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# NEW BIOPLASTICS BRING CHITIN OUT OF ITS SHELL

Shrimp heads, crab carapaces, lobster shells — many billion tonnes of shellfish waste are generated globally per year. Very little of it is put to good use. This could be about to change, as EU-funded researchers have developed an innovative way to transform this briny refuse into plastic.

The shells of crustaceans and molluscs contain chitin, a natural polymer that can be transformed into tiny filaments called nanofibrils. The partners involved in the **n-Chitopack** project use these nanofibrils to develop compostable bioplastics that offer a more sustainable alternative to petroleum-derived plastics for a variety of applications. The nanofibrils are extracted using a process patented by Italian SME MAVI Sud, the lead partner.

The project has already created a number of products based on this invention. These notably include coffee capsules, shopping bags and a variety of food packaging materials, such as hard and soft containers.

## From prawns to polymers

n-Chitopack's bioplastics are not just biodegradable; they are compostable, says project coordinator Pierfrancesco Morganti of MAVI Sud, who notes that more than 150 billion tonnes of shellfish waste are produced annually around the world. "Some things that are biodegradable actually generate toxic compounds as they break down," he explains. "It's important to make sure that products degrade into compounds that are of some benefit, and not harmful to humans or to the environment."

The project's emphasis on sustainability is not just reflected in the final product. It has shaped the entire process developed by the partners, says Morganti — starting with the extraction of the nanofibrils. Care was taken to design a method that consumes little energy, allows for recycling of all the water used in the process and generates no toxic residues. "The powder that remains at the end of the process is used as fertiliser," says Morganti.

The resulting bioplastics could replace conventional plastics for a number of uses, such as coffee capsules, for example. "Millions and millions of these are thrown away every day, and they are usually not compostable," Morganti notes. "This has created a problem we didn't have before."

The n-Chitopack partners decided to rise to the challenge and made the development of greener coffee capsules one of its priorities. The team is currently exploring options to produce their flexible, robust bio-capsules on an industrial scale.

## It's a wrap

The materials developed by n-Chitopack are based on chitin nanofibrils, but they also contain a certain amount of chitosan, another substance derived from chitin. The project has, for instance, blended the two to produce food packaging film.

This food wrap benefits from a particularly useful property that chitosan adds to the mix: it stops the growth of germs. Tests that focused on packaging fish confirmed this effect, Morganti reports. "There were no bacteria on the film that was in contact with the food," he notes.

## The full package

n-Chitopack's bioplastics could thus help to address several problems simultaneously: they could help to reduce the vast amounts of chitin waste going to landfill, they could transform part of the world's avalanche of discarded packaging into a slow-release supply of nutrients, and they could further protect resources by slowing down the spoilage of perishable foods.

Food packaging is, however, just one of several possible applications. Chitin nanofibrils also show promise for use in medicine, says Morganti, more specifically for the production of bandages, where the materials' ability to keep microbes in check are particularly valuable. They also have potential for a range of environmental solutions, including filtering systems for air or water.

There are still a few technical issues to address before commercial roll-out can begin, says Morganti. However, he expects the large-scale manufacture.

**Below coffee capsules made from chitin nanofibrils and polylactic acid**



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*Source: https://ec.europa.eu/programmes/horizon2020/en/news/new-bioplastics-bring-chitin-out-its-shell*
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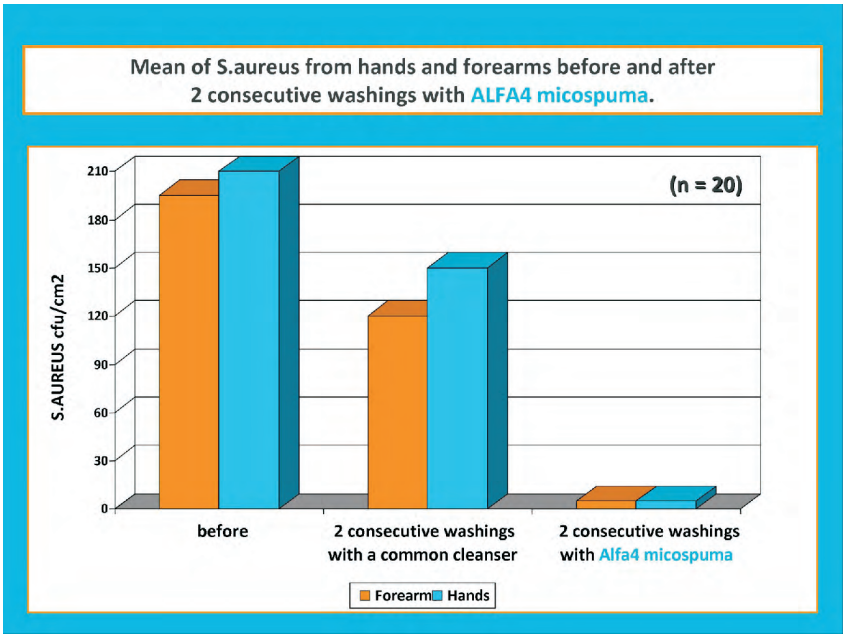


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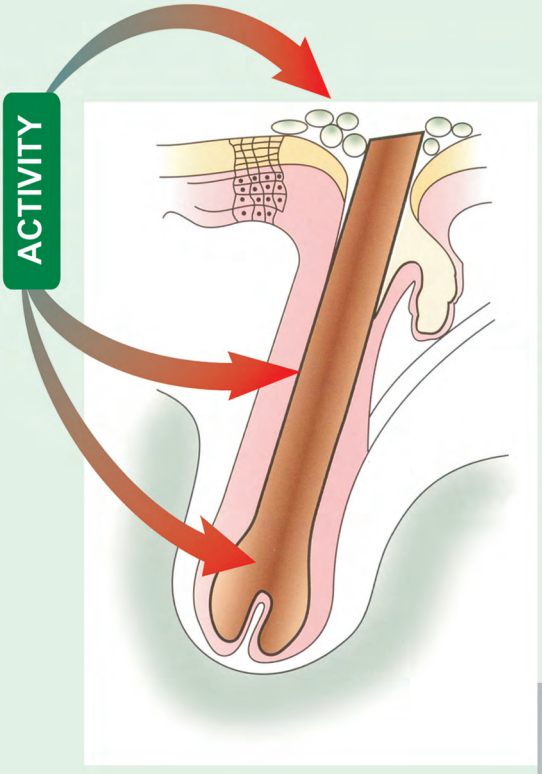


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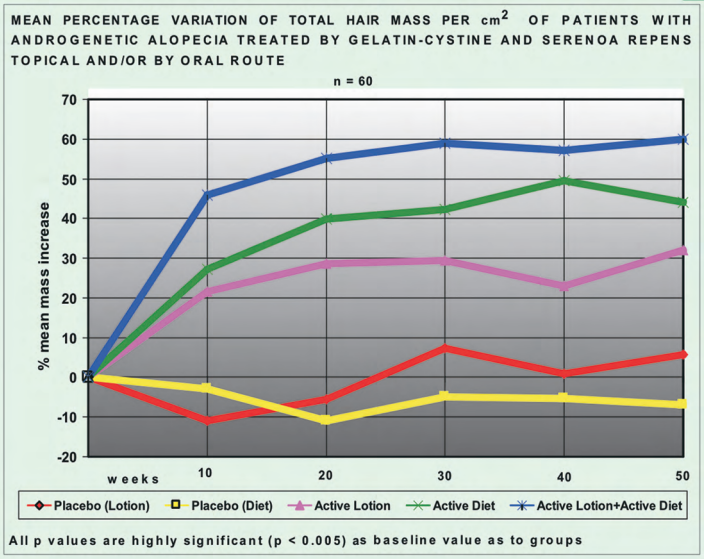


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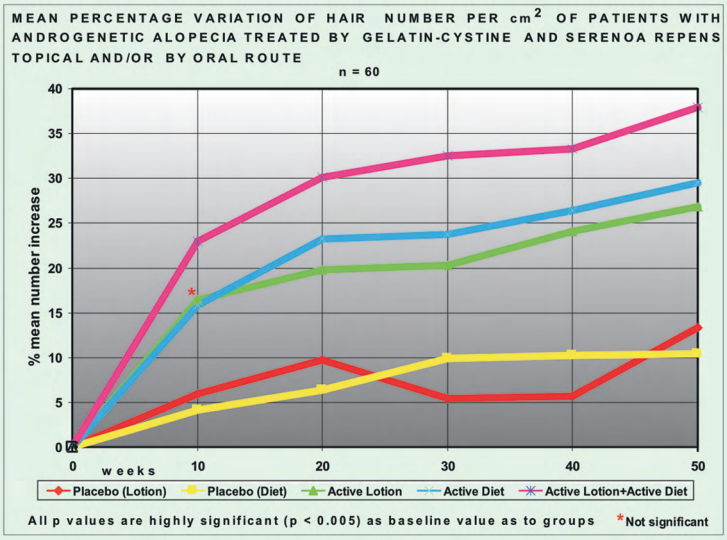


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2) Strehler BL (1977) Time, cells and aging 2nd edn. Academic Press, New York
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**We Wish to dedicate this issue of the Journal of Applied Cosmetology to the memory of a well known dermatologist, Professor Wolfgang Raab.**

*Another friend of mine and fellow of the International Society of Cosmetic Dermatology is no more among us.*

*I personally collaborated with him on several scientific occasions and in particular in organizing the unforgettable ISCD Congress Progress in Cosmetic Dermatology in 1998, in Vienna.*

*Wolfang wrote many books and hundreds of scientific papers on the problems affecting skin and hair.*

*As an expert in Cosmetic Dermatology, he wrote also for our Journal appreciated papers on the light border separating Cosmetology from Dermatology*

*I remember his clever talks on the doubts the Dermatology community had about the cosmetic efficacy, because considering cosmetics not as drug adjuvants but as holist products only.*

*Fortunately today, the medical mentality changed thanks also to Wolfang's scientific battles. Hence cosmetic products today are considered essential in combination with drugs for a better resolution of some diseases. An example, is the use of urea for skin xerosis which plays and important activity in many cosmetic formulations. On urea effectiveness Wolfang wrote many papers presented in International Meetings.*

*His death is a great misfortune not only for is family but also for all the international scientific and medical community, and our association.*

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# Trimestrale di Dermatologia Cosmetologica
# Quarterly Review of Cosmetic Dermatology

## Contents

# 'Bacterial Growth Inhibition' – A novel treatment strategy for Acne

**Janani S., Gayathri Rajagopal**
Dr. JRK's Siddha Research and Pharmaceuticals Pvt., Ltd, Chennai, India

***Received:*** *January, 2015*

***Key words:*** *Anti-acne pack; Bacterial growth; Skin adhesion; Water resistance capacity; Mexameter;*

## Summary

The present study reports a novel treatment strategy for the treatment of acne. The strategy is the effective use of topical agents to inhibit the bacterial growth. This was achieved through increased skin residency and water resistance capacity. The study provides scientific evidence for the above claim.

## Riassunto

Il presente studio riporta i risultati di una nuova strategia utilizzata nel trattamento dell'acne. Il trattamento si basa sulla verifica dell'attività svolta da agenti topici nell'inibire la crescita batterica, sul controllo, sul tempo di permanenza sulla cute e sulla resistenza al risciacquo con acqua.
Lo studio riporta alcune evidenze scientifiche a supporto.

# INTRODUCTION

*Propionibacterium acnes* is considered the principal cause of pimples (acnes) (1). Therefore, the most anti-acne preparations targeted towards *P. acnes* have a high bactericidal activity.

Among them, clindamycin is the widely used anti-acne agent (2). Even though Clindamycin has high anti-microbial activity, its residency on skin alone can ensure the treatment success. Therefore, beyond the spectrum of high anti-microbial activity, high residency of the agent(s) on the skin alone could prevent the bacterial growth.

We have evolved the inhibition of bacterial growth as a new strategy in the treatment of acne.

The present study reports the effect of an anti-acne pack* as an agent in inhibiting the bacterial growth of *P. acnes in vitro*. The above finding was shown by studying the water resistance capacity of this anti-acne pack controlled on volunteers.

The present study assumes significance in the treatment of acne in the light of the prolonged residency of anti-acne pack along with the effective inhibition of bacterial growth.

Findings are presented in this paper.

# MATERIALS & METHODS

The standard culture of *Propionibacterium acnes* (MTCC 1951) was procured from MTCC, Chandigarh. The culture was revived as per the standard procedures and was sub cultured onto Propionibacter isolation agar (Hi-media, India) with supplement. 48 hours grown culture was used for preparing inoculum.

## Description of the test material

The anti-acne pack tested for the study is a cosmetic formulation of Dr. JRK's Siddha Research & Pharmaceuticals, Pvt. Ltd. containing Bentonite, Zinc oxide, Calamine, Titanium dioxide, Salicylic acid, *Aloe vera, Ocimum sanctum*.

## Preparation of sample

The sample was weighed accurately and dissolved in normal saline to achieve the following concentrations viz. 100, 500 & 1000 mg/ml respectively.

## Determination of contact time versus death of Propionibacterium acnes[3]

The 48 hours grown *P. acnes* culture in normal saline was adjusted to an absorbance of 0.6 at 450 nm.

One hundred (100) microlitre of the standardized inoculum was inoculated into the sample suspension (100 mg/ml, 500 mg/ml & 1000 mg/ml) in triplicate and was incubated for 10 minutes.

After 10 minutes, 0.1 ml of sample was drawn from each tube and was plated onto Propionibacter isolation agar and incubated anaerobically for 48 hrs. Untreated inoculum was maintained as control.

## Determination on inhibition of bacterial growth

The concentrations such as 100 mg, 300 mg, 500 mg, 800 mg & 1000 mg of anti-acne pack were weighed separately in petri dishes and then dissolved in 1 ml of normal saline. Then, 15 ml of the media at molten stage was added to each plate, mixed well to ensure uniform dispersion of the sample with the media. The plates were then allowed to solidify.

* *Trade name: Verdura anti-acne pack by Dr. JRK's Siddha Research and Pharmaceuticals Pvt., Ltd., Chennai.*

After solidification, 0.1 ml of the standardized inoculum of *P. acnes* was inoculated onto the plate and incubated for 48 hours in an anaerobic environment. Triplicate sets were maintained. Alongside, control plates inoculated with 0.1 ml of the inoculum was also maintained.

### *Water resistance as established by skin adhesion post wash – Mexameter-based study*[4]

To establish the effective adhesion and *water resistance capacity* of anti-acne pack, a study was conducted by evaluating the erythema index, post exposure to sun.

In the volar forearm region, varying concentrations of anti-acne pack was applied evenly on 2 $cm^2$ areas. After 15 minutes, the skin area was washed with distilled water. Then the $cm^2$ area of the skin was exposed to sun for 15 minutes by using window patch made by a thick black sun impermeable cloth. Similarly the control site, without application of anti-acne pack was also exposed to sun by the same method.

The erythema reading was taken using Mexameter. The erythema value of the skin on exposure to sun with and without the application of the cream was measured and compared.

## RESULT

Irrespective of the concentration, the anti-acne pack ranging from 100 to 1000 mg/ml, did not affect the survival of *P. acnes*. Further, the CFUs (Colony Forming Units) of *P. acnes* remain practically with reference to control (Table I).

**TABLE I**

*Contact time versus death.*

| S.No. | Concentration of the test material (mg/ml) | Number of colony forming units (CFUs) in average |
|---|---|---|
| 1. | Control | 4000 |
| 2. | 100 | 3920 |
| 3. | 500 | 3860 |
| 4. | 1000 | 3779 |

When the organism was allowed to grow in media plate containing varying concentrations of anti-acne pack and incubated for 48 hours, there was a small decline in the CFUs of *P. acnes* from the concentration of 100 mg/ml to 1000 mg/ml and the number of CFUs was 3300 for 100 mg/ml and 250 CFUs for 1000 mg/ml. Whereas, the CFUs of the control was 4000 (Table II).

When the control plates were incubated for a further period of 72 hours to 5 days, the growth of *P. acnes* turns to TNTC (bacteria too numerous to count).

On the contrary, the CFUs of *P. acnes* in 100 mg i.e. (the least concentration of the sample) showed only a marginal increase in the CFUs. The trend was almost the same in other concentrations as well up to a maximum period of 5 days (Table II).

After sun exposure to sun for 15 minutes, significant increase in erythema formation was observed in control skin region (Table III).

The cumulative % difference in erythema value found decreased with increased dose of anti-acne pack from 5 mg/cm$^2$ to 15 mg/cm$^2$. The effect of anti-acne pack post wash in reducing erythema formation suggests the water resistance capacity of the anti-acne pack (Table III).

The cumulative erythema index in control was -6.6 as against 3.7, 4.1 & 4.9 respectively for 5, 10 & 15 mg/cm$^2$ of anti-acne pack (Table III).

**TABLE II**

*Effect on bacterial growth inhibition.*

| S.No. | Concentration of the test material (mg/ml) | Number of colony forming units (CFUs) in average | | | |
|---|---|---|---|---|---|
| | | 24 hours | 48 hours | 72 hours | 5 days |
| 1. | Control | 4000 | 7300 | TNTC | TNTC |
| 2. | 100 | 3300 | 4200 | 4560 | 5020 |
| 3. | 300 | 2540 | 2230 | 1890 | 1640 |
| 4. | 500 | 1754 | 1520 | 1289 | 946 |
| 5. | 800 | 645 | 530 | 478 | 382 |
| 6. | 1000 | 250 | 218 | 194 | 156 |

**TABLE III**

*Reading of erythema value post exposure to sun by Mexameter.*

| Volunteer | Control | | | 5 mg | | | 10 mg | | | 15 mg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | % diff | Before | After | % diff | Before | After | % diff | Before | After | % diff |
| 1. | 492 | 510 | -4 | 430 | 410 | 5 | 455 | 435 | 5 | 440 | 420 | 5 |
| 2. | 399 | 432 | -8 | 310 | 305 | 2 | 399 | 381 | 5 | 350 | 322 | 8 |
| 3. | 375 | 399 | -6 | 370 | 366 | 1 | 385 | 375 | 3 | 355 | 330 | 7 |
| 4. | 452 | 468 | -4 | 488 | 460 | 6 | 475 | 425 | 12 | 456 | 424 | 7 |
| 5. | 463 | 475 | -3 | 394 | 390 | 1 | 415 | 402 | 3 | 390 | 378 | 3 |
| 6. | 489 | 508 | -4 | 488 | 465 | 5 | 456 | 440 | 4 | 490 | 473 | 3 |
| 7. | 466 | 480 | -3 | 470 | 434 | 8 | 449 | 445 | 1 | 460 | 440 | 4 |
| 8. | 309 | 325 | -5 | 472 | 445 | 6 | 389 | 375 | 4 | 412 | 400 | 3 |
| 9. | 390 | 412 | -6 | 415 | 410 | 1 | 411 | 400 | 3 | 432 | 418 | 3 |
| 10. | 425 | 470 | -11 | 469 | 459 | 2 | 447 | 440 | 2 | 470 | 455 | 3 |
| 11. | 445 | 480 | -8 | 475 | 469 | 1 | 447 | 460 | 4 | 517 | 490 | 5 |
| 12. | 395 | 464 | -17 | 457 | 440 | 4 | 429 | 406 | 5 | 455 | 410 | 10 |
| 13. | 459 | 485 | -6 | 424 | 395 | 7 | 442 | 408 | 8 | 430 | 400 | 7 |
| 14. | 418 | 450 | -8 | 459 | 445 | 3 | 460 | 450 | 2 | 475 | 455 | 4 |
| 15. | 491 | 525 | -7 | 501 | 479 | 4 | 470 | 455 | 3 | 492 | 489 | 1 |
| **Sum** | 6468 | 6883 | -98.3 | 6622 | 6372 | 54.8 | 6559 | 6297 | 61.6 | 6624 | 6304 | 73.75 |
| **Average** | 431.2 | 458.9 | **-6.6** | 441.5 | 424.8 | **3.7** | 437.3 | 419.8 | **4.1** | 441.6 | 420.3 | **4.9** |

## DISCUSSION

The present study has brought a new strategy for the treatment of acne.

The acne treatment is always approached from the angle of killing the causative agent (5). Even the effective microbicidal agents are proven to be less effective in treating acne, this phenomenon could not be due to a lack of efficacy of such agents, but may be due to their poor residency over the skin. Further, any preparations, when applied over the face, would likely to occlude the sweat glands activity. Hence, such occlusion may accelerate profuse sweating (6). Due to the consequent profuse sweating, the possibility of anti-acne agents to be washed off is quite high (7). Therefore, if the residency of the anti-acne preparations is increased along with the water resistance capacity, such products may offer an effective answer to acne problems.

If the residency of the products could be increased, even with topical agents of *P. acnes* also, we can achieve greater treatment success.

Our present study clearly shows that the anti-acne pack is quite effective in preventing the bacterial growth. However the above product did not show great microbicidal activity at short contact period.

The reason we wish to attribute to the obtained effect of anti-acne pack in inhibiting the bacte-

rial growth, is its high residency over skin combined with its good water resistance.

The water resistance capacity of the anti-acne pack was established by using a very sensitive instrument called Mexameter useful to measure the skin erythema value. 15 minutes of contact time with the anti-acne pack was sufficient to have a greater residency over the skin.

After 15 minutes when the cream was washed and the skin was exposed to sun activity, the recovered erythema was extremely low in skin regions treated with higher concentration of anti-acne pack. This suggests that the cream not only has a greater affinity and residency over the skin structure but also it is resistant to water washing.

This study based on volunteers reaffirms our laboratory finding about the effect of our anti-acne pack in inhibiting the bacterial growth. Although, the anti-acne pack could not affect the life of bacteria, certainly it seems to inhibit their growth. Once the microbial growth is inhibited, the acne eruptions can be significantly reduced.

The above finding clearly establishes a new strategy for the treatment of acne even with static preparations.

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# Topical treatment of psoriasis with an ointment containing liver oil from ratfish (Chimaera Monstrosa). A Pilot study.

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***Key words:*** *Plaque psoriasis; Ratfish liver oil; Microencapsulation; Clinical study;*

## Summary

Long-term treatment of psoriasis can be a challenge, mainly due to the tolerability problems with the potent corticoids used. Atrophy is a frequent problem in this respect. Intermittent treatment with other topical substances following the active drug period is therefore often used. The liver oil from ratfish (Chimaera Monstrosa) contains alkoxyglycerol and squalene. These substances have been reported to have excellent emollient effects on the skin and alkoxyglycerol seems to have immunostimulant properties.

On this background, it was decided to carry out a clinical study with an ointment containing 10 % ratfish liver oil in patients with psoriasis of the plaque type.

In an open clinical pilot study for 4 weeks, we obtained impressive results in the treatment of psoriasis of the plaque type.

A group of 30 patients participated in the study using an ointment containing 10% microencapsulated liver oil from ratfish (Chimaera Monstrosa). The liver oil consists mainly of squalene and alkoxyglycerol and was microencapsulated in β-cyclodextrin in order to mask the sticky odor of the oil. The patients had suffered from psoriasis in average for 8.8 (SD 1.0) years and all of them had tried most of the available therapies for the treatment of psoriasis. Of the 30 patients participating in the 4-week study, seven patients had minor psoriasis, of 16 patients had moderate psoriasis and seven patients had severe psoriasis of plaque type.

The result indicated that the ratfish liver oil ointment might be an important and promising tool in the intermittent treatment of psoriasis. More clinical documentation in form of randomized controlled studies is needed before a final answer can be given.

## Riassunto

I trattamenti a lungo termine per la psoriasi rappresentano una vera sfida terapeutica soprattutto a causa dei problemi di tollerabilità legati all'uso prolungato di corticosteroidi molto attivi.
Gli effetti collaterali che si presentano più di frequente sono rappresentati, ad esempio, dall'atrofia cutanea. Si cerca di superare questo problema mediante l'uso alternativo di altri prodotti topici che seguono l'applicazione dei farmaci. L'olio del fegato di aringhe (Chimaera Monstrosa) contiene squalene e alcossigliceroli, ingredienti che hanno dimostrato di possedere rispettivamente interessanti attività emollienti e immunostimolanti.
Partendo da questi presupposti, è stato deciso di condurre uno studio clinico aperto della durata di 4 settimane su 30 pazienti affetti da psoriasi a placche, trattandoli con un unguento contenente il 10% di questo olio.
I risultati raggiunti sono stati molto interessanti. L'olio è stato incapsulato in ciclo-destrine per mascherarne l'odore poco gradevole. I pazienti trattati, che soffrivano di psoriasi mediamente da 8.8 anni (SD 1.0), erano stati sottoposti a diversi trattamenti terapeutici. Dei 30 pazienti sottoposti allo studio per 4 settimane, 7 erano affetti da fenomeni psoriasici minori,16 da una moderata psoriasi ed altri 7 presentavano psoriasi a placche.
I risultati ottenuti dimostrano come l'olio di aringa possa rappresentare un promettente trattamento di ausilio per le persone affette da psoriasi. Naturalmente sono necessari ulteriori studi clinici in forma randomizzata per poter dare una risposta finale.

## INTRODUCTION

Patients with different skin diseases are often seeking alternative treatment either as monotherapy or in combination with drugs. Even if substantial developments have been performed in the treatment of immune-related skin diseases like psoriasis and atopic dermatitis during later years, it is still many patients that have unsatisfactory treatment results.

Essential fatty acids, omega 3 as well as the omega 6 series, have in well-controlled clinical studies (RCT) been shown to have some effects on psoriasis and atopic dermatitis after oral intake (1).

Chimaera Monstrosa (ratfish) is a deep-sea fish, living, among other places along the Norwegian coastline. For centuries, fishermen from Norway have used oil from Chimaera Monstrosa to treat wounds, to aid in respiratory problems, to ward off colds and flu and for overall well-being. Chimaera Monstrosa is a by-catch of a number of deep water fisheries. The liver comprises 15-20% of the fish's total weight and contains a considerable amount of oil, predominantly in the form of squalene and alkoxyglycerols.

The shark is a member of a subclass of fish that includes ratfish. Several reports have indicated an extremely low incidence of cancer in sharks due to n-3-polyunsaturated fatty acids (PUFA) and other shark liver oil (SLO) components that may exert anti-carcinogenic effects (2).

Squalene is a long chain unsaturated hydrocarbon (C30H50) and has antioxidant and bactericidal properties. It has its benefits as a health food as well as external use in cosmetics. Squalene has an excellent emollient effect when applied as a component of a topical cream. Human sebum contains 10% squalene, and in addition to its skin, enhancing effect is thought to have fungicidal properties and provide protection against sunburn.

Alkoxyglycerols have been extensively studied since the 1950's (3). Deep-sea shark liver oil contains 10-30% alkoxyglycerols.

Alkoxyglycerols are important components of human breast milk (0.1%), helping to build up disease resistance in babies. They are found in bone marrow (0.2% of the lipids) and the spleen, and are involved in white blood cell formation that is so important in immune function. Alkoxyglycerols are also present in cow milk at 0.01%. Research undertaken by Swedish researchers Hallgren et al identified that alkoxyglycerols activate and enhance the body's immune system and diminish harmful side effects from radiation therapies Research has also shown that they stimulate the brain, benefit brain development in young people and act as an anti-depressant (4-6).

Shark liver oil (SLO) has a characteristic and unpleasant smell and this could be a hindrance for people using the ointment. In order to reduce the odor it was decided to microencapsulate the SLO by using β-cyclodextrin. This is a well documented method for reducing odor, prevent oxidation, and improve skin penetration (7-9).

Based on the composition of shark liver oil (SLO) containing squalene and alkoxyglycerols, we felt that it could be of interest to test the SLO on skin ailments requiring an emollient as well as an immune stimulating effect.

We decided therefore to carry out a pilot study in order to have some preliminary data on the effect of an ointment containing SLO on psoriasis vulgaris. By searching the literature, we could only find one publication documenting the effect of SLO on a skin indication (10).

## PSORIASIS IN THE POPULATION

Psoriasis affects as many as 7.5 million Americans or 2.2% of the population. It is the most prevalent autoimmune disease in the US and worldwide, 125 million people worldwide,

2-3 percent of the total population suffer from the disease according to the World Psoriasis Day Consortium. Studies have shown that between 10 and 30% of people with psoriasis also develop psoriasis arthritis, and nearly 40% with psoriasis arthritis reported their disease to be a large problem in everyday life (11). Also patients with moderate to severe psoriasis experienced negative impact on their quality of life (12).

Especially in women and younger patients psoriasis has greater impact negatively on their quality of life. The disease often has its onset between the ages of 15 and 25, However, it has been seen developing also in earlier life stages (13).

In our study a group of 30 patients with minor psoriasis (7), moderate psoriasis (16) and severe psoriasis (7) participated in the study. Mild psoriasis is defined by the National Psoriasis Foundation as effecting less than 3 percent of the body, while 3% to 10% is considered moderate. More than 10% is considered severe. Your hand is considered one percent of the skin surface, but the severity is also measured by how much the disease affects the daily life. Nearly one-quarter of people with psoriasis have moderate to severe psoriasis.

Annually, the total direct or indirect health care costs of psoriasis are in the US calculated up to $ 26.000 per person or $ 135 billion annually. Direct costs, which include the cost of treatment and doctor's visits, can amount to $ 8000 a year per person (14).

Study has shown that approximately 60% of psoriasis patients missed an average of 26 days of work a year due to their disease (15).

About one out of three people with psoriasis report having a relative with psoriasis. If one parent has psoriasis, a child has about a 10% chance of having psoriasis. If both parents have psoriasis, a child has approximately a 50% chance of developing the disease.

## METHODS

Thirty patients (20 women and 10 men) with a psoriasis of plaque type and with an average age of 46.2 years (18 to 74 years of age), an average height of 171.0 cm and with an average weight of 72.4 kg volunteered to participate in an open 4 week study. All of them had signed the written consent form before the study started. None of the participants reported any allergy to fish or nuts or certain alpha linolenic acid or omega-3-fatty acids products.

The thirty subjects had suffered from psoriasis of plaque type in average for 8.8 (SD 1.0) years and their psoriasis was diagnosed by dermatologist. All of them had tried most of the available therapies for the treatment of psoriasis. All of them were given an ointment containing liver oil from ratfish (Chimaera Monstrosa). The liver oil consisted mainly of squalene and alkoxyglycerol and was microencapsulated in β-cyclodextrin in order to mask the sticky odor of the oil. The oil used, here Dermar$^{R}$ 2112, was separated from the liver by mechanical separation, and oil is not exposed to heat nor to chemical treatment. After separation the oil has gone through a filtration process.

Of the 30 patients who participated in the open study lasting for four weeks, seven patients had minor psoriasis, 16 patients had moderate psoriasis and seven patients had severe psoriasis.

Mild psoriasis is defined by the National Psoriasis Foundation as effecting less than 3% of the body, while 3% to 10% is considered moderate. More than 10% is considered severe. The human hand is considered one percent of the skin surface, but the severity is also measured by how much the disease affects the daily life.

## RESULTS

After the end of the 4-week study, the patients and the doctor performed an independent evaluation of the effect of the treatment according to a 4 points scale (0=no effect,1=mild effect, 2 =good effect, 3= very good effect). The results are shown in Table I. According to the table there was almost complete agreement in the evaluation of the effect of the treatment by the doctor and the patients. The doctor evaluated the effect to very good in 87% of the study participants, while the patients' own evaluation showed very good effect in 93% of the subjects. Twentyseven patients (90% of study participants) wanted to continue with Dermar[R] 2112, 3 participants wanted to discontinue ( 2 due to lack of effect and 1 due to the smell of the ointment). Should read Twentyfour patients rated the cosmetic properties of the ointments as very good, four patients rated the ointment as good and only two patients rated is as unsatisfactory due to the smell. Thirteen patients meant the smell was disturbing, 17 meant it was satisfactory. None reported any side effects (only the strong smell) during the study period.

## DISCUSSION

The results of this open 4 week study on psoriasis plaque treated with ointment containing oil from ratfish are encouraging. We do not know at this point, which of the ingredients in the oil gave such good therapeutic effects. Earlier studies have shown good effect of topical administration of shark liver oil on wounds (16) but later controlled clinical studies have not been able to confirm these However, a certain effect of cod liver oil on wound healing has been reported (18). Marine oils are rich in essential fatty acids and contain a great amount of alkoxyglycerols and A, D and E vitamins. Oil from ratfish has a higher content of alkoxyglycerols than shark liver oil. However, it is unlikely that alkoxyglycerol alone is responsible for the good effect in patients with psoriasis. Moreover, it is possible that the ratfish oil contains trace element that are not easy traceable.

Ratfish is found in abundance along the Norwegian Coast Line. Several research projects are performed in Norway today in order to investigate the possible commercial utilization of ratfish (Personal communication Moere Research Norway).

Over the years, alkoxyglycerols have been regarded as having anti-inflammatory and antibacterial effects, being able to protect skin against radioactive radiation, wound healing and inhibiting growth of cancer tumors.

Medical research indicate that shark liver oil can be beneficial to certain health conditions the ointment can be an important tool in the intermittent treatment of psoriasis (19, 20). However, there is a need for more studies to further understand the pharmacological effect of the components in the SLO.

**TABLE I**

*The doctor and the patients evaluation of effect of treatment on the psoriasis plaque after 4 weeks of treatment.*

| | | |
|---|---|---|
| Total of patients | 30 | 30 |
| Effect of treatment | Doctor evaluation | Patient evaluation |
| No effect | 2 | 2 |
| Mild effect | 2 | 0 |
| Good effect | 9 | 9 |
| Very good effect | 17 | 19 |

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# From the circular economy to a green economy. Note 1. Chitin Nanofibrils as natural by-products to manage the human and environment ecosystems

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## Summary

The transition to a high level of human development has created a negative ecological footprint, putting a disproportionate burden on the environment. Thus the necessity for increasing the resource efficiency, minimizing both harmful greenhouse gas emissions and waste material, to transform the actual circular economy to a green economy with waste near to zero. The transition to a green economy could reduce the risks of global climate changes and ameliorate the energy security, because of its capacity to use in a better way both natural resources and waste materials. The annual cost in natural capital degradation, in fact, is estimated at US$ 7.3 trillion, almost six time the cost of greening the economy, while ~2 billion tons of wasted food is produced on the planet together with 50 million tons of electrical waste. Therefore, the necessity to change our way of living is a must of our society.

Among the use of industrial by-products, a major use of raw materials, as chitin nanofibrils obtained from crustaceans waste, will certainly contribute to accelerate the passage from a circular economy to a green economy, safeguarding the planet biodiversity also.

Data and examples of this use will be reported.

## Riassunto

Il rapido progresso tecnologico accompagnato da uno sviluppo economico troppo repentino, ha favorito una evidente degradazione dell'ambiente che ci circonda, causa primaria dei continui disastri naturali ai quali assistiamo da diversi anni. Di qui la necessità di incrementare l'uso più efficiente delle risorse disponibili, riducendo l'emissione dei gas serra ed utilizzando materiali di rifiuto al fine di trasformare l'attuale economia circolare in una vera e propria economia verde.
Il passaggio ad una economia verde potrebbe ridurre, infatti, i rischi legati al cambiamento climatico e migliorare l'utilizzazione delle fonti energetiche.
Il costo globale annuo della degradazione ambientale è stimato essere pari a circa 7,3 trilioni, sei volte il costo necessario per una politica verde, mentre si continuano a produrre 2 miliardi di tonnellate di rifiuti alimentari e circa 50 milioni di tonnellate di rifiuti elettrici/elettronici.
Cambiare il nostro modo di vivere è diventato un dovere della nostra società!
L'uso delle nanofibrille di chitina ricavate dagli scarti di lavorazione dei crostacei, insieme all'uso di altri prodotti di rifiuto, faciliterà il passaggio da una economia circolare ad una economia verde salvaguardando la biodiversità del nostro pianeta.
In questo articolo verranno riportati alcuni esempi concreti di tale utilizzazione.

# INTRODUCTION

The transition to high level of human development has created a negative ecological footprint, putting a disproportionate burden on the environment (Fig. 1) (1).

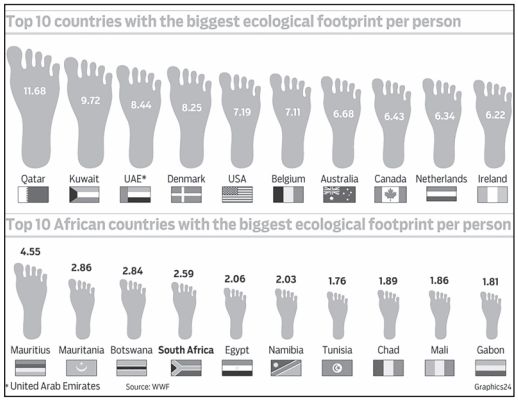


***Fig. 1*** *Ecological footprint.*

As a result, some countries live well while others live within the limit of the planet eco-sustainability (Fig. 2). Thus the necessity for increasing the resource efficiency, minimizing both harmful greenhouse gas emissions (GHGs) and waste materials to obtain the ecosystem resilience, maintaining also environment biodiversity and human well-being (Fig. 3).

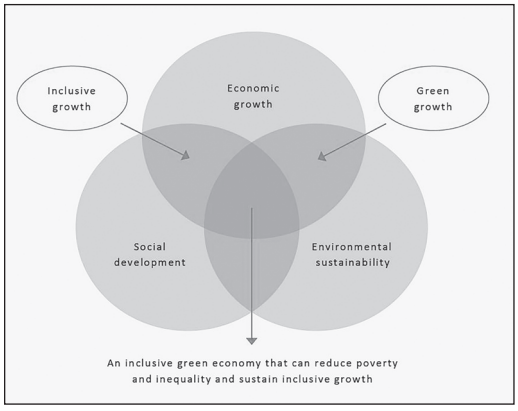


***Fig. 2*** *Correlation between ecological footprint (2008) and the human development index (2012).*

***Fig. 3*** *Minimizing the greenhouse gas emissions for a better environment.*

So doing it will be possible to promote a *renaissance* of the European industry for managing an eco sustainable production integrated with a correct use and consumption of raw materials and goods. In any way, it would be possible to transform the actual *circular economy* to a *green economy*, with waste near to zero (Fig. 4) (2). To achieve this result, it will be necessary a better management of water, energy, natural raw materials, and land biodiversity, integrating environment, sociality and politics into the main economic sectors for a sustainable development (Fig. 5).

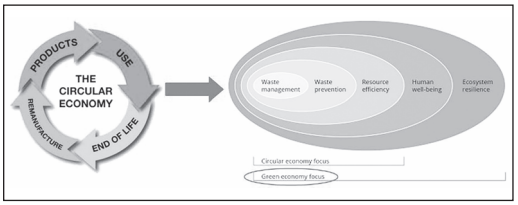


***Fig. 4*** *From a circular economy to a green economy. Source: SOER 2015.*

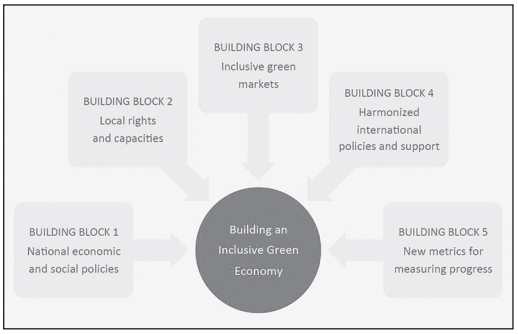


***Fig. 5*** *The sustainable development.*

This is why the optimization of natural resources together with a drastic reduction of waste conti-

nues to be a must of our Society towards a sustainable low-carbon world (3, 4). Stale air, noise, and pollution (Fig. 6), in fact, continue to cause serious health impacts, so that in 2011 about 430.000 premature deaths have been attributed to fine particulate matter (5-7).

***Fig. 6*** *Noise pollution.*

Each year in EU, the exposure to environmental noise and O3 contributed to at least 10,000 deaths, for hearth diseases and strokes (8). However, the transition to a *green economy* requires not only more fundamental changes in the global production, but also a new strategy in the consuming systems, mobility, energy and food. The EU food waste, in fact, has been estimated at some 89 million tons, corresponding to 180 Kg per person per year. Thus, ~2 billion tons of all food produced on the planet - i.e. 30-50%- is lost before reaching the human stomach. Additionally, every year the global population bins around 50 million tons of electrical waste. But a sustainable consumption means not only to reduce consumption/waste, but also to consumption and waste better! It is estimated for example that, restoring worldwide the 2 billion hectares of degraded agricultural land, could boost food production by up 79% - or feed up to 2.25 billion people. It is to remember, in fact, that currently 60% of the Earth's ecosystems are degraded, augmenting the impact of natural disasters and lowering the productivity of land and marine ecosystems (Fig. 7) (9). By these reasons, the loss of Ecosystem service is projected to result in a 25% reduction in the world's food production by 2050 (10).

***Fig. 7*** *Sea degradation.*

## *The four pillars of the EU economy*

For all these reasons, the European Community has been based its economy on 4key pillars (11): *implementation, integration, information* and *investments*, strengthening science and polity-society to interface citizen engagement, in long-term perspectives as important elements of transition processes (Fig. 8).

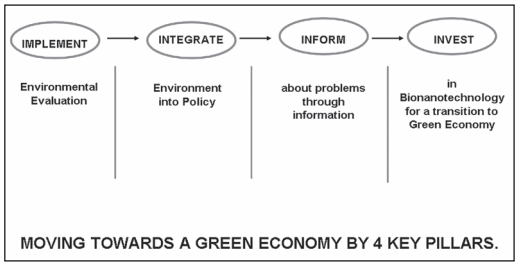


***Fig. 8*** *The key pillars of EU economy.*

(a) The *implementation* of environmental regulations plays an important role not only in protecting ecosystems, but also contributing to enhance the resource-efficiency by incentivizing Companies to invest in eco-innovation. Human health and well-being, in fact,

are intimately linked with the quality of the environment because its good quality can provide multiple benefits to physical, mental, and social wellbeing. Unfortunately, despite the last substantial improvements, environment and health challenges remain considerable.

(b) The *integration* of environment into policies induces companies to optimizing water; energy and land consume to obtain fiscal-economical facilities. Unfortunately, "the growth of marine activities such as transport offshore, renewable energy generation, tourism, and extraction of living and non-living resources is taking place without the full understanding of the complex interactions between natural and human-induced changes on water pollution, as well as on the aspects of marine biodiversity and ecosystems" (12, 13). Furthermore, the unequal distribution of environmental sources contributes to pervasive health and social inequalities (14, 15). From these considerations, the necessity to better analyzes the actual relations existing between the environment and health with production and consumption systems (8, 16). Thus, while it will be necessary to ensure coherence between the so called green growth and the policy objectives of halting the loss of biodiversity, it will be useful to achieve a good environmental status by long-term ecosystem resilience. It has been shown, for example, that the qualitative, quantitative, ecological and chemical status of European water can significantly affect human health and wellbeing. Until now, there is a lack of access to good quality drinking water and to its adequate sanitization. On the contrary people are exposed to contaminated bathing and drinking water consume. Despite considerable European progress in reducing the discharged water pollutants in the last years, nutrients, pesticides, industrial chemicals, and household chemicals continue to affect quality of land and marine waters (12, 15).

(c) Better *information* and an *expanded knowledge* on the environmental problems and biodiversity may enable policymakers, businesses, and consumers to take the right decisions. This knowledge, essential to determine the allocation of private and public capital for a harmonic and economic development, must have a fundamental role for taking right regulatory measures and creating market-based instruments. Such instruments will be also important in correcting the market and policy failures that too often distort the economic incentives for improved environmental and ecosystems management. Therefore, considering that the implementation of the existing environmental policies is likely to reduce specific health burdens, the need for more systemic approaches to reduce health risks has been recognized in recent EU policies by the new amended Environmental Impact Assessment Directive (17). Promoting good health and reducing inequalities, in fact, is a central theme in EU health policy (18, 19) together with its smart and inclusive growth objectives (20).

(d) *Investments*, therefore, have a fundamental role in the transition to a Green economy, impacting the functioning of these new systems, as well as the viability of the alternative productive processes based on the bio-nanotechnologies. Naturally, they will have to be supported by innovative financing and fiscal reform. According to the last IEA BLU Map scenario, global investments of US$ 46 trillion should be necessary by 2010 to 2050, for a successful Green economy (21). At this purpose, the World Economic Forum and Bloomberg New Energy Finance calculated that clean energy investment must rice US$ 500 billion per year to restrict global war-

ming to 2 °C (22). Moreover, it has been estimated that the transition to a low Carbon economy will see the necessary investment of US$ 10 trillion from 2010 to 2020 (23).

In sum, moving towards a green economy has to become a strategic economic policy agenda for achieving the goal of a sustainable development. By these investments, the quality of human life might be improved, eradicating the poverty, stopping the global climate changes and the energy insecurity. At the same time, the food scarcity will be reduced, as well as the planet's biodiversity will be protected.

## Transition to a green economy

The transition to a green economy reduces the risks of global climate changes and ameliorates the energy security, improving the livelihood of poor people because of the existing link between ecological scarcity of water and the poverty problem. Millions of poor people in developing countries, in fact, have no access to water and to modern energy services.

Thus, EU, UNEP and OECD consider the green economy as a strategic approach for reducing the global environmental degradation, because of its capacity to modulate natural resources and the waste materials. So doing the right utilization of the unused fishery's and plant biomass, will be increased to obtain a sustainable production with an increasing workers employment and industrial competitiveness (24-26). It is to remember, for example, that each year in Europe, 27 billion of waste are produced, ~ 89 million of which originated from food, i.e. 179 kg pro capita (27). On the other hand, the aggregate impacts of housing and infrastructural account for around 15-30% of all the consumption-related environmental pressures, contributing to produce annually ~2.5 tons of CO2 pro capite (28). According to the International Labour Organization (29), the greening of economy is "a net generator of decent good-jobs, which offer adequate wages, safe working conditions, reasonable career prospects and worker rights". This economical approach, in fact, goes further the circular economy (Fig. 9), with the goal to maintain both environmental biodiversity and human well-being (30, 31). Moreover as previously reported it is a prerequisite for a sustainable and irreversible socioeconomic development and poverty eradication. Investing to improve the sustainability of agriculture, fisheries, forestry and animal husbandry will ensure a long-term human well-being, without depleting the finite resources of the planet (Fig. 10) (32). So doing "we might ensure a life to dignity for all" (33).

***Fig. 9*** *Human health and well-being, according to EU ecosystems.*

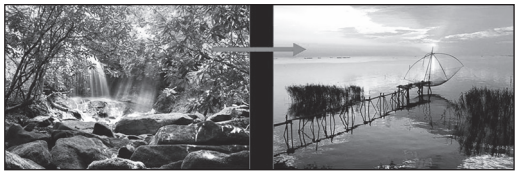

***Fig. 10*** *To improve sustainability of agriculture, fishery's, forestry, and husbandry for maintaining the planet ecosystem.*

## Resource efficiency: chitin-derived as natural raw material

As already mentioned, the annual cost in natural capital degradation is actually very high, estima-

ted at US$ 7.3 trillion/year, almost six times the cost of greening the economy. Thus, our responsibility to manage the economic and social benefits of a *green economy*, maximizing the supply of natural materials, land, and money, became increasingly compelling. Preserving the environment and producing goods with minimum wasted effect and expense, is a MUST for our society. For this reason, both UN and EU recognize that "investment in cleaner industrial processes, technologies, and cities have the power to positively transform economies and societies" (33). The recommendation is to reduce waste, support cleaner investments, and transfer to consumers and businesses the knowledge about the needs to maintain the earth' precious resources. But "economic growth and social development cannot be sustained with the current consumption and production patterns". We have to change out way of living!

Considering, for example, the waste material, one of the biggest problems is represented from plastic polymers, made prevalently of material that earth cannot digest, because they do not undergo bacterial decomposition (Fig.11). These polymers breaking down into smaller particles, not only attract toxic materials, but also swallow by wildlife in the ocean and land where form a large garbage patches, contaminating the food chain also (Fig.12). At this purpose, it is to underline that the growth rate in polymer production has been significantly fast during the 60-year period from 1960 to 2010, ranging 196 million tons from 1960 to 2005, with an average annual growth rate of 8.1% (Fig.13) (36, 37). By the last estimations, this number will probably continue to escalate to over 510 million tons in 2020, with a conservative yearly rate of 3.9% to 6.5% (38,39). In any way, in EU the plastic production has been stabilized in 2013 after the 2009 turn-down, so that the actual level are similar to those in 2012.

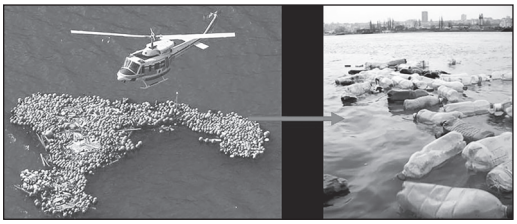

***Fig. 11*** *Plastic polymer's bottles remaining in the environment as waste.*

***Fig. 12*** *Plastic materials contaminating land and sea.*

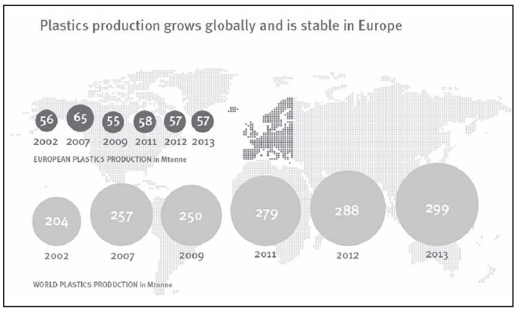


***Fig. 13*** *European plastic production in Mtons. Source: PlasticsEurope -The fact 2014-2015.*

Additional statistics show that in 2008 an average of 24.9 megatons of plastic waste was produced in EU27, corresponding to 534kg/person! Waste problem, with its negative impact on the environment, led to new interest in the area of degradable and compostable biopolymers, derived from renewable resources, such as simple sugar, complex carbohydrates and ligno-cellulosic compounds (40). As a consequence, the

development of nanoengineering biopolymeric composites has rapidly triggered a new class of materials, as an alternative to conventional material petrol-derived (41). Among waste materials, polysaccharides, such as chitin nanofibrils (CN), are to be taken into account for their capacity to develop greener nanocomposites and human-environmentally friendly goods. Particular interest in chitin increased in the last years, during which this natural polysaccharide, organized as nanocrystals and nanofibers was recognized as new source of nanopolymers characterized by interesting properties (Fig. 14) (42-44). Worldwide production of chitin, in fact, ranges about $10^{11}$ tons per annum, making it one of the most abundant natural on the earth (45).

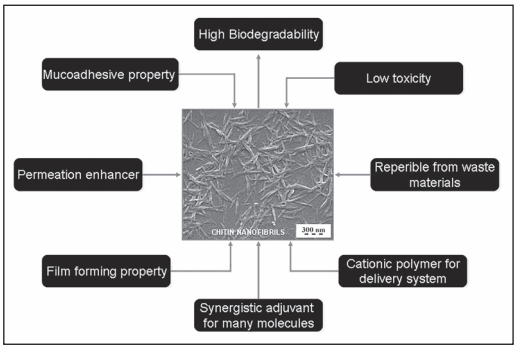


***Fig. 14*** *The interesting properties of Chitin Nanofibrils to ameliorate the mechanical properties of other polymers.*

Following multiple extractions, purification, and other industrial steps, chitin and chitin-derived compounds have been used for the production of structural and functional nanocomposites, useful to make innovative cosmetics, new food packaging and advanced medications (46). Thus, due to the matrix reinforcement effect of the CN-nanofiller, the physical properties of the obtained composites have been improved at molecular level, ameliorating their mechanical, thermal and barrier properties without affecting the polymer processing.

This result has been obtained, for example, by the use of chitosan and CN to produce thin and transparent films by the casting technology or by polylactic acid (PLA), to produce hard and flexible containers for cosmetic and food purpose. Moreover, by the use of CN, lignin and other polymers, non-woven tissues have been made to produce beauty masks and advanced medications by the electrospinning technology (47-49). Naturally, the properties of the obtained nanocomposites are dependent on the polymer selected, quality and quantity of CN-nanoparticles used, and the extent of their dispersion into the polymer matrices. Thus for example, by the use of SEM it was possible to show the ameliorated mechanical properties of the final nanocomposite, controlling the cross-sectional structure of chitosan, into which CN was embedded as filler (Fig.15) (50). On the other hand PLA-CN bio composite, characterized and compared in terms of crystal morphology, chemical structure, and water resistance, has shown a better thermal stability, mechanical property and storage modulus, compared to thermoplastic PLA without the filler CN (51, 52). These results are probably due to the good dispersion of the nano-sized CN-filler into the matrix-PLA, because of the relative strong adhesion established between them (filler-matrix) by the hydrogen bonding interactions. In any way, it has been shown that the final properties of the produced bio composites were dependent on concentration, dimension, and crystallinity of the CN used as filler and introduced into the chitosan water suspension or into the thermoplastic PLA matrix.

It is interesting to underline that the unique feature of CN, among polysaccharides, is its content in nitrogen under the form of amine site, useful for different derivative processes. As reported from Raab et al. (53) (Fig.16), the crystal chitin is organized in nature as regularly structured fibrils of nano-sized materials. Because of its natural origin CN, obtained by raw chitin in its pure crystalline structure, may find application in various areas, such as food,

cosmetics and medicine (Fig.17). Easily metabolized from the human and environment enzymes (54), this polymer is recognized as safe and non toxic material (55). It is interesting, in fact, to remember, that the human families of enzyme chitotriosidases (chitinases) degrade more quickly chitin than chitosan, having a relative weak preference versus the acetylated subsites (56). This probably the reason of the safeness and effectiveness recovered in cosmetic and medical products, based on the use of CN (57-59).

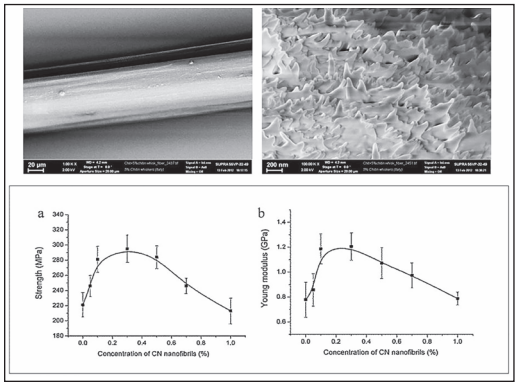


***Fig. 15*** *Mechanical properties of the composite chitosan-chitin nanofibrils. By courtesy of V.E. Yudin (2015).*

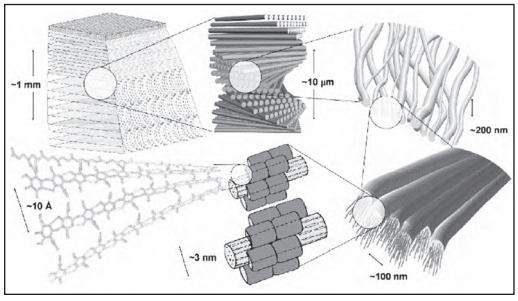


***Fig. 16*** *Chitin organization in nature. Source: D. Raabe et al (2005), J Crystal Growth, 283:1-7.*

In conclusion, considering the actual ecological and environmental pressure, there is an increasing industrial demand for natural by-products to produce low-cost and biodegradable nanocomposite polymers. Chitin nanofibrils, isolated from crustacean waste as highly crystalline and natural structure, seem to be an ideal candidate for this purpose. They, in fact, exhibit an higher cristallinity, mean dimension of 240x7x5 nm, a molecular weight of 2x106 Dalton, an acetylating degree higher than 0. 90 with a superior mechanical stiffness (at least 150 4Pa), developing a surface area up to 400 m2/g (60, 61).

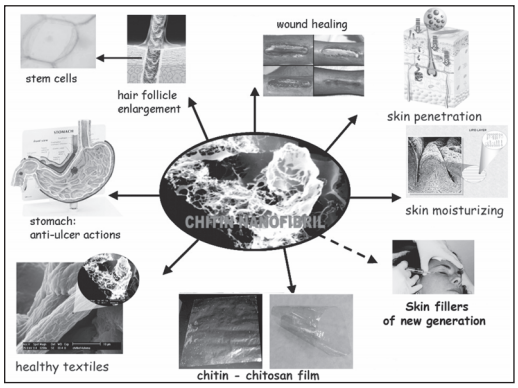


***Fig. 17*** *Different uses of chitin nanofibrils*

Additionally, CN is non-toxic, odourless, biocompatible with living tissues, biodegradable and compostable in the environment, presenting also an antibacterial and moisture retention activity. Finally, it shows interesting healing characteristics, because of the capacity to form microfibrillar arrangements in living tissues (62-65). In conclusion, a major use of natural discharged raw materials, as CN, will certainly contribute to accelerate the passage from a circular economy to a green economy, safeguarding the planet biodiversity.

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# Actinic Keratosis

**By H.P. Soyer, T.W. Prow and G.B.E. Jemec**

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Actinic keratosis is the topic of this book organized in 21 chapters. Actinic keratosis (AKs), also known as solar keratosis, are common pre-cancerous skin lesions that, occurring predominantly in the middle-aged and elderly, affect sun-exposed areas, such as face, V of chest, and backs of the arms and hands. They are of public health importance because their presence significantly raise risks of skin cancers, such as basal cell carcinoma, squamous cell carcinoma (SCC) and melanoma. AKs are usually less than one centimetre in size and appear as slightly elevated, rough surfaced lesions. The presence of hyperkeratosis may make it difficult to distinguish between an actinic keratosis and a squamous cell carcinoma or an irritated seborrheic dermatitis.

Although the natural history of AK is poorly understood, it is associated with immunosuppression so that the immune surveillance and the sun protection play a key role to prevent the skin tumour genesis. However, it is clear from studies conducted in many different populations that AKs are a public health burden in sun-sensitive people living without adequate sun protection at low latitudes. Moreover, the major risk factors are male sex, advanced age, sensitive complexion, high lifetime sun exposure, and prolonged immunosuppression. In any way, a very small proportion of AKs undergo malignant transformation, also if the precise rate of transformation is unknown due to the inaccuracies in monitoring these skin lesions over time. For example, in a study on 1.040 people with actinic keratoses who were followed over a 12-month period, it has been reported a spontaneous remission of 26% of all the lesions and only 0.24% incident of squamous cell carcinoma for each keratosis present.

What the perspectives on AK? Many factors influence patient's perspectives, depending also on the extent of patients' emotional reactions regarding the risk of getting skin cancer, the worsening of the AKs conditions, the losing control and participating in UV-related activities, and the treatment that may cause some time pain, diminishing the quality of life (QoL). For these reasons attention has to be paid to the patient's profile, personal preferences, and medical history when choosing an AK treatment. It is recommended to emphasise to patients that full compliance will result in lesion resolution and improved cosmetic appearance. In particular, women find it important to consider therapeutic options that minimise the risk of scarring and pain. However, patients with AKs have to stay out of the sun, protecting their skin from UV rays. This topic is reported on **Chapters 1** and **2.**

UV-induced genetic damage and the suppression of anti-tumour immunity are both causative for skin cancer, the initiation and progression of which is driven from actinic keratosis. UV radiations, in fact,

damage many cellular constituents, including lipids, proteins and DNA, all of which are likely to contribute to UV-induced skin cancer. Photodamage to these cell constituents, which create mutations in the genes and immunosuppression, contribute to carcinogenesis, interfering with the cellular signalling and repairing processes. Thus, while chronic sun exposure is recognized as a central etiologic factor in the development of skin cancer. UVB has been demonstrated to have the ability to trigger the initiation, promotion and progression of both non-melanoma and melanoma skin cancer. These phenomena occur in part for the alterations in epigenetic mechanisms, which silence tumour suppression genes and drive proliferation. After UV exposure, skin cells under go cell cycle arrest to allow for the repair of damaged cells. If the damage cannot be repaired, the cells undergo apoptosis. Thus, the failure of DNA repair mechanisms or of apoptotic machinery contribute to carcinogenesis. However the precise genetic changes, critical for the initiation and progression of these lesions, are incompletely understood because of its great complexity. However, the central role of the Epidermal Growth Factor has been recently recognized. In any way it is highly likely that UV driven many of these events, and, therefore, understanding the mechanisms involved will allow for the design of novel treatment options. These the themes discussed on **Chapters 3** and **4**.

The link between AK, SCC, and a fully functional immune system is until now poorly understood. However, the large proportion of AKs that regress spontaneously provides strong evident that these premalignancies can be kept in check by the immune system. It may be that SCC lesions are protected from the destructive potentials of effector T cells and other immune cells. They could be regulated by mechanisms, such as those governed by suppressive T-regs, mast cells, or invariant natural killer T cells that, under normal circumstances, protect healthy skin from damaging immune responses. At this purpose, the application of newer technologies for the examination of the local genomic and proteomic environment of SCC and its precursor AK lesions, may give clues to facilitate the development of new approaches to the therapy of this common disease. These and others the topics reported on **Chapters 5, 6** and **7**.

The clinical continuum between AK, intraepidermal carcinoma (IEC) and SCC makes extremely difficult a reliable distinction between these entities because of its variable morphology due to an atypical keratinocyte proliferation. The cytopathological changes shown in the individual cells of AK and SCC are, in fact, identical and indistinguishable from one another. However, today by specific dermoscopic patterns it seems possible to have a correct clinical diagnosis to differentiate actinic keratosis from intraepidermal carcinoma, and invasive squamous cell carcinoma, necessary to establish the treatment of choice and monitor its response. A future clinical workflow, ideally combining both clinical and imaging techniques, might benefit from low-cost and ubiquitous digital imaging systems, such as that found on smartphones, for the first line of assessment.

After regional photography, Optical Coherence Tomography (OCT) or Reflectance Confocal Microscopy (RCM) could be used to provide a robust, in-clinic diagnosis of suspicious lesions with the sane level of confident as histopathology. RCM, in fact, is a non-invasive clinical imaging modality that results in quasi-histological, en face skin images. On the other hand OCT can produce cross-sectional, non-invasive, real-time images of skin. This technology produces high-resolution images at a micrometre resolution and has a maximum 2-mm penetration depth, which places OCT in the imaging gap between ultra sound and confocal microscopy. Thus OCT, which can reliably differentiate between normal and lesioned skin is of great importance when tumour borders, prior to surgical and non-invasive treatments of keratinocyte neoplastic lesions, have to be identified.

Another convenient and accessible methodology for both patients and doctors is Teledermatology, tested for its safety, feasibility and accuracy for many dermatological conditions, including the early

detection of skin cancer. In addition Teledermatology has the potential application of monitoring topical products in regard to side effects and management, as well as of assessing the treatment efficacy, among all the dermatologists involved. All these topics are discussed and reported by interesting histological photos from **Chapters 8** to **15**.

**Chapters 16** to **21** are entirely dedicated to the therapy of AK. No surgical procedures are the first-line treatment for AK, so that many data are available on the efficacy and tolerability of conventional therapies, such as cryotherapy, photodynamic therapy, or treatment with 5-fluorouracil (5-FU), diclofenac, or imiquimod.

Cryotherapy is recommended to treat single AK lesions (lesion-direct therapy), while topical medical therapies are used to treat multiple lesions on an entire sun damaged area (field therapy), having the advantage of highlighting and treating both visible and invisible lesions. Combined or sequential use of a surgical/ablative procedure and a topical medical treatment has been proposed to improve treatment efficacy, while medication breaks between treatment cycles or lowering drug concentrations is used to increase treatment tolerability/adherence. However, 5-FU, available as 5 ,2,1,or 0.5% cream or solution combined or not with 10% salicylic acid, is an antimetabolilte that acts as a pyrimidine antagonist, interfering with the synthesis and functioning of DNA and RNA; diclofenac, available as a 3% sodium salt in 2.5% Hyaluronic acid gel is a non selective non steroidal anti-inflammatory drug with cyclooxygenase-1 and cyclooxigenase-ω inhibitory function, inhibiting the tumour cell proliferation; imiquimol, available as a 5 or 3.75% cream, is an immune-modulating imidazoquinolite compound, acting as a toll-like receptor agonist that targets cytokine-producing cells; ingenol mebutate, diterpene ester extracted from *Euforbia peplus,* seems to damage the tumour vasculature, activating the protein kinase C pathway. Its mechanism of action primarily involves the induction of primary necrosis and initiation of an inflammatory response, characterized by the migration of neutrophils to the treated area. Finally nicotinamide, that may be used to prevent malignant and premalignant skin lesions, seems able to reduce the formation of AKs and accelerate their regression, enhancing DNA repair and reducing UV immunosuppression. It is interesting to underline that treatment of an entire area rather than individual lesions allows for the elimination of both clinical and preclinical lesions within an area of skin exposed to a carcinogenesis and in which cancer potentially may develop over longer period of time. At this purpose, nicotinamide, able to modulate the activity of various cytokines and the genes involved in apoptotic pathways, seems to be a promising agent to prevent the incidence of AKs, also for its safeness and effectiveness. In any way, surgical procedures are the treatment of choice when suspicion of progression to invasive squamous cell carcinoma arises, i.e. when AK is hyperkeratotic, inflamed, bleeding, and/or painful.

In conclusion, knowledge of the molecular genetic changes in UV-irradiated keratinocytes shows the necessity and importance of not only treating clinically visible non-melanoma skin cancer, but also all the 'sleeping' cells in the surrounding skin. Additionally, the risk-benefit factor of the available therapies has to be considered carefully when deciding on treatment options for an individual patient, always remembering the antique Romans citation "primum non nocere".

This interesting book, describing all the more important biological and clinical processes involved in the AKs, and reporting an update of all the used therapies, represents a necessary tool for all the scientists, dermatologists, plastic surgeons, and cosmetic chemists who wish to know the last studies reported on this pathology.

P. Morganti
Editor-in-Chief

# Composite Materials. Design and Applications. *Third Edition*

**By Daniel Gay**

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A composite material can be defined as a combination of a matrix and a reinforcement which, when combined, gives properties superior to the properties of the individual components, showing particular strengths and weakness. This is the topic of thebook organized in 4 sections and 20 chapters, going from the *Principles of Construction of composite materials to their relative Applications*.
Currently, composite materials refer to materials containing strong fibers embedded in a weaker matrix. The Matrix keeps the geometric arrangement of fibers, transmitting the load acting on the composite component. The resulting composite has superior mechanical performance, presenting also other specific properties. The bonding between fibers and matrices, created during the manufacturing phase of the composite material, significantly influences its final mechanical properties. Other types of reinforcement are also used as *fillers*, represented from full or empty microspheres, powders, and nano-reinforcements.
The nano-reinforcement offers to the final material other significant benefits in terms of resistance to fire, electrical, optical, and surface properties. The verified interactions at the atomic level, in fact, became more complex than for the interfaces matrix-reinforcement of conventional composites. However, manufacturing a nanocomposite material is essential to ensure a homogeneous distribution of the nanoparticles in the material, that is to avoid particles to congregate in clusters, which would result in loss of all the expected properties.
For polymeric matrices, for example, the manufacturing process require action at level of the polymer/nanoparticle interfaces to ensure the dispersion of nanoparticles:grafting of compounds onto the surface of the nanoparticles; introduction of ions, so-called organophilic: and introduction of graft polymers.
It is to underline that today the development of composite reinforced with natural fibers is rapidly emerging, because of the significance of the environmental impacts. The mechanical properties of this type of composite depend on the volume fraction of fibers, orientation of these fibers, and quality of bonding between fiber and matrix. Thus, for technical natural fibers, such nanochitin or nanocellulose crystallites, a prior surface treatment are a clear need in view of improving the fiber-matrix linkage. In addition for a complete recycling, the use of natural fibers as part of composite respectful of the environment must be associated with a biodegradable biopolymer as matrix.
The physical properties of composite materials, as well as their manufacturing process are reported on the **Chapters 1-3**. The *Sandwich structures*, which occupy an important place in the manufacture

of composite parts, are the topic reported on **Chapter 4**. These structures result from the assembly of two thin facings or skins on a lighter core, that maintains a predetermined spacing between the two skins. The properties are particularly interesting being characterized from a very light weight, an high flexural rigidity, and excellent thermal insulation properties. Assembly of the skins and the core is achieved by bonding with adhesives or directly with the resin, impregnating the fibers of skins. The bonding quality is, of course, fundamental to obtain the best performance and durability of the sandwich part. How to design the typical area of a laminate so to sustain loads, is the topic discussed on **Chapter 5**, *Conception, Design and Drawing;* **Chapter 6** reports the problems regarding the attachments and joint of the laminates between them. In any mechanical component, the presence of holes generates stress concentration of factors. Especially in composite parts, in fact, holes (moulded-in holes or drilled holes) induce local reduction of the failure strength in comparison to the same location but without holes. Thus, many are the examples reported to show the different assembly solutions involving riveting, bonding of a composite part to another composite part, as well as a composite part to a metallic part.

**Chapter 7**, *Composite, Materials and Aerospace Construction*, reports the side variety of composite components used in aircraft to reduce both weight and cost, without reducing its performance. However, the introduction of composite in aircraft is limited to certain structure areas, representing no more than 25% of the structural mass.

**Chapter 8**, *Composite Materials for Various Applications*, is focused on the area of the activities (excluding Aerospace industry) where nanocomposites have been introduced and used in a significant way, such as civil engineering, road and Raikkonen transports, electricity and electronic, consumer goods, wind turbines, pipes and thanks, shipbuilding. Just to give an example, the polymer solutions for the car save its weight up to 60%, compared to a metal solution. At this purpose it is to underline that when the mass increases by 10%, the fuel consumption increases by 4-6% and the road transport sector is the major emitter of carbon dioxide!

While **Section I** reports the anisotropic properties of a composite material from a qualitative point of view, **Sections II, III,** and **IV** by **Chapters 9-12, 13-17** and **18-20** respectively have been dedicated to the justification and expected results obtainable by these properties.

In conclusion, it is to remember that the growth of nanocomposites, nanoparticles and nanoclays has an annual global rate of 5-6% and the relative tonnage is expected to grow in units' terms from 225,060 metric tons (MT) of 2014 to nearly 584,984 MT in 2019, with an annual growth rate of 21,1%. Global consumption of nanocomposites, in fact, has increased significantly since BCC Research published its last market analysis in early 2012, reaching 190,562 MT, with an estimated value of over $ 1.2 billion in 2013, expected to reach close to 584,984 MT, or $4.2 billion in value terms, by 2019.

This interesting book, covering the important field of nanocomposite and biocomposite materials, reports the latest manufacturing processes and applications in the aerospace, automotive, naval, wind turbine, and sporting goods industries. Moreover, it provides design and reports original studies of composite beams and plates wrote and discussed in a way to be understandable to both graduate and under graduate students, as well as to engineers, chemists, and technicians who wish to enhance their knowledge on the fascinating field of nanocomposites and bio composites

P. Morganti
Editor-in-Chief

# THE CALL FOR CLIMATE ACTION IS CLEAR

*in-cosmetics Group and Soil Association release recommendations to help the global cosmetics supply chain become greener*

**18 November 2015** – As world governments press public companies to disclose more non-financial information, such as carbon emissions data, sustainability is becoming more deeply embedded in operations. And with new global Sustainable Development Goals and the forthcoming UN Conference of the Parties (COP21) shaping climate policies for the next 15 years, the in-cosmetics Group – organiser of the world's leading personal care ingredients events – has teamed up with the Soil Association to call on the cosmetics industry to take more action on environmental sustainability.

The global beauty market is increasingly sensitive to environmental concerns as manufacturers and consumers seek out the most sustainable products and solutions. To protect the planet and human health, companies are trying to use energy and water more efficiently, while producing fewer carbon emissions and waste. Ultimately, those taking the biggest strides to manage their environmental footprint will be best placed for long term success.

The personal care industry has a complex multi-country supply chain and a global distribution network. It includes a huge variety of natural, raw materials, base, fine and specialty chemicals. In 2010, the International Energy Agency (IEA) estimated that the global chemical industry produced 1.2 gigatonnes of carbon emissions, and predicted that to almost double by 2050. Major chemical companies – including many that supply the beauty manufacturers – are now taking steps to measure and reduce their emissions.

The cosmetics sector has been introducing other practices to 'green' the supply chain for some 10 years. Green chemistry, in particular, is steadily being incorporated into formulating, with suppliers reducing waste, becoming more energy efficient, using solvent-free extraction methods and optimising ambient or cold-processing. Additionally, some companies including Clariant, Evonik and Lubrizol, have introduced their own internal Renewable Carbon Index to define the amount of materials that comes from non-petroleum based or derived products.

When it comes to carbon reduction targets, BASF is one of the most ambitious in the chemical industry. It aims to reduce specific GHG emissions per metric tonne of sales product by 40 percent by 2020 compared to 2002. It already claims to have achieved a decrease of 33.9 percent, and is now seeking to improve efficiency in its production processes by 35 percent on 2002 levels.

To encourage continued progress and debate in the sector, the in-cosmetics Group – supported by the Soil Association – has outlined four key recommendations in a new whitepaper, launched today, titled 'Environmental Sustainability in the Cosmetic Supply Chain' – authored by industry analyst, Nica Lewis.

1) **Set science-based targets for $CO_2$ emissions reduction** – Targets in carbon reduction are a useful tool for driving long-term sustainability and climate action. Setting those targets in relation to climate science can help limit global warming. Leading cosmetics suppliers have set targets, but more can join in to support decarbonisation of the chemicals sector.
2) **Optimise Responsible Care®** – More can be done to leverage the chemical industry's global charter for safety and sustainability and engage other cosmetic chemical suppliers, especially in some of the world's most energy-intensive countries.

3) **Invest in renewable energy** – Clean energy can lower costs, improve profitability, reduce emissions and enhance a company's reputation. To help decarbonise the beauty supply chain, cosmetic chemical suppliers should start to buy renewable energy, generate their own solar or wind power or set renewable energy targets to green their power supply in the future.
4) **Further educate the sector** – A lot of work is being done, but unless businesses promote or are rewarded for their sustainability achievements it will be difficult to get others to follow. Awards and conferences should help highlight environmental and social initiatives throughout the cosmetics supply chain.

Lucy Gillam, Director of the in-cosmetics Group, commented: "By working collaboratively at local, national and global level, we think the cosmetics industry can have a major, positive impact on sustainability throughout the supply chain.

"Some great work has already be done, but there are plenty of opportunities for the sector to position itself as the leading sustainable industry. This whitepaper is all about highlighting success stories and providing ideas to help businesses in the cosmetics market become more environmentally sustainable."

Emma Reinhold, Trade Relations Manager, Health, Beauty & Textiles at the Soil Association, added: "The cosmetics industry is certainly moving in the right direction when it comes to sustainability. A lot of initiatives are underway to reduce water usage and carbon emissions, while there is an increased focus on sourcing organic raw materials that have less of an impact on the environment.

"Having historically been involved in organic food and farming, the Soil Association has expanded its mission to cover more areas including cosmetics and personal care. The success we have had in enhancing the organic credentials of other industries will help us bring fresh thinking to the cosmetics industry, and highlight how a business' processes and machinery can be used in a way that respects our environment."

The full whitepaper can be downloaded from
http://www.in-cosmetics.com/Form/Whitepaper-Download-Form/

**More information about in-cosmetics:**
in-cosmetics is the leading global event for personal care ingredients. The exhibition brings together over 700 exhibitors of ingredients, fragrances, lab equipment, testing and regulatory solutions with over 9,000 cosmetic manufacturers worldwide. in-cosmetics is the global launch pad for innovations in ingredients and technologies, delivering high-level scientific education and consumer insights for formulators, R&D and regulatory professionals. Shaping future global industry trends, in-cosmetics offers the most cost-effective business and networking opportunities for the world's personal care ingredients community.

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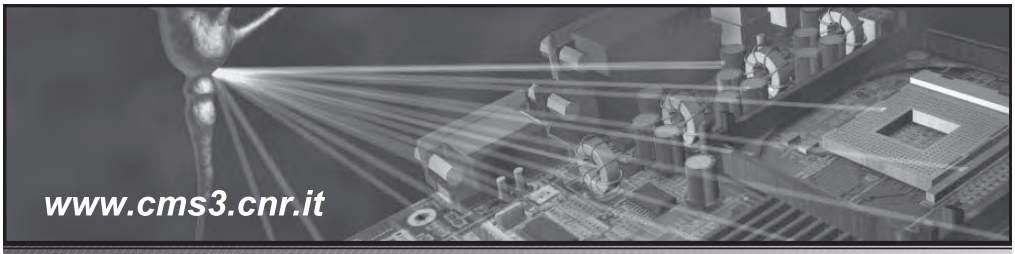


# Cell Model Systems Summer School

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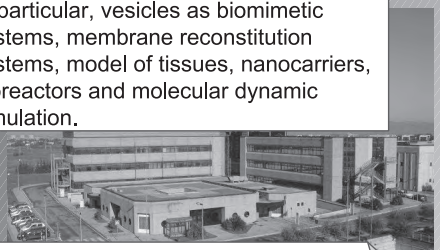

**APPLICATIONS AND FUNDING**
Participants must have a degree in either Physics, Mathematics, Engineering, Chemistry, Biology or Medicine, as well as a basic working knowledge of experimental research. Preference will be given to Ph.D. student and junior scientists under 35, who have less than 5 years research exp. Closing date for applications: **May 6th, 2016.** The School can accept a maximum of 18 students. Registration fee 150 eur. To sign up for the school: **cms3.cnr@gmail.com**

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# Trimestrale di Dermatologia Cosmetologica
# Quarterly Review of Cosmetic Dermatology

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# Trimestrale di Dermatologia Cosmetologica
# Quarterly Review of Cosmetic Dermatology

## Contents

J. Appl. Cosmetol. **33,** 123-128 (July/December 2015)

# Complimentary Benefits from Contradicting Agents - Science of a Novel Cream for Melanogenesis

**Aruna.V, Gayathri R.**
Dr. JRK's Siddha Research and Pharmaceuticals Pvt., Ltd., Chennai – India.

***Received:*** *January, 2016*

***Key words:*** *Melagain; Melanogenesis; Mexameter; Sun protection; Vitiligo;*

## Summary

The combined effect of the extracts of *Wrightia tinctoria, Indigofera tinctoria, Eclipta alba, Psoralea corylifolia and Emblica officinalis* and some sunscreens (dual technology) in the process of melanogenesis was verified evaluating by Mexameter how such technology may be useful during sun exposure.
The findings are presented in this paper.

## Riassunto

L'obiettivo di questo studio è stato quello di verificare l'effetto combinato degli estratti di *Wrightia tinctoria, Indigofera tinctoria, Eclipta alba, Psoralea corylifolia ed Emblica officinalis* associati all'uso di filtri solari (doppia tecnologia) nel processo di melanogenesi valutato con l'uso di Mexameter durante l'esposizione al sole.
Lo studio riporta i dati ottenuti.

## INTRODUCTION

The treatment of vitiligo essentially requires medicaments that support / augment the process of melanogenesis (1). However, the amelanotic skin remains vulnerable to photodamages. Therefore photo protective agents (sunscreens) are considered equally essential to protect the vitiliginous skin. Sun exposure is also considered as one of the treatment methods to control vitiligo (2).

The in-study active cream* is formulated with dual active constituents useful to increase at the same time melanogenesis offering a sun protection effectiveness. Combination of the above may appear contradictory to each other for the treatment of vitiligo.

To understand the complimentary role of supposedly contradicting agents (ingredients that induce melanogenesis and agents that offer sun protection), the present study was undertaken.

The aim of the present study is to establish the effect of herbal constituents in increasing tanning. This kind of effectiveness is unaffected by the sun screening agents present in the cream. The aim is also to justify the role of the sunscreens agents and their importance in the treatment of vitiligo.

The tanning property of the cream with and without sunscreens and sun exposure was evaluated by Mexameter (3), reporting the obtained results below.

## MATERIALS & METHODS

The in-study cream contains the extracts of *Psoralea corylifolia, Ecliptia alba, Wrightia tinctoria, Indigofera tinctoria* and *Emblica officinal*is as herbal ingredients to induce the process of pigmentogenesis (4, 5, 6), together with Bentonite, Calamine, Titanium dioxide, Zinc oxide, as physical sunscreens (7, 8).

For the present study we have prepared two separate formulations viz.

1. Cream base only with herbal actives (No Bentonite, Calamine, Titanium dioxide and Zinc oxide)
2. Cream with both herbal and sunscreens – active cream*

A total of 26 volunteers willing to participate in the study were included. The volunteers were divided into two equal groups of 13 volunteers in each group.

In the volar left forearm of 13 volunteers, the active cream* was applied (2 mg/cm2) then exposed to sun for 15 minutes. Similarly in the volar right forearm of the same volunteers the cream containing only the herbal actives was applied and then exposed to sun for 15 minutes. After 15 minutes exposure, the reading of tanning was taken using Mexameter.

Three separate readings were taken from the volar forearm regions before and after cream application and sun exposure. Suitable control was also maintained. In the other 13 volunteers, the active cream* and the control cream with only herbal actives were applied respectively in the right or left volar forearm, waiting for 30 minutes.

After 30 minutes, the volar forearm regions were gently washed and pat dried. Then the tanning activity of the tested creams was verified by using Mexameter, as described above.

The statistical significance of the result obtained for active cream was done by Paired t-test using graph pad software.

* *Trade name: Verdura Melagain cream. Dr. JRK's Siddha Research and Pharmaceuticals Pvt., Ltd., Chennai – India.*

## RESULTS

The extent of tanning (cumulative average) was 4.4 with a baseline of 2.2 in the volunteers who used the active cream* and not subjected to sun exposure. When the cream with only herbal actives were used and not exposed to sun, the extent of tanning was 4.9 under the above conditions (Table I).

The extent of tanning has increased to 5.3 from 2.2 in volunteers who used the active cream* and exposed to sun for 15 minutes. When the cream with only herbal actives were used and exposed to sun, the extent of tanning was 8.2 under the above conditions (Table I).

**TABLE I**

*Individual and complimentary role of dual actives the active cream**

| No | Untreated | | % diff | Without Sun exposure | | | | | | After Sun exposure | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Active cream Complete | | % diff | Only actives | | % diff | Active Cream complete | | | Only actives | | % diff |
| | B | A | | B | A | | B | A | | B | A | % diff | B | A | |
| 1 | 585 | 595 | -1.7 | 518 | 525 | -1.4 | 508 | 525 | -3.35 | 537 | 550 | -2.4 | 515 | 590 | -14.6 |
| 2 | 652 | 665 | -2.0 | 553 | 565 | -2.2 | 536 | 555 | -3.54 | 580 | 600 | -3.4 | 700 | 750 | -7.1 |
| 3 | 467 | 468 | -0.2 | 449 | 465 | -3.6 | 399 | 410 | -2.76 | 438 | 440 | -0.4 | 543 | 580 | -6.8 |
| 4 | 571 | 580 | -1.6 | 566 | 580 | -2.5 | 602 | 635 | -5.48 | 580 | 611 | -5.4 | 590 | 600 | -1.7 |
| 5 | 471 | 485 | -3.0 | 517 | 535 | -3.5 | 536 | 565 | -5.41 | 508 | 520 | -2.4 | 475 | 490 | -3.2 |
| 6 | 462 | 470 | -1.7 | 462 | 475 | -2.8 | 543 | 585 | -7.73 | 489 | 515 | -5.3 | 464 | 495 | -6.7 |
| 7 | 646 | 655 | -1.4 | 671 | 690 | -2.8 | 668 | 685 | -2.54 | 662 | 690 | -4.3 | 702 | 755 | -7.5 |
| 8 | 504 | 510 | -1.2 | 420 | 450 | -7.1 | 448 | 470 | -4.91 | 457 | 485 | -6.0 | 503 | 535 | -6.4 |
| 9 | 384 | 400 | -4.2 | 397 | 420 | -5.8 | 470 | 515 | -9.57 | 417 | 452 | -8.4 | 431 | 480 | -11.4 |
| 10 | 388 | 394 | -1.5 | 376 | 395 | -5.1 | 373 | 385 | -3.22 | 379 | 420 | -11 | 360 | 425 | -18.1 |
| 11 | 503 | 520 | -3.4 | 473 | 495 | -4.7 | 485 | 500 | -3.09 | 487 | 520 | -6.8 | 554 | 595 | -7.4 |
| 12 | 491 | 495 | -0.8 | 453 | 489 | -7.9 | 486 | 495 | -1.85 | 477 | 501 | -5.1 | 478 | 525 | -9.8 |
| 13 | 296 | 315 | -6.4 | 265 | 285 | -7.5 | 259 | 285 | -10.0 | 273 | 295 | -7.9 | 265 | 280 | -5.7 |
| S | 494 | 504 | -2.2 | 471 | 490 | -4.4 | 486 | 508 | -4.9 | 483 | 508 | -5.3 | 506 | 546 | -8.2 |

Abbreviations- B= Before, A= After, S= Average

### *Statistical analysis*

Statistical evaluation of the data was done using Paired t-test.

**Statistical significance of active cream in inducing melanogenesis (without sun exposure)**
The two-tailed P value is less than 0.0001 and which is statistically significant with confidence interval of 95 %
t = 9.0441
df = 12
standard error of difference = 2.118

**Statistical significance of active cream in inducing melanogenesis (with sun exposure)**
The two-tailed P value is less than 0.0001 and which is statistically significant with confidence interval of 95 %
t = 8.2543
df = 12
standard error of difference = 2.936

**Statistical significance of only herbal actives in inducing melanogenesis (without sun exposure)**
The two-tailed P value is less than 0.0001 and which is statistically significant with confidence interval of 95 %
t = 7.1255
df = 12
Standard error of difference = 3.206

**Statistical significance of only actives in inducing melanogenesis (with sun exposure)**
The two-tailed P value is less than 0.0001 and which is statistically significant with confidence interval of 95 %
t = 7.4033
df = 12
standard error of difference = 5.403

## DISCUSSION

The present study clearly shows that the active cream* induces tanning.
Tanning as immediate reaction of melanocytes to UV rays, transferring melanin to keratinocytes cannot be directly extrapolated from the process of melanogenesis required in the case of vitiligo. Thus, the kindling effect of tanning by the active cream* suggests its effect in increasing melanogenesis making it useful for the treatment of vitiligo (9).
The extent of tanning was expected to be higher when sun exposure was given (2). When only herbal actives were tested for tanning effect in the presence and absence of sun exposure, we found great difference i.e. 8.2 and 4.9 respectively. On one hand, the increased tanning observed for the cream that contain only herbal actives under sun exposure may be due to the vulnerability of the skin to sun exposure. On the other hand, when the active cream* was tested for its tanning effect in the presence and absence of sun exposure, we observed that the values were 5.3 and 4.4 respectively.
The statistical analysis clearly show that the effect of active cream with and without suns creeners and with or without sun exposure augment melanogenesis and the process of melanin formation was statistically significant in all the groups.
The above findings suggest that the herbal actives are inducing tanning, irrespective of sun exposure, and simultaneously the sunscreens minimizes the solar vulnerability of the skin. It means that both the herbal and sunscreens act independently without conflicting with each other, although these ingredients may appear to have a conflicting activity.
The in-vitro study on the active cream* (data submitted for publication elsewhere) has shown that the cream is effective in inducing synthesis of tyrosinase enzyme by melanocytes and

increasing melanin synthesis.

The anti -oxidant effect of the cream against the free radical molecules, 2,2-diphenyl-1-picrylhydrazyl (DPPH) and nitric oxide assumes greater importance as melanocytes are susceptible to oxidative damage (5).

The efficacy of the active cream* as established through in-vitro studies and the tanning effect proved by the present investigation undoubtedly supports the clinical use of the cream in the treatment of vitiligo.

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# Development & Optimization of Anti-Dandruff Shampoo by Modifying its Rheological Behavior

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***Key words:*** *Ketoconazole; Stability; Rheology; Temperature; pH;*

## Summary

Pharmaceutical product stability is an important issue in pharmaceutical industry. The rheological behavior of a pharmaceutical product affects its stability and performance characteristics such as, foaming properties and filling process during production. Ketoconazole, imidazole antifungal agent, is a weak base with two pKa-values 6.15 and 2.94. It is unstable in aqueous medium and vulnerable to degradation if not properly formulated. Oxidation and hydrolysis are the most degradation routes affecting its stability. The aim of this study to assess the effect of formulation factors such as, pH, the amount of the rheology modifier, rheological behavior and temperature on the stability of ketoconazole in aqueous media.

Different formulations of 2 gm% ketoconazole were prepared, using different percent concentrations of the rheology modifier (NaCl) as 0.8 gm%, 0.2 gm%, 0.4 gm%, 0.1 gm% at different pH values 5.5, 6.5 and 7.5. Experimental formulations were prepared at different temperature and time intervals. The measurements of pH and viscosity of the prepared shampoo were evaluated during stability. Stability studies were carried out as per ICH guidelines for 18 months and monitored by validated stability indicating HPLC method (linearity: 60-140 µg/mL; $R^2$=0.9995; acceptable accuracy and precision %RSD < 1.0%).

The rheological behavior of the system possess a yield point (minimum shear stress for flow to commence) and time dependency. A reduction in viscosity occurs on shearing with time and rebuilding of viscosity on standing. The key is the rate at which the structure is rebuilt. This is a function of the nature of the thixotropic agent, its concentration in the vehicle or medium, and the amount of agitation before use. The prepared ketoconazole shampoo was high stable at high pH (6.5-7.5) and at temperature < 30 °C during the manufacturing process. Furthermore, the amount of rheology modifier had a high significant effect on the stability of ketoconazole. Formulations containing 0.1 gm% NaCl showed better stability and exhibited ideal thixotropic rheological behavior.

The rheology of dispersed systems is among the most important of their physical properties, which influences not only the physical stability of the systems, but often also profoundly affects the performance features, their quality, and their utility. In dealing with rheological parameters, and in case of thixotropic systems, long shearing times should be avoided. Temperature changes can also produce spurious results, since shear stress at a constant shear rate, is also a function of temperature. It is important to consider the optimum pH for the product, since the properties of the product, particularly rheology, can be quite dependent on the pH of the system. In conclusion, the expected shelf life of the final ketoconazole formulation was stable for 18 months.

## Riassunto

La stabilità di un prodotto farmaceutico o cosmetico risulta molto importante per il suo uso. Le proprietà reologiche di un prodotto ne influenzano, infatti, sia la stabilità che le caratteristiche finali, quali ad esempio le proprietà schiumogene e la rapidità di riempimento nei contenitori durante le fasi di produzione.
Il ketoconazolo è un antiinfiammatorio imidazolico caratterizzato da un pKa che va da 6.51 a 2.94. E' instabile in un mezzo acquoso e, se non propriamente formulato, facilmente degradabile. L'ossidazione e l'idrolisi sono i due fenomeni più frequenti che ne provocano la degradazione.
Lo scopo di questo studio è di controllare gli effetti provocati da alcuni parametri quali il pH, gli eventuali modificatori reologici e la temperatura sulla formulazione e sulla stabilità del prodotto finale in un mezzo acquoso.
A tal proposito, sono state controllate diverse formulazioni contenenti concentrazioni del 2% di ketoconazolo, preparate utilizzando come modificatore reologico NaCl a percentuali variabili dello 0.8 , 0,4,0, 2 e 0,1% in peso, e a diversi pH 5.5 ,6.5 e 7.5. Le formulazioni sono state preparate utilizzando diverse temperature e diversi tempi di intervallo.
Durante il periodo di stabilità sono stati verificati pH e viscosità degli shampoo formulati. Gli studi di stabilità sono stati condotti secondo le linee guida ICH per 18 mesi, monitorando la relativa stabilità per mezzo dell'HPLC/linearità (60-140ug/ml; $R^2$= 0,9995 accuratezza e precisione con %RSD<1,0%).
Il comportamento reologico del sistema è caratterizzato da un punto di rendimento legato al tempo. Si verifica una riduzione di viscosità durante la lavorazione ed un ulteriore incremento durante la fase di riposo. La soluzione è nel tempo dedicato alla ristrutturazione della soluzione/emulsione finale che dipende dalla natura dell'agente tixotropo, dalla sua concentrazione nel veicolo e dall'intensità del sistema emulsionante.
Durante il processo di lavorazione, la preparazione dello shampoo al ketoconazolo si è rivelata più stabile a pH più alti (6,5-7,5) ed alla temperatura di 30°C. Inoltre, la presenza del modificatore reologico è risultata importante per la stabilità del ketoconazolo. Le formulazioni contenenti 0,1% in peso di NaCl hanno dimostrato di essere più stabili e di mantenere una densità ideale.
Lo stato reologico dei sistemi risulta essere il più importante tra i sistemi fisici perche influenza profondamente non soltanto la stabilità fisica del prodotto finito, ma anche l'aspetto, la qualità ed il relativo modo d'uso. La variazione dei parametri reologico e delle temperature può provocare la formazione di sistemi poco stabili nel tempo, legati anche al loro pH.
In conclusione, tenendo presenti tutti questi parametri, la vita media del prodotto formulato con ketoconazolo è risultata stabile per 18 mesi.

# INTRODUCTION

Ketoconazole, an antifungal agent, is an imidazole derivative structurally related to miconazole and clotrimazole. It possesses some antibacterial activity (1,2,3). Ketoconazole is a weak base with two pKa values 6.51 and 2.94 (Fig.1).

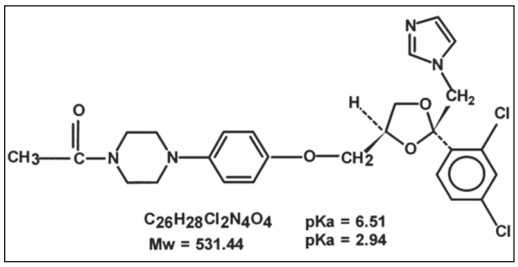


***Fig. 1*** *Chemical and Molecular Structure of Ketoconazole.*

It acts as antifungal by interfering with the fungal synthesis pathway of ergosterol, a constituent of cell membranes, in susceptible organisms. It has activity against yeast specially candida and cryptococcus spp., fungi, and dermatophytes (3,4,5). In animal studies, topical ketoconazole was found to be very effective on the treatment of skin dermatophytosis, skin and vaginal candidiasis (4,6). Ketoconazole is marketed in different dosage forms and routes of administration such as, orally (i.e. tablets) and topically (i.e. creams, gels, lotions and shampoos) (1,2). In fact, different topical formulations of ketoconazole have been introduced and presented in the market for antidandruff purposes with short-term stability.

Product stability is an important issue in pharmaceutical industry. A thorough knowledge of the chemical and physical stability of drugs and dosage forms is critical in the development and evaluation of pharmaceuticals. Drug products are complex mixtures of drug and excipients, and, as such, their chemical and physical stability kinetics are complex. The chemical and physical stability of these complex dosage forms, starting with pre-formulation studies and continuing through to studies of the final products, including the role of packaging. Many drugs are susceptible to physical and chemical degradation, especially in aqueous solution. Ketoconazole is vulnerable and extremely sensitive to degradation. Oxidation and hydrolysis are the most degradation pathways affecting its stability. Due to the delicate nature of ketoconazole, especially in aqueous formulations; further investigations are needed to improve the stability of ketoconazole in aqueous formulations, and elucidate the physicochemical parameters affecting its stability.

Rheology is the science of flow and deformation of matter, and describes the interrelation between force, deformation and time. In turn, fluid rheology is the consistency of different products, normally by the two components viscosity and elasticity. By viscosity is usually meant resistance to flow or thickness, and by elasticity usually stickiness or structure. Rheological behavior plays an important role on the stability of a pharmaceutical product, and determines its flow behavior and storage condition (7).

The elementary rheological properties of most products could be described in terms of shear rate and stress. In our study, the behavior of the system possessed a yield point (minimum shear stress for flow to commence) and time dependency. A reduction in viscosity occurred on shearing with time and rebuilt of viscosity on standing. During mixing, the yield stress was exceeded, and the product flowed. The structure began to re-form after cessation of shear. However, it did not re-form immediately. It took time to rebuild the order or structure that existed when the system was at rest. The key was the rate at which the structure was rebuilt (8). This was a function of the nature of the thixotropic agent (NaCl), its concentration in the aqueous medium, and the amount of agitation before use. The usage of surfactant-thickening agents' complex has shown the most stable thixotropic

system. A blend of ionic and non-ionic surfactants was preferable. The choice of surfactants was based on physicochemical characteristics of each surfactants, hydrophilic-lipophilic balance of non-ionic surfactant, critical micelle concentration of ionic surfactants; in addition to, stability and hydrodynamic of the molecules at the interfacial phase, interfacial film formation kinetics, and interactions between molecules on the surface (9).

In conclusion, the aim of this study was to assess the effect of formulation parameters such as, pH, the amount of the rheology modifier and temperature on the stability of ketoconazole in aqueous solution.

# MATERIALS AND METHODS

## *Materials*

Ketoconazole was purchased from Sigma-Aldrich, USA. Sodium lauryl ether sulphate, disodium mono lauryl ether sulfosuccinate, PEG-120 methyl glucose dioleate, coconut fatty acid diethanolamide, imidurea, hydrochloric acid, sodium hydroxide and sodium chloride were kindly supplied by Sigma Pharmaceutical Co., Egypt. All other reagents used were of analytical grade.

## *Method of Preparation*

A vessel was charged with purified water, sodium lauryl ether sulphate and concentrated hydrochloric acid, then mixed using a mechanical overhead stirrer (IKA® RW 20 digital, Staufen, Germany) at speed 36 rpm/min. for 10 mins. Ketoconazole was added and homogenized using high-speed homogenizer (IKA® T-25 ULTRA-TURRAX Digital, Staufen, Germany) at speed 200 rpm/min. for 20 mins, followed by mixing at speed 60 rpm/min. for 30 mins.

Disodium mono lauryl ether sulfosuccinate was subsequently added and mixed at speed 60 rpm/min. for 15 mins. Temperature was controlled in all preparation steps to be 25 °C ± 2. PEG-120 methyl glucose dioleate and coconut fatty acid diethanolamide were gradually added and mixed at speed 36 rpm/min. for 10 mins. Imidurea solution, colorants and fragrances were subsequently added and mixed at speed 60 rpm/min. for 10 mins. pH was adjusted to 6.5 ± 0.5 by using sodium hydroxide and mixed at speed 80 rpm/min. for 15 mins.

Finally, sodium chloride solution was portionwisely added and homogenized at speed 200 rpm/min. for 5 mins, followed by mixing at speed 80 rpm/min. for 30 mins. The amount of sodium chloride (0.1 gm%) was necessary to obtain a stable thixotropic system.

# PHYSICAL, CHEMICAL, VISCOSIMETRY AND RHEOLOGICAL CHARACTERIZATION

## *Physical Appearance and Visual Inspection*

The prepared shampoo were evaluated in terms of clarity, transparency, homogeneity, foaming producing ability, fluidity, color intensity and stability.

## *Determination of pH*

pH was measured at 25 °C ± 2 °C, by using pH meter (Digital pH meter, 827pHlab, Metrohm, Switzerland).

## *Determination of the Percentage of Solid Contents*

Four grams of the prepared shampoo were placed in a dry clean previously weighted evaporating dish. The dish and shampoo were weighed

to confirm the exact weight of the shampoo. The evaporating dish with the prepared shampoo was placed on the hot plate until the liquid portion was totally evaporated and solids were precipitated. The percent weight of solids after drying was calculated.

## Measurement of Surface Tension

The stalagmometric method (10) was used for measuring the surface tension of the prepared shampoo. A dry stalagmometer was filled up to the mark with 10 gm% of the prepared shampoo diluted with purified water.

Diluted shampoo were released to the weighting bottle and number of drops were calculated according to the following equation:

$$R_2 = [(W_3-W_1)n_1/(W_2-W_1)n_2] \times R_1$$

Where $W_1$ is the weight of empty beaker, $W_2$ is the weight of beaker with purified water, $W_3$ is the weight of beaker with diluted shampoo, $n_1$ is the number of drops of distilled purified water, $n_2$ is number of drops of diluted shampoo, $R_1$ is surface tension of purified water and $R_2$ is surface tension of diluted shampoo.

## Dirt Dispersion

Two drops of the prepared shampoo and one drop of India ink were added in a test tube containing 10 ml of purified water, stoppered well and allowed to shake for ten times. The amount of ink in the foam was evaluated as none (N), light (L), moderate (M), or heavy (H) (11).

## Foamability and Foaming Stability

Cylinder shake method was used for determining foaming ability of the prepared shampoo. 50 ml of 1% of the prepared shampoo was placed in a hand-closed 250 ml graduated cylinder and shaken for 10 times.

The total volume of the foam content after shaking for 1 min. was recorded. Foam stability was evaluated by shaking the volume of foam at 1 min. intervals for 4 mins (12).

## Viscosimetry and Rheological Study

The viscosity of the prepared shampoo was determined at 25 °C ± 2 using Brookfield Viscometer (DV-E Viscometer, Brookfield Engineering Laboratories Inc., USA) rotated at 20 rpm, using spindle 64 and torque > 50%. The temperature and sample container's size was kept constants during measurements.

## Stability Studies

Stability studies of the prepared shampoo were carried out as per ICH guidelines (13). Shampoo samples were stored at 30 °C ± 2 °C / 65% RH ± 5% RH in stability chambers for a period of 18 months. Samples were withdrawn at regular interval 3, 6, 9, 12 and 18 months for physical and chemical stability evaluation.

## Analytical Method for Chemical Stability Evaluation

A stability indicating analytical method was developed for determination of ketoconazole in the aqueous shampoo.

The HPLC method was specified to separate ketoconazole, using octasilyl (C8) stationary phase column (4.6 mm x 150 mm x 5 $\mu$m) and a mobile phase composed of filtered a degassed mixture of 0.025 M phosphate buffer solution and acetonitrile in ratio of 60:40. pH was adjusted to 4.0 ± 0.5 using phosphoric acid or sodium hydroxide. Flow rate was 1.0 ml/min. UV detection was at wavelength 223 nm.

The method was linear over the range 60–140

$\mu$g/mL with $R^2$=0.9995. Accuracy and precision were acceptable with %RSD < 1.0%. The method was found to be specific for ketoconazole by separating ketoconazole from its degradation byproducts formed under acid and alkaline stress conditions (Fig. 2).

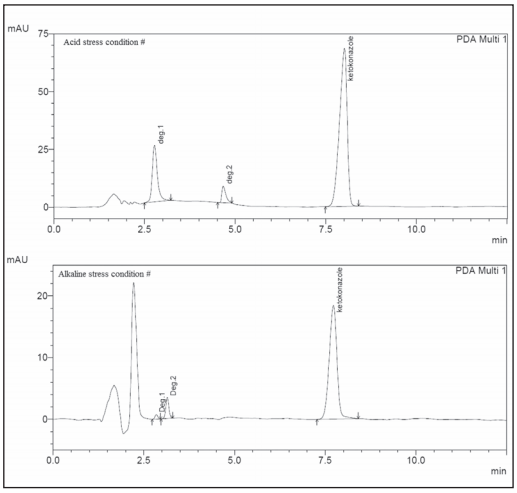


***Fig. 2*** *HPLC Method for Determination and Separation of Ketoconazole.*

# RESULTS AND DISCUSSION

## Evaluation of the Prepared Ketoconazole Shampoo

### Physical Appearance and Visual Inspection

The prepared shampoo was evaluated for the physical characteristics such as clarity, transparency, homogeneity, foaming producing ability, fluidity, color intensity and stability. Our prepared shampoo was clear, transparent, homogenous, semi-viscous aqueous solution, pink in color and had characteristic odor (Table I). No significance changes were observed in physical evaluation during stability, indicating the high stability index of the prepared shampoo.

## Effect of pH on Ketoconazole Stability

Most shampoos are formulated as either neutral or slightly acidic to minimize the damage to the hair. The pH of shampoo helps in minimizing irritation to the eyes, prevents swelling, promotes tightening of the scales, enhances the qualities of hair and maintain the hair, and maintains ecological balance of the scalp (14). pH-stability studies of 2% ketoconazole were conducted as per ICH guidelines (13) for 18 months at 30 °C ± 2 °C / 65% RH ± 5% RH and results are shown in (Table II). The most stable formula was at pH 6.5 as shown in (Fig. 3).

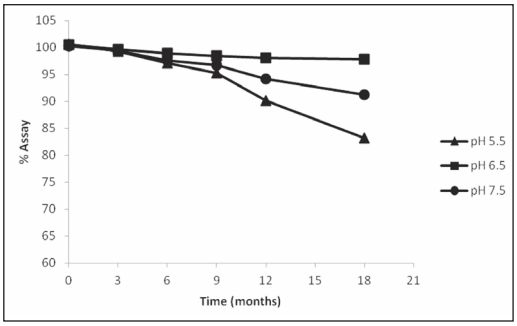


***Fig. 3*** *Effect of pH on % Assay of Ketoconazole during Stability.*

## The Percentage of Solid Contents

In fact, if the shampoo has too many solid contents; it will not be easy to be applied and wash out from the hair. Good shampoos usually have 20 to 30% of solid contents (15). If it has low percent of solid contents; it will be too watery and wash away quickly. In turn, if it has too many solids; it will be hard to wash out. The percent of solid contents of the prepared shampoo was from 20–24% (i.e. easily washable) as shown in (Table I).

**TABLE I**

*Physicochemical Evaluation of the Prepared Shampoo during Stability.*

| Parameters | 0 month | 6 month | 12 month |
|---|---|---|---|
| Physical Appearance and Visual Inspection | Clear, Transparent, Homogenous, Pink in color | Clear, Transparent, Homogenous, Pink in color | Clear, Transparent, Homogenous, Dark Pink in color |
| pH | 6.50±0.03 | 6.48±0.04 | 6.47±0.08 |
| Solid Contents (%) | 23.12±0.24 | 22.56±0.18 | 21.08±0.30 |
| Surface Tension Measurement (dy./cm) | 34.12±0.24 | 33.19±0.22 | 33.85±0.26 |
| Foamability and Foam Stability (ml) | Good Foaming Foam Type: Compact, Condense Foam Volume: 86 ml | Good Foaming Foam Type: Small, Condense Foam Volume 84 ml | Good Foaming Foam Type: Small, Condense Foam Volume 90 ml |
| Viscosity (cp) | 4700 | 4656 | 4536 |
| % Assay of Ketoconazole | 100.6±0.16 | 98.7±0.25 | 97.2±0.48 |
| Results are mean ± SD (n = 3) | | | |

**TABLE II**

*Effect of pH on % Assay of Ketoconazole during Stability.*

| Time | pH Values | | |
|---|---|---|---|
| (months) | 5.5 | 6.5 | 7.5 |
| 0 | 100.6 | 100.5 | 100.3 |
| 3 | 99.3 | 99.7 | 99.4 |
| 6 | 97.1 | 98.9 | 97.6 |
| 9 | 95.3 | 98.4 | 96.7 |
| 12 | 90.2 | 98.1 | 94.2 |
| 18 | 83.2 | 97.8 | 91.2 |

## *Measurement of Surface Tension*

It is an indication of the amount of surfactant required to reduce the surface tension of the shampoo. The well formulated shampoo should be able to reduce the surface tension of purified water to 40 dynes/cm (16). Reduction of the surface tension is one of the mechanisms applied to detergency. In our study, the prepared shampoo showed a good reduction in surface tension to 34.12 dynes/ cm which indicated its good cleaning and detergent actions (Table I).

## *Dirt Dispersion*

Dirt dispersion is one of the most important parameters for evaluating the cleansing action of the shampoo. When shampoo causes the ink to concentrate in the foam, it will be difficult to wash out, then deposit on the hair. In this case, it is considered of poor quality. In our study, the prepared shampoo showed a good quality (i.e. none (N) in accordance to cleaning ability) (11).

## Foamability and Foaming Stability

Foaming is an important parameter in evaluating the efficacy of the shampoo for customers. Generally, foaming of the shampoo is a result of the activity of surfactants. In our study, the prepared shampoo generated a compact, condensed and stable foam volume 86 ml. It persisted for 5 mins indicating that it has good stability (12). The higher foaming property of the prepared shampoo may result from the successful blend of non-ionic surfactants with an ionic surfactant to achieve a high HLB value (Table I).

## Effect of Sodium Chloride (NaCl) Concentration on Ketoconazole Stability

Decreasing the amount of rheology modifier (NaCl) from 0.8 gm% to 0.1 gm% showed a great improvement in the stability of ketoconazole shampoo in aqueous formulations, particularly at pH 6.5. The effect of NaCl concentrations on the shelf life were compared as shown in (Table III). Results showed that formulations containing 0.8 gm% NaCl had a shorter shelf life than formulations containing 0.1 gm% NaCl that have better stability and rheological behavior (Fig. 4a and 4b).

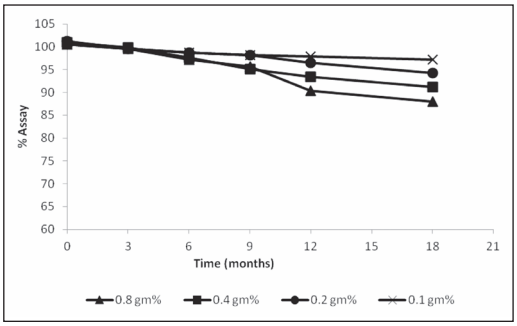


***Fig. 4a*** *Effect of Nacl Concentration on % Assay of Ketoconazole during Stability.*

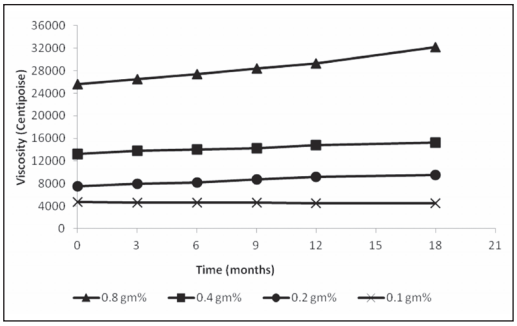


***Fig. 4b*** *Effect of Nacl Concentration on Viscosity of Ketoconazole during Stability.*

**TABLE III**

*Effect of Nacl Concentration on Stability and Viscosity of Ketoconazole.*

| Time (months) | Concentration of NaCl at pH 6.5 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.8 gm% | | 0.4 gm% | | 0.2 gm% | | 0.1 gm% | |
| | P | H | P | η | P | η | P | η |
| 0 | 100.5 | 25590 | 100.9 | 13265 | 101.2 | 75.23 | 100.6 | 4700 |
| 3 | 99.5 | 26478 | 99.8 | 13825 | 99.6 | 7950 | 99.6 | 4680 |
| 6 | 97.2 | 27450 | 97.6 | 13995 | 98.7 | 8251 | 98.7 | 4656 |
| 9 | 95.6 | 28380 | 95.1 | 14256 | 98.2 | 8781 | 98.2 | 4602 |
| 12 | 90.3 | 29256 | 93.4 | 14835 | 96.5 | 9231 | 97.9 | 4559 |
| 18 | 87.9 | 32231 | 91.2 | 15235 | 94.2 | 9535 | 97.2 | 4536 |

P is % assay of ketoconazole; η is viscosity (Centipoise)

### *Effect of Temperature during Preparation on the Stability and Viscosity of Ketoconazole*

Temperature is as key factor in rheology building systems. The effect of temperature on the viscosity of ketoconazole shampoo was observed during the preparation. Results indicated that while during preparation, temperature should not exceed 30°C for obtaining an ideal thixotropic system and to maintain the stability of ketoconazole.

## CONCLUSION

The rheology of dispersed systems is among the most important of their physical properties, which influences not only the physical stability of the systems, but often also profoundly affects the performance features, their quality, and their utility. In dealing with rheological parameters, and in case of thixotropic systems, long shearing times should be avoided.

In turn, short shearing times at different time intervals are necessary to obtain a thixotropic system. Temperature changes can also produce spurious results, since shear stress at a constant shear rate, is also a function of temperature. It is important to consider the optimum pH for the product, since the properties of the product, particularly rheology, can be quite dependent on the pH of the system. Ketoconazole was found to undergo less hydrolysis at mild acidic pH and temperature below 30°C. Furthermore, the viscosity of the prepared shampoo was stable at the same pH and exhibited thixotrophy. Decreasing the amount of rheology modifier 0.1% gm was effective to maintain the rheological behavior of the system and stability of ketoconazole during stability. pH of the final formulation was concluded to be pH 6.5 that have been shown good physical and chemical characteristics during long-term stability studies.

## AUTHORS' CONTRIBUTIONS

*All authors contributed equally to this work*

## CONFLICT OF INTERESTS

*The authors declare that there is no conflict of interests concerning the publication of this paper.*

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# Can Gamma Rays be an Alternative to preservative Agents in Cosmetics?

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## Summary

The goal of this work was to experiment and characterize the treatment of finished products with gamma rays, aiming to new cosmetic formulations preservative-free.

This paper presents the intermediate results obtained in this framework so far. The research activity was focused on the representative most used cosmetic formulations such as O/W, W/O emulsions and detergents, characterized by different water and lipid phase content, viscosity and additives; among these, colorants were used as probe of stability.

The idea behind the project was to exploit the effects of the gamma rays and verify the cosmetic chemico-physical parameters after irradiation, correlating type of formulation, water content and viscosity with formulation stability. This approach has been particularly focused on the situations where one may believe the irradiation less attractive in keeping the product characteristics. In fact azodyes, known to be easily degraded, were found to longer resist at a dose of 10 kGy, when included in high viscosity grade house-formulated and commercial shower gels formulations, in a low water content environment and in presence of antioxidant phenols, such as butyl hydroxyl anysole (BHA). This behavior was found consistent with a mechanism of azodyes degradation involving water hydroxyl radical attack to the azo functional group, reduced by the presence of antioxidants and in high viscosity and ”water-caged” formulations. As a further confirmation of this mechanism, the powder dyes in solid state and no water were found completely stable upon gamma irradiation.

These results were also confirmed in emulsion formulations. Viscosimetric evaluation showed that gamma rays treatment did not significantly affect the viscosity grade and emulsion texture in all the formulations. Through these preliminary studies it has been shown that, by adjusting the appropriate formulation ingredients, it is possible to tailor cosmetics products, which maintain their chemico-physical properties and texture, when treated by gamma rays.

## Riassunto

Lo scopo di questo lavoro è stato quello di sperimentare e caratterizzare il trattamento con raggi gamma di prodotti finiti, orientandosi verso nuove formulazioni cosmetiche prive di conservanti. Questo articolo presenta i risultati intermedi ottenuti finora in questo ambito.
L'attività di ricerca si è concentrata sulle formulazioni cosmetiche più utilizzate quali le emulsioni ed i detergenti O/A e A/O, caratterizzati da un diverso contenuto d'acqua e olio, viscosità e additivi; fra questi, i coloranti sono stati usati come indicatori di stabilità. L'idea di sviluppo del progetto prevede di sfruttare gli effetti dei raggi gamma e verificare i parametri chimico-fisici dei cosmetici dopo l'irraggiamento, correlando i tipi di formulazione, il contenuto in acqua e la viscosità con la stabilità del prodotto. Questo approccio è stato particolarmente focalizzato su quelle situazioni in cui l'irraggiamento è ritenuto meno attraente dal punto di vista del mantenimento delle proprietà dei prodotti.
Nei fatti si è riscontrato che i coloranti azoici, noti per degradare facilmente, resistono maggiormente ad una dose di 10 kGy quando vengono inclusi in formulazioni di shampoo a basso contenuto acquoso e ad alto grado di viscosità, commerciali o formulati in laboratorio, in presenza di antiossidanti fenolici, come ad esempio il butilidrossianisolo (BHA). Tale comportamento si è rivelato coerente con un meccanismo di degradazione dei coloranti azoici che coinvolge i radicali idrossilici dell'acqua nell'attacco del gruppo funzionale azo, attenuato dalla presenza di antiossidanti, dall'alta viscosità e da formulazioni "water-caged".
Come ulteriore conferma di questo meccanismo, i coloranti in polvere privi di acqua si sono dimostrati altamente stabili una volta irraggiati. Questi stessi risultati sono stati confermati anche per quanto riguarda le emulsioni. L'analisi viscosimetrica ha mostrato che il trattamento mediante raggi gamma non influisce significativamente sul grado di viscosità e sulla struttura delle emulsioni in tutte le formulazioni considerate. Mediante questi studi preliminari si è evidenziato che, scegliendo e dosando in modo appropriato gli ingredienti delle formulazioni, è possibile ottenere prodotti cosmetici che mantengano le loro proprietà chimico-fisiche e la loro struttura quando sottoposti a trattamento gamma.

## INTRODUCTION

Cobalt-60 has been known and industrially used for over 50 years for a variety of applications, such as sanitation, sterilization and chemical irradiation. Applications of gamma rays delete any microorganisms, therefore gamma irradiation is known as a "cold sanitation process", since the temperature of the processed product does not significantly increase during the irradiation process.

Gamma rays from Co-60, as electron beams and x-rays, are used to sterilize the medical devices used in surgery and other healthcare treatments. Implants, artificial joints, syringes, blood-bags, gowns, and dressings are sterilized using radiation. Other industries that benefit from radiation processing include packaging, pharmaceutical, cosmetic, food and automotive industries. Radiation sterilization, as a physical cold process, has been widely used in many countries for the sterilization of health care products.

Earlier, a minimum dose of 25 kGy was routinely applied for many medical devices, pharmaceutical products and biological tissues; now, as recommended by the International Organization for Standardization (ISO), the sterilization dose must be set for each type of product depending on its bio-burden. Generally, the determination of sterilization dose is one of the principal medical product manufacturer responsibility, who must have access to a well qualified microbiology laboratory.

Gamma irradiation has been used for microbial decontamination of food, herbs, cosmetic raw materials and cosmetic products, and according to one study, the technology was applied to botanical raw materials at doses between 4 and 30 kGy and 10 to 40 kGy for uncommon high contaminated samples (1).

Irradiation of cosmetic products was also studied at doses of 5, 7.5 and 10 kGy founding that the suitable doses for decontamination were approximately 5 kGy; observations confirmed that there were no effects on skin irritation (2). Low dose ionizing radiation processing plays an increasingly important role in the microbial decontamination of pharmaceutical and medicinal herbal products as well as health food and botanical health products. Nevertheless, irradiation can be applied only when it has been experimentally proved and well documented that no harmful side effects occur, owing to possible qualitative and quantitative alterations of the irradiated materials.

It is well known, as an example, that most colored material undergo bleaching or color changes when exposed to ionizing radiation (3). When an aqueous solution is irradiated under gamma ray, the interaction between gamma rays and water molecules generate primary species such as hydroxyl radical, hydrated electron, hydrogen radical, di-hydrogen and water oxygen; radical species can react rapidly with organic compound and lead to alteration of their chemical structure (4).

According to these evidences, beside the already validated and widely studied decontamination of raw materials used for industrial production process, the aim of this work was to apply the treatment with gamma rays to cosmetic finished products. Gamma rays can represent a valid alternative to reach the quality standards required for cosmetic products, such as a longer shelf-life of personal care products and the microbiological profile, expected to be as safe as possible to protect products from degradation and consumers from health hazard.

Further on, raw materials handling and production process can affect finished product quality because of microbial contamination, so gamma rays applied to the finished product can represent a strategic solution, leading to a production process optimization and new cosmetic formulations preservative-free, highly required by many industries interested into this claim.

# EXPERIMENTAL

In order to investigate the effect of gamma rays on cosmetic formulations chemical stability, in this study different types of products were realized, taking into account the most used formulations among personal care products. HPLC and viscosimetric analysis to determine the optimal dose of irradiation for finished product treatment and chemical stability were performed on irradiated and non-irradiated products.

# FORMULATIONS

Shower gels and emulsions were evaluated in this work.

## *Shower gels*

In house-made shower gels (5) were realized with demineralized water, sodium laureth sulfate, cocamidopropylbetaine, cocamide DEA, sodium chloride, lactic acid. All the chemicals were mixed and the formulation was omogenized with a turbo-emulsifier.
Tartrazine (19140), Sunset Yellow FCF (15985), Carmoisin (14720), Ponceau 4R (16255), Patent Blue V (42051), Indigotin (73015), Brilliant Black (28440), Acid Red (17200), Acid Violet 43 (60730), Brilliant Blue FCF (42090), Allura Red AC (16035), Quinoline Yellow (47005), Solvent Violet 13 (60725), Fast Green FCF (42053), Acid Orange 7 (15510), Orange G (16230) were added to in-house made shower gels formulations.
Seven commercial shower gels with different composition and dyes's content were also studied; in house formulated and commercial products were both treated with gamma rays at 10 kGy and analyzed with HPLC-UV-Vis-DAD to evaluate the influence of water content on azo-dyes stability. Viscosity, related to increasing stress rate, was determined with two different kind of viscosimeters.

## *Emulsions*

In house O/W emulsions were obtained with Brij 56, glyceryl monostearate, wheat germ oil, vitamin E acetate, glycerin, propylene glycol 5, sorbitol, glycolic acid solution, demineralized water. Oil phase was dropped into acqueous phase at the same temperature and mixed with a turbo-emulsifier.
In house W/O emulsions were realized with: beeswax, Liquid wax jojoba, oil vaseline, hydrogenated castor oil, olive oil, spermaceti, vitamin E acetate, sodium borate, demineralized water. Acqueous phase was dropped into oil phase at the same temperature and mixed with a turbo-emulsifier.
Three different viscosity levels in both emulsion formulations were obtained with increasing carbopol content (0% - 0.5% - 2%). Solvent Violet 13 (60725) and Brilliant Blue FCF (42090) were added to both emulsion formulations.
Gamma treatment was performed on packed products in plastic containers. Emulsions contained in PP vials were irradiated at increasing doses from 5 to 10, 20 and 30 kGy.
Powder dyes in solid state (10 mg) contained in PP vials were irradiated at 10 kGy and analyzed by UV-VIS spectrophotometry.

# METHODS

## *HPLC analysis*

Shower gels were dispersed and homogenized with MeOH in a volumetric flask, mixed and filtered on 0.5 μm Whatman PTFE filter, while emulsions were extracted with THF in a volumetric flask, mixed and filtered. Samples were injected in the HPLC system (Agilent, Infinity 1260 Binary pump system and Diode Array Detector, Palo Alto, CA). Chromatographic analyses were carried out on a C18 reversed phase stationary phase (Kinetex XB-C18 100 Å,

150x4.6 mm I.D.) with a C18 safeguard pre-column (SecurityGuard Cartridge Phenomenex), under gradient conditions, by using as mobile phase 0.1 M sodium acetate aqueous solution at pH 6.7 (A) and Acetonitrile (B) (99% to 65% (A) in 21 min) with a flow rate of 1 ml/min. UV-Vis detection was accomplished in the 400 to 630 nm range for azodyes' quantification, and at 260 nm for methylparaben.

### Spectrophotometric analysis

UV-Vis spectrophometric analysis was performed with a double-beam spectrophotometer on aliquots of 10 mg of powder dyes, dissolved in demineralized water and/or methanol and diluted in a volumetric flask to 0.02 mg/mL or 0.050 mg/mL.
UV-VIS spectra of the resulting solutions were registered in the UV-Vis range comprised between 400 and 630 nm. Formulations with additives and antioxidants, added together or separately, were extracted and diluted with methanol. UV-Vis spectra were registered in the UV-Vis range comprised between 400 and 630 nm.

### Viscosimetric analysis

Reological analyses were carried on the non irradiated and irradiated emulsions samples to evaluate the effect of different irradiation doses on emulsion stability.
Viscosimetric analysis was carried out by a rotational viscometer (Viscometer Rotational BROOKFIELD mod. DVII+PRO), for formulations 1 and 2 of O/W emulsions, and rotational rheometer (Rheometric Scientific SR5 Universal Stress Rheometer) for formulations 3 of O/W and 1,2 and 3 of W/O emulsions. SR 5 Rheometer was used for measuring dynamic rheological properties. Shear stress was applied to a sample of emulsion sandwiched between two parallel plates (25 mm) and resulting shear stress was monitored as a function of frequency.
Based on stress measurements, viscosity can be obtained at different temperatures, frequencies and strain levels for samples. Measurements were taken at 25° C and samples were sandwiched between two parallel plates set at the distance of 0.5 mm, one of which is fixed and the other one is an oscillating type.

## RESULTS

### Shower gels

Gamma treatment of cosmetic products was performed in order to identify the best conditions for different type of formulation and additives. In fact, irradiation dose may affect products stability, especially when labile additives are present. On the basis of these evidences, the 10 kGy irradiation dose for all the shower gels formulations, containing the dyes reported in Table I, was chosen to perform a safe decontamination, based on a validated process and experimental evidences.
The irradiated in house formulations did not show any difference in texture and macroscopic stability, while color appeared significantly changed in most of the formulations. Dyes' resistance, in particular, is strongly influenced by the applied irradiation dose (6).
In order to identify dyes degradation molecular mechanisms in shower gels, the evaluation of chemical stability was accomplished by HPLC (7,8). Dyes'determination in washing products was carried out after gamma treatment: in particular, molecular differences between azodyes and other classes of dyes (Table I) were found to play an important role.

**TABLE I**

*Dyes added to cosmetic formulations.*

| Dyes | Color index | Chemical structure | UV detection at Λmax (nm) |
|---|---|---|---|
| Tartrazin | 19140 | Azo | 414 |
| Sunset Yellow FCF | 15985 | Azo | 482 |
| Ponceau 4R | 16255 | Azo | 515 |
| Blu Patent V | 42051 | Triphenylmethane | 637 |
| Indigotin | 73015 | Indigoids | 612 |
| Brilliant Black BN | 28440 | Azo | 575 |
| Acid Violet 43 | 60730 | Antraquinone | 568 |
| Brilliant Blue FCF | 60725 | Triphenylmethane | 630 |
| Allura Red AC | 42053 | Azo | 498 |
| Solvent Violet 13 | 15510 | Antraquinone | 576 |
| Fast Green FCF | 47005 | Triphenylmethane | 623 |
| Acid Orange 7 | 16035 | Azo | 485 |
| Acid Yellow 3 | 16230 | Indigoids | 414 |
| Orange G | 42090 | Azo | 478 |

The first test to assess chemical stability of azo dyes in low-viscosity formulations, in order to identify the optimal conditions for gamma treatment, was carried out by performing in house-made shower gels treatment at a dose of 10 kGy, that has led to the disappearance of the color in each of the aliquots irradiated.

The hypothesis for the explanation of this phenomenon regards dye's concentration and the ability, by gamma radiation, to produce water activation leading to the formation of free radicals able to create destructive interactions with the dyes (9). Considering the structure of the dyes, mostly belonging to the class of azo compounds, it must be considered that the disappearance of coloration is due, probably, to a breakage in the azo groups. Since the color is mainly due to the azo groups conjugated with the other parts of the molecules (10), the first effect of radiation is most probably the breakage of the double bond of these groups. The radiolysis of aqueous solutions produces reactive species that may react with the additives in the solution.

As OH radical is a strong oxidizing agent, oxidation of the additive solute generally occurs. The number of OH radicals formed is a function of the absorbed dose; therefore, the irradiation dose determines the number of solute molecules that may be oxidized (11).

To exclude other variables and to understand whether the formulation itself is responsible for a poor stability, due to the pH or the presence of not appropriate preservatives, seven commercial formulations characterized by a lower water content and higher viscosity grade, containing dyes of the same range used in previous rounds, were considered.

The formulations were placed inside glass jars and treated by gamma irradiation at a dose of 10 kGy. Among the seven irradiated products some showed a more subdued color, others resulted more opaque while others became practically transparent. When treated at 10 kGy, azodyes, known to be easily degraded, were found to longer resist if included in high viscosity grade house-formulated, or commercial shower gels

formulations in a low water content environment.
This behavior was found consistent with a mechanism of azodyes degradation involving water hydroxyl radical attack to the azo functional group (12) reduced by the presence of antioxidants and additives as butylhydroxyanisole (BHA) and methylparaben in high viscosity and 'water-caged' formulations.
In order to clarify the mechanism of degradation of azodyes in shower gels, two different types of antioxidant agents were added to the formulations with high water content: methylparaben and buthylhydoxyanisole (BHA) together or separately to formulations at 0.5% w/w.
Among the chemical structures considered, Brilliant Blue FCF (c.i. 42090), a triphenylmethane derivative, resulted the most resistant dye, presumably because of the absence of azo-functional group, less-attractive for hydroxyl radicals. Both in commercial and in-house made containing antioxidants formulations, Brilliant Blue was found to be significantly more visible and stable after gamma treatment.
As a further and important confirmation of this mechanism involving water radicals, the powder dyes in solid state and no humidity, irradiated at 10 kGy showed high stability grade after gamma irradiation. Even in this case, among the non-azo dyes, Brilliant Blue FCF, showed the highest resistance. UV-VIS spectra of the powder solid dyes were registered, showing that the remaining percentage was very high with no significant changes in color perception. This evidence led to a further confirmation of the dye instability by irradiation due to high water content.
As a matter of fact, water content exerts a strong influence on the chemical stability of dyes; according to the previous evidences, the influence of O/W and W/O emulsions, characterized by low water content and higher viscosity grade, was evaluated.

## Emulsions

In house preservatives-free emulsions as moisturizers were formulated with natural raw materials (13) and no labile functional groups.
Three different levels of O/W and W/O emulsions with increasing viscosity and carbopol content from 0 to 2% were formulated (Table II); non-azo dyes as Solvent Violet 13 and Brilliant Blue FCF were added as probes of stability and showed high resistance.

**TABLE II**

*In house prepared emulsions.*

| **O/W Formulation** | **% carbopol** | **dyes** |
|---|---|---|
| **1:** low viscosity | 0% | Solvent Violet 13 |
| **2:** medium viscosity | 0.5% | Brilliant Blue FCF |
| **3:** high viscosity | 2% | Brilliant Blue FCF |
| | | |
| **W/O Formulation** | **% carbopol** | **dyes** |
| **1:** low viscosity | 0% | Solvent Violet 13 |
| **2:** medium viscosity | 0.5% | Brilliant Blue FCF |
| **3:** high viscosity | 2% | Brilliant Blue FCF |

In both O/W and W/O formulations, Solvent Violet 13 remained unaltered up to 30 kGy (Figure 1), a very high dose if we consider that the typical dose for cosmetic product decontamination is 10 kGy. This effect is probably due to a more lipophilic profile of the dye and a higher affinity to the oil phase, less attractive for hydroxyl radicals from water. The chemical analysis performed by HPLC showed a low degradation only at values higher than 10 kGy.
Brilliant Blue FCF, more hydrophilic, showed good stability from 0 to 10 kGy and a significative degradation only at values higher than 10 kGy.

***Fig. 1*** *Solvent Violet 13 before and after gamma treatment in O/W and W/O emulsions.*

As one of the most important aspect in emulsions stability, rheological/textural properties of cosmetic products such as creams, lotion and gels as well as rheological behaviour of human skin (14), were evaluated by viscosimetric analysis on O/W and W/O emulsions before and after treatment at different doses, by using a rheometer. The rheometer simulates the action of a human finger touching the surface and probing the properties of the formulation. Results showed that gamma rays treatment did not significantly affect the viscosity grade and emulsion texture in all the analyzed formulations (15, 16). As mentioned above, emulsion stability plays very important role in personal care products processing. In the present study the effect of total irradiation dose on cosmetic product emulsion stability has been observed (17). The formulations reported no appreciable changes in viscosity and in homogeneity of the biphasic system, which indicates a good resistance to treatment, in particular up to 10 kGy. No phase separation in irradiated aliquotes, even at higher doses, was registered, when compared to non-irradiated sample, and texture maintained rheological characteristics unchanged.
For 1- and 2-O/W formulations, characterized by a high fluidity grade, a rotational viscometer was used. This instrument is able to detect viscosity, measured in mPa·s, values expressed as the force exerted by a metal cylindrical rotor inserted into the product.
This measurement allowed to appreciate for up to 10 kGy irradiated formulations non-significant differences in the values of viscosity in the samples, while greater differences may be noticed at higher doses (20-30 kGy).
For formulation 3-O/W (Figure 2), characterized by a higher viscosity, due to the addition of a greater amount of texturizing agent, a rotational rheometer was used, so that the viscosity was measured at room temperature by applying a stress in a range of frequencies between 0.1 and 15 Hz.

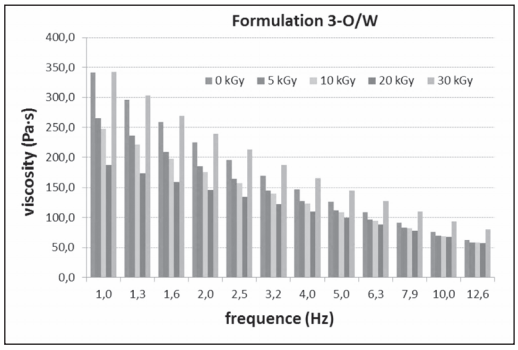


***Fig. 2*** *Viscosity evaluation of O/W emulsion for Formulation 3-O/W (see Table II).*

The behavior of the formulation was almost the same for all the doses considered, despite the initial values of viscosity resulted to be slightly different. In particular from 0 to 20 kGy, we noted a progressive decrease of the initial value of viscosity with an increase at 30 kGy; however,

stress increasing, the viscosity decreased to reach values almost identical for all aliquots. Instead, the dosages of 5 and 10 kGy show an evolution trend and initial values of viscosity very similar.

As in the case of the O/W formulations, the W/O emulsions viscosity showed a similar pattern, under rheometer increasing stress. Nevertheless, in this case some rises of the viscosity appear at intermediate dosing levels. This phenomenon, that seems to make the latter parameter adjustable according to the irradiation intensity, will be investigated in our future research steps. However, by increasing the irradiation dose, initial viscosity values were found slightly different, then reaching similar values at higher applied stress.

The gap of the initial values of viscosity is wider for formulations characterized by higher fluidity, while decreasing in the case of the formulation 3-W/O (Figure 3), characterized by a high viscosity, thanks to the presence of a higher amount of texturizing agent (carbopol). The reason behind this phenomenon may be due to different texture that characterizes the formulations, highlighting the important role of thickening agent in reducing the fluidity of the system and increasing the 'caged' water.

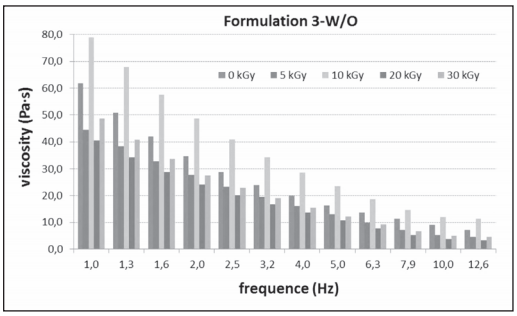


***Fig. 3*** *Viscosity evaluation of W/O emulsion for Formulation 3-W/O (see Table II).*

# CONCLUSIONS

These preliminary studies demonstrated that by adjusting the appropriate formulation ingredients it is possible to tailor cosmetic products, which maintain their chemico-physical properties and texture, when sanitized by gamma rays.

Azodyes were used as probe of stability and found to be easily degraded when inserted in high water content environment in low viscosity formulations; thanks to the absence of the azo group, Brilliant Blue, a triphenylmethane derivative, and Solvent Violet 13, were found to be resistant when included in emulsions formulation with lower water content.

Additional antioxidant, such as BHA, protected dyes from degradation and confirmed the mechanism of azodyes degradation involving water hydroxyl radical attack to the azo functional group. This phenomenon can be reduced by the presence of antioxidants, in high viscosity and "water-caged" formulations.

When treated up to 10 kGy, the typical dose for cosmetic raw material and finished product decontamination, emulsions showed good stability related to texture, color persistence and phase homogeneity.

These encouraging results are a good starting point to accomplish further studies aimed to develop stable cosmetic formulations tailored to be sanitized by gamma rays.

Further analytical studies are ongoing focused on chemical stability of the single ingredients of cosmetic formulation to reinforce the application of this technology in cosmetic field.

Raw material, finished products and inorganic dyes will be deeply investigated before and after treatment to deepen mechanisms and behaviors to find out the best conditions to apply gamma treatment.

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# Alopecias. Practical Evaluation and Management

**by D. Ioannides and A.Tosti**

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The human hair growth is cyclical so that its follicle undergoes intermittent periods of growth when a new hair is produced, followed by periods of quiescence, when resting hair is retained. All human hairs show various stages of hair growth: the so called anagen or growth phase that lasts about 6 years; the regression catagen phase of about 3 weeks, and the resting telogenic phase of about 3 months. While on one hand anagen duration varies depending on age, season, anatomic region, sex, hormonal levels, and genetic predisposition, on the other hand the physiological trigger mechanism for the initiation of each hair cycle remains the main problem concerning the control of hair growth. Thus, it is estimated that the healthy individual loses 100 hairs daily and each follicle completes its cycle 10-20 times over a life-time. Unfortunately, the mechanism of cycle activation is unknown, but could involve a diffusible direct cell-cell contact. The biologic clock determining the end of the anagen phase and the beginning of the cartagen-telogen phase is, in fact, a complex phenomenon in which multiple proteins partecipate.Various metabolic and physiologic changes are capable of adjusting this biologic clock within hair follicles, and it is possible to enter the telogen phase simultaneously for abnormally large number of hairs. When this happen, approximately 300 hairs are shed daily. However, hair growth on the scalp can last for several years, and the duration is dependent on the continued activity of the matrix cells. But hair cycle is also affected during the aging process, especially with respect to the duration of the growth and resting phases. As an individual ages, the duration of telogenic become longer, probably as a consequence of the declining capability of hair follicle stem cells to initiate the anagen cycle. These and other news are reported on **Chapter 1:** *Normal and Aging Hair Biology and Structure "Aging and Hair"*.

*Evaluation of Hair Loss* is the topic discussed on **Chapter 2**. The evaluation of a patient problems is, in fact, a fundamental step for the correct diagnosis of disease, so that time should be spent to get all the necessary anamnesis data. It includes a clinical history and patient evaluation followed some time by invasive and non-invasive tests, such as, for example, dermoscopy. In any way, when approaching a patient with hair problems, it is mandatory to consider the strong psychological impact of hair diseases, often associated with severe emotional distress. Thus, the reason for the consultation should be asked the patient and the visit should be carried out in a well-lit area with a lamp to increase its illumination.

Clinical evaluation includes the hair aspect, size, density and its distribution at the marginal areas, such as front, temples, parietal and occipital. The fronto-temporal hair margin is typically involved in male androgenic alopecia, as well as the thinning of the hair of the fronto-parietal areas, is often the only symptom in chronic telogen effluvium, while loss of eyelashes is a typical feature of frontal fibrosing alopecia. Moreover a careful evaluation of the skin is also necessary both on the face and on the whole body which may reveal an increased number of hairs and increased hair size hirsutism, as well as localized or diffuse hypertrichosis or diffuse or patchy alopecia. Finally the pull test should be utilized together with trichogram, tug test, hair weight and hair card test, all techniques useful for a correct diagnosis.

Trichoscopy enhances the diagnosis of different forms of hair loss, thus reducing the need for scalp biopsy. It, in fact, represents a valuable non-invasive technique for the evaluation of patients with loss that allow for magnified visualization of the hair and scalp skin. Particularly, this technique enhances the diagnosis of androgenic alopecia, telogen effluvium, trichotillomania, congenital triangular alopecia, scarring alopecia, tinea capitis and hair shaft disorders. However, trichoscopy is a method simple, quick, well accepted by patients, and easy to monitor both treatment and follow-up. This topic amply treated and discussed on **Chapter 3:** *Scalp Trichoscopy or Trichology.*

Male baldness is a genetically determined condition androgen-determined by dihydrotestosterone that might significantly impact quality of life, reducing self-esteem and increasing stress. This topic, reported on **Chapter 4**, *Androgenic, Diffuse and Senescent Alopecia in Men: Practical Evaluation and Management*, encompasses the most important aspects of the practical evaluation and management of male baldness. The majority of men seeking dermatological consultation concerning hair loss are easily diagnosed by clinical exam alone, according to the characteristic distribution of hair loss with a decreased density of hair in the superior scalp. Scalp hair follicles, in fact, decrease in size and activity during the hair cycles so that terminal hair become thinner, shorter and less pigmented. This miniaturizing process is driven by an inhibitory follicle response to the androgen hormone dihydrotestosterone (DHT) at the level of dermal papilla cells.

DHT is a metabolite of testosterone and androstenedione, formed through the action of the enzyme 5-alpha-reductase. The binding of DHT to its receptor in hair follicles leads to the increased production of some cytokines, such as transforming growth factor beta 1 and 2 (TNF-beta), which promote senescence in the dermal papilla cells. Established the diagnosis, it is important to explain to the patient the natural course of the condition and the possible treatments, which may vary individually. Oral finasteride and topical minoxidil are the only US Food and Drug Administration-approved as effective medications to treat and prevent the progression of male baldness, also if their mechanism of action remain unclear.

*Female Pattern Hair Loss* is the topic focused on **Chapter 5.** Female pattern hair loss (FPHL), or female pattern androgenetic alopecia, is nonscarring alopecia with a multi-factorial aetiology affecting postmenopausal women. The clinical picture is a diffuse rarefaction of scalp hair over the crown and frontal scalp without signs of inflammation or scarring. Although the disease poses only a cosmetic concern, it is chronic and may have negative psychological impact on the affected person. The diagnosis of FPHL is based on the clinical picture that includes an inquiry about the patient's medical family and social history together with appropriate hair evaluation methods. Various are the available treatments, also if remains unclear which are the most effective. However, while the aim of treating FPHL is to reduce hair loss, the early initiation of treatment combined with different

modalities seem to be more effective than the monotherapy.

Hair problems are not uncommon in the paediatric group, but its patterns are different from those seen in adults. They occur relatively frequently in a wide range of conditions that may be congenital or acquired. Additionally in children, these disorders can have psychological effects that can interfere with growth and development. However, a number of disorders may occur as part of a multisystem syndrome. Thus, a detailed clinical history accompanied by a right examination of hair and scalp are essential for an accurate diagnosis of the pathology, as well as it is important to have a good knowledge of the normal hair cycle, its embryology accompanied by clinical features. However, pediatric hair disorders causes psychological and emotional stresses in both children and parents. A proper diagnostic process helps to distinguish between acquired and congenital hair diseases, and their management has to be adapted according to the age of the patient also if for many of these disorders there is no effective therapy. This interesting topic has been discussed on **Chapter 6:** *Hair loss in Children*.

*Alopecia Areata* is reported on **Chapter 7.** Alopecia Areata (AA) is a common, non-scarring pathology, both genetic and autoimmune, that usually presents well-circumscribed patches of sudden hair loss and affects 0.1-0.2% of the population. It has a significant effect on a patient's quality of life, addressing the psychological aspects of the subjects affected. While the diagnosis of AA is usually made on clinical ground, the treatment of choice remains the intralesional and systemic corticosteroids, also if minoxidil, topical immunotherapy, and anthralin may be used as alternative therapies. Naturally a successful treatment should be focused on the improvement of the psychological impact also.

Scarring alopecia or cicatricial alopecia results from a follicular damage that is sufficient to cause the destruction and replacement of pill sebaceous structures by scar tissue. These alopecias represent a group of disorders that primarily affect the hair follicles as opposed to secondary scarring alopecias, which affect the dermis and secondarily cause follicular destruction. The differential diagnosis requires pathological examination because the clinical features are usually not diagnostic. Cicatricial alopecias that involve lymphocytic inflammation include discoid lupus erythematosus, lichen planopilarus, frontal fibrosing alopecia, central centrifugal alopecia, and pseudopelade (Brocq). On the contrary, when neutrophilic inflammation is involved, cicatricial alopecias include folliculitis decalvans, tufted folliculitis, and dissecting cellulitis of the scalp. Naturally clinical presentations are different and therapies give variable results. This is the topic of chapter 8, Primary Scarring Alopecias, where the different disorders are reported together with a wide discussion on the relative prognosis and treatments.

*Molecular Genetics of Alopecias* is the topic focused on **Chapter 9.** Although hereditary hair disorders are considered to be rare, it is not unlikely for the practicing dermatologist to encounter them in his clinic. Better knowledge of these conditions is, therefore, important for accurate diagnosis and management. The recent understandings of genetic conditions, due also to the developments of new methods and research techniques, have given interesting advancements to the complex regulation of hair growth at molecular level. This improvement has also affected the large scope of genotrichoses, or hereditary hair diseases, which have long been obscure. In addition, the unveiling of the molecular pathways and players that take part in the complex regulation of hair growth, can offer new therapeutic modalities, not only for monogenic genotrichoses but also for more common hair disorders.

The most common alopecias due to drugs and other disorders are discussed on **Chapter 10:**

*Alopecias due to Drugs and Other Skin and Systemic Disorders*. It covers epidemiology, etiology, clinical picture, diagnosis, and current treatments of the more common alopecias, such as telogen effluvium (TE) (acute and chronic), anagen effluvium, folliculotropic mycosis fungoides, folliculitis due to bacteria, fungi and parasites, human immunodeficiency, virus disease, lupus erythematosus, and sarcoidosis. Among all, acute TE is one of the most common causes of hair loss in women, due often to physiologic post-partum or post surgical processes, UV radiation, seasonal changes, crash diets, iron deficiency, urban environment and triggers like contact sensitizers, such as hair dyes.

Chronic TE is a primary idiopathic disease most commonly affecting middle-aged women with a complaint of increased hair shedding and bitemporal recession. In any way, similar to the skin, the hair is exposed to noxious environmental factors and is subject to intrinsic or physiologic aging as well as extrinsic or premature aging due to external factors. The prototypes of intrinsic aging are familiar premature greying and androgenetic alopecia, while the extrinsic factors include exposure to UVR and tobacco smoke. UV degrades hair, attacking its pigments, proteins and lipids, while cigarette smoke contains over 4,800 chemicals, many of which are known to be toxic to cells inducing imbalance in the intra and perifollicular protease/anti-protease systems controlling tissue remodelling may also affect the hair follicle growth cycle. Moreover, smoking-induced oxidative stress and a disequilibrium of the anti-oxidant systems may lead to the release of pro-inflammatory cytokines from follicular keratinocytes, from follicular keratinocytes, which by themselves have been shown to inhibit the growth of isolated hair follicles in culture. Thus, increasing public awareness of the association between smoking and hair loss seems to offer a good opportunity for the prevention or cessation of smoking, since it plays an important role in the overall physical appearance and self-perception of people. Finally, the quantity and quality of hair are closely related to the nutritional state of an individual.

Because the hair shaft is composed almost entirely of protein, the protein components of the diet are critical for the production of normal healthy hair. These topics are reported and discussed on **Chapter 11:** *Effect of Ultraviolet Radiation, Smoking and Nutrition on Hair.*

Alternatively, alopecia can be effectively camouflaged or worsened through the use of hair care techniques and dying. Since hair is a nonliving fiber it is important to minimize its damage because it is permanent, as repair is not possible. However, with time, the hair undergoes weathering due to the trauma that it sustains from combing, brushing, shampooing, heat, wind friction and UV exposure. All these events cause the cuticular scale to loosen and shed from the hair shaft. As the cuticle is lost, the weak cortex is exposed, producing a phenomenon medically known as trichoptilosis and commonly known as spit end. At this purpose it is to underline that alopecia patients may develop an obsession with their hair appearance, resulting in excessive combing and brushing, encouraging the cuticle loss. This is the topic focused on **Chapter 12**, *Hair Care and Dying,* that examines how cosmetic procedures can be used to camouflage alopecia while minimizing hair damage as well as how to use hair care products and hair dying in the patient with hair loss.

Humans are social mammals that communicate disproportionately via potent genetic signals imbued in the skin and hair. Hair follicle (HF) pigmentary unit is, therefore, a wonderful tissue for studying mechanisms genetically regulating hair greying and aging, because age-related hair pigment loss become the inescapable signal of the disappearing youth. And *Age-Related Hair Pigment Loss* is the topic reported and discussed on **Chapter 13**. Given that follicular melanocytes are regulated by the hair cycle, this cycle is likely to impact the process of aging in the HF pigmentary unit. Regardless

hair greying, an age-related imbalance seems to be involved in the tissue's oxidative stress impacting not only the melanogenesis process but also melanocyte stem cell and melanocyte homeostasis and survival. At this purpose, some emerging evidences suggest that the HF pigmentary unit may have regenerative potential by cytokines-induced activation, even after it has begun to produce white hair fibers. Therefore the future looks bright for human hair pigmentation research, focused especially on the function of the follicular dermal papilla and amelanotic melanocytes distributed in the outer root sheath of human scalp HFs.

The management of hair and scalp conditions is difficult in any patient, also because the emotional and psychological implications of hair loss cannot be underappreciated. In the ethnic patient, the treatment of these diseases has an extra layer of complexity, because of his/her varied hair shaft and architecture, as well as the different grooming and hair care practices. It is imperative that the physician be knowledgeable about these practices and phenotypic differences seen in ethnic hair in order to appropriately diagnose and treat these patients. Traction alopecia, for example, affects almost all black women to some degree of severity. This is the topic focused on **Chapter 14**, *Ethnic Hair Disorders,* where the most prominent conditions of ethnic hair have been reviewed, such as acquired trichorrhexis nodosa, traction alopecia, central centrifugal cicatricial alopecia, pseudo folliculitis barbae, dissecting cellulitis, and acne keloidalis nuchae, reporting both diagnosis and treatments.

The last **Chapter 15**, *Advanced in Hair Transplantation: Longitudinal Partial Follicular Unit Transplantation* reports the different techniques dedicated to the most known hair transplantation methods.

Featuring contributions by well known experts in the field, this interesting book covers important scientific and clinical aspects of the alopecias reporting their diagnosis and therapy. Academic and industrial pharmaceutical researchers as well as students in medicine, and in cosmetic dermatology will find the book an essential guide to try to solve the difficult problems regarding all the pathological aspects of the hair alopecias.

P. Morganti
Editor-in-Chief

# Carbohydrate Chemistry: State of the Art and Challenges for Drug Development

**by Laura Cipolla**

2016. Pages 506. Hardcover
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The circulating glucose serves as a fuel for energy metabolism and as substrate for biosynthesis of polysaccharides, lipids, nucleic acids, and proteins. The growing knowledge about carbohydrate involvement in physiological and pathological states has spurred renewed interest in the chemistry, biology and therapeutic for the potentialities of these natural compounds. Moreover, the need of carbohydrate multivalent activities has led to the synthesis of a plethora of compounds based on different scaffolds. Their language requires, in fact, a huge effort to be learned, but is meant to be one the most spoken in the future of drug development.

This book organized in **V Parts and 19 Chapters**, reports and discusses the key aspects of carbohydrate biology and chemistry, fundamental to design and market novel therapeutics.

**Part I:** *Structure and Biological Function of Glycoconiugates*, introduces the reader to the fields of glycoproteins, gangliosphingolipids and bacterial lipo-polysaccharides giving a wide report on their chemical structure and biological roles. On **Chapter 1**, *Glycoproteins: Chemical Features and Biological Roles*, the important biological role of glycoproteins is focused. They can serve as structural components, lubrificants, protective agents, transport molecules, inhibitors, hormones, and enzymes. The N-Glycans in glycoproteins, for example, affect the folding, stability, solubility, function, and activity of different proteins, while O-glycosylated mucins form viscous gels functioning as cell chemical signalling and barrier. In addition, the terminal sequences of N-and O-GalNAc-glycans serve as recognition molecules and sites for cell-attachment.

Among glycoprotein therapeutics, antibody-based drugs are the largest and fastest growing category and have a wide range of applications, particularly in cancer, immune disorders, and infectious diseases. Establishing cost-efficient and robust system possibilities to produce humanized therapeutic glycoproteins with improved functions and homogeneous forms at industrial scale is reported and discussed on this chapter.

The lipid moiety of vertebrate glycosphingolipids (GSLs) consists of either a shingoid or a ceramide, which is a sphingoid base linked to a fatty acid through an amide bond. Most of the structural variability of gangliosides and GSLs is born by the carbohydrate domain that exhibits a staggering structural diversity. They are important compounds of the plasma membranes involved in many cellular functions, mainly supported by the glycine moiety of gangliosides.This the topic focused on **Chapter 2** *Gangliosphingolipids: Structure and Biological Roles*.

**Chapter 3** reports an overview on the structure, biosynthesis, and immunological activity of the bac-

terial Lipo-polysaccharides (LPSs), also known as *endotoxins*. As the major component of the outer membrane of almost all Gram-negative bacteria and some Cyanobacteria, they have the capability to activate the immune system. LPSs are amphiphilic molecules which contribute to the protection and integrity of the bacterial envelop, organized as a highly ordered structure of a lipid mono layer of low fluidity, stabilized by electrostatic interactions between bivalent cations and negatively charged groups present on LPS molecules. Among all the other activities, LPSs have been shown to be the most potent immunostimulant molecules, playing a key role in the pathogenesis of Gram-negative infections, triggering the immune system in a wide range of organisms ranging from insects to humans.

**Part II** is focused on the latest techniques used to investigate the structure and biological role of carbohydrates, including their interactions with proteins and receptors; it is comprised by chapters 4-7 reporting the most advanced methods necessary to develop the synthesis of carbohydrate-based therapeutics, such as Mass Spectrometry (**Chapter 4**), where the new methodological and analitical aspects about for example, of the glycols moiety of glycoconjugates is reported and discussed. Due to the high importance of glycoconjugates in biology and medicine, in fact, an entire generation of chemists has been involved in solving the structural intricacies of carbohydrates, developing new methodologies for studying the primary structures of the glycan moieties attached to proteins. Advanced NMR techniques, that provide scientists the possibility to study, in solution and at atomic scale, the structure of carbohydrates, is the topic of **Chapter 5.**

Glycoarrays for Glycomics, i.e. the high-throughput bioanalytical screening to evaluate thousand of individual glycan-receptor binding events in a single experiment and with minimum reagent use, is reported on **Chapter 6**.

**Chapter 7**, on the other hand, summarizes the current software and databases that have been developed reporting informatics and analytical tools for glycans analysis and biotherapeutics. The chemical synthesis of complex carbohydrates, in fact, has been a challenge for more than a century due to the diversity and complexity of their structures recovered in mammalians and, composed by building blocks of monosaccharide units. Thus, the first step in the assembly of a complex oligosaccharide is its retro synthetic analysis and, afterwards, the choice of the appropriate building blocks.

The creation of the corresponding building blocks is, therefore, the most time-consuming part of the complete synthesis performed and generated by numerous steps. The different methodologies used have been reported in **Chapter 8**, first chapter of **Part III**, where the chemical synthetic problems solved by the use of enzymes are focused. Enzymatic strategies are an open field of research, with significant applications in glycosciences and industrial biotechnology, addressing the need for simple end efficient methodologies to access structurally defined oligosaccharides, polysaccharides, and glycoconjugates.

The screening of new enzymes and engineered methods is the topic reported and discussed on **Chapter 9**, and the novel technologies for the automation of oligosaccharides synthesis have been discussed on **Chapter 10**. However, until today further development of existing automated synthesis remains a significant area of research and the manual synthesis still remains an important tool to obtain complex oligosaccharides of particularly challenging sequences.

**Part IV**, developed in 8 chapters, is entirely dedicated to the carbohydrate-based compounds used for medical applications.

On **Chapter 11** are summarized the potential possibilities the iminosugers have to mimic some bio-

logical activities, acting as immune modulators and pharmacological chaperons of misfolded proteins. Iminosugers, in particular, are sugar analogs with nitrogen in place of the ring oxygen of the corresponding sugar, while naturally occurring iminosugers are one of the most interesting discoveries and the most fascinating nature arts in the fields of natural product chemistry. The first interest for these compounds was based on their properties as glycosidase inhibitors, while today scientists are also studying their ability for other potential activities.

**Chapters 12, 13,** and **14** are all dedicated to the routine production and use of vaccines, characterized for their high diversity. From the list of 15 vaccines ranked by sales and representing the 15 top-selling of 2012, for example, six are carbohydrate-based vaccines. However, despite the advent of antibiotics, implementation of national vaccination campaigns and intensive care support, bacterial meningitis continues to be an important cause of morbility and mortality among high-risk groups. The common feature of the organisms that cause most of the bacterial meningitis is a carbohydrate capsule with different oligosaccharide patterns that act as both a virulence determinant and target of protective antibody. Therefore, antibodies specifically against bacterial surface polysaccharides may enhance the elimination of pathogenic bacteria. This the reason of cancer immunotherapy, based on tumour-associated carbohydrate antigens (TACAs), as promising alternative to antitumoral treatments, such as surgery, chemo-and/or radiotherapies, often cause of undesired side effects. However, the presence of TACAs in vaccine formulation is indeed necessary to activate B lymphocytes, but are not sufficient to produce high titers of antibodies and to induce reproducible and long-lasting immunity against tumors. In any way, new generations of structures associating 3 and 4 components and unimolecular multiantigenic constructions, represent author bases for further optimization of future vaccine candidates.

**Chapters 15-18** are focused respectively to specific inter cellular adhesion molecule-3 graffing non-integrin (DC-SIGN) that play a key role in human immunodeficiency virus (HIV) transmission, biomaterials and tissue engineering applications, carbohydrate multivalent systems, and antitubercular drugs based on carbohydrate-derived.

On one hand, much work remains to allow the selection of polyvalent scaffolds, ligands and biomaterials optimal in size, shape, and valency, tuned to the supramolecular architecture for antagonizing the majority of pathogens structures that infect humans. On the other hand, early research and fortuitous accidents, linking material chemistry to biological responses, have provided a rationale basis for developing new biomaterials, significantly affected by the biology revolution and the advanced knowledge in genomics, proteomics, and glycomics. At this purpose, it is interesting to underline that carbohydrate structures encode information that modulates interceptions between cells and the extracellular matrix (ECM). Thus, saccharidic motifs are undoubtedly interesting cues to be used for the upgrading of synthetic or natural polymers to smart biomaterials with the ability to cross-talk with their biological environment.

In any way, despite the increasing development of glycomics and methods at disposal for the oligosaccharide synthesis, the application of glycoscience is still scarce and remain a difficult challenge.Glycans are, in fact, not only an important source of metabolic energy, but play also a key role in many relevant biological processes, expressed as glycoconjugates on the surface of the cells. In recent years, there has been an increasing amount of research on the utilization of natural polymeric materials as drug, covering several therapeutic niches, or as drug delivery vehicles due to their high biocompatibility and biodegradability. Their potential uses have not been completely under-

stood yet and probably the future will hold new and challenging opportunities to create many other structures and drugs with interesting biological and therapeutic potential. While the exploration of polysaccharides for their multifaced roles is still in its infancy, the introduction of targeting moieties carbohydrate-based will certainly improve their therapeutic efficacy, reducing also undesired side effects.

This interesting book offers an ample overview of all the fundamental chemical and biological aspects of carbohydrates. Its intelligent editorial organization represents an indispensable guide for the academic and industrial researchers of the medical and chemical communities who wish to be introduced or to understand in a better way the fascinating structural chemical and therapeutic activity of these natural compounds. Moreover its reading may be of great help for students in chemistry or medicine who wish to enter into the mechanisms regulating the cell life in healthy or pathological state.

P. Morganti
Editor in Chief

ICCD 12th
The International Congress of Cosmetic Dermatology
JAKARTA 2016

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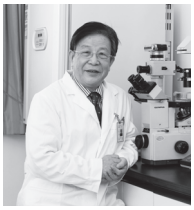

International Society of Cosmetic Dermatology Application & Research

# Greetings from the International Society of Cosmetic Dermatology

Dear friends and colleagues,

The International Society of Cosmetic Dermatology (ISCD) is the first non-profit society of cosmetic dermatology. It was founded in 1982 in Rome and has a scientific history of long run. Its official journal (Journal of Applied Cosmetology) started its first issue in 1983. As you may see on our website (www.iscd.it) the Society has organized 11 international congresses, together with many other regional meetings, held in various locations among both eastern and western countries around the world. These meetings were actively participated by distinguished dermatologists and biologists, such as P.Agache, H Amamatsu, JP Bentley, RN Butler, HD Chen, AC DeGroot, DT Dowing, FJG Ebling, BA Gilchrest, E Handog, S Jablonska, C Jacobson, A Jarret, S Kang, FH Kemper, AM Kligman, N Konnikov, SH Lee, H Lim, T Lotti, HI Maibach, P Morganti, W Montagna, CE Orfanos, JP Ortonne, TJ RyanJ, S Strauss, A Tosti, EJ Van Scott, J Wepierre, W Westerhof, J Uitto and many other scientists worldwide known for their papers and discoveries. Drs. Jian-Zhong Zhang and Xing-Hua Gao, as presidents of the 11th International Congress of Cosmetic Dermatology in Beijing 2014, have contributed a lot to the great success of the last congress.

The future program of ISCD would focus on not only cosmetic dermatology itself but also other disciplines involved in the progress of cosmetic dermatology such as biology, physiology, histopathology, chemistry as well as the multidisciplinary biomaterial science, which involves bioengineering chemistry, clinical and medical medicine, regulatory affairs, bioethics, business administration and commercialization transition. The motto of this Congress in Jakarta is “New Horizon in Cosmetic Dermatology”. We are grateful to Dr. Abraham Arimuko, Dr. Lilik Norawati, and Dr. Irma Bernadetta, as President, Secretary-General and Vice President of this congress respectively, as well as the organizing committee for their hard work in planning and organizing this congress. We wish this congress to be another great success.

Jakarta is the capital city of Indonesia, the close neighbor and good friend of China. This congress in Jakarta will provide us good opportunities to learn from each other and make friends with each other just like Indonesia, Italy and China. Hope countries all over the world maintain the friendships just like the dermatologists and cosmetologists do. Then there will be no war in the world!

We wish all participants enjoy this congress in Jakarta!

Best Regards,

Chen, Hong-duo

Hong-Duo Chen
President ISCD

Pierfrancesco Morganti
Secretary General ISCD

## 12TH INTERNATIONAL CONGRESS OF COSMETIC DERMATOLOGY
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| | Saturday, 2 April 2016 | | |
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| **07:00 – 07:30** | Registration | | |
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| **07:30 – 08:30** | Basic Filler - Hassan Galadari (UAE) | Strategies for Effective Treatment Outcome in Acne – Cheong Wai Kwong (Singapore) | Hyperpigmentation |
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| **07:00 – 08:00** | Registration | | |
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| **08:30 – 09:00** | Coffee Break | | |
| | | | |
| **09:00 – 09:30** | Opening | | |
| | | | |
| | Plenary Session – What's New in Cosmetic Dermatology | | |
| **09:30 – 10:00** | New Horizon in Cosmetic Dermatology: Pierfrancesco Morganti (Italy) | | |
| **10:00 – 10:30** | Trends and Future in Skin Aging Treatment: Hassan Galadari (UAE) | | |
| **10:30 – 11:00** | Acne: Giuseppe Micali (Italy) | | |
| | | | |
| **11:00 – 11:30** | Break | | |
| | | | |
| | SYMPOSIA | | |
| **11:30 – 12:50** | **I. Acne** | **II. Aging Skin Update** | **III. Total Face Approach with CPM & Ultrasound** |
| 11:30 – 11:50 | Update on Acne Pathogenesis Dae Hun Suh (South Korea) | Stem Cell for Aging Skin Yohanes Widodo (Indonesia) | See The Beauty of Sound with Ultrasound Therapy – Edwin Djuanda (Indonesia) |
| 11:50 - 12:10 | Dermocosmetics in Acne Giuseppe Micali (Italy) | Glutathione: Superpower Antioxidant & Skin Lightening – Abraham Arimuko (Indonesia) | Recent Advances in Filler Through CPM Technology – TBA |
| 12:10 - 12:30 | International Consensus in Acne Management – Cheong Wai Kwong (Singapore) | Aging and Grey Hair: News from Melanocyte Biology and Clinical Practice Torello Lotti (Italy) | Harmonized Total Face Approach with Filler & Ultrasound Therapy – TBA |
| 12:30 – 12:50 | Efficacy of Nicotinamide Plus Cream as Adjunctive Therapy for Acne: Indonesia Experience – Irma Bernadette (Indonesia) | Hormonal Aspects in Skin Aging Edwin Djuanda (Indonesia) | Low Concentration Hyaluronic Acid for Fine Lines and Skin Hydration Lis Surachmiati (Indonesia) |
| **12:50 - 13:50** | Lunch | | |
| | | | |
| | SYMPOSIA | | |
| **13:50 – 15:10** | **IV. Update on Light Sources in Dermatology** | **V.Miscellaneous Anti Aging** | **VI. What's New in Cosmetics** |
| 13:50 - 14:10 | Phototherapy for Rejuvenation Henry W. Lim (USA) | Glutathione Precursors as Skin Lightening – Titi Moertolo (Indonesia) | Herbal Cosmetics – Anna Setiadi Ranti (Indonesia) |
| 14:10 - 14:30 | Phototherapy for Acne Vulgaris Keyvan Nouri (USA) | The Importance of Hyaluronic Acid in Keeping The Skin Young Edwin Djuanda (Indonesia) | Enhancement of Drug's Topical Delivery – Joshita Djajadisastra (Indonesia) |
| 14:30 – 14:50 | PDT for Aesthetic Indications – Henry W. Lim (USA) | Antioxidants and Low Dose Oral Cytokines and Growth Factors - The Novel Paradigm in Photoprotection and in Photoaging - Torello Lotti (Italy) | The Role of Growth Factors in Wound Healing – Danu Mahandaru (Indonesia) |
| 14:50 - 15:10 | Laser for Nail Disorders – Keyvan Nouri (USA) | Epigenetic Changes in Skin Aging in Vivo Sewon Kang (USA) | The Side Effect of Cosmetics Retno Widowati Soebaryo (Indonesia) |
| | | | |

| 15:10 – 16:30 | VII. IMCAS | VIII. What's New in Laser, Light, and Energy-Based Device System | IX. Nanotechnology in Cosmetics |
|---|---|---|---|
| 15:10 - 15:30 | From Anatomy to Main Indications: a 2016 Updated (Orbit, Nose, Mid & Lower Face, Neck, Décolleté, Temple, Hands) – Benjamin Ascher (France) | State of The Art in Tattoo Treatment: New Lasers and Concepts - Andreas Widiansyah (Indonesia) | Technological Aspects of Nanocosmetics Etik Mardliyati (Indonesia) |
| 15:30 – 15:50 | Concepts of Asian Beauty: Trends, Structural Anatomy, and Augmentation Adri Prasetyo (Indonesia) | New Perspective in Lasers and EBD Treatment for Pigmented Problems David Sudarto Oeiria (Indonesia) | International Regulation of Nanocosmetics – Sonia Selletti (Italy) |
| 15:50 - 16:10 | The Microwave Technology in treating Axillary Hyperhidrosis and Osmidrosis Po Han Huang – (Taiwan) | Laser for Acne – Prof. Goh Chee Leok | Use of Nanotechnology in Plastic Surgery Department Tommaso Anniboletti (Italy) |
| 16:10 – 16:30 | Restructuring Aesthetic Learning with IMCAS – Benjamin Ascher (France) | Scars Wars: Laser and EBD for The Treatment of Scars and Keloids – Aryani Sudharmono (Indonesia) | Indonesian Regulation on Nanocosmetics – Hary Wahyu (Indonesia) |
| | | | |
| **16:30-17:00** | Coffee Break | | |
| | | | |
| | SYMPOSIA | | |
| **17:00 – 18:20** | | **X. Hair Disorders** | **XI. Free Paper Communication** |
| 17:00 - 17:20 | | Common Hair Loss and Related Diseases – Rataporn Ungpakorn (Thailand) | |
| 17:20 – 17:40 | | Pathogenesis of Seborrheic Dermatitis – Dae Hun Suh (South Korea) | |
| 17:40 - 18:00 | | Hair Transplant – Gunawan Budisantoso (Indonesia) | |
| 18:00 – 18:20 | | The Latest Treatment of Alopecia – Iwan Trihapsoro (Indonesia) | |
| | | | |
| **18:20 – 18.50** | Door Prize | | |

## 12TH INTERNATIONAL CONGRESS OF COSMETIC DERMATOLOGY
## TEACHING COURSE

| | **Sunday, 3 April 2016** | | |
|---|---|---|---|
| | | | |
| **07:00 – 07:30** | Registration | | |
| | | | |
| **07:30 – 07:50** | Laser Treatment for Congenital or Acquired Pigmentary Lesions in Asian Skin – David Soedarto Oeiria (Indonesia) | An Improved Technique for Isolation of Adipose Derived Stem Cells and Its Transplantation as Stromal Vascular Fraction in Combination with Biomaterial Scaffolding: Dermatology Aspect Reza Y. Purwoko (Indonesia) | Advanced Filler Hassan Galadari (UAE) |
| **07:50 – 08:10** | Keys of Success in The Treatment of Melasma and Pigmentation with Lasers in Asian Skin – Aryani Sudharmono (Indonesia) | | |
| **08:10 – 08:30** | Laser Tattoo Removal in Asian Skin – M. Yulianto Listiawan (Indonesia) | | |

## 12TH INTERNATIONAL CONGRESS OF COSMETIC DERMATOLOGY
## SYMPOSIUM PROGRAM PLAN

| | **Sunday, 3 April 2016** |
|---|---|
| | |
| **08:30 – 09:00** | Coffee break |
| | |
| | **Plenary** |
| **09:00 – 09:30** | Challenges for Dermatologist in Cosmetic Dermatology – Xing-Hua Gao (China) |
| **09:30 – 10:00** | Melanocyte Biology - Amit G. Pandya |
| **10:00 – 10:30** | Regulation and Ethical Aspects of Cosmetic Dermatology – M. Nasser (Indonesia) |
| | |
| **10:30 – 11:00** | Break |

| | SYMPOSIA | | |
|---|---|---|---|
| **11:00 – 12:20** | **XII. Acne Scar Management Update** | **XIII. Hyperpigmentation Update** | **XIV. Master Class on Vitiligo** |
| 11:00 – 11:20 | Pathogenesis of Acne Scars<br>Sewon Kang (USA) | Update on Management of Hyperpigmentation Disorder<br>Amit G. Pandya (USA) | Pathogenesis and Overview of Vitiligo<br>Tjut Nurul Alam (Indonesia) |
| 11:20 – 11:40 | Treatment of Acne Scar – Goh Chee Leok (Singapore) | Combination Peel for Hyperpigmentation<br>FX. Hanny Suwandhani (Indonesia) | What's New, What's True in 2016: The Therapeutic Pipeline for Vitiligo<br>Torello Lotti (Italy) |
| 11:40 – 12:00 | Moisturizer in Acne – Irma Bernadette (Indonesia) | Management of Erythema and Hyperpigmentation Post Acne<br>Lili Legiawati (Indonesia) | Phototherapy in Vitiligo – Henry Lim (USA) |
| 12:00 – 12:20 | Sunscreen in Acne, How and When?<br>Rataporn Ungpakorn (Thailand) | Pro and Cons in Hyperpigmentation Management – Rointan Simanungkalit (Indonesia) | Non Steroid Immunomodulators in Management of Vitiligo Progression<br>Torello Lotti (Italy) |
| | | | |
| **12:20 – 13:20** | Lunch | | |
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| | SYMPOSIA | | |
| **13:20 – 14:40** | **XV. Master Class on Vitiligo** | **XVI. Aging Skin Update** | **XVII. Pharmacology of Cosmetic** |
| 13:20 – 13:40 | Fractional Laser-aided Penetration of Slow-releasing Corticosteroid Plus NB-UVB to Treat Recalcitrant Stable<br>Xing-Hua Gao (China) | The Role of Growth Factors in Skin Care and Management for Elderly People<br>Ahmed Al Qahtani (USA) | Pharmacology of Cosmetic Ingredients<br>Widji Soeratri (Indonesia) |
| 13:40 – 14:00 | Biobanking Specimens for Vitiligo<br>Yan Valle (USA) | Kudzu Acetic Acid: A New Natural Peel for Facial Rejuvenation – Kim Won-Serk (South Korea) | Green Ingredients in Cosmetic Dermatology – Pierfrancesco Morganti (Italy) |
| 14:00 – 14:20 | Punch, Blister and Cellular Grafting for Vitiligo – Amit G. Pandya (USA) | The Latest Trend of Laser and Energy Based Devices for Skin Rejuvenation<br>Amaranila Lalita Drijono (Indonesia) | Chemical Body Peel with Bearberry Extract – Abraham Arimuko (Indonesia) |
| 14:20 – 14:40 | Major Mistakes in Approaching the Vitiligo Patients – Torello Lotti (Italy) | Fractional Microneedle RF and Fractional CO2 Laser: How to Choose and Combine These Two Fractional Techniques to Achieve Optimal Results<br>Dr Michaël Naouri | Men's Cosmetic Update – Reti Hindritiani (Indonesia) |
| | | | |
| **14:40 – 16:00** | **XVIII. Miscellaneous** | **XIX. Skin Tightening** | **XX. Free Paper Communication** |
| 14:40 - 15:00 | IPL for Aesthetic Indications – Khunadi Hubaya (Indonesia) | Threadlift: Does It Really Work?<br>Abraham Arimuko (Indonesia) | |
| 15:00 – 15:20 | Body Contouring – Elizabeth Houshmand | Mini Facelift – Syarief Hidayat (Indonesia) | |
| 15:20 – 15:40 | Nano Fractional RF for Advanced Skin Rejuvenation – 4D Multi-Polar RF & PMEF Technology for Face, Neck, and Body – Elizabeth Houshmand (USA) | Skin Tightening and Contouring With Laser and Energy Based Devices: How Far Can We Go? – M. Yulianto Listiawan (Indonesia) | |
| 15:40 – 16:00 | Metals in Cosmetic Ingredients<br>Sondang P. Sirait (Indonesia) | Vaginal Tightening – TBA | |
| | | | |
| | SYMPOSIA | | |
| **16:00 – 17:20** | **XXI. Invasive Procedures in Cosmetic Dermatology** | **XXII. Cosmetic Dermatology for Skin of Color** | **XXIII. Miscellaneous** |
| 16:00 – 16:20 | Face Anatomy Unit for Flaps and Grafts<br>Dr. Sri Lestari KS | Traditional Eastern Cosmetic – Idrianti Idrus (Indonesia) | Green Treatment in Skin Aging<br>Tommaso Anniboletti (Italy) |
| 16:20 – 16:40 | Liposuction - Susanti Budiamal (Indonesia) | Emerging Cosmetics and Cosmeceuticals<br>Sjarif M.Wasitaatmadja (Indonesia) | What is Sensitive Skin? Is There an Agreed-On Definition? – Irma Bernadette (Indonesia) |
| 16:40 – 17:00 | Bromhidrosis – Indah Yulianto (Indonesia) | Role of Dermocosmetic in Dermatology<br>Cheong Wai Kwong (Singapore) | The Trend and Future of Cosmetic Dermatology – Retno I. Tranggono (Indonesia) |
| 17:00 – 17:20 | Invasive Procedure for Eyebag<br>Kun Jayanata (Indonesia) | Antioxidant in Aging Skin<br>Theresia L. Toruan (Indonesia) | How to Prevent Side Effect in Acne Therapy – Sjarif M.Wasitaatmadja (Indonesia) |
| **17:20 – 17:50** | Door Prize and Closing | | |

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**Electrospinning of Chitin Nanofibrils (CN) at SEM**


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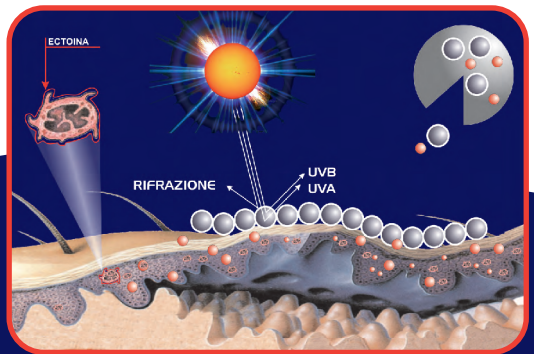


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