Vincience

Quintescine

PATENT PENDING

Quintescine

Antioxidant Peptide

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Quintescine

Presentation

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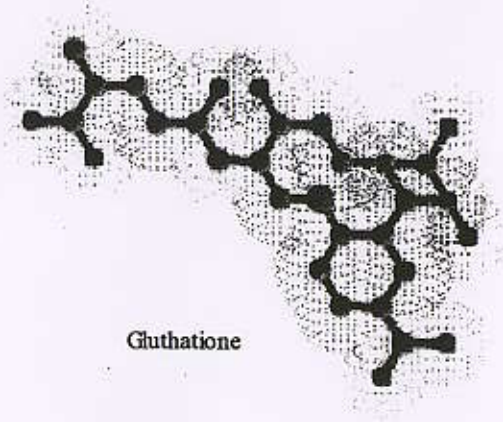
Quintescine is a dipeptide (Cys-Gly) whose structure is very close to glutathione, a natural tripeptide (Gly-Glu-Cys) with strong cellular antioxidant properties.



Quintescine exhibits remarkable antioxidant properties:

- It reinforces the activity of Cu/Zn SOD and catalase, thus favoring the elimination of Reactive Oxygen Species (ROS),
- It decreases protein carbonylation and DNA damage, while increasing cell viability.

Quintescine operates on a succession of cellular antioxidant mechanisms, offering thus a genuine physiological protection, likely increasing skin comfort and preventing premature aging.

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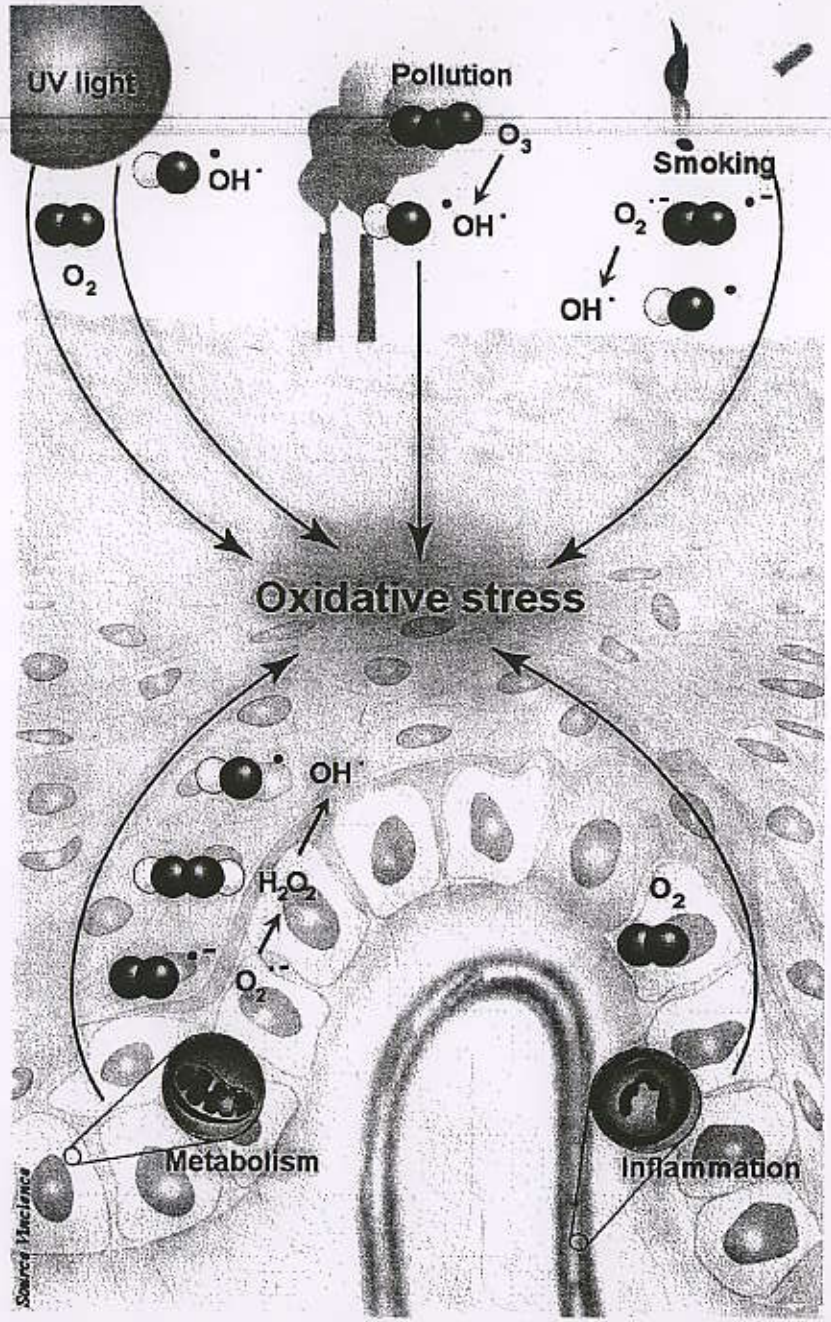
The world of Reactive Oxygen Species

ROS are generated either by the environment (UV, smoke, pollution, etc.) or by normal cellular functioning (mitochondrial metabolism and immune activation).

ROS include the free radicals superoxide ($O_2^{\cdot -}$) and hydroxyl ($OH^{\cdot}$), and non radical oxygen species such as hydrogen peroxide (H_2O_2).

The skin is a primary target for oxidative damage induced by ROS.



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ROS and cellular homeostasis

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Cellular homeostasis reflects a balance between the production of ROS, and their destruction by endogenous systems of protection. Oxidative damages occur when this equilibrium is disrupted.

The frequent exposure to UV, smoke or other factors of oxidative stress increases ROS production, disrupting the balance and leading to cell damages and skin disorders.

Moreover, a common feature of aging is a progressive decline in the ability to provide an efficient ROS protection, another factor of imbalance leading to acute cell damages and chronic skin disorders.

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Cellular oxidative damages

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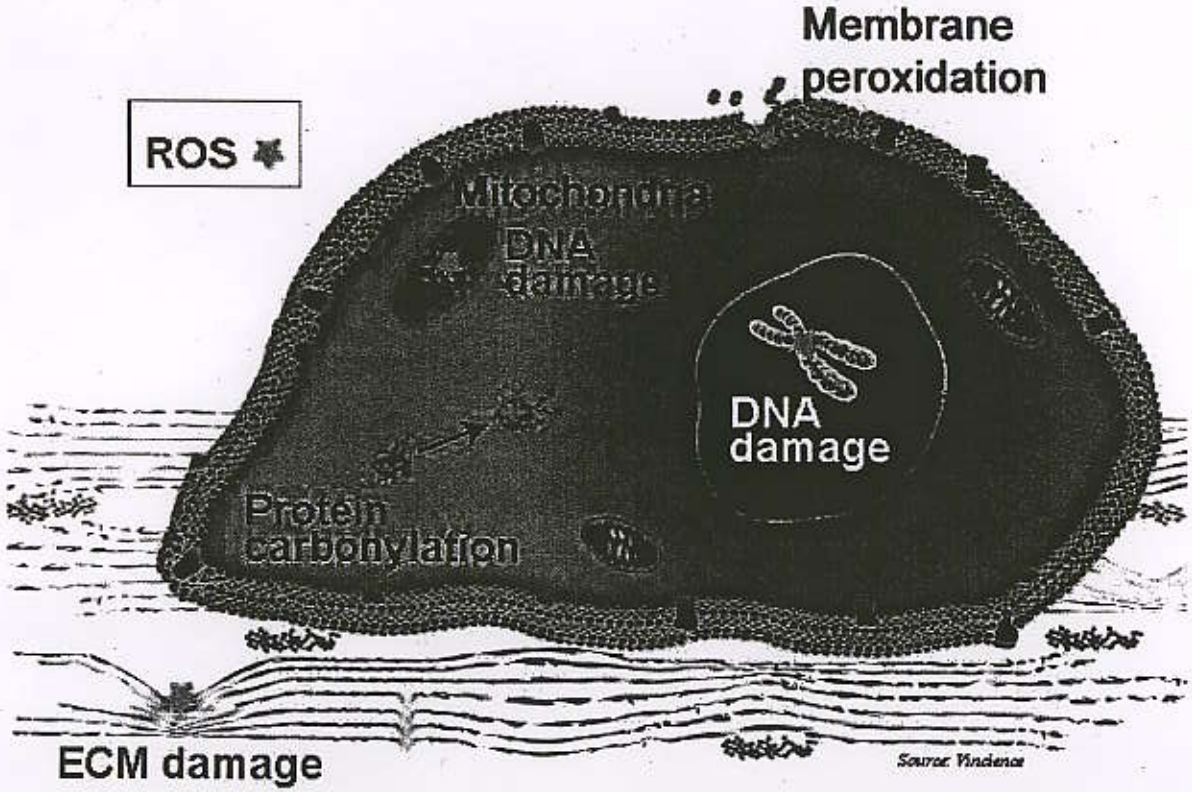
Non-regulated accumulation of ROS results in oxidative damages that include DNA damage, protein oxidation, such as the generation of protein carbonyl derivatives, and membrane peroxidation.



Repeated oxidative damages can greatly impair cell functions and tissue integrity, leading to increased sensitivity and premature aging.

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SOD and catalase: antioxidant enzymes

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The endogenous protection from oxidative stress is ensured by non-enzymatic antioxidant systems (eg vitamins) and by antioxidant enzymes, such as SODs (superoxide dismutases) and catalase.

$$O_2^{\cdot -} + O_2^{\cdot -} \xrightarrow[\text{dismutation}]{\text{SOD}\ Zn^{++}, Cu^{++}} H_2O_2 + O_2 \xrightarrow{\text{Catalase}} H_2O + O_2$$

superoxide radicals — oxygen peroxide — oxygen — water — oxygen

SOD and catalase are centrally involved in the protection of the skin from UV-oxidative stress, and thereby, in the aging process of the skin.

In case of increased ROS generation, SODs and catalase may be overwhelmed, resulting in oxidative stress.

Quintescine reinforces the skin natural antioxidant enzymes by increasing Cu/Zn SOD and catalase activity.

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Protein oxidation: carbonylation

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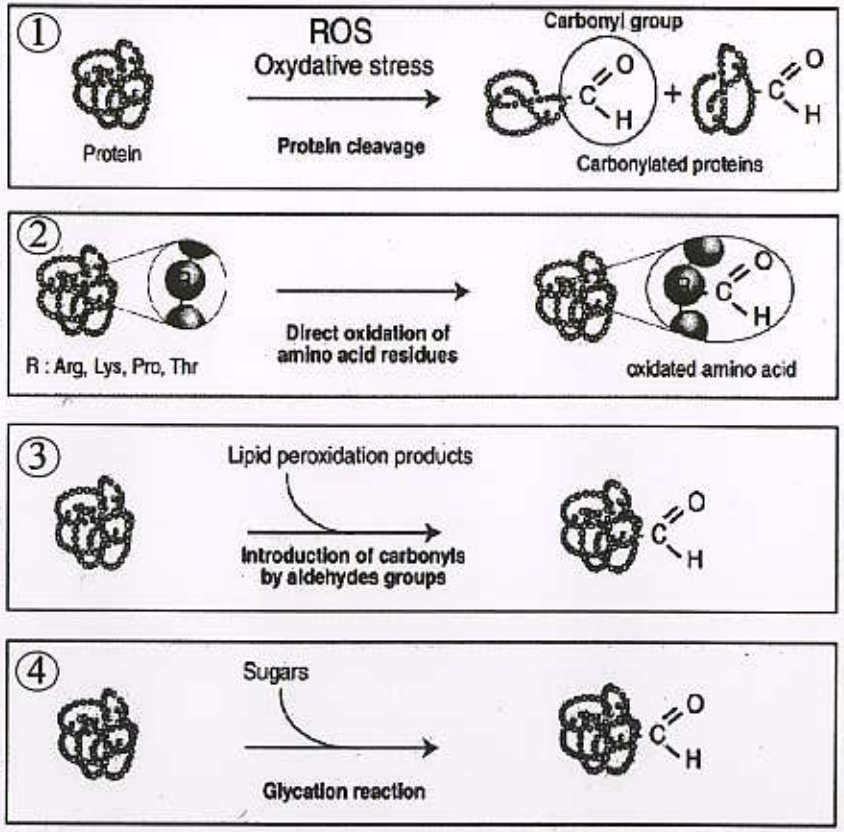
Proteins are important targets for oxidative modifications. ROS cause modifications of the amino acids of the proteins that result in functional changes of structural or functional proteins.

Protein carbonyls may be formed by:

1. Oxidative cleavage of proteins,
2. Direct oxidation of lysine, arginine, proline and threonine residues,
3. Carbonyls groups may be introduced into proteins by reactions with aldehydes produced by lipid peroxidation,
4. Interaction with reactive carbonyls derivatives generated as a consequence of glycation reactions.



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Quintescine increases Cu/Zn SOD expression level

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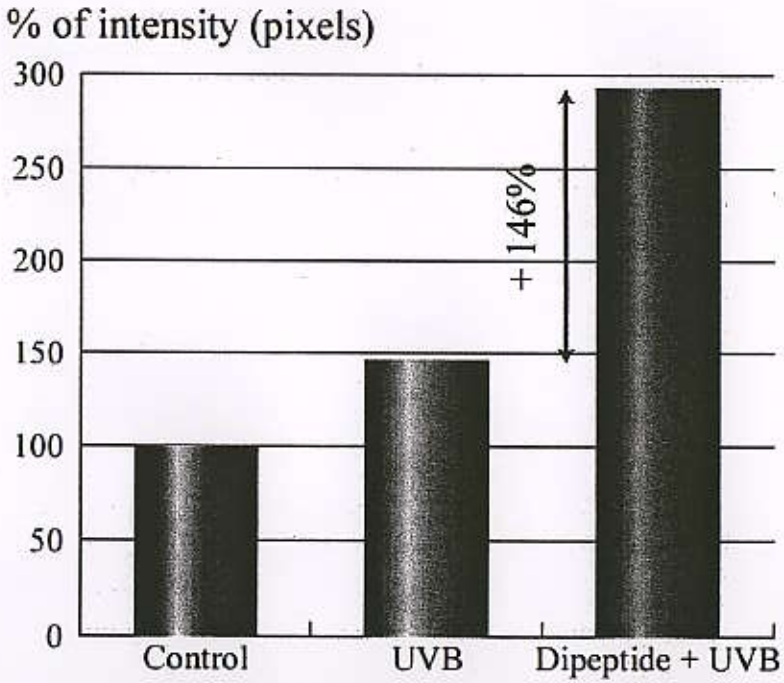
Cell culture: human fibroblasts
Dose: Quintescine 1%
Application time: 24 h prior and during UV exposure
UVB stress: 100 mJ/cm^2



Quantitative analysis of electrophoresis results show that Quintescine increases by 146% Cu/Zn SOD expression in UV-stressed cells, compared to untreated and UV-stressed cells.

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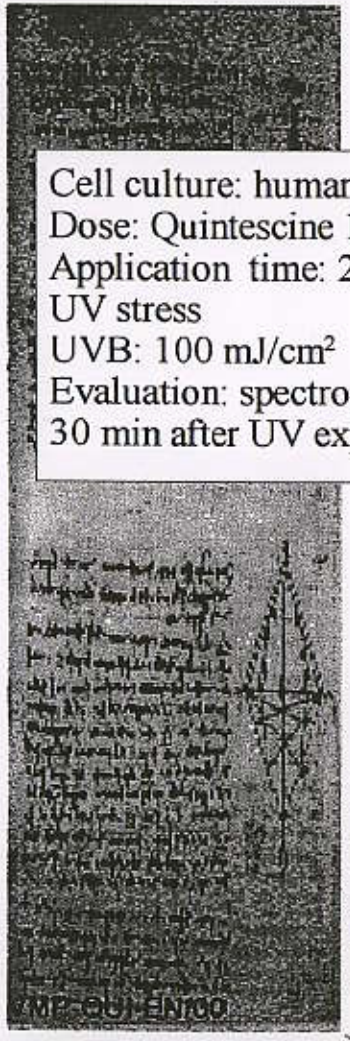
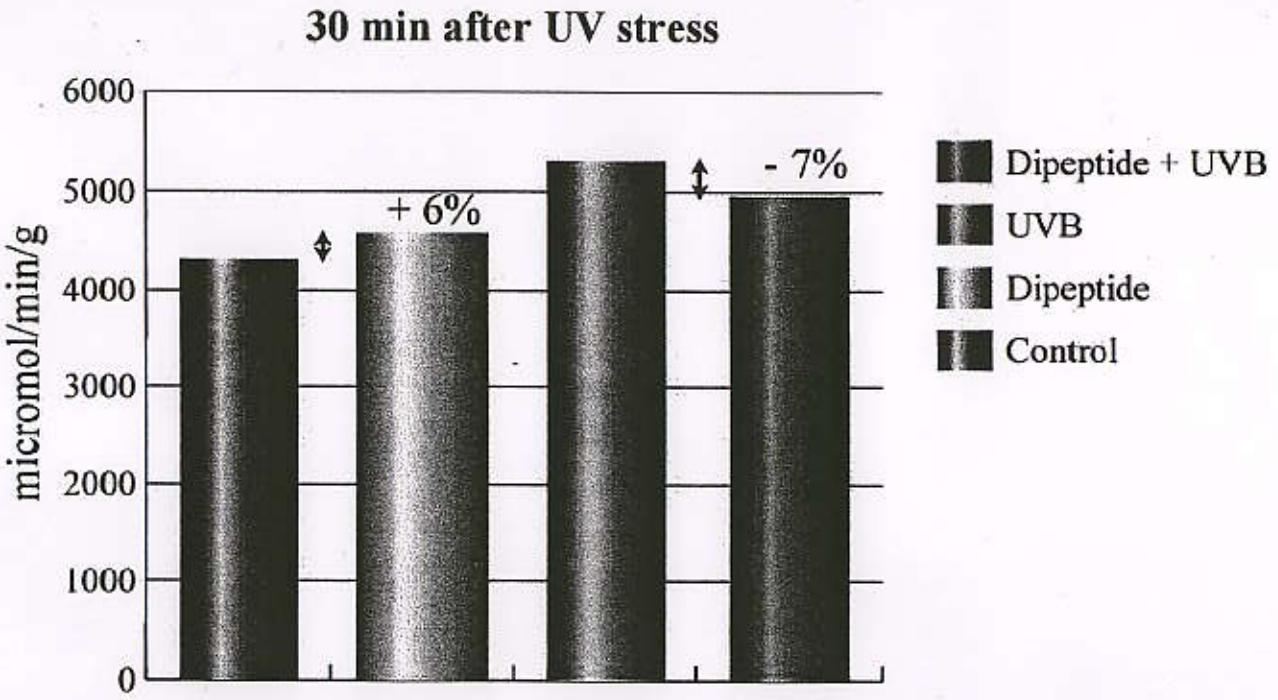
Quintescine enhances catalase expression

PATENT PENDING



Cell culture: human fibroblasts
Dose: Quintescine 1%
Application time: 24 h prior UV stress
UVB: 100 mJ/cm²
Evaluation: spectrophotometer 30 min after UV exposure



Quintescine increases catalase expression in unirradiated cells. When the cells are submitted to UV stress, they exhibit a moderate increase in catalase level, since they have already been prepared with a higher level of protective catalase activity.

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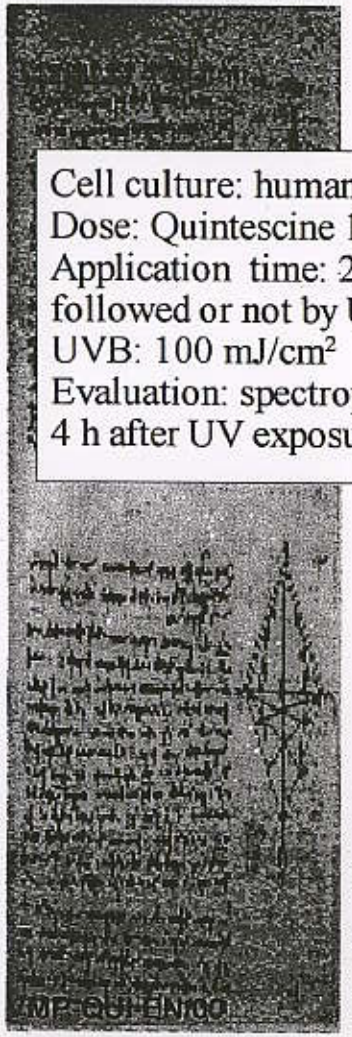
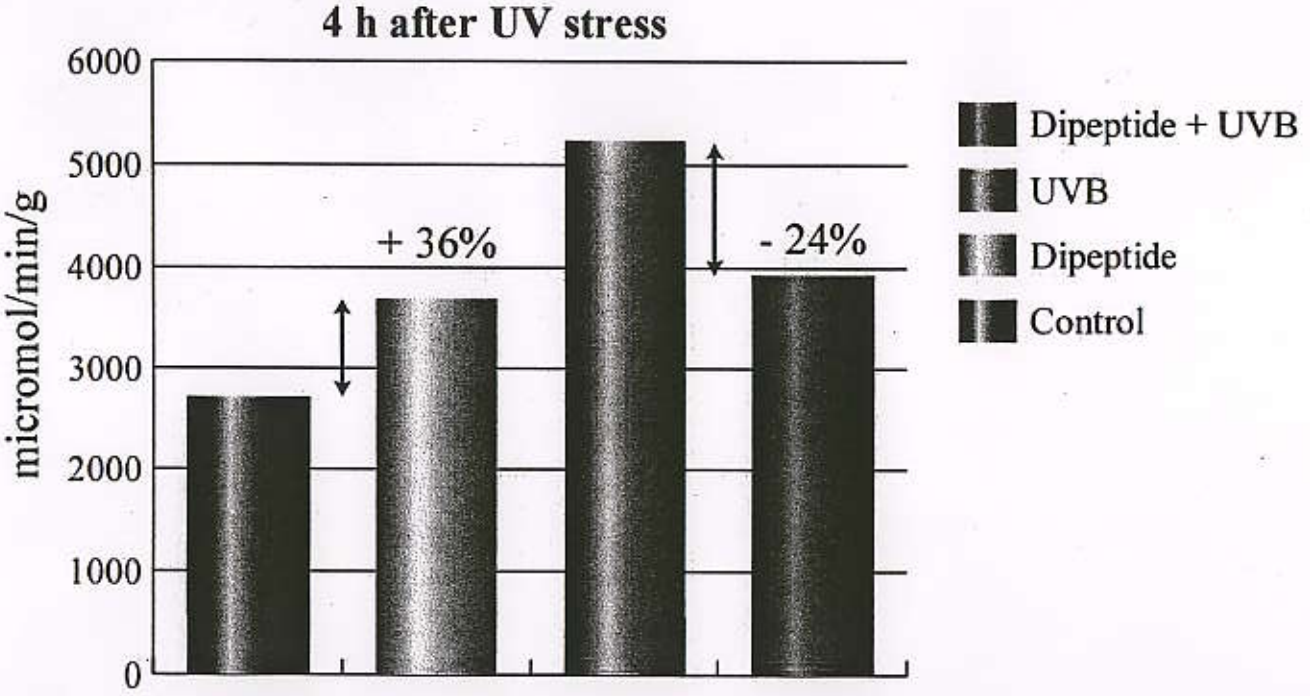
Quintescine enhances catalase expression

PATENT PENDING



Cell culture: human fibroblasts
Dose: Quintescine 1%
Application time: 24 h
followed or not by UV stress
UVB: 100 mJ/cm²
Evaluation: spectrophotometer
4 h after UV exposure



These results confirm our prior results: Quintescine increases catalase level in unirradiated cells, and better prepares cell to face stress. The effect is more prominent at 4 h, suggesting a time-dependent effect.

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Quintescine increases cell viability

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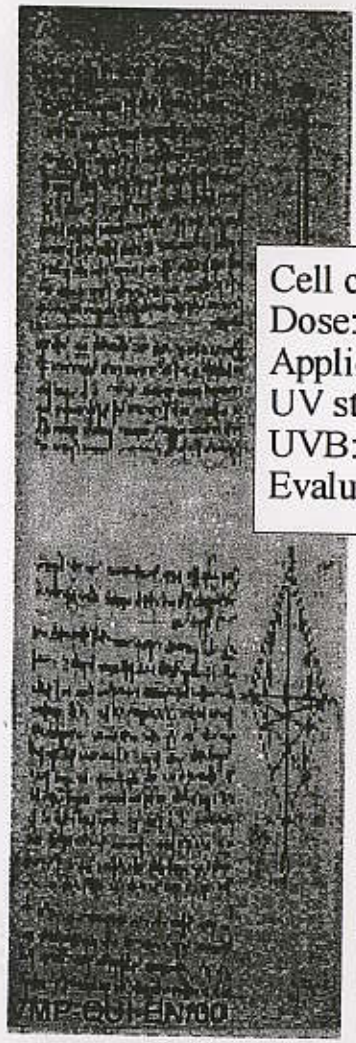
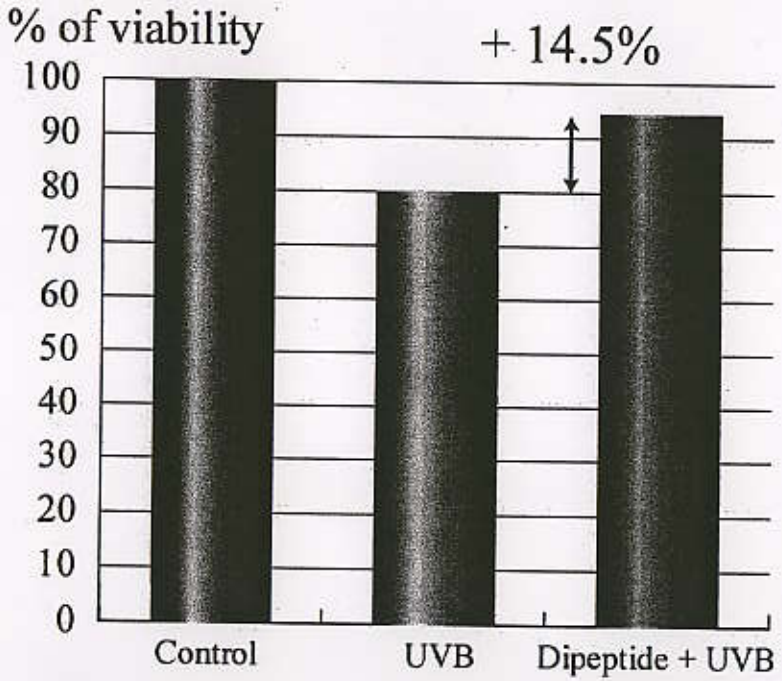


Cell culture: human fibroblasts
Dose: Quintescine 1%
Application time: 24 h prior
UV stress
UVB: 100 mJ/cm²
Evaluation: MTT test



The results show that Quintescine enhances cell viability by 14.5% in UV-irradiated cells, which suggests that Quintescine-treated cells are better armed against UV-oxidative stress.

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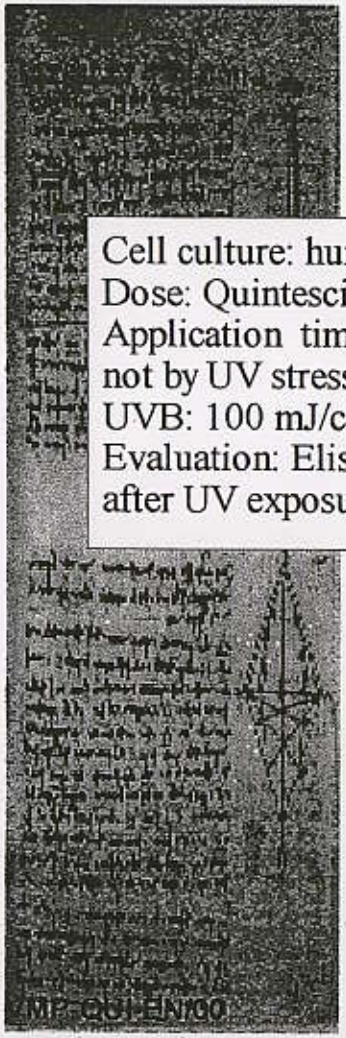
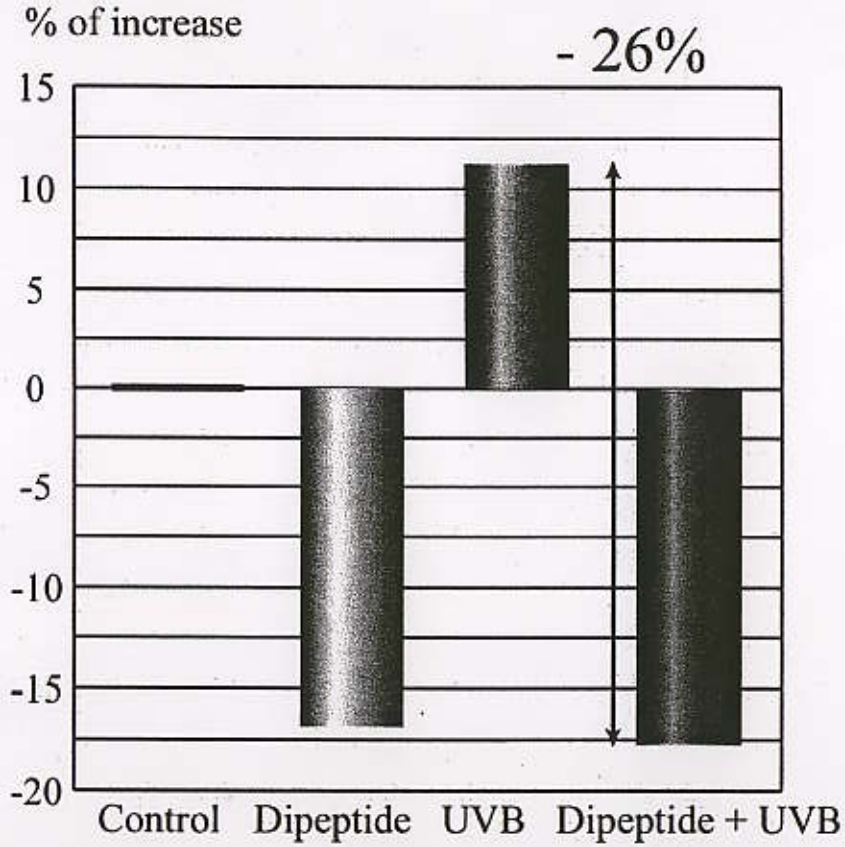
Effect of Quintescine on protein carbonylation immediately after UV exposure

PATENT PENDING



Cell culture: human fibroblasts
Dose: Quintescine 1%
Application time: 24 h followed or not by UV stress
UVB: 100 mJ/cm²
Evaluation: Elisa assay immediately after UV exposure



Quintescine decreases UV-induced carbonyl formation by -26% compared to untreated and irradiated cells.

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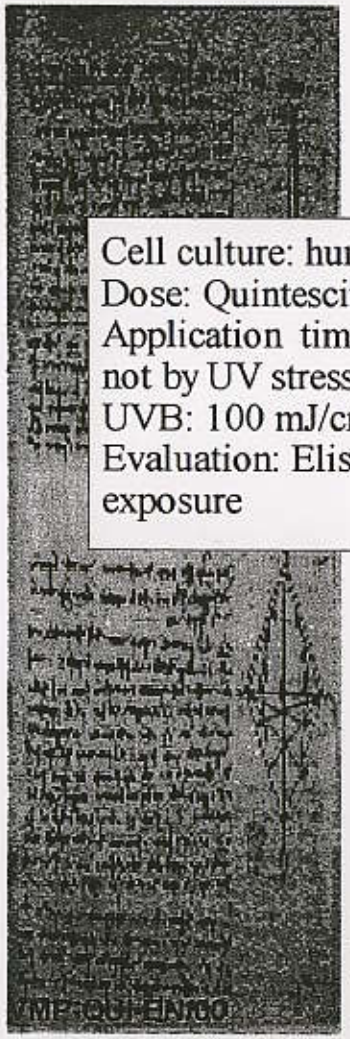
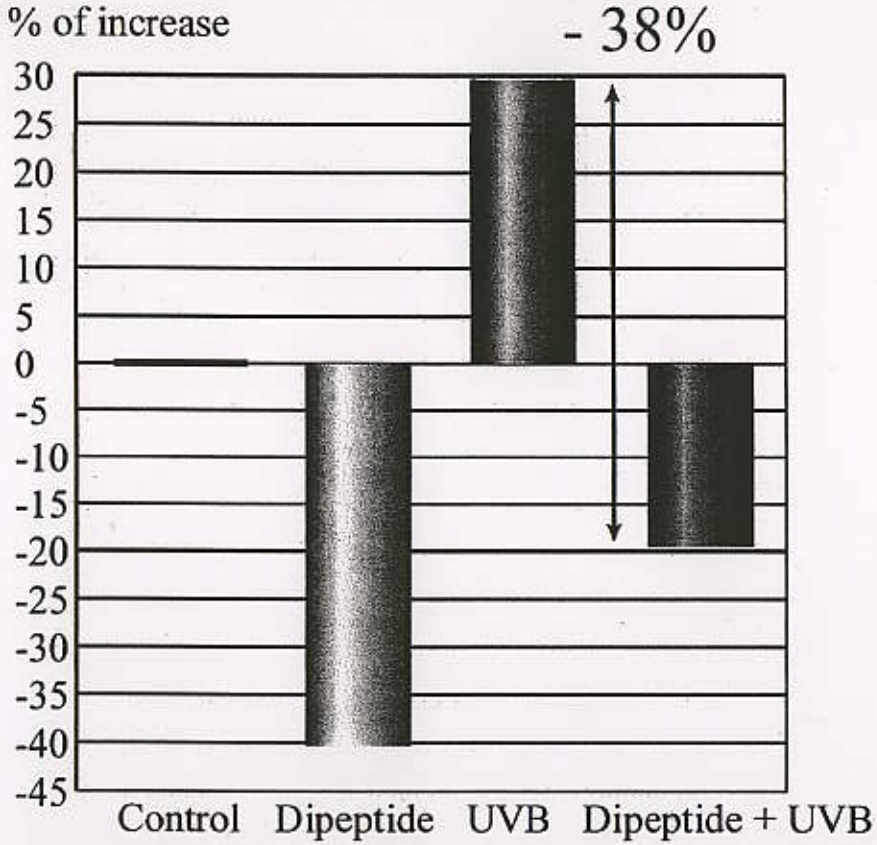
Effect of Quintescine on protein carbonylation 4 h after UV exposure

PATENT PENDING



Cell culture: human fibroblasts
Dose: Quintescine 1%
Application time: 24 h followed or not by UV stress
UVB: 100 mJ/cm²
Evaluation: Elisa assay 4 h after UV exposure



Quintescine decreases protein carbonylation and these results are more significant 4 h after UV stress (-38%), which confirms our prior results.

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Quintescine

Cosmetic applications

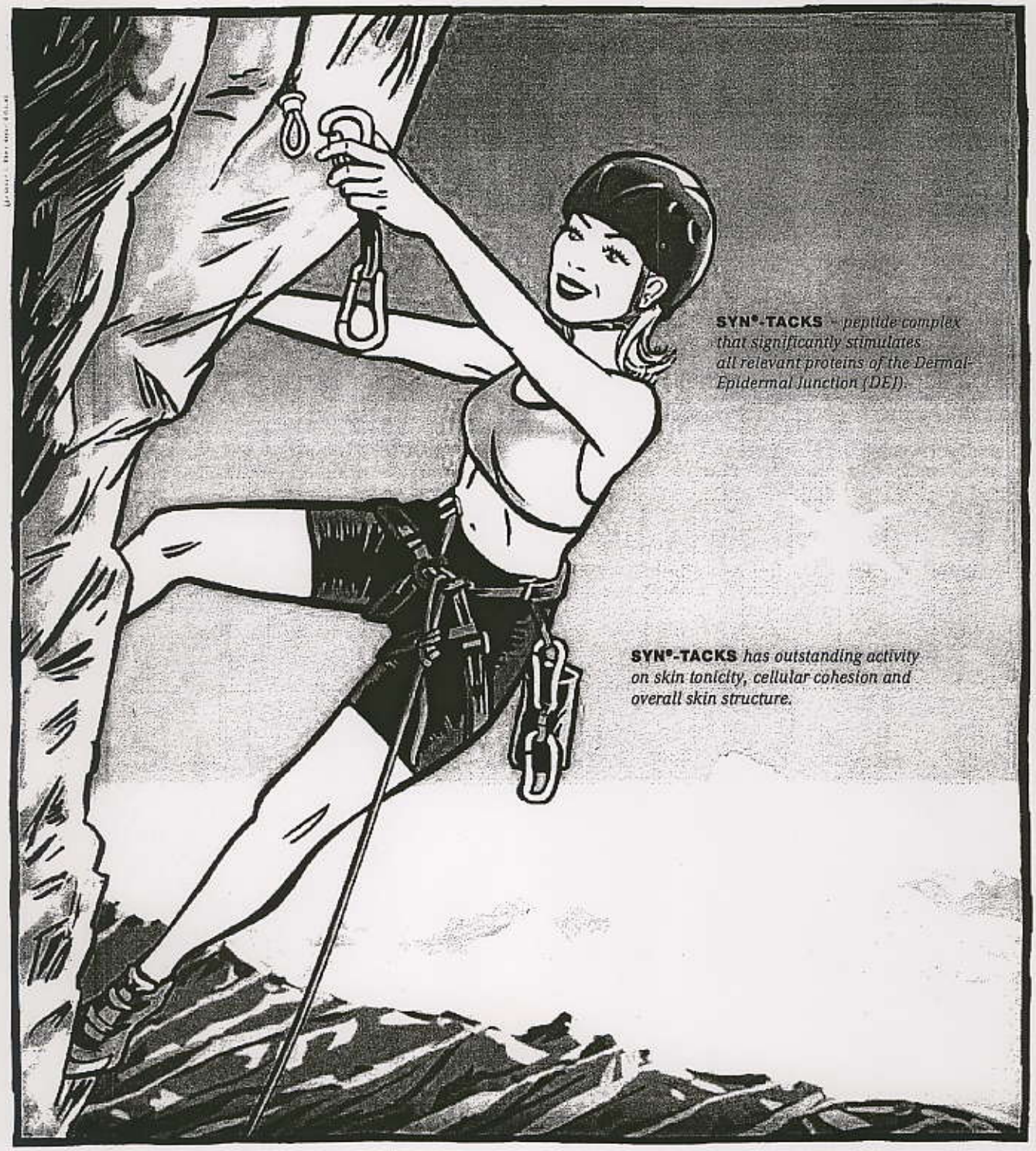
PATENT PENDING

Quintescine is a peptide with strong antioxidant properties:

- A common feature of modern life is the frequent exposure of the skin to ROS generated by UV, pollution, toxins, etc. Quintescine is perfectly adapted to day care products, and specifically, to anti-pollution, anti-stress products, etc.
- As chronic and acute photodamage is mediated by depleted antioxidant enzyme expression, Quintescine is a central ingredient to antiage products.
- As ROS are involved in inflammatory skin disorders, Quintescine is likely to alleviate sensitive skins.
- Melanocyte DNA is also a target to UV-oxidative stress, and therefore, Quintescine may help treat skin pigmentation disorders.
- Quintescine is also adapted to suncare products to reinforce antioxidant defenses and fight UV-oxidative stress.

Recommended percentages: 1%

SYN®-TACKS *organizes your Dermal-Epidermal Junction (DEJ) to reach the "top of beauty".*



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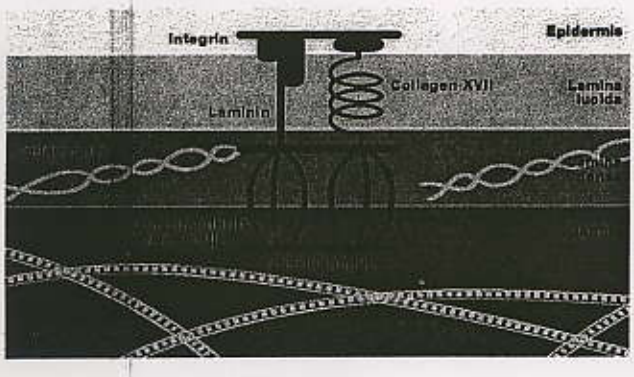
SYN®-TACKS

Helping skin to behave in a healthy way is the major target of cosmetic research. However, traditional approaches to skin aging appear today to be incomplete, particularly considering changes occurring at the dermal-epidermal junction (DEJ) and the evaluation of the changes of key proteins therein. The functionality of the DEJ that provides structural and functional integrity to the skin starts to change at around the age of 30. This process goes along, and is even accelerated by external influences such as UV light, with decreasing skin compactness, elasticity and a lack of skin firmness.

Mature skin → DEJ even → wrinkles, less elasticity and firmness

Properties:

SYN®-TACKS, the combination of two peptides offers for the first time the possibility to interact with the most relevant protein structures of the dermal-epidermal junction (DEJ). **SYN®-TACKS** significantly stimulates Laminin V, Collagen type IV, VII and XVII and Integrin at once. Only by this broad spectrum activity it is guaranteed to achieve the utmost structural benefit for the skin. By increasing the activity of these proteins the whole structure of the DEJ is improved. This finally leads to a visible cosmetic benefit.



Function of SYN®-TACKS:

- improved structural integrity
- improved epidermal nourishment
- improved molecular communication within the skin

this leads to:

- improved skin compactness
- reduced wrinkles
- increased skin tonicity
- increased skin firmness

Cosmetic application:

- Skin compactness and skin restructuring treatments
- Anti aging cure and anti wrinkle products
- Skin protecting elixir and sun-care lines
- Barrier function and skin repair treatments

Formulations:

SYN®-TACKS is offered as a glycerine-based aqueous solution that can easily be incorporated into the aqueous phase of a formulation even at elevated temperatures up to 80°C.

Suggested concentration:

For skin care preparations, we recommend the addition of 1% **SYN®-TACKS**.

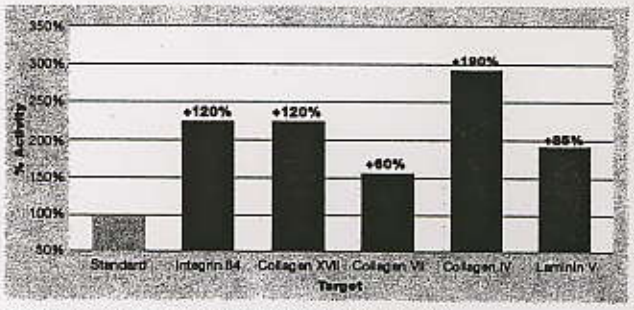
INCI name:

Glycerin, Palmitoyl Dipeptide-5 Diaminobutyloyl Hydroxythreonine, Palmitoyl Dipeptide-6 Diaminohydroxybutyrate

Efficacy tests:

In vitro tests:

Stimulation of the relevant DEJ proteins by Palm-Lys-Val-Dab-Thr (50 µM, in red) and Palm-Lys-Val-Dab (100 µM, in orange).

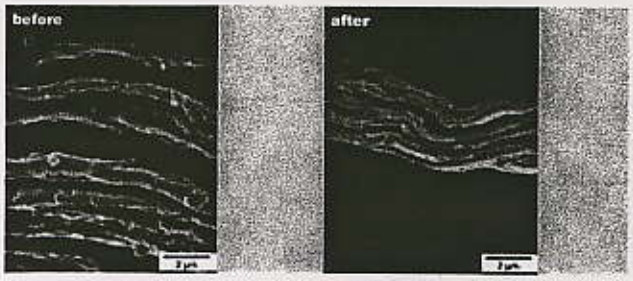


All tested proteins are significantly up-regulated.

In vivo tests:

In various clinical studies the product has been tested at a 1% level. Measurements have been performed either at day 56 or day 84 depending on the protocol.

*Macro photograph of a 45 year old volunteer after 56 days of treatment with 1% **SYN®-TACKS**.*



*Scanning Electron microscopy of the epidermis (tape strips) of a 62 year old volunteer after 84 days of treatment with 1% **SYN®-TACKS**.*

Summary of clinical investigation

- **SYN®-TACKS** improves after only two months skin tonicity by **32%**.
- **SYN®-TACKS** improves skin anisotropy up to **62%**.
- **SYN®-TACKS** improves cellular cohesion up to **23%**.
- Scanning electron microscopy shows a significant skin benefit.
- Macro photographs show the benefit of using **SYN®-TACKS**.
- **SYN®-TACKS** got excellent ratings in the evaluation questionnaire, **87%** would purchase the product again.

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Presents

NATURAL AMINO ACID

"TORCH OF LIFE"*
SUPPLIER AND PROTECTOR

THIOTAINE

AGI Dermatics

*Torch of Life terminology first used by Lavoisier, 1789)

INTRODUCTION - MITOCHONDRIA, OXYGEN, ENERGY & WELL-BEING

1. Oxygen/ATP in Mitochondria
2. DNA in Mitochondria
3. UV-A and UV-B and Aging
4. Thiotaine - Natural Amino Acid

PART ONE: Energy in Mitochondrias

PART TWO: Thiotaine is an Anti-Oxidant

1. Role as an Anti-Oxidant in UV-A Attack
    a) Quenching Activity against O_2^-
    b) MMP-1 mRNA Expression

2. Role as an Anti-Oxidant in UV-B Attack
    a) Scavenging Ability Against O_2^-
    b) TNF-Alpha Expression by UV-B Irradiation

PART THREE: Thiotaine, as a Clarifier

SPECIFICATIONS

MATERIAL SAFETY DATA SHEET

BIBLIOGRAPHY

INTRODUCTION: MITOCHONDRIA, OXYGEN, ENERGY AND WELL-BEING

1. Oxygen/ATP in Mitochondria

Energy is the moving force of life. It is a fundamental and indispensible element in cellular activity. All cells must produce energy to survive, and oxygen consumption is fundamental to the process. Lavoisier understood this in 1789, and dubbed mitochondria the "torch of life."

In our daily life we associate oxygen with "outdoor activity." We go to the mountains for fresh air. In trendy shopping areas we can visit oxygen bars. Oxygen is associated with health, with looking and feeling good.

It is also known that Olympic long-distance runners train in the mountains to increase the oxygen levels in their blood to help give them a competitive edge. Respiration also takes place in the body, not only in the lungs. At the cell level the energy is made by hundreds to thousands of mitochondria per cell (Figure 1), the powerhouse of the cells.

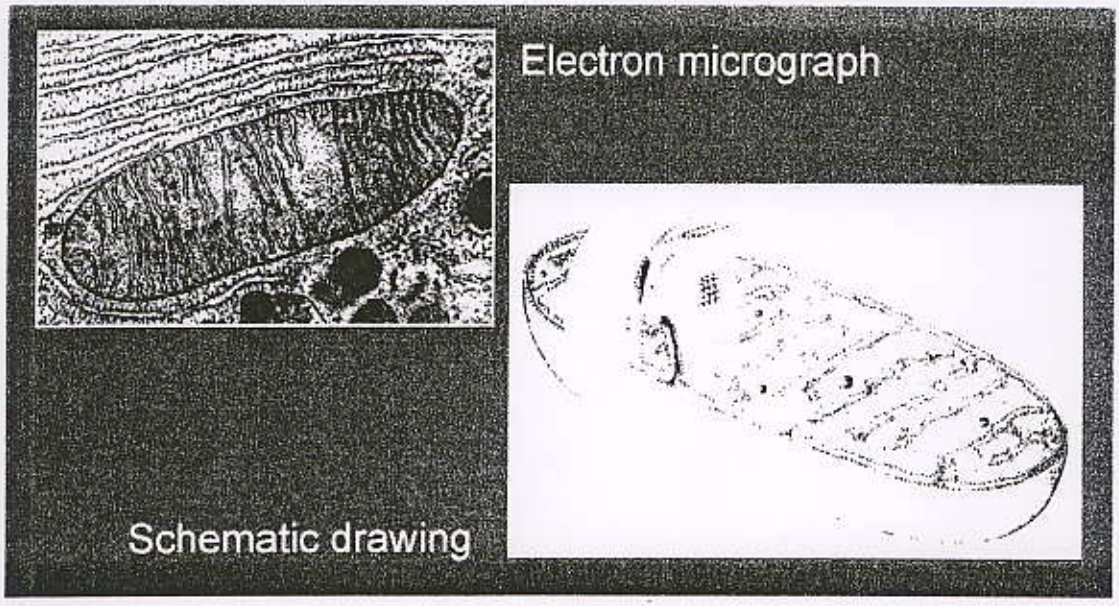


Figure 1: Mitochondria

Energy and oxygen are related and Thiotaine is a molecule that helps assure efficient use of oxygen for more efficient energy production. Thiotaine is also an anti-oxidant, reduces 8-oxo-guanine synthesis and reduces MMP-1 release, according to Obayashi et. al (1), all assuring the well-being aof the cells and mitochondrias.

Skin energy production declines from youth as there is a decrease in ATP (*Greco et al., FASEB J. 17:1706, 2003*) and in increase in lactic acid (*Goldstein et al., J. Cell Physiol. 112:419, 1982*).

Mitochondria created a symbiotic relationship with the host cells billions of years ago. Mitochondria breathes; they use fatty acids and oxygen to produce CO_2 and ATP.

ATP is the "currency energy" (Figure 2).

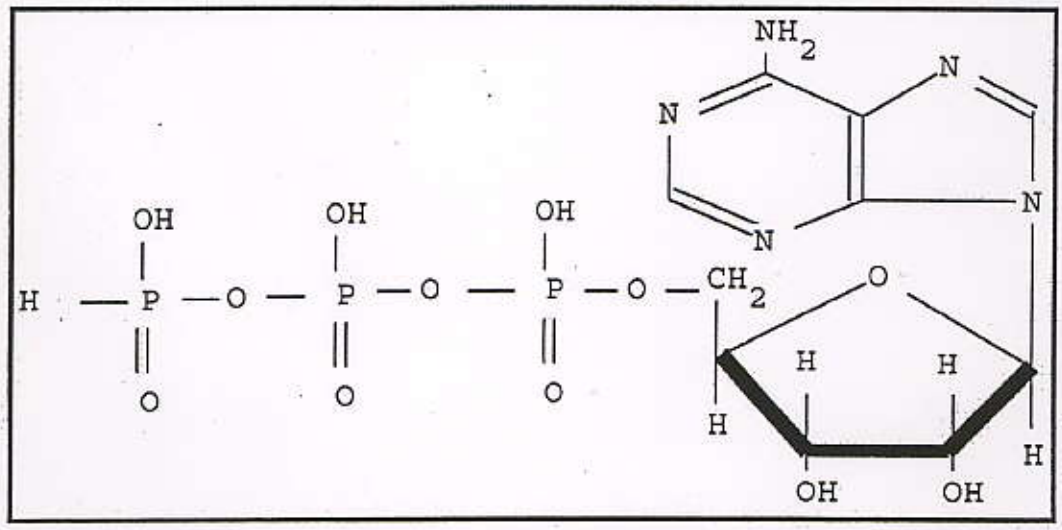


Figure 2: ATP Chemical Structure
(energy currency)

The corresponding process is:

$C_6H_{12}O_6 + 6O_2 \Rightarrow 6H_2O + 6CO_2 + ATP$
(carbohydrate)

2) DNA in Mitochondria

Mitochondria have 1-2% of the total DNA. This circular DNA is important because mitochondrial DNA code for sub-units of

--- ATP Synthase (linked to ATP synthesis)
--- NADH dehydrogenase (linked to respiration)
--- Cytochrome Oxidase

...for a total of 13 units.

NADH Hydrogenase is involved in the process of NADH recycling and is key to respiration (Figure 3).

Figure 3: Respiration Process

Integrity of mitochondrial DNA is therefore important.

OK: $O_2 \longrightarrow H_2O$

WRONG: $O_2 \longrightarrow O^*_2$

$O_2 \longrightarrow H_2O_2$

H_2O_2 leads to DNA damage in the form of 8-oxo-guanine and in increase in MMP-1 release.

3) UV-A and UV-B and Aging

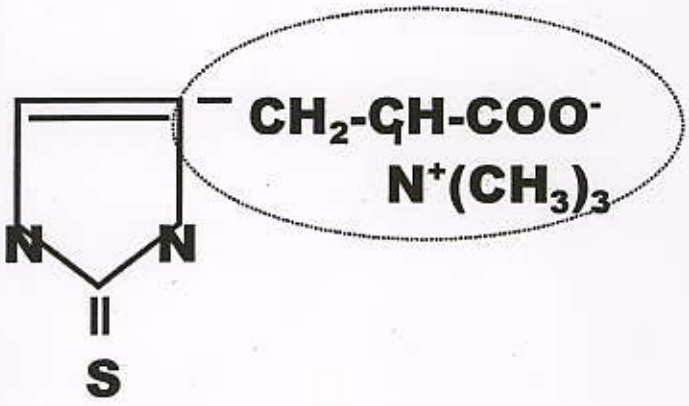
Recently, the increase in the aged population and the increase in UV at the earth's surface (2) have focused on the public's concern on the long-term effects of UV-A (320 nm - 400 nm) and UV-B (290 nm -320 nm), especially the acceleration of premature skin aging. Photoaged facial skin is characterized by the appearance of deep wrinkles at the corner of the eyes and around the mouth. Many studies have demonstrated that the alterations of the extracellular matrix at the papillary dermis, collagen and elastin substantially contributes to the formation of photoaged skin (3-9). The decrease of collagen fibers and the disappearance of elastin fine fiber and oxytalan fiber has been observed in photoaged skin. These alterations are caused by repeated UV exposure.

4) Thiotaine - Natural Amino Acid

Thiotaine (Ergothioneine) is a natural antioxidant and an amino acid not incorporated into protein, whose sulfur is predominantly in the thione form (Figure 4). Thiotaine is a fungal metabolite that cannot be endogenously synthesized by mammals; it must be taken up in the diet (10). Is is found in many mammalian tissues in millimolar quantities (10). Thiotaine is generally regarded as an antioxidant, although results are conflicting. Some regard it as a scavenger of hydrogen peroxide (11), while others contend that it does not readily react with hydrogen peroxide but does scavenge hydroxyl radicals (12). Also, some date indicate that Thiotaine quenched O_2 by monitoring 1270-nm phosphorescence derived from O_2 (13).

In this study, we examined the scavenging abilities of Thiotaine against O_2^- and $^1O_2$ using chemical and biological systems to identify antioxidative characters. Also, the effects of Thiotaine on UV-induced cellular responses such as expression of TNF-Alpha and MMP-1 were evaluated.

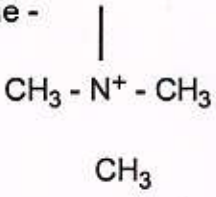
Figure 4: L-ergothioneine chemical structure



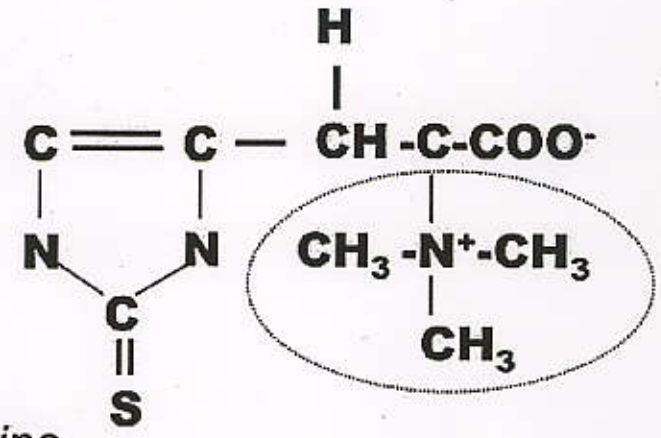
PART ONE - THIOTAINE: ENERGY in MITOCHONDRIAS

Role in Energy Production and Fatty Acid Transport

The transferring group of Thiotaine -

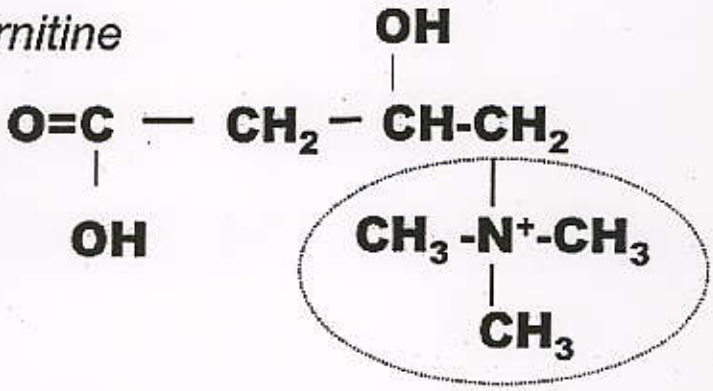


- is also present in Carnitine



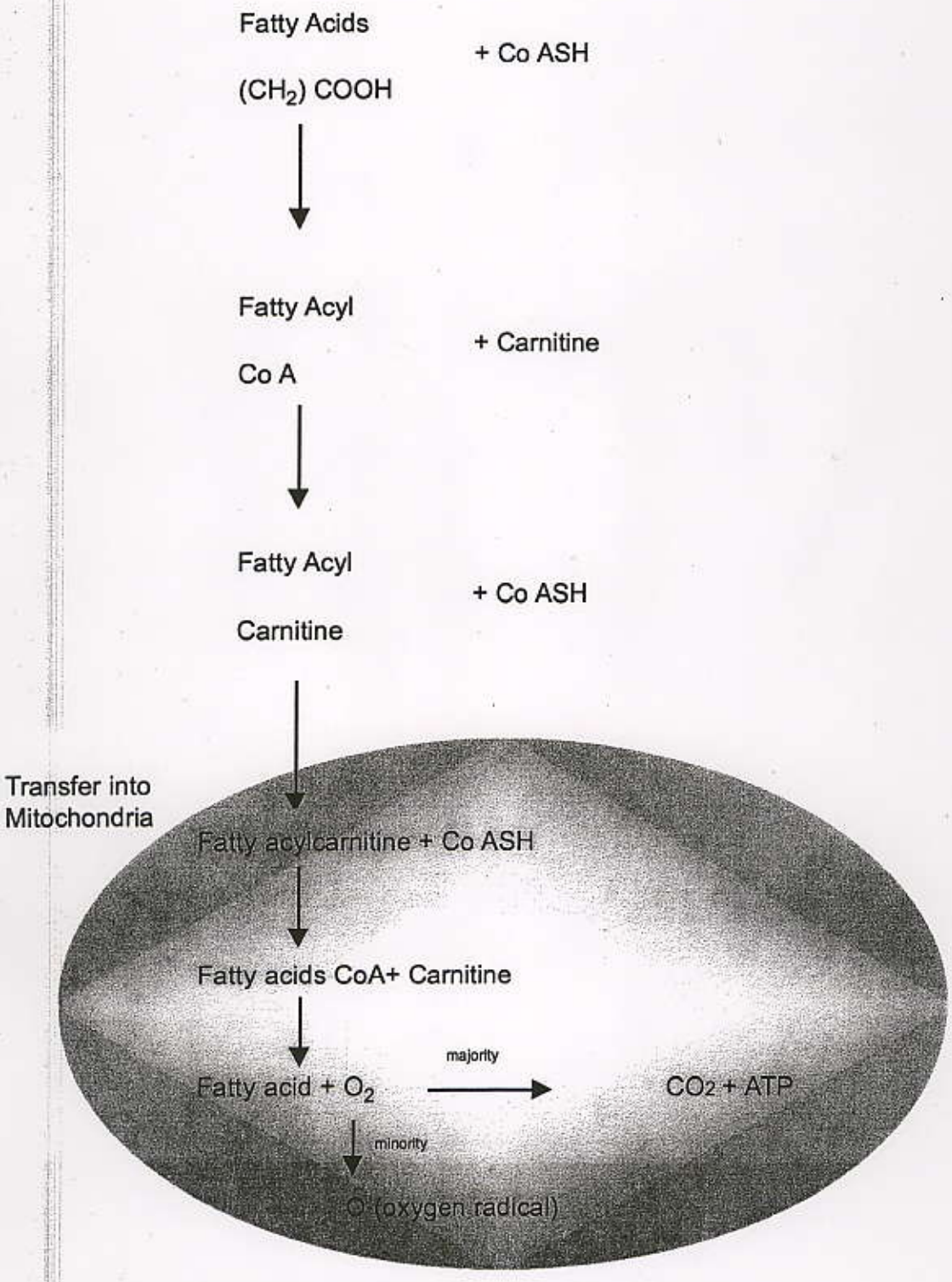
Thiotaine

Carnitine



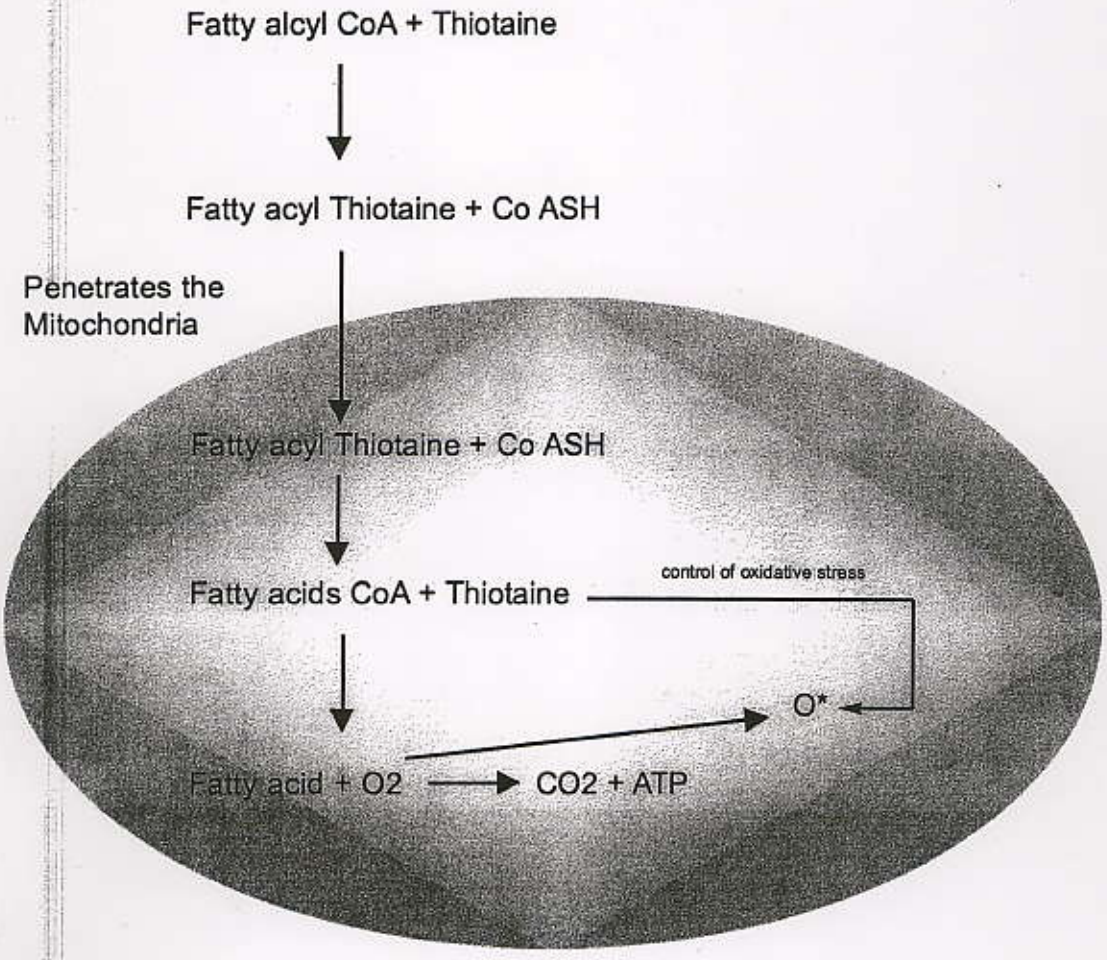
Carnitine is used in slimming products. It helps to transfer fatty acid in the mitochondria and the oxygen present will burn the fatty acid.

Carnitine's mode of action is described below.



Consequence: Less Fatty Acid; More Energy

Thiotaine's mode of action is similar.



Consequence: Less Fatty Acid, More Energy

But Also: Control of Oxidative Stress by the second group of Thiotaine:
The Thiol

PART TWO: THIOTAINE IS AN ANTI-OXIDANT

1) Role as Anti-Oxidant in UV-A attack

UV-A radiation generates singlet oxygen (O_2) (type II photosensitization) through photosensitization reactions with several intracellular chromophors such as NADH, NAPDH, and flavine protein (14). It has been reported that O_2 generated by UV-A mediates the induction of MMP-1 through the pathway of IL-6 and IL-1 (15,16).

UV-A exposure to dermal fibroblasts leads to the reduction of collagen synthesis (17) and the excess elevation of matrix metalloproteinase-1 (MMP-1)/interstitial collagenase (18). MMP-1 is a member of the MMP's, a superfamily of endopeptidase that is capable of degrading extracellular matrix components (19). Excess expression of MMP-1 by skin fibroblasts causes subsequent damage of dermal connective tissue. The imbalance between the synthesis and degradation of collagen critically contributes to the process of matrix alteration (20) and leads to photoaging.

a) Quenching Activity Against O_2

The quenching activity of Thiotaine was measured by using the ESR spin-trapping method and lipid peroxidation (LPO) initiated by O_2. In general, hematoporphytin produces O_2 during UV-A irradiation. As a source of O_2 the hematoporphytin and UV-A system was used. The ESR spectrum of the $^1O_2$ is shown in Figure 5. The addition of Thiotaine showed a decrease of O_2^- derived TEMP radicals in a dose-dependent manner. These results indicated that Thiotaine effectively quenched O_2.

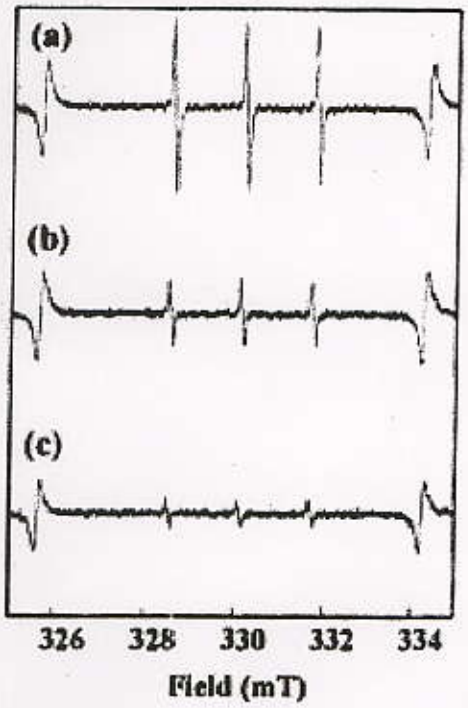


Figure 5. Singlet oxygen quenching effect of Thiotaine by ESR study
(a) Control (without Thiotaine)
(b) Thiotaine 10 mg/ml
(c) Thiotaine 20 mg/ml

The results for LPO initiated by $^1O_2$ are shown in Table 1. Rose bengal plus visible light was used as the source of $^1O_2$. The LPO level of control liposomes was 23.81 nmol/ml, and the exposure to O_2 increased LPO to 91.84 nmol/ml. The addition of Thiotaine reduced LPO to 26.53 nmol/ml, a 96% reduction.

Table 1. Inhibition of Thiotaine on Lipid Peroxidation Initiated by Singlet Oxygen

	nmol LPO/ml
Liposomes alone	23.81
Liposomes + rose bengal	91.84
Liposomes + rose bengal + 20 µM Thiotaine	26.53

As a source of singlet oxygen, the photo-irradiated rose bengal system was used. Liposomes prepared from phosphatidyl choline with 10 mM rose bengal were irradiated using a Sylvania 150W slide projector. Oxidation products in the liposomes were assayed with K-Assay™ LPO-CC from Kaniya Biomedical Company (Seattle, WA). Data are expressed as mean value from dependent examinations in duplicate.

b) MMP-1 mRNA Expression

Fibroblasts exposed to UV-A enhance MMP-1 production with up-regulation of MMP-1 mRNA expression. Thus, we examined the effect of Thiotaine on MMP-1 mRNA expression in cultured normal human fibroblasts, exposed to UV-A. MMP-1 mRNA in human fibroblasts was elevated 1.25-fold at 24 h post UV-A irradiation. Thiotaine reduced MMP-1 mRNA expression levels in a dose-dependent manner (Figure 6). The results indicated that Thiotaine down-regulated MMP-1 mRNA expression of fibroblasts induced by UV-A irradiation.

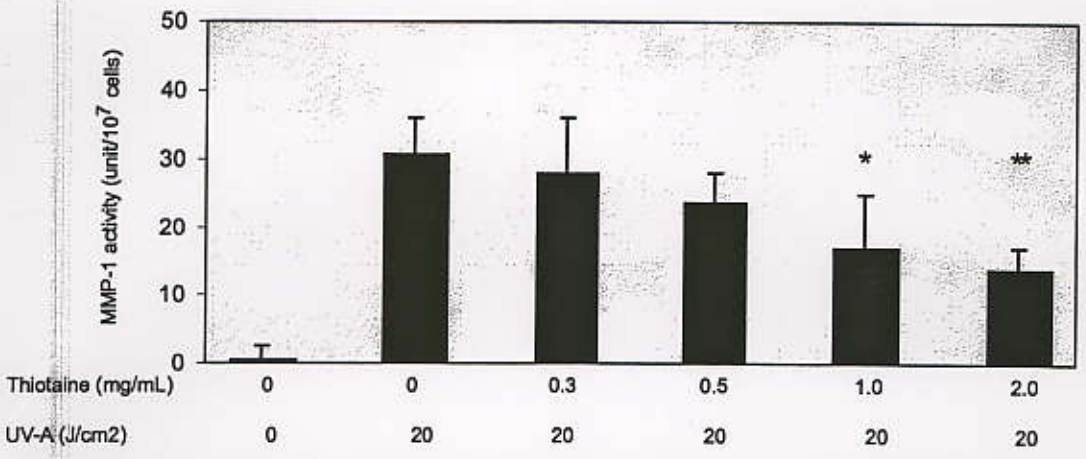


Figure 6. Thiotaine-suppressed MMP-1 production induced by UCV-A irradiation. Human fibroblasts were exposed to UV-A at a dose of 20 J/cm2 in the presence of various concentrations of Thiotaine in HBS. MMP-1 activity and cell numbers were measured after UV-A irradiation for 24 hours. n = 4. Significance: *p< 0.05; **p < 0.01.

2) Role in Anti-Oxidation in UV-B attack

UV-B radiation creates superoxide anion (O_2^-) (type I photosensitization) due to reaction with water, activation of mitochondrial function and release of peroxides by inflammatory cells (21). UV-B causes acute damage in the skin, such as DNA damage and apoptosis of keratinocytes, even in dermal cells. In addition, UV-B induces the production of cytokines, hormones and chemical messengers IL-1, TNF-alpha, propiomelanocortin-derived hormones and prostaglandin E2, which consequently leads to erythema and inflammation in the dermis (22).

a) Scavenging Ability Against O_2^-

The scavenging ability of Thiotaine against O_2^- was evaluated using the hypoxanthine and xanthine oxidase system as a source of O_2^-. Thiotaine showed scavenging activity against O_2^- in a dose-dependent manner in the micromolar range (Figure 7).

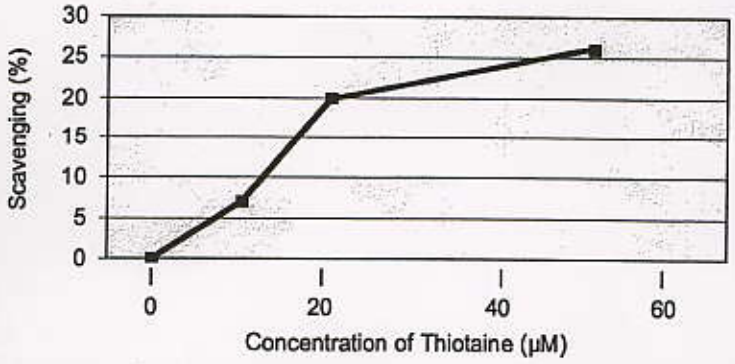


Figure 7. Scavenging the effect of Thiotaine against superoxide anion generated by hypoxanthine-xanthine oxidase system. The OD_{560nm} in the absence of Thiotaine was set as 0% scavenging. The scavenging percent was calculated as the reduction in OD divided by the starting OD X 100.

In addition, we examined the effects of Thiotaine on lipid peroxidation (LPO) of liposomes initiated by O_2^- generated by alloxan. The base level of LPO in the control liposome was 17.37 nmol/ml, and the addition of alloxan to the system was increased to 50.31 nmol/ml. Thiotaine (20 µM) reduced LPO to 22.12 nmol/ml, an 85% reduction, and exhibited superior effects among other sulfur-containing antioxidants that were tested at the same concentration (Figure 8, following page).

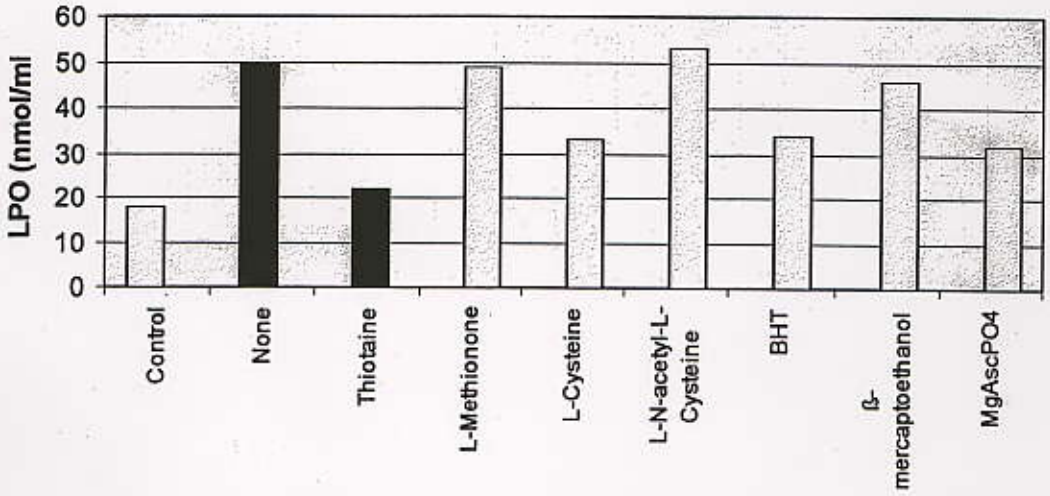


Figure 8. Scavenging effect of antioxidants against superoxide anion generated by alloxan. Lipid peroxides (LPO) were generated in liposomes by alloxan without addition (none). The level of LPO in samples with 20 µM antioxidants was measured after 60 minutes.

b) TNF-alpha Expression by UV-B Irradiation

To examine the effects of Thiotaine on UV-B induced TNF-alpha expression, we carried out a reporter assay using fibroblast cell line XPTNF2, which is an SV40 fibroblast line deficient in DNA repair and carrying the TNF-alpha promoter chloramphenicol acetyl-transferase (CAT) reporter gene. UV-B irradiation of these cells increased the promoter activity, and as a result exhibited a CAT activity of 39.87 nmol/mg/h. Twenty µM and 50 µM Thiotaine reduced CAT activities to 15.97 and 22.07 nmol/mg/h, respectively (Table II).

Table II
Induction of TNF-alpha by UV-B in Fibroblasts

Treatment	Net CAT Activity (nmol/mg/h)
UV-B (100 J/m^2)	39.87
UV-B + 20 µM Thiotaine	15.97
UV-B + 50 µM Thiotaine	22.07

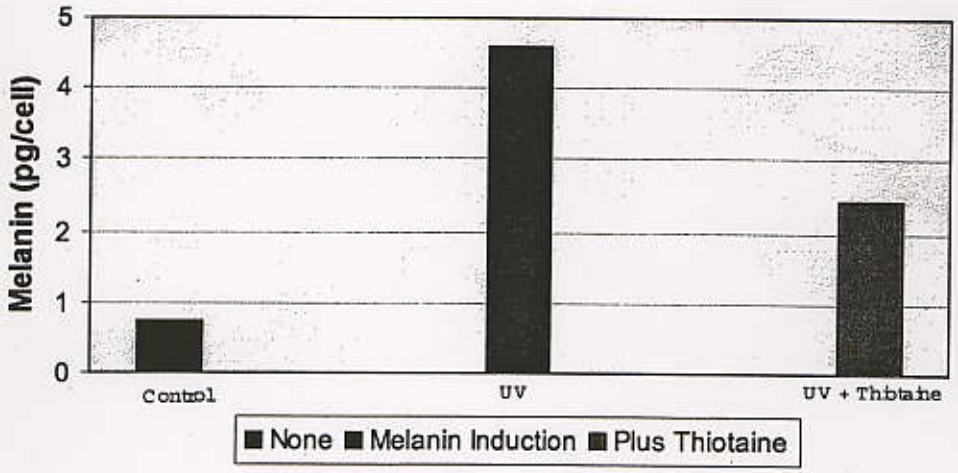
Fibroblast line XPTNF2, which is an SV40 fibroblast line deficient in DNA repair and carrying the TNF-alpha promoter chloramphenicol acetyltransferase (CAT) reporter gene. Assay of TNF-alpha promoter activity as described in text. Assays in duplicate, background subtracted, and results averaged.

PART THREE: THIOTAINE AS A CLARIFIER

Clarifier:

Thiotaine acts like a clarifier because it is:

* A metal chelator like Kojic Acid
* An antioxidant like Vitamin C
* It inhibits tyrosinase and also inhibits melanin in cell culture at 1% use level



Thiotaine

PRODUCT SPECIFICATIONS

INCI Name: L-Ergothioneine
CAS #: 497-30-3

Test	Specifications
HPLC ANALYSIS: L-ERGOTHIONINE	1.8 - 2.2 MM
APPEARANCE	CLEAR AND COLORLESS SOLUTION
ODOR	CHARACTERISTIC
BACTERIA AND FUNGI	<100 ORGANISMS/GRAM
PATHOGENS	<1 CFU/GRAM
PHENOXYETHANOL	1.0 - 1.2%
PH	7.0 - 8.0

MATERIAL SAFETY DATA SHEET

Barnet Products Corp.
140 Sylvan Avenue
Englewood Cliffs, NJ 07632

Tel: 201-346-4620
Fax: 201-346-4333

1. CHEMICAL PRODUCT IDENTIFICATION

Product Name:	Thiotaine
Manufacturer's Name	AGI Dermatics
Common Chemical Name:	Ergothioneine & Water
INCI Name:	Ergothioneine & Water

2. COMPOSITION/INFORMATION ON INGREDIENTS

Substance/Preparation:	Preparation
Information on hazardous ingredients	N/A

Chemical Name	%	EINECS No.	CAS Number
Ergothioneine			497-30-3
Water			7732-18-5

Preservative: Phenoxyethanol 1%

3. HAZARD IDENTIFICATION

Human Health Hazards:	None known

4. FIRST AID MEASURES

Effects and Symptoms:

Ingestion:	No adverse effects known. Low toxicity.
Inhalation	No adverse effects known.
Skin Contact	No adverse effects known.
Eye Contact	No adverse effects known.

First Aid Measures:

Ingestion:	Induce vomiting if large amounts are ingested and seed medical attention.
Inhalation:	Remove to fresh air. Seek medical attention if breathing is labored.
Skin contact:	Wash thoroughly with soap and water. Call a doctor if irritation develops.
Eye contact:	Flush with water for 15 minutes. Seek medical atten tion.

5. FIRE FIGHTING MEASURES

Extinguishing Media

Suitable:	Not flammable
Special Firefighting Procedures:	None
Hazardous Thermal (de)composition Products:	N/A
Protection of Firefighters:	N/A

6.ACCIDENTAL RELEASE MEASURES

Personal Precautions:	Avoid contact with skin and eyes.
Environmental Precautions:	No special precautions necessary.
Methods of cleaning up	Remove excess. Wash area with detergent and water.

7. HANDLING AND STORAGE

Handling:	Avoid contact with skin and eyes.
Storage:	Store at 20-25° C. Do not freeze. Keep away from light.

8. EXPOSURE CONTROL/PERSONAL PROTECTION

Respiratory System Protection:	No special respirator necessary.
Skin and Body Protection:	Wear suitable protective clothing.
Hand Protection:	Wear impervious gloves.
Eye Protection:	Wear goggles with side shields.

9. PHYSICAL AND CHEMICAL PROPERTIES

Physical State:	Liquid
Color:	Clear
Odor:	Characteristic
pH:	7.0 - 8.0
Flash Point	>200° C
Solubility:	
Water	Soluble

10. STABILITY AND REACTIVITY

Conditions to avoid:	None expected if stored and handled properly.
Materials to avoid:	None expected if stored and handled properly.
Hazardous Decomposition Products:	N/A

11. TOXICOLOGICAL INFORMATION

Skin Irritation:	Low irritation
Eye Irritation:	Low irritation
Sensitization:	Not tested

12. ECOLOGICAL INFORMATION

13. DISPOSAL CONSIDERATIONS

Method of Disposal:	As per federal, state and local regulations.

14. TRANSPORT INFORMATION

Land - Road/Railway	Non-hazardous material
Inland Waterways	Non-hazardous material
Sea	Non-hazardous material
Air	Non-hazardous material
National Transport Regulations	Non-hazardous material

15. REGULATORY INFORMATION

Label Name:	Thiotaine

16. OTHER INFORMATION

History	
Date of issue	March 20, 2002

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UNICHONDRIN ATP

THE MODERN ACTIVE AGENT CONCEPT FOR LASTING PRESERVATION OF YOUTHFUL SKIN

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1. Introduction

The main task of modern skin care cosmetics is without doubt the preservation of a youthful and healthy condition of the skin. In addition, it can also be expected of effective skin care products that they eliminate minor deviations from ideal conditions due to stress and environmental factors and that they ensure an optimal equilibrium between all the skin functions. Nevertheless, despite regular daily care, the natural ageing process with its undesirable consequences cannot be arrested. However, premature ageing of the skin due to our modern stressful lifestyle and detrimental environmental factors can nevertheless be specifically counteracted with modern active agent cosmetics. According to recent biochemical findings, the visible consequences of the inexorable ageing process can be demonstrably and increasingly effectively reduced with potent active agents.

The external appearance of the skin depends very considerably on the connective tissue. The extremely complex processes in the connective tissue of the skin determine its hydration capacity, elasticity, pliability, and not least the presence or absence of wrinkles. The age-related changes affecting specifically the connective tissue of the skin is the subject of continuous research, and this is constantly discovering new findings. This is the scientific basis of modern cosmetics.

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2. Concept of the active agent complex Unichondrin ATP

The connective tissue of the skin consists of connective tissue cells or fibroblasts and an extra cellular matrix that occupies the space between the cells. This matrix consists of a complex network or reticulum of a wide variety of macromolecules called biopolymers. It is these biopolymers that determine the mechanical properties of the tissue. The matrix consists partly of amorphous gelatinous substances and partly of structural fiber proteins. The biosynthesis of the constituents takes place in the fibroblasts. The amorphous biopolymers consist of glycosaminoglycans (GAG) (also called glucosaminoglycans or mucopolysaccharides), glycoproteins (also called glucoproteins or mucoproteins) and proteoglycans.The fiber proteins are mainly collagen, elastin and reticulin.

Glycosaminoglycans (= mucopolysaccharides) are formed from aminosaccharides and uronic acids. The best known of the glycosaminoglycans is without doubt hyaluronic acid. Hyaluronic acid is used widely in cosmetics and has the following structure:

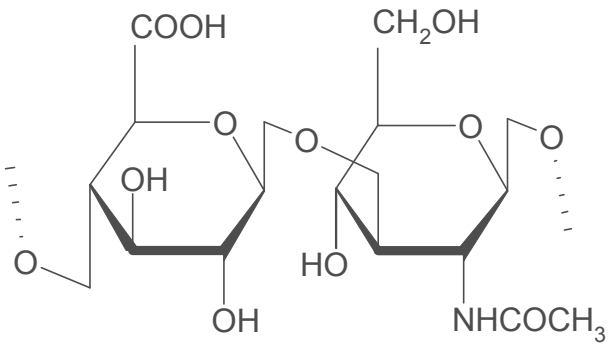

Figure 1: Hyaluronic acid

Hyaluronic acid is formed from N-acetylglucosamine and glucoronic acid in the ratio 1:1 and has a molecular mass of between 1 and 15 million depending on the conditions.

Hyaluronic acid is degraded by the enzyme hyaluronidase.

Another building block no less important for the structure of the extracellular matrix is chondroitin sulfate. This glycosaminoglycan consists of N-acetylgalactosamine and glucuronic acid. It is known to exist as various isomers, and it is mainly types A and C with the structures described below:

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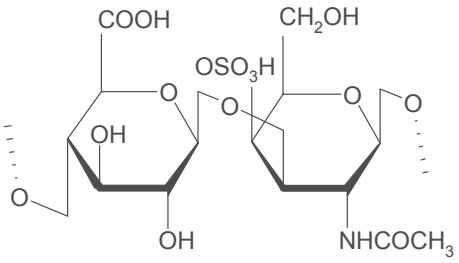

Figure 2: Chondroitinsulfat A

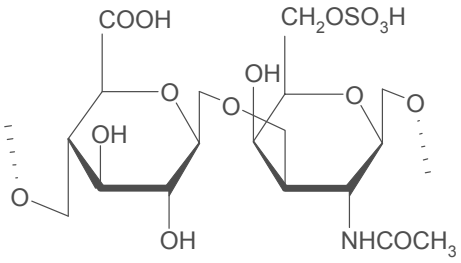

Figure 3: Chondroitinsulfat C

The molecular mass is between 5,000 and 50,000 and is thus several orders of magnitude smaller than that of hyaluronic acid.

The free sulfate groups give chondroitin sulfate a pronounced anionic character and thus very considerably improve the substantivity. Furthermore, chondroitin sulfate is not degraded by hyaluronidase. Chondroitin sulfates reduce the activation energy for the formation of collagen fibers and thus assists their generation.

Chondroitin sulfates are the most important constituents of the proteoglycans. Proteoglycans are structurally similar to glycoproteins, i.e., glycosaminoglycans are bound as side chains to peptide chains („core protein“) of various lengths. Proteoglycans form a three-dimensional reticulum of varying density in the extracellular space, and the other connective tissue structures are embedded into this reticulum. These proteoglycans show a wide range of structural variation, and not all details of their functions are yet known. The most important functions definitely include, for example, the water-binding ability, the binding of positively charged substances, ion exchange, and cohesion of the matrix.

Recent investigations also show that proteoglycans not only have mechanical functions but also perform important biochemical tasks that influence cell and tissue behavior.

The points of special interest to cosmetics chemists are the possible changes occurring in the connective tissue in response to every day stress and skin ageing and how these changes can be delayed.

Various investigations have shown that the fibrils in the connective tissue become thinner with increasing age and the proportion of soluble collagen decreases because the intermolecular cross-linkages lower the solubility. The degree of cross linking is partly a function of age, but cross-linking is also accelerated by environmental factors such as exposure to UV radiation and free radicals. The moisture retention capacity decreases as the degree of cross linking increases, and this leads to the visible changes in ageing skin. With increasing age there is also a reduction in the regeneration capacity of the fibroblasts and thus also of the extracellular matrix.

The content of chondroitin sulfates in particular also decreases markedly as skin ages. Unfortunately, it is the glycosaminoglycans and thus also the chondroitin sulfates that counteract cross linking of the collagen. A chondroitin sulfate deficit in the skin thus accelerates the ageing process.

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In view of the above results, it is rational to use chondroitin sulfates in cosmetics. Although the molecules of chondroitin sulfate are considerably smaller than those of, for example, hyaluronic acid, it cannot be assumed that they can be absorbed through the skin and thus made available to metabolism of the fibroblasts. Instead, the macromolecular chondroitin sulfates form a film of high substantivity on the surface of the skin, and as a result of the outstanding water-binding capacity of these molecules, brings about an improvement in the moisture retention capacity of the skin and thus an immediate effect that can be both felt and seen.

The lasting preservation of a healthy and youthful condition of the connective tissue requires optimal cellular metabolism of the fibroblasts. The extracellular matrix is the result of an extremely complex system of interactive anabolic processes of the intermediate metabolism. The maintenance of these processes requires energy. In order to meet this energy requirement, nature has devised an extraordinarily efficient system that is present in every living creature. The energy supplied to the body through the food chain is stored in the form of adenosine-5'-triphosphate (abbreviation: ATP), which is a very energy-rich molecule. During the energyconsuming biosynthesis of the glycosaminoglycans (= mucopolysaccharides) in the fibroblasts, ATP is cleaved into adenosine diphosphate and orthophosphate in a process that releases energy:

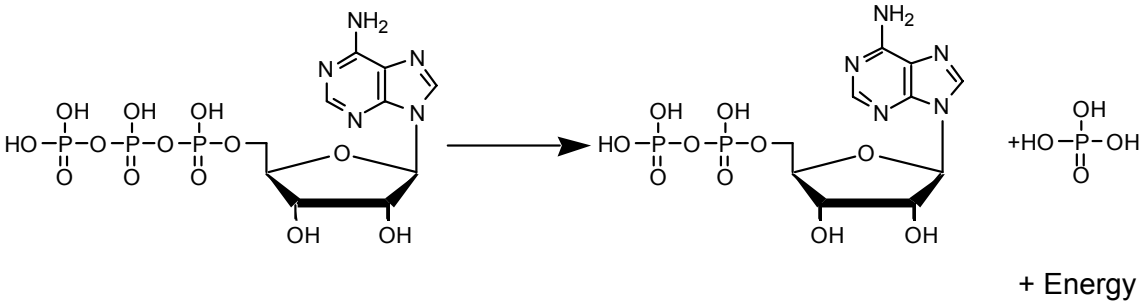

Figure 4: Biosynthesis

A variety of in-vitro studies on cell cultures have shown that addition of ATP actually stimulates the cellular metabolism and promotes the formation of extracellular matrix substances. For this reason, ATP is often called a „biocatalyst“ in specialist literature.

The high energy content of ATP has the consequence that, particularly in aqueous solution, ATP is not very stable. However, the presence of protein hydrolysates reduces the rate of breakdown of ATP very considerably. It therefore appears rational to use ATP in cosmetic products only in conjunction with protein hydrolysates. Protein hydrolysates are also biopolymers and are used in cosmetics to improve the moisture retention capacity of the skin.

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The points described above form the scientific basis that explain the rational and clear route to the concept of the active agent complex Unichondrin ATP:

- Chondroitin sulfate is a biopolymer with a pronounced moisture retention comparable to that of hyaluronic acid but with a higher substantivity that occurs in the connective tissue of the skin and thus, as a component of the active agent complex
  Unichondrin ATP, brings about an immediate effect on the skin that can be both felt and seen.

- ATP is a biocatalyst that stimulates the cellular metabolism and thus assists the fibroblasts in the formation of the extracellular matrix of the connective tissue and forms the basis for the lasting effect of the active agent complex Unichondrin ATP.

- The protein hydrolysate contained in Unichondrin ATP not only assists the hydrating properties of chondroitin sulfate but also stabilizes the ATP present in the active agent complex.

- The greatest possible hydration is the best precondition for penetration of the hydrophilic ATP molecules through the skin. Unichondrin ATP therefore contains a high proportion of 1,3-butylene glycol.

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3. Efficacy

3.1 General

The aim of the active agent complex Unichondrin ATP is to delay the ageing processes in the connective tissue of the skin and to preserve its youthful appearance, as manifested by improved hydration and better skin topography (wrinkle depth, wrinkle density, wrinkle length, roughness). These assessment criteria can be measured objectively with a high degree of reliability on living human skin. For the assessment of the efficacy, Unichondrin ATP was blended into a neutral base cream to form a test cream with a concentration of 2.5%. The same base cream without addition of the active agent was used as the placebo comparison product.

Experience has shown that, despite comparative investigations with placebo products, the efficacy of a cosmetic active agent can be influenced by the composition of the base cream used to generate the test cream. It is therefore of little benefit to perform investigations of this type on as many subjects as possible. The validity can, however, be increased by lengthening the application and assessment periods. The efficacy studies described below were performed on 4 subjects according to the established study designs of the Consumer Product Testing in the USA.

3.2 Skin moisture

The efficacy of the active agent complex Unichondrin ATP was tested for skin moisturization using the electrical conductivity of the skin of the forearm. The subjects were forbidden to use any cosmetics other than soap during the 7 days preceding the test phase. The test phase lasted 28 days, during which the test cream and the placebo cream were applied twice daily. The electrical conductivity of test patches on the skin was determined on day 1 (before the start of treatment), on day 15 (after 2 weeks) and on day 29 (after 4 weeks). The results can be summarized as follows:

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The skin moisture content increased by 12% more after two weeks of application of Unichondrin ATP test cream than placebo cream, and by 62% more after four weeks of application of Unichondrin ATP test cream than placebo cream.

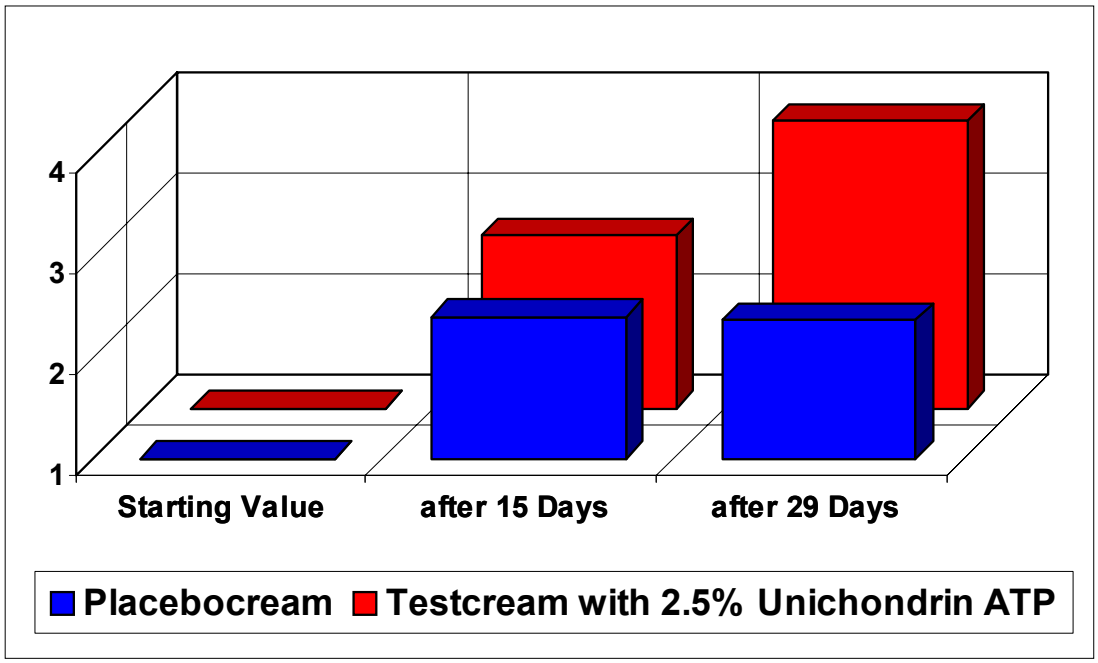

Figure 5: Comparison placebo cream with test cream with 2.5% Unichondrin ATP

The skin moisture content did not increase further during further treatment with the placebo cream after 2 weeks. By contrast, a marked additional improvement was achieved with the test cream during a further two weeks of treatment. From this, it may be concluded that the active agent complex Unichondrin ATP already brings about a clear immediate effect after a short duration of application, and also shows a lasting long term effect.

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3.3 Skin topoqraphy

In order to assess the influence of the active agent complex Unichondrin ATP on the skin topography, silicone replicas of the outer canthus of the right and left eyes were made before and after the treatment phase. The subjects were forbidden to use any cosmetics other than soap during the 7 days preceding the test phase. The test phase lasted 28 days, during which the test cream was applied twice daily to one side of the face and the placebo cream applied twice daily to the other side. The silicone replicas were analyzed using computer aided image analysis. The results can be summarized as follows:

Average amplitude (RZ):	Test cream:	46% reduction
	Placebo cream:	35% reduction
Number of peaks (RN):	Test cream:	67% reduction
	Placebo cream:	29% reduction
Residual length (RS):	Test cream:	58% reduction
	Placebo cream:	54% reduction
Primary wrinkle (RT):	Test cream:	42% reduction
	Placebo cream:	25% reduction
Roughness:	Test cream:	42% reduction
	Placebo cream:	30% reduction

These results can be seen as plots below as well as digitized image analyses of the silicone replicas before and after the 28 days of treatment with Unichondrin ATP.

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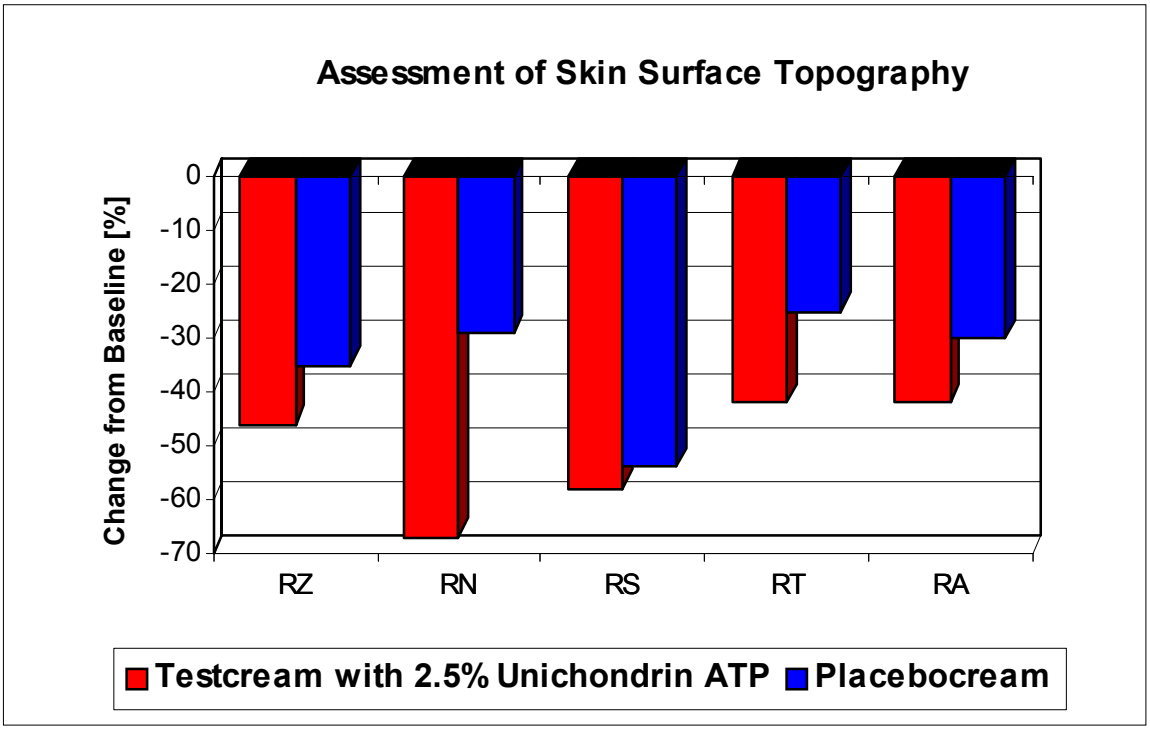

Figure 6: Assessment of skin surface topography

RZ: Average amplitude
RN: Number of peaks
RS: Residual length
RT: Primary wrinkle
RA: Roughness

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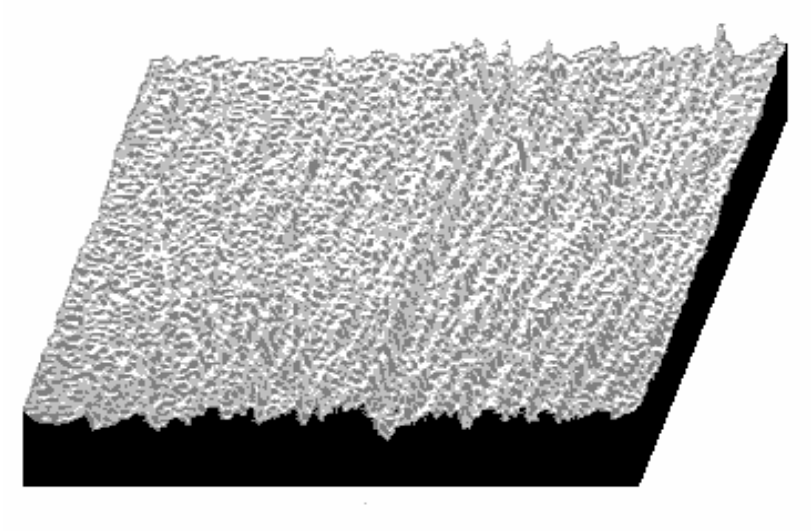

Figure 7: 3-D representation of digitized image - Basisline

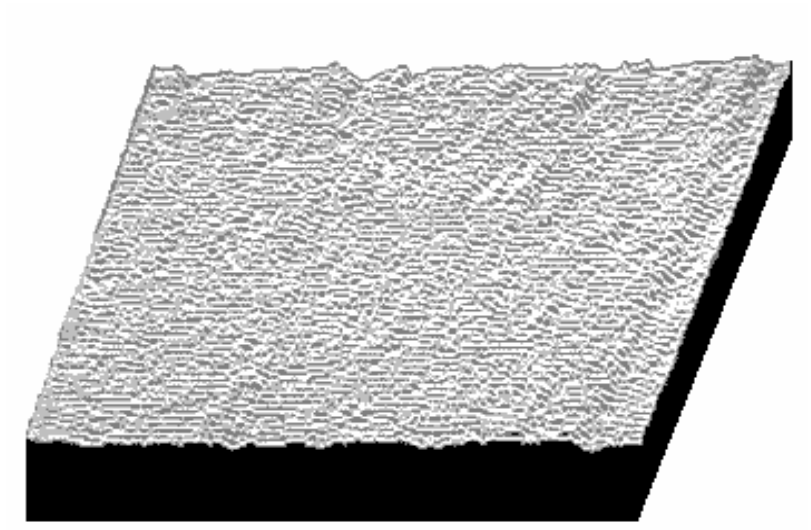

Figure 8: 3-D representation of digitized image - Final

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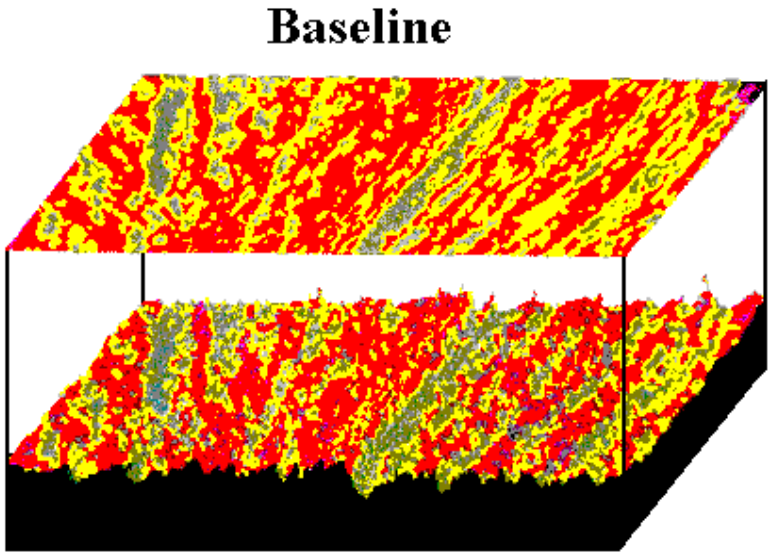

Figure 9: 3-D representation of digitized image with 2-D projection – Basisline

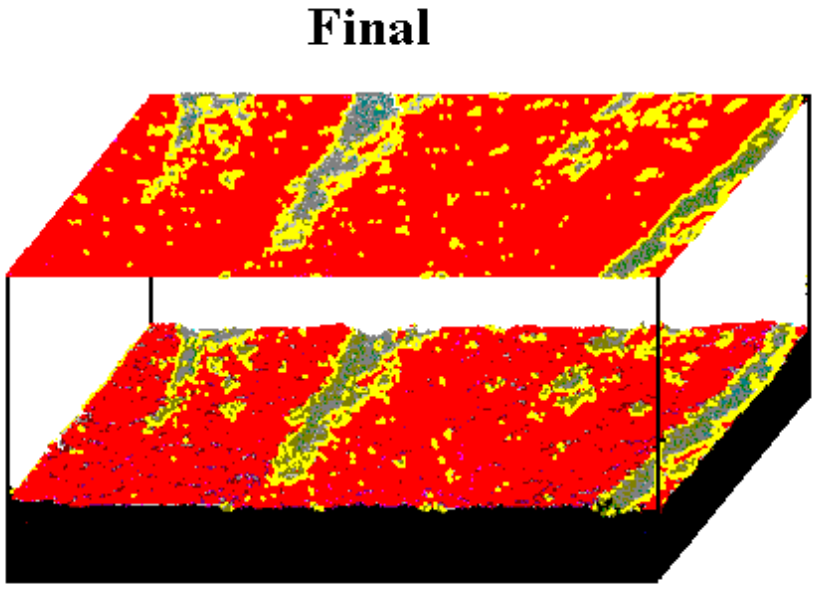

Figure 10: 3-D representation of digitized image with 2-D projection - Final

Yellow :	Peaks
Red :	Transitions
Green :	Valleys

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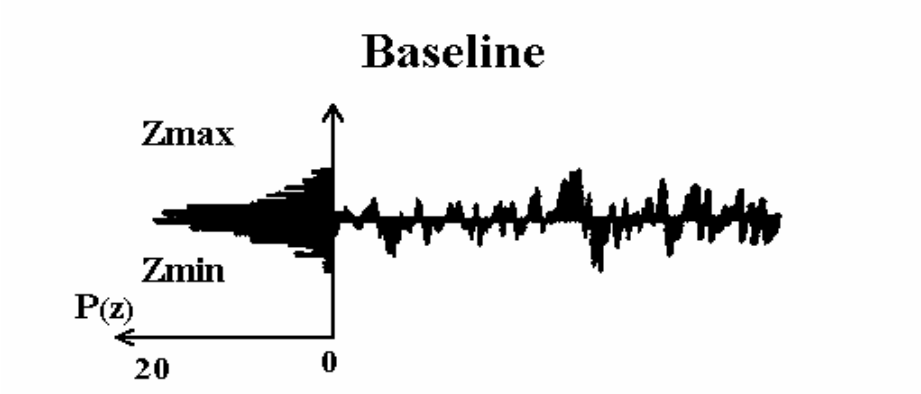

Figure 11: Line density graph (*) – Basisline

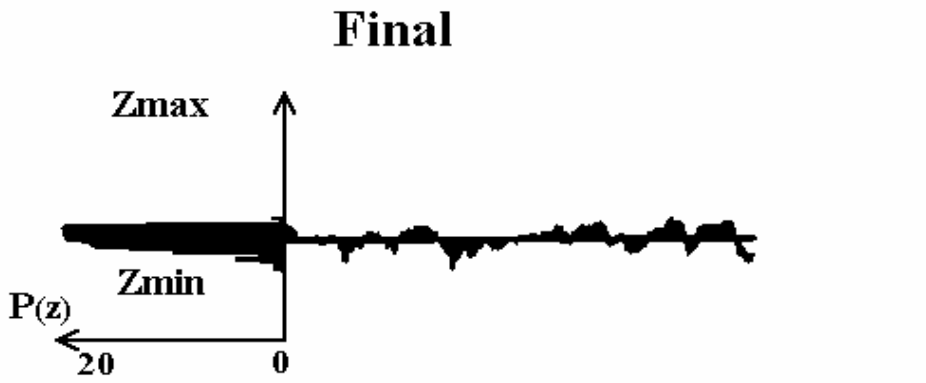

Figure 12: Line density graph (*) - Final

* Profile of one line selected from two dimensional digitized image and quantitated (planar) density of same line.

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4. Skin tolerance

Unichondrin ATP has been investigated extensively in comprehensive patch tests, and is well tolerated by the skin without problems.

5. Use

Unichondrin ATP is a potent active agent complex for high quality cosmetic skin care products for lasting preservation of youthful skin. Unichondrin ATP is water soluble and therefore suitable for blending into all types of emulsions, lotions, gels, etc.
On the basis of the efficacy studies described in Section 3, we recommend a concentration for Unichondrin ATP of between 2.5 and 5%.

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6. Characteristics

Composition	Unichondrin ATP is a water soluble active ingredient complex consisting of chondroitin sulfate (sodium salt), adenosin triphosphate, hydrolyzed vegetable protein and butylene glycol. Unichondrin ATP contains no preservative (self-preserving).
Appearance	Slightly viscous liquid.
Analytical data	See specifications.
Solubility	Miscible in all proportions with water Soluble in propylene glycol. Soluble in aqueous ethanol. Insoluble in lipids
Storage	Storage conditions: see safety data sheet Shelf life: see specifications
Processing	Unichondrin ATP is relatively stable and can easily be processed under conditions common in the production of cosmetics. However, temperatures over 70°C should be avoided. Intolerance reactions may occur with cationic substances.

Identification	**INCI name**	**CAS-No**
.	Butylene glycol	107-88-0
	Hydrolyzed vegetable protein	100209-45-8
	Adenosine triphosphate	56-65-5
	Sodium chondroitin sulfate	9007-28-7

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