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RESEARCH ARTICLE

Formulation and *In-vitro* Antibacterial Activity of Gel containing Ethanolic extract of Purple Sweet Potato Leaves (*Ipomoea batatas* (L.) Loaded Poly Lactic Co-Glycolic Acid Submicroparticles against *Staphylococcus aureus*

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ABSTRACT:
Staphylococcus aureus has been resistant to various antibiotics including erythromycin, clindamycin, penicillin, trimethoprim-sulfamethoxazole, tetracyclines, chloramphenicol, and piperacillin-tazobactam so that an alternative treatment is needed. The purple sweet potato leaves (*Ipomoea batatas* (L.) Poir) contain flavonoid compounds that have antibacterial activity by inhibiting nucleic acid, protein synthesis, cell membrane, and energy metabolism in bacteria. In this study, ethanolic extract of purple sweet potato leaves is loaded to poly lactic-co-glycolic acid submicroparticles to increase the stability of flavonoids and the antibacterial effect. Submicroparticle gel was prepared with various concentrations of hydroxypropyl methylcellulose ie F1, F2, and F3 respectively 3%, 5%, and 7%. The antibacterial activity of submicroparticles gel compared with a gel containing extracts without submicroparticle and erythromycin gel as a positive control. Phytochemical test results that the ethanolic extract of purple sweet potato leaves contains flavonoids. Based on the research results, the best formula was F1(3%) with pH, homogeneity, viscosity, dispersibility, adhesion, and washability, respectively 7.4±0.0361; homogeneous; 8358.9±228.1391 cps; 4.2667±0.3005cm; 45.333±2.5166 seconds; 11.6667±1.5275mL. F1 was also shown to have strong antibacterial activity with an inhibition zone value of 13.67±4.04mm.

KEYWORDS: Purple sweet potato leaves (*Ipomoea batatas* (L.) Poir), Flavonoids, Hydroxypropyl Methylcellulose, *Staphylococcus aureus,* Antibacterial, Submicroparticles.

INTRODUCTION:

Bacterial resistance is a growing problem throughout the world, including in Indonesia. One of the bacteria that has been resistant to various antibiotics is *Staphylococcus aureus*. *Staphylococcus aureus* has been resistant to penicillin, methicillin, oxacillin, vancomycin, daptomycin, erythromycin, clindamycin, trimethoprim-sulfamethoxazole, tetracycline, chloramphenicol, ampicillin-sulbactam, and piperacillin-tazobactam.[1,2] So that, alternative treatment is needed to avoid this problem using a natural compound.[3]

The plant that is known to have antibacterial activity is purple sweet potato (*Ipomoea batatas* (L.) Poir).

Purple sweet potato leaves contain secondary metabolite compounds such as alkaloids, tannins, saponins, and flavonoids.[4]

Research conducted by Osuntokun et al.[5] stated that the ethanolic extract of purple sweet potato leaves has antibacterial activity against several bacteria, one of them is the *Staphylococcus aureus*. A concentration of 50mg/mL of ethanolic extract of purple sweet potato leaves act as a moderate antibacterial by producing an inhibition zone diameter of ±10mm and a minimum inhibitory concentration of 12.5mg/ml.

Secondary metabolites that act as antibacterial agents in purple sweet potato leaves are flavonoids.[6,7,8] Flavonoids have antibacterial activity by inhibiting nucleic acid synthesis, cell membrane function, energy metabolism, and protein synthesis.[9] Flavonoids are compounds that are unstable against the effects of oxidation, light, and chemical changes, so that when oxidized their structure

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will change and their function as an active ingredient will decrease.[10,11,12] The stability of flavonoids can be improved by making them into the form of submicroparticles.

Submicroparticle preparations have the advantage such as can protect the active substance, being enhancers, and can be efficient in drug dosage.[13,14] The polymer used in the manufacture of submicroparticle preparations is PLGA (Poly - Lactic - co - Glycolic Acid) with PVA (PolyVynil Alcohol)[15] as a stabilizer using the Emulsion solvent evaporation method. PLGA was chosen because it is biodegradable, biocompatible, non-toxic, and has been approved by the FDA.[16] PLGA polymers are capable of delivering drugs and producing small particle sizes ranging from 180-200nm.[17] The submicroparticles formulated into a gel preparation so that it is easy for the patient to use.

A gel is topical preparation which is usually applied through the skin or mucous membranes. The gel contains a lot of water components and has good drug delivery capabilities.[18] The gelling agent used in this study was Hydroxypropyl methylcellulose (HPMC). HPMC can form a clear, neutral gel and has a stable viscosity.[19] The concentration of HPMC is playing important role in topical preparation. A high concentration of HPMC will produce a viscous gel. When the viscocity of gel is high, the gel will be more resistant to dilution or erosion.[20] This will have an impact on drug release. Thus, gel with high viscocity will exhibited slower drug release.[21]

Based on the description above, in this research, ethanolic extract of purple sweet potato leaves will be formulated into submicroparticle and submicroparticle will be formulated into gel. Submicroparticles of ethanolic extract of purple sweet potato leaves will be seen antibacterial activity against S. aureus by determining the inhibition zone. Antibacterial activity testing was divided into 5 groups, namely negative control (gel containing submicroparticles without active substances), positive control (erythromycin gel), and treatment groups F1, F2, F3 with HPMC variations of 3%, 5%, and 7%.

MATERIALS AND METHODS:

Materials:

The materials used in this study were purple sweet potato leaves (South Sumatra), 96% ethanol (DiraSonita®), 10% Pb Acetate (Bratachem®), 20% NaOH (Bratachem®), PLGA (SigmaAldrich®), PVA (Bratachem®), Aquadest. (DiraSonita®), ethyl acetate (Bratachem®), hydroxypropyl methylcellulose (Bratachem®), propylene glycol (Bratachem®), methylparaben (Bratachem®), propylparaben (Bratachem®), *Staphylococcus aureus* (Biomeriux®), nutrient broth (Merck®), nutrient agar (Merck®), erythromycin (Erymed®), and McFarland's solution (Merck®).

Plant Collection and Determination:

The plant was collected from Pagar Alam, South Sumatra, Indonesia. The determination of this plant was conducted in Herbarium of Andalas University Andalas, Padang, Indonesia.

Preparation of Ethanolic Extract:

The leaves taken are greenish. The leaves that have been picked then washed under running water. The drying process is protected from direct sunlight for 7 days. The dried leaves are powdered using a grinding machine. The extract was made using the maceration method. The simplicia powder of purple sweet potato leaves was dissolved in 96% ethanol solvent with a ratio of simplicia and solvent of 1:20. The filtrate obtained is evaporated at a temperature of 60^{o}C and 80 rpm so that a thick extract is obtained.

Phytochemical Test for Flavonoid Compound:

A 1 ml of test solution was inserted into three test tubes. Tube 1 as a control. Tube 2 was added with 1 mL of 10% Pb acetate (lead acetate) solution, the positive result for flavonoids if there is a yellow precipitate. Tube 3 added with a few drops of 20% NaOH forms a yellow color if it contains flavonoids.[22]

Preparation of Submicroparticles*:*

Submicroparticles were made using the Emulsion Solvent Evaporation Method. The ethanolic extract of purple sweet potato leaves was dispersed with 96% ethanol, Poly Lactic-Co-Glycolic Acid (PLGA) was dissolved in ethyl acetate and PolyVinyl Alcohol (PVA) was dissolved in distilled water. Extract solution containing 150mg of purple sweet potato leaf extract was dissolved with PLGA solution containing 50 mg of PLGA in a beaker glass using a Magnetic Stirrer at 750 rpm (oil phase). PVA solution containing 50mg of PVA act as a water phase. Emulsify the oil phase into the water phase by dropping it using a 50µL Micropipette (O/W emulsion) on a Magnetic Stirrer. The emulsification process is left for 1 hour at a speed of 750 rpm. In the next step, the solution was homogenized using ultra turrax at a speed of 12.0 x 1000rpm for 5 minutes. The particle solution was evaporated to remove the remaining organic solvent on the Magnetic Stirrer for 24 hours.[23]

Preparation of Submicroparticles Gel:

The gel was made of four formulas. The three formulas containing submicroparticle of the ethanolic extract with variations in the concentration of HPMC, namely 3%, 5%, and 7% and one formula containing ethanolic extract without submicroparticles. The formulas for each are shown in Table 1.

Table 1. Formula Gel

Materials	Quantity			
	F1	F2	F3	F4
Submicroparticle of the ethanolic extract of purple sweet potato leaves	150 mg	150 mg	150 mg	-
Ethanolic extract of purple sweet potato leaves	-	-	-	150 mg
HPMC	3 g	5 g	10 g	*
Propilene Glycol	15 mL	15 mL	15 mL	15 mL
Methylparaben	0.18 g	0.18 g	0.18 g	0.18 g
Propylparaben	0.02 g	0.02 g	0.02 g	0.02 g
Aquadest	Ad. 100 mL	Ad. 100 mL	Ad. 100 mL	Ad 100 mL

Note : * Refers to optimum formula between F1, F2, F3

HPMC is dissolved in hot water in a ratio of 1:20 until it forms a gel mass. Methylparaben and propylparaben were dissolved in propylene glycol and added little by little to the gel mass and then stirred until homogeneous. Submicroparticles of ethanolic extract of purple sweet potato leaves are added gradually to the gel mass, then add 100mL of distilled water, stirring until homogeneous, then stored in a tightly closed container.

Evaluation of Submicroparticles Gel:

a. Organoleptic Test:

The organoleptic test in this study was carried out directly observing the texture, color, and smell.

b. pH Test:

The pH of the gel was determined using a digital pH meter. An amount of submicroparticles gel was stirred in distilled water and the pH of the solution was measured.

c. Homogeneity Test:

The homogeneity test was carried out by applying the gel to a transparent glass preparation. It was observed visually. If there were no particles so the gel was homogenous.

d. Viscosity Test:

Measurement of the viscosity of the submicroparticle gel was carried out using a viscometer. A total of 30mL of gel preparation in a beaker is placed on the viscometer by inserting the rotor into the beaker and setting the speed to 60rpm. Observe the needle manually on the tool pointing to the number on the viscosity scale. The viscosity value is characterized by a stable needle movement and is expressed in cP.

e. Spreadability Test:

An excess of gel was placed in between two glass slides and then 125-gram weight was placed on slides for 1 min and then the diameter formed is measured Weight.

f. Adhesion Test:

An 0.25-gram gel was placed in between two glass s and then 1 kg weight was placed on slides for 5 min. Then added weight 80gram to pan and determine the time required to separate the two slides.

g. Washable Test:

The gel is applied on the surface of human skin, then flattene, and then run with water until the stains of the gel preparation disappear. Record the volume of water used.

h. Cycling Tets:

The submicroparticles gel was kept in the refrigerator at 4±2°C for 24 hours and subsequently moved to 40±2°C for 24 hours. The organoleptic, pH, homogeneity, and syneresis phenomenal were determined.[24]

***In vitro* Antibacterial Activity Test:**

Antibacterial activity was evaluated using the disk diffusion method to determine the value of the inhibition zone. The bacterial suspension was made by diluting some colonies in stock bacterial to the nutrient broth. The bacterial suspension of *Staphylococcus aureus* was compared visually with 1.5 McFarland Standard. The treatments were divided into 6 groups as shown in Table 2. Erythromycin gel was selected as a positive control and submicroparticle placebo gel as a negative control.

Table 2. Treatment Group

S. No.	Group	Treatment
1	Negative Control	Submicroparticles placebo Gel
2	Positive Control	Erythromycin Gel
3	F1	Submicroparticles Gel with 3 % HPMC
4	F2	Submicroparticles Gel with 5 % HPMC
5	F3	Submicroparticles Gel with 7 % HPMC
6	F4	Ethanolic Extract Gel with optimum concentration of HPMC

First, the 100µL of bacterial inoculums containing were spread over plates containing Nutrient agar. The disc with a diameter of 6 mm impregnated to agar and the gel was placed on the disc. The plates were incubated for 24 h at 37°C, and the experiments were performed in triplicate. The diameters of inhibition zones were measured.

Data Analysis:

The data were analyzed by Shapiro-Wilk to see the normality of the distribution. If the data is normally distributed, then the test is carried out using ANOVA One Way. From this test, then proceed with the Post Hoc Test if the p-value is < 0.05.

RESULT:

Preparation of Ethanolic Extract:

The purple sweet potato leaves were macerated using 96% ethanol. This solvent is used because it is universal

so that it can dissolve polar and non-polar compounds and has a good ability to extract low molecular weight compounds such as flavonoids.[25] The filtrate produced during the maceration process was concentrated using a rotary evaporator at 60°C and obtained 56.36 g of thick and blackish-brown extract with a yield of 9.39%.

Phytochemical Test for Flavonoid Compound:
The phytochemical test carried out on the extract was the flavonoid test. This is because flavonoid compounds play a role in antibacterial activity. The ethanolic extract of purple sweet potato leaves positively contained flavonoids as evidenced by the formation of a yellowish precipitate when Pb acetate was added and the formation of a brick red color when 20% NaOH was added.

Preparation of Submicroparticles:
Submicroparticles were prepared using the emulsion solvent evaporation method. Submicroparticles are made by mixing the extract solution into the PLGA solution, this aims to form an oil phase which will then be mixed into the PVA solution (water phase). The oil phase is mixed into the water phase with a micropipette to form an O/W emulsion. Then the emulsion is evaporated. During the evaporation process, the emulsion will become a suspension and the remaining content after the evaporation process is only the active substance of the ethanolic extract of purple sweet potato leaves encapsulated by PLGA and PVA as a stabilizer in the water phase. The submicroparticle formulation is expected to increase the stability of flavonoids and increase their antibacterial activity so that the resulting effect is maximized. The submicroparticles solution obtained in this study can be seen in Figure 1.

Figure 1. Submicroparticles Solution

Preparation of Submicroparticles Gel:
Preparation of submicroparticle gel of ethanolic extract of purple sweet potato leaves requires ingredients such as HPMC as a gelling agent, propylene glycol as a humectant, methylparaben and propylparaben as a preservative and aquadest as a solvent. HPMC is able to form a gel by absorbing solvents and forming a compact liquid mass. HPMC is used as a gelling agent because HPMC can form a clear and neutral gel and has a stable viscosity and has good drug delivery capability.[18] In this study, three gel formulas (F1, F2, F3) were made by variation concentration of HPMC ie 3%, 5%, and 7%.

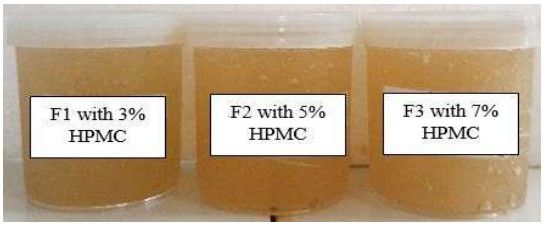

Figure 2. Submicroparticles Gel

Evaluation of Submicroparticles Gel:
Gel evaluation carried out in this study was an organoleptic test, pH test, homogeneity test, viscosity test, spreadability test, adhesion test, washability test, and cycling test. The results of the gel evaluation can be seen in Table 3.

Table 3. The Result of Evaluation of Submicroparticles Gel

Parameter	Formula		
	F1	**F2**	**F3**
Organoleptic	Light yellow, characteristic smell of extract, semi-solid	Light yellow, characteristic smell of extract, semi-solid	Light yellow, characteristic smell of extract, semi-solid
pH	7.40±0.04	7.44±0.06	7.48±0.05
Homogeneity	Homogenous	Homogenous	Homogenous
Viscosity	9093.9±248.2 cps	12020.4±379.1 cps	14546.3±156.5 cps
Spreadability	4.3±0.3 cm	3.6 ±0.1 cm	2.5±0.2 cm
Adhesion	45.3±2.5 s	724±2.6 s	1794.3±5.5 s
Washability	11.7±1.5 mL	15.3±1.5 mL	21.3±2.1 mL

Based on the result in Table 3, F1 was chosen as optimum formula because of the viscosity value is not too high so the resulting gel has a soft texture than the others.

***In-vitro* Antibacterial Activity Test:**
Antibacterial activity test was carried out by measuring the diameter of the inhibition zone. The results of the antibacterial activity test can be seen in Table 4.

Table 4. Inhibition Zone Measurement Results for Gel Preparations

Group	Average Inhibition Zone Diameter±SD (mm)
Negative Control	0±0*
Positive Control	13±1.73
F1	10.23 ± 0.69**
F2	5.78 ± 1.39*
F3	4.0 ± 0.0*
F4	1.89±1.54*

Notes: Statistical significance for each condition compared to positive control (*P<0.05; **P>0.05)

Based on the results of the antibacterial activity test above, F1 has antibacterial activity that is not significantly different from the positive control while the other two formulas had significant differences. This proves that the use of HPMC concentration has an effect on antibacterial activity.

DISCUSSION:

Ethanolic extract of purple sweet potato leaves obtained in this study was thick and blackish-brown extract with a yield of 9.39%. Ethanol extract in this study is proven to contain flavonoid compounds. This is in accordance with research conducted by Kim et al[26], who succeeded in isolating the ethanolic extract of purple sweet potato leaves and obtained 3 types of flavonoids, namely quercetin-3-O-β-D-glucopyranoside, isoquercitrin, and kaempferol 3-O-β-glucopyranoside. Quercetin-3-O-β-D-glucopyranoside has been researched and proven to have antimicrobial activity.[27,28] But, quercetin are compounds that has low stability, poor water solubility and also low bioavailability.[29] Quercetin is thermally unstable, has low stability when in aqueous solution so that it is easily hydrolyzed, and unstable in the presence of light and oxygen which causes oxidation.[30] The stability of flavonoids can be improved by making them into the form of submicroparticles.In this study, PLGA used as polymer and PVA used as stabilizer in submicroparticles. PLGA will encapsulate the ethanolic extract of purple sweet potato leaves due to ionic interactions. Ionic interactions between the drug and polymer will result in higher incorporation in the non-end-capped polymers while if the interaction shows hydrophobic features, the end-capped polymers will show greater incorporation.[31] The presence of PVA will increase the stability of submicroparticles because PVA acts as an emulsifying agent. During the manufacture of submicroparticles, hydrophobic bonds will occur between the acetyl group in PLGA and the hydrolyzed PVA.[32] The presence of PVA will strengthen the encapsulation of PLGA-ethanolic extract of purple sweet potato leaves.

The submicroparticles formulated into a gel preparation. In this study, submicroparticles formulated into three formula gel with various concentrations of hydroxypropyl methylcellulose ie F1, F2, and F3 respectively 3%, 5%, and 7%. Based on the results of the gel evaluation in Table 3, the organoleptic test, pH test, homogeneity test and cycling test between the three formulas did not show a significant difference ($p > 0.05$). The gel produced from the three formulas is light yellow, has the distinctive smell of the extract, has a semi-solid, and homogenous texture. The pH results of the three formulas show that the pH is in the range of 7. Ideally, topical preparations have the same or similar pH value to the skin pH, namely 4.5-6.5 to avoid irritation of the skin. However, the gel at a pH of 7 can still be tolerated by the skin and has not irritated. The resulting gel pH tends to be high due to the influence of PVA on submicroparticles. PVA has a pH range of 5-8, the higher concentration of PVA used, the more hydroxyl ions (OH-) from PVA are likely to be released and will shift the pH value to higher.[33] In the viscosity test, the spreadability test, the adhesion test, and the washability test, there was a significant difference ($p<0.05$) which indicated that there was an effect of the HPMC concentration used on the test. Increasing the amount of gelling agent can strengthen the gel constituent matrix so the viscosity will increase. In addition, the presence of PVA also affects the viscosity value. HPMC and PVA are polymers that can enter the cavity formed by water molecules so that hydrogen bonds occur between the hydroxyl (-OH) groups of the polymer and water molecules.[34,35] This hydrogen bond plays a role in hydration in the swelling process.[36] The results of this viscosity test are inversely proportional to the results of the spreadability and washability tests but are directly proportional to the results of the adhesion test. The higher the viscosity result, the dispersibility and washability's result will smaller, but the adhesion will be stronger. The physical stability test (cycling test) also showed no significant difference between the three formulas ($p> 0.05$). The parameters observed in this test included organoleptic (color, smell, and texture) and changes in pH. The results of the observations obtained were that there was no organoleptic change in the three formulas, each formula had a light yellow color, the distinctive odor of the extract, semi-solid texture, and homogeneous. The three formulas do not indicate a syneresis phenomenon. Based on the gel evaluation and stability results, the F1 formula with a concentration of 3% HPMC was chosen as the optimum formula in making submicroparticle gel and used as the basis for making purple sweet potato leaves ethanolic extract gel which not formulated into submicroparticles for antibacterial activity testing.

Based on the results of the antibacterial activity test above, the three formulas gel containing the ethanolic extract of purple sweet potato leaves in the form of submicroparticles had antibacterial activity. F1 with the smallest HPMC concentration of 3% has the largest inhibition zone diameter compared to F2 and F3. The antibacterial activity result also depends on the viscocity of the gel. Viscocity of the gel can affect to the drug release from the vesicle. Increase in viscocity will resulted in slower drug release and the effect of antibacterial will be reduced.[37,38] Viscosity of gel was directly proportional to the concentration of gelling agent used so in this study F1 with the smallest concentration had the largest inhibition zone diameter. The negative control did not produce inhibition because the component of submicroparticle gel without an active substance did not have antibacterial activity. The

positive control of erythromycin gel had the largest inhibition zone diameter was 13±1.73mm. Erythromycin has antibacterial activity by binding to the ribosome subunit 50s so that protein synthesis is inhibited in bacteria.[39,40]

Based on the data in Table 4, it can be seen that there is an increase in antibacterial activity after the ethanolic extract of purple sweet potato leaves is formed into submicroparticles. F4 or gel contain extract which not formulated into submicroparticles with an optimum concentration of HPMC (3%) can only cause inhibition of 1.67±2.08mm. In the research of Osuntokun et al.[5] ethanolic extract of purple sweet potato leaves with a concentration of 50mg/ml gives an inhibition zone diameter of 10mm. In this study, the amount of extract used was 150mg/100ml and gave an inhibition zone of 1.67±2.08mm. However, when it was formed into submicroparticles, it was able to provide an inhibition zone diameter of 10.23±0.69mm. This proves that the submicroparticle can reduce dose usage.

Submicroparticle preparations can also increase the contact surface area because the resulting particle size is microparticle size so that the penetration of the active substance will increase and the antibacterial effect increases.[41] Flavonoids can act as an antibacterial by inhibiting protein synthesis. Protein synthesis from bacteria occurs in the cytoplasm so that by increasing the penetration power of flavonoids into bacterial cells, more flavonoid molecules can inhibit protein synthesis in bacteria. In addition, the flavonoids formulated into submicroparticle preparations have better stability. Submicroparticle polymers protect flavonoids by encapsulating flavonoid molecules so they are protected from chemical disturbances. The mechanism for the release of active substances from PLGA submicroparticles can go through 4 ways, namely diffusion through water-filled pores, diffusion through the polymer, osmotic pumping, and erosion. In general, the mechanism for releasing the active substance from PLGA submicroparticles is by diffusion through water-filled pores. The water molecules around the submicroparticle will enter the system and cause swelling so that the formation of pores which allows the encapsulated active substance to leave the submicroparticle system constantly until the erosion stage where the PLGA polymer as a submicroparticle maker begins to degrade.[42,43] Submicroparticles reach the target site of bacterial also assisted by propylene glycol used in the gel. Propylene glycol as a penetration enhancer works by extracting lipids and proteins from the stratum corneum to form pores in the stratum corneum. Propylene glycol also changes the solubility parameters of the stratum corneum so that it affects the thermodynamic activity of the submicroparticles contained in the gel formula. This pushes the submicroparticles into the stratum corneum thereby increasing the penetration of the submicroparticles and increase antibacterial activity.[44,45,46]

The results of the shapiro-wilk statistical analysis showed that the data for all groups were normally distributed. One Way ANOVA statistical analysis showed the significance value $p < 0.05$ so it can be concluded that there is a significant difference in the results of the antibacterial activity test of all treatments. In the post hoc test, it can be seen that there is a significant difference in the antibacterial activity of the positive control group with all treatment groups, except F1. From this result, we can conclude that F1 has similar antibacterial activity to positive control.

CONCLUSION:

Based on the results of the research, there was an effect of the HPMC concentration on the results of the physical evaluation of the gel preparation. The higher concentration of HPMC used will cause the resulting gel to be viscous so that it will affect the releasing drug from the gel matrix. F1 with a concentration of 3% HPMC was chosen as the optimum formula because physically good, stable, and produces the best antibacterial effect among the three formulas. In addition, the use of submicroparticle preparations as a carrier for ethanolic extract of purple sweet potato leaves has also been shown to increase antibacterial activity, be able to efficiently use dosages, and can be used as an alternative treatment for infection to prevent resistance.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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