Retinaldehyde cyclodexrin complex for topical skin therapy

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Abstract
Retinaldehyde (retinal) has been identified as having superior topical activity, unrivaled topical bioavailability, and is less irritating than most other vitamin A derivatives. However, it has not received its deserved market attention possibly due to formulation-related issues. A novel compound, Retinaldehyde γ-Cyclodextrin Complex (RCC), has been developed to address the principal issues preventing retinaldehyde to enter the marketplace. Gene expression data of RCC have shown certain unique skin care attributes that are not present in retinaldehyde, including significantly less topical irritation.

Introduction
Retinaldehyde (Retinal) is gaining in popularity in anti-aging cosmetic products. It is well known that all forms of Vitamin A have positive effects for reducing fine lines and wrinkles of the face associated with skin aging [1]. The biology of skin aging process consists of two types; intrinsic or chronological aging, and photoaging. Retinoids have been popular for the treatment of skin aging and acne [2,3]. Amongst the retinoids, Tretinoin is possibly the most widely investigated retinoid for photoaging and acne treatments [4]. However, irritant reactions such as burning, scaling and/or dermatitis associated with retinoid therapy limit their acceptance by patients. This problem seems more prominent with Tretinoin and Tazarotene whereas retinaldehyde and retinol seem to be less irritating. Novel drug delivery systems have been developed to minimize these side effects. In particular, nanoparticles have shown good potential in improving the stability, tolerability and efficacy of retinoids [5]. However, nanoparticle have developed certain less favorable consumer attention for their potential safety issues. Retinaldehyde has shown to be unstable in typical cosmetic formulations. This intrinsic instability has posed problems in the inclusion of retinaldehyde and other retinoids in topical anti-aging products [6-8]. The approaches to retinal stability include certain Schiff’s bases with polylysine [9], retinaldehyde - hyaluronic acid fragments [10], and combinatorial treatments [11].

A novel compound, Retinaldehyde γ-Cyclodextrin Complex (RCC), has been developed to open retinaldehyde to wider applications in the marketplace [12]. RCC and related compounds are prepared by the reaction of a polyene aldehyde, such as retinal, with a cyclodextrin, such as γ-cyclodextrin [13].

Materials and methods
Chemical structure study

Structure 1: Retinaldehyde γ-cyclodextrin complex (RCC).

The mass spectra (ms) of RCC, purified via hplc, do not show a molecular ion. However, fragments at m/e 279, 285, 297, 299, and 371 arise from the fragmentation proposed in Figure 1. These fragments are not present in ms spectra of either γ-cyclodextrin or retinaldehyde.

Gene expression study
The objective of the study was to understand how a topical material influences gene expression in the skin. The current study [14] was conducted using a full thickness in vitro skin culture model (MatTek, Epiderm EFT-400). Two test materials, RCC powder, and a 99% pure form of crystalline retinaldehyde (retinal), were each diluted in 100% dimethylsulfoxide (DMSO) to a final retinaldehyde concentration of 0.1%. A 15-μL volume of each test material was applied to the surface of each test culture. Cultures treated with 15 μL of 100% DMSO served...
Figure 1. Mass Spectral Fragmentation of Retinaldehyde γ-Cyclodextrin Complex (RCC).
### Table 1. Gene-Expression Data.

| Gene ID | Gene Name                        | Retinol 0.5% | Retinol 0.10% | Retinaldehyde 0.10% | RCC 0.10% | Gene Function                                      |
|---------|----------------------------------|-------------|--------------|---------------------|----------|---------------------------------------------------|
| DSC1    | desmocollin                      | -11.89      | -2.38        | -6.97               | -12.36   | Extracellular matrix/Cell adhesion                |
| TNF     | tumor necrosis factor alpha      | n/a         | n/a          | -3.78               | -5.92    | Inflammatory response, Extracellular matrix breakdown |
| FLG     | epidermal filaggrin              | -2.35       | -0.47        | -3.64               | -5.60    | Barrier function                                  |
| LOR     | loricrin                         | n/a         | n/a          | -3.82               | -4.32    | Keratinocyte differentiation/Barrier function     |
| BMP4    | bone morphogenetic protein 4     | n/a         | n/a          | -2.16               | -3.39    | Whitening/Melanogenesis                           |
| DSG1    | desmoglein 1                     | -5.33       | -1.07        | -2.26               | -2.95    | Extracellular matrix, Cell adhesion/Barrier function |
| CDSN    | comeodesmosin                    | n/a         | n/a          | -2.57               | -2.74    | Barrier function                                  |
| PTGS2   | cyclooxygenase 2 (COX-2)         | 4.35        | 0.87         | n/a                 | -2.60    | Cytokine/Chemokine/Inflammatory response          |
| LIF     | leukemia inhibitor factor         | 10.93       | 2.19         | n/a                 | -2.45    | Inflammatory response                             |
| KRT1    | keratin 1                        | -6.30       | -1.26        | n/a                 | -2.30    | Keratinocyte differentiation                      |
| LCE3D   | late cornified envelope 3D       | n/a         | n/a          | -2.00               | -2.15    | Barrier function                                  |
| NGF     | nerve growth factor              | -7.97       | -1.59        | n/a                 | -2.06    | Inflammation/Collagen synthesis/Repair            |
| IL6     | interleukin 6                    | 3.18        | 0.64         | n/a                 | -2.04    | Cytokine/Chemokine/Inflammatory Response          |
| IL1A    | interleukin 1 alpha              | 3.76        | 0.75         | n/a                 | -2.02    | Cytokine/Chemokine/Inflammatory response          |
| IL8     | interleukin 8                    | 11.84       | 2.37         | n/a                 | -1.92    | Cytokine/Chemokine/Inflammatory response          |
| MMP1    | matrix metalloproteinase 1/collagenase | n/a       | n/a          | n/a                 | -1.82    | Extracellular matrix breakdown                    |
| TGM1    | transglutaminase                 | n/a         | n/a          | n/a                 | -1.70    | Keratinization/Barrier function                   |
| BMP2    | bone morphogenetic protein 2     | 4.44        | 0.89         | n/a                 | -1.69    | Whitening/Melanogenesis                           |
| HMOX1   | hemeoxygenase 1                  | n/a         | n/a          | 2.12                | -1.49    | Anti-oxidant/Oxidative Stress                     |
| VEGFA   | vascular endothelial growth factor A | n/a       | n/a          | n/a                 | -1.47    | Growth factor/Cell proliferation/ Wound healing    |
| MITF    | microphthalmia-associated transcrption factor | -1.85    | -0.37        | n/a                 | -1.46    | Whitening/Melanogenesis                           |
| DSG3    | desmoglein 3                     | 1.99        | 0.40         | 1.92                | 1.68     | Extracellular matrix, Cell adhesion/Barrier function |
| KLK8    | kallikrein 8                     | n/a         | n/a          | 2.13                | 1.88     | Desquamation/Extracellular matrix breakdown       |
| ITGB4   | b4 integrin                      | n/a         | n/a          | n/a                 | 1.89     | Cell adhesion/Barrier function                    |
| KLK5    | kallikrein 5                     | n/a         | n/a          | n/a                 | 1.96     | Desquamation                                      |
| TGFBI   | transforming growth factor beta 1 | 2.04        | 0.41         | 2.20                | 2.17     | Extracellular matrix integrity, Cell adhesion/Barrier function |
| TP65    | tumor protein p65; tp73-like     | -1.41       | -0.28        | n/a                 | 2.22     | Cell cycle/proliferation                          |
| GSTT1   | glutathione S transferase theta 1| n/a         | n/a          | n/a                 | 2.44     | Anti-oxidant/Oxidative Stress                     |
| KLK7    | kallikrein 7                     | 1.62        | 0.32         | 3.13                | 3.02     | Desquamation/Extracellular matrix breakdown       |
| AQP3    | aquaporin 3                      | n/a         | n/a          | 4.85                | 5.96     | Keratinocyte proliferation, Differentiation, Hydration |
| CLDN7   | claudin 7                        | 7.04        | 1.41         | 7.79                | 9.29     | Barrier function                                  |
| KLK6    | kallikrein 6                     | 13.49       | 2.70         | 11.28               | 12.99    | Inflammation/Barrier function, Extracellular matrix breakdown |
| AQP10   | aquaporin 10                     | -96.92      | -19.38       | n/a                 | n/a      | Hydration                                          |
| AQP7    | aquaporin 7                      | -88.08      | -17.62       | n/a                 | n/a      | Hydration                                          |
| CAT     | catalase                         | -2.34       | -0.47        | n/a                 | n/a      | Anti-oxidant/Oxidative Stress                     |
| CLDN1   | claudin 1                        | -1.74       | -0.55        | n/a                 | n/a      | Barrier function                                  |
| COL4A1  | collagenn IV a1                  | 1.87        | 0.37         | n/a                 | n/a      | This gene encodes type IV alpha collagen chain    |
| FGF2    |                                  | 1.92        | 0.38         | n/a                 | n/a      | Regulation of cell survival, cell division, angiogenesis, cell differentiation and cell migration |
as the control group. Cultures were collected 24 hours post-application for gene expression analysis.

Gene expression was analyzed using validated Taqman gene expression assays in the Taqman Low Density Array (TLDA) format. Analysis was carried out using the Genemarkers Standard Skin Panel, which contains assays for 92 target genes and four endogenous control genes. One additional target gene, HSP47, was assayed using a 96-well format. All genes in both formats were assayed in duplicate. A summary of the genes with statistically significant FC values is shown in Table 1. Negative values indicate decreased gene expression (down-regulation) and positive values indicate increased gene expression (up-regulation). RNA yield and quality was ensured using qPCR metrics based on up/down regulation of genes. NA=fold-change values were not greater than or equal to 2.0. Changes in gene expression greater than or equal to 2.0 are reported as linear fold change differences.

### Exceptional Results

The gene-expression data (Table 1) clearly indicate RCC provides a topical method of treating, reducing the occurrence of, or improving the symptoms associated with melanogenesis, oxidative damage, inflammation, skin irritation from inflammation, loss of cell adhesion, loss of desquamation, extra-cellular including connective tissue matrix breakdown and skin tone loss thereof, loss of keratinization, cellular senescence, skin aging from cellular senescence, loss of skin whiteness, loss of skin barrier function, loss of skin firmness, inflammation from rosacea, skin disfigurements and skin discoloration from rosacea, inflammation from acne, skin wrinkles and fine lines from cellular senescence, cellular oxidation, loss of skin barrier function, loss of skin firmness, inflammation from rosacea, skin disfigurements and skin discoloration from rosacea, inflammation from acne, skin wrinkles and fine lines from cellular senescence, cellular oxidation, loss of skin barrier function, loss of skin firmness, inflammation from rosacea, skin disfigurements and skin discoloration from rosacea, inflammation from acne, skin wrinkles and fine lines from cellular senescence, cellular oxidation, loss of skin barrier function, loss of skin firmness, inflammation from rosacea, skin disfigurements and skin discoloration from rosacea, inflammation from acne, skin wrinkles and fine lines from cellular senescence, cellular oxidation, loss of skin collagen, and topical wounds.

### Conclusion

Retinaldehyde γ-Cyclodextrin Complex (RCC) now provides marketing opportunities for high-performance cosmetics that wish to utilize retinaldehyde into their line-up with unprecedented skin care attributes.

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