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The Effect of Nanotechnology in the Formulation of Butterfly Pea Flower (*Clitoria ternatea*) Extract Cream on the Antibacterial Activity of Acne-Causing *Propionibacterium acnes*

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Abstract: Acne is a chronic inflammatory skin disease caused by the bacteria *Propionibacterium acnes*. Common therapy using topical antibiotics can cause resistance if used long term. It is necessary to develop therapy using natural ingredients of butterfly pea flower (*Clitoria ternatea*) which has the potential for antibacterial activity and is made into a cream formulation with nanoparticle technology that can increase drug bioavailability. This study used an experimental method with the stages of maceration extraction of butterfly pea flowers using 96% ethanol, making nanoparticle extracts using the ionic gelation method (sodium alginate and $CaCl_2$), and making nanocreams using the high-energy emulsification method. The formulation formulations consisted of formula 1 extract cream, formula 2 extract nanoparticle cream, and formula 3 butterfly pea flower extract nanocream with a concentration of 5%. Particle size characterization was carried out using the Particle Size Analyzer (PSA), while the antibacterial activity test was carried out using the well diffusion method against *Propionibacterium acnes* bacteria. The characterization results showed that the size of the extract nanoparticles was 378 nm, the extract nanoparticle cream was 4402 nm, and the nanocream was 465 nm. Physical evaluation showed that all three formulas met good standards and were classified as O/A type creams. The nanocream formulation had the highest antibacterial activity with an average inhibition zone of 6.3 mm (moderate category), while the extract cream and extract nanoparticle cream showed lower inhibition, 4.2 mm and 1 mm respectively (weak category), so that the telang flower extract nanocream formulation was the most effective in inhibiting the growth of *Propionibacterium acnes*.

Keywords: *Clitoria ternatea*, formulation, nanotechnology, nanoparticles, nanocream, *Propionibacterium acnes*, antibacterial.

INTRODUCTION

Acne (Acne vulgaris) is a common chronic inflammatory skin disease involving sebaceous glands, excessive bacterial colonization, and complex immune responses. This condition has a significant impact not only on aesthetic aspects but also on the psychosocial well-being of sufferers (Madelina & Sulistiyaningsih, 2018). In Indonesia, the prevalence of acne is very high, reaching 80–85% in adolescents and remains significant in the adult population, emphasizing the need for effective therapeutic solutions (Sibero *et al*., 2019). One of the main factors involved in the pathogenesis of acne is Propionibacterium acnes (now classified as Cutibacterium acnes), a skin commensal bacterium that triggers inflammation through the hydrolysis of triglycerides into free fatty acids (Leung *et al*., 2021).

Topical therapy is the first-line option for the treatment of mild to moderate acne. Reliance on topical antibiotics such as clindamycin and erythromycin has raised the issue of bacterial resistance, which reduces the effectiveness of treatment in the long term (Fox *et al*., 2016; Madelina & Sulistiyaningsih, 2018). This problem emphasizes the urgency of finding alternative antibacterial agents, especially from natural sources, to reduce the risk of side effects and resistance (Wardania *et al*., 2020).

Indonesia's biodiversity provides great potential for the development of natural medicinal ingredients, one of which is the butterfly pea flower (*Clitoria ternatea*). This plant is traditionally used because it has anti-inflammatory, analgesic, and antibacterial effects (Lijon *et al*., 2017). The content of bioactive compounds such as alkaloids, saponins, and flavonoids contributes to broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria. The mechanism of action includes disruption of peptidoglycan synthesis, increased cell membrane permeability, and damage to bacterial protein structures leading to growth inhibition and cell death (Febrianti *et al*., 2022; Widhowati *et al*., 2022; Pisacha *et al*., 2023). A study by Khumairoh (2020) showed that the ethanol extract of butterfly pea flowers had significant inhibitory power against P. acnes, indicating its potential use as a natural antibacterial agent.

Topical formulations such as creams are considered strategic in the use of plant extracts because of their ease of application and even distribution ability on the skin surface (Sulastri & Sari, 2016). Previous research on butterfly pea flower extract cream (Putri *et al*., 2022) revealed obstacles related to the large molecular size of the active compound, low solubility, and possible interactions with the cream base, which can affect antibacterial effectiveness.

The application of nanotechnology provides an innovative approach to overcome the limitations of conventional formulations. Reducing the size of extract particles to the nanometer scale has been shown to increase bioavailability, skin penetration, and effectiveness of active compounds, and even has the potential to reduce the risk of microbial resistance (Jahan *et al*., 2016; Mba & Nweze, 2021). Nanoparticle-based formulations, either in the form of nanoparticle extract creams or nanocream, are expected to optimize the delivery of active compounds of butterfly pea flowers to target P. acnes bacteria.

This study aims to formulate and evaluate the antibacterial activity of various nanotechnology-based butterfly pea flower extract cream formulations. Three types of formulations were compared, namely conventional extract cream, nanoparticle extract cream, and butterfly pea flower extract nanocream. All three used 96% ethanol extract of butterfly pea flowers with a concentration of 5%. Nanoparticles were formulated using the ionic gelation method using sodium alginate and calcium chloride ($CaCl_2$), while nanocream was prepared using a high-energy emulsification technique. Evaluation was carried out by testing the physical characteristics and antibacterial activity against Propionibacterium acnes using the well diffusion method. The results of this study are expected to provide scientific contributions in the development of more effective and sustainable acne therapy based on natural ingredients.

METHODS

This study is an experimental laboratory study using a quantitative approach. The purpose of this study was to determine the antibacterial activity of cream and nanocream formulations of butterfly pea flower extract (*Clitoria ternatea*) against Propionibacterium acnes. The research procedures included formulation of simplicial, extraction using the maceration method with 96% ethanol solvent, formulation of extract nanoparticles through the ionic gelation method with sodium alginate and calcium chloride ($CaCl_2$), formulation of cream and nanocream formulations, and evaluation of physical characteristics and antibacterial activity tests against P. acnes using the well diffusion method.

Tools and materials

The equipment used in the study included a blender, oven, analytical balance, rotary evaporator, UV-Vis spectrophotometer, micropipette, spectrophotometer, hotplate with magnetic stirrer, sonication bath, Particle Size Analyzer (PSA), and microbiology tools such as autoclave, incubator, laminar air flow cabinet, and petri dish.

The main ingredient used is fresh butterfly pea flower from Semarang City and botanically identified in the Biology Laboratory of FMIPA UNNES. The solvent used is 96% ethanol. Additional ingredients include sodium alginate, NaOH, $CaCl_2$, and Aquadest for making nanoparticles. The cream formulation formula consists of stearic acid, cetyl alcohol, triethanolamine (TEA), glycerol, methylparaben (nipagin), propylparaben (nipasol), and 2% erythromycin as a positive control. The culture medium used is Nutrient Agar, and P. acnes suspension is obtained from the FK Undip pure culture collection.

Research Procedures

Plant Identification and Material Collection

Plant identification and material collection were carried out in Semarang City, the parts of the plant identified were the flowers and leaves, after identification the entire plant was taken.

Determination of Butterfly Pea Plants

Determination of butterfly pea plants is done by observing all parts of the plant, including flowers, leaves, stems, and roots. The flowers that will be used in the study are purplish blue butterfly pea flowers.

Formulation of Butterfly Pea Flower Simple Powder

The butterfly pea flower raw material is collected and then wet sorted to separate dirt or other impurities. Then washed with clean water to remove soil, microbes and other dirt that sticks, then cut into small pieces, making it easier for the drying and smoothing process. Then the raw material is dried in an oven at a temperature of 50 ° C for 4 hours.

Drying is done to obtain a simple drug that is not easily damaged, so that it can be stored for a long time. Further dry sorting is done to separate foreign objects such as unwanted plant parts and other impurities that are

still present and left behind in the dry simple drug. Then the butterfly pea flower simple drug is ground using a blender until a powder form is obtained, then the dry weight of the simple drug powder is weighed.

Butterfly Pea Flower Simple Powder Extraction

500 grams of butterfly pea flower powder was put into a glass jar and 96% ethanol solvent was added (1:3), then covered with aluminum foil. After that, it was left for 24 hours and stirred 3 times repeatedly, then the maceration results were filtered using filter paper and the remaceration process was carried out on the dregs 2 times. Then all the filtrates obtained were collected. The 96% ethanol extract was evaporated using a rotary evaporator and concentrated with a water bath at 45 ° C, after obtaining the concentrated extract, the results of the resulting thick extract were weighed. Then the extract yield was calculated (Wijaya *et al*., 2018

Phytochemical Screening of Ethanol Extract of Butterfly Pea Flowers

Flavonoid Test

Weigh 0.5 grams of ethanol extract of butterfly pea flowers, add 1.5 mL of 96% ethanol, then add a little magnesium powder and 6 drops of concentrated hydrochloric acid, if there are flavonoid compounds, an orange-red color will form (Rismayuti *et al*., 2024).

Saponin Test

Weigh 0.5 grams of ethanol extract of butterfly pea flowers, add 2 mL of distilled water, then shake until foam forms. If there is a saponin compound, foam will form for 10 minutes and will not disappear if hydrochloric acid is dripped on it (Rismayuti *et al*., 2024).

Alkaloid Test

Weighed as much as 0.5 grams of ethanol extract of butterfly pea flowers then dissolved using hydrochloric acid. Next, the existing filtrate is filtered and given 2-3 drops of Mayer's reagent, if there is an alkaloid compound, a white or yellow precipitate will form. Then 2-3 drops of Dragendorff's reagent are added, if there is an alkaloid compound, a yellow - orange - red - brown precipitate will form (Rismayuti *et al*., 2024).

Determination of Total Flavonoid Content of Ethanol Extract of Butterfly Pea Flowers

A total of 10 mg of quercetin powder was dissolved in 10 mL of ethanol pa, from a solution of 1000 ppm concentration, a 100 ppm solution was made, and a series of concentrations of 2, 4, 6, 8, 10 ppm were made. The series of concentration solutions were added with 0.2 mL of 10% $AlCl_3$ and 0.2 mL of 1 M sodium acetate, after being left for 30 minutes, it was pipetted and then inserted into a microplate using a micropipette along with a blank (ethanol pa). Then the absorbance was measured and the maximum wavelength was determined at a wavelength of 400-800 nm. Take 10 mg of extract sample added with 10 mL of 96% ethanol, take 1 mL of 1000 ppm extract solution, then add 0.2 mL of 10% $AlCl_3$ and 0.2 mL of 1 M sodium acetate. After being left for 30 minutes, the absorbance of the reference solution was measured by UV-Vis Spectrophotometry of visible light at a previously measured wavelength. Then the total flavonoid content was calculated using a linear regression equation from the previously measured quercetin calibration curve (Styawan & Rohmanti, 2020).

Making of Butterfly Pea Flower Extract Nanoparticles

A 0.1% sodium alginate solution was made by dissolving 0.1 gr of sodium alginate powder in 100 mL of NaOH, then a 0.01% $CaCl_2$ solution was made by dissolving 0.01 gr of $CaCl_2$ powder in 100 mL of aquadest. A total of 0.5 gr of ethanol extract of butterfly pea flowers was dissolved and made up to 100 mL using aquadest. Furthermore, 4 mL of 0.1% sodium alginate solution was put into a vial then stirred, then 5 mL of butterfly pea flower extract was added and stirred for 30 minutes. Next, add 1 mL of 0.01% $CaCl_2$ solution to the mixture and stir again for 30 minutes. Then after the mixture is homogeneous, sonication is carried out for 60 minutes, the stirring and sonication process is carried out in 3 cycles (Ariani & Purwanto, 2021).

Characterization of Butterfly Pea Flower Extract Nanoparticles

The Particle Size Analyzer tool is prepared, then the settings are made on the tool. Furthermore, the extract of butterfly pea flower nanoparticles can be directly inserted into the cuvette until it is filled 2/3 of the cuvette. After that, the cuvette is inserted into the tool and closed with a sensor, the tool will produce particle size results in the form of numbers and graphs (Nuraeni *et al*., 2013).

Cream and Nanocream Formulation Formulation

The cream formulation formula, nanoparticle extract cream and ethanol extract nanocream of butterfly pea flower were obtained based on the formula in previous research with modifications (Andini & Raharjo, 2024):

Table 1. Modified Butterfly Pea Flower Extract Cream and Nanocream Formula

No.	Material	Function Material	Formula				
			I	II	III	K+	K-
1.	Extract Ethanol Butterfly Pea Flower	Active Ingredients	5%	-	5%	-	-
2.	Nanoparticle Extract Butterfly Pea Flower	Active Ingredients	-	5%	-	-	-
3.	Stearic Acid	Emulsifier	5%	5%	5%	-	5%
4.	Cetyl Alcohol	Thickener	0.2%	0.2%	0.2%	-	0.2%
5.	Glycerol	Emollients	1%	1%	1%	-	1%
6.	TEA	Emulsifier	0.4%	0.4%	0.4%	-	0.4%
7.	Nipagin	Preservative	0.02%	0.02%	0.02%	-	0.02%
8.	Nipasol	Preservative	0.01%	0.01%	0.01%	-	0.01%
9.	Aquades	Solvent	add 100%	add 100%	add 100%	-	add 100%
10.	Erythromycin	Comparator	-	-	-	Cream 2%	-

Information: FI: 5% concentration ethanol extract cream of butterfly pea flower; FII: 5% concentration of butterfly pea flower extract nanoparticle cream FIII: 5% concentration of butterfly pea flower ethanol extract nanocream K+: Positive control with 2% erythromycin cream; K-: Negative control with cream base

Making Nanocream from Butterfly Pea Flower Extract

Each ingredient in the formula was weighed, then the oil phase (stearic acid and cetyl alcohol) and the water phase (propyl, methyl, distilled water, TEA, and glycerol) were each heated on a hotplate. The oil phase and water phase were mixed using a mixer for 15 minutes, then the weighed ethanol extract of butterfly pea flowers was added and stirring was continued for 20 minutes, after which sonication was carried out for 30 minutes (Andini & Raharjo, 2024).

Making of Base, Extract Nanoparticle Cream and Ethanol Extract Cream of Butterfly Pea Flower

Each ingredient in the formula is weighed, then the oil phase (stearic acid and cetyl alcohol) and the water phase (propyl, methyl, distilled water, TEA, and glycerol) are each heated on a hotplate. The oil phase and water phase are mixed in a hot state using a mortar and pestle, after mixing, the weighed ethanol extract of butterfly pea flowers is added, then the cream mixing process is continued, as well as for the extract nanoparticle of butterfly pea flowers.

Characterization of Extract Nanoparticle Cream and Nanocream of Butterfly Pea Flower Extract

Dissolve the extract nanoparticle cream and nanocream of butterfly pea flower extract using distilled water as a dispersing agent. Furthermore, the Particle Size Analyzer tool is prepared and the settings are made on the tool. The solution of the extract nanoparticle cream and nanocream of butterfly pea flower extract is then put into the cuvette until it is filled 2/3 of the cuvette. After that, the cuvette is put into the tool and closed with a sensor, the tool will produce particle size results in the form of numbers and graphs (Nuraeni *et al*., 2013).

Evaluation of Physical Characteristics of Cream

Evaluation of the physical properties of cream and nanocream formulations was carried out to assess the pharmaceutical quality and stability of the resulting formulations. Organoleptic examination includes visual observation of the color, odor, and form of the formulation to ensure uniformity of physical appearance. Homogeneity testing was carried out by applying a thin layer of the formulation to a glass slide to observe the uniformity of distribution of the active ingredient and carrier; the formulation was declared homogeneous if no coarse grains or color gradation were found. pH measurements were carried out on 1 gram of the formulation that had been diluted in 10 mL of aquadest, then dipped in pH paper, to ensure that the pH value was within a safe range

for the skin (pH 4.5–6.5). Spreadability testing was carried out by placing 1 gram of the formulation in the center of the glass slide, then covered with another glass slide and given a load weighing 200 grams for one minute. The diameter of the spread formed was measured to assess the ability of the formulation to spread on the skin surface. The adhesion test is carried out by clamping the formulation between two glass objects, then given a load of 150 grams for five minutes, and the time required for the two glasses to separate is recorded as an indicator of the formulation's adhesion to the skin. Determination of the emulsion type is carried out by dripping methylene blue dye solution on the surface of the formulation; if the color spreads evenly, then the formulation is categorized as an oil-in-water emulsion (O/W), while if it does not mix, then it is included in the water-in-oil (W/O) type.

Antibacterial Activity Test

Antibacterial activity tests are carried out through several standardized stages. Sterilization of tools and materials is carried out using the wet heat method with an autoclave at a temperature of 121°C for 20 minutes, while the loop needle is sterilized by being heated on a Bunsen burner (Bassy *et al*., 2023). The formulation of Nutrient Agar (NA) media is carried out by dissolving 11.5 grams of NA powder in 500 mL of distilled water, stirring using a hotplate with a stirrer until completely dissolved, then sterilized using an autoclave at a temperature of 121°C for 20 minutes. After that, 20 mL of the media is poured into each sterile petri dish and stored in the refrigerator (Bassy *et al*., 2023). Bacterial rejuvenation was carried out using the scratch method, namely by inoculating one loop of pure Propionibacterium acnes culture in a zigzag manner on NA media aseptically, then incubating at 37°C for 24 hours (Noviyanti & Sumiati, 2016). To make a test bacterial suspension, one loop of bacterial colonies was taken with a sterile loop needle and then suspended in 10 mL of 0.9% NaCl infusion solution and homogenized using vortex. The turbidity of the suspension was then adjusted to the McFarland standard of 0.5 (Halimathussadiah *et al*., 2021). The antibacterial activity test was carried out in a laminar air flow cabinet that had been turned on previously. The test bacterial suspension was inoculated onto the entire surface of the solid NA media using a sterile cotton swab until evenly distributed. Furthermore, five wells were made in the media using a cork borer, then each well was filled with test formulation, positive control, and negative control. The petri dishes were then incubated in an incubator at 37°C for 24 hours. Antibacterial activity was determined based on observations of the diameter of the inhibition zone (clear zone) formed around the well (Lukman La Bassy *et al*., 2022).

Data analysis

Antibacterial activity test was analyzed statistically using SPSS One Way ANOVA data processing program if both requirements (normality and homogeneity) were met. If the requirements of One Way ANOVA test were not met, statistical analysis was used with Kruskal-Wallis test and continued with Duncan test to determine significantly different cream formulas. Data analysis used SPSS version 16.0 application.

RESULT AND DISCUSSION

Butterfly Pea Flower Simple Powder Extraction

The extraction process begins with cleaning and sorting fresh flowers, followed by drying using an oven at 50°C for 4 hours, then ground to increase the efficiency of the extraction process. The maceration method is used with 96% ethanol solvent, because this solvent is semi-polar and can extract active compounds such as flavonoids and anthocyanins. Maceration was carried out for three days, repeated twice, and produced a total of 4.5 liters of filtrate. The filtrate was evaporated using a rotary evaporator and thickened in a water bath at 45°C, producing a thick blackish green extract with a distinctive aroma and a yield of 28.4%. This yield is quite high and indicates the success of the extraction process and a high content of active metabolites.

Phytochemical Screening of Ethanol Extract of Butterfly Pea Flowers

The secondary metabolite compounds of ethanol extract of butterfly pea flowers screened in this study were flavonoids, saponins, and alkaloids. The secondary metabolite compounds were selected based on previous studies which stated that these compounds have antibacterial activity in butterfly pea flower extract (Febrianti *et al*., 2022). The results of the phytochemical screening carried out were in accordance with the literature obtained (Hataningtyas *et al*., 2024).

Table 2. Phytochemical Screening Results of 96% Ethanol Extract of Butterfly Pea Flowers

Chemical Content	Colors Formed	Information
Flavonoid	red	+
Saponins	foamy	+
Alkaloid	Mayer's reagent: white precipitate Dragendorff's reagent: red precipitate	+

Determination of Total Flavonoid Content of Ethanol Extract of Butterfly Pea Flowers

After the phytochemical screening test was carried out, the next procedure was to determine the total flavonoid content in the extract. The standard used in this study was quercetin, this is because quercetin is the most widely distributed compound in plants (Styawan & Rohmanti, 2020). The maximum wavelength was read in the range of 300-800 nm, and the maximum wavelength of quercetin was 424 nm. The results obtained are in accordance with the literature obtained and meet the requirements for the maximum wavelength range of quercetin, which is 400-450 nm (NWL Puspitasari *et al*., 2024).

Furthermore, the absorbance measurements of the quercetin series and blank solutions were carried out and a linear regression equation was obtained, namely y = 0.0241x - 0.0233 with an R2 value of 0.9722. The R value approaching 1 can be interpreted that there is a good and linear relationship between the concentration value and the absorbance value (Sixca *et al*., 2023).

Table 3. Results of Total Flavonoid Content of Ethanol Extract of Butterfly Pea Flowers

Absorbance	Concentration		FP	KTF mgQE/g
	µg/mL	mg/mL		
0.13	6,3610	0.0064	1	6.4
0.14	6,776	0.0068	1	6.8
0.14	6,776	0.0068	1	6.8
Average Standard Deviation				6.7 ± 0.2345

The results of the absorbance values were then calculated for concentration and the results were 6.3610 ppm, 6.776 ppm, and 6.776 ppm. Furthermore, the concentration was converted into mg/mL units to calculate the total flavonoid content and the results were 0.0064 mg/mL, 0.0068 mg/mL, and 0.0068 mg/mL. The results of the calculation of the total flavonoid content obtained were 6.7 ± 0.2345 mgQE/g. The total flavonoid content obtained from the study was greater when compared to the literature, which was 2.8107 mgQE/g (NWL Puspitasari *et al*., 2024). These results are influenced by the solvent factor used, in the study 96% ethanol was used while in the literature 70% ethanol was used.

Differences in ethanol solvent concentration can affect the polarity level of a solvent and can affect the solubility of flavonoid compounds in the solvent. To obtain the most effective levels of flavonoid compounds in the butterfly pea flower (*Clitoria ternatea*) extraction process is to use 96% ethanol solvent. The results of the study are in accordance with the literature which states that 96% ethanol solvent is said to be the best for producing total flavonoid compound levels (Pujiastuti & El'Zeba, 2021).

Butterfly Pea Flower Extract Nanoparticles

The manufacture of nanoparticles from butterfly pea flower extract in this study used the ionic gelation method with sodium alginate polymer and CaCl2. The ionic gelation method was chosen because it has the potential to be used in various things, for example in the pharmaceutical, cosmetic, and food sectors. In addition, the ionic gelation method is simple and the materials used are also easy to obtain (Latupeirissa *et al*., 2022). Sodium alginate polymer was chosen because its use has not been widely carried out, besides sodium alginate has neutral properties (does not have antibacterial activity against Propionibacterium acnes) (Friedman *et al*., 2012). Because the research conducted was an antibacterial activity test, a polymer that was neutral was chosen so that it would not affect the results of the antibacterial activity test.

The selected polymer pair is CaCl2 solution based on the reference that this compound can improve the stability of nanoparticles. Because Ca2+ ions react with alginate and form a strong and stable three-dimensional network structure, it can increase stability and prevent aggregation in particles (Maharani *et al*., 2022). The reason for choosing the CaCl2 concentration in the formulation is that in previous studies, a CaCl2 concentration of 0.01% produced a smaller particle size when compared to a concentration of 0.4% (Ngafif *et al*., 2022). A higher concentration of CaCl2 can reduce the surface charge and increase the occurrence of aggregation in particles. The nanoparticle formula in this study refers to research (Ariani & Purwanto, 2021) which found that the optimal

concentration ratio for ethanol extract is 0.1% sodium alginate and 0.01% CaCl2.

The ratio of the nanoparticle extract made is 4:1:5 (sodium alginate : CaCl2 : ethanol extract of butterfly pea flower), the nanoparticles are made with the help of a stirrer to ensure the polymer and solution are mixed well. The stirrer can also help break up large aggregates to produce smaller particles. Next, a sonication process is carried out with the aim of homogenizing the size and making the particle size smaller compared to without using the sonication method (Delmifiana & Astuti, 2013). The process of making nanoparticles begins with making a 0.1% sodium alginate solution by dissolving 0.1 gram sodium alginate powder using NaOH and making up to 100 mL. NaOH functions as a base that ionizes the carboxyl group in sodium alginate into an anion form that is more water soluble and interacts more easily with nanoparticles.

The next step is to make a $CaCl_2$ solution with a concentration of 0.01%, by weighing 0.01 grams of $CaCl_2$ powder then dissolving it and adding 100 mL to distilled water. Ethanol extract of butterfly pea flowers is weighed as much as 0.5 grams then dissolved in distilled water and added to 100 mL. The mixing process begins by adding 4 mL of sodium alginate solution and 5 mL of butterfly pea flower extract solution then stirred using a stirrer for 30 minutes. When the stirring process is carried out, the container is covered with aluminum foil to avoid evaporation and wasting of the solution. Next, 1 mL of $CaCl_2$ solution is slowly added and stirred again for 30 minutes.

After that, the solution was taken and put into a sonicator for one hour to help the particles break down faster and become more homogeneous. This process was carried out in three cycles with a total time of 3 hours for stirring with a stirrer and 3 hours for sonication. The cycles carried out are expected to maximize the results of particle size gradually and increase the efficiency of nanoparticle formation (Maharani *et al*., 2022). Organoleptically, the results of the nanoparticle extract formed were a light green liquid, clear without sediment, and had a distinctive odor. These results must be stored first before the particle size test is carried out because the particles formed are not stable after the stirring and sonication process is carried out. The nanoparticles made are stored in the refrigerator to avoid aggregation and changes in particle size before the particle size is tested later (NI Putri *et al*., 2024).

Characterization of Butterfly Pea Flower Extract Nanoparticles

Particle size testing is important in nanotechnology manufacturing because it can see the properties of the material and ensure the safety and effectiveness of nanotechnology applications. Smaller particle sizes produce larger surface areas and volumes, thus producing greater activity potential (Ngo, 2022). The previously made nanoparticles are inserted into the cuvette until it is 2/3 full, because it is already in solution form, aquadest is no longer used as a dispersing agent. After the cuvette is inserted into the device and the computer is operated, measurements will be carried out by utilizing the principle of light scattering using the dynamic light scattering method (Jia *et al*., 2023).

The advantages of nanoparticles measured by the dynamic light scattering (DLS) method are the ability to analyze very small particles and measurements in a wide concentration range (Jia *et al*., 2023). The particle size results obtained in the study were 378 nm. The results obtained are within the range of the literature, namely <500 nm for nano sizes intended for drug delivery (Zeb *et al*., 2019). Particle size is very important to ensure the effectiveness and stability of the formulation. Sizes that are too small can cause aggregation and cause uncontrolled drug release, while sizes that are too large can reduce bioavailability and drug delivery efficiency (Wilar *et al*., 2024).

Formulation of Formulations

Three cream formulations were developed, namely extract cream (Formula 1), extract nanoparticle cream (Formula 2), and extract nanocream (Formula 3). All formulas used a 5% extract concentration. Cream was chosen as the dosage form because it has a longer contact time with the skin, increasing the effectiveness of the active compound (Milanda *et al*., 2021). The formulated cream is an oil-in-water (O/W) type, which is light, easily absorbed, and non-sticky. Nanocream was made by adding a sonication process for 30 minutes after mixing, aiming to maintain the particle size in the nano range. PSA characterization showed that the extract nanoparticle cream (Formula 2) had a particle size of 4402 nm, far above the nano size, indicating particle aggregation. In contrast, the extract nanocream (Formula 3) had a particle size of 465 nm, which is still included in the nano category and shows better formulation stability.

The previously prepared extract nanoparticle cream and nanocream were first dispersed using distilled water so that the measurement results would be more accurate. Then it was put into a cuvette until it was 2/3 full, after which the particle measurements were carried out again by utilizing the principle of light scattering using the dynamic light scattering method (Jia *et al*., 2023). The results of the size of the extract nanoparticle cream obtained were 4402 nm, while for the nanocream formulation the results were 465 nm. The results of the nanocream size obtained were within the range of the literature, namely <500 nm for the nano size intended for drug administration (Zeb *et al*., 2019). Nano formulations have the advantage of being able to increase the effectiveness of the formulation and reduce side effects (Pudyastuti *et al*., 2023).

Physical Properties Test of Cream

Organoleptic Test

Table 4. Results Organoleptic Test of Formulations

Observation	Base	Formula 1	Formula 2	Formula 3
Color	White	Dark Green	Greenish White	Light green
Smell	-	distinctive smell extract	distinctive faint odor extract	distinctive smell extract
Form	semi solid	semi solid	semi solid	semi solid

Organoleptic tests are carried out by observing the cream formulation that has been made including color, odor, and shape. The color and odor results obtained from the entire formula are influenced by the form of extract used and the method of making the formulation. Because the color of the extract is blackish green, when mixed with a white base it changes to dark green, while for the nanocream formulation it becomes light green due to the influence of the stirring process. The cream formulation with nanoextract is greenish white because the extract used is already in liquid form.

Homogeneity Test of Formulations

Table 5. Homogeneity Test Results of Formulations

Formula	Homogeneity	Literature
Base	Homogeneous	Homogeneous
Formula 1	Homogeneous	Homogeneous
Formula 2	Homogeneous	Homogeneous
Formula 3	Homogeneous	Homogeneous

Homogeneity test is conducted to determine whether the active ingredients of the formulation and the base have been mixed well (Arifin *et al*., 2023). A cream formulation is said to be homogeneous if there are no visible particles that clump or do not mix. The physical characteristics of a homogeneous cream can ensure a more even distribution of the formulation on the skin, so that the active ingredients become more effective and prevent irritation (Wijayanti *et al*., 2014).

pH Test of Formulation

Table 6. Formulation pH Test Results

Formula	pH	Literature
Base	6	4.5 – 6.5
Formula 1	6	4.5 – 6.5
Formula 2	7	4.5 – 6.5
Formula 3	6	4.5 – 6.5

The pH test of the formulation was carried out to ensure that the cream made was safe and did not cause skin irritation. A good pH value for topical formulations is 4.5 - 6.5. A pH value that is too acidic will cause skin irritation, while if it is too alkaline, the skin will become scaly or dry (Pratasik *et al*., 2019). The increase in pH that occurred in formula 2 was caused by the addition of a basic NaOH solution during the process of making extract nanoparticles.

Spreadability Test of Formulation

Table 7. Spreadability Test Results of Formulations

Formula	Spread Power (cm)	Literature (cm)
Base	6	5 – 7
Formula 1	5.5	5 – 7
Formula 2	5.55	5 – 7

The cream spreadability test is carried out to determine the ability of the formulation to spread on the skin. If the cream spreadability is good, the contact of the formulation on the skin becomes wider and the absorption process becomes faster (Pratasik *et al*., 2019).

Adhesive Power Test of Formulations

Table 8. Results of the Adhesion Test of the Formulation

Formula	Adhesion (seconds)	Literature (sec)
Base	3.28	2 – 300
Formula 1	4.88	2 – 300
Formula 2	3.67	2 – 300
Formula 3	3.50	2 – 300

The adhesion test of the formulation is carried out to determine the ability of the cream to stick to the skin. Good adhesion ensures that the cream does not come off easily or disappear during use. Based on the literature obtained, a cream that adheres well can help achieve the desired effect (Tari & Indriani, 2023).

Cream Type Test

Table 9. Cream Type Test Results

Formula	Cream Type	Literature
Base	M/A	M/A
Formula 1	M/A	M/A
Formula 2	M/A	M/A
Formula 3	M/A	M/A

The cream formulation type test was carried out to determine the type of cream made, whether it was O/W or A/M. The reagent used in this study was methylene blue, if the cream was evenly mixed in the reagent, the cream type was O/W. The results obtained in the study were the O/W cream type, because the amount of oil phase (dispersed phase) was less than the water phase (dispersing phase). The O/W cream type is often used in cosmetic formulations because it is lighter, non-sticky, and easy to clean (Kumalasari *et al*., 2020).

Based on all the cream properties tests conducted on the extract nanoparticle cream (formula 2) and nanocream (formula 3), it can be interpreted that with the influence of nanotechnology, cream can be formulated into a formulation that has good physical characteristics.

Antibacterial Activity Test

The antibacterial activity test of Propionibacterium acnes carried out in this study was the well diffusion method with nutrient agar media. The reason for choosing the well diffusion method is because it provides a more accurate picture of antibacterial activity. This is because the results of the diameter of the inhibition zone formed in the media become easier to measure, because the formulation has activity not only on the agar surface (Kirtanayasa, 2022). Nutrient agar media was chosen because it has sufficient nutritional content for the growth of Propionibacterium acnes bacteria and is the most common and practical media as a test medium (Retnaningsih *et al*., 2019). The positive control used in this study was 2% erythromycin cream which was selected and adjusted based on the form of the formulation to be tested. Another reason is based on the literature, the first line of acne treatment is topical formulations and the most commonly given is in the form of antibiotics (Sibero *et al*., 2019).

Table 10. Antibacterial Activity Test Results

Formulation	Replication	Zone Diameter Resistance (mm)	Average (mm)
Positive Control	1	20	18.7 (strong)
	2	18	
	3	18	
Negative Control	1	0	0 (none)
	2	0	
	3	0	
Formula 1	1	3.5	4.2 (weak)
	2	5	
	3	4	
Formula 2	1	1	1 (weak)
	2	1.3	
	3	0.7	
Formula 3	1	5	6.3 (moderate)
	2	6	
	3	8	

The antibacterial activity test conducted in the next study was processed using the SPSS application. The results of the data obtained were tested for normality and homogeneity first. The results of the homogeneity test obtained were <0.05, which means that the data is distributed inhomogeneously, so the data will be tested using the Kruskal-Wallis test. The results obtained are sig. <0.05, so it can be concluded that there is at least one significant difference between the formulas tested. Furthermore, the Duncan test was carried out to determine which formulas had significant differences.

Table 11. Duncan Test Results Antibacterial Activity

Formula		1	2	3	4
Cream Base	3	,000			
Formula 2	3	1,000			
Formula 1	3		4,167		
Formula 3	3			6,333	
Positive Control	3				18,667
Sig.		,218	1,000	1,000	1,000

Based on the data in the table, it can be said that formula 2 and the base are included in the same group and there is no significant difference. This means that the nanoparticle cream formulation of butterfly pea flower extract has less antibacterial activity of Propionibacterium acnes. Based on the literature that is the reference for this study, antibacterial activity is not optimal because the difference in polymers used (Damanis *et al*., 2019). Antibacterial activity can also be less than optimal because if in the literature the extract nanoparticles are used directly, but in this study the extract was added to the cream base, so that the effectiveness was reduced (Deniyati & Priscilly, 2023). So it can be said that the form of nanotechnology in the extract is not suitable for use in cream formulations that have antibacterial activity.

The data results in the table also show that formula 3 has significantly different antibacterial activity. This means that the butterfly pea flower nanocream formulation has the most effective antibacterial activity of Propionibacterium acnes when compared to formulas 1 and 2. When compared to the previous extract nanoparticle cream formulation, the differences that can be taken are the concentration of the extract used and the method of making the formulation. The nanocream made as a whole has a small particle size, while the size of the extract nanoparticles in the cream has changed due to the addition of the formulation excipients. The results obtained are in accordance with the literature which states that with nano size, the effectiveness of the formulation can increase and become more optimal (Nurayu *et al*., 2023).

CONCLUSION

Based on the results of the study, it can be concluded that the formulation of butterfly pea flower extract cream formulated with nanotechnology has good physical characteristics and meets the requirements of topical formulations. Antibacterial activity tests against *Propionibacterium acnes* showed that the butterfly pea flower extract cream formulation had a weak inhibitory power of 4.2 mm, the extract nanoparticle cream showed a very weak inhibitory power of 1 mm, while the nanocream formulation showed an inhibitory power in the moderate category of 6.8 mm. These results indicate that the butterfly pea flower extract nanocream formulation has a significantly higher antibacterial effectiveness compared to the extract cream and nanoparticle cream formulations, so that the nanocream formulation shows superior potential as an antibacterial formulation against *P. acnes.*

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CONFLICT OF INTEREST

We declare that we don't have any conflict of interest.

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