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The Inhibitory Effect of East Indonesia Endemic Plant Itchy Leaves on *Staphylococcus epidermidis* as a Normal Skin Flora

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ABSTRACT

Itchy leaf (*Laportea decumana*) is one of the plants endemic to Eastern Indonesia. People usually use itchy leaves as an alternative treatment for pain and soreness by rubbing it on the surface of the body. Itchy leaves are very useful because they contain abundant secondary metabolites. The application of itchy leaves by rubbing can certainly affect normal skin flora such as *Staphylococcus epidermidis*, leading to health problems. This study aimed to investigate the effect of methanol extract of itchy leaves on the normal skin flora of *S. epidermidis*. This test was conducted using the disk diffusion method. The results of this study showed that all concentrations of itchy leaf extract inhibited the growth of *S. epidermidis*. The highest inhibitory activity was observed at 50% concentration (23.00 ± 7.20), categorized as very strong, followed by 100% concentration (15.00 ± 2.90), 25% (18.00 ± 11.3), 12.5 (13.40 ± 3.51), and 6.25 (10.40 ± 3.10), all categorized as strong. These findings indicate that the prolonged use of itchy leaves may affect the growth of normal flora, resulting in health problems. On the other hand, itchy leaves have the potential to be developed as an antibacterial agent in the future.

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INTRODUCTION

About 350,000 species of Tracheophyta plants, also known as vascular plants, are found on Earth, with 10% of these species being used as medicines (Borsch et al., 2020; Salmerón-Manzano et al., 2020). The use of Tracheophyta species as medicinal plants has been practiced since ancient times to prevent or cure diseases, and it continues to be used by the community as a primary form of health care (Henri et al., 2022; Ikhsan et al., 2021). About 80% of the world's population, or four billion people, living in developing countries use herbal medicinal products as an alternative to primary traditional medicine (Ekor, 2014; Maldonado Miranda, 2021; Okaiyeto & Oguntibeju, 2021). On the other hand, the use of herbal medicine has also been widely accepted in many developed countries such as America, Australia, the UK, and parts of Europe, as complementary and alternative medicine (Ekor, 2014). In addition, according to WHO (World Health Organization), 40% of medicines considered important are derived from plant products, such as aspirin, artemisinin, and treatments for childhood cancer (World Health Organization, 2023).

In Asian societies, medicinal plants have been used for thousands of years to treat health problems (Musa et al., 2023). Data on medicinal plants in Asia shows that the number of medicinal plants used by the community in each country varies greatly, such as Thailand (2187 species), China (274 species), Laos (8,000-11,000 species), Korea (1,819 species), Cambodia (50 species), Philippines (1500 species), Malaysia (8711 species), Myanmar (472 species) and Indonesia (30,000-40,000 species) (Belgica et al.,

2021; Cahyaningsih et al., 2021; DeFilipps & Krupnick, 2018; Ehrman et al., 2007; Ibrahim et al., 2022; Liu, 2021; Soejarto et al., 2012; Yun et al., 2021). Medicinal plants used come from leaves, stems, roots, fruits, buds and flowers (Shaik et al., 2023). Asians commonly use medicinal plants by oiling, brewing, cooking, mashing, dipping, and direct consumption (Nugroho et al., 2022).

Indonesia, one of the countries in Southeast Asia, has also used herbal plants for medicine, a practice that has been passed down through generations (Ikhsan et al., 2021). About 30.1% of the Indonesian population uses traditional medicines and practices traditional medicine (Suryawati et al., 2023). In general, Indonesian people cultivate medicinal plants in their yards or gardens, on the edge of rice fields, or in forests where they grow wild (Rosmini et al., 2021; Siahaan et al., 2023; Sri Pujihastuti et al., 2020). The use of herbal plants in Indonesia is practiced by the local wisdom of each tribe, especially in rural communities and those in remote or inland areas (Hastuti et al., 2022; Mulyani et al., 2020). In Eastern Indonesia, especially in Maluku and Papua regions, local populations also rely on alternative endemic medicinal plants, one of which is itchy leaves (*Laportea decumana* (Roxb.)).

Itchy leaf is a genus of *Laportea* that is used by people in Maluku and Papua as a topical remedy for fatigue, soreness, and pain relief (Basy et al., 2022; Simaremare, D. N. Putri, et al., 2022; Thalib et al., 2021). Itchy leaves are known to have various benefits, such as antimicrobial, antioxidant, antidiabetic, cytotoxic, and analgesic effects. The efficacy of itchy leaves is inseparable from the content of secondary metabolites they contain, such as alkaloids, glycosides, and topical triterpenoids (Assaf et al., 2020; Rollando et al., 2022; Thalib et al., 2022). Moluccans and Papuans usually use itchy leaves directly by rubbing or patting them onto areas of skin experiencing soreness or pain (Simaremare et al., 2019). The effect of patting or rubbing the itchy leaves is the onset of burning, itching, and heat, causing an analgesic effect on the skin.

As is well known, the skin is the outermost physical defense of humans and is home to a normal flora consisting of millions of microbes such as bacteria, fungi, and viruses. However, most researchers do not classify viruses and parasites as members of the normal skin flora because they are not commensal and harmful to the host. Normal flora plays a role in helping the skin protect the body against pathogens. Some types of normal flora found on the skin include *Propionibacteria*, *Micrococci*, *Streptococci*, and *Staphylococcus epidermidis*. The *S. epidermidis* population accounts for more than 90% of the entire aerobic microbiota on the skin (Fournière et al., 2020). *S. epidermidis* has a self-defense mechanism that helps the skin protect the body by producing proteases and bacteriocins that can inhibit the formation and growth of opportunistic pathogens on the skin. In addition, *S. epidermidis* can produce molecules that have antimicrobial activity against pathogenic bacteria, such as *Streptococcus pyogenes* and *Staphylococcus aureus*, known as Phenol Soluble Modulin (PSM). (Glatthardt et al., 2020). Antimicrobial Peptide (AMP), which is produced through the activation of innate immunity by *S. epidermidis*, synergize with PSM to kill the pathogen (Pastar et al., 2020).

In previous studies, antimicrobial activity of *L. decumana* against *Candida albicans* was tested with the most effective results to inhibit fungal growth at a concentration of 500ppm using ethanol solvent. Testing against *S. aureus* bacteria showed the best results at a concentration of 500ppm using n-hexane solvent with an inhibition zone diameter of 11 mm (Simaremare et al., 2020).

These findings demonstrate that *L. decumana* has potential as an anti-bacterial. However, to date, no research has been conducted to examine the effect of *L. decumana* on normal skin flora, especially *S. epidermidis* bacteria, which play a crucial role in protecting the skin from other pathogenic microorganisms. Therefore, the purpose of this study was to investigae the effect of *L. decumana*, which is usually used on the skin to relieve pain and soreness on the growth of the normal skin flora *S. epidermidis*.

MATERIALS AND METHODS

Study Area

This research was conducted from July to August 2024. Antibacterial testing was carried out at the Microbiology Laboratory, Faculty of Medicine, Universitas Pattimura. The extraction process was carried out at the Biochemistry Laboratory, Faculty of Mathematics and Natural Sciences, Universitas Pattimura. The sampling of itchy leaves (*Laportea decumana*) was carried out in Mamala Village, Leihitu District, Central Maluku Regency, Maluku Province (3°33'34.7"S 128°11'32.0"E). A pure culture of *Staphylococcus epidermidis* bacteria was obtained from PT Agritama Sinergi Inovasi, with strain code ATCC-12228.

Sample Preparation

The part of the *L. decumana* plant used was the dark green leaves. A total of 3 kg of leaves were washed thoroughly using running water and air-dried overnight. The dried leaf samples were cut into small pieces and dried using an oven (Memmert, Germany) at 60°C until fully dried (Pardua et al., 2018; Ren et al., 2020). Next, the leaves were pulverized using a blender until they became powder.

Extraction of Itchy Leaves

The extraction process was carried out using the maceration method. A total of 350 grams of dry powder was soaked in methanol solution for three days at a ratio of 1:10. The solvent was added every 24 hours along with stirring. The extract was concentrated using a vacuum rotary evaporator (RE100-ProD-Lab) to get a thick extract, then filtered using filter paper (Whatman) (Elfita et al., 2019; Mulia et al., 2023). The calculation of the yield percentage was carried out referring to previous research by (Isac-García et al., 2016):

$$\text{Yield (\%)} \frac{\text{Mass pf leaves extract yield}}{\text{Mass of leaves powder}} \text{x100}$$

Furthermore, the extract was diluted using sterile distilled water to obtain the desired concentrations of 6.25, 12.5, 25, 50, and 100% (Warella et al., 2021, 2023).

Preparation of *Staphylococcus epidermidis*

Rejuvenation of *S. epidermidis* was done by inoculating the bacteria into a petri dish containing sodium agar medium (Merck). The isolates were streaked on the available medium under sterile conditions to avoid contamination. The isolates were then incubated for 24 hours at 20-35°C (Aviany & Pujiyanto, 2020). The preparation of bacterial suspension was made by taking 1 Ose of *S. epidermidis* bacteria into a test tube containing 10 mL of 0.9% physiological NaCl and vertexing (Gemmy VM-300, Taiwan) until homogeneous. The suspension was then adjusted to match the McFarland 0.5 (1,5 x 10^{-8}) standard solution (Odo et al., 2023; Rizki et al., 2021).

Bacterial Growth Inhibition Test

The bacterial inhibition test was conducted using the Kirby-Bauer disc paper diffusion method. *L. decumana* extracts used were 6.25, 12.5, 25, 50, and 100%, with tetracycline as a positive control and 10% DMSO as a negative control. A total of 10 mL of Muller Hintor Agar media (Merck) was put into a Petri dish and cooled to solidify. Then, 0.2 mL of *S. epidermidis* bacterial suspension was evenly inoculated onto the surface of the medium utilizing a spread plate method. Paper disks were soaked in *L. decumana* extracts at various concentrations of 6.25, 12.5, 25, 50, and 100% for 15 minutes and attached to the surface of the media. The positive control and negative control were also placed on the surface of MHA. The Petri dish was then incubated at room temperature (25-35°C) for 24 hours (Warella et al., 2023). The observation of the inhibition zone was carried out by measuring the clear zone using a caliper. Clear zone measurements were calculated using the formula by Rosa et al. (2020) (Figure 1): (AB-ab + CD-cd)/2, where AB is the diameter of vertical zone of inhibition, CD is the diameter of horizontal zone of inhibition, and ab & cd are the diameter of paper discs.

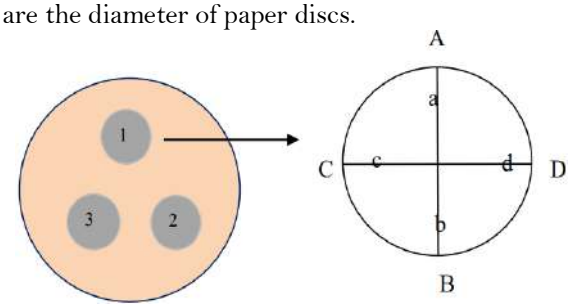

Figure 1. Measurement of clear zone diameter

Data Analysis

The data obtained were presented in tables and figures and assessed descriptively. Assessment of the effectiveness of the inhibition of *L. decumana* extract based on different concentrations was analyzed using the Statistical Package for the Social Science (SPSS) software application. First, the data normality test was conducted using Shapiro-Wilk test, then the homogeneity test was conducted using the Levene Test. If the data were normally distributed and homogeneous, a one-Way ANOVA statistical test was carried out to assess the differences in the inhibition measurement at each concentration.

Ethical Consideration

The ethical approval for this research was issued by the Health Research Ethics Committee, Faculty of Medicine, Universitas Pattimura, Ambon, Indonesia, under certificate No: 076/FK-KOM.ETIK/VIII/2024.

RESULTS AND DISCUSSION

Itchy leaf (*L. decumana*) is a plant endemic to Eastern Indonesia that is often used in traditional medicine. People use itchy leaves as anti-analgesics, antioxidants, antipyretics, antidiabetic, antibacterials, anti-inflammatory agents, antiandrogens, pre-gestational agents, anti-estrogens, and others (Basy et al., 2024; Simaremare et al., 2020; Thalib et al., 2021). The part of the plant used in medicine is the leaves, with which have a broad surface and are covered with trichomes (Ariastuti et al., 2018; Simaremare, Tolip, et al., 2022). Ethnobotanical data of itchy leaves used in this study can be found in Figure 2 and Table 1.

In this study, the extraction of itchy leaf was carried out using the maceration method with methanol solvent. Methanol is an organic solvent that is effective in extracting high amounts of phytochemical compounds. The ability of methanol is influenced by the nature of the solvent, which is polar or soluble in water and is universal because it can extract active compounds with polar and non-polar components (Mahasuari et al., 2020; Riyadi et al., 2023). The polarity of methanol is higher than that of ethanol. This allows the methanol solvent to act as a molecular hydrogen acceptor or donor by forming stronger hydrogen bonds (Lee et al., 2024). Based on this principle, methanol can extract compounds more quickly and efficiently with maximum extraction results. The percentage yield obtained using methanol solvent is presented in Table 2.

Research conducted by Borges et al. (2020) compared several types of solvents and found that methanol was able to extract the most active compounds, demonstrating the highest antimicrobial ability in inhibiting the growth of *Staphylococcus aureus* and *Escherichia coli* bacteria, with an inhibition zone of 16.7 mm. In addition, a study by (Truong et al., 2019) found that methanol was the most effective solvent to produce a high extraction yield (32.2%), as well as phytochemical content (phenolic, flavonoid, alkaloid, terpenoid). Moreover, it exhibited a high antioxidant capacity (IC_{50}:16.99 µg/mL) and demonstrated anti-inflammatory activity in vitro. The extraction effectiveness comes from the interaction between solvent capability and the relative solubility of the plant sample. Extraction can be optimized if the solvent is able to form hydrogen bonds with the solute (Gil-Martín et al., 2022). Therefore, the greater the diffusivity of the solvent in the cell matrix, the easier it is to destabilize the hydrogen bonds in its structure and the higher the solvency of the target compound (Alara et al., 2021).

The extraction of itchy leaves produced 50 ml of extract. These results are supported by Saafi et al. (2009), who used conventional methods with methanol solvents on 100 g samples to obtain high amounts of phenolic compounds, ranging from with 209.42 to 447.73 mg. The right extraction technique will produce high yields with stable compound components (Ghenabzia et al., 2023). This is also related to the fact that the greater the ratio of solvent to solute, the higher the extraction yield. If the ratio of solvent to solute is too high, it can lead to excessive used of the solvent and result in a longer extraction time to achieve the desired yield (Zhang et al., 2018). In addition, a higher the percentage yield often correlates with the production of active compounds (Pawarti et al., 2023). Some factors that affect the extraction yield and active compound content, including the extraction method, temperature, type of solvent, time, and agitation speed (Dhanani et al., 2017). This is supported by research from Haido et al. (2024), who compared extraction methods, solvent types, and extraction times, and found that the soxhlet method had the highest extraction yields

Figure 2. *Laportea decumana* (Roxb.) Wedd

Table 1. Ethnobotanical data on medicinal plants selected for antibacterial tests

Ecthnobotanical data	Type of plant
Plant Spesies	*Laportea decumana* (Roxb.) Wedd
Family	*Urticaceae*
Local Name	Beep Bangii (Kiwirok, Papua), Bulum / Bugum (Mimika, Papua), Kafa' (Sorong), Daun Gatal Putih (Ambon),
Common Name	Daun Gatal
Plant part used	Leaves
Color plant	Dark green

Table 2. Yield percentage of *Laportea decumana (Roxb.)* Wedd

Charactics	Yield
Extraction method	Maceration
Solvent	Methanol
Weight of Simplisia	300 grams
Amount of Solvent	3 Liters
Total Extract	50 ml
Yield (%)	16.6%
Color yield	Dark green
Texture Ekstract	Liquid

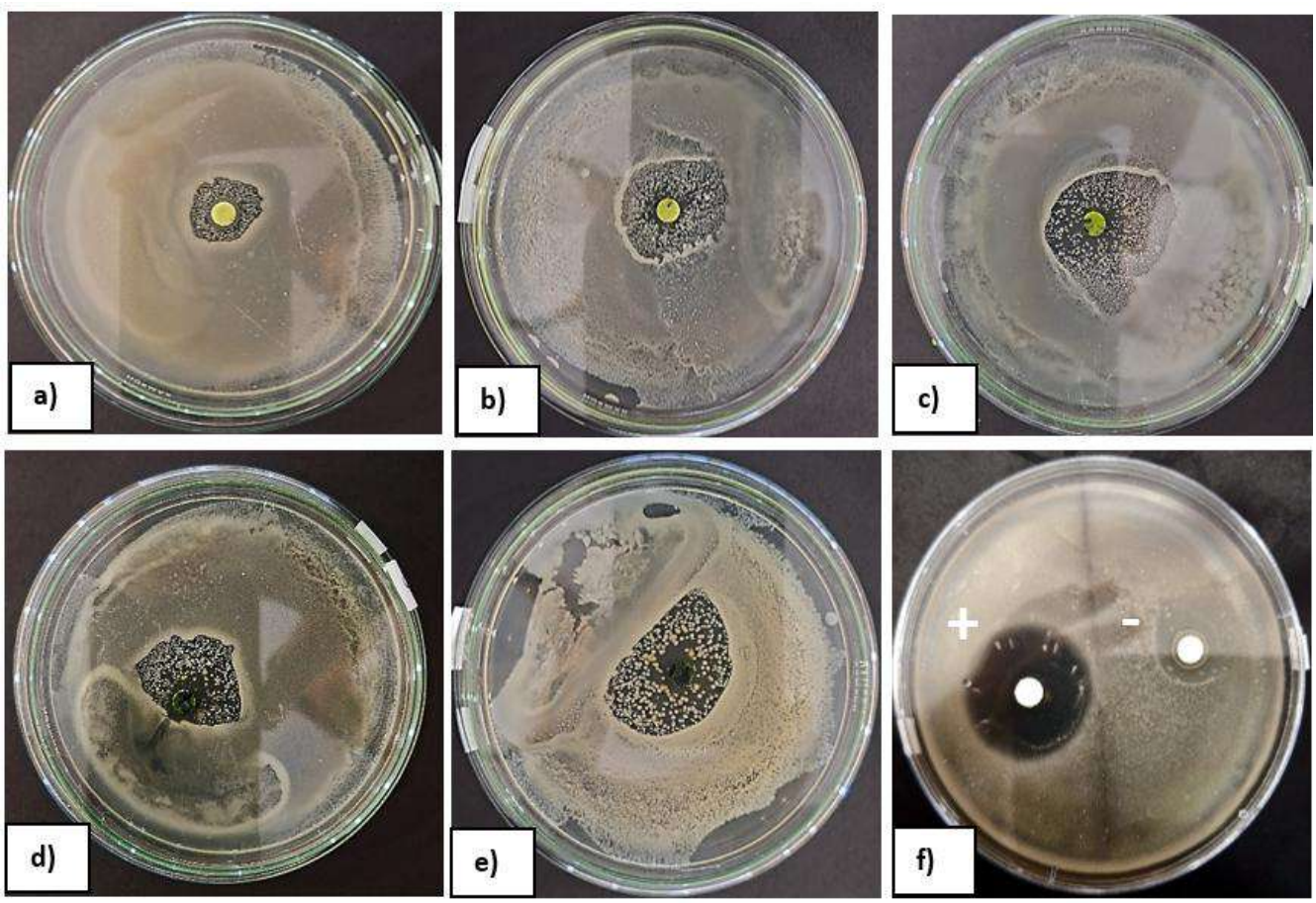

Figure 3. The clear zone around the *S. epidermidis* colony indicates the inhibition of the extract against bacterial growth: a) inhibition zone at 6.25%, b) 12.5%, c) 25%, d) 50%, d) 100%, f +) positive control, f -) negative control

Table 3. Disk diffusion test result of methanol extract of itchy leaves against *S. epidermidis*

Concentration (mg/mL)	Inhibition zones (mm)		Analisis Data			
	Diameter of inhibition zone (Mean ± SD) mm	Inhibitory activity (Davis and Stout)	Sapiro-Wilk	Levene Test	One-way Anova	
					F	p<0.05
100%	15.00 ± 2.90	Strong	.960*			
50%	23.00 ± 7.20	Very strong	.248*			
25%	18.00 ± 11.3	Strong	.552*			
12.5%	13.40 ± 3.51	Strong	.492*	0.157*	2.037	0.128**
6.25%	10.40 ± 3.10	Strong	.603*			
Control (+)	23.80 ± 0.96	Very strong	-			
Control (-)	0.00 ± 0.00	-	-			

Note: (**) = not significant with a p-value (p<0,05),
(*) = significant with a p-value (p>0,05)

while the maceration method had lower yields. In this study, we found that the methanol extract of itchy leaves was able to inhibit the growth of *S. epidermidis* at all test concentrations with varying inhibition zones. The results of the zone of inhibition measurement of itchy leaves against the growth of normal flora *S. epidermidis* are presented in Table 3.

Table 2 and Figure 3 show the ability of itchy leaf extract to inhibit *S. epidermidis* bacteria at all test concentrations. The results of the Shapiro-Wilk normality test indicated that the data were normally distributed with a significant value greater than 0.05 (p>0.05). Then, the homogeneity test was conducted using the Levene Test, which revealed that the data exhibited homogeneous variance with a significant value of 0.157 (p>0.05). Based on the results of the assumption test, the one-way ANOVA test was conducted to analyze whether there was a difference in the average of each concentration. The results of data analysis using one-way ANOVA showed insignificant results, as indicated by F = 2.037 and p = 0.128 (p-value <0.05), suggesting that there was no significant difference between the means of each concentration of *L. decumana* extract.

The results of this study showed that the higher the concentration, the greater the inhibition zone produced. However, at a 100% concentration (15.00 ± 2.90), a decrease in the diameter of the inhibition zone was observed. The decrease in the diameter of the inhibition zone can be caused by extracts that do not fully penetrate the paper disk and extracts that are difficult to diffuse in the test media, resulting in a smaller inhibition zone. This finding is supported by Bubonja-Šonje et al. (2020), who suggested that the diameter of the inhibition zone is influenced by the extract solubility , diffusion time, and evaporation. At a concentration of 100%, the extract tends to be concentrated, which affects its permeability and and slows down the diffusion process into the paper disk. This correlates with antimicrobial activity because the content of active compounds absorbed in the disk paper decreases.

Itchy leaves are known to have several secondary metabolites, including flavonoids, alkaloids, phenolics, and terpenoids (Basy et al., 2022). The role of secondary metabolites may vary in inhibiting bacterial growth, particularly *S. epidermidis*. Flavonoids are secondary metabolites found in all types of plants because they have many functions, such as promoting growth, attracting pollinating insects, and protecting against biotic and abiotic stresses. According to Dias et al. (2021), flavonoids can act as effective antioxidants to control the accumulation of reactive oxygen species (ROS), thereby playing an important role to environmental stress. Flavonoid compounds are known to inhibit the growth of *S. epidermidis* by damaging the complex structure of the cell membrane, inhibiting DNA and RNA synthesis by intercalating hydrogen bonds, which leads to an accumulation of nitrogenous bases (Alamsjah et al., 2024). In addition, the flavonoid quercetin has been known to inhibit the formation of *S. epidermidis* biofilms by reducing the production of the ICA gene, which results in reduced synthesis of Polysaccharide Intercellular Adhesin (PIA) (Mu et al., 2021).

Other secondary metabolites found in itchy leaves are alkaloids. Alkaloids are important compounds due to their abundant presence and structural diversity. Previous research found that alkaloids have potential as natural antibiotics with a broad antibacterial spectrum, low toxicity, and a

tendency not to induce resistance (Yan et al., 2021). This makes alkaloids a promising alternative for antibiotic development in reducing the spread of bacterial resistance. The mechanism of action of alkaloids involves in inhibiting the synthesis of nucleic acids, which affect cell division, inhibit the process of cell respiration and the process of enzyme synthesis, disrupt the outer membrane of gram-negative bacteria, depolarize the membrane of gram-positive bacteria, and disrupt the function of genes responsible for virulence (Othman et al., 2019). In *S. epidermidis* bacteria, alkaloids can inhibit biofilm formation by 50% (Li et al., 2016). This finding is supported by Jia et al. (2020), who discovered that total alkaloids more effectively damage the biofilm structure of *S. epidermidis* than ciprofloxacin, without causing resistance .

In addition, phenolic compounds are known to effectively inhibit the growth of *S. epidermidis*. Research by (Pinho et al., 2014) found that phenolic compounds have high antibacterial activity on gram-positive bacteria, such as *S. epidermidis* and *S. aureus*, at low concentrations. Phenolic is a secondary metabolite compound produced by plants, fungi, and bacteria. Phenolic compounds have many benefits, including anti-inflammatory, antimicrobial, and antioxidant properties (Kauffmann & Castro, 2023). This is supported by research by Sagini et al. (2024), which foundthat phenolic compounds show antibiofilm activity by inhibiting the formation of *S. epidermidis* biofilm by 90%. Several types of phenolic compounds, such as eugenol, vanillin, carvacrol, and syringic acid can inhibit the function of efflux pumps to prevent bacterial resistance (Waditzer & Bucar, 2021).

Another secondary metabolite present in itchy leaves is terpenoids. Terpenoids are the main constituent of essential oils produced by certain plant tissues. Terpenoid compounds are known to have antimicrobial, anti-inflammatory, and antioxidant activities (Siddiqui et al., 2024). Research by Guimarães et al. (2019) found that terpenoid compounds showed higher activity than sulfanilamide. Terpenoid compounds function by eliminating the integrity of cell membrane, resulting in leakage and cell death. In addition, terpenoid compounds and their derivatives have bacteriostatic and bactericidal activities against pathogenic bacteria (Mahizan et al., 2019).

CONCLUSION

Itchy leaf (*L. decumana*) exhibits a high activity in inhibiting the growth of *S. epidermidis*. The results of this study showed that itchy leaves were able to inhibit the growth of normal flora at all concentrations of 6.25, 12.5, 25, 50, and 100%. The best results were shown at a concentration of 50%, with an inhibition zone of 23.00 ± 7.20, categorized as very strong. Therefore, itchy leaves have the potential to be developed as an antibacterial agent. However, the antibacterial activity of itchy leaves can reduce the presence of normal skin flora. This may occur if people use itchy leaves continuously to produce analgesic effects without considering the antibacterial effect on normal skin flora. Nonetheless, further investigation needs to be done to confirm the MIC and MBC limits of the itchy leaf extract.

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