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FORMULATION AND ACTIVITY TESTS OF EUPHATORIUM LEAF (Eupatorium Oradatum L) ETHANOL EXTRACT GEL ON BURNS HEALING OF RABBITS

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ABSTRACT

A gel is a semisolid system consisting of small inorganic particles or large organic molecules suspended in a liquid. This study aims to determine if Eupatorium leaf extract can be formulated into a gel preparation that meets the physical quality requirements and to determine the activity of Eupatorium leaf extract gel on rabbit burn wound healing. This type of research was a laboratory experiment with gel preparation formulations and activity tests on rabbit burn wound healing. Preparation of Eupatorium leaf extract by maceration with 96% ethanol solvent. In this study, FI gel preparations (negative control), FII (2.5% extract), FIII (5% extract), FIV (10% extract), and FV (Bioplacenton positive control). Furthermore, a physical stability test was carried out on the Eupatorium leaf extract gel which included; an organoleptic test, homogeneity test, pH test, spreadability test, adhesion test, viscosity test, and accelerated stability test. Then the activity of Eupatorium leaf extract gel on the healing of rabbit burns. In this test, 5 rabbits were used. Each rabbit was made a wound with an area of 2 cm on the back area which was divided into 3 wound areas. Each wound area is given the same concentration. Observations were made every 3 days of treatment. The results showed that Eupatorium leaf extract could be formulated into a gel preparation and met the physical stability requirements of the gel, and the activity test on the healing of rabbit burns obtained an average percentage of burn wound healing, namely FI (11.83%), FII (24.50), FIII (31.33%), FIV (54.17%) and FV (66.17%). Based on the results of statistical analysis tests with one-way ANOVA, it was shown that there were significant differences in the healing activity of rabbit burns between all treatment groups where the value of p <0.05.

Keywords*: Eupatorium leaf, Extract, Gel, Burns healing, Rabbits*

INTRODUCTION

Burns are a local response of a tissue, with or without a systemic response to energy transfer from physical sources (mechanical, thermal, radiation, electrical) or chemical sources These injuries can be caused by friction between the skin and a rough surface, heat, radiation, chemicals such as hydrochloric acid, or electrical sources, but the majority of burns are caused by the heat of a high-temperature melt or solid, or fire. (Sanjaya *et al*., 2023). Burns often have detrimental effects on humans both psychologically and physically. This is because this type of injury is a severe form of trauma that has caused humans to suffer since ancient times. (Ananta, 2020)

Burns are a major problem for society globally, resulting in permanent damage to appearance and loss of work. According to WHO, 90% of burns occur in lower-middle-class countries. WHO states that women in the Southeast Asia region have the highest incidence of

burns, namely 27% of all deaths, and ± 70% of them are women (Kemenkes RI, 2013) On the skin, burns can cause skin damage and disrupt the skin's thermoregulatory, sensory, protective, metabolic and sexual signal functions. This incident is one of the most severe forms of trauma that humans have suffered from in the past and for years researchers have carried out trials to obtain improvements in the final results of a series of treatments for burns. (Ananta, 2020)

One alternative for wound healing treatment is using traditional medicine. Traditional medicine has become the nation's cultural heritage that needs to be developed so that it can be utilized optimally to improve health services. Medicinal plants have a variety of chemical contents that have broad biological and medical activity, with a good level of safety, are easy to obtain, and are cheap to use.

The Kirinyuh plant is one of the plants used in traditional medicine with the Latin name *Chromolaena odorata (L.) R.M. King H. Rob* is a group of plants in the Asteraceae family. This plant is a weed that is easy to grow and spreads widely and quickly in tropical areas so that grass cannot grow in grasslands. In various regions, C. Odorata L. is known as Kirinyuh. It has many chemical contents, namely it is proven to be rich in three compounds, glycosides, terpenoids, and phenols. Several other compounds such as tannins, saponins, flavonoids, betacyanins, quinones, and alkaloids (Putry *et al*., 2021)

Research has been out by (Yenti et al., 2016) Explained that the ethanol extract of kirinyuh leaves can be formulated in the form of a cream used in wound healing. Cream with a 10% concentration of kirinyuh leaf extract showed a faster wound-healing effect than the comparison with a povidone-iodine concentration of 10%. Then kirinyuh leaf extract can heal cut wounds. This is indicated by accelerated healing on the macroscopic level (hyperemia, granulation, crusting, pus production, and wound contraction). A concentration of 20% is the most optimal in reducing hyperemia and wound contraction. Meanwhile, a concentration of 10% is the most optimal in forming granulations, preventing crusting and pus production. The 20% concentration is the most optimal in increasing epidermis thickness, number of fibroblasts, and amount of collagen. (Amfotis *et al*., 2022)

Based on the description above, the author wants to examine in more depth the benefits of Kirinyuh leaf extract as a wound-healing medicine. The novelty of this research was the formulation of Kirinyuh leaf extract in a gel preparation to determine the consistency of the extract in preparation, then an activity test was carried out on healing rabbit burns intending to determine the effect of Kirinyuh leaf extract in a gel preparation. The test animal used was a local male white rabbit because it has several advantages compared to other test animals, namely the body size (including the back) which is quite large as a test area, making it easier to shave hair, easy to handle (not easy to stress).

METHOD

Tools and materials

The tools used in this research are rotary evaporator (Labmart®), viscometer (Brookfield®), analytical balance (Kern®), maceration vessel, test animal cage, surgical tools, tweezers, porcelain dish, Petri dish, filter paper, aluminum foil, tube, gauze, plaster, label paper, cover. Hands, masks, and glassware (Pyrex®). The materials used in this research were Kirinyuh leaves, Ethanol 96% (one med), Carbopol 940, Propylene glycol, Methylparaben, TEA (Tritenolamine), Aquades, Bioplacenton, and Ethyl chloride.

Simplicia processing

The Kirinyuh leaves that have been taken are then wet sorted. Wet sorting is carried out to separate raw materials from foreign objects that are involved in the raw material collection process. Then wash it to separate dirt or foreign objects that stick to it. Next, the chopping

process is carried out to facilitate the drying process so that it does not rot easily, after that it is dried by airing it protected from direct sunlight until dry. After it is sorted dry avoid foreign objects that may be involved in the drying process. Then put it in a tightly closed container and ready for extraction.

Making extract

Weighed 500 grams of Kirinyuh leaf simplicia then put it into a maceration vessel, then added 10 parts of 96% ethanol, then soaked for the first 6 hours while stirring occasionally, then macerated for 18 hours. The liquid extract obtained was separated by filtration or filtration. The filtering process was repeated at least twice with the same type of solvent and the volume of solvent was half the volume of solvent in the first filtering, all the extracts obtained were collected and then evaporated using a rotary evaporator until a thick extract was obtained. (Astuti *et al.*, 2021)

Making gel

Table 1. Gel composition

Material	Base (F1%)	FII (%)	FIII (%)	FI (%)	Utility
Leaf Kirinyuh extract	-	2,5%	5%	10%	Active substance
Carbopol 940	2%	2 %	2%	2%	*Gelling agent*
Propylene glycol	15%	15 %	15 %	15%	solvent
Methylparaben	0,3%	0,3 %	0,3 %	0,3 %	Preservative
Tritenolamin (TEA)	0,4%	0,4 %	0,4 %	0,4%	Neutralizing agent
Aquades ad	Ad 100 ml	Ad 100 ml	Ad 100 ml	Ad 100 ml	Solvent

The tools and materials used are prepared, and then a gel preparation based on carbopol 940 is developed in 10 parts of distilled water in a mortar and left to swell. Then TEA was added and homogenized. Next, propylene glycol was added which had previously been dissolved in hot distilled water at 90°C, and methylparaben, was stirred until homogeneous. Kirinyuh (*Eupatorium odoratum* L.) leaf extract was mixed into the base, the remaining water was added to the base and stirred until a homogeneous gel mass was formed. After that, put it in a tightly closed receptacle. (Slamet *et al*., 2020)

Evaluation of gel preparations

a) Organoleptic test
   The organoleptic test was carried out to see the physical appearance of the gel preparation by observing the shape, color, and odor of the preparation that had been made.
b) pH test
   pH testing was carried out using universal pH paper which is dipped into the diluted gel sample. The color changes that occur are matched with universal pH standards. Gel preparations generally have a pH value between 4-6 (Rahmadani et al., 2021)
c) Homogeneity test
   This observation is purposeful to see significant changes in the final preparation that has been made. The preparation was tested using two object glasses, where the sample was placed on one of the object glasses and placed evenly. A good preparation must be homogeneous and free from particles that are still lumpy.
d) Spread power test

This test was carried out by weighing 0.5 grams of gel, then placing it in a round glass, placing another glass on top, and leaving it for 1 minute. After that, 150 grams of load was added and left for 1 minute and the constant diameter was measured.

e) Sticking power test
The adhesion test was carried out by placing 0.5 grams of gel on top of another object and giving it a load of 1 kg for 3 minutes. Determining adhesive force the time of release of the two object glasses was recorded. The adhesion requirement is more than 4 seconds.

f) Viscosity test
The viscosity test of the preparation was carried out using a Brookfield viscometer by inserting the spindle on the viscometer into 100 grams of the preparation which had been placed in a beaker glass and at the appropriate speed. The viscosity of the preparation was seen on a scale in the tool after stability had been achieved.

g) Stability faster test
The physical preparation was tested using an accelerated test method by storing the gel preparation at a temperature of 4ºC for 24 hours and storing it at a temperature of 40ºC for 24 hours, called 1 cycle. This work was carried out in 6 cycles, namely for 2 days with observations before and after accelerated storage. (Nurhayana *et al*., 2022)

Burn Test

First, the rabbit's back is anesthetized using ethyl chloride by spraying it on the skin of the rabbit's back where the burn will be made. Burns was made using a metal plate with a diameter of 20 mm by heating the plate for 3 minutes. After that, stick it on the rabbit's back for 5 seconds, and a burn wound forms. Then, treatment was given by applying each Kirinyuh leaf gel extract to 5 groups consisting of 5 rabbits, namely:

Group I: Gel Base (negative control)
Group II: Kirinyuh leaf gel extract 2.5%
Group III: Kirinyuh leaf gel extract 5%
Group IV: Kirinyuh Leaf gel extract 10%

The treatment was carried out for 15 days while being observed every 3 days before and after treatment. (Rahmadani et al., 2021)

Data Analysis

The data obtained was then analyzed statistically using the One-way ANOVA method to see whether the gel made had a healing effect on burn wounds. If the ANOVA test result shows a probability value <0.05, a difference in the effect of healing burns between each treatment. The statistical test was then continued using LSD (*Least Significant Difference*) to see whether there were significant or non-significant differences between each treatment. (Prasongko *et al.*, 2020)

RESULTS AND DISCUSSION

Research Result

Based on the results of research conducted on the formulation and activity test of the Kirinyuh Leaf (*Eupatorium Odaratum* L.) Ethanol Extract Gel Preparation for Healing Rabbit Burns, the following research results were obtained:

Table 2.Organoleptic Test result

Treatment	Formula	Room temperatur	After testing Accelerated Stability (4˚& 40˚C)
Color	I	White	White
	II	Green	Green
	III	Green	Green
	IV	Green	Green
Smell	I	Typical	Typical
	II	Typical	Typical
	III	Typical	Typical
	IV	Typical	Typical
Texture	I	Semi-solid	Semi-solid
	II	Semi-solid	Semi-solid
	III	Semi-solid	Semi-solid
	IV	Semi-solid	Semi-solid

Information:
F I : Carbopol 940 gel base (negative control)
F II : Gel extract 2.5%
F III : Gel extract 5%
F IV : Gel extract 10%

The organoleptic test was carried out to observe the physical stability of the preparation which includes changes in shape/texture, color, and aroma of the preparation of each formula when stored at room temperature or after accelerated stability testing. Leaf Gel Preparation The kirinyuh produced with a distinctive aroma has a semi-solid shape/texture and, a green color in formulations II, III, and IV, while in the formulation I (base) it has a clear color. During accelerated stability testing, the Kirinyuh Leaf Gel preparation did not experience changes (stable).

Table 3. pH test result

Formula	Replication	Room temperature	After accelerated stability testing (4˚and 40˚C)	Interpretation (SNI 06-2588)
I	1	6.76	6.57	4,5-7
	2	6.75	6.53	
	3	6.58	6.43	
II	1	6.18	6.13	
	2	6.17	6.10	
	3	6.15	6.08	
III	1	6.09	6.03	
	2	5.10	6.05	
	3	5.01	5.89	
IV	1	5.55	5.32	
	2	5.64	5.45	
	3	5.62	5.42	

Information:
F I : Carbopol 940 gel base (negative control)
F II : Gel extract 2.5%
F III : Gel extract 5%
F IV : Gel extract 10%

The results of pH testing on the Kirinyuh leaf extract gel preparation showed that all formulas had a pH that met the gel preparation requirements, provided that the pH value for the gel preparation was 4.5-7 (Prasongko *et al*., 2020a)

Table 4. Homogeneity test result

Formula	Room temperature	After accelerated stability testing (4˚and 40˚ c)	Interpretation
I	Homogeneous	Homogeneous	Homogeneous
II	Homogeneous	Homogeneous	
III	Homogeneous	Homogeneous	
IV	Homogeneous	Homogeneous	

Information:
F I : Carbopol 940 gel base (negative control)
F II : Gel extract 2.5%
F III : Gel extract 5%
F IV : Gel extract 10%

The homogeneity test on the Kirinyuh leaf extract gel preparation was carried out by smearing a small amount of the preparation on a glass object and paying attention to the presence of separate parts and the presence of small granules on the preparation. The results of the homogeneity test at room temperature and after accelerated stability testing showed that formulas I, II, III, and IV had no coarse grains and did not experience changes or continued to show homogeneous physical quality properties during storage.

Table 5. Spread power test result

Formula	Replication	Room temperature	After accelerated stability testing (4˚and 40˚ c)	Interpretation (SNI)
I	1	6.50	6.30	5-7 cm
	2	6.70	6.40	
	3	6.80	6.60	
II	1	6.40	6.20	
	2	6.20	6.00	
	3	6.10	5.90	
III	1	5.90	5.70	
	2	5.80	5.50	
	3	5.70	5.40	
IV	1	5.30	5.20	
	2	5.20	5.00	
	3	5.50	5.40	

Information:
F I: Carbopol 940 gel base (negative control)
F II : Gel extract 2.5%
F III : Gel extract 5%
F IV: Gel extract 10%

The results of the spreadability test on the Kirinyuh leaf extract gel preparation showed that the preparation had good spreadability as a gel in all gel formulas tested.

Table 6. Sticking power test result

Formulas	Replication	Room temperature	After accelerated stability testing (4˚and 40˚ c)	Interpretation
I	1	4.14	4.35	More than 4 seconds (SNI 06 – 2588)
	2	4.07	4.20	
	3	4.32	4.39	
II	1	4.78	4.89	
	2	4.92	5.15	
	3	4.84	5.03	
III	1	5.37	5.52	
	2	5.01	5.26	
	3	5.42	5.61	
IV	1	5.76	5.92	
	2	5.89	6.03	
	3	6.17	5.40	

Information:
F I : Carbopol 940 gel base (negative control)
F II : Gel extract 2.5%
F III : Gel extract 5%
F IV : Gel extract 10%

The results of the adhesion test showed that all the formulas tested had good adhesion as gel preparations.

Table 7. Viscosity test results

Formulas	Replication	Room temperature	After accelerated stability testing (4˚and 40˚C)	Interpretation
I	1	3260	46820	3.000-50.000 cP SNI 16-4380-1996
	2	42660	45300	
	3	44160	48800	
II	1	24660	29320	
	2	22260	26020	
	3	26820	32200	
III	1	20940	25320	
	2	21000	26940	
	3	21060	27420	
IV	1	20700	23820	
	2	20820	23940	
	3	20620	24800	

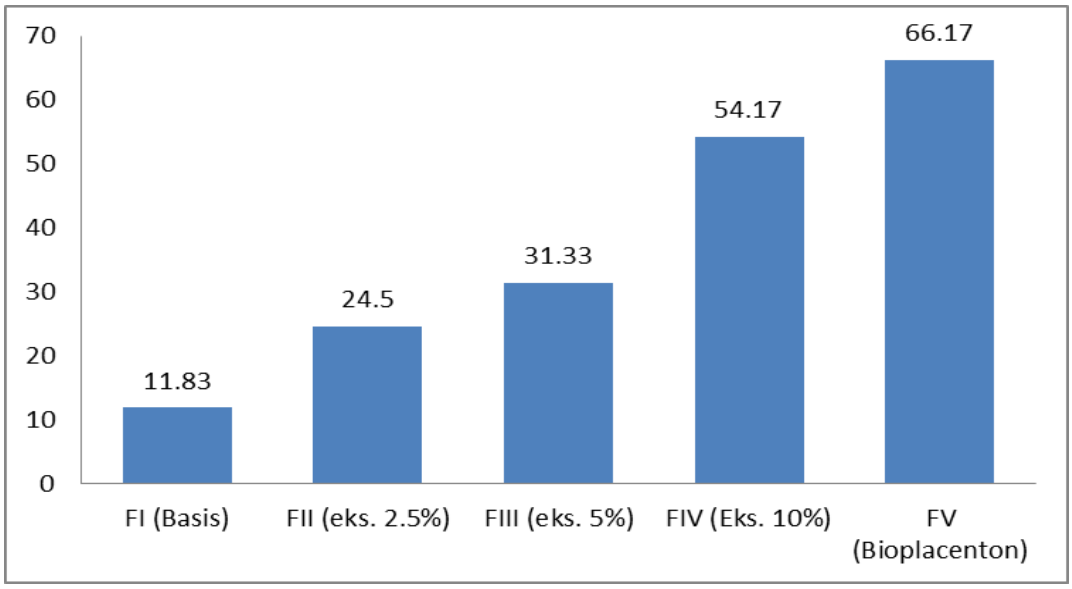
Information:
F I : Carbopol 940 gel base (negative control)
F II : Gel extract 2.5%
F III : Gel extract 5%
F IV : Gel extract 10%

The results of viscosity testing on the preparations showed that all the formulas tested met the viscosity value requirements for the Kirinyuh leaf extract gel preparation, with the viscosity requirement being 3000-50,000 cP. (Ambari *et al*., 2021)

Table 8. Average percentage results of burn wound healing tests in Rabbits

Replication	FI (K -) Basis	F II Ekst. 2,5%	F III Ekst.5%	F IV Ekst.10%	FV (K +) Bioplacenton
I	10.5	23.5	31.5	55.5	65
II	11.5	25.5	29.5	55	63.5
III	13.5	24.5	33	52	70
Amount	35.50	73.50	94.00	162.50	198.50
Average	11.83	24.50	31.33	54.17	66.17

Picture 1. Histogram of the average percentage of burn wound healing in rabbits



DISCUSSION

Research has been carried out regarding the formulation and activity test of Kirinyuh (*Eupatorium odaratum* L.) leaf extract gel preparations for healing rabbit burns. This research aims to create a formulation of kirinyuh leaf gel extract and to determine the concentration of kirinyuh leaf gel extract that meets the physical quality test requirements as a burn wound healing gel. In this study, a gel formula was made from Kirinyuh leaf extract, formula I was based on carbopol 940 (negative control), formula II was 2.5% Kirinyuh leaf extract, formula III was 5% Kirinyuh leaf extract, and Formula IV was 10% kirinyuh leaf extract and F V Bioplacenton (control positive). The tests carried out to evaluate the Kirinyuh leaf gel preparation included an organoleptic test, homogeneity test, pH test, spreadability test, stickiness test, viscosity test, and a stability test carried out on the gel preparation using the Cycling test method.

The results of the physical quality test on the gel, namely the organoleptic test, were carried out to observe the physical stability of the preparation which includes changes in shape/texture, color, and aroma of the preparation for each formula at room temperature storage or after accelerated stability testing. The resulting Kirinyuh leaf gel preparation with a

distinctive aroma has a semi-solid shape/texture and, green color in formulations II, III, and IV while in formulation I (base) it has a clear color. During accelerated stability testing, the Kirinyuh Leaf Gel preparation did not experience changes (stable).

The homogeneity test on the Kirinyuh leaf extract gel preparation was carried out by smearing a small amount of the preparation on a glass object and paying attention to the presence of separate parts and the presence of small granules on the preparation. The results of the homogeneity test at room temperature and after accelerated stability testing showed that formulas I, II, III, and IV had no coarse grains and did not experience changes or continued to show homogeneous physical quality properties during storage. This means that this complies with the requirements for the kirinyuh leaf extract gel preparation which must show a homogeneous composition and the absence of coarse particles. This is because a gel preparation is said to have to be homogeneous and evenly distributed so as not to irritate when used on the surface of the skin. Homogeneity is indicated by the absence of coarse grains.

A pH test is carried out to find out whether the pH of the gel matches the pH of the skin. Topical preparations that have a very high or very low pH can endanger the skin's absorption capacity, so they are made according to the skin's pH, namely 4.5-7. The pH test is carried out using a pH meter by dipping the electrode into the gel preparation until the pH meter shows the correct pH still. Observation results both at room temperature and after accelerated pH stability testing of the Kirinyuh leaf extract gel preparation were said to be stable because they had pH values ranging from 6.24 to 6.87 in the skin pH range. Increasing the extract concentration did not have a significant effect on the pH of the preparation. Because the pH of the preparation meets the skin pH criteria, namely in the interval 4.5-6.5.

The results of measuring the viscosity of the Kirinyuh leaf extract gel preparation were carried out using a Brookfield viscometer with spindle number 64 and speed 6. Viscosity testing is an important factor because it affects the spreadability parameters and release of active substances from the gel preparation. A gel preparation that has optimum viscosity will be able to hold the active substance dispersed in the gel base and increase the concentration of the gel preparation. The results of viscosity testing at room temperature show that the four formulas have viscosity values ranging from 3000 cp to 50000 cp. The difference in viscosity values is influenced by the higher the concentration of the extract used in each formula, the lower the viscosity value, it can be seen that formula II has a higher viscosity, namely 26820 cp with a concentration of kirirnyuh leaf extract of 2.5% when compared with formula IV containing the extract. Kirinyuh leaves 10% with a viscosity value of 20620. Meanwhile, the viscosity value after accelerated stability testing (4ºC and 40ºC) experienced an increase in viscosity, namely between 29320 cp to 23820 cp. This is because storage time affects viscosity, the longer the storage time, the higher the viscosity of the preparation. This increase occurs because the longer the storage time, the longer the preparation is affected by the environment such as air. Poor packaging can cause the preparation to absorb water vapor from the outside, thereby increasing the volume of water in the preparation. However, all formulas still meet the gel viscosity value requirements. (Ambari *et al*., 2021)

Testing the spreadability of the Kirinyuh leaf gel extract aims to see the ability to spread the gel preparation over the skin surface when used. Based on the results of testing the dispersion capacity of the gel preparation, it can be concluded that as the concentration of the extract increases, the absorbency of the gel preparation will decrease. After accelerated stability testing (4ºC and 40ºC) the spreadability value decreased, and the spreadability decrease occurred because the viscosity value of the gel preparation increased. Viscosity increases due to the difference between two varying temperatures during storage. However, all the formulas tested met the gel spreadability test requirements because they were in the range of 5-7 which is the requirement for good spreadability for gels (Prasongko *et al*., 2020)

The results of testing the adhesive strength of the preparations for each formula in storage before accelerated stability testing (25ºC), showed that the four formulas had adhesive strength values ranging from 4.07 to 6.17 seconds. Meanwhile, after accelerated stability testing (4ºC-40ºC), the kirinyuh leaf extract gel preparation was said to be stable because it had an adhesion value ranging from 4.20 to 6.28 seconds, which still met the requirements. After all, the adhesion power obtained was still by the requirements, namely the adhesion value. a good one over 4 seconds.

Based on the results of research that has been carried out on rabbit burn wound healing activity tests, it shows that administration of Kirinyuh leaf extract gel shows rabbit burn wound healing activity with a concentration of 2.5% (F II) with an average percentage of 24.50%, a concentration of 5% (F II) with an average percentage of 31.33 and a concentration of 10% (F III) with an average percentage of 54.17%. Bioplacenton® as a positive control had a better effect, namely 66.17%, this shows that the positive control had a better effect compared to Kirinyuh leaf gel extract and the negative control. This is because Bioplacenton® contains 10% placenta extract which works to trigger the formation of new tissue and for wound healing, and contains 0.5% neomycin sulfate to prevent or treat infections of gram-negative bacteria in the wound area. Meanwhile, in the negative control group with a base that did not affect wound healing, the group experienced a normal healing process where burn wounds could heal within 2 weeks, however, healing was not optimal as was obtained by administering kirinyuh leaf gel extract and also the positive control.

Saponin in Kirinyuh leaves can cure burn wound infections, saponin can act as a cleanser and antiseptic which functions to kill or prevent the growth of microorganisms that appear in wounds so that the wound does not experience serious infections. Kirinyuh leaves also contain flavonoid compounds which are thought to be able to increase collagen fibers, flavonoids inhibit peroxidase so they can increase collagen fibers and vascularization as well as prevent cell damage and help collagen synthesis. Vascularization is blood vessels that supply oxygen and nutrients to the wound area. Vascularization itself will take place well if the healing process is fast, while areas that have poor vascularization will take a long time to heal (M Kaihena, 2021)

The results of statistical analysis of the burn wound healing activity test of Kirinyuh leaf extract gel in rabbits using one-way ANOVA showed that there were significant differences between treatment groups, namely formula I base Carbopol 940 (negative control), formula II (ext. 2.5%), formula III (ext. 5 %), formula IV (ext. 10 %) and F V Bioplacenton (positive control) where the results obtained show each treatment group with a p-value = 0.00 or sig value. smaller than 0.05 ($p<0.05$). However, the effect of Bioplacenton formula V (positive control) was still better for healing burns in rabbits compared to formula IV (ext. 10%) as the formula with the highest concentration of Kirinyuh leaf extract.

CONCLUSION

The results obtained from physical quality testing show results that are by SNI. Based on the results of research conducted and the results of data analysis, it can be concluded that Kirinyuh leaf gel extract can be formulated into a gel preparation that meets physical quality requirements and Kirinyuh leaf extract gel has burn wound healing activity in rabbits with concentrations of 2.5%, 5%, and 10%.

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