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The use of cysteamine as a hyperpigmentation brightening agent in Indonesian women

Zastosowanie cysteaminy jako środka rozjaśniającego przebarwienia u kobiet pochodzenia indonezyjskiego

ABSTRACT

There are many depigmenting preparations available on the cosmetic market, which often cause side effects such as dry skin, flaking, redness or burning. Intensive research is being conducted on substances with comparable efficacy but a better tolerability profile. One such substance is cysteamine.

This study aimed to evaluate the effectiveness of combining 2.5% cysteamine with 2% *Galactomyces* ferment filtrate, 2% *Saccharomyces* ferment filtrate, 2% saccharide isomerate and 4% niacinamide. The study was conducted using a dual-application technique of serum and cream with a brightening effect on facial hyperpigmentation among women in Indonesia. An open-label pre-post-test clinical trial was used.

After six weeks of treatment, there was a significant decrease in the melanin index of the study participants. The use of cysteamine serum and cream appears to be a promising approach for treating hyperpigmentation disorders on the face.

Keywords: brightening agent, cysteamine, facial hyperpigmentation, melanin, depigmentation

STRESZCZENIE

Na rynku kosmetycznym dostępnych jest wiele preparatów o działaniu depigmentacyjnym, które często powodują skutki uboczne, takie jak suchość skóry, łuszczenie, zaczerwienienie czy pieczenie. Trwają intensywne badania nad substancjami o porównywalnej skuteczności, ale lepszym profilu tolerancji. Jedną z takich substancji jest cysteamina.

Celem badania była ocena skuteczności połączenia 2,5% cysteaminy z 2% filtratem fermentu *Galactomyces*, 2% filtratem fermentu *Saccharomyces*, 2% izomeratem sacharydowym i 4% niacynamidem. Badanie przeprowadzono z zastosowaniem techniki podwójnego nakładania serum i kremu o działaniu rozjaśniającym przebarwienia, na skórę twarzy kobiet w Indonezji. Zastosowano otwarte badanie kliniczne typu pre-post-test.

Po sześciu tygodniach terapii odnotowano istotny spadek wskaźnika melaniny u uczestniczek badania. Zastosowanie serum i kremu z cysteaminą wydaje się obiecującym podejściem w leczeniu zaburzeń hiperpigmentacji na twarzy.

Słowa kluczowe: środek rozjaśniający, cysteamina, przebarwienia na twarzy, melanina, depigmentacja

INTRODUCTION

Skin hyperpigmentation is a dermatological condition characterized by a darker skin tone due to various internal and external factors, including hormonal changes, inflammation, trauma, acne, eczema, medications, and exposure to ultraviolet (UV) light. Alterations in melanocyte production or melanin distribution can lead to hyperpigmentation disorders. Topical use of conventional depigmentation agents, such as hydroquinone, has been the gold standard in the management of hyperpigmentation problems, but it is currently banned in cosmetics in the European Union (EU) [1]. However, long-term use of these agents can lead to various side effects and complications, such as allergic contact dermatitis, hypopigmentation or ochronosis [2]. Therefore, many researchers are currently conducting various experiments to find depigmentation agents that have the same potential as conventional ones, but have minimal side effects. One such agent currently being investigated is cysteamine, which acts as an antioxidant by increasing intracellular glutathione resulting in a shift of eumelanin synthesis to pheomelanin [1, 3].

This study aimed to determine the effectiveness of the combination of serum and cream containing cysteamine with *Galactomyces* ferment filtrate, *Saccharomyces* ferment filtrate, saccharide isomerate, and niacinamide as a safe and effective brightening agent for hyperpigmentation on the face.

MATERIAL AND METHODS

Study design

This study was experimental research with an open-label pre-post-test clinical trial design conducted at the Department of Dermatology & Venereology, Dr. Wahidin Sudirohusodo General Hospital and Hasanuddin University Hospital, Makassar City, South Sulawesi, Indonesia, from September 2023 to March 2024. This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University, Makassar, with number 635/UN4.6.4.531/PP36/2023.

Subject

The total number of subjects was 17, female, aged between 20-40 years, and Fitzpatrick skin type III-V. All participants in the study signed an informed consent form. The exclusion criteria were pregnancy, breastfeeding, suffering from chronic inflammation of the facial skin, and being treated with topical and systemic whitening agents for six months to a year before the study began.

Study Protocol

A total of 17 study subjects were assessed before and after treatment. Baseline melanin index (MI), L-value, and UV spot values were measured using Mexameter®, Chromameter®, and Janus-III Facial Analysis System® tools at week 0. All study participants received a combination of serum and cream containing 5% cysteamine with 2% *Galactomyces* ferment filtrate, 2% *Saccharomyces* ferment filtrate, 2% saccharide isomerate, and 4% niacinamide and were obligated to apply it for six weeks. Two drops of serum were used, followed by application of one fingertip unit (FTU) of cream containing the same ingredients, twice a day on the entire face. The participants were also given a facial wash that was used twice a day before the application of serum and cream. The total duration of the study was six weeks, with an interval of every two weeks. During each session, MI value, L-value, and UV spot were measured as well as clinical assessment by camera documentation.

The Mexameter® MX 18 (Courage Khazaka, Germany) used 16 LEDs to emit light at three wavelengths: 568 nm (green), 660 nm (red), and 880 nm (infrared). The melanin index (MI), which corresponds to the skin melanin level, and the erythema index (EI) were obtained using a computerized examination.

The Chromameter® (Konica Minolta, Japan) objectively measured skin color by analyzing the reflection of a xenon lamp perpendicular to the probe at 450 nm, 560 nm, and 600 nm. The resulting parameters were represented by the numbers L, a, and b. The L-value parameter represented the brightness of the skin colour (100 for white and 0 for black).

The Janus-III Facial Analysis System® (PIE Inc, South Korea) was a facial analysis system that uses a high-resolution camera to objectively assess various skin issues such as pigmented spots, wrinkles, skin tone, UV spots, and sebum production.

All data were analyzed using Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS. Inc) with Repeated Measure ANOVA test and Dependent Samples T-Test. All the data had a normal distribution. Statistically significant values were obtained when the p-value was <0.05. All data results were presented in tables and graphs.

RESULTS

The mean age of the participants was 35.27 years. All subjects were categorized as Fitzpatrick skin type III-V (table 1). Overall, there was a significant decrease in the melanin index score in the study subjects before and after the six-week therapy ($p=0.016$) (table 2). The melanin index decreased consistently and significantly when entering the second week (fig. 1).

Based on the results of the L-value score, an increase in value was found in all research subjects for six weeks after therapy compared to before therapy. The L-value increased by 2.4 from 48.59 at week 0 to 50.99 at week 6. There was a significant difference from week 0 to week 6 or in other words, there was an effect of therapy on the L-value ($p<0.001$) (table 3). A significant increase occurred when entering week 2, after which it gave another increase at week 6 (fig. 2).

Table 1 Demographics characteristics

CHARACTERISTICS	NUMBER (%)
Female	17 (100%)
Age (year)	35.27
Fitzpatrick's skin type	
III	3 (17.64%)
IV	8 (47.05%)
V	6 (35.29%)

Source: Own studies

Table 2 Comparison of melanin index scores in research subjects during six-week therapy

WEEK	MELANIN INDEX SCORE *(MEAN± SD)*	P-VALUE
0	242.55±42.97	0.016
2	230.36±55.34	
4	210.47±37.85	
6	209.14±37.72	

Source: Own studies

Table 3 Comparison of L-values in research subjects during six weeks of therapy

WEEK	L-value *(MEAN± SD)*	P-VALUE
0	(48.59±3.72)	<0.001
2	(49.25±4.11)	
4	(49.58±3.86)	
6	(50.99±3.32)	

Source: Own studies

Table 4 Comparison of UV spot values in research subjects during six-week therapy

WEEK	UV SPOT *(MEAN± SD)*	P-VALUE
0	(83.08±21.02)	0.094
2	(82.04±24.03)	
4	(79.30±25.19)	
6	(67.15±30.81)	

Source: Own studies

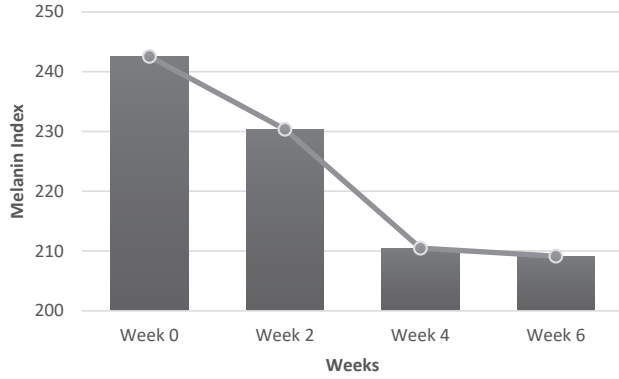

Fig. 1 Decrease in melanin index score in research subjects during six-week therapy
Source: Own studies

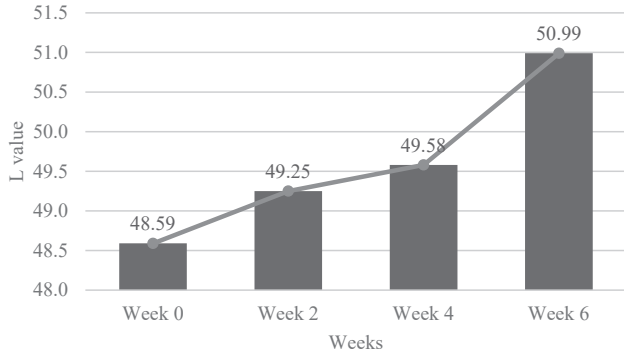

Fig. 2 Increase in L-value in the research subjects during the six weeks of therapy
Source: Own studies

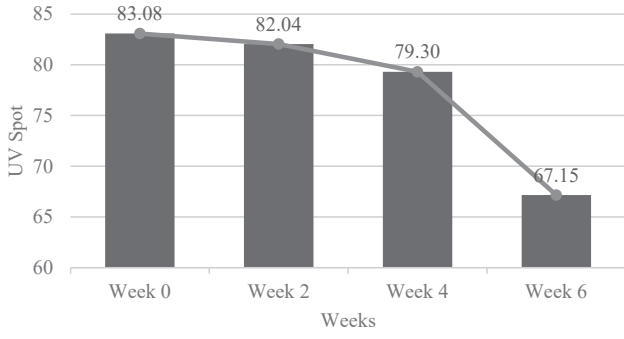

Fig. 3 Decrease in UV spot values in research subjects during six-week therapy
Source: Own studies

Based on the UV spot results in table 4, there was a decrease in value of 15.93 from 83.08 in week 0 to 67.15 in week 6 (p=0.094). The UV spot value had a decreasing effect over time (fig. 3).

Comparison of the clinical changes that could be seen in the subjects is presented in figures 4-7. No side effects occurred after using the combination of serum and 2.5% cysteamine cream for six weeks.

Fig. 4 Clinical changes in hyperpigmentation on the woman's face before (W0) and after therapy (W6) **Source:** Own studies

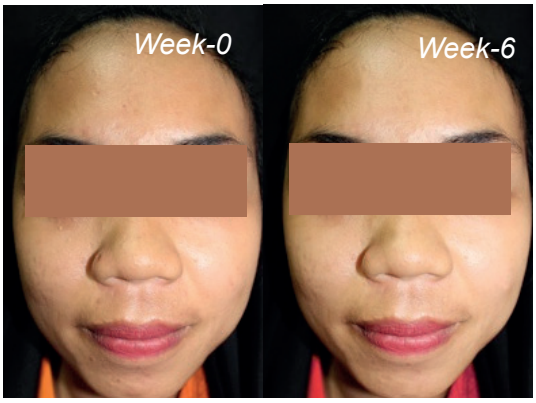

Fig. 6 Clinical changes in hyperpigmentation on the woman's face before (W0) and after therapy (W6) **Source:** Own studies

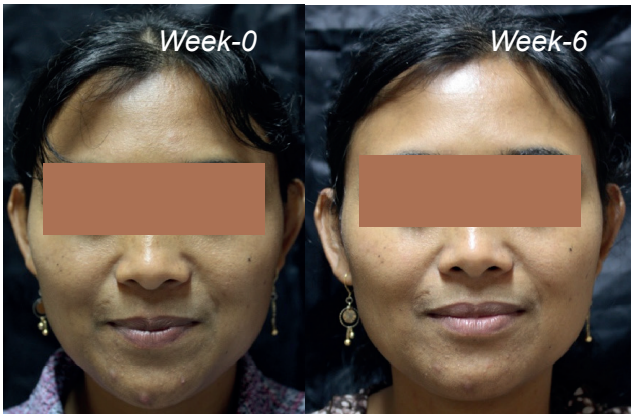

Fig. 5 Clinical changes in hyperpigmentation on the woman's face before (W0) and after therapy (W6) **Source:** Own studies

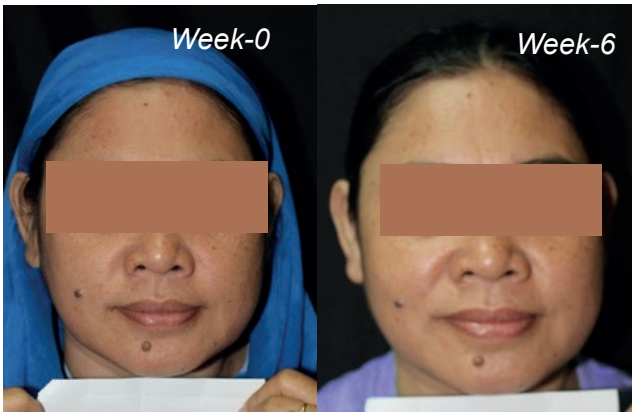

Fig. 7 Clinical changes in hyperpigmentation on the woman's face before (W0) and after therapy (W6) **Source:** Own studies

DISCUSSION

Hyperpigmentation is a common dermatological condition characterized by an increase in the amount of melanin pigment produced by melanocytes in the skin layers. Hyperpigmentation disorders such as melasma, post-inflammatory hyperpigmentation, ephelids (freckles), and lentigo are common cosmetic concerns and are commonly found in the young adult female population with Fitzpatrick skin types III-VI. These abnormalities can impair psychological health and affect the quality of life. Topical therapy is the gold standard in the management of hyperpigmentation problems, but its longterm use can cause side effects, complications and decreased compliance [1].

This study assessed the efficacy of low-dose cysteamine by bilayering method in serum and cream as a potential agent for hyperpigmentation disorders on the face using the parameters of MI, L-value, and UV spot. The results showed a decrease in MI value, an increase in L-value, and a decrease in UV spot value, indicating an improvement in skin brightness after six weeks of serum and cream use consistently in all study subjects. The decrease in MI value by 3.6%, increase in L-value by 1.02%, and decrease in UV spot value by 5.14% occurred before and after therapy. The clinical changes that occurred in all study subjects were statistically significant, especially for MI value and L-value. No adverse effects occurred in all samples during the study period.

Topical hydroquinone is a first-line management of hyperpigmentation disorders that has been used for more than 60 years. It inhibits the tyrosinase enzyme, preventing pigment production by melanocyte cells and is melanocytotoxic [2]. The combination of 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide, known as Kligman's modified formula, is also one of the first-line treatment options for topical depigmentation agents [1, 4]. Long-term use or excessive doses of hydroquinone can cause carcinogenic effects and mutagenic activity. The use of hydroquinone as a brightening agent for cosmetic concerns is restricted in some countries and EU regulations have banned it [2].

Recent studies have reported the use of topical cysteamine as a depigmenting agent in hyperpigmentation disorders [2, 3, 5]. L-cysteamine (β-mercaptoethylamine hydrochloride) is an aminothiol compound with antioxidant and brightening

effects [3, 4]. It is widely available as a capsule and eye drop solution used as therapy for cystinosis [3]. Cysteamine has non-melanocytotoxic and non-mutagenic properties, so it is considered safe for long-term use [2, 4]. Topical cysteamine 5% is effective in inhibiting tyrosinase and peroxidase enzymes, increasing intracellular glutathione antioxidants, preventing dopaquinone formation, and regulating the chelation of iron and copper ions that play a role in the melanin synthesis pathway [3, 4, 6]. Nguyen et al. (2020) reported that the use of topical cysteamine 5% as a depigmentation agent for mild-moderate cases of melasma, compared to 4% hydroquinone, had the same effectiveness after 16 weeks [2]. The study by Lima et al. (2020) reported that the use of topical cysteamine 5% was safe and effective for melasma cases for 17 weeks, but the effect was inferior compared to hydroquinone [3].

The choice of topical combination therapy is more effective than monotherapy for the treatment of hyperpigmentation disorders, not only because there are various pharmacokinetic properties exhibited by other agents, but the use of different agents can also reduce the potential side effects [4]. In this study, the serum and cream containing 2.5% cysteamine with 2% *Galactomyces* ferment filtrate, 2% *Saccharomyces* ferment filtrate, 2% saccharide isomerate, and 4% niacinamide were combined.

Galactomyces ferment filtrate is a fungal derivative that is often used in the cosmetic field as an anti-aging and antioxidant ingredient [7]. It can inhibit the enzyme tyrosine hydroxylase so as to increase skin brightness [8]. In addition, it can also develop the expression of aryl hydrocarbon receptors that express filaggrin, so as to enhance skin hydration [9]. *Saccharomyces* is a group of fungi that can suppress the activity of tyrosinase enzyme through the fermentation residue of *Saccharomyces cerevisiae*, thus inhibiting melanin formation [10, 11]. Both fungal derivatives are a group of postbiotics that can also maintain the balance of the skin microbiome [12]. Saccharide isomerate is a bioactive natural substance formed from the transformation of corn kernel sugar into complex carbohydrates. This chemical is similar to the natural moisturizing factor in the stratum corneum that can bind water and has a hydrating effect on the skin barrier [13]. Niacinamide is an active form of niacin, a vitamin B3 derivative, which can block the transfer of melanosomes to keratinocytes, thus preventing pigmentation [4, 6]. Liu et al. (2023) reported the use of cysteamine and isobionicamide combination therapy in post-inflammatory hyperpigmentation cases for 16 weeks and showed a decrease in melanin index values compared to placebo [4].

This study was the first to assess the efficacy of using a combination of serum and cream contained cysteamine with *Galactomyces* ferment filtrate, *Saccharomyces* ferment filtrate, saccharide isomerate, and niacinamide for hyperpigmentation disorders on the face. The cysteamine was combined with various fungal derivatives in cosmetic products because these two agents have a synergistic role in inhibiting melanogenesis through suppression of the tyrosinase enzyme. The combination can reduce the irritative side effects of cysteamine, through the hydrating role of fungal derivatives and niacinamide, so this product can be used for hyperpigmentation cases with sensitive or dry skin types. The study we conducted gave significant results in all research subjects and similar results were obtained in a study conducted by Anwar et al. (2024) using 1% cysteamine, 3% tranexamic acid, 2% *Galactomyces* ferment filtrate, and 4% niacinamide as a brightening agent with bilayering technique in females aged 31-50 years with Fitzpatrick IV skin type for eight weeks [9]. Another study *by Anwar et al.* (2022) also reported significant results on the use of 1% cysteamine, 3% tranexamic acid, *Galactomyces* ferment filtrate 2%, and niacinamide 4% for epidermal-type melasma cases for seven weeks [14]. Overall, there was clinical improvement in all research subjects, but significant differences were only found in MI values and L-values, so further studies are needed in the form of research with a randomized controlled trial design, a larger sample size, and a longer duration to assess maximum effectiveness.

CONCLUSIONS

The combination of serum and cream containing 2.5% cysteamine with 2% *Galactomyces* ferment filtrate, 2% *Saccharomyces* ferment filtrate, 2% saccharide isomerate, and 4% niacinamide is a potential agent that can be used for hyperpigmentation disorders on the face.

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