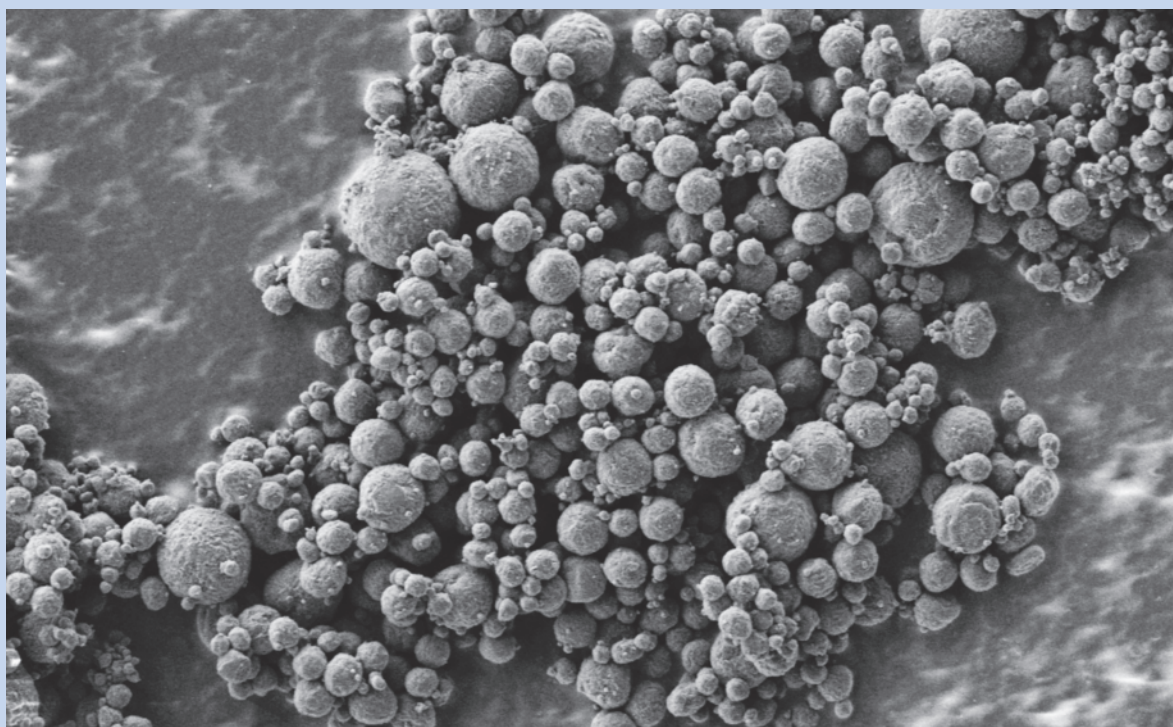


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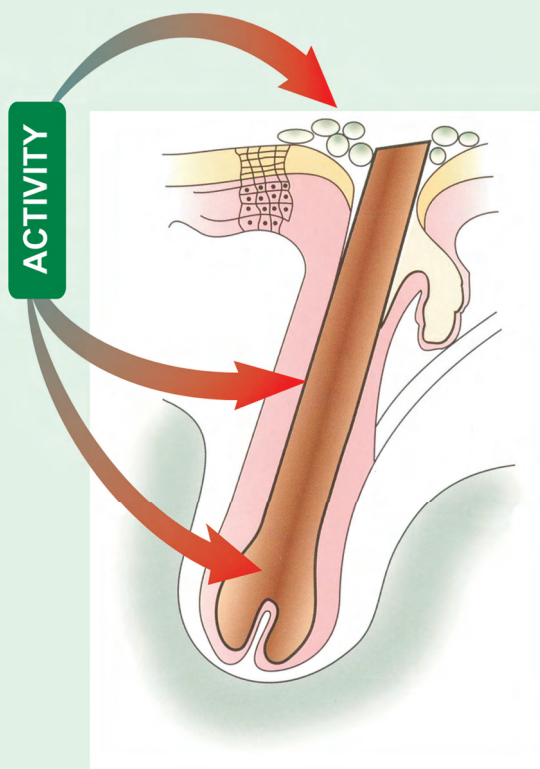


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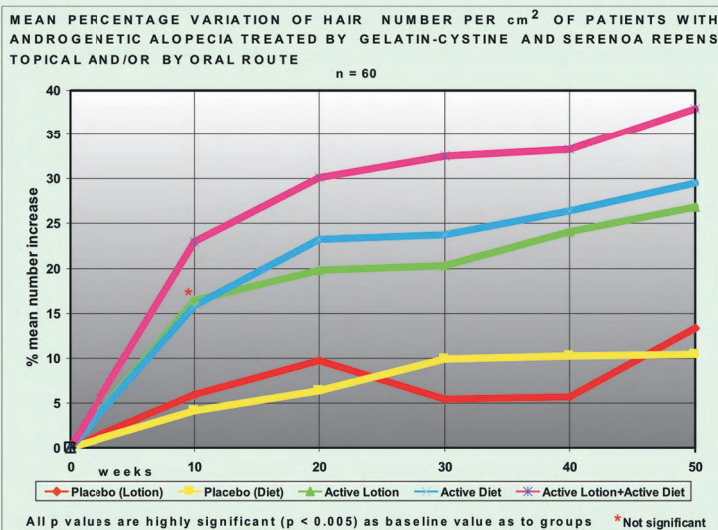
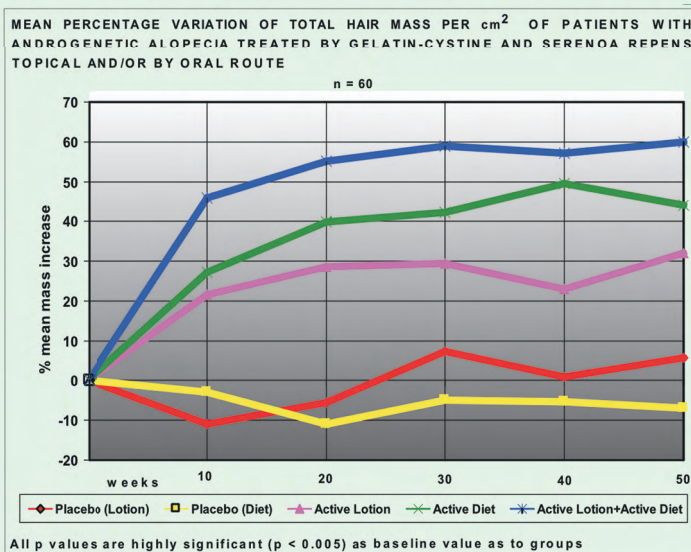
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Trimestrale di Dermatologia Cosmetologica

Quarterly Review of Cosmetic Dermatology

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***In vivo* study of the nanofiber-based composite wound dressing intended for treatment of deep skin wounds**

I. P. Dobrovolskaya^{1,2}, V. E. Yudin^{1,2}, P. V. Popryadukhin^{1,2}, I. O. Lebedeva¹, A. S. Shabunin¹, R. G. Stoyanovsky³, M. S. Asadulaev³, E. M. Ivan'kova^{1,2}, P. Morganti⁴

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Received: May 2016

Key words: *Aliphatic copolyamide; Chitosan; Chitin nanofibrils; Electrospinning; Wound dressing; Composite nanofiber;*

Summary

Electrospinning technique was used for preparation of two-layer wound dressing consisting of a layer of aliphatic copolyamide nanofibers and a layer including chitosan nanofibers and chitin nanofibrils. Experimental studies (*in vivo* treatment of deep skin wounds with this dressing) demonstrated that complete epithelialization of wound surface was achieved after 28 days. Histological analysis of scar tissue indicated the presence of insignificant amount of capillaries and low amount of infiltrate cells. The survival of animals was 100%. At the same time, in the control group of animals, the lethality was observed in 10% of cases, and suppurative complications were observed in 100% of cases.

Riassunto

Attraverso l'elettrofilatura è stata realizzata una nuova medicazione avanzata costituita da due strati; uno esterno formato da nanofibre di copoliammide alifatica ed uno interno basato su nanofibre di chitosano e nanofibrille di chitina. I nostri studi sperimentali *in vivo* (trattamento di ferite profonde con tale medicazione) hanno dimostrato la completa riepitelizzazione della ferita in 28 giorni.

Le analisi istologiche condotte sul tessuto cicatriziale hanno posto in evidenza una presenza non significativa di capillari e un basso quantitativo di infiltrati cellulari.

La sopravvivenza degli animali è stata del 100%. Al contrario, nel gruppo di controllo è stata verificata una mortalità del 10% accompagnata da complicanze suppurative pari al 100%.

INTRODUCTION

Nowadays, healing of skin and soft tissue wounds is a topical problem in cosmetology. The main factors which inhibit epithelialization and granulation processes are tissue dystrophy, oxidative damage, moisture imbalance in wound, infections and other complications in the area of surgical resection, trauma or burn. Formation of scar tissue or other structural defects at the wound site reduces a patient's quality of life. Currently, there are a number of techniques which allow intensification of wound healing process. In the majority of these methods, wound dressings of various compositions and structures are used (1-3).

Wound dressing should facilitate the optimal gas and moisture exchange which is necessary for cell vital activity, should reproduce wound surface relief, i.e. possess elasticity and provide ease of surgical manipulations. Another important property of modern wound dressings is atraumaticity; that is, the formed epithelium layer should not be traumatized or destroyed during removal of a dressing from wound. Finally, a dressing should prevent wound infection (invasion of pathogenic microflora from external medium).

These properties can be achieved in porous type films based which are obtained by electrospinning of polymeric solvents. This method allows preparing fibers with diameters ranging from tens to hundreds of nanometers from various polymers. Nanofiber-based films possess low density, high porosity, water permeability and gas permeability (4-7). Recently, these porous films have found practical use as matrices for cell technologies. Chemical structure and porosity of these materials facilitate adhesion of stem or somatic cells onto fiber surface, and promote metabolic processes which are necessary for efficient cell proliferation and differentiation. Preparation of nanofibers from alcohol-soluble

aliphatic copolyamide (CoPA) (copolymer of poly(ϵ -caprolactam) $[-NH-(CH_2)_5-CO-]_n$ and poly(hexamethylene diamine adipate) $[-NH(CH_2)_6NHCO(CH_2)_4CO-]_n$) is described in (5). Good adhesion of stem cells and the absence of cytotoxicity were demonstrated.

Chitosan is another polymer which is widely used in developing materials for medicine. This biocompatible and biodegradable polysaccharide consists of β -(1-4)-D-glucosamine and N-acetyl-D-glucosamine units (8). Products of chitosan biodegradation are non-toxic; as decomposition proceeds, these products are involved in usual metabolic reactions of organism. However, it is known (8-10) that processing fibers from chitosan solutions by electrospinning is difficult, since this polymer is a polyelectrolyte. For preparation of chitosan-based fibers by electrospinning, water-soluble polymers, e.g. poly(ethylene oxide), poly(vinyl alcohol), methyl cellulose, poly(vinyl pyrrolidone), are introduced into aqueous solution of acetic acid. Addition of these polymers (up to 50 wt.% with respect to mass of chitosan) has a detrimental effect on properties of the end product, e.g. leads to increase in hygroscopicity and deterioration in mechanical properties.

Some authors (11-13) described a patented method of preparing chitin nanofibrils intended for use in cosmetology. Chitin nanofibrils were used as a filler in chitosan-based composite fibers obtained by wet spinning (14) also. It was demonstrated that the chitosan-based composite fibers containing chitin nanofibrils with a diameter of 20 nm and a length ranging from 600 to 800 nm possess enhanced mechanical strength and elasticity. Besides, introducing chitin nanofibrils into chitosan spinning solution stabilizes the spinning process.

Properties and structure of the composite nanofibers obtained by electrospinning and containing chitin nanofibrils as a filler are described in (15). It was established that introducing chitin nanofi-

brils into chitosan solution leads to significant increase in the rate of nanofiber formation, and results in the formation of materials with lesser amount of defects. In addition, introducing chitin nanofibrils into chitosan-based composite nanofiber allowed lowering the necessary amount of poly(ethylene oxide) (PEO), which is water-soluble polymer added into solution in order to facilitate formation of fibrous structures during electrospinning.

In the present work, we suggest the method for preparation of the composite wound dressing consisting of a layer of CoPA-based nanofibers and a layer of composite nanofibers including chitosan and chitin nanofibrils. Nanofibers from non-resorptive CoPA impart the necessary mechanical properties to wound dressing, facilitate metabolism between a wound and external environment and create a barrier for pathogenic microflora. The layer of chitosan nanofibers and chitin nanofibrils which is in direct contact with wound surface simultaneously affords hemostatic and bactericidal action and atraumaticity of dressing. In the process of integration with active biological medium, gradual resorption of chitosan and chitin nanofibrils occurs. After removing dressing, non-resorptive CoPA layer is separated from wound surface, while the chitin-chitosan layer remains and facilitates epithelialization of a wound.

The aim of the present work was development of the wound dressing based on CoPA nanofibers and composite nanofibers containing chitosan and chitin nanofibrils as well as *in vivo* studies of these materials as wound dressings for treatment of deep skin wounds.

MATERIALS & METHODS

The materials based on CoPA and chitosan nanofibers were obtained from polymeric solutions by electrospinning (5). The method of processing composite nanofibers from chitosan and fil-

lers (chitin nanofibrils), and the properties of these materials are described in (16). Films were prepared by electrospinning of composite chitosan-based nanofibers onto the surface of porous film made from CoPA nanofibers. The thickness of CoPA nanofibers was 150 μm , and the thickness of the layer of composite nanofibers was 50 μm . Electrospinning was performed using a NANON 01 instrument (Japan) at a voltage of 18 kV; the distance between electrodes was 0.15 m.

The structure of nanofibers and nanofiber-based materials was studied by scanning electron microscopy. The measurements were carried out using a Supra 55VP electronic microscope (Carl Zeiss, Germany).

Composite wound dressings based on nanofibers were tested on scalped wounds of skin. For this purpose, the model of a full-thickness skin wound in small laboratory animals (rats) was developed. The incision in the back of an animal was made with a scalpel; then separation of skin from surface fascia was performed with the use of scissors and surgical tweezers (Fig. 1a). Skin edges of a wound were fixed with interrupted musculocutaneous inverting sutures to its own fascia (Fig. 1b). Diethyl ether was used for inhalation anesthesia in animals. This method allows to avoid early wound closing by primary intention and to reliably assess efficiency of wound treatment preparations.

Eighteen animals were used in the experiments (Wistar-Kyoto male rats, mass 200-250 g). The animals were divided into two groups (the control group and the experimental group, each including 9 animals). In the experimental group, after modeling full-thickness mechanical skin wound (10% from the animal surface area), wound surface was covered with chitosan/copolyamide dressings. The animals were observed for four weeks.

In 28 days, the experiments were completed; tissue samples were taken from wound area, and

morphological studies of this tissue were carried out. Tissue samples were fixed in 10% solution of neutral formalin in phosphate buffer (pH = 7.4) for 24 hrs, then treated with ethanol solutions of increasing concentrations and embedded

in paraffin. Paraffin sections (5 μ m thick) were dyed with hematoxylin and eosin (Bio-Optica, Italy). Microscopy analysis and registration of images were performed with the use of a Leica DM750 light microscope (Germany).

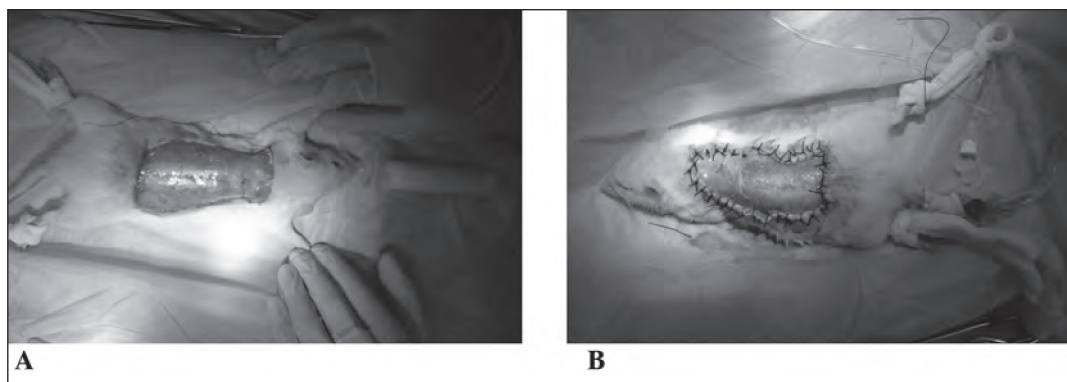


Fig. 1 Formation of a scalped wound in rat: before suturing (a); after suturing (b).

RESULTS AND DISCUSSION

Figure 2 presents microphotographs of CoPA nanofibers and chitosan-based composite nanofibers containing 20 wt.% of chitin nanofibrils. It can be seen that the average diameter of CoPA fibers is about 600 nm, and the average diameter of chitosan-based composite fibers is 150 nm. Two-layer composite material was applied to wounds in such a way that the layer containing nanofibers of chitosan and chitin nanofibrils was in direct contact with a wound.

All animals from the experimental group, which were treated with the two-layer wound dressing, were alive in 28 days after beginning of the experiment; complete epithelialization of wound surface was observed in all cases (Fig. 3a). Scar areas were significantly smaller than those in the animals from the control group, which were not treated with the developed wound dressing (Fig. 3b). Histological studies of scar tissue demonstrated the presence of a small amount of capil-

laries and insignificant amount of infiltrate cells (Fig. 4).

Observation of the animals from the control group demonstrated that lethality occurred in 11% of cases; suppurative complications were registered in 100% of cases. In 11% of cases, large amounts of pus were accumulated under scar tissue (Fig. 3b). Histological studies of scar tissue (Fig. 4) revealed the presence of a large amount of capillaries and dense infiltrate.

Efficiency of using chitosan nanofibers is confirmed by the experiments in which we employed wound dressings prepared from CoPA nanofibers without the layer of composite nanofibers. In all animals with deep skin wounds which were treated with these dressings, large amounts of pus were accumulated under scars.

Morphological studies showed that in the animals of the control group, in the scar area, neutrophilous leukocytes prevailed over other infil-

trate cells; maturation of granulation tissue was less pronounced. This granulation tissue covers rather large area compared to that of the experimental group.

At the same time, only in some cases from the experimental group, complete epidermization of wound surface (Fig. 5) and formation of new

connective tissue (Fig. 6) were observed; the connective tissue occupied rather small area in comparison to that of the control group. These morphological features may be indicative of more intense regeneration of wound surface in experimental animals as a result of using the developed wound dressing.

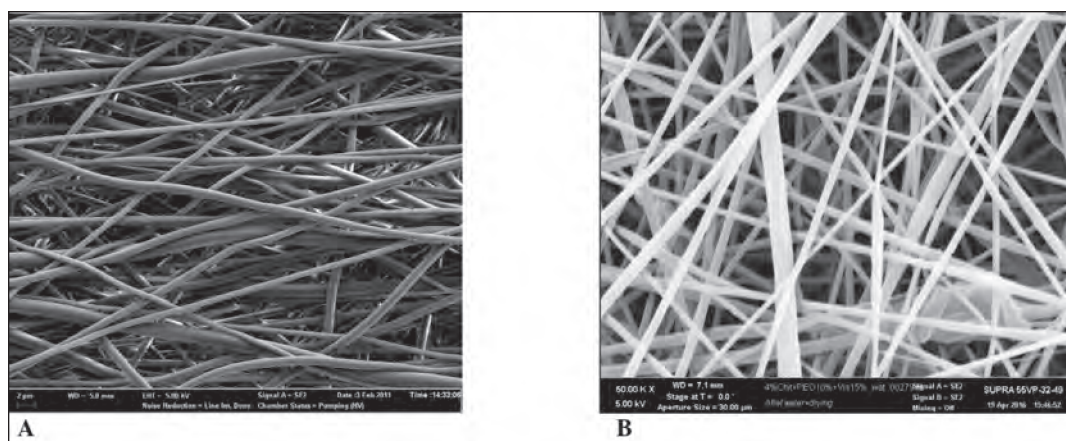


Fig. 2 Microphotographs of CoPA fibers (a) and chitosan-based composite nanofibers containing chitin nanofibrils (b).

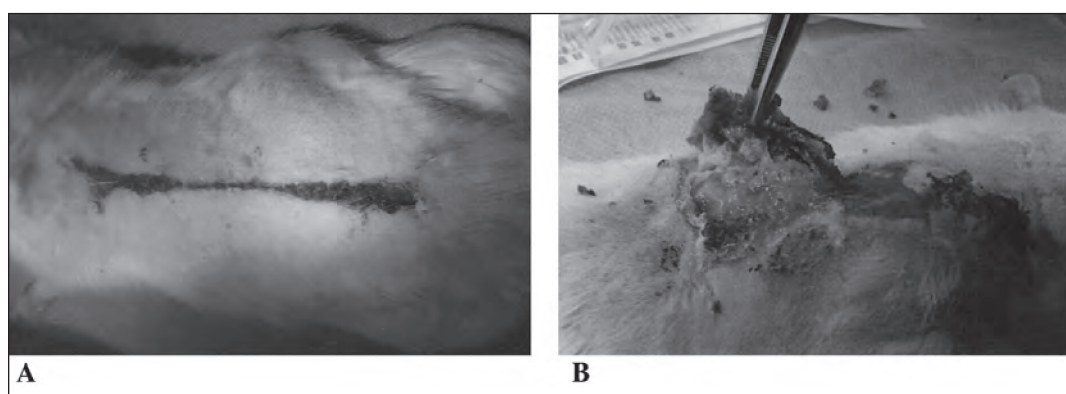


Fig. 3 Visual appearance of the wound surface in an animal after applying the composite wound dressing (a) and in an animal from the control group (b).



Fig. 4 Histological view of the scar area of a rat from the control group (magnification X10).

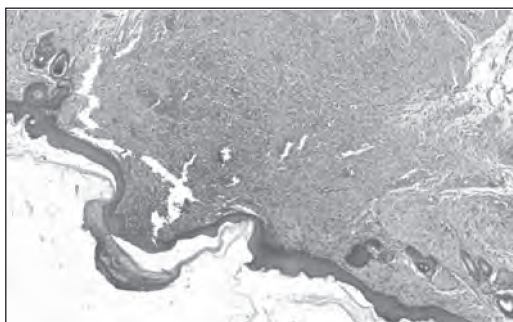


Fig. 5 Histological view of the scar area of a rat from the experimental group (magnification X5).

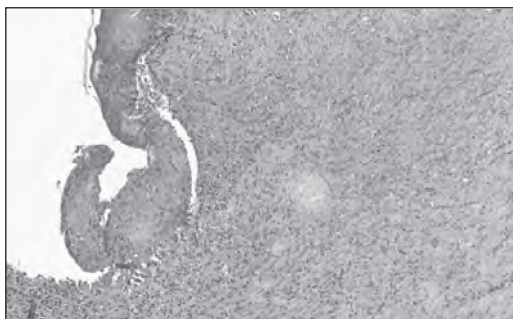


Fig. 6 Histological view of the scar area of a rat from the experimental group (magnification X10).

combined with chitin nanofibrils was developed. The *in vivo* experiments demonstrated high efficiency of this dressing in treatment of deep skin injuries.

CONCLUSIONS

The two-layer wound dressing including a layer of fibers from non-resorptive polymer (aliphatic copolyamide) and a layer of chitosan nanofibers

ACKNOWLEDGEMENTS

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Safety evaluation of skin fresh intense moisturizer bar

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Key words: Safety evaluation; Safety studies; Fibroblast toxicity; MTT assay; Zein protein hydrolysis; Collagen swell test;

Summary

Skin fresh intense moisturizer bar¹ is a well-researched bathing bar for the treatment of dry skin in psoriasis conditions.

Sufficient scientific data is available on the efficacy of conditions in the treatment of dry skin in psoriasis.

In the present study reports the complete safety assessment of the skin fresh intense moisturizer bar and its importance.

Riassunto

Skin fresh intense moisturizer bar¹ è un sapone sintetico formulato per il trattamento della cute estremamente secca in quanto affetta da psoriasi.

Lo studio riporta alcuni dati sperimentali che pongono in evidenza la sicurezza d'uso di questo trattamento cosmetico.

¹ Trade name: Verdura skin fresh intense moisturizer bar is the product of Dr. JRK's Siddha Research and Pharmaceuticals Pvt., Ltd., Chennai - India.

INTRODUCTION

Use of herbal products in healing various skin problems are well known in the system of alternative medicine (1). In most instances the herbs are directly extracted into vegetable oils like coconut oil, ginger oil, sun flower oil etc.

The herbs used for preparing such oils can be in wet or shade dried form. Skin fresh intense moisturizer bar is a well-researched and uniquely formulated bathing bar using the herbal oil extracts. The bathing bar is formulated with 10% both Aloe vera and *Wrightia tinctoria* oil extracts. These oils were incorporated into melt and pour bathing bar base².

Skin fresh intense moisturizer bar is used for treating dry skin, psoriasis skin, geriatric dry skin, also if bathing bar may cause various dermatological problems, skin irritation etc., during prolonged usage to establishing the primary safety of such product is therefore necessary.

The present study reports the safety profile of the in-study bar as product for the treatment of dry skin, and psoriasis skin.

MATERIALS AND METHODS

Fibroblast toxicity- MTT Assay

Toxicity on fibroblast cells was measured by treating the cells with the in-study bar at various concentrations and the reduction in cell proliferation was measured using MTT assay (2, 4).

The cell proliferation is based on the ability of the mitochondrial succinate-terazolium reductase system to convert 3-(4, 5- dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) to a blue colored formazan. The test denotes the survival cells after exposure to the test samples. The 3T3 Fibroblast cell line was used for this study. The cell lines was maintained and sub cul-

tured in 25mm² tissue culture flasks using 5 ml of minimum essential medium (MEM) supplemented with 10% fetal bovine serum, 3% L-glutamine, penicillin (100 IU/ml), streptomycin (100 µg/ml), Amphotericin B (20 µg/ml), phenol red.

The pH of the medium was adjusted to 7.2-7.4 with 7.5% sodium bicarbonate and all flasks were incubated at 37°C in a humidified 5% CO₂ / 95% O₂ incubator.

Cells were grown in an appropriate growth media and seeded at concentrations of 5×10⁴ cells per ml of media in 24 well plate. Cells were allowed to adhere for 12 hours followed by treatment with different concentrations of the in study-bar viz., 50, 40, 30, 20 and 10 mg/ml and incubated for 48 hours at 37 °C with 5 % CO₂. After treatment of 48 hours, cells were treated with 10% MTT in media for 4 hours in 37 °C and 5 % CO₂. Media was then aspirated and the adherent cells with formazon product was dissolved in DMSO, centrifuged at an RPM of 5000 for 15 minutes to remove debris and the spectrophotometric absorbance of the sample was measured using a microplate reader. The wavelength used to measure the absorbance of formazan product was 570 nm and the percentage of reduction in cell proliferation was determined.

Zein Protein Hydrolysis

The purpose of the zein protein hydrolysis test is to investigate the irritation potential of skin fresh intense moisturizer bar. Skin fresh intense moisturizer bar is diluted in water with the addition of 0.5% glycerine. The predicted protein hydrolysis was determined by the amount of zein solubilised i.e. zein value (3).

Initial weight of the filter paper is noted. 0.5% and 1% solution of the test sample was prepared. 0.5% of SLS is also prepared as irritative surfac-

² Trade name: TBB-Melt and Pour flakes, Galaxy SN 930, Galaxy surfactants Ltd, India.

tant control. Accurately weight predetermined amount of zein was added to the three solutions as mentioned. The solution was poured onto the filter paper, seated inside the ceramic tunnel, and filtered under vacuum; filtrate and filter paper were placed on the aluminum dish, and the same was dried overnight in a 45°C oven, recording the final weight of zein. The following formula was used for evaluating the zein value:

Total Zein (g) added to the solution - Total Zein after drying x 100

Total Zein (g) added to the solution

Collagen Swell Test

Because the swelling of collagen film by anionic surfactants correlates well with the skin irritation (5), this film was also treated with the skin fresh intense moisturizer bar in a solution to identify the ratio of swelling compared to control (collagen). According to our experience, the irritation potential of surfactants could be identified through this test, attesting the mildness and moisturizing properties on the skin of the in-study bar. The collagen swelling test was adapted using a piece of collagen sheet (1 cm²). It was incubated for 24 hours, at 50°C, in different solutions con-

centrations at 1, 2, 3, and 5%. The collagen was weighed before and after incubation to determine the amount of swelling. The more the collagen swells, the more irritating the product results. The results are expressed as follows:

CSW = (weight after incubation – initial weight) / initial weight

RESULT

Fibroblast toxicity- MTT Assay

Up to a concentration of 50 mg/ml the in-study bar did not affect either the viability or proliferation of fibroblast. The percentage inhibition as measured by the formation of formzan clearly shows that the effect of skin fresh intense moisturizer bar in the viability of fibroblast cells was insignificant (Table I).

Zein Protein Hydrolysis

When the in-study bar was tested for its irritant potential through Zein protein hydrolysis assay keeping 0.5% Sodium Lauryl Sulphate (SLS) as positive control. Findings of the study reveal that skin fresh intense moisturizer bar is completely non-irritant (Table II).

TABLE I		
% of viability of fibroblast cells.		
S.No	Skin fresh intense moisturizer bar (mg/ml)	% inhibition
1	50	29
2	40	19
3	30	11
4	20	10
5	10	5

Collagen Swell Test

Skin fresh intense moisturizer bar was tested for its irritant potential through collagen swell test

keeping 0.5% Sodium Lauryl Sulphate (SLS) as positive control. Findings of the study reveal that skin fresh intense moisturizer bar is completely non-irritant (Table III).

TABLE II
% Zein protein hydrolysis.

S.No	Skin fresh intense moisturizer bar (mg/ml)	% Zein protein hydrolysis
1	0.5% SLS	90
2	1% Sample	19
3	0.5% sample	7

TABLE III
% Collagen swelling.

S.No	Skin fresh intense moisturizer bar (mg/ml)	% Collagen swelling
1	0.5% SLS	80
2	1% Sample	20
3	2% sample	30
4	3% sample	40
5	5% sample	45

DISCUSSION

The present study undoubtedly established the safety profile of skin fresh intense moisturizer bar with reference to the following tests such as fibroblast toxicity, zein protein hydrolysis and effect on collagen swelling.

The findings of the in-study bar did not show any cytotoxic effect in the growth and viability of fibroblasts. It has shown a low inhibition rate at high concentrations also. Similarly this natural bar also did not show any irritant potential by the zein protein hydrolysis test in comparison with the 90% hydrolysis due to 0.5% SLS.

Furthermore, it did not show any irritancy by the collagen swelling test even at 5% concentration when compared to 0.5% SLS. Thus the non-irri-

tancy of the in-study bar is reassured in collagen swell test.

When products are tested for efficacy testing the safety is equally important. In that respect skin fresh intense moisturizer bar seems to be very safe for prolonged usage for the treatment of dry skin, also psoriasis skin. In the above circumstances the proven safety of the in-study bar with battery of safety tests, can be prescribed predominantly for psoriatic patients.

Therefore it can be assumed that skin fresh intense moisturizer bar seems to be safe for psoriatic patients also.

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New Horizon in Cosmetic Dermatology

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Key words: Circular economy; Bionanotechnology; Cosmetic Dermatology; Sustainability; Recycling process; Chitin Nanofibrils; Chitosan; Lignin;

Summary

The new Cosmetic Dermatology horizon of keeping materials, products, and tools at their highest value by the Circular Economy, could be part of a transition towards a restorative and regenerative economic cycle. This new way of thinking and working, will move Dermatologists, Plastic surgeons, Biologists, and Cosmetic chemists from wasteful resource use to foster lower cost products and services, characterized by less carbon emissions and more employment possibilities.

Circular economy, in fact, is based on a functional model service in which manufacturers, retailers, and professional people retail the ownership of their products and replace the concept of the consumer with that of the user. Eliminating waste from the industrial and consumer chain will save cost and reduce resource dependence.

As an example, nanochitin and nanolignin, obtained from crustacean by-products and plant biomass respectively, used to produce cosmetic and pharmaceutical carriers, food packaging, and advanced medications completely biodegradable and compostable. This innovative way to produce goods and services could eradicate poverty and improve social equity.

Riassunto

Il nuovo modo di operare nell'ambito della Dermatologia Cosmetologica di utilizzare materiali e prodotti al massimo del loro valore, secondo i canoni dettati dall'Economia Circolare, dovrebbe caratterizzare il futuro ciclo economico. Questo nuovo modo di pensare ed agire porterà il dermatologo, il chirurgo plastico, il biologo ed il chimico cosmetologo ad utilizzare prodotti ricavati dall'uso di materiali di recupero che, oltre a risultare economicamente più convenienti, contribuiranno a ridurre l'emissione di CO₂, incrementando anche i posti di lavoro. Infatti, l'economia circolare è basata su un modello di sviluppo secondo il quale i produttori, i distributori ed i professionisti coinvolti nella

produzione e commercializzazione dei diversi prodotti, dovranno considerare non come un semplice consumatore ma come un vero e proprio utilizzatore. Così anche l'eliminazione degli sprechi della catena produttiva fino al consumo finale potrà contribuire a ridurre i costi ed a conservare le materie prime naturali per le generazioni future. Un esempio viene dall'uso delle nanofibrille di chitina e della nanolignina che, ricavate rispettivamente dalla lavorazione dei crostacei e della biomassa vegetale, vengono utilizzate per produrre cosmetici innovativi, imballi alimentari biodegradabili e compostabili, e medicazioni avanzate.

Questi nuovi prodotti realizzati con l'uso di bionanotecnologie, risulteranno utili per ottenere prodotti e servizi indispensabili per eliminare la povertà e raggiungere un miglior equilibrio sociale.

Nel lavoro sono riportati alcuni esempi di prodotti ottenuti con l'uso delle nanofibrille di chitina e dei suoi complessi con acido ialuronico o con lignina.

INTRODUCTION

Cosmetic Dermatology has to gain increasing attention to Circular Economy from day to the incoming years. Circular Economy, in fact, will offer a major opportunity to increase resource productivity, decrease resource and waste dependence, offering the opportunity to create new employment and growth (1). At this purpose, the actual European studies provide evidence that this new economical vision, enabled by the bionanotechnology revolution (Fig. 1), allows Europe to grow resource productivity by up to 3 per cent annually. This would generate a primary resource benefits of as much as € 0.6 trillion per year by 2030 to Europe's economy. In addition, it would generate €1.2 trillion in non-resource and externality benefits, bringing the annual total benefits to around €1.8 trillion versus to day (2). Thus, the Circular Economy (Fig. 2) has the potential to help all Countries to make better decisions about resource use, designing out waste, increasing growth and profitability, fostering innovation through novel business models, necessary to increase the worldwide prosperity and maintain environmental sustainability for future generations. By combining efficiency and effectiveness, the worldwide economy would experience win-win results benefiting the environment and boosting competitiveness and resi-

lience by the use of waste materials with a low consume of water and energy.

At this purpose, Cosmetic Dermatology could open an new horizon of values, being part of transition towards a restorative and regenerative economic cycle. This new way of thinking and operating will move Dermatologists, Plastic Surgeons, Biologists, and Cosmetic Chemists from wasteful resource use to foster lower cost products and services, being also characterized by less carbon emissions, and more employment possibilities (3) (Fig. 3). It is time to rethink our technologies for a better economic future!

The New Horizon: Circular Economy

This new horizon goes beyond different mechanisms of production and consumption of drugs, medical devices, cosmetics, and services to obtain an economy in which the today's goods are the tomorrow's resources (Fig. 4). At this purpose for example, one of the many challenges for marketers and professional people is to differentiate their sustained and prescribed drug/cosmetics from competing and publicizing products and to communicate this to consumers, and for, consumers to recognize what makes a product more sustainable.

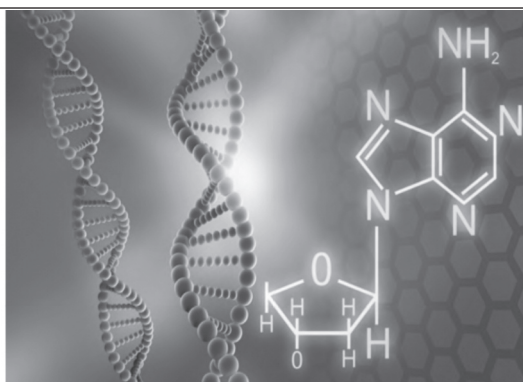


Fig. 1 *The Bionanotechnology revolution.*

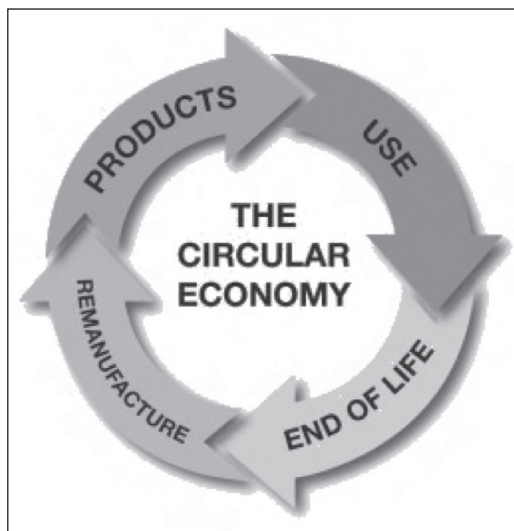


Fig. 2 Significance of Circular Economy.

Thus, Circular Economy advocates the need for a functional service-model in which manufacturers or retailers increasingly retain the ownership of their products, replacing the concept of the consumer with that of the user. In order to materialize the savings, associated with a circular

system by reusing resources inputs to the maximum degree, the companies need to increase the rate at which their products are collected and subsequently reused and/or their components/materials recuperated. So doing, eliminating waste from the industrial chain by reusing materials to the maximum extent possible, Circular economy will save the production cost and reduce the resource dependence by recycling processes (Fig. 5). Based on a product modelling scenario, the annual material cost saving for Europe should be of US\$ 340 to 630 billion for a transition scenario and US\$ 520 to 630 for an advanced scenario, based on 2010 GDP all net of the material used in the reverse-cycle processes (1). This new economic vision is to be considered strategic not just for industry but also for customers, serving as sources of both efficiency and innovation. For example, technical and natural polymers and other man-made materials may be designed to be used again with minimal energy and highest quality retention, to produce nanoparticles, nanowires, and nanofibers (4).



Fig. 3 The use of waste material induces lower costs.

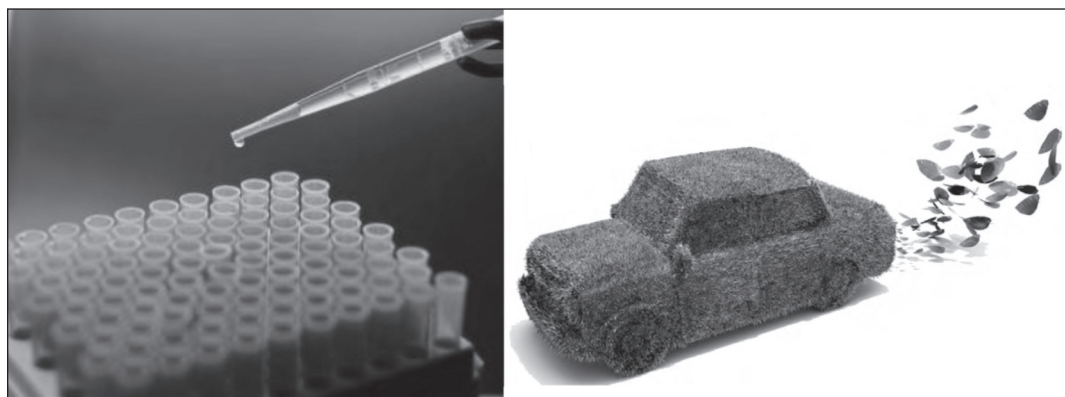


Fig. 4 The future green goods.



Fig. 5 The necessity of the recycling process.

New Goods from Biomass

In this direction are going, production and use of chitin nanofibrils (CNs), obtained from crustaceans waste, and/or lignin from plant biomass, utilized both as basic raw materials to produce advanced medications, innovative pharmaceutical and cosmetic delivery systems, and new food packaging (Fig. 6) (5,6). Following multiple extractions, purification, and other industrial steps, chitin, chitin-derived, and lignin have been used for making structural and functional bio-nanocomposites useful for making innovati-

ve goods, and reduce the fossil-based products (7-9). Thus, it has been shown a matrix reinforcement effect obtained by the use of CN as nanofiller. Its use, in fact, improves the physical properties at molecular level of the produced composites. As a consequence their mechanical, thermal and barrier properties result ameliorated, without affecting the polymer processing. An example is the use of CN as filler, to make more soft, resistant and regular the surface of chitosan fiber (Fig.7) (10-12).

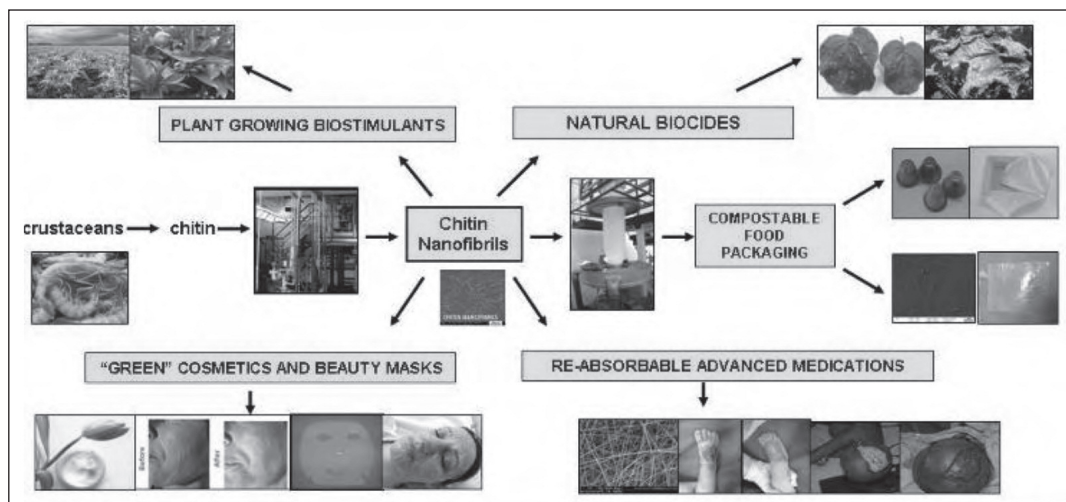


Fig. 6 Different products made by chitin nanofibrils.

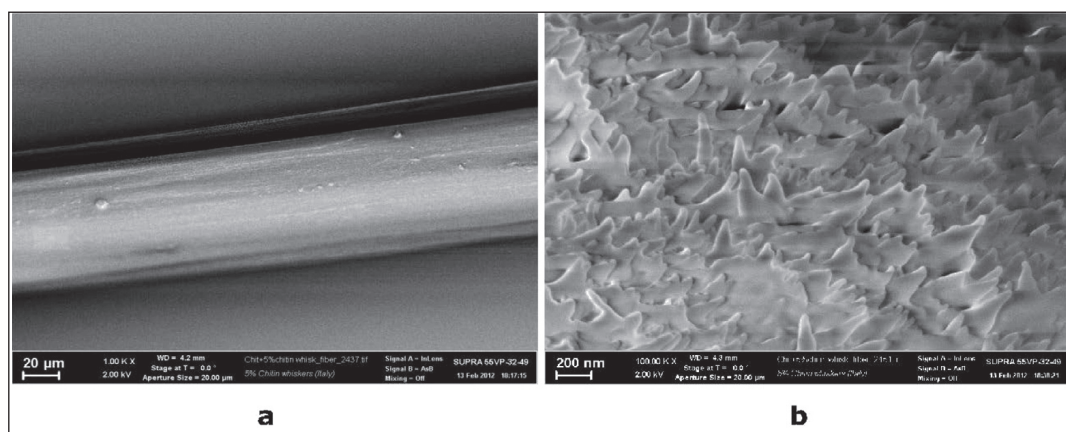


Fig. 7 The smooth surface of a chitosan fiber containing CN as filler. a: the surface; b: chitin nanofibrils disposition into the fiber structure (By courtesy of Prof. V.E. Yudin).

Thus, this natural polymer can be used for making transparent films (Fig. 8) which, characterized for their biodegradability and compostability may result useful to make innovative cosmetic beauty masks or advanced medicated tissues (13), according to the different active ingredients entrapped into the film or non-woven tissue by the casting or the electrospinning methodologies (Fig. 9), before being processed. It is interesting to underline that both CN

and chitin-based materials are versatile polymers that can be optimized for many regenerative or haemostatic purposes (14-15), such as for example to culture stem cells (Fig. 10) (16), or to increase filaggrin and involucrin biosynthesis when used as carrier for medical and cosmetic purpose (Fig. 11) (17-19). CN and CN-based nanoparticles and polymers, in fact, are characterized for their high porosity, biodegradability, structural integrity, biocompatibility, and non-

toxicity to cells. Moreover, these biopolymers can be easily processed into various products, such as hydrogels, membranes, nanofibers, micro/nanoparticles, scaffolds, sponges, etc to be used in different fields from food packaging to cosmetics and biomedical applications (20,21).



Fig. 8 Transparent film made by chitin nanofibrils.

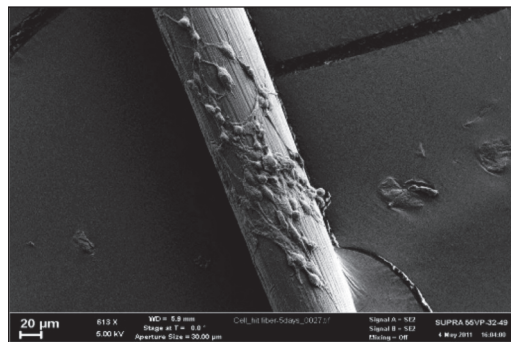


Fig. 10 Reproduction of Stem cells on a Chitosan/chitin fiber.

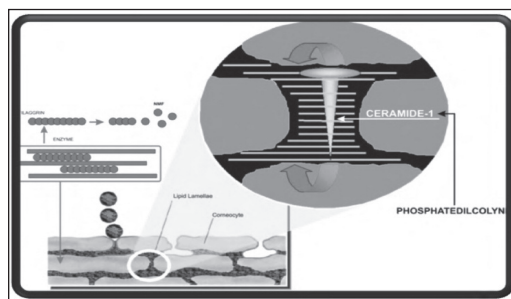


Fig. 11 The filaggrin cycle.



Fig. 9 The electrospinning and casting methods.

CONCLUSION

In conclusion, the innovative products made by these natural polymers are a today reality to be remembered from dermatologists, plastic surgeons, biologists, cosmetic chemists, and marketing managers (Fig. 12) who should know and increase their use from their customers/patients. However, the goal of this new way to produce/consume is to generate a synergistic relationship between ecological and economical systems. Moreover according to OECD Innovation strategy," new sources of growth are urgently needed to help the world for a stronger, more inclusive and sustainable growth path, following the financial crisis so that "innovation can be a critical part of the solution (22). In any way," the combination of innovation policies

and related governance need to be aligned with the capabilities of each country in terms of policy making and policy implementation "(22). Additionally, Circular Economy will involve large scale investments in new technologies, equipments, buildings, and infrastructures (Fig.13). These investments will deliver social and economic benefits by improving resource efficiency and inducing Companies and Professional organizations to innovate, for obtaining a competitive edge, capable also to eradicate poverty and improve social equity (Fig. 14). This has to be the new horizon of Cosmetic Dermatology to obtain a sustainable development by the use of innovative green biopolymers and bionanotechnologies, biocompatible and environmentally friendly (23-26)



Fig. 12 Innovative food packaging made by Chitin Nanofibrils.



Fig. 13 New technological equipment to produce and control Chitin Nanofibrils. A: the pilot plant; B: SEM.

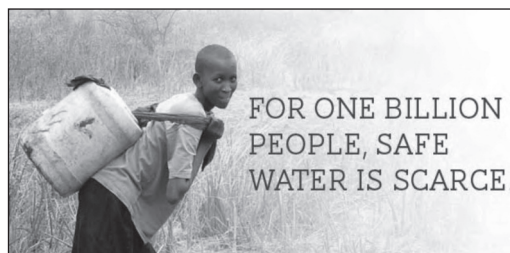


Fig. 14 The necessity to improve the social equity.

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An Unforgettable Meeting

P. Morganti

Prof. of Skin Pharmacology, Dermatology Institute, 2nd University of Naples, Italy

Visiting Professor, Dermatology Depart., China Medical University, Shenyang, China

R&D Director, Nanoscience Centre, Mavi Sud, s.r.l, Italy

In the wonderful city of Jakarta, surrounded by an unusual skyscrapers setting of the Ritz Carlton Hotel Pacific Place (Fig. 1), the 12th Congress of the International Society of Cosmetic Dermatology has been held on April 2-3, 2016, in collaboration and in occasion of the 50th anniversary from the foundation of the Indonesian Society of Dermatology and Venereology (PERDOSKI).



Fig. 1 Carlton Hotel Pacific Place.

Abraham Arimuko, President of the Indonesian Cosmetic Dermatology Study Group and Chairmen of the Committee together with Syarief Hydayat, President of Perdoski have been the organizers.

New Horizon in Cosmetic Dermatology was the general topic of this interesting meeting participated by 1200 dermatologists with more than 100 speakers and industrial boots. Actual and future trends in dermo-cosmetic treatments of the main dermatological diseases, such as psoriasis, vitiligo and acne together with the update solutions to slowdown the aging processes, have been the main topic reported and discussed.

The main frame of this meeting was the necessity to obtain the best therapeutic and aesthetic result by the use of products and tools skin-friendly and environmentally-friendly.

The challenge to maintain the human wellness of our body, alleviating the environmental burdens by innovations reducing the poverty is the to-day necessity for maintaining the biodiversity of our planet also (Fig. 2).

According to the circular/green economy, Innovation support not only productivity, but also a green growth, addressing global and social challenges by a sustainable production. Education and training systems are core to Innovation and productivity, also in the Cosmetic and Pharmaceutical fields, while policy has to facilitate the Development of enduring linkages and networks among researchers, academic professional people, such as Dermatologists, Plastic Surgeons, Cosmetic Chemists, and Innovators across countries worldwide. Innovation involves the creation and diffusion of new products, processes, and methods necessary to support higher living standards.



Fig. 2 The planet biodiversity.

Circular Economy, in fact, advocates the need for a functional service model in which manufacturers or distributors increasingly retail the ownership of their products replacing the concept of the consumer with that of the user.

To obtain environmental, economic, and social equity benefits by the 3-E biomass utilization (Fig.3), the patient has to solve his/her problems in a short time without suffering of side effects being not considered as a simple consumer! This the reason why Cosmetic Dermatology has to give increasing attention to Circular Economy from today to the incoming years, according to lectures that opened the Congress with the interventions among all of Hong-Duo Chen, President of the ISCD, Pierfrancesco Morganti, Secretary General of ISCD, Syarief Hidayat, President of PERDOSKI and Abraham Arimuko, Chairman of the Committee and organizer in chief of the meeting.

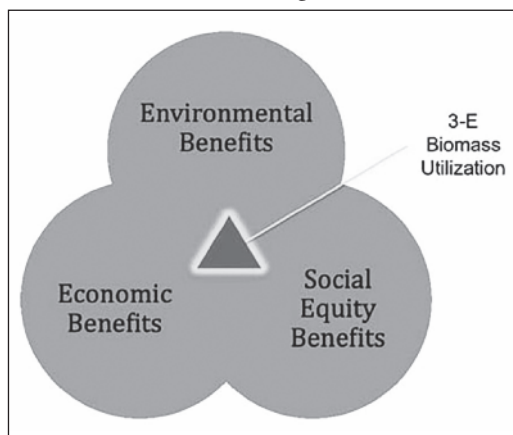


Fig. 3 The 3-E biomass utilization.

Likewise, most recent advanced from interdisciplinary academic approaches have provided important perspectives to understand the whole spectrum of acne physiopathology, according to the lecture of Dae Hun Suh, Department of Dermatology, Seoul National University College of Medicine, South Korea, Giuseppe Micali, Head Department of Dermatology, University of Catania, Italy, and Cheong Wai Kwong, from the Medical University of Singapore. Moreover, the management of acne requires cooperation between doctors and patients, because based on the pathogenic, clinical and Psychological aspects. At this purpose, the use of dermocosmetic agents provides significant improvement to increase the compliance treatment of this disease, according to Irma Bernardette Sitohang, Department of Dermatology, University of Indonesia, Jakarta. Additionally effective moisturizing agents, when property used, may improve the tolerability of acne therapy by decreasing the stinging and dryness effect of some drugs. Moreover, according to Rathporn Ungpakorn, from Bangkok, Thailand, selected sunscreens can protect the skin from infrared rays by inhibition of Matrix metalloproteinases (MMPs); reducing both the acne inflammatory manifestations and the consequential hyperpigmentation on some localized areas of the skin. These results are in accordance to the experience of our group also, who has used an acne cosmetic therapy based on the use of sunscreen gels free of any greasy agents, in combination with an emulsion having as active ingredients phosphatidylcholine linoleic-acid-rich and nicotinamide.

What are the future trends in Cosmetic Dermatology?

Nowadays the interest in Cosmetic therapies incorporating mind-body concepts has growing among scientists and clinicians, so that the use

of Clinically Correct Cosmetics combined with the right diet, food supplements, exercise, alternative therapies and drugs, could become a total concept to slow down the aging processes also, according to Retno I.S. Tranggono of the Ristra Indolab. The aging processes, in fact, has a significant Impact on the renewal of the skin cells, where the proliferation rate of the keratinocytes in the basal layer becomes progressively reduced. It is, in fact, up 50% slower in people 80 and more years old. Thus, the reduced production of many key elements leads to an impaired function and quality of skin barrier with a loss of the antioxidant and immunocompetent network of the epidermis, so that the skin appears less healthy. Proper balance between antioxidant compounds, in fact, is considered crucial to the resolution of prolonged inflammation, for obtaining regular skin turnover and subsequent skin integrity, according to my topic on green ingredients.

The main goal of Cosmetic Dermatology is to formulate Clinically Correct Cosmetics based on the use of bionanotechnology and effective green ingredients and carriers capable to modulate the intercellular lipid and the filaggrin synthesis together with the water content in the epidermis and the fibroblast activity in the dermis for obtaining the right collagen synthesis. These innovative carriers, entrapping selected active ingredients, as, for example, vitamin C and melatonin (antioxidant compounds) and niacinamide and beta-glucan (immunomodulant compounds) must be capable to improve a controlled delivery of therapeutics or cosmetic active ingredients for inducing collagen synthesis and reducing the irritative phenomena. This the topic reported from Tommaso Anniboletti, plastic surgeon in the Saint Eugenio Hospital, in Rome, Italy.

The oxidative stress is a problem of skin cells so that endogenous and exogenous antioxidants could play an important role in skin aging, pro-

tecting them from the membrane damages and DNA mutations, according to the topic on aging and wrinkling discussed from Theresia L. Toruan, Depart. Dermatology, Sriwiya University, Palembang, Indonesia.

Threadlift, does it really work?

This is one of the topics reported and discussed from Abraham Arimuko. Reporting the results obtained by the use of polydioxanone (PDO), he concluded that the success of this procedure depends on the right indication, the seek action of thread provided, and the application of the correct techniques used. Other topics brilliantly reported from Dr. Arimuko were the use of glutathione diet supplement as whitening agent to reduce the appearance of the skin hyperpigmentation. Glutathione, recognized as antioxidant compound, should have effectiveness in increasing body compartment store of the tripeptide cysteine-glycine-glutamate. It could affect the melanogenetic process involving tyrosinase function and melanine cellular transport. This new therapy could be used in combination with topical whitening agents and chemical peelings. The use of low doses of antioxidant compounds and oral, cytokines was one of the topics reported also from Torello Lotti, Head of Dermatology Department, University G. Marconi, Rome, Italy.

Prevention and therapy of low-grade chronic inflammation, in accordance with the principle of low dose medicine (LDM), represent the modern approach to facilitate the natural process of physiological aging.

In healthy condition, the slow progress of the so called inflamm-aging leads, in fact, to physiologically deterioration of biological functions in advanced age; conversely, the presence of chronic diseases, resulting in a state of low-grade chronic inflammation, is able to anticipate the aging process by reducing lifespan. Thus, accor-

ding to recent studies, some of the most important dermatological chronic inflammatory autoimmune diseases and skin aging processes can today be approached with LDM. On the other hand, the modulation of inflammatory phenomena and immune response, the restoration of keratinocytes-melanocytes axis with specific low dose of interleukins, and the antibodies and basic fibroblast growth factors, seems to represent also an innovative therapeutic approaches for vitiligo treatment. Moreover, other studies show that fibroblast growth factor and its terminal undecapeptide are able to enhance melanogenesis in both epidermal and bulb hair melanocytes, at picomolar concentration.

This may represents a new therapeutic approach for contrasting the aging and grey hair phenomena, according to other topics of Torello Lotti. Speaking on vitiligo and according to Xing-Hua Gao, Head Dermatology Department, China Medical University of Shenyang, there is a general rule that affects the treatment responses on vitiligo. Its treatment on hand/foot or body prominence is more recalcitrant than on face/neck or torso, so that in these areas conventional mono therapies are unsatisfactory. Thus in the hospital a combination method with CO₂ fractional laser plus betamethasone injection and NB-UVB treatment was used with a great success. A self controlled trial comparing this novel combination to conventional methods showed a remarkable superiority of the adopted triple combination therapy for the vitiligo recalcitrant areas.

The revolutionary progress in nanoscience has posed the milestone to develop novel, safe and biocompatible biomaterials, which can easily delivery bioactive ingredients for treating wound healing and skin aging. The hospital use of advanced medications made by chitin nanofibrils-lignin have been reported and discussed from Tommaso Annibolletti, Plastic and Reconstructive Surgery and Burn Center, Saint

Eugenio Hospital of Rome, Italy. The plastic surgeon has shown how these innovative and biodegradable non-woven tissues are capable to rapidly repair the burned skin in a week, contemporary counteracting the microorganism's growth without any side effect. This interesting study, developed on baby and adult skin affected by burns of 1st and 2nd grade, was realized in hospitalized people with the collaboration of Marco Palombo and Paolo Palombo, head of the Plastic Surgery Department, Saint Eugenio Hospital.

Cosmetic dermatology, using the words of Abraham Arimuko, "is an ever-changing and evolving field with a strong demand from the patients". The meeting has given many replies to these demands by many interesting topics presented and discussed thoroughly by more well-known speakers coming from many countries. Among the leakers it is also to remember Hassan Galadary from UAE who, evidencing the importance of mid cheek augmentation, has shown the different techniques used today for enhancing this and other skin areas of the face by the use of filler natural, or man made. On the other hand, Henry Lim Lom, Department of Dermatology, Henry Ford Hospital, Detroit, USA has underlined the importance of phototherapy for the skin rejuvenation and the photodynamic therapy (PDT) for the treatment of actinic keratoses. PDT therapy seems to be effective for treatment of acne vulgaris also, according to CL Goth, from Skin Centre of Singapore. However, according to Tal Nachlieli from Atidim Medical Center of Tel Aviv, Israel, skin laxity and deep facial wrinkles may be treated by less aggressive treatments using radiofrequency devices with reduced risks and side effects.

As framework to all the medical/chemical topics, the interesting lectures of legal matter, reported from the lawyer Sonia Selletti, from the well-known Studio Astolfi of Milano, Italy and the lawyer-medical doctor Nasser Muk,

Chairman of the Ethical Court of Perdoski, have open the mind of the attendants on national and international regulations regarding some aspects of Cosmetics and Drugs used in the field of Cosmetic Dermatology. The lawyer Selletti has reported in a very clear way the EU regulations on nanomaterials used for the Cosmetic formulations. According to the EU rules "for every Cosmetic product that contains nanomaterials, a high level of protection of human health shall be ensured".

On the other hand dr Nasser with the double experience of lawyer and medical doctor has attested that "doctor or other professional can't use their authority to make a prescription in pharmacy that unclear in reaction or function". She/he has to understand that the dermatological service "Is a professional activity based on professional rules and "not a cosmetic business"? She/he "has not to give excessive hope to patient without backed by proper research/accurate source" as well as has not "to promote specific product because of financial benefit/considerations". This foul play is considered "a heavy ethical violation" from the Indonesian rules. These were some of the many topics presented during this interesting meeting where the promise of a New Horizon in Cosmetic Dermatology has been completely performed. Apart the scientific sessions, the events organized during the two-days meeting i.d. the Welcome dinner, sponsored from Menarini Company and the Cultural night Gala Dinner, sponsored by Galderma, has been very interesting and joyful. The organization of these two special dinners together with the VIPs area, where all the speakers had the possibility to test and taste the local food for all the days, have underlined the great hospitality and gaiety of Indonesian people. The cheer fullness of all Indonesian women and man has broken out in the Cultural night, during which characteristics historical dances have been organized. Moreover, some of the

speaker-guests have been invited to wear local historical trouser suits for dancing as mark of friendship. In the same way, the closure of the meeting has been suddenly wonderful and joyous with the projection and remembering of all the past ISCD meetings gladdened by fireworks. In conclusion the 12th International Congress of ISCD will be remembered as one of the best organized meeting of the association long life.

Views of Jakarta



President of the Italian Republic visiting Jakarta.



Popular shopping market



Kota Tua Square



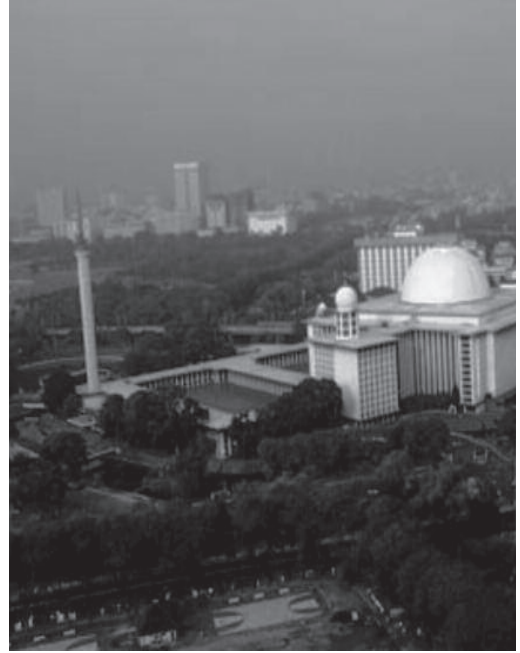
Dutch restaurant in Jakarta



Dutch street in Jakarta



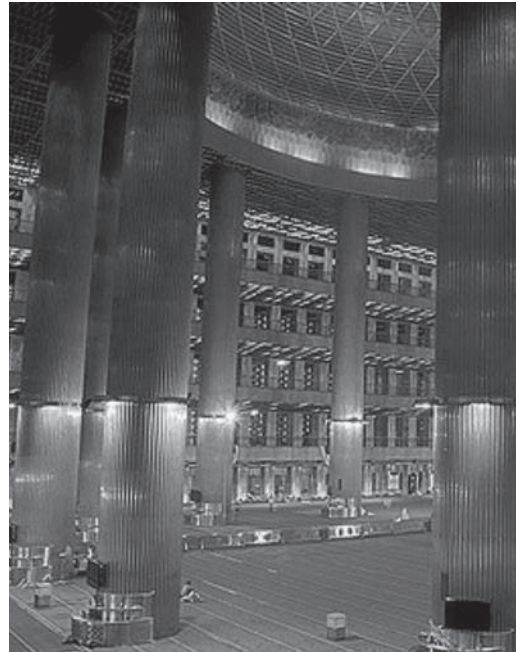
Typical Indonesian food in Jakarta



The mosque



The Column - symbol of Jakarta



The mosque interior

Opening Ceremony



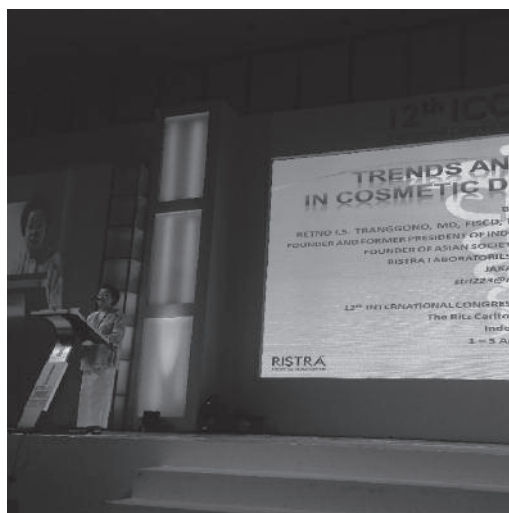
Prof. P. Morganti



Prof. G. Micali.

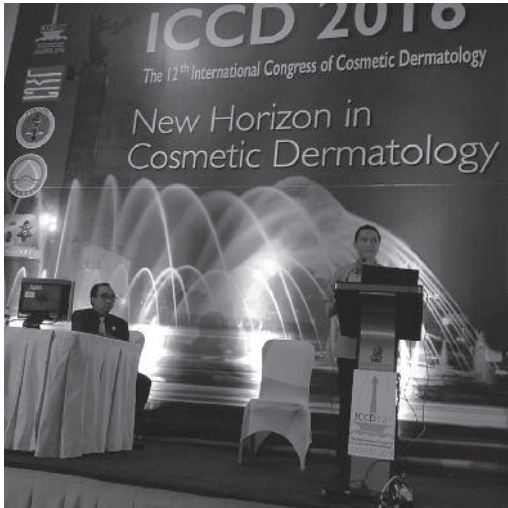


Prof. H. Galadali



Prof. Tranggono

From the Congress



The Opening Ceremony. Dr. Arimuko, Chairman of the Congress Committee.



Exhibition area: T. Anniboletti, P.Morganti, and a participant.



Hong-Duo Chen, A. Arimuko, P.Morganti before the opening of the cultural night.



P. Morganti, T. Anniboletti and R.A.A. Tranggono into the meeting room.

Some Speakers



Dr. Arimuko, prof Chen, President of ISCD, and prof Hydayat, President of Perdoski.



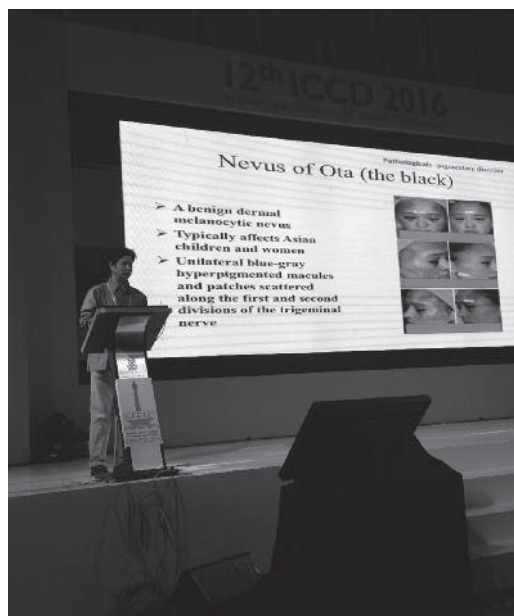
Prof. Hong-Duo Chen.



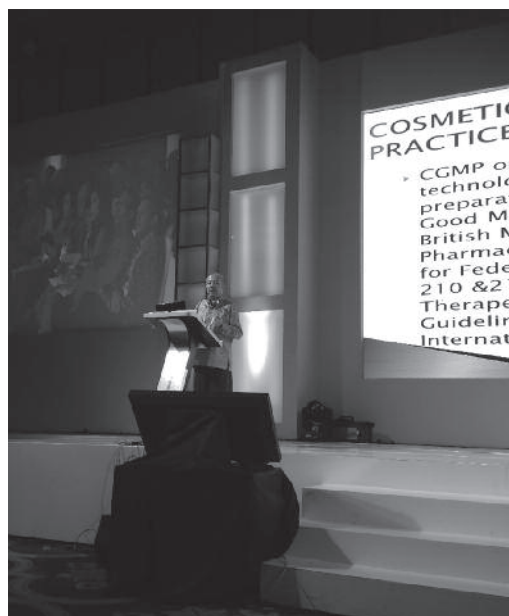
Dr. T. Anniboletti.



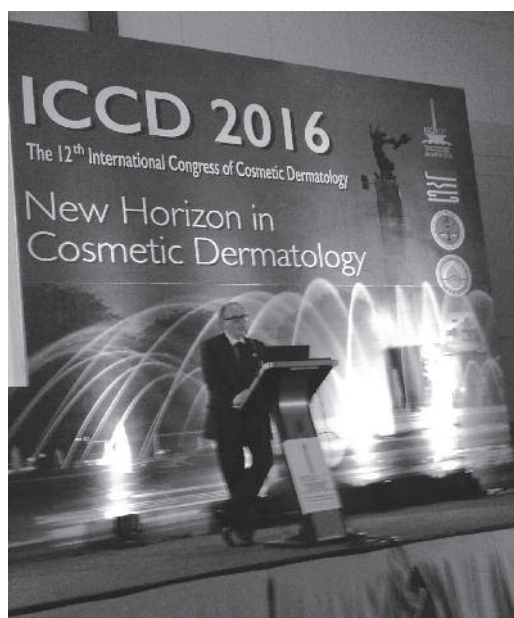
Avv. S. Selletti.



Prof. X. Gao



Dr. Nasser



Prof. Lotti

Cultural Night



Hong-Duo Chen, P.Morganti with local dress



Local Dance.



Local Dance.



Local Dance.

The Closing Ceremony



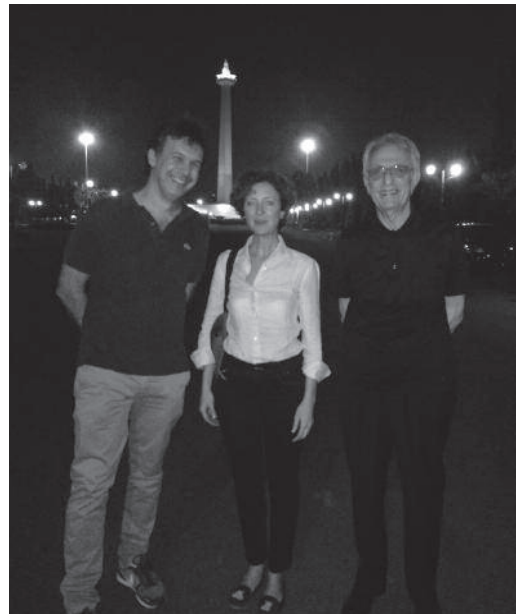
Arimuko, H.D. Chen and Hydayat.



Before leaving the meeting.



The Jakarta Mosque.



The famous column, symbol of Jakarta.



Ordine dei Medici Chirurghi e Odontoiatri
della provincia di Monza e Brianza
(Ente di Diritto Pubblico D.L.C.P.S. del 13/09/1946 n. 233)

SEVESO, L'EVENTO DIOSSINA 40 ANNI DOPO: UN CONVEGNO PER PARLARE DEGLI STUDI EFFETTUATI, DEI RISULTATI OTTENUTI E DELLE SCELTE PRESE NEL 1976 CHE SI RIVELARONO FONDAMENTALI A LIVELLO MONDIALE

Durante il convegno, organizzato dall'OMCeO di Monza e Brianza, sono intervenuti numerosi medici che in questi 40 anni di storia hanno continuato a studiare gli effetti del disastro diossina.



Monza, 14 maggio 2016 – Si è tenuto oggi, presso l'Auditorium del Centro Pastorale Ambrosiano di Seveso, il convegno **“L'EVENTO DIOSSINA 40 ANNI DOPO: quali insegnamenti”** alla presenza di circa 150 medici del territorio interessati ad approfondire quello che ha rappresentato il disastro dell'ICMESA di Seveso e gli studi che sono stati effettuati da allora. Ricerche rese possibili anche grazie allo **spirito visionario dei medici operanti in quel periodo che, fin dal primo momento, conservarono i campioni di sangue** raccolti: una condizione particolare e unica al mondo che ha permesso in seguito di studiare la relazione fra l'esposizione alla diossina e i suoi possibili effetti. Nel corso del convegno è stato ricordato più volte come, a seguito di questo tragico evento, sia risultato **essenziale il senso civico della popolazione, dei medici e delle Istituzioni** che, insieme, riuscirono a far fronte alla situazione nella quale versava non solo Seveso, ma anche i territori circostanti.

Dopo i saluti introduttivi di **Carlo Maria Teruzzi**, *Presidente OMCeO MB*, hanno preso parola **Guido Marinoni**, *Consigliere Nazionale FNOMCeO*; **Paolo Butti**, *Sindaco di Seveso* e **Matteo Fumagalli**, *Presidente Fondazione Lombardia per l'Ambiente*. Ad aprire gli interventi scientifici è stato il **Prof. Paolo Mocarelli**, già

Direttore del Servizio Universitario Medicina di Laboratorio - H. Desio con l'intervento "Impatto dell'Evento e scelte effettuate", seguito dal **Prof. Pietro Alberto Bertazzi**, Clinica del Lavoro - Università degli Studi di Milano che ha presentato una relazione dal titolo: "Studi epidemiologici di mortalità e di incidenza tumori". Tra gli ospiti della mattinata, anche Sua Eminenza **Cardinale Dionigi Tettamanzi**, Arcivescovo Emerito della Diocesi di Milano e testimone partecipe all'epoca dei fatti. La sessione mattutina si è conclusa con l'intervento "Effetti della diossina sull'uomo" a cura di **Paolo Mocarelli** e **Paolo Brambilla**, Docente di Biochimica Clinica Università Milano Bicocca e Direttore del Servizio Universitario Medicina di Laboratorio - H. Desio e con l'intervento "Art.5 Codice di Deontologia Medica Valutazione impatto sanitario (V.I.S.) – Esperienze attuali e prospettive future" a cura di **Raimondo Ibba** - Presidente OMCeO Cagliari e Referente Comitato Centrale FNOMCeO per Ambiente, Salute e Sviluppo Economico.



*"I medici hanno la responsabilità nell'affrontare le questioni di salute, sempre più spesso correlate all'ambiente, non solo sul singolo paziente ma sull'intera comunità – ha dichiarato **Carlo Maria Teruzzi**, Presidente dell'Ordine dei Medici Chirurghi e Odontoiatri della Provincia di Monza e Brianza – Questo convegno è un'occasione importante anche per capire quale eredità, quell' "evento diossina", ha lasciato ad una generazione che dovrà dimostrare una particolare sensibilità per le questioni ambientali".*

Il convegno è proseguito nel pomeriggio con la sessione titulata ***Cosa è cambiato da allora nel rapporto tra ambiente e salute, che è stata aperta*** con l'intervento "Le patologie croniche nella popolazione: dati dell'Agenzia Tutela della Salute delle Brianza" a cura di **Luca Cavalieri D'Oro**, Servizio di Epidemiologia ATS della Brianza; seguito da **Roberto Romizi**, Presidente Associazione Medici per l'Ambiente – ISDE Italia che ha tenuto un intervento dal titolo "Medici Sentinella sulle malattie di origine ambientale"; **Ian Marc Bonapace**, Docente di Patologia Generale e Oncologica Molecolare – Università dell'Insubria con l'intervento titolato "Il ruolo dell'epigenoma negli effetti a lungo termine delle esposizioni ambientali". La sessione si è conclusa con l'intervento "Direttiva Seveso 3: evoluzione delle norme europee e nazionali per la prevenzione negli stabilimenti industriali a rischio di incidente rilevante" a cura di **Luca Zucchelli**, Regione Lombardia, D.G. Ambiente, Energia e Sviluppo Sostenibile.

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Trimestrale di Dermatologia Cosmetologica

Quarterly Review of Cosmetic Dermatology

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Reconstruction of a scalp defect with exposed bone following burn injury: our experience

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Key words: *Matriderm® 1mm; Artificial dermis; Scalp burn; Burn calvaria exposure management; One stage reconstruction scalp burn;*

Summary

The reconstruction of large losses of substance through burns affecting the scalp in a full thickness-way is very demanding, especially when the cranial theca is exposed and has sustained heat damage. There are many surgical options: neighbouring flaps, autologous epidermal skin graft, dermal replacement graft with subsequent skin graft, galea flap with immediate thin epidermal skin graft. Dermal replacement and immediate cutaneous grafts could also be indicated, but this method has rarely been reported in specialist literature. We illustrate the case of a psychiatric patient who, in a suicide attempt by throwing his head into the flames of a fireplace gained a third-degree burn of a diameter of around 13 cm, also affecting the cranial theca, and a large burn of about 20% of the total body surface area. The treatment involved, in a single procedure: the removal of the lesion, including the non-vital bone part, the immediate implant of a dermal prothesis (Trademark: Matriderm® 1 mm) and the skin graft. The eschar of the trunk and the upper limbs was removed at the same time and the wound grafted with thin autologous skin. The patient was operated on the 5th day following the incident and discharged with a healed wound after 16 days from the surgery with new cutaneous coverage of the cranium of a good thickness and quality. The option of carrying out the entire reconstructive surgery in a single intervention was very useful for reducing recovery time and therefore facilitating the rapid healing of a difficult patient.

Riassunto

La ricostruzione di grosse perdite di sostanza dovute ad ustioni a tutto spessore del cuoio capelluto è molto impegnativa, soprattutto quando la teca cranica è esposta ed ha subito danni dovuti al calore. Ci sono molte opzioni chirurgiche: lembi di vicinanza, innesto di cute autologo, innesto di sostituto

dermico con innesto successivo cute, innesto di galea con immediato innesto di cute sottile. Illustriamo il caso di un paziente psichiatrico che, in un tentativo di suicidio gettando la testa tra le fiamme di un camino ha riportato un'ustione di terzo grado per un diametro di circa 13 centimetri, interessando anche la teca cranica, e un'ustione di circa 20% della superficie corporea totale. Il trattamento in questione interessa in un unico procedimento: la rimozione della lesione, compresa la parte non vitale dell'osso, l'impianto immediato di un sostituto dermico (Matriderm® 1mm) e l'innesto cutaneo. L'escara del tronco e degli arti superiori è stato rimosso allo stesso tempo e le aree innestate con innesto autologo sottile. Il paziente è stato operato il 5° giornata postoperatoria e dimesso guarito dopo 16 giorni dalla chirurgia con nuova copertura cutanea del cranio di un buon spessore e qualità. La possibilità di effettuare tutta la ricostruzione in un singolo intervento è stata molto utile per ridurre il tempo di recupero e quindi agevolare la rapida guarigione di un paziente con ferite difficili.

INTRODUCTION

Although burn is among the most common traumatic accidents in the world, it is relatively rare for the scalp to be the burn site (1-2). Unfortunately when the burn is third-degree and the damage involves bone tissue, healing becomes a complex therapeutic challenge, as it is necessary to rapidly protect the valuable tissue within the skull (3).

The wound can be closed using many solutions (4). The most simple, after having achieved a good bed, is immediate dermo/epidermal graft. The procedure is simple and fast, however the aesthetic and functional result is mediocre because of a thin and unstable post operative surface.

An alternative procedure to cover the damaged cranial theca with healthy tissue of appropriate thickness is the immediate use of an adjacent skin flap; in this case the problem, where there is a wide loss of substance, is that the area of the rotated strip would remain uncovered, this surface must in turn be covered by a skin graft, but this would reproduce the problem of the coverage of bone with thin and unstable skin tissue (5-6). In addition, where the skin of the scalp is severely damaged at multiple sites, circulation is mediocre or the patient's general condition is deteriorating, coverage of the wound via a strip must often be delayed, this gives rise to problems associated with extended periods of time with no coverage of the cranial wound.

We present a case of a psychiatric patient, with third-degree burns on more than 20% of the body surface area, cranium included, who underwent a one-step surgery. The wound, of a maximum diameter of 13 cm, in the scalp with bone damage was treated in a single surgical procedure with the use of the skin prosthesis Matriderm® 1mm Single-layer and thin autologous skin graft (7).

PATIENT AND METHOD

A 43-year-old Caucasian man, suffering from psychiatric problems threw himself on the fire of his fireplace in an attempt to destroy the voices he was hearing in his head. First-aid from his family members reported 2nd and 3rd degree burns on more than 20% of the total of the body surface area, especially the trunk, the upper limbs and the scalp, without inhalation damage. Admitted after a few hours at our Burns Center, he underwent rehydrating and antibiotic therapy and also deep sedation after psychiatric assessment. His understanding of the clinical process was poor. After 5 days from the incident the patient underwent general anaesthesia and escharectomy and mesh skin grafts all over the body apart from the scalp.

The scalp wound, in the occipital parietal region, measured about 13 cm at the largest diameter and was a full thickness defect, including the external bone walls of the cranial theca (Figure 1).

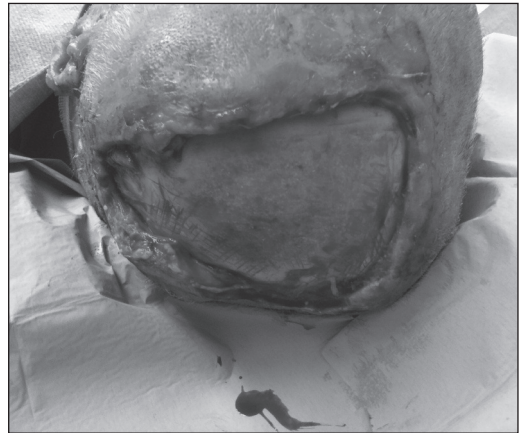


Fig. 1 View of the scalp defect.

Then the non-vital bone matrix was removed via abrasion with mechanical cutting tools, until achieving homogeneous bleeding. While one team prepared the Matriderm® for receiving the

graft, another harvested a whole graft from the anterolateral side of the right thigh. Then the skin graft was perforated with a number 11 blade to promote drainage. Lastly, after a thorough new disinfection of the operating area, gloves changing, one sheet of Matriderm® measuring 148 mm x 105 mm, 1mm thick was applied using tweezers, then it was cut around to match the receiving site, paying attention to avoid air bubbles or empty spaces between the product and the receiving bed: then the dermal prosthesis was rehydrated using a gauze soaked in physiological solution (Figure 2). The entire thin autologous demo/epidermal skin graft was then placed over the Matriderm® 1 mm single layer (Figure 3). The dermal prosthesis and the overlying skin graft were secured to the healthy tissue using staples. About 6 layers of sterile paraffin gauze (Jelonet®) were layered above the graft to prevent dead spaces or detachment from the receiving bed and the whole was covered with 3 covering gauzes. Then the cranium was bandaged moderately compressive with elastic bandages. The dressing was removed after slightly more than 96 hours, where the patient presented around 90% engraftment of the skin graft. The dressing of the graft harvesting site was not removed until complete healing. 16 days after surgery, the patient was discharged with complete coverage. There was no blood or serum collection; no topical antibiotics were used. The harvesting site was dressed with sterile paraffin gauze (Jelonet®). The patient was discharged with systemic antibiotic therapy and locally moisturising cream for the scalp. The patient attended only for a checkup after around 3 months, the wound and the thickness of the grafted skin were satisfactory. (Figure 4) The grafts on the other burn areas of the body were perfectly healed.



Fig. 2 Scalp defect with Matriderm® in situ.



Fig. 3 Scalp defect with Matriderm® and skin graft in situ.



Fig. 4 Result after 3 months.

DISCUSSION

Burn scalp are one of the major surgery problems worldwide, especially when full thickness with bone involvement.

A simple graft on the periosteum is a rapid and effective solution, but the result is poor from an aesthetic point of view and reconstruction does not take account that there is usually dermal tissue and the galea between the skin and bone. In emergency, skin graft can be a solution, at least temporary.

Coverage of the wound with a rotation flap is an effective option, but in the initial phase its failure is very dangerous, therefore it is preferable to use a flap of galea (8) with immediate thin autologous skin graft; this technique is not however simple and needs a rather long learning curve; lastly, when the patient is a heavy smoker, or presents vascular disease or diabetes the option of the skin flap must be taken carefully or replaced with a two-stage intervention, where the first involves flap autonomisation, rotated after about 20 days. This temporary dilation significantly increases the infection risk. In addition, at the flap donor site, it will almost never be possible to close by first intention, but it will almost always be necessary to cover the periosteum with a thin dermo/epidermal graft: thereby revisiting the poor aesthetic and functional result which the immediate skin graft on the cranial bone tissue carries.

The coverage of the defect with free flap is also a possible option.

In our opinion in case of burn trauma is a secondary choice. In fact there is a high risk of damaged vascular receiving structures. In addition the free flaps area could be involved in the burn surface. In this case the poor patient compliance was a further indication against (9).

Alternatively, it is possible to expand the scalp flap using cutaneous expanders, before using it to cover the loss of material resulting from the

burn; this, the most aesthetically valid method, requires up to 90 days for an intervention to cover the lesion by grafts. The use of the skin expander in the scalp requires compliance from the patient and the absence of concomitant diseases such as diabetes.

The use of the dermal prosthesis, in a single surgery, below the skin graft offers a better final aesthetic quality as well as simplicity of technique and enables a rapid solution of sufficient quality, including in the case of patient non-collaboration (10). Also the one-step for covering the skin wound reduces the risk of infection, which is very important considering the value of the content of the skull. There is evidence in literature relating to the use of dermal prostheses in the treatment of full thickness scalp wounds (11-11). A comparable result to those described in the literature was the one we obtained using the dermal prosthesis called Matriderm 1 mm thickness. This product is a three-dimensional matrix for dermal regeneration comprising bovine collagen type I, III and V with a natural elastin structure extracted by hydrolysis. Its function is to form a matrix for the skin reconstruction by promoting first haemostasis and then the scarring process: in actual fact, it promotes the colonisation of vessels and fibroblasts, enabling the nutrition of the overlying skin graft via its very low thickness. When the wound produces its own collagen matrix via fibroblasts, the Matriderm® 1 mm is reabsorbed, on average within 6 weeks. A few months after the wound, the skin reconstructed with the Matriderm appears more elastic. The product can be grafted immediately with autologous whole or mesh skin grafts. The graft presented an engraftment index equal to the autologous skin graft without the dermal prosthesis and did not present any problems with the post-operative wound management (13-14).

CONCLUSIONS

The use of the autologous skin graft on Matriderm® 1 mm single-layer in a one-step procedure for third-degree burns also affecting the cranial theca is, in our experience, a potential option. In the same way as using other dermal prostheses, it offers the option for quickly covering the lesion and then protecting the vital structures contained within the skull without a lower engraftment index than an autologous skin graft. The quality of the graft, evaluated by an external plastic surgeon 30 days following surgery, was good from an aesthetic and functional point of view being thinner and more elastic than a simple skin graft performed directly on the bone matrix. The method illustrated can also be used as a temporary option before a definitive reconstruction, perhaps by means of expanded scalp flap. In conclusion, the option in our experience was appropriate, rapid and safe.

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Scientific proof for the use of a cell repair oil formulation for Psoriasis

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Key words: Psoriasis; Cell repair; Elastase; Anti-oxidant; Scientific proof; Collagenase; Protein glycation process; Non-cytotoxic; Inflammation; Free radicals;

Summary

The present article deals with the clinical efficacy of cell repair oil in the treatment of psoriasis. The *in vitro* findings prove that the oil inhibits elastase, collagenase and protein glycation process besides having anti-oxidant effect. Safety of the oil is also established through Zein protein hydrolysis and Fibroblast toxicity assay (MTT assay). Findings are discussed in the article.

Riassunto

Questo articolo riporta l'efficacia clinica di un olio cosmetico in grado di intervenire nella riparazione cellulare della cute affetta da psoriasi.

Le prove *in vitro* evidenziano come quest'olio sembri inibire l'attività dell'elastasi e della collagenasi intervenendo nel processo della glicazione con un effetto antiossidante.

La sicurezza d'uso dell'olio è stata evidenziata attraverso il metodo idrolitico effettuato sulle proteine del grano e attraverso il metodo MTT sui fibroblasti.

INTRODUCTION

Psoriasis is an autoimmune disease difficult to manage, so that, the effective management approach with right choice of medicaments alone, can help to improve the quality of life of the patients. Keeping the skin symptom free for longer duration is considered to be one of the key strategies in the treatment of psoriasis (1). Necessary life style changes are also equally important for improving the morbidity and to prevent sufferings and psoriasis associated complications.

In most occasions, the clinical cycle of psoriasis pass through a short acute/severe inflammatory phase and later it is accompanied by prolonged/long term remission phase. The treatment of severe inflammatory phase of psoriasis involves the use of steroids and other medicaments such as calcipotriol, methotrexate etc.

Although the complete remission phase is not possible to achieve in case of psoriasis, by the use of drug, a greater patient's comfort can be achieved by the use of an adjuvant therapy. One of the proven and accepted management approaches for maintaining long term remission phase of psoriasis seems to be the use of select adjuvant moisturizers.

The cell repair oil formulation tested is a cosmetic oil able to give intense moisturization benefit especially for psoriasis and extreme dry skin problems*.

Through *in vitro* studies we have tried to prove that the in-study cell repair oil inhibits elastase, collagenase and glycation events. Besides that, it also posses' antioxidant activity against both DPPH and Nitric oxide induced oxidation.

The safety tests such as Fibroblast cytotoxicity and Zein protein hydrolysis also have proved that cell repair oil is safe for long term use.

In the light of the above findings, cell repair oil

could have a significant clinical value for the management of psoriasis during remission phase.

MATERIALS AND METHODS

In vitro assays

Anti-oxidant Assay - DPPH Free Radical Scavenging Assay

DPPH is a common abbreviation for an organic chemical compound 2,2 diphenyl-1-picrylhydrazyl. It is a dark colored crystalline powder composed of stable free radical molecules capable to monitor the chemical reactions involving free radicals (2). Most notably it is a common antioxidant and a standard to control the intensity of the electron paramagnetic resonance signals.

The DPPH assay method is based on the reduction of DPPH, a stable free radical (3). The free radical DPPH with an odd electron gives a maximum absorption at 517 nm (purple colour). When antioxidants react with DPPH, the molecule is reduced to the DPPHH and as consequence the absorbance decreases. The reduction of DPPH to DPPH-H results in more or less decolorization (yellow colour) with respect to the number of electrons captured.

More the decolorization, more is the reducing ability of the test material. This test has been the most accepted model for evaluating the free radical scavenging activity of many chemical compounds (4). When a solution of DPPH is mixed with the in-study substance, it can donate a hydrogen atom giving rise to the reduced form of di phenyl picryl hydrazine; a non-radical with the loss of violet colour (although there would be a residual pale yellow colour from the picryl group if present).

* Trade name: Psoronorm cell repair oil by Dr. JRK's Siddha Research and Pharmaceutical Pvt Ltd., Chennai, India.

DPPH free radical scavenging activity of cell repair oil was evaluated according to this standard methods (2).

Different doses (10, 20, 30, 40 and 50 mg/ml) of the oil was added to ethanol solution of DPPH radical. The final concentration was adjusted to 0.1mM. The mixture was shaken vigorously for 1 minute by vortexing and left to stand at room temperature in dark condition for 30 minutes. The absorbance of the samples was measured using UV 160 spectrophotometer at 517nm against ethanol blank. A negative control was taken after adding DPPH solution to 0.2ml of water. The percent of DPPH discoloration of the sample was calculated according to the equation $\% \text{ discoloration} = [1 - (\text{sample}/\text{control})] \times 100$. The free radical scavenging activity of the product was expressed as an equivalent of Trolox (water soluble analogue of Vitamin E).

Inhibition of Nitric Oxide (NO) Production

Nitric oxide (NO) is a diatomic free radical produced from L-arginine by constitutive and inducible nitric oxide synthase (eNOS and iNOS) in numerous mammalian cells and tissues (5).

Nitric oxide (NO), superoxide ($O_2^\bullet$) and their reaction product peroxynitrite ($ONOO^\bullet$) may be generated in excess as the host response to a viral and antibacterial infections, they, therefore, may contribute to some pathogenetic diseases by promoting oxidative stress, tissue injury and even cancer.

Oxidative damage, caused by free radicals, may initiate and promote the progression diseases indicative of the inflammation process. The mechanism of inflammation injury may be attributed, in part to release the reactive oxygen species (ROS) from activated neutrophils and macrophages. ROS propagate inflammation by stimulating release of mediators such as NO and cytokines.

METHODS

Macrophages were seeded at the density of 5×10^3 cells per well in a micro titer plate. The plate was incubated for 12 h at 37°C with 5% CO_2 . Then media of each well was aspirated and fresh FBS-free DMEM media was replaced. Different concentrations of the aqueous preparation of the oil (10–50 mg/ml) were used for testing. After 1 h treatment with the oil, cells were stimulated with $1 \mu\text{g/ml}$ of LPS for 24 h. The presence of nitrite was determined in cell culture media using commercial NO detection kit (3,4). After 10 minute incubation, the absorbance was measured at 540 nm. The amount of nitrite in the media was calculated from sodium nitrite (NaNO_2) as standard curve.

Collagenase Assay

Collagenase is believed to be important for cell migration and collagen remodeling during tissue repair and regeneration. Collagenases are endopeptidases that digest native collagen in the triple helix region. Collagens are the major fibrous component of animal extracellular connective tissue. Bacterial collagenases differ from vertebrate collagenases because of their broader substrate specificity. Unlike animal collagenases that split collagen in its native triple-helical conformation, bacterial collagenase is unique because it can degrade both water-insoluble native collagens and water-soluble denatured ones. It can attack almost all collagen types, and is able to make multiple cleavages within triple helical regions.

The assay employed was based on spectrophotometric method with some modifications. The assay was performed in 50 mM Tricine buffer (pH 7.5 with 400 mM NaCl and 10 mM CaCl_2). Collagenase enzyme from *Clostridium histolyticum* was dissolved in buffer with the initial concentration of 0.8 unit/ml (as per the activity

data). The synthetic substrate N-[3-(2-furyl)acryloyl]-Leu-Gly-Pro-Ala (FALGPA) at 2 mM was dissolved in Tricine buffer. Different concentration of the aqueous preparation of the oil was incubated with the enzyme in the buffer and was incubated for 15 minutes. Then the substrate was added to the above to start the reaction. Water was used as negative control. Absorbance at 335 nm was measured soon after adding the substrate and the reading was taken continuously for 20 minutes using a Micro-plate Reader (6,7) Epigallocatechin gallate (EGCG), 250 μ M (0.114 mg/ml) was used as a positive control.

Elastase Inhibition Assay

Elastases are matrix degrading enzymes involved in the tissue homeostasis and are mainly produced by the epithelial cells in the skin, lungs and neutrophils etc. The neutrophil-derived elastases play a major role in the regulation of vascular injury and inflammation, such as ischemia-reperfusion injury. Elastases are available both as membrane bound and intracellular forms. Intracellular elastases break down the foreign proteins, whereas the extracellular elastases released by neutrophils and mostly bound to the neutrophil plasma membrane, assists neutrophil migration to the inflammation sites by degrading various host proteins, such as extracellular matrix proteins.

Under normal conditions these enzymes are under control by endogenous inhibitors like elafins α 1-antitrypsin (α 1-AT), secretory leukocyte proteinase inhibitor and α 2-macroglobulin. However, large amounts of oxygen radicals and proteases released by leukocytes recruited to inflammation sites can inactivate these endogenous inhibitors leading to severe inflammatory flare-ups and injuries to the tissues. Hence potential elastase inhibitors could serve as targets in the anti-inflammatory therapy.

The other important target organ of elastase is

the matrix protein in skin which imparts the structural and functional integrity to it. During the process of chronological ageing, the metabolic events like formation of advanced glycation end products in the skin draws inflammatory infiltrates leading to the formation of wrinkles. Hence the elastase inhibitors could serve multiple treatment options for various dermatological problems.

Porcine pancreatic elastase was assayed spectrophotometrically using SANA as substrate. The aqueous preparation of Verdura cell repair oil at concentrations of 50, 40, 30, 20 and 10 mg/ml were incubated in a mixture of 200mM Tris buffer (pH 8.0) and 1 unit of enzyme for 15 minutes. The enzyme reaction was initiated by the addition of the substrate and then the mixture was further incubated for 15 minutes at 37 °C. The absorbance value was read at 410nm using UV spectrophotometer (6,8).

Anti-glycation Assay

Glycation is the key molecular basis of several diabetic complications like diabetes retinopathy, nephropathy, neuropathy and some cardiovascular diseases. This is a non-enzymatic reaction between amino groups of proteins and carbonyl groups of reducing sugars forming fluorescent, insoluble Advanced Glycation End Products that accumulate on long lived proteins thus compromising the physiological function.

Glycation is a non-enzymatic condensation reaction between reducing sugars and amino groups of proteins that undergo rearrangements to stable ketoamines, leading to the formation of advanced glycation end products (AGEs).

Antiglycation activity was determined using the Bovine Serum Albumin assay with slight modification. In the experiment, the final reaction volume was 1.0 ml and carried out in 1.5 ml Eppendorf tubes (9).

Bovine Serum Albumin 500 μ l (1 mg/ml con-

centration) was incubated with glucose 400 μ l (500 mM final concentration) and different concentrations of the sample viz., 50, 40, 30, 20, 10 mg/ml. 100 μ l of phosphate buffer saline was used as the sample control and 100 μ l Arbutin as the reference standard. A negative control was carried out at the same time with BSA 500 μ l (1 mg/ml concentration), 400 μ l phosphate buffer saline and the different concentrations of the sample (as described above) incubated under the same conditions. The reaction was allowed to proceed at 60 °C for 24 hours and was terminated by adding 10 μ l of 100% (W/V) trichloroacetic acid (TCA). The TCA added mixture was kept at 4 °C for 10 minutes and then centrifuged for 4 minutes at 13000 rpm. The precipitate was re-dissolved in alkaline phosphate buffer saline (pH 10) and was quantified for the relative amount of glycated BSA based on fluorescence intensity by Fluorescent Microplate Reader. The excitation and emission wavelength that used were 370 nm and 440 nm respectively.

Each concentration of the sample was analyzed thrice. Percentage of inhibition was calculated and the sample concentration required for the 50% of inhibition was calculated using the formula

$$\% \text{ of inhibition} = \frac{\text{OD blank} - (\text{OD sample} - \text{OD sample negative})}{\text{OD blank}} \times 100$$

Safety assays

Zein Protein Hydrolysis

The purpose of the Zein protein hydrolysis test is to investigate the irritation potential of the test substance. The sample was diluted in water to a specific concentration. The predicted protein hydrolysis is determined by the amount of Zein protein that got solubilized i.e. Zein value (10). Initial weight of the filter paper was noted. 0.5% and 1% solutions of the test sample was prepared

and similarly 0.5% of SLS was used as positive control. Accurately weighed Zein protein was added to the above solutions. Then filter the solution through a filter paper seated inside the ceramic funnel and then dried the filter paper overnight at 45°C. Finally Zein protein hydrolysis was calculated using the formulae

$$\frac{\text{Total Zein (g) added to the solution} - \text{Total Zein after drying}}{\text{Total Zein (g) added to the solution}} \times 100$$

$$\text{Total Zein (g) added to the solution}$$

Fibroblast Toxicity Assay

Toxicity on fibroblast cells was measured by treating the cells with Verdura cell repair oil and the reduction in cell proliferation was measured using MTT assay (9).

MTT Assay:

The cell proliferation is based on the ability of the mitochondrial succinate-terazolium reductase system to convert 3-(4, 5- dimethylthiazol-2-yl)-2, 5- diphenyltetrazolium bromide (MTT) to a blue colored formazan. The test denotes the survival cells after exposure to the test samples. The 3T3 Fibroblast cell line was used for this study. The cell lines was maintained and sub cultured in 25mm² tissue culture flasks using 5 ml of minimum essential medium (MEM) supplemented with 10% fetal bovine serum, 3% L-glutamine, penicillin (100 IU/ml), streptomycin (100 μ g/ml), Amphotericin B (20 μ g/ml), phenol red. The pH of the medium was adjusted to 7.2-7.4 with 7.5% sodium bicarbonate and all flasks were incubated at 37°C in a humidified 5% CO₂/95% O₂ incubator.

Cells were grown in appropriate growth media and seeded at concentrations of 5 ×10⁴ cells per ml of media in 24 well plate. Cells were allowed to adhere on to the plate for 12 hours followed by treatment with different concentrations of the test sample viz., 50, 40, 30, 20 and 10 mg/ml and

incubated for 48 hours at 37 °C with 5 % CO₂. After treatment of 48 hours, cells were treated with 10% MTT in media for 4 hours in 37 °C and 5 % CO₂. Media was then aspirated and the adherent cells with formazon product was dissolved in DMSO, centrifuged at an RPM of 5000 for 15 minutes to remove debris. And then, spectrophotometric absorbance of the sample was measured using a microplate reader.

The wavelength used to measure the absorbance of formazan product was 570 nm and the percentage of reduction in cell proliferation was determined.

RESULTS

In vitro Assays

Anti-oxidant assay: DPPH and NO (Nitric oxide) Inhibition

Cell repair oil inhibited DPPH at 50 mg/ml as against Ascorbic acid at 1.52 mg/ml concentra-

tion (Table I).

Similarly the cell repair oil also inhibited Nitric oxide synthesis induced by LPS at 50 mg/ml concentration (Table II).

Elastase Inhibition Assay

Cell repair oil inhibited elastase activity by 18% at 50 mg/ml concentration (Table III).

Collagenase Assay

Cell repair oil at 50 mg/ml inhibited 11 % of collagenase enzyme as against epi galacto catacheine at 250 µM (Table IV).

Anti-glycation Assay

Cell repair oil exhibited anti glycation activity at 75 mg/ml as against Arbutin at 2mg/ml. (Table V).

TABLE I

% of viability of fibroblast cells.

Ascorbic acid (Positive control)	IC50 of 1.52 mg/ml
Cell repair oil	IC 50 at 50 mg/ml

TABLE II

Inhibition of Nitric Oxide (NO) Production

% of Nitric oxide inhibition versus concentration of the product.

S.No	% of Nitric oxide inhibition versus concentration of the product	
	Test details	% nitrate production (Cell repair oil)
1	Only LPS (Lipo Poly Saccharide-Positive control)	73
2	LPS +50 mg of oil	39
3	LPS +40 mg of oil	45
4	LPS +30 mg of oil	59
5	LPS +20 mg of oil	62
6	LPS +10 mg of oil	61
7	Untreated cells	22

Cell repair oil inhibits the production of NO with IC 50 value of 50 mg/ml.

TABLE III*inhibition of elastase enzyme Vs Conc. of product.*

S.No	% inhibition of elastase enzyme Vs Conc. of product	
	Conc. of product mg/ml	%Elastase inhibition (Cell repair oil)
1	50	18
2	40	11
3	30	6
4	20	2
5	10	1

TABLE IV*% inhibition of collagenase.*

Products	concentration	% inhibition of collagenase
Cell repair oil	50 mg/ml	11%
Epigallocatechin gallate	250 μ M (0.114 mg/ml)	40%

TABLE V*Anti glycation activity.*

Cell repair oil	75 mg/ml
Arbutin	2.0

Safety assays

Zein protein hydrolysis

Cell repair oil hydrolyzed zein protein by 9% as against SLS at 90% (Fig. 1).

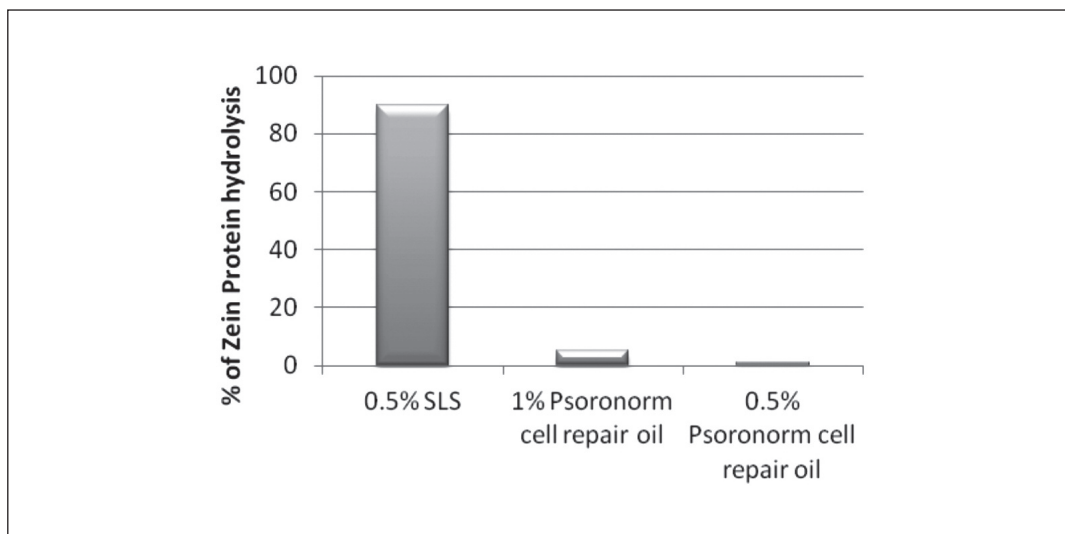


Fig. 1 Zein protein hydrolysis assay.

Fibroblast Toxicity Assay

Cell repair oil inhibited fibroblast by 9% at 50 mg/ml. (Table VI).

TABLE VI

Cell repair oil inhibited fibroblast by 9 % at 50 mg/ml.

Concentration (mg/ml)	% inhibition (Cell repair oil)
50	9
40	2
30	1
20	1
10	1

DISCUSSION

Finding of the present study has clearly revealed that cell repair oil is quite useful for managing the remission phase of psoriasis.

Reduction in erythema in erythrodermic and inverse psoriasis and reduction in scaling in Plaque psoriasis after use of cell repair oil assumes greater clinical importance. Similarly, reduction in itching and dryness in all patients after use of cell repair oil also clearly reveals its clinical efficacy and usefulness in the management of psoriasis.

We assume the above clinical benefits may not due to the mere moisturization effect of cell repair oil only.

The detailed in vitro study of cell repair oil has clearly revealed that cell repair oil inhibits elastase, collagenase and glycation events. Similarly, the oil also has shown to have definite antioxidant property (11).

The role of elastase and collagenase in worsening the clinical manifestation of psoriasis is known (12).

Similarly the protein glycation process is known to decrease cell maturation time and increase cell senescence.

The effect of cell repair oil in inhibiting elastase, collagenase and glycation activity as established by in vitro studies clearly suggests the functional role of cell repair oil in managing psoriasis, besides its moisturizing effect.

The involvement of oxidative damages and the role of antioxidants in the treatment of psoriasis is also known. Several studies have shown that the natural antioxidant – Glutathione synthesis gets lowered significantly in Psoriatic patients. Therefore inactivation/ attenuation of free radicals of both general and specific are important for psoriasis.

The in vitro evaluation of the antioxidant effect of cell repair oil has revealed that it inhibits both DPPH and Nitric oxide induced oxidative damage.

The above findings clearly points towards the multi-level clinical effect of cell repair oil and only due to such effects, greater solace could be achieved in various signs and symptoms of psoriasis by the patients in the present study.

The prolonged use of cell repair oil is also known to be safe as we have established its non-cytotoxic property using fibroblast cell lines and Zein protein hydrolysis. The cell repair oil was found to be absolutely safe through the above tests.

Further the above findings expand the definite scope of the cell repair oil for the management of psoriasis.

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Green Ingredients in Cosmetic Dermatology. Molecular Aspects of Ingredients and Carriers

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Summary

In healthy skin keratinocytes provide the essential function of self-renewing themselves, regularly communicating with each other, with dermis and the immune system by a delicate balance of biochemical signals and cellular responsiveness, which slow down during the aging and photoaging phenomena. The main goal of Cosmetic Dermatology is to formulate Clinically Correct Cosmetics based on the use of effective and safe natural active ingredients and carriers, skin and environmentally-friendly. It has been shown by different studies that nanochitin-hyaluronan (CN-HA) and nanochitin-lignin (CN-Lignin) block copolymeric nanoparticles may contemporarily act as active carriers and ingredients ameliorating the skin sensible and prematurely aged. On one side they entrap into their structure and load different active ingredients, such as, for example, antioxidant and immunomodulant compounds, releasing them at the right skin site at the right time. On the other side they are metabolized from the enzymes to glucosamine, acetyl glucosamine, glucose, hyaluronic acid (CN-HA) or to polyphenols (CN-lignin), and used from the skin cells as raw material and energy useful to repair their damages, caused from the environment and the aging processes. The paper reports some example of the results obtained *in vitro* and *in vivo* by use of CN-HA and CN-Lignin, entrapping different active ingredients, to produce innovative Cosmetics and advanced medications.

Riassunto

Nella cute sana i cheratinociti svolgono la funzione essenziale di un loro continuo rinnovo, svolto attraverso l'uso di segnali intercellulari interscambiati dell'epidermide con il derma e con il sistema immunitario. La produzione di questi segnali rallentano con l'invecchiamento della pelle aggredita dall'ambiente. Il principale scopo della Dermatologia Cosmetologica è di formulare cosmetici clinicamente corretti basati sull'uso di ingredienti e veicoli, possibilmente naturali, efficaci, privi di effetti collaterali e rispettosi sia della cute che dell'ambiente.

Diversi studi hanno posto in evidenza come i complessi naturali nanochitina-acido ialuronico e nanochitina-nanolignina siano, in grado di agire come veicoli e principi attivi apportando benefici alla cute sensibile e precocemente invecchiata. Questi complessi innovativi da una parte intrappolano e trasportano diversi ingredienti attivi, quali ad esempio antiossidanti e immunomodulanti, cedendoli ai giusti siti cutanei nei tempi prestabiliti. Dall'altra parte, vengono metabolizzati da appositi enzimi a glucosammina, acetil glucosammina, glucosio e acido ialuronico, CN-HA, o a polifenoli, CN-lignina, per essere utilizzati dalle cellule come materiale ed energia necessari per riparare i danni cutanei provocati dall'ambiente e dai processi di invecchiamento.

Lo studio riporta alcuni esempi dei risultati sperimentali ottenuti, *in vitro* ed *in vivo*, dall'uso di questi nuovi principi attivi naturali utilizzati per produrre cosmetici innovativi e medicazioni avanzate.

INTRODUCTION

The skin, composed of several layers, such as epidermis, dermis and hypodermis, acts as a biological barrier with a thickness of less than 2 mm, preventing water loss and protecting the body's organs from the external environment and foreign substances (Fig. 1) (1, 2).

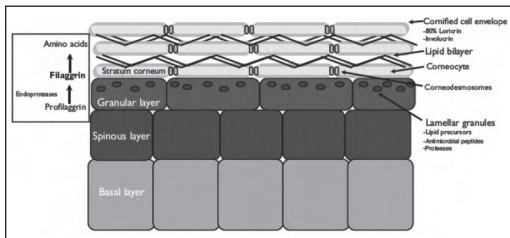


Fig. 1 The skin composed of epidermis and dermis acts as biological barrier of the body's organs.

While the stratum corneum(SC), composed of corneocytes, represents the primary barrier as outermost layer of epidermis, the dermis, composed of the extracellular matrix (ECM), counteracts oxidative stress and inflammation also (3, 4). To achieve these purposes, the corneocytes, filled with keratin filaments and enclosed by a protein envelope, are surrounded by a semi-continuous matrix of highly organized lipids, called lamellae, dominated by three lipid classes: ceramides (~50%), cholesterol (~25%), and free fatty acids (~15%) in equimolecular ratio 1:1:1(5, 6).The filaments are aggregated by a variety of enzymes and the protein filaggrin (FLG), which by degradation accounts in part for the water holding capacity and maintenance of SC' acidic pH. Linked to this protein layer the non polar lipids, referred to as the lipid envelope, seems to act as a template for the formation of the intercellular lipid layers (lamellae). On one hand, the epidermis corneocytes have to be considered important components for the structural and mechanical integrity of the skin, while their degradation results necessary to control desqua-

mation, lipid synthesis, inflammatory phenomena and, therefore, the epidermal barrier homeostasis. On the other hand collagen and elastic fibers, synthesized by fibroblasts represent the structural protein of ECM (Fig. 2).

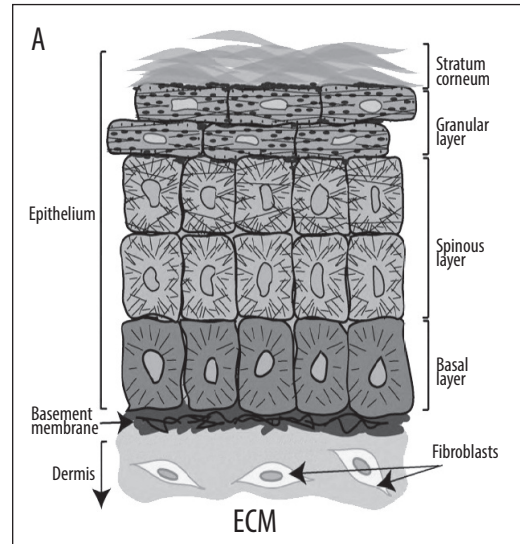


Fig. 2 Collagen and elastic fibers represent the structural proteins of the extracellular matrix.

Thus, the integrity of both SC and ECM, compromised by the environmental aggressions and the aging processes, results essential to skin health. The integrity of the skin, in fact, depends on specific intercellular signalling and attachments of its keratinocytes to ECM and to each other, on their regular turnover, and the intrinsic cellular capacity to counteract the increased formation of reactive oxygen species (ROS), modulate contemporary the inflammatory mediators and allow mtDNA mutagenesis (7). Thus, the thicker SC is associated with decline of aging skin with a steady reduction of the Trans Epidermal Water Loss (TEWL), a gradual decline in immune function and a reduced allergen responses. For all these reasons, the cutaneous inflammation displays a significantly higher threshold, compared to young adult and infant skin(8-10).

Thus, the epidermis keratinocytes, attached to the basal lamina through hemi-desmosomes rich of glycoproteins, have to be protected in their molecular mechanisms and processes in order to allow these cells to regularly migrate and proliferate (Fig. 3).

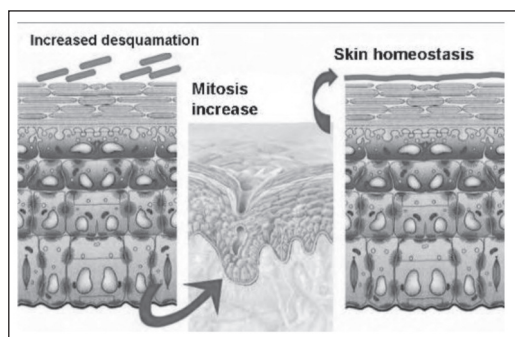


Fig. 3 The structural integrity of both SC and ECM is based on the regular migration and turnover of keratinocytes.

Moreover, the cellular structure of dermis, results necessary to maintain and protect the cellular signal transduction pathways, including the mitogen activated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B) (11). As a consequence, the expression of the ECM genes and structure of the ECM proteins, have to be continuously regenerated, because normally altered by the oxidative stress and inflammation. The altered keratinocytes and lipid lamellae turnover and differentiation (12), together with a compromised and reduced gene expression, and an increased degradation of fibrillar collagen, manifest, in fact, wrinkling with an aged skin appearance. In addition, environmental exposure to ultraviolet radiation (UV), smoking, wind, and chemicals, result in roughness, fine lines, sagging, irregular pigmentation, and decreased skin elasticity (13, 14).

As a consequence, collagen is degraded by matrix metalloproteinases (MPs), while the photochemical generation of ROS (Radical Oxygen Species) produces damages at level of nucleic

acid, lipids and proteins. For these reasons the skin protects itself with natural occurring antioxidants, such as vitamins C and E with polyphenols which, donating electrons, neutralize the ROS activity (Fig. 4) (15-17). Additionally, the enzymatic proteinases are thought to facilitate the keratinocyte movement by remodelling ECM proteins, and modulating intra cellular signalling, secretion, bio-activation, and stability of cytokines and growth factors (Fig. 5) (18).

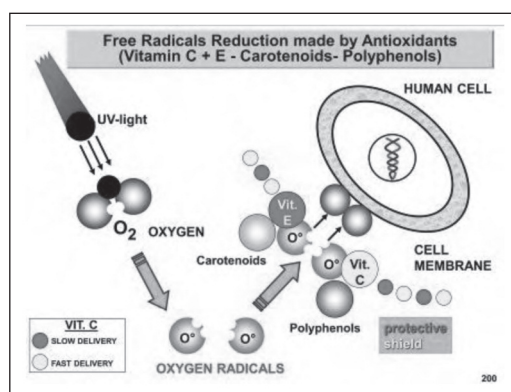


Fig. 4 The antioxidant activity of vitamins and polyphenols neutralizes the ROS activity.

A proper balance between antioxidant compounds and proteinases is thus considered crucial to the resolution of prolonged inflammation and regular skin turnover, subsequent to the skin integrity.

In conclusion, the normal functioning of the skin directly depends on the organization of the lipid bilayers, thickness of SC, number and layers of corneocytes, their size and cohesion, and regular organization of ECM (19, 20).

Cosmetic Dermatology and skin aging

In healthy epidermis keratinocytes recognize what function has to be performed at any particular time. Thus, these specialized cells may provide the essential function to self-renewing

themselves, by regularly communicating with each other, with dermis and the local immune system (21). The skin coordinate degradation and regenerative process require, therefore, a delicate balance of biochemical signals and cellular responsiveness, which slow down during the aging and photoaging phenomena (22). In response to environmental injuries, the basal keratinocytes of the skin surface, hair follicles and sweat gland ducts has to be regenerated during the aging process by regulated migration, mitosis, and maturation sequence, mediated by locally released growth factors, cytokines and chemokines. The main goal of Cosmetic Dermatology is to formulate clinically correct cosmetics based on effective and safe green ingredients and carriers skin and environmentally friendly. They must be capable to counteract and slow down the skin aging phenomena, mini-

mizing also the skin sensitivity. Thus, they have to play an active role in modulating intercellular lipids and moisturizing agents by an increased filaggrin synthesis (23, 24). As a consequence the abnormal desquamation as well as the water content of lipid lamellae and differentiation of corneocytes are regulated.

So doing it will be possible to obtain a normalization of the SC barrier function. In addition, the fibroblast activity has to be regulated for inducing the right and regular collagen production, beneficial to maintain strength and durability of a healthy and younger skin (25, 26).

However, it is important to underline that, while the selection of the active ingredients is fundamental for the effectiveness and safeness of the final cosmetic formulation, the role of the carrier (vehicle) has not to be underestimated, when dealing with biological surfaces.

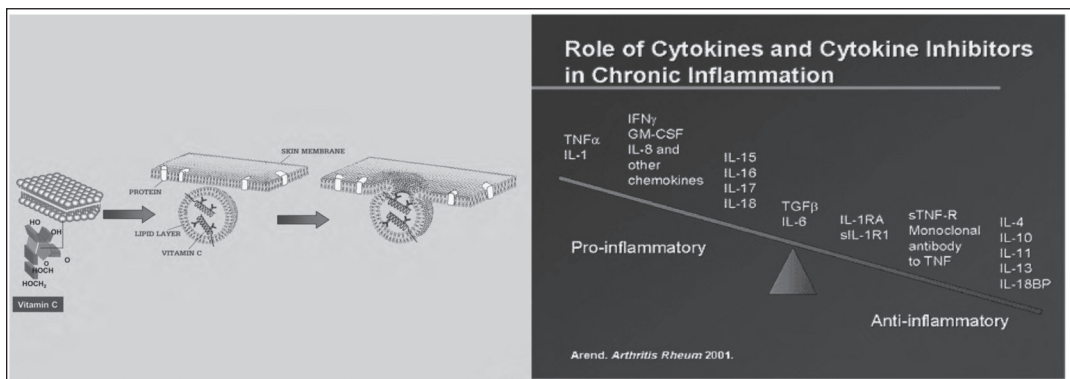


Fig. 5 Role of the cellular signals and enzymes in modulating the keratinocytes' turnover and skin inflammation.

The carrier effectiveness

The carrier could have proper active properties, while it should be also capable to load and deliver the active ingredients at the right skin/cellular layers, at the right dose, and time (27). As an example, the natural polymers nano-chitin and nano-chitosan could have a greater potential for future development in different fields of science, namely drug delivery, gene delivery, cell imaging sensors and also in treatment and diagnosis of some diseases, like cancer (28). They, in fact, appositely and differently modified for their nano-structure, possess superior physical and chemical, properties such as high surface area, porosity, tensile strength, conductivity, photoluminescence and increased mechanical properties, as compared to technical chitin and chitosan (29). Moreover chitin nano-fibrils (CN) (30), while have shown to bond many molecules of water (at least 3 trillion for 1ml!), evidence a high moisturizing effectiveness, having also the capacity to load as carrier different active ingredients (31-33). At this purpose, it is interesting to underline the characteristics of CN-Lignin nanoparticles (Fig.6) used from our group as innovative new carrier and active agent, to enhance the biological activities of CN (34-36).

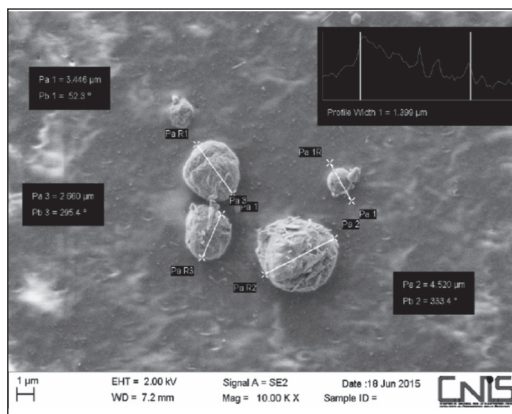


Fig. 6 The innovative carrier Chitin nanofibril-Lignin at SEM.

As bivalent carrier, composed of CN positively charged and Lignin negatively charged, these nanoparticles are capable to load into their molecular structure many active ingredients carrying and releasing them at the right skin site, at the right dosage, and the right time (37). On one hand, CN is a nano polymer which, composed of about 25 molecules of glucosamine and acetyl glucosamine with a mean dimension of 240x7x5 nanometers(nm), shows the same backbone of hyaluronic acid (Fig. 7) (38).

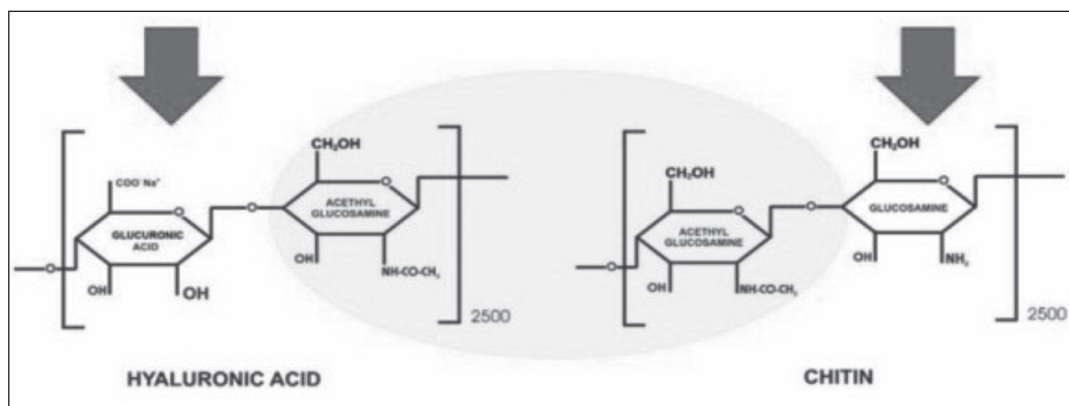


Fig. 7 Chitin Nanofibril shows the same backbone of hyaluronic acid.

For its own specific characteristics, this natural polymer has the capacity to bond many molecules of water, acting as moisturizing compound probably capable as glycerine do, to increase the aquaporine-3 expression (39). Moreover, it has been shown that CN has also the capacity to modulate the regular synthesis of skin lipids and their organization in lipid lamellae (40). Finally, being rich in acetyl chains, it is easily recognized and metabolized from the chitotriosidases expressed by lipid-laden tissue macrophages in man (41, 42). Thus, it could be totally used from the skin cells, as glucosamine and acetyl glucosamine to repair cartilage, or as energetic compound for the mitochondria activity. On the other hand, the component lignin with a mean dimension of about 270 nm and possessing antimicrobial, antioxidant and UV absorption properties could be metabolized to produce polyphenol compounds, necessary to reinforce the antioxidant network of the skin (43,44), or to increase its photoprotective activity, acting as a booster of natural or man made sunscreen agents (45).

Thus, CN-lignin could act both as carrier and active ingredient useful to reinforce the moisturizing and defensive networks of the skin, supporting the filaggrin synthesis also.

The active agents

It has been shown as the nanoparticles of CN and the block polymeric nanoparticles CN-Hyaluronan (CN-HA) and CN-lignin can easily bond and load many active ingredients, increasing their effectiveness and slowing down their possible side effects (46-48). Thus, CN, for example, has the ability to form block polymeric nanoparticles with zinc pyrithion or pyrithion olamine, increasing their effectiveness to eliminate the hair dandruff (Fig. 8) (49); to bond Zn ion and load it on the hair surface, ameliorating the gloss measurements of UV-exposed hair (Fig. 9) (50) and accelerating the repairing acti-

vity of damaged hair by load amino acids and peptides on its damaged structure (Fig.10) (50); to induce the regular disposition of collagen in a wounded skin, accelerating the skin reconstruction and reducing the risk of the keloids formation (Fig.11) (51).

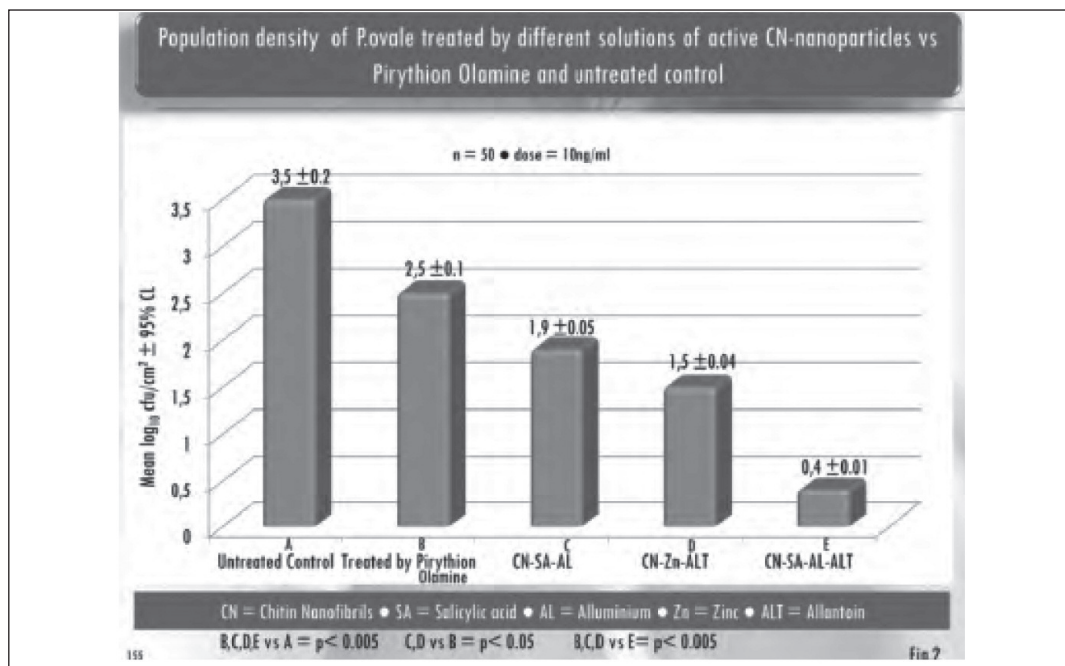


Fig. 8 CN has the ability to complex Zinc pyriithion and Zinc olamine, increasing their antidandruff effectiveness.

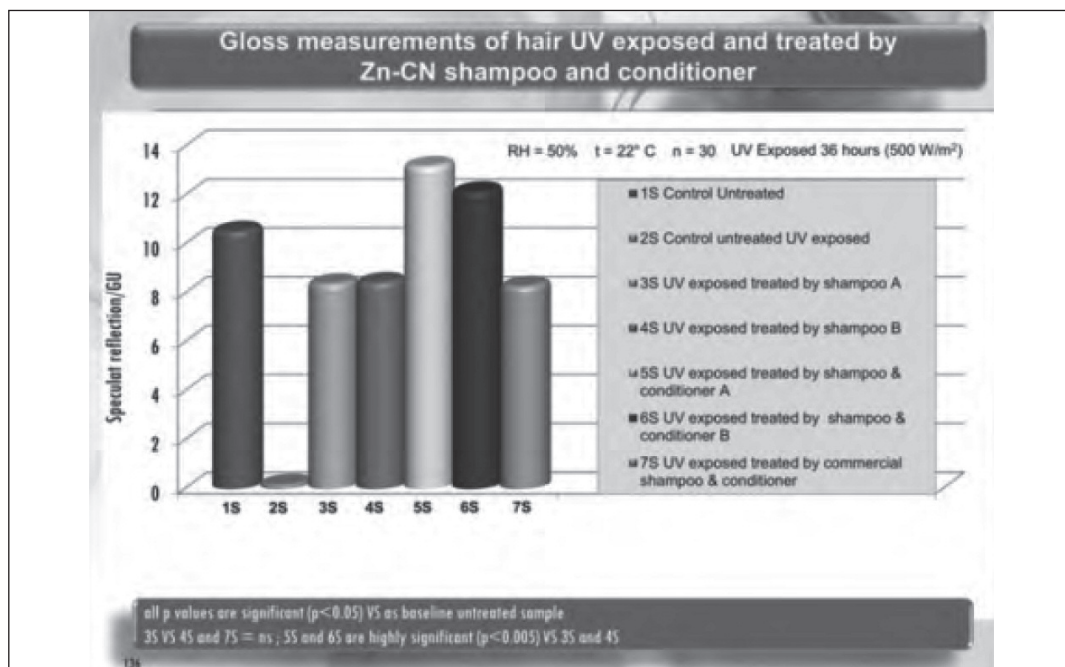


Fig. 9 CN bonds and loads Zinc ion on the hair surface, ameliorating its gloss.

Moreover, CN-HA has evidenced its capacity to modulate the metalloproteinase and collagenase release (Fig. 12) (52, 53), increase the antioxidant capacity of vitamin C-derived compounds (Fig. 13) (54), to decrease the melanin synthesis and/or the melanosomes transfer to keratinocytes, increasing the whitening activity of the final

product (Fig.14) (54).In addition, CN-lignin has shown to favour the synthesis of the human protective peptides, known as defensins (Fig. 15) (55), enhancing the DNA repairing activity of nicotinamide and boosting the activity of UVB-UVA screens (56).

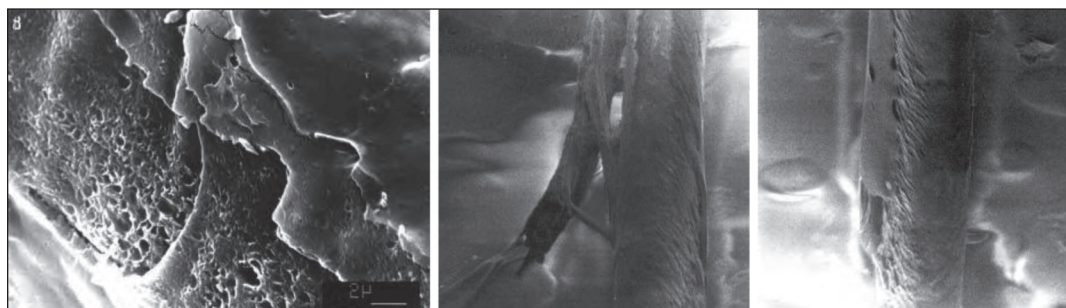


Fig. 10 CN bonds and loads amino acids and peptides on the surface of damaged hair ameliorating the structure of its fibers.

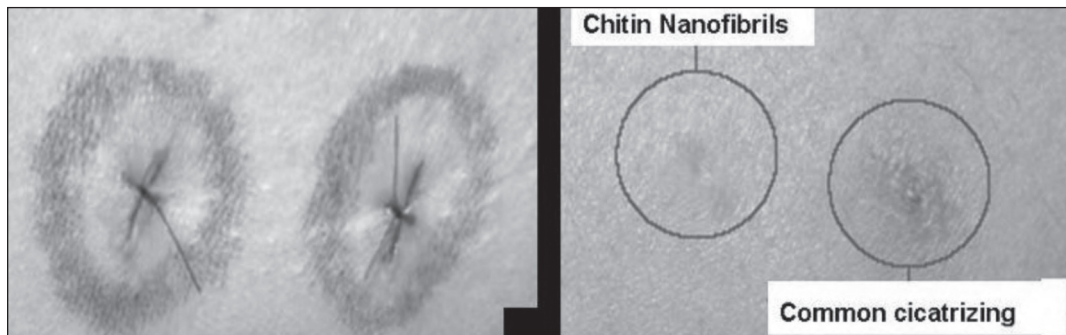


Fig. 11 CN induces the regular disposition of the collagen' fibers reducing the risk of the keloid formation.

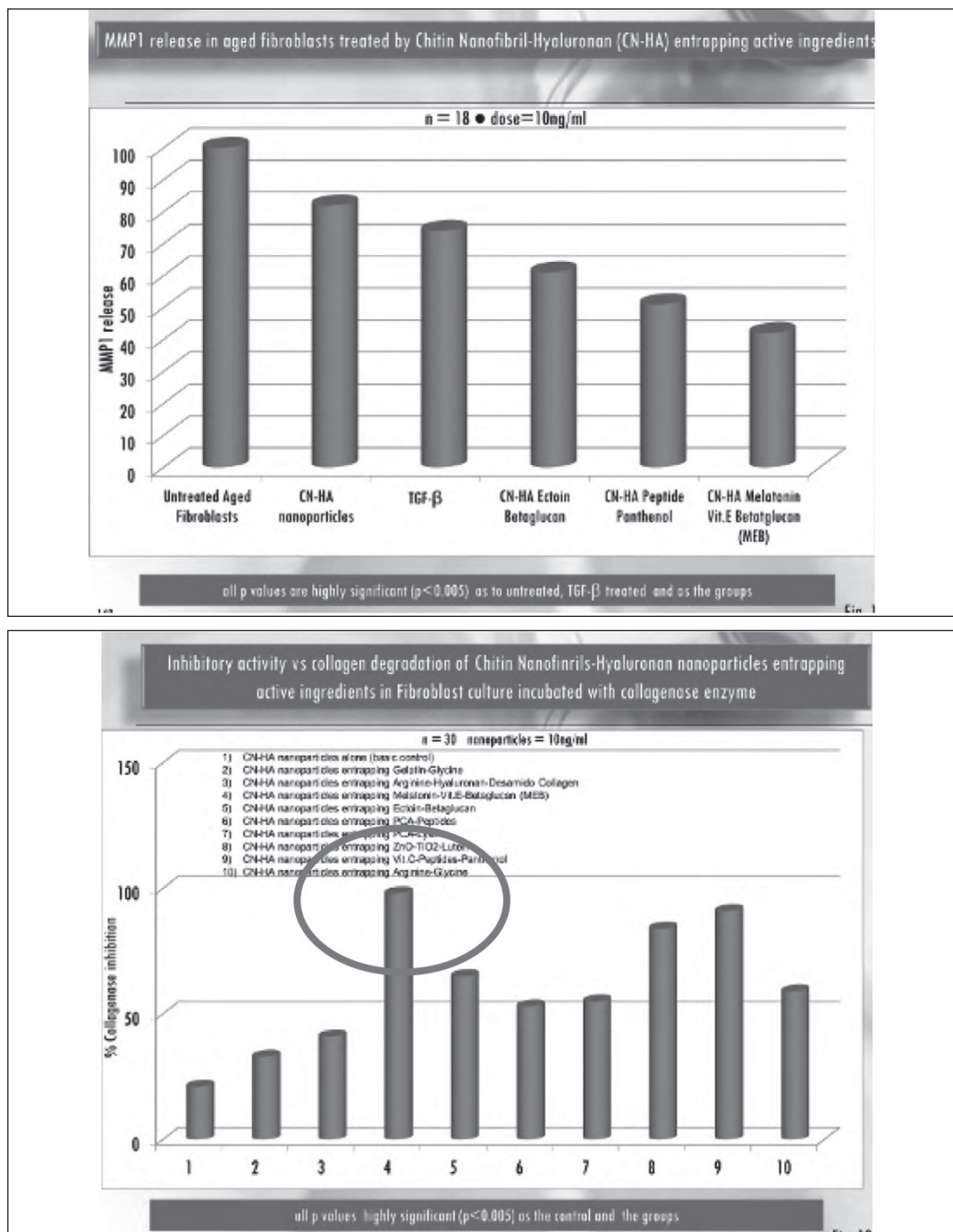


Fig. 12 CN-HA modulate the metalloproteinase and collagenase release.

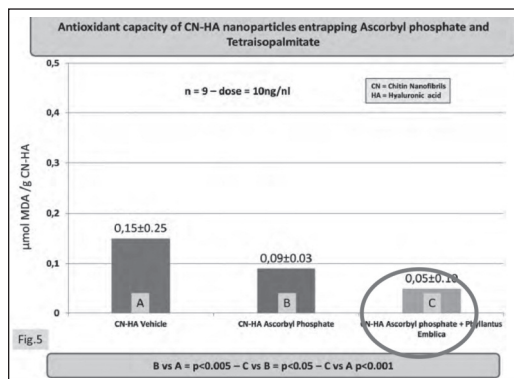


Fig. 13 CN-HA increases the antioxidant capacity of vitamin C-derived compounds.



Fig. 14 CN-HA increases the whitening effectiveness of different active ingredients.

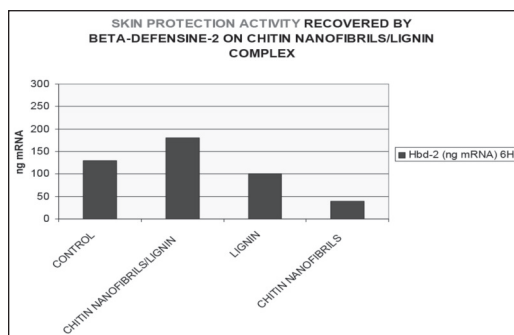


Fig. 15 CN-lignin favours the synthesis of defensins.

CONCLUSION

As conclusive remarks, it is interesting to underline that the natural polymers CN and lignin, obtained from the industrial and agricultural waste and classified as green components, are not only 100% biodegradable and skin friendly, but are considered useful to save the environment and the planet biodiversity, safeguarding the actual natural raw materials for the future generations (57-59). Moreover, the use of these innovative and active nano-carrier gives the possibility to deliver the selected active ingredients in the best dosage and at the right site, increasing their bioavailability, enhancing the ingredient's effectiveness, reducing their possible side effects, and improving the patient compliance (60, 61).

In conclusion the use of natural active ingredients, as chitin nanofibrils and lignin, obtained from waste materials by the use of bio-nanotechnologies could provide new approaches for delivering green ingredients at the best dose possible in a controlled release, to specific tissues and cells, enriching and modifying the dermatologist and plastic surgeon's armamentarium with the vision to live in a future greener and more safe planet.

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Skin Barrier Function

by T. Agner

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Skin acts as a biological barrier protecting the body from external insults; externally protecting it from pathogens, chemicals, UV radiation, and allergens; internally helping to maintain the homeostasis and protect the body from enhanced loss of water, electrolytes and proteins. The permeability barrier function is situated in the epidermis and primarily in the stratum corneum (SC) that, representing the outermost 10-20 μm of the epidermis, is made up of corneocytes, flattened dead squamous cells, filled with keratinocyte filaments enclosed by an envelops of cross-linked proteins, and surrounded by a semi-continuous, highly organized, lipid lamellae matrix. These filaments are aggregated by filaggrin (FLG) protein which, next together with several other proteins, is cross-linked into a mechanically robust cornified cell envelop. This envelop, that provides a scaffold for the extracellular lipid matrix, is an important component for the SC structural and mechanical integrity. Moreover, the products of FLG degradation account in part for the water-holding capacity and maintenance of acidic pH of the SC, necessary to regulate the activity of different enzymes which control desquamation, lipid synthesis, inflammation, and, therefore, the epidermal barrier homeostasis. Experimental mechanisms by which FLG deficiency affect skin barrier are reported and discussed on **chapter 1** of this book, organized in IV sections and 15 Chapters.

The SC lipid matrix represents another fundamental component of the skin barrier function. Its role is to prevent excessive water loss through the epidermis and to avoid that compounds from the environment, permeating into the viable epidermal and dermal layers, may provoke consequential immune response. Also if the particular role of each individual lipid class remains to be elucidated, the lipid matrix is dominated by three lipid groups: ceramides (~ 50%), cholesterol (~25%) and free fatty acids (~15%) (present in SC in an equimolar ratio) and some minor lipid components. These lipids are organized in an ordered 3-dimensional structure of stacked densely packed layers, known as lipid lamellae. Because of the cornified envelope and bound lipids, they form a continuous structure. They originate from precursors, phospholipids, glucoceramides, sphingomyelin and free sterols delivered to SC by the lamellar bodies in the stratum granulosum (SG). Moreover, the lamellar bodies contain enzymes (hydrolases and proteases) important for further lipid processing in the SC and are involved to regulate the desquamatory process. This intercellular lipid matrix acts as the main penetration pathway for the diffusion of substances through the skin and is considered important for the skin barrier. Another important component for the structure of the cornified envelope is filaggrin, necessary for the skin miniaturization. Its metabolites, in fact, are part of the natural moisturizing factor

(NMF), responsible of the equilibrated SC hydration. The explanation of the lipid organization and its general structure, the expression of the enzymes involved in lipid metabolism, and their role in healthy subjects and atopic dermatitis patients, is the topic reported on **chapter 2**.

The skin barrier consists of several barriers among which Tight Junctions (TJs) play an important role. TJs, in fact, are complex cell-cell junctions that form a barrier in the stratum granulosum of mammalian skin, influencing other skin barriers ,i.e. the stratum corneum, the chemical network, the microbiome and the immunological barrier. At this purpose, it has been shown that, for example, the impaired barrier function leads to up-regulation of some specific interleukins, which in turn influence the amount of NMF. The central role of these transmembrane proteins in skin barrier is reported and discussed in **chapter 3**, where it is underlined how one barrier can lead to a deterioration of other barriers, therefore resulting in an accumulation of negative effects or even a vicious circle. In any way, TJs are pivotal for innate tolerance and their regulation could enhance our knowledge to understand the mechanisms of some diseases and find new treatment options.

As reported, the skin constitutes the body's contact zone barrier protecting us from invading pathogenic microbes and harmful organisms. An important part of this barrier is represented from antimicrobial peptides (AMPs), which with their role of direct antibiotic-like activity, are in the center of epithelial defence mechanisms, forming also an important part of the innate immune system. Most of these peptides, in fact, have an overall positive charge, allowing them to interact with negatively charged phospholipids in the cell walls of microbial and anionic components of fungi and viruses, resulting in cell lysis. However keratinocytes, as dominant source of AMPs, play an important role in forming both a physical barrier by the production of lipids. They create an immunologic shield, alert the immune system, producing pro inflammatory mediators, thus creating a strong barrier and defence against harmful microorganisms and environmental aggressions. AMPs are produced in the suprabasal layers and basal stratum of the epidermis and transported by lamellar bodies to the SC, where they play their important role. Moreover, they influence the cell migration, proliferation and differentiation and the cytokines production, playing an important role in linking innate and adaptive immune responses. Finally, it seems that the recovered synergism between host commensalism and AMPs might be another important function in protecting the skin, playing a role in maintaining the homeostasis of the skin barrier's microflora. These are the topics discussed in **chapter 4**.

Inherited genetic variants, negative environmental or extrinsic factors, and age determine a person's predisposition to a skin barrier defect, appearing clinically as dryness/*xerosis*, such as in atopic dermatitis (AD) or ichthyosis. However, the structure and function of the skin barrier may vary greatly during the aging processes, the inheritable genetic differences, and the environmental impact. With aging the metabolic activity of the skin slows down, resulting in slower epidermal turnover and desquamation, reduction in Trans Epidermal Water Loss (TEWL), reduction in water hydration and skin elasticity for altered filaggrin, lipid and collagen synthesis, and decline of immune function with consequent changing in allergen responses. Nevertheless, the causes of the skin barrier defect are highlighted by the gene-gene and gene-environment involved, for example, in the development of AD. Thus, the treatment and prevention of dry skin conditions will require an understanding of the subclinical variation in the structure and function of skin barrier between individuals. This the topic developed in **chapter 5** by which ends the *Section I: Basic Parameters*.

Experimental models for studying penetration through the skin barrier are good and validated

approaches, enabling percutaneous penetration between different chemicals and formulations. Thus many research methods have been developed for sampling, measuring and predicting the skin penetration both *in vitro* and *in vivo*, together with mathematical models for predicting the rate of penetration. In line with a pharmacological approach, the dose-effect can also be established for functional ingredients that have to reach the site of action, at the right dose and time. At this purpose, various target sites on or within the skin have to be considered: the outside layer of the SC, the SC or the lipid lamellae outside and between the corneocytes, or the corneocytes themselves within the SC, the viable epidermis, and the dermis. However, other structural entities such as the hair follicle, the sebaceous or the eccrine glands, or specific units, such as melanocytes or Langerhans cell can be targeted. Therefore, the big issue in skin delivery is to carry and release the functional molecules in the specific skin layers. Thus the quantification of TEWL with non-invasive bioengineering methods has gained popularity as one of the most reliable methods to assess the barrier function of the skin. Studies on the insensible water loss in healthy and in different disease conditions such as psoriasis or atopic dermatitis have been published. Quantifying TEWL, in fact, provides the most direct measure of the barrier function.

Other non-invasive bioengineering methods are used, such as SC hydration, colorimetric values, skin surface, pH, and sebumetry, to provide information on different characteristics of the skin and its condition, also if these are no direct measures of skin barrier function. However, their more or less frequent use is determined not only by the scientific problems studied, but also by their practicability and cost. A novel investigative method, such as the *in vivo* Raman confocal spectroscopy (RCS), is employed to study the structural components of the epidermal barrier (lipids, proteins, NMFs and water gradient) and compounds penetrating the epidermis both in a space-resolved manner. To monitor the penetration of exogenous substances and their transformation in the epidermis, RCS seems to be an useful method to study the skin pharmacology and physiology *in vivo*, without altering the epidermis properties. Thus, a combination of *in vivo* measurements, complemented by analytical methods, may help to improve the understanding of the barrier responses to specific irritants and to identify sensitive redoubt parameters, for studying skin irritation in healthy and diseases conditions. Irritative compounds, interacting with different components of the skin, elicit a cascade of homeostatic or pathological responses that could be investigated by both *in vitro* and *in vivo* methods.

At this purpose, skin irritation leads to the release of IL-1 and TNF-alpha, which affecting the function of antigen-presenting cells and promoting their migration to local lymph nodes, increase the probability of contact sensitization (CS) and ultimately the development of contact allergy (CA). However, the relationship between common dermatoses such as psoriasis, AD and irritant contact dermatitis (ICD) and the development of CA is complex, and depends on immunologic responses and the skin barrier status, connected with the percutaneous penetration of exogenous compounds. It is to remember that the variation in the penetration rate between skin areas is not directly related to the thickness of the skin, but rather to factors such as number of follicles, thickness of the SC, sebum composition as well as the exposure conditions, the distance between capillaries, and the surface of the skin. Moreover, all these factors change as a function of increasing age during which the repair mechanisms become less effective causing barrier damage that, remaining for longer period of time, increases the penetration rate. In conclusion, the best experimental approach depends on the research problems to be solved, also if the *in vitro* models are seen as a simpler design at lower costs, requiring less time and ethical considerations, than the *in vivo* methods.

All these topics are reported and discussed on *Section II: External Factors Influencing Skin Barrier* by **chapters 6-10**.

As previously reported, the barrier function of the skin is submitted to a continuous turnover, being driven by the epidermis in close relationship with the dermis. The skin integrity and its normal functioning depend, therefore, on keratinocytes' perpetual process that provides its own self-renewing by a cycle of 2/4 weeks. In healthy epidermis, keratinocytes slowly proliferate in the basal layer and differentiate in the suprabasal layers, communicating not only with each other, but also with dermis and local immune system. Within moments of burning, for example, these cells communicate the urgent need to repair the broken barrier, also alerting the defence mechanisms for the incoming pathogens. Thus, the coordination of degradative and regenerative processes of skin barrier requires a delicate balance of biochemical signalling and cellular responsiveness, mediated by specialized biochemical signals, such as growth factors, cytokines and chemokines, which may act in an autocrine or paracrine manner. Restoring the skin barrier function in people with defects by the use of specific treatments may, for example, help to prevent the development of atopic eczema, and halt the development and progression of allergic diseases. Selected lipids may change the lamellae organization and the packing of the lipid matrix, as well as moisturizing agents may influence the desquamatory enzyme proteases, altering the thickness of the SC. Both lipids and moisturizing agents, such as glycerine and urea, have been reported to influence barrier repair in experimentally damaged human skin.

On one hand, topically applied lipids may enter the epidermis content, increasing cell differentiation and reducing skin permeability. On the other hand water content in the moisturizing cream gives a temporary increase in skin hydration by its absorption rate into the epidermis. Thus, the right mixture of the required lipids and moisturizers in the correct proportions is essential for the reconstitution of the epidermal lipid bilayers, contributing to the repair of the epidermal barrier. They, in fact, would not only form an occlusive layer on the skin but would also deliver the raw materials required to create new lamellar bodies. These are the reasons for applying emollients and moisturizers to the skin with the aim not only for changing its tactile and visual characteristics, but also for delaying the relapse of eczema. These and other interesting topics regarding the occupational skin diseases, are also reported, documented and discussed on the last III session: *Optimizing Skin Barrier Function* by **chapters 11-15** of this interesting book.

Edited by an expert team of distinguished researchers, focused on the skin barrier function, this book has to be considered the most up-to-date information of all the biochemical and clinical aspects regarding dry skin and related diseases. Ideal for dermatologists, plastic surgeons, cosmetic chemists, biologists, pharmacologists, clinical scientists, and people interested in the treatment of xerotic skin conditions and experts in related industries, it may be considered a reference book for generating innovative products and applications in dry skin biology.

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Editor-in-Chief

Introduction to Nanoscience and Nanomaterials

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Nanotechnology is a technology that deals with small structures or small-sized materials with the dimension that spans from subnanometer to several hundred nanometers, where a nanometer (nm) is one billionth of a meter. According to the EU rules "nanomaterial means a natural, incidental or manufactured material containing particles in a bounded state or as an aggregate or as an agglomerate where, for 50% or more of the particles in the number size distribution, one or more external dimensions are in the size range of 1-nm-100 nm".

Apart the different opinions regarding nanotechnology, it is identified in EU as a key-enabling technology driving innovation. At "this dimension level", in fact, "the physical, chemical, and biological properties of materials differ in fundamental and valuable ways from the properties of individual atoms and molecules of bulk matter". The industrial strategies to be adapted for producing at nano level are not yet clear, but the processing techniques may have the top-down or bottom-up approaches. Attrition or milling is a typical top-down method in making nanoparticles, whereas the colloidal dispersion is a good example of bottom-up approach in the synthesis of nanoparticles. Among others, the biggest problem with top-down approach is the imperfection of the surface structure, such as the crystallographic damage in lithography. In any way, bottom-up is the way all the plant and biological structures are making, combining a simple nanostructure to form higher level building block hierarchical structures. They form higher level building blocks that further self assemble to give the next level of structure and so on.

Compared to the general bottom up processing techniques, top-down fabrication techniques for producing nano structures follow the same approaches based on micro fabrication. However, limitation of size less than 100nm in the top-down process could damage the surface of the nanostructures and nanodevices fabricated with negative consequence on their physical properties and performance. Although the bottom-up approach is nothing new, it plays an important role in the fabrication and processing of nanostructures and nanomaterials. These the considerations reported on **chapter 1**.

On **chapter 2**, the role of the surface in determining the properties of nanomaterials are reported and discussed, illustrating the relative applications also. In the nanomaterials, the surface to volume ratio is very high and increases rapidly as the relevant dimension decreases, so that for a 3 nm diameter particle approximately 90% of the atoms reside on the surface. Therefore, nanostructures and nanomaterials possess a large fraction of surface atoms per unit volume with a consequent increase of surface energy, which in turn depend on the dimension of the material. Consequently these materials are

thermodynamically unstable or meta stable. In any way, the surface atoms of nanostructures differ from the bulk atoms in many ways and their chemical activity increase drastically as the particle size reaches the dimension of few nm. Thus, synthesis, processing, self assembly and properties of nano-scale objects are very sensitive to parameters such as specific surface area, surface structure, surface curvature, and surface energy. When the dimension of the nanoparticles is sufficiently small and quantum effects are observed, quantum dots are the common term used to describe such nanoparticles.

A quantum dot is a nanoparticle displaying quantum effects. And many are the changes observed in electronic and optical properties due to quantum effects. The quantum dots, in fact, are very attractive light sources due to their large radiative efficiency, nearly monochromatic emission.

On **chapter 3** some selected topics in physics are reported for trying to explain and understand the properties of these optical changes. It covers specific zero dimensional nanostructures such as the semiconductor quantum dots, the metal nanoparticles, the magnetic nanostructures, the colloidal particles and colloidal crystals. Many are the experimental observations reported and discussed considering, for example, the different phenomena observed on bulk and nano solids structures, necessary to understand the changes in the band gap and other electronic and optical properties, connected with the different sizes of the structures. However, it seems that changes in properties such as the band gap, the photoluminescence, the optical absorption etc, can only be understood on the basis of the quantum mechanics. Nanoparticles or quantum dots can be prepared by phase segregation through annealing appropriately designed solid materials at elevated temperature. However, the quantum dots can be fabricated by several methods such as colloidal chemistry, lithography and epitaxy all growth.

The colloidal chemistry methods are suitable for producing a suspension of quantum dots for biological and medical applications, while the method of epitaxy is more compatible with the semiconductor processing. Epitaxy, in fact, is a very special process that refers to the formation or growth of a single crystal on top of a single crystal substrate or seed. Epitaxial growth can be further divided into homoepitaxy and heteroepitaxy. While homoepitaxy is the growth of a film on the substrate of the same material, heteroepitaxy refers to films and substrates made by different materials. Both are well-established techniques that found wide applications, particularly in electronic industry.

The fabrication of semiconductor quantum dots is the topic of **chapter 4**, where the epitaxial deposition of semiconductor films on slightly mismatched substrates are reported and discussed together with their properties and energetic necessities.

One manifestation of the effect the particle size has on the properties of the semiconductor quantum dots is the appearance of distinct colours. The nanoparticles suspensions of some metals show bright colours by the phenomenon of the surface plasmon resonance. It is a dipolar excitation of the entire particle between the negatively charged free electrons and its positively charged lattice. The energy of the surface plasmon resonance depends on both the free electron density and the dielectric medium surrounding the nanoparticle. It represents, therefore, the coherent excitation of all the free electrons within the conduction band, leading to an in-phase oscillation. Thus, when the size of a metal nanocrystal is smaller than the wavelength of incident radiation, a surface plasmon resonance is generated. This the topic developed on **chapter 5** while spintronic and the applications of super paramagnetic and other material are discussed on **chapter 6**.

A magnetic field can be represented by *lines of force* which can be visualized, for example, by

sprinkling iron powder near a bar magnet. By convention, the lines are assumed to be emitted from the North Pole of a magnet, and the force is called magnetic flux. Several the length scales characterizing magnetism, such as the exchange length, the domain wall width, the maximum equilibrium single domain particle size, the super magnetic radius at 300 K, etc. Therefore, some new effects should be expected when the object size approaches any of these characteristics lengths. One of the important effects observed is the phenomenon of superparamagnetism in nanometer ferromagnetic crystals, in the range of 19-200 nm.

The phenomenon of giant magnetic resistance arises due to the spin of the electrons, observed in a stack of alternating, nanometer thick, magnetic and non magnetic layers. The ability to control and manipulate the spins of electrons, has given rise to the new field of *spintronics*. The field of spintronics seeks to use the spin of electrons to develop new non-volatile devices in which logic operations, storage and communication are combined.

Colloids, colloidal crystals and suspensions are the systems reported and described on **chapter 7** where the explanation for the electrical interactions between the particles in suspension, tuned by changing the pH, the electrolyte concentration, and other parameters, are discussed.

A model colloidal system is a suspension of particles having diameters ranging from 1 nanometer to 10 micrometers in a liquid. The particles may be either dissolved macromolecular structures formed from smaller structural units, or they may constitute a separate phase. Such suspensions are of interest in nanotechnology for the preparation of nanoparticles, their modifications and their assembly to yield nanomaterials and nanodevices used in many industrial products, such as paints, cosmetics, drugs, etc.

In order to be stable, the micro/nanoparticles of the suspension have to possess the essential presence of a repulsive force between them. Such repulsive interactions are produced either by the presence of electrical charges or by the adsorption of some polymers on the particle surface. One kind of force, always present between two particles in a suspension, is the van der Waal's force, the interaction of which plays an important role during the fabrication and manipulation of nanostructures. At this purpose, the carbon nanostructures such as nanotubes have found a large number of applications because of their remarkable properties. This is the subject of **chapter 8**. Carbon is the most important element on earth, forming the backbone of the organic and biologic molecules, many of which have nano dimensions. All the nanostructures of carbon can be thought as derived from the sheets of carbon atoms which make up the structure of graphite. In the graphite, these sheets called graphene sheets are stacked one above the other. Both the fullerene and the carbon nanotubes can be imagined to form by folding a graphene sheet in different ways.

The structure of graphene consists of carbon atoms located at the corners of hexagons, each carbon atom being shared by three hexagons. The unit cell is a hexagon with $6/3 = 2$ atoms per unit cell. A fullerene is a carbon sheet closed upon it self to form a sphere, the most abundantly produced of which contains 60 carbon atoms. A single carbon nanotube can be imagined to be made by taking a rectangular strip of graphene sheet, rolling it into a cylinder and welding the two edges. It is important to underline that the carbon-carbon (C-C) bond is one of the strongest bond known. Thus, it is not surprising that the carbon fibers constitute a class of the strongest materials available and are used extensively in structural components of aircraft and space vehicles, where light weight together with strength and modulus are needed. However, the full potential of the C-C bond to produce composites is represented by nanotubes that are found to have much higher strength and modulus with

less defects compared to carbon fibers.

After the discovery of carbon nanotubes, efforts were intensified to prepare nanotubes of other material so that at present, synthesis strategies are available to produce one dimensional nanostructure from almost any material. In addition to the tubular morphology, nanostructures having several other one dimensional morphologies have been observed depending on the growth technique and growth conditions. These include shapes, such as nanowires, nanoribbons, nanosprings, dendritic shapes, etc. Nanowires of materials other than carbon is the topic treated on **chapter 9**. One dimensional nanostructure, in fact, is being investigated for applications in sensors, photoelectric energy generation, fine effect transistors and other devices. It has a large surface area and, in comparison to the nanoparticles, are easier to handle and to assemble. Few nanowires realized on a chip can act as a working electrode.

Due to their small size, the nanowires can respond to fast electron kinetics, while for their low surface area, their small capacitance they detect faster reactions. In any way, on one hand several issues regarding the integration of semiconductor nanowires in the based technology remain to be solved. On the other hand, nanowires of semiconductors and metals are also being looked at as building blocks which might lead to the realization of invisible cloaks!

The two dimensional (2D) nanostructures are defined as structures in which two dimensions are large, while the third dimension along the z axis is less than 100nm. Preparation of the 2D nanostructures is carried out by the techniques of thin film deposition, used also for the preparation of core-shell particles, hollow shells, functionalization of particles and surface, and other miscellaneous structures.

The other chemical deposition techniques such as chemical vapour deposition (CVD), atomic layer deposition (ALD) and layer-layer-deposition (LBL), known from many decades, are now being actively investigated for the preparation of novel nanostructures consisting of both inorganic and organic constituents. In the layer-by-layer growth the particles, are bonded more strongly to the substrate than to themselves. A layer covering the whole substrate is deposited first. This is followed by the deposition of the next layer, in the epitaxial growth, as previously described.

In the PVD methods atoms from a source, called target, are removed and deposited on the substrate. The removal of the atoms is effected either by heating the target so as to vaporize it or by impinging energetic ions on it to knock out atoms. CVD deposition is also used as the PVD technique, for the deposition of inorganic materials. In this process, reactants in the vapour or the gaseous form are brought near a heated substrate and react to form a solid film on the substrate. The PVD and CVD techniques of thin film deposition have relatively high rates of deposition and have been routinely used in the manufacture of integrated circuits.

Multilayers of different organic molecules or multilayer composites consisting of organic and inorganic layers are of interest for several reasons. Although the organic molecules having a wide range of functionalities are available, some mechanical stability is necessary to effectively use them in a nanostructure. This structure can be imparted making a composite consisting of organic molecules and an inorganic component. Furthermore, it may be also possible to combine the functionalities of two different types of molecules if they can be arranged in layers with determined position and orientation. LBL deposition provides this capability. Many of these deposition techniques in 2D structures are reported on **chapter 10**, which reports also their multilayer applications for mechanical engineering. Nanocrystalline metals and nanocomposites offer material with higher strengths and mechanical pro-

perties when compared to the bulk nanostructured materials. The hardness and strength of these nanocrystals, in fact, increase with decreasing grain size. Their preparation and properties are reported and discussed on **chapter 11**, while in Appendix II the mechanical properties of solids are provided.

Polymer nanocomposites are the topic of **chapter 12** where their processability and barrier properties are reported. But what composite means? Nanocomposite refers to a material consisting of at least two distinct materials with one disperse in another that is called matrix and forms a three-dimensional network, whereas nano-grained materials are generally multi-grained single phase polycrystalline material. While each material maintains its identity having a distinct interface in the finished structure, the reduced particle size promotes the densification of nanocomposite and the polycrystalline materials, due to the large surface area and short diffusion distance.

The continuous phase of the composite is called matrix and the discontinuous phase is called filler or reinforment. Thus, a major concern in its preparation is to achieve a good dispersion of the filler in the matrix, as well as the mechanical properties of a composite are a strong function of the properties of the filler. Moreover, to explain all the observed properties of nanocomposites, it is also necessary to remember the so called *nano effect* due to the small size of the particles which is not expected on the basis of the macroscopic theories. **Chapter 13** is entirely dedicated to describe the many molecules used in soft matter, such as polymers, biopolymers, surfactants and dendrimers, the self assembly of which is discussed in **chapter 14**.

Most of the synthetic polymers have a backbone of C-C bonds, so that polymers, formed by linking together a large number of monomers to form chains, have to be characterized by an average molecular weight. The polymers having weak bonds between the chains are called thermoplastics. These compounds can be brought into a viscous liquid form by heating them to a temperature high enough to inactivate the weak bonds between the chains. On cooling from the molten state, some polymers form an amorphous solid while others form mixtures of amorphous and crystalline solids.

At slightly lower temperatures, the ability of the chains to slide past each other decreases but the chains can still uncoil rapidly. The uncoiling of the chain produces large elongations and the polymer behaves as a rubber. However, polymer fibers tend to have a high crystalline fraction because during the drawing process the chains get extended and can easily organize into a crystalline structure. Thus, self-assembly and soft matter are the basic materials used in the fields of nanomaterials and nanotechnology to produce lithographic stamps, novel nanostructures, conducting nanowires, implants and scaffolds for tissue engineering, etc.

In conclusion this interesting book, emphasizing the increasing interest devoted to nanoscience, nanotechnology, and nanomaterials to realize innovative goods, gives a comprehensive and coherent picture of the nanostructure field.

For the clarity of the explanation reported, it could serve as general introduction to nanotechnology for under graduate students as well as for teaching and self-study purposes. Moreover, it may be considered a references book for Cosmetic chemists, Biologists, Medical doctors, and other scientists who have interest to understand and better know the fascinating field of nanoscience.

Pierfrancesco Morganti
Editor-in-Chief

MR SOLUTIONS, partner of the Integrated Magnetic resonance and Positron emission tomography in Preclinical Imaging (IMAPPI) consortium takes over the completion of phase 2 for a sequential PET/MR imager, and phase 3 for a simultaneous PET/MR imager



Dijon, France and Guildford, United Kingdom

MR Solutions, the pioneer and leading supplier in cryogen-free superconducting MRI up to 7.0T, has been chosen by the IMAPPI consortium among the historical partners to complete the project replacing the previously selected partner. The IMAPPI project is supported by a French Government grant managed by the French National Research Agency (ANR) under the program “Investissements d’Avenir” (with reference ANR- 10-EQPX-05-01/IMAPPI Equipex).

In March 2016, MR Solutions installed phase 2 of the IMAPPI project which consists of an in-line PET module with a high field MRI system where the data are acquired sequentially and co-registered together automatically.

The final phase of the project, phase 3, will consist of a large bore high field MRI with a PET module inserted in the field of view of the MRI for simultaneously acquiring PET and MR data. The simultaneous PET/MR system will be installed before fall 2016. Both phase 2 and phase 3 systems are designed for the imaging of rodents.

MR Solutions is one of the most innovative companies in recent years in the MRI area, and today with its PET modules, the company can demonstrate its full capabilities in multimodality imaging.

According to Dr François Brunotte, project coordinator and Professor of nuclear medicine, “we truly believe that multi-parametric and quantitative images from the IMAPPI PET/MR imager will bring crucial advantages in oncology and cardiovascular research due to its high soft tissue contrast and high resolution. Beside the expertise brought by MR Solutions, the project takes advantage from the close presence of hospitals, labs and companies in various fields such as physics, chemistry, biology, medical imaging. The installation of the imager in the department of Nuclear Medicine at the Centre Georges-François Leclerc-CGFL, specialising in oncology makes easy an efficient translation from bench to the clinic.”

Dr David Taylor, Chairman and CEO of MR Solutions Ltd explains: “we are extremely delighted to be the company that will complete the IMAPPI project. Only a company with strong expertise in MRI, as MR Solutions, can achieve the integration of a PET scanner with a high field MR system. MR Solutions has been investing massively in the multi-modality area with an innovative approach and we are pleased to become the key player in the IMAPPI project.”

Since the IMAPPI project has started, MR Solutions has been a reliable partner. “The company has demonstrated strong means and capabilities to achieve smoothly the Phase 3” states Mr Jean-Jacques Wawrzyniak, Directeur General of the Fondation de Cooperation Scientifique (FCS) Bourgogne Franche-comté, the coordinating IMAPPI project partner.

Fabrice Chaumard, VP Sales and Marketing at MR Solutions Ltd, adds “as one of the initiators of the IMAPPI project, I’m glad to have MR Solutions as the leading partners and to work again in close collaboration with the all the partners in Dijon. This project, binding two modalities, PET and high-field MRI generates a huge amount of interest in the research community looking at translational imaging to the clinic. MR Solutions brings its expertise from the preclinical area but also from the clinical area.”

About MR Solutions:

MR Solutions, Guildford, Surrey, UK, has over 30 years’ experience and in excess of 1000 installations across the world. Its scanners are renowned for their excellence in terms of superior soft tissue contrast and molecular imaging ability. Operating out of offices in the UK, USA and with distributors in all the major markets, maintenance and service coverage is offered across the globe. MR Solutions has its global headquarters at Ashbourne House, The Guildway, Old Portsmouth Road, Guildford, Surrey GU3 1LR.

In copertina / Front cover
Polvere di Nanofibrille di Chitina.

Foto al microscopio elettronico a scansione – Su gentile concessione del CNIS, Centro Ricerca per le Nanotecnologie applicate all'Ingegneria, Univerisità La Sapienza, Roma – Italia.

Chitin Nanofibrils powder.

Scanning Electron Microscopy (SEM) micrographs. On kind permission of CNIS, Research Center for Nanotechnology Applied to Engineering, University of Rome “La Sapienza, Roma - Italy.

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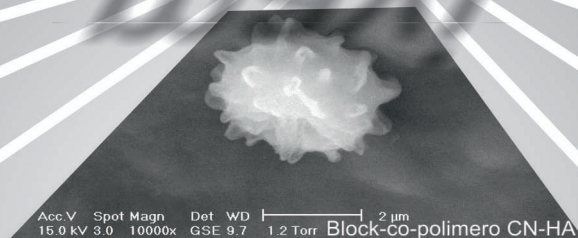


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