

# Effectiveness of application of serum and cream containing combination of tranexamic acid, galactomyces ferment filtrate, niacinamide, and alpha arbutin using layering technique in melasma

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## Original Article

# Effectiveness of application of serum and cream containing combination of tranexamic acid, galactomyces ferment filtrate, niacinamide, and alpha arbutin using layering technique in melasma

含傳明酸、半乳桿菌發酵濾液、煙酰胺和甲型熊果素結合的精華和乳膏層疊式塗抹在黃褐斑的應用效果

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**Objective:** This research aimed to determine the effect of tranexamic acid 3% in combination with several brightening agents including *Galactomyces* ferment filtrate 2%, niacinamide 4% and alpha arbutin 2%, in melasma treatment. **Methods:** This was a multi-centre trial which was held Hasanuddin University hospital in Makassar, South Sulawesi, Indonesia and Gatot Soebroto Central Army hospital in Jakarta, Indonesia. A total of 66 patients with epidermal and/or mixed-type melasma were instructed to apply tranexamic acid in combination serum containing 3% tranexamic acid, 2% *Galactomyces* ferment filtrate, 4% niacinamide, and 2% alpha-arbutin, followed by cream with the same content (layering technique) for four weeks. The clinical appearance was assessed using melasma severity score (MSS) while skin analyser Janus Facial Analyses System® was used to assess the spot ultraviolet (UV) (parameter for dermal hyperpigmentation) and spot polarised (PL) (hyperpigmentation in the epidermis). The MSS score, spot UV and spot PL were measured at baseline and at follow up every two weeks and four weeks. **Results:** MSS score showed significant reduction in week 2 (1.33%) and week 4 (1.47%) compared to baseline (1.65%). There was a significant decrease of spot UV value from baseline (22.6%) compared to week 2 (20.1%) and week 4 (19.8%). However, no significant differences in spot PL value from baseline to week 2 and week 4. **Conclusion:** Application of combination of tranexamic acid 3% with *Galactomyces* ferment filtrate 2%, niacinamide 4% and alfa arbutin 2% in serum and cream preparation using layering technique was effective in treating melasma.

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目的：本研究旨在確定 3% 傳明酸混合數種增白劑（包括 2% 半乳發酵濾液、4% 煙酰胺和 2% 甲型熊果素）的組合用來治療黃褐斑的效果。方法：這是一項多中心臨床試驗，在印度尼西亞南蘇拉威西省望加錫的哈桑努丁大學醫院和印度尼西亞雅加達的加托特·索布羅託中央軍醫院進行。總共 66 名表皮或混合型黃褐斑患者，按指示先塗抹含有 3% 傳明酸、2% 半乳發酵濾液、4% 煙酰胺和 2% 甲型熊果素結合的精華，再重複塗多一層相同成分的乳劑，持續四個星期。我們使用黃褐斑嚴重度分數來評估臨床外觀，同時使用皮膚分析儀 Janus 面部皮膚檢測系統® 評估點紫外線（真皮層色素沉著過度的參數）和點極化（表皮色素沉著過度）。分別在基線、第二周和第四周跟進時，測量黃褐斑嚴重度分數、點紫外線和點極化。結果：與基線（1.65%）相比，黃褐斑嚴重度分數評分在第二週（1.33%）和第四週（1.47%）顯著降低。第二週（20.1%）和第四週（19.8%）的點紫外線值亦較基線（22.6%）低。反之，基線到第 2 周和第 4 週的點極化值無顯著差異。結論：將 3% 傳明酸與 2% 半乳發酵濾液、4% 煙酰胺和 2% 甲型熊果素結合的精華和乳膏層疊式塗抹能有效治療黃褐斑。

**Keywords:** Alfa arbutin, *Galactomyces ferment filtrate*, melasma, niacinamide, tranexamic acid

關鍵詞：甲型熊果素、半乳桿菌發酵濾液、黃褐斑、煙酰胺、傳明酸

## Introduction

Melasma is characterised by irregular light brown to gray macules or patches on sun-exposed sites, such as the cheek, forehead, nose, and chin. This condition may occur in any skin types, ethnic group, or gender, but is more common in skin types III and IV and in women of reproductive age. The exact aetiology is still unknown but factors such as ultraviolet (UV) exposure, genetic predisposition, and hormonal status lead to increased melanosome synthesis and their transfer to keratinocyte.<sup>1</sup>

The treatment of melasma is especially challenging as the main goal is to obtain clinical improvement without hypopigmentation.<sup>2</sup> Hydroquinone remains the gold standard therapy.<sup>3</sup> However, side effects such as irritation, erythema, and ochronosis are not rare and thus a new treatment approach is required.<sup>4</sup>

Tranexamic acid, originally developed as an antifibrinolytic agent, has recently come into surface as an alternative treatment for melasma. An *in-vitro* study has shown that tranexamic acid can inhibit melanin synthesis by disrupting the interaction between melanocyte and keratinocyte. This is done through the inhibition of plasminogen/plasmin system which

downregulates tyrosinase activity and results in decreased melanin synthesis.<sup>5</sup> Topical tranexamic acid the preferred route of administration due to its minimal systemic absorption.<sup>6</sup>

A trial showed that a tranexamic acid combination serum containing 3% tranexamic acid, *Galactomyces ferment filtrate* (GFF), niacinamide, and alpha arbutin was superior to 4% hydroquinone and placebo in increasing skin whitening.<sup>7</sup> In addition, a preliminary data showed that the application of tranexamic acid combination serum followed by cream of the same ingredient resulted in a more significant increase in skin whitening compared to serum only (unpublished data).<sup>8</sup>

This study aims to evaluate the effectiveness of topical application of tranexamic acid combination serum and cream using layering technique in patients with melasma.

## Methods

### Study design, place, and time

This multi-centre pre-post interventional study was carried out in the Department of Dermatovenereology, Hasanuddin University, Makassar, South Sulawesi, and Department of

Dermatovenereology, Gatot Soebroto Central Army Hospital, Jakarta, Indonesia from May-June 2018.

### Subjects

Women with epidermal or mixed-type melasma diagnosed by experienced dermatologists were recruited using consecutive sampling. Subjects 35-50 years old with Fitzpatrick skin type II, IV, and V who worked indoors for a minimum of eight hours per day were included in this study. Those who were pregnant, using hormonal contraception, any melasma treatment in the past month, history of systemic tranexamic acid in the past three months, and facial skin inflammatory disorders were excluded. This study was approved by the research ethics committee of the Faculty of Medicine, Hasanuddin University, Indonesia.

### Study protocol

Initially, information such as the duration of melasma, sunscreen use, length of daily sun exposure was collected through history taking. The melasma severity score (MSS) was calculated and Woods' lamp examination was done to determine the type of melasma. In addition, the spot UV, spot polarised (PL), skin tone, and sebum score were analysed in each subject using Janus Facial Analysis System<sup>®</sup>. Clinical photographs were taken using 16.1-megapixel Sony<sup>®</sup> digital camera.

The subjects were then instructed to apply the 3% tranexamic acid combination serum containing 3% tranexamic acid, 2% *Galactomyces* ferment filtrate, 4% niacinamide, and 2% alpha-arbutin, followed by 3% tranexamic acid combination cream with the same composition as the serum (WLW SynergiLab, Ltd) twice daily in the morning and evening after face washing. No topical preparations were to be applied on the face except for sunscreen with SPF 35 which was applied every morning, one minute after applying the cream.

Subjects were followed-up every 14 days for a total of 28 days. The clinical improvement, MSS, and results from the Janus Facial Analysis System<sup>®</sup> from each visit were assessed and compared.

### Janus Facial Analysis System<sup>®</sup>

Janus Facial Analysis System<sup>®</sup> (PSI, Korea) is a facial analysis device with 10-megapixel ultra-high-resolution camera. It is equipped with chin supports and forehead clamps, thus ensuring the stabilisation of the subject's head. Facial images are captured and analysed with the internal image analysis program. Spot UV denotes the hyperpigmentation area in the dermis while spot PL denotes the hyperpigmentation area in the epidermis. Skin tone, on the other hand, is a measure of skin brightness with a value of 0-100%. The score 0 and 100 represent the color black and white, respectively.

### Statistical evaluation

Data analysis was done by Statistical Package for Social Sciences (SPSS) 18.0 for Windows (SPSS Inc. Chicago, IL, USA). The statistical tests used were Mann-Whitney test and Wilcoxon signed-rank-test. A p-value <0.05 was considered as significant.

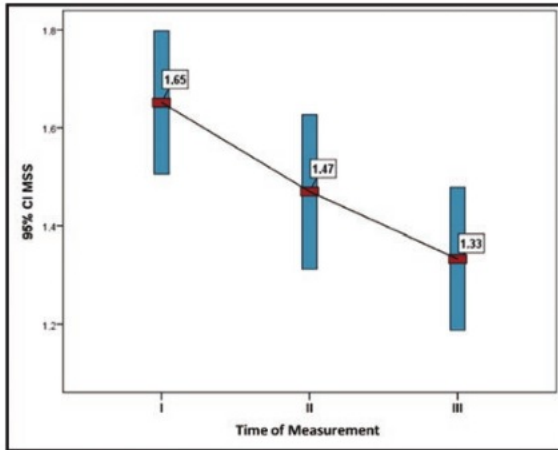
### Results

A total of 66 subjects with epidermal or mixed-type melasma participated in this study. Thirty-four subjects (3 dropped out) and 32 subjects (2 dropped out) were recruited in Department of Dermatovenereology, Hasanuddin University and Department of Dermatovenereology, Gatot Soebroto Central Army Hospital, respectively. Figure 1 shows a significant MSS reduction from an initial value of 1.65 after 14 days (1.47) and 28 days of application (1.33), respectively ( $p < 0.05$ ).

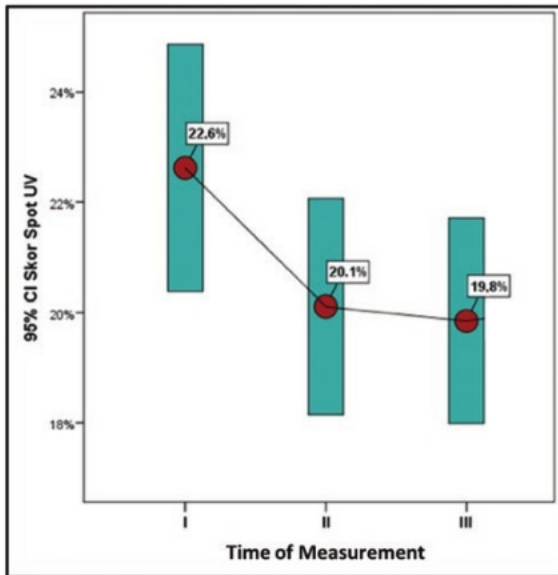
A significant reduction in spot UV but not in the spot PL levels were shown in Figures 2 and 3, respectively. The spot UV level was decreased from 22.6% to 20.1% and to 19.8% after two and four weeks of application, respectively.

A significant reduction in skin tone (Figure 4) and sebum levels (Figure 5) as measured by Janus Facial Analysis System<sup>®</sup> was also observed after 14 days

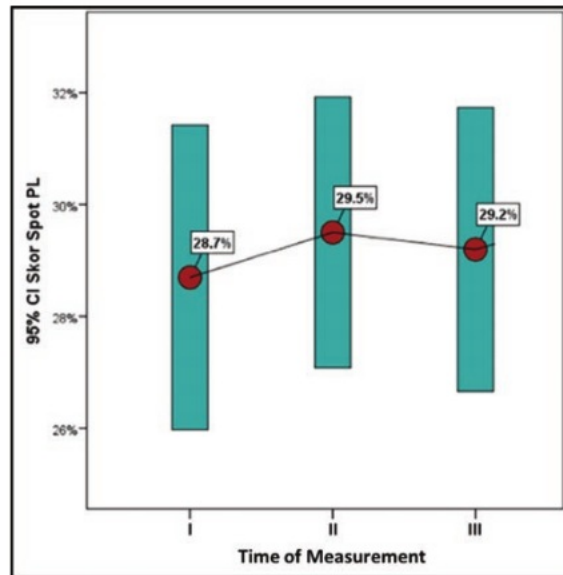
and 28 days of application ( $p < 0.05$ ). The skin tone was found to decrease from 42.3% to 42.1% and 41.8%, after two and four weeks of application, respectively. A similar trend was also shown by the sebum level measurement after four weeks of application, from 87.6% to 66.8%.



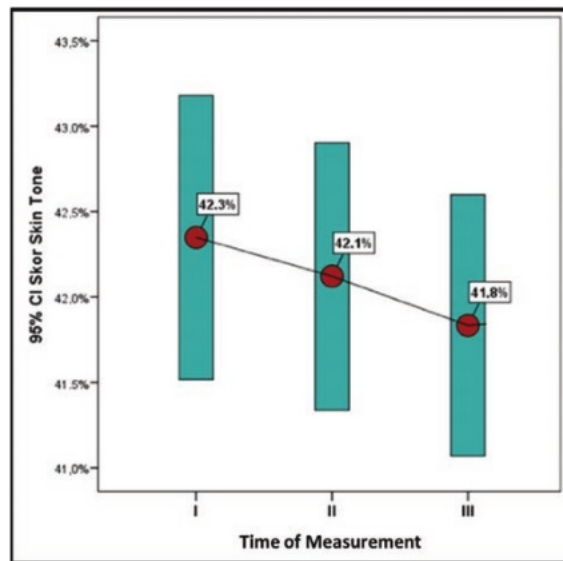
**Figure 1.** Results of MSS measurement.



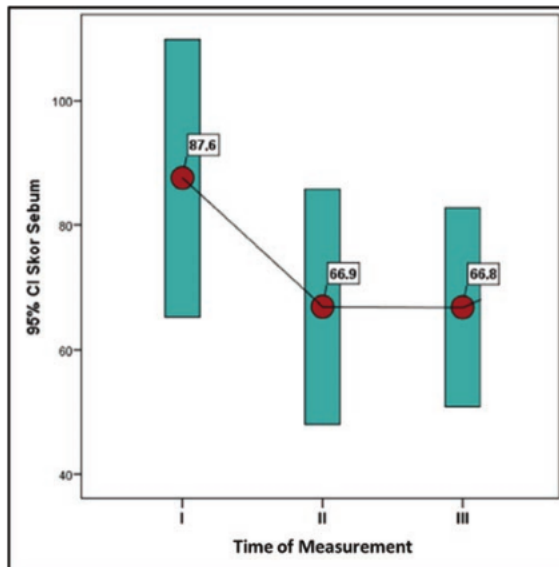
**Figure 2.** Changes in spot UV.



**Figure 3.** Changes in spot PL.



**Figure 4.** Changes in skin tone.



**Figure 5.** Changes in sebum level.

## Discussion

The change in MSS is shown in Figure 1, where a significant reduction in MSS was evident after two and four weeks of application ( $p < 0.05$ ). MSS is a simple and practical approach to score the pigmentation intensity of the skin.<sup>9</sup> It is divided into four grades, grade 0 (absence of melasma), grade 1 (mild melasma), grade 2 (moderate melasma), and grade 3 (severe melasma).<sup>10</sup> This result shows that the application of tranexamic acid combination cream using layering technique resulted in significant improvement in skin pigmentation.

Figures 2 and 3 show the change in spot UV and spot PL. It is interesting to see that the change in skin hyperpigmentation is more pronounced in the deeper level (dermis) as shown by the significant reduction in the spot UV level. This result indicates that the application of tranexamic acid combination serum and cream using layering technique is especially effective in the deeper layer of the skin.

The skin tone was shown to decrease significantly as shown in Figure 4. This result was different from

what was expected with the decrease of the spot UV level, the pigmentation should be also decreasing, which corresponds to the increase in skin tone. However, the data instead showed a decreasing trend (becoming darker). This result can be due to two reasons. First, the melanin from the applied site might have dispersed to the surrounding area. A study showed that although the melasma index (MI) after 8-week of topical and oral tranexamic acid on the applied site showed a significant reduction, an increased MI was found in the surrounding area.<sup>11</sup> In addition, topical tranexamic acid was also shown to induce erythema in the application site.<sup>11</sup> The induced erythema may be interpreted by the device as a decrease in skin tone.

Data in Figure 5 showed a decrease in facial sebum level after four and eight weeks of topical application. This could be attributed to the GFF content in this combination preparation. Lee et al showed a 64.17% sebum reduction after the application of 97% GFF.<sup>12</sup> In addition, they also found a decrease in the number of comedones and enlarged pores. The exact mechanism of how GFF reduces sebum remains to be elucidated. Further study is required to reveal the mechanism.

The side effects reported in this study included oedema and erythema reported by one subject, acne reported by 13 subjects, and facial soreness and pruritus experienced by four subjects. However, the side effects did not require therapy cessation.

## Conclusion

The application of tranexamic acid combination serum and cream using layering technique resulted in an improvement in melasma, both subjectively and objectively, and reduced sebum level. Future studies with longer follow-up period need to be conducted to evaluate the skin tone and spot PL levels.

## References

1. Achar A, Rathi SK. Melasma: a clinico-epidemiological study of 312 cases. *Indian J Dermatol* 2011;56: 380-2.
2. Gupta AK, Gover MD, Nouri K, Taylor S. The treatment of melasma: a review of clinical trials. *J Am Acad Dermatol* 2006;55:1048-65.
3. Sarkar R, Arora P, Garg VK, Sonthalia S, Gokhale N. Melasma update. *Indian Dermatol Online J* 2014;5: 426-35.
4. Gandhi V, Verma P, Naik G. Exogenous ochronosis after prolonged use of topical hydroquinone (2%) in a 50-year-old Indian female. *Indian J Dermatol* 2012;57: 394-5.
5. Maeda K, Tomita Y. Mechanism of the inhibitory effect of tranexamic acid on melanogenesis in cultured human melanocytes in the presence of keratinocyte-conditioned medium. *Journal of Health Science* 2007; 53:389-96.
6. Kanechorn Na Ayuthaya P, Niumphradit N, Manosroi A, Nakakes A. Topical 5% tranexamic acid for the treatment of melasma in Asians: a double-blind randomized controlled clinical trial. *J Cosmet Laser Ther* 2012;14:150-4.
7. Santoso GL, Anwar Al, Tabri F, Djawad K, Madjid A, Seweng A. The Effectiveness of Combination Serum of Tranexamic Acid, Galactomyces Ferment Filtrate, Niacinamide And Alpha Arbutin in Enhancing Skin Brightness. *Int J Med Rev Case Rep* 2018;2:169-73.
8. Anwar Al, Tabri F, Djawad K, Madjid A. The Effectiveness of Combination Serum and Cream of Tranexamic Acid, Galactomyces Ferment Filtrate, Niacinamide And Alpha Arbutin Using Layering Technique in Enhancing Skin Brightness 2017 (Unpublished Work).
9. Majid I, Haq I, Imran S, Keen A, Aziz K, Arif T. Proposing Melasma Severity Index: A New, More Practical, Office-based Scoring System for Assessing the Severity of Melasma. *Indian J Dermatol* 2016;61:39-44.
10. Thng TGS, Chuah SY. The Scoring Aid: MASI and Modified MASI. In: Handog EB, Enriquez-Macarayo MJ, editors. *Melasma and Vitiligo in Brown Skin*. India: Springer India; 2017:p.63-70.
11. Na JI, Choi SY, Yang SH, Choi HR, Kang HY, Park KC. Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. *J Eur Acad Dermatol Venereol* 2013;27:1035-9.
12. Lee M, Kim HS, Cho A, Jeon SH, Lee NK, Ahn KJ, et al. The Effects of Essence-Formed Cosmetic Ingredients Containing the Galactomyces Ferment Filtrate on Skin Improvements in Keratinization, Pores, Sebum Excretion, Brightness and Acne. *Kor J Aesthet Cosmetol* 2014;12: 77-84.

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**3** ATM Rezaul Karim, Shayesta Parvin Sadeque, Afreen Ferdous, Md Abdul Latif Khan, Md Habibur Rahman, Ahmed Rafi, Abdullah Masum. "Treatment of Melasma Cases by Oral Tranexamic Acid: A Randomized Control Trial", Journal of Armed Forces Medical College, Bangladesh, 2020  
Publication % **1**

**4** [www.gssrr.org](http://www.gssrr.org) Internet Source % **1**

**5** Song, E. J., J. A. Lee, J. J. Park, H. J. Kim, N. S. Kim, K. S. Byun, G. S. Choi, and T. K. Moon. "A study on seasonal variation of skin parameters" % **1**

in Korean males", International Journal of  
Cosmetic Science, 2014.

Publication

6

S. WAHYUNI, J. J. HOUWING-DUISTERMAAT,  
SYAFRUDDIN, T. SUPALI, M.  
YAZDANBAKHSI, E. SARTONO. "Clustering of  
filarial infection in an age-graded study: genetic,  
household and environmental influences",  
Parasitology, 2004

Publication

% 1

7

[www.pubmedcentral.nih.gov](http://www.pubmedcentral.nih.gov)

Internet Source

% 1

8

Submitted to Cardiff University

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[www.ijord.com](http://www.ijord.com)

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11

Anis I. Anwar, Siswanto Wahab, Widya Widita,  
Airin R. Nurdin, Suci Budhiani, Arifin Seweng.  
"Randomized control trial outcomes of  
tranexamic acid combination serum as a  
depigmenting agent for the use in healthy  
individuals", Dermatologic Therapy, 2019

Publication

<% 1

12

"Melasma and Vitiligo in Brown Skin", Springer

Science and Business Media LLC, 2017

Publication

<% 1

13

"Original Research", European Heart Journal  
Supplements, 2017

Publication

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academic.oup.com

Internet Source

<% 1

15

Mona Sadeghpour, Jeffrey S. Dover, Thomas E.  
Rohrer. "Advances in the Treatment of  
Melasma", Advances in Cosmetic Surgery, 2018

Publication

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WORDS