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RESEARCH ARTICLE

Activity test of kitolod (*Isotoma longiflora*) leaf ethanol extract gel against *acne* bacteria

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Abstract

Background: *Propionibacterium acnes* is a bacterium that causes acne. Flavonoids, alkaloids, and saponins are believed to be present in kitolod leaves, potentially serving as antibacterials. This extract is formulated in a gel preparation to facilitate its use. **Objective:** Discover the antibacterial activity of kitolod leaf ethanol extract gel against *Propionibacterium acnes* bacteria, and the results on days 0, 7, and 14 were related to organoleptic, physical stability, homogeneity, pH, dispersion, and adhesion. **Method:** The maceration method was employed for extraction over five days using 96% ethanol as the solvent. The disc diffusion method was then used to test the antibacterial activity, measuring the diameter of the inhibition zone formed around the disc paper that had been inoculated with the test bacteria. **Result:** The result showed that the kitolod leaf ethanol extract gel has antibacterial activity against Propionibacterium acnes bacteria. FI (extract concentration of 25%), FII (extract concentration of 45%), and FIII (extract concentration of 65%) have an average diameter of each inhibition zone of 5.52 mm, 11.83 mm, and 17.67mm. All gel formulations on days 0, 7, and 14 were physically stable and met the requirements. **Conclusion:** The higher the concentration of kitolod (*Isotoma logiflora*) leaves extract gel, the higher the inhibition zone produced.

Introduction

Acne, also known as acne vulgaris, is a skin condition that often occurs in teenagers aged 16-19 and adults aged 30. The presence of acne can have a psychological impact, reducing a person's self-confidence and affecting their quality of life (Wardani, 2020). *Propionibacterium acnes* is the cause of acne, which is a type of bacteria that breaks down free fatty acids in skin lipids by producing lipase and plays an essential role in the pathogenesis of acne vulgaris (Hasanah & Novian, 2020). Until now, most anti-acne drugs on the market contain antibiotics, whether used orally or topically. Using acne medication that contains antibiotics can cause adverse reactions, such as irritation, resistance, organ damage, and even hypersensitivity reactions (Putra, 2020). An alternative method for reducing the use of synthetic drugs to treat acne is to utilise antibacterial active ingredients derived from plants. Kitolod (*Isotoma longiflora*) is a wild plant that is still relatively unknown to the public. The leaves and flowers of this plant offer numerous health benefits. Kitolod leaves contain secondary compounds, including alkaloids, saponins, and flavonoids (Pawar *et al*., 2020. This compound exhibits pharmacological effects that include anti-inflammatory, antioxidant, anticancer, antidiabetic, antibacterial, antimalarial, antitumor, antimicrobial, antifungal, anti-insecticidal, and antiseptic properties (Fazil *et al*., 2017).

Previous research has shown that the thick extract of kitolod leaves (*Isotoma longiflora*) with a concentration of 300 mg/mL produced an antibacterial inhibitory potency of 14.3 mm against Staphylococcus aureus, which falls within the high category (Nisa, 2019). Another study showed that kitolod leaf extract (*Isotoma longiflora*) with a concentration of 65% produced an antibacterial inhibitory potency for Staphylococcus epidermidis of 4.23 mm (Lestari & Setiawan, 2017).

The direct use of kitolod (*Isotoma longiflora*) leaf extract is considered less efficient, so it needs to be

formulated into a gel to facilitate the use process. The gel formulation was chosen as a topical anti-acne treatment because it does not contain oil and features a hydrogel formulation, which prevents the skin from drying and helps prevent acne from worsening (Nisa, 2019). Thus, due to the problems arising in the background of this research, it is the study's interest to conduct research entitled Activity Test of Kitolod Leaf Ethanol Extract Gel (*Isotoma longiflora*) against *Propionibacterium acnes* bacteria. This research was conducted to determine the antibacterial activity of kitolod (*Isotoma longiflora*) leaves in gel dosage form against *Propionibacterium acnes* bacteria.

Methods

Design

This research employs experimental methods, a research approach used to investigate the influence of two variables under conditions determined by the researcher (Lestari & Setiawan, 2017). The approach used in this research is the cross-sectional method. The population in this study consisted of 11 kg of fresh kitolod (*Isotoma longiflora*) leaves collected in Pecangaan District, Jepara Regency. The sample used was kitolod (*Isotoma longiflora*) leaves obtained from Pecangaan Wetan Village, Pecangaan District, Jepara Regency. The kitolod leaves used are 5.5 kg of fresh, young, and light green leaves picked directly from wild plants. The sample collection technique used in this research was purposive sampling, which was employed to select samples of kitolod (*Isotoma longiflora*) leaves from the Jepara Regency area that met the inclusion criteria. A simple random sampling technique was then used to randomly select samples of kitolod (*Isotoma longiflora*) leaf extract for antibacterial testing.

Assessment

In this study, gel preparations were prepared with five formulations, as shown in Table I. In this study, a qualitative phytochemical screening was conducted to identify the presence of flavonoids, alkaloids, and saponins. Antibacterial testing was carried out using the disc diffusion method. The bacterial inhibition zone parameter is the diameter of the inhibition zone, which grows and develops in the area of the well of the bacterial growth medium. The diameter of the inhibition zone is measured with a calliper or ruler in millimetres (mm). The physical stability of the ethanol extract gel from kitolod leaves was tested using organoleptic, homogeneity, pH, spreadability, and adhesiveness tests on days 0, 7, and 14.

Data analysis was then carried out after obtaining the results of antibacterial testing and physical stability of the kitolod leaf ethanol extract gel during 14 days of storage. The data analysis technique was carried out quantitatively using SPSS with a one-way analysis of variance.

Table I: Kitolod leaf ethanol extract gel formulation

Material	Function	F0	FI	FII	FIII
Ethanol extract of kitolod leaves	Active substance	0%	25%	45%	65%
Carbopol	*Gelling agent*	2%	2%	2%	2%
Propilenglikol	Humectant	10%	10%	10%	10%
TEA	*Alkalising agent*	1%	1%	1%	1%
Gliserin	Aqueous gel	5%	5%	5%	5%
Methylparaben	Preservative	0.2%	0.2%	0.2%	0.2%
Aquadest	Solvent	Ad 100	Ad 100	Ad 100	Ad 100

The selection of the concentration of kitolod leaf extract, i.e., 25%, 45%, and 65%, is based on previous research, which showed that kitoloid leaf extract with a concentration of 65% exhibited an antibacterial inhibitory potency against *Staphylococcus* epidermidis of 4.23 mm (Lestari & Setiawan, 2017). The gel was prepared by dispersing Carbopol in a portion of distilled water heated to 70°C, allowing it to swell, and stirring until a homogeneous mixture was achieved. After that, glycerin and propylene glycol are added. Next, the ethanol extract of kitolod leaves (*Isotoma longiflora*) and methylparaben are dissolved in a portion of water that has been heated in a water bath. Then triethanolamine and distilled water were added. After that, it is added to the gel base that has been formed. Stir until a homogeneous gel forms, then package it in a gel container (Rowe *et al*., 2009; Borman *et al*., 2015).

Results

Sample extraction results

Eight hundred grams of kitolod leaf simplicia were used, which were extracted using the maceration method using 8,000 ml of 96% ethanol solvent for three days, resulting in a thick extract of 140.55 grams with a dark green extract and a distinctive smell of kitolod leaf extract (*Isotoma longiflora*) and received the yield (Table II).

Table II: Calculation results of the kitolod leaf extract yield

Simple weight (g)	Solvent volume (mL)	Type of extract	Extract weight (g)	Rendement (%)
800	8.000	Thick	140.55	17.57 %

Phytochemical screening

The results of qualitative phytochemical screening tests stated that kitolod (*Isotoma longiflora*) leaf extract is positive for containing flavonoids, alkaloids, and saponins, which are compounds that play an essential role as antibacterials (Table III).

Table III: Results of identification of kitolod leaf extract using qualitative methods

Active compound	The results are formed	Conclusion
Alkaloid	There is a white precipitate	Positive for alkaloids
Flavonoid	An orange colour forms	Positive for flavonoids
Saponin	There is 2.5 cm of foam	Saponin positive

Gel physical stability test results

Organoleptic test

Observation of the physical appearance of preparation, including shape, colour, and odour, through organoleptic tests (Table IV). Based on the results of the shape, smell, and colour of the kitolod leaf extract gel, it has a thick shape, a distinctive smell of the extract, and a green colour, where the resulting green colour has a difference with the higher concentration of the extract in the gel formula, the colour of the gel preparation will be more intense.

Table IV: Organoleptic stability test results of kitolod leaf extract gel

Formulation		Characteristics		
		Colour	Smell	Form
FI	Day 0	Green	Characteristic odour of extract	Semi-solid
	Day 7	Green	Characteristic odour of extract	Semi-solid
	Day 14	Green	Characteristic odour of extract	Semi-solid
FII	Day 0	Dark green	Characteristic odour of extract	Semi-solid
	Day 7	Dark green	Characteristic odour of extract	Semi-solid
	Day 14	Dark green	Characteristic odour of extract	Semi-solid
FIII	Day 0	Deep green	Characteristic odour of extract	Semi-solid
	Day 7	Deep green	Characteristic odour of extract	Semi-solid
	Day 14	Deep green	Characteristic odour of extract	Semi-solid

Homogeneity test

Table V presents the results of the homogeneity stability test. The three formulations exhibited comparable characteristics, characterised by homogeneity and a coarse-grained structure.

Table V: Results of the homogeneity stability test of kitolod leaf extract gel

Formulation	Observation result		
	FI	FII	FIII
Day 0	Homogeneous, coarse grains do not appear	Homogeneous, coarse grains do not appear	Homogeneous, coarse grains do not appear
Day 7	Homogeneous, coarse grains do not appear	Homogeneous, coarse grains do not appear	Homogeneous, coarse grains do not appear
Day 14	Homogeneous, coarse grains do not appear	Homogeneous, coarse grains do not appear	Homogeneous, coarse grains do not appear

Test pH

Table VI presents the pH stability of the kitolod leaf extract gel. Formulation FIII demonstrates a marginally lower pH compared to the other two formulations. Over an extended period, a slight decrease in pH is observed across all formulations.

Table VI: Results of pH stability test of kitolod leaf extract gel

Formulation	Observation result (Average)		
	FI	FII	FIII
Day 0	6.15	6	5.64
Day 7	6	5.95	5.61
Day 14	5.82	5.74	5.54

Spreadability test

Table VII presents the results of the stability test conducted on the spreadability of the kitolod leaf extract gel. It is noteworthy that all three formulations exhibited the highest levels of spreadability on day seven.

Table VII: Results of the stability test for the spreadability of kitolod leaf extract gel

Formulation	Observation result (Average)		
	FI	FII	FIII
Day 0	5	5.2	5.1
Day 7	5.5	5.4	5.5
Day 14	5	5.2	5.1

Adhesion test

Table VIII presents the results of the adhesion stability test. The stability of adhesion among the three formulations increases gradually over time.

Table VIII: Results of the stability test of the adhesion of kitolod leaf extract gel

Formulation	Observation result (Average)		
	FI	FII	FIII
Day 0	5s	6s	5s
Day 7	7s	6s	8s
Day 14	8s	7s	9s

Antibacterial test results

Table IX presents the results of the antibacterial activity assessment of the kitolod leaf extract gel. The concentration of 65% demonstrated the most significant inhibition zone in comparison to the other concentrations examined.

Table IX: Results of antibacterial activity test of kitolod leaf extract gel

Sample	Inhibition zone formed (mm)			Average ± SD	Category
	Repetition 1	Repetition 2	Repetition 3		
Concentration 25%	5	6.25	5.3	5.52 ± 0.6	Currently
Concentration 45%	10	12	13.5	11.83 ± 1.7	Strong
Concentration 65%	15	18	20	17.67 ± 2.5	Strong
Positive control (+) (Clindamycin gel)	30	32.5	33.4	31.97 ± 1.7	Very strong
Negative control (-)	0	0	0	0 ± 0	-

Figure 1 illustrates the results of the antibacterial activity test conducted with the kitolod leaf extract gel displayed in Petri dishes. Additionally, the inoculation of *Propionibacterium acnes* bacteria is presented in Figure 2.

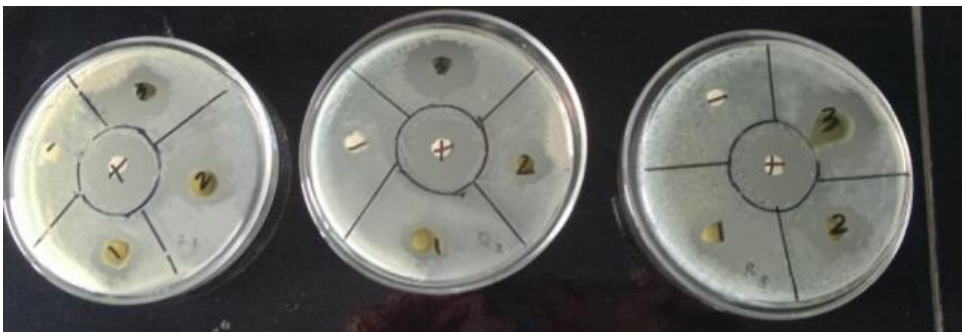

Figure 1: Antibacterial activity test results of kitolod leaf extract gel

Figure 2: *Propionibacterium acnes* bacteria inoculation

Discussion

Kitolod leaf ethanol extract gel was tested for homogeneity, and the results showed that all gel formulations had good homogeneity during storage. A good gel to use must have good homogeneity. The homogeneity test is conducted to ensure that the cream ingredients are mixed evenly and free from clumped particles, thereby preventing irritation when applied topically to the skin. Gel homogeneity can be visually determined and observed under a microscope to assess the uniformity of the particles at each gel concentration.

A good gel pH score is almost identical to the skin's pH, which typically ranges from 4.5 to 6.5. If the pH value is too acidic compared to the skin's pH, it is feared that it will irritate the skin. Conversely, if the pH is too alkaline compared to the skin's pH, the skin will become dry (Sayuti, 2015). The decrease in pH during 14 days of storage at room temperature in the gel preparation was caused by the gelling agent of the preparation, namely, carbopol, which is acidic. Triethanolamine (TEA) cannot cover the acidic properties of the carbopol base during storage. The decrease in pH of the preparation is still within the normal skin pH range, making it still acceptable (Slamet *et al*., 2020).

Spreadability refers to the ability of the preparation to spread evenly on the skin area after application (Forestryana *et al*., 2020). Based on the spreadability test, the results obtained for the three formulas during 14 days of storage were 5-5.5 cm. This means that it meets the requirements for good spreadability of topical preparations, which is 5-7 cm. This proves that the spreading diameter for the antiseptic gel formula meets the gel spreading diameter requirements. Based on the results of the spreadability test, it was found that the spreadability value fluctuated on day zero and day seven, and all formulations experienced an increase. The longer the storage time, the more the spreadability results will increase (Mahdalin *et al*., 2017). However, on the 14th day, all formulations experienced a decrease in spreadability values. This can happen due to several factors, including unstable storage temperature (Forestryana *et al*., 2020). An adhesion test is conducted to determine how long the gel adheres to the skin before the gel preparation is removed. Adhesion that is too strong will block the skin pores, whereas adhesion that is too weak will not achieve the therapeutic effect (Slamet *et al*., 2020).

This is due to the adhesion test requirements, as theoretically, the adhesion potency that meets the requirements for cosmetic preparations is more than one second (Irianto *et al*., 2020) and increases during 14 days of storage. This reasonably high result indicates that the concentration of the gelling agent affects the adhesive force. The greater the concentration, the more the sticking time will increase (Forestryana *et al*., 2020). Additionally, the increase in adhesion is attributed to the increase in viscosity of the gel preparation during storage. This viscosity increase is attributed to the evaporation of ethanol during storage in the gel preparation (Affandy *et al*., 2021).

In research on the antibacterial activity of kitolod (*Isotoma longiflora*) extract gel, five formulas were used: F1 (25%), F2 (45%), F3 (65%), a negative control, and a positive control (clindamycin gel). This antibacterial activity test determines the ability of the kitolod (*Isotoma longiflora*) extract gel preparation to inhibit the growth of Propionibacterium acnes bacteria, as indicated by the clear zone that forms around the paper disc. Clindamycin gel was used as a positive control because clindamycin is an antibiotic used to treat diseases caused by gram-positive anaerobic bacterial infections (Agistia *et al*., 2021). After all, it exhibits high activity against various facultative anaerobic bacteria and Gram-positive organisms, one of which is the bacterium Propionibacterium acnes, which is the bacterium responsible for causing acne (Kumalasari *et al*., 2020).

The concentrations of the ethanol extract of kitolod leaves (*Isotoma longiflora*) used in the research were 25%, 45%, and 65% to determine the amount of inhibitory potency equal to the concentration found in the kitolod leaves ethanol extract (*Isotoma longiflora*) on gel availability. At a concentration of 25%, the diameter of the bacterial inhibition zone, on average, is approximately 5.52 mm, indicating moderate inhibition, as determined by the results obtained at this concentration. At a concentration of 45%, the average diameter of the bacterial inhibition zone was 11.83 mm, which is within the classification of inhibitory solid potency. At a concentration of 65%, the average diameter of the bacterial inhibition zone was 17.67 mm, which is within the classification of inhibitory solid potency. In the positive control (clindamycin), the average diameter of the bacterial inhibition zone was 31.97 mm, whereas the results obtained in the positive control (clindamycin) were classified as potent inhibition. The results of this research showed that the largest zone of inhibition was observed in the gel preparation with an extract concentration of 65%, specifically 17.67 mm. In this research, it is evident that the higher the extract concentration used, the greater the resulting inhibitory potency.

Greetham demonstrated that the ethanol extract of kitoloid leaves, at concentrations of 65%, 70%, 75%, and 100%, exhibited inhibitory potency against Staphylococcus epidermidis bacteria, with IC50 values of 6.1 nm and 4.23 nm, respectively (Lestari & Setiawan, 2017). Greet (2013) demonstrated that ethanol extracts of kitoloid leaves, with concentrations of 65%, 70%, 75%, and 100%, exhibited inhibitory potency against Staphylococcus epidermidis bacteria, with IC50 values of 6.1 nm for 65% and 4.23 nm for 70%. Oktaviani (19) demonstrated that ethanol extracts of kitoloid leaves at concentrations of 100 mg/mL, 150 mg/mL, 200 mg/mL, and 300 mg/mL exhibited inhibitory potency against Staphylococcus aureus bacteria, with the 300 mg/mL concentration yielding a zone diameter of 14.3 mm (Nisa, 2019).

Inhibition of antibacterial activity occurs due to chemical reactions involving the compound. The chemical compounds in the ethanol extract of kitolod leaves contain flavonoids, alkaloids, and saponins. The mechanism of action of flavonoid compounds consists in forming a complex with soluble extracellular proteins. Thus, it can cause damage to bacterial cell membranes and the release of intracellular compounds (Kumalasari *et al*., 2020). Alkaloid compounds exhibit antibacterial activity against the peptidoglycan component found in bacterial cells. Thus, a layer on the cell wall will not form, which is the cause of cell death (Kumalasari *et al*., 2020). Saponin compounds have an antibacterial mechanism of action that decreases surface tension, thereby increasing permeability and allowing cells to leak, and facilitating the escape of intracellular compounds (Kumalasari *et al*., 2020). In the one-way ANOVA test, the results were 0.000 < 0.05, indicating a significant influence between variations in the concentration of the ethanol extract gel of kitolod leaves (*Isotoma longiflora*) and the diameter of the inhibitory potency produced.

Conclusion

From the results of qualitative phytochemical screening, there were secondary metabolite groups of flavonoids, alkaloids, and saponins in kitolod (*Isotoma longiflora*) leaves. Kitolod (*Isotoma longiflora*) leaf ethanol extract gel exhibits antibacterial activity against Propionibacterium acnes bacteria, with higher extract concentrations yielding higher inhibitory potency results. The highest inhibitory results are observed in formulation three, which contains a *65% kitolod (Isotoma longiflora) ethanol extract in the* solid category. Where variations in the concentration of kitolod leaf ethanol extract in the gel preparation influence the diameter of the inhibitory zone of the *propionibacterium acnes* bacteria, all gel preparation formulations were physically stable during 14 days of storage. The formulation of kitoloid leaf extract gel can be further developed, i.e., through in vivo testing on test animals and in clinical trials on humans, to assess its effectiveness as an antibacterial agent and its safety.

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