The Efficacy and Safety of 3% Caffeine Cream on Reduction of Periorbital Hyperpigmentation

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Abstract

Addressing periorbital hyperpigmentation or dark circles is challenging due to its multifactorial nature, and effective, widely applicable treatments are still lacking. To bridge this gap, our study investigates the potential of 3% caffeine cream in periorbital hyperpigmentation treatment, utilizing both objective and subjective measurements. This 12-week open-label clinical study evaluates the efficacy and safety of 3% caffeine cream in reducing periorbital hyperpigmentation. The 18 participants (12 females, six males, aged 26-40) with Fitzpatrick's skin types 3-4 underwent objective measurement of mean melanin index using a Mexameter, along with subjective assessments using Global Satisfaction Scores from two independent doctors and participants' satisfaction scores. All 18 participants completed the study, demonstrating a statistically significant reduction in the mean melanin index on both sides at the *0.05* level ($p<0.001$). The mean difference and percentage change of the mean melanin index at the 8^{th} and 12^{th} weeks were significantly lower than the baseline at the *0.05* level ($p<0.05$). The application of 3% caffeine yielded high scores on dermatologists' evaluations and patients' satisfaction scales, with scores increasing with longer application times. Notably, no participants exhibited a positive patch test, and no severe side effects were reported. Hence, the findings suggest that 3% caffeine holds promise as an alternative skin-whitening agent in cosmetics for periorbital hyperpigmentation.

Keywords**:** *Caffeine, Periorbital Hyperpigmentation, Dark Circles, Efficacy, Safety*

1. Introduction

Extrinsic aging (the skin's reaction to external damage) and intrinsic aging (natural consequences and heredity) contribute to skin aging. Hyperpigmentation or dark circles, diminished skin elasticity and laxity, wrinkles and fine lines, dilated blood vessels, uneven skin texture, enlarged pores, swollen or puffy eyes, keratosis (abnormal skin growth), etc. are all indications of ageing skin (Chiu, Chan, Lin, & Chiu, 2007).

As a result of redox imbalances, external environmental irritants or their metabolites function as intrinsic oxidants, directly or indirectly triggering the generation of various reactive oxidants, specifically reactive oxygen species (ROS). The most prevalent free oxygen radicals, ROSs, have a role in numerous physiological and pathological skin processes (Xu et al., 2017).

Deep face architecture, soft tissue alterations, and skin-related factors are just a few of the causes of periorbital hyperpigmentation, a frequent and complicated problem in the field of cosmetic medicine. It is difficult to treat, has a complex pathophysiology, and lacks simple, repeatable therapy alternatives. The development of periorbital hyperpigmentation beneath the eyes at any age is of major aesthetic concern since it may portray the person as depressed, worn out, worried, and old. It can happen to both young and older adults. Using pigmentation-reducing topicals stands out as the frequently documented approach in clinically managing periorbital hyperpigmentation. Of these, retinoids, dihydrochalcone, α-arbutin, caffeine, cyanidin-3-glucoside, hyaluronic acid, lactic acid, lycopene, and niacinamide are noted to demonstrate considerable advantages (Sawant, & Khan, 2020).

Caffeine (1,3,7-trimethylxantine, CAF) is a naturally occurring xanthine alkaloid in numerous plant species, such as coffee and tea. Strong antioxidant effects exist in caffeine. It aids cell defense against UV radiation and photo-carcinogenesis and reduces the skin's photoaging and photodamaging process. Additionally, caffeine in cosmetics improves the microcirculation of blood in the skin (Herman, & Herman, 2013; Koo et al., 2007; Leon-Carmona, & Galano, 2011). In an in vitro study, it was observed that caffeine interacts with tyrosinase at specific binding sites, namely Lys379, Lys376, Asp357, Glu356, Thr308, Gln307, Asp312, and Trp358. This interaction induces alterations in the binding sites of L-tyrosine and the loop conformation adjacent to the active center. Furthermore, the study revealed that caffeine exerts a significant inhibitory impact on both intracellular tyrosinase activity and melanin production in B16-F10 melanoma cells, with the inhibitory efficacy exhibiting a concentration-dependent response (Yang et al., 2019).

Currently, caffeine, along with other antioxidants, are frequently included in cosmeceuticals, often promoted for its benefits in reducing facial creases and periorbital hyperpigmentation (Adolf, & Kurt, 2005). However, there was not any solid evidence to prove these claims. Moreover, studies are scarce regarding topical caffeine, an inexpensive substance that penetrating easily through human skin. In cosmetic products, caffeine formulation with concentrations of up to 3% is considered highly safe, and it is readily absorbed by the human skin (Dias et al., 1999).

A randomized, double-blinded, placebo-controlled study demonstrated the ability of a 3% caffeine-based gel to penetrate the lower eyelid skin and diminish the lower eyelid oedema (Amnuaikit, et al., 2011). Another study found that the caffeine pad containing vitamin K in an Emu oil base shows an improvement in eye counter appearance with anti-periorbital hyperpigmentation capacity and as an emollient after four weeks (Ahmadraji, & Shatalebi, 2015). However, this evidence was not strong enough to support the claims of anti-periorbital hyperpigmentation of caffeine.

The researcher got great interest in studying the antioxidant properties, photoprotective properties, and tyrosinase inhibitor effect of 3% caffeine, which is a safe concentration and has been used in previous studies (Ahmadraji, & Shatalebi, 2015; Amnuaikit et al., 2011; Dias et al., 1999), would be advantageous and helpful in the reduction of periorbital hyperpigmentation. Therefore, the main reason for this research is to study the effectiveness of 3% caffeine cream for the treatment of periorbital hyperpigmentation.

2. Objectives

1) To compare the anti-periorbital hyperpigmentation effect of 3% caffeine cream from baseline periorbital hyperpigmentation to follow-up visits assessed by measurement of mean melanin index using Mexameter.

2) To evaluate the improvement of periorbital hyperpigmentation using a global satisfaction score by two independent doctors at the end of the study.

3) To evaluate participants' satisfaction with the 3% caffeine cream.

4) To observe the side effects of 3% caffeine cream.

3. Materials and Methods

3.1 Participants

The sample size was calculated with the statistical formula for the comparison of two means from a similar research article titled "Effective reduction of post-inflammatory hyperpigmentation with the tyrosinase inhibitor isobutylamido-thiazolyl-resorcinol (Thiamidol) (Study III)" (Roggenkamp et al., 2021). Means and standard deviations were utilized in the sample size calculation. After calculation, n = 15.1877 was obtained. A dropout rate of 20% was expected. Therefore, 18 volunteers (n=18) were recruited. The participants were selected and included according to the following criteria: (1) healthy male and female

volunteers aged between 20 and 50 years old with periorbital hyperpigmentation, (2) not having problems around the eye, (3) Fitzpatrick skin phototype 2-5. Participants who met one or more of the following criteria were excluded from the study: (1) being allergic to caffeine cream (at least +1 level of adverse event), (2) having active skin diseases in the eye area or ocular pathology, prominent eye bags, prominent wrinkles, or visible vessels without pigmentation under the eye area, (3) having a history of allergic or hypersensitivity reaction to any cosmetic ingredients, (4) having received eye filler procedures, peeling, and any ablative or non-ablative laser treatment six months before the study, (5) working under the sun for a long amount of time (more than 5 hours/days, especially from 11:00 am – 3:00 pm) such as construction workers, agriculture workers, golf groundkeepers, etc., (6) taking any medication that interferes with melanogenesis such as OC pill, phenytoin, and spironolactone, (7) pregnant and breastfeeding women.

3.2 Test Materials

The caffeine cream produced by the SKIN INTIMATE company in tubes contained 30g of the 1-month usage. The cream used in the research has been approved by the Thailand FDA (12-1-6500044073). The cream's ingredients include 3% W/W Caffeine, Water, Sodium Chloride, Glycerin, Cyclopentasiloxane, PEG-10 Dimethicone, Disteardimonium Hectorite, Dimethicone, Caprylic/Capric Triglyceride, Hydroxyacetophenone, Caprylyl Glycol, Dipropylene Glycol, and Dipotassium.

3.3 Methodology

The research is designed as an open-label quasi-experimental study involving 18 healthy males and females aged between 26-40 years, with a duration of 12 weeks. The protocol and informed consent were reviewed and approved by the Ethics Committee of Mae Fah Luang University, Thailand, on April 27, 2023 (acceptance code: EC 23004-20). Participants are required to apply a 3% caffeine cream on both sides of the periorbital area twice a day. Follow-up appointments are scheduled for the 4th, 8th, and 12th weeks. Prior to the study, volunteers were thoroughly informed about the research purpose, detailed procedure, and anticipated risks and benefits. Informed consent was obtained through signed forms, and a patch test for the 3% caffeine cream was conducted. The mean melanin index was measured at the landmark three times, and then the mean values were, using Mexameter MX 18 at baseline, 4th, 8th, and 12th weeks. Participants were photographed using the VISIA® at baseline and the 12th week to evaluate the Global Satisfaction Score at the end of the study period by two independent doctors who were blinded using a scale ranging from -1 to 4. Physicians monitored participants for adverse effects, and participants' satisfaction was recorded.

3.4 Statistical Analysis

The data collected from the study were statistically analyzed using SPSS software and Microsoft Excel 2019. This analysis was conducted at Mae Fah Luang University Hospital in Bangkok, Thailand. For statistical data analysis of the mean melanin index by Mexameter, repeated ANOVA measures and multiple comparisons by the Bonferroni method were used to analyze and compare the data. Descriptive data analysis was used for global and patients' satisfaction scores.

4. Results and Discussions

4.1 Results

4.1.1 Baseline Characteristics of the Participants

Table 1 Baseline characteristics

General characteristics	n = 18
Sex, n (%)	
Male	6
Female	12
Age (years)	
mean±SD	29.61±3.74
min – max	26 - 40
Occupation, n (%)	
Student	12
Employee	3
Government officer	3
Fitzpatrick skin type, n (%)	
III	7
IV	11
Sunlight exposure minutes/day)	
median (IQR)	10 (5, 37.5)
min – max	5 - 60
Periorbital skin care, n (%)	5
Underlying disease, n (%)	0
Treatment history within six months, n (%)	0
Food / Drug allergy, n (%)	0

IQR: Interquartile range

4.1.2 Mean melanin index

According to the statistical analysis result from Table 2, the mean melanin index on the right side at baseline, follow-up 4th, 8th, and 12th weeks were 219.02±46.31, 211.96±41.92, 202.74±39.40, and 193.70±37.45, respectively. The mean melanin index on the right side showed a statistically significant decrease at each visit at the 0.05 level ($p<0.001$). The mean melanin index on the left side at baseline, follow-up 4th, 8th, and 12th weeks were 206.63±44.64, 202.94±41.29, 199.09±39.71, and 187.44±36.76, respectively. The mean melanin index on the left side showed a statistically significant decrease at each visit at the 0.05 level ($p = 0.002$).

Table 2 Statistical analysis of mean melanin index on the right and left side at baseline, follow-up 4th, 8th, and 12th week (n=18)

Right side	Left side

	Mean±SD	Mean difference[a] (%change)	Mean±SD	Mean difference[a] (%change)
Baseline	219.02±46.31		206.63±44.64	
4th week	211.96±41.92	-7.06 (-3.22%)	202.94±41.29	-3.69 (-1.79%)
8th week	202.74±39.40	-16.28 (-7.43%)	199.09±39.71	-7.54 (-3.65%)
12th week	193.70±37.45	-25.31 (-11.56%)	187.44±36.76	-19.19 (-9.29%)
P-value	<0.001*		0.002*	

Data were analyzed with Repeated measure ANOVA
Statistically significant at the 0.05 level
a: compared with baseline

Table 3 Multiple comparison analysis (posthoc test) of mean melanin index on the right and left side (n=18)

	Right side	Left side
	Mean difference (P-value)	Mean difference (P-value)
Baseline vs. 4th week	-7.06 (0.382)	-3.69 (0.889)
Baseline vs. 8th week	-16.28 (0.010*)	-7.54 (0.594)
Baseline vs. 12th week	-25.31 (0.002*)	-19.19 (0.016*)
4th week vs. 8th week	-9.22 (0.036*)	-3.85 (1.000)
4th week vs. 12th week	-18.26 (0.004*)	-15.50 (0.023*)
8th week vs. 12th week	-9.04 (0.014*)	-11.65 (0.019*)

Multiple comparisons by the Bonferroni method
*The mean difference is significant at the 0.05 level (α = 0.05)

According to the multiple comparison analysis results from Table 3, the mean melanin index on the right side in the8th week was lower than the baseline (Mean Difference=-16.28, p=0.010) and the 4th week (MD=-9.22, p=0.036) both statistically significant at the 0.05 level. Similarly, the mean melanin index on the right side at the 12th week was lower than baseline (MD=-25.31, p=0.002), the 4th week (MD=-18.26, p=0.004), and the 8th week (MD=-9.04, p=0.014) all statistically significant at the 0.05 level. Additionally, the mean melanin index on the left side at the 12th week was lower than baseline (MD=-19.19, p=0.016), the 4th week (MD=-15.50, p=0.023), and the 8th week (MD=-11.65, p=0.019) all statistically significant at the 0.05 level.

4.1.3 Patients' satisfaction score

The patient's satisfaction after the study in the 12th week was evaluated the results with the grading scale as follows:

-1 = worse
0 = no improvement
1 One= fairly improvement (1-25%)
2 = moderate improvement (26-50%)
3 Three= good improvement (51-75%)
4 = excellent improvement (76-100%)

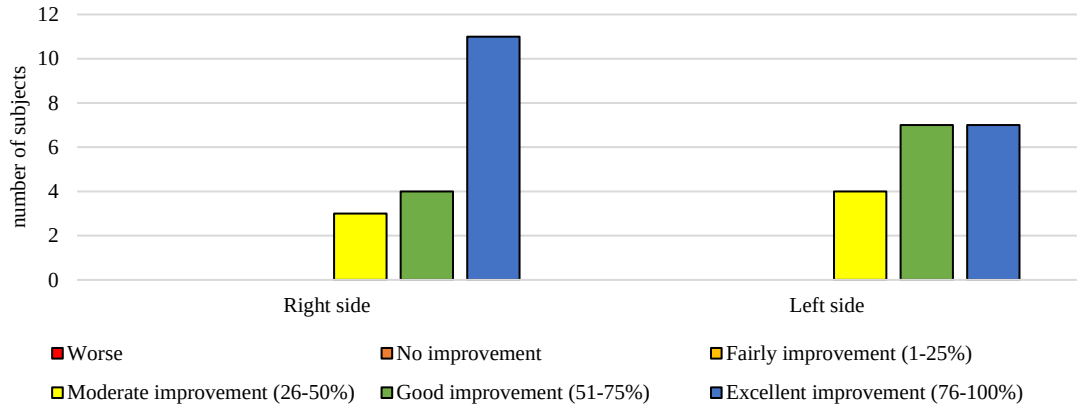

Figure 1 Bar graph displaying the frequencies of patients' satisfactory scales at the 12th week

According to the result from Figure 1, eleven subjects rated the patients' satisfaction on the right side as excellent improvement. Following that, four subjects reported good improvement, and three subjects reported moderate improvement. On the left side, seven subjects rated excellent and good improvement. Following that, four subjects reported moderate improvement. The median of patients' satisfaction scores on the right and left sides were 4 (IQR 3, 4) and 3 (IQR 2.75, 4).

4.1.4 Dermatologists' Evaluation Score

The dermatologists' evaluation after the study in the 12th week, conducted by two independent physicians, assessed the results with the grading scale as follows:

-1 = worse
0 = no improvement
1 = fairly improvement (1-25%)
2 = moderate improvement (26-50%)
3 = good improvement (51-75%)
4 = excellent improvement (76-100%)

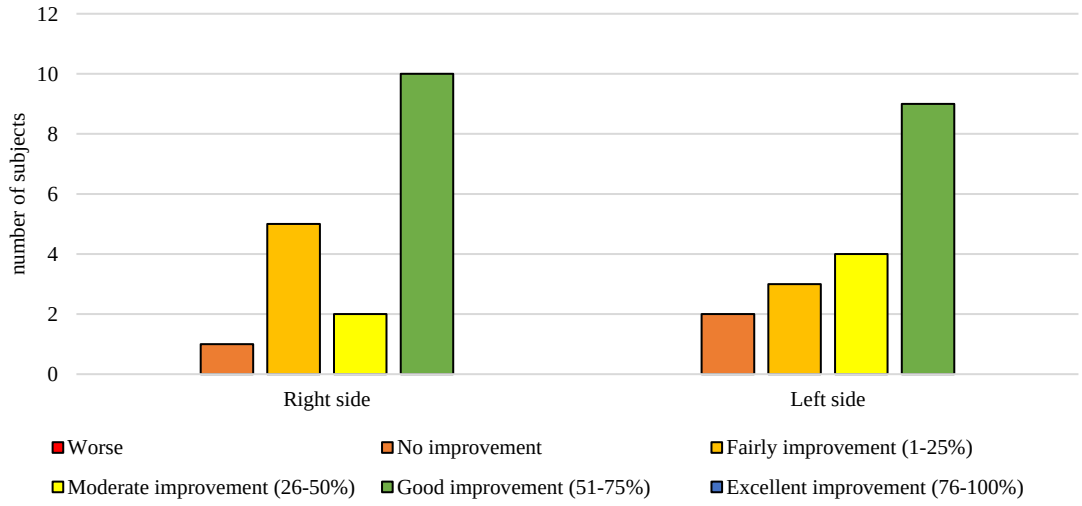

Figure 2 Bar graph displaying the frequencies of dermatologists' evaluation scale at the 12th week

According to the result from Figure 2, the dermatologists' evaluation on the right side was rated as a good improvement by ten subjects. Following that, five subjects reported some improvement; two subjects reported moderate improvement, and one subject reported no improvement. On the left side, nine subjects rated good improvement. Following that, four subjects reported moderate improvement; three subjects reported fairly improvement, and two subjects reported no improvement. The median of dermatologists' evaluation scores on the right and left sides were 2.5 (IQR 0.5, 3) and 2.25 (IQR 1, 3).

4.2 Discussion

The development of periorbital hyperpigmentation beneath the eyes at any age is of major aesthetic concern since it may portray the person as depressed, worn out, worried, and old. This condition can affect individuals of all ages. The most frequently employed approach to managing periorbital hyperpigmentation involves using topical depigmenting agents in a clinical setting. According to current research, the ingredients α-arbutin, caffeine, cyanidin-3-glucoside, dihydrochalcone, hyaluronic acid, lactic acid, lycopene, niacinamide, and retinol have been found to provide notable benefits (Sawant, & Khan, 2020). Nowadays, caffeine and other antioxidants are frequently included in cosmeceuticals, often promoted for their benefits in reducing facial creases and periorbital hyperpigmentation, hair loss prevention, and alopecia areata treatment (Adolf, & Kurt, 2005). Typically, topical caffeine formulations contain up to 3% caffeine concentration, which is generally safe and easily absorbed by the skin (Dias et al., 1999; Herman, & Herman, 2013). In this open-label clinical quasi-experimental study, 3% caffeine cream was investigated for the treatment of periorbital hyperpigmentation by using objective and subjective measurements.

A previous study by Lee, Bharadwaj, Yadava, and Kang (2019) investigated the potential of caffeine as a therapeutic agent against photoaging. The study examined caffeine's inhibitory effects on collagenase, elastase, and tyrosinase activity. The findings showed that caffeine had a molecular interaction activity profile against tyrosinase of 2.86 kcal/mol and demonstrated statistically significant inhibitory activity for tyrosinase (13.72%) in the in-silico study (Lee et al., 2019). Another recent study showed that caffeine has the potential to significantly inhibit melanoma cell melanin production and intracellular tyrosinase activity, which is believed to be from the mechanism of inhibition of tyrosinase, the key enzyme that initiates melanin biosynthesis. This effect is achieved through caffeine binding to the binding sites of L-tyrosine in a concentration-dependent manner (Yang et al., 2019). In this research study, the researcher used 3% caffeine in topical cream form to assess the efficacy of caffeine in reducing periorbital hyperpigmentation by measuring the melanin index without any side effects. As a result, this study can validate the findings of those previous studies, which stated that the application of 3% caffeine cream has good efficacy in reducing periorbital hyperpigmentation.

These findings align with previous research, a randomized, double-blinded, placebo-controlled study that applied caffeine gel to dark puffy eyes. The study showed promising results, including reduced soft tissue swelling and lightening of dark complexions (Amnuaikit et al., 2011). Nevertheless, this study employs the mean melanin index, a widely recognized metric for pigment assessment, to quantify the outcomes. This method enhances objectivity and precision in measurement, contributing to the study's credibility and reliability. Additionally, a significant improvement in periorbital hyperpigmentation was observed in our study, which is consistent with prior research utilizing a 3% caffeine pad containing vitamin K in an Emu oil base. This earlier research demonstrated improved eye contour appearance and anti-periorbital hyperpigmentation effects after four weeks (Ahmadraji, & Shatalebi, 2015). However, the previous study, spanning a duration of 4 weeks, although providing valuable insights, might be considered relatively short in the context of observing significant and long-term impacts. Therefore, this study, with an extended timeline of up to 12 weeks, contributes more to the depth and reliability of the study findings.

To evaluate the efficacy of 3% caffeine cream in melanin production for periorbital hyperpigmentation improvement, in this study, the mean melanin index by Mexameter, global satisfaction score by two independent physicians, patients' satisfaction score, and adverse effects were measured. For statistical data analysis of the mean melanin index by Mexameter, repeated ANOVA measures and multiple comparisons by the Bonferroni method were used to analyze and compare the data. Descriptive data analysis was used for global and patient' satisfaction scores. Comparing the results from follow-up visits to baseline visits, it was found that there was a statistically significant reduction in the mean melanin index.

The results of the experiment that evaluated the efficacy of a 3% caffeine cream showed that, according to the statistical analysis, the results of the mean melanin index on both sides were reduced statistically significantly at the level of 0.05 ($p<0.001$). The mean difference and percentage change of mean melanin index on follow-up 8th and 12th weeks were lower than baseline statistically significant at the level of 0.05 ($p<0.05$). However, the mean difference and percentage change on follow-up 4th week compared with baseline are not statistically significant at the level of 0.05. Compared to a previous study, the changes in pigmentation were statistically significant only after the 3rd week of applying caffeine pads ($p<0.05$) compared with baseline. Still, there was no significant change between the 3rd week and the 4th week (Ahmadraji, & Shatalebi, 2015).

The median evaluation scores of dermatologists and satisfaction scores of subjects were presented due to the non-parametric nature of the data, which was confirmed by a normality test. Most dermatologists' evaluations resulted in good improvement on both sides, with a median of 2.5 (IQR 0.5, 3) and 2.25 (IQR 1, 3) for the right and left sides, respectively. Similarly, the satisfaction scores of subjects in the 12th weeks showed a majority of excellent and sound improvements. The median satisfaction scores for participants on the right and left sides were 4 (IQR 3, 4) and 3 (IQR 2.75, 4), respectively. Therefore, using 3% caffeine resulted in high scores on both the dermatologists' evaluation and patients' satisfaction scales, with scores increasing with longer application times.

According to a previous study, conducted by Gajewska et al. (2015), topical application of caffeine is safe and does not cause any harm to liver cells. The liver cell survival was not affected by oral or skin ingestion of caffeine at doses up to 5.33 mg/kg BW (Gajewska et al., 2015). Moreover, none of the participants in the study showed a positive patch test, and no severe side effects were reported. These results indicate that using 3% caffeine as a topical treatment is safe and well-tolerated by the participants. However, there should be more future research studies for better results.

5. Conclusion

This research study concluded that 3% caffeine can achieve good efficacy in improving periorbital hyperpigmentation and safe topical application. According to this study, the results of the mean melanin index on both sides were reduced statistically significantly, proving the periorbital hyperpigmentation capacity of 3% caffeine. Moreover, the 3% caffeine cream highly fulfilled participant's satisfaction, and no adverse effect was reported throughout the study. Hence, it is believed that 3% caffeine has the potential to be used as an alternative skin-whitening agent in cosmetics for periorbital hyperpigmentation.

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