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Antioxidant and Anti-*Propionibacterium acnes* Activities of Citronella Oil and Clove Oil, and their Formulation Into Emulgel

Nur Aji*, Arum Puspitasari, Haevia Nafisah, Levina Hadi Vania Armilda

Pharmacy Department, Politeknik Kesehatan Kementerian Kesehatan Tasikmalaya
Cilolohan No. 35 Tasikmalaya, 46115, Indonesia
*Corresponding author email: nuraji090689@gmail.com

ABSTRACT

Propionibacterium acnes is a common acne-causing bacteria in adolescents and adults. The combination of citronella oil and clove oil has the potential to inhibit the growth of *Propionibacterium acnes*. Both essential oils are also known to have antioxidant effects. The combination of the two essential oils is expected to have better activity. The purpose of this research was to determine the activity of the Fractional Inhibitory Concentration (FIC) index against *Propionibacterium acnes*, antioxidant activity, and formulation in emulgel. Antibacterial assay of combination citronella oil and clove oil using the FIC index. Antioxidant assay by DPPH (2,2-diphenyl-1-picrihydrazil) method. The emulgels formulation uses Viscolam AT 100P as the base of the emulgels. The results showed that the combination of citronella and clove oil an antibacterial activity with an FIC index is 2 (indifferent), antioxidant citronella oil had an IC_{50} of a moderate category (185.04 µg/mL) and clove oil in a very strong category (23.48 µg/mL) so that it could be formulated in an emulgel with good characteristics. The most preferred formula in terms of color, scent, consistency, and texture is a formula with a concentration of 5% viscolam AT 100P.

Keywords: Antioxidant, citronella oil, clove oil, emulgel, *Propionibacterium acnes*

Background

Acne is a skin disease that generally occurs during adolescence to adult. Acne is characterized by a symptom such as blackheads, pustules, papules, cysts, and nodes on the neck, face, upper arms, back, and chest. Acne can affect a person's quality of life by giving a bad psychological effect for sufferers in the form of the way a person assesses, responds to, and views his condition and situation (Sugiarti *et al.*, 2020). The prevalence of acne in Indonesia ranges from 80-85% in adolescents at 15-18 years old, 12% in women is more than 25 years old and 3% at 35-44 years old (Sekar and Halim, 2017). The pathophysiology of acne occurs by the colonization of *Propionibacterium acnes*, follicular hyperkeratinization, inflammation, and increased sebum production (Zouboulis, 2004).

P. acnes is a common bacteria cause of acne. These bacteria are prime targets in antibacterial treatments for acne. *P. acnes* acts by producing several inflammatory substances (such as chemotactic factors, and lipase enzymes) that induce the development of acne lesions (Dréno *et al.*, 2018). *P. acnes* is an anaerobic bacterium that is often found in acne and grows slowly and is Gram-positive (Radji, 2010). These bacteria produce lipase enzymes that function to break down triglycerides which is one of the components of sebum into free fatty acids. This free fatty acid is a good medium for the growth of *P. acnes*. Furthermore, bacteria multiply, cause inflammation, and form micro comedones which are factors in the formation of acne (Burkhart, Burkhart and Lehmann, 1999).

The use of antibiotics is one of the effective therapies in the treatment of acne such as clindamycin, erythromycin, and tetracycline (Tan, 2004). But the use of inappropriate antibiotic therapy can lead to resistance. This can cause synthetic antibiotic materials to become ineffective and sometimes even cause side effects in their use (Sholih, Muhtadi and Saidah, 2015). Therefore, alternative therapies are needed that are effective, efficient, and safe. One of them is by using plants that contain essential oils that can potentially as antibacterial to *P. acnes* (Dewi and Hanifa, 2021). Essential oils act as antibacterial by interfering with the process of forming membranes or cell walls so that they are not formed or formed imperfectly. Essential oils that are active as antibacterial generally contain hydroxyl (-OH) and carbonyl functional groups (Ergüden, 2021). The various medicinal plants available, citronella (*Cymbopogon nardus* L.) and cloves (*Syzygium aromaticum* L.) are plants that contain essential oils and have antibacterial activity (Lamlertthon, Luangnarumitchai and Tiyaboonchai, 2007; Fu *et al.*, 2009).

Besides having antibacterial activity, Citronella oil and clove oil have antioxidant activity. The content of citronella and clove oils that cause antioxidant activity are citronellal and eugenol (Sinha, Biswas and Mukherjee, 2011; Gülçin, Elmastaş and Aboul-Enein, 2012). The effect of antioxidants on the skin is known to increase cell regeneration so that in the case of acne vulgaris, it is expected to increase the speed of cell regeneration in acne wounds (Ahmed, 2018).

However, the combination of emulgel from citronella essential oil and clove oil as an antibacterial against *P. acnes* has never been reported, so the novelty of this study is the formulation and evaluation of the emulgel combination of citronella and clove oil which has the potential as an antibacterial to *P. acnes*. Emulgel was chosen because this dosage forms are suitable for topical use.

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Instrument

The instrument used in the research: micropipette (Accumax) and biological safety cabinet (Type-11001162-x, biobase), incubator (Memmert), vortex mixer (H-VM-300), UV-Vis spectrophotometer (Agilent Carry 60), pH meter (ATC), and viscometer NDJ-8s (MRC).

Materials

The materials used in this research: essential oils from clove oil (Happy Green) and citronella oil (Happy Green). The bacteria used in this research is *P. acnes* ATCC 11827. Materials used to Anti-bacterial assay include Nutrient Agar (Oxoid), blank paper disc Ø 6 mm (Machercy-Nagel), dimethyl sulfoxide/ DMSO (Merck), and sterile 0.9% NaCl (OTSU). Gel ingredients: viscolam AT 100P (RITA), propylene glycol (VWR), propylparaben (Acme-Hardesty), methylparaben (Acme- Hardesty), alpha-tocopherol (Santa). The material used for the type emulsion test is Sudan III (Pudak Scientific). The material antioxidant assay used a solution of 2,2-Diphenyl-1-picrylhydrazyl (DPPH) (Sigma Aldrich) and methanol pro analysis (Emsure).

Antibacterial Combination of Citronella and Clove oil

The antibacterial activity used the disk diffusion method. The concentration of the test solution used is the concentration of clove oil which produces the most optimal inhibition against *P. acnes*. The samples were dripped as much as 20 µL on blank paper disc. This experiment was repeated triplicate with the ratio of the concentrations of clove oil and citronella oil in each petri dish in Table 1.

The cultures were incubated at 37°C for 24 hours in anaerobic conditions. The results of inhibition zone obtained were then calculated the mean value and deviation standard (DS). The presence of antibacterial activity from the sample was indicated by the formation of a clear zone around the paper disc on the media and calculated using the FIC Index using equation 1 (Robiyanto, 2021), with the FIC Index category as shown in Table 2.

$$\text{FIC Index} = \frac{\text{MIC A in combination}}{\text{Single MIC A}} + \frac{\text{MIC B in combination}}{\text{Single MIC B}} \quad (1)$$

Table 1. The concentration of combination citronella and clove oil

	Citronella oil (%, w/w)				
		1.68	0.84	0.42	0.00
Clove Oil (%, w/w)	2.25	2.25: 1.68	2.25: 0.84	2.25: 0.42	2.25: 0.00
	1.13	1.13: 1.68	1.13: 0.84	1.13: 0.42	1.13: 0.00
	0.56	0.56: 1.68	0.56:0.84	0.56:0.42	0.56: 0.00
	0.00	0.00: 1.68	0.00: 0.84	0.00: 0.42	0.00: 0.00

Tabel 2. FIC index category (Altaweel, Ahmed and Abood, 2021)

Category	**Score**
Synergy	<0.5
Addition	0.5-1
Indifference	1-4
Antagonism	>4

Antioxidant Assay

The citronella oil was made stock solution 8,400 µg/mL, while the clove oil sample was made stock solution 1,126 µg/mL which was then added with ethanol and 100 µg/mL DPPH according to Table 3.

The solution concentration series were incubated at 37°C for 30 minutes, protected from light. After that, the absorbance at a wavelength of 510 nm was calculated using a UV-Vis spectrophotometer (Agilant Carry 60) and the percent inhibition (Pi) using equation 2 (Tristantini *et al.*, 2016). *Ab* is the control absorbance, while *As* is the sample absorbance. After the percentage of inhibition was obtained, then IC_{50} was determined using a linear regression equation. The IC_{50} category can be seen in Table 4.

Emulgel Formulation Combination of Citronella and Clove Oil

The formulations were made in three formulas (Table 5), where the difference of each formula in the concentration of viscolam AT 100P is the emulgel base. The characteristics of the emulgel were carried out to determine whether the emulgel were made following the requirements including organoleptic, homogeneity, viscosity, spersibility, pH, and emulsion type.

$$\text{Pi} = \left[\frac{Ab - As}{Ab}\right] x\ 100\% \quad (2)$$

Table 3. DPPH and sample volume

Sample	**Volume of methanol (mL)**	**Volume of samples (mL)**	**Volume of DPPH (mL)**
Control	5	0	5
A1	4.95	0.05	5
A2	4.90	0.10	5
A3	4.50	0.50	5
A4	4.00	1.00	5
A5	3.50	1.50	5

Table 4. IC_{50} Category (Zamzani and Triadisti, 2021)

Antioxidant Intensity	Score IC_{50} (µg/mL)
Very strong	<50
Strong	50-100
Moderate	100-250
Weak	250-500

Table 5. Formulation of emulgel combination of citronella and clove oil

Materials	Formulation (%, w/w)		
	Formula 1	Formula 2	Formula 3
Viscolam AT 100P	2	3.5	5
Methyl parabene	0.18	0.18	0.18
Propyl parabene	0.02	0.02	0.02
Prophylene glikol	10	10	10
α-Tocopherol	0.5	0.5	0.5
Citronella oil	1.68	1.68	1.68
Clove oil	2.25	2.25	2.25
Water	83.37	81.87	80.37

Results and Discussion

Antibacterial Activity and FIC Index

The antibacterial effectiveness of citronella oil and fragrant clove oil on the growth of *Propanibacretium acnes* by diffusion test. The diameter of the inhibition zone was measured using a caliper. Concentrations are made in several different sizes, 1.68%; 0.84%; 0.42% and 0% (w/w).

Based on the combination and single antibacterial activity test using the FIC index, it was found that the combination of clove and citronella oil with a ratio of 2.25%: 1.68% had the greatest inhibition zone value of 4.9 ± 1.75 mm. While the smallest inhibition zone value is in the 0:0 ratio, which means that 99% DMSO does not produce an inhibition zone.

The measurement of the FIC Index value aims to see the effects that occur in combinations. Calculation of the FIC Index value by determining the combined MIC and single MIC values. The results of the FIC index calculation based on observations can be seen in Table 6. The results show the single MIC of clove oil and the combined MIC of citronella oil is 1.13%. Meanwhile, the single MIC of citronella oil and the combined MIC of clove oil was 0.42%. So the FIC Index value in the combination of citronella and clove oil is 2, which is indifferent category. It is said to be indifferent because according to the characteristics of the combination based on the FIC index value 1 to 4. Indifferent means that the effect produced after the combination is almost the same as a single effect (Konaté *et al.*, 2012; Apridamayanti *et al.*, 2021).

Citronella oil has an active substance as an antibacterial agent described by (Moustafa *et al.*, 2021) that the main components of citronella oil are citronella and geraniol. Based on research by (Moustafa *et al.*, 2021), the active substance in clove oil is Eugenol, which is one of the phenolic compounds as antibacterial. Citronellol and geraniol are monoterpene alcohol compounds while eugenol is a phenolic compound.

The mechanism of action of monoterpene alcohol compounds begins when they enter the cell by diffusion, causing disruption of cell membranes, causing disruption of phospholipids, and ion leakage. This effect disrupts the osmotic balance of cells through the loss of ions, making membrane-associated proteins inefficient due to increased membrane disruption which eventually leads to inhibition of cell growth or cell death. The mechanism of phenolic compounds is to damage the cell wall structure, interfere with active transport and proton strength in the bacterial cytoplasmic membrane. Furthermore, stated that these compounds will denature and inactivate proteins such as enzymes. Therefore, the bacterial cell wall will be damaged due to a decrease in permeability. It can allow disruption of the important transport organic ions that will enter the bacterial cell. This phenomenon can also disturb metabolism and lead to cell death. The hydrophobic eugenol makes it easier to penetrate lipopolysaccharide's bacteria cell walls (Chen and Viljoen, 2010).

Antioxidant Activity

Antioxidant activity can be tested using the measurement method by 2,2-diphenyl-1-picrylhydrazyl (DPPH). The IC_{50} value interprets the results to determine the concentration of the compound that can reduce radicals as much as 50%. The higher activity antioxidant is seen from the lowest value of IC_{50}. Based on observations (Table 7), citronella oil has an IC_{50} of 184.04 ± 1.55 µg/mL, and clove oil has an IC_{50} of 23.48 ± 0.25 µg/mL. Its means that the IC_{50} value category of citronella oil is included in the medium category, while clove oil IC_{50} is included in the very strong category.

The main compound of clove oil as an antioxidant is eugenol which includes phenolic compounds. The mechanism of phenolic compounds as antioxidants is described by Moustafa *et al.*, (2021), through the ability of the phenol group to bind free radicals by donating a hydrogen atom to produce phenoxyl radicals through the Hydrogen Atomic Transfer (HAT) reaction with DPPH (Figure 1). The phenoxyl radicals formed as a result of the reaction of phenol with free radicals will then be stabilized through the resonance effect. For this reason, phenol derivatives are good hydrogen donors that can inhibit reactions that occur by radical compounds. Phenol compounds are also known as radical inhibitors (Lu *et al.*, 2011).

Citronella oil has antioxidant activity derived from geraniol and citronellol. The two compounds are alcohol monoterpene derivatives that have antioxidant activity due to the presence of an OH group that can donate a hydrogen atom through the reaction of HAT with DPPH. In addition to the OH group in the aliphatic chain, there is a double bond

and this also causes geraniol and citronellol to have antioxidant activity. However, when compared with phenolic compounds, monoterpene alcohol compounds have less reactivity to DPPH (Greever, 1995). This causes the antioxidant activity of clove oil to be higher than citronella oil.

Table 6. MIC value of citronella and clove oil

Sample	MIC combination (%, w/w)	MIC single (%, w/w)	FIC index
Clove oil	1.13	1.13	1
Citronella oil	0.42	0.42	1
Amount			2

Table 7. Antioxidant activity

Sample	Correlation Coefficient	Regression Equation	IC_{50} (µg/mL)	Mean (µg/mL)	DS
Clove oil	0.9951	y = 2.0667x + 1.8121	23.32	23.48	0.25
	0.9949	y = 2.0671x + 1.8643	23.29		
	0.9949	y = 2.0613x + 1.9477	23.83		
Citronella oil	0.9888	y = 0.2493x + 3.3513	187.12	185.04	1.55
	0.9903	y = 0.2509x + 3.6846	184.60		
	0.9914	y = 0.2533x + 3.543	183.41		

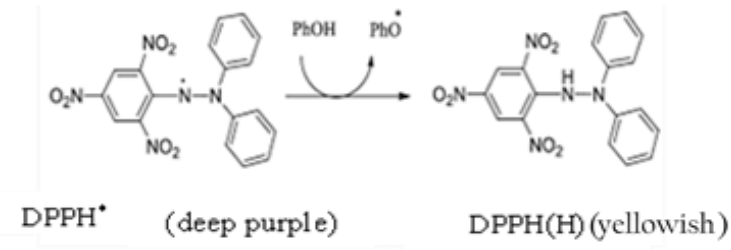

Figure 1. Mechanism of HAT reaction by phenolic compounds against DPPH (Prakash, Rigelhof, dan Miller, 2001)

Emulgel combines of Citronella and Clove Oil

Emulgel are pharmaceutical dosage forms combining emulsion and gel. The delivery of hydrophobic drugs for deep penetration through the skin is the main goal of the emulgel formulation (Mutmainnah, 2015). Emulgel has been chosen because it has several advantages, according to Tristantini, Dewi Ismawati, Alifah Pradana and Jonathan, (2018) the presence of an oil phase component in the emulsion system, as a good carrier for hydrophobic active substances, causes the emulgel to be thixotropic, greaseless, easy to spread, easy to wash, emollient, non-staining, soluble in water. This research, make three formulations were made with the different formulations being in the concentration of the viscolam emulgel base, which of course affected on the viscosity of the emulgel. After obtaining the results of the three formulations, we can find out which formulation is the most suitable for the characteristics of a good emulgel.

The essential oil used is a combination of citronella and clove oil, this combination is a novelty of this research. The ingredients used are citronella and clove oil because many references state that each of these essential oils has anti-acne properties. In addition to being efficacious substances, citronella and clove oil also act as the oil phase in the manufacture of emulgel. The emulgel base used in this formulation is viscolam AT 100P, because it can form a good based emulgel system. Viscolam AT 100P contains three compounds: sodium polyacryloydimethyl taurate which functions as a thickener, emulsifier, and bulking agent, hydrogenated polydence which functions as an emollient, trideceth-10 is the polyethylene glycol (PEG) ether of tridecyl alcohol, with 10 units of ethylene oxide in the molecule. It is seen in a variety of cosmetics and personal care products as both a surfactant and emulsifier (Personal Care Products Council, 2021).

The active substance has an oil solubility so that an oil-soluble antioxidant is α-tocopherol so that it can maintain the stability of the emulgels from oxidation (Ahmad *et al.*, 2012). The oil and water phases in the formulation can be mixed due to the presence of an emulsifier located on the emulgel base, trideceth-10. The emulsifier belongs to the surfactant group which has a hydrophobic side and a hydrophilic side. When the emulsifier is added to the mixture of emulsion system materials, the hydrophilic side will interact with water phase. While the hydrophobic side will interact with oil phase so that two phases are not separated from each other and the emulsion system becomes more stable.

Emulgel Characteristic

The results of the homogeneity measurement of the three formulas produced homogeneous (Figure 2), its was because the

three samples fulfil the homogeneity test requirements including uneven color, coarse granules were not found in the emulgels. This can happen because in the process the essential oils from citronella and cloves have been homogeneously dispersed. The homogeneity test is related to the dose rate release. The homogeneous emulgel, will give an even dose. In addition, the homogeneity test is important because emulsion is said to be stable when an emulgel is visually uniform and there is no separation between the emulgel base and the aqueous phase (Wardiyah, 2015).

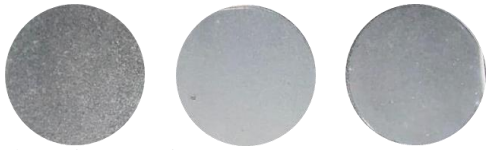

Figure 2. Emulgel formulation homogeneity test results: (left) formula 1, (middle) formula 2, (right) formula 3

The results of microscopic observations with a magnification 100 times is oil in water (O/W) type emulsion. The oil phase this indicated by the red oil droplet. Sudan III is an oil-soluble dye when mixed with emulgel, if the droplets are stained, it shows the O/W type because the droplets are the oil phase. The addition of Sudan III to the emulgel in a combination of citronella and clove oil type O/W caused the water phase (dispersion medium) to be colorless and the oil phase (differentiated phase) to be red (Figure 3) (Josi, 2010).

Figure 3. Emulgel type: (left) formula 1, (middle) formula 2, (right) formula 3. The red color is an oil soluble dye of Sudan III where the medium is white

The viscosity results of the three formulas showed that Formula 3 with the highest emulgel base concentration of 5% had a viscosity value of 160,800 m.Pa.s. The result is an equal consistency of semi-solid. The difference in the viscosity of the emulgel is influenced by the concentration of the emulgel base used. The higher emulgel base added, causes an increased viscosity value. High viscosity will provide stability to the emulsion system in emulgel, because it will minimize the movement of droplets in the dispersed phase so that changes in droplet size to larger sizes can be avoided and the possibility of coalescence can be prevented (Laverius, 2011). Increasing the viscosity of the emulgels will also increase the retention time at the site of application, but will reduce the dispersibility of the emulgel (Garg et al., 2002). This can be seen in Figure 4, where formula 3 has the highest viscosity value.

The viscosity of emulgels will affect the flow properties to facilitate the process of removing from the tube. This type of emulgel flow combination of citronella and clove oil is included in the pseudoplastic type. The pseudoplastic type has a shear rate that increases steadily over time and will break down when the thermodynamic state of the aggregate system is kinetically unstable. Pseudoplastic type at least close to the origin at low shear rates and shows a decrease in viscosity with the increasing rate (Delfiyanti, 2016).

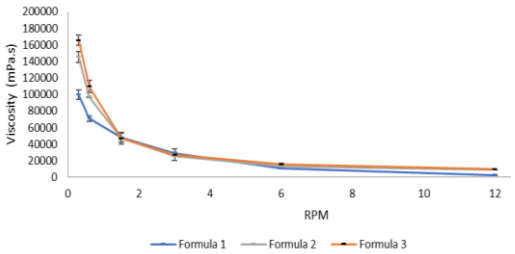

Figure 4. Viscosity of emulgels

The results of the spreadability test (Figure 5) showed that all formulas had a dispersion value below 5 cm, that all formulas had good dispersion. Formula 3 has a spreadability value of 3.85 cm, which is better than Formula 1 (5.12 cm) and formula 2 (4.89 cm). It means that the emulgel formulas 2 and 3 are in the semi-stiff category that has a high viscosity. While formula 1 is included in the semifluid category that has tended to be runny viscosity (diameter is 5 cm to 7 cm) (Daud *et al.*, 2018). Spreadability is influenced by dosage form, which has an inverse relationship with viscosity. The viscosity of formula 1 and formula 2 is very high so that the dispersion power is lower.

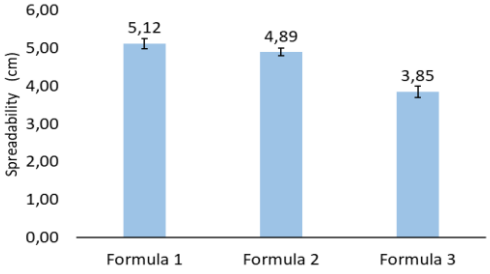

Figure 5. Spreadability of emulgels

The emulgel pH value parameter must be within the skin pH range. The same concentrations of citronella oil and clove oil in formula 1-3, resulted in a different pH of the sample emulgels. The formula 2 had a higher pH value than formulas 1 and 3, but blank 2 had a lower pH than blanks 1 and 3. Citronella oil has

the main components of citronellol and geraniol which are monoterpene alcohol groups while clove oil has the main content of eugenol. The content of essential oils has acidic properties so that it can decrease the emulgel pH (Tambun *et al.*, 2016). However, the pH of the emulgels ranged from pH 5.8 to 6.4. So that the resulting emulgel is safe to use and does not irritate.

Conclusion

The combination of citronella oil and clove oil has a FIC index with an indifference category. The antioxidant activity of Citronella oil has IC_{50} in the medium category and clove oil in the very strong category. The combination of citronella and clove oil can be formulated in emulgel with good characteristics. The most preferred formula in terms of color, scent, consistency, and texture is formula 3 with a concentration of 5% viscolam AT 100P.

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