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Formulation And Testing The Effectiveness Of Gel Extract Of Red Ginger (Zingiber officinale Var. Rubrum) As Antiinflamatory In White Male Rats (Rattus norvegicus).

Nurjannah Bachri[1], Nielma Auliah[2], Sri Wahyuningsih[3,*], Husna Dewi[4]
[1]S1 Pharmacy Study Program,Tarumanagara Collage Of Health Sciences of Jakarta, Indonesia
[2,3,4] Pharmacy Faculty, Megarezky University, Makassar, Indonesia

Abstract: *Red Ginger is a type of rhizome that is widely used as an ingredient in traditional medicine in Indonesia. The efficacy of red ginger has been widely studied as an effective anti-inflammatory. One of the main components of red ginger is the gingerol class of compounds. This study aims to determine the anti-inflammatory effect that is applied to the red ginger extract gel (Zingiber officinale var. Ruburum) gel preparation with the HPMC gel-forming ingredient. The gel preparation was then tested for stability up to day 7 and evaluated for its anti-inflammatory power against white rats (Rattus norvegicus). The method used was the artificial inflammation ordering method, where the test was carried out by injection of carrageenan as a mediator for inflammation of the thighs of white rats, then topically giving Red Ginger extract gel with a concentration of 1%, 3% and 5%, HPMC as a negative control and diclofenac sodium as a Positive control. Measurements were carried out every 8 hours every day after being induced by carrageenan to use a caliper. The results showed that the reduction in inflammation to reduce the diameter of 1% after induction was 1.76 cm and decreased to 1.22 cm, the concentration of 3% after induction was 1.68 cm and decreased to 1.33 cm, the concentration of 5% after induction was 1 , 79 cm and decreased to 1.35 cm. Data were statistically analyzed using ANOVA showing that the negative HPMC controls did not show any anti-inflammatory effects. It can show that 1%, 3% and 5% Red Ginger ethanol extract gel has anti-inflammatory effects and the greatest effect is that the 5% concentration has an anti-inflammatory effect.*

Keywords: *Gel, Red Ginger, Anti-inflammatory, Carrageenan*

1. INTRODUCTION

Indonesia has a variety of medicinal plants or spices as a national cultural heritage. People are increasingly accustomed to using natural medicinal preparations, one of which is in the form of traditional herbal medicine to maintain a healthy body, prevent disease, treat disease, and restore disease, and increase immunity. [7]

There are several types of ginger which in Indonesia are known as three types of ginger, namely elephant ginger, emprit ginger, and red ginger or known as sunti ginger. Big white / yellow ginger or also known as elephant ginger or rhino ginger has bigger and fatter rhizome, the rhizome is more bulging than the other two varieties. The essential oil content is greater than elephant ginger so it tastes spicier, in addition to its high fiber. 8. Red ginger Zingiber officinale var. Its rhizome ruburum is red and smaller than small white ginger. Just like small ginger, red ginger is always harvested when it is old, and also has the same essential oil content as small ginger. Among the three types of ginger, red ginger has a high essential oil content. [9]

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Zingiber officinale var. Ruburum, has a distinctive taste that is spicy and warm and has been known for a long time and is used as a medicinal plant. The use of ginger as a medicinal plant is growing rapidly along with the use of natural ingredients for treatment. [5]

Based on its pharmacological effects, red ginger has benefits for blood circulation, boosts the immune system, warms the body, is anti-inflammatory, and increases appetite and has anti-inflammatory effects. [5]

The content of red ginger is 1-3% essential oil with components of zingiberen, sesquipeladren, beta-bisabolone and oleoresin by 1-2.5% with gingerol and sogaol components. Gingerol in red ginger rhizome is an active compound that is responsible for the inflammatory process, namely the inhibition of cyclooxygenase and lipoxygenase activity in arachidonic acid, causing a decrease in the number of prostaglandins and leucotrin. [10]

Red ginger has anti-inflammatory activity that has been studied both in vitro and in vivo. The active compound that acts as an anti-inflammatory is gingerol. [3]

In formulating red ginger extract that is used as an anti-inflammatory, it is necessary to make red ginger extract in topical preparations. The advantages of topical use include avoiding difficulty in absorption of drugs through the gastrointestinal tract caused by enzyme activity and drug-food interactions, and being able to stop drug effects quickly if clinically necessary 2 The available classes of drugs for inflammation include NSAIDs (Anti inflammatory Drugs), which are known as non- steroidal anti-inflammatory drugs, the use of anti-inflammatory drugs that cause gastroteintestinal disorders and kidney damage 12. For that, look for safer alternative treatments for inflammation using plants or herbs one of them is red ginger Anti-inflammatory testing was carried out on male mice (Rattus norvegicus), intramuscularly as much as 0.1 ml using caragenin 1% which is not reactive and then closed for 24 hours. After 24 hours, the bandage is opened and the test area is cleaned with water to remove the residue of the test material.At 24.48.72 hours the changes were observed as a skin reaction to the test substance and assessed by giving a score of 0 to 4 depending on the severity of the skin reaction seen.

This study used eleven male rats to test the swelling of the thighs of male rats divided into five groups, group I was negative control, group II was positive control, group III was 1% extract concentration gel, group IV consisted 3% concentration gel, and group V consisted of 3% concentration gel. The gel extract concentration was 5%. After application of red ginger extract gel on the rats' thighs, the effect of the preparation until day 7 was observed to observe the changesthat occurred which were marked by edema.

2. MATERIALS AND METHODS

Preaparation of Sample

Samples of red ginger rhizome (Zingiber officinale var. Ruburum) that had been collected were selected which were in good condition, the rhizome then flowed clean with running water, dried by aerating and not exposed to direct sunlight during the drying process. Until dry simplicia is formed, the dried rhizomes are pollinated using a blender and sieved using a sieve, then weighed. The simplicia preparations were extracted using the maceration method using 96% ethanol as a liquid and solvent.

Formulation of Gel

Red ginger extract (Zingiber officinale var. Ruburum) is designed in a gel formula with a gel concentration of 1%, 3%,5%.

Table 1. Gel Formulation

Composition	**Function**	**Concentration (%)**			
		F1	**F2**	**F3**	**F4**
Ginger red Extract	Active Substance	0	1	3	5
HPMC	Basis Gel	10	10	10	10
propylenglycol	Humectant	10	10	10	10
Triethanolamine	Increased viscosity	5	5	5	5
Glycerin	Humectant	10	10	10	10
Aquadest	Solventad	100 ml	100 ml	100 ml	100 ml

Notes :

F I: Control Formula (No extract), F II: 1% Red Ginger Extract Formula and Additional Substances, F III: 3% Red Ginger Extract Formula and Additional Substances, F IV: 5% Red Ginger Extract Formula and Additional Substances. **Making a gel base**

The base is made by dispersing HPMC with 60 ml of distilled water, pouring the distilled water gradually and increasing the volume with the remaining 60 ml of distilled water then homogenized.

Methode Gel Making

Making ginger root extract gel (*Zingiber officinale var. Ruburum*) with a concentration of 1% is made by dispersing HPMC with 60 ml of distilled water, which has been added with sodium benzoate, stirring until homogeneous, then adding the remaining 650 ml distilled water. Then stored in the first container.

The gel preparation of red ginger rhizome extract (*Zingiber officinale var. Ruburum*) with a concentration of 3% and 5% was made in the same manner as at a concentration of 1%, where HPMC was dispersed with 60 ml of distilled water, stirred until homogeneous, then stored in the first container.

Then in the second container, the red ginger extract (*Zingiber officinale var. Ruburum*) is dispersed in glycerin, propylenglycol and triethanolamine until homogeneous, enter the base contained in the first container into the second container and homogenize it.

Preparation of Test Animals

The experimental animal used was 11 male rats weighing 150 g and divided into 5 groups. Test animals are treated in the same way, namely placed in each cage and fed in the form of pellets and mineral drinks or boiled water. Before testing, experimental animals are kept for 1 week in a cage that has good ventilation and is always kept clean. A healthy animal, characterized by showing agile movements. Each time the treatment was finished, the rabbits were rested for 2 weeks, then the rabbits could be used again for the next treatment.

Preparation of Inflammation Inductors (Carrageenan 1%)

Carrageenan 1% is made by weighing as much as 100 mg Carrageenan, then put in a 100 ml volumetric flask then distilled water is sufficient, to the mark. Then incubated at 37ºC for 24 hours.

Anti-inflammatory effect test in Male Rats.

Before testing, the rats were fasted for 18 hours while still given drinking water, the rats were divided into 5 treatment groups, namely negative control testing, testing of test materials (red ginger ethanol extract gel concentration of 1%, 3%, and 5%) and positive control testing. (diclofenac sodium gel).

The irritation test was done by shaving the hairs on the rats' thighs until they were clean. After that, the rats' thighs were measured 1x1 inch each. Before applying the test material, the rats' skin was cleaned using a cotton swab moistened with alcohol, then rubbed with red ginger extract gel (0.5 gr). Then smeared on the thighs of rats and covered with a thin plastic for 3 times a day. After that the test animals are returned to their cages. The next day at the next hour, the plaster is opened and the skin is cleaned with aquadest from the remaining test compounds that have stuck. The symptoms that were observed were primary irritation in the form of edema every 8 hours a day. Then each mouse was injected

intramuscularly with 0.1 ml of 1% carrageenan, one hour after injection of 1% carrageenan, each rat was treated topicallyon the thigh that had been induced by carrageenan.

Group I : Given the Voltadex® (+) Gel

Group II : Given the gel without ethanol extract as a control (-)Group III : Given Red Ginger Ethanol Extract Gel 1%

Group IV : Given 3% Red Ginger Ethanol Extract GelGroup V : Given Red Ginger Ethanol Extract Gel 5%

60 minutes after treatment, the volume of the rats' thighs was measured again using a caliper. Measurements were made every 8 hours for 360 minutes. Changes in the degree of swelling that occurred were recorded as rat thigh volume (Vt).

The volume of inflammation (inflammation) is the difference in the volume of the rats' thighs after and before injection of Carrageenan 1%. The boundary mark on induction of the thigh should be clear. The thighs of rats should be measured to a limit made to minimize the risk of errors in measurement of inflammation in the calipers, then the data obtained from the treatment are recorded.

Statistic Analysis

Observation data were collected based on the results of observations and One Way ANOVA testing.

Result and Discussion

A total of 5 kg of dried red ginger rhizome (Zingiber officinale var. Ruburum) was put into a maceration vessel which was added with 96% ethanol as much as 2000 ml, after a day the liquid was replaced with new 96% ethanol as much as 2000 ml. replacement of the filter fluid is done once every 2 days with the same number of sprays. Fluid replacement is carried out 3 times. The 96% ethanol liquid extract obtained was then collected and evaporated using a maceration vesseland put into a desiccator until a thick extract was obtained.

Table 2. Extraction Results

Sample	Sample weight (g)	Extract weight (g)	yield (%)
Red Ginger	800	71.25 g	8.90

The extraction method used in this research is maceration extraction, because the maceration method is a cold method

(extraction process without heating) besides gingerol is not resistant to heating which can cause damage to chemical content and simplicia. In addition, maceration extraction has the advantage that all parts of the sample can come into contact with the solution.

Maceration was carried out by soaking 800 g of simplicia in 96% ethanol filter liquid. Ethanol is used as a solvent, because it is able to attract polar and non-polar compounds. In addition, it was chosen as a solvent because ethanol is very effective in producing the optimal amount of active ingredients, the ethanol solvent is allowed to immerse the simplicia powder sample well, extraction is carried out for 3x24 hours to attract the chemical components contained in the simplicia and every 24 hours the ethanol solvent is replaced while stirring occasionally. Solvent replacement is carried out to speed up the extraction process because the first solvent is saturated with the expected compound, then the filtered filtrate is evaporated until a thick extract is obtained, organoleptic observations for red ginger ethanol extract are thick, brownish yellow in color, have a distinctive smell and taste spicy.

Before making red ginger extract gel (Zingiber officinale. Var. Ruburum), a gel base was first made using HPMC (Hidroxy Propyl Methyl Celullose) base, lumped separately, the base was made by heating 100 ml of distilled water to 70 ºC. . A total of 100 ml of hot distilled water is put into a measuring cup as much as 80 ml is mixed into a mortar containing HPMC (Hydroxy Propyl Methyl Celullose) then crushed constantly.

After the base is formed, glycerin and red ginger extract are added, propylene glycol and tea, the addition of glycerin is intended to maintain moisture in the preparation so that the preparation does not dry out during use, keeps the skin moist and makes the skin feel soft.

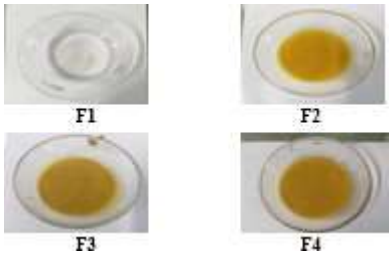

Figure 1. Gel Red Ginger Extract

Organoleptic Result Research

Table 3. Organoleptic Test, , Ph Test, and Viscosity Test.

Gel Formulation	Organoleptic	Observation Result				
		Early Cycle		End Cycle		Difference
F1	Scent	Unique	Unique	Unique	Unique	
	Consistency	Thic	Thic	Thic	Thic	
	Color	Clear	Yellow	Yellow	Yellow	
	Form	Gel	Gel	Gel	Gel	
	pH	6.0		6.3		
	Viscosity	21.00 mPa's		23.00 mpa's		2.00 mPa's
F2	Scent	Unique	Unique	Unique	Unique	
	Consistency	Thic	Thic	Thic	Thic	
	Color	Yellow	Yellow	Yellow	Yellow	
	Form	Gel	Gel	Gel	Gel	
	pH	6.0		6.3		
	Viscosity	25,99 mPa's		27,50 mPa's		1,51 mPa's
F3	Scent	Unique	Unique	Unique	Unique	
	Consistency	Thic	Thic	Thic	Thic	
	Color	Yellow	Yellow	Yellow	Yellow	
	Form	Gel	Gel	Gel	Gel	
	pH	6.0		6.3		
	Viscosity	35,00 mPa's		36,50 mPa's		1,50 mPa's
F4	Scent	Unique	Unique	Unique	Unique	
	Consistency	Thic	Thic	Thic	Thic	
	Color	Yellow	Yellow	Yellow	Yellow	
	Form	Gel	Gel	Gel	Gel	
	pH	6.0		6.3		
	Viscosity	27,00 mPa's		37,50 mPa's		2,50 mPa's

Stability test which includes organoleptic test where in this organoleptic test the things that are considered are the smell, consistency, color and shape of the gel preparation starting from the time the preparation is formulated until the end of the determined cycle using the sense of smell, and the sense of sight is carried out to determine purity. a preparation while the chemical stability test is checking the pH of the gel preparation.

On the pH check for the initial cycle for concentrations of 1%, 3% and 5%, it shows a value of 6. and the results obtained from the Final Cycle for concentrations of 1%, 3% and 5% show a value of 6.3. The occurrence of a less significant pH change could be caused by uncontrolled temperature conditions that have become below or even exceeding the specified temperature.

Evaluation Results of Gel Form

Table 4. Evaluation Result of Gel Form

Form	Sample Weight (g)	Time	Result (cm)
Control (-)	1	01:00.38	0-5.5
1%	1	01:00.65	0-5
3%	1	01:00.99	0-6
5%	1	01:01.65	0-5

In the test of the spreadability test on the red ginger ethanol extract gel (Zingiber officinale var. Rubrum), it was carried out by using 1 g of gel in the middle of the tool with a diameter of 15 cm, the one glass was left on it for 1 minute, then the measured gel diameter was put 50 g additional load, let stand for 1 minute and measured the diameter of the gel that spreads. This was repeated until a significant diameter was obtained, and the results were obtained in the control (-) with a sample weight of 1 gram in a time of 01: 00.38 so that the results were 0 to 5.5 cm, at a concentration of 1% with a sample weight of 1 gram within 01: 00.65 so that the results are 0 to 5cm, a concentration of 3% with a sample weight of 1 gram in 01: 00.99 so that the results are 0 to 7cm and a concentration of 5% with a sample weight of 1 gram within 01: 01.65, the results are 0 to 5cm according to (Robertus et al. al, 2015) test results of good gel dispersion between 5-7 cm.**Homogeneity Data of Gel Form**

Table 5. Homogenity Data of Gel Form

pH			
F1	**F2**	**F3**	**F4**
Homogen	Homogen	Homogen	Homogen

Notes :

F I: Control Formula (No extract), F II: 1% Red Ginger Extract Formula, F III: 3% Red Ginger Extract Formula, F IV:5% Red Ginger Extract Formula.

After making and testing the stability of gel preparations in this experiment, inflammation testing was carried out on research animals, the research animal used was white male rats (Rattus norvegicus) with body weights ranging from 150- 184 grams with 3 months of age, the selection of male sex in mice was the test results are not influenced by the hormoneestrogen.

Table.6 Data from the measurement of edema diameter in research animals until day 7

Gel Form	Experimental Animal	Induction	Diameter of the day						
		After	Before	1	2	3	4	5	6	7
(+)	1	1,24 cm	1,78 cm	1,65 cm	1,54 cm	1,44 cm	1,38 cm	1,24 cm	1,24 cm	1,24 cm
(-)	1	1,11 cm	1, 54cm	1,51 cm	1,47 cm	1,42 cm	1,40 cm	1,35 cm	1,23 cm	1,20 cm
1%	1	1,22 cm	1,76 cm	1,67 cm	1,60 cm	1,55 cm	1,41 cm	1,30 cm	1,24 cm	1,22 cm
	2	1,28 cm	1,65 cm	1,60 cm	1,57 cm	1,43 cm	1,39 cm	1,30 cm	1,28 cm	1,28 cm
	3	1,30 cm	1,61 cm	1,55 cm	1,52 cm	1,48 cm	1,42 cm	1,37 cm	1,33 cm	1,30 cm
3%	1	1,33 cm	1,68 cm	1,60 cm	1,55 cm	1,42 cm	1,39 cm	1,35 cm	1,33 cm	1,33 cm
	2	1,28 cm	1,65 cm	1,57 cm	1,54 cm	1,47 cm	1,30 cm	1,30 cm	1,28 cm	1,28 cm
	3	1,19 cm	1,59 cm	1,54 cm	1,49 cm	1,35 cm	1,29 cm	1,26 cm	1,19 cm	1,19 cm
5%	1	1,35 cm	1,79 cm	1,65 cm	1,54 cm	1,39 cm	1,38 cm	1,35 cm	1,35 cm	1,35 cm

On the day of testing, the rats were weighed and grouped randomly into five groups of rats consisting of 3 rats from each group, after which the initial diameter of the rats 'thighs was measured to determine the diameter of the rats' thighs before being given further treatment using a caliper. This method of measuring calipers is one of the methods often used in anti-inflammatory tests, relatively simple, from the treatment process, observation, measurement to data processing.

Then each treatment group was induced using carrageenan on the thighs of male rats using 1% carrageenan with an injection volume of 0.1 ml, because the resulting edema can be clearly observed. The use of carrageenin intramuscularly can cause inflammation which is indicated by the presence of edema in test animals, carrageenan is a foreign substance (antigen) that plays a role in the body which stimulates the release of inflammatory mediators such as histamine causing inflammation due to the body's antibodies reacting to these antigens to fight its effects then measured the rats thighs to know the diameter after induction Then given the ethanol extract of red ginger (Zingiber officinale. Var. Ruburum) with a concentration of 1%, 3% and 5%, control X and HPMC base according to the treatment group. Measured diameter reduction of edema for 3 times a day every 8 hours due to reducing the risk of infection after treatment and accelerating wound healing.

Based on the results of the study, it was found that giving X inflammation control increased where the edema diameter after induction was 1.78 cm, decreased successively on

day 1 to 1.65 cm, day 2 to 1.54 cm on day 3 to 1, 44 cm, day 4 became 1.24 cm and began to decline on day 1 and continued on day 7. It means that the potential for inhibition of control X is greater than that of negative control. This is because diclofenac sodium works by stabilizing lysosomes, inhibiting the release of inflammatory mediator activity (histamine, serotonin, prostaglandins).

In the control group HPMC did not affect the maximum reduction in the percentage of inflammation, in the HPMC group the percentage of inflammation produced did not decrease significantly, with a diameter after induction of 1.54 cm. On observations of days 1 to 7 after giving the dosage, each obtained a diameter of 1.51 cm, 1.47 cm, 1.42 cm, 1.40 cm, 1.35 cm, 1.23 cm and 1.20 cm , which has not returned to normal, namely 1.11 cm. This is because HPMC is only a drug solvent so that there is no stimulation in the form of drugs to reduce inflammation.

On the first and second day of the administration of red ginger (Zingiber officinale. Var. Ruburum) ethanol extract, the diameter of edema in rats for a concentration of 1% with a diameter after induction of 1.76 cm decreased on the first day to 1.67 cm, day 2 became 1 , 60 cm, day 3 becomes 1.55 cm, day 4 becomes 1.41 cm, day 5 becomes 1.30 cm on day 6 becomes 1.24 cm which returns to normal to 1.22 cm. The results of the reduction in edema that occurred every day were due to improvements in skin tissue due to the addition of extracts, where this preparation gave a better effect than the negative control.

At a concentration of 3% with a diameter after induction of 1.68 cm decreases on the first day to 1.60 cm, day 2 becomes 1.55 cm, day 3 becomes 1.42 cm, day 4 becomes 1.39 cm, day 5th to 1.35 cm on the 6th day to 1.33 cm which returns to normal to 1.33 cm. The results of the reduction in edema that occur every day are due to improvements in skin tissue due to the addition of extracts, where this preparation gives a better effect than the 1% concentration dosage.

At a concentration of 5% with a diameter after induction of 1.79 cm decreased on the first day to 1.65 cm, day 2 to 1.54 cm, day 3 to 1.39 cm, day 4 to 1.38 cm, day 5th becomes 1.35 cm where back to normal becomes 1.35 cm. The result of the reduction in edema that occurred for 7 days was due to the improvement in skin tissue due to the addition of the extract, the red ginger extract gel preparation with a concentration of 5% gave the fastest inflammatory healing effect, compared to the concentrations of 1% and 3%, where the inflammatory healing process was faster. namely on day 5, this is because the higher the concentration in the preparation, the faster it has an effect on experimental animals and the content of gingerol compounds contained in red ginger which plays an important role in the

inhibition of prostaglandins (PGE) and lipoxygenase (LOX), the mechanism of gingerol in inhibiting gingerol. the process of inflammation, which plays a role in inhibiting the formation of inflammatory mediators, both the cyclooxygenase pathway and the direct inhibition of phospholipase, so that prostaglandin and leukotriene synthesis is disrupted (Singh, 2008).

In testing in this study using the One Way Anova data analysis method which aims to determine the significant difference of each treatment for each day.

Based on the data obtained, it is processed by using the One Way Anova statistical analysis as for the results from appendix 4. It is an overview of the data analyzed, the highest mean value is obtained in the 5% group and diclofenac sodium is 1.608 in the Homogeneity of Variances data analysis as evidence can be obtained using One Way Anova, where significant> 0.05 is obtained so that it can be concluded that the data has the same variance (homogeneous), because the data is homogeneous, followed by Anova, a significant value of 0.000 <0.05 means that the data is significant.

The anti-inflammatory effectiveness of red ginger extract can be seen in the results of Tukey's BNJ test analysis (real difference to be honest) The results of edema measurements in rats after being analyzed using One Way Anova data analysis in Table 8, gave significant results (p <0.05) on edema measurements in white rats between positive controls, concentrations of 1%, 3%, and 5%. The results of statistical analysis of the homogeneity of variance test on edema of white rats on days 5 and 6 gave significant results.

3. CONCLUSION

Based on the results of the research that has been done, it can be concluded that the ethanol extract gel of red ginger (Zingiber officinale var. Ruburum) at a concentration of 1%, 3% and 5% has the greatest anti-inflammatory effect, which is 5% among the concentrations used. However, when compared with the comparison preparations, Control X had the maximum anti-inflammatory effect.

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