# Antiaging Effects of Topical Lactobionic Acid: Results of a Controlled Usage Study

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There are numerous clinical publications supporting the use of traditional α-hydroxy acids (AHAs), including glycolic acid, lactic acid, and citric acid, to counter aging. Studies have demonstrated significant dermal effects, including increased deposition of glycosaminoglycans, improved elastic fiber quality, and collagen gene induction. These dermal effects provide antiaging benefits to skin. Lactobionic acid, a next-generation AHA possessing a polyhydroxy structure (a so-called polyhydroxy acid), has been shown to provide textural and smoothing benefits to skin and to increase skin thickness via digital caliper measurements, thereby providing multiple antiaging benefits. Lactobionic acid is also an antioxidant chelating substance that suppresses matrix metalloproteinase enzymatic activity, helping to protect against further sun damage. Lactobionic acid has also been shown to be gentle to skin without causing the stinging and irritation associated with some AHAs. This study was conducted to assess the efficacy of topical lactobionic acid 8% to reduce the visible signs of aging skin on the face and to determine histologic and dermal thickness changes on the arm during 12 weeks of controlled usage. Results indicate significant improvements in clinically graded parameters, a significant reduction in mild preexisting irritation, and significant increases in skin firmness and thickness. Histologic examples of reduced matrix metalloproteinase-9 activity and increased staining for glycosaminoglycans were observed. When used alone, either as a preventive or an active treatment, lactobionic acid provides beneficial antiaging effects. Owing to its gentleness, it may also be used in combination with cosmetic procedures.

The process of keratinization is normalized by α-hydroxy acids (AHAs) by diminishing corneocyte cohesion in the stratum granulosum, thus enhancing the process of cell turnover in skin.[1,2] AHAs also stimulate epidermal cell production, reverse basal cell atypia, and normalize melanin disbursement in photodamaged skin.[1,3,4] Significant dermal benefits have also been demonstrated, including increased deposition of glycosaminoglycans, improved elastic fiber quality, and collagen gene induction, an early indicator of increased collagen synthesis.[3-5]

Lactobionic acid (4-O-β-D-galactopyranosyl-D-gluconic acid, MW 358, pKa 3.8) (Figure 1) is a polyhydroxy bionic acid derived from lactose; it is comprised of one molecule of the sugar D-galactose and one molecule of D-gluconic acid (a polyhydroxy acid), attached via an acetal linkage.[6] It is called a *bionic acid* owing to the attachment of a sugar unit (galactose) to the traditional polyhydroxy acid (gluconic acid) structure. Lactobionic acid has numerous beneficial

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properties as a result of its polyhydroxy bionic AHA structure, making it ideal for use in skin care. Notably, the compound is a strong humectant, is nonirritating to skin, and provides skin-smoothing and skin-moisturizing benefits.[7,8] It is capable of forming a thin hydrofilm, which provides unique aesthetics to a topical formulation. Lactobionic acid has antioxidant properties that are at least in part due to metal chelation and, as a result, is a major constituent of organ preservation fluids for use during transplantation procedures. In this regard, lactobionic acid chelates iron and suppresses oxidative tissue damage during organ storage and tissue reperfusion with iron-rich blood.[9,10] The antioxidant properties of lactobionic acid may also help prevent aging-related skin changes.

In addition, studies in the field of organ preservation have revealed that lactobionate is an inhibitor of matrix metalloproteinase (MMP) enzymes.[11] MMP enzymes are necessary for normal cellular function and are responsible for degrading the skin's extracellular matrix to facilitate cellular migration, among other beneficial effects.[12] However, excessive MMP activity decreases the structural integrity of the skin's extracellular matrix, causing wrinkles, skin laxity, and telangiectasias. Increased MMP activity, along with a natural age-related decline in the inhibitors of MMP activity, is one of the consequences of photoaging.[13] In particular, MMP9 is a gelatinase enzyme that attacks gelatin, elastin, and collagen types IV, V, and X as substrates. $Zn^{2+}$ and $Ca^{2+}$ chelating agents are potent inhibitors of the MMP enzymes.[14] Chelation may be the mechanism by which lactobionic acid functions as an MMP inhibitor.

The current study was conducted to assess the efficacy of topical lactobionic acid 8% to reduce the visible signs of aging skin on the face and to determine histologic and dermal thickness changes on the arm during 12 weeks of controlled usage.

## METHOD

The study was conducted as a prospective, controlled usage evaluation of female subjects having mild to moderate periocular fine lines, periocular coarse wrinkles, and mottled hyperpigmentation on the face. The subjects participated in a 3- to 5-day washout prior to baseline, during which time they discontinued the use of all topical products on the face and arms except for their regular facial cleansers and beauty products. During the study, participants applied a research formulation containing 8% lactobionic acid in a simple cream vehicle (pH 3.8) to the entire face twice daily and to the left or right sun-exposed outer forearm 3 times per day according to a randomization schedule. The other forearm was left untreated as a control; no products were applied to the control arm. Subjects also resumed use of their regular facial cleansers and beauty products and continued using them throughout the study.

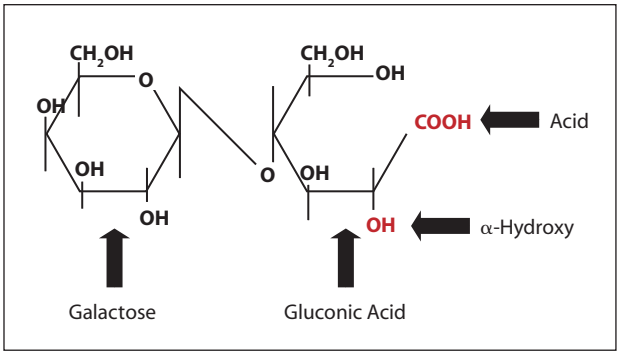


**Figure 1.** Chemical structure of lactobionic acid.

The study was conducted in North America over a period of 12 weeks between February and May. Subjects were instructed to avoid sun exposure and artificial tanning. Product efficacy was evaluated via visual and tactile clinical grading, as well as by physical measurements of skin firmness and skin thickening, as described below. Biopsy specimens of the outer forearms of a small subset of subjects were collected at end point. The protocol received institutional review board approval, and informed consent was obtained prior to implementation of any of the study procedures.

Product efficacy on the face was evaluated visually via clinical grading at weeks 0, 6, and 12 by a trained assessor using an anchored 0- to 10-point scale that allowed the use of 0.25-point increments for increased sensitivity. The clinical grading site and definitions of low and high extremes of the scales are defined in Table 1 for each of the graded parameters.

Digital photographs were taken of the face positioned at a 45° angle using a facial positioning device to ensure standardization and reproducibility.

Self-assessment questionnaires were administered at weeks 0, 6, and 12.

### Irritation and Safety

Global evaluation of objective evidence of irritation and safety (dryness, erythema, and edema) was conducted at weeks 0, 6, and 12 by a trained assessor. Evaluation of subjective evidence of irritation (burning, stinging, itching, tightness, and tingling) was also conducted. Parameters were graded using a 0- to 3-point scale with the following descriptors: none, mild, moderate, severe. Half-point increments were used to provide increased grading sensitivity for conditions that fell between the full-point descriptors.

### Firmness

Pinch recoil is a recognized indicator of skin resiliency and firmness and relies on a trained assessor to visually observe and record skin recoilability.[15,16] Pinch recoil

measurements were collected at weeks 0, 6, and 12. The skin was pinched, and the time to full recovery was recorded with a stopwatch (in hundredths of a second). The measurements were performed in triplicate, and the average score was reported.

### Total Skin Thickness (Plumping)

Skin thickness measurements were collected for each subject at weeks 0 and 12 on the outer forearms using a hinged pinching device and digital calipers as previously described.[3] Duplicate measurements representing a 2-fold thickness of skin were taken and averaged for both the treated forearm and the untreated control arm.

### Histology

Three-millimeter punch biopsy specimens of the outer forearms of several study participants were collected at end point. The specimens were stored in 10% formalin and were subsequently processed for immunohistochemical analysis. Colloidal iron was used to stain mucopolysaccharides, including hyaluronic acid and chondroitin sulfate compounds. An immunohistochemical stain specific to MMP-9 was used to assess MMP enzymatic activity.

### Statistics

The statistics for this study were planned and performed by a statistician independent of the sponsor company.

### Visual Grading and Pinch Recoil

The mean values for all visually graded efficacy and irritation parameters and pinch recoil measurements at weeks 6 and 12 were compared with the baseline values using a paired *t* test at the $P \leq .05$ significance level. The mean percent change from baseline was calculated for all attributes at all time points by averaging each subject's individual percent change from baseline.

### Skin Thickness

The mean values from both the treated and untreated arms at week 12 were statistically compared with the baseline values using a paired *t* test at the $P \leq .05$ significance level. The mean percent change from baseline was calculated at end point by averaging each subject's individual percent change from baseline. Comparisons were made between the treated and untreated arms using analysis of variance, with paired comparisons using Fisher's Least Significant Difference test at the $P \leq .05$ significance level.

Self-assessment questionnaires were tabulated, and top box versus bottom box analysis was performed.

## RESULTS

Thirty-three women enrolled in the study. Two subjects discontinued the study for reasons unrelated to test product usage. Thirty-one women (29 white, 2 Asian), 39 to 60 years of age, with Fitzpatrick skin types II and III, completed the study. In accordance with inclusion criteria, study participants had mild to moderate periocular fine lines, periocular coarse wrinkles, and mottled hyperpigmentation on the face. A smaller subset of the study population (n=16) agreed to undergo punch biopsies.

Compared with the baseline parameters, all clinically graded parameters improved significantly at both week 6

Table 1

**Visual Grading Scale for the Face for Subjects Treated With Lactobionic Acid 8% for 12 Weeks**

| Parameter | Site for Grading | Low Extreme of Scale | High Extreme of Scale |
|---|---|---|---|
| Fine lines | Eye area | 0=none | 10=severe |
| Coarse wrinkles | Eye area | 0=none | 10=severe |
| Pore size | Cheek | 0=invisible | 10=very large |
| Laxity | Cheek | 0=firm, unpliable | 10=loose, pliable |
| Roughness | Cheek | 0=soft, smooth | 10=rough, coarse |
| Sallowness | Face | 0=light, nonyellow | 10=dark, matte |
| Clarity | Face | 0=dull, matte | 10=clear, radiant |
| Mottled pigmentation | Face | 0=even tone | 10=mottled, uneven tone |

The faces of subjects were visually graded by a trained assessor at baseline, week 6, and week 12 using a 0- to 10-point scale with defined anchors. Increments of 0.25 points were allowed to enhance grading sensitivity.

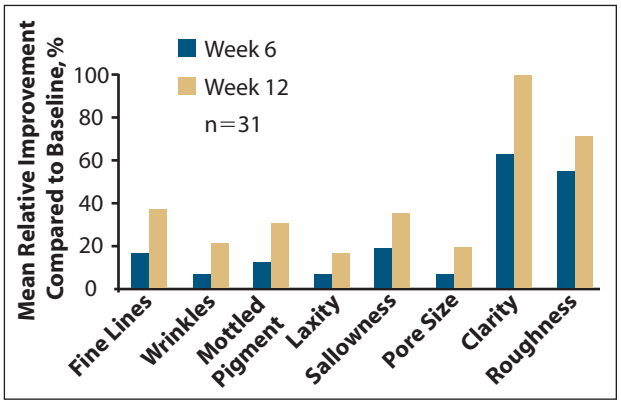


**Figure 2.** Antiaging effects of lactobionic acid 8%. Clinical grading revealed significant improvements in all of the graded parameters at weeks 6 and 12 compared with baseline ($P<.05$).

and week 12 ($P<.05$) (Table 2, Figure 2). Compared with the baseline measurements, pinch recoil measurements also improved significantly at both week 6 and week 12 ($P<.05$), with a 14.5% increase in skin firmness and elasticity at end point (Table 2, Figure 3). Skin thickness increased significantly relative to baseline (6.9%; $P<.05$) and relative to the untreated control (1.9%; $P<.01$) (Figure 4).

The lactobionic acid 8% cream was well tolerated, and there were no significant increases in average irritation scores over the 12-week treatment period (Table 2). Mild preexisting facial erythema significantly improved at week 6 compared with baseline ($P<.05$), and dryness significantly improved compared with baseline at weeks 6 and 12 ($P<.05$). Preexisting forearm dryness improved by 20% ($P<.05$) at week 6, representing a statistically

TABLE 2

## Clinical Grading Results for Subjects Treated With Lactobionic Acid 8%: Baseline Versus Week 12

| Variable | Grading Site | Mean Baseline Score | Mean 12-Wk Score | Mean Change | Standard Deviation | Statistical Significance ($P<.05$) | Change From Baseline, %* |
|---|---|---|---|---|---|---|---|
| Pore size | Cheek | 5.02 | 4.10 | −0.92 | 0.58 | ↓ | −20.7 |
| Roughness | Cheek | 3.89 | 1.23 | −2.66 | 1.13 | ↓ | −70.8 |
| Laxity | Cheek | 5.56 | 4.72 | −0.84 | 0.34 | ↓ | −16.4 |
| Fine lines | Eye | 3.98 | 2.61 | −1.37 | 0.49 | ↓ | −37.0 |
| Coarse wrinkles | Eye | 5.10 | 4.05 | −1.05 | 0.28 | ↓ | −21.4 |
| Mottled pigmentation | Face | 4.48 | 3.26 | −1.22 | 0.47 | ↓ | −30.9 |
| Sallowness | Face | 3.65 | 2.53 | −1.12 | 0.33 | ↓ | −35.6 |
| Clarity/radiance | Face | 3.87 | 7.59 | 3.72 | 0.91 | ↓ | 100.1 |
| Pinch recoil | Face | 1.65 | 1.40 | −0.25 | 0.11 | ↓ | −14.5 |
| Erythema | Face | 0.45 | 0.24 | −0.21 | 0.59 | None | −7.0 |
| Edema | Face | 0.00 | 0.00 | 0.00 | 0.00 | None | 0.0 |
| Dryness | Face | 0.24 | 0.06 | −0.18 | 0.46 | ↓ | −5.9 |
| Burning | Face | 0.03 | 0.00 | −0.03 | 0.18 | None | −1.1 |
| Stinging | Face | 0.00 | 0.06 | 0.06 | 0.25 | None | 2.2 |
| Itching | Face | 0.00 | 0.00 | 0.00 | 0.00 | None | 0.0 |
| Tightness | Face | 0.40 | 0.32 | −0.08 | 0.90 | None | −2.7 |
| Tingling | Face | 0.00 | 0.00 | 0.00 | 0.00 | None | 0.0 |

n=31. Data show mean baseline scores, mean 12-week (end point) scores, mean change from baseline, standard deviation, and statistical significance for each variable (end point vs baseline) at $P<.05$. Asterisk indicates the mean percent change from baseline (calculated on an individual basis and then averaged).

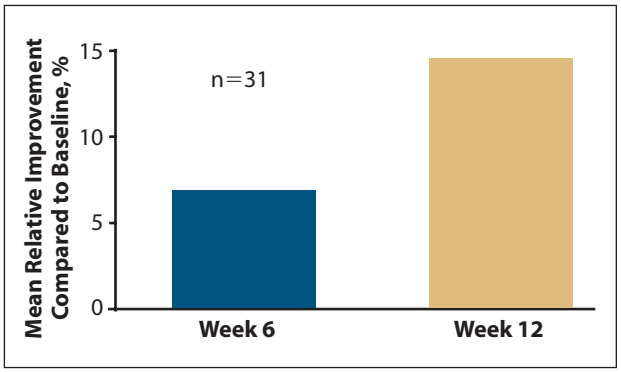


**Figure 3.** Pinch recoil measurements in subjects treated with lactobionic acid 8% at 6 and 12 weeks. Firmness and elasticity were significantly improved at weeks 6 and 12 compared with baseline ($P<.05$).

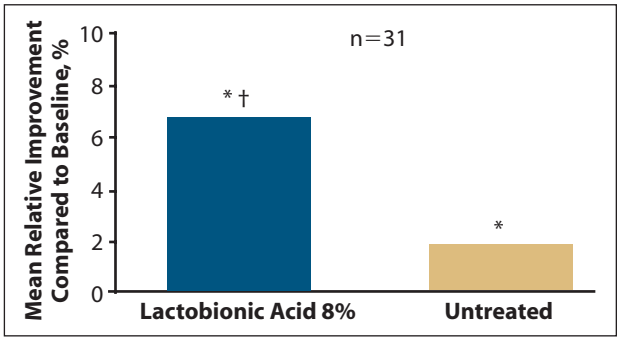


**Figure 4.** Mean relative percent of improvement in skin thickness measurements on the forearms of subjects treated with lactobionic acid 8% for 12 weeks compared with baseline. Asterisk indicates significant increase in skin thickness (plumpness) compared with baseline ($P<.05$); dagger, significantly thicker than untreated skin ($P<.01$).

TABLE 3

## Self-Assessed Improvements to Skin Quality in 12-Week Clinical Study of Subjects Treated With Lactobionic Acid 8%

| Parameter | Subjects Scoring Excellent, Very Good, and Good for Improvement to Parameter, % |
|---|---|
| Skin texture and smoothness | 94 |
| Elasticity | 84 |
| Healthier-looking skin | 81 |
| Skin plumpness | 81 |
| Dryness | 77 |
| Redness/irritation | 74 |
| Fine lines | 71 |
| Wrinkles | 68 |
| Decreased acne breakouts | 68 |

Significant self-assessed skin improvements were noted ($P<.05$). These findings support the clinical grading and efficacy measurements.

significant improvement relative to baseline, and improved significantly ($P<.05$) relative to the untreated control arm, which worsened slightly (1.1%) over the 12-week treatment period. (Six-week data and arm data are not shown.)

Responses to self-assessment questionnaires revealed a significantly greater proportion of subjects answering positively (excellent, very good, good) rather than negatively (fair, poor) to questions regarding photoaging parameters ($P<.05$) (Table 3). Two thirds (68%) of participants rated the lactobionic acid 8% test formulation better than the products they were currently using. These findings provide evidence of consumer-perceivable benefits and also support the clinical grading results of a trained assessor.

Photography revealed significant improvements to skin texture and laxity. There were demonstrable improvements to firmness of the eyelid (Figure 5) and malar (Figure 6) skin.

Histologic samples demonstrated findings consistent with those of previous AHA histologic studies. Epidermal structure was thickened, and the stratum corneum was more compact (Figure 7). Mucopolysaccharides were increased (Figure 8), representing an increase in water-binding glycosaminoglycans, which plump and firm the dermal matrix. In addition, there was an observable decrease in keratinocyte MMP-9 staining (Figure 9). Inhibition of MMP-9 enzymes helps to protect and preserve the dermal matrix, thereby providing a preventive aspect to the treatment of photoaging.

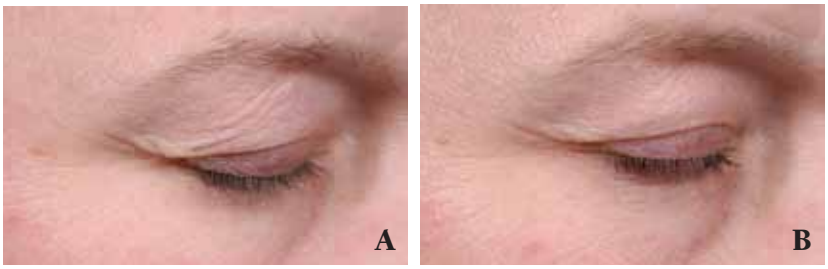


**Figure 5.** Eyelid skin before (A) and after (B) 12 weeks of treatment with lactobionic acid 8%. Diminished periocular fine lines and improved eyelid skin texture are shown.

## SUMMARY

Lactobionic acid is a polyhydroxy bionic acid with numerous benefits for skin. It is a moisturizer and an antioxidant and is nonirritating to skin. This study reveals the measurable and consumer-perceivable antiaging effects of a lactobionic acid 8% cream formulation. The observed benefits include clinically graded improvements in skin texture, clarity, and roughness; increased skin firmness and elasticity; and increased skin thickness (plumping). Self-assessment demonstrated significant improvements in skin texture, elasticity, fine lines, and wrinkles, and no irritation. Histologic specimens showed benefits to skin consistent with previous AHA data, including increased viable epidermal thickness with a more compact stratum corneum and increased dermal glycosaminoglycan content, which corresponds to and supports the increased skin plumping demonstrated using skin thickness measurements. Histologic studies also showed reduced keratinocyte staining of MMP-9. MMP-9 is a gelatinase enzyme


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**Figure 6.** Malar skin before (A) and after (B) 12 weeks of treatment with lactobionic acid 8%. Improvements to skin laxity and texture of malar skin are shown.

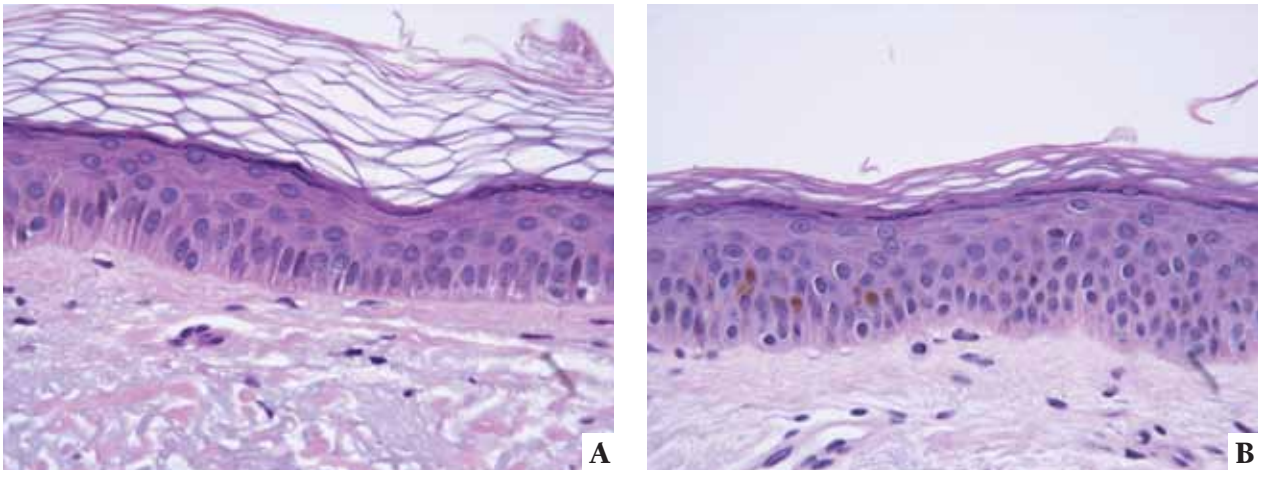


**Figure 7.** Epidermal structure of untreated control skin (A) and skin treated with lactobionic acid 8% (B) for 12 weeks. Increased viable epidermal thickness and a more compact stratum corneum are shown. (H&E, original magnification ×400).

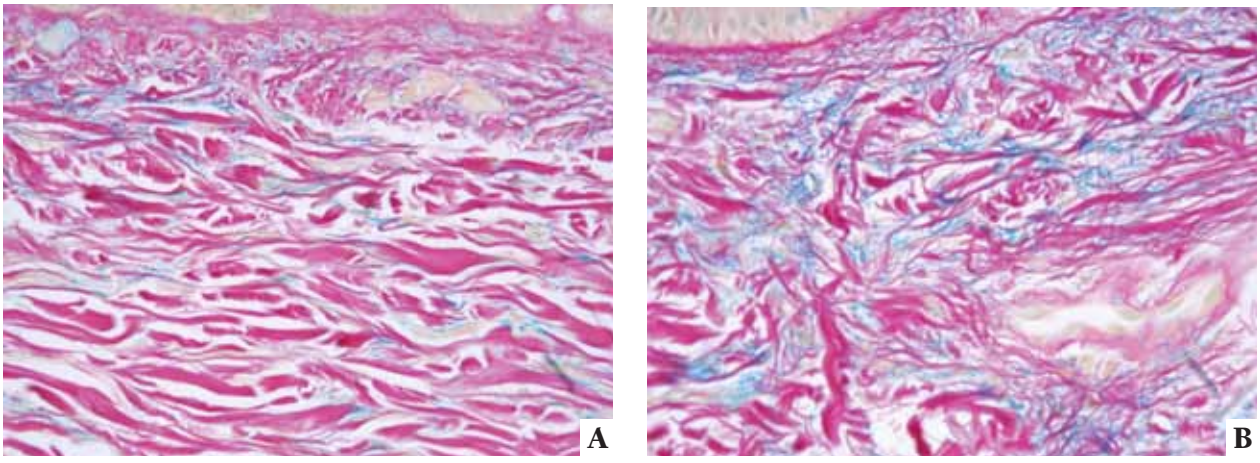


**Figure 8.** Glycosaminoglycans in untreated control skin (A) and skin treated with lactobionic acid 8% (B) for 12 weeks. Increased density of dermal colloidal iron staining (blue color) representing glycosaminoglycans/acid mucopolysaccharides is shown (original magnification ×400).

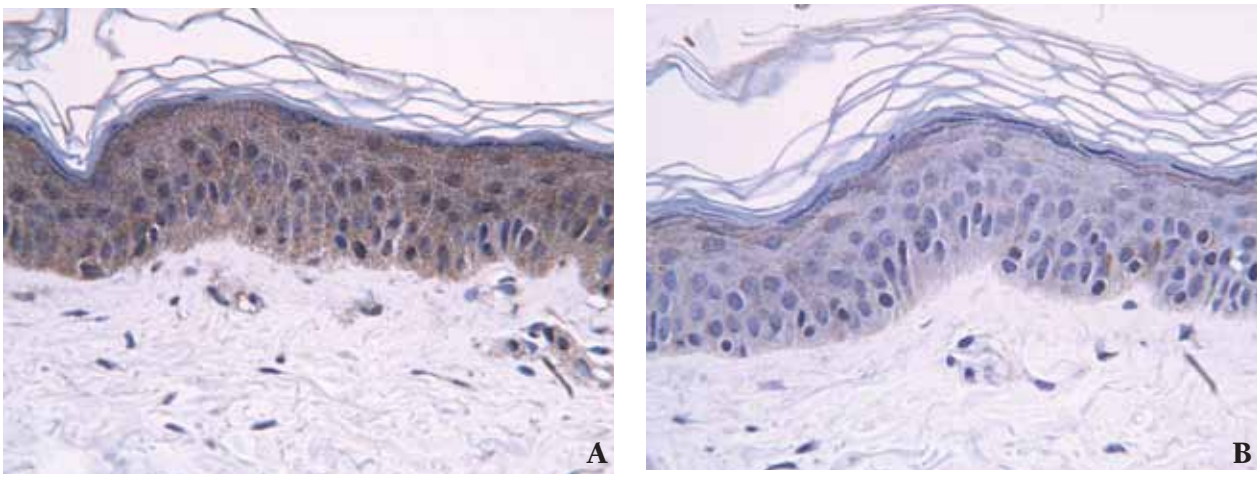

**Figure 9.** Matrix metalloproteinase-9 (MMP-9) in untreated control skin (A) and skin treated with lactobionic acid 8% (B) for 12 weeks. Decreased density of MMP-9 staining (brown color) within keratinocytes is shown (immunohistochemical stain, original magnification ×400).

that attacks gelatin, elastin, and collagen types IV, V, and X as substrates. The latter finding supports prevention of photoaging owing to a reduction in activity of skin matrix–degrading MMP enzymes.

Lactobionic acid provides benefits to all of the layers of the skin, including the stratum corneum, epidermis, and dermis. In addition, it is nonirritating and nonstinging, as well as moisturizing. It is also an antioxidant. When used alone, lactobionic acid is ideal for all skin types to achieve antiaging effects. Owing to its gentleness, it may also be used in combination with cosmetic procedures to help achieve optimal improvements to photoaged skin.

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