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# Randomized control trial outcomes of tranexamic acid combination serum as a depigmenting agent for the use in healthy individuals

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**Abstract**

To compare the effectiveness of tranexamic acid (TA) combination serum with hydroquinone, the gold standard in whitening agents for healthy populations. This was a three-arm randomized controlled trial. The subjects were divided into three groups: the first group received 3% TA combination serum (3% TA, 4% galactomyces ferment filtrate, 2% niacinamide, and 4% alpha arbutin), the second group received 2% TA combination serum, and the third group received 4% hydroquinone. One milliliter of each serum was applied on three holes: Hole A, which was located 4 cm from the left cubital fossa, Hole B, which was located 4 cm from the first hole, and Hole C, which was located 4 cm from the right cubital fossa. The skin brightness and pigmentation intensity were evaluated each week for 4 weeks using a chromameter. A total of 44 subjects were recruited for this study. All groups showed a significant improvement in skin brightness and pigmentation intensity after 4 weeks ( $p < .001$ ). There were no differences between the treatment groups and hydroquinone ( $p > .05$ ). TA serum (2 and 3%) combined with 4% galactomyces ferment filtrate, niacinamide, and alpha arbutin is an effective depigmenting agent.

**KEYWORDS**

depigmenting agent, topical tranexamic acid

## 1 | INTRODUCTION

Women, including those in Asian and Western countries, often dream of having a bright skin. In Eastern Asian countries, such as China and Korea, fair skin is regarded as a symbol of elegance and nobility (Leong, 2006). In South Asian countries, women with dark skin are thought to be laborers or field workers, while those with pale skin are considered as to be aristocratic lineage and are thought of as high-class citizens (Shankar & Subish, 2016). A high demand for a fair complexion has produced an overflowing supply of skin whitening products with various proposed mechanisms (Couteau & Coiffard, 2016).

In recent years, tranexamic acid (TA) has emerged as a promising depigmenting agent with multiple mechanisms of action. The depigmenting property this agent has been extensively studied, particularly in the field of hyperpigmentation disorders, such as melasma (Zhang et al., 2018). As a novel agent, different preparations and concentrations have been used, either alone or as an adjunctive treatment, in multiple clinical trials, producing variable results (Kim, Moon, Cho, Lee, & Sung Kim, 2017; Zhang et al., 2018).

Recent evidence has shown that topical TA (2 and 3%) application is effective in treating melasma (Chung, Lee, & Lee, 2016; Ebrahimi & Naeini, 2014). However, no study has compared the effectiveness of these concentrations relative to hydroquinone, the current gold standard

for depigmenting agents. TA is thought to be effective solely in the treatment of ultraviolet-induced hyperpigmentation disorders and has never been studied as a whitening agent in a healthy population (Atefi, Dalvand, Ghassemi, Mehran, & Heydarian, 2017). In addition, currently available hydroquinone alternatives, such as galactomyces ferment filtrate, niacinamide, and alpha arbutin, are still inferior to hydroquinone; thus, the quest for an alternative for hydroquinone remains (Sarma et al., 2017).

The objective of this study was to assess the effectiveness of TA serum in combination with galactomyces ferment filtrate, alpha arbutin, and niacinamide as a whitening serum in a healthy population.

## 2 | METHODS

This was a three-arm randomized controlled trial. The study was conducted at the dermatovenereology clinic of Hasanuddin University Hospital, Makassar, Indonesia between April and May 2018. We included subjects that were 25–50 years of age with a Fitzpatrick skin type ranging from III to V. The exclusion criteria included pregnancy, lactation, inflammatory dermatoses on the arm, history of hypersensitivity to substances used in this study, history of any medical procedures or depigmenting agents on the arms within 1 month prior to the study, or use of systemic TA within 3 months prior to the study. Approval from the ethical committee had been obtained prior to the initiation of this study.

After signing an informed consent form, all subjects received three treatments with identical sera used for each subject: combination serum with 3% TA (3% TA, 4% galactomyces ferment filtrate, 2% niacinamide, and 4% alpha arbutin), combination serum with 2% TA (2% TA, 4% galactomyces ferment filtrate, 2% niacinamide, and 4% alpha arbutin), and 4% hydroquinone (PT LipWih SynergyLab,

Indonesia), which were randomly labeled as A, B, and C. To ensure uniform serum application sites on the flexor side of both forearms, we used a special sleeve made of elastic material with two holes for serum application: the first hole (A) was located 4 cm from the left cubital fossa, and the second hole (B) was located 4 cm from the first hole. One milliliter of each serum was then applied to the appropriate locations each morning and evening for 28 days. Additionally, serum C was applied to the right forearm following the same procedure.

The subjects were evaluated each week for a total of 4 weeks by taking standardized photographs from a fixed position and distance as well as measuring the skin brightness, pigmentation intensity, and erythema using a chromameter<sup>®</sup> (CR-400, Minolta, Japan). The chromameter is used to assess the reflective colors of a surface by taking into account three variables,  $L^*$ ,  $a^*$ , and  $b^*$ , where  $L^*$  denotes color brightness, ranging from 0 (black) to 100 (white),  $a^*$  denotes degree of erythema, and  $b^*$  denotes changes from yellow to blue. In addition, the individual typology angle (ITA) score was calculated by using the formula  $ITA = [\arctan(L^*-50)/b^*] \times 180/3.14159$ . The ITA score was validated using Fontana-Mason staining and was shown to correlate with skin melanin content and distribution. (Del Bino, Sok, Bessac, & Bernerd, 2006) Three measurements for each variable were determined each week, and the average values were recorded. Adverse events were also recorded at each visit.

All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL). The differences in skin brightness and pigmentation between all groups were assessed using one-way ANOVA, which, when significant, was further assessed by least significant difference tests. The intragroup analysis was assessed using paired  $T$  tests. Changes in measurements in each group over time were assessed using Pearson's correlation.  $p$  values less than .05 were considered to be statistically significant.

## 3 | RESULTS

Of the 44 subjects enrolled in the study, 26 (59.1%) subjects were 30 years-of-age or younger (Table 1). Thirty-seven (84.1%) subjects worked as nurses.

Table 2 shows the changes in the chromameter values after 28 days of topical treatment with 4% hydroquinone, 2% TA combination serum, and 3% TA combination serum. At baseline, no significant differences in skin brightness ( $L^*$ ), erythema ( $a^*$ ), or pigmentation

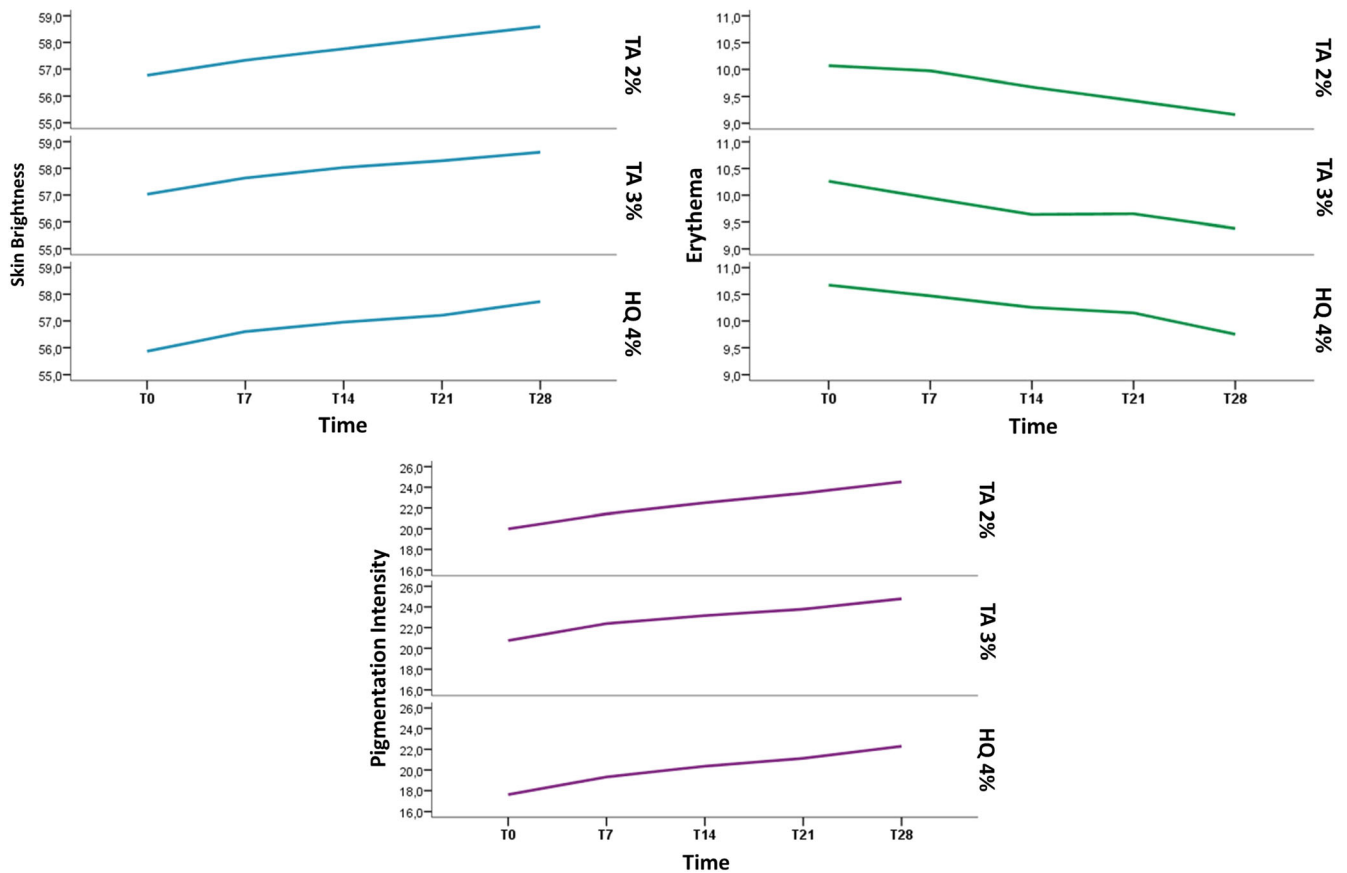
**TABLE 1** Characteristics of the subjects

Variable		<i>n</i>	%
Age	<30 years	26	59.1
	30–39 years	14	31.8
	≥40 years	4	9.1
Occupation	Nurse	37	84.1
	Staff	7	15.9

**TABLE 2** Changes in skin brightness ( $L^*$ ), erythema ( $a^*$ ), and pigmentation intensity (ITA score) after 28 days

Parameter	HQ*				TA** 2%				TA** 3%			
	T0	T28	<i>p</i> Value	<i>R</i> Value <sup>Δ</sup>	T0	T28	<i>p</i> Value	<i>R</i> Value <sup>Δ</sup>	T0	T28	<i>p</i> Value	<i>R</i> -Value <sup>Δ</sup>
$L^*$ axis	55.87	57.73	.000	.255	56.77	59.59	0.000	0.263	57.03	58.60	.000	.215
$a^*$ axis	10.67	9.75	.000	-.285	10.07	9.16	0.000	-0.335	10.26	9.38	.000	-.322
ITA score	17.61	22.29	.000	.217	19.99	24.53	0.000	-0.322	20.74	24.79	.000	.177

Note: No significant difference in skin brightness was observed between HQ, TA 2%, and TA 3% serum at baseline and after 28 days. \*HQ, hydroquinone. \*\*TA, tranexamic acid combination serum. <sup>Δ</sup>All  $R$  values were statistically significant ( $p = .000$ ).



**FIGURE 1** Changes in all chromameter values. There was an increase in both skin brightness and pigmentation intensity, and there was a decreasing trend of erythema



**FIGURE 2** Clinical picture before (left) and after (right) 28 days of tranexamic acid combination serum

intensity (ITA score) were observed within the groups ( $p > .05$ ). After 28 days of intervention, intragroup analysis showed a significant improvement of all chromameter values in all treatment groups ( $p < .05$ ). No significant differences were among the groups ( $p > .05$ ).

Figure 1 shows that the skin brightness and pigmentation intensity values showed an increasing pattern, while a decrease in erythema was evident after treatment for 28 days. Pearson's correlation analysis showed that both trends were statistically significant ( $p < .05$ ; Table 2).

## 4 | DISCUSSION

This study shows that TA serum (2 and 3% concentrations), in combination with galactomyces ferment filtrate, alpha arbutin, and niacinamide, was as effective as 4% hydroquinone, the gold standard depigmenting agent, when applied for skin brightening.

In the initiation of this study, the baseline values for  $L^*$ ,  $a^*$ , and ITA score were measured, and no significant difference was found between the treatment and control groups ( $p > .05$ ). This result shows that the randomization was successful and ensured homogeneity among treatment sites.

This study shows that skin brightness and pigmentation intensity, as demonstrated by the  $L^*$  scores and ITA scores, respectively, significantly improved in all groups after 28 days of treatment ( $p < .05$ ; Figure 2). Although the figures did not visually impressive, our objective measurement confirmed a significant improvement. These results are further supported by the result of the Pearson's correlation analysis, which suggests a statistically significant trend toward improvement in all groups, with the largest  $R$  value found in the 2% TA group. These data suggest that in addition to treating hyperpigmentation disorders, TA is an effective depigmenting agent in healthy individuals, as opposed to the classical view that TA is only effective in the treatment of ultraviolet-induced pigmentation (Atefi et al., 2017).

Topical TA is postulated to inhibit plasminogen from binding to keratinocytes by various mechanisms. It is thought to interfere with the lysin binding sites on keratinocytes which in turn downregulates prostaglandin, a stimulator of tyrosinase, resulting in a decline in tyrosinase activity and melanogenesis (Li, Shi, Li, Liu, & Feng, 2010; Poojary & Minni, 2015). TA is also found to block the Sc-uPA pathway and affect the plasminogen plasmin system, which eventually reduces hyperpigmentation (Maeda & Tomita, 2007).

The relative equal effectiveness of 2 and 3% concentrations of TA in this study may be explained by the compensating depigmenting effects of other substances contained in the combination sera. In a double-blind, randomized, controlled trial, niacinamide was found to decrease pigmentation after 8 weeks of application (Navarrete-Solís et al., 2011). This effect was thought to be mediated via reduction in melanosome transfer and its photoprotective effect (Hakozaki et al., 2002). On the other hand, alpha arbutin contributes to depigmentation by inhibiting tyrosinase, the enzyme that plays a central role in melanogenesis (Sardesai, Kolte, & Srinivas, 2013). Galactomyces ferment filtrate further augments this effect by inhibiting tyrosine hydroxylase and dampening oxidative stress (Cooper & JàNay, 2018; Woolridge et al., 2014).

To our knowledge, most studies on topical TA have been directed toward melasma treatment. This is the first study to show that, aside from treating hyperpigmentation disorders, topical TA is a promising whitening agent for the healthy population.

The short follow-up period in this study may explain the similar effectiveness of the combination serum treatments and hydroquinone. The clinical effect of niacinamide was suggested to be evident after 8 weeks of treatment, compared to 4 weeks with hydroquinone.(Navarrete-Solís et al., 2011) Future studies with

longer follow-up durations are needed to confirm the clinical significance of adding multiple substances in augmenting the depigmentation effect. In summary, this study showed that TA serum, in combination with galactomyces ferment filtrate, alpha arbutin, and niacinamide, is a safe and effective depigmenting agent in a healthy population.

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