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Effectiveness and Safety Test of Antiaging Serum Combination of Ceremai Fruit (*Phyllantus acidus*) and Watermelon Rind (*Citrullus lanatus*) In Vivo

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ABSTRACT: Antiaging serum is a cosmetic to prevent skin damage due to aging factors. The antiaging serum from the combination of ceremai fruit extract (*Phylantus acidus*) and watermelon rind (*Citrullus lanatus*) has been tested ad an antioxidant, antihyperpigmentation and anti-wrinkle activities. However, its efficacy, safety, and toxicity had not yet been tested in vivo. This study aimed to evaluate these parameters using four groups of rats over four weeks. Two formulations (F1 and F2) contained the combination of ceremai fruit extract and watermelon rind, while the negative control (NC) used only the base serum, and the positive control (PC) contained a known antiaging compound. Results showed that all formulations affected moisture content, pigmentation, collagen, and skin elasticity. Notably, F2 demonstrated the most effective outcomes: it increased skin moisture by 11.2%, improved elasticity by 10.6%, enhanced collagen levels by 14.7%, and reduced pigmentation by 21.1%, without stimulating excess sebum. These results were significantly different from the negative control ($p < 0.05$). In addition, the results of the F2 serum toxicity test showed no toxic symptoms to the test animals because there was no irritation.

Keywords: **antiaging; *Citrullus lanatus*; efektivitas; *Phyllantus acidus*; serum.**

Introduction

The skin has various functions such as providing a physical permeability barrier, protection from infectious agents, protection against ultraviolet (UV) rays and skin regeneration [1]. Skin is also very complex, elastic and sensitive, which is affected by climate, age and race [2]. Clinically, the skin can experience aging which is characterized by loss of hydration, rough texture, pigmentation, discoloration, wrinkles, thinning of the skin, and fine lines [1]. Aging can be caused by a variety of factors, namely intrinsic and extrinsic factors. Intrinsic factors include an increase in the activity of certain enzymes involved in the skin aging process such as elastase enzymes, hyaluronidase enzymes, collagenase enzymes and tyrosinase enzymes [3]. The increase in the effect of skin damage by factors that trigger aging, it is necessary to make efforts to prevent and develop *antiaging* therapy. The natural ingredients used as products can be combined with other cosmetic ingredients to provide maximum effectiveness for skin care [4]. One of the most widely used cosmetic preparations is serum preparations.

One of the ways of development is by utilizing natural ingredient extracts as serum active substances. Natural materials that can be developed are Ceremai Fruit (*Phyllantus acidus*) and Watermelon Fruit (*Citrullus lanatus*).

P. acidus fruit is reported to contain flavonoids, alkaloids, terpenoids, saponins, glycosides, and vitamin C [5]. P.acidus *fruit methanol extract* has strong antioxidant activity with an IC50 value of 5.96 µg/mL [6,7]. P. acidus *fruit* with ethanol solvent has antioxidant activity with an IC50 value of 75.44 ppm [8].

The skin of *C. lanatus* contains retinol (Vitamin A), thiamin (Vitamin B1), Riboflavin (Vitamin B2), niacin (Vitamin B3), pyridoxin (Vitamin B6), and Vitamin C [9]. Saponins, tannins, alkaloids, flavonoids and total phenolic 0.087 (mg/g) [10]. The skin of *C. lanatus* fruit has strong antioxidant activity with an IC50 value of 79.87 bpj [3]. This is in line with other studies that show that C. *lanatus* fruit rind extract has an

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IC50 value of 102.19 µg/mL [8].

Previously, a serum formulation containing a combination of *P. acidus fruit extract and* C. lanatus *fruit rind* with an antioxidant concentration of P. acidus *fruit extract* of 76.76 µg/mL and C. lanatus *fruit rind* extract of 102.19 µg/mL had been carried out. The antioxidant activity of serum F2 has the best activity compared to serum F1 with an IC50 value of 326.71 µg/mL [8].

The results of the serum tyrosinase enzyme inhibition test of the combination of P. acidus fruit extract and C. lanatus fruit rind were 1.025 µg/mL [11].

Based on the results of the study, it can be concluded that a combination serum of ceremai fruit extract (*P. acidus)* and watermelon rind (*C. lanatus)* has the potential to be an *antiaging* serum in *vitro*. To complete the results of the study, it is necessary to continue testing the effectiveness and safety of serums before efficacy is carried out on humans [12]. Through in vivo testing of serum formulations by checking the level of elasticity, wrinkles, smoothness, and moisture of the skin and then tested for safety through dermal sensitization and acute dermal toxicity.

Methods

Tools and Materials

Ceremai fruit extract (*Phyllantus acidus*), watermelon rind extract (*Citrullus lanatus*), xhantan gum (PT. Dwilab Mandiri Scientific, Indonesia), butylene glycol (PT. Sheva Mutiara, Indonesia), methylparaben (PT. Dwilab Mandiri Scientific, Indonesia), aquaadas (PT. Palapa Muda Perkasa, Indonesia), 70% ethanol (PT. Dwilab Mandiri Scientific, Indonesia), Sodium dodecylsulfate (SDS) 10 % (PT. Intralab Ekatama, Indonesia).

Animal Ethics Review

Animal ethics review was carried out at the Biology Study Program, State University of Jakarta with letter number 024/KEH-BIO/UNJ/2024.

This study was carried out over 24 days to ensure the welfare of the experimental animals, and the Five Freedoms principle was applied. This principle includes the freedoms from: hunger and thirst; discomfort; injury, illness and pain; fear and suffering; and the ability to express normal behaviour.

Extraction

The sample was taken from the Pandeglang area, Banten. The sympilation powder is extracted by maceration with a 70% ethanol solvent for 3 x 24 hours. Then the maserat is concentrated with a rotary evaporator at a temperature of 50oC until a thick extract is obtained.

Serum Formulations

The serum formula is made with a modified reference formula [8] Table 1.

Serum Preparation Effectiveness Test

The anti-aging activity test approach uses Pre Test and Post Test Control Group Design with modifications [13]. The entire group of rats was shaved on the back of a 2x2 cm2 area. Measurement of the condition of test animals before and after using the Skin Analyzer EH 900 (China) including moisture content, sebum, collagen, elasticity and pigment. UVA and UVB irradiation to all mice was carried out for 10 minutes every day for 4 weeks. The dose of UVA irradiation is 630 µW/cm2 and UVB is 105 µW/cm2. The distance of the dorsal skin of the rat to the UV lamp is 15 cm. The application of anti-aging ingredients by means of the negative control group (NC), positive control group (PC), F1 and F2 treatment groups, smeared with a serum formula. The material is applied 2 times per day, namely 2 hours before UV irradiation, and 15 minutes after UV irradiation at a dose of 2 mg/cm2 for 4 weeks.

Table 1. The serum formula.

NO	Material	Function	Formula %		
			NC	F1	F2
1	Ceremai Fruit Extract	Active substances	-	0.76	1.53
2	Watermelon Rind Extract	Active substances	-	0.5	1
3	Xhantan Gum	Thickener	0.4	0.4	0.4
4	Methylparaben	Preservatives	0.3	0.3	0.3
5	Butylene Glycol	Humektan	10	10	10
6	Aquades	Ad 100 mL			

Safety Test

Cosmetic safety test according to BPOM regulation No. 10 of 2022. Non-Clinical Toxicity Test in vivo [14]. The cosmetic safety tests carried out in this study were dermal sensitization tests and acute dermal toxicity tests.

Dermal Sensitization Test

The test animal used was a white rat (*Rattus norvegicus*) strain of *Sprague dawelay,* a young and healthy adult, male sex with a weight of 160-300 g according to the weight of the test animal according to BPOM RI for the dermal sensitization test. The sampling technique of test animals uses simple random sampling with *posttest-only control group design*. The test animals were grouped into 4 groups, namely normal control (no treatment), negative control (NC), F1 and F2 sample groups [15]. This study uses the principles of *the Guinea Pig Maximization Test* (GPMT) method to assess the dermal sensitization reaction to rat skin [16] [14]. The experimental mice were acclimatized for 5 days before use. Each experimental group went through two test stages, namely the preliminary test stage and the main test. Test animals are given test samples in the nape area for preliminary tests and back areas at the main test. The sample is given for 24 hours by being wrapped in gauze and then covered with *an occlusive patch*. Observations were made for a preliminary test for 24 hours then continued to the main test on rat skin starting from day 0 (the beginning of the intradermal induction phase), the 1st, and 7th (the beginning of the topical induction phase). Observation was continued in the topical induction phase on day 9 with 10% sodium deodesilsuate (SDS) to see erythematic and edema reactions if the topical induction phase on day 7 did not see erythema and edema reactions. The observation was then continued on the 11th day until the challenge test phase on the 22nd, 23rd, and 24th days by scoring erythema and edema according to the Magnusson and Kligman scales (Table 2).

Acute Dermal Toxicity Test

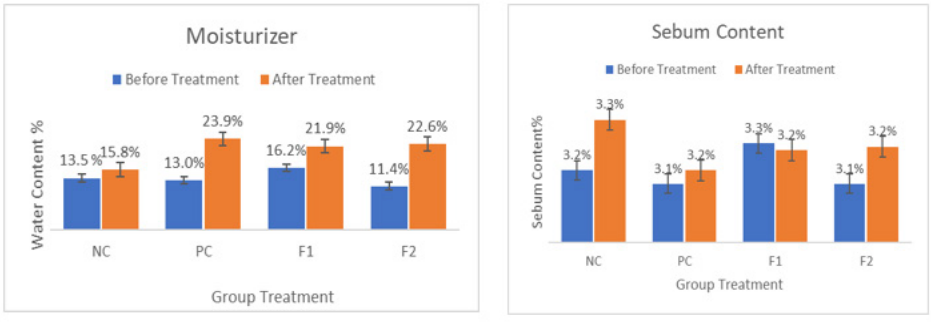
The dose used for liquid test preparations is as much as 0.5 mL. Test animals are adapted (acclimatized) first before testing. The test animal test consisted of 4 treatment groups, including treatment 1 rat smeared by positive control (commercial serum), treatment 2 smeared with negative control (NC), treatment 3 rats smeared with serum formula (F1) and treatment 4 smeared with serum formula (F2). The hair of the test animal is shaved on the back with an area of 3x3 cm until it is clean before the application of the sample. The test preparation is presented in an area of ± 6 (2 x 3) cm2 skin then the exposure site is covered with gauze and a non-irritating plaster. All test animals should be observed for the presence or absence of erythema and edema, assessment of response is performed at hours 1, 24, 48, and 72 after the opening of the skin reaction patch is assessed.

Result and Discussion

Results of Antiaging Effectiveness Test of Serum Preparations

The effectiveness of antiaging was evaluated based on the observation of sebum content, moisture content, pigmentation, collagen level and elasticity. In this study, the test animals used were male Sprague Dawley white rats because of their similarity to human skin in terms of structure and response to aging due to exposure to ultraviolet (UV) light, so it is suitable for use as a topical antiaging test animal [17].

Previously, the mice were shaved off the pugroot part to be exposed to UV irradiation simulated using UV A and



(A) (B)

Figure 1. Comparison of water content before and after treatment (A), Comparison of sebum content before and after treatment (B).

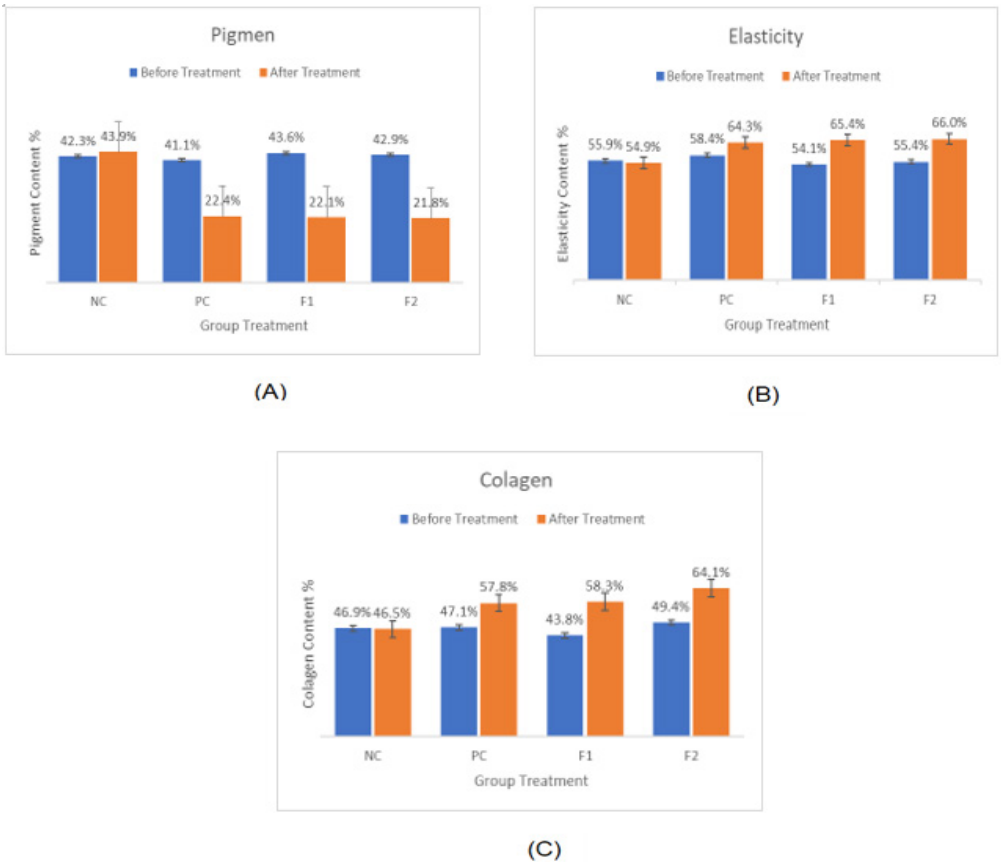


Figure 2. Comparison of pigment levels before and after treatment (A), Comparison of elasticity levels before and after treatment (B), Comparison of collagen levels before and after treatment (C).

UV B lamps which are close to exposure to sunlight [18]. The application of anti-aging ingredients by means of a negative control group (NC) smeared with a serum base, a positive control group (PC) smeared with commercial serum, treatment groups 1 (F1), 2 (F2) smeared with a serum formula combining *P. acidus* fruit extract and *C. lanatus fruit rind.*

The results of the observation of water content before treatment and after treatment after using serum for 4 weeks there was a significant change in F2, namely an increase in water content of 11.2% while NC experienced a decrease in water content in week 4, which was 2.3%, this result can be seen in Figure 1 (A). The criteria for dry or dehydrated skin is to have a value of 3-4%, aging conditions of 4-10%, normal 10-15% and high moisture content of 15-30% which can be read on the skin analizer tool. This is because F1 and F2 have flavonoid content in ceremai fruit extract and watermelon rind. Flavonoids have hydroscopic properties that allow them to attract and hold water molecules on the surface of the skin. This can help maintain skin moisture by preventing excessive evaporation of water. With their ability to maintain water content, flavonoids have an important role in maintaining skin moisture [19]. Antioxidants also affect the skin's moisture content. Low water content in the negative control group is caused by the absence of antioxidants that protect the stratum corneum lipids in the epidermis from the oxidation of free radicals by UV radiation Oxidative damage causes cell cohesion and mechanical integrity of the stratum corneum to decrease, followed by increased water transepidermal loss (WTL), and finally the stratum corneum water content decreases [13].

Sebum has amphiphilic properties because it contains free fatty acids and wax. This makes the skin moisturized. Sebum plays a role in protecting against intensive dehydration of the skin. In addition, sebum has a nutritional function for beneficial bacterial species in the organism, while ensuring protection against fungal static activity and functional qualities, the rate of hair sebum secretion reaches its highest level in adolescence and decreases gradually thereafter [20]. The results of the observation of sebum levels in test animals using a skin analyzer for 4 weeks can be seen in Figure 1 (B) where F1 is 3.2%, F2 is 3.2%, F0 is 3.2%, PC is 3.2% and NC is

Table 2. Average results of observation of dermal sensitization reaction in the preliminary test.

Treatment groups	Day 0 (Intradermal Induction)	Day 1 (Topical Induction)
CN	0	0
PC	0	0
NC	0	0
F1	0	0
F2	0	0

3.3%. This value is included in the condition of dry skin, it can be concluded that all preparations do not affect the sebum level in the skin of rats

Observations on the Image 2 (A) showed a decrease in black spots (pigments) on the skin of rats before and after treatment. F2 showed a decrease in the percentage of black spots by 21.1% it can be proven that a combination serum of ceremai fruit extract and watermelon rind has an influence in accelerating the recovery process of black spots. The decrease in the percentage of black spots in F1 and F2 was influenced by the active compounds contained in the serum preparation of a combination *of P. acidus* fruit extract and *C. lanatus* fruit rind. Phytochemical compounds show potential for several biological actions, e.g. flavonoids with the effect Its antioxidants play a role in inhibiting the enzyme tyrosinase [21]. Dark spots or hyperpigmentation affected by tyrosinase enzyme [22]. Flavonoids in ceremai fruit extract and watermelon rind inhibit the pigmentation process or the appearance of spots by directly inhibiting tyrosinase activity in the melanogenesis process. Tyrosine is also one of the phenolic compounds that can suppress melanin synthesis. Phenols and flavonoids have a similar structure to tyrosine, therefore phenols and flavonoids can also act as substrate analogue inhibitors against melanogenesis [1].

Observations on elasticity before and after treatment can be seen in Figure 2 (B). There was a change in elasticity after 4 weeks of serum use where F2 produced an increase of 10.6%, this value was higher than that of PC with a percentage of 5.4%. Meanwhile, NC experienced a decrease in the percentage of elasticity. In this study, an increase in skin elasticity was seen after 4 weeks of treatment. This is suspected because ceremai fruit extract has compounds such as phenolics, vitamin C, alkaloids, tannins, sesquiterpenes and flavonoids that can work synergistically to inhibit the activity of the elastase enzyme that causes wrinkles [23]. The elastase enzyme is able to break down elastin, an insoluble elastic fibrous protein that along with collagen contributes to the mechanical strength of connective tissue. Some studies show that skin aging and anti-wrinkle effects are significantly associated with reduced elastase activity. Similar results were also reported by Astuti, 2021 [13]. An increase in elasticity was seen after 4 weeks of treatment using *Centella asiatica extract.*

Skin is a complex structure with elastic and supple properties. The elastic properties of the skin depend on

Table 3. Results of observation of the average dermal sensitization reaction in the topical main test on day 11 to day 24 of the challenge test.

Treatment Groups	Day 11	Day 22	Day 23	Day 24
CN	0	0	0	0
PC	0	0	0	0
CN	0	0	0	0
F1	1	1	1	1
F2	1	1	1	1

Information:
CN: Control Normal
PC: Positif Control
NC: Negatif Control
F1: Formula 1 sample group
F2: Formula 2 sample group

Table 4. Average results of observation of dermal acute toxicity test

Treatment Groups	Irritation Effects	1 hour	24 hour	48 hour	72 hour
CN	Eritema	0	0	0	0
	Edema	0	0	0	0
PC	Eritema	0	0	0	0
	Edema	0	0	0	0
NC	Eritema	0	0	0	0
	Edema	0	0	0	0
F1	Eritema	0	0	0	0
	Edema	0	0	0	0
F2	Eritema	0	0	0	0
	Edema	0	0	0	0

the collagen and elastin fibers in the dermis. Collagen is the most abundant component of the extracellular matrix, a protein that determines skin physiology by maintaining the structure of the skin and allowing its various functions [1]. The results of the observation of collagen levels after and after the treatment can be seen in the Figure 2 (C). It can be concluded that there is an increase in collagen levels in F2 by 14.7%, which is significantly different from NC. This condition is categorized as high collagen in the skin based on the results of readings on a skin analyzer. This is influenced by the content of terpenoid and flavonoid compounds in P. *acidus fruit extract and* C. lanatus *fruit rind* providing a synergistic effect functioning as an antioxidant. Antioxidants and flavonoids work stimulates the formation and production of skin collagen and prevents collagen degradation. Meanwhile, in NC, collagen levels decreased

Antiaging Serum Safety Test Results

Dermal sensitization test

Furthermore, the test continued in the challenge test for the sample group on the 22nd, 23rd and 24th days respectively having a score of 1 in the F1 and F2 groups. An interpretation for a score of 1 indicates mild erythema or erythema patches. The results of the experiment showed a dermal sensitization reaction. The sensitization reaction can be seen because between the intradermal induction test and the topical test there is an incubation period of at least 1 week during which the hypersensitivity condition can develop. Thus, the results obtained showed the presence of sensitization reactions in test animals compared to the normal group, positive control group and negative group.

The sensitization reaction to a health product is a reaction mediated by cells involving the body's immune system. The sensitization phase occurs when the allergen manages to penetrate the epidermal barrier and meets Langerhans cells or dermal dendritic cells that recognize it as a foreign body. The foreign object referred to in this study is sodium dodecyl sulfate and serum combined with ceremai fruit extract and watermelon rind. This can occur due to repeated use of a product which is characterized by redness and swelling/edema.

Results of The Dermal Acute Toxicity Test

Dermal acute toxicity test is a test that involves experimental animals to detect the presence of toxic effects caused in a short time (72 hours) after the test preparation is exposed through the dermal route in a single administration [25]. Male white rats with *the spragedawley strain* were used as research subjects because they are a group of lactating animals that are not much different from humans, have a rapid response, are used by males because they do not experience an estrus cycle so that the sample becomes homogeneous and is expected to be accurate [26]. The observations carried out are qualitative observations and quantitative observations [27]. Qualitative observations were made by looking at whether or not erythema and udema effects occurred after exposure to the test preparation on the skin of the rats' backs. Meanwhile, quantitative observations were carried out by grouping the effects of erythema and udema that occurred according to the score. The results of the observations can be seen in table 4 all experimental groups of rat back skin, the irritation index score or primary irritation was zero (0) so it was included in the category of non-meaningful because there was no irritation characterized by the absence of erythema and udema. This shows that

the formulation used does not cause an irritating effect on the skin so it is safe to use. In addition, the ingredients used have a synergistic effect characterized by the absence of side effects visible on the skin of the rats' backs.

Conclusion

The results of the observation of the effectiveness of serum antiaging after 4 weeks of treatment showed changes in the level of water content, collagen content, pigmentation and elasticity while the sebum level had no significant effect. The treatment using F2 demonstrated superior antiaging effects compared to the treatments with F1, the negative control (NC), and the positive control (PC). Where F2 has better results than the formulations of F1, NC, and PC. F2 serum can increase moisture content by 11.2%; does not cause sebum formation, can reduce hyperpigmentation by 21.1%; increase skin elasticity by 10.6%; and increased collagen levels by 14.7%. The results of the observation of serum sensitization showed that F1 and F2 indicated erythema spots in the challenge test with a mild category while in the toxicity test there was no irritation.

Conflicts of Interest

The author has no conflict of interest regarding this research.

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