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ORIGINAL PAPER

Whitening effect of L-ascorbate-2-phosphate trisodium salt on solar lentigos

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Abstract

Little is known about the anti-pigmenting effects of whitening agents on solar lentigos (SLs), which comprise ~ 60% of hyperpigmented facial lesions of Asian subjects. Lotions with or without 6% L-ascorbate-2-phosphate trisodium salt (APS) [test lotion (TL) and placebo lotion (PL), respectively] were applied twice daily for 24 weeks in a double-blind half-face study of 27 Japanese females with SLs on both sides of their faces. Pigmentation scores were evaluated using a photo-scale and the skin colors were assessed using a color difference meter and a mexameter for SLs and the non-lesional surrounding skin (NLS). Although the pigmentation scores were not significantly different between the TL and PL-treated SLs after 24 weeks, the *L* values of TL-treated SLs and NLS increased significantly with a significantly higher ΔL value in SLs than in NLS. In contrast, the *L* values of PL-treated SLs and NLS remained unchanged after the treatment. The number of subjects with > 2.0 ΔL was 7 of 27 (TL) and 0 of 27 (PL) in SLs and 3 of 27 (TL) and 0 of 27 (PS) in NLS. In contrast, the melanin index in TL-treated SLs and NLS significantly decreased with a significantly higher △melanin index in SLs than in NLS. Similarly, the melanin index of PL-treated SLs and NLS were significantly decreased with a significantly higher △melanin index in SLs than in NLS. These findings strongly indicate that APS has a weak but significant anti-pigmenting effect on SLs and a significant whitening effect even on normally pigmented healthy skin.

Keywords L-Ascorbate-2-phosphate trisodium salt · Solar lentigo · Double-blind half-face study · Pigmentation · *L* value · Melanin index

Abbreviations

SLs	Solar lentigos
APS	L-Ascorbate-2-phosphate trisodium salt
AMP	L-Ascorbate-2-phosphate Mg
EDN	Endothelin
SCF	Stem cell factor
NLS	Non-lesional surrounding skin

Yuko Ishikawa and Takao Niwano contributed equally to this work.

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Introduction

Most epidermal hyperpigmentary disorders occur due to the activation of melanocytes via the interaction of the skin with external and internal environments which include UV radiation [5–7], hormonal and nutritional factors [26–28] as well as several melanogenic cytokines or chemokines [5–8]. In Asian subjects, the most frequently appearing epidermal hyperpigmentary disorder is solar lentigos (SLs), which generally occur on the face. SLs develop on sun-exposed skin, especially on the face and they never disappear. The reason that SLs are more permanent has been speculated to result from the fact that the repeated UVB radiation of keratinocytes in the lesional epidermis may cause significant levels of cumulative DNA damage. Those lesional keratinocytes with UV-induced mutations may then begin to continuously produce tumor necrosis factor-α which stimulates the expression of endothelins (EDNs) and stem cell factor (SCF) in an autocrine fashion, leading in turn to the continuous activation of neighboring melanocytes [3, 9]. Little is known about the potential anti-pigmenting effects of those whitening

agents on SLs, which comprise ~ 60% of hyperpigmentary lesions that appear on the faces of Asian subjects.

L-Ascorbate-2-phosphate Mg (AMP) was the first whitening agent approved in Japan and was reported to act as a tyrosinase inhibitor after AMP is dephosphorylated by intrinsic epidermal phosphatases and is converted to ascorbic acid [1, 10, 14, 17, 21, 24, 25, 29, 32]. AMP is also used as an anti-acne agent with a mechanism of action distinct from tyrosinase inhibition [4, 12, 15, 16]. L-Ascorbate-2-phosphate trisodium salt (APS) (Fig. 1) is another approved whitening agent in Japan [1, 2, 18] that is also used as an anti-acne agent [13, 22, 30]. APS is a modified derivative of AMP that improves its stability, namely its aggregation due to the Mg salt [11]. Based on the requirement for the approval of whitening agents in Japan, it is well established that topical application of AMP or APS for 21 days on UVB (2MED)-exposed human skin significantly inhibits the UVB-increased pigmentation measured as *L* values at 21 days post-UVB irradiation. However, there is no published study on the anti-pigmenting effect of topical treatment with APS or AMP on SLs in a double-blind half-face study although a whole-face study using AMP on SLs for 3 months was reported to have some efficacy [10], although that study was flawed due to the lack of a placebo control. In this study, to characterize the effects of APS on SLs, we conducted a double-blind half-face study of 27 Japanese female subjects with SLs using lotions with or without 6% APS (test lotion and placebo lotion, respectively) applied twice a day for 24 weeks. Here we show for the first time that APS has a weak but significant anti-pigmenting effect on SLs and also a significant whitening effect even on non-lesional normally pigmented skin.

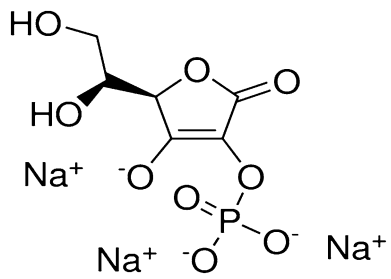

Fig. 1 Chemical structure of APS

Materials and methods

Test materials

The test lotion comprised 6% APS and other ingredients as listed in Table 1. The placebo lotion comprised the same components as the test lotion except it did not include APS.

Study design

This study was performed from October 2017 to March 2018, in the Ebisu Skin Research Center, Inforward Co. LTD, Tokyo, Japan. Lotions with or without 6% APS (test lotion and placebo lotion, respectively) were applied twice a day for 24 weeks. Thus, 27 Japanese female volunteers with SLs on both the right and left sides of their faces applied in a double-blind manner the test lotion to one-half of the face and the placebo lotion to the opposite side.

Compliance with ethical standards

Ethical approval

All procedures performed in studies involving human subjects were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The present study adhered to the tenets of the Declaration of Helsinki and was reviewed and approved by the Japanese Society of Aesthetic Dermatology Examination Ethics Committee (#TV-2017-09-001). A formal informed consent was obtained from each subject before the study. Following screening by a dermatologist, 27 Japanese female volunteers with SLs on the right and left sides of their faces attended this evaluation.

Evaluation of pigmentation level

Pigmentation levels were evaluated using a photo-scale ranging from 1.0 to 5.0 of SLs on the face by a dermatologist (KN). The pigmentation level on facial skin was measured using a color difference meter CM-700d(KONICA MINOLTA JAPAN, INC) for *L* value and using a Mexameter

Table 1 Full ingredients list of the test lotion (with 6% APS) and the placebo lotion (without APS)

With or without 6% APS, ammonium glycyrrhizate 0.1, water, alanine, saccharide isomerate, *Scutellaria baicalensis* root extract, *Chamomilla recutita* (Matricaria) flower extract, *Glycyrrhiza Glabra* (Licorice) root extract, zinc glycinate, *Tremella fuciformis* polysaccharide, *Pyrus communis* (Pear) twig extract, *Glycine soja* (Soybean) seed extract, *Ziziphus jujuba* fruit extract, hydrolyzed *Codonopsis pilosula* root extract, betaine, sodium hyaluronate, *Bellis perennis* (daisy) flower extract, sodium PCA, *Callicarpa japonica* fruit extract, polyphosphorylcholine glycol acrylate, saxifraga sarmentosa extract, *Rosmarinus officinalis* (rosemary) leaf extract, rosa centifolia flower water, glycerin 4.0, diglycerin, 1,2-hexanediol, pentylene glycol, butylene glycol 6.5, citric acid, sodium citrate, sodium lactate, phenoxyethanol

MX18 (Courage + Khazaka Electronic GmbH) [19] for melanin index (MI) at weeks 0 and 24.

Statistics

All data are expressed as means ± standard deviation (SD) unless noted otherwise. For pairwise comparisons, Student's *t* test was applied. p values < 0.05 are considered statistically significant.

Results

Changes in pigmentation level of SLs after treatment for 24 weeks

The use of lotions with or without 6% APS (test lotion and placebo lotion, respectively) was performed twice daily for 24 weeks as a double-blind half-face study of 27 Japanese female subjects with SLs on both the right and left sides of their faces. The pigmentation level of SLs was evaluated using a photo-scale ranging from 1.0 to 5.0 by a dermatologist (KN) and revealed no significant difference between test lotion and placebo lotion-treated SLs after daily treatments for 24 weeks. However, the pigmentation scores of SLs slightly decreased to a similar extent following treatment with the test lotion or the placebo lotion for 24 weeks (data not shown).

Observations of SLs and NLS before and after treatment for 24 weeks

Representative photographs of the faces of subjects No. 012 and No. 016 before and after treatment showing that the pigmentation level of the test lotion-treated SLs appeared to slightly decrease in concert with a slight decrease in the test lotion-treated NLS (Fig. 2). In contrast, the pigmentation level of the placebo lotion-treated SLs and the NLS appeared to remain unchanged.

Changes in *L* values of SLs after treatment for 24 weeks

L values measured using a color difference meter of test lotion-treated SLs significantly increased from 59.68 ± 2.32 to 60.99 ± 2.19 after treatment for 24 weeks

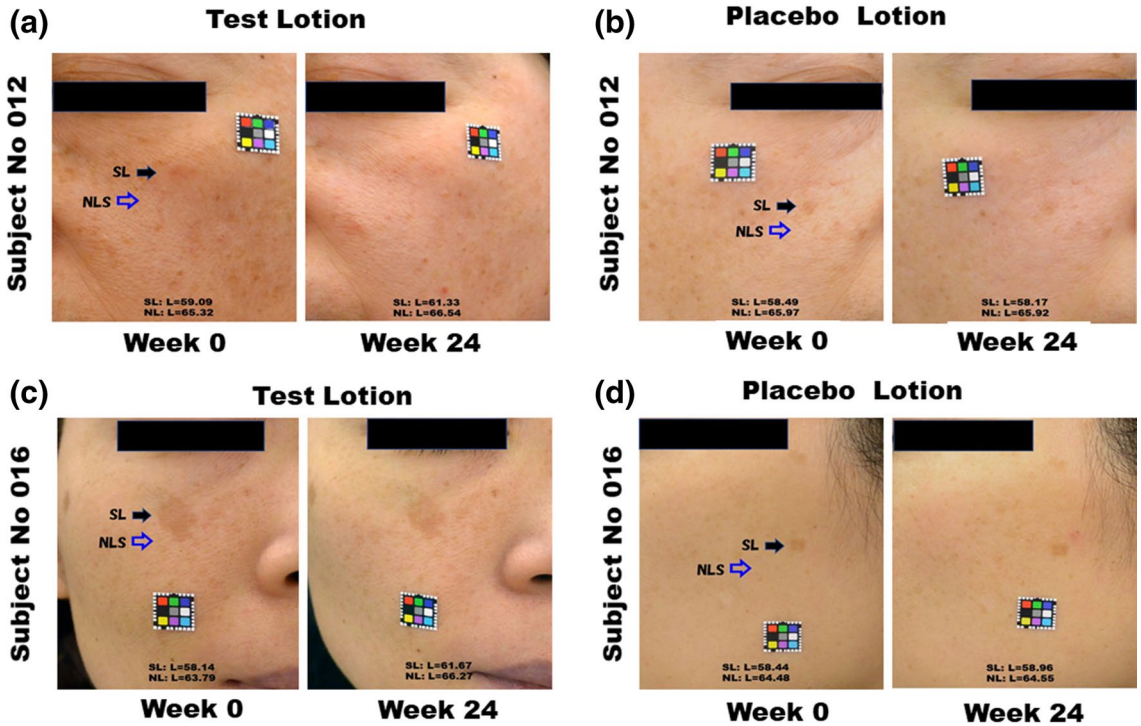

Fig. 2 Photographs of SLs and NLS before and after treatment for 24 weeks. **a, b** Subject No. 012: L values at 0 and 24 weeks of treatment with the test lotion were 59.09 and 61.33 on SLs and 65.32 and 66.54 on NLS, respectively. *L* values at 0 and 24 weeks of SLs treated with the placebo lotion were 58.49 and 58.17 and were 65.97 and 65.92 on the NLS, respectively. **c, d** Subject No. 016: *L* values at 0 and 24 weeks of SLs treated with the test lotion were 58.14 and 61.67 and 63.79 and 66.27 on the NLS, respectively. *L* values at 0 and 24 weeks of SLs treated with the placebo lotion were 58.44 and 58.96 and were 64.48 and 64.55 on the NLS, respectively. Black arrows point to SLs, and white arrows point to NLS

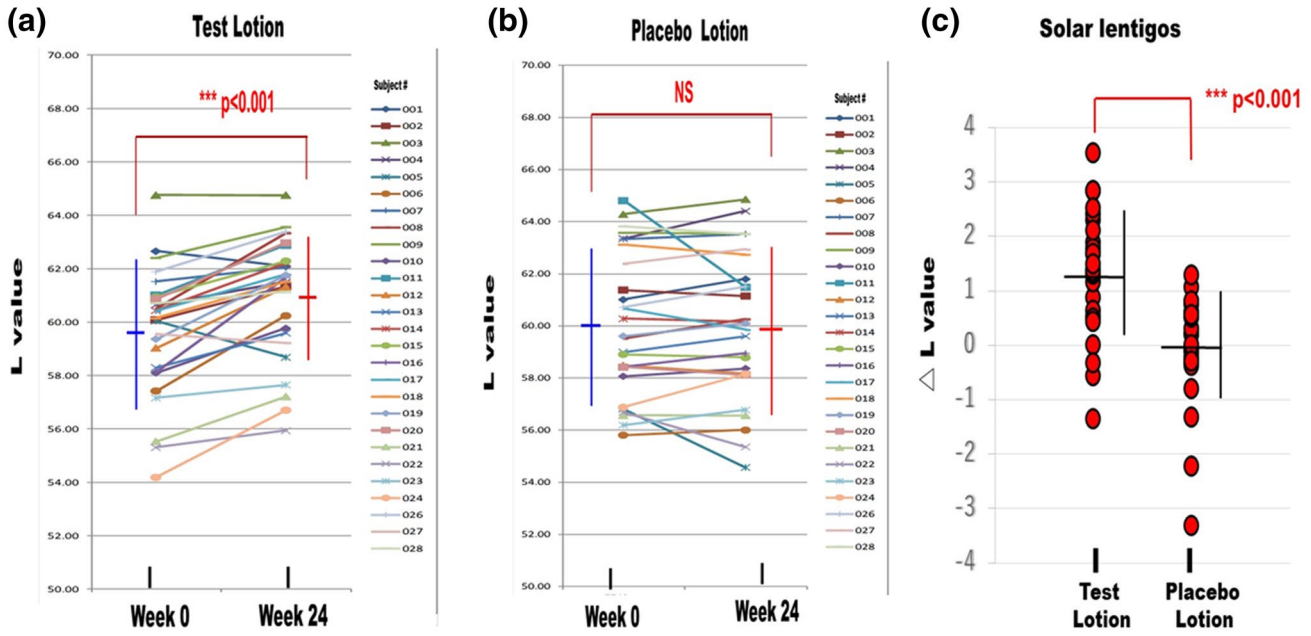

Fig. 3 Changes in L values of SLs after treatment for 24 weeks. **a** Test lotion, $N=27$, **b** placebo lotion, $N=27$, **c** $\triangle L$ values between weeks 0 and 24. $N=27$, $^{***}p<0.001$

(Fig. 3a). In contrast, L values of placebo lotion-treated SLs remained unchanged after the same treatment period (Fig. 3b). Comparisons of $\triangle L$ values before and after the treatments demonstrated that the test lotion-treated SLs had a significantly higher $\triangle L$ value than the placebo lotion-treated SLs (Fig. 3c). While more than a 2.0 $\triangle L$ is a visibly recognizable level, the ratio of subjects with more than a 2.0 $\triangle L$ of SLs was 7 of 27 (test lotion) and 0 of 27 (placebo lotion). These findings suggest that the test lotion has a significantly stronger anti-pigmenting effect on SLs than the placebo lotion.

Changes in *L* values of NLS after treatment for 24 weeks

L values of test lotion-treated NLS significantly increased from 64.44 ± 2.24 to 65.34 ± 2.34 after the treatment for 24 weeks (Fig. 4a). In contrast, L values in placebo lotion-treated NLS remained unchanged after the same treatment period (Fig. 4b). Comparison of $\triangle L$ values before and after the treatments demonstrated that the test lotion-treated NLS had a significantly higher $\triangle L$ value than the placebo lotion-treated NLS (Fig. 4c). The ratio of subjects with more than a 2.0 $\triangle L$ of NLS was 3 of 27 (test lotion) and 0 of 27 (placebo lotion). These findings suggest that the test lotion has a significantly stronger whitening effect on NLS than the placebo lotion.

Comparison of $\triangle L$ values between SLs and NLS

Comparison of the anti-pigmenting effects between SLs and NLS revealed that $\triangle L$ values before and after treatment with the test lotion were significantly higher in SLs than in the NLS (Fig. 5a). In contrast, in placebo lotion-treated SLs and NLS, the $\triangle L$ values were similar in the SLs and NLS without any significant difference between them (Fig. 5b).

Changes in melanin index of SLs after treatment for 24 weeks

The melanin index measured using a Mexameter MX18 in test lotion-treated SLs significantly decreased from 212.50 ± 33.83 to 188.65 ± 33.16 after treatment for 24 weeks (Fig. 6a). Similarly, the melanin index of placebo lotion-treated SLs also significantly decreased from 211.00 ± 36.12 to 198.81 ± 41.30 after the same treatment period (Fig. 6b). Comparison of changes in the melanin index before and after treatment demonstrated that the test lotion-treated SLs had a significantly lower $\triangle$ melanin index than the placebo lotion-treated SLs (Fig. 6c). These findings suggest that the test lotion has a significantly stronger anti-pigmenting effect on SLs than the placebo lotion.

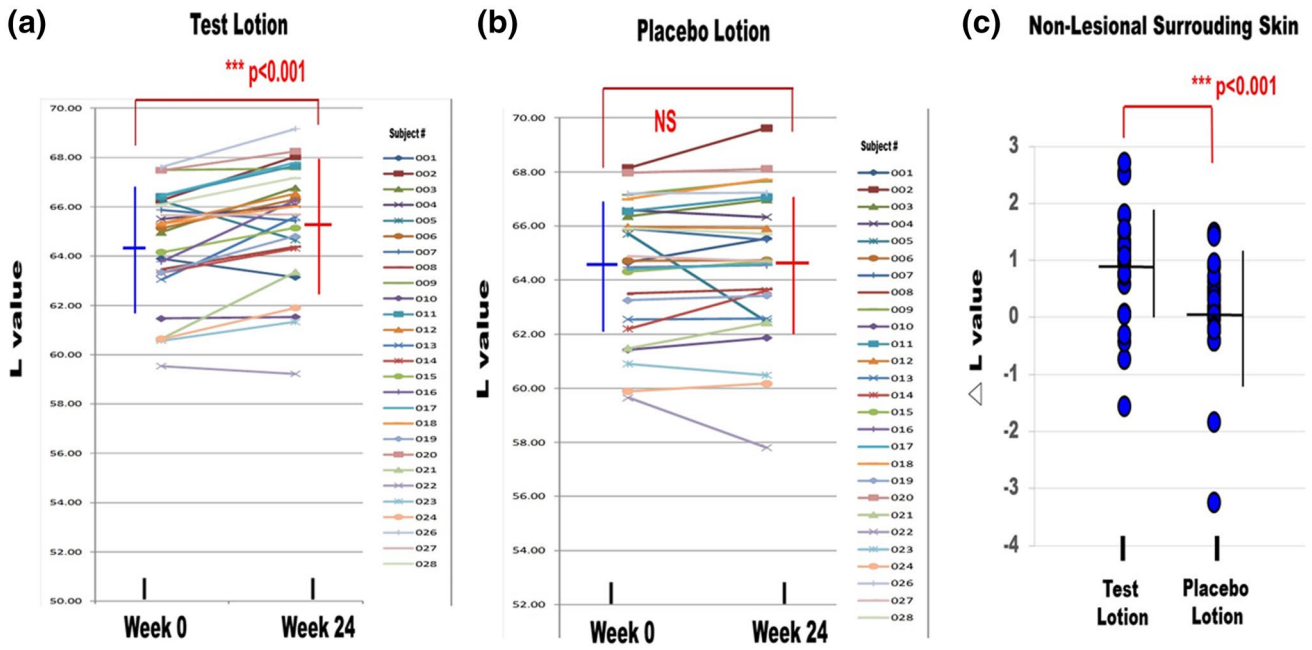

Fig. 4 Changes in L values of NLS after treatment for 24 weeks. **a** Test lotion, $N=27$, **b** placebo lotion, $N=27$, **c** ΔL values between weeks 0 and 24. $N=27$, $^{***}p<0.001$

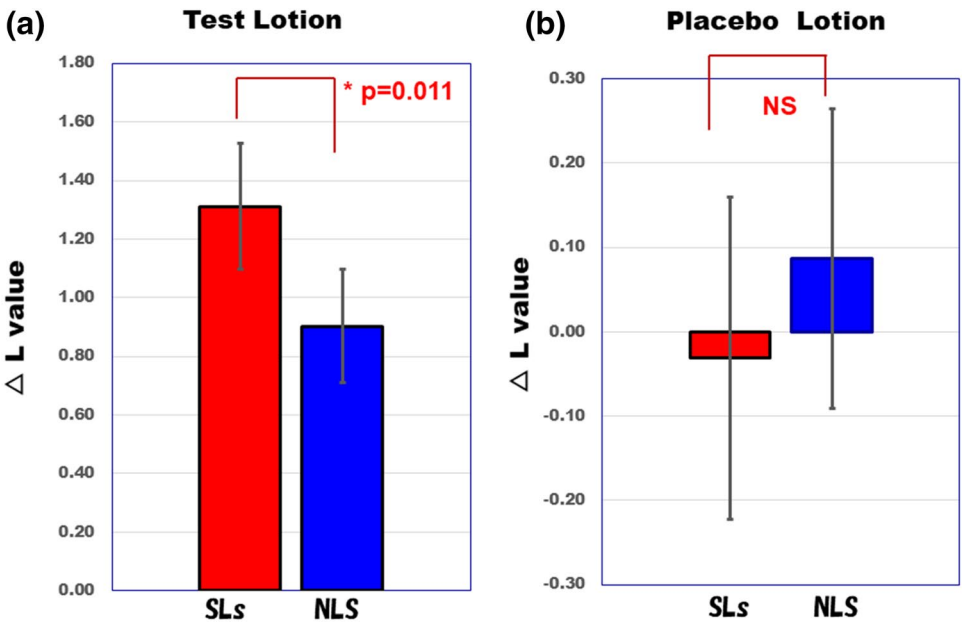

Fig. 5 Comparison of ΔL values between SLs and NLS. **a** Test lotion, $N=27$, **b** placebo lotion, data represent means ± standard error (SE). $N=27$, $^{*}p<0.05$

Changes in melanin index of NLS after treatment for 24 weeks

The melanin index in test lotion-treated NLS significantly decreased from 150.65 ± 29.73 to 125.13 ± 26.58 after treatment for 24 weeks (Fig. 7a). Similarly, the melanin index in placebo lotion-treated NLS also significantly decreased from 147.44 ± 29.60 to 140.54 ± 27.64 after the same treatment period (Fig. 7b). Comparison of the △ melanin index before and after treatment demonstrated that the test lotion-treated NLS has a significantly lower △ melanin index than the placebo lotion-treated NLS (Fig. 7c). These findings suggest that the test lotion has a significantly stronger anti-pigmenting effect on NLS than the placebo lotion.

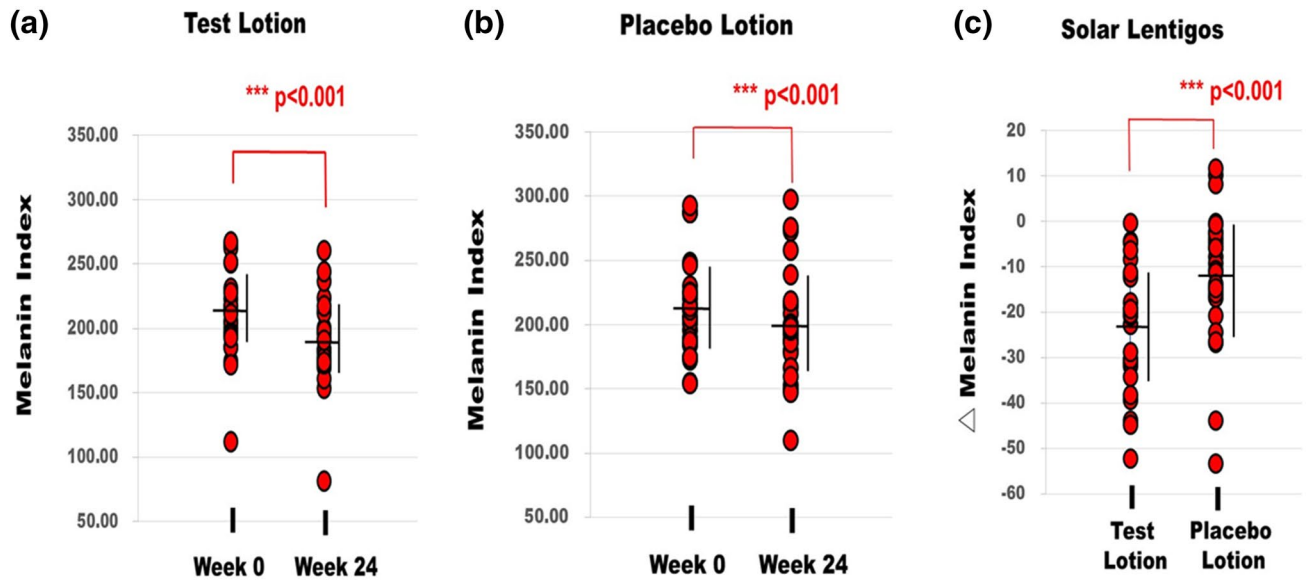

Fig. 6 Changes in melanin index of SLs after treatment for 24 weeks. **a** Test lotion, $N=27$, **b** placebo lotion, $N=27$, **c** △ melanin index between weeks 0 and 24. $N=27$, $^{***}p<0.001$

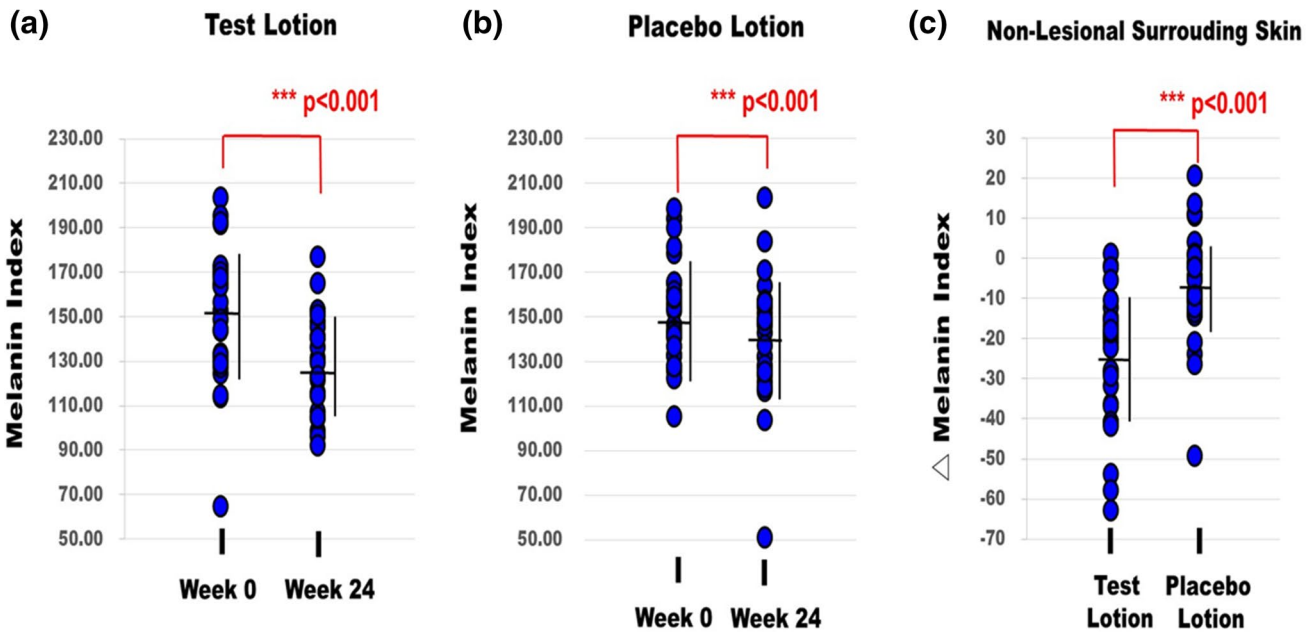

Fig. 7 Changes in the melanin Index of NLS after treatment for 24 weeks. **a** Test lotion, $N=27$, **b** placebo lotion, $N=27$, **c** △ melanin index between weeks 0 and 24. $N=27$, $^{***}p<0.001$

Discussion

Since APS serves as a tyrosinase inhibitor following its conversion to ascorbic acid after its dephosphorylation by phosphatase upon penetrating into the epidermis, it was intriguing to determine whether the hyperpigmentation of SLs is associated with an accentuated activity of tyrosinase in the lesional melanocytes. The mechanistic connection of the hyperpigmentation in SLs with the up-regulated expression of the key melanogenic enzyme tyrosinase has been already established since there are higher numbers of tyrosinase-positive melanocytes in the SL lesional epidermis than in the non-lesional epidermis and mRNA

levels of tyrosinase are significantly up-regulated in the SL lesional epidermis compared with the non-lesional epidermis [9]. It is well known that the up-regulated expression of tyrosinase in human melanocytes is generally mediated via the activation of the SCF and/or EDN1-triggered intracellular signaling cascades, at the terminal point of which the cyclic AMP responsive element CREB is phosphorylated and activated. That in turn stimulates the expression of the melanocyte-specific master transcription factor MITF, which leads to the increased expression of tyrosinase [5, 6, 8, 19, 20, 23, 31]. Consistently, our findings [3, 9] that the expression of SCF and EDN1 is distinctly up-regulated at the gene, protein and immunostaining levels in the SL lesional epidermis of SLs strongly suggested that the over-production of SCF and/or EDN1 by lesional keratinocytes in SLs triggers neighboring melanocytes via activation of their corresponding receptors, c-KIT and EDNRB. The activation of those receptors stimulates the corresponding major melanogenic signaling cascades and results in the up-regulation of melanization in the lesional melanocytes. As for the mechanistic connection of the EDN1/EDNRB axis with the activation of a melanogenic signaling cascade that leads to the stimulated expression of MITF as well as tyrosinase and subsequently to the hyperpigmentation of SLs, we have already demonstrated that the pigmentation level of SLs on the face was significantly improved by topical treatment for 6 months with a *M. chamomilla* extract, which can act as an antagonist of the EDN/EDNRB signaling cascade to down-regulate the EDN1-stimulated expression of melanocyte-specific proteins including tyrosinase [7]. In contrast, there have been no in vivo reports to show the effects of tyrosinase inhibitors on SLs that quantitatively measures pigmentation levels and therefore, little was known about the potential anti-pigmenting effects of tyrosinase inhibitors such as AMP or APS on SLs. Whereas it was anticipated that inhibiting the up-regulated level of tyrosinase activity would serve as an effective therapeutic approach for the hyperpigmentation of SLs, major concerns about its possible hypopigmenting effect on non-lesional, healthy normally pigmented skin should be noted because topical treatment is not generally confined only to the lesional skin.

In the present double-blind half-face study of subjects with SLs, we found that in spite of no significant difference in the slightly decreased pigmentation scores of SLs between the test lotion and the placebo lotion after daily treatments for 24 weeks, the *L* values in the test lotion-treated SLs significantly increased from 64.44 ± 2.24 to 65.34 ± 2.34, which represents a distinct and significant anti-pigmenting effect on SLs. In contrast, the *L* values of the placebo lotion-treated SLs remained unchanged. It should be noted that whereas the ratio of subjects with more than a 2.0 ΔL, which is generally thought to be the minimum recognizable level for a visible difference in pigmentation level, was 7 of 27 subjects treated with the test lotion, but was 0 of 27 subjects treated with the placebo lotion. This result also indicates a distinct anti-pigmenting effect on SLs by the test lotion. On the other hand, the melanin index in the test lotion-treated SLs significantly decreased from 212.50 ± 33.83 to 188.65 ± 33.16 after the treatment for 24 weeks, which also represents a distinct and significant anti-pigmenting effect on SLs. Similarly, the melanin index in the placebo lotion-treated SLs also significantly decreased from 211.00 ± 36.12 to 198.81 ± 41.30 after the same treatment period although the test lotion-treated SLs had a significantly higher Δ melanin index than the placebo lotion-treated SLs, which indicates that the melanin index reflects a seasonal decline of the pigmentation level and/or some other possibility as discussed below.

Interestingly, we found that *L* values in the test lotion-treated NLS also significantly increased from 64.44 ± 2.24 to 65.34 ± 2.34, whereas *L* values in placebo lotion-treated NLS remained unchanged. It should be noted that the ratio of subjects with more than a 2.0 ΔL in NLS was 3 of 27 treated with the test lotion, it was 0 of 27 subjects treated with the placebo lotion. On the other hand, the melanin index in the test lotion-treated NLS significantly decreased from 150.65 ± 29.73 to 125.13 ± 26.58 after treatment for 24 weeks. Similarly, the melanin index in placebo lotion-treated NLS also significantly decreased from 147.44 ± 29.60 to 140.54 ± 27.64 after the same treatment, while the test lotion-treated NLS had a significantly higher Δ melanin index than the placebo lotion-treated NLS. Comparisons between *L* values and the melanin indices for all measurements indicate that there is a marked distribution shift toward a lighter color in the test lotion-treated SLs and NLS, whereas there are no such distinct distribution shifts in placebo lotion-treated SLs and NLS. The sum of the above findings indicates that the test lotion has a significantly higher anti-pigmenting effect on SLs as well as the NLS than the placebo lotion and suggests that APS has a weak but significant anti-pigmenting effect on SLs as well as a significant whitening effect on the NLS.

According to the mathematical formula calculated as "$y = -10.01x + 797.14$" for the relationship between the *L* value and the melanin index (data not shown), a 2.0 ΔL value appears to be approximately equivalent to a 20 Δ melanin index. This function may reflect the significant decrease in the melanin index (but not in the *L* value) observed even with the placebo lotion-treated SLs and the NLS. There are at least two possible explanations for the significant decrease in the melanin index of the placebo lotion-treated SLs and NLS as follows: (1) the naturally diminished level of pigmentation in SLs and in the NLS, which occurs during the period from October to March in Japan seems to be significantly detectable by the melanin index but not by the *L* value. The observation that treatment of SLs and NLS with

the placebo lotion elicited a significant decrease in the melanin index indicates that seasonal factors especially related to a decreased UV energy during the period from October to March have a distinct influence on the naturally occurring decrease in pigmentation level. Thus, it is likely that during the period from October to March in Japan, the pigmentation level of SLs as well as the NLS detectable only by the Mexameter is gradually diminished. (2) It is also possible that some of the extracts included in the placebo lotion have the potential to slightly inhibit tyrosinase activity, resulting in the weak but melanin index detectable decrease in pigmentation level in both the SLs and the NLS.

In this study, there was a discrepancy between the pigmentation scores of SLs evaluated by a dermatologist and the quantitative evaluation of the pigmentation level by the *L* value. Thus, whereas the pigmentation scores of SLs were not significantly improved after 24 weeks of treatment with the test lotion, 7 of the 27 subjects had more than a 2.0 ΔL value before and after the treatment. This may be due to the fact that the significant increase of *L* values in both the SLs and the NLS after treatment with the test lotion for 24 weeks may not result in a distinct decrease in the visible skin pigmentation level between SLs and the NLS, and does not lead to an improvement in the pigmentation scores of SLs despite the fact that their pigmentation levels were substantially diminished.

In conclusion, the sum of the above findings indicates that APS has a weak but significant anti-pigmenting effect on SLs and a significant whitening effect even on normally pigmented skin in concert with high safety without the risk of eliciting vitiliginous skin.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors state no conflict of interest.

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