ORIGINAL ARTICLE

Smart Medical Journal

Smart Medical Journal (SMedJour) April 2024, Vol. 7, No.2, pp :118 - 128
DOI: https://doi.org/10.13057/smj.v7i2.92213
E-ISSN: 2621-0916 | P-ISSN: 2621-1408

The Effect of Citronella oil Concentration on Physicochemical Properties of Laponite Hydrogel and Antimicrobial Activity Test to *Streptococcus aureus* ATCC 25923 and *Candida albicans* ATCC 14053

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Recived: 19/08/2024
Accepted: 18/10/2024
Published: 29/10/2024

ABSTRACT

Introduction: The Citronella plant produces 78 -85% citral oil. This oil has antimicrobial activity. The oil was developed as an antimicrobial topical and incorporated into laponite hydrogel for optimal use. Laponite hydrogel has a cooling sensation and is compatible with polar and non-polar active substances. This study aims to evaluate the effect of citronella oil concentration on physicochemical properties and examine its antimicrobial activity. **Methods:** The Citronella plant was distilled using the steam distillation method and analyzed using the GC-MS. The laponite hydrogel was prepared with three concentrations: 6%, 8%, and 10%. Physicochemical properties included pH value, viscosity, stickiness, spreadability, and organoleptics, and the chosen formula was tested for antimicrobial activity. The research data were compared with relevant literature, and *ANOVA* statistics were analyzed with a confidence level of 95%. **Results:** Based on the research results, increasing the concentration of citronella oil caused the laponite hydrogel to become increasingly cloudy, viscosity, and sickness but decreased the pH and spreadability. Citronella oil concentration of 8% is the chosen formula that fulfills the best hydrogel preparation with evaluation results of pH value of 7.24 ± 0.064, spreadability of 5.68 ± 0.320 cm, thickness of 1.25 ± 0.012 seconds, and viscosity of 23596.3 ± 227.55 mPa. s. The citronella oil hydrogel has antibacterial and antifungal properties and moderate strong inhibitory.
Conclution: As a delivery system for citronella oil, Laponite can be developed as a pharmaceutical preparation to treat mouth ulcers as an alternative synthetic product with good antimicrobial potential.

Keywords: citronella oil; antimicrobial; laponite hydrogel; topical preparation; physicochemical properties

INTRODUCTION

Oral mucosal health is part of health that can represent overall body health. Based on National Basic Health Research, the prevalence of oral health ~~problems~~ issues in Indonesia was 25.9%. This was due to the need for more public awareness and knowledge regarding the importance of dental and oral health, which can cause disease around the oral cavity[1]. In the oral cavity, there are various bacteria, including *Streptococcus, Lactobacillus, Staphylococcus*, and *Corynebacterium*, as well as types of anaerobic bacteria, such as *Bacteroides*. These bacteria can be commensal, but if the condition of the oral cavity is poor, the number of pathogenic bacteria will cause infectious diseases in the oral cavity[2].

The oral cavity contains normal flora bacteria that are not pathogenic in healthy conditions, including *Candida albicans*. *Candida albicans* is an opportunistic fungus that can cause candidiasis. The incidence of oral candidiasis due to this microbe is reported to be 20% - 75%. Fungi in the oral cavity are often found on the tongue, labial mucosa, buccal mucosa, posterior dorsum of the tongue, circumvallate papillae, and the palate area. *Candida albicans* is found around 30 – 40% in the oral cavity of healthy adults, 45% in neonates, 45 – 65% in healthy children, 65 – 88% in people taking long-term medication, 90% in acute leukemia patients who are undergoing chemotherapy and is most often found in patients who wear removable teeth, around 50 – 65%. *Candida albicans* accounts for 75% of fungal infections in humans. About 40% of healthy adults carry this species in the oral cavity[3]. Oral *Candida species* can lead to oral candidiasis and denture stomatitis[3]. Oral candidiasis, commonly known as oral thrush, appears as creamy white or yellowish, crusty, curd-like patches with cracks in the corners of the mouth, lips, tongue, palate, and buccal cheeks.

The oral cavity, inhabited by various microbes, can cause various diseases, including caries, gingivitis, and other oral dental diseases[4]. The prevalence of canker sores in the oral cavity was estimated to reach more than 25% of the population worldwide. Canker sores are inflammation that occurs on the mucosa of the oral cavity, such as the cheeks, gums, tongue, lips, and floor of the mouth[5]. The oral mucosal tissue that becomes inflamed and causes canker sores was characterized by lesions that are concave in shape, have clear boundaries, were white, and subjectively cause pain. Thrush can occur due to microorganisms that cause infection or disease[6]. Medicines for canker sores on the market contain chemicals such as antibiotics and policresulen, which, if consumed incorrectly, will cause side effects that were detrimental to health. Side effects caused by antibiotics include rash, fever, urticaria, and chills[7]. The side effect of policresulen is causing cell damage and dead [8]. Antifungal drugs have been produced ~~and sold~~ to treat fungal infections that attack the oral cavity. However, overusing for a long period will also cause problems of microbial resistance to the drug. Therefore, treatment has been developed using natural ingredients, which are expected to minimize side effects but have equivalent effectiveness to chemical drugs.

Herbs have been used for centuries to prevent and control dental disease. Herbal extracts are effective because they interact with specific chemical receptors within the body. Herbal medicines have less side-effects in comparison with traditional medicines, but side-effects do occur. Citronella oil is a kind of plant essential oil extracted from *Cymbopogon nardus* (L.) Rendle, mainly composed of monoterpenes about 80%, including citronellal, citronellol and geraniol[9]. Citronella oil is traditionally used as a flavoring and antimicrobial agent in the food industry because of its strong flavoring and aromatic properties, as well as its antifungal, antibacterial and antioxidant biological activities. The oil was found effective against all the six tested bacteria strains namely *Bacillus subtilis, Staphylococcus epidermidis, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia* and *Escherichia coli*, which revealed that citronella oil could be applied for the treatment of infections caused by various gram positive or negative pathogenic organism. Using essential oils as active ingredients in topical preparations requires an appropriate drug delivery system. Hydrogel was chosen because it provides an astringent effect and is also easily absorbed, light, and cool compared to cream or paste.

Synthetic magnesium lithium silicate (laponite) is a synthetic hydrophilic layered silicate insoluble in water but hydrates and expands when water is added. Laponite has advantages in terms of productivity, purity, and efficiency. This makes laponite suitable for application as a filler and thickener for aqueous preparations in the industrial sector[10]. Laponite is a type of synthetic smectite clay in the form of a fine, dense white powder with a bulk density of around 1g/cm^3. The size of the laponite is in nanoparticles range, so the laponite suspension has a considerable gel strength[11]. Laponite can disperse active ingredients that have both lipophilic and hydrophilic properties without additional emulsifiers. Laponite delivers the active ingredient with a sustained release mechanism so that the bioavailability of the active ingredient reaches more than 72 hours. Research conducted by Ghadiri et al.[12] stated that the

tetracycline antibiotic incorporated into the laponite system showed resistance to changes in pH so that the active antibiotic ingredient was more stable. This research basis underlies the development of innovation in designing citronella oil formulations incorporated into laponite as a gel preparation to help overcome oral health problems. Gel formulations of essential oils in the laponite system have never existed before, making this research a novelty.

The concentration of laponite used was 2.5% because the orientation of the laponite base had been carried out, and optimal gel results were obtained, namely at a concentration of 2.5%.[13] In this research, we will observe the effect of variations in the concentration of citronella oil incorporated into the laponite based on the gel preparation's physicochemical properties and antimicrobial activity. The concentration variations used were 6, 8, and 10%. Hopefully, this will reveal the optimal concentration that produces an excellent oral gel preparation and reduces the bitter taste, heat, and irritating effects of citronella oil when applied to the oral mucosa area. Laponite provides an incredible feeling and can release active ingredients periodically for a long time, thereby reducing the frequency of drug use and making patients more compliant in using drugs.

METHOD

Material: Laponite (BYK-Chemie GmbH Abelstraße 4546483 Wesel, German), aqua dest (Repacking by Ramayana, Indonesia), citronella essential oil (UMKM “Surya Wulan” in Kulon Progo), propylene glycol (Repacking by CV Cipta Kimia, Indonesia), citric acid (Repacking by CV Cipta Kimia, Indonesia), Phenoxyethanol (Repacking by CV Cipta Kimia, Indonesia), Staphylococcus aureus ATCC 25923 (Thermo Science, United Kingdom), Candida albicans ATCC 14053 (Thermo Science, United Kingdom), Muller Hinton Agar medium (Merck) and Potato medium Dextrose Agar (Merck).

Instrumet: Analytical balance (Radwag AS220-R2, Poland), Petri dish (pyrex, Germany), adhesion tester, pH meter (Lutron-TMPH-207), magnetic stirrer and spin bar (Thermo Cimarec+BioSafety Cabinet (BIOBASEBSC1100IIA2), Brookfield viscometer type RV and spindle 1 (NDJ-SS, China), micropipette (Dragon Lab, China).

Sample preparation

Samples of citronella oil resulting from steam distillation using dried leaves as a fuel. This oil was producted by UMKM Suryowulan Kulonprogo Yogyakarta. The oil samples were analyzed for eugenol content using the Gas Chromatography-Mass Spectrometry (GC-MS) method. This method was chosen because lemongrass oil is an essential oil that evaporates quickly. GC-MS chromatography has advantages that include high sensitivity and good separation results.

Citronella oil Hydrogel

Table 1. Citronella oil hydrogel using various concentation of citronella oil

Ingredients	Concentration (%)			Function
	Formula 1	Formula 2	Formula 3	
Citronella oil	6.0	8.0	10.0	Active ingredients
Laponite powder	2.5	2.5	2.5	Hydrogel matrix
Propylene glycole	0.5	0.5	0.5	Co-solvent
Citric acid	qs	qs	qs	pH adjusting
phenoxyethanol	0.5	0.5	0.5	Preservatives
Water	Add 100.0	Add 100.0	Add 100.0	Solvent

Gel formulation with the active ingredient citronella essential oil was carried out by weighing all the ingredients used according to the formulation listed in Table 1. Laponite was dispersed in distilled water using a magnetic stirrer at a speed of 450 rpm until homogeneous, and a gel was formed. Then, the other ingredients, phenoxyethanol, propylene glycol, and citric acid, are mixed into the gel and then

homogenized. Finally, the citronella essential oil, according to the percentage, is added and stirred until homogeneous.

Physicochemical properties of Citronella oil hydrogel

Direct observation of the gel's consistency, color, and odor made with human senses. The gel is usually evident in color with a semi-solid consistency[14,15]. The electrode on the Lutron-PH-207 pH meter is calibrated using distilled water; then, the calibration button is pressed and adjusted. Next, the electrode is dipped into pH four buffer, washed with distilled water, and dipped into pH seven buffer, washed with distilled water, pressed on the calibration button, and adjusted. The electrode is then dipped into the preparation and waited until the reading is stable. According to SNI 16-4399-1996, the range of quality requirements for leather preparations is 4.5-8.0.

The spreadability test was carried out by placing 0.5 grams of gel on a round glass, placing another glass on top, and leaving it for 1 minute. After that, 150 grams of load was added, left for 1 minute, and the constant diameter was measured. The criteria for good spreadability of gel preparations according to SNI-06-2588 standards is 5-7 cm.

A total of 0.5 g of the gel preparation was placed on an object glass attached to a glass cabinet and attached to a rope, then covered with another object glass, given a load of 1 kg for 5 minutes, and released. A weight weighing 80 g is attached to the rope while the stopwatch is turned on, and the time required for the two object glasses to be released is recorded. The criteria for good adhesion of a gel preparation are less than 10 seconds.

The viscosity test was measured using a Brookfield-type NDJ-8S viscometer. The test sample is placed in a beaker glass; then, the device is turned on. The spindle is installed on the tool and placed right in the middle of the preparation. The viscosity value parameter for gel preparations based on SNI 16-4399-1996 is 2,000 – 50,000 mPa.s[14,15].

Antimicrobial Activity Test

Muller Hinton Agar media is made by weighing 38 g of MHA powder dissolved in 1.0 L of distilled water, if necessary, with the help of heating. Next, the media was sterilized by autoclaving at 121°C for 20 minutes. The pure strain of *S. aureus* ATCC was suspended in BHI (Brain Heart Infusion) media; then, the media was incubated at 37°C for 24 hours. Next, *S. aureus* bacteria were planted on blood agar media, then incubated at 37°C for 24 hours. The ready NA (Nutrient agar) media solution was put into several test tubes of 5 mL each and then sterilized using an autoclave for 15 minutes at 1 atm pressure, temperature 121°C. One dose of each bacterial culture was taken and streaked into a test tube containing slanted NA media. The bacteria in the slanted NA medium were then incubated for 12-18 hours in an incubator at 37°C. The colonies that form show bacterial growth and are ready for further testing. One ose of bacterial colonies from slanted NA media was diluted using a sterile 0.9% NaCl solution until it had turbidity by Mc standards. Farland (107 – 108 CFU/mL). A sterile cotton swab is inserted into a bacterial suspension tube and then streaked evenly onto the MHA media. A total of 20 µL of sample solution was injected onto a blank disk paper using a micropipette. After the solution has been completely absorbed, the sample paper disk is placed on MHA media containing the test bacteria and then incubated at 37°C for 24 hours. The clear zone formed around the disk indicates that the sample can inhibit bacterial growth, and its diameter can be determined[16].

Potato Dextrose Agar (PDA) media is made by boiling 250 grams of potatoes, 20 grams of agar, and 20 grams of sugar. Put the weighed agar and sucrose into a glass beaker containing potato solution and add distilled water until the solution is 1000 mL. The solution was stirred homogeneously until it boiled, then poured into an Erlenmeyer and sterilized using the autoclave method 121°C for 15 minutes. The *Candida albicans* fungus was dispersed in a test tube containing 3 mL of 0.9% NaCl solution, then mixed until homogeneous, indicated by the liquid turning turbid according to the McFarland turbidity

standard. The *Candida albicans* fungus culture was inoculated using a sterile cotton swab by smearing it on the surface of solid PDA media in a petri dish; 5 wells were made using a boorprof with a diameter of 6 mm on solid PDA media (3 gel preparations of the selected formula, 1 for negative control using gel base, and 1 for positive control using citronella oil). The selected formula gel preparation, positive control, and negative control were dropped as much as 50 µL using a micropipette. Next, the test material was incubated at 25°C for five days, and the changes that occurred were observed, and the diameter of the clear zone around the well was measured[17,18].

Data analysis

The data obtained from the test results is then compared with parameters from several sources or libraries. The data obtained was then analyzed statistically using IBM SPSS statistics 25 software, which uses the One-Way Anova method if the sig. <0.05.

RESULT

Analysis of eugenol concentration was carried out at the LPPT Test-Laboratory, Universitas Gadjah Mada, Yogyakarta, which resulted in a eugenol concentration in UMKM Suryowulan steam distilled citronella oil of 8.65%. Based on previous research conducted by Setyaningsih et al.[19], the concentration of citronella essential oil is between 2.4% - 18.2%. This proves that citronella essential oil production by UMKM Suryowulan has a eugenol concentration that meets the requirements.

The gel base can influence the physicochemical properties of the gel. Gelling agents in gel formulas increase the strength of the gel structure and viscosity, but excessive use can make application difficult on the skin[20]. This research used a laponite hydrogel matrix as a gelling agent. Laponite can disperse active ingredients that have both lipophilic and hydrophilic properties without additional emulsifiers. Based on research by Stealey et al.[21], laponite has accessible properties and is suitable for application as a drug delivery agent where drug molecules interact electrostatically with laponite particles. The concentration of laponite used in this research was 2.5% because the previous orientation of the laponite base had been carried out with concentrations of 2%, 2.5%, and 3%. So, we get a 2.5% concentration with the best consistency of gel.

In this study, the gel was made with variations in the concentration of the active ingredient of citronella essential oil, where in formula 1, it was 6%, formula 2 was 8%, and formula 3 was 10%. Other ingredients are used to make gel, including phenoxyethanol, propylene glycol, citric acid, and distilled water. *Phenoxyethanol* is an alcohol derivative that is an antimicrobial preservative[22]. Preservatives protect preparations from microbial contamination during use or storage. Phenoxyethanol has low sensitivity to the skin, does not affect the pH stability of gel preparations, and is a safe preservative[23]. *Propylene glycol* is a clear liquid that is colorless and odorless. Apart from being a humectant, propylene glycol can also be used as a solvent, extractant, preservative, and disinfectant. Propylene glycol is stable at low temperatures and in closed containers because it is protected from oxidizing agents[24]. According to research by Patil et al.[25], propylene glycol is used 0.5% - 4% to get a good gel. In this research, citric acid was used as an acidity regulator. Citric acid is used as an acidity regulator, color enhancer, and preservative. Aqaudest, namely laponite, was used as a solvent and dispersing base in this research.

[a] [b] [c]

Figure 1. Visual results of citronella oil gel with variations in citronella oil concentration of 6% (a), 8% (b), and 10% (c) respectively

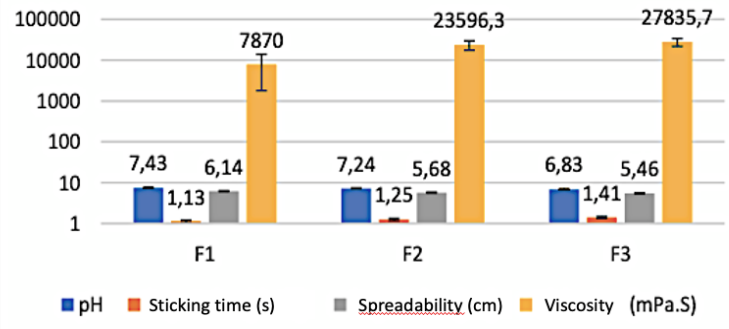
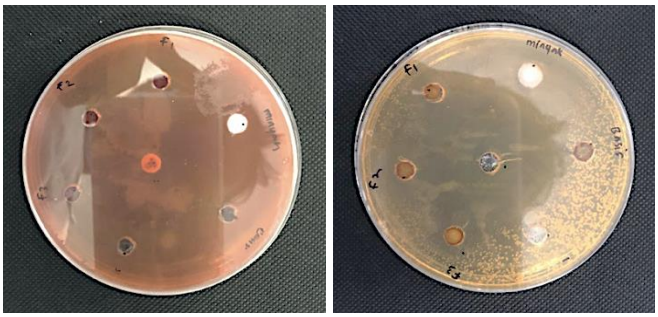


Figure 2. Graph of analysis results of the physicochemical properties of citronella gel with varying concentrations of citronella oil where formula 1 is 6%, formula 2 is 8%, and formula 3 is 10%



[a] [b]

Figure 3. The results of the antimicrobial activity using difusion methods of the citronella oil gel preparation are as follows: image [a] is the antibacterial activity of *S. aureus*, and image [b] is the antifungal activity of *C. albicans*

DISCUSSION

Physicochemical properties of citronella oil hydrogel

In research, laponite hydrogel has a pH value of more than 8; this is based on research conducted by Jatav and Joshi[26], which states that laponite has a pH of around 9. Citric acid was added to adjust pH; citric acid has a pH of 3, while citronella oil has a pH of 3. The skin's pH is 4.5 – 8.0 according to SNI 16-4399-1996. This is based on research by Setyaningsih et al.[19], with the pH value of citronella oil being 4.80. From the pH test results, all formulas evaluated met good pH quality standards according to the pH test requirements set by SNI 16-4399-1996. The statistical analysis results using the One-Way ANOVA test produced a significance value of 0.000. A significance value of less than 0.05 indicates a difference in averages between groups. The conclusion is that variations in the concentration of citronella oil significantly influence the pH of citronella essential oil gel preparations.

Spreadability affects the efficacy of topical therapy in pharmaceutical preparations and the extent of preparation spread when applied. Testing the spreadability of citronella essential oil gel preparations with variations in the concentration of the active ingredient of citronella oil resulted in variations in spreadability values. The difference in dispersion power greatly influences the diffusion speed of the active substance through the membrane. The wider the membrane through which the preparation spreads, the greater the diffusion coefficient, which increases the diffusion of the drug. Hence, the greater the dispersion power of preparation, the more optimal it is during its application[27]. This is based on research conducted by Daud and Suryanti[28], which stated that the higher the

concentration of essential oils, the lower the spreadability value. Ermawati et al.[18] [15] stated that the viscosity of a dosage form influences the spreadability of the dosage form, where viscosity is inversely proportional to spreadability. The higher the viscosity, the lower the spreadability value.

According to Isna et al.[29], the relationship between viscosity and spreadability is caused by the cohesive force between particles in a liquid. The higher the viscosity of a preparation, the higher the cohesive force. The higher the cohesion force that occurs, the higher the time required for the preparation to spread. The spreadability test on F1, F2, and F3 is included in the excellent spreadability category because it meets the requirements for a good gel preparation spreadability test according to the SNI-06-2588 standard, which is 5 – 7 cm[30]. The One-Way ANOVA test, which produces a significance value of 0.000 ($p<0.05$), shows a difference in averages between groups. Variations in the concentration of citronella essential oil significantly affect the spreadability of citronella oil gel preparations.

The results of the adhesion test of citronella essential oil gel preparations showed (Figure 2) that increasing the concentration of citronella oil resulted in more prolonged adhesion. The viscosity of a preparation can influences Stickiness. Ermawati et al.[18] stated that apart from affecting spreadability, viscosity also affects the adhesion power of the preparation, where viscosity is directly proportional to adhesion power. The higher the viscosity, the higher the adhesive force value. The adhesion test for all formulas is included in the excellent adhesion category because it meets the requirements, namely, namely, less than 10 seconds[30]. The One-Way Anova test, which produces a significance value of 0.000 ($p<0.05$), shows that there is a difference in averages between groups. Variations in the concentration of citronella oil significantly affect the adhesive power of citronella essential oil gel preparations.

The higher the viscosity value, the more excellent the resistance[31]. Therefore, the proper viscosity of the gel is critical so that application can be carried out comfortably and effectively[27]. Viscosity relates to the ability of a liquid to flow. Viscosity is inversely proportional to spreadability; the higher the viscosity, the lower the spreadability value. Viscosity also determines the length of stickiness of the preparation on the skin so that the preparation can stick well. The higher the concentration of lemongrass oil added, the viscosity of the gel preparation also increases. This is based on research conducted by Daud and Suryanti[28], which states that differences in essential oil concentrations affect viscosity values. The higher the concentration of essential oil added, the higher the viscosity value. High viscosity will stabilize the emulsion system in gel preparations because it will minimize the movement of droplets in the disperse phase so that changes in droplet size to larger sizes can be avoided. The possibility of coalescence can be prevented[28]. Based on the SNI 16-4380-1996 standard, the desired viscosity range for gel preparations is 2000 – 50000 mPa.s. From the results obtained, the gel formula with varying concentrations of citronella essential oil meets the requirements.

Antimicrobial activity

ATCC (American Type Culture Collection) *Staphylococcus aureus* as test bacteria. ATCC is a standard bacterium that is recommended for use as a test for research. Apart from that, ATCC bacteria are also not easily contaminated. MHA media is used because it has good nutritional content for culturing most bacteria. MHA is also neutral, so it does not affect antibacterial test procedures[16]. *Staphylococcus aureus* bacteria are suspended by taking one dose of bacteria and then placing it in a test tube containing 3 mL of physiological NaCl, stirring until homogeneous. The turbidity of the suspension is standardized to the McFarland standard[32]. Test the antibacterial activity of the gel preparation where citronella essential oil was the positive control, gel base was the negative control, and citronella essential oil gel was the test sample with three replications. The diameter of the inhibition zone is categorized by the level of response based on the classification of weak (<5 mm), moderate (5 – 10 mm), strong (11 – 19 mm), and very strong (≥20 mm) [30]. The results showed that the gel preparation with a concentration of citronella oil of 8% had moderate inhibitory power (5 – 10 mm).

Candida albicans ATCC 14053 as the test fungus. The diameter of the citronella oil gel's inhibition area was measured by measuring the well's diameter and the total diameter around the hole using a caliper. The diameter data obtained is then converted in the area using the formula for the area of a circle, namely $L = \pi r^2$, with $\pi = 3.14$ and r (radius) = 1⁄2 diameter, so that the total area and area of the well will be obtained. The obstruction area is obtained from the total area minus the area of the well [14]. The type of antibacterial activity of citronella essential oil is bacteriostatic, which is determined by bacteriostatic and bacteriocidal tests, where citronella essential oil can inhibit the growth of bacteria but does not kill them[32]. The results obtained by gel preparations with a concentration of citronella oil of 8% had moderate inhibitory power (5 - 10 mm). The mechanism action of essential oil to inhibit both bacteria a fungal are they be completely lysed in the presence of essential oil could elucidate the antmicrosidal mechanism of due to cell damage. Essential oil demonstrates a capability to disintegrate the cell wall and further decrease its permeability, which subsequently causes cell death. Eugenol was found to disturb the cell wall integrity by increasing cell fluidity and permeability. It has also been reported that ergosterol, which forms part of the fungal cell, is the target site for antifungal agents to bind within the cell. The binding causes depolarization of the bactria and fungal cell and creates polar pores. This allows proteins and cations (monovalent and divalent protons) to leave the cell easily, and eventually causes a decrease in cell permeability which could lead directly to cell death. Eugenol is also capable of denaturing proteins and reacting towards the phospholipid bilayer of cell walls, thus altering their permeability[9].

CONCLUSION

Variations in the concentration of citronella essential oil affect the physicochemical properties of the hydrogel preparation. Increasing the concentration of citronella oil causes the hydrogel to become cloudy, increases viscosity and sticking times, but reduces spreadability and pH value. The concentration of citronella essential oil at 8% produced a hydrogel preparation with the best physicochemical properties. This formula produces a pH value of 7.24 ± 0.064, a spreadability of 5.68 ± 0.320 cm, a sticking time of 1.25 ± 0.012 seconds, and a viscosity of 23596.3 ± 227.55 mPa.s. Hydrogel shows antibacterial and antifungal activity with moderately strong inhibitory. As a delivery system for citronella oil, Laponite can be developed as a pharmaceutical preparation to treat mouth ulcers as an alternative synthetic product with good antimicrobial potential.

ACKNOWLEDGEMENT

This research was funded by RKAT PTNBH Universitas Sebelas Maret Fiscal Year 2023 through the FUNDAMENTAL GRANT RESEARCH Research scheme (PF-UNS).

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