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Irritation Test of Cream Preparations Made from Purple Cabbage Extract Against Healthy Skin Using The Path Test Method

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Abstract
Testing for skin irritation caused by new substances is a critical component of safety evaluation procedures. Pharmaceutical formulations and active ingredients intended for topical application have the potential to cause skin irritation, necessitating thorough safety assessments prior to public distribution. This study aimed to evaluate the primary irritation potential of a purple cabbage extract cream using the patch test method on healthy older adults. The experimental research involved 18 volunteers, who were administered 0.625% purple cabbage extract cream and a placebo preparation without the test substance. The test materials were applied twice daily over a period of 72 hours. Observations were conducted at baseline (0 hours) and at 24, 48, and 72 hours post-application. The degree of skin irritation was then calculated based on the recorded data. The results indicated a primary irritation index of 0.1, suggesting that the purple cabbage extract cream did not cause skin irritation. It can be concluded that the purple cabbage extract cream is safe for skin application in the tested population. Future research should explore the effects of purple cabbage cream on different skin locations, as skin sensitivity can vary across different areas of the body.

Keywords: Irritation Test, Patch Test, Purple Cabbage Extract Cream.

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1. INTRODUCTION

Indonesia's abundant natural wealth means that it contains various natural ingredients that are beneficial to human health. Purple cabbage (*Brassica oleracea*) is a plant that grows widely in Indonesia and has various health benefits because of its rich contents of retinol, vitamin B, ascorbic acid, alpha-tocopherol, minerals, potassium, calcium, phosphorus, sodium, and iron. Purple cabbage has an attractive color that is produced by the anthocyanin content (Mizgier, et al., 2016; Jin, et al., 2018; He, et al., 2020; Fenger et al., 2021; Araújo, et al., 2023).

Previous studies have shown that the anti-inflammatory effect of cabbage is due to its high antioxidant content (Kim, 2020; Kwak, et al., 2020; Ryou, et al., 2021; Oh, et al., 2024; Sabin, et al., 2024). Cabbage plants, including purple cabbage, are known for their significant health benefits due to their rich content of antioxidants and other bioactive compounds (Favela-González, et al., 2020; Moreb, et al., 2020; Zayed, et al., 2023; Wulandari et al., 2024). Other studies have shown that cabbage can reduce inflammation and act as a cytoprotective agent by preventing oxidative damage and stimulating cell regeneration (Uuh-Narvaez, & Segura-Campos, 2021). Previous research on the topical anti-inflammatory effects of purple cabbage (*Brassica oleracea*) extracts and fractions has demonstrated that the methanol fraction of purple cabbage exhibits more optimal anti-inflammatory effects, making it suitable for cream preparations to enhance the anti-inflammatory effect of purple cabbage (Deswani et al., 2022).

Cream is a semi-solid preparation containing one or more medicinal ingredients dispersed and dissolved in a suitable base material (Pradeepa, Kumar, & Murali, 2023). The improper use of chemicals can cause skin irritation. Irritation is the reaction that occurs when an irritating material is used. Evaluation of the irritating properties of topical preparations is crucial. This test was conducted to ensure that the topical preparation used was safe for human skin. The irritation test can employ the patch test method on human skin by observing the presence of erythema and edema that arise when the preparation is used (Foti, et al., 2021; Raabe et al., 2024).

Based on the results of previous preclinical research, the Purple Cabbage Extract (EKU) cream formulation with an irritating effect of 0.2 was categorized as very slightly irritating in rat test animals. Anti-inflammatory studies have been conducted to test the anti-inflammatory effects of the ethyl acetate extract (Deswani et al., 2022). Therefore, there is a need for research on the development of a purple cabbage extract cream innovative product as an anti-inflammatory phytopharmaceutical product for arthritis in the elderly. Specifically, This study aimed to evaluate the primary irritation potential of a purple cabbage extract cream using the patch test method on healthy older adults.

2. RESEARCH METHOD

A pre-experimental study used a group pre-test and post-test design to discover cause-and-effect linkages in one group of participants (Nursalam, 2013). An exploratory strategy was used to ascertain whether the treatment had an irritating effect on the skin. Application of cream containing purple kale extract. To determine if the qualities shown in experimental animals were also evident in humans, purple cabbage extract cream was tested in healthy volunteers (60–70). This stage establishes a connection between the dose and the results produced. This phase I clinical study was conducted in an open manner, without comparison or cover-up.

The clinical experiment was open/undisguised (open trial or open-label), and both the researcher and subject were aware of the therapy being administered. Based on inclusion and exclusion criteria, 18 people consisting of men and women test subjects were chosen based on the inclusion and exclusion criteria. Age requirements of 60 years or older, healthy knee skin, a lack of a history of topical medicine allergies, the ability to carry out daily activities on one's own inside the facility, a doctor's certification of good health, and agreement and signature of informed consent are all requirements for inclusion. Elderly people, joint symptoms, a history

of allergies, partial knee skin, and medications that may interfere with skin responses (such as steroids, anti-allergy medications, and topical immune modulators within one month of testing, according to data from the subjects) are given treatment with intensive observation by trained health personnel (nurses and doctors) and carried out in a place with adequate facilities for monitoring or observation during the trial. The irritation test was carried out with a cream containing an active substance consisting of the water fraction of purple cabbage extract 0.3%-10%; Cera Alba 3-30%; Span 80 5-20%; Paraffin Liquid 20-40%; Glycerin 0.5-2%; Aquades, where the amount of distilled water is not more than 50%. The placebo cream contained all substances except purple cabbage extract 0.3%-10%. The material is attached or applied to the part of the knee marked with a marker or a mark with a diameter of 2.5 cm.

A Test step the intervention carried out was applying purple cabbage cream or placebo cream to the skin of the subject's right and left knee joints. The dose was 2 × a day, where each knee was given the same medication for 3 × 24 h. Participants and survey personnel (nurses) could not differentiate between placebo drugs and drugs containing active substances. The drug code was only known by the researcher; the subject's knee was coded the same as the drug code to avoid errors in administration.

Figure 1. Left knee: Drug code 1

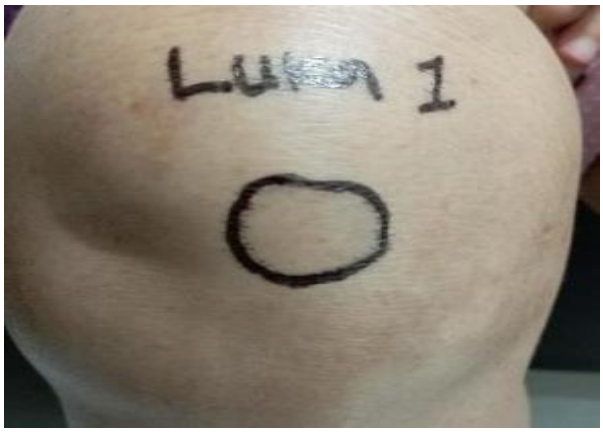
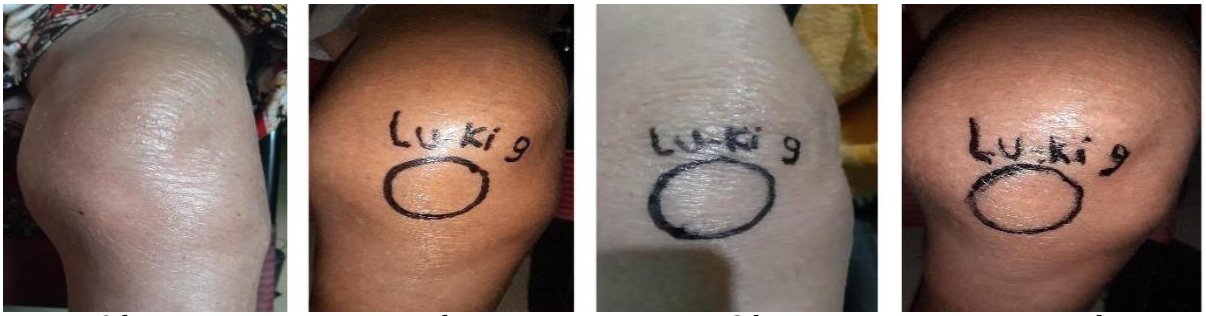


Figure 2. Right knee: drug code 2



0 hours 24 hours 48 hours 72 hours

Figure 3. Trial results with irritation and edema index of 0

Observations of the irritation effects were carried out at intervals of 0, 24, 48, and 72 hours following the application of the test substance. Erythema and edema on the skin area where the test substance was applied are indicators of a skin irritation reaction in healthy skin (Raabe et al., 2024). The skin condition was viewed daily, and images taken before and after administration were used to measure and screen the results. General practitioners performed evaluations before and after treatment (Heje, Vedsted, & Olesen, 2011).

The nurse applied the medicine and assessed the condition of the patient's skin before applying the medicine. If there were signs of redness, the nurse immediately consulted the doctor-in-charge. During the assessment, volunteers could shower or wash their knees without soap for at least 1 h after applying the medication. To ensure the smooth implementation of clinical trials and the success of treatment, cream administration is performed by nurses, and

the medicine is stored by the nurse in charge. Two nurses were responsible for to 4-5 volunteers. Medication is given after bathing in the morning and evening at the same time to maintain patient compliance and other provisions that apply during clinical trials. Evaluation was carried out at 0 h before administering the test preparation, and 24 hours, 48 hours, and 72 hours after administering the test preparation. Furthermore, each skin condition is assigned a value as follows (Draize, 1944):

a. Erythema
   - No erythema = 0
   - Very mild erythema = 1
   - Mild erythema = 2
   - Moderate erythema = 3
   - Severe erythema = 4

b. Edema
   - No edema = 0
   - Very mild edema = 1
   - Mild edema = 2
   - Moderate edema = 3
   - Severe edema = 4

Analysis of test result data was carried out by calculating the irritation index using the following formula: (erythema score 24+48+72 hours)+(edema score 24+48+72 hours).

The number of volunteers The irritation index obtained was compared with the irritation score to determine the severity of the irritation reaction, not irritating: 0.0. Very slight irritation 0.1-0.4, slight irritation 0.41-1.9, moderate irritation 2.0-4.9, and severe irritation 5.0-8.0. This research met the requirements to carry out research with a certificate of ethical suitability description of ethical approval" (letter number No. LB.02.02/08670/2023 issued by the Jakarta III Health Polytechnic Committee of the Ministry of Health.

3. RESULTS AND DISCUSSION

Table1. Irritation Index calculation results

Volunteer	Irritation Index	
	Active substance	No Test Substance
1	0.2	0.1
2	0	0
3	0	0
4	0.1	0
6	0	0
7	0	0
8	0	0
9	0.2	0.2
10	0	0
11	0.1	0
12	0	0
13	0.2	0
14	0	0.1
16	0	0
17	0.2	0.2
18	0	0
19	0	0
20	0.2	0

Volunteer	Irritation Index	
	Active substance	No Test Substance
Amount	1.2	0.6
Average results	0.1	0.03

Note: *0.03-0.1 that means very little irritation*

Table 1 shows the results of the testing preparations with active ingredients, with an irritation index of 0.1. The test results for the preparations were included in the very mild irritation category because they range from 0.1 to 0.4. Likewise, the test results for preparations without active substances had an irritation index of 0.03, which is also included in the very mild irritation category.

DISCUSSION

The irritation test was performed on 20 volunteers, consisting of 10 men and 10 women, who met the criteria as a positive control and purple cabbage cream as a negative control. The number of volunteers in this study met the level of sample representativeness based on the minimum requirements for phase 1 clinical trials (Wang, & Ji, 2020). In the elderly, arthritis often occurs because increasing age causes human physiological functions to decline, which reduces quality of life (Cai et al., 2024). The inclusion of men and women in equal numbers ensures a balanced representation of gender, which is crucial for obtaining reliable and generalizable results. The use of a positive control and a negative control is a standard practice in clinical trials to validate the efficacy and safety of the test substance, in this case purple cabbage cream. The adherence to phase 1 trial requirements indicates that the study's design is rigorous and aligns with the established research standards.

Elderly individuals have sensitive skin, which makes them suitable subjects for this study. The final results of this study were also aimed at overcoming joint inflammation, which often occurs in the elderly. Joint inflammation can be managed using herbal ingredients. Purple cabbage is an herbal ingredient commonly used by the elderly. Previous research has highlighted the properties of purple cabbage, particularly the methanol extract, which has demonstrated antioxidant and anti-inflammatory effects (Ha, & Lee, 2014). Research on purple cabbage as a treatment for joint inflammation in elderly individuals has substantial potential. By focusing on a population with sensitive skin and common inflammatory conditions, this study aimed to provide practical solutions to enhance the management of arthritis. The antioxidant and anti-inflammatory effects of purple cabbage further support its potential use as a therapeutic agent. Successful outcomes from this study could lead to new, effective, and natural options for improving the health and well-being of older adults, particularly those affected by chronic joint inflammation.

Pharmaceutical preparations administered via the topical route may cause side effects, such as irritation of the skin at the site where the product is applied. This irritation can be caused by two components of the preparation: the formula and active substance used. Therefore, it is necessary to conduct safety testing as one of the requirements for preparation before it is marketed to the wider public. Irritation testing can be carried out using various methods, including the Draize, acute dermal, and patch tests (Barthe et al. 2021).

Test materials and methodology. This study aimed to evaluate the side effects of two types of creams: one containing purple cabbage extract as the active ingredient and a placebo cream that did not include this extract. The study utilized an open patch test methodology to assess the skin response to both creams applied to the knee area, a standard method for evaluating dermatological reactions to cosmetic and pharmaceutical products.

Cream composition and methodology. The tested creams included active cream which contained 0.625% purple cabbage extract within a base cream consisting of Cera Alba, Span 80, Liquid Paraffin, Glycerin, and distilled water. Placebo cream which contained all the base ingredients listed above but excluded the purple cabbage extract. The use of base ingredients in the cream was aimed at identifying potential irritation or allergic reactions caused by either

the active component or base ingredients. According to Foti, et al., (2021), the open patch test is widely used to evaluate skin reactions to topical products. This method involved applying the cream to skin areas marked with a 2.5 cm diameter, allowing systematic assessment of skin reactions on consistent sites. This approach ensures that the results obtained are reliable and can accurately identify skin responses to both active and placebo creams.

Evaluation of side effects. The primary objective was to observe whether the purple cabbage extract caused any irritation or allergic reactions compared with the placebo cream. A recent study conducted by Garg, Brod, & Gaspari, (2021), supported the effectiveness of open patch testing in detecting skin reactions caused by active ingredients in cosmetic formulations. The results from this test provide clear insights into the potential side effects of purple cabbage extract as well as the base cream ingredients. Iliopoulos, Sil, & Evans, (2022), highlighted that innovations in topical formulations require a comprehensive evaluation of both active components and excipients to ensure product safety and efficacy. This study aligns with the current trends in dermal testing, focusing on understanding skin reactions to active ingredients and base formulation components. By employing a standard patch test methodology, this research contributes valuable information to the safety assessment of new cosmetic products, particularly regarding the use of active ingredients, such as purple cabbage extract.

Thus, it can be concluded that the irritation test using both active and placebo creams applied to marked skin areas allows for thorough identification of skin reactions to the active ingredient and base components. This approach confirmed the effectiveness of open patch testing as a reliable tool for evaluating dermal responses to topical products. This study supports the use of this methodology to assess the safety and potential side effects of the new formulations.

The results of this study demonstrated that minimal irritation was observed in the test preparation without active ingredients, suggesting that participants experienced very mild irritation reactions. This finding is consistent with the nature of cream, which is a semi-solid preparation of a thick emulsion containing no less than 60% air, specifically formulated for external use. The creams tested in this study were prepared as water-in-oil (W/O) emulsions. The emulsifiers used in these formulations, which are typically anionic, cationic, or nonionic surfactants, occasionally cause mild irritation. This observation is consistent with recent research, highlighting that such surfactants may contribute to minor skin reactions, particularly in topical formulations.

Recent studies have expanded this understanding. Schmidt et al. (2011) investigated the effects of various surfactants, including anionic, cationic, and nonionic types, on skin irritation within water-in-oil emulsions. Their findings align with our observations, indicating that, while these surfactants can occasionally induce mild irritation, the reactions are generally minimal and within acceptable limits for cosmetic use. The impact of emulsifiers in water-in-oil emulsions confirmed that different surfactants can cause varying degrees of skin irritation. Their review underscores that even well-tolerated emulsifiers in water-in-oil formulations might cause mild skin reactions in some individuals, which is consistent with the minor irritation observed in our study. Similarly, Kim et al. (2023) explored skin sensitivity and irritation using various topical formulations containing different emulsifiers. Their research supports the notion that emulsifiers, which are essential for emulsion stability, can contribute to mild irritation, particularly in sensitive skin types. The use of different types of surfactants and emulsifiers in topical formulations can lead to varying degrees of skin irritation, depending on their concentration and type. In this study, observations of the irritation effect were conducted at baseline (0 hours before application), 24, 48, and 72 hours after applying the test substances. A positive skin irritation reaction was identified by the presence of erythema and edema, which were measured using a micrometer.

The application of cream containing purple cabbage extract demonstrated an irritation index of 0.1, indicating very mild irritation (Pradeepa, Kumar, & Murali, 2023). This mild irritation can be attributed to the presence of saponins in purple cabbage extract. Saponins are surfactants that can cause skin irritation at high concentrations. However, in the study conducted by Santoso et al., (2006), surfactants could induce irritation at concentrations of approximately 10%, whereas the concentration of purple cabbage extract used in our study was 0.625%. This concentration was significantly lower, ensuring that the saponin content remained below the tolerance limit and unlikely to cause substantial irritation.

Purple cabbage (*Brassica oleracea*) has been recognized for its potential anti-inflammatory properties, attributed to its rich antioxidant and phytochemical contents. Recent research supports these claims, highlighting the role of purple cabbage in mitigating inflammation in various body parts such as the intestine and joints. This study aimed to evaluate the safety of purple cabbage extract by performing an irritation test using the Draize method over a 24-hour period. The goal was to assess the potential for skin irritation following application of the test material and to establish the safety profile of the preparation.

Irritation test results showed that the formula containing purple cabbage extract had a mild irritation index, indicating minimal irritation. The control formula, which lacked the extract, did not cause irritation. These findings are consistent with those of recent studies that emphasized the safety and efficacy of purple cabbage extract in topical applications. A recent study by Chandrasenan, et al., (2016) examined the anti-inflammatory and antioxidant properties of purple cabbage and found that its phytochemical components, particularly anthocyanins and flavonoids, contribute significantly to its anti-inflammatory effects. Their research reinforces the benefits of purple cabbage in reducing inflammation while supporting its general safety in topical formulations (Chandrasenan, et al., 2016).

Overall, the evidence suggests that purple cabbage extract, owing to its antioxidant and anti-inflammatory properties, is a safe ingredient for topical applications. The mild irritation index observed in our study, along with the lack of irritation from the control formula, support the safety and efficacy of purple cabbage extract in dermatological formulations.

4. CONCLUSION

Based on the conducted research, purple cabbage cream, tested using the patch test method on elderly participants, did not cause any noticeable irritation. Specifically, no erythema was observed on the knees of healthy elderly individuals. This result falls within the category of negligible irritation, indicating that the cream does not induce significant topical irritation in human skin. Therefore, purple cabbage cream was deemed safe for further investigation. Future research should explore the effects of purple cabbage cream on different skin locations, as skin sensitivity can vary across different areas of the body. Additionally, expanding the research to include various types of inflammation beyond arthritis could provide a broader understanding of the potential therapeutic benefits of this cream.

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