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AGEs Blocker™ (Goji Berry, Fig, and Korean Mint Mixed Extract) Inhibits Skin Aging Caused by Streptozotocin-Induced Glycation in Hairless Mice

Jin Hee Yoo[1], Je Sung Lee[2], Ji Hwan Jang[2], Jae In Jung[3], Eun Ji Kim[3], and Su-Young Choi[4]

[1]Functional Ingredient Development Team and [2]New Technology Business Team, COSMAX NS, Inc., Gyeonggi 13486 Korea
[3]Industry coupled Cooperation Center for Bio Healthcare Materials, Hallym University, Gangwon 24252, Korea
[4]Functional Ingredient Development Team, COSMAX NBT, Inc., Gyeonggi 13487, Korea

ABSTRACT: Glycation is a cause of skin aging. This study investigated in a glycation-induced skin aging mouse model the effects on skin and mechanism of action of AGEs Blocker™ (AB), which contains goji berry, fig, and Korean mint mixed extract. This study sought to demonstrate the antiglycation effect of streptozotocin, thereby improving skin aging, by measuring advanced glycation end products (AGEs) and various skin parameters, including collagen; matrix metalloproteinases (MMPs); inflammatory cytokines; activities of oxidative enzymes; and skin wrinkles, elasticity, and hydration. This study found that skin wrinkles, elasticity, and hydration improved with AB. Particularly, the oral administration of AB suppressed AGEs, receptors of AGEs, and carboxymethyl lysine in blood and skin tissue. In addition, AB increased the activities of antioxidative enzymes, reduced inflammatory cytokines, suppressed MMP-9 expression, and increased the contents of collagen and hyaluronic acid, ultimately suppressing skin wrinkles and increasing skin elasticity and hydration. Therefore, AB can inhibit skin aging through its antiglycation effect and is thus considered a good ingredient for skin care products.

Keywords: advanced glycation end products, antiglycation, N(6)-carboxymethyllysine, receptor for advanced glycation end products, skin aging

INTRODUCTION

Skin aging can be classified into intrinsic and extrinsic aging (photo aging). The features of intrinsic aging include fine wrinkles, dry skin, and reduced elasticity (Naylor et al., 2011). Compared with intrinsic skin aging, extrinsic skin aging features thick and deep wrinkles and fine wrinkles caused by ultraviolet (UV) radiation, chemical compounds, pathogens, and air pollutants. In severe cases, skin dryness and pigment disorders are increased, while skin elasticity is decreased (Yaar and Gilchrest, 2007).

Recent studies have shown that glycation is a cause of skin aging. Glycation is a nonenzymatic reaction between sugars, such as glucose, and protein. This reaction generates advanced glycation end products (AGEs) (Pageon et al., 2017). AGE deposits have been identified in fibronectin, laminin, collagen, and elastin (Jeanmaire et al., 2001). Skin proteins modified by glycation reactions reduce skin elasticity and cause wrinkle formation (Ichihashi et al., 2011). In addition, AGEs bind to receptors of AGEs (RAGE), thereby increasing the production of proinflammatory cytokines, matrix metalloproteinases (MMPs), and reactive oxygen species (ROS) (Han et al., 2016).

Goji berry (*Lycium barbarum*), a dried fruit of the tree belonging to the Solanaceae family, is native or cultivated in Korea, China, and Taiwan and is widely used in oriental medicine (Lee et al., 1998). Goji berry contains carotenoids, choline, zeaxanthin, physalin (dipalmitoylzeaxanthin), vitamin B1, β-sitosterol, betaine, rutin, and unsaturated fatty acids, such as melissic acid (Kim et al., 2019). Goji berry also exhibits anticancer effects (Park et al., 2002) and enhances immune (Park et al., 2000) and liver function (Kang et al., 2006). Furthermore, the polysaccharides in goji berry inhibit glycation (Deng et al., 2003).

Fig (*Ficus carica* L.) is a plant belonging to the family Moraceae, with more than 600 species distributed worldwide. Traditionally, fig oils have been used for rashes, ulcers, and hemorrhoids. Figs are known to promote digestion and relieve constipation (Jeong et al., 2005). Figs are also known for their antibacterial, antioxidative, antican-

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Correspondence to Su-Young Choi, E-mail: sychoifwp@cosmax.com

cer, antipyretic, emollient, and hypocholesterolemic activities (Debib et al., 2016). Fig contains carotenoids, such as lutein, cryptoxanthin, and lycopene; flavonols such as quercetin-3-*O*-rutinoside and quercetin; and phenolic acids, such as chlorogenic acid (Wojdyło et al., 2016).

Agastache rugosa O. Kuntze is a perennial plant belonging to the family Labiate, also called Kwakhyang, Bang-a, or Korean mint. Geographically, it is distributed throughout Korea and Northeast Asia. The leaves of *A. rugosa* have been traditionally used as a spice for various dishes, such as fish stew (Kim et al., 2017). It is also used as medicinal treatment for abdominal pain, anorexia, nausea, vomiting, and diarrhea. It is effective against scabies and psoriasis (Kim et al., 2017). *A. rugosa* contains essential oils, such as methyleugenol, estragole, eugenol, and transanethole; and flavonoids, such as acacetin-7-*O*-β-D-glucopyranoside (tilianin), acacetin, linarin, agastachoside, and rosmarinic acid (Li et al., 2013). *A. rugosa* extract has antibacterial (Shin and Kang, 2003; Shin, 2004; Wang et al., 2015), anti-dementia (Cho et al., 2014), hepatoprotective (Vincent et al., 2001), anti-inflammatory, and anti-arteriosclerotic effects (Moon et al., 2015) and inhibits cell damage caused by oxidative stress (Oh et al., 2006). Previously, *A. rugosa* extract was shown to have anti-photo aging and antioxidative effects in UVB-irradiated human skin cells and UVB-irradiated hairless mice (Seo et al., 2019; Yun et al., 2019).

We hypothesized that AGEs Blocker™ (AB) exerts an antiaging effect on the skin via the antiglycation of goji berry polysaccharides, antioxidation of fig, and antiphoto aging of Korean mint. Therefore, this study investigated skin improvements and the mechanism of action of AB in a glycation-induced mouse model.

MATERIALS AND METHODS

Sample preparation

The samples were procured from COSMAX NS Inc.. To prepare the AB, dried raw *L. barbarum*, *F. carica*, and *A. rugosa* were mixed and extracted at 95°C for 4 h in hot water. The extract was filtered and concentrated using a vacuum evaporator, added with maltodextrin (40%), and spray dried.

Animal experiment

Seven-week-old hairless mice were purchased from Dooyeol Biotech. The mice were maintained under well-controlled conditions, including a 12-h light/dark cycle, 23±3°C temperature, and 50±10% relative humidity. Mice were freely fed water and pelleted food (Cargill Agri Purina, Inc.). All animal experiments were conducted according to protocols approved by the Institutional Animal Care and Use Committee of Hallym University (Hallym 2021-84).

Streptozotocin (STZ)-induced skin aging model

After an adaptation period of 1 week, the mice were randomly divided into four groups (n=10 per group): normal control (NOR, vehicle-administered group), STZ 150 mg/kg+vehicle (CON), STZ 150 mg/kg+10 mg/kg/d AB (AB10), and STZ 150 mg/kg+100 mg/kg/d AB (AB100). The treatments were orally administered once a day for 6 weeks. Two weeks after the start of treatment, the mice were intraperitoneally injected with STZ (150 mg/kg body weight). At the end of the experimental period, the mice were anesthetized with tribromoethanol diluted in tertiary amyl alcohol. Blood and dorsal skin specimens were collected immediately for further analysis.

Evaluation of skin wrinkle formation

After administering the ingredients for 6 weeks, the mice were anesthetized using tribromoethanol diluted with tertiary amyl alcohol. For skin wrinkle formation analysis, pictures of the dorsal skin of mice were captured using a digital camera. Skin replicas (SILFLO, Flexico Developments Ltd.) were fabricated and photographed with a stereomicroscope. Wrinkle formation was observed with a Skin Visiometer® (SV600, CK Electronic GmbH), and the skin wrinkle index was analyzed.

Evaluation of skin hydration and elasticity

Skin hydration was measured using a Corneometer® CM 825 (Courage-Khazaka Electronics), and skin elasticity was measured using a Cutometer® MPA 580 (Courage-Khazaka Electronics).

Serum biochemical analysis

Serum was obtained by centrifuging blood samples (600 *g* for 10 min) and stored at −70°C until analysis. Serum AGEs, RAGE, and carboxymethyl lysine (CML) concentrations were determined using enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource).

ELISA

Skin tissue samples were homogenized with phosphate-buffered saline. The homogenates were centrifuged for 10 min at 1,000 *g*, and the supernatants were analyzed. Total proteins in the supernatant were analyzed using a BCA protein assay kit (Thermo Fisher Scientific). The concentrations of AGEs (MyBioSource), RAGEs (MyBioSource), CML (MyBioSource), tumor necrosis factor-α (TNF-α, R&D Systems), interleukin-6 (IL-6, R&D Systems), hyaluronic acid (R&D Systems), collagen (Abcam), MMP-1 (MyBioSource), and MMP-9 (R&D Systems) were determined by ELISA, according to the manufacturer's instructions. Activities of superoxide dismutase (SOD, Cayman Chemical) and catalase (Cayman Chemical) were

determined by ELISA according to the manufacturer's instructions.

Statistical analysis

All data are expressed as mean±standard deviation. Statistical analysis was conducted using one-way analysis of variance, and Tukey's multiple test was performed using IBM SPSS Statistics ver. 21 (IBM Co.). Significant differences were denoted as $P<0.05$ or $P<0.01$.

RESULTS

AB improved wrinkle formation, skin hydration, and elasticity in STZ-induced hairless mice

Compared with that in the NOR group, skin in the CON group was dry, and wrinkles were observed. Skin dryness and wrinkles improved in the AB10 and AB100 groups (Fig. 1A). Skin roughness (R1), average roughness (R2), and maximum roughness (R3), which indicate the depth of wrinkles, were significantly higher in the CON group than those in the NOR group and lower in the AB100 group. Smoothness depth (R4), the skin roughness index, and arithmetic average roughness (R5), the fine wrinkle depth index, were significantly higher in the CON group than in the NOR group ($P<0.05$) and lower, but not significantly, in the AB100 group than in the CON group (Fig. 1B).

Changes in skin moisture content were measured using a Corneometer®. Skin hydration was significantly lower in the CON group than in the NOR group ($P<0.01$) and increased in a dose-dependent manner when AB was administered. Particularly, skin hydration was significantly higher in the AB100 group than in the CON group ($P<0.01$; Fig. 1C). Skin elasticity was significantly lower in the CON group than in the NOR group ($P<0.01$) and significantly higher in the AB100 group than in the CON group ($P<0.01$; Fig. 1D).

AB reduced skin glycation-related factors in STZ-induced hairless mice

To confirm the induction of glycation, AGE contents in blood and skin tissue were measured. The numbers of AGEs in the CON group were significantly increased in skin tissue and blood compared with those in the NOR group ($P<0.01$). However, AGE contents were decreased in a dose-dependent manner in both AB-administered groups and were significantly decreased in the AB100 group compared with those in the CON group ($P<0.01$; Fig. 2A and 2D). The amounts of CML, a type of AGE, were measured in the blood and skin tissue. CML content was significantly increased in the CON group compared to that in the NOR group ($P<0.01$), decreased in the AB-administered groups, and significantly decreased in skin tissue of the AB100 group compared to that in the CON group ($P<0.01$; Fig. 2B and 2E). RAGE contents were significantly increased in the blood and skin tissue of the CON group compared to those in the NOR group ($P<0.01$), and the contents were decreased when AB was administered, but there was no significance (Fig. 2C and 2F).

AB improved factors related to skin aging, such as collagen, MMP-9, and hyaluronic acid in STZ-induced hairless mice

Collagen, one of the constituent proteins of the skin, was measured in skin tissue. The collagen content was significantly lower in the CON group than in the NOR group. Compared with that in the CON group, collagen was significantly higher in the AB10 group and tended to increase in the AB100 group (Fig. 3A). MMP-9, a collagenase in skin tissue, was significantly higher in the CON group compared than in the NOR group ($P<0.01$). With AB treatment, MMP-9 levels were lower in both AB groups than in the CON group, but the difference was not significant (Fig. 3B). To determine the effect of glycation on skin moisturization, hyaluronic acid, a significant factor in skin moisturization, was measured. Hyaluronic acid content was significantly lower in the CON group than in the NOR group and increased in both AB treatment groups; however, no significant difference was found (Fig. 3C).

AB increased antioxidative activity

The effect of glycation induction on the activities of antioxidative enzymes in skin tissue was investigated. SOD activity in skin tissue was significantly lower in the CON group than in the NOR group ($P<0.01$) and was also increased in both AB groups. However, no significant difference was found (Fig. 4A). In addition, catalase activity was significantly lower in the CON group than in the NOR group ($P<0.01$). Both AB groups tended to have increased activity of these two enzymes, but this was not significant (Fig. 4B).

AB inhibited inflammatory cytokines

The levels of inflammatory cytokines in skin tissue were measured to confirm the effect of AB on the inflammatory response in the skin induced by glycation. TNF-α in the skin tissue was significantly higher in the CON group than in the NOR group (Fig. 5A). The TNF-α content was lower in the AB100 group than in the control group, but the difference was not significant. In addition, IL-6 was significantly higher in the CON group than in the NOR group and decreased dose-dependently in both AB treatment groups. The TNF-α content was lower in the AB100 group than in the control group, but no significant difference was observed. Notably, the AB100 group had significantly lower IL-6 levels than the CON group (Fig. 5B).

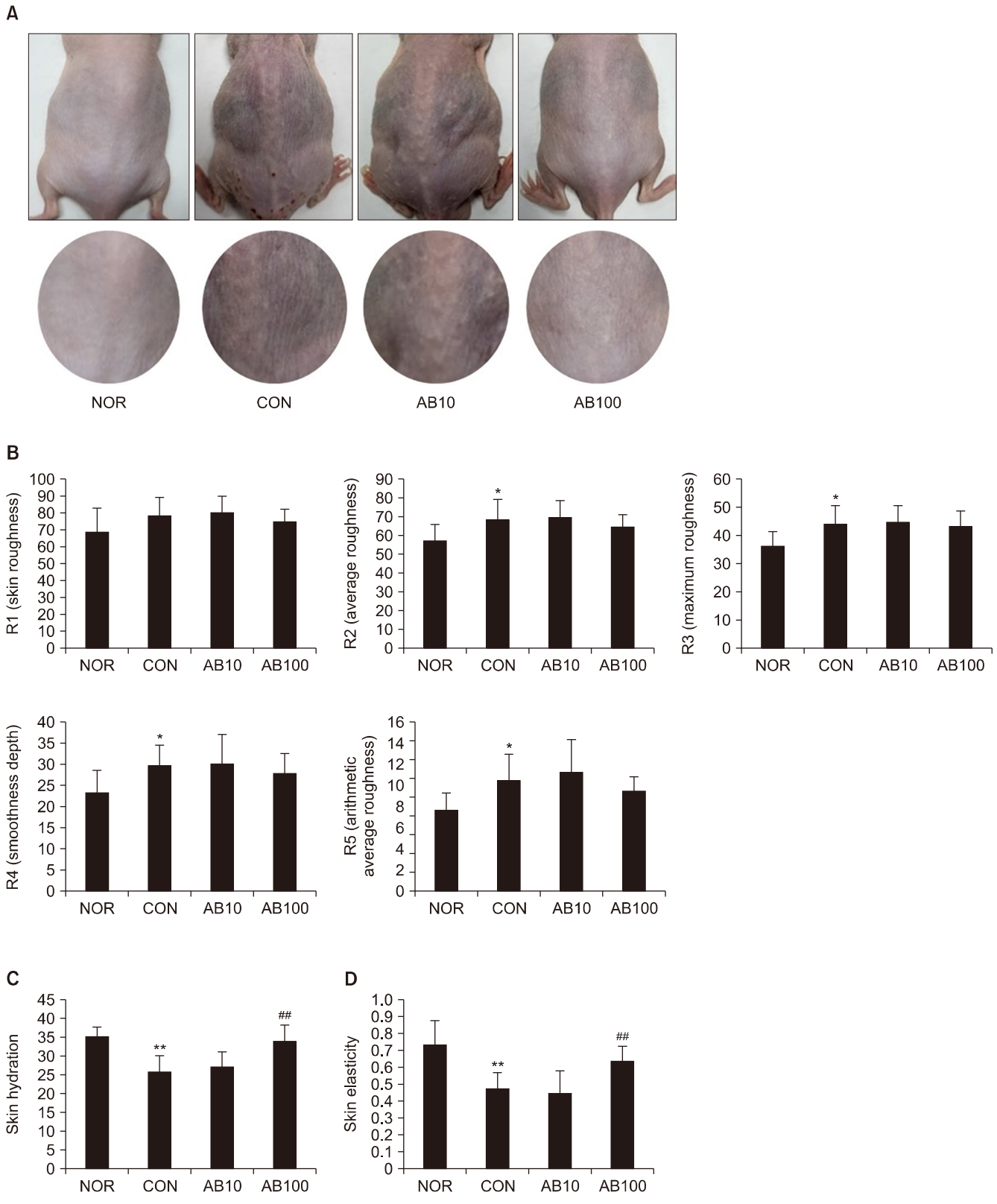

Fig. 1. Effects of advanced glycation end products Blocker™ (AB) on wrinkle formation, skin hydration, and skin elasticity in streptozotocin (STZ)-induced hairless mice. (A) Representative dorsal skin specimens were photographed. (B) The wrinkle index values were measured using skin replicas. (C) Skin hydration was measured using a Corneometer® CM825 (Courage-Khazaka Electronics). (D) Skin elasticity as measured using a Cutometer® MPA 580 (Courage-Khazaka Electronics). Significant differences at $^{*}P<0.05$ and $^{**}P<0.01$ compared with the normal control (NOR) group. Significant differences at $^{\#\#}P<0.01$ compared with the STZ + vehicle (CON) group. AB10, 10 mg/kg/d AB; AB100, 100 mg/kg/d AB.

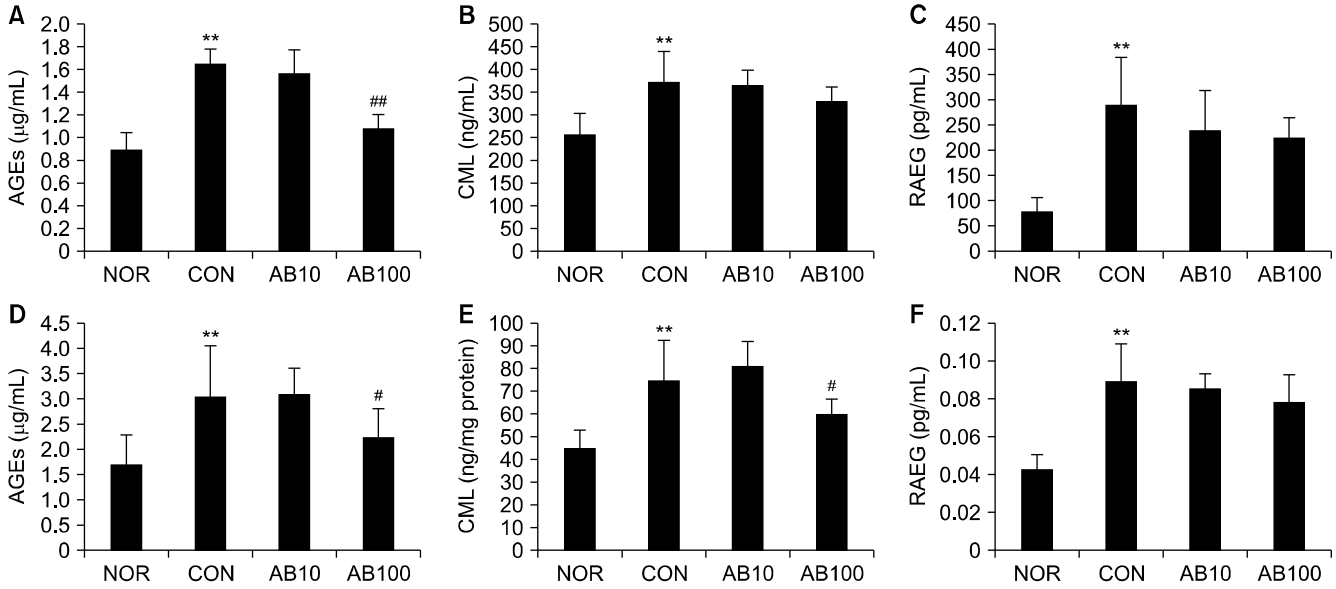

Fig. 2. Effects of advanced glycation end products (AGEs) Blocker™ (AB) on skin glycation-related factors in streptozotocin (STZ)-induced hairless mice. The AGEs content was measured in blood (A) and skin tissue (D). The carboxymethyl lysine (CML) content was measured in blood (B) and skin tissue (E). The concentration of receptors of AGEs (RAGE) was measured in blood (C) and skin tissue (F). Significant differences at $^{**}P<0.01$ compared with the normal control (NOR) group. Significant differences at $^{\#}P<0.05$ and $^{\#\#}P<0.01$ compared with the STZ + vehicle (CON) group. AB10, 10 mg/kg/d AB; AB100, 100 mg/kg/d AB.

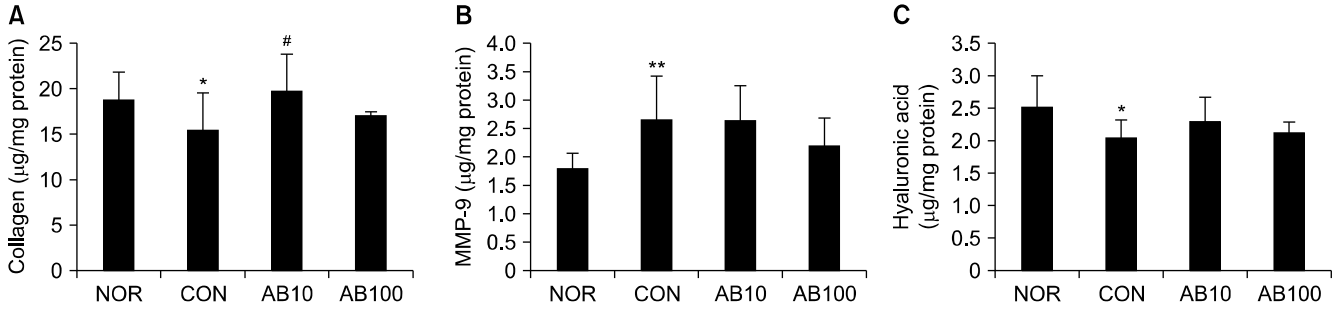

Fig. 3. Effects of advanced glycation end products Blocker™ (AB) on the production of collagen (A), matrix metalloproteinase (MMP)-9 (B), and hyaluronic acid (C) in streptozotocin (STZ)-induced hairless mice. Significant differences at $^{*}P<0.05$ and $^{**}P<0.01$ compared with the normal control (NOR) group. Significant differences at $^{\#}P<0.05$ compared with the STZ + vehicle (CON) group. AB10, 10 mg/kg/d AB; AB100, 100 mg/kg/d AB.

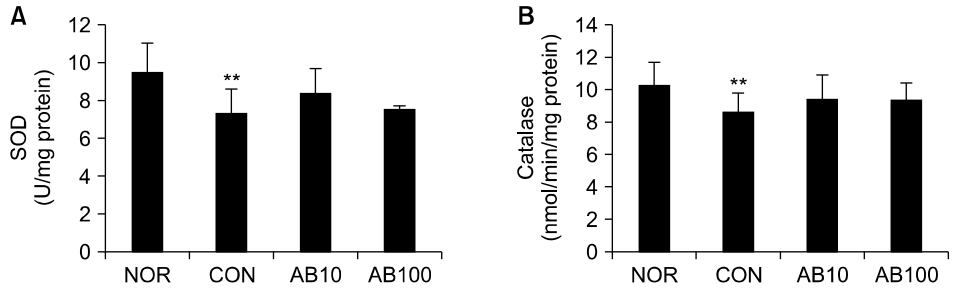

Fig. 4. Effects of advanced glycation end products Blocker™ (AB) on superoxide dismutase (SOD) (A) and catalase (B) activities in streptozotocin-induced hairless mice. Significant differences at $^{**}P<0.01$ compared with the normal control (NOR) group. AB10, 10 mg/kg/d AB; AB100, 100 mg/kg/d AB.

DISCUSSION

The accumulation of AGEs produced by glycation reactions cause skin aging by modifying skin proteins. In addition, the accumulation of AGEs further promotes skin aging by inducing oxidative stress and inflammation (Lee et al., 2016). A previous study in an animal model has found that an increase in STZ-induced AGEs and MMPs and/or reduction of collagens caused skin aging (Lee et al., 2017).

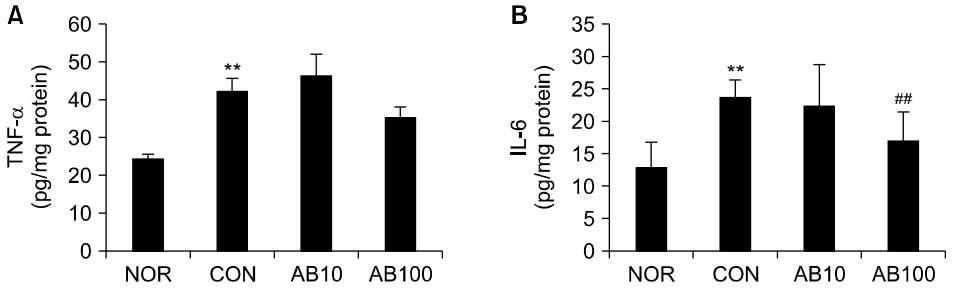

Fig. 5. Effects of advanced glycation end products Blocker™ (AB) on the production of tumor necrosis factor-α (TNF-α) (A) and interleukin-6 (IL-6) (B) in streptozotocin (STZ)-induced hairless mice. Significant differences at $^{**}P<0.01$ compared with the normal (NOR) group. Significant differences at $^{\#\#}P<0.01$ compared with the STZ + vehicle (CON) group. AB10, 10 mg/kg/d AB; AB100, 100 mg/kg/d AB.

The present study aimed to demonstrate whether AB can inhibit skin aging by reducing AGEs and improving various skin parameters, such as wrinkle formation, elasticity, and hydration, through antiglycation. To accumulate AGEs and induce glycation, we used a diabetes mouse model induced by STZ treatment to which AB was orally administered. We then analyzed AGE factors, skin wrinkle-related factors, skin moisturizing-related factors, activities of antioxidative enzymes, and inflammation-related factors to identify the effect of inhibiting skin aging.

We found that these skin parameters were lower in the CON group, where glycation was induced by STZ treatment. However, skin wrinkles, elasticity, and hydration improved after treatment with AB (Fig. 1). In addition, AGEs, CML, and RAGEs, which were increased by glycation, were reduced by AB. CML is the most representative non-cross-linked AGE and accumulates, not only by binding with collagen but also with the epidermis, resulting in reduced skin elasticity and increased dullness. Moreover, when CML collagen binds to RAGE, the mitogen-activated protein kinase (MAPK) pathway is activated (Hori et al., 2012). Stimulation of MAPK activates the activator protein-1 (AP-1) complex composed of c-Jun and c-Fos (Heng, 2013; Lu et al., 2016). Activated AP-1 promotes the expression of MMPs in the nucleus (Watson et al., 2014), while MMPs accelerate the breakdown of collagen or gelatin, which makes up the extracellular matrix, thus destroying the cell structure and ultimately promoting wrinkle formation.

In the present study, the collagen content decreased, while the MMP-9 content increased because of glycation. AB was expected to inhibit the production of AGEs, CML, and RAGEs induced by glycation; inhibit the breakdown of collagen; and decrease MMP-9 production. In addition, AGE-RAGE binding activates NF-κB and promotes the production of inflammatory cytokines, resulting in an inflammatory response (Pageon et al., 2017). The present study demonstrated that AB treatment suppressed the production of inflammatory cytokines TNF-α and IL-6, which were increased by glycation.

Glycation causes oxidative stress. ROS were significantly generated upon exposure to UV light. Furthermore, ROS increase AGEs. Simultaneously, AGEs directly generate ROS. Since UV or ROS increase AGEs, which increase ROS, an increase in AGEs essentially increases oxidative stress. Furthermore, the expression of RAGEs is increased when the skin is exposed to UV rays. RAGE activation reduces SOD and catalase activity (Gkogkolou and Böhm, 2012). The present study found that SOD and catalase activities increased with AB administration. Therefore, AB can reduce oxidative stress caused by glycation by increasing the activity of antioxidative enzymes.

The decrease in hyaluronic acid in the skin due to aging is one of the direct causes of skin wrinkles, decreased elasticity, and decreased moisture content (Song et al., 2013). The present study revealed that hyaluronic acid content decreased with glycation and increased with AB treatment. Therefore, AB promotes skin moisturization by increasing hyaluronic acid levels.

In conclusion, oral administration of AB suppressed AGEs in both blood and skin tissues, increased the activities of antioxidative enzymes, reduced inflammatory cytokines, suppressed MMP-9 expression, and increased the contents of collagen and hyaluronic acid. These effects ultimately suppressed skin wrinkles and increased skin elasticity and hydration. These results thus indicate that AB can inhibit skin aging by promoting antiglycation and is thus highly applicable as a good ingredient that improves skin.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: JHY, EJK, SYC. Analysis and interpretation: JHY, JIJ. Sample Production: JSL, JHJ. Data collection: JIJ, EJK. Writing the article: JHY, SYC. Critical revision of the article: EJK, SYC. Final approval of the article: all authors. Statistical analysis: JHY, JIJ. Obtained funding: SYC. Overall responsibility: SYC.

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