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Retinaldehyde cyclodextrin 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.

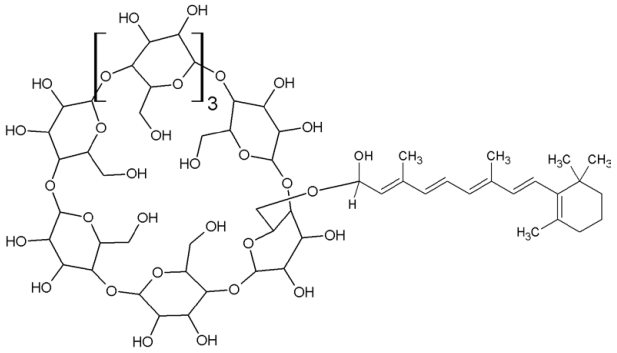
Introduction

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 is 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

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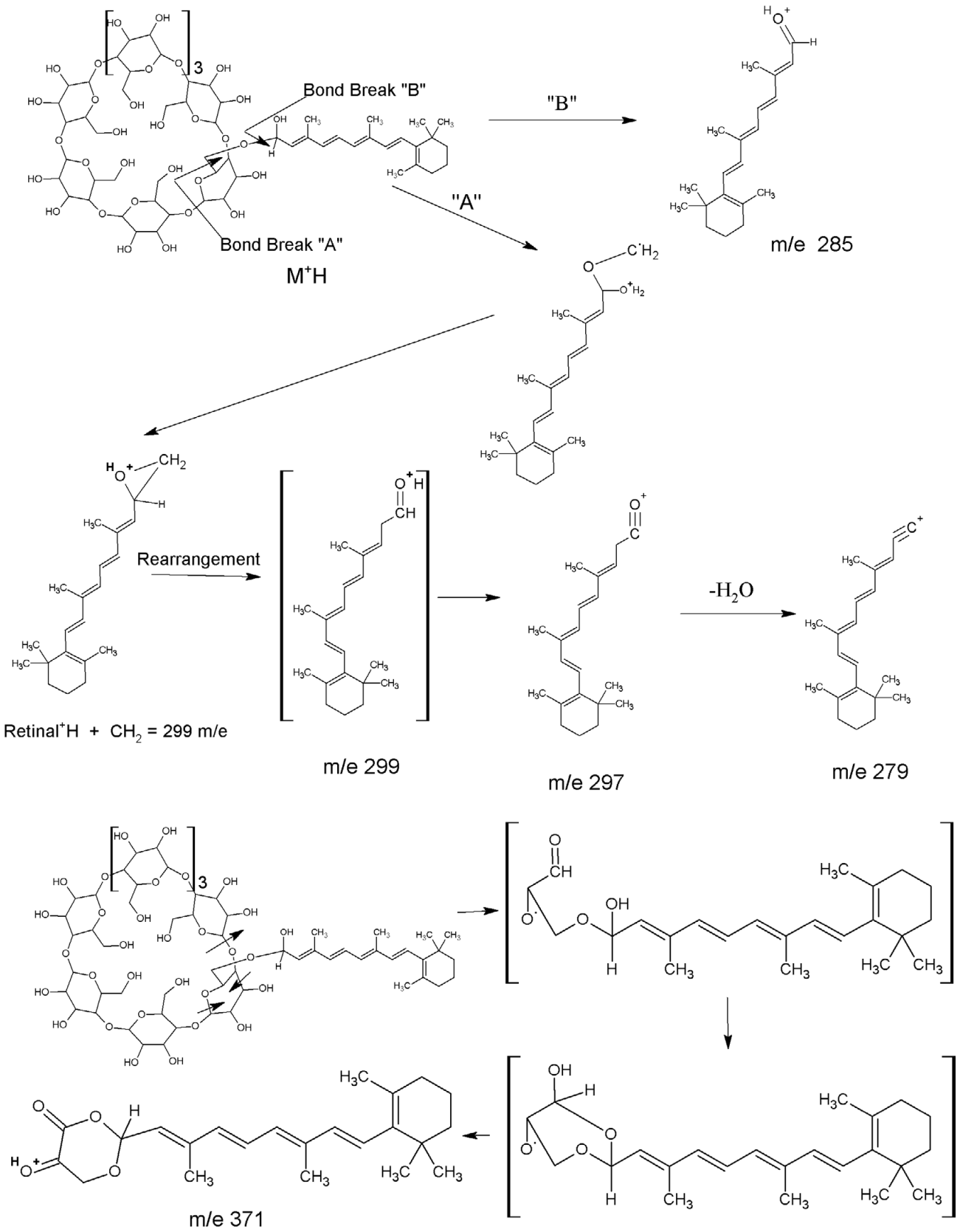

Figure 1. Mass Spectral Fragmentation of Retinaldehyde γ-Cyclodextrin Complex (RCC).

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	corneodesmosin	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 metallopeptidase 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	micropthalmia-associated transcription 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 breakdwon
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
TGFB1	transforming growth factor beta 1	2.04	0.41	2.20	2.17	Extracellular matrix intergrity, Cell adhesion/Barrier function
TP63	tumor protein p63; 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 breakdwon
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	-0.35	n/a	n/a	Barrier function
COL4A1	collagen 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, celldifferentiation and cell migration

HBEGF	heparin-binding EGF-like growth factor	7.73	1.55	1.90	n/a	Growth factor/Keratinocyte migration
IL1B	interleukin 1 beta	9.95	1.99	2.39	n/a	Cytokine/Chemokine/Inflammatory response
ITGB1	b1 integrin/Fibronectin 1 receptor	n/a	n/a	1.59	n/a	Cell adhesion/Barrier function
IVL		2.49	0.50	n/a	n/a	Component of keratinocyte crosslinked envelope
KRT10		-6.84	-1.37	n/a	n/a	This gene encodes a member of the type I cytokeratin family
KRT5		-3.03	-0.61	n/a	n/a	This type II cytokeratin is in the basal layer of the epidermis
MC1R		-2.12	-0.42	n/a	n/a	This gene encodes the receptor protein for melanocyte-stimulating hormone (MSH).
MKI67		-2.28	-0.46	n/a	n/a	This gene encodes a nuclear protein necessary for cellular proliferation
MMP3		2.85	0.57	n/a	n/a	This gene encodes an enzyme which degrades fibronectin, laminin, collagens III, IV, IX, and X, and cartilage proteoglycans
MT2A		2.76	0.55	n/a	n/a	MT2A (metallothionein 2A) is a protein-coding gene that bind various heavy metals
PCNA		-2.38	-0.48	n/a	n/a	Auxiliary protein of DNA polymerase delta involved in the control of eukaryotic DNA replication
PKP1		-2.04	-0.41	n/a	n/a	Plakophilin proteins involved in molecular recruitment and stabilization during desmosome formation
TNC	tenascin C	n/a	n/a	-1.73	n/a	Extracellular matrix
TP73		-2.85	-0.57	n/a	n/a	Participates in the apoptotic response to DNA damage.
TXN	thioredoxin	n/a	n/a	2.12	n/a	Anti-oxidant/Oxidative Stress
TXNRD1	thioredoxinreductase 1	1.96	0.39	3.80	n/a	Anti-oxidant/Oxidative Stress
VCAN		-2.07	-0.41	n/a	n/a	This gene is involved in cell adhesion, proliferation, proliferation, migration and angiogenesis

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 between test material and control groups (paired t-tests, $p \leq 0.05$, N=4).

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 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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