TRANSPUBLIKA INTERNATIONAL RESEARCH IN EXACT SCIENCES (TIRES)

EFFECTIVENESS TESTING CREAM OF CASSAVA LEAF ETHANOL EXTRACT (*Manihot Usculenta Crantz*) ON CONJUSES OF RABBIT (*Lepus Negricollis*)

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Abstract

Cassava leaves (Manihot esculenta Crantz) have been clinically studied to contain ingredients such as saponins and flavonoids, which have wound-healing and anti-inflammatory effects. This study aims to determine the effectiveness of cassava leaf (M. esculenta Crantz) ethanol extract cream on bruises in rabbits (Lepus nigricollis). The research is a laboratory experimental study testing the effectiveness of cream preparations with varying concentrations of cassava leaf ethanol extract on bruise healing in rabbits. Cream preparations were made in four formulations: 25%, 50%, 75%, and 100% concentrations. Physical tests of the cream preparations included organoleptic, homogeneity, pH, and spreadability tests. Test animals were divided into treatment and control groups. The treatment group received cream preparations of different concentrations (25%, 50%, 75%, and 100%), while the control group received no treatment. Bruise healing was observed for color changes daily. Physical test results of all cream preparations met the requirements for good cream preparations. In the treatment group, 25% and 50% concentrations showed similar healing processes, with greenish bruises still present on day 14. The 75% and 100% concentrations resulted in the fastest healing, with bruises disappearing and fur regrowth by day 14. The control group's healing process was similar to the 25% and 50% treatment groups. Therefore, the cassava leaf ethanol extract cream was most effective at 75% and 100% concentrations compared to 25% and 50%.

Keywords: *Cassava Leaves (Manihot Usculenta Crantz), Extract Cream, Bruises*

1. INTRODUCTION

Indonesia has been known for its extraordinary natural wealth. All types of plant products in Indonesia can be utilized for the benefit of the community. In the past, Indonesians have used various concoctions from leaves, roots, and tubers to gain health and cure various diseases. Thus, Indonesia is known as the second country with the most traditional medicinal plants (Delarosa & Wulansari, 2019). Indonesian people use many medicinal plants in traditional medicine. Plants are one of the sources of raw materials in traditional and modern medicine systems. More than 60% of pharmaceutical products come from plants (Sukmawati et al., 2021). Indonesia is a country rich in medicinal plants, of the many thousands of medicinal plants, there are still many plants whose properties are not yet known. One of these medicinal plants is the cassava plant or cassava or cassava, or in English called cassava (Manihot utilissima pohl). Cassava plants originated in Brazilia but are now spread almost all over the world. Indonesia is one of the world's main cassava producing countries (Azizah et al., 2020).

Cassava leaves have various contents, one of which is flavonoids. The main flavonoid content of cassava leaves is rutin which is a quercetin glycoside with

disaccharides consisting of glucose and rhamnose. Rutin is used to reduce capillary fragility, reduce capillary permeability by tissues, and treat retinal hemorrhage (Azizah et al., 2020). Cassava leaves (Manihot esculenta Crantz) are widely used for alternative medicine. Cassava leaves pharmacologically have activity as anti-inflammatory, antibacterial, antioxidant, and have wound healing activity. The content of cassava leaves that plays a role in wound healing includes vitamin C, flavonoids, triterpenoids, tannins and saponins (Sukmawati et al., 2021).

Ethanol, also called ethyl alcohol or alcohol, is the most commonly used alcohol in everyday life. Because of its non-toxic nature, this material is widely used as a solvent in the pharmaceutical world and the food and beverage industry. The chemical properties of ethanol are: BM46.07, volatile, flammable, smokeless and bluish flame, less than specific gravity (Anggraini et al., 2017). Cream is one of the pharmaceutical preparations used topically for the treatment of various skin diseases. Apart from its practical use, it is also easy to clean from the skin and is not sticky like ointments or other pharmaceutical preparations. Cream is a solid preparation containing one or more medicinal ingredients dissolved in a suitable base material. Creams have traditionally been used for semi-solid drug preparations that have a relatively liquid consistency formulated as water-in-oil or oil-in-water emulsions (Megawati & Kurniasih, 2020). Nowadays, the limitation is more directed to products consisting of oil-in-water emulsions, which can be washed off with water or are more intended for cosmetic and ointment use (Wijaya et al., 2013).

A contusion is the discharge of blood into the surrounding tissue as a result of blunt trauma. Contusions are the most common cases of examination of injuries that are treated by doctors both for healing and for medicolegal purposes. A contusion itself is the result of blood extravasation into the tissue (Hendrawati et al., 2019). This reaction is one of the inflammatory responses characterized by the release of neutrophils from blood vessels as the body's defense mechanism system against injury. Neutrophils are part of leukocytes, besides neutrophils there are several other leukocyte cells, namely eosinophils, basophils, monocytes, lymphocytes and sometimes plasma cells (Faisal et al., 2018). Bruising occurs due to blunt force injury resulting in bleeding under the skin tissue (hematoma) (Wuri et al., 2021).

Cassava leaves are known to inhibit tyrosinase enzyme activity with flavonoids in the form of quarsetin, which based on research has high biological activity (Toha et al., 2020). Quarsetin is an active substance of the flavonoid group that is known to have free radical inhibiting activity. High antioxidant activity in quercetin can trigger collagen production and an increase in vascular endothelial growth factor (VEGF) which is the most important endogenous in burn wound healing (Rahman et al., 2022). Based on the description above, cassava leaves have effectiveness in wound healing and there is no research information about Cassava Leaf Ethanol Extract (Manihot Usculenta Crantz) in cream preparations as a healer of Bruises in Rabbits (Leppus Negricollis). Therefore, researchers are interested in conducting research on ethanol extract of cassava leaves in cream preparations for healing bruises in rabbits (Leppus Negricollis) " (Hakim & Saputri, 2020).

2. LITERATURE REVIEW

Cassava leaves are one part of the cassava plant that is commonly used as human food. Cassava leaves are known to contain many calories, protein, phosphorus, hydrate charcoal and iron. The vitamin content in cassava leaves consists of vitamin A, B1, and vitamin C (Dewi et al., 2013). In addition, cassava leaves contain tannin and a number of phytopharmaceuticals which are very good for maintaining endurance and overcoming a number of diseases. Seeing so many benefits from cassava leaves, moreover this leaf is quite economical. The benefits of cassava leaves as medicine include anticancer, preventing constipation and anemia, and increasing endurance. The content of vitamins A and C in cassava leaves acts as an antioxidant that prevents the aging process and increases the body's resistance to disease (Tuhenay, 2018).

Rabbits are mammals of the Leporidae family, which can be found in many parts of the earth. Rabbits reproduce by lambing called viviparous. Formerly, this animal is a wild animal that lives in Africa to mainland Europe. In 1912, rabbits were classified in the order Lagomorpha. This order is divided into two families, namely Ochtonidae and Leporidae. The origin of the word rabbit comes from the Dutch language, namely *konijntje* which means "rabbit child". This shows that the people of the archipelago began to recognize rabbits during the colonial period (Nurhikmah & Amrullah, 2022). A bruise is a closed wound where tissue damage is carried by the skin and only appears as a lump when viewed from the outside. This bruise causes a bluish or blackish area on the skin when there is sufficient bleeding, the onset of bleeding in a limited area is called a hematoma. The location, shape and extent of the bruise are influenced by various factors such as the amount of violence, the type of object that causes it (rubber, wood, iron), the condition and type of tissue (loose connective tissue, fatty tissue), the fragility of blood vessels (Tilaar et al., 2020).

The depth of the bruise and skin pigmentation can have an effect on color appearance and detection. At the time of bruising, the color is red, then turns purple or black; after 4-5 days it will be green which will then turn yellow in 7-13 days, and finally disappear in 15-21 days. The color change takes place starting from the edge and the time can vary depending on the degree and various factors that affect it. One of the factors that affect the discoloration of bruises is skin color, skin color can be caused by several factors (Faisal et al., 2018).

Ethanol (ethyl Alcohol) with the chemical formula C2H5OH is one of the derivatives of hydroxyl compounds or OH gugu (Gugule et al., 2019). Ethanol has colorless, volatile, easily soluble in water, has a molecular weight of 46.1, boiling point 78.3 ºC, freezes at a temperature of -117.3 ºC, density 0.789 at 20ºC, calorific value 7077 cal / gram, latent heat of vaporization 204 cal / gram and octane number 91-105. Ethanol is an organic solvent that is often used for the extraction process and there have been very many reports or research articles from the use of ethanol (Isnatin, 2021). Some reasons for the wide use of ethanol include the fact that ethanol is relatively non-toxic compared to acetone and methanol, low cost, can be used in various extraction methods, and is safe for extracts that will be used as medicines and foods. Another reason is because ethanol is a solvent that is easily available, efficient, safe for the environment, and has a high extraction rate (Chen et al., 2020).

Cream is one of the topical dosage forms that can be used as skin medication. Cream preparations for the skin can function as a good protector for the skin. A good cream

preparation must meet certain requirements such as having adequate physical stability (Riski & Sami, 2015). Cream preparation is one of the pharmaceutical preparations used topically for the treatment of various skin diseases. Creams are more widely used because of their practical nature where they are easier to use, cause a feeling of cold, are easy to wash, are not fatty, can be used in hair-covered areas, provide a sense of comfort that is not irritating, are easily cleaned from the skin, allow contact with the application site longer, and are not sticky like ointments or other pharmaceutical preparations (Setyani et al., 2016).

3. RESEARCH METHODS

The type of research used is laboratory experimental (Intan & Khariri, 2020). This research was conducted to test the effectiveness of cream preparations from each concentration of cassava leaf ethanol extract (*manihot usculenta crantz*) on bruise wound healing on rabbits (*leppus negricollis*). In accordance with the theory above, the type of research is by classifying cassava leaf extract (25%, 50%, 75% and 100%) and then given treatment to test animals. The population in this study were local male rabbits (*Lepus Negricollis*). The samples used in this study were experimental animals, namely 5 local male rabbits (*Lepus Negricollis*) which would be divided into 2 groups (treatment group and control group). Analysis of data obtained from observations of the quality of cream preparations in the form of qualitative descriptive data. Qualitative descriptive data was carried out to determine the effectiveness of cassava leaf ethanol extract cream with different concentrations, bruise healing in rabbits, organoleptically test observations, homogeneity test, pH test and cream spread ability.

4. RESULTS AND DISCUSSION

4.1. Research Results

a. Extraction

Making cassava leaf extract using maceration method using 70% ethanol solvent. The cassava leaves used were 3015 grams and for dry weight cassava leaves or leaves that have been dried are 677 grams. So that a thick extract of 27.43 grams was obtained and the extract yield was 15.166%. The results of making the yield can be seen in the table below:

Table 1. Results of Cassava Leaf Extract

Weight of Simplicial Powder (gr)	Solvent (70% Ethanol)	Extract weight (gr)	Result
416 gr	4 liters	27,43 gr	15,166 %

b. Evaluation of Physical Properties of Cream Preparations

The results of the physical properties test of cassava leaf ethanol extract cream preparation can be seen in table 2. The physical properties tested include organoleptic, homogeneity, pH, and cream spread ability.

Table 2. Results of Physical Properties Test of Cassava Leaf Ethanol Extract Cream Preparations

Test type	Result			
	Concentration 25%	Concentration 50%	Concentration 75%	Concentration 100%
Organoleptic	Semi solid, Greenish White, Odor Typical of extracts	Semi-solid, light green, Odor Typical of extracts	Semi-solid, dark green, Odor Typical of extracts	Semi-solid, brownish green, Odor Typical of extracts
Homogeneity	No coarse grains	No coarse grains	No coarse grains	No coarse grains
Ph	6,36	5,29	5,64	5,05
Spread ability (cm)	5,05 cm	5,05 cm	5,03 cm	5,00 cm

4.2. Discussion

In this study, the effectiveness of cassava leaf ethanol extract cream (*manihot utilissima crantz*) on bruises in rabbits (*lepus negricolis*) was tested. The plant material used in this study was cassava leaves (*manihot utilissima crantz*).

Making cassava leaf extract using maceration method using 70% ethanol solvent, maceration method is a fairly simple and practical method by soaking the simplisia powder with solvent. In the process of extracting using powder material in order to expand the surface so that the solvent is easier to attract compounds contained in simplisia (Fahmi et al., 2019). One of the advantages of using 70% ethanol solvent is that it is easy for the solvent to dissolve organic compounds contained in cassava leaf simplisia and can inhibit the growth of microorganisms (Dwitiyanti & Kusuma, 2015).

Cassava leaf simplisia powder that has been prepared as much as 416 grams is put into 4 containers with the same size/weight into a 1000m beaker glass. Cassava leaf simplisia powder is soaked using 70% ethanol solvent as much as 4000m where each container is 1000m, in a ratio of 1: 1. Then, the soaked powder is allowed to stand for 3 days while occasionally stirring it aims to increase contact between the powder and the solvent in order to get optimal results. After 3 days, filtering will be carried out using filter paper coated with tissue, so that the results of the macerate obtained are cleaner from the pulp. The results obtained are 3920 m of liquid extract which will then be thickened using a rotary evaporator to obtain a thick extract free from ethanol. Thickening is done in order to remove 70% of the liquid extract which is ethanol contained in the liquid extract. The results of the thick extract obtained were 27.43 grams. Extract yield is the ratio between the weight of the extract obtained after the thickening process and the weight of the initial simplisia.

The results of the yield calculation obtained the yield value of cassava leaf extract which is quite high, namely 15.166%. The extract yield is carried out to determine the amount of extract obtained during the extraction process. In addition, the yield data has a relationship with active compounds if the amount of yield is more, the number of active compounds contained is also more (Hasnaeni & Wisdawati, 2019). So, if the active

compounds contained in cassava leaf extract are more and more, the healing process of bruises in rabbits will be maximized.

The process of making cassava leaf ethanol extract cream, namely by preparing all the tools and materials. then the ingredients contained in the formula are separated into oil and water phases. The oil phase includes stearic acid, cera alba, parifin liquid, and nipasol melted in a vaporizer cup on a heater at a temperature of 70-75% until melted. The aqueous phase includes: TEA, distilled water, and nipagin were dissolved in an erlemeyer using hot temperature and stirred using a stirring rod until dissolved. Then, the two phases are mixed by putting the oil phase into a hot mortar and then crushed or crushed, after which the water phase is added slowly while continuing to be crushed at a constant speed until homogeneous and creamy. Finally, the cassava leaf extract that has been weighed is then dissolved a little with hot water and then mixed into the cream base little by little until homogeneous.

Organoleptic tests were conducted to observe changes in shape, color, and odor of each cream preparation. From the observation of cassava leaf ethanol extract cream, it was found that there was no difference in shape and odor. However, the distinguishing factor among the cream preparations was the color, which varied due to the addition of active substances from the ethanol extract of cassava leaves. At a concentration of 25%, the color obtained was greenish white, attributed to the addition of 25% active substance. At a concentration of 50%, the color was light green due to the inclusion of 50% active substance. At a concentration of 75%, the color was dark green, resulting from the addition of 75% active substance. At a concentration of 100%, the color obtained was brownish green, due to the incorporation of 100% active substance. The more cassava leaf ethanol extract used, the more intense the color of the preparation.

This homogeneity test is carried out once and to determine whether the active substances and ingredients used are well mixed, namely the preparation must show a homogeneous composition and no coarse grains are visible (Roosevel et al., 2019). The results of the homogeneity of the cream preparation with concentrations of 25%, 50%, 75%, and 100% show that the cassava leaf ethanol extract cream preparation does not have coarse grains on the glass object, so the cassava leaf ethanol extract cream preparation is declared homogeneous. This research is in line with research conducted by Putri (2019) which states that the homogeneity of a cream is evidenced by the even color of the cream for each formula and the absence of particles in the cream because the ingredients in the cream are well mixed and there are no coarse grains.

The ideal topical preparation is not irritating to the skin. The cream pH test is carried out to determine whether the preparation is in accordance with the pH of the skin so that it is safe to use the preparation to avoid skin irritation (Roosevelt et al., 2019). Then skin irritation will be very influential if the cream preparation is too acidic or too basic, the pH requirement of topical preparations is between 4.5-6.5 (Ulaen et al., 2012). The results of pH testing based on the average results of the four cassava leaf ethanol extract cream formulations meet the requirements of a good pH test (can be seen in the table). Where the results obtained from the pH of the cassava leaf ethanol extract cream preparation the highest pH was at a concentration of 25% with a pH of 6.37, followed by a concentration of 50% with a pH of 5.29 then a concentration of 75% with a pH of 5.64 and the lowest concentration of 100% with a pH of 5.06%.

The spreadability test has a spreadability requirement for topical preparations, which is around 5-7 cm (Bintang, 2019). Testing the spreadability of the cream is done to determine the ability of the speed of spreading the cream on the skin when applied to the skin. Based on table 10, it is known that in the observation of the spreadability test carried out once the test obtained the results of each preparation, namely in the preparation with a concentration of 25% and 50% the results obtained were 5.05cm in the preparation with a concentration of 75% obtained the result of 5.03cm, while in the preparation with a concentration of 100% obtained the result of 5.00cm. Normal spreadability ranges between 5-7 cm which is good for a cream preparation.

In this study, the test animals used were male local rabbits (*Leppus negricolis*) aged 3-4 months and weighing 1.2-1.5 kg. Test animals were previously acclimatized for 1 week. A total of 5 rabbits were grouped into 2 different groups. Consisting of 4 rabbits in the treatment group and 1 rabbit in the control group. Where in the treatment group rabbits will be applied with cassava leaf ethanol extract cream, namely with concentrations of 25%, 50%, 75% and 100%, while the control group is not given any spread. Before being given a cream preparation, the test animals were shaved first on the back of the rabbit. Then the rabbits were given bruises by dropping a metal ball with the percentage of the upper range with a load weight of 129-204% of the rabbit's weight, and had a low height of 18-30 cm.

The results of the observation of the bruise test carried out on the back of the test animal by applying 4 cream preparations with different concentrations to 4 rabbits and 1 rabbit that was not given any treatment. This test was conducted on 5 rabbits with 4 wound areas so that the results obtained were more accurate and reduced the error rate, thus proving that the preparation of cassava leaf ethanol extract cream can have an effect on the healing of bruises in rabbits. This study shows that the preparation of cassava leaf ethanol extract cream (*manihot utilissima crantz*) can provide a bruise wound healing effect carried out for 14 days with preparations applied 1 x a day to the wound on the back of rabbit test animals. This is obtained from the results of observations made by researchers every 1x a day which shows that there is an effectiveness of cassava leaf ethanol extract cream (*manihot utilissima crantz*) on bruise wound healing in rabbit test animals (*lepus negricollis*).

Observations of bruise wound healing were observed, namely changes in initial wound color with changes in wound color on day 14, where faster color changes indicate effective bruise wound healing with increasing color changes from day to day. In the observations made, the wound began to change color on day 3 from the initial red color to purplish, this occurred due to the lack of oxygen supply in the area around the bruise, as a result of which the red hemoglobin turned purplish. Meanwhile, on days 9 to 14 the color of the bruise changed until it faded and the hair on the rabbit test animals began to return as before. This shows that the preparation of cassava leaf ethanol extract cream has the effectiveness of healing bruises in rabbits.

From the observation of bruise healing on the first day to day 14, it was found that the treatment group applied with 100% cassava leaf ethanol extract cream preparation gave significant results, at this concentration the bruise healing was faster than all groups. Where the healing results were obtained on day 14, the bruises disappeared slowly and returned to the original color of the skin and the hair on the rabbits grew back as before. Then followed by the treatment group applied with 75% cassava leaf ethanol extract

cream, the results were observed on day 14 where the color of the bruise turned lighter, namely pale yellow or light brown, this stage is the final stage of the bruise healing process.

Then in the healing of test animals applied with 50% and 25% cassava leaf ethanol extract cream, the results on the 14th day of observation of the bruise changed color to greenish purple, indicating that the colored hemoglobin contained in the blood began to break down and the healing process was underway and the hair coat began to grow and cover the bruise. The 50% and 25% concentrations experienced the same healing process. Then followed by the control group where the observation results obtained on day 14 of the bruise turned greenish purple, indicating that the colored hemoglobin contained in the blood began to break down and the healing process was underway and the hairs began to grow and cover the bruise. The wound healing process at this concentration is similar to the bruise healing process at 50% and 25% concentrations. This may be caused by differences in each concentration of the test preparation which can affect the speed of change of the bruises of each group, so that different results are obtained for the test animal groups, where the higher the concentration of the test preparation, the faster the speed of wound healing.

So, it can be concluded that the treatment with the administration of cassava leaf ethanol extract cream provides effectiveness with the improvement of bruise wound healing faster in experimental animals and the higher the concentration of the extract, the better the bruise wound healing. Chemical compounds that are thought to play a role in this wound healing process are flavonoid compounds that are anti-inflammatory because of their ability to prevent oxidation. As well as saponin compounds that have the ability as cleaners and antiseptics that function to kill or prevent the growth of microorganisms that arise in the wound so that the wound does not experience infection (Paju., 2019). Saponins also have benefits in increasing the number of fibroblast cells and stimulating collagen formation (Nur., 2020). Tannins are known to have antioxidant activity in some medicinal plants. Antioxidants play a role in capturing free radicals that can cause damage to cell membranes (Price & Wilson, 2006)

Previous research conducted by Sukmawati et al (2021) proved that the effectiveness of cassava leaf ethanol extract on wound healing in rabbits. Where what shows the results of the analysis that the ethanol extract of cassava leaves with a concentration of 5%, 10% and 20% is effective for closing the incision wound, namely the ethanol extract of cassava leaves with a concentration of 20%, which means that the higher the concentration of the extract, the faster the closure of the incision wound in rabbits (Sukmawati et al., 2021). The results of other studies from Anggraini et al (2017) which can be concluded from their research are that the administration of cassava leaf extract (*manihot usculenta*) has effectiveness in treating burns on the skin of the back of male rats. The good level of cassava leaf extract (*manihot usculenta*) seen from the percentage of burn healing is the concentration in the 3rd group because it has a healing effect with increasing concentrations, namely 75% and 100% concentrations contained, which shows the more effective and faster the healing process of bruises.

5. CONCLUSION

After conducting research on the Effectiveness of Cassava Leaf Ethanol Extract Cream (Manihot Utilissima Crantz) Against Bruises in Rabbits (*Lepus Negricollis*), it can be concluded that cassava leaf ethanol extract cream (*manihot utilissima crantz*) has an effect as a bruise wound healing which is characterized by a rapid change in bruise color and the start of hair growth in the bruise area in rabbits, ethanol extract cream of cassava leaves (*manihot utilissima crantz*) which has the effectiveness of healing bruises in rabbits is found in cassava leaf ethanol extract cream with concentrations of 100% and 75% resulting in the fastest healing compared to cassava leaf ethanol extract cream with concentrations of 25% and 50%, the healing period between the treatment group and the control group, each of which has similarities and some are different, at concentrations of 25% and 50% have the same healing process as in the control group, while at concentrations of 75% and 100% have a faster healing rate compared to the control group.

For further researchers, it is expected to be able to make observations of cassava leaf plants more broadly, by providing the latest proposals about the efficacy of cassava leaves other than as healing bruises, can be used as a reference or reference for students of Abulyatama University Aceh. As for other suggestions, namely providing information and knowledge to the public about the benefits of cassava leaves (*manihot utilissima crantz*) which are usually only used for vegetables, but cassava leaves also have properties in healing wounds.

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