

ACTIVE INGREDIENTS

TECHNICAL FILE

MDI COMPLEX™

NEUTRALIZES MMPS

Marine glycosaminoglycans

-

To erase dark circles, varicose veins and rosacea

TECHNICAL FILE

MDI COMPLEX™

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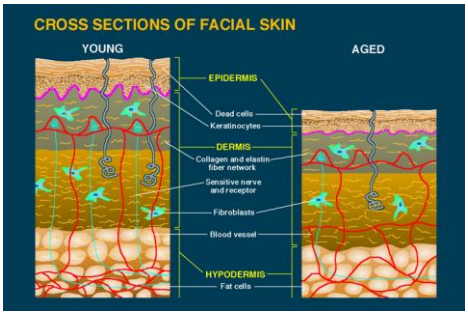
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SUMMARY

INCI NAME **CAS** **EINECS**	INCI name: Glycosaminoglycans CAS: 94945-04-7 EINECS: 305-682-6
ORIGIN	Glycosaminoglycans derived from marine bio-mass
COSMETIC PROPERTIES	
SKIN BENEFITS / POTENTIAL CLAIMS	• Reduces dark circle • Reduces the appearance of rosacea & spider veins • Reduces the appearance of varicose veins • Increase resistance to physical damages
APPLICATIONS	• Anti-aging • Firming • Sun Care & After sun-care • Slimming • Eye care • Dermoceuticals
RECOMMENDED DOSAGE	1 to 5%
USAGE pH RANGE	4.0 to 8.5
INCORPORATION	MDI COMPLEX™ should be incorporated at the end of the manufacturing process, at a temperature of **20/40°C**.
INCOMPATIBILITIES	Protein reducing agents, denaturing agents and strong alcohol solutions

INTRODUCTION

Skin aging involves major changes in the conjunctive tissue elements of the skin. Many molecules forming the extracellular matrix are produced by the keratinocytes of the epidermis and the fibroblasts of the dermis. Those molecules include collagen, elastin, proteoglycans, fibronectin and other glycoproteins. Deterioration of this matrix plays an important role in the aging phenomenon and implies a progressive diminution in dermal thickness, collagen content and protein organization. These qualities of the skin are essential to a young-looking skin and destructive enzymes such as the collagenases negatively impact the firmness, elasticity and maintenance of the extracellular matrix. Therefore, a collagenase inhibitor such as the MDI COMPLEX™ , can potentially control signs of aging skin and help maintain a young-looking skin.



MDI COMPLEX™ : A product of High Technology

The MDI COMPLEX™ , developed by Lucas Meyer Cosmetics Inc., is an inhibitor of the enzymes that destroy the skin's collagen network. The exclusive patented manufacturing process, using state-of-the-art molecular fractionation technology, is performed at low temperature with sophisticated ultra-filtration units to allow the selection of specific molecules and insures the maintenance of their potency. The product is aseptically filtered at the end of the manufacturing process and kept at room temperature. Each of the manufacturing steps is carefully supervised in accordance with strict quality control criteria. The MDI COMPLEX™ final product is a highly purified, quality cosmetic ingredient. It was designed to meet the highest quality requirements of the cosmetic industry as well as to provide its users with many benefits. The MDI COMPLEX™ is easily incorporated in formulation because it is 100% water soluble. In fact, it can be incorporated in a variety of cosmetic preparations, such as lotions, creams and gels. It is compatible with most of the water-soluble ingredients of a cosmetic formulation. Incompatibility might occur however, with compounds such as protein reducing agents, denaturing agents and strong alcohol solutions.

MDI COMPLEX™ : An Evolution in Cosmetic Care

The cosmetic applications of the MDI COMPLEX™ are numerous. It has demonstrated biological activities *in vitro* and has proven its efficacy in several clinical trials in reference to different skin conditions along with an excellent safety profile. It can also be incorporated into all kinds of cosmetic "anti-aging" formulations as the main active ingredient or used in combination with other cosmetic active ingredients. Clinical trials have demonstrated the MDI COMPLEX™ 's potential to improve the protective functions of the skin as well as to reduce the appearance of spider veins of the face, leg varicose and periorbital dark circles. Moreover, a study has shown that MDI COMPLEX™ may also reduce skin irritation, which implies that many other cosmetic applications may be possible. Thus, MDI COMPLEX™ may improve any cosmetic formulations to:

- reduce the appearance of rosacea and eye dark circles;
- reduce the appearance of the leg varicose and spider veins;
- reduce damage caused by sun exposure.
- decrease skin redness;
- increase cohesion of the extracellular matrix;
- increase skin firmness and elasticity;
- retard appearance of skin sagging and fine lines;

Proteolytic Enzymes and Skin

Proteolytic enzymes are a family of proteins involved in the degradation of necrotic debris derived from cell breakdown. They are produced endogenously often as precursor proteins whose activation is precisely regulated. These activated enzymes serve many functions in normal as well as pathologic situations. In particular, they are involved in the regulation of cell maturation and multiplication; collagen synthesis and turnover; the development and removal of the perivascular fibrin cuffs found in venous insufficiency and leg ulceration and the removal of dead tissues following inflammation (Sinclair and Ryan, 1994).

The degradative events in remodeling connective tissues are mediated through the actions of one or more of the matrix metalloproteinase (MMP) family and conversely, members of the tissue inhibitors of metalloproteinase (TIMP) family act to attenuate proteolysis (Stricklin and Nanney, 1994). Reorganization of the extracellular matrix is thus an important function in biological and pathophysiological processes (Langhilz et al., 1995). In particular, the extracellular connective tissue matrix of the skin is a complex aggregate of distinct collagenous and non-collagenous components. Optimal quantities of and complex interactions among these components are necessary to maintain normal physiological properties (Uitto et al., 1989).

As the skin ages, its physiology undergoes significant modifications. These changes are due to the structural and functional alterations that occur in the skin naturally with the passage of time, along with those provoked by exposure to the environment. Nevertheless, the skin continues to carry out functions, including protection, absorption, secretion, excretion, thermoregulation, pigmentogenesis, sensory perception and immunity, all of which are essential to the survival of the human body. With aging, these functions are performed less efficiently (Cerimele et al., 1990).

Atrophy of the skin's extracellular matrix is a common event during the aging of connective tissue (West et al., 1989). Besides synthesis of the extracellular matrix, its regulated degradation by various matrix-metallo-proteinases determines the amount and composition of the extracellular matrix within the dermis and the basement membrane of the dermo-epidermal junction. Hence, unbalanced synthesis of matrix metalloproteinases potentially contributes to the dissolution of dermal and basement membrane compounds, ultimately leading to blister formation and photoaging (Herrmann et al., 1993). Among the representative metalloproteinases of the extracellular matrix, interstitial collagenase has an important function in remodeling the extracellular matrix since the activity of this enzyme forms the initial and limiting step in collagen degradation (Childers and Stricklin, 1989). The participation of interstitial collagenase in the process of aging skin is thus very important, since all of the previously mentioned functions of the skin are affected by its activity and by the degradation of the extracellular matrix. Furthermore, the increased collagenolytic activity of senescent fibroblasts cultured in the presence of a low serum concentration suggests that aging fibroblasts may become increasingly fibroclastic, causing many of the age-associated alterations in dermal collagen which are observed during aging *in vivo* (West et al., 1989).

The initial event in the inflammatory response (to exogenous substances) is percutaneous absorption. Percutaneous absorption consists of two basic steps: (1) penetration through the layers of the epidermis and (2) absorption into the blood stream. Since the main purpose of this document is related to the cosmetic industry, we will focus the discussion on percutaneous absorption and penetration into the layers of the epidermis. Step 1 depends on factors such as stratum corneum barrier function and hydration of the stratum corneum. The degree of stratum corneum barrier function is in turn dependent on the number of cell layers and the amount and type of intercellular lipids (Stricklin et al., 1993). Transepidermal water loss (TEWL), an indicator of barrier impairment from irritation, is often used as a skin barrier function measurement.

In inflamed tissue sites characterized by active matrix degradation, the matrix metalloproteinases are secreted as latent precursors which are capable of proteolysis after extracellular activation (Harvell et al., 1994). As an example, collagenase enhanced by chronic inflammation attacks the intact collagen molecule, making it susceptible to further digestion by other proteases that are also products of inflammation (Saarinen et al., 1994). Puffiness of the eye area and dark circles around the eyes are among some of the skin problems associated, in part, with irritation and inflammation. Puffiness of the eye area is usually caused by edema but it may also be accentuated by allergies (chemical or environmental), poor blood circulation which may involve increased capillary pressure and permeability or mild irritation that can lead to the release of inflammatory mediators. Similarly, allergy resulting in edema contributes to a darkening of the eye lids, often

times producing dark circles. The lack of inhibitors of matrix metalloproteinases associated with the formation of inflammatory mediators is one of the reasons dark circles form. The latter have also been attributed to lack of sleep, fat deposits, which can impart a yellow coloration to the eyelid and proliferation of blood vessels in the eye area (Abramson et al., 1987).

EFFICACY STUDIES



IN VITRO MMP-2 INHIBITION ASSAY

BACKGROUND

Gelatinase 72 kDa (MMP2) is a member of the family of the matrix metalloproteinases (MMP's), which are capable of breaking down the extracellular matrix.

PROTOCOL

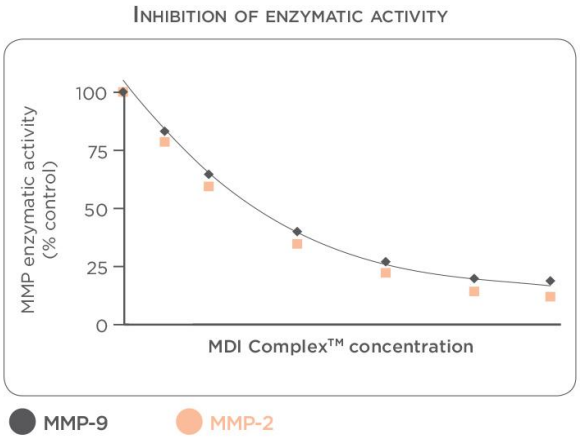
Principle

In this assay the enzyme, matrix metalloproteinase type-2 (MMP-2), is incubated in the presence of a synthetic peptide substrate and different amounts of the MDI COMPLEX™ . The peptide substrate contains a MMP-2 cleavage site bordered by a fluorescent residue and a quenching residue. In the intact peptide substrate, fluorescence emission is hampered by the quenching residue. Upon cleavage of the peptide, the quenching residue is released and fluorescence emission can be measured. The increase in fluorescence intensity reflects the extent of enzymatic cleavage of the peptide substrate.

Results analysis

The MDI COMPLEX™ inhibits in a concentration-response fashion the enzymatic activity of the MMP-2

RESULTS



CONCLUSION

MDI COMPLEX™ strongly inhibits the collagenase activity of MMP-2 *in vitro*.

MDI Complex™ helps maintain ECM integrity

CLINICAL STUDIES

EFFECT OF THE MDI COMPLEX™ ON THE PROTECTIVE FUNCTIONS OF THE SKIN

OBJECTIVE

A clinical study was designed to study the effect of the MDI COMPLEX™ on skin after 4 weeks of use. Barrier function of the skin was tested by gentle removal of the stratum corneum with simple scotch tape stripping, followed by measurement of transepidermal water loss (TEWL) as a marker of skin barrier condition.

PROTOCOL

Test conditions

When assayed in clinical trials, the MDI COMPLEX™ was used at concentrations ranging from 1% to 5% (w/w) in the final formulation unless otherwise stated.

Subjects

A panel of six healthy volunteers participated in the study and the panelists received the products to be applied on the right and left forearms, twice a day for four weeks. The measurements were obtained before treatment and after 2 and 4 weeks of treatment. The panelists applied the treatment cream (containing the MDI COMPLEX™) on the left arm and the vehicle cream on the right arm.

Six qualified female participants, ages 21-45, were selected for the study. To qualify for the study, the subjects were in normal health with no evidence of acute or chronic disease, including dermatologic or ophthalmologic problems.

Methods

A vehicle cosmetic cream was used as a placebo and the MDI COMPLEX™ was introduced in the same vehicle cream as the treatment product.

Subjects exhibiting sunburn, rashes, burn marks etc., which might interfere with evaluation of test results, were excluded from the study. The test site was devoid of warts, nevi, moles, sunburn, suntan, scars and any active dermal lesions observed upon examination. Written informed consent was obtained from each volunteer before entrance into the study.

On the day of the test, the panelists were instructed to refrain from using any lotions, creams or other products. During the course of measurements, the panelists were allowed to relax and had to refrain from conversing or getting excited. The panelists were allowed to acclimate for at least 30 minutes prior testing in a controlled environment of 20-21°C and 40% relative humidity.

The test sites were the right and left volar forearms. A small area (1.5" X 3") was marked on each arm and baseline TEWL measurements were obtained from three sites within this area (Pinnagoda 1990, Grove 1994).

A sticky (Tuck) tape was used to cover the test area and, after a firm stroke in both directions, the tape was peeled off (Elias 1993). A total of 5 strippings were performed and TEWL was recorded again. Strippings followed by TEWL measurements were continued in groups of 5. The strippings were stopped when the TEWL approached 18 g/m2/hr. TEWL was measured again at the end of the last stripping sequence.

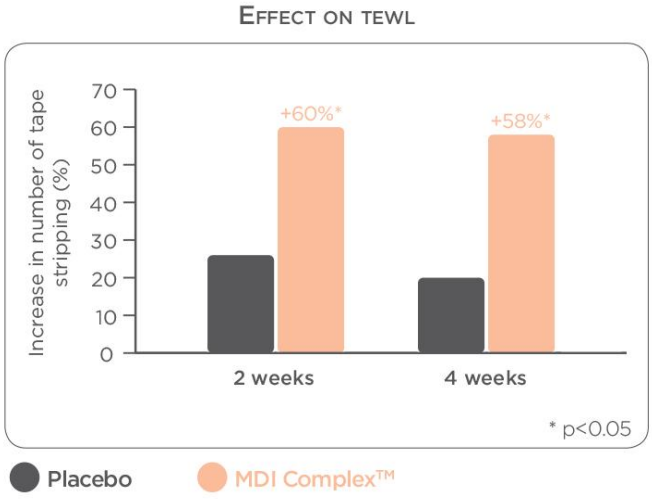
The number of strippings required to damage the skin barrier (TEWL of 18 g/m2/hr) was calculated at each time point.

RESULTS

The results were analyzed for statistical significance between treatments versus baseline at various time points, using the one-tailed rank coefficient Z test.

Vehicle-treated arms did not appear to exhibit much improvement, since only 26% and 21% (non-significant) more strippings were required to damage skin after 2 weeks and 4 weeks of treatment, respectively.

There was a significant improvement ($p<0.05$) in barrier condition of each of the panelists after treatment with the MDI COMPLEX™ product for 2 and 4 weeks, since 60% and 58% more strippings, were respectively required to disrupt skin barrier. The histogram below demonstrates the results obtained with both the vehicle cream and the MDI COMPLEX™ cream.



CONCLUSION

The MDI COMPLEX™ is significantly effective ($p<0.05$) in strengthening the skin barrier function against physical damage.

MDI Complex™ increases skin resistance to acute physical damage

EFFECT OF THE MDI COMPLEX™ ON SPIDER VEINS OF THE FACE

OBJECTIVE

This clinical study was designed to study the effect of the MDI COMPLEX™ on the reduction of the appearance of spider vein telangiectasia of the face.

PROTOCOL

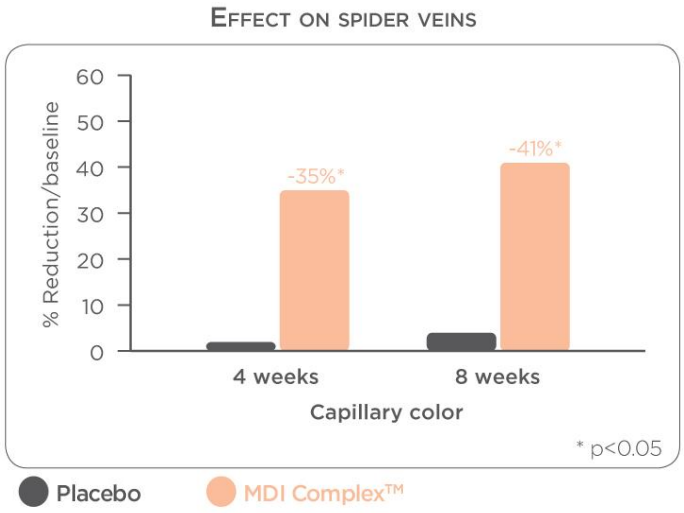
Subjects

A total of sixteen (16) healthy panelists participated in the study.

The panelists had visible but not excessive telangiectasia on the face. The panelists were provided with the product cream containing the MDI COMPLEX™ to be used on the full face, twice a day for 8 weeks. A fiber optic surface microscope was used to obtain images of a minimum of 4 sites on the face showing spider veins. The images were analyzed for gray values via the Zeiss Ibas Image Analyzer. Integrated Optical Density (IOD) was calculated for each site for each panelist. The values of the four sites from each panelist were averaged for each time point.

RESULTS

As observed in the graph below, there was a 35% significant decrease in the IOD after 4 weeks and this efficacy raised up to 41% after 8 weeks.



CONCLUSION

MDI COMPLEX™ is significantly effective ($p<0.05$) in reducing the appearance of spider veins of the face.

MDI Complex™ reduces the appearance of spider veins

EFFECT OF THE MDI COMPLEX™ ON LEG VARICOSE

OBJECTIVE

This clinical study was designed to study the effect of the MDI COMPLEX™ on the reduction of the appearance of leg varicose.

PROTOCOL

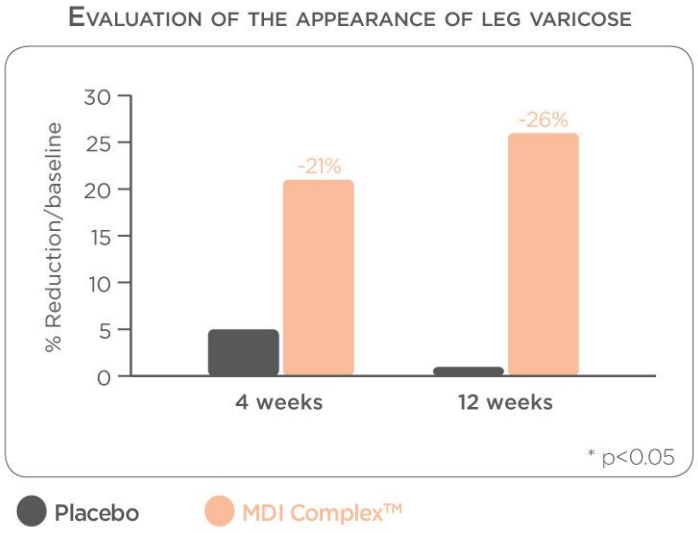
Subjects

A total of twenty (20) healthy panelists participated in the study.

The panelists had visible but not excessive leg varicose. The panelists were provided with the product cream containing the MDI COMPLEX™ to be used on the full leg, twice a day for up to 12 weeks. A fiber optic surface microscope was used to obtain images of a minimum of 4 sites on the leg where varicoses were present. The images were analyzed for gray values via the Zeiss Ibas Image Analyzer. Integrated Optical Density (IOD) was calculated for each site for each panelist. The values of the four sites from each panelist were averaged for each time point.

RESULTS

As observed in the graph below, there was a 21% significant decrease in the IOD after 4 weeks and this efficacy was 26% after 12 weeks.



CONCLUSION

MDI COMPLEX™ is significantly effective ($p<0.05$) in reducing the appearance of leg varicose.

MDI Complex® reduces the appearance of leg varicose

ANTI-IRRITANCY EFFECT OF MDI COMPLEX™

OBJECTIVE

This trial was aimed at verifying the effect of a topical application of the MDI COMPLEX™ on induced skin irritation.

PROTOCOL

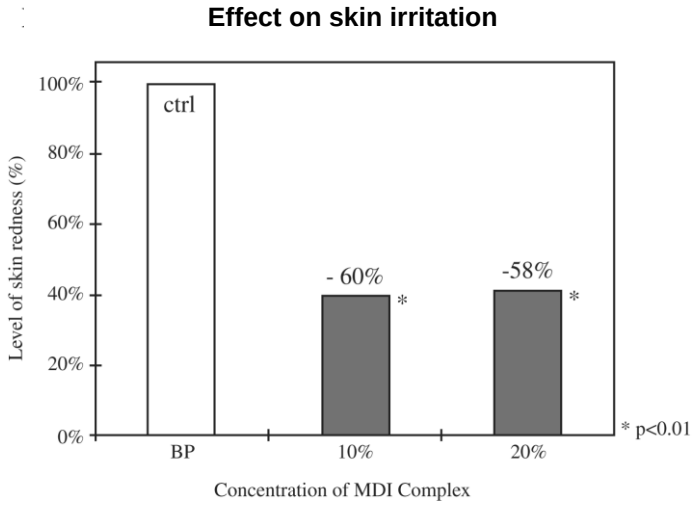
Methods

Volunteers with a history of skin sensitivity to Balsam of Peru were chosen for the studies. The MDI COMPLEX™ was applied on the ventral forearms of the panelists. It was allowed to absorb for twenty minutes and then Balsam of Peru, an irritant, was applied on the test sites. Skin irritation was measured in terms of increase in skin redness. The degree of redness was measured with the Minolta Chromameter and compared with the positive control.

The control (fully irritated skin) was the redness of skin treated with Balsam of Peru alone. Statistical significance was calculated via two tailed probability T-Test.

RESULTS

The MDI COMPLEX™ was effective in reducing skin irritation by 60% and 58% ($p<0.01$) at concentrations of 10% and 20% respectively.



CONCLUSION

The MDI COMPLEX™ is significantly effective ($p<0.01$) in reducing skin irritation.

MDI Complex® protects against induced skin irritation

EFFECT OF THE MDI COMPLEX™ ON PERIORBITAL DARK CIRCLES

OBJECTIVE

This study was designed to verify the effect of the MDI COMPLEX™ on the appearance periorbital dark circles.

PROTOCOL

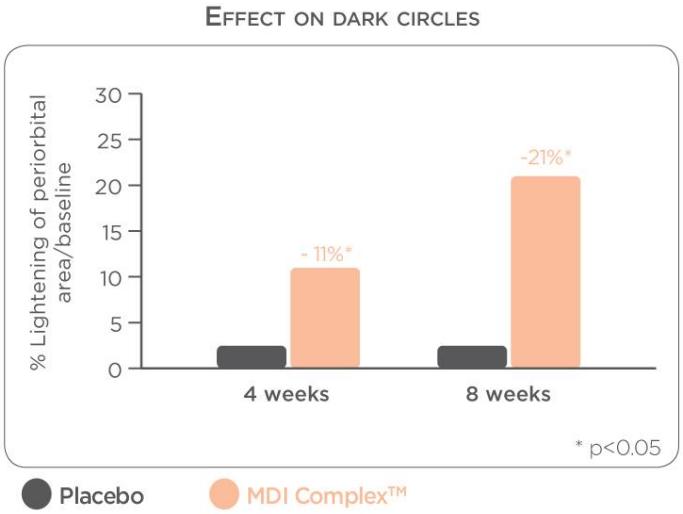
Subjects

A total of 18 female volunteers, aged between 18 to 65, participated in the study. The panel was divided in two groups, 10 volunteers were provided the cream base containing the MDI COMPLEX™ and 8 volunteers received the cream base alone as a control. Exclusion criteria included sunburn, rashes, burn marks, scars, etc.

The panelists applied the products around the eye area at least twice a day for 8 weeks. Measurements were obtained at baseline, and after 4 weeks and 8 weeks. At each visit photographs were obtained and analyzed via Image Analysis for the grey value which depicts darkness/lightness of skin.

RESULTS

The MDI COMPLEX™ significantly ($p<0.05$) reduced the intensity of periorbital dark circles. After treatment with the MDI COMPLEX™ for 4 weeks and 8 weeks, there was 11% and 21% lightening of the skin in the periorbital area respectively. Vehicle did not exhibit any notable change.



CONCLUSION

The MDI COMPLEX™ is significantly effective ($p<0.05$) in reducing the appearance of periorbital dark circles.

MDI Complex™ reduces the appearance of periorbital dark circles

EFFICACY OF THE MDI COMPLEX™ IN ROSACEA: SUMMARY OF A CLINICAL INVESTIGATION

PROTOCOL

Rosacea is characterized by the development of a dense network of microcapillaries. Essentially, rosacea is a cutaneous vascular disorder associated with flushing and erythema. Flushing increases blood flow in superficial dermal tissues, leading to an accumulation of extracellular fluid that overwhelms cutaneous lymphatic vessels. When these facial lymphatic vessels are damaged and fail to function, inflammatory edema occurs. Early-stage rosacea is characterized by simple erythema, which reflects an increase of erythrocytes in the inflamed superficial vasculature. In more advanced stages, the mechanical integrity of upper dermal extracellular matrix is compromised, causing the appearance of telangiectasia. Rosacea is also associated with increased activity of matrix metalloproteinases (MMP) that are responsible for the disorganization of the extracellular matrix surrounding lymphatic and blood vessels. The deterioration of the matrix around the blood vessels allows passive vasodilation revealed in the form of telangiectasia. Actual management of rosacea, such as with metronidazole, mainly targets overall erythema. Even though often successful, such treatements may leave behind telangiectasia that becomes even more visible on a fair skin background.

The MDI COMPLEX™ is a cosmetic ingredient that has been shown to inhibit the activity of matrix metalloproteinases (MMPs), enzymes that cause the degradation of components of skin's extracellular matrix. In vitro, the MDI COMPLEX™ inhibits MMP-2, -9 and -12. The clinical efficacy of the MDI COMPLEX™ has already been demonstrated in numerous clinical trials for different skin conditions and statistically significant responses were obtained in all trials. One of the evaluated condition was the efficacy of the MDI COMPLEX™ on facial and body telangiectasia. The favorable results on this trial prompted us to test the efficacy of the MDI COMPLEX™ for telangiectasia associated with skin redness problems. The efficacy of the MDI COMPLEX™ has been tested in a controlled, randomized (left/right) split-face, double-blind clinical trial for telangiectasia associated with skin redness problems with 23 subjects. Assessment of facial dryness, overall facial erythema, capillary color, capillary clarity, capillary branching and capillary length were made at week 0 (baseline) and week 12. The MDI COMPLEX™ scored positively and statistically compared to the placebo after 12 weeks of application in telangiectasia parameters. The effect on facial dryness and erythema confirmed the safety profile of the MDI COMPLEX™ . The MDI COMPLEX™ represents an efficacious ingredient to reduce the appearance of telangiectasia associated with skin redness problems such as rosacea.

Study design and evaluation

The efficacy of the MDI COMPLEX™ was tested in a randomized (left/right) split-face, double-blind rosacea clinical trial. Results were obtained with 23 subjects suffering of rosacea with visible telangiectasia. The assessments were made at week 0 (baseline) and week 12 by an expert grader. All visual exams were conducted in an environmentally controlled room (68-72 °F, 38-42%RH) in order to minimize vascular changes due to temperature. Each subject acclimated to the room for 30 minutes prior to each examination. Each subject applied a cream formulation containing 5% MDI COMPLEX™ to one side of the face and a cream without MDI COMPLEX™ to the other side of the face.

Six clinical parameters were evaluated during the 12-week study period. The parameters were facial dryness, overall facial erythema, capillary color, capillary clarity, capillary branching and capillary length. Among them, facial dryness and facial erythema were mainly monitored as safety purposes.

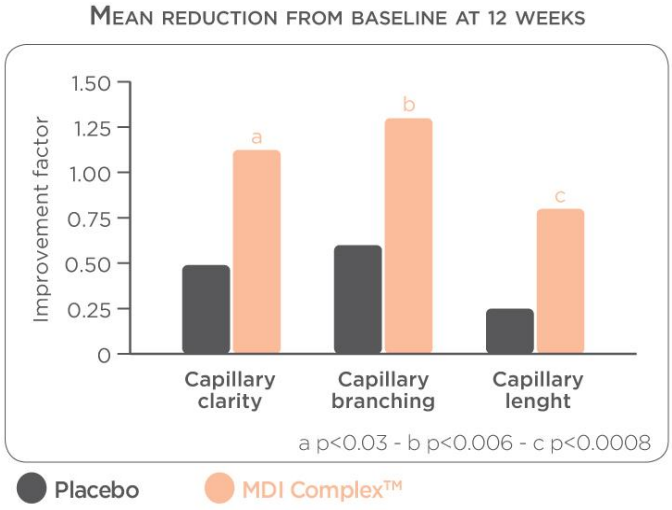
Subjects were visually graded as follows:

- Capillary Color: Measure of capillary darkness (0 to 5, light to dark)
- Capillary Clarity: Degree of definition of capillary margins (0 to 5, fuzzy margins to sharply defined margins)

- Capillary Branching: An estimate of the total number of capillary branches on each side. A clear sheet of acetate was used to trace a selection of vessels and to subsequently chart the progress of individual branches (0 to 5, no branching to extensive branching)
- Capillary Length: One prominent capillary on each side of the face was measured lengthwise using a caliper and measurements were repeated at each exam (measured in millimeters).
- Dryness: Measure of facial dryness (0 to 5, normal to dry skin)
- Erythema: Measure of facial erythema (0 to 5, normal to erythematous skin)

At week 12, the MDI group was compared with respect to the change from baseline. The changes between baseline and week 12 are shown in Figure 1. Figures 2 and 3 summarize the effect on facial dryness and facial erythema, respectively. The significance of the mean changes was determined using a paired t-test. The expert grader judged that 74% of subjects showed a greater overall improvement over baseline on the side on which the MDI COMPLEX™ was applied.

RESULTS



Improvement factor for the capillary color, capillary clarity, capillary branching and capillary length parameters. The improvement factors are obtained by comparing the clinical evaluation grade between time point Week 12 and baseline. A, b and c indicate the statistical difference between MDI COMPLEX™ and placebo at Week 12.

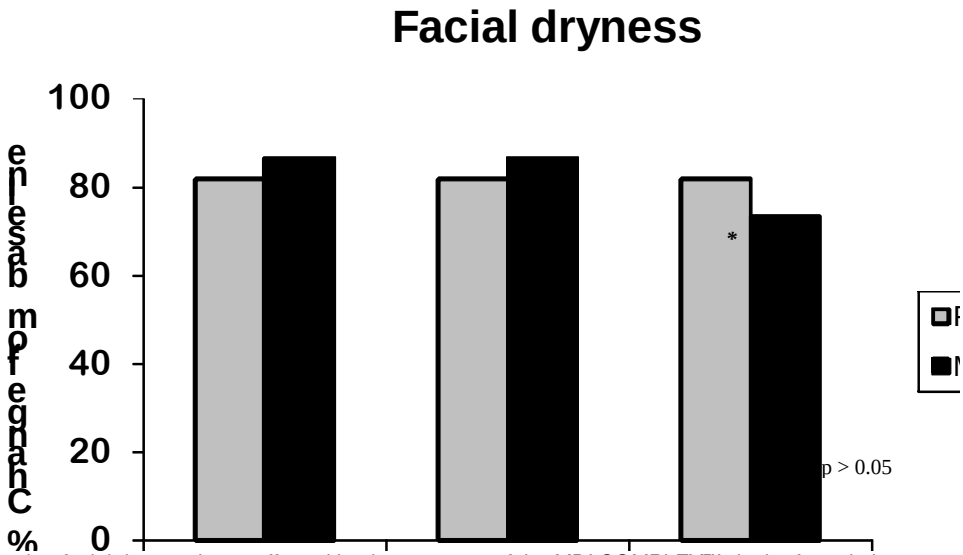
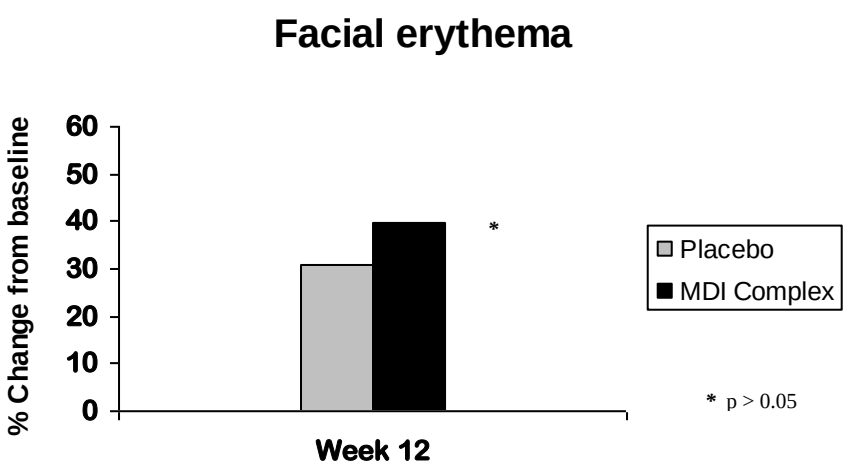


Figure 2 demonstrates that facial dryness is not affected by the presence of the MDI COMPLEX™ in the formulation.



MDI COMPLEX™ has a slight improvement, although not significant,over the placebo for facial erythema after 12 weeks.

CONCLUSION

Rosacea is an intricate skin condition in which extracellular matrix degradation (1), vasodilation (2) and possibly angiogenesis (3) are involved. Interestingly, the telangiectasia parameters such as capillary color, clarity, branching and length showed improvement after application of the MDI COMPLEX™ . Actual anti-rosacea treatments have little or no efficacy on these angiogenic parameters. Based on its spectrum of biological activity, the MDI COMPLEX™ can certainly be beneficial for this skin condition as demonstrated here. The action on MMPs could result in an amelioration of the integrity of the extracellular matrix thereby reducing the phenomenon of vasodilation. Haemodynamic parameters are also known to play a role in the proliferation of new blood vessels (4). In addition, since extracellular matrix degradation is a key event in vasodilation, the anti-collagenolytic action of the MDI COMPLEX™ could explain the reduction of the appearance of telangiectasia, possibly the most visible and less responsive signs of rosacea using currently available therapies.

The MDI COMPLEX™ has proven to be an active cosmetic ingredient in providing benefits for a skin condition already difficult to treat in dermatology. Therefore, the MDI COMPLEX™ may figure as a key product in the management of rosacea.

1. Wilkin JK. Rosacea. Pathophysiology and treatment. ***Arch Dermatol*** 1994 Mar;130(3):359-62.
2. Goldman MP, Bennett RG. Treatment of telangiectasia: a review. ***Am Acad Dermatol*** 1987 Aug;17(2 Pt 1):167-82.
3. Lachgar S, Charveron M, Gall Y, Bonafe JL. Inhibitory effects of retinoids on vascular endothelial growth factor production by cultured human skin keratinocytes. ***Dermatology*** 1999;199 Suppl 1:25-7.
4. Nasu R, Kimura H, Murata T, Tanaka Y. Blood flow influences vascular growth during tumour angiogenesis. British Journal of Cancer 1999;79 (5/6):780-786.

CONCLUSION

The deterioration of the extracellular matrix is a common phenomenon of aging conjunctive tissues and implies the progressive diminution in dermal thickness, collagen content and protein organization. Proteolytic enzymes, such as the interstitial collagenases, play a major role in the atrophy of the skin's extracellular matrix related to aging.

The MDI COMPLEX™, developed and manufactured by Lucas Meyer Cosmetics Inc., is a natural inhibitor of the above enzymes in the skin and is prepared from marine extract. As described in this document, the MDI COMPLEX™ showed strong *in vitro* inhibition of collagenase activity. This *in vitro* biological activity profile translates into many clinical studies as per the demonstration of the reduction of spider veins of the face, leg varicose, maintenance of protective functions of the skin (TEWL), anti-irritancy effects and reduction of the dark circles around the eyes.

Finally, the MDI COMPLEX™ is very easy to incorporate into a cosmetic formulation because of its complete hydrosolubility and it is very safe when used topically, as demonstrated by the safety tests performed.

COSMETIC APPLICATIONS

- Anti-aging
- Firming
- Sun Care & After sun-care
- Slimming
- Eye care
- Cermoceuticals



RECOMMENDATION OF USE

MDI COMPLEX™ should be incorporated at the end of the manufacturing process, at a temperature of **20/40°C**.

MDI COMPLEX™ is very easy to use. Its formulation does not pose any particular problem. Incompatibility might occur however, with compounds such as protein reducing agents, denaturing agents and strong alcohol solutions.

Recommended dosage:

1 to 5%

FORMULATIONS

EYE CREAM

PHASE	INGREDIENT	%W/W
A	M.O.D (Octyldodecyl Myristate) [1]	4.0
	Isopropyl Palmitate (Isopropyl Palmitate)	3.0
	Rofetan OE (Dicaprylyl Ether) [2]	2.0
	Apricotkernel Oil (Prunus Armeniaca (Apricot) Kernel Oil)	3.0
	Jojoba Oil Golden (Simmondsia Chinensis (Jojoba) Seed Oil)	2.0
	dl-α-Tocopherol (Tocopherol)	0.1
	Aristoflex AVC (Ammonium Acryloyldimethyltaurate/ VP copolymer)[3]	1.5
	Dow Corning 9041(Dimethicone (and) Dimethicone Crosspolymer)[4]	1.0
	PROTELAN ENS (Glyceryl Stearate, Cetearyl Alcohol, Stearic Acid, Sodium Lauroyl Glutamate) [7]	4.0
	Antioxidant	q.s.
B	Water (Aqua (Water))	up to 100
	EDTA (Tetrasodium EDTA)	0.05
C	MDI COMPLEX™ (Glycosaminoglycans)[5]	5.0
	Hydriame (Water (and) Glycosaminoglycans (and) Sclerotium Gum)[5]	1.0
	Lanachrys (Propylene Glycol & Water & Chrysanthellum Indicum Extract)[5]	1.0
	Dekluron M (Sodium Hyaluronate)[6]	1.0
	α-Bisabolol (Bisabolol)	0.05
	Perfume (Parfum (Fragrance))	0.2
	Preservative	q.s.

Our raw material suppliers:

(1) www.gattefosse.com, (2) www.dhw-ecogreenoleo.de, (3) www.fun.clariant.com,
(4) www.dowcorning.com, (5) www.lucasmeyercosmetics.com, (6) www.jandekker.com (7) www.zsm.com

Mixing Procedure	Part A): Mix the above oil components and Aristoflex AVC to a homogenous dispersion. Then add Dow Corning 9041 and PROTELAN ENS. Heat up to approx. 70°C. Part B): Heat up to approx. 70°C. Add part B) to part A) and homogenize directly. Cool down to approx. 35°C, add part C) and stir to homogeneity. Adjust the pH value to approx. 7.0 and homogenize again.

The above results have been obtained from trials in our laboratory and plant. In the light of changing conditions, they can serve only as a guide, and are therefore offered without obligation. We ask that the possible rights of third parties are observed.

ANTI-AGING CREAM

(With MDI COMPLEX™ and PRE Complex®)

PHASE	INGREDIENT	%W/W	SUPPLIER
A	Water	74.65	----------
	Glycerin	5.00	Charles Tennant & Co.
	Nipagin M	0.40	Nipa
	Triethanolamine	0.10	Dow Chemical
B	Promulgen D	5.00	Amerchol
	Tegosoft OP	1.00	Goldschmidt
	Blandol Mineral Oil	3.00	Witco Petroleum Specialties
	Shea Butter	2.00	Fanning Corporation
	Glyceryl Stearate SE	2.00	Stepan
	Lipovol Soy	2.00	Lipo Chemicals Inc.
	Vitamin E Acetate	0.10	Roche Vitamins & Fine Chemicals
	Nipasol M	0.20	Nipa
	Irgasan DP 300	0.30	Ciba Specialty Chemicals
C	Fragrance 700F46	0.25	Flavor & Fragrance Specialties
	MDI COMPLEX™	**2.00**	**Lucas Meyer Cosmetics**
	PRE Complex®	2.00	Lucas Meyer Cosmetics

Mixing Procedure	1. In a 316SS steam jacketed kettle, add the ingredients of sequence A. Heat to 75-80°C and mix with a lightening mixer using a marine type propeller at about 500 rpm. 2. In a second 316SS steam jacketed kettle, combine the ingredients of sequence B. Heat to 75-80°C and mix until uniform with a lightening mixer using a marine type propeller at about 500 rpm. 3. When A and B are both at 75-80°C and uniform, add B to A with mixing. Insert homogenizer and homogenize for 30 minutes at 2000 rpm. Heat to the kettle may be turned off during this step. Remove homogenizer and continue mixing with lightening mixer at about 800 rpm. 4. Begin cooling to 40°C with continued mixing. 5. At approximately 40°C, add sequence C. Mix until uniform. 6. Continue mixing and cool to room temperature or 30°C. 7. Remove from kettle and store in polypropylene lined drums.
Colour	White
Fragrance	light citrus
pH	7.0 - 7.5

CREAM FOR DARK CIRCLES

	INGREDIENTS	INCI NAMES	%
A	Purified Water	Water	74.70
	Glycerin	Glycerin	5.00
	Nipagin M	Methylparaben	0.40
	TEA 99%	Triethanolamine	0.10
	Irgasan DP300	Triclosan	0.30
B	Promulgen D	Cetearyl Alcohol (and) Ceteareth-20	5.00
	Tegosoft OP	Ethylhexyl Palmitate	1.00
	Blandol	Mineral Oil	4.00
	Shea Butter	Butyrospermum Parkii (Shea) Butter	1.00
	GMS-SE	GMS-SE	2.00
	Lipovol Soy	Glycine Soja (Soybean) Oil	1.00
	Vitamin E Acetate	Tocopheryl Acetate	0.10
	Nipasol M	Propylparaben	0.20
C	Fragrance 700F48	Fragrance	0.20
	MDI Complex™	Glycosaminoglycans	5.00

Mixing Procedure	1. In a 316SS steam jacketed kettle, add the ingredients of sequence A. Heat to 75-80°C and mix with a lightening mixer using a marine type propeller at about 500 rpm. 2. In a second 316SS steam jacketed kettle, combine the ingredients of sequence B. Heat to 75-80°C and mix until uniform with a lightening mixer using a marine type propeller at about 500 rpm. 3. When A and B are both at 75-80°C and uniform, add B to A with mixing. Insert homogenizer and homogenize for 30 minutes at 2000 rpm. Heat to the kettle may be turned off during this step. Remove homogenizer and continue mixing with lightening mixer at about 800 rpm. 4. Begin cooling to 40°C with continued mixing. 5. At approximately 40°C, add sequence C. Mix until uniform. 6. Continue mixing and cool to room temperature or 30°C. 7. Remove from kettle and store in polypropylene lined drums.
Colour	White
Fragrance	light citrus
pH	7.0 - 7.5
Viscosity	30,000 to 40,000 cps (LVT sp 3, 1.5 for 1 min., F=800)

SKIN CREAM FOR SPIDER VEINS AND VARICOSE VEINS

PHASE	INGREDIENT	%W/W
A	Purified Water	76.70
	Glycerin	5.00
	Methylparaben	0.40
	TEA 99%	0.10
	Irgasan DP300	0.30
B	Promulgen D	5.00
	Tegosoft OP	1.00
	Blandol Mineral Oil	3.00
	Shea Butter	2.00
	GMS-SE	2.00
	Lipovol Soy	2.00
	Vitamin E Acetate	0.10
	Propylparaben	0.20
C	Fragrance 700F48	0.20
	MDI COMPLEX™	**2.00**

Mixing Procedure	1. In a 316SS steam jacketed kettle, add the ingredients of sequence A. Heat to 75-80°C and mix with a lightening mixer using a marine type propeller at about 500 rpm. 2. In a second 316SS steam jacketed kettle, combine the ingredients of sequence B. Heat to 75-80°C and mix until uniform with a lightening mixer using a marine type propeller at about 500 rpm. 3. When A and B are both at 75-80°C and uniform, add B to A with mixing. Insert homogenizer and homogenize for 30 minutes at 2000 rpm. Heat to the kettle may be turned off during this step. Remove homogenizer and continue mixing with lightening mixer at about 800 rpm. 4. Begin cooling to 40°C with continued mixing. 5. At approximately 30°C, add sequence C. Mix until uniform. 6. Continue mixing and cool to room temperature or 30°C. 7. Remove from kettle and store in polypropylene lined drums.
Colour	white
Fragrance	light citrus
pH	6.5 - 7.5
Viscosity	30,000 to 40,000 cps (LVT sp 3, 1.5 for 1 min., F=800)

WHITENING AND ANTI-WRINKLE SKIN CREAM

(With MDI COMPLEX™ and Ascorbyl PM)

PHASE	INGREDIENT	%W/W	SUPPLIER
A	Purified Water	60.15	----------
	Propylene Glycol	10.00	Canada Colors & Chemicals
	MAP SL	3.00	Ikeda Corporation
	Nipagin M	0.40	Nipa
	Sodium Citrate	0.50	Charles Tennant Company
	Irgasan DP300	0.30	Ciba Specialty Chemicals
B	Promulgen D	8.00	Amerchol
	Tegosoft OP	1.00	Goldschmidt
	Blandol Mineral Oil	3.00	Witco Petroleum Specialties
	Shea Butter	2.00	Fanning Corporation
	GMS-SE	4.00	Stepan
	Lipovol Soy	2.00	Lipo Chemicals Inc.
	Vitamin E Acetate	0.10	Roche Vitamins & Fine Chemicals
	Nipasol M	0.20	Nipa
C	Fragrance 700F47	0.35	Flavor & Fragrance Specialties
	MDI COMPLEX™	**5.00**	**Lucas Meyer Cosmetics**

Mixing Procedure	1. In a 316SS steam jacketed kettle, add the ingredients of sequence A. Heat to 75-80°C and mix with a lightening mixer using a marine type propeller at about 500 rpm. 2. In a second 316SS steam jacketed kettle, combine the ingredients of sequence B. Heat to 75-80°C and mix until uniform with a lightening mixer using a marine type propeller at about 500 rpm. 3. When A and B are both at 75-80°C and uniform, add B to A with mixing. Insert homogenizer and homogenize for 30 minutes at 2000 rpm. Heat to the kettle may be turned off during this step. Remove homogenizer and continue mixing with lightening mixer at about 800 rpm. 4. Begin cooling to 40°C with continued mixing. 5. At approximately 30°C, add sequence C. Mix until uniform. 6. Continue mixing and cool to room temperature or 30°C. 7. Remove from kettle and store in polypropylene lined drums.
Colour	White
Fragrance	light citrus
pH	7.0 - 7.5
Viscosity	range 30,000 to 40,000 cps (LVT sp 3, 1.5 for 1 min., F=800)

REFERENCES

Abramson M, Huang CC, Localization of collagenase in human middle ear cholesteatoma, Laryngoscope, 1977, May, 87(5 Pt 1): 771-791.

Cerimele D, et al., Physiological changes in aging skin, Brit J Dermatol, 1990, 122 (Sup.13-20.)

Childers JW, Stricklin GP, Increased immunostaining of collagenase and TIMP in eruptive xanthoma, Am J Med Sci, 1989, Sep., 298(3): 172-176.

Harvell JD, et al., Percutaneous absorption and inflammation in aged skin : A review, J Am Acad Dermatol, 1994, Dec., 31(6): 1015-1021.

Herrmann G, et al., UVA irradiation stimulates the synthesis of various matrix-metalloproteinases (MMPs) in cultured human fibroblasts, Exp Dermatol, 1993, Mar., 2(2): 92-97.

Langholz O, et al., Collagen and collagenase gene expression in three-dimensional collagen lattices are differentially regulated by alpha 1 beta 1 and alpha 2 beta 1 integrins, J Cell Biol, 1995, Dec., 131(6 Pt 2): 1903-1915.

Oresajo C, et al., Eye area problems : Puffiness, Bags, Dark circles and Crowsfeet, Cosmetic & Toiletries, 1987, Jul., Vol. 102: 29-33.

Saarinen J, et al., Activation of human interstitial procollagenase through direct cleavage of the Leu83-Thr84 bond by mast cell chymase, J Biol Chem, 1994, Jul., 269(27): 18134-18140.

Sinclair RD, Ryan TJ, Proteolytic enzymes in wound healing : the role of enzymatic debridement, Australas J Dermatol, 1994; 35(1): 35-41.

Stricklin GP, Nanney LB, Immunolocalization of collagenase and TIMP in healing human burn wounds, J Invest Dermatol, 1994, Oct., 103(4): 488-492.

Uitto J, et al., Extracellular Matrix of the skin : 50 Years of Progress, J Invest Dermatol Suppl., 1989; 92(4): 61S-77S.

West MD, Pereira-Smith OM, Smith JR, Replicative senescence of human skin fibroblasts correlates with a loss of regulation and overexpression of collagenase activity, Exp Cell Res, 1989, Sep., 184(1): 138-147.

Dupont, E., et al., Extracts of shark cartilage having an anti-angiogenic activity and an effect on tumor regression; process of making thereof, United States Patent No. 5,618,925, April 8, 1997.

Elias, P. M., Epidermal lipids, barrier function and desquamation, J Invest Dermatol, 1993, 80: 044s-049s.

Frosch P. J., and Kligman A. M., Recognition of chemically vulnerable and delicate skin, in Principles of Cosmetics for the Dermatologist, Philip Frost and Stephen N Horwitz, eds, St Louis MO: CV Mosby, 1982, 287-296.

Grove G, Age related differences in healing of superficial wounds in humans in the effect of aging in oral mucosa and skin, Edited by C. A. Squier and M. W. Hill, CRC Press, 1994, 124-125.

Laden K, Studies on irritancy and stinging potential, J Soc Cosmet Chem, 1973, 24: 385-393.

Moses M. A., and Langer R., Inhibitors of angiogenesis, Biotechnology, 1991, Jul., 9: 630-634.

Moses M. A., et al., Identification of an inhibitor of neovascularization from cartilage, Science, 1990, June, 248: 1408-1410.

Oikawa T, et al., A novel angiogenic inhibitor derived from Japanese shark cartilage (I). Extraction and estimation of inhibitory activities towards tumor and embryonic angiogenesis. Cancer Letters, Elsevier Scientific Publishers Ireland Ltd., 1990, 51:181-186.

Oresajo C, et al., Eye area problems: Puffiness, Bags, Dark circles and Crowsfeet, Cosmetic & Toiletries, 1987, Jul., Vol. 102: 29-33.

Pinnagoda J, et al., Guidelines for transepidermal water loss (TEWL) measurement, Contact Dermatitis, 1990, 22: 164-178.

Walker M, The effect of liquid shark cartilage and other live proteins, Explore, 1994, 5(4): 5-10.