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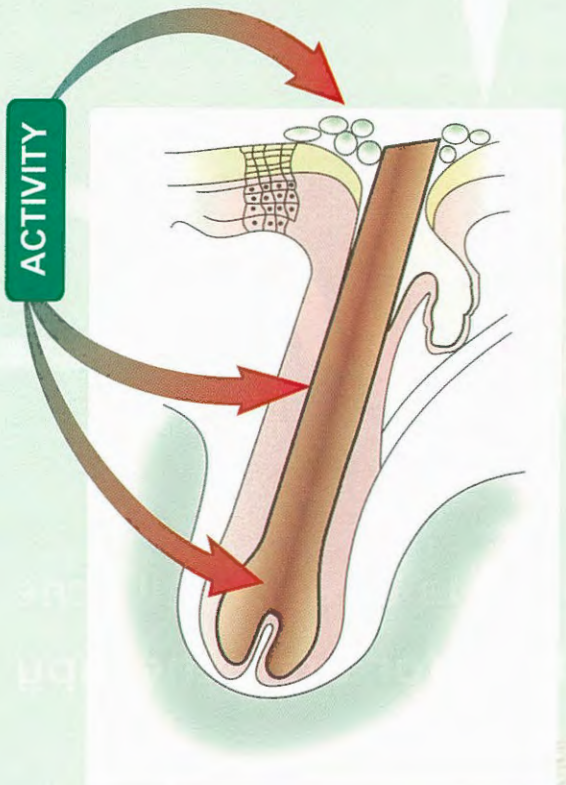

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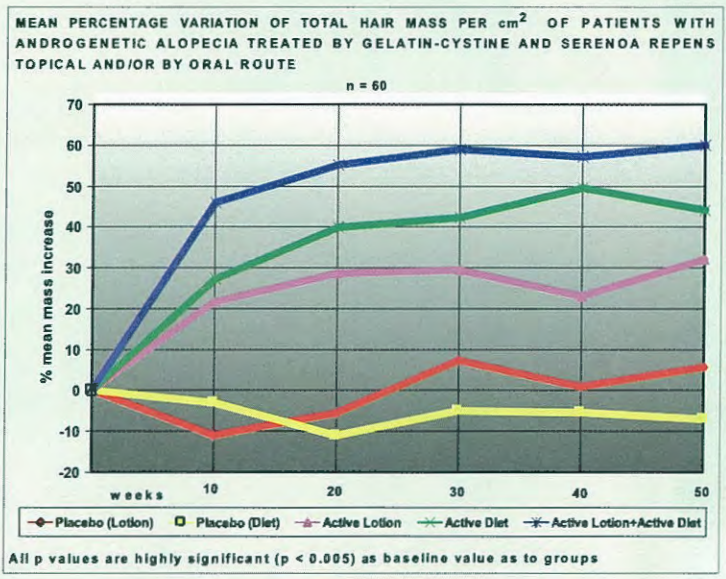

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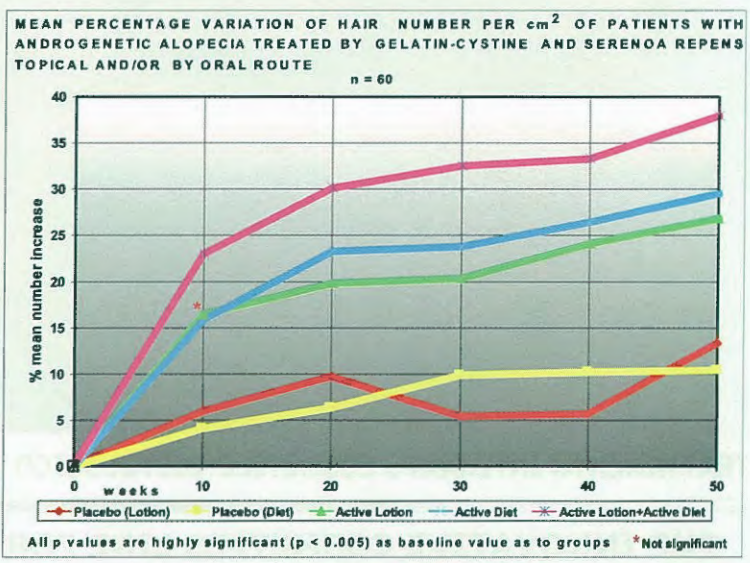

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[1] Morganti P, Fabrizi G, James B, Bruno C, *J. Appl. Cosmetol.* **16**,57,1998

[2] Fabrizi G, Morganti P, (1999),*SÖFW-Journal*, **125**, 2/3 :10-13

[3] Morganti P, (1999),*Eurocosmetics* **9**: 30-32

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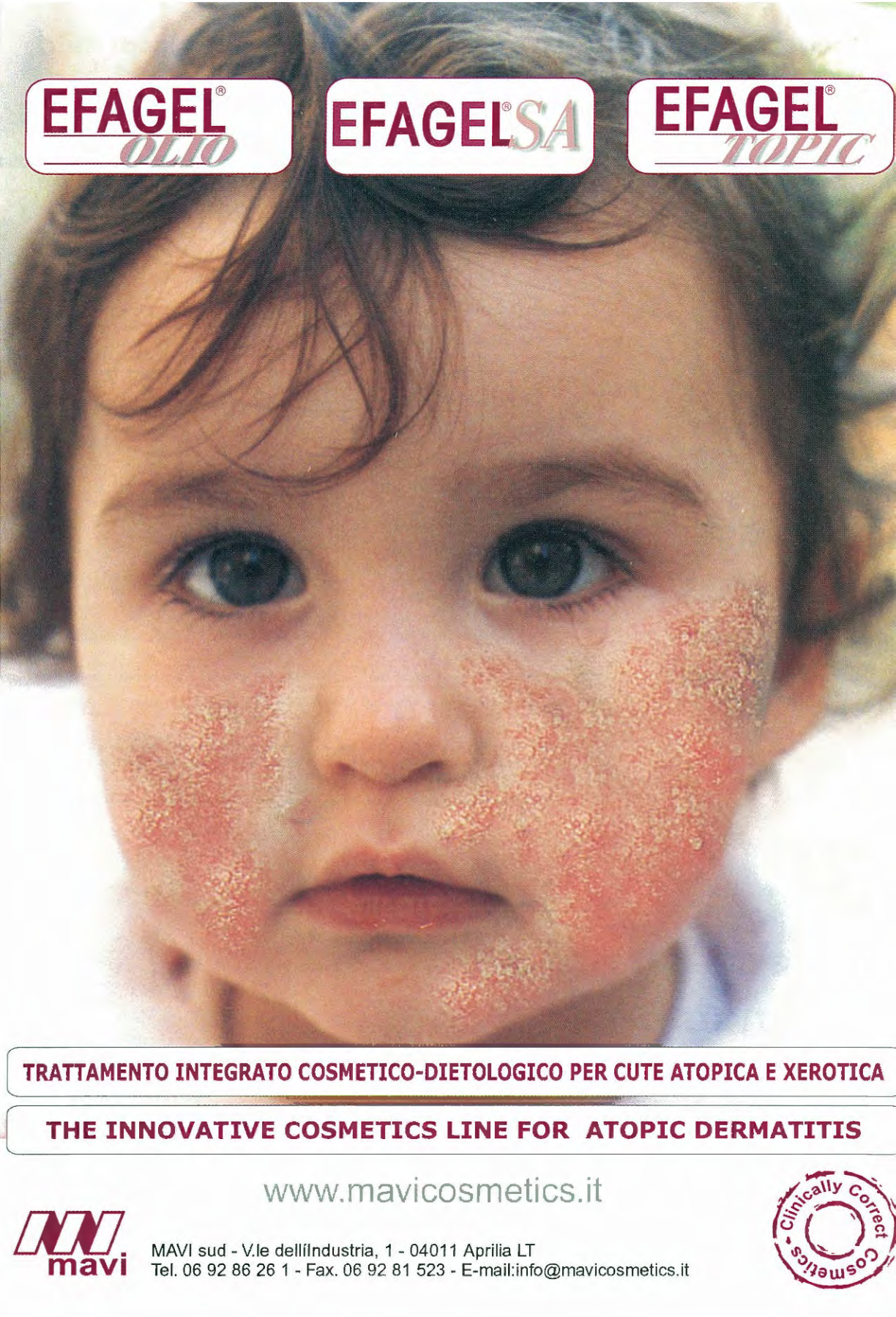
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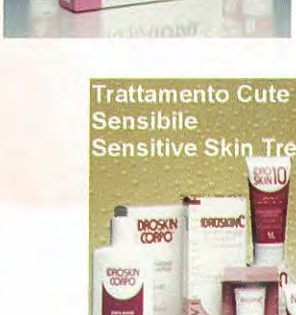

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Trimestrale di Dermatologia Cosmetologica
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Trimestrale di Dermatologia Cosmetologica
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J. Appl. Cosmetol. **21,** 01-08 (January/March 2003)

Hair and nail structure and function

Alfredo Rossi, PhD, Luca Barbieri, MD, Giuseppe Pistola, MD, Paola Bonaccorsi, MD, and Stefano Calvieri, PhD
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Key words: *Hair; Nail; UV Protection*

Summary

The hair and nail are skin appendages that share with the skin a common origin from the ectodermal layer. They fulfil important protective and cosmetic physiologic function. After intrauterine life, hairs are divided, by size in two major types: vellus and terminal. Terminal hair is described as being substantial or large in size with a diameter of about 60mm. The scalp hair is a typical terminal hair. Vellus hairs are smaller, more lightly pigmented and the diameter is less than 30mm. The hair has a growth cycle consisting in different phases: anagen, telogen , catagen.
The nail provides protection to the distal digit as well as aesthetic adornment and dexterity. Hair and nail disorders have a deep impact in the patient self-confidence and relation life. A vast spectrum of nail or hair alterations can be observed during the course of systemic disease although a causative association is seldom proved. A deep knowledge of the structure and physiology of the nail is necessary to correctly approach the pathogenesis of nail disorders.

Riassunto

I capelli e le unghie sono annessi cutanei che con la cute hanno in comune la derivazione ectodermica. Questi rivestono un importante funzione fisiologica di protezione e vestigiale. I peli terminali presentano un diametro di circa 60 micron. Il capello è un tipico pelo terminale. I peli vello sono più sottili, depigmentati, con diametro di circa 30 micron. Il ciclo del pelo consta di diverse fasi: anagen, telogen, catagen.
Le unghie forniscono protezione alle falangi distali delle mani e dei piedi, sono un adornamento estetico e favoriscono l'esecuzione dei movimenti fini. Le malattie dei capelli e delle unghie hanno un considerevole impatto sulla vita sociale e di relazione del paziente. Un vasto spettro di alterazioni delle unghie e dei capelli può essere osservato in corso di malattie sistemiche sebbene il nesso causale sia raramente provato. Una approfondita conoscenza della struttura anatomica e della fisiologia dell'unghia consentirà un corretto approccio patogenetico.

HAIR ANATOMY

Two main types of hair are present after birth, although intermediate forms are also seen: vellus hair (fig.1), unmedullated, unpigmented or lightly pigmented, growing to a maximum of 2 cm, are usually located in body areas normally considered "hairless", such as a child's cheek; on the contrary, terminal hair (fig.2) are medullated and variously pigmented.

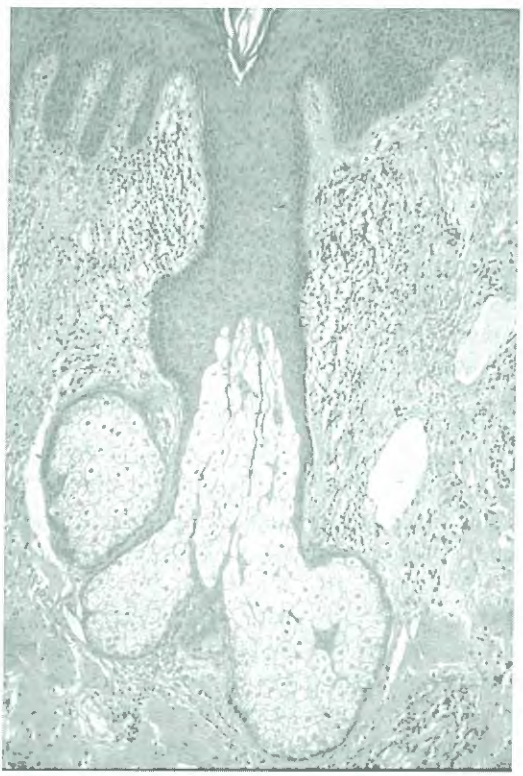

***Fig. 1** Histological aspects of a vellus hair.*

They can grow to considerable length and are best defined by their size relative to vellus hair (ca. 2x diameter). Terminal hair is the typical hair of the scalp throughout life in normal individuals. Each hair shaft is produced by an hair follicle, a mainly epithelial structure which protrudes down through the dermis, often into subcutaneous adipose tissue.

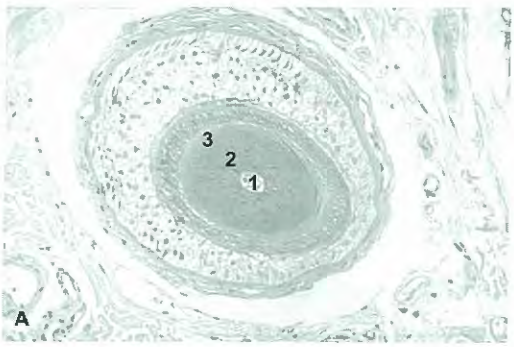

***Fig. 2** Histological aspects of a terminal hair*

The hair follicle consists of a complex system of multiple tissue compartments that are clearly distinguishable by their morphology and type of differentiation. As hair follicle is associated with a sebaceous gland, arrector pili muscle and apocrine sweat gland, the conventional designation for the pilo-sebaceous unit fails to do justice to it, both linguistically and morphologically. In fact the unit is not a "hair-sebaceous" one, but it is a folliculo-sebaceous-apocrine smooth-muscled and nervous and vascular unit [1].
On average, the entire body surface of an adult contains 5.000.000 follicles [2] (Tab. I).

Table I.
Hair follicles number.

Total hair follicles	5,000,000
Head	1,000,000
Scalp	100,000

The maximum number of hair follicles is present at birth. Scalp biopsies have shown 700-800 follicles per cm2 at birth, that decrease approssimately to 300 per cm2 in adult life. As seen in Tab. II, hair follicle morphology varies according with race. A wide range of variation is also present in hair colour. Depending on the of presence of eumelanin, pheomelanin or oxymelanin the hair can be black or brown, blond or red respectively.

Table I.
Hair follicle morphology: racial variations.

Caucasoids	Variable from straight to helical
Negroids	Helical follicle
Mongolian	Straight follicle

Anatomically, each hair can be divided in two parts: an external one, named hair shaft and an inner one, named hair follicle. The mayor structure of the hair shaft is the cortex. It consists of elongated cells that run parallel to the fiber axis. Within these cells are located tbe tonofilaments and interfilamentous matrix material that are responsible for most of the physicochemical properties characteristic of whole hair. It is surrounded by a cuticle of overlapping flattened cells with their free margins pointing upwards to the hair tip. Thick hairs have a central zone of more loosely organized keratinised material, the medulla (figg.3a-3b) [3].

In the hair follicle, the hair shaft is surrounded (from central to peripheral) by the inner root sheath, the outer root sheath, the basement membrane and the perifollicular sheath of connective tissue.

A mature follicle in anagen, as viewed in sections oriented vertically and by conventional microscopy, can be divided in two parts: an upper segment and a lower segment. This subdivision has a relevance even from a biological point of view. In fact, while the upper segment is permanent, the lower segment is the part of a follicle that undergoes changes during the hair cycle, marked by growing, involuting and resting. The upper segment extends from the ostium of the follicle to the attachment site of the arrector pili muscle. It is dividend in two parts: the upper infundibulum, from the ostium of the follicle to the point at which the sebaceous duct enters the follicle, and the isthmus which extends from the inferior boundary of the infundibulum to the insertion of the arrector pili muscle (fig.4).

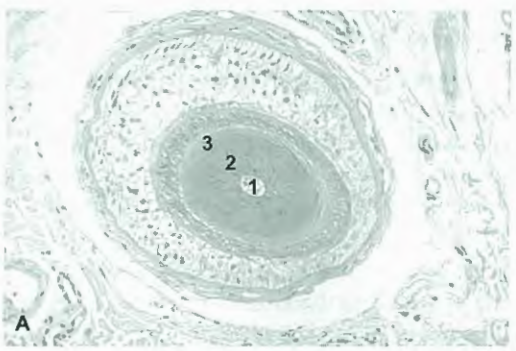

Fig. 3A *Histological aspect of a transverse section of hair: 1) medulla, 2) cortex, 3) cuticle.*

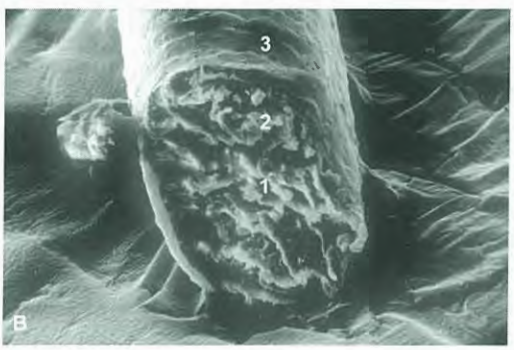

Fig. 3B *Ultrastructural aspect of hair shaft transverse section: 1) medulla, 2) cortex, 3) cuticle.*

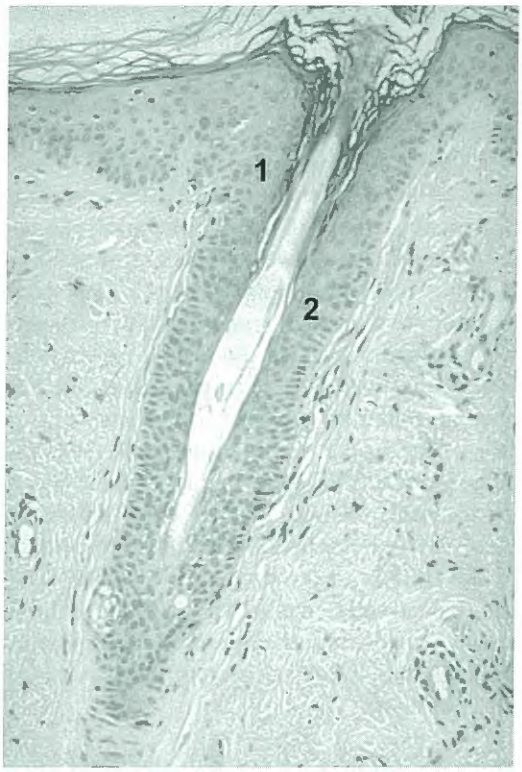

Fig. 4 *Histological aspects of the upper segment of a hair follicle: 1) infundibulum, 2) isthmus.*

The bulge (fig.5) is a localized thickening of the outer sheath and it is a proliferation of cells of the outer sheath at isthmus.

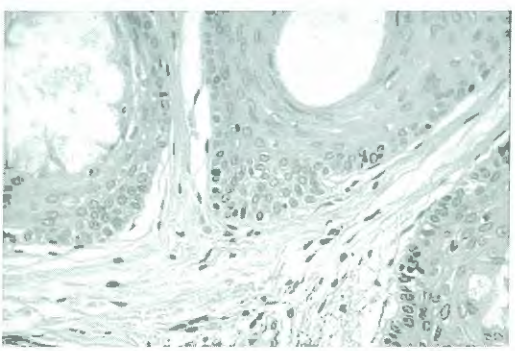

Fig. 5 *Histological aspect of the bulge.*

This proliferation is more marked at the site of attachment of the arrector pili muscle. The bulge is probably the source of germinative cells that enables a follicle to be reconstituited at the end of telogen [4-6].

The lower segment extends from the insertion of the arrector pili muscle to the base of the follicle and is divided in the stem and the bulb.

The stem [1] is the upper part of the lower segment. It extends from the upper boundary of the bulb to the base of the isthmus.

The lowest part of the follicle is named the bulb (fig.6).

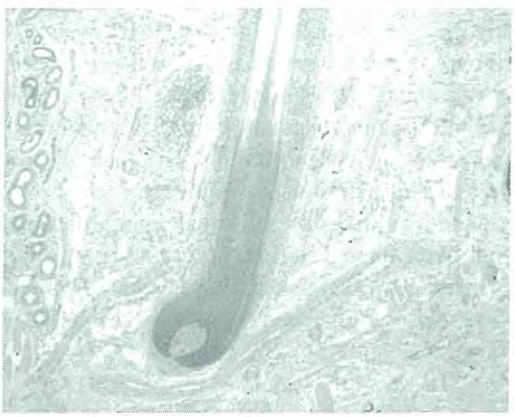

Fig. 6 *Histological aspect of the bulb.*

It is composed by the matrix, the supramatrical zone and the keratogenous zone.

The matricial zone extends from the base of the bulb to the site where the bulb has the widest diameter which is called the critical line of Auber.

The supramatrical zone spans from the critical line of Auber to the B-Fringe which defines the area where keratinization in the Henle's layer of the inner root sheath begins and where the onter root sheath becomes stratified.

The keratogenous zone boundaries are defined by the B-fringe proximally and the A-Fringe (Adamson's fringe) distally. The A-fringe is the site where tbe cornification of the cortical keratinocytes is first observed and where Huxley's layer loses its trichohyalin granules (fig.7).

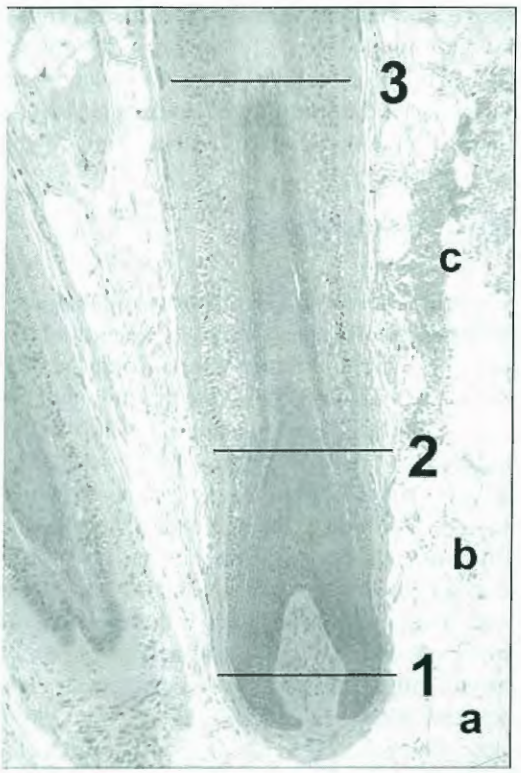

Fig. 7 The three areas of the bulb: 1) critical line of Auber, 2) B-fringe, 3) A-fringe, a) matrical zone, b) supramatrical zone, c) keratogenous zone.

The matrix contains the proliferating pool of undifferentiated cells that give rise to the three components of the inner sheath and to the hair shaft. Although the matrix has been assumed to be the source of the outer root sheath, that has not yet been demonstrated. Above the matrix, in the supramatrical zone, begins the differentiation of the progenitor cells. In the keratogenous zone the cells begin to die and cornify.

The anagen hair follicle contains an assembly of specialized fibroblasts, the dermal papilla (fig.8), which is located in the center of the hair bulb and surrounded by the epidermally derived germinative epithelium.

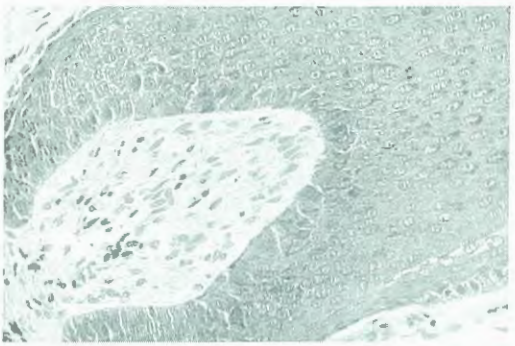

Fig. 8 The dermal papilla.

The dermal papilla is composed by various cellular types (fibroblasts, Langherans cells, lymphocytes, mast cells), extracellular matrix, blood vessels and nervous fibres and is probably responsible for inducing differentiation of the hair bulb matrix [7-8]. This parallels embryologic events, where development of the epithelial component is dependent upon inductive stimuli from the mesenchyme [9]. There is also evidence that the size of the hair follicle and the volume of the hair fiber are determined by the volume of the dermal papilla [10-11]. In the hair follicle, hair shaft is surrounded by the inner root sheath, which is composed, moving inward, of Henle's layer, Huxley's layer and the cuticle of the inner root sheath. The inner root sheath stretches from the base of the bulb to the isthmus, where the cornified cells desquamate. The outer root sheath is located from the inner root sheath and extends from the base of the follicle to the lower boundary of the infundibulum. It is composed by epithelial cells that changes gradually in width and colour, through the follicle length. At last, the dermal sheath is a connective tissue that surrounds the outside of the hair follicle (fig.9).

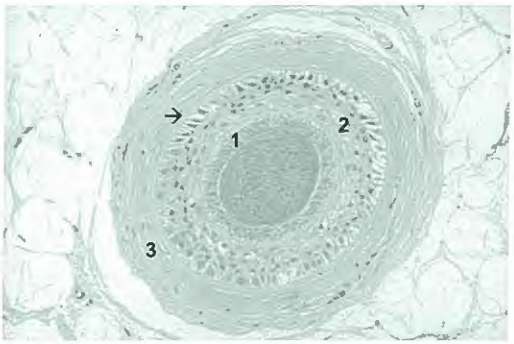

Fig. 9 Histological aspect of the root sheaths: 1) inner root sheath, 2) outer root sheath, 3) dermal sheath, the basement membrane (arrow).

HUMAN HAIR FUNCTIONS

Hair is an important element of human appearance that is commonly used for recognition and is one determinant of physical attractiveness [12]. Across the centuries, the decoration of scalp hair has been a medium of social communication and a display of social identity or status. Several studies have shown the negative psychological impact of various conditions associated with hair loss [13-15]. For many years hair has been regarded as important only for these aesthetic functions, but recently hair follicle epithelial cells and their contribution to healing skin have attracted particular attention [16]. It is believed that epithelial outer root sheath cells provide replacement cells for the epidermis in response to wounding. Moreover, the dermal sheath probably contains progenitor cells that become important in the wound healing process [17]. Hair plays an important role even in skin repigmentation. In adult follicle, melanocytes are found in the bulb epithelium, aud in the epithelial outer root sheath cells at the infundibulum and at the lower part of the follicle. While only active (DOPA-positive) melanocytes exist in the epidermis of normal skin, there are some inactive (DOPA-negative) melanocytes in the outer root sheath of the lower part of a normal hair follicle. These latter cells appear to form a melanocyte reservoir in the skin. Under certain circumstances, for example during repigmentation of vitiligo, outer root melanocytes proliferate and migrate to the epidermis [18]. At last hair offers a valid UV protection of the scalp skin.

NAIL ANATOMY

Like hair, the nail unit forms by invagination of the epidermis into the dermis. It consists of the nail plate and the tissues that surround it. The nail plate is a fully keratinized structure that covers the dorsal distal phalanges of the fingers and toes. It results from maturation and differentiation of the epithelial nail matrix cells and is firmly attached to the nail bed, which partially contributes to its formation. The nail bed is the structure upon which the nail rests. It extends from the distal margin of the lunula to the epidermis of the hyponychium and, normally, appears pink because of a blood-filled vascular network that is visible through the translucent plate. The nail bed keratinization produces one fifth of the total mass of the nail plate which consists of a thin, horny layer that forms the ventral nail plate.

The nail matrix is a specialized epithelial structure that lies underneath the proximal nail fold. The epithelium of the nail matrix consists of basal cells that differentiate into spinous cells and subsequently into the orthokeratotic cells that compose the nail plate. The matrix appears as a convex crescent and consists of a proximal or dorsal portion and a distal or ventral portion. The proximal portion of the matrix is the predominant supplier of cornified cells that constitute the dorsal nail plate, whereas the distal matrix (lunula) contributes the intermediate nail plate.

Proximally and laterally the nail plate is surrounded by the nail folds, which cover its lateral and proximal margins. The hyponichium is the anatomic limit between the nail bed and the free margin of the nail plate.

HUMAN NAIL FUNCTIONS

Probably, the most important function of the fingernails consist in enhancing tactile discrimination and fine movements. Furthermore, fingernails are utilized for scratching and grooming and are an efficient natural weapon [19]. Toenails protect the distal toes and contribute to pedal biomechanics. The nails also contribute to the aesthetic appearance of the hand and foot.

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BOTANICALS FOR INNOVATIVE COSME-NUTRI-CEUTICALS

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Received: *February, 2002*

Key words: *Skin aging, LEUCOSELECT™, procyanidins*

Summary

Cutaneous aging is a complex biological process affecting various layers of the skin, but the major changes are seen in the dermis. There are two biologically independent aging processes that occur simultaneously. The first is intrinsic aging and affect skin as it probably affects the internal organs. The second is extrinsic aging, the results of exposure to the elements, primarily ultraviolet irradiation.
There is the need to protect the skin from premature aging by tools able to counteract the action of the proteases on the dermis and the disappearance of the antioxidant defences from the skin.
On the basis of recent findings it is possible to suggest the use of some active ingredients of botanical origin which, besides to be strong and bioavailable antioxidants, are well known to be vascular protectors and anti-senescence as well.
LEUCOSELECT™ PHYTOSOME® is the linkage between the pharmaceutical usage of natural polyphenols in the field of vascular protection and the epidemiological evidences on their high dietary intake and low incidence of chronic vascular diseases.
Moreover, it is a potent quencher of reactive oxygen species, it preserves the integrity of PUFAs, and it prevents the erythema development.
LEUCOSELECT™ PHYTOSOME® is also a bioavailable form, both by oral and topical route of administration, which guarantees grape procyanidins the reaching of target tissues. There they can exert their antioxidant and antiproteasic properties, having a potential role in the prevention of photoaging and, probably, photocarcinogenesis.

Riassunto

L'invecchiamento cutaneo è un complesso processo biologico che influenza i vari strati della pelle; i maggiori cambiamenti avvengono però nel derma. Vi sono due processi di invecchiamento che avvengono simultaneamente. Il primo è l'invecchiamento intrinseco e influenza la pelle come pure gli organi interni. Il secondo è l'invecchiamento estrinseco, risultato dell'esposizione agli elementi, principalmente le radiazioni ultraviolette.
Vi è la necessità di proteggere la pelle dall'invecchiamento prematuro con strumenti capaci di contrastare l'azione delle proteasi nel derma e la scomparsa delle difese antiossidanti della pelle.
Sulla base di dati recenti è possibile suggerire l'uso di alcuni ingredienti attivi di origine vegetale che, oltre ad essere antiossidanti potenti e biodisponibili, sono ben noti come protettori vascolari e sostanze anti-senescenza.
Il LEUCOSELECT™ PHYTOSOME® è l'anello fra l'uso farmaceutico dei polifenoli naturali nel

campo della protezione vascolare e le prove epidemiologiche basate sulla loro elevata assunzione con la dieta, accompagnata da una bassa incidenza di malattie vascolari croniche.
Inoltre, è un potente "quencher" di specie reattive dell'ossigeno, protegge l'integrità dei PUFA, e previene lo sviluppo dell'eritema.
Il LEUCOSELECT™ PHYTOSOME® è anche una forma biodisponibile, sia per via di somministrazione orale che topica, garantendo alle procianidine il raggiungimento dei tessuti bersaglio. Esse possono così realizzare le loro proprietà autiossidanti e antiproteasiche, svolgendo un importante ruolo potenziale nella preveuzione del fotoinvecchiamento e, con tutta probabilità, della fotocarcinogeuesi.

INTRODUCTION

A remarkable new phenomenon is occurring throughout the world: older ages are becoming far more common; and in several countries the fastest growing age group is the oldest. Many fears about aging are related to the concept that everything declines with aging. In fact, a number of important physiologic variables do decline with aging mainly affecting central nervous and cardiovascular systems, and also the skin. Cutaneous aging is a complex biological process affecting various layers of the skin, but the major changes are seen in the dermis. There are two biologically independent aging processes that occur simultaneously. The first is intrinsic aging and affect skin as it probably affects the internal organs. The second is extrinsic aging, the results of exposure to the elements, primarily ultraviolet irradiation (Figures 1, 2). In

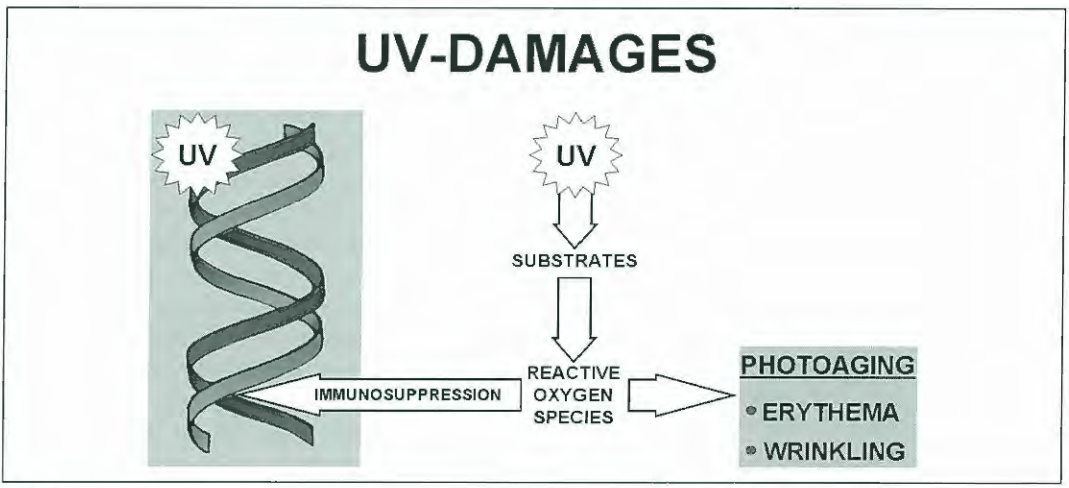


Fig. 1

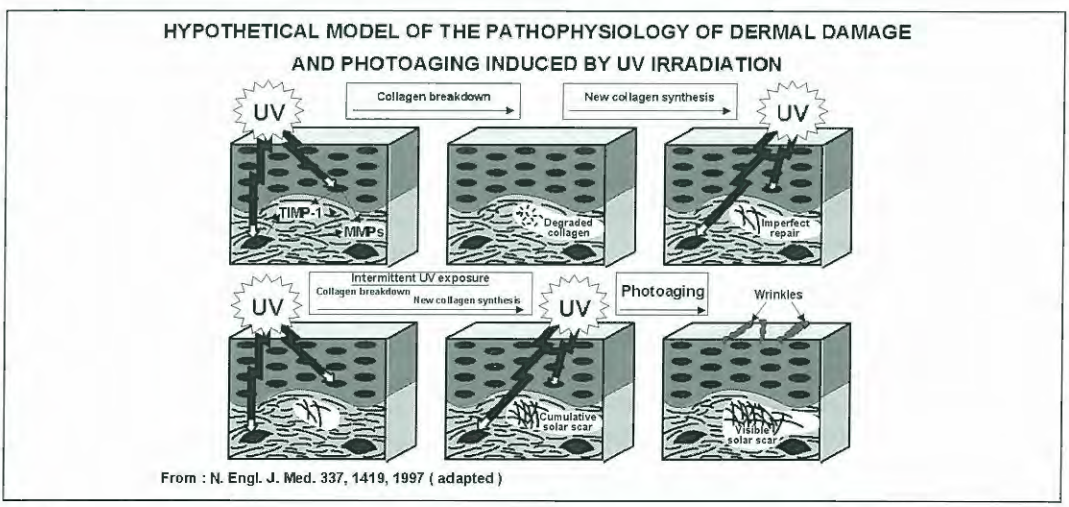


Fig.2

areas exposed to the sun, particularly the face and the backs of the hands, damage from photoaging is superimposed on tissue degeneration from innate aging. Thus, the most noticeable changes on facial and neck skin, the primary area that patients are concemed about, results from a combination of intrinsic and extrinsic aging processes.

From a biochemical standpoint, photoaging is thought to be provoked mainly by:

- the action of some proteases, mainly metalloproteases, overproduced by keratinocytes and fibroblasts because of the interaction with ultraviolet irradiation (these proteases are degradative enzymes able to irreversibly damage collagen, elastin and hyaluronic acid, bringing about dermis scars and visible wrinkles);
- the oxidative stress, able to eliminate the normal skin antioxidant defences in a very short time.

On the basis of these general considerations, it looks clear the need to protect the skin from premature aging by tools able to counteract the action of the proteases on the dermis (increasing at the same time the capability of fibroblasts to produce and release new collagen fibers) and the disappearance of the antioxidant defences from the skin.

Even though it is maybe impossible to totally abolish skin damage due to age, on the basis of recent findings it is possible to suggest the use of some active ingredients of botanical origin which, besides to be strong and bioavailable antioxidants, are well known to be vascular protectors and anti-senescence as well.

In formulating cosmetic products containing these herbal derivatives, the main problem is to guarantee the better possible bioavailability, in order to be sure that the active principles effectively can reach their site of action: in this case, the dermis. Quite surprisingly, the experience demostrated that both by oral and topical route the vehiculation with the phospholipids can improve absorption of several classes of substances. In the first case, because gastrointestinal absorption is favored when the substance is in a lipophilic form, in the second, because this form is able to enter the skin barrier. So, conceptually there are no significant differences between treating the dermis with a topical or an oral formulation, provided that the actives arrive in a concentration able to give the desired effects.

FROM VITAMIN P TO THE "FRENCH PARADOX"

Some decades ago Hungarian investigators discovered that flavonoids, commonly present in the human diet, were provided with relevant properties in respect of the cardiovascular system.1 Flavonoids and other polyphenols were than described to exert a sort of vitaminic action, which the investigators called vitamin P activity, mainly connected witb the capacity to improve capillary resistance and to normalize an altered capillary permeability. In the following years, a controversial debate took place in the scientific community about the validity of the term vitamin P, and finally this denomination was rejected since the role of polyphenols were recognized to be not comparable to that of vitamins. Nevertheless what remained well demonstrated by a number of pharmacological tests, pharmacokinetics evidences and clinical trials was the tropism of some polyphenols for the cardiovascular system. Within tbis huge family of natural products, some specific compounds such as the case of grape procyanidins, demonstrated a particularly elevated specificity in the targeting to the cardiovascular system. This constituted the basis for the development of prescription drugs containing standardized extracts from grape seeds (the part of the plant particularly rich in procyanidins) and devoted to the relief of disturbances of the microcirculation. These pharmaceuticals are widely used in European countries and particularly in France they are still within the top reimbursed products.

Recently, another interesting finding coming in this case from epidemiology suggested that grape polyphenols, present also in red wine, could act as preventive agents in respect of the development of chronic diseases of the cardiovascular system, such as atherosclerosis (2).
This evidence came out mostly from the evaluation that the low incidence of cardiovascular diseases in France, is paralleled by a very high dietary intake of lipids, but concomitantly also by an elevated consumption of red wine (Figure 3). Scientists agree that this last event well explains the apparent "French Paradox" and they suggest that the "antioxidant properties" of red wine polyphenols could be good candidates as responsible for the preventive effect (3,4).
Nowadays, hundreds of papers are available dealing with the antioxidant properties of natural polyphenols, most of the studies being conducted *in vitro* and concentrated on monomeric products. In this respect studies on grape procyanidins constitute a unique among natural antioxidants since they deal with oligomeric polyphenols and include both *in vitro* and *in vivo* investigations.
At the light of these considerations it is not an overestimation to indicate grape procyanidins as a really unique example of pharmacologically and clinically proved biologically-active antioxidant, provided with a specific indication in the prevention and therapy of cardiovascular diseases.

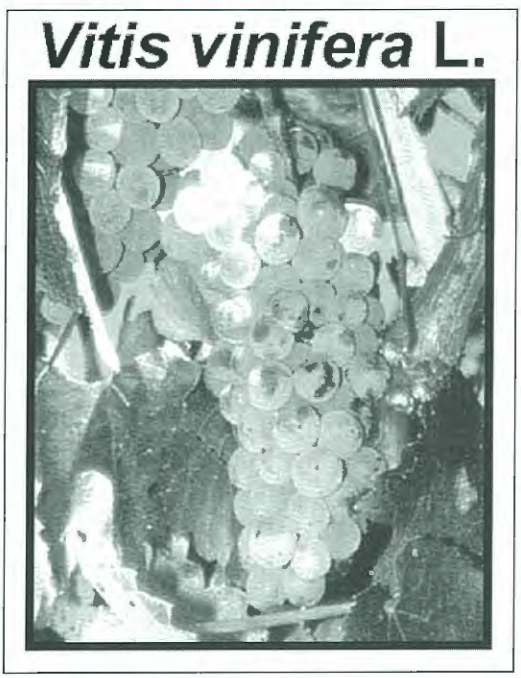


Fig. 3

GRAPE SEEDS EXTRACT AS A STANDARDIZED SOURCE OF GRAPE PROCYANIDINS

Most of the studies performed on grape procyanidins were made possible by the availability of standardized extracts which could guarantee the constancy of composition of a so complex chemical mixture. Recently, the definition of the industrially produced grape seeds extract LEUCOSELECT™ has been completely elucidated by using fractionation with Sephadex® and by analyzing the isolated fractions with HPLC-UV, GPC, HPLC-TSP MS and ES-MS (5).
The composition of LEUCOSELECT™ (Figures 4, 5) has the following pattern:

- (+)-catechin, (-)-epicatechin (15%)
- (-)-epicatechin gallate, dimers, trimers, tetramers and their gallates (80%)
- pentamers, hexamers, heptamers and their gallates (5%)

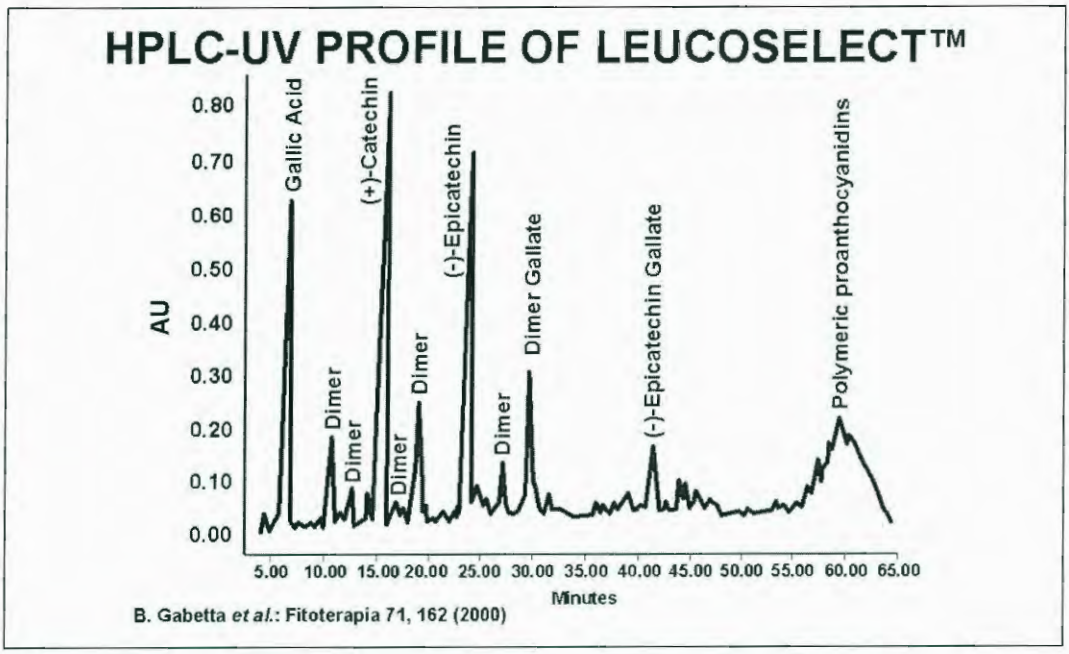

HPLC-UV PROFILE OF LEUCOSELECT™
AU
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Gallic Acid
Dimer
Dimer
(+)-Catechin
Dimer
Dimer
(-)-Epicatechin
Dimer
Dimer Gallate
(-)-Epicatechin Gallate
Polymeric proanthocyanidins
5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00
Minutes
B. Gabetta et al.: Fitoterapia 71, 162 (2000)

Fig. 4

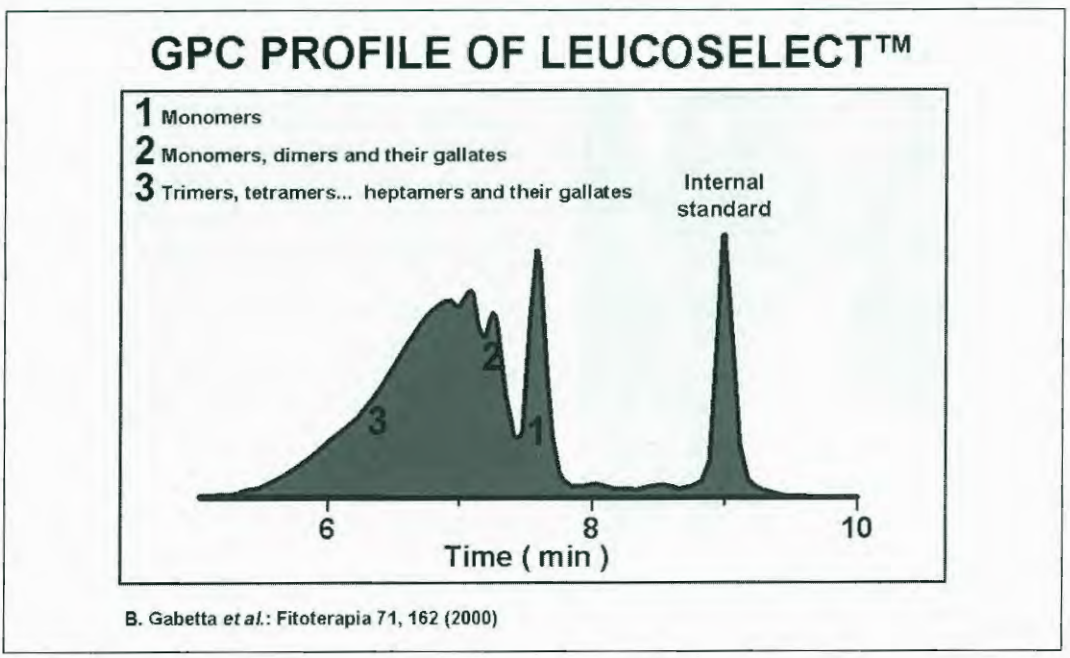

GPC PROFILE OF LEUCOSELECT™
1 Monomers
2 Monomers, dimers and their gallates
3 Trimers, tetramers... heptamers and their gallates
Internal standard
3
2
1
6
8
10
Time (min)
B. Gabetta et al.: Fitoterapia 71, 162 (2000)

Fig. 5

LEUCOSELECT™: ONE OF THE MOST EFFECTIVE NATURAL ANTIOXIDANTS

The antioxidant effect seems to be responsible for most of the biological properties reported for grape procyanidins. In this light the availability of a standardized extract such as LEUCOSELECT™ allowed the detailed *in vitro* definition of the antioxidant profile along with other biochemical properties such as the inhibitory effect on several proteases (including collagenase and jaluronidase) which has been proved (Figure 6) in several experimental models (6,8):

- DPPH scavenging activity (Figure 7)

IN VITRO INHIBITION OF PROTEASES BY LEUCOSELECT™

	IC_{50} (µmol/L)	
	LEUCOSELECT™	Catechin
Xanthine oxidase	2.40	300
Elastase	4.24	uneffective
Collagenase	38.00	1800
Hyaluronidase	80.00	uneffective
ß-Glucuronidase	1.10	75

R. Maffei Facino *et al.*: Arzneim. Forsch./Drug Res. 44 (I), (1994) 592-601

Fig. 6

- hydroxyl radical entrapping capacity after water sonolysis (ESR study)
- superoxide anion quenching action in a non-enzymatic generating system
- peroxyl radical scavenging activity in PCL (phosphatidylcholine liposomes) and MLM (methyl-linoleate micelles) stimulated by ultrasounds and UV
- iron (II)/copper (II)-chelating properties
- sparing effect on α-tocopherol
- regenerating effect on α-tocopherol
- protection of rabbit heart from ischemia/reperfusion injury
- stimulation of prostacyclin release from isolated rabbit hearts

LEUCOSELECT™ : RADICAL SCAVENGING ACTIVITY

1. DPPH radical	IC_{50} (µM)
LEUCOSELECT™	1.3
Catechin	9.5
Ascorbic acid	19.0
α-tocopherol	19.0

2. Tocopheroxy radical	IC_{50} (µM)
Ascorbic acid	15
LEUCOSELECT™	50
Catechin	640

R. Maffei Facino *et al.*: Arzneim. Forsch./Drug Res. 44 (I), (1994) 592-601

Fig.7

This panel of properties makes LEUCOSELECT™, at least *in vitro*, a complete natural antioxidant and from a biochemical standpoint one of the most efficient among botanical derivatives known until now. This was a strong basis to investigate the activity *in vivo*.

For this purpose we relied on our previous experience in the field of polyphenols which, once isolated, are very well known to be generally provided with a very low and erratic bioavailability (Table 1). In order to overcome this gap, we investigated several formulations and among these, one in particular (resembling the natural affinity of polyphenols for phospholipidic substrates), succeeded in improving the absorption at gastrointestinal level. This new formulation, PHYTOSOME®, is based on the complexation between the botanical derivative and the polar heads of the soy phospholipidic mixture which has used as lipidic vehicle (Figure 8).

By using this process, we obtained LEUCOSELECT™ PHYTOSOME®9 (EP 0 275 224; US Patent 4, 963, 527; WO 99/29331) which has been tested in vivo for its antioxidant properties both in experimental animals and in human volunteers.

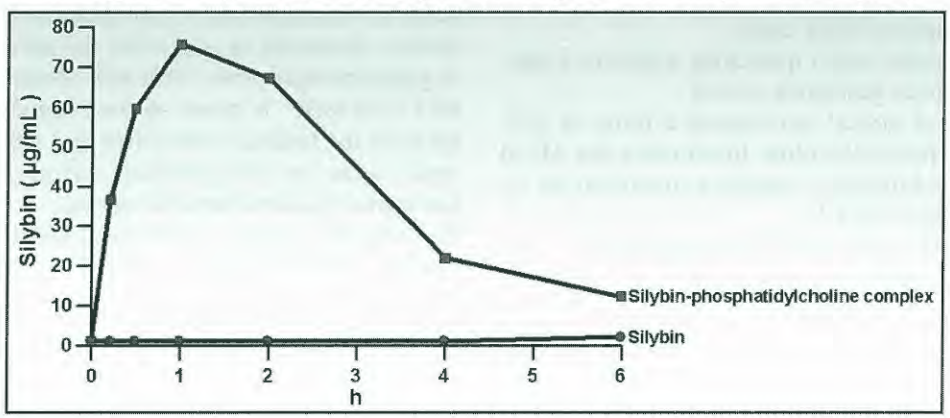
MAJOR GAPS FOR THE USAGE OF NATURAL POLYPHENOLS *IN VIVO*

- Extensive intraluminal degradation
- Poor absorbability due to chemical-physical characteristics
- Intensive presystemic metabolism

Tab. 1

EFFECT OF COMPLEXATION WITH PHOSPHATIDYLCHOLINE ON THE BIOAVAILABILITY OF NATURAL POLYPHENOLS

Mean plasma levels of total silybin after oral administration of 200 mg/kg of silybin and silybin-phosphatidylcholine complex in rats (n=6)



P. Morazzoni *et al.*: Eur. J. Drug Metabol. Pharmacokinet. 17, 39 (1992)

Fig.8

LEUCOSELECT™ PHYTOSOME®: THE BIOAVAILABLE ANTIOXIDANT FOR THE PROTECTION OF THE CARDIOVASCULAR SYSTEM

Several investigations have been performed in order to establish the capacity of the product to exert its properties after oral administration to both experimental animals and human volunteers:

- effect on total antioxidant capacity and physiological antioxidant defences of plasma in young and old rats (Figures 9, 10) fed on diet containing LEUCOSELECT™ PHYTOSOME® at the concentration of 2.4% for 30 days (10)
- effect on ischemia-reperfusion induced damages (Figures 11, 12) in the heart of rats fed on diet containing LEUCOSELECT™ PHYTOSOME® at the concentration of 2.4% for 30 days (10)
- effect on experimental atherosclerosis induced in rabbits by using balanced cholesterol-rich diets with controlled intermediate conditions of hypercholesterolemia (11)
- effect on experimental atherosclerosis induced in rabbits by using a cholesterol-rich diet with severe condition of hypercholesterolemia (12)
- effect on total antioxidant capacity and physiological antioxidant defences of plasma in healthy volunteers (Figure 13) with controlled dietary supply of polyphenols (13)
- effect on plasma oxidative status in healthy volunteers after a fat-rich meal (14)
- effect on LDL-susceptibility to oxidation (Tables 2, 3) in aged smoking men (15)
- effect on oxidative stress in diabetic (NIDDM) patients (16)
- preventive effect on the UV erythema (Figure 14) in healthy volunteers (17)

CONCLUSION

LEUCOSELECT™ PHYTOSOME® is the linkage between the pharmaceutical usage of natural polyphenols in the field of vascular protection and the epidemiological evidences on their high dietary intake and low incidence of chronic vascular diseases.

Moreover, it is a potent quencher of reactive oxygen species, it preserves the integrity of PUFAs, and it prevents the erythema development.

LEUCOSELECT™ PHYTOSOME® is also a bioavailable form, both by oral and topical route of administration, which guarantees grape procyanidins the reaching of target tissues. There they can exert their antioxidant and antiproteasic properties, having a potential role in the prevention of photoaging and, probably, photocarcinogenesis.

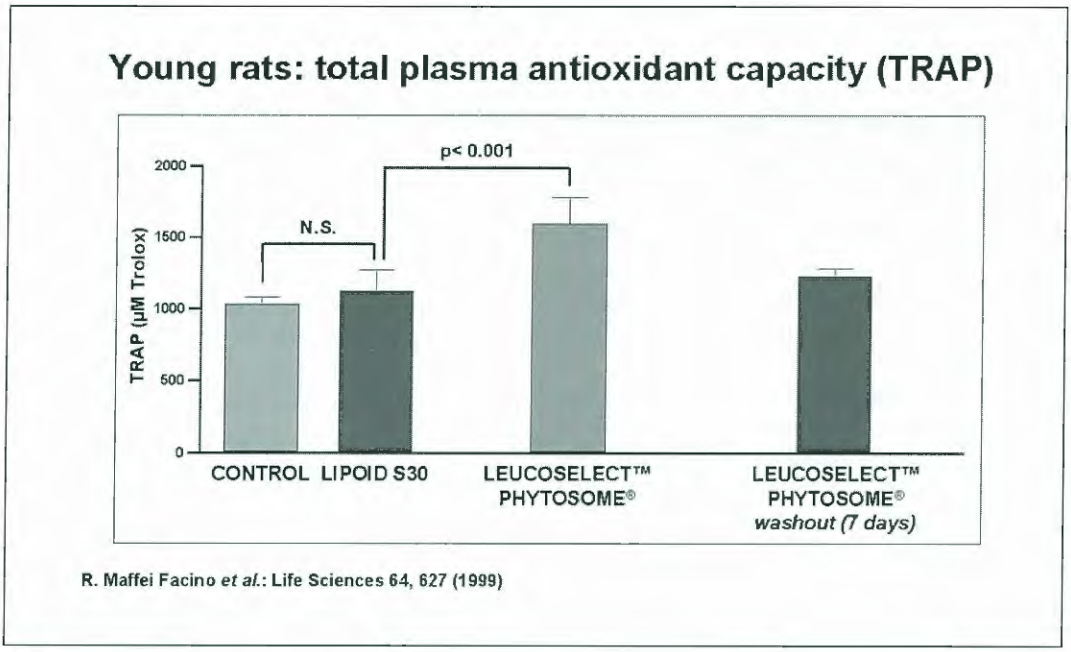

Young rats: total plasma antioxidant capacity (TRAP)
TRAP (µM Trolox)
2000
1500
1000
500
0
p< 0.001
N.S.
CONTROL
LIPOID S30
LEUCOSELECT™ PHYTOSOME®
LEUCOSELECT™ PHYTOSOME® washout (7 days)
R. Maffei Facino et al.: Life Sciences 64, 627 (1999)

Fig.9

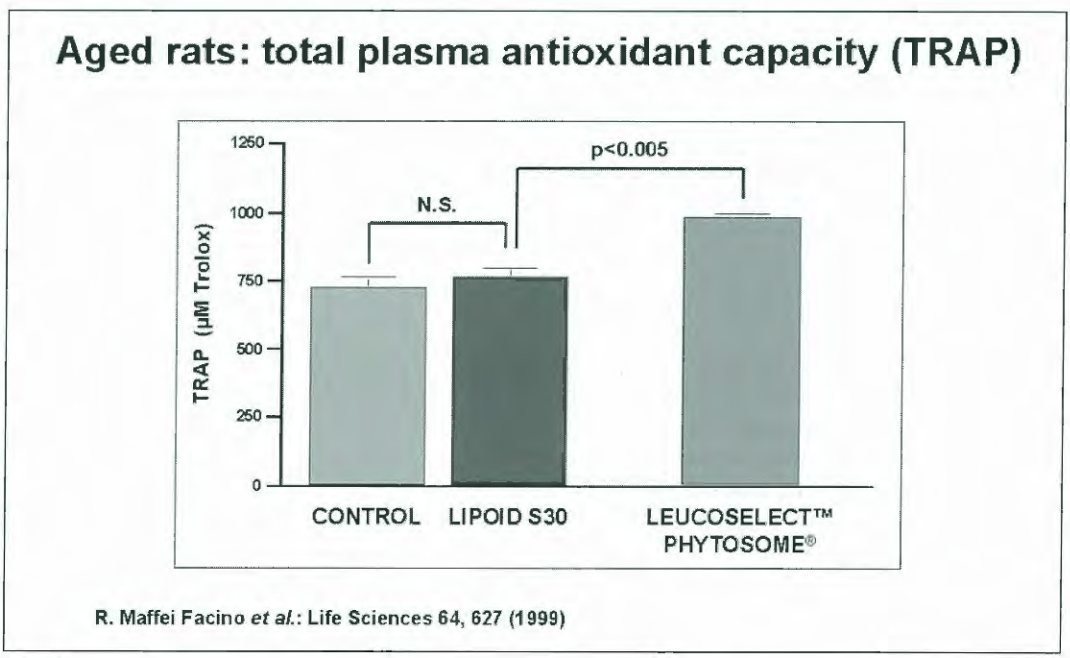

Aged rats: total plasma antioxidant capacity (TRAP)
TRAP (µM Trolox)
1250
1000
750
500
250
0
p<0.005
N.S.
CONTROL
LIPOID S30
LEUCOSELECT™ PHYTOSOME®
R. Maffei Facino et al.: Life Sciences 64, 627 (1999)

Fig.10

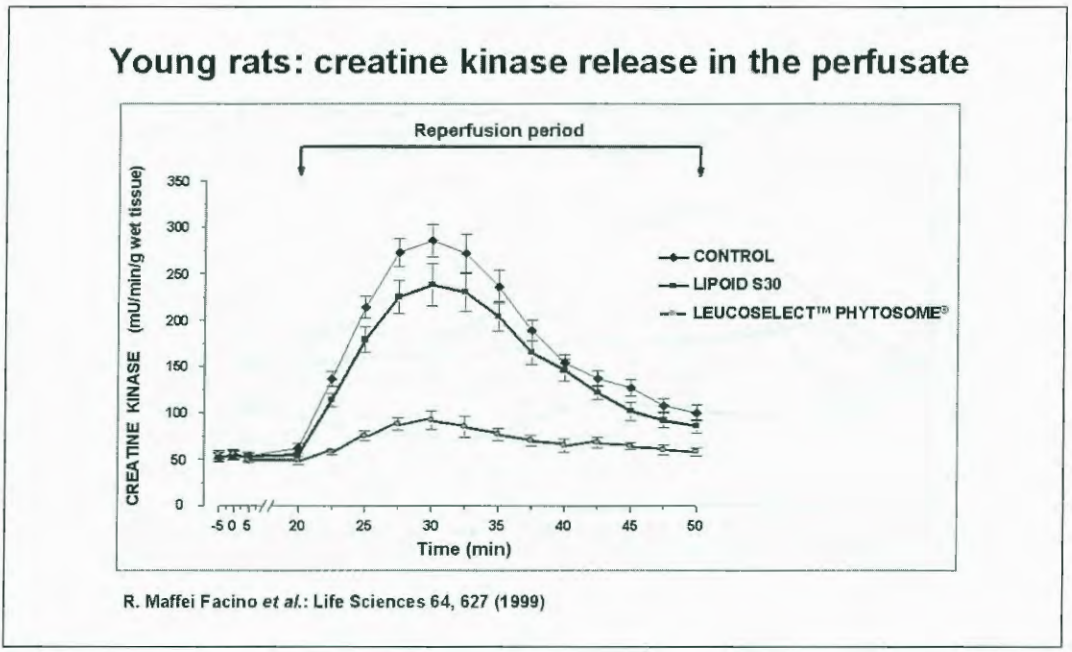

Young rats: creatine kinase release in the perfusate
Reperfusion period
CREATINE KINASE (mU/min/g wet tissue)
350
300
250
200
150
100
50
0
-5 0 5
20
25
30
35
40
45
50
Time (min)
CONTROL
LIPOID S30
LEUCOSELECT™ PHYTOSOME®
R. Maffei Facino et al.: Life Sciences 64, 627 (1999)

Fig.11

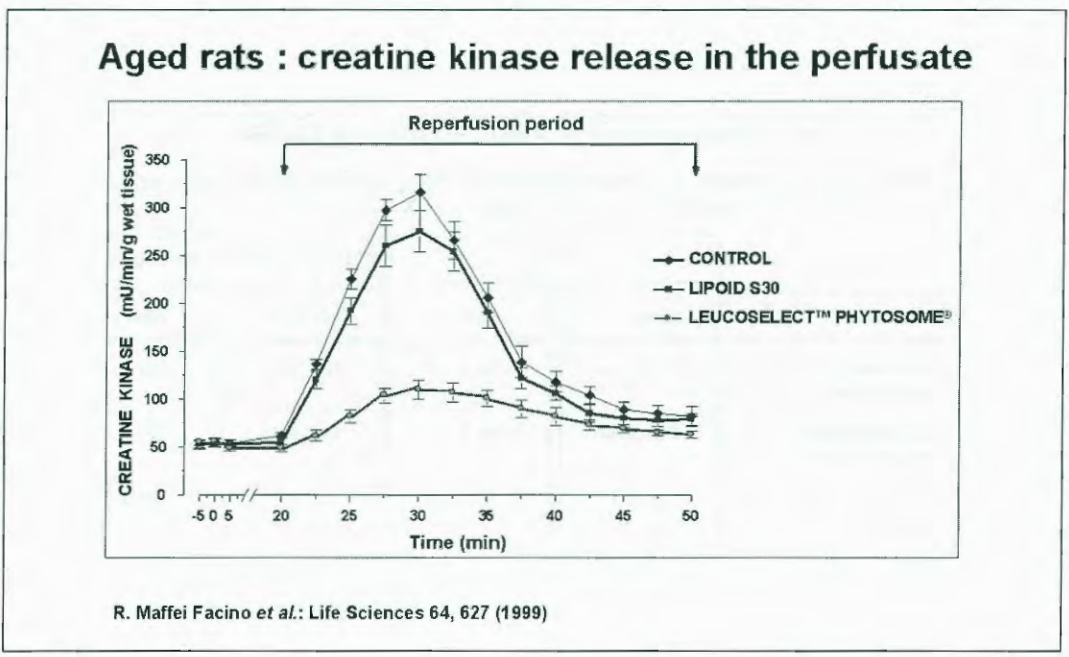

Aged rats : creatine kinase release in the perfusate
Reperfusion period
CREATINE KINASE (mU/min/g wet tissue)
350
300
250
200
150
100
50
0
-5 0 5
20
25
30
35
40
45
50
Time (min)
CONTROL
LIPOID S30
LEUCOSELECT™ PHYTOSOME®
R. Maffei Facino et al.: Life Sciences 64, 627 (1999)

Fig.12

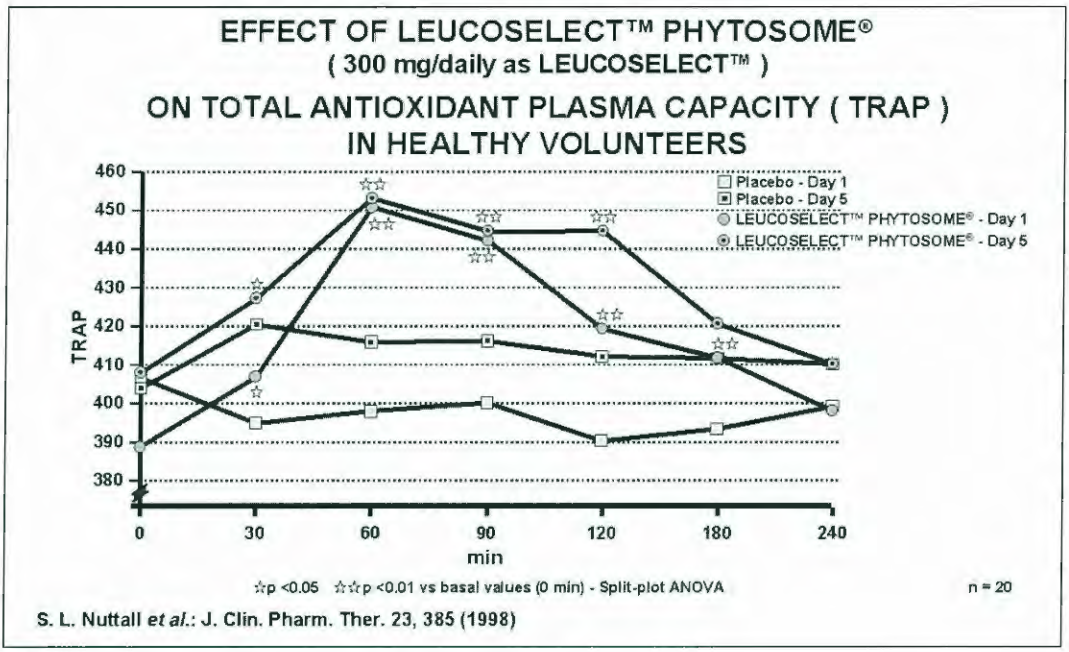


Fig.13

EFFECT OF LEUCOSELECT™ PHYTOSOME® ON LDL-SUSCEPTIBILITY TO OXIDATION IN AGED SMOKING MEN

RANDOMIZED DOUBLE-BLIND CROSS-OVER STUDY

SERUM TOTAL CHOLESTEROL, LDL-CHOLESTEROL, HDL-CHOLESTEROL, TRIGLYCERIDES
(baseline and after 4 weeks of treatment)

	Placebo		LEUCOSELECT™ PHYTOSOME®	
Parameter	baseline	week 4	baseline	week 4
Total cholesterol (mg/100 mL)	235 ± 35	234 ± 34	228 ± 39	235 ± 37
LDL-cholesterol (mg/100 mL)	160 ± 34	160 ± 33	156 ± 33	160 ± 36
HDL-cholesterol (mg/100 mL)	42 ± 11	42 ± 10	43 ± 11	43 ± 11
Triglycerides (mg/100 mL)	169 ± 66	160 ± 56	147 ± 55	163 ± 78

G. B. Vigna *et al.*: XIIth International Symposium on Atherosclerosis, June 25-29, 2000 - Stockholm, Sweden

TAB. II

EFFECT OF LEUCOSELECT™ PHYTOSOME®
ON LDL-SUSCEPTIBILITY TO OXIDATION IN AGED SMOKING MEN

RANDOMIZED DOUBLE-BLIND CROSS-OVER STUDY
FLUORESCENT LIPIDIC PRODUCTS (FLP), LDL-OXIDATIVE PARAMETERS AND MALONDIALDEHYDE
(baseline and after 4 weeks of treatment)

	Placebo			LEUCOSELECT™ PHYTOSOME®		
Parameter	baseline	week 4	Δ %	baseline	week 4	Δ %
FLP (RFU/mL plasma)	20.2± 6.0	20.3± 3.9	+ 4.6	22.1± 5.1	20.8± 6.9	- 2.9
Lag phase (min)	59.0±13.0	57.7± 9.8	- 0.13	52.9± 7.6	61.1±15.6 •	+ 15.4 ♦
Propagation Rate (nmol/min/mg LDL-C)	7.2± 1.3	7.5± 1.3	+ 5.6	7.9± 1.5	7.5± 1.6	- 3.6
Malondialdehyde (nmol/mg proteins)	0.56±0.10	0.57±0.08	+ 5.0	0.64±0.11	0.54±0.13 •	- 14.7 ☆

RFU: Relative Fluorescence Unit • p <0.005 vs baseline ♦ p <0.05 vs Placebo ☆ p <0.005 vs Placebo

G. B. Vigna *et al.*: XIIth International Symposium on Atherosclerosis, June 25-29, 2000 - Stockholm, Sweden

TAB. III

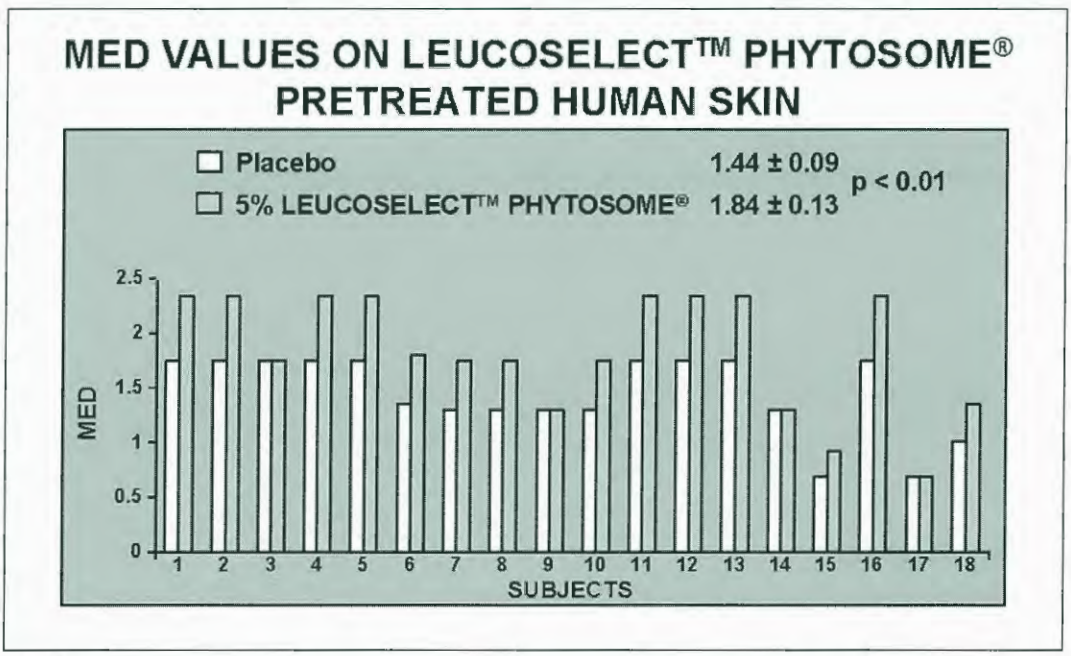


Fig.14

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Prevention/Repair cream: What's new?

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Key words: *Cosmetics; Nutricosmeceuticals; Prevention; Repair; Legal requirement; Stabilisation; Encapsulation; Delivery system; Packaging technology; Oxidative stress; Efficacy test system; Antioxidative protection; UPE (ultraweak-photon-emission); Safety test system; Comet Assay; Coenzyme Q 10; AGR (Alpha Glucosyl Rutin); Retinol; Vitamin A; Wrinkle reduction; Photoprovocation; DNA damage; PLE (polymorphous light eruption); UVA Erythema.*

Summary

Nutricosmeceutical is an artificial word . It tries to describe products that contain ingredients derived from food with high proven efficacy used in cosmetics. There is no legal background for nutricosme-ceuticals in contrast to pharmaceuticals, drugs, cosmetics and nutrients which have to meet individual specific regulations in economic regions or countries.
The following major topics will be covered :
- Present situation = Today's position of these products in the cosmetic field.
There are clear legal regulations for cosmetics, pharmaceuticals, drugs and food in the EU, US, Australia and in Asian countries, which should not be muddled up, even if similar criteria are valid for some ingredients, technologies and test approaches. The process of harmonisation of cosmetic laws on an international level is in progress.
- Problems / Open questions = Which relevance have these products to the consumer ? Which benefits / problem solution is looked for ?
Today, consumer demands for creams have dramatically changed in comparison to what they were some years ago. Prevention gets more and more important because life conditions have changed as well as unlimited youth via repair is the dream of many.
- Solution concept = Which new solutions for the consumer do they offer ? What is needed to reach these objectives ?
UV filters, to protect the skin, are commonly known, but today's prevention creams contain many additional ingredients like antioxidants used until now in the food sector. Furthermore to get repair effects, cosmetic formulas are enhanced with food additives. The key issue from a cosmetic point of view for many of these food derived ingredients is to get them stabilised and effective in cosmetic formulations. Therefore new pathways have been found to encounter these obstacles as innovative encapsulations, new formulation types and / or packaging technologies and innovative test strategies to prove efficacy and safety using appropriate non invasive instruments and methods.
- Future vision: Where will these products lead us ? Cosmetics stand for effectiveness but also for well-being i.e. psychological wellness. Holistic concepts, "Body, spirit and soul", could even be more enlarged.

Riassunto

Nutricosmeceutico è un termine con il quale si cerca di descrivere un prodotto che contiene ingredienti di alta e provata efficacia utilizzabili e utilizzati anche nei cosmetici.
Per questa categoria di prodotti non esiste ancora una regolamentazione giuridica a differenza di quanto avviene per i farmaci per i presidi medici, per i cosmetici o per gli alimenti ed i dietetici.
Vediamo cosa avviene nel mondo a livello giuridico e quali sono le aspettative dei consumatori sulle diverse categorie di prodotti menzionati.
Per i cosmetici, i farmaceutici e gli alimenti, la regolamentazione è chiara in Europa, negli USA, in Australia e nelle nazioni asiatiche, anche se necessitano ancora di una armonizzazione che è però in fase avanzata di realizzazione.
Problemi e quesiti ancora aperti: quale rilevanza hanno questi prodotti per il consumatore?
Come si cerca di risolvere le diverse problematiche?
Oggi, ad esempio, rispetto al passato la domanda del consumatore nei confronti dei cosmetici è notevolmente cambiata. La prevenzione delle patologie è la maggiore richiesta assieme al mantenimento di una cute ed un aspetto generale più giovane.
Quali sono le soluzioni offerte al consumatore?
Quali sono le strade possibili da percorrere per raggiungere gli obiettivi richiesti?
I filtri solari per proteggere la cute sono usati comunemente, ma sempre più vengono utilizzati anche gli antiossidanti di uso più frequente negli alimenti. Inoltre si utilizzano molti principi attivi di uso alimentare quali la vitamina C che debbono essere protetti per svolgere un azione durevole.
Per tutti questi motivi sono stati condotti molti studi sulle nuove tipologie di veicoli, quali la microincapsulazione, in grado di rendere più sicuri ed efficaci i prodotti cosmetici.
Il futuro: come saranno questi prodotti?
I cosmetici saranno sempre più efficaci ed utili per il benessere globale del corpo e dello spirito, ma probabilmente anche dell'anima.

INTRODUCTION

There are clear and legal regulations for cosmetics on an international level and there is no need for a new nutri-cosme-ceutical subcategory.
Nowadays, demands of consumers for creams have dramatically changed in comparison to what they have been for years: prevention and repair have become extremely important. Consumers endeavour to keep a younger looking skin as long as possible. Nutri-based ingredients can help and are therefore integrated in modern cosmetic formulations.
Major challenges for cosmetics are stabilisation/bioavailability, stronger efficacy and guaranteed higher safety. Thus new ideas about innovative encapsulation and / or packaging technologies as well as new test strategies to prove efficacy and safety have been developed. Today, cosmetics not only stand for rational efficacy but also for personal, emotional well-being.
Nutri-based ingredients will inspire and contribute to a more holistic product concept of "Body, Spirit and Soul" in the near future.

The following topics will be covered:

- First, some background information with reference to topical regulations of cosmetics on an international level, especially referring to overlaps between cosmetics, tbe pharmacy and/or the food sector.
- Second, the relevance of nutri-cosme-ceuticals in the cosmetic field: Which problems do occur and which benefit for the consumer can or do these products offer ?
- Third, the 3 major challenges that we face in Cosmetics: the stabilisation / bioavailability of the product, highly proven efficacy and last but not least guaranteed safety.
- Finally the future aspect: Where can these products lead to?

Definition of the artificial word "nutri-cosme-ceutical":

"Nutri" means ingredients, derived from food "cosme" means used in cosmetics and "ceutical" means products with highly proven efficacy

The present situation

From a legal point of view a nutri-cosme-ceutical category does not exist.
On an international level in the US there are 4 major categories: cosmetics, over-the-counter drugs, drugs and food.
In Japan there are 4 categories with different legal background in comparison to the US: cosmetics, quasi drugs, drugs and food.
In Europe there are only 3 categories existing, cosmetics, drugs and food, whereas, in Australia the categories are defined as cosmetics, non prescription drugs, prescription drugs and food.
In cosmetics there are various approaches towards harmonisation:
– harmonisation between EC and US
– Japan and Korea opening slowly their legislation, getting also closer to US / EC
– in South America the „Mercusor".
The process of harmonisation for cosmetic regulations on an international level is running. The position of the cosmetic industry therefore is, that the existing cosmetic regulations are sufficient. There are more products with higher efficacy, there must be a clear balance of efficacy and guaranteed safety, but there is no need of a legal subcategory for cosmetics.

The relevance of nutri-cosme-ceuticals for cosmetics and consumers

Customers have been faced with a dramatic change in living over the last years: The intact environment, clean air and healthy food were more and more replaced by pollution, ozone,

fast food and stress factors. Additionally, people are having a higher life expectancy. Despite all those "negative" life changes, the consumer desires to stay as young as possible as long as possible. To reach this, the consumer requires - better protection / prevention („An ounce of prevention is worth a pound of cure") as well as more repair / anti-aging products.
Those benefits can be found in nutri-based products, for example :
In the past, classical UV filters were used for cosmetics as sunburn protection. Nowadays, this is not enough and antioxidants derived from food play an important role as supplements for protection / prevention.
In the past, alpha hydroxy acids were used to get repair effects, whereas now cosmetics already work with products containing vitamin A.
Generally, more and more ingredients of food origin are transferred to the cosmetic sector:
- Vitamins: among them vitamin A, C, E and K
- From the enzyme sector: Coenzyme Q 10, Gluthathion Peroxidase, Gluthation Reductase, Superoxid-Dismutase or Subtilisin
- Plant extracts: oils of green tea, lavender, evening prime rose oil, soy bean derived-, yeast derived- or sugar derived- ingredients which are used e.g. as emulsifiers or emollients, and single ingredients like Alpha Glycosyl Rutin/ AGR, Quercitin or other flavonoids.

3 major challenges

To be able to use those nutri-derived extracts or ingredients for products, the cosmetic industry faces 3 major challenges :
- the challenge of stabilisation / bioavailability
- the challenge to prove their even higher efficacy
- the challenge of safety, the must in cosmetics.

Stabilisation / bioavailability

The first challenge was and still is, getting the new innovative nutri-derived ingredients , as e.g. Q 10, Alpha Glucosyl Rutin or vitamin A, stablised in cosmetic formulations.
To achieve stabilisation, the cosmetic formulators have to be very creative and look for new approaches: such as innovative encapsulations, new formation types (e.g. w/o/w) or they even integrate new packaging technologies such as airless pump systems or 2 chamber packaging (neatly copying the food industry's müsli- yoghurt packaging = the product is activated on the spot, adding chamber 1 to chamber 2).
Today, formulators can choose from a large selection of highly sophisticated delivery systems which exist at a great variety: Rheological systems, multiple emulsions, molecular – or micro- encapsulations, liposomes or nanobodies are only some of them (see figure 1).
Which delivery system the formulator will use depends on the ingredients and the benefits it should provide the consumer with.

Efficacy

It is remarkable and new, that there are more and more *in vitro* and *in vivo* test systems occurring to prove stronger efficacy. The major in vivo tests in cosmetics are e.g. (see figure 2) the hydration / moisture test systems (done by TEWL transepidermal waterloss or Corneometer),the skin surface tests (performed via skin replica, profilometry , etc...), the skin elasticity test (done via Ballistometer, GBE or Cutometer), the antioxidative protection via UPE (Ultraweak-Photon-Emission), etc.

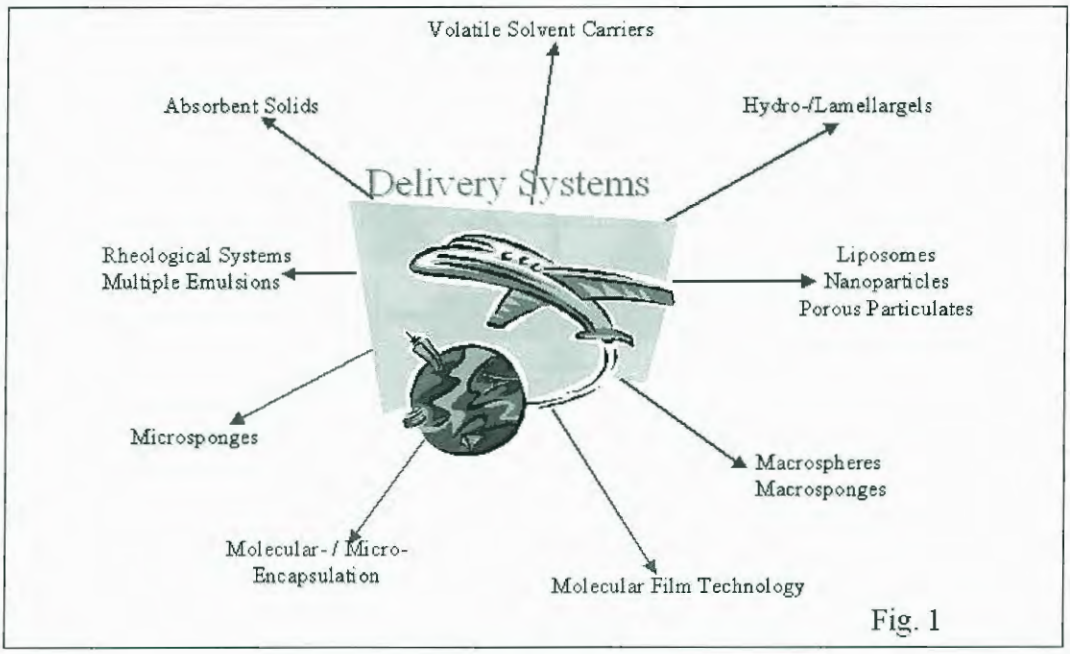

Volatile Solvent Carriers
Absorbent Solids
Hydro-/Lamellargels
Delivery Systems
Rheological Systems
Multiple Emulsions
Liposomes
Nanoparticles
Porous Particulates
Microsponges
Macrospheres
Macrosponges
Molecular-/ Micro-
Encapsulation
Molecular Film Technology

Fig. 1

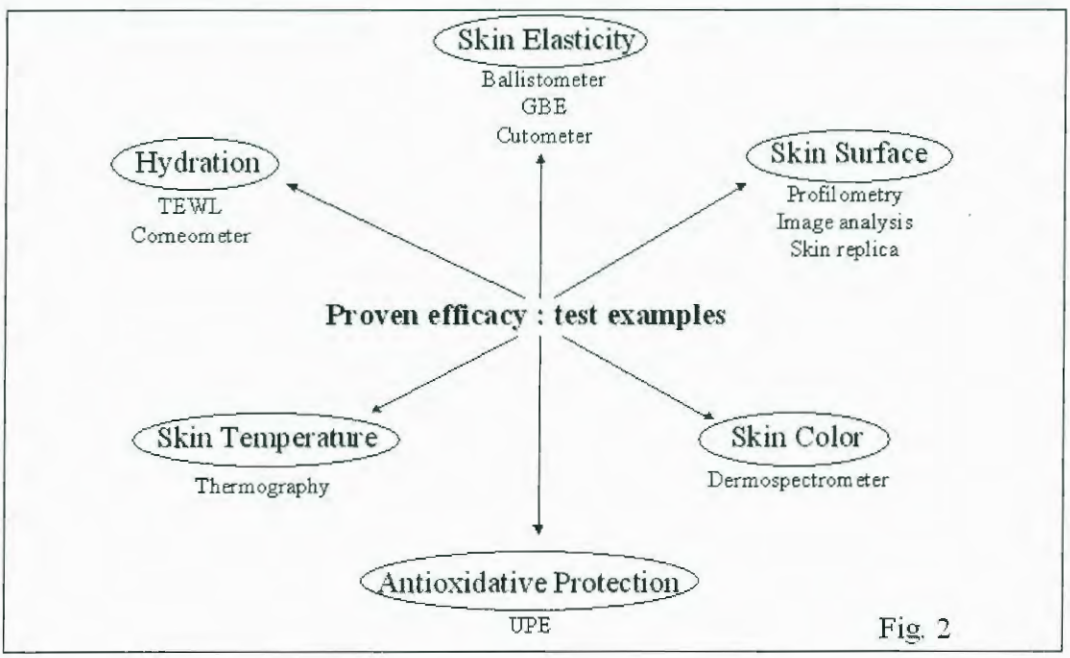

Skin Elasticity
Ballistometer
GBE
Cutometer
Hydration
TEWL
Corneometer
Skin Surface
Profilometry
Image analysis
Skin replica
Proven efficacy : test examples
Skin Temperature
Thermography
Skin Color
Dermospectrometer
Antioxidative Protection
UPE

Fig. 2

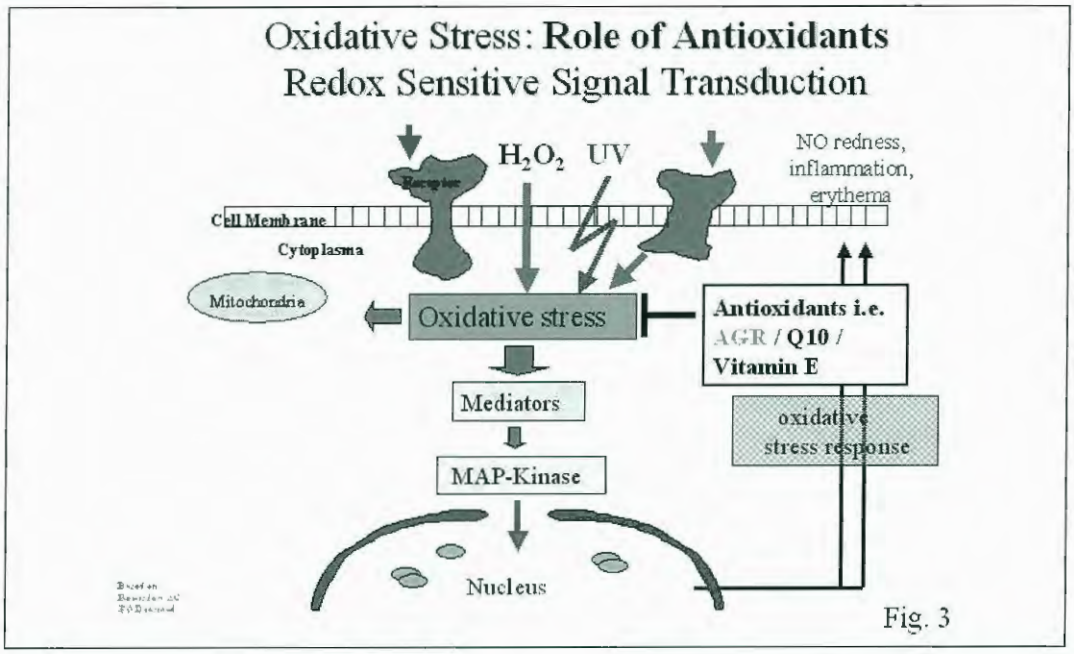

Oxidative Stress: Role of Antioxidants
Redox Sensitive Signal Transduction
H_2O_2 UV
NO redness, inflammation, erythema
Cell Membrane
Cytoplasma
Mitochondria
Oxidative stress
Antioxidants i.e. AGR / Q10 / Vitamin E
Mediators
oxidative stress response
MAP-Kinase
Nucleus

Fig. 3

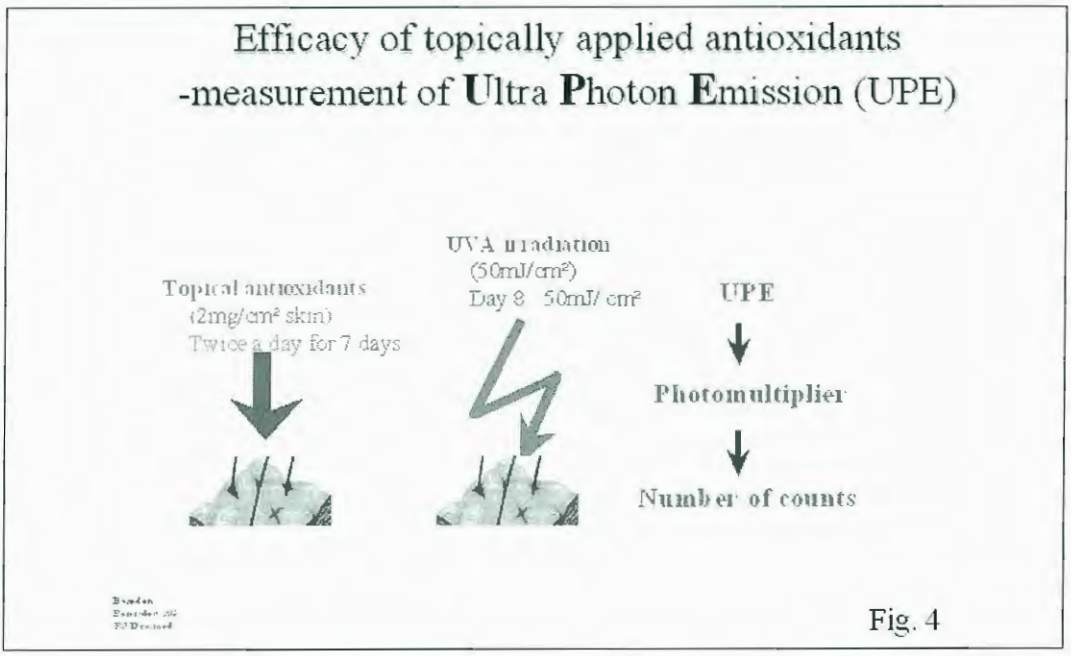

Efficacy of topically applied antioxidants
-measurement of Ultra Photon Emission (UPE)
Topical antioxidants
(2mg/cm² skin)
Twice a day for 7 days
UVA irradiation
(50mJ/cm²)
Day 8 50mJ/ cm²
UPE
Photomultiplier
Number of counts

Fig. 4

Prevention is a major target for the consumer. Before going into any detail concerning the antioxidative protection testing we focus on background information referring to both, the ingredients and the test methods. Either are results from body and skin research, based on the free radical theory of aging.
In skin, free radicals can damage the chemical structure and function of lipids, proteins and the DNA. Oxidative stress, induced for example by UV, can activate mediators like the kinase systems: stress signals from the cell membrane are directed to the nucleus via a cascade of enzymatic phosphorylation reactions. There, the transcription of specific stress-associated genes induced, resulting in the expression of stress proteins like ICAM1 or IL1, well known mediators of inflammation. The final result of this oxidative stress response can be seen on the skin as redness, inflammation and / or erythema.
Specific antioxidants as Alpha Glycosyl Rutin, Q 10 or vitamin E counteract these stress-induced transduction cascades and protect skin structures against direct oxidative damages. Thus no redness, inflammation or erythema occurs (see figure 3).
This antioxidative protection can be measured by the non invasive in vivo UPE, the Ultraweak-Photon-Emission measurement.
In this test the chemiluminescence is measured before and after UV irradiation. This enables the quantitative evaluation of chemically and / or UV induced oxidative stress. Antioxidants (2 mg / cm2) were applied prior to the UV radiation (50 mJ / cm2). The number of counts of UPE were measured via photomultiplier before and after the radiation (see figure 4).
The product with Coenzyme Q 10 reaches very good results (see figure 5).
The simple rule for the evaluation of the results is: The lower the UPE the better is the antioxidant state of the investigated skin. Q 10 therefore is a valid antioxidant.
To demonstrate a repair, antiwrinkle effect we have used the skin surface image analysis. Ingredients as vitamin A and Q 10, though acting biochemically totally different, have antiwrinkle qualities. The results of a vitamin A containing product, are shown in figure 6: an objective facial lines / wrinkle reduction via image analysis of replicas and parallel a subjective evaluation by an expert grader.

The panel sized 25 people. We see, that this product is very effective in reducing lines and wrinkles. The second example (see figure 7) shows a product containing Q 10: After 10 weeks we have a more than 30 % wrinkle reduction. And if you look at longer term results, after 6 months (see figure 8), the skin gets a clear and smooth appearance.

Safety

In cosmetics – other than in pharmacy – safety problems, in other words negative side effects, are unacceptable. Therefore according to the 6th amendment of the EU cosmetic directive, toxicological evaluations for each ingredient are compulsory to ensure full safety of the products. In addition to this, we use more and more in vitro and in vivo safety tests for finished products. There are various in vitro tests existing to prove either the safety like the well known HET CAM, the Red Blood Cell or the vitality of keratinocytes. Other test systems as e.g. the Comet Assay have been used to prove antixodant efficacy effects hut could also be used as a part of a safety test.
Figure 9 shows the in vitro results of the Comet assay of the antioxidant Alpha Glucosyl Rutin (AGR), a plant derived flavonoid. AGR protects significantly the DNA of primary keratinocytes against UVA-induced damage and therefore ensures higher safety requirements.

Antioxidant efficacy of Q10 containing product *in vivo*

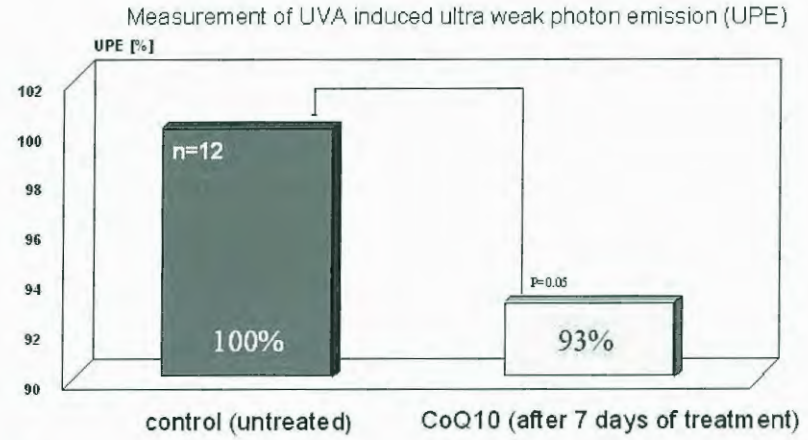
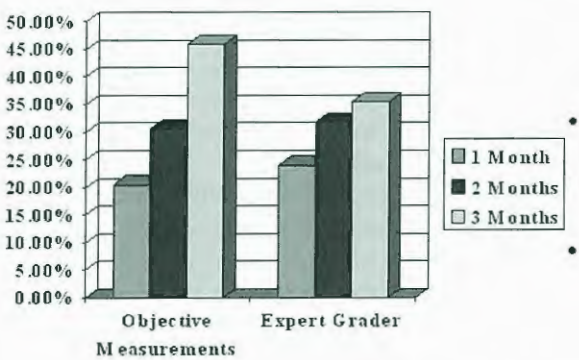


Fig. 5

Challenge 2 : Proven Efficacy Repair
"Antiwrinkle effect"
Test Model "antiwrinkle cream" with Retinol



- Objective : Image Analysis Skin replica
- Subjective : Expert grader

Fig. 6

Reduction of wrinkles after treatment with CoQ10-containing product

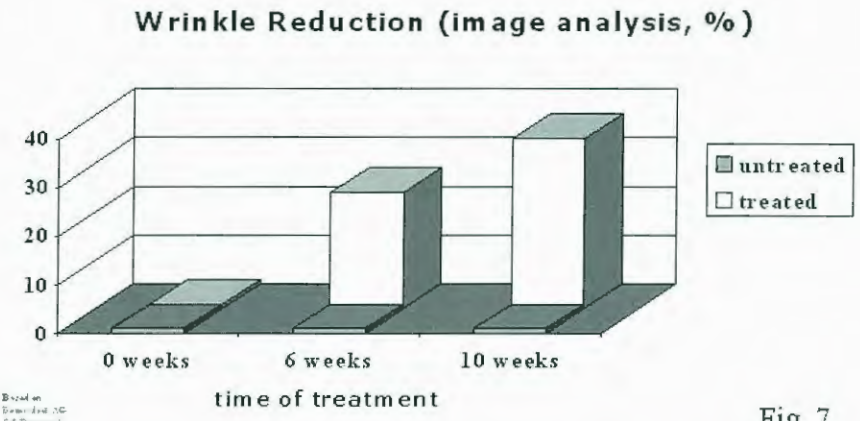
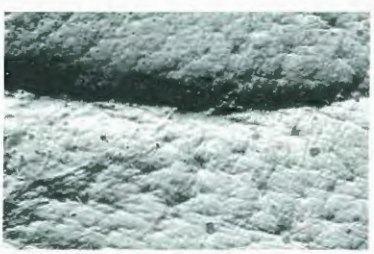


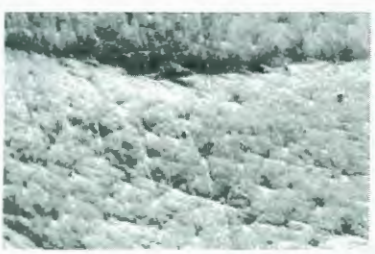
Fig. 7

Challenge 2:
Proven Efficacy **Repair** Antiwrinkle Effect

Test Model "antiwrinkle cream" with Q_{10}



Before treatment



After 6 months of treatment

Fig. 8

AGR protects against UVA-induced DNA damage - Comet Assay -

- primary human keratinocytes -

(24 hour preincubation with/without 150µM AGR)

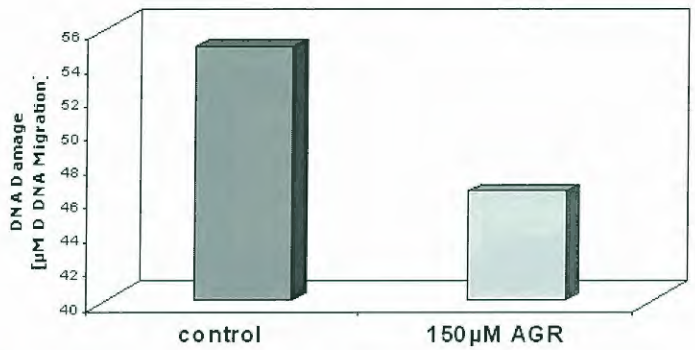


Fig. 9

AGR protects against Polymorphous Light Eruption (PLE) and UVA Erythema

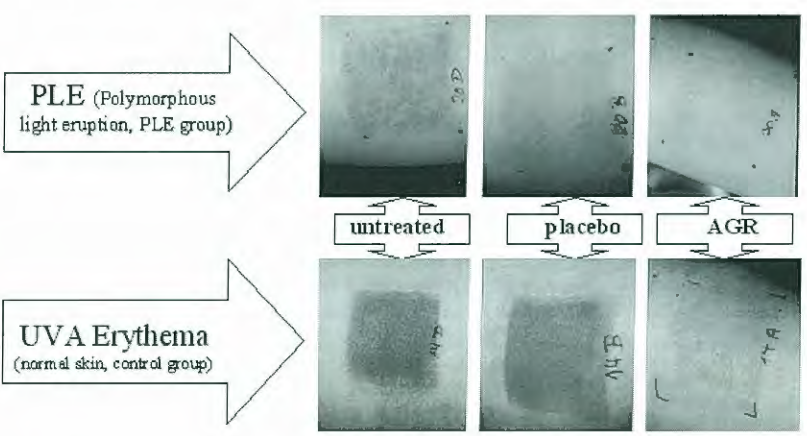


Fig. 10

The in vivo safety test batteries of finished products can be open or closed epicutan (patch) tests, RIPTs (repeated insult patch test), ophtalmological tests (eye safety) or in use field studies and – for sun protecting products - phototox- and / or photoallergy- studies etc...
Take as an example the design of a clinical photoprovocation study: A placebo formula containing 1 % Vit. E and the verum with 0.25 % AGR included were applied twice a day for 11 days. Both formulae contained no UV-filters. They were applied on skin sites of the upper volar forearms and further there was one site left untreated. There were two groups, one of PLE (Polymorphous Light Eruption) patients and another one of healthy volunteers, the control group. On day 8, photoprovocation tests were conducted applying 60 J UVA/ cm2 skin daily, from day 8 to 11. The scoring of the clincal symptoms were done daily from day 8 to 11.
Figure 10 shows examples of the clinical figure of PLE (PLE group) and of UVA-erythema (control group) on day 11. In comparison to untreated or placebo treated skin sites, AGR can protect impressively against PLE and against UVA-erythema in normal skin, even at these high, repeatedly applied UVA-doses used in this photoprovocation test. This means higher safety to the consumer using this product.

The future vision of nutri-cosmeceutical products

To start with, we all profit from the increasing knowledge of skin and body functions, thus understanding aging processes more thoroughly. Communication systems and mediators to trigger processes will be more and more known.
The second challenge, using nutri- derived ingredient products, is and will be to achieve higher efficacy while safety aspects have to be still guaranteed.
Next, cosmetics in general, but especially the nutri-cosme-ceuticals have always 2 bridges to cross : they have to be rationally effective –and give subjective well-being, a totality of psychological aspects. There are still a lot of grey zones. One of them is the measuring of wellbeing. Highly sensitive test methods will have to be developed considering carefully the aspects behind the secret why a consumer states "I BELIEVE in this product".
Finally, this will also challenge our marketing colleagues making them more aware of getting the right holistic approach to a product: to position, to market and promote it, appealing to consumers on an emotional level.
Therefore a holistic vision based on "body, spirit and soul" is essential - and nutri-derived ingredients inspire this approach.

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CLINICAL STUDY ON THE EFFECT OF A COSMETIC EMULSION IN IRRITATED SKIN

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Summary

The skin is constantly exposed to the environment and therefore is susceptible to a variety of problem among which dermatitis involve an increasing number of people due to environmental aggressive factors and to individual reaction or physio-pathological predisposition. Although the clinical classification of dermatitis is accurate, the identification of factors contributing to the genesis and maintenance of skin disorders is frequently unclear, and this makes the clinical approach to prevention and care of dermatitis sometimes difficult. As a consequence prevention recommendations and pharmacological therapy of dermatitis is frequently unspecific and it includes a number of adjuvant preparations.

KVDS is a cosmetic formulation that has been shown in previous study to be effective as an adjuvant in treating seborrheic dermatitis, and the present study has been undertaken with the aim of assessing its activity and tolerability in other skin disorders. To this end KVDS has been investigated in 20 subjects with atopic dermatitis, and its activity has been evaluated by instrumental cutaneous tests such as skin electric capacitance, TEWL, D-squame and others have been carried out. Its soothing efficacy was also assessed in cutaneous erythema induced by UV irradiation of the skin.

The results already reported for seborrheic dermatitis and those obtained in the present study suggest that KVDS might be effective in different types of dermatitis thanks to its beneficial action in improving the cutaneous barrier, to its protective function and its soothing activity.

Riassunto

La pelle è costantemente esposta all'ambiente esterno ed è quindi soggetta a numerosi problemi, tra cui le dermatiti che coinvolgono un numero crescente di persone e possono essere causate da aggressioni di agenti esterni, reazioni individuali o predisposizione fisio-patologica.

Sebbene la classificazione clinica delle dermatiti sia accurata, l'identificazione dei fattori che contribuiscono al loro scatenamento è spesso non chiara, e questo rende difficoltoso l'approccio clinico alla loro prevenzione e cura. Come conseguenza le raccomandazioni per prevenire l'instaurarsi di tali affezioni sono spesso generiche ed il loro trattamento farmacologico include parecchie preparazioni coadiuvanti.

KVDS è una preparazione cosmetica che si è dimostrata efficace nel trattamento della dermatite seborroica, ed il presente studio è stato intrapreso al fine di verificarne l'attività e la tollerabilità in altre affezioni cutanee.

Ha coinvolto 20 soggetti con anamnesi positiva per la dermatite atopica, e l'attività della formulazione in studio è stata valutata con test quali la capacità elettrica cutanea, la perdita d'acqua transepidermica (TEWL), la misura della desquamazione cutanea (D-Squame) ed altri. L'effetto emolliente è stato verificato trattando degli eritemi cutanei causati artificialmente mediante raggi UV.
I risultati già riportati per quanto riguarda la dermatite seborroica e quelli ottenuti nel presente studio suggeriscono che KVDS è efficace in vari tipi di dermatiti grazie alla sua azione protettiva, emolliente e di ripristino della barriera cutanea.

INTRODUCTION

The skin is constantly exposed to the environment and therefore is particularly susceptible to a variety of problems among which dermatitis involve an increasing number of people, likely due to raising of pollution and climate alterations on one side and to the strength of the physio-pathological reaction on the other. In addition to chemical and physical factors, a number of health conditions, such as allergies, genetic factors, diet, physical and mental stress can provoke or aggravate dermatitis possibly by altering the normal defensive mechanisms.

The term eczema, or eczematous dermatitis, is applied to specific non-infectious inflammatory reactions of the skin that are dependent on individual predisposition, and covers a number of etiologically heterogeneous conditions with common features in terms of clinical presentation and pathogenesis that account for approximately 20% of the dermatological disorders (2). According to the American Academy of Dermatology, dermatitis affects about one in every five people at some time in their lives, and has an high individual and socio-economical impact.

Dermatitis include skin alterations characterized by swollen, reddened and itchy skin that make people feeling uncomfortable, and the morphology of this skin disorders may vary in the acute or chronic stages, as it is characterized by erythematous and papulo-vesicular aspect when acute, and erythematous and scaling morphology with or without fissures and lichenification when chronic.

By a clinical point of view, the most frequent forms of dermatitis have been classified as: atopic, irritant and allergic, seborrheic and microbic dermatitis (2).

Atopic dermatitis (3) is a chronically relapsing inflammatory skin disease with altered immune and pharmacological responses (4,5). Atopic dermatitis is prevalent in children, it affects approximately 5% of children in Italy, and commonly appears during early childhood (infantile eczema). Inherited factors seem to be of importance, as there is nearly always a family history of dermatitis or asthma, and it often occurs with allergies and frequently runs in families in which other family members have asthma or hay fever. Signs and symptoms include itchy, thickened, fissured skin, most often in the antecubital and popliteal region. Generally, atopic dermatitis symptoms become less serious in adulthood, unless people are exposed to allergens or irritants.

Irritant or allergic contact dermatitis commonly results from direct contact with one of many irritants or allergens causing more trouble in subjects who have a tendency to atopic dermatitis. This includes frequent handling of water, use of common irritants, including laundry and skin soaps, cleaning products, detergents, solvents or harsh chemicals perfume, or of possible allergens, such as rubber, metals, jewelry, perfume, cosmetics and some weeds. The clinical signs that occur include redness, itching and vesicles, while in severe cases hlisters and weeping sores may appear, generally limited to site of contact with the irritant or the allergen. In general it takes a large amount of an irritant over a longer time to cause contact dermatitis, while in people sensitized to a given allergen dermatitis can be caused by just a brief exposure to a small amount of that allergen.

Seborrheic dermatitis is characterized by greasy, scaling areas at the sides of the nose, between the eyebrows, behind the ears or over the sternal region, and it can appear as itchy dandruff, usually due to mild seborrheic dermatitis of the scalp, or as a "cradle cap", that is crusty, scaly skin on baby's scalp. The fact that Malassezia furfur yeast (Pytisporum ovale) plays a part in seborrheic dermatitis is well established but the mechanism of the exact relationship has not been established. An increase in inflammatory interleukins, as well as in the regulatory interleukins, in combination with complement activation indicate that an irritant stimulation of the immune system plays an important role in se-

borrheic dermatitis (6). Predisposition to seborrheic dermatitis is often inherited and the disease occurs during periods of psychological stress or in people suffering from neurological conditions such as Parkinson's disease (7).
Microbic or infective dermatitis is provoked by bacterial or fungal infection of particular areas of the skin.
Despite the accurate clinical classification, the identification of the factors contributing to the genesis and maintenance of the skin disorders is frequently unclear, and this makes difficult the clinical approach to the prevention and care of the different types of dermatitis as well as the formulation of strategies for the protection of the skin.
As a matter of facts, with only few exceptions, prevention recommendations and/or protecting procedures are intended for the dermatitis in general, and include: use of suitable soaps, shampoo and detergents; use of suitable clothing; protection of the skin from irritant agents, including dust, solvents, detergents, and from physical injuries; use of emollients, that should be applied with continuity, particularly after bathing and when the skin is itchy; use of moisturizing agents to prevent dry skin.
As far as pharmacological therapy of dermatitis (8,9), is concerned, it includes drugs and preparations that are commonly used for the different types of dermatitis. In fact they include 1) topical steroids, used as cream or ointment that should be applied once or twice daily to the red and itchy areas only for a 5 to 15 day course: different topical steroids may be used either for different parts of the body or for differing grades of dermatitis; systemic steroids are also used; 2) antihistamines preparations are of particular importance for reducing irritation and itching, and particularly useful at night; 4) antibiotics if infection, most commonly caused by Staphylococcus Aureus or Streptococcus Pyogenes, is complicating or causing the dermatitis. Other promising treatments have been introduced quite recently, e.g. topical immuno-modulators with proved anti-inflammatory activity (10). In addition to the mentioned therapies a large number of adjuvant treatments have been introduced so far and contain different active principles.
The present study was undertaken with the aim of investigating the tolerability and the pharmacological activity of a cosmetic emulsion (KVDS*) in skin irritation and atopy.

Materials and methods

Investigations have been carried out in 20 healthy volunteers, 19 females and 1 male aged 13 to 58 years (average 36 years). All the enrolled subjects had clinically diagnosed atopy according to the criteria indicated by Hanifin and Rajka[4]. Other inclusion criteria and procedures were similar to the first group. Exclusion criteria were the following: pregnancy or lactation, presence of skin disorders in the areas of treatment, systemic pathologies. The study consisted of two sets of experiments:
1- In use skin testing: Each subject applied the product on the right or left deltoid region twice a day, in the morning and in the evening, for 4 consecutive weeks according to a previously defined randomized schedule. At T_0 (basal conditions), T_{15} (15^{th} day of treatment) and T_{28} (28^{th} day) the clinical examination for tolerability and the following instrumental evaluations were performed:
1) cutaneous hydration (11) (Corneometer CM820, Courage-Khazaka, Köln, Germany) has been evaluated indirectly by evaluating the electrical capacitance of skin surface. In order to reduce the variability of the method, three measures on the same skin area were taken for each volunteer, and the adjusted mean was taken as the hydration value at that time.
2) Trans Epidermal Water Loss (TEWL), i.e. the expression of the epidermal barrier, was mea-

* *KVDS is sold as: KOURILES®, SEBODERM®, DERMOPUR® and EMULZE K®*

sured by Evaporymeter device (Servo Med, Sweden), and the water loss rate was expressed as the amount of water evaporated per unit area of the skin in the absence of sweating.

3) measurement of the surface lipid content (Derming Tester model STC20, Monza, Italy).
4) measurement of skin surface pH (12) (Skin-pH-meter PH900, Courage-Khazaka, Köln, Germany).
5) cutaneous micro-topography was evaluated by computerized image analysis of skin replicas obtained with a silicon representing the skin surface impression. The subsequent analysis of the cutaneous casts (13,14) was carried out by computerized image elaboration. The pictures, taken with a high-resolution camera, were analyzed through the study of the Fast Fourier Transform and the identification of the mathematical parameter describing the skin micro-relief.
6) D-Squame® for the evaluation of the cutaneous scaling (15) was carried out by taking samples of skin scales from skin surface using a special adhesive tape (D-Squame®, Difa Cooper, Italy). The samples were then submitted to computerized analysis of the image for the measurement of the following parameters: mean area, perimeter, major and minor axes of the scales. Calculation of the respective desquamation index was made according to the following formula:

$$D.I = \frac{2A + \sum_{n=1}^{5} T_n * (n-1)}{6}$$

where A - is area occupied by the scales (percentage); Tn - is the percentage of the scales related to their thickness; n is the level of scale thickness, scores from 1 to 5.

2- Soothing activity: The soothing efficacy of KVDS has been investigated. in 20 volunteers, 18 females and 2 males, aged 13 to 58 years (average: 36 years), whose informed consent had been obtained. For the subjects under 18 a written consent was signed by one of the parents according to previously defined protocol. Among these subjects, 70 % had clinically diagnosed atopy, while 30 % had a positive anamnesis for hyperactivity to sun radiation. Exclusion criteria were the following: pregnancy or lactation, presence of skin disorders in the areas of treatment, systemic pathologies. The skin erythema was induced by ultraviolet radiation of discrete areas of the skin according to Diffey et al. (16). After the minimum erythematous dose (MED) of UV was assessed for each subject , a twice as high dose of UV (2MED) was administered on three well identified, contiguous areas of the skin of the back: an untreated control area, a second pre-treated area, in which KVDS was applied before UV irradiation, and a third post-treated area in which KVDS was applied 24 hours after UV irradiation.

KVDS was applied in the fixed amount of 0.1ml per treatment by the same operator, by gentle rotating massage until it was completely absorbed. Clinical score and instrumental evaluation of the erythema index (E.I., by means of optical densitometry (17) were performed at T_0 (before application) T_8 and T_{24} (respectively 8 and 24±4 hours from the application of the product).

All instrumental measurements were performed under standard environmental conditions (Temperature 20±2°C, Relative Humidity 45±5%). Before each visit the volunteers were acclimatized under relax conditions for at least 15 min. During 3 hours before the visit, the volunteer had not to smoke, drink coffee or strong drinks and not to use other products on the skin test areas during all the duration of the study. Once verified their distribution, obtained data from instrumental measurements were statistically evaluated using the parametric Student's "t" test.

Results

1- In use skin testing: The repeated application of KVDS was well tolerated by the subjects in-

cluded in the present study, since neither irritation signs nor dropout occurred during treatment. The results obtained with the instrumental tests can be summarized as follows:

1) the treatment with KVDS did increase the electric capacitance of skin surface (Tab. 1 and Fig. 1) and the recorded values were already significantly increased from 82 to 97 U.A. ($p<0.001$) at T_{15} and were still higher than control at the end of treatments (T_{28} = 93 U.A., $p<0.001$).

Table I.

Effect of the repeated treatment with KVDS on the electric skin capacitance of 20 subjects with atopic dermatitis.

n. volunteers. 20	control (T_0) AU	2nd week (T_{15}) AU	4th week (T_{30}) AU
Mean	82	97	93
SEM	2,01	3,17	2,95
Student "t" test		p<0,001 [1]	p<0,001 [2]

1) T_{15} vs T_0; 2) T_{28} vs T_0; AU: arbitrary units

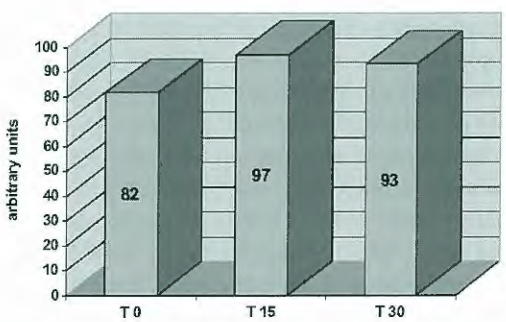

Fig. 1 Effect of KVDS on the electric skin capacitance.

2) The measurement of trans-epidermal water loss (TEWL) allows to objective monitoring of the responses to cosmetic treatments: a marked decrease in water loss rates indicates skin surface occlusion by the treatments, while a shift from high water loss rates to normal rates in subjects with altered skin barrier function likely expresses skin lipid replacement and restored barrier function. Data obtained in the present study and included in Tab 2 (Fig. 2), show that the treatment with KVDS® caused a significant decrease in this parameter compared to the values recorded at T_0 (control). In fact mean trans-epidermal water loss values decreased from 6.53 g/m²/h (control value) to 5.73 g/m²/h ($p<0.05$) at T_{15}, and it was 5.22 g/m²/h ($p<0.001$) at T_{28}.

Table II.

Effect of the repeated treatment with KVDS on the Trans Epidermal Water Loss (TEWL) of 20 subjects with atopic dermatitis.

n. volunteers. 20	control (T_0) g/m²/h	2nd week (T_{15}) g/m²/h	4th week (T_{30}) g/m²/h
Mean	6,53	5,73	5,22
SEM	0,35	0,35	0,25
Student "t" test		p<0,05 [1]	p<0,001 [2]

1) T_{15} vs T_0; 2) T_{28} vs T_0

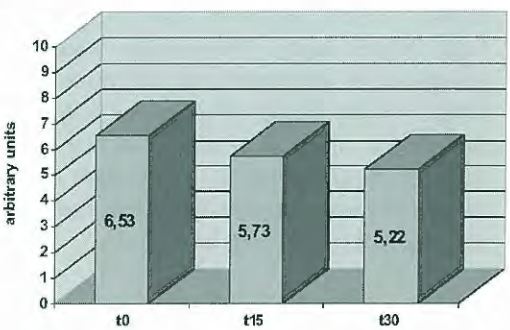

Fig. 2 Effect of KVDS on the Trans Epidermal Water Loss (TEWL).

3) the treatment with KVDS did not alter the superficial lipid content. In fact the small variations in the mean values relative to this parameter recorded at T_{15} and T_{28} did not differ significantly from those recorded at T_0;

4) the average skin pH was increased significantly from 6.2 UA to 6.4 ($p<0.05$) at T_{15} of treatment, but this change was only transient

as cutaneous pH was again 6.3 at T_{28} (Tab. 3).

Table III.
Effect of the repeated treatment with KVDS on the cutaneous pH of 20 subjects with atopic dermatitis.

n. volunteers. 20	control (T_0) IU	2nd week (T_{15}) IU	4th week (T_{30}) IU
Mean	6,2	6,4	6,3
SEM	0,1	0,1	0,1
Student "t" test		p<0,05 [1]	NS [2]

1) T_{15} vs T_0; 2) T_{28} vs T_0

5) The analysis of the computerized image of skin replicas allows the evaluation of the regularity of skin surface micro-relief and therefore the variations of these characteristics after the use of topical products: micro-relief regularity is elevated in well hydrated skin, while xerotic skin, as that caused by strong detergents, is characterized by a very irregular superficial draw. The computerized analysis of the cutaneous casts carried out in our investigation clearly shows that the treatment with KVDS® did not alter the cutaneous micro-relief. In fact the Fourier spectra of the images of the cutaneous replicas, as the values for X and Y axes obtained at the different experimental times, T_0 (control), T_{15} and T_{28}, were almost unchanged (Tab. 4).

Table IV.
Effect of the repeated treatment with KVDS on cutaneous micro-topography in 20 subjects with atopic dermatitis.

n. volunteers. 20	control (T_0) amplitude X-axis	Y-axis	2nd week (T_{15}) amplitude X-axis	Y-axis	4th week (T_{30}) amplitude X-axis	Y-axis
Mean	249,9	249,5	234,3	233,7	230,2	230,1
SEM	33,03	15,3	15,3	15,3	22,4	22,4
Student "t" test			NS [1]	NS [1]	NS [2]	NS [2]

1) T_{15} vs T_0; 2) T_{28} vs T_0

6) the effect of KVDS treatment on scaling resulted in a significant 33 % reduction of the mean scale area at T_{15} that was maintained at T_{28}, (Tab 5 and Fig. 3), and a significant 37 and 29 % decrease in the mean scale perimeter at T_{15} and T_{28} respectively (Tab 5 and Fig.3); reduction of the major and minor axes of the scales were also obtained at the second week of treatment (T_{15}) and maintained throughout the treatment period.

At the same time, the skin desquamation index was significantly reduced from 0.52 to 0.34 after 2 weeks of treatment and it was still 0.37 at the end of treatment (see Tab 6 and Fig 3), thus supporting the previous clinical data concerning the effect of KVDS® on desquamation.

A typical example of cutaneous micro-topography before and at different times of treatment with KVDS T_{15} and T_{28} is illustrated in Fig. 4

Table V.
Effect of the repeated treatment with KVDS on cutaneous scaling (D-Squame test) in 20 subjects with atopic dermatitis.

n. volunteers. 20	control (T_0) area perim. mm^2 mm	2nd week (T_{15}) area perim. mm^2 mm	4th week (T_{30}) area perim. mm^2 mm
Mean	136,1 0,59	91,33 0,37	91,3 0,42
SEM	4,7 0,03	14,4 0,05	14,4 0,07
Student "t" test		p<0,01 [1] p<0,01 [1]	p<0,05 [2] p<0,05 [2]

1) T_{15} vs T_0; 2) T_{28} vs T_0

Table VI.
Effect of the repeated treatment with KVDS on the desquamation index in 20 subjects with atopic dermatitis.

n. volunteers. 20	control (T_0) AU	2nd week (T_{15}) AU	4th week (T_{30}) AU
Mean	0,52	0,34	0,37
SEM	0,00	0,05	0,06
Student "t" test		p<0,01 [1]	p<0,05 [2]

1) T_{15} vs T_0; 2) T_{28} vs T_0; AU: arbitrary units

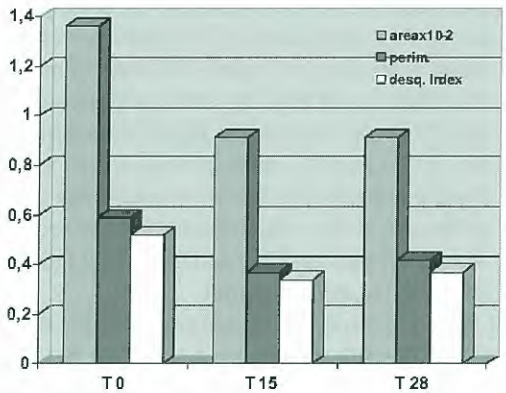

Fig. 3 Effect of KVDS on skin scaling.

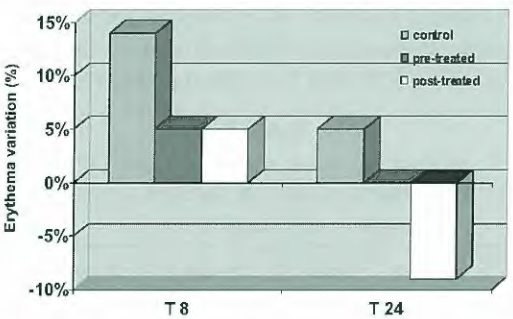

Fig. 5 Optical densitometry test Changing of the erythema percentage versus T0 (Students't test : t_0 vs. t_8 = $p<0.01$ (control area) and $p<0.05$ t_0 vs. t_{24} (post treated area))

2- Soothing activity: The application of KVDS significantly reduced the cutaneous erythema at the irradiated skin areas results show a significant reduction of the clinical scores on post-treated areas at T_{24} (T_0 vs. T_8 and T_{24}, $p<0.05$). Regarding the comparison between control and pre-treated areas, a trend towards the reduction in the clinical scores for erythema was detected at T_{24} also on control area, but this was not statistically significant.

Instrumental evaluation of erythema (optical densitometry): at the level of control area (irradiated and untreated area) a marked, significant 14 % increase of the erythema index (E.I.: $p<0.01$) was found at T_8, while on pre- and post-treated areas the increase was only 5 % (Fig. 5). The soothing activity was particularly evident at the level of post-treated areas at T_{24} with a statistically significant 9 % reduction of average E.I. (T_0 vs. T_{24}, $p<0.05$).

CONCLUSION

It has recently been published that effective therapeutic agents for dermatitis are limited in number and that they may have long-term toxic side-effects (18). This situation prompted many patients to turn to alternative medical approaches, and the options included over-the-counter (OTC) products (20) so-called natural products or cosmetic preparations as adjuvant treatments. In this study we investigated the therapeutic activity of KVDS®, a cosmetic preparation containing piroctone olamine (Octopirox), hyaluronic acid, Sebomine SB12, oxidative enzymes plus lactoferrine, and Norgel, which was already been shown to be effective as an adjuvant in the treatment of seborrheic dermatitis (19,20,21,22) due to its antifungal, antimicrobial and antioxidant activities coupled with an effective moisturizing action. The role of hyaluronic acid (HA) in skin disorders (23) as well as in aging skin (24) is well known and its efficacy in wound healing (25) has been proved in recent clinical investigations. In addition it has been suggested that, due to its physicochemical properties and to the binding to HA receptors, hyaluronic acid might have a value as a novel drug delivery system (26). The antimicrobial activit Octopirox as well as its anti-dandruff activity are well established (27,28). Antimicotic activity has also been reported for Sebomine which contains lactoferrin, a biological protein endowed with antimicrobial (29) fungicidal (30) and antiviral activities (31). Recent studies have also proved that lactoferrin possess anti-inflammatory (32) and immuno-modulating properties(33). Norgel has

been shown to improve skin hydration, an action that is of particular importance in subjects with dry skin. Thus the demonstrated clinical activity of KVDS® on dermatitis seems to be based on the specific activity of each of its components. KVDS® formulation had been showed in previous studies to be effective as an adjuvant in the treatment of subjects with seborrheic dermatitis.

The results obtained in the present investigation confirm the therapeutic effectiveness demonstrated by KVDS® in seborrheic dermatitis, and show that KVDS® is endowed with a remarkable soothing activity in the atopic patients included in the present study. This is accompanied by efficacious hydrating action, significant reduction of trans-epidermal water loss, indicating an improvement of the condition of the cutaneous barrier and improvement of its protective function. Quite interestingly, KVDS® also reduced to a significant extent cutaneous scaling in treated areas.

In conclusion the overall results obtained in our investigation clearly indicate that KVDS® should be advantageously added to the therapeutic armamentarium for atopic dermatitis, as well as for other cutaneous situations in which the changes in skin surface parameters are dependent on the state of hydration, as indicated by changes in electrical capacity, trans-epidermal water loss and surface micro-relief. Moreover, the favorable results previously obtained in seborrheic dermatitis patients and those obtained in the present study in subjects with atopic dermatitis suggest that KVDS® might represent an efficacious tool for the treatment of different types of dermatitis due to its beneficial action in improving the protective function of the cutaneous barrier and to its remarkable soothing activity.

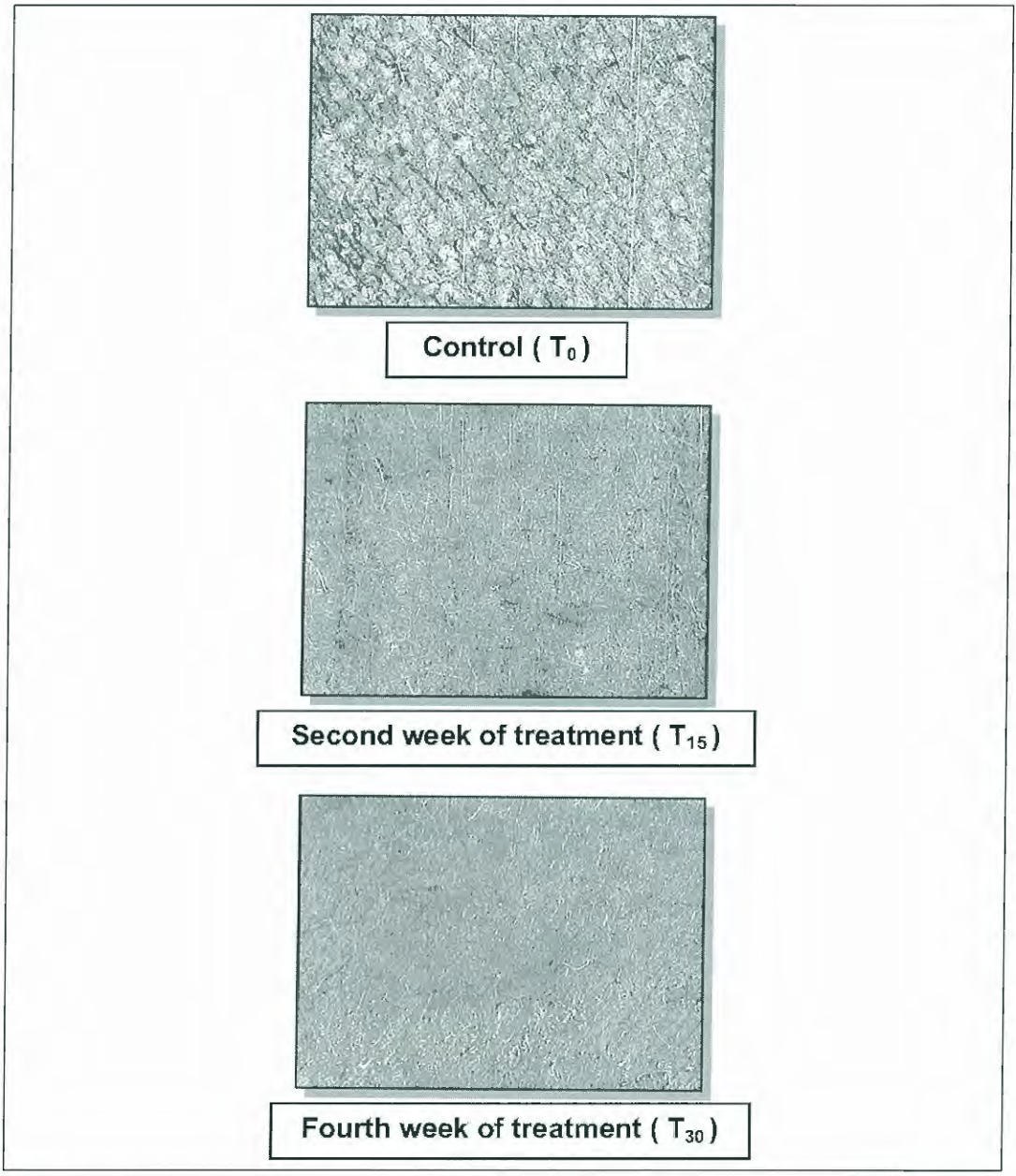

Fig. 4 *Typical example of cutaneous micro-topography records obtained before (T0) and during the treatment with KVDS Emulsion (T_{15} and T_{28})*

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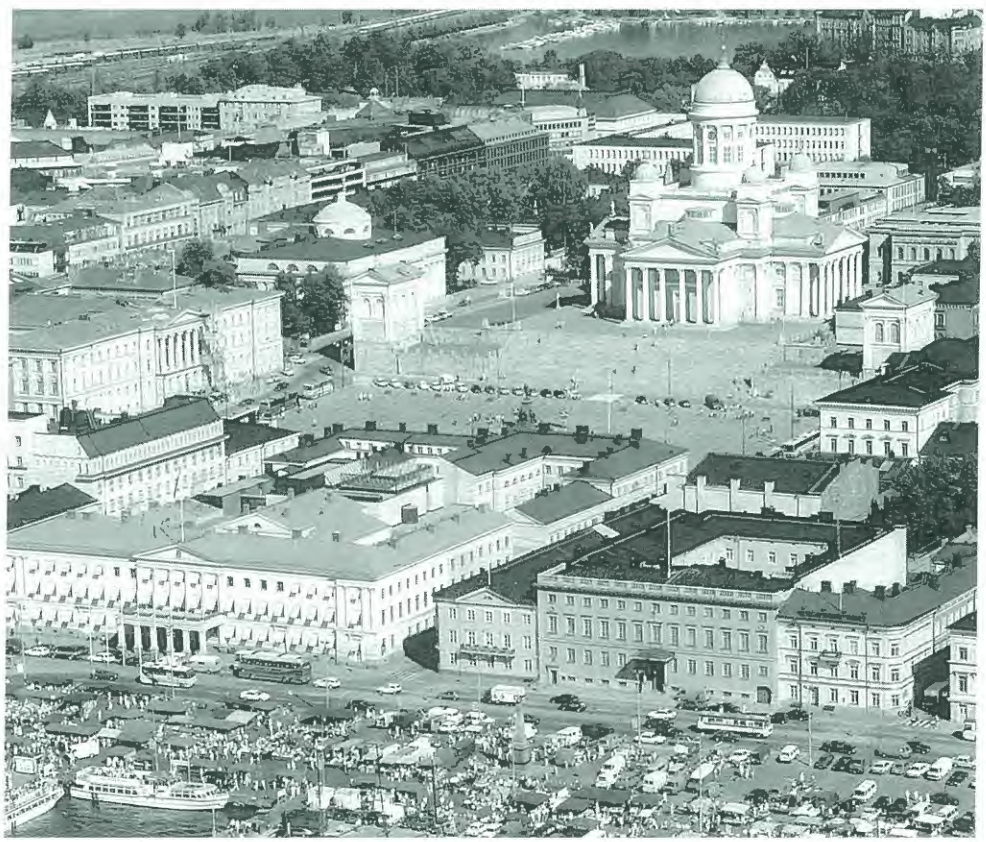
First Announcement

First World Congress on Work-Related and Environmental Allergy (1ST WOREAL)

&

Fourth International Symposium on Irritant Contact Dermatitis (ICD)



9-12 July 2003
1ST WOREAL
Helsinki, Finland

Helsinki, Finland, 9 - 12 July 2003
www.woreal.org
e-mail: secretariat@woreal.org

General Information

Venue. The congresses will take place at Marina Congress Center, in central Helsinki by the passenger harbour.

The Second Announcement and Call for Papers is scheduled for October 2002. It will include detailed programmes, registration information and a call for free communications and posters. To receive it, please mail the attached request-slip or send a request via e-mail.

The social programme will include a get-together party, a reception at City Hall and a banquet. For accompanying persons there will be excursions in Helsinki and its environs. Post-congress tours will include Estonian Tallinn and Russian St. Petersburg.

Medical/technical exhibition. Suppliers of products and services to physicians and researchers will find an opportunity to meet with an estimated 600 medical specialists from some 40 different countries.

The Allergy School is a satellite event organised by Professor Tari Haahtela. For information contact

Ms. Sinikka Hänninen
Skin and Allergy Hospital
Helsinki University Central Hospital
e-mail: sinikka.hanninen@hus.fi

The 7th International Niva Course on Work-Related Respiratory Hypersensitivity is a satellite course organised by the NIVA Institute. For information contact

Ms Pirjo Turtiainen
Finnish Institute of Occupational Health
Telephone +358 9 47 47 23 49
e-mail: pirjo.turtiainen@ttl.fi

Hotel accommodation and transport. All categories of accommodation will be offered. One of the hotels is Scandic Hotel Grand Marina just across the street from the congress venue. For information on travel and hotels contact

Congreszon Ltd.
Ms. Terttu Seppänen
Itälahdenkatu 22 A
FIN-00210 Helsinki, Finland
Telephone: +358 9 58 40 93 51
Telefax: +358 9 58 40 95 55
e-mail: terttu.seppanen@congreszon.fi

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Weather. July is mostly sunny and warm in Helsinki. The sun is up more than 18 hours. The average afternoon temperature is 20 degrees, and the risk of rain is 29 percent.

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9th World Congress on

Cancers of the Skin

May, 7 - 10, Sevilla (Spain), 2003

PRELIMINARY PROGRAM

MEETING AND EXHIBIT LOCATION

Hotel Alcora Sevilla (Spain).
May 7 to 10th, 2003

LANGUAGE

The official language of the meeting is English.
Spanish-English translation is planned for the Scientific Sessions only depending on sponsor support.

TECHNICAL EXHIBITION

The technical exhibition will take place within the Conference Centre of the Hotel, in close proximity to the main meeting rooms. Exhibit space may still be available on a first-come, first-served basis.

Contact:

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PROGRAMMA

13.30	**Registrazione Partecipanti**
14.00	**Benvenuto ed Apertura dei lavori**
14.10	**Topici e Biostimolanti**: attività, assorbimento ed efficacia su cute e mucose
15.10	**Peeling cutanei:** scopi e funzioni
16.10	**Filler cutanei:** modalità d'uso e tecniche iniettive recenti
17.10	**Acne:** metodologie terapeutiche topico-sistemiche
18.10	**Cheloidi e cicatrici:** funzioni terapeutiche delle tecniche occlusive e della biostimolazione
19.10	**Integratori alimentari:** efficacia in Dermatologia e Ginecologia Cosmetologica
20.00	**Chiusura dei lavori e Cocktail**

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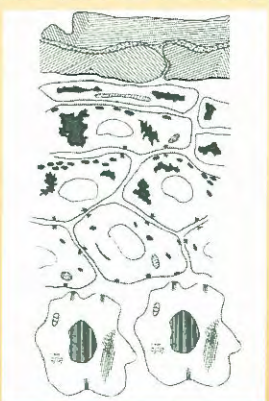

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