still somewhat underestimated so far. With the present work we highlight the pivotal role of IL-36 cytokines in plaque psoriasis and among the first suggest that also IL-37 but not IL-38 is involved in psoriatic skin inflammation.

## Conflict of interest

The authors have no conflict of interest to declare.

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Letter to the Editor

# Beneficial effects of blood group antigen synthesis-increasing natural plant extracts and monosaccharides on extracellular matrix protein production *in vivo*

*Keywords*
ECM protein
Natural plant extract
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Anti-aging
Blood group antigen

Skin aging is clinically characterized by the wrinkle formation associated with damage of dermal extracellular matrix (ECM) [1]. Recent study has indicated that expression of ABO blood group antigens (ABH antigens) are reduced in the sun exposed skin, suggesting that ABH antigens may be implicated in photoaging process [2]. Hence, the present study was aimed to investigate the possible anti-aging potential of ABH antigen synthesis-increasing materials on ECM protein production in human skin, which are mixtures of natural plant extracts (*Camellia sinensis* (Green tea) leaf extract, *Polygonum cuspidatum* root extract; Biospectrum, Seongnam, Republic of Korea; *Ginkgo biloba* leaf extract, *Cynara scolymus* (Artichoke) leaf extract, *Selaginella tamariscina* extract; kindly gifted from Amorepacific R&D Institute, Yongin, Republic of Korea) and ABH antigen-composing monosaccharides (D-Glucose, D-Galactose, L-fucose, *N*-acetyl-D-glucosamine, *N*-acetyl-D-galactosamine; Sigma–Aldrich, St. Louis, MO), increasing ABH antigen expression in HaCaT cells and human skin (Suppl. Figs. S1 and S2), by immunohistochemical determination of ECM proteins.

*Abbreviations:* ECM, extracellular matrix.

Firstly, we performed one-time topical application of the minimally-effective vehicle cream solution (gifted from Amorepacific R&D Institute), composition TYPE I, containing five kinds of natural plant extracts (1%, *C. sinensis* (Green tea) leaf extract; 3%, all other extracts, respectively) in the vehicle cream, and composition TYPE II, containing five kinds of monosaccharides (1%, respectively) in the vehicle cream, to the healthy female human buttock skin (age range; 44–57 yr, mean age ± standard error (SE); 49.2 ± 5.0 yr, $n = 6$). At 48 h after application, 2 mm punch biopsy was performed, and their frozen sections were analyzed by immunohistochemistry. This study was approved by the institutional review board of Seoul National University Hospital (IRB No. C-1207-100-418), and all of the subjects gave written informed consent, which was reviewed by the board.

The immunohistochemistry showed that, the staining of ECM proteins, including procollagen 1α, mainly composing dermal collagen fibers, tropoelastin and fibrillin-1, composing elastic fibers, perlecan, one of basement membrane proteoglycans supporting epidermal proliferation, and biglycan, one of supporting proteoglycans for collagen and elastic fibers, in TYPE I or II-applied skin tissues were tended to be increased, compared to the vehicle cream-applied skin tissues. Visual grading analysis (Grade 0–5) performed by 3 dermatologists revealed that the increase of perlecan staining by application of TYPE I and the increase of fibrillin-1 staining by application of TYPE II were statistically significant, using Wilcoxon-signed rank test ($p = 0.044$ for perlecan, $p = 0.042$ for fibrillin-1, Fig. 1A). Representative staining results for the perlecan for TYPE I and fibrillin-1 for TYPE II are shown in Fig. 1B. These results suggest that these ingredients may help ECM protein production in human skin.

Therefore, we next performed the double blind long-term application (24-week) experiment to the facial skin with vehicle cream and composition TYPE III, containing all of the ingredients with same concentration in the vehicle cream. Healthy female volunteers (age range; 42–72 yr, mean age ± SE; 54.9 ± 7.8 yr, $n = 44$), whose visual grade of wrinkle is same or greater than 3 [1], were double-blindly divided into vehicle-treated group or composition TYPE III-treated group by block randomization ($n = 22$, per each group). All volunteers were treated with their vehicle or TYPE III composition by themselves in their facial skin 2 times a day for 24 weeks, under direction of using SPF30 sunscreen and avoiding long time sun exposure. Eye wrinkles and elasticity were measured in the 2 cm-away area from the eye at 0 week (baseline), 8-week, 16-week, and 24-week treatment, using the Skin-Visiometer SV 600 and Cutometer MPA 580 (Courage & Khazaka Electronic, Köln, Germany), and all the measurements were performed in a controlled environment room with a constant room temperature (20∼25 °C) and humidity (45∼55%). Among the volunteers, 12 volunteers (5 volunteers from vehicle-applied group and 7 volunteers from composition TYPE III-applied group), who gave the written informed consent in accordance with the principles of the Declaration of Helsinki, provided the 2 mm-punch biopsies of the skin at 3 cm-away from

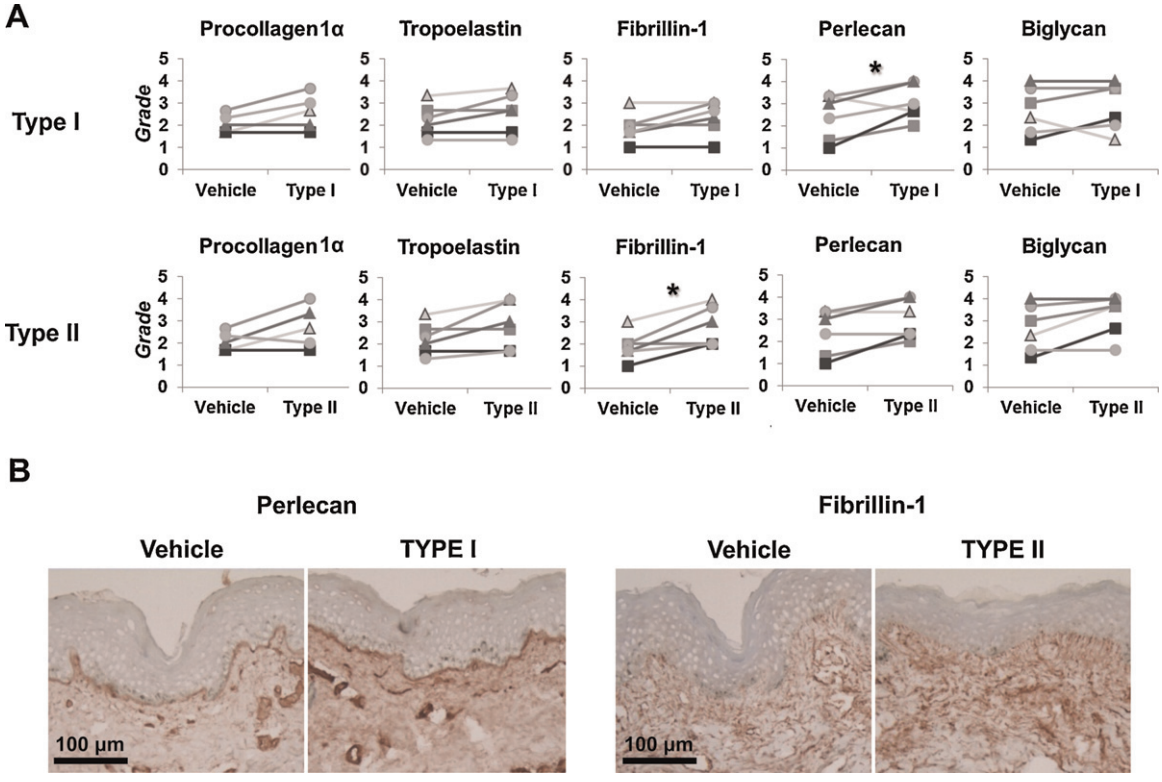


**Fig. 1.** One-time topical application with mixtures of natural plant extracts and monosaccharides in human buttock skin
(A) One-time topically applied human buttock skin tissues from 6 Korean women (44–57 yr, 49.2 ± 5.0 yr) with composition TYPE I (natural plant extracts), TYPE II (monosaccharides), or vehicle cream were biopsied at 48 h after application, and the immunohistochemistry was performed with their frozen sections, using primary antibodies for procollagen 1α (SP1.D8, Developmental Studies Hybridoma Bank, University of Iowa, USA), tropoelastin (Elastin Products, Owensville, MO, USA), fibrillin-1 (11C1.3, Neomarkers, Fremont, CA, USA), perlecan (A7L6, Santa Cruz Biotechnology, SantaCruz, CA, USA), and biglycan (R&D systems, Minneapolis, MN, USA). The degree of immunostaining intensities was ranked using a 5-point scale, from 0 (unstained) to 4 (very intensively stained) by three independent dermatologists. All values were presented as mean of semi-quantitative visual grading results. $^*p < 0.05$, between vehicle and TYPE I, or vehicle and TYPE II, by Wilcoxon signed rank test. (B) Representative staining results for the perlecan for TYPE I and fibrillin-1 for TYPE II were shown.