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## IRRITATION TEST OF BAWANG DAYAK (*Eleutherine bulbosa* (Mill.) Urb.) EXTRACT CREAM WITH HUMAN PATCH TEST METHOD

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### ABSTRACT

Topical agents indicated for the treatment of acne have the potential to cause irritation or allergic contact dermatitis. This study investigates the irritancy potential of anti-acne cream of bawang dayak (*Eleutherine bulbosa* (Mill.) Urb.) previously tested for microbiological effectiveness with the lowest concentration of 5% and the highest concentration of 20%. The method used in this study is the human patch test. A total of 20 volunteers were recruited for the patch test study, testing the cream. The result showed that all volunteers did not experience irritation both in the 5% or 20% bawang dayak extract cream formulations. However, the interview results were found that some volunteers experienced a slight itching without any significant skin adverse reactions on the cream application. Therefore, based on these initial findings it can be safely concluded that the cream of bawang dayak does not cause significant skin adverse reaction and good enough for further development for anti-acne cream dosage form.

**Keywords:** Acne, Bawang dayak, Cream, Patch test

## 1. INTRODUCTION

Acne vulgaris is one of the skin issues that can affect anyone. Acne vulgaris is a disease that causes inflammatory (papules, pustules, or nodules) or non-inflammatory lesions (open and closed comedones) (Tan et al., 2018). Typically located on the forehead, upper chest, or back with the highest density of sebaceous follicles (Mahto, 2017). Acne vulgaris may affect all age groups but are typically experienced by adolescents who experience puberty when hormonal changes occur at 85% (Saviuc et al., 2017). While acne is a common skin issue, sometimes it can also make adolescents feel uneasy and make a significant contribution to psychological distress. The research has shown that acne faced by adolescents tends to reduce adolescent self-esteem, making them insecure or anxious (Oon et al., 2019; Prabhakar et al., 2020).

Propionibacterium acnes are Gram-positive bacteria, the normal anaerobic flora of the skin that is an essential component of the skin microbiota (Platsidaki et al., 2018). Administering antibiotics for acne treatment is most frequently done to minimize the bacterial population. However, excessive use of antibiotics may lead to bacterial resistance. Increasing the use of antibiotics worldwide without the development of new antibiotics is a very urgent problem (Canavan et al., 2016). Therefore, it is important to consider or turn from now on to using non-antibiotic preparations as far as possible (Rathi, 2011), such as exploring local anti-acne plants. Based on previous research, an ethanolic extract of bawang dayak and cream formulation have antibacterial activity against acne-causing (*P. acnes*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*), the result of the minimum inhibitory concentration (MIC) test was 0.19% (Novaryatiin & Ardhany, 2019; Novaryatiin & Ardhany, 2020). The inhibition caused by

the ethanolic extract of bawang dayak which has been tested for phytochemical compounds containing secondary metabolites such as alkaloids, flavonoids, tannins, and saponins which have antioxidant and antibacterial potential activity (Górniak et al., 2019; Othman et al., 2019; Maisetta et al., 2019; Tagousop et al., 2018; Yazdani et al., 2019; Hassan et al., 2019). Besides, the primary irritation test results in rabbits showed the ethanolic extract of bawang dayak did not irritate topically (Ardhany et al., 2019). Based on this background, it is necessary to research the irritation test on human skin further using the human patch test method to determine whether the cream is safe to use on human skin before it is used as anti-acne.

## 2. METHODS

### Plant Collection and Identification

Fresh bulbs of bawang dayak were collected from the farmer in Sei Gohong Bukit Batu, Palangka Raya, Central Kalimantan and authenticated by Dr. Joeni Setijo Rahajoe from Indonesian Institute of Sciences Research Center for Biology, Bogor Indonesia.

### Preparation of Plant Extract

The bawang dayak were cut into pieces and dried at a temperature of not more than 40°C. The dried bulb is then crushed with a grinder to become a powder. The powder of the bulbs bawang dayak was extracted with 96% ethanol using a percolator until the solvent's color returned colorless, and once the process was finished, all extracts were concentrated in a rotary evaporator.

### Formulation of Cream Preparation

Bawang dayak bulbs after the extraction process were formulated as creams by different concentration, the lowest (5%) and the highest (20%) based on the study before (Ardhany & Novaryatiin, 2019) with adding cinnamon, honey, and aqua *Menthae piperitae* to improve the odor of cream formulation as shown in Table 1. *Menthae piperitae* also can give a better creamy smell, so it is more comfortable to use (Elsaie et al., 2016).

Table 1. Bawang dayak extract cream formulation

Materials	5% bawang dayak extract cream	20% bawang dayak extract cream	Cream base
Bawang dayak ethanol extract	1250 mg	5000 mg	-
Cinnamon powder	2500 mg	2500 mg	2500 mg
Honey	2000 mg	2000 mg	2000 mg
Oil phase			
Stearic acid	5000 mg	5000 mg	5000 mg
Adeps lanae	750 mg	750 mg	750 mg
Paraffin liquid	6250 mg	6250 mg	6250 mg
Aqueous phase			
Triethanolamine	375 mg	375 mg	375 mg
Nipagin	25 mg	25 mg	25 mg
aqua <i>Menthae piperitae</i>	20 mL	20 mL	20 mL
Aquadest ad	25000 mg	25000 mg	25000 mg

### Study Design

This study was approved by the Health Research Ethics Committee of Universitas Aisyiyah Yogyakarta with ethical approval No. 1638/KEP-UNISA/V/2020. Study design of this study is pre-post-test-controlled design. Written informed consent was obtained from all participants. The inclusion criteria of this study were a healthy person, 18-30 years old, there is no history of allergic-related illness, cooperate well and willing to be volunteer for this study. The exclusion criteria of this study were an unhealthy person (excessive sweating, the skin has a wet wound, or unnormal skin). Patch test of cream ethanolic extract Bawang dayak was

conducted on 20 healthy individuals used two hands each participant, one for control and one for the cream test. The 20 volunteers tested at the same time and concentration both base and cream test, each 10 volunteers for cream with 5% w/w or 20% w/w on right hand and base on left hand. The volunteers will be informed to don't excessive activities causing sweat.

### Patch Test Study

A total of 20 volunteers were recruited for the patch test study, and each volunteer used two hands for the base and cream test. The first study for the cream test (right hand) consisted of 20 subjects, including nine men and 11 women with an age range of 19-25 years were living in Palangka Raya city, while the second study for the base test with the same volunteers (left hand). A patch test was done on the forearm of each volunteer on the first day of skin testing. The test was conducted by applying cream and base on the forearm with a diameter of  $\pm 3$  cm, 100 mg of the base, and 100 mg of cream formulation applied on the left and right forearm of the volunteers which was previously marked with a size of 4 x 2.5 cm, respectively. The method of application of cream to the volunteer forearm is shown in [Figure 1](#). After applying base and cream formulation, it was then enclosed with the help of surgical post-op bandages. Then the patch was left to stand for 24 hours to observe for any irritation on the volunteers' skin. The duration of contact for 24 hours was reported to be optimal in observing the irritation test of topical preparations on the skin ([Horita et al., 2014](#)). After 24 hours, the patch test was removed, and the forearm was washed with normal saline solution, after which erythema was determined by using a score scale ([Aktar et al., 2014](#)) as presented in [Table 2](#).

Table 2. Skin reaction scoring criteria

Score	Reaction
0	No response
1	Well-defined erythema
2	Erythema with slight to moderate edema
3	Vesicles (small blister) or papules (small, circumscribed elevations)
4	Bullous (large blister), spreading, or other severe reaction

### 3. RESULTS AND DISCUSSION

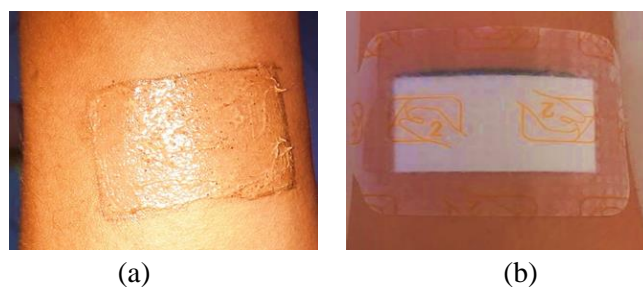
Bawang dayak is one of the typical plants of Central Kalimantan, which has several secondary metabolites such as flavonoids, alkaloids, saponins, and tannins ([Novaryatiin & Ardhany, 2019](#)). Based on some literature, these metabolites have activities that can inhibit the bacteria that cause acne with their respective mechanisms, such as flavonoids with antioxidant mechanisms that generally synergize with antibacterial activity ([Freitas et al., 2012](#); [Kim et al., 2018](#); [Otuechere et al., 2019](#); [Massoud & Reihaneh, 2020](#); [Kumari et al., 2020](#); [Perumal et al., 2020](#)). Other studies have also reported that other secondary metabolites from bawang dayak, such as eleutherol A are known to inhibit cell wall synthesis from bacteria ([Pratama & Aziz, 2019](#)). This is very important to know before making a preparation. The human patch test results showed that neither the formulations used nor the cream base showed an irritating reaction to all the volunteers involved. The visualization of the results of cream application to volunteer samples is presented in [Figure 2](#); [Figure 3](#); [Figure 4](#), while a recapitulation of the skin reaction scores is presented in [Table 3](#).

In previous studies, the primary irritation test for bawang dayak extract cream was carried out on the rabbit, showing that it does not irritate the test animal skin ([Ardhany et al., 2019](#)). This study is then continued to the evaluation stage of skin irritation in humans as one of the essential things a product can be used by the public, especially cosmetics for long-term use ([Ali et al., 2013](#)). The method used in this study is the human patch test. Patch testing helps confirm the presence of an allergy and identify the most common allergen and cosmetic products, causing dermatitis ([Kumar et al., 2014](#)).

**Table 3.** The results of irritation tests on volunteers

Sample	5% bawang dayak extract cream	20% bawang dayak extract cream	Cream base
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	0	0	0
20	0	0	0

Volunteer skin irritation score



**Figure 1.** (a) Application of cream on the forearm; and (b) the site of application of the cream is covered with a post-op bandage

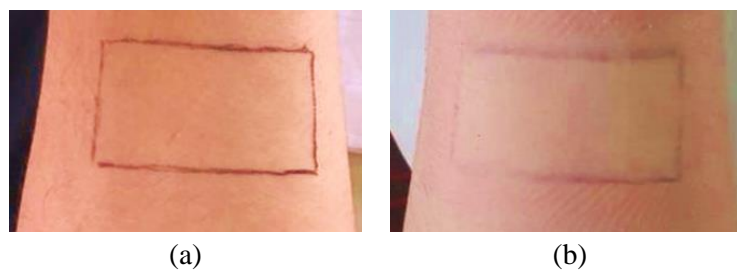


**Figure 2.** Appearance of irritation test results on the forearm: (a) before; and (b) after application of 5% bawang dayak extract cream for 24 hours



**Figure 3.** Appearance of irritation test results on the forearm: (a) before; and (b) after application of 20% bawang dayak extract cream for 24 hours





**Figure 4.** Appearance of irritation test results on the forearm: (a) before; and (b) after application of cream base for 24 hours

Apart from visual observation of irritation, the volunteers were also interviewed verbally to determine a particular sensation in each treatment. The interview results will provide information about irritation symptoms that are not visible visually, including an itching and pain sensation (Zuuren et al., 2017; Daud et al., 2018). From interviews with all volunteers, it was found that the two cream formulations did not cause itching—only some volunteers who report a slight itching from the use of the cream base. However, the itching sensation was reported to be minimal and did not cause the feeling of scratching the area. The itching sensation may be due to unfamiliar volunteers with a cream base that contains a fair amount of oil phase. Cream preparations contain a relatively large amount of oil phase, especially those with the water in oil (W/O) type (Moldovan et al., 2017). In contrast to other topical preparations such as gels, which contain more water and rarely cause an itching sensation (Putri et al., 2019). However, cream preparations will provide an advantage of longer contact time between the active ingredients and the skin (Purnamawati et al., 2017).

Although it seems simple, the irritation test for cream preparations made from active plant extracts against humans by the patch test method is rarely reported. Some studies only report the results of irritation tests on test animals like mice and rabbits, as reported by Ali et al. (2013) and Lukelal et al (2019). In humans, irritation tests of creams with active extracts of natural ingredients have previously been reported on *Ficus carica* (Khan et al.,2014), *Averrhoabilimbi* (Sutriningsih et al., 2018), *Mangifera indica* (Satria & Siahaan, 2017), and *Curcuma longa* (Wattanakrai et al., 2007), all of which reported no irritation to the skin of volunteers. Meanwhile, the irritation test on human volunteers from a cream made from bawang extracts has never been reported before. This study's results are expected to provide valuable information in the development of cream preparations made from bawang dayak extract, especially as an anti-acne cream.

#### 4. CONCLUSION

The results of this study indicate that the bawang dayak extract cream with a concentration of 5 and 20% w/w does not irritate human skin. This study is a continuation of previous studies to get additional data to produce a suitable formulation without causing harmful effects on the skin. Further research is needed to develop testing effectiveness cream of bawang dayak in humans with acne faces to produce an anti-acne product with reasonable safety and high quality.

#### 5. ACKNOWLEDGMENT

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#### 6. CONFLICT OF INTEREST

The authors declare that there no competing conflicts of interest.

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