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Study On The Treatment Effect Of Atopic Dermatitis Using Aloe Vera PDRN-Based Aptamer And Vitis Vinifera Viniferin And Its Application To NDS And TDS

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Abstract
Many studies have been conducted to treat atopic dermatitis, but these treatments have generally been inadequate or failed due to side effects. In this study, we investigated the efficacy of Vitis vinifera viniferin containing aloe aptamer (ALOVEtamer) obtained from a preliminary study based on Aloe vera plant PDRN (Polydeoxyribonucleotide) in a mouse model of atopic dermatitis. For the experiment, Nc/Nga mice were exposed to house dust mite extract (HDM) to induce atopic dermatitis. The mice were divided into four groups: positive control, ALOVEtamer topical treatment group, ALOVEtamer dietary treatment group, and ALOVEtamer topical + dietary treatment group. There was no significant difference in serum IgE concentration between the two groups, but the serum cytokine antibody array showed an enrichment of genes related to immune response. A significant difference in skin lesion scores was observed between the two groups, and skin lesions were confirmed to be alleviated in the ALOVEtamer topical treatment group and the ALOVEtamer dietary treatment group compared to the control group. Interestingly, almost normal structures were observed within the skin lesions of the ALOVEtamer topical + dietary treatment group. Overall, the mixture of viniferin extract and aloe aptamer was found to be effective in the treatment of atopic dermatitis, and thus its development as a therapeutic agent and functional cosmetic material in the future is expected.

Keywords: *Atopic dermatitis; Aloe vera aptamer; plant PDRN (Polydeoxyribonucleotide); House dust mite; Nc/Nga mouse; Vitis vinifera viniferin*

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I. Introduction

Atopic dermatitis is a common chronic inflammatory skin disease, and its prevalence is increasing due to environmental deterioration, and its socioeconomic burden is increasing, raising it as a global public health problem [1]. Approximately 20% of the world's population suffers from AD [2], and the age of onset of atopic dermatitis varies from infants to adults, and one study showed a high increase rate of 42.8% in adults. In addition, approximately 57.6% of adult patients showed a persistent and chronic atopic dermatitis pattern, and lichen planus/exudative flexural dermatitis, the most common in adult patients, accounted for 58.5%, which is accompanied by eczema and pruritus [3]. Many trials have been conducted to overcome atopic dermatitis, including antihistamines, glucocorticoids, and antibiotics. More advanced treatments, such as immunotherapy, have also been used to treat atopic dermatitis. However, these treatments have not been successful due to lack of efficacy or side effects [4]. A number of novel drugs, including specific monoclonal antibodies and novel topical molecules that are expected to block one mechanism of atopic dermatitis, such as Tofacitinib, Crisaborole, and Dupilumab, have been developed, opening a new era in the treatment of AD [5], but these have not been satisfactory in the treatment of atopic dermatitis. Therefore, recent studies have focused on alternative medicine and oligonucleotide or PDRN (Polydeoxyribonucleotide) aptamer nanotechnologies to control atopic dermatitis [6–8].

Plant aptamers are nucleic acid ligands designed to target compounds derived from plants. Aptamers are short strands of PDRN (Polydeoxyribonucleotide) or RNA that can bind to specific molecules with high affinity and specificity, performing a function similar to antibodies. Plant aptamers have a variety of biological and medical applications. Aptamers targeting plant compounds as drug delivery systems can be used to treat certain diseases. For example, they can be utilized as delivery systems for drugs, including natural compounds [9]. In addition, aptamers can be used as biosensors due to their inherent high affinity and specificity, making them useful for the detection and quantification of analytes in plant biology [10]. Recently, it has been used for gene regulation

and editing in plants in combination with the CRISPR/Cas9 system [10], and for new drug discovery and target validation, and research is being conducted to develop new therapeutics based on plant compounds [11].

Aloe vera (*Aloe vera* (L.) Burm.f.) is well known for its moisturizing effect [12], soothing effect [12], antioxidant and anti-aging effect [12], wound healing and inflammation relief [12], whitening and UV protection effect [13], and recently, our laboratory has studied it as a cosmetic material for atopic diseases, etc. through a prior art study on Aloe Aptamer (called ALOVEtamer) [6–8].

Viniferine (*Vitis vinifera* L.) has been reported to have a whitening effect that is 62 times stronger than vitamin C and 13 times stronger than arbutin as a cosmetic material, and it prevents and brightens dark spots on the skin by inhibiting melanin production. In addition, it has a strong antioxidant effect (22 times stronger than quercetin, 28 times stronger than tocopherol), which helps prevent skin aging and maintain healthy skin ((https://www.ingr.kr/service/nature/index.jsp, https://www.cosinkorea.com/news/article.html?no=46103), and in recent studies, it has been known as a material that improves wrinkles caused by aging and reduces atopic dermatitis by maintaining skin elasticity and suppressing skin damage and inflammation when administered orally [14].

In this study, the efficacy of *Aloe vera* PDRN (Polydeoxyribonucleotide)-based aptamer and *Vitis vinifera* viniferin was investigated in an atopic disease-induced mouse model.

II. Materials And Methods

Animals

For the atopic disease mouse model, 20 female Nishikinezumi Cinnamon/Nagoya (Nc/Nga, 8 weeks old) mice were purchased from Central Laboratory Animal Inc. (Seoul, Korea). The experimental protocol complied with ethical guidelines and was approved by the Institutional Animal Care and Use Committee of the Korea Research Institute of Bioscience and Biotechnology (KRIBBE-240921-3). Mice were housed in an air-conditioned general room maintained at 24±2C and 55±15% humidity. The mice were divided into four groups: positive control (house dust mite extract (HDM) treatment only), Synbio-glucan topical treatment (Synbio-glucan topical treatment in HDM-treated mice), Synbio-glucan dietary treatment (Synbio-glucan dietary treatment in HDM-treated mice), Synbio-glucan topical + dietary treatment group (Synbio-glucan topical + dietary treatment in HDM-treated mice) (n = 5 in each group).

ALOEtamer, Viniferin extract and Reagents

Aloe vera PDRN (Polydeoxyribonucleotide)-based aptamer and *Vitis vinifera* viniferin was purchased from Kim Jung-moon Aloe Farm Co., Ltd., a pre-research institute, and was purified from fresh *Aloe vera* leaves by KJM Bio Research Institute Co., Ltd. Patent technology [6-8] was manufactured. Then, a complex containing PLL (Polylysine) and PAMAM (Poly(amidoamine)) was prepared with aloe aptamer-Viniferin derivatives together with viniferin extract (called ALOVEtamer) as in the previous study [6-8]. The ALOVEtamer diet consisted of a standard diet (containing 18% protein rodent diet) and 2% ALOVEtamer preparation (Koatech, Gyeonggi-do, Korea). HDM allergen ointment consisting of Dermatophagoides farinae was purchased from Biostir Inc. (Kobe, Japan). Viniferin extract was purchased from the laboratory of Guro Hospital, Korea University [15]. HDM allergen ointment composed of Dermatophagoides farinae was purchased from Biostir Inc. (Kobe, Japan).

Induction of Atopic Dermatitis

To destroy the skin barrier, the hair on the back was shaved and treated with 100 μL of 4% (w/v) sodium dodecyl sulfate (SDS; Sigma-Aldrich, St. Louis, MO, USA) to induce the disease. After drying the SDS, 100 mg of HDM allergen (HDM, Biostir Inc., Kobe, Japan) per mouse was applied to the exposed skin area twice a week for 4 weeks (Figure 1).

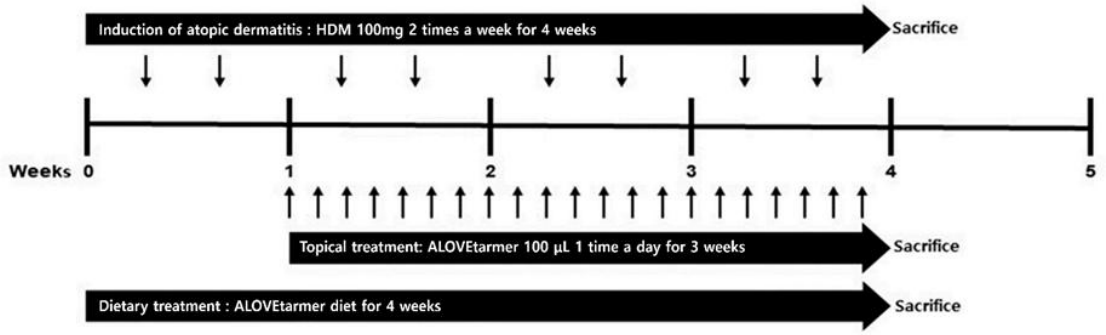

Figure 1. Atopic dermatitis induction experiment scheme

ALOVEtamer Treatment in NC/Nga Mice

For the ALOVEtamer topical treatment group, the skin area where HDM was applied was treated with 100 μL ALOVEtamer daily for 3 weeks starting from 1 week after HDM treatment. After drying the ALOVEtamer topical treatment skin, the mice were returned to their original housing cases. All mice in this group were fed a standard diet. For the ALOVEtamer diet treatment group, the ALOVEtamer diet was fed for 4 weeks starting from the beginning of the experiment. For the positive control group (HDM treatment only), 100 μL PBS was used instead of ALOVEtamer topical for 3 weeks starting from 1 week after HDM treatment. All mice in this group were fed a standard diet. The ALOVEtamer topical and diet treatment groups were fed an ALOVEtamer diet for 4 weeks starting from the beginning of the experiment. The skin area where HDM was applied was treated with 100 μL ALOVEtamer daily for 3 weeks starting from 1 week after HDM treatment (Figure 1).

Serum IgE Concentration Assay

Serum was collected from sacrificed mice. Total serum IgE concentration was measured using an ELISA kit (Fujifilm Wako Shibayagi Corporation, Shibukawa, Japan) according to the manufacturer's instructions. Plates were analyzed at 450 nm with a SpectraMax ABS Plus Microplate Reader (Molecular Devices, LLC, San Jose, CA, USA).

Serum Cytokine Antibody Assay

Sera (50 μL) from sacrificed mice were used in the array protocol. Relative serum cytokine levels were measured using the Mouse Cytokine Antibody Array L308 Membrane Kit (RayBiotech, Inc., Norcross, GA, USA), and 100 μL of serum from five mice per group was used for the cytokine array. Diluted pooled serum (1:10) was examined according to the manufacturer's protocol to determine cytokine profiles. The fold change of cytokines was calculated as the relative value of the treatment group to the control group.

Skin Lesion Scoring

The degree of erythema/hemorrhage, scarring/dryness, edema, and abrasion/erosion was individually scored as 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The total skin score was the sum of the individual scores [18,19] (Supplementary Material Figure S1). Scoring was performed weekly during the experimental period.

Histological Analysis

At the end of the experiment, mice were perfused via the heart with 0.1 M phosphate-buffered saline (PBS) after deep anesthesia with high-dose Zoletil 50® (Virbac, Carros, France). Fixation was then performed using 4% paraformaldehyde in 0.1 M PBS. Skin was collected and fixed with the same fixation for 24 h at 4°C. Tissues were dehydrated and embedded in paraffin. Embedded tissues were cut into 5-μm-thick sections using a microtome (Leica Microsystems GmbH, Wetzlar, Germany). Tissues were mounted on slides (Muto Pure Chemicals Co., Ltd., Tokyo, Japan) and stained with hematoxylin and eosin (H&E) and toluidine blue (TB) using standard protocols.

Statistical Analysis

Data were analyzed using statistical analysis software (GraphPad Prism, Ver. 5.01, San Diego, CA, USA). The values presented are the experimental means of each group. Differences between means were identified using the Mann-Whitney and Kruskal-Wallis tests. Statistical significance was considered to be p-value < 0.05.

III. Results

Comparison of Serum IgE Levels Between Groups

Atopic dermatitis was induced in Nc/Nga mice. These mice were treated with ALOVEtamer topical, dietary, dietary and topical, or not treated. In general, atopic dermatitis tends to produce excessive IgE levels. Serum from all groups was collected from sacrificed mice and the serum IgE levels of the groups were compared. The serum IgE levels of mice in all groups were similar (p = 0.2560). The serum IgE levels were similar in the positive control group, ALOVEtamer topical treatment group (p = 0.5476), ALOVEtamer diet treatment group (p = 0.3095), and ALOVEtamer topical + diet treatment group (p = 0.3095). Serum IgE levels in the ALOVEtamer diet treatment group (p = 0.3095), ALOVEtamer topical + diet treatment group (p = 0.3095), and ALOVEtamer topical treatment group were similar. Serum IgE levels in the ALOVEtamer diet treatment group and ALOVEtamer topical + diet treatment group were similar (p = 0.1508) (Figure 2).

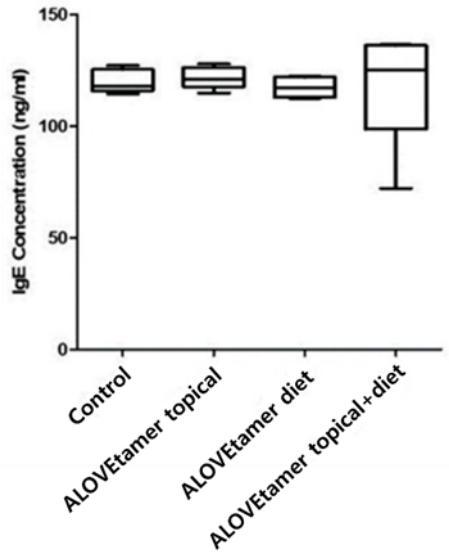

Figure 2. Comparison of serum IgE levels between groups. Serum IgE levels are expressed in optical density units. Serum IgE levels were similar in all groups. Control group; positive control group, ALOVEtamer topical treatment group, ALOVEtamer diet treatment group, ALOVEtamer topical + diet treatment group.

Comparison of Serum Cytokine Antibody Arrays Between Groups

Figures 3A–C show the antibody array scatter plots. The scatter plots represent the fold change of serum cytokines between the treatment groups and the positive control group. The plots show the change in signal intensity between the ALOVEtamer topical treatment group and the positive control group (Figure 3A), the ALOVEtamer diet treatment group and the positive control group (Figure 3B), and the ALOVEtamer topical + diet treatment group and the positive control group (Figure 3C). The red and green lines represent 2-fold up- or down-regulated expression, respectively. The data indicated by the red and green dots above the red and green lines are presented in the table. These results confirmed the pattern of change in serum cytokines between the treatment groups and the positive control group.

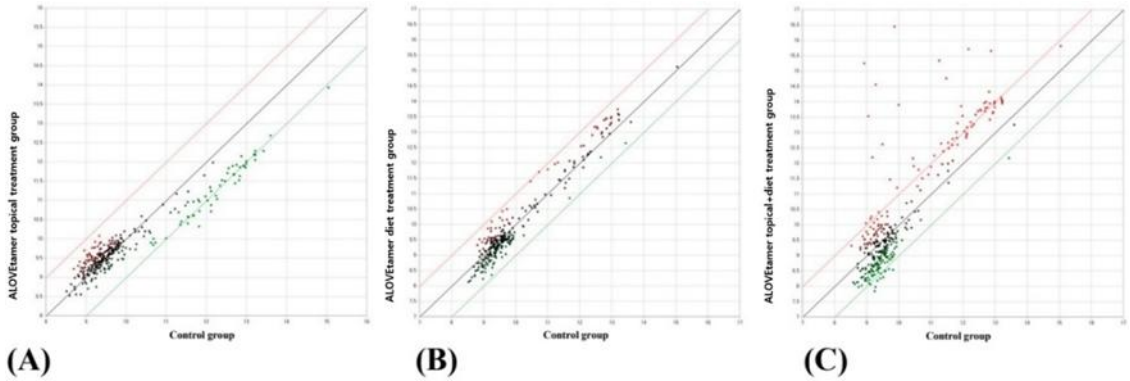

Figure 3. (A) Signal changes between ALOVEtamer topical treatment group and positive control group, (B) ALOVEtamer dietary treatment group and positive control group, and (C) ALOVEtamer topical + diet treatment group and positive control group. Red and green lines represent 2-fold up- or down-regulated expression, respectively. The scatter plot shows the pattern of serum cytokine changes between the treatment groups and the positive control group. (D) Functional analysis of the antibody array results after ALOVEtamer topical treatment. The most enriched GO_BP term was response to lipopolysaccharide, and the most enriched KEGG category was cytokine-cytokine receptor interaction. (E) Functional analysis of the antibody array results after ALOVEtamer dietary treatment. The most enriched GO_BP term was immune response, and the most enriched KEGG category was cytokine-cytokine receptor interaction. (F) Functional analysis of the antibody array results after ALOVEtamer topical + diet treatment. The most enriched GO_BP entry was immune response, and the most enriched KEGG category was cytokine-cytokine receptor interaction.

The serum cytokine arrays in each treatment group were compared to the positive control group to identify up- or down-regulated proteins. In the ALOVEtamer topical treatment group, 27 proteins were significantly down-regulated (>2-fold change from normalized values; *t*-test p-value < 0.05; Table 1). In the ALOVEtamer dietary treatment group, there were 27 significantly up-regulated proteins (>2-fold change from normalized values; *t*-test p-value < 0.05; Table 2). In the ALOVEtamer topical + dietary treatment group, 45 up-regulated and 12 down-regulated proteins were identified (>2-fold change from normalized values; *t*-test p-value < 0.05; Table 3).

Table 1. Serum cytokine antibody array representing the significantly downregulated proteins in the ALOVEtamer topical treatment group compared to the positive control group based on the fold-change rank.

Rank	Antibody Name	Fold-Change	Gene Symbol	Swiss-Prot Entry
	Downregulated			
1	IFN-beta	0.354	Ifnb1	P01575
2	GDF-8	0.377	Mstn	O08689
3	Common gamma Chain/IL-2 R gamma	0.408	Il2rg	P34902
4	Endostatin	0.412	Col18a1	P39061
5	IGFBP-3	0.423	Igfbp3	P47878
6	SPARC	0.424	Sparc	P07214
7	WISP-1/CCN4	0.432	Wisp1	O54775
8	TLR2	0.440	Tlr2	Q9QUN7
9	SLPI	0.450	Slpi	P97430
10	MIP2	0.453	Cxcl2	P10889
11	VEGF-B	0.456	Vegfb	P49766
12	CCL28	0.458	Ccl28	Q9JIL2
13	ICAM-1	0.460	Icam1	P13597
14	Fas/TNFRSF6	0.461	Fas	P25446
15	CXCR6	0.465	Cxcr6	Q9EQ16
16	IL-1 RI	0.475	Il1r1	P13504
17	IGFBP-1	0.475	Igfbp1	P47876
18	b FGF	0.482	Fgf2	P15655
19	Prolactin	0.483	Prl	P06879
20	M-CSF	0.485	Csf1	P07141
21	TGF-beta RII	0.485	Tgfbr2	Q62312
22	CRP	0.488	Crp	P14847
23	Lymphotoxin beta R/TNFRSF3	0.488	Ltbr	P50284
24	Frizzled-6	0.496	Fzd6	Q61089
25	IL-27	0.499	Il27	Q8K3I6
26	IL-23 R	0.499	Il23r	Q8K4B4
27	TCCR/WSX-1	0.499	Il27ra	O70394

All proteins were identified from antibody array analysis and further analyzed according to the categories of The Database for Annotation, Visualization and Integrated Discovery (DAVID) and Kyoto Encyclopedia of Genes and Genomes (KEGG). DAVID is a database resource for analyzing biological gene functions. KEGG is a database resource for analyzing pathways related to biological systems. Fifty-five components were significantly enriched in Gene Ontology_Biological Process (GO_BP) by the DAVID results in the ALOVEtamer topical treatment group. Among them, the top 10 enriched GO_BP terms were response to lipopolysaccharide, inflammatory response, immune response, response to glucocorticoid, innate immune response, regulation of cell proliferation, wound healing, response to ethanol, response to drugs, and immune system process (Figure 3D). Among the KEGG categories, 23 pathways were significantly enriched in the ALOVEtamer topical treatment group. The five most enriched KEGG categories were cytokine-cytokine receptor interaction and PI3K-Akt signaling pathway, Chagas disease (American trypanosomiasis), TNF signaling pathway, and osteoclast differentiation (Figure 3D).

Table 2. Serum cytokine antibody array showing proteins significantly upregulated in the ALOVEtamer diet treatment group compared to the positive control group, ranked by fold change.

Rank	Antibody Name	Fold-Change	Gene Symbol	Swiss-Prot Entry
	Upregulated			
1	IL-9	83.568	Il9	P15247
2	Dtk	62.380	Tyro3	P55144
3	FGF R3	24.767	Fgfr3	Q61851
4	GFR alpha-4/GDNF R alpha-4	16.304	Gfra4	Q9JJT2
5	Thymus Chemokine-1	14.052	Ppbp,	Q9EQI5
6	TRAIL/TNFSF10	9.431	Tnfsf10	P50592
7	Follistatin-like 1	8.738	Fstl1	Q62356
8	VE-Cadherin	6.714	Cdh5	P55284
9	BLC	6.328	Cxcl13	O55038
10	ICAM-2/CD102	5.753	Icam2	P35330
11	IL-22	5.632	Il22	Q9JJY9
12	IL-10 R alpha	5.608	Il10ra	Q61727
13	WIF-1	4.277	Wif1	Q9WUA1
14	MIP-3 beta	3.753	Ccl19	O70460
15	MIP-1alpha	3.608	Ccl3	P10855
16	LIF	3.496	Lif	P09056
17	VEGF-D	3.197	Figf	P97946
18	RANTES	3.117	Ccl5	P30882
19	Decorin	2.988	Dcn	P28654
20	P-Selectin	2.687	Selp	Q01102
21	IL-13	2.309	Il13	P20109
22	IL-1 Ra	2.288	Il1r1	P13504
23	IL-1 R4/ST2	2.245	Il1rl1	P14719
24	PDGF-C	2.180	Pdgfc	Q8CI19
25	CD27 Ligand/TNFSF7	2.173	Cd70	O55237
26	ICK	2.153	Ick	Q9JKV2
27	SDF-1	2.074	Cxcl12	P40224

As determined by applying GO_BP, 58 components of the protein list regulated in the ALOVEtamer diet treatment group were significantly enriched. The top 10 enriched GO_BP terms among the proteins were immune response, chemokine-mediated signaling pathway, inflammatory response, cell-cell signaling, positive regulation of phosphatidylinositol 3-kinase signaling, positive regulation of ERK1 and ERK2 cascade, cell chemotaxis, chemotaxis, lymphocyte chemotaxis, and protein kinase B signaling (Figure 3E). Among the KEGG categories, seven pathways were significantly enriched in the ALOVEtamer diet treatment group. Among the pathways, the five most abundant categories in KEGG were cytokine-cytokine receptor interaction, Jak-STAT signaling pathway, chemokine signaling pathway, rheumatoid arthritis, and NF-kappa B signaling pathway (Figure 3E).

In the GO_BP results of ALOVEtamer topical + dietary treatment group, 109 components in the protein list were significantly enriched. Among them, the top 10 enriched GO_BP items were immune response, positive regulation of peptidyltyrosine phosphorylation, chemotaxis, chemokine-mediated signaling pathway, positive regulation of cell proliferation, inflammatory response, positive regulation of inflammatory response, cell chemotaxis, negative regulation of cell proliferation, and negative regulation of viral genome replication (Figure 3F). In the KEGG results, 12 pathways were significantly enriched. The top 5 enriched pathways were cytokine-cytokine receptor interaction, Jak-STAT signaling pathway, chemokine signaling pathway, hematopoietic cell lineage, and PI3K-Akt signaling pathway (Figure 3F).

Comparison of Skin Lesion Scores Between Groups

Skin lesions included erythema/hemorrhage, scarring/dryness, edema, and abrasion/erosion (Figure 4A). These clinical signs were more severe in the positive control group and ALOVEtamer diet treatment group than in the other groups. Compared with the positive control group, the lesion scores of the ALOVEtamer topical treatment group (p = 0.0432) and the ALOVEtamer topical + diet treatment group (p = 0.0273) showed a significant difference, but there was no difference in the ALOVEtamer diet treatment group (p = 0.8294). The skin lesion scores were similar among the ALOVEtamer topical treatment group, the ALOVEtamer diet treatment group (p = 0.0532), and the ALOVEtamer topical + diet treatment group (p = 0.7449). Skin lesion scores were significantly different between the ALOVEtamer diet treatment group and the ALOVEtamer topical + diet

treatment group (p = 0.0345) (Figure 4B).

Comparison of Histological Results Between Groups

H&E staining of positive control tissues showed epidermal and dermal hyperplasia, excessive keratinization, and lymphocytic infiltration. Compared with the positive control, the other groups showed amelioration of tissue, epidermal and dermal hyperplasia, keratinization, and lymphocytic infiltration. The ALOVEtamer topical treatment group showed a greater alleviation of epidermal and dermal hyperplasia, keratinization, and lymphocytic infiltration than the ALOVEtamer diet treatment group. Interestingly, almost normal structures were observed within the epidermis, dermis, subcutaneous layer, and muscle layer in the ALOVEtamer topical + diet treatment group (Figure 5A).

TB staining results showed that the number of mast cells in the dermis was prominent in the positive control group. The number of mast cells decreased in the ALOVEtamer topical treatment group and the ALOVEtamer diet treatment group. The mast cells decreased more in the ALOVEtamer topical treatment group than in the ALOVEtamer diet treatment group. Most prominently, mast cells were reduced in the ALOVEtamer topical + diet treatment group (Figure 5B).

Table 3. Serum cytokine antibody arrays representing proteins that were significantly up- or down-regulated in the ALOVEtamer topical + dietary treatment group compared to the positive control group. Based on fold change ranking.

Rank	Antibody Name	Fold-Change	Gene Symbol	Swiss-Prot Entry
	Upregulated			
1	Dtk	95.560	Tyro3	P55144
2	IL-9	80.615	Il9	P15247
3	GFR alpha-4/GDNF R alpha-4	38.326	Gfra4	Q9JJT2
4	FGF R3	22.346	Fgfr3	Q61851
5	Follistatin-like 1	16.970	Fstl1	Q62356
6	Thymus Chemokine-1	14.916	Ppbp,	Q9EQI5
7	ICAM-2/CD102	11.732	Icam2	P35330
8	VE-Cadherin	9.709	Cdh5	P55284
9	TRAIL/TNFSF10	8.673	Tnfsf10	P50592
10	Decorin	8.051	Dcn	P28654
11	IL-1 Ra	6.894	Il1r1	P13504
12	ICK	3.760	Ick	Q9JKV2
13	Frizzled-7	3.344	Fzd7	Q61090
14	GDF-5	3.263	Gdf5	P43027
15	IL-1 R4/ST2	2.961	Il1rl1	P14719
16	Common gamma Chain/IL-2 R gamma	2.836	Il2rg	P34902
17	CXCR6	2.769	Cxcr6	Q9EQ16
18	Lungkine	2.718	Cxcl15	Q9WVL7
19	VEGFC	2.509	Vegfc	P97953
20	Glut2	2.441	Slc2a2	P14246
21	Endostatin	2.422	Col18a1	P39061
22	RANTES	2.364	Ccl5	P30882
23	CTACK	2.329	Ccl27	Q9Z1X0
24	LIF	2.310	Lif	P09056
25	IL-28/IFN-lambda	2.298	Il28b	Q8CGK6
26	TCA-3	2.284	Ccl1	P10146
27	IGFBP-2	2.246	Igfbp2	P47877
28	IL-17 R	2.232	Il17ra	Q60943
29	Eotaxin-2	2.216	Ccl24	Q9JKC0
30	IL-31	2.192	Il31	Q6EAL8
31	BLC	2.174	Cxcl13	O55038
32	IL-11	2.150	Il11	P47873
33	HVEM/TNFRSF14	2.145	Tnfrsf14	NP_849262
34	CCL28	2.135	Ccl28	Q9JIL2
35	CRP	2.127	Crp	P14847
36	FLRG(Follistatin)	2.105	Fstl3	Q9EQC7
37	beta-Catenin	2.103	Ctnnb1	Q02248
38	Soggy-1	2.091	Dkkl1	Q9QZL9
39	GDF-8	2.064	Mstn	O08689
40	IGFBP-5	2.040	Igfbp5	Q07079
41	LIX	2.017	Cxcl5	P50228
42	Frizzled-6	2.015	Fzd6	Q61089
43	b FGF	2.011	Fgf2	P15655
44	IFN-beta	2.007	Ifnb1	P01575
45	CCL1/I-309/TCA-3	2.001	Ccl1	P10146
	Downregulated			
1	Activin A	0.373	Inhba	Q04998
2	Gremlin	0.403	Grem1	O70326
3	IL-4	0.408	Il4	P07750
4	SLPI	0.416	Slpi	P97430
5	Angiopoietin-like 2	0.425	Angptl2	Q9R045
6	Frizzled-1	0.446	Fzd1	O70421
7	Growth Hormone R	0.447	Ghr	P16882
8	IL-6 R	0.456	Il6ra	P22272
9	ICAM-5	0.469	Icam5	Q60625
10	IL-1 Rb	0.473	Il1r2	P27931
11	Axl	0.475	Axl	Q00993
12	Flt-3 Ligand	0.487	Flt3l	P49772

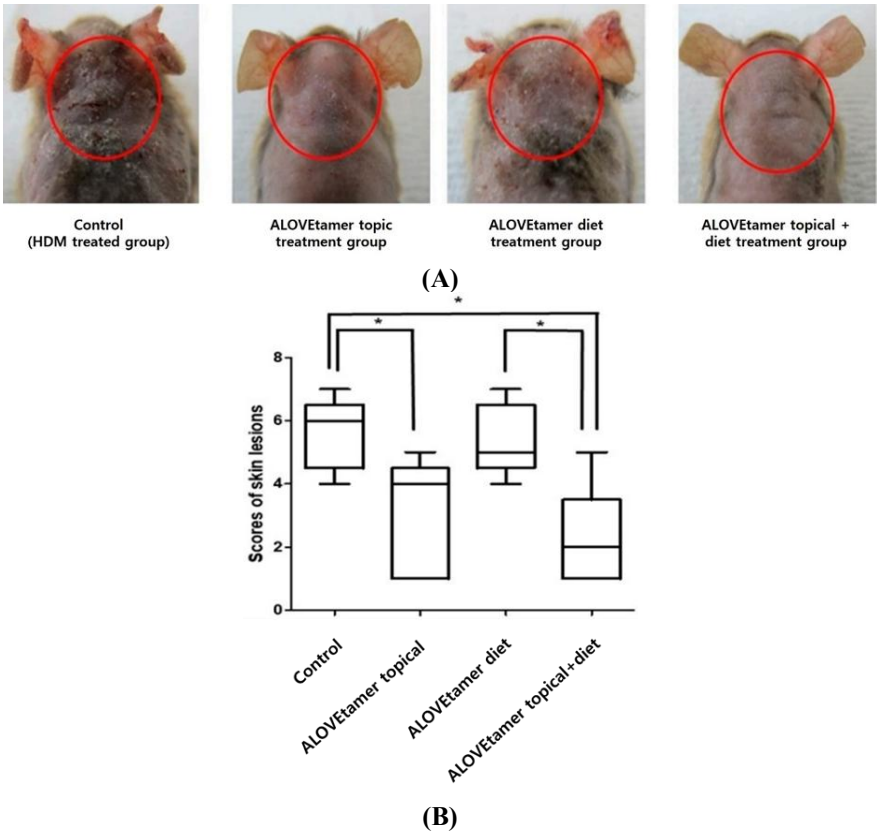

Figure 4. Skin lesion scores. (A) Representative clinical symptoms of the positive control group, ALOVEtamer topical treatment group, ALOVEtamer diet treatment group, and ALOVEtamer topical + diet treatment group. (B) Skin lesion scores of all groups were significantly different, except for the scores between the positive control group and ALOVEtamer diet treatment group, between the ALOVEtamer topical treatment group and ALOVEtamer diet treatment group, and between the ALOVEtamer topical treatment group and ALOVEtamer topical + diet treatment group. Control group; Positive control group, ALOVEtamer topical treatment group, ALOVEtamer diet treatment group, ALOVEtamer topical + diet treatment group. *$p < 0.05$.

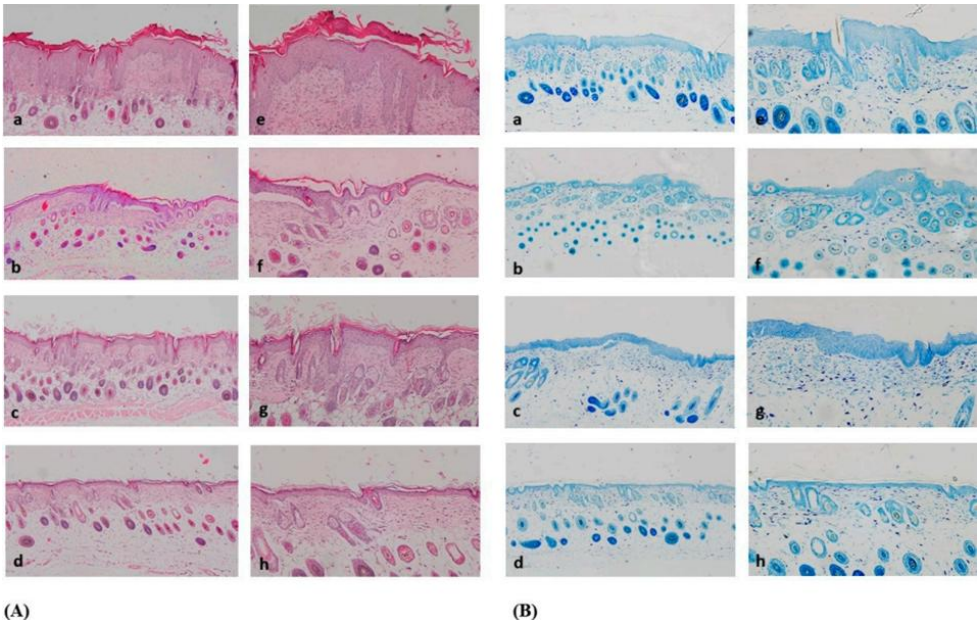

Figure 5. (A) H&E staining. Inflammatory cells were excessively expressed in a, e. This pattern was reduced in b, c, f, and g. Inflammatory cells were almost absent in d, h. (B) TB staining. Mast cells were prominent in a, e. This pattern was reduced in b, c, f, and g. In d, h, the pattern was almost normal.; Figures a, e: positive control group, Figures b, f: ALOVEtamer topical treatment group, Figures c, g: ALOVEtamer diet treatment group, Figures d, h: ALOVEtamer topical + diet treatment group.

IV. Discussion

ALOVEtamer was applied to the Nc/Nga mouse model induced with atopic dermatitis by HDM administration. ALOVEtamer is a nucleic acid ligand of *Aloe vera* designed to target compounds derived from *Vitis vinifera* extract. ALOVEtamer is a short PDRN or RNA strand that can bind to specific molecules of *Vitis vinifera* extract with high affinity and specificity, and performs antibody-like functions. ALOVEtamer has various biological and medical applications. In the future, ALOVEtamer targeting viniferin derivatives of *Vitis vinifera* extract as a Drug Delivery System (DDS) and Skin Delivery System (SDS) can be used for the treatment of specific diseases and cosmetics. For example, it can be utilized as a delivery system for drugs or active ingredients including natural compounds. Recently, our laboratory has studied aloe aptamer as a cosmetic material for atopic diseases through a preliminary study of aloe aptamer technology [6-8]. Viniferine (*Vitis vinifera* L.) has been reported to have a whitening effect that is 62 times more powerful than vitamin C and 13 times more powerful than arbutin as a cosmetic material, and prevents and brightens dark spots on the skin by inhibiting melanin production. In addition, it has a strong antioxidant effect (22 times that of quercetin, 28 times that of tocopherol), which helps prevent skin aging and maintain healthy, and in recent studies, it has been known as a material that improves wrinkles caused by aging and reduces atopic dermatitis by maintaining skin elasticity and suppressing skin damage and inflammation even when administered orally [15].

In this study, the efficacy of *Aloe vera* PDRN-based aptamer and *Vitis vinifera* viniferin was investigated in an atopic disease-induced mouse model. As a result of skin lesion score and histological analysis, ALOVEtamer topical + dietary therapy significantly alleviated skin lesions. Both ALOVEtamer topical therapy and ALOVEtamer dietary therapy Improved skin lesions. In contrast, the improvement of skin lesions was significantly lower in the ALOVEtamer diet. In this study, the skin lesion scores were similar to those of the positive control group, but histological analysis showed that skin lesions were improved compared to the control group. This difference in results may be due to the ratio of the aloe and viniferin extract dietary supplement. Therefore, further studies using a high ratio of ALOVEtamer derived from aloe and viniferin extracts will be needed to explain this difference in dietary effects. Nevertheless, our results showed that topical application together with dietary administration was more effective than dietary administration alone on skin lesions induced by atopic dermatitis. Atopic dermatitis is a biphasic chronic inflammatory skin disease with erythema, edema, excoriation, or lichenification. Atopic dermatitis is a Th2-type disease in which various immune cells infiltrate and stimulate B cells in the early stage. In the later stage, Th1 cytokines effectively promote cellular immune responses [16,17]. Among the antibody array containing 308 cytokines in the ALOVEtamer topical treatment group, only 27 cytokines were downregulated by more than 2-fold. The least downregulated was IFN-β, which has antiviral, antiproliferative, and immunomodulatory activities. In immune cells, IFN-β is naturally produced in the skin by dermal dendritic cells under biological or chemical stimulation [18]. The downregulated IFN-β in this study may be related to the decrease in dendritic cell numbers and immunomodulatory functions. On the other hand, few studies have been reported on IFN-β in relation to atopic diseases. Therefore, more studies are needed to prove the correlation between IFN-β and atopic diseases.

Many studies have reported high levels of IL-9 expression in atopic dermatitis [19,20]. Interestingly, although the lesions were alleviated in the local and dietary treatment groups, IL-9 was strongly expressed in the dietary treatment group and the local + dietary treatment group, except for the local treatment group. The types and expression levels of cytokines in each treatment group were identified using a serum cytokine antibody array. Furthermore, the activated biological processes and pathways could be identified. The overall expression of cytokines and biological processes and pathways when aloe aptamer or viniferin extract was applied to the AD-induced mouse model is unclear. GO is an ontology widely used in bioinformatics to annotate large-scale genes and gene products [21]. KEGG is a practical database resource for genome sequencing and high-molecular experimental techniques [22]. In this study, GO and KEGG were used to analyze biological gene functions and pathways related to biological systems.

V. Conclusion

This study investigated the efficacy of aloe aptamer and viniferin extract in an atopic disease-induced mouse model. The results confirmed that ALOVEtamer could improve lesions in an atopic disease-induced mouse model with HDM. Based on previous studies, this study is the first study to treat atopic disease and dermatitis by mixing aloe aptamer with a viniferin derivative. It is expected to be developed as an atopic skin disease treatment agent or a Nutrient Delivery System (NDS) and Transdermal Delivery System (TDS) after human clinical trials.

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