Antibacterial Activity of SNEDDS-Based Parijoto Fruit Extract (*Medinilla speciosa* Blume) Against *Staphylococcus aureus* ATCC 25953

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ABSTRACT

Staphylococcus aureus ATCC 25953 is a Gram-positive bacterium that can cause various infections in humans. Parijoto fruit (Medinilla speciosa Blume) contains bioactive compounds such as flavonoids, tannins, saponins, and phenolics that exhibit antibacterial potential. However, its application is often limited by the poor solubility and bioavailability of its active compounds. This study aimed to evaluate the antibacterial activity of parijoto fruit ethanol extract formulated into a Self-Nanoemulsifying Drug Delivery System (SNEDDS) against Staphylococcus aureus ATCC 25953.The ethanol extract of parijoto fruit was formulated into SNEDDS using a combination of oil, surfactant, and cosurfactant. The SNEDDS was characterized by percent transmittance, particle size, polydispersity index (PDI), and zeta potential analyses. Antibacterial activity was evaluated using the agar diffusion method at concentrations of 25, 50, 75, and 100 mg/mL.The results showed that the SNEDDS had a transmittance value of 96.22 ± 0.55%, an average particle size of 9.742 ± 0.461 nm, a PDI value of 0.389 ± 0.013, and a zeta potential of -16.46 ± 0.88 mV. The antibacterial assay demonstrated inhibition zone diameters of 3.5, 6.4, 7.9, and 9.10 mm at concentrations of 25, 50, 75, and 100 mg/mL, respectively. The SNEDDS formulation of parijoto fruit extract exhibited favorable nanoemulsion characteristics and antibacterial activity against Staphylococcus aureus ATCC 25953, indicating its potential as a natural product-based antibacterial delivery system

Keywords: antibacterial activity; SNEDDS; Medinilla speciosa Blume; Staphylococcus aureus ATCC 25953; nanoemulsion

INTRODUCTION

Acne is a common skin condition that affects the face, neck, chest, and back(1). Several factors contribute to acne, including genetics, race, season, psychological factors, hormonal factors, and bacterial infections. However, acne is generally caused by a bacterial infection(2). This bacterial infection occurs due to blockage of the pilosebaceous glands, which causes inflammation due to blocked ducts in the epidermis(3). The bacteria that cause acne are Propionibacterium acnes and Staphylococcus epidermidis. These bacteria play a role in acne formation by participating in the process of photogenesis and producing lipase, which breaks down free fatty acids in the skin(4).

Parijoto (*Medinilla speciosa*) is an endemic plant that grows wild in tropical climates, particularly in mountain slope forests at altitudes of around 800-2,300 m above sea level. In Asia, parijoto is found in Malaysia, the Philippines, and Indonesia. In Indonesia, parijoto is found in the areas of Mount Muria (Kudus, Central Java), Mount Merapi (Yogyakarta), and Mount Kinabalu (Kalimantan) (5)(6)(7). Parijoto fruit contains phytochemical compounds such as phenolic compounds, flavonoids, saponins, tannins, alkaloids, glycosides, and cardenolin. The pharmacological activity of parijoto fruit is influenced by these phytochemical compounds. Some pharmacological activities that have been identified from parijoto fruit are antioxidant, anti-inflammatory, antibacterial, antidiabetic, and anticancer(8). Several studies have been conducted on the pharmacological activity of parijoto fruit. The results of research by Advistasari and Vifta (9) showed that blood sugar level lowering activity occurred after administration of ethanol extract of parijoto fruit. Other research shows that parijoto fruit extract has a cytotoxic effect on HeLa cells (cervical cancer cells) and WiDr cells (colon cancer cells) (10).

The flavonoid compounds contained in parijoto fruit have low water solubility and tend to be unstable(11). It is estimated that 40% or more of natural compounds have low water solubility (12). In general, oral flavonoid bioavailability is low, ranging from 2-20% (13). Low water solubility and lack of penetration to penetrate absorption barriers can affect the bioavailability of natural compounds in the body. Therefore, nanoparticles are considered to provide a good solution in this situation, namely the stability of the active compound, and nanoparticles are able to provide pharmacological effects at smaller doses (14). One technology that utilizes a combination of nanoparticles is the Self-Nanoemulsifying Drug Delivery System (SNEDDS).

SNEDDS is used as an effective drug delivery strategy for substances with low water solubility. SNEDDS is an isotropic mixture of oil, surfactant, and co-surfactant that, when mixed spontaneously with water, forms an oil-in-water nanoemulsion with only gentle stirring (15). SNEDDS has the ability to spontaneously form nanoemulsions with droplet sizes ≤200 nm upon contact with gastrointestinal fluids, thereby increasing drug release and absorption, resulting in increased bioavailability. SNEDDS can produce more stable preparations both biologically and chemically in the absence of water. Due to its ability to form droplets in the range of ≤200 nm, it can increase the solubility of water-insoluble drugs and their physical stability. In addition, increased intestinal permeability increases bioavailability (16). According to research by Sugiarti and Fitrianingsih (2018), ethanol extract of parijoto leaves can inhibit the activity of *Propionibacterium acnes* and *Staphylococcus aureus* bacteria starting at a concentration of 6.25 mg/mL. The results of this study indicate that the ethanol extract of parijoto leaves has the potential as an antibacterial against the growth of acne-causing bacteria, so it needs to be further developed in the form of a parijoto fruit SNEEDS formula. The purpose of this study was to determine the ability of the Self-Nanoemulsifying Drug Delivery System (SNEDDS) formulation of parijoto fruit extract (*Medinilla speciosa* Blume) in its antibacterial activity against *Staphylococcus aureus* ATCC 25953.

METHODS

A. Research Tools and Materials

The tools used in this study were analytical scales, stirring rods, measuring cups (Herma), beakers (Pyrex), horn spoons, blenders, ovens, dropper pipes, micropipettes, test tubes, wooden clamps, mortars and stamfers, water baths, porcelain cups, watch glasses, sonicators, hot plates, ultrahomogenizers, 5 ml vials, 5 ml volumetric flasks, 10 ml volumetric flasks, blue tips, vortexes, pH meters, glass objects, pH meters, UV-Vis spectrophotometers, Particle Size Analyzers. Zeta potential analyzers. The materials used in this study were parijoto fruit (Medinilla speciosa Blume) 96% ethanol, Tween 80, Aquadest, 96% Ethanol, Ethyl acetate.

B. Research Procedure

This research was conducted in the Pharmacy Laboratory of the Faculty of Health Sciences, Duta Bangsa University, Surakarta, and the Chemistry and Biology Laboratory of the Integrated Technical Implementation Unit (UPT) of Sebelas Maret University, Surakarta.

1. **Sample Preparation and Preparation of Simple.** Parijoto fruit was obtained from Mount Muria, Kudus, Central Java, washed and sorted, then dried in an oven for 40 hours at 40-60°C. The fruit was then ground to size using a grinder. The resulting parijoto fruit powder was sieved using a 30-mesh sieve. The parijoto fruit powder that passed the 30-mesh sieve was stored in an airtight container until further use(17).

2. **Preparation of Parijoto Fruit Extract with Ultrasonic Assisted Extraction Method**. The parijoto fruit extraction method with ultrasonic-assisted extraction was carried out according to previous research by Kunarto and Sani (2020). A total of 20 grams of dry parijoto fruit powder was placed in a beaker, then ethanol was added as a solvent with a ratio of parijoto fruit powder and ethanol of 1:10 (w/v). The variation in the concentration of the ethanol solvent used was 70%. The sample was extracted using Ultrasonic Assisted Extraction (UAE) at a frequency of 40 kHz with an extraction temperature of 35°C and for 31 minutes. Next, filtration and evaporation were carried out at the boiling temperature of ethanol until a thick extract was obtained(18).

3. **Uji Skrining Fitokimia**
    a. **Anthocyanin.** The extract was dissolved in 1 ml of distilled water, then the filtrate was taken and 2 M HCl was added. The solution was then heated at 100°C for 5 minutes. A red color appeared. 2 M NaOH was then added dropwise while observing the color change. A bluish-green color appeared (19).
    b. **Alkaloids.** A test tube containing one milliliter of sample solution was filled with one milliliter of 2 N HCl. After heating for two minutes in a water bath, the solution was cooled. In the first test tube, the extract sample was filtered and 3-5 drops of Dragendorff's reagent were added. A red precipitate will form if the alkaloid is positive. In the second test tube, the extract sample was placed in the test tube and 2 drops of Mayer's reagent were added, resulting in the formation of a white precipitate. In the third test tube, the extract sample was placed in the test tube and 2 drops of Wagner's reagent were added, resulting in the formation of a brown or orange-brown precipitate (20).
    c. **Flavonoids.** One mL of sample solution is taken, then 0.2 g of magnesium is added and a drop of concentrated HCl and amyl alcohol is added to the test tube. A positive result for flavonoid compounds is indicated by a color change from yellow to red (21).
    d. **Phenol.** A test tube is filled with one mL of sample solution and one mL of 1% $FeCl_3$. The presence of phenolic compounds can be determined by the formation of a blackish-green precipitate (22).
    e. **Saponin.** 2 mL of sample solution is shaken with 2 mL of hot water. If a white foam appears that persists for 10 minutes, it indicates a positive result for saponin compounds (23).
    f. **Steroids/Triterpenoids.** 1 mL of sample solution is taken, then Liebermann-Burchard reagent (anhydrous CH_3COOH: concentrated H_2SO4) is added. The presence of steroids is indicated by a blue or green color, while triterpenoids are indicated by a red or purple color (24).
    g. **Tannin.** One mL of sample solution is obtained, then one milliliter of 1% gelatin solution with NaCl is added. The presence of tannin compounds can be identified from the formation of white deposits (25).

4. **Ethanol Soluble Extract Level Test.** The ethanol soluble extract level test was carried out by weighing 2.5 grams of extract, then dissolving it in 50 mL of ethanol to produce a 5% ethanol solution. From this solution, 20 mL was taken and filtered using filter paper. The filtrate was placed in a steam dish, then evaporated at 100°C until all the solvent had evaporated and only a residue remained. The percentage of ethanol soluble extract level was calculated using the following formula (26):

$$\textbf{Ethanol soluble extract} = \frac{\textbf{W2} - \textbf{WO}}{\textbf{W1}} \textbf{X 100\%}$$

Description:
W0 = Weight of empty cup (gr)
W1 = Weight of initial extract (gr)
W2 = Weight of final extract (gr)

5. **Water-Soluble Essence Test**

A total of 1.25 grams of extract (W1) was dissolved in 25 mL of distilled water. 20 mL of this solution was taken and filtered. The resulting filtrate was placed in a pre-weighed evaporating dish (W0). The solution was then evaporated over a water bath at 100°C until all the solvent had evaporated, leaving a residue. The resulting residue was then weighed (W2) to calculate the water-soluble essence content. The percentage of water-soluble essence was calculated using the following formula(26):

$$\textbf{Water soluble Essence} = \frac{\textbf{W2} - \textbf{WO}}{\textbf{W1}} \textbf{X 100\%}$$

Description:
W0 = Weight of empty cup (gr)
W1 = Weight of initial extract (gr)
W2 = Weight of final extract (gr)

6. **SNEDDS (*Self-Nanoemulsifying Drug Delivery System*) Formulation**. The SNEDDS formulation of parijoto extract was adapted from research (Prianai et al., 2020)(27). Parijoto extract nanoemulsion was made using Tween 80. Then, surfactant (0.24 g) was added, and the mixture was thoroughly homogenized. Next, 2.76 g of deionized water was added and stirred again until the surfactant was completely dispersed in the water. The solution was then sonicated in a sonicator at 35°C, 20 kHz, and 100% power for 60 minutes. To produce a good nanoemulsion, homogenization was performed using high-shear homogenization at 10,000 rpm at 4°C for 15 minutes.

7. **Uji Evaluasi SNEDDS**
   a. **Zeta Potential Test**. The SNEDDS preparation was tested for zeta potential using a Particle Size Analyzer (PSA) instrument. The sample was placed in a cuvette, then the cuvette was inserted into a sample holder. The zeta potential (ZP) value must be less than -30 mV or greater than +30 mV to be stable (28).
   b. **Particle Size Analyzer Test.** The SNEDDS preparation containing parijoto fruit extract was tested for particle size using a particle size analyzer. A 0.1 ml sample was suspended in 100 ml of water. A 10 mL sample was taken and placed into the cuvette. The cuvette must first be cleaned to prevent affecting the analysis results. The cuvette filled with the sample was then placed in the

sample holder and analyzed by the instrument. The observed results were particle size and polydispersity index (PDI), which describe the variation in the sample. Preparations with a PDI value close to 0 indicate monodisperse (29)

c. **Transmittance Testing.** SNEDDS preparations were tested for transmittance using UV-Vis spectrophotometry at a wavelength of 254 nm. A suspension of 0.1 ml of the sample was mixed with 10 ml of distilled water (27).

8. **Test on Bacteria.** A 100 µL bacterial suspension with a cell density equivalent to 0.5 McFarland was prepared and put into a sterile petri dish, then nutrient agar was added, after which it was shaken in a figure eight shape slowly, when the media had solidified, the discs that had been saturated with each concentration of the SNEEDS formula and controls (positive and negative) were inserted into the media at a predetermined distance and then incubated for 18 hours at 37°C.

RESULTS

1. Sample Preparation and Extraction Results

The UAE extraction yield of parijoto fruit can be seen in Table 1.

Table 1. UAE Extraction Results of Parijoto Fruit

Dry Simplicia Weight (g)	Thick Extract Weight (g)	Extraction Yield (%)
20	5,214	26,07

2. Phytochemical Screening Test Results

The results of the phytochemical screening test for parijoto fruit extract can be seen in Table 2.

Table 2. Phytochemical Screening Results of the Sample Extract.

Phytochemical Screening	Positive Result According to Literature	Observation Result	Conclusion
Flavonoids	Color change from yellow to red	Color changed from reddish-brown to transparent yellow	+ (Positive)
Alkaloids	- Dragendorff's reagent produces a red precipitate	Red precipitate was formed	+ (Positive)
	- Mayer's reagent produces a white precipitate	White precipitate was formed	+ (Positive)
	- Wagner's reagent produces a brown precipitate	Brown precipitate was observed	+ (Positive)
Phenols	Formation of a dark green to blackish-green precipitate	Dark green to blackish-green precipitate was formed	+ (Positive)
Saponins	Presence of persistent foam or froth	Persistent foam or froth was observed	+ (Positive)
Steroids/Triterpenoids	Blue or green color indicates steroids, while red or purple color indicates triterpenoids	Reddish-brown color change was observed	+ (Triterpenoid)
Tannins	Formation of a white precipitate	White precipitate was formed	+ (Positive)
Anthocyanins	Color changes to green after addition of NaOH	Green color was formed	+ (Positive)

3. Results of the Ethanol-Soluble Essence Test

Table 3. Ethanol-Soluble Extractive Value of the Sample

Replicate	Ethanol-Soluble Extractive Value (%)
1	15.97
2	16.34
3	16.15
Mean ± SD	16.1530.15107

4. Results of the Water-Soluble Essence Test

Table 4. Results of Water-Soluble Extractive Content (%)

Replicate	Water-Soluble Extractive Content (%)
Replicate 1	10.33
Replicate 2	11.18
Replicate 3	10.42
Mean ± SD	**10.64 ± 0.381**

5. Results of the SNEDDS (Self-Nanoemulsifying Drug Delivery System) Formulation for Parijoto Fruit Extract

Table 5. SNEDDS Formulation for Parijoto Fruit Extract

Material	Concentration (%)	Weight (gram)
Tween 80	12	6
Deionized water	80,5	40,25
Parijoto fruit extract	7,5	3,75

6. Results of the Percent Transmittance Test

These results indicate results above 90% so it can be assumed that the SNEDDS made is already nano-sized. The results of the percent transmittance test for Parijoto fruit extract can be seen in Table 6.

Table 6 Results of the % Transmittance Test of SNEDDS Parijoto Fruit Extract

Replicate	% Transmitan
1	95,700
2	96,200
3	96,500
4	95,600
5	97,100
Mean ± SD	96,22 ± 0,54918

7. Results of the *Particles Size Analyzer* Test

The results of the SNEDDS particle size analyzer test on parijoto fruit extract can be seen in Table 7.

Table 7 Results of the SNEDDS Particle Size Analyzer Test on Parijoto Fruit Extract

Replicate	Particle Size (nm) Range	Range	PDI
1	9.118	6,88-11,7	0,401
2	10.17	7,47-13,5	0,390
3	10.09	7,33-13,4	0,401
4	10.10	7,32-13,5	0,365
5	9.232	6,95-11,9	0,390
Mean ± SD	9,742±0,4613		0,389±0,0131

8. Results of the Nilai *Zeta Potential* Test

The results of the SNEDDS zeta potential test for parijoto fruit extract can be seen in Table 8.

Table 8 Results of the SNEDDS Zeta Potential Test for Parijoto Fruit Extract

Replicate	Zeta Potensial (mV)
1	-15.7
2	-16
3	-17.7
Mean ± SD	-16,46±0,8806

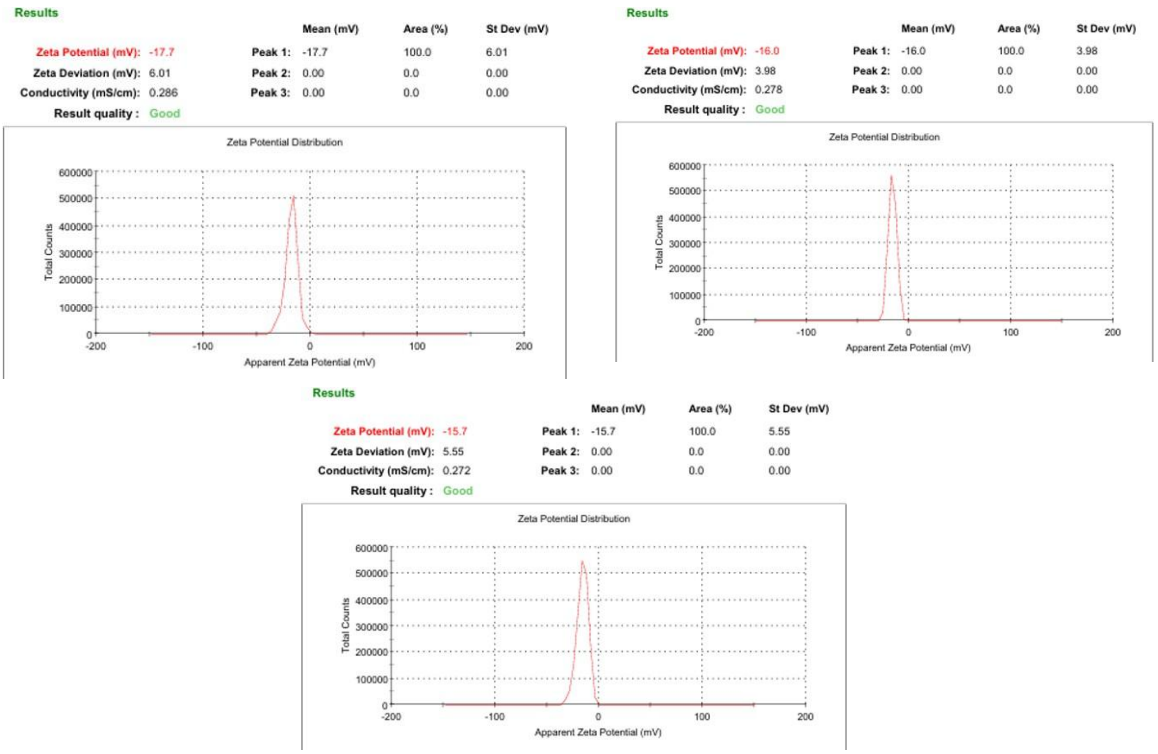

Figure 1. Results of the SNEDDS Zeta Potential Test for Parijoto Fruit Extract

9. Test on Bacteria.

Table 9. The results of the antibacteria test on SNEDDS parijoto fruit extract

Replicate(mg/ml)	Snedds Concentrations
25	3,5
50	6.4
75	7.9
100	9.10
Clindamisine (2 ug/ml)	11,5
Sterile water	-

DISCUSSION

1. Sample Preparation and Extraction Results

Ultrasonic Assisted Extraction (UAE) is an extraction method that utilizes the phenomenon of cavitation in liquid media, namely the formation, growth, and collapse of microbubbles. The rupture of these bubbles produces high temperatures and pressures, which, when occurring near a solid surface, can damage cell walls, thereby releasing compounds within the cells. The advantages of this method include shorter extraction times and processes, increased extraction yields, the use of safer solvents, and the ability to extract thermolabile compounds without compromising quality. Furthermore, this method is easy to implement, flexible, and lower cost than other modern techniques (Puspita et al., 2024). The sonication method has limitations, including excessive exposure to ultrasonic waves that can cause degradation of sensitive compounds such as anthocyanins. Furthermore, the application of UAE on an industrial scale still faces technical challenges, particularly the need for specialized equipment and strict control of process parameters.

2. Phytochemical Screening Test Results

Phytochemical screening is used to qualitatively identify chemical compounds. Phytochemical screening is a preliminary test that describes the compound content of a plant under study. Visually identified color changes will provide an indication of the compound's content. The presence of secondary metabolic compounds in parijoto fruit extract was determined using phytochemical testing in test tubes.

3. Results of the Ethanol-Soluble Essence Test

These results demonstrate consistency between replicates and illustrate the extract's ability to optimally dissolve active components in ethanol. According to Materia Medika Indonesia Volume VI, the standard ethanol-soluble extract content for herbal medicines or herbal extracts is not less than 6%. Therefore, the obtained ethanol-soluble extract content of the parijoto fruit extract meets and exceeds the established quality requirements.

This high ethanol-soluble extract content indicates that the extract contains a significant amount of secondary metabolites, the majority of which are soluble in ethanol, such as flavonoids, phenolic compounds, tannins, and saponins. The use of 70% ethanol as the extraction solvent plays a crucial role in the high ethanol-soluble extract content. Ethanol is semi-polar, effectively dissolving polar to semi-polar compounds. Furthermore, the application of the Ultrasound-Assisted Extraction (UAE) method increases extraction efficiency through cavitation, which can damage the cell walls of the herbal medicines and accelerate the transfer of active compounds into the solvent.

4. Results of the Water-Soluble Essence Test

These results demonstrate consistency between replicates and illustrate the extract's ability to optimally dissolve active components in water. According to Materia Medika Indonesia Volume VI, the standard water-soluble content for herbal drugs or extracts is no less than 6%.

5. Results of the SNEDDS (Self-Nanoemulsifying Drug Delivery System) Formulation for Parijoto Fruit Extract

The formulation of SNEDDS parijoto extract was adapted from the research of Ananingsih et al., (2024) parijoto extract nanoemulsion was made with Tween 80. Tween 80 was added, and the mixture was thoroughly homogenized. Then, deionized water was added and stirred again until the surfactant was completely dispersed in the water. The solution was then sonicated in a sonicator at a temperature of 35°C, a frequency of 20 KHz, and 100% power for 60 minutes. To produce a good nanoemulsion, homogenization was carried out using high shear homogenization at a speed of 10,000 rpm with a temperature of 4°C for 15 minutes. SNEDDS was made using the spontaneous emulsification (SE) technique. This technique uses surfactants and cosurfactants that spontaneously produce emulsions. Tween 80 surfactant has an HLB <10 (15) which makes the emulsion spontaneously. SNEDDS stirring should not be too fast or too slow. Stirring too fast will cause turbulence so that the particle size is too large and stirring too slow will make it difficult to achieve homogeneity.

6. Results of the Percent Transmittance Test

The transmittance test aims to determine its clarity which is shown in percentage form. A good transmittance test for nanoemulsion is to have a clear appearance and a transmittance percentage of 90-100% or close to water clarity, which is close to 100%. A higher transmittance value indicates that the nanoemulsion is nanometer (nm) in size. The size of the dispersion will affect the appearance of the nanoemulsion. The nanometer size will make it easier for light to pass through so that the light beam will be transmitted until the solution is transparent and the transmittance percentage value will be greater. The results of this study showed an average transmittance value of SNEDDS ethanol extract of parijoto fruit of 96.22%. These results indicate results above 90% so it can be assumed that the SNEDDS made is already nano-sized.

***7.* Results of the *Particles Size Analyzer* Test**

Measurement of SNEDDS particles of parijoto fruit extract using a particle size analyzer (Malvern, UK). The test results on five replications showed a relatively narrow and overlapping particle size range, which was in the range of 6.88–13.5 nm. The average particle size of 9.742 ± 0.4613 nm with a polydispersity index (PDI) value of 0.389 ± 0.0131 indicated that the resulting nanoparticle system had a relatively homogeneous and reproducible size distribution. These results mean that the particle size of SNEDDS parijoto fruit extract has met the nanoparticle size standard (10–1000 nm). A PDI value within the 0.3 range indicates that the resulting nanoemulsion has a consistent particle size distribution or a similar degree of uniformity. Non-uniform particle size is caused by particles clumping together to form large aggregates.

8. Results of the Nilai *Zeta Potential* Test

The zeta potential value reflects the surface charge of particles and affects colloidal stability. A high zeta potential can prevent particle aggregation due to electrostatic repulsion. The zeta potential value of SNEDDS ethanol extract of parijoto fruit of -16.46 ± 0.88 mV indicates that the particles have a negative surface charge, but the magnitude

of the charge is not high enough to provide a strong electrostatic repulsion between particles. The ideal potential range for nanoparticle stability is (-30 to 20 mV or +20 to +30 mV). This condition has direct implications for PSA results and particle size distribution.

In the PSA SNEDDS analysis of parijoto fruit extract, the dominant size was around 9–10 nm with a relatively narrow size range (±7–12 nm), indicating that the primary particles were successfully formed and relatively homogeneous in number. However, the intensity-based PSA analysis detected larger particles, indicating aggregation. This difference in the results between the number and intensity distributions can be explained by the zeta potential value which is in the low–moderate stability range. Although the number of aggregates is relatively small, their size is large enough to contribute significantly to the intensity of scattered light in DLS measurements. Therefore, particle aggregation is more influenced by the limitations of electrostatic repulsion due to the moderate zeta potential value, rather than by the failure of nanoparticle formation (5).

9. Test on Bacteria.

Bacterial growth activity is inhibited by the presence of secondary metabolites contained in the fraction, including flavonoids, which attack the phosphate group in the cytoplasmic membrane, causing membrane damage, and tannins, which react with the cell membrane and inhibit essential enzymes or genetic material, resulting in hydrophobic bonds that cause denaturation and metabolic disruption. This may be due to differences between the two bacteria, which have varying properties and resistance to antibacterial agents, even though they belong to the same bacterial group, and differences in the compounds absorbed in the two solvents.

CONCLUSION

Formulation of Medinilla speciosa Blume fruit ethanol extract into a Self-Nanoemulsifying Drug Delivery System (SNEDDS) resulted in a nano-sized delivery system with desirable physicochemical properties and effective antibacterial activity against Staphylococcus aureus ATCC 25953. The increased inhibition observed at higher concentrations indicates that SNEDDS may improve the delivery and antibacterial efficacy of parijoto fruit bioactive compounds, supporting its potential development as a natural antibacterial agent.

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