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Formulation and Characterization of Soursop Leaf extract (*Annona muricata* L.) Nanoemulsion Using VCO and Tween 80

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Abstract. Methanol extract of soursop leaves contains various bioactive compounds such as alkaloids, saponins, tannins, and flavonoids. To increase the absorption of these compounds, a nanoemulsion formulation of soursop leaf extract was carried out. Extraction was carried out using the maceration method using 96% methanol, followed by a thickening process using a rotary evaporator and freeze drying to obtain the dry extract. The nanoemulsion preparation was made from methanol extract of soursop leaves (*Annona muricata L.*) using Virgin Coconut Oil (VCO) as the oil phase and Tween 80 as a surfactant. The nanoemulsion was formulated using a high-energy method using an ultrasonicator. Two formulas were tested (F1 and F2) and evaluated through organoleptic tests, clarity (transmittance), physical stability (centrifugation), solubility, emulsion type, storage test (freeze-thaw), and measurement of droplet size and polydispersity index with a Particle Size Analyzer (PSA). The results showed that formula F1 had the most optimal characteristics, with a clarity of 80% indicating better droplet dispersion with an average droplet size of 13.96 nm and a polydispersity index of 0.216 indicating the successful formation of a stable and uniform nanoemulsion. Nanoemulsions showed good physical stability, were soluble in polar and semi-polar solvents, and were oil-in-water (O/W) type supporting increased solubility and availability of active compounds in air-based systems. These results indicate that F1 is the most potential formula to increase the bioavailability of active compounds in soursop leaves and can be further developed as a carrier system candidate in pharmaceutical preparations.

Keywords: *nanoemulsion, Annona muricata L., soursop leaves, extract, methanol, VCO, tween 80*

Abstrak. Ekstrak metanol daun sirsak memiliki senyawa bioaktif yang beragam seperti alkaloid, saponin, tanin, dan flavonoid. Untuk meningkatkan penyerapan senyawa-senyawa tersebut dilakukanlah formulasi nanoemulsi ekstrak daun sirsak. Ekstraksi dilakukan dengan metode maserasi menggunakan metanol 96%, diikuti proses pengentalan menggunakan rotary evaporator dan *freeze drying* untuk memperoleh ekstrak kering. Sediaan nanoemulsi berbahan dasar ekstrak metanol daun sirsak (*Annona muricata* L.) *menggunakan Virgin Coconut Oil* (VCO) sebagai fase minyak dan Tween 80 sebagai surfaktan. Nanoemulsi diformulasikan dengan metode energi tinggi menggunakan ultrasonikator. Dua formula diuji (F1 dan F2) dan dievaluasi melalui uji organoleptik, kejernihan (transmitan), stabilitas fisik (sentrifugasi), kelarutan, tipe emulsi, uji penyimpanan (*freeze-thaw*), serta pengukuran ukuran droplet dan indeks polidispersitas dengan *Particle Size Analyzer* (PSA). Hasil menunjukkan bahwa formula F1 memiliki karakteristik paling optimal, dengan kejernihan sebesar 80% yang menandakan dispersi droplet yang lebih baik dengan ukuran droplet rata-rata 13.96 nm serta indeks polidispersitas 0.216 menunjukkan keberhasilan pembentukan nanoemulsi yang stabil dan seragam. Nanoemulsi menunjukkan kestabilan fisik yang baik, larut dalam pelarut polar dan semi-polar, serta bertipe minyak dalam air (O/W) mendukung peningkatan kelarutan dan ketersediaan senyawa aktif dalam sistem berbasis air. Hasil tersebut menunjukkan bahwa F1 menjadi formula paling potensial untuk meningkatkan bioavailabilitas senyawa aktif daun sirsak dan dapat dikembangkan lebih lanjut sebagai kandidat pembawa (carrier system) dalam sediaan farmasi.

Kata kunci: *nanoemulsi, Annona muricata L., daun sirsak, ekstrak, metanol, VCO, tween 80*

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INTRODUCTION

The use of plants in traditional medicine has been widely recognized as alternative treatments (Widiastusti *et* al., 2022). Soursop is well-suited to cultivation in warm and humid tropical climate with humidity levels of 60–80% and annual rainfall between 1.500 and 2.500 mm (Putri and Diliarosta, 2022).

Soursop leaves (*Annona muricata*), as part of the plant, have been widely used in traditional medicine, particularly in tropical countries. The leaves are pinnate in shape, ovate to lanceolate, measuring 6–18 cm in length and 3–7 cm in width. They are light to dark green in color, with a shiny upper surface and a rough texture on the underside. The leaf apex is pointed (Rasyidah, 2019).

The use of soursop leaf in oral dosage forms can affect the body's absorption process due to the poor solubility of its active compounds (Sopyan et al., 2019). Therefore, advanced formulation technologies are required to enhance bioavailability, such as nanoemulsion systems, as previous studies have mainly focused on crude plant extracts. Nanoemulsion is a thermodynamically stable system consisting of water and oil phases dispersed with the aid of surfactant molecules at the interfacial layer (Zulfa et al., 2019). These systems are characterized by their nanoscale droplet size, typically ranging from tens to several hundred nanometers (Wilson et al., 2022).

The bioactive constituents of soursop leaves, particularly lipophilic fractions such as acetogenins, are known to have very low solubility in aqueous media, thus limiting the dissolution process, stability, and absorption efficiency during oral and topical administration. This condition has been reported as one of the main obstacles in the development of soursop leaf extract-based formulations (Artanti *et al.,* 2021). The nanoemulsion-based approach is considered capable of overcoming this problem, because this system provides nanometer-sized droplets that increase the contact surface area, improve effective solubility, and facilitate increased permeation of lipophilic compounds into the aqueous phase and biological membranes (Piazzini *et al.,* 2017). Thus, nanoemulsions offer a relevant formulative solution to enhance the bioavailability of active components of soursop leaves.

Virgin coconut oil (VCO) was used as the oil phase in nanoemulsion formulations due to its good solubility with various bioactive compounds found in soursop leaf extract (Mah et al., 2024). The incorporation of VCO into nanoemulsions can enhance the absorption of these bioactive compounds in the digestive system. VCO is rapidly absorbed through the intestinal wall and transported to the liver via the portal vein, which facilitates the rapid metabolism and activation of the encapsulated compounds (Gerrard et al., 2023).

Tween 80 is one of the most widely used non-ionic surfactants due to its ability to reduce interfacial tension between the water and oil phases, thereby facilitating the formation and stabilization of oil-in-water (O/W) nanoemulsions (Zulfa et al., 2019). It possesses a Hydrophilic-Lipophilic Balance (HLB) value of approximately 15, which makes it highly suitable for the formulation of O/W nanoemulsion systems (Yuwanti et al., 2011).

Therefore, this study was conducted to formulate and characterize a soursop leaf extract-based nanoemulsion system using VCO as the oil phase and Tween 80 as a

surfactant, and to evaluate the characteristics of clarity, droplet size and distribution, emulsion type, and physical stability in order to identify the most optimal formula in increasing the solubility and absorption potential of lipophilic bioactive compounds.

MATERIAL AND METHODS

Materials

The materials used in this research include soursop leaves (*Annona muricata* L.), methanol 96% (Merck), distilled water (OneLab), hydrochloric acid (HCl) 32% (Merck), magnesium powder (Merck), sulfuric acid (H_2SO_4) 2N, Dragendorff's reagent, Mayer's reagent, Wagner's reagent, ferric chloride ($FeCl_3$) 1%, acetic acid (CH_3COOH), Tween 80 (Sigma-Aldrich), pure virgin coconut oil (VCO), propylene glycol (Merck), universal pH indicator, *n*-hexane, and ethyl acetate.

The equipment used includes a blender, volumetric flasks, measuring cylinders, rotary evaporator, amber glass bottles, filter paper, glass funnels, vial bottles, analytical balance, spatulas, glass rods, dropper pipettes, volumetric pipettes, micropipettes, hot plate with magnetic stirrer, centrifuge, cuvettes, UV-Vis spectrophotometer, and Particle Size Analyzer (PSA).

Procedure

Extraction

The sample of soursop leaves was extracted twice using the maceration method over 3 × 24 hours at room temperature in a closed container protected from direct sunlight. Maceration was carried out using 96% methanol as the solvent, with a sample-to-solvent ratio of 1:5. After each maceration period, the extract was filtered using filter paper to separate the liquid extract from the plant residue. The residue was then subjected to re-maceration following the same procedure to ensure maximum extraction of bioactive compounds. The combined filtrates were concentrated using a rotary evaporator at 50°C to obtain a condensed extract. To remove residual solvent and obtain a stable dry extract, freeze-drying (lyophilization) was performed. This process yielded a dry extract that is stable, easy to quantify, and suitable for long-term storage without degrading the bioactive constituents. The yield percentage (% yield) was calculated using an initial sample weight of 200 grams, according to Equation 1:

$$\%\text{Yield} = \frac{\text{mass of concentrated extract (gr)}}{\text{mass of dried extract (gr)}}\ x\ 100$$

Nanoemulsion formulation

The nanoemulsion formulation was prepared using a high-energy method, involving specific tools such as ultrasonication. VCO was used in the oil phase, with Tween 80 as the surfactant, propylene glycol as the co-surfactant, and concentrated methanol extract of soursop leaves. The mixture was then brought to a final volume of 100 mL with the water phase (Budiarto et al., 2021). The formulation is presented in Table 1.

Table 1. Nanoemulsion formulation of methanol extract of soursop leaves

Materials	Nanoemulsion Formulation	
	F1	F2
Soursop leaf extract	0.4	0.4
VCO (gram)	1.96	2.16
Tween 80 (gram)	15.68	15.48
propylene glycol (PG) (gram)	1.96	1.96
Aquades (ml)	Add 100	Add 100

The concentrated methanolic extract of soursop leaves was dissolved into VCO according to the predetermined formulation, along with the surfactant (Tween 80) and co-surfactant (propylene glycol). The nanoemulsion mixture was stirred using a magnetic stirrer at 250 rpm for 3 hours. To form submicron droplets and enhance the oil–water interface, the formulation was further processed using a bath-type sonicator at 40 kHz for 2 hours until a stable nanoemulsion was obtained.

Nanoemulsion characterization

1. ***Organoleptic test***

   The organoleptic test was conducted by observing the odor, color, and clarity of the nanoemulsion. (Ma'arif et al., 2023).

2. ***Clarity test***

   A 1 mL sample was diluted with distilled water to 100 mL using a volumetric flask. Then, the absorbance was measured by UV-Vis spectrophotometry at a wavelength of 650 nm (Nasiro et al., 2023).

3. ***Centrifugation test***

   The physical stability of the nanoemulsion was evaluated using a centrifugation test at 2750 rpm for 1 hour (Nasiro et al., 2023).

4. ***Solubility***

   Each 5 mL nanoemulsion sample was mixed with various solvents—namely methanol, ethyl acetate, n-hexane, and distilled water—in a 1:1 ratio. Solubility was evaluated by observing the extent to which the sample dissolved in each solvent. (Nasiro et al., 2023).

5. ***Emulsion type test***

   This test was conducted by mixing the nanoemulsion with methylene blue on a watch glass, followed by stirring and visual observation. If the methylene blue dissolved, the nanoemulsion was identified as an oil-in-water (O/W) type. However, if agglomeration occurred, it was classified as a water-in-oil (W/O) nanoemulsion (Rahmawati et al., 2021).

6. ***Storage test***

   This test was carried out using a freeze–thaw cycle method over 6 cycles in 12 days, where each cycle involved storing the sample for 24 hours. The nanoemulsion was stored and observed at 4 ± 2 °C (refrigerator temperature) and 25 °C (room temperature) for each cycle. (Risma et al., 2020).

7. ***Droplet size and polydispersity index***

   This test was conducted using a PSA. A portion of the sample was taken and measured to determine the droplet size and polydispersity index values (Ma'arif et al., 2023).

RESULT AND DISCUSSION

Extraction

The extraction process was conducted using a sample-to-solvent ratio of 1:5. Two hundred grams of soursop leaf powder was measured and macerated with 1000 mL of 96% methanol for 3 cycles of 24 hours each. After maceration, the mixture was filtered to separate the filtrate and residue. The residue was then subjected to remaceration following the same procedure.

The macerated extract was then concentrated using a rotary evaporator at 50 °C to obtain a thick extract. The concentrated extract was subsequently stored in a freeze dryer to ensure complete removal of the solvent. The freeze-drying process involved freezing the extract below its freezing point, followed by primary and secondary drying

stages to remove water vapor through sublimation. This process was carried out under low pressure to prevent degradation of active compounds. The final yield of the extract was considered good, reaching 15.79%, which exceeds the minimum threshold of 10% (Wardaningrum, 2019).

Organileptic test

This test was conducted to observe and identify the organoleptic characteristics of the nanoemulsion. The parameters observed included color, odor, and clarity. The resulting nanoemulsion was dark green in color, had a pleasant aroma similar to pandan leaves, and appeared clear. The result is presented in Figure 1.

Figure 1. Organoleptic Test

This result is similar to the previous research conducted by Jusnita and Syurya (2019) in which the nanoemulsion was reported to be clear, brownish-green in color, and had a leafy aroma.

Clarity test

The clarity test was conducted to evaluate the transparency level of the formulated nanoemulsion. The clarity of the nanoemulsion is a parameter that indicates perfect dispersion (Ma'arif et al., 2023). The result is shown in Table 2.

The clarity of the nanoemulsion system occurs because the droplet size decreases, resulting in a reduction of the system's surface free energy.

Table 2. Clarity test

Nanoemulsion Formula	Transmittance percentage (%)
F1	80.2
F2	77.1

Notes:
F1 = soursop leaf extract 0.4 g: VCO 1.96 g: Tween 80 15.68 g: Propylene Glycol 1,96 ml: distill water added 100 ml:
F2= soursop leaf extract 0.4 g:
VCO 2.16 g: Tween 80 15.48 g: Propylene Glycol 1.96 ml: distill water added 100 ml

Physical stability test

This test used centrifugation to assess the thermodynamic stability of the nanoemulsion, so it can be stored for a long period without phase separation (Nasiro et al., 2023). The result is shown in Table 3.

Table 3. Physical stability test

Nanoemulsion Formula	Physical Stability
F1	No separation phase
F2	No separation phase

Notes:
F1 = soursop leaf extract 0.4 g: VCO 1.96 g: Tween 80 15.68 g: Propylene Glycol 1.96 ml: distill water added 100 ml:
F2= soursop leaf extract 0.4 g: VCO 2.16 g: Tween 80 15.48 g: Propylene Glycol 1.96 ml: distill water added 100 ml

The test result was categorized as good and stable, as there was no separation after centrifugation. This is consistent with previous research by Nasiro (2003), which stated that a nanoemulsion is considered good if no separation occurs.

Solubility Test

Solubility is one of the key parameters in achieving the therapeutic concentration of a drug in systemic circulation, which produces the desired pharmacological response (Dara and Husni, 2017). The results are shown in Table 4.

This test showed that the nanoemulsion was soluble in polar and semi-polar solvents, indicating that the formulation had polar characteristics. It also showed that the nanoemulsion system could increase the

solubility of lipophilic compounds (the chemical properties of substances that tend to dissolve in fats, oils, liquids, and non-polar solvents) in polar and semi-polar solvents, thus potentially increasing the bioactivity of the active compounds contained therein (Shakeel et al., 2012).

Table 4. Solubility test

Nanoemulsion	Solvent				
	1	2	3	4	5
F1	D	D	D	D	ND
F2	D	D	D	D	ND

Notes:
D = Dissolved; ND = Not Dissolved
1= distilled water ; 2= methanol ; 3= ethanol ; 4= ethyl ; 5= N-Hexane

Emulsion Type Test

The determination of the nanoemulsion type was conducted by adding methylene blue to the nanoemulsion. The emulsion was identified as an O/W type if the methylene blue dissolved and diffused throughout the entire nanoemulsion. In contrast, for the W/O type, methylene blue did not dissolve and instead clustered on the surface (Budiarto et al., 2021). The results are shown in Figure 2.

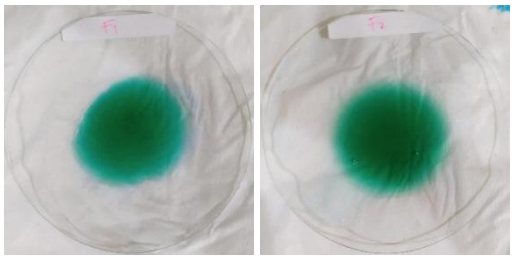

Figure 2. Emulsion type test

The results indicated that the nanoemulsion is O/W type, as shown by the methylene blue dissolving in the continuous (aqueous) phase, resulting in a blue-colored dispersion medium. Meanwhile, the dispersed phase droplets remained colorless., according to (Shakeel et al., 2012).

Storage Test

This test was conducted to evaluate the short-term stability of the nanoemulsion. It can accelerate potential changes that might occur under normal conditions. The results are shown in Table 5.

Table 5. Storage test

Notes	F1		F2	
	before	after	before	after
Clarity color	Green	Green	Green	Green
Odor	Characteristic	Characteristic	Characteristic	Characteristic
Separation phase	No	No	No	No
pH	4.17	4.5	4.06	4.6

The results showed that there were no observable changes in the nanoemulsion. This stability is attributed to the hydrophilic groups in the system, which became frozen at low temperatures. During the freeze-thaw process, these frozen hydrophilic groups returned to their original form, enabling them to surround and protect the droplets, thereby maintaining a high level of steric hindrance. The high steric hindrance prevented the droplets from merging, which contributed to the continued stability of the nanoemulsion (Budiarto et al., 2021).

The increase in pH after the freeze-thaw test was caused by several factors related to chemical stability and the physical system. One of the contributing factors was the degradation of the bioactive compound, which is acidic, due to exposure to extreme temperatures. This degradation process can produce neutral or basic compounds. Additionally, the release of ions from excipients such as non-ionic surfactants (e.g., Tween 80) during the freeze-thaw cycle also contributed to the increase in the pH system (Koroleva et al., 2018).

Droplet Size and Polydispersity Index Test

The nanoemulsion droplet size test was conducted to determine whether the formulation could be categorized as a nanoemulsion, characterized by droplet sizes smaller than 100 nm. Meanwhile, the polydispersity index test was carried out to assess droplet varieties (Rismarika, 2020).

The results from all tests showed that F1 exhibited better characteristics than F2. Therefore, F1 was selected as the most suitable candidate for the PSA test. The droplet size result of F1 is presented in Table 6.

Table 6. Droplet size and polydispersity index test (n = 3).

Replicate	Droplet size (nm)	Polydispersity Index
1	13.9	0.307
2	14.1	0.206
3	13	0.136
average	13.996	0.216

This result is consistent with previous research conducted by Budiarto et al. (2021). Their study showed that the nanoemulsion droplets were smaller than 100 nm, with a polydispersity index (PDI) value of less than 1, indicating a homogeneous droplet distribution.

Statistical comparison between the two formulas shows that F1 has superior physical performance compared to F2. The clarity value of F1 was recorded at 80.2%, higher than F2 which reached 77.1%, with a difference of 3.1% which illustrates a better level of light dispersion and a more homogeneous droplet distribution. The droplet size of F1 which is in the range of 13–14 nm (average 13.96 nm) indicates the successful formation of a stable nanoemulsion and is far below the nanoemulsion characterization limit (<100 nm). These results confirm that the combination of higher clarity and small droplet size makes F1 the formula with the most optimal characteristics compared to F2.

CONCLUSION

Methanolic extract of soursop leaves can be developed in the form of a nanoemulsion. Based on several tests, including organoleptic properties, solubility, emulsion type, storage stability, droplet size, and polydispersity index, the F1 formulation demonstrated the most optimal characteristics. The nanoemulsion produced had an average droplet size of 13.96 nm with a polydispersity index of 0.216, and showed good stability and homogeneity. It also exhibited an O/W type, which is appropriate for increasing the solubility of bioactive compounds in polar systems. These results indicate that F1 is the most potential formula for increasing the bioavailability of active compounds in soursop leaves and can be further developed as a candidate carrier system in pharmaceutical preparations.

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