P-ISSN: 2304-3075; E-ISSN: 2305-4360
International Journal of Veterinary Science
www.ijvets.com; editor@ijvets.com

Research Article https://doi.org/10.47278/journal.ijvs/2024.001

Potential of Red Fruit Oil as an Ointment for Burns on Rabbits (*Oryctolagus cuniculus)*

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Article History: 23-315 Received: 07-Oct-23 Revised: 27-Nov-23 Accepted: 23-Dec-23

ABSTRACT

Herbal medicine in Indonesia is often used as a healing medium. Red fruit as one of the endemic medicinal plants in Papua has a high content of various active ingredients and antioxidants so it can treat various diseases. The use of topical medicinal preparations in the form of ointments for the treatment of burns is considered the easiest to apply to livestock. The antioxidant content in red fruit accelerates the regeneration of dead skin cells so it is hoped that it can be used as a topical treatment for burns. Antioxidant therapy for burn management has been widely researched. This study aims to determine the quality and effectiveness of red fruit oil herbal from Papua in the ointment preparations for healing burns in rabbits (*Oryctolagus cuniculus*). This study used a completely randomized design (CRD) which consisted of 4 treatments. The treatment given was P0 = Vaseline without red fruit oil (negative control); P1 = Red fruit oil ointment 15%; P2 = Red fruit oil ointment 30%; P3 = Red fruit oil ointment 45%. Variables to be measured and observed in this study include the stability of the ointment preparation (organoleptic test, homogeneity test, spreadability test, ointment pH test, and freeze-thaw cycle stability test and the effectiveness of red fruit oil ointment against burns in rabbits. The quality of red fruit oil ointment for the treatment of burns in rabbits (*Oryctolagus cuniculus*) was the best in the P3 formulation (45% red fruit oil) but in the spreadability test, it was still relatively low.

Key words: Burn, Rabbit, Ointment, Red Fruit.

INTRODUCTION

People in Indonesia still often use herbal medicines as a medium for healing various diseases. Red fruit as one of the endemic herbal medicinal plants from Papua is often used in treating various diseases and maintaining health. Papuan society uses the fruit of this plant as a food mixture, which can increase stamina and is also used to treat worms and skin diseases (Inayatilah et al. 2022). The habitat of red fruit is mainly dominated by the texture of clay combined with dust and sand. Red fruit needs space for moist growing which is often found in Papua (Wawo et al. 2019). Red fruit contains a variety of active ingredients and is quite high so that it can prevent and treat various diseases. Red fruit contains various active components, namely α-carotene, β-carotene, β-chipstosantin, and α-tocopherol, as well as unsaturated fatty acids, especially oleic acid, linoleic and palmitoleic (Surono et al. 2008).

Burns is one of the health problems that often occur in daily life both humans and livestock. Burns are damage to the skin protection function accompanied by the loss of continuity of epithelial tissue with or without damage to other tissues such as muscles, bones, and nerves caused by several factors, namely: pressure, incision and wound due to surgery (Ryan 2014). Burns are injuries of the epidermis, dermis, and hypodermis caused by contact with heat sources such as fire, hot water, chemicals, and electrical, and electromagnetic energy (Rose and Chan 2003). According to the World Health Organization (WHO), in 2017 there were approximately 180,000 burn-related deaths where 2/3 parts focused on Africa and South-East Asia. Burns are a global health problem in poor countries and those injuries are associated with high costs in public health systems, because of prolonged hospitalization periods and rehabilitation with possible infectious processes that can lead to death from sepsis (Martínez-Higuera et al. 2021).

The use of topical drug preparations in the form of ointments for the rehabilitation of burns is considered the easiest to apply to livestock. The antioxidant content can accelerate the regeneration of dead skin cells so it is expected to be a topical treatment for burns. Red fruit oil ointment is a semi-solid topical preparation with red fruit extract content in the form of, a soft mass that is easily

Cite This Article as: Purwanta and Timur NPVT, 2024. Potential of red fruit oil as an ointment for burns on rabbits (*Oryctolagus cuniculus*). International Journal of Veterinary Science 13(4): 508-513. https://doi.org/10.47278/journal.ijvs/2024.001

applied and used for the use of epidermis and dermis mainly protects wounds, moisturizes wounds, and removes necrosis tissue and controls infections/avoid contamination, comfortable to use and reducing pain when changing wound bandages. This study aims to determine the quality and effectiveness of the herbal ointment of red fruit oil against the healing of burns in rabbits (*Oryctolagus cuniculus*).

MATERIALS AND METHODS

Ethical Approval

Before the research was carried out, the research team submitted an Ethical Clearance (EC) to the Animal Ethics Committee of the Udayana University Faculty of Veterinary Medicine which takes approximately 1 to 3 months. The purpose of this procedure is that in experimental animal research, it remains in conditions that are guaranteed by the 5 principles of animal welfare. This research was approved by the Animal Ethics Committee with the Animal Ethics Approval Certificate Number: B/84/UN14.2.9/PT.01.04/2022.

Study Period and Place

The study was conducted from 3 February 2022 to 18 May 2022 and was held in two places, namely, in the Integrated Livestock Laboratory, Campus I of the Manokwari Agricultural Development Polytechnic, and at TEFA Campus II of the Manokwari Agricultural Development Polytechnic, Manokwari, West Papua.

Research Material

The research tools used were digital sitting scales, analytical scales, glass bowls, scissors, tweezers, 100 mL pot cream, pH meters, glass, labels, room thermometers, refrigerators, hair shaver, bunsen burner, rabbit cages, and equipment. The research materials used include red fruit oil, white album Vaseline, aquadest, physiological NaCl, 70% alcohol, local anesthesia cream, and 20 rabbits and forage feed.

Making Red Fruit Oil Ointment

The white Vaseline was weighed on the cup and then 0.1mL of liquid paraffin was added, then red fruit oil was added according to the specified formulation. Then stir until the Vaseline was added gradually into the mortar while grinding and then put into the container.

Stability Test for Preparation of Red Fruit Oil Ointment

Organoleptic Test

An organoleptic test was carried out by observation of the ointment preparation from the shape, smell, and color of the preparation. According to the Department of Health of the Republic of Indonesia, the specifications for the ointment that must be met are choosing a semi-solid form, the color must comply with the specifications at the time of initial manufacture of the ointment and the smell is not rancid (Sari and Maulidya 2016).

Homogeneity Test

The homogeneity test of the ointment preparation was carried out by applying the ointment to a piece of glass or other transparent material which must show a homogeneous composition. A homogeneous ointment was characterized by the absence of lumps in the smearing results, a flat structure, and a uniform color from the starting point of application to the end point of application. The tested ointment was taken in three places, namely the top, middle, and bottom of the ointment container (Sari and Maulidya 2016).

Spreadability Test

Five grams of ointment was placed on a round glass with another glass placed on it and left for 1 minute. The spread diameter of the ointment was measured. After that, 100 grams of weight were added and allowed to stand for 1 minute and then a constant diameter was measured (Pratimasari et al. 2015). The diameter of good ointment spreadability is between 5-7 cm (Sari and Maulidya 2016).

pH Ointment Test

Measurement of the pH value using a pH meter tool dipped in 0.5g of ointment which has been diluted with 5 mL of distilled water. The pH value of a good ointment is 4.5-6.5 according to the pH value of human skin (Sari and Maulidya 2016).

Stability Test of Freeze-Thaw Cycle

The physical stability test was carried out using the freeze-thaw cycling method. Freeze-thaw cycling was carried out by storing the preparations at 4°C for 24 hours and then being transferred to 40°C for 24 hours (one cycle). Stability testing was carried out for 6 cycles (Suryani et al. 2017). Warnida et al. (2016) states that the stability test with freeze-thaw cycling is carried out to see the stability of the preparation of the temperature factor. Observations were made by observing physical changes in the form of organoleptic, scattered power, adhesion, pH, and viscosity before and after freeze-thaw cycling. Inadequate can arise because of the storage process at extreme temperatures compared to room temperature.

The Effectiveness Test of Red Fruit Oil Ointment

Experimental Animal Treatment

Twenty experimental animals were divided into 4 treatment groups. Experimental animals were treated with second-degree burns on the left side of the back. Started with shaving the left back of the rabbit with an area of 5 x 5 cm.

Previously, topical administration of anesthetic was carried out on the surface of the skin which would be induced by burns. The anesthetic used was lidocaine 39.9% in topical cream preparations. Use this drug in the following way (according to the recommendations for using the drug on the brand label). After confirming that the rabbits were under anesthesia, it was then followed by disinfection on the left side of the rat's back that had been shaved, using 70% alcohol. Burns was made by using a metal plate that has a measurement extensive of 2 cm x 2 cm. The iron metal plate was preheated with a fire at 100°C for 30s. Then an iron metal plate was affixed to the dorsal left side of the rabbit alternately for 20s to form a second-degree burn (Khoo et al. 2010). The action ends with giving red fruit oil ointment. Red fruit oil ointment formulations using variation ointment base are presented in Table 1. Each treatment group received the following treatment:

P0 = Vaseline without red fruit oil (control)
P1 = Red fruit oil ointment 15%
P2 = Red fruit oil ointment 30%
P3 = Red fruit oil ointment 45%

Red fruit oil ointment and Vaseline without red fruit oil were applied topically 2 times a day for each group, namely at 07.00 AM and 07.00 PM for 21 days starting on the first day after second-degree burns were performed on the research. Measurements were taken once every 7 days, for 21 days. After completing the treatment, on the 21st day, another examination was carried out on the healing of burns in the experimental animals to monitor the effect of the red fruit oil ointment given to the experimental animals.

Burns Examination Technique

Examination of burn healing was carried out using a millimeter block has been modified to determine the burns extensive in experimental animals during treatment. The parameter used in this study to determine burn healing is the reduction in the burns extensive in mm (millimeters) (Milzam et al. 2021).

Burns Healing Activity Test

The test was carried out using 5 rabbits which were first adapted to the new environment for 3 days. After being adopted, the rabbit is ready to be used as a test animal. Experimental animal rabbits were shaved on their backs as much as 1 part with a size of 5 x 5cm, before being induced with a heat induction device in the form of a metal plate with a diameter of 2cm which was heated for 30s and affixed to the rabbit's back for 20s (Khoo et al. 2010). Each experimental animal was given 1 part of the wound, wound I (control), and wounds II, III, and IV (treatment). Before the induction procedure with hot metal, the rabbit was applied anesthetic topically to the skin surface to induce the burns. The anesthetic used was lidocaine 39.9% in topical cream preparations. Use this drug in the following way (according to the recommendations for using the drug on the brand label).

Each burn was treated according to its respective group where each part of the wound was treated with ointments with various treatment formulations (15%, 30%, and 45%). Basting was done twice a day. Observations were made on the healing effect of burns every day for 21 days of observation or until the burns healed.

Data Analysis

The method used in this study was an experiment using a completely randomized design (CRD) consisting of 4 treatments and 5 replications. The treatment given was P0 = Vaseline without red fruit oil (control); P1 = red fruit oil ointment 15%; P2 = red fruit oil ointment 30%; P3 = red fruit oil ointment 45%. Variables to be measured and observed in this study include the stability of the ointment preparation (organoleptic test, homogeneity test, spreadability test, ointment pH test, and freeze-thaw cycle stability test and the effectiveness of red fruit oil ointment against burns on rabbits.

RESULTS

Quality of Red Fruit Oil Ointment

The results of the stability test of the red fruit oil ointment stability that has been carried out are as follows:

Organoleptic Test

Organoleptic test result from the application of red fruit ointment with various concentrations on rabbits are presented in Table 2. The organoleptic test showed the same characteristics as the red fruit ointment and the red fruit oil, specifically in smell and color. The ointment texture was semi-solid in each determined concentration percentage.

Homogeneity Test

Homogeneity test results from the application of red fruit oil ointment with various concentrations on rabbits can be seen in Table 3. The homogeneity test of red fruit oil ointment showed a fairly flat structure at the top, middle, and bottom of the ointment that has been homogeneous and shows a uniform color according to the original color, namely, the color of the fruit oil red.

Spreadability Test

Spreadability test results from the application of red fruit oil ointment with various concentrations on rabbits are presented in Table 4. The spreadability test showed a varied spread diameter for each determined percentage concentration. The biggest spread diameter with ballast was 3.6cm showed in P3 which is 45% concentration and the smallest was 2.3cm in P2 which is 30% concentration.

Table 1: Red fruit oil ointment formulations using variation ointment base on rabbits

Formulation	Concentration (g)			
	P0 (control)	P1 (15% RFO)	P2 (30%RFO)	P3 (45%RFO)
Ointment-based	100	85	70	55
Red Fruit Oil	0	15	30	45

Table 2: Organoleptic test result from the application of red fruit ointment with various concentrations on rabbits

Treatment	Form	Smell	Color of preparation
P0	Semi-solid	Not rancid and typical ointment	White
P1	Semi-solid	Typical of red fruit oil and not rancid	Red
P2	Semi-solid	Typical of red fruit oil and not rancid	Maroon
P3	Semi-solid	Typical of red fruit oil and not rancid	Maroon

Table 3: Homogeneity test result from the application of red fruit oil ointment with various concentrations on rabbits

Treatment	Structure	Color	Average Number of Lumps
P0	Flat Structure	Uniform	2
P1	Flat Structure	Uniform	4
P2	Flat Structure	Uniform	7
P3	Flat Structure	Uniform	2

Meanwhile, the biggest spread diameter without ballast was 1.8 cm in P2 and the smallest was P3.

Spreadability Test

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Table 4: Spreadability test result from the application of red fruit oil ointment with various concentrations on rabbits

Treatment	The diameter of the spreadability without ballast (cm)	The diameter of the spreadability with ballast (cm)
P0	0.5	3
P1	2	3.5
P2	1.8	2.3
P3	1.5	3.6

Ointment pH

The pH 4.5 in P3 and pH 5 in P0, PI and P2 were recorded.

Stability Test of Freeze-Thaw Cycle

Observation results of freeze-thaw cycling test of red fruit oil ointment with various concentrations on rabbits are presented in Table 5. The physical stability test was carried out by the freeze-thaw cycling method toward organoleptic, homogeneity, spreadability, pH and viscosity, before and after freeze-thaw cycling. The test showed that the ointment was stable in all parameters.

Table 5: Observation results of freeze-thaw cycling test of red fruit oil ointment with various concentrations on rabbits

Treatment	Original Condition	Close Condition
P0	Stable	Stable
P1	Stable	Stable
P2	Stable	Stable
P3	Stable	Stable

Effectiveness Test of Red Fruit Oil Ointment in Healing Burns on Rabbits

The average reduction of extensive burns on each week is presented in Table 6. Examination of burn healing was performed using a modified millimeter block to determine the area of burns in the animal trial during treatment. Reduction of burns was measured every week on the seventh day, for 21 days (3 weeks) hence that data is obtained for three weeks. Data from the reduction result of burns extensive on each week was then analyzed by the Duncan Test as presented in Table 6. The best burn wound healing in the first week was in P2 (RFO 30%), this is indicated by the average reduction of the largest burn wound in this group. The best burn wound healing in the second and third week was in P3 (RFO 45%), this is indicated by the average reduction of the largest burn wound in this group. However, the final results showed that P3 was the best treatment for rabbit burn wound healing in this study.

DISCUSSION

Several studies reported the pharmacological effects of red fruit extract as antimicrobial, both as an anti-fungal, anti-bacterial, and as an anti-viral agent including as inhibitory power on *Escherichia coli* and *Staphylococcus aureus* bacteria (Asrianto et al. 2021; Tharukliling et al. 2021), *Streptococcus mutant*, *Streptococcus saungunis* (Damayanti et al. 2020) and *Enterococcus faecalis* (Herdiyati et al. 2020). Red fruit extract contains chemical compounds of flavonoids, tannins, alkaloids, steroids, and triterpenoids. The results of the bioactivity test for red fruit extract were not sensitive to the fungus *Candida albicans* (Asrianto et al. 2023).

Ointment (*unguenta*) is a preparation of external drugs in a semi-solid form that is easily applied and used for the skin or lender membrane (Anwar 2012). Organoleptic testing is performed by observing the ointment preparation from the preparation's shape, odor, and color. According to the Indonesian Department of Health, the ointment must meet it's including selecting semi-solid shape, the color must be by the specifications when making the early ointment and the smell should not rancid. The organoleptic test of the ointment compared the ointment and the red fruit oil. The organoleptic test showed similar characteristics specifically in smell and color. The ointment of each determined concentration percentage showed semi-solid texture. All the results met the condition of good ointment quality parameters which are semi-solid, typical-smelling, and colored-like to the original. Hence, the formulated ointment was determined as a good quality ointment by the organoleptic test.

The homogeneity test of ointment preparation is performed by applying ointment to a glass or other transparent material that must show a homogeneous arrangement. The homogeneous ointment is characterized by the absence of lumps on the results of the application, the flat structure, and a uniform color from the starting point of the processing to the end point of the processing. The ointment tested was taken in three places, namely the top, middle, and bottom of the ointment container (Sari and Maulidya 2016).

Table 6: Mean reduction in burn area per week (mm^2) results with various concentrations on rabbits

Treatment Groups	Week 1	Week 2	Week 3
P0 (control)	121.4±71.76a	193.6±74.29a	58.4±31.60a
P1 (15% RFO)	157.6±91.34ab	159.4±101.70a	28.8±27.80a
P2 (30% RFO)	244.4±32.25b	168.8±20.99a	106.0± 45.62b
P3 (45% RFO)	210.8±21.16 ab	307.2±34.50b	158.2±41.59c

Values with different alphabets in a column differ significantly ($P<0.05$).

The spread diameter of good ointment is between 5-7 cm (Sari and Maulidya 2016). The spreadibility test of the formulated ointments showed spread diameters below the standard. It might be caused by the low ability of ointment to bind with the base, resulting in easier separation of the active ingredient from its base. The use of red fruit oil might also affect the spreadability result. Ointment preparations have lower extensive than other topical preparation such as gels and cream, so their spread is generally lower than other topical preparation. The pH test showed pH 4.5 in P3 and pH 5 in P0, PI, and P2. This result has met a good pH standard for the ointment, which is 4.5-6.5 (Sari and Maulidya 2016).

Giving red fruit ointment with a concentration of 45% (P3) provides a faster wound-healing process. Red fruit contains bioactive molecules such as tocopherols, alpha-tocopherols, beta-carotene, tannins, and flavonoid components which have the ability to help the wound healing process. Red fruit contains nutrients needed for wound healing such as vitamin A and vitamin C (Asri 2017). Antioxidant, considered as the first line of defense mechanism against free radical damage, delays, removes, and prevents oxidation process that may harm target molecules (Yadav et al. 2019).

The tocopherol in the red fruit is natural vitamin E which can play a role in strengthening the immune system by stabilizing cell membranes and protecting the skin. Meanwhile, beta-carotene in the body will be converted into vitamin A, which is an important substance for healing burns. Tannin helps the wound-healing process by increasing the number of capillaries forming. Flavonoids act as antioxidants that function to delay or inhibit oxidation reactions by free radicals (Asri 2017). Antioxidant supplementation is a viable adjuvant therapy option that has shown promise for the suppression of burn conversion in severe burn cases (Wardhana and Halim 2020).

The administration of red fruit ointment with diverse concentrations demonstrates divergent weekly disparities in the healing process. The experimental group treated with P0, which consisted of white vaseline without red fruit, had a slower rate of healing. The treatment using P0 was specifically identified as the control group in the study. The findings presented in P1, P2, and P3, wherein red fruit oil concentrations of 15, 305 and 45% respectively, indicate a correlation between the concentration of red fruit oil and the rate of burn wound healing. A positive correlation exists between the concentration of red fruit and the rate of healing, whereby a higher concentration of red fruit is associated with a faster healing process.

This study represents the inaugural investigation into the potential impact of the application of red fruit ointment on the process of burn wound healing. The ointments with a 45% concentration of red fruit have demonstrated the most rapid healing process, which was attributed to their elevated levels of antioxidants compared to other concentrations. This heightened antioxidant content is believed to enhance the efficiency of the healing process, resulting in accelerated wound recovery. This research is in line with research that has been carried out previously on mice wounds. There is an effect of red fruit oil gel emulsion on the length of the incision wound on day 7 and day 14. There is an effect of red fruit oil gel emulsion on the thickness of the skin epithelium and on the average number of fibroblast cells (Inayatilah et al. 2022). The conducted study investigated the impact of red fruit oil, derived from red fruit, on the wound healing process in mice. The findings revealed that higher concentrations of red fruit oil resulted in an accelerated healing process. The enhanced epithelialization process and reduced mucosal permeability resulting from the elevated flavonoid and tannin levels in red fruit contribute to the reinforcement of mucosal linkages, hence impeding the infiltration of microbes and chemical irritants into the wound (Saa et al. 2022).

Di Lonardo et al. (2019) found that α-tocopherol acetate as vitamin E (an essential micronutrient with strong antioxidant activity) can stimulate granulation tissue, it seems to reduce bacterial growth, modulate angiogenesis, improve epithelialization, and advanced the healing of potential infective burn wounds. This research is in line with the case study conducted by Firdaus and Pramono (2015) regarding diabetic wound healing. The evaluation of the results found was that the use of primary dressings with the active ingredient red fruit could cover the wound and heal within one month. This is because antioxidants reduce inflammation and stimulate skin regeneration. Preparations in the form of oil-based ointments retain more skin moisture thereby accelerating the healing of diabetic wounds.

The use of herbal plants for the treatment of burn wounds has been explored across several plant species, such as the application of ointment derived from kitolod leaves (*Isotoma Longifora*) (Ghofroh 2017), soyogik leaf ethanol, despite the dispersion test power is still relatively low (Tumigolung et al. 2019) and aloe vera (Halwa 2018). The study on the use of red fruit ointment shows effectiveness in healing burns wound healing process even though the spreadibility test of the ointment has not met the required standard. Despite the absence of satisfactory findings in the spreadability test conducted on the red fruit ointment formulated for burn treatment in this study, it is important to note that the presence of antioxidant properties in red fruit still contributes to the acceleration of burn wound healing. The exploration of other preparations may be deemed worthy of consideration. The study conducted by Kusumawardhani et al. (2015) examines the efficacy of betel leaf extract (Piper betle Linn) essential oil in the treatment of burn wounds. The findings of the study indicate that the use of betel leaf extract can expedite the healing process of burns and enhance the development of capillaries and fibroblasts.

Conclusion

The quality of red fruit oil ointment for the treatment of burn on rabbits (*Oryctolagus cuniculus*) is the best in the formulation of P3 (45% red fruit oil) however, the scattered power test is still relatively low. The effectiveness of red fruit oil ointment with P3 treatment (45% red fruit oil) is the best treatment for healing burns on rabbits (*Oryctolagus cuniculus*).

Acknowledgments

My sincere gratitude to colleagues of Manokwari Agricultural Development Polytechnic for their assistance and cooperation during the performance of this research, and to all parties who have assisted so that this research can run smoothly.

Author's Contribution

Purwanta and Ni Putu Vidia Tiara Timur designed the study, carried out the practical, and data tabulation. Ni Putu Vidia Tiara Timur wrote the manuscript. All authors revised and approved the final version of the manuscript.

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