Vol. 2 No. 1 2025 || E-ISSN 2997-7258

The Journal of Academic Science

journal homepage:
https://thejoas.com/index.php/

Formulation, Physical Stability Test, and Irritation Test of Gambir (Uncaria Gambir Roxb.F) Leaves Extract Nanogel Medicine

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KEY W O R D S

Gambir leaves,
Nanogel, Concentration,
Physical Stability Test

A B S T R A C T

Gambir leaves (Uncaria gambir Roxb.) are widely available in Indonesia, especially on the island of Sumatra. Gambir leaf extract (Uncaria gambir Roxb.) if used topically is less desirable by the public because it smells languorous or herbal. In addition, secondary metabolites of catechins found in gambier leaves have low bioavailability. Nanogels are nanoscale particles produced by three-dimensional cross-linked polymers with hydrophilic or amphiphilic macromolecular chains that can be ionic or non-ionic. This research began with making gambier leaf extract which was then made into nanogel preparations with concentrations of 1%, 2% and 3%. Physical evaluation of nanogel preparations in the form of organoleptic, homogeneity, pH, adhesion, viscosity, particle size and zeta potential. The results obtained were a brownish orange nanogel preparation with a pH between 4.5 to 6.5 and was homogeneous. The highest adhesion results were found at F3 (1.752 ± 0.037) cm with a zeta potential value and particle size of 30.6 ± 0.17 mV 142.567 ± 0.3055 nm. The conclusion obtained in this research is that the 3% concentration of gambier leaf extract nanogel preparation has the best results in terms of physical evaluation compared to other concentration nanogel preparations.

1. Introduction

Gambir leaves (Uncaria gambir Roxb.) are widely available in Indonesia, especially on the island of Sumatra. Empirically, many people use gambier leaves as a traditional medicine to reduce heat in children, traditional medicine for diarrhoea, traditional medicine for throat or cough, as a food preservative and an addition to betel nut. Research by Isriza and Minda (2022) states that gambier is one of the native Indonesian plants that contains high levels of catechins. Catechins are very potential to be used for medicinal raw materials because of their proven effects as antibacterial, antiviral, and antidyslipidemia. Catechins have positive effects on human health and are not potentially mutagenic.

Kurniatri et al (2019) stated that catechins and their derivatives can be useful as high antioxidants which can be used as antibacterial and antiviral. Catechins from gambir can also be developed for its potential as antidyslipidaemia. Preclinical studies have shown a positive correlation between catechin consumption in green tea and heart health through many mechanisms, namely antioxidation, antihypertension, anti-

inflammatory, antiproliferation, antithrombogenic, and lowering fat levels.

Gambir leaf extract (Uncaria gambir Roxb.) if used topically is less desirable by the public because it smells languorous or herbal. In addition, secondary metabolites of catechins found in gambier leaves have low bioavailability. Nanogels are nanoscale particles produced by three-dimensional cross-linked polymers with hydrophilic or amphiphilic macromolecular chains that can be ionic or non-ionic. Nanogels consist of various natural polymeric materials, synthetic polymers, or combinations thereof that play a role in the encapsulation of small molecular particles, oligonucleotides, and proteins (Yin at al, 2020). Nanogels are often used in drug delivery systems especially in cancer therapy, local anaesthesia, bone regeneration, antibacterial, antimicrobial, and anti-inflammatory.

The advantages of nanogel preparations compared to other conventional preparations are precise drug delivery, enabling more targeted drug delivery, good drug stability of nanogel preparations can protect the drug from degredation before reaching its target, increased bioavailability the small size of nanogels enables increased bioavailability of the drug by improving absorption and distribution in the body. Nanogels can be designed to release drugs gradually, providing better control of drug release in the body, tissue penetration the small size of nanogel preparations allows better penetration into biological tissues reaching target areas that are difficult to reach, biocompability nanogel preparations generally have a high degree of biocompatibility thus minimising adverse reactions in the body, improved therapeutic efficiency with advanced delivery capabilities nanogel preparations can improve the therapeutic efficiency of drugs and can reduce the dose required, multi-functional applications of nanogel preparations are designed to carry more than one type of drug or bioactive ingredient which increases the ability of combination therapy, reduced drug side effects nanogel preparations are designed to go directly to where it is needed and can help reduce side effects associated with high doses, innovations in therapeutic nanogel preparations continue to inspire innovation in the field of drug therapy and medical diagnosis (Maniraman et al., 2023).

Baharlouei and Rahman (2022) stated that the use of synthetic drugs is still the main choice, while the use of natural ingredients as wound medicines is still rarely optimised into pharmaceutical preparations. For this reason, researchers are interested in formulating gambier leaf extract into nanogel preparations and conducting physical stability tests and irritation tests.

2. Methodology

2.1. Preparation of Simplified Leaf Powder

Fresh gambier leaves were washed, then separated from the twigs, and dried in a drying cabinet at 30-40oC for 5 days or until the leaves were dry enough. The dried leaves are then ground into powder and sifted with a 40 mesh sieve (Indonesian Herbal Pharmacopoeia Second Edition 2017).

2.2. Preparation of Gambir Leaf Ethanol Extract

Gambir leaf powder of 5000 g was extracted using 96% ethanol solvent (in order to filter most of the secondary metabolites contained in the simplisia powder) of 20,000 mL. Soaked for the first 6 hours while occasionally stirring, then allowed to stand for 18 hours. Separated the maserat by filtration. The process was repeated twice with the same type of solvent and the amount of solvent volume was half the amount of solvent volume in the first extract. Collected all the maserat, then evaporated with rotavapor, until a thick extract was obtained. (Indonesian Herbal Pharmacopoeia Second Edition 2017).

2.3. Determination of Total Flavonoid Content of Gambir Leaf Extract Using HPLC (High Performance Liquid Cromatography)

2.3.1. Determination of Mobile Phase

The mobile phase to be used is a mixture of 25% distilled water in 75% methanol.

2.3.2. Preparation of catechin standard solution

Weighed 10 mg of catechin then dissolved in a 100 ml flask with ethanol solvent, thus obtaining 1000 ppm mother liquor. Taken 10 ml of 1000 ppm mother liquor and diluted into a 50 ml flask. Dilution was carried out to obtain a series of standard solutions of 100; 50; 25; 10; and 5 ppm in a 25 ml flask with ethanol solven.

2.4. Nanogel Formulation

Nanogel preparations of gambier leaf extract can be seen in the following Table 1.

Table 1 Gambir Leaf Extract Nanogel Formulation

Ingredients	F 0	F 1 (g)	F 2 (g)	F 3 (g)
GLEE	-	1	2	3
Carbhopole 940	1	1	1	1
Prophylenglycol	5	5	5	5
Methyl paraben	0.5	0.5	0.5	0.5
Prophyl paraben	0.02	0.02	0.02	0.02
TEA	0.3	0.3	0.3	0.3
Tween 80	0.5	0.5	0.5	0.5
Aquades	100	100	100	100

2.5. Preparation Procedure of Gambir Leaf Extract Nanogel

Making the gel base and then making the emulsion and combining the two to form the nanogel are the three main steps in making the nanogel formulation. Carbopol 940 was chosen as the gelling agent and developed using hot distilled water and then crushed in a mortar until homogeneous. Then methyl paraben and propyl paraben were added as preservatives to the nanogel preparation. Next, an emulsion was made consisting of an oil or organic phase and an aqueous phase. The organic phase consisted of gambier leaf extract dissolved in distilled water, and propylene glycol added and mixed using a magnetic stirrer for 15 minutes at 350C with a speed of 1000 rpm. The aqueous phase consists of Tween 80 dissolved in distilled water mixed using a magnetic stirrer for 1 hour at 350C with a speed of 1000 rpm. Then the organic phase was dispersed into the water phase and TEA was added. Stirred with a magnetic stirrer for 1 hour at 350C with a speed of 1000 rpm to form an emulsion. The emulsion formed from the combination of the organic phase and the aqueous phase was subjected to particle size analyser (PSA) to determine whether the emulsion had a nano size. After obtaining good PSA test results, the nanoemulsion that has been formed is re-dispersed in the gel base to become a nanogel (Harahap, 2021).

2.6. Physical Evaluation of Nanogel Preparation

Physical evaluation of nanogel preparations in the form of organoleptic, homogeneity, pH, adhesion, viscosity, particle size and zeta potential.

2.7. Irritation Test of Gambir Leaf Extract Nanogel Formula

The irritation test was performed by shaving the hair on the rabbit's back until it was clean. After that, the animal's back was divided into 4 square sections with a size of 1x1 inch each. Before applying the test material, the rabbit skin was cleaned using a cotton swab soaked in distilled water. The cotton swab was applied with gambier leaf extract nanogel, then attached to the rabbit's back and covered with thin plastic and plaster for 24 hours. After that, the test animals were returned to their cages. The next day at the same hour, the plaster was removed and the skin of the test animals was cleaned with distilled water

from the remaining test compounds. The symptoms observed were primary irritation in the form of erythema and oedema for 24 hours, 48 hours, and 72 hours. At the time of observation of the primary irritation test, the irritation was read in the form of oedema and erythema. Each test material was calculated with the primary irritation index calculation formula (Lu, 1995).

$$\text{Primary Irritation Index} = \frac{\Sigma \text{ etythema score} + \Sigma \text{ erythema score}}{2}$$

Description:

Erythema score = sum of erythema scores (24 hours + 48 hours + 72 hours)

Edema score = sum of edema score (24 hours + 48 hours + 72 hours).

3. Result and Discussion

3.1 Results of Simplisia Characteristic Examination

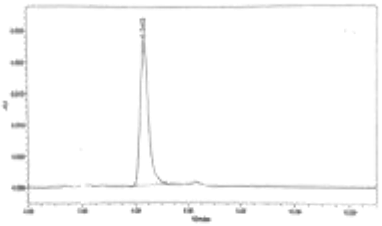
The results of the examination of simplisia characteristics, namely water content, ash content, acid insoluble ash content, water soluble juice content, ethanol soluble juice content. The results of the simplisia characteristics can be seen in Table 2 below.

Table 2 results of examination of simplisia characteristics

Determination of simplisia content	FHI (%)	Gambir Leaf Simplisia Result (%)
Determination of moisture content	<10	8.70
Determination of ash content	<10	4.732
Determination of acid insoluble ash content	<0.7	0.597
Determination of water soluble essence content	>18	44.28
Determination of ethanol soluble essence content	>8	15.09

3.2. Peak area and retention time of catechin standard at 10% concentration

Determination of peak area and retention time at 10% concentration obtained based on HPLC (High-Performance Liquid Chromatography) testing. The results of peak area and retention time can be seen in Figure 1 below.



Peak #	Ret. Time	Area	Heigh	Conc.%	Name	Unit
1	4.940	0.015	262911	10	Katekin baku	
Total						

3.3. Determination Result of Calibration Curve for Catechin of Gambir Leaf Extract

The determination of the calibration curve of gambier leaf extract begins with the measurement of the standard comparator of catechin compounds with concentrations of 5, 10, 25, 50, and 100 ppm. The results of the calibration curve obtained based on HPLC (High-Performance Liquid Chromatography) testing obtained the area. The results of the calibration curve and the area of the standard comparator can be seen in Table 3 below.

Table 3 Results of calibration curve determination of gambier leaf extract catechins

Concentration (mcg/ml)	Area
5	0.013
10	0.015
25	0.018
50	0.02
100	0.024

3.4. Antioxidant Test of Total Flavonoid Level of Gambir Leaf Ethanol Extract Nanogel Preparation

The total flavonoid content of gambier leaf nanogel extract and preparation was determined based on the regression equation of the standard catechin. The regression equation is y = 0.000107x + 0.01393, with a value of R = 0.9655. The total flavonoid content of the extract and nanogel preparation can be seen in Table 4 below.

Table 4 Antioxidant test results of total flavonoid content of gambier leaf ethanol extract nanogel preparation

Formula	Average ± SD
Gambir leaf extract	2095.985 ± 208.399
Gambir leaf extract nanogel at 1% concentration	1160.578±195.466
Extra gambier nanogel at 2% concentration	1633.266±350.539
Gambir leaf extract nanogel at 3% concentration	1783.389±345.804

3.5. Organoleptic Test Results of Gambir Leaf Ethanol Extract Nanogel Preparation

The results of the Organoleptic Test of Gambir Leaf Ethanol Extract Nanogel Preparation can be seen in Table 5 below.

Table 5 Organoleptic Test Results of Gambir Leaf Extract Nanogel

Storage Duration (week)	Organoleptic								
	Colour			Smell			Shape		
	F1	F2	F3	F1	F2	F3	F1	F2	F3
0	J	JK	JM	Kh	Kh	Kh	SK	SK	SK
1	J	JK	JM	Kh	Kh	Kh	SK	SK	SK
2	J	JK	JM	Kh	Kh	Kh	SK	SK	SK
3	J	JK	JM	Kh	Kh	Kh	SK	SK	SK
4	J	JK	JM	Kh	Kh	Kh	SK	SK	SK

Description:

F1 : Nanogel 1 gram gambier leaf ethanol extract
F2 : Gambir Leaf Ethanol Extract Nanogel 2 grams
F3 : Gambir Leaf Ethanol Extract Nanogel 3 grams
J : Orange
JK : Brownish Orange
JM : Reddish Orange
Kh : Typical
SK : Slightly Thick
K : Thick.

3.6. Homogeneity Test Result of Gambir Leaf Extract Nanogel Preparation

The results of the Homogeneity Test of Gambir Leaf Extract Nanogel Preparation can be seen in Table 6 below.

Table 6 Homogeneity Test Results of Gambir Leaf Extract Nanogel Preparations

Lama Penyimpanan (Week)	Homogeneity			
	F 0	**F1**	**F2**	**F3**
0	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains
1	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains
2	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains
3	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains
4	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains	Homogeneous / no coarse grains

Description:
F 0 = nanogel base
F 1 = 1% concentration gambier leaf extract nanogel
F 2 = 2% concentration gambier leaf extract nanogel
F 3 = 3% concentration gambier leaf extract nanogel

3.7. Results of pH Test of Gambir Leaf Extract Nanogel Preparation

pH is one of the test parameters to determine whether the preparation produced is acceptable for skin pH or not. The results of pH testing on the four formulas can be seen in Table 7.

Table 7 Results of pH Test of Gambir Leaf Extract Nanogel Preparations

Formula	pH of gambier leaf extract nanogel preparation ±SD
F 1	4.83±0.020
F 2	4.87±0.018
F 3	5.17±0.034

3.8. Adhesion Test of Gambir Leaf Extract Nanogel Preparation

The adhesion test is one of the parameters carried out to determine the ability of the nanogel preparation to adhere to the skin surface when used. The results of the adhesion test on Nanogel of gambier leaf ethane extract can be seen in Table 8.

Table 8 Adhesion Test Results of Gambir Leaf Extract Nanogel

Formula	Adhesion of gambier leaf extract nanogel ±SD (detik)
F 0	1.080±0.047
F 1	1.426±0.038
F 2	1.552±0.013
F 3	1.752±0.037

3.9. Viscosity of Gambir Leaf Ethanol Extract Nanogel Preparation

Viscosity is a statement of the resistance of a liquid to flow. The viscosity of gambier leaf extract nanogel can be seen in Table 9.

Table 9 Viscosity of Gambir Leaf Extract Nanogel Preparations

Time (Day)	Dosage Formula			
	F 0	**F 1**	**F 2**	**F 3**
0	2882	2912	2931	2943
7	2540	2710	2727	2829
14	2460	2612	2642	2823
21	2328	2412	2432	2712
28	2116	2120	2224	2508

3.10. Results of Particle Size and Zeta Potential of Gambir Leaf Extract Nanogel Preparation

Zeta potential and particle size of gambier leaf extract nanogels were measured using a PSA (Particle Size Analyser) tool with the Microtac brand. The results of zeta potential and particle size can be seen in Table 10.

Table 10 Results of Particle Size and Zeta Potential Measurements of Gambir Leaf Extract Nanogel Preparations

Formula	**Zeta Potential (mV)**	**Particle Size (nm)**
F 0	26.733±0.49	274.367±0.057
F1	25.733±0.11	272.833±0.493
F2	28.066±0.49	257.9±7.7078
F3	30.6±0.17	142.567±0.3055

3.11. Anti-irritation Test of Gambir Leaf Ethanol Extract Nanogel Using Animal Experiment (Rabbit)

Table 11 Anti-irritation test results of gambier leaf ethanol extract nanogel preparation on experimental animals (male white rabbits).

Animal Test (Rabbit)	**Irritating Effects**	**Kelompok Uji (skor)**			
		Nanogel base	**NEDG (1%)**	**NEDG (2%)**	**NEDG (3%)**
Rabbit 1	Erythema	0	0	0	0
	Oedema	0	0	0	0
Rabbit 2	Erythema	0	0	0	0
	Oedema	0	0	0	0
Rabbit 3	Erythema	0	0	0	0
	Oedema	0	0	0	0
Score		0	0	0	0

Irritation testing was carried out on 3 test animals (rabbits) which were selected to fulfil the criteria for irritation testing. The test material consists of nanogel base without gambier leaf extract, nanogel with 3% extract, and 3% concentration of gambier leaf extract gel. Testing without extract serves to determine the effect of irritation that may be caused by the cover material. The sticking of the test material was carried out on the rabbit's back which was cleaned first by shaving the back hair and by cleaning with ethanol which was then divided into 4 parts.

<table>
<tr><td colspan="2">Head</td></tr>
<tr><td>1</td><td>2</td></tr>
<tr><td>2</td><td>1</td></tr>
<tr><td colspan="2">Teal</td></tr>
</table>

Discussion

Determination of water content is the measurement of water content in simplisia that has been dried and pollinated. The purpose of determining the water content is to provide a minimum limit to the range of water content in the simplisia powder. The requirement for water content of simplisia according to the applicable standard parameters is no more than 10%. The result of determining the water content in gambier leaf simplisia is 8.70%. This means that gambier leaf simplisia meets the requirements for water content.

Determination of total ash content aims to determine the total mineral content in simplisia. Based on the results of the research that has been carried out, the total ash content of gambier leaf simplisia is 4.732%. It can be interpreted that the total ash content of gambier leaf simplisia meets the requirements of FHI. The results of the research on the total ash content of acid insoluble simplisia used in this study showed that the total ash content insoluble in acid for gambier leaves was 0.597%.

Determination of water-soluble juice content of gambier leaves aims to obtain an initial picture of the number of compounds that can be extracted with water solvents, the water-soluble juice content of gambier leaves is 44.28%. Determination of the content of juice dissolved in ethanol is done by weighing a total of 0.5 grams of powdered macerated simplisia, 20 ml of filtrate is evaporated to dry in a cup that has been tare, the residue is heated at a temperature (100oC) until the weight remains. The content is calculated in per cent of ethanol-soluble compounds calculated in the initial extract. The ethanol-soluble juice content of gambier leaves was 15.29%.

Organoleptic test with gambier leaf extract nanogel was conducted to observe the colour, odour, and shape of the preparation. The test is carried out by using the sense of sight to see the colour, the sense of smell to see the smell, and the sense of touch to see the shape of the preparation. (Ratna et al, 2024).

Homogeneity testing is carried out to determine whether the preparation is made homogeneous, because topical preparations must be homogeneous and free of particles that are still clumped and not too coarse (Klindangen et al., 2018). Based on the test results, the preparations from weeks 0 to 4 were homogeneous and did not contain coarse grains. However, the bubbles generated during the stirrer manufacturing process, as well as the impact of using carbopol, showed an increase in bubble concentration (Danishe and Frigaard, 2023). The nanogel base contained bubbles, formula 1 contained few bubbles, formula 2 contained few bubbles, formula 3 contained few bubbles.

According to the test results shown in Table 7, the pH of the three formulations meets the requirements of ideal topical preparations, in accordance with (Ariani and Wulandari, 2021) which states that, this is in accordance with the literature, that the pH of the skin ranges from 4.5-6.5. If the pH of nanogel preparations

with a pH of less than 4 will irritate the skin, while nanogels with a pH of more than 8 will cause the skin to become scaly (Ariani and Wulandari, 2021). Judging from the results of each nanogel preparation formulation, the value is almost uniform, which means that the data on the pH results of gambier leaf extract nanogel preparations meet good requirements in pH testing.

The purpose of adhesion testing is to determine how long the nanogel needs to adhere to the skin in order to function properly in drug delivery. However, the adhesion of semi-solid preparations should be more than one second, although there is no specific requirement for this test (Kindangen, 2018). The table shows the results of the nanaogel adhesion test of formulas 1,2,3 and the base show that they meet the requirements because the adhesion results reach more than 1 second. According to the theory, the adhesion of topical preparations is positively correlated with the viscosity value (Ariani and Wulandari 2021). Then, the longer the gel adheres to the skin surface, the longer the gel will provide a therapeutic effect, thus allowing greater drug absorption through the skin and providing optimal treatment (Kindangen et al., 2018).

From the table of results, the viscosity of gambier leaf extract nanogel preparation was found to decrease slightly. Increasing temperature can affect the stability of the preparation where the durability of the emulsion will be disturbed at high temperatures, which reduces the viscosity and increases the motion of the dispersed phase. The process of increasing temperature will increase and molecular flexibility so that viscosity will decrease. However, from the four formulas, the decrease in viscosity still shows the stability of the preparation. The viscosity value can be seen in the table. Viscosity should not be too low so that it spreads everywhere on the skin surface, or too thick so that it makes the skin sticky and too oily.

Zeta potential is the surface potential or charge present on the surface of the nano film layer, which generates an electric force between the oil droplets to avoid coalescence. The low zeta potential value is due to the presence of tween 80 surfactant which is a nonionic surfactant that has no charge on its hydrophobic group, so the surface of oil droplets covered by this surfactant tends to be uncharged (Wahyuningsih and Putranti, 2015). Zeta potential values close to ±30 mV indicate a high level of nano-stability (Lowry et al., 2016).

Nanogels are nanoparticles composed of hydrogels with crosslinked hydrophilic polymers with a particle size of 100-200 nm (Garg et al. 2012). The table shows that the particle size measurement of formula 3 is included in the good size of 100-200 nm. The less oil phase used, the smaller the droplet diameter size and if the amount of oil phase is greater, causing the nanoemulsion droplet size to be larger. This is due to the lack of surfactant concentration used. The use of increasing concentrations of Tween 80 will reduce the nanoemulsion globules, this is due to an increase in surfactant absorption between oil-water surfaces, and a decrease in surface tension in the system so as to support the formation of nanoemulsion systems with smaller droplet sizes (Riquelme et al., 2019). The use of surfactant Tween 80 and interacting with propylene glycol can reduce particle size. This is because the absorption of surfactants on the oil surface can reduce the interfacial tension in the nanoemulsion system resulting in a small particle size and the use of co-surfactants causes the nanoemulsion to be stable. Then the less active substance, the larger the particle size and the more active substance, the smaller the particle size is because it is difficult to penetrate the semi-permeable membrane.

Based on the results of anti-irritation testing using 3 experimental animals (rabbits). Observations were made on the irritation test for 24, 48, and 72 hours after being given the nanogel base formula, 3% EEDG nanogel and 3% EEDG Gel comparison. By observing the skin reaction that arises with two parameters of observation, namely the level of erythema (redness reaction) and the level of edema (swelling) that arises. Observations were made at 24, 48, and 72 hours after the bandage was removed to

determine the possibility of delayed irritation reactions, then the results of these observations were scored 0 to 4 according to their severity. The level of irritation is calculated based on the calculation of the observation score. (Peranginangin, 2018).

Erythema is a reddish skin reaction that occurs as a side effect of using topical preparations. Redness is also characterised by the appearance of prominent patches scattered symmetrically. The symptoms are not only erythema (redness), but also vesiculation (watery) accompanied by itching (heat). While udema is a swelling reaction in the skin that arises from the side effects of using topical preparations. Udema occurs due to the increase in the volume of fluid outside the cells (extracellular) and outside the blood vessels (extravascular) that accumulates in the tissues of the body (Periad et al, 2018).

From the results of observations made on test animals (rabbits) for 24, 48, and 72 hours by testing the erythema and oedema scores obtained on the nanogel base nanogel base at 24 hours got a score of 0, 48 hours score 0, and 72 hours score 0. Then at nanogel of gambier leaf ethanol extract at 24 hours with a score of 0, 48 hours score 0, and 72 hours score 0. Then on the gel of ethanol extract of gambier leaves at 24 hours with a score of 0, 48 hours score 0, and 72 hours score 0. It can be concluded that from the results obtained by testing the preparation of gambier leaf extract nanogel not irritating.

4. Conclusion

The conclusion obtained in this research is that the 3% concentration of gambier leaf extract nanogel preparation has the best results in terms of physical evaluation compared to other concentration nanogel preparations.

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