salsabila and Nusadewiarti, 2023). Candidiasis can be transmitted by direct or indirect contact through objects contaminated with fungi, for example, bathroom floors, beds, towels, clothes, etc. (Salsabila and Nusadewiarti, 2023). Cases of candidiasis which are still a problem and increasing microbial resistance to drugs have encouraged the search for sources of antimicrobial medicines from natural ingredients (Utami et al., 2023). The use of drugs

from plants is believed to have few side effects (Oktaviani et al., 2021), the dangers and risks posed are lower when compared to chemical-based medicines, and are cheap in terms of price (Fahdi and Sari, 2022).

One of the plants that is efficacious as a traditional medicine is the Kalanchoe pinnata plant. Kalanchoe pinnata is used to treat several diseases including skin diseases, wound healing, kidney stones, gallstones, and diabetes. The pharmacological activity of Kalanchoe pinnata leaves has been reported as anti-inflammatory, antioxidant, and antimicrobial (Lestari et al., 2022). The Kalanchoe pinnata plant contains flavonoids, saponins, triterpenoids, and other chemical elements (Lestari et al., 2022; Temarwut, 2022). This content has the potential to act as an antifungal (Meilia et al., 2022; Rodiah et al., 2022). Candidiasis treatment mostly uses topical medications. The dosage form that is suitable as a vehicle for topical use is an ointment, which is a semi-solid preparation that is easy to apply and use as an external medicine. Based on this description, researchers formulated Kalanchoe pinnata leaf extract into an ointment. This research aimed to determine the physical quality and antifungal activity of Kalanchoe pinnata leaf extract ointment against Candida albicans.

Materials and Methods

This research uses laboratory experimental research methods. The equipment used includes an oven (Memmert), grinder, 60 mesh sieve, Erlenmeyer (Pyrex), glass funnel, water bath (Equitron), analytical balance (Labex), stir bar, L-bar, dropper pipette, measuring cup (Pyrex), cup. Porcelain, mortar, glass plate, pH meter, round diameter glass, weight, object glass, stopwatch, autoclave (Hirayama Autoclave HVE-50), tube needle, tweezers, spirit burner, petri dish, hot plate, test tube (Pyrex), glass beaker (Pyrex), caliper, vortex (Thermo Scientific), incubator (Vienna), steel pan. The materials used include Kalanchoe pinnata leaves, 70% ethanol, vaseline album, adeps lanae, sterile distilled water, Sabouraud Dextrose Agar (SDA) media, McFarland standard solution, nystatin ointment (Myco-Z), 0.9% NaCl, filter paper, aluminum foil. Research procedures include the preparation of raw materials, making Kalanchoe pinnata leaf extract, formulation and the making of ointment, physical quality evaluation, and antifungal activity test of the ointment.

Preparation of raw materials

Kalanchoe pinnata leaves are obtained from Boyolali Regency, Indonesia. The selected Kalanchoe pinnata leaves refer to the literature with the following characteristics: plant height is around 70 cm, Kalanchoe pinnata leaves are thick, contain lots of water, oval or long round shape, blunt leaf tip, rounded leaf base, curved leaf edges, and glabrous leaf surface. The leaves used are whole leaves that are not damaged, not moldy, and not yellow. The color Kalanchoe pinnata leaves obtained were made simply by collecting materials, wet sorting, washing, chopping, drying, and dry sorting. Drying was carried out in an oven for 3 days at a temperature of 40°C (Djumaati, 2018). The dried samples were ground using a blender and sieved using a 60-mesh sieve to obtain simplicia powder that was fine and uniform in size (Meilia et al., 2022).

Making Kalanchoe pinnata extract

The process of making Kalanchoe pinnata leaf extract is carried out using the maceration method. 400 grams of c Kalanchoe pinnata leaf powder was macerated with 3000 ml of 70% ethanol in a vessel covered with aluminum foil and left for 3 days with occasional stirring. Then the macerate is filtered using a glass funnel lined with filter paper, then evaporated over a water bath at a heating temperature of around 70°C so as not to damage the resulting extract (Putri et al., 2019).

Formulation and preparation of ointments

The formulation of the ointment preparation is made according to *Table 1*. which refers to several previous studies (Fahdi et al., 2022; Temarwut, 2022). The ingredients used are weighted according to the measurements in each formula. The bases used for making ointments are Adeps Lanae and Vaseline album. Adeps lanae is put into a porcelain cup and then melted in a water bath. After that, transfer the adeps lanae into a mortar then add the album vaseline little by little, and grind until homogeneous. Then, add Kalanchoe pinnata leaf extract according to the concentration in the formula, then grind until homogeneous, the finished ointment is placed in an ointment pot and labeled. The ointment is made in 100 grams.

Table 1. *Formulation of Kalanchoe pinnata leaf extract ointment.*

Formulation	Function	Concentration (%)			
		F0	F1	F2	F3
Kalanchoe pinnata leaf extract (gr)	Active ingredients	-	5	10	15
Adeps lanae (gr)	Ointment Base	15	20	15	10
Vaseline album (gr)	Ointment Base	85	75	75	75
m.f salep	-	100	100	100	100

Note: F0 (Ointment formula without added extract), F1 (Ointment formula with 5% Kalanchoe pinnata leaf extract), F2 (Ointment formula with 10% Kalanchoe pinnata leaf extract), F3 (Ointment formula with 15% Kalanchoe pinnata leaf extract).

Evaluation of ointment

Evaluation of ointment includes organoleptic tests, homogeneity tests, pH tests, and spreadability tests. (1). Organoleptic examination included the shape, color, and odor (Jamilatun et al., 2023a) of Kalanchoe pinnata leaf extract ointment. The quality parameters of a good ointment are a semi-solid dosage form, the ointment having a characteristic smell of the extract used, and a color like the extract. (2). The homogeneity test of the preparation was carried out by observing the results of applying the ointment to a glass plate (Jamilatun et al., 2024). The homogeneous ointment is characterized by the absence of lumps when applied, an even structure, and a uniform color from the start point of application to the end point of application. (3). The pH value of the ointment preparation is measured by dipping the pH meter (Jamilatun et al., 2023b) into the ointment preparation. A total of 50 mL of distilled water in a beaker was used to dissolve 0.5 g of ointment (Sari, 2023). The pH value is seen on a scale in the tool and recorded after the pH value is stable (Sandi and Musfirah, 2018). (4). The spreadability test was carried out by placing a sample of 0.5 g on a round glass with a diameter of 15 cm, another glass was placed on top and left for 1 minute then measuring the spread diameter of the ointment (Jamilatun et al., 2023a). After that, add a load of 100 gr and then 150 gr alternately every 1 minute and then measure the constant spreading power diameter (Rawung et al., 2020).

Antifungal activity test

The SDA media that has been made is poured into a sterile petri dish with a volume of ±20 ml (Jamilatun et al., 2020b). The SDA media was left at room temperature to solidify for around 30 minutes. Then 0.5 ml of Candida albicans suspension was inoculated on SDA media so that the suspension was mixed evenly on the surface of the media. A hole is made in the SDA media that has been inoculated with the test fungus with a diameter of 6 mm using a steel spatula or with a sterilized cork punch. Fill the hole with the tested ointment F1, F2, F3, positive control (nystatin), negative control (ointment base without extract/F0). And prepare a petri dish containing SDA media as a media control. Then incubated at 37°C for 24-48 hours and the clear zone formed was measured (Saputri et al., 2022). Observations were made during the 24-48 hour incubation period. The diameter of the inhibition zone is measured in millimeters (mm) using a caliper, by means of the overall diameter (vertical diameter plus horizontal diameter divided by two) minus the hole diameter of 6 mm (Rawung et al., 2020). Classification of inhibition zone diameter includes: >20 mm (very strong), 10-20 mm (strong), 5-10 mm (moderate), <5 mm (weak) (Lukito et al., 2024; Jamilatun et al., 2020a).

Results and Discussion

As a result of the extraction process of 400 grams of Kalanchoe pinnata leaf simplicia powder, 35.12 grams of thick extract was obtained, with a yield of 8.78%. These results are from previous research, the results of extracting Kalanchoe pinnata leaves obtained a yield of 8.14% (Meilia et al., 2022). Kalanchoe pinnata leaf extract is then formulated into an ointment with a predetermined concentration. The ointments were evaluated for physical quality which included organoleptic tests, pH tests, homogeneity tests, spreadability tests, and antifungal activity tests. The results of the physical quality of the ointment preparation of Kalanchoe pinnata leaf extract can be seen in *Table 2*. The results of organoleptic observations of Kalanchoe pinnata leaf extract ointment can be seen in *Table 2*. The F0 or ointment base is light yellow, semi-solid in shape, and has a distinctive ointment odor. In F1, F2, and F3, the Kalanchoe pinnata leaf extract ointment has a brown to dark brown color, semi-solid shape, and a distinctive odor of Kalanchoe pinnata leaf extract. These results are from previous research, where ointments that meet the requirements for ointment dosage form are semi-solid form, non-rancid odor, and color according to the active ingredient used (Sandi and Musfirah, 2018). The higher the concentration of the extract used in the ointment, the stronger the distinctive aroma of the extract and the more intense the color of the ointment (Fahdi et al., 2022).

***Table 2**. Physical quality of Kalanchoe pinnata leaf extract ointment.*

Formulation	Organoleptic			Homogenitas	pH	Spreadability (cm)
	Color	Texture	Smell			
F1	Yellow	Semi-solid	Typical ointment aroma	Homogeneous	5,90	5,77
F2	Chocolate	Semi-solid	The distinctive aroma of Kalanchoe pinnata leaf extract	Homogeneous	5,63	5,61
F3	Dark brown	Semi-solid	The distinctive aroma of Kalanchoe pinnata leaf extract	Homogeneous	5,54	5,39
F4	Dark brown	Semi-solid	The distinctive aroma of Kalanchoe pinnata leaf extract	Homogeneous	5,37	5,22

Note: F0 (Ointment formula without added extract), F1 (Ointment formula with 5% Kalanchoe pinnata leaf extract), F2 (Ointment formula with 10% Kalanchoe pinnata leaf extract), F3 (Ointment formula with 15% Kalanchoe pinnata leaf extract)

Homogeneity testing is carried out to assess the uniformity of the ointment, which is characterized by the absence of particles or granules (Sari, 2023). Based on the results in *Table 2*, it can be seen that the Kalanchoe pinnata leaf extract ointment has homogeneous results, when tested there were no lumpy particles found, the structure was even, and when applied it had a uniform color. The ointment homogeneity test shows that the resulting ointment is homogeneous. This indicates that the active ingredients and additives are mixed and distributed evenly, and the addition of the extract does not affect the physical stability of the ointment (Jacob et al., 2022). pH testing is carried out to determine the degree of acidity in the ointment to determine the safety of the preparation when used so that it does not irritate the skin. Based on the results in *Table 2*, it can be seen that the pH value at F0 is 5.90; F1 of 5.63; F2 of 5.54; and F3 of 5.37. These results show that the pH of the ointment meets pH standards that are safe for the skin. These results are to the literature in previous research that the pH requirements for topical preparations are between 4.5-6.5 (Sandi and Musfirah, 2018). The higher the extract concentration, the lower the pH of the ointment, because the greater the amount of extract added (Ambarwati, 2021). This is caused by the presence of organic compounds in the extract which tend to be acidic, so they can influence the acidity of a preparation (Ambarwati, 2021). The ideal topical preparation does not irritate the skin, because topical preparations require prolonged contact with the skin. Skin irritation if the preparation is too acidic or too alkaline (Rumanti et al., 2022). Based on the pH value obtained, Kalanchoe pinnata leaf extract ointment at various concentrations is safe for topical preparation (Novasella et al., 2022). Based on the pH value obtained, Kalanchoe pinnata leaf extract ointment at various concentrations is safe for topical preparation.

Testing the spreadability of the ointment, the ointment must be able to spread well without any pressure so that it is easy to apply to the skin. The difference in spreading power greatly influences the diffusion speed of active substances through the membrane. The wider the membrane through which the preparation spreads, the greater the diffusion coefficient, resulting in increased drug diffusion, so the greater the spreadability of preparation, the better it is (Djumaati, 2018). The results of the spreadability test on the Kalanchoe pinnata leaf extract ointment preparation, at F0 it had a spreadability of 5.77 cm; F1 had a spread of 5.61 cm; F2 had a spread of 5.39 cm; and F3 had a spread of 5.22 cm. The highest spreading power is at F0 and the lowest is at F3. The results of the spreadability test at the widest F0 show that the consistency of the ointment is softer due to the use of a large amount of album vaseline so that with each addition of a larger load the spreadability also changes. Meanwhile, F1, F2, and F3 show that the higher extract concentration causes the ointment to become thicker and spread less widely (Sandi and Musfirah, 2018). Overall, the spreadability test results for each formula are by the requirements for good ointment spreadability, namely around 5-7 cm. The antifungal test of the Kalanchoe pinnata leaf extract ointment preparation was carried out using the good diffusion method with SDA media. This test was carried out to determine the ability of the Kalanchoe pinnata leaf extract ointment to inhibit the Candida albicans fungus. The antifungal activity of the ointment preparation from Kalanchoe pinnata leaf extract can be seen in *Table 3*.

***Table 3**. Antifungal activity of Kalanchoe pinnata leaf extract ointment.*

Formulation	Inhibition zone (mm)	Category
K(+)	15,11	Strong
F0	0	Weak
F1	4,31	Weak
F2	8,04	Currently
F3	12,28	Strong

Note: K(+) (Positive control/nystatin ointment), F0 (Ointment formula without added extract), F1 (Ointment formula with 5% Kalanchoe pinnata leaf extract), F2 (Ointment formula with 10% Kalanchoe pinnata leaf extract), F3 (Ointment formula with 15% Kalanchoe pinnata leaf extract).

The results of the antifungal activity test in Table 3 show that the positive control has an inhibition zone of 15.11 mm, F0 has no inhibition zone, F1 has an inhibition zone of 4.32 mm with a weak classification, in F2 there is an inhibition zone of 8.04 mm. with a moderate classification, and at F3 there is an inhibition zone of 12.28 mm with a strong classification. In the positive control, nystatin was used (Aruan, 2018), with strong antifungal activity because this drug is effective in treating candidiasis and can inhibit the growth of Candida albicans. The antifungal nystatin works by irreversibly binding to ergosterol which is the main component of fungal cell walls. At sufficient concentrations, it will form pores in the fungal cell membrane which causes potassium leakage and fungal cell death (Permataningrum et al., 2020). In the negative control used was ointment base or F0, the same base was used for all formulas, the results of no inhibition showed that the inhibition zone produced by each formula in F1, F2, and F3 came from the active substance of the extract (Novasella et al., 2022). The highest inhibition zone is at F3 and the lowest inhibition zone is at F1. The results obtained show that the greater the concentration of Kalanchoe pinnata leaf extract, the greater the inhibition zone formed (Fahdi et al., 2022; Rajab et al., 2021). The larger the inhibition zone, the better the activity of the test material against microbes. Previous research stated that Kalanchoe pinnata leaf extract has antifungal activity against Candida albicans, with an inhibition zone of 11.67 mm (Widyanti, 2015). Kalanchoe pinnata leaves contain alkaloids, flavonoids, saponins, triterpenoids, tannins, and phenols (Fahdi and Sari, 2022). Alkaloids are antifungal because they can inhibit the growth of fungi by inserting between the cell wall and DNA so that fungal growth is disrupted (Qomaliyah et al., 2023). Alkaloids are antifungal because they can inhibit the growth of fungi by inserting between the cell wall and DNA so that fungal growth is disrupted (Maisarah and Chatri, 2023). Flavonoids are antifungal because they are lipophilic which can damage microbial membranes, phenolics in flavonoids damage cell cytoplasm and cause leakage of fungal cell nuclei (Ningsih and Advinda, 2023). Saponin acts as an antifungal by reducing surface tension so that cell permeability increases, cells become leaky, and intracellular compounds contained in the cells come out, causing metabolic substances, enzymes, proteins, and nutrients in the cells to come out and the fungi die (Yulia et al., 2023). Triterpenoids as antifungals react with pores in the outer membrane of the cell wall, forming strong polymer bonds thereby reducing cell wall permeability (Chatri et al., 2022). Tannin acts as an antifungal by inhibiting the biosynthesis of ergosterol, which is the main sterol that makes up fungal cell membranes. Sterols are structures and regulatory components found in fungal cell membranes (Lathifah and Chatri, 2022). Phenol as an antifungal works by increasing the amount of reactive

oxygen species (ROS), thereby triggering fungal cell apoptosis and inhibiting hyphae formation (Lathifah and Chatri, 2022).

Conclusion

The physical quality of the Kalanchoe pinnata leaf extract ointment preparation meets the requirements. The results of the F0 organoleptic test are yellow, semisolid, and have a characteristic ointment odor. Meanwhile, F1, F2, and F3 are brown to dark brown, semisolid, and have a distinctive smell of Kalanchoe pinnata leaf extract. The homogeneity test results show that each formula has homogeneous properties. The results of the pH test on F0, F1, F2, and F3 were respectively 5.90; 5.63; 5.54; and 5.37. The results of the spreadability test at F0, F1, F2, and F3 respectively yielded results of 5.77 cm, 5.61 cm, 5.39 cm, and 5.22 cm. The results of the antifungal activity test at F0, F1, F2, and F3 respectively yielded results of 0 mm, 4.31 mm, 8.04 mm, and 11.50 mm.

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Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

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