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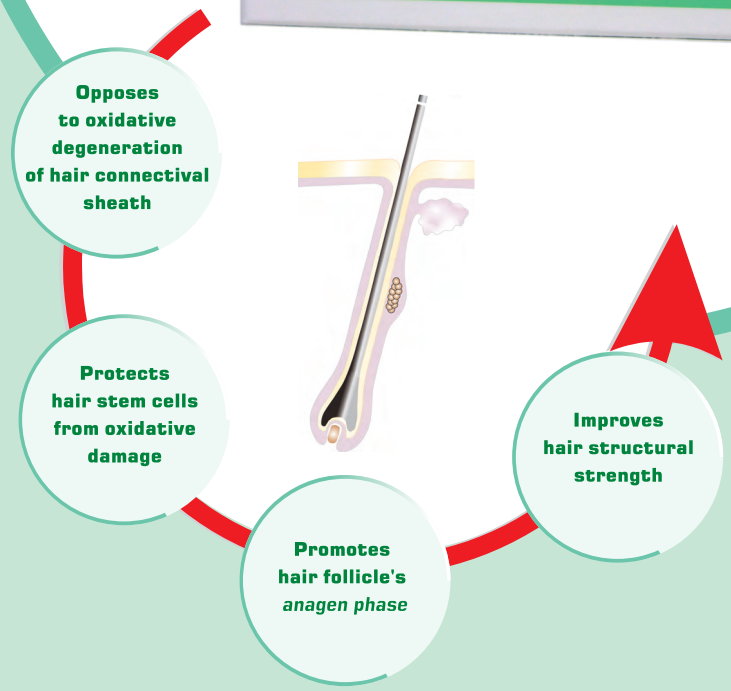

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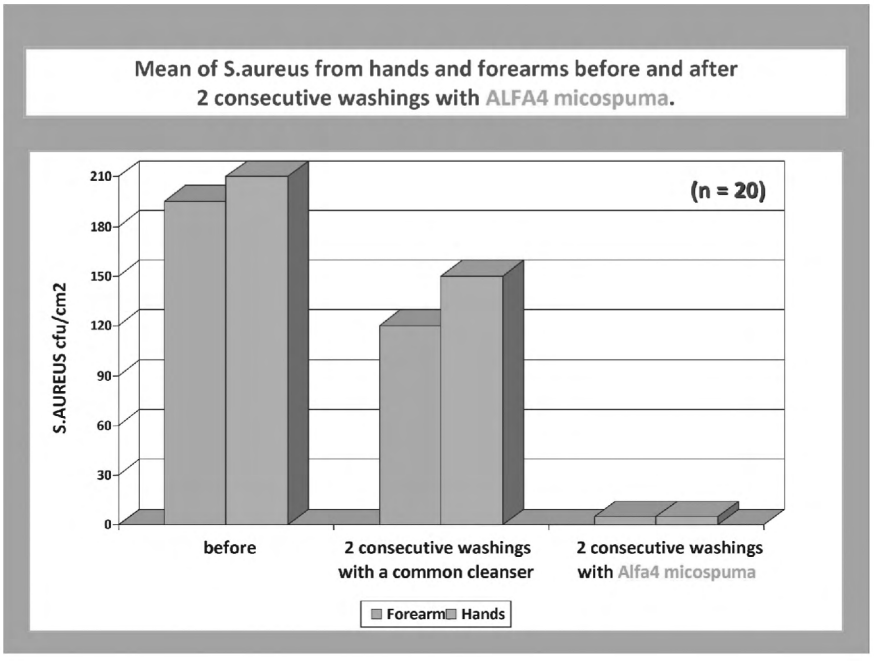

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Contents

ERRATA CORRIGE

volume 31- page 1

La redazione si scusa per aver erroneamente riportato il nome Francesco Guarneri come coautore dell'articolo 'New Insights on Anti-Aging Activity of Chitin Nanofibril-Hyaluronan Block Copolymers Entrapping Active Ingredients: In Vitro and In Vivo Study'.
Il nome corretto è Fabrizio Guarneri.

The Editorial staff apologizes for misspelling the name of one of the authors of the paper 'New Insights on Anti-Aging Activity of Chitin Nanofibril-Hyaluronan Block Copolymers Entrapping Active Ingredients: In Vitro and In Vivo Study' which is Fabrizio Guarneri, not Francesco Guarneri.

Introductory remarks Nanotechnology and wellbeing

Health and well-being have just become a must of people worldwide, being not only the most influential current trend for drugs , cosmetics and food, but also opening up a wellsprings of innovation opportunities for industrial and university's R&D research centres.

In particular, convergence and the gradual overlap of the food, the cosmetic, and the pharmaceutical industries, are leading to create new borderline inter-industry segments such as cosmeceutical, nutraceutical and nutricosmetics products. Given the necessity of recovering strategies to obtain new functional healthy ingredients and carriers, innovative solutions are therefore required.

Nanotechnology seems to play the right critical role to solve this problem, constructing ingredients at molecular level, just as the human body do.

Thus a cleansing emulsion, designed as a system of nano-machines appositely organized, could do a better and more selective job of cleaning than any product can today. According to Eric Drexler "it could remove the right amount of dead skin cells, together with excess fatty acids, add missing free fatty acids, apply the right amount of natural moisturizing factors", maintaining the skin homeostasis. "A cosmetic cream could be therefore a smart material with smooth-on, peel-off convenience".

In the same way may be designed a drug, so that a medical nano-device could, for example, augment the immune system by finding and disabling unwanted bacteria and viruses, as well as waste and dirt materials would be transformed in food.

However, because of the cross-cutting nature of nanotechnologies, its effective governance requires a high level of interaction between, those who develop, manufacture, sell and regulate nanotechnology-based products, and representatives of civil society, such as dermatologists, plastic surgeons, cosmetic chemists, politicians etc.

In this way it will be possible to implement a proactive and adaptive governance platform capable of supporting the development of these novel technologies across clear boundaries, defining the roles and responsibilities of all the stakeholders and institutions involved.

However, the governance and regulation of nanotechnologies must be considered a dynamic affair that needs to be continuously adapted to the consumer requests. In anyway, according with a Nanotechnology Industry Association' study the general EU consumer attitude towards the possible use of nanostructured products seems positive at 71% according to the group of people especially for medicine, surface cleaning and clothing.

This special review' issue will report some scientific papers for introducing the readers to this fascinating field.

P. Morganti
Editor-in-Chief

J. Appl. Cosmetol. ***31,*** *89-96 (July/December 2013)*

Saving the Environment by Nanotechnology and Waste Raw Materials: Use of Chitin Nanofibrils by EU research projects

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Key words: *Chitin nanofibrils; Climate change; Nanoparticles; Electrospinning; Casting; Plant biomass; Fishery waste; Non-woven tissues; Food packaging; Cosmetics;*

Summary

While hazardous waste may affect the health, its prevention and recycling help address global climate change by decreasing the amount of pollution and saving energy.
The rationale and intelligent use of industrial byproducts from fishery processing and plant biomass towards the production of durable components, easy to reuse, remanufacture, or recycle is becoming a must for our society to save the integrity and biodiversity of our planet.
The use of chitin nanofibrils and other natural polymers to produce innovative goods seems to go in this direction by some EU research projects described in this short communication.

Riassunto

Mentre i rifiuti generati dall'industria e dalle coltivazioni agricole creano problemi per la salute umana, una loro produzione più razionale assieme al loro pieno utilizzo e intelligente riciclo risultano utili per ridurre sia l'inquinamento generale che il consumo di energia.
L'utilizzazione degli scarti industriali provenienti dalle lavorazioni di pesci e crostacei sono alla base della produzione delle nanofibrille di chitina che, complessate con altri polimeri di provenienza vegetale, vengono impiegate per produrre prodotti innovativi, proprio per cercare di migliorare la qualità della nostra via, salvaguardando l'integrità dell'ambiente.
Alcuni risultati ottenuti attraverso progetti europei sono riportati in questo lavoro.

The hazardous waste as problem

Every year are generated about 140 billion tons of industrial and agricultural waste driving also by processing of animal and plant' raw materials into intermediate and final products (1, 2). Of 13 billion tons/year of world plant biomass waste, only 3% are used for making goods, while of 154 billion tons/ year of fishery and crustacean processing with a waste of 30 million tons (Fig. 1), only 20% are transformed in chitin, chitosan, and oligosaccharides.

Fig. 1 *Plant biomass by-products.*

Moreover, these by-products, generated in all sorts of ways and volumes, depend on consumption patterns and economical structures of the different Countries involved.

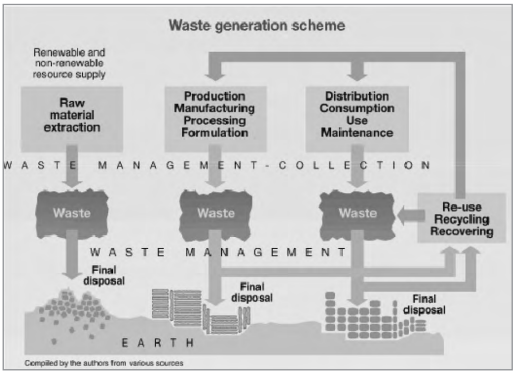


Fig. 2 *Vital Waste Graphics (UNEP - DTIE).*

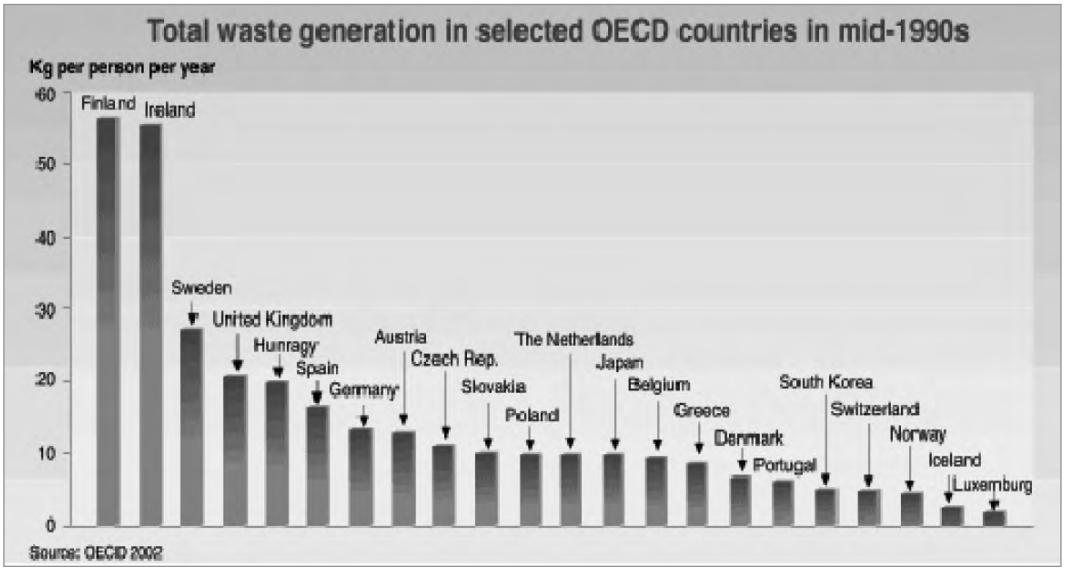
They, in fact, may be generated during the raw materials processing, the consume of goods and services, or from other human activities. Thus, each stage of the production process or way of consume generates a specific type of waste and requires a specific management solution (Fig. 2), also if we have no idea about the raw material and energy extracted from the environment that are needed to produce, transport, distribute, and use it (3).

Therefore, while it is fundamental to have a comprehensive overview of the amount waste generated in every Country from every individual and from the different industrial and agricultural sectors (Fig. 3), it should be necessary to have the capacity for evaluating the life cycle of every typology of product consumed (Fig. 4), as well as to know in a deeper way the development, use and regulation of biological systems for remediation of contaminated environments, and for organizing environment-friendly processes (green manufacturing technologies and sustainable development).

In every way, about the 30 million tons/year of waste, generated from the fish and crustacean processing, are thrown into the sea (Fig. 5), provoking its eutrophication, or remain on the land causing environmental and public health concerns, because of their high perishability and high polluting effect (4, 5).

The EU Projects as solution

Many EU research projects are trying to solve this important problem. Among them the group of researchers working in n-Chitopack project (www.n-chitopack.eu), coordinated by the Italian SME MAVI Sud, are studying the possibility to produce hard and soft films necessary for food packaging, but useful for cosmetics also.



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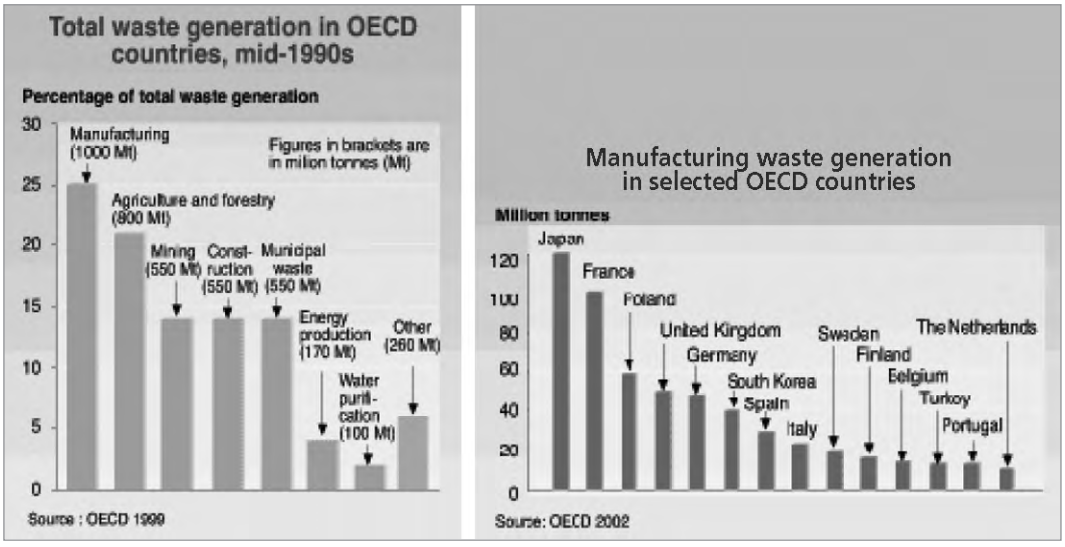

Fig. 4 *Vital Waste Graphics (UNEP - DTIE).*

As basic raw material Chitin Nanofibrils (CNs) will be used, obtained from crustacean waste as pure nano-Crystals of 240x7x5 nanometers (nm)in dimension (6, 7). It is to remember that a bacterium is about 1000 nm long, while the hair diameter is about 50, 000 nm (Fig. 6)!

Fig. 5 *Fishery waste thrown into the sea.*

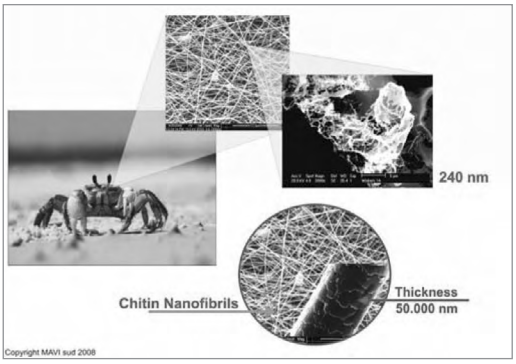

Fig. 6 *Chitin Nanofibrils dimension.*

These nano-crystals, which have into their own structure about 15, 000 -NH2 chemical groups, are covered of positive charges on their surface (Fig. 7) (8). Through their numerous electrical positive charges, these natural crystallin polymers may bind many other electronegative polymers man-made or obtained from natural animal or vegetal sources, such as fishery or plant biomass (8-10). From their union it has been possible to obtain micro/nanolamellae or globular nanoparticles, encapsulating different active ingredients (Fig. 8) (11) increasing their skin activity.

These innovative micro/nano carriers, which can be covered by negative or positive charges, depending on the adopted processes, are able to penetrate at different skin layers and in different times by the formation of specific *tunnels*, according to the nanoparticles size, the active(s) ingredients entrapped, and the electrical charges covering the nanoparticle surface (12, 13).

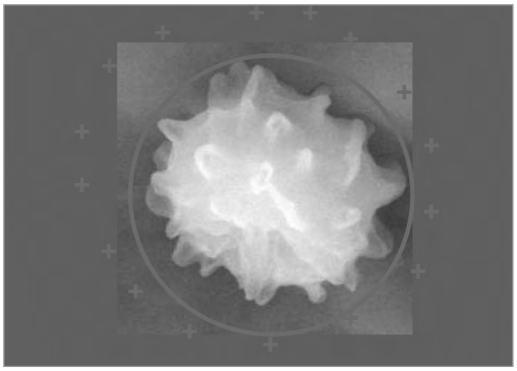

Fig. 7 *Chitin Nanoparticle positively charged at SEM.*

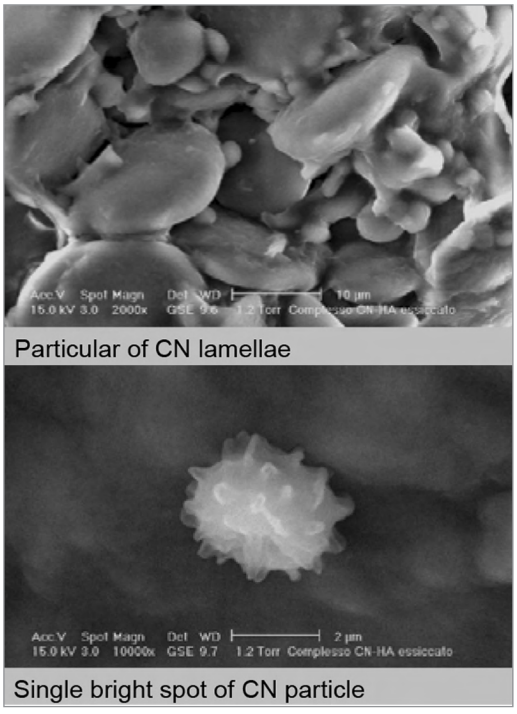

Fig. 8 *Lamellae and single bright spot of CN at SEM.*

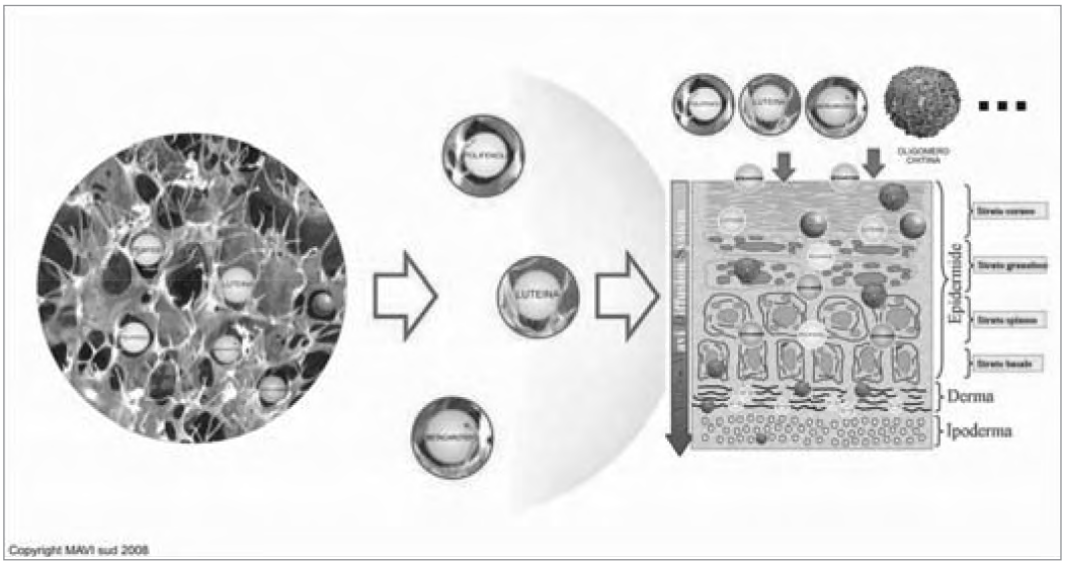

Fig. 9 *Skin penetration of CN particles.*

Naturally, charge and dimension drive the cession of the actives at the skin level and at the desired time, determined by the designed formula (Fig. 9). This interesting productive process, used also by the EU project Bio-Mimetic coordinated by P&G UK (www.biomimetic-eu-project.eu) will give the possibility to entrap the nanoparticles into cosmetic emulsions or fibers naturally made by the electrospinning methodology. In this way it will be possible to produce innovative cosmetic products and beauty masks made by a conceptually new process (14-17). Through another project named Chitofarma, coordinated by MAVI sud (www.mavicosmetics.it) and based on the same use of CNs, the production of a new generation of advanced medications is in progress.

These particular non-woven tissues, characterized by the use of natural polymers, have shown to accelerate the granulogenesis process of cutaneous tissue, facilitating the quick regeneration of wounded or burned skin, just thanks to the activity of these chitin nanocrystals capable to modulate and regularize the collagen production (Fig. 11). It is well known, in fact, how hyperthrophic scars and keloids seem to be provoked by an excessive production of collagen from the fibroblast cells, so that collagen fibrils, made in a too short time, result disposed irregularly and in a disordered way. (Fig. 10). In conclusion, these and other EU research projects, are trying to use raw material obtained from industrial and agricultural waste without impoverish the environment from precious and useful materials, necessary to all the earth inhabitants, contemporary slowing down the production of CO2 and the greenhouse gas emissions. Therefore, according to Baker E et al (3) it could be "essential that governments and corporations face up to waste, using what we know about reduction, recycling and reuse, but also developing new low-cost technologies", in order to increase productivity and achieve a good mass and energy balance in eliminating the industrial and agricultural by-products.

This include "the intelligent use of raw materials and steering production towards the use of durable non-toxic components that are easy to reuse,

remanufacture, or recycle".
In conclusion, it will be necessary to obtain a zero-food-waste that wound require a revolution in the way to consume and produce food and other goods.
This is not only the objective of the European Union, but also the actual goal of MAVI which will find to achieve it with all the Companies that feel proud of accept this important challenge.

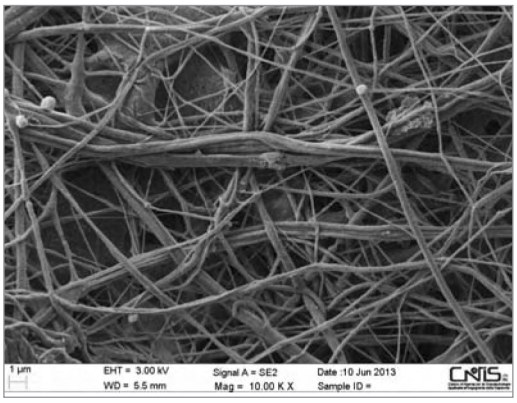

Fig. 10 *Sample of non-woven tissue made by Chitin Nanofibrils and plant polymers.*

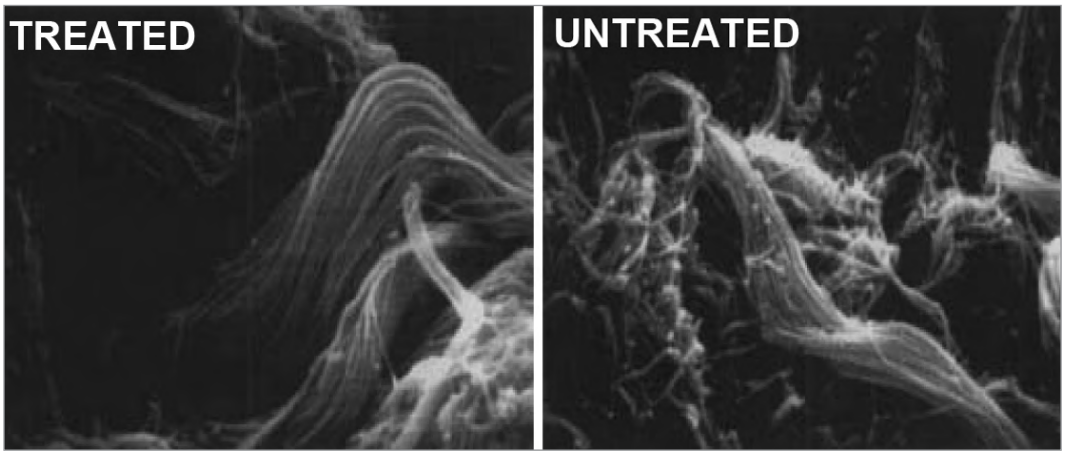

Fig. 11 *Regular collagen fibers disposition in skin samples treated by Chitin Nanofibrils.*

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Nanomaterials: Progress in Science of Healthcare and Public Awareness

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Summary

Nanotechnologies are the protagonists of numerous scientific publications, patents and research studies, and it is not surprising that the subject is topical not only in research centers but also often the "media" science dedicated to the public.
From the scientific point of view, nanotechnology is known for many years (the first significant work can be traced back to 1959), but in the last 10 years have seen an exponential increase of interest in many disciplines, including not less health sciences.
The wide diffusion of publications on the topic of nanotechnology brings to the attention of experts and the public a large amount of information, which does not always lead to a clear understanding of the bases, the state of the art and prospects of this important branch of research scientific.
In parallel to the great interest and prospects always considered the most critical aspects regarding the impact on the environment and health, evidenced by the intense activity at the European Commission and the U.S. FDA on this issue.
The increasing of products and technologies which claim the use of nano materials is accompanied by a proportionate and appropriate knowledge and awareness?
This review aims to summarize and update not only the status of progress and the availability of nanotechnology, but also the public perception and awareness about this topic: fundamental aspects so that a promising branch of science can express all their potential in improving the knowledge and the quality of life without shadows and doubts about the safety.

Riassunto

Le nanotecnologie sono protagoniste di numerose pubblicazioni scientifiche , brevetti e studi di ricerca, e non è sorprendente che il tema sia di attualità non solo in ambito specialistico, ma spesso anche in ambiti mediatici dedicati al grande pubblico.
Dal punto di vista scientifico le nanotecnologie sono note da molti anni (il primo lavoro significativo può essere fatto risalire al 1959), ma negli ultimi 10 anni hanno visto un aumento esponenziale di coinvolgimento nell'ambito di molte discipline, tra le quali non meno coinvolte le scienze della salute.
L'ampia diffusione di pubblicazioni sul tema delle nanotecnologie porta all'attenzione degli esperti e del pubblico una grande quantità di informazioni, che non sempre aiutano una chiara comprensione delle basi, lo stato dell'arte e le prospettive di questo importante ramo della ricerca scientifica.
In parallelo al grande interesse e le prospettive anche in merito agli aspetti più critici per quanto riguarda l' impatto sull'ambiente e sulla salute, testimoniano l'intensa attività presso la Commissione Europea e la FDA degli Stati Uniti su questo tema.
Ma l'incremento di prodotti e tecnologie che vantano l' uso di materiali nano è accompagnato da una conoscenza e consapevolezza proporzionate e appropriate?
La presente review mira a riassumere e aggiornare non solo lo stato di avanzamento e la disponibilità delle nanotecnologie, ma anche la percezione pubblica e la consapevolezza su questo argomento: aspetti fondamentali per una branca promettente della scienza che può esprimere tutta la propria potenzialità nel migliorare la conoscenza e la qualità della vita senza ombre e dubbi sulla sicurezza.

INTRODUCTION

We can say that the concept of "nano materials" has been addressed for the first time by Richard Feynman (1) in 1959, when he presented to the international scientific community the prospect of a horizon oriented to extremely small particles as a new frontier of physics.

He wondered, in the historical article, if it were possible to write the 24 volumes of the Encyclopaedia Britannica on a pinhead. Calculation that followed demonstrated the enormous potential of the material in the ability to differentiate and "transduce" signals in extremely high concentrations compared to the size.

Today this ability to concentrate information in a small space is much less surprising.

The technologies in the electronics world has made the usual capacity to store data in comparable amount to much more of an Encyclopedia Britannica in static memories of a few millimeters in size. So you can say that, at least as order of magnitude, we are not far from the exercise shown theoretically by Feynman.

But the research field of nanomaterials have plenty to say and to give.

The great insight of Feynman comes from an acute reflection on the potential of materials in small scale, their interactions with substrates, their ability to interact with the biological matrices and their ability to "transmit" or "transducer " signals and messages.

In addition to predicting with great accuracy the potential of "communication" enclosed in a pinhead, Feynman explores the consequences of a miniature robot in the form of "pantograph". The technology of 1959 led to the examples of lathes that could produce goods at a reduced scale of one quarter (a real case of that time). The projection of this progress raises the question of what could be the result of work conducted by 2 billion back the size of 1/4000 of a lathe common: the surprising conclusion is that 2 billion large lathes just 1/4000 of a lathe common occupy less space than in a normal lathe. It was demonstrated in 1959 that can be achieved with a much lower amount of material. Perhaps today we would calculate the energy used to produce 2 billion small lathes and on how much carbon dioxide will enter the environment. But the value of the reflection of Feynman remains unchanged: the relationship between the volume and efficiency of the machines is becoming more favorable with decreasing size scale. From this point of view of the reduction of scale was seen as a function of the new prospects, well beyond mere size.

An important step in the historical article by Feynman deals with the difference between the concept of nanotechnology and the “miniaturization”. The needle that brings the Encyclopedia Britannica is not attributable to the definition of "nanomaterial". But the tiny lathes or "little hands" is definitely part of the action. While suitably enlarged needle will allow us to read an encyclopedia (which could be done easily by reading books, or today looking up your laptop or a smartphone), 2 billion small lathes or hundreds of tiny hands can make products that no hand or lathe any dimension "normal" can get.

This was the real meaning: nanotechnologies can get us results that are not obtainable otherwise.

The development of nanomaterials and nanotechnology from 1959 to date has been impressive, as we can guess from the selection of the research described below; it has produced results that have contributed to the development of many fields of science and technology.

Consequently, the health authorities for years have started to assess the impact of these technologies on the environment and health of the consumer, for years defining a strategy for managing such innovations so as not to constitute a health hazard.

We will see in the conclusion that recent surveys show that the public underestimates the impact of nanotechnology in everyday life, and percep-

tions regarding nanotechnology is a blend of understatement and optimism.

Progress in Health Science related to Nanomaterials

The research in nanotechnology has produced impressive results and impressive. Below is a selection of some important developments in health sciences.

Fullerenes

The progress and development of nanomaterials has continued in the years after 1959, but development and applications in the health sciences have undergone a significant acceleration since the early '90, probably also driven by the discovery of the class of fullerenes (2-7).

Harold Kroto, the University of Sussex, James Heath, Sean O'Brien, Robert Curl and Richard Smalley from Rice University, discovered the C60 and other fullerenes in 1985. Kroto, Curl and Smalley were awarded the Nobel Prize for chemistry in 1996.

As a result of the important discovery of the allotropic form of carbon, in few years at beginning of the '90, fullerene has been the subject of innumerable research projects to both the characterization and to functionalization: water soluble form was obrained by embedded form with ciclodextrin (8), virucidal activity of water soluble forms (9). The 5-mercapto-substituted was found to inhibiting the replication of virus type 1 associated to human immunodeficiency (10). Radical reactions have been examinted (11), as well as multi-hydroxy additions (12), aminoderivatives (13, 14), diphenylfulleroids (15), spirolinked C-Glycosides (16).

During the second half of the '90s were investigated and implemented researches in field of the pharmacokinetics. A derivative of bis(monosuccinimide) of p,p'-bis(2-aminoethyl)diphenyl-C60 (MSAD-C60), prepared by the fulleroid route, was found to be active against human immunodeficiency virus type 1 (HIV-1) and HIV-2, as well as it was developed a high-performance liquid chromatographic analytical methodology for MSAD-C60 and to characterize the preclinical pharmacokinetics of the compound in rats (17, 18).

Effect against *Escherichia coli*-induced meningitis was evaluated as C60 fullerenes appeared to be promising anti-bacterial meningitis agents (19).

The water-miscible form of 14C-fullerene was object of studies on labeling, absorption, distribution, excretion and acute toxicity (20)

In the case of photosensitivity was estimated the oxidative damage induced by fullerene C60 (21), but at the same time it has been shown that the carboxy fullerenes prevent the iron-induced oxidative injury in the nigrostriatal dopaminergic system in rat brain (22)

The controversy about the safety of nanomaterials are born almost immediately with the researches, and are the source of an enormous effort by the health authorities. From a scientific point of view it is not surprising that the new "entity", so responsive and innovative way may, from time to time, result in promising antimicrobial or antiviral and other areas may instead reveal behaviors and alarming results.

As we shall see later, in almost all areas of research on nanomaterials, are followed encouraging results and alarming results.

The researches on fullerenes/modified fullerenes brought to the evidence of significative harmful effects like the C60fullerenes on mouse embryos *in vitro* and *in vivo* (23), the adverse effects of fullerenes on endothelial cells (Fullerenol C60(OH)24 induced tissue factor and ICAM-1 membrane expression and apoptosis *in vitro*) (24), the capacity to bind fullerenol C60(OH)24 to dsDNA (25).

The study on Salmonella typhimurium revealed the mutagenicity of fullerene and some of its

derivatives (26).
Studies over the past decade have confirmed this alternation between efficacy trials and the start of a promising class of drugs, at the same time alarming data on toxicity, as is usual for such a category of new active molecules.
So the fullerenes are shown in many studies, promising matrices for the development of new classes of antibacterial and antiviral products (27, 28), accompanied by evidence to show that the cytotoxicity (29-32).
In products for topical use, the fullerenes provide promising results of both as enhancers and as a transdermal drug (33,34)

Silica Nanoparticles

The silica is used for many years in numerous products for topical use, both because of the mechanical characteristics (abrasive) both for the ability to produce gel systems with polar and aprotich solvents such as glycols or glycerine.
One of the research fields on nanomaterials as most active in the development and modification of silica nanoparticles.
A recent study has focused its attention on the prerogatives of some silica nanoparticles that have the property of improving the delivery of functional molecules for topical use, such as trans-retinol coming from o/w emulsions(35). It is demonstrated the release of retinol and the targeted dermal delivery.
In the event that the retinol is included in the silica nanoparticles, it is shown the release of the same retinol in the epidermis.
Moreover, in subsequent studies, the ability to increase the transdermal transport of lipophilic molecules coexists with exposure to inflammatory and cytotoxic effects, as well as the potential implications homeostatic due to platelet aggregation. Such effects are related to cardiovascular problems due to exposure to silica nanoparticles (36- 40).

Polystyrene

A type of nanomaterial that has been facing more recently the scene of nanomaterials for therapeutic use, is polystyrene. Interestingly the study pertaining to the development of polystyrene nanoparticles hold promise for the development of new therapies for lung diseases (41).

Titanium Dioxide

Titanium Dioxide is one of the substances most traded worldwide, because of the well-known applications such as white mineral pigment widespread in virtually all white objects that surround us.
It is widely used as pharmaceutical excipient, and in cosmetics, which is also used as a UV filter for sunscreen products (42).
Biggest concerns about Titanium Dioxide nanoparticles deal with inhalation (43), the reactive oxygen species given by the photoexcitation in human skin (44), the penetration of titanium dioxide microparticles in sunscreen formulations in the horny layer and in the follicular orifice (45).
Confirming the views on the nanoparticles, which are always accompanied by controversy, data from a publication claimed the photogenotoxicity (46) just before the admission of titanium dioxide as a sunscreen. Few years later, a publication that highlights the stratum corneum of the skin that prevents the transcutaneous passage of the micronized forms of titanium dioxide (47).
A comprehensive table on the percutaneous absorption studies on cosmetic products has been published by Morganti, P. (58), and demonstrates unequivocally that the nano particles of titanium dioxide do not penetrate through the skin or the penetration is limited to the superficial layers of the stratum corneum.

Proteins

The development of peptide-based nanoparticles, in my opinion is remarkably interesting and promising, for several reasons.
First of all it must be considered that the realization of oligomers and oligopeptides is based on a branch of biochemistry already highly specialized and evolved since the years 70s recognizing them as "cellular messengers". Therefore have been published dozens of articles of scientific literature concerning the procedures for implementation of oligo peptide complex matrices.
Another non secondary element is inherent the nature of the peptide matrix: we would consider that the cellular physiology of the matrices of the target- organs (or the skin, in the case of cosmetic products) is very rich in receptors and "signal transducers", so if it is true that most of the field concerning the nanoparticles-receptor interactions is currently unexplored, we can expect a strong affinity and a significant predisposition to "transduction" of the "signal" (so a strong effect due to the interactions between the peptide-nanoparticles and the receptor target) in the case of matrices so thoroughly consistent in origin.
A strategy of synthesis involves the fusion of interesting structures of oligomers in repetitive structures which are assembled into nanohedrich bolls.
The strategy “nanohedra” (48) allows to obtain the formation of both particles that have cavities of well-controlled size and shape, and both tubular structures, in analogy with the well known category of nanotubes (49-53).

Self-Assembly processes

A further and even more recent evolution of nanohedra is given by self-assembly supramolecular structures
An additional and even more recent evolution of the nanohedric systems is given by the supramolecular self-assembling structures. Between the supramolecules these soluble systems appear to be the most promising because of their "dynamic" structure which can change depending on the conditions of 'environment in which they are placed. The structure made of rigid blocks connected by flexible bridges, allows to change by external signals.
The ability to manage and "remote controlling” the structural (and functional) changes can suggest the beginning of a completely new class of nanoparticles of enormous potential (54).

Immune System

Thinking to a class of compounds characterized by high bioavailability, selectivity, and reactivity, we must consider important interaction with the body's immune system.
Thus, the nanoparticles have to be studied and controlled for their impact in relation to their probable and not well predictable activity and function towards the body’ receptors. Moreover, because of their selectivity and the ability to produce and control a localized dose and for their nano-dimension,these nanoparticles represent an advanced frontier in the search for vaccines and immune stimulants (55-57).

Cosmetics: innovation related to the nanotechnologies. Importance of nanoparticles and nanotechnologies

Relating to cosmetic products, should focus attention on two important recent publications, which provide a wide and updated on the latest innovations and prospects: Morganti, P. (58) and Mihranyan, A. et al. (59).
In the large overview given in the review of Morganti (58) , the importance and significance of the development of nanotechnology in cosmetics are examined. The development of delivery

system related to nanoparticles, and nanoparticles of Titanium Dioxide and Zinc Oxide and Chitin nanofibril are deeply evaluate for their potential as dermatological functional ingredients.

The attention and interest for nano-particle systems in the cosmetic field are demonstrated by both the number of compounds used for years by cosmetic companies, such as titanium dioxide or zinc oxide (58) (in 2009 13% of nano materials produced were intended for the cosmetics sector, (59)), both from the attention by the EU health authorities (60, 61).

The cosmetic companies, strongly oriented towards innovation, are always looking for delivery systems, biocompatible, efficient and highly selective (58).

Safety, Regulations and Standards in Cosmetics

Cosmetic Containing nanomaterials, the point of view of the EU commission (62):

What are the rules in Europe for the use of insoluble nanoparticles in cosmetics?

What specific measures has the Commission taken to address the safety of insoluble nanoparticles? What is the Commission doing in terms of research?

The European Commission as expressed by the questions and answers provided on the site, has invested significant resources to assessing the safety of nanotechnology products in recent years. Since 2004 it has been approved and published the strategy that the Commission would then follow in the coming years (63). Following that publication, were published two further updates (64, 65).

On the 12th May 2004, the **European Commission** adopted the **Communication** "Towards a European Strategy for Nanotechnology" COM(2004) 338.

The scheme proposed in the program was the following: clear and ambitious. An important commitment.

Actions: A European Research Area for nanotechnology

1. *To remain at the forefront of nanosciences and nanotechnologies, the EU should reinforce its commitment to R&D. While ensuring synergy with programmes at national level, the Commission calls upon the Member States to:*

(a) *substantially increase public investment in nanosciences and nanotechnologies in a coherent and coordinated manner by a factor of 3 by 2010 bearing in mind the Lisbon and "3%" objectives;*

(b) *promote excellence in nanosciences through competition at European-level;*

(c) *boost R&D in nanotechnologies with a view to wealth-generating applications with emphasis on the involvement of SMEs;*

(d) *to maintain a concentration of R&D activities in the next FP in order to secure critical mass and synergy between the development of nanosciences, nanotechnologies, related engineering and safety aspects;*

(e) *ensure effective coordination of the national programmes;*

(f) *reinforce roadmap and foresighting efforts at European level with the contribution of centres of excellence and institutes such as the IPTS.*

Other significative actions in that Strategic plans were concerning: Infrastructure (creating "poles of excellence"), Investing in human resources, Industrial innovation, Integrating the social dimension (in order to ensure public awareness and confidence with nanotechnologies), Public health and International cooperation.

On the 7th June 2005, the European Commission adopted the **Action Plan** "Nanosciences and nanotechnologies: An action plan for Europe 2005-2009" (COM(2005) 243). This Action Plan defines a series of articulated and interconnected

actions for the immediate implementation of a safe, integrated and responsible strategy for nanosciences and nanotechnologies, based on the priority areas identified in the above-mentioned Communication.

Nanosciences and Nanotechnologies: An action plan for Europe 2005-2009.

First Implementation Report 2005-2007. On 6 September 2007, the European Commission adopted the Communication "Nanosciences and Nanotechnologies: an action plan for Europe 2005-2009.

First Implementation Report 2005-2007". This reports progress in virtually all areas of the Action Plan.

The commitment of the European Commission under the regulatory framework for nanotechnology is evidenced by strategies and actions aimed at supporting the development of nanotechnology.

Last October 2011 the update on definition of nano material was given (66):

2. *'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm.*
   In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.
3. *By derogation from point 2, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1nm should be considered as nano¬ materials.*

The nanomaterials are fully included in the comprehensive legislation concerning chemicals for which there is an "interaction" with consumers: the so-called legislation "REACH" (67).

The obligations of the REACH provide for the registration of substances produced in excess of 1 tonne, at the European Chemical Agency (ECHA) (68), depending on the chain purchasing and related end-use of the substance. In other words, the REACH legislation will require (at the end of the adjustment process, which ends in 2018) a study and approval by the authorities on the end use of any substance, which must be studied and supported as a function of 'end use. Nanomaterials are no exception in this sense, although because of their innovative nature ,is expected to obtain more support informations.

and Chemical Agency (ECHA) will receive the lettering and the Agency plays a central role in the collection, evaluation and dissemination of information on substances and preparations, including nanomaterials.

In 2010, the Directorate General Environment of the European Commission has launched a project in collaboration with the Joint Research Centre (JRC): "Scientific support in the evaluation of nanomaterials in REACH registration dossiers and appropriateness of the information available."

EU topics on Cosmetics: the new EU Regulation 1223/2009, a little "revolution" that is focused also on nanomaterials

The great attention paid towards nanotechnology in cosmetics is demonstrated also by the new European Regulation on Cosmetics (69), which includes a chapter specifically devoted to nano materials, which will be highlighted on the product label (with the "nano") and contrary to all cosmetic products "common", which may be notified to the European authorities just prior to launch, in the case of cosmetics containing nano materials, you must notify the authorities of the European presence at the first 6 months, to give way to the authorities of the same take direct

action against the company requesting for the verification of information relating to the safety of nano materials (EU Regulation 1223/2009, chapter 16 (69)).

The Nanomaterials seen from outside: the public perception

The history of discoveries and innovations in science teaches that the public opinion and perception can significantly influence the development of a new branch of science, or creating important and unexpected obstacles. It is therefore crucial to assess the actual perception of the work conducted by research centers and companies, as seen by the public.

It was conducted a very interesting study in Italy with the purpose to examine the perception of Italians according to demographic variables and heuristics most influential in shaping public perceptions of the benefits and risks of nanotechnology (70).

In that study it was investigated the role of four demographic (age, gender, education, and religion) and one heuristic (knowledge) predisposing factors.

According to the results of the study, regardless of age and religion, the Italians have a different perception of how nanotechnology will affect their lives in the next two decades, according to sex, education and level of knowledge. Another important aspect that joins the opinions of group of people addressed is the optimism about the applications of nanomaterials, and particularly those related to nanomedicine.

CONCLUSION

The survey on developments relating to nanomaterials and nanotechnology in particular concerned with the health sciences, shows a very vital branch of science and generous results and excellent growth prospects. Feynman's insight in 1959, from an encyclopedia written on a pinhead we wanted to see and provocative thinking to new frontiers, has resulted in a new science that is providing new areas of research and innovation. At the same time nanotechnology provides almost endless possibilities of applications in the field of healthcare. As with all great innnovations, are still huge areas to explore, and especially the great potential of new materials will still be supported by appropriate verification tools so that, just as a source of powerful energy, is conveyed in the direction of a constructive use, controlled, and safe.

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Nanotechnology in Cosmetics

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Summary

Substances in the nano-sized dimensions perform newer properties which determine new benefits and special uses in cosmetics. Nano-materials may have special interactions with biological systems and physiological effects that are different from conventional or bulk ingredients. Concerns about the non-controlled potential penetration of nano-materials through the skin have been raised.
This issue considers that they are so new that cannot have been adequately tested up to now to ensure sufficient safety. As consequence, the new EU legislation considers with special attention formulations containing nano-sized ingredients.

Riassunto

Tutte le sostanze di dimensioni "nano" mostrano proprietà nuove rispetto alle loro forme fisiche usuali, che mostrano speciali vantaggi e suggeriscono nuovi impieghi nelle formule dei cosmetici.
I Nano-materiali possono interagire in modo speciale con i sistemi biologici, mentre gli effetti sulla fisiologia dell'organismo sono differenti di quelli in forme convenzionali. Sono sorte preoccupazioni circa il potenziale di penetrazione transdermica incontrollata dei nano-materiali.
Di fatto, la considerazione in proposito è che questa forma della materia sia così nuova da non poter ancora disporre di prove sufficienti sulla sicurezza di impiego.
Come conseguenza, la nuova legislazione UE dedica speciale attenzione alle formule dei cosmetici contenenti nano-materiali.

INTRODUCTION

The distinctive features in the nanotechnology world are that nano-sized substances exhibit size-related properties that differ significantly from those observed in larger materials. Indeed, as the size of particles decreases, their specific surface area per volume unit increases, and the physicochemical and biological properties are altered, compared with the bulk characteristics (1). Nano-materials may have also special interactions with biological systems and physiological effects that are different from conventional or bulk ingredients. Nano-structures in cosmetic formulations are found to improve the stability of various cosmetic ingredients such as unsaturated fatty acids, vitamins or antioxidants, by encapsulating them. Nanotechnology also increases the efficacy and tolerability of organic UV filters applied onto the skin surface. Moreover, it enhances the penetration of some active ingredients through the epidermis. In general, nanoparticles make cosmetic products more aesthetically pleasing (2). On these grounds is based the growing success of this special physical form.

Market and norms

The global production of engineered nano-materials is estimated to increase from 1,100 tons in 2003-2004 to 5,700 tons in 2020 (3) whereas the world market for products that contain nano-sized substances is expected to reach $2.6 trillion by 2015 (1).

Today, almost all the major cosmetic manufacturers use nano-materials in their products. In 2006, the European Commission estimated that 5 % of cosmetic products contained nanoparticles (4). The global market for cosmetics using nanotechnology is now projected to reach 156 million dollars in 2012 (5).

The EU Regulation for Cosmetic Products (EC/1223/2009) (6) was the first legislation describing specific requirements for nano-materials, including a technical definition of this term. As there was a need for a horizontal definition which could be applied across several sectors, the EU adopted in 2011 a Commission recommendation (7) with a second general definition. The EU Commission is today planning to align the two differing definitions used for the term "nano-material" to make them applicable specifically to cosmetic products within the new legal requirements for cosmetics containing nano-materials, entered into force in 2013 (8).

Currently, there is no official globally recognized definition of "nanomaterial". It is however generally accepted that nano-scale substances are single particles ranging from 1 to 100 nm. Their agglomerates may be larger than that and some researchers consider even particles larger than 100 nm as part of the category.

Applications

Nano-sized substances perform newer properties which determine new benefits and some special uses in cosmetics which are common since some decades. The first is that they enhance or limit the transdermal delivery of specific ingredients. Indeed liposomes and other types of nanostructures were used in the cosmetic industry as delivery vehicles for a long time. The second is the use of nanoparticles as sun filters for UV protection. Titanium dioxide (TiO_2) and zinc oxide (ZnO) are the main compounds used in such applications (9).

Accordingly, a number of nano-materials such as liposomes, polymeric nanocapsules, solid lipid nanoparticles and nanostructured lipid carriers, nano-crystals, nano-emulsions and metal oxide nanoparticles have been increasingly investigated for cosmetic applications.

Nanostructures for ingredient delivery

Many modern cosmetic products contain nano-sized components. Emulsions and vesicular carriers are the most diffused delivery systems used today.

Nano-emulsions

Nano-emulsions are metastable dispersion of nano-scale droplets of one liquid within another. The nano-sized droplets can move easily through the stratum corneum, resulting in good delivery of the actives into the dermis. Antioxidants such as gamma-oryzanol and coenzyme Q10 were reported to be used in nano-emulsions. Furthermore, oils with high antioxidant activity can be used in nano-emulsions as both oil vehicles and functional actives (10). Nano-emulsions are transparent due to the tiny droplet size, furthermore they remain stable for a long period. Mostly used in deodorants, sunscreens, shampoos, and skin and hair care products, they show good sensorial properties i.e. rapid absorption, light textures and hydrating power (11). Significant improvements in the aspect of dry hair after several shampoos, with prolonged effects, are obtained after using a cationic nano-emulsion: the hair become more fluid and shiny, less brittle and non-greasy (12). A great deal of effort is currently being put into the development of aqueous-based nail lacquers, based on aqueous polymer emulsions. They reportedly adhere well to the nails, are characterized by good gloss, exhibit good water resistance after drying and do not develop any solvent odour (13).

Liposomes

Liposomes are globular vesicles with single or multi-layer structures. Their size can vary from 15 nm up to several micrometers. Liposomes with vesicles in the range of nanometres are called nano-liposomes. Liposomes have been formed to facilitate the continuous supply of agents into the cells over a sustained period of time. Thanks to their aqueous core, liposomes can entrap a variety of active molecules. This improves stability and/or skin delivery and, as consequence, the cosmetic efficacy. Skin care preparations with empty or moisture-loaded liposomes reduce the transdermal water loss and are therefore suitable for the treatment of dry skin. They also enhance the supply of lipids and moisture to the stratum corneum (13). In 1986, the first application in the cosmetic story was created by the Christian Dior brand, that introduced liposomes in its “Capture” line. Since that time, many cosmetics manufacturers started incorporating nanotechnology in their formulations. The liposomes delivery system is the ideal candidate for the delivery of molecules to regenerate unbalanced epidermis. Several active ingredients, vitamins and antioxidants have been incorporated into liposomal membranes to increase their skin delivery (14).

Polymeric nanocapsules

Polymeric nanocapsules are spherical hollow structures surrounded by rigid polymer shells. The interior space can be loaded with active ingredients in order to protect sensitive substances, control their release or avoid all incompatibilities with other cosmetic ingredients. The core is often filled with oils, which can dissolve lipophilic active ingredients. The major benefit of nano-capsules is the possibility to functionalize polymers to meet specific aims, as to release the payload depending on the environment. An example of this mechanism is a hydrogel that can be used as facial mask with a temperature-dependent release: the gel shrinks and releases active substances only if the temperature is

increased (from room to body temperature) (9).
Hydrophobically modified nanocapsules have also been investigated as sunscreen carrier. Nanocapsules decrease the percutaneous absorption of the sunscreen filter benzophenone-3, which should constantly remain onto the skin surface to efficiently protect the skin from UV radiation (2).
In perfumery products long-lasting fragrance is desired. To prevent fragrance from being diluted or washed off, it can be encapsulated in nanocapsules with strong affinity to the skin. The adhesion of the perfume to the skin and its lasting during the day result improved (15).
Generally, polymeric nanoparticles are unable to cross the intact stratum corneum. Even if the inter-corneocyte spaces are ~100 nm wide, they are filled with multiple lipid bilayers. Therefore, it seems unlikely for a ~50 nm nanosystem to traverse the SC via the trans-cellular route. Their rigidity and ability to form a film of polymeric nanoparticles further undermines the possibility of their permeation across the stratum corneum (16).

Solid Lipid Nanoparticles and Nano-structured Lipid Carriers

Solid Lipid Nanoparticles (SLNs) are little more than o/w emulsions in which the fluid oil droplet has been replaced by solid fat droplets. In other words, the dispersed droplets are made of lipids which are solid at the body temperature and stabilized by surfactants. SLNs were originally considered just an improvement over liposome delivery systems. An additional advantage is their nature made of biocompatible ingredients, capable of including both water- and lipid-soluble actives. In addition, their membrane permeability and consequential release of actives can be tuned via the creation of single or multiple lamellar vesicles (17).
The second generation technology of Nano-structured Lipid Carriers (NLCs), produces them by blending a solid lipid with a fluid lipid, the blend being solid at the body temperature. Compared to SLNs, NLCs show a higher loading capacity for a number of active compound, a lower water content of the particle suspension and minimal potential expulsion of active compounds during storage (11).
After topical application, SLNs and NLCs can form occlusive adhesive films on the skin surface, which prevent skin dehydration and make them ideal for use in skin creams (18). The occlusive feature of SLNs makes them attractive to use in sunscreens: the lipid film formed at the skin surface retards the penetration of molecular sunscreens, thus enhancing the UV-resistant capacity and reducing the potential toxicity of filters(19).
Recently, research devoted to SLNs and NLCs has gradually increased in the field of cosmetics. Many active ingredients such as retinol, tocopherol acetate, ascorbyl palmitate, coenzyme Q10, omega-3 and omega-6 unsaturated fatty acids, titanium dioxide and other sunscreens (20) are now incorporated with success.

Nano-crystals

Another way to deliver hydrophobic active principles to the skin is via nano-crystals. They are crystalline aggregates which perform a supersaturation of actives in the water phase of formulations. Thus, the gradient between the concentration of one ingredient in the formulation and in the skin increases. In this way, poorly soluble actives can penetrate more easily by diffusion. Actives penetrating from the water phase into the skin are rapidly replaced in the aqueous phase by the active released from the dissolving nano-crystals in the formulation (21). For example, rutin is a sparingly soluble antioxidant that could not previously be used in topic products. A water-soluble rutin derivative, rutin glucoside, is

typically used as alternative. Once formulated as nano-crystals, rutin becomes dermally available as measured by its antioxidant effect in the skin. When compared with creams containing rutin glucoside, the rutin nano-crystals patented formula shows 500x more bioactivity, based on the measured SPF (22).

Cosmetic actives interesting for the nano-crystal structures include many polyphenols, such as catechines, flavonoids, isoflavones, coumarines and resveratrol. Also triterpenes with anti-inflammatory activity like those from *Boswellia* serrata, actives extracted from *Centella asiatica* (asiaticoside, asiatic acid, madecassic acid) or 18β-glycyrrhetinic acid from *Glycyrrhiza glabra* can be used with success under this form. In addition, unstable active molecules like andrographolide, forskolin, glabridin, mangiferin, gamma-oryzanol or vitamin derivatives like ascorbyl palmitate and retinyl palmitate may adopt this way of delivery. Of relevant interest are also some cosmetic actives which possess a relatively high water-solubility but show insufficient penetration into the skin for lack of affinity for the stratum corneum (22).

Metal oxide nanoparticles for sunscreens

In cosmetics, nano-materials are predominantly found in sun care: titanium dioxide and zinc oxide are the most widely used metal oxide as UV filters. They are especially used in their "nano-sized" version, to provide enhanced protection in sunscreens. Indeed, the smaller the particles, the higher their surface, the lower the empty spaces between particles onto the skin, the better the coverage of the epidermis. The unique size-dependent properties of nano-materials mean also that in some ways they behave like new chemicals. For a particle size of about 35 nm, nanoparticles are big enough to scatter and reflect short-wavelength UV radiation without affecting the longer-wavelength visible light. In this way, the sunscreen formulation is transparent. The optimum particle size for a high UVB and UVA attenuation but also a good transparency in the visible region is between 40 and 60 nm (see Figure 1) (23). Other benefits of the reduced size are the ease in preparing dispersions and the pleasant skin feel.

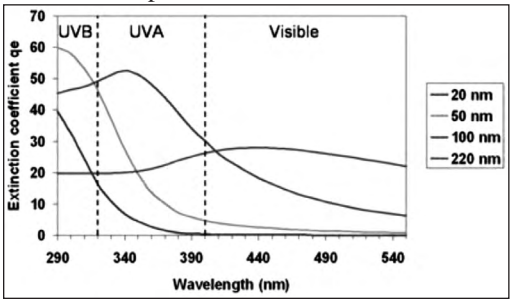

Fig. 1 *(from Reference 23). The effect of particle size on the UV attenuating properties of titanium dioxide. Reduction of particle size moves the peak of UV attenuation to shorter wavelengths, while improving transparency.*

Safety issues

Concerns about the non-controlled potential penetration of nano-materials through the skin have been raised. Much of the concern around nano-sized materials considers that they are so new that cannot have been adequately tested up to now to ensure sufficient safety. Moreover, treating all nano-materials as though they pose the same degree of risk is not a reasonable approach. Most of the vesicles and nano-emulsions are made by GRAS (generally recognised as safe) ingredients and are designed to penetrate the skin, break down into their individual ingredients and deliver their content in depth, therefore their potential side effects are minimal. Thus, in terms of risk assessment, these materials act the same as conventional cosmetic emulsions and delivery systems.

Different considerations have to be made for insoluble substances which are intended to

remain on the surface of the epidermis, e.g. metal oxides. Examining the matter from the point of view of the theoretical principles of skin penetration, it might be concluded that there is no significant penetration of particulate matter into the viable epidermis, and hence the predictable exposure to the ingredient is very, very small, as results from a detailed prediction by Professor Johann Wiechers (23).

A number of experimental evidences are also available. A big number of studies have been executed and have failed to show the particles to penetrate beyond the stratum corneum. A few studies did show somewhat deeper penetration, but in these cases, the results could be attributed to the methodologies used. No strong experimental evidences have till now supported the argument that nanoparticles penetrate the skin (24).

In a recent publication, the Department of Dermatology, Venereology and Allergology of the University of Berlin reports that zinc oxide nanoparticles penetrate only into the outermost layers of stratum corneum, furrows and into the orifices of the hair follicles but do not reach the viable epidermis (25). The United States Food and Drug Administration recently indicated that nano-scale titanium dioxide may have better efficacy than other filters while lacking toxicity. The concerns arising from this material when dermally applied appear to be primarily related to the product quality and its adequate characterization, rather than to safety considerations (26). But concerns remain because the complete safety of these particles could not be irrefutably shown. In fact, safety can never be shown because it is impossible to demonstrate the presence of an absence. Penetration into the deeper parts of the skin and systemic absorption should be avoided for their possible, but still unknown, interactions with some biological systems.

New light and new norms appearing

Finally, in the field of inorganic sunscreens, researchers can only show a lack of evidence, but the public opinion remains concerned. This is the reason why a precautionary principle is currently adopted in the cosmetic field. In fact, the new EU legislation introduces the need of a special safety assessment procedure for the products containing nano-materials.

The Commission published this year the Guidance on the Safety Assessment of Nanomaterials in Cosmetics. The document was drafted by the Scientific Committee on Consumer Safety (SCCS) to guide the cosmetics industry on the essential elements that would be required in a manufactured nanomaterial safety dossier i.e. physicochemical characterisation; toxicological evaluation, exposure assessment etc. (27). Prior to placing the cosmetic product on the market, the responsible person should submit the following information to the Commission: the presence of substances in the form of nano-materials; their identification including the chemical name (IUPAC) and other descriptors; the reasonably foreseeable exposure conditions. All ingredients present in the form of nano-materials shall also be clearly indicated in the list of ingredients on the labels of cosmetic products. Their names shall be followed by the word "nano" in brackets (28).

Silver, copper, gold, chitosan, silicone, silica nanoparticles, nano-scale chitosan structures and fullerenes as radical-scavenger have also been reported as new nano-scale ingredients for cosmetics (9, 29). And there are still infinite opportunities to exploit other benefits of the nanotechnology in the cosmetic field. At the same time, this will create infinite associated safety issues. The risk to human health consequent to cosmetic applications is the subject of an increasing amount of researches as is the strive for higher performances. New and safe is the need for all future cosmetic ingredients.

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Nanopharmaceutics. The Potential Application of Nanomaterials

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While nanoscience is research focused on multifunctional devices and biomaterials at nanoscale from tens to hundred nanometers, nanomedicine is a a multidisciplinary field using nanotechnology for medical applications. Thus nanomedicine can provide an opportunity for improved drug development so that the USA National Nanotechnology Initiative in 2009 allocated € 1.5 billion to different funding agencies, reflecting a steady growth in addition to the € 8 billion invested since 2001. This book, composed of **20 Chapters**, addresses the specific nanoplatforms used for delivery imaging, therapy and toxicity of nanomaterials for pharmaceutical applications by a multidisciplinary interactive approach, where engineers, chemists, and physical scientists are teaming up with biologists and clinicians.

Nano-emulsions are one of the most important nanocarriers in nanomedicine because they seem to achieve new and effective ways of treating and preventing cancer and other pathological diseases to ultimately change the lives of patients worldwide. Cancer remains, in fact, one of the most complex diseases affecting humans and, despite the impressive advances that have been made in molecular and cell biology, how cancer progress through carcinogenesis and acquire their metastatic ability is still widely debated. In any way, the complexity of cancer combined with an avalanche of basic science research uncovering the plethora of pathways that feed into cellular growth control reveal many potential therapeutic targets. However, there is a critical need for not only specific, effective therapies without side effects, but also mechanisms for early detection to ensure that therapies have the best opportunity to be timely and effective.

Thus, in order to increase therapeutic benefit, it would be advantageous to protect, for example, the *silent* RNA in *packaging* while specifically delivering the cargo to the intended target cell or tissue. The goal in particular is where nanotechnology will shine, enhancing bio-distribution of the active ingredients, increasing their therapeutic efficacy, while reducing the toxicity of the active compounds by the use of well designed nanoemulsions.

Design, production and use of nano-systems for drug and gene delivery are reported and discussed on **Chapters 1** and **2**. Safety and efficacy for protein pharmaceuticals are as important as for another medicinal product. For any protein, it is essential to maintain its active form and avoid introduction of structural changes or aggregation. One of the main adverse effects of protein therapeutics are believed, in fact, to be triggered by the presence of non-native or aggregated protein, provoked during pharmaceutical processing. This is why the therapeutic application of peptides and proteins

present us with several challenges.
Since protein molecules are often surface active, adsorption to various surfaces can occur during processing, in the product under storage, and after administration, leading to loss of protein from the product and increased rate of physical degradation. Moreover, degradation and conformational changes can led to loss of biological activity and can also induce adverse effects. Once a protein is administered into the body, it will rapidly come into contact both with proteases that can promote hydrolysis of the amino acid backbone, and the immune system which can be activated producing antibodies against the injected protein. This is the topic reported and discussed on **Chapter 3**.
With completion of the Human Genome Project, proteomics has become the point of interest for a deeper insight into the cellular processes.
A deep understanding of the structure and property of nanomaterials and interdisciplinary applications of nanotechnology to proteomics will certainly be revolutionary and intellectually rewarding. The large surface-to-volume ratio of nanomaterials, in fact, could facilitate mass transfer and increase of the separation, providing also a platform for attaching a large number of functionalities to the surface for specific separations. However, to achieve revolutionary advances in nanotechnology-based proteomics, a deeper understanding of the structure and property of nanomaterials and their relationship with bio-molecules are needed. This the topic of **Chapter 4**.
Cancer, which affects over 10 million people around the world, is characterized by rapid and uncontrolled proliferation of normal cells. While surgery offers the greatest chance for the cure of many types of cancer, chemiotherapy and radiotherapy present efficient treatment strategies to deplete cancer cells, also if a large group of patients experience dose-limiting adverse effects. One of the key elements in improving cancer therapy lies in the development of drugs and carriers that are more selective to cancer cells.
Nanopharmaceuticals represent an effective strategy to take care of these issues, as a new area of interdisciplinary research which bridges biology, chemistry ,engineering, and medicine to further major advances in diagnosis and treatment of cancer. On **Chapters 5** and **6**, this fascinating topic is discussed reporting results of the use of antibody mimetics, delivered by appropriate and well designed carriers made of lipidic nanoparticles to be used in gene delivery as non-viral vectors.
The activities of modified chitosan, chitin and their derivatives are summarize on **Chapter 7**. This chapter is focused on various factors influencing inclusion complex formation because an understanding of the same is necessary for proper handling of these natural and versatile materials. These positively charged polymeric systems, having the capacity to bind negatively charged molecules by chemical and ionic cross-linking, find a wide range of applications useful to solve numerous biomedical problems. Modified chitin and chitosan are easily degraded within the biological systems over time, and furthermore their degradation rate is easily engineered on the amount of deacetylation that occurs during processing. This allows drugs to be released into the body in a controlled manor to be as effective as possible. The ability chitin/chitosan have to be used in various forms, such as gels, copolymeric-films or non-woven tissues, is another characteristic that make them attractive materials for drug transport.
Owing to their well-defined structure and multivalent cooperativity, dendrimers have attracted particular attention as ideal nanocarriers for nucleic acid delivery. Thus, **Chapter 8** highlights the current status of dendrimers as non-viral nanovectors for both DNA and siRNA (silent RNA). Ranging in size from 1 to 10 nm, these particular vehicles are based on the unique molecular architecture with

cascade-branched units emanating from a focal point and numerous end groups on the surface. They are composed of three distinct domains: (1) a central core that is either a single atom or a group bearing at least two identical chemical functionalities, (2) growing units containing at least one branch junction repeated in a geometrically organized fashion, and (3) a large number of terminal groups located at the dendrimer surface. Unlike conventional polymers, their structure can be precisely controlled thanks to their characteristic stepwise synthesis.

Thus, various chemical modifications such as surface modifications, PEGylation, ligant and antibody conjugation have been performed with a view of increasing delivery efficiency, reducing nonspecific toxicity and promoting targeted delivery.

Any way, the today challenge is oriented to developing multifunctional biodegradable dendrimeric delivery platforms for nucleic acid based gene therapy with the aim of maximizing the delivery efficacy and minimizing the complicated side effects.

Chapters 9 and **10** are dedicated to platinum cancer therapy. Despite of its toxicity, platinum-based drugs continue being the support of therapy for many different kinds of cancer. Thus the wide variety of materials used to synthesize the best delivery systems in chemotherapy for platinum-based compounds are reported and discussed in these chapters. Delivery systems based on its chemical conjugation are able to avoid premature releasing of this drug that shows a better targeting efficacy as well as physical encapsulation by the use of polymeric systems capable to increase its biodegradability, biocompatibility and its more easy release. In any way, *resistance* appears the major problem limiting the efficacy of drug treatment of cancer.

Improved tumor-delivery strategies and co-administration with specific modulators of prevalent platin-resistance mechanisms might provide future clinical benefits. By nanotechnology it seems possible to develop customized solutions for optimizing the delivery of platinum and other pharmaceutical agents. It could positively impact the rate of absorption, distribution, metabolism, and excretion of the drugs in the body.

In addition, nanoparticles delivery can allow the drug to reach its target in a more active form.

Nanomedicine offers unique tools to address intractable medical problems in cancer and cardiovascular diseases, based on the use of compounds at molecular level, for molecular imaging, an emerging technique capable to give new perspectives.

The promise of molecular imaging lies in its potential to use selective biomarkers or molecular targets as reporter for the selectivity of targeting. Development of an efficient molecular imaging agent depends on well-controlled high-quality experiment design involving target selection, agent synthesis ,and its *in vitro* and *in vivo* characterization before its application in humans. The majority of these agents are used for Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT), and Magnetic Resonance Imaging (MRI). In any way, molecular imaging as an important tool is based on the concept that targeted delivery of contrast agents can specifically increase the signal-to-noise ratio by targeting the difference between diseased and normal tissues.

Among the theranostic options emerging in the new wave of biotechnology development, the perfluorocarbon nanoparticles have shown robust potential *in vivo* for diagnosing, characterizing, treating and following proliferating cancers, progressive atherosclerosis, rheumatoid arthritis, and much more. The different opportunities of imaging use and application are reported and discussed on **Chapters 11** and **12**.

Novel nanomaterias are playing key roles in nanotechnology innovations and their application in

biomedicine presents myriad of opportunities and challenges.
Nanomedicine is expected to enhance human capabilities and promises the ability of health care professionals to diagnose, treat, and share medical information nearly instantaneously , but it is necessary to understand in a better way the potential impact on nanomaterials, environment, health and society by undertaking their proactive risk assessment.
Understanding the contribution of physicochemical characteristics of nanomaterials to toxic effects would allow safety to be built into the design of nanomaterials and other applications, to allow their safe integration into products. Many studies on the toxicological aspects of SiO2, ZnO and TiO2 in the form of nanoparticles were focused and discussed on **Chapter 13**.
Any assessment of a nanoscale material's safety has to consider the potential toxicity arising from oxidative damage. Nanotoxicity mechanism of nanomaterials, facilitating the molecular transfer of electrons , seems to involve an oxidative damage due to generation of free radicals and other reactive oxygen species. Thus the necessity to detect rapid and predictive methods to assess the oxidative damage elicited by nanoscale materials.
Chapter 14 discusses the use of electrospin resonance (ESR) to determine and identify the free radicals. By this method it is possible to directly assess antioxidant quenching or prooxidant generation of free radicals and reactive oxygen species. ESR is, in fact, sensitive at optical spectroscopy, and has additional advantage to detect and identify free radicals unambiguously.
From the biological perspective, the natural bone matrix is a typical combination of organic/inorganic composite material consisting of a naturally occurring polymer (collagen) and a biological mineral (apatite), and blending with inorganic material can modify not only properties but also the degradation rates of materials. Moreover, this natural composite material also has an excellent balance between strength and toughness, superior to either of its individual components. Thus the necessity to fabricate scaffolds of similar characteristics that meet all requirement necessary to improve the orthopedic implants. This is the topic of **Chapter 15** where methods of production and use of nanostructured hydroxyapatite (HAp) scaffolds are discussed. Highly nanoporous HAp-based composite materials have been characterized on the basis of their biodegradability and biocompatibility through *in vitro* and *in vivo* tests. Recent studies have suggested, in fact, that nanocrystalline HAp powders may improve its natural similarity and enhance the bone densification due to its greater surface area, which may improve the bone fracture toughness, as well as other mechanical properties. Due to the chemical similarity between HAp and mineralized human bone, it exhibits a strong affinity to host tissues, showing biocompatibility and biodegradability *in situ*, possessing also a good osteoconductivity and osteo-inductive capability. For all these reasons, HAp is considered an ideal candidate for orthopedic and dental implants or component of bone implants.
Neurological disorders in humans can be modelled in animal using standardized procedures that recreate specific pathogenic events and behavioural outcomes. The problem is that human brain is protected from penetration of microoganisms or toxins by the physiological barrier called hemathoencephalic barrier that serves as highly selective filter. Thus, the drug delivery to the brain remains a big challenge, so that the encapsulation of active ingredients, as dopamine, inside an inorganic nanostructured matrix seems to be a promising way to deliver the drugs. They may be incorporated either by adsorption into an already existing structure or during the structure formation ,namely the synthesis of the matrix, also when its solubility influences the possibility of its encapsulation. These problems are focused on **Chapter 16**, where the treatment of Parkinson's disease

is reported.

Recent research on drug delivery approaches indicates that engineered nanosystems may bring positive effect on the improvement of current antiretroviral therapy. This is the topic focused on **Chapter 17** and it is also the reason why nanotechnology may become a potential approach in the field of HIV/AIDS treatment and prevention. According to the report of Joint Nations Programme on HIV/AIDS, by November 2009, about 32.8 million people are living with AIDS, but the death of HIV patient decreased by 19% in the last five years thanks to the new therapies and drug delivery systems. Today, in fact, nanotechnology-based delivery systems can been used to control drug release, reduce its toxicity, improve bioavailability and targets to affect special tissues or cells. This is why nanotechnology brings a new world of drug design and probably resulting in technology revolution. Thus may be that one day could be possible drive away virus completely and cure AIDS. The advantages of using nanoparticles for site-specific drug delivery, to obtain stability *in vitro* and *in vivo*, as well as reduced side-effects compared to conventional drugs, have made them the next generation therapy for the treatment of many diseases. However, toxicological studies have revealed that the uptake of novel nanomaterials may pose serious threats to health by the way of immune responses. But recent studies have shown that the parameters such as uptake, impact and final fate of the nanoparticles, depends on the surface state of the materials. Thus, engineering the surface of the nanomaterials with the help of biological molecules, can help in immune acceptance without triggering any undesirable inflammatory response. The fate of the nanoparticle upon interaction with the immune system is dependent on the cellular and humoral immune response which can distinguish self from non-self.

The use of nanomaterials for immunotherapy or immunomodulation seems, therefore, relevant as nanomaterials can be designed or manipulated on the basis of physical properties, encapsulating ligands and surface ligands in order to activate the immune system to fight back diseases. The interaction of nanoparticles with the immune system and their significance in drug-design and development is the topic discussed on **Chapter 18**.

Nanotechnology has become a distinctive field of research, aimed to modernize the way scientists have addressed urgent needs and sophisticated problems, towards the achievement of unprecedented discoveries. Biocompatibility and biodegradability are the two most important characters acquired to nanostructures when used in biological and medical fields. Thus, during these last two decades there was a shift from biostable biomaterials to biodegradable biomaterials for medical and health applications. The main advantage of biodegradable materials is the disappearance of implanted foreign materials from the body ,which might elicit foreign-body reactions from the host's defense system during their long-term contact, thus helping the body to repair and regenerate the damaged tissues without causing unacceptable degree of harm to the body. On the other hand, biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effect, but generating the most appropriate beneficial cellular or tissue response. In any way, up today a total biodegradable/biocompatible carrier is a dream in the development of a drug delivery system that can delivery the drug at a rate dictated by the needs of the body over a specified period of treatment. These topics are reported on the final **Chapters 19** and **20**.

This book provides a wide overview of the many problems connected with nanomaterials to be used in the pharmaceutical field, from their biological activities and toxicity potential for human and

environmental concern.
For its multidisciplinary approach to the emerging field of cancer nanotechnology, the reported design of the new nano-emulsions and innovative nanoparticles, the nanoscaled proteomic analysis, the interaction with the immune system, and the interesting discussion on the biocompatibility and biodegradability characteristics, *Nanopharmaceutics* may be a useful support for researchers involved not only in the pharmaceutical field, but also in nanomedicine in general, such as biologists, material and biomedical engineers, clinical oncologists and other scientists having interest on nanobiomaterials and regenerative medicine.
In conclusion the book is very interesting and well organized and just for this reason, it is a pity that many chapters do not report the references list according to *Index Medicus*.

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Editor-in-Chief

Lignin and Lignans. Advances in Chemistry

by C. Heitner, D.R. Dimmel, J.A. Schmidt

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Since the realization of global sustainability depends on renewable sources of materials and energy, there is an ever-increasing need to use plant biomass to develop bio-based goods able to replace petroleum-based one.

Biomass crops, woody species or grasses consist primarily of cell walls, composed of a complex matrix in which cellulose are embedded in a network of cross-linking hemicellulose polysaccharides. *Lignin* acts to harden the wall, providing structural rigidity and a physical barrier to fungi and insects, and assists movement and transport of water in plants.

As complex compound, it forms a barrier for evaporation, helping to channel water to critical areas of the plant and, while its content and structure that depends on the type of tree, can vary within the same plant. Furthermore, lignin has an interesting redox potential containing more diverse reactive chemical groups, such as aromatic and aliphatic hydroxyl, carboxyl, and carbonyl moieties. However, it is a polymer that, built up by the combination of three basic monomer types (p-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol), is formed from oxidative coupling of hydroxycinnamyl alcohols and related compounds such as hydroxycinnamaldehydes.

The polymerization which occurs in the cell wall, especially in the secondary cell walls at the level of the water-conducting xylem vessels and sclerenchyma fibers, is mediated by peroxidases and/or laccases. Variation in lignin composition is a function of plant species, age, and tissue type. However, it is interesting to remember that lignin has historically been viewed as a waste product with little intrinsic value, while today, with the desire to maximize the use of all components of the biomass, efforts are being made to identify additional uses of this interesting polymer also.

For all these considerations and because of the increasing economical interest to the global use of plant biomass, a deeper knowledge of lignin's chemistry has to be taken in great consideration. This the scope of *Lignin and Lignans*.

The goal of this book, comprised of **17 Chapters**, is to provide a source for reporting an update knowledge of *lignin* in the key areas of more specific interest.

Due to its complexity, non-uniformity, and conjunctive bonding to other compounds, *lignin* has been difficult to isolate for determining its structure, and converting this complex compound in useful consumer products.

Chapters 1 and **8** give the reader a coherent picture of lignin properties reporting data on its thermal stability and molecular motion when isolated. It is difficult, in fact, to measure a single component in a biocomposite such as wood, since it contains three macromolecular species: cellulose, hemicellulose, and lignin. X-ray diffractograms indicate that the isolated lignin, frozen in the glassy

state (i.e. a nonequilibrium state) is represented by a broader distribution of structures in comparison with synthetic polymers, such as polystyrene. Moreover the molecular motion of hydrophilic polymers is enhanced in the presence of water. Water molecules break intermolecular hydrogen bonds and make segmental motion occur easily.

However, the molecular motion of lignin, having phenyl groups in the main chain, is similar to that of synthetic polymers but because of the presence of many hydroxyl groups, its motion is influenced by the hydrogen bonds water molecules. In any way, the real problem with the structural studies is to obtain a sample of lignin not been significantly altered by its isolation from the other plant components. This polymer seems not to be a stand-alone polymer, but has linkages to polymeric carbohydrates. Some data of *in situ* lignin are, however, discussed according to results that have recently been obtained using new methods, such as thermal analysis and viscoelastic measurements.

One of the greatest challenge in the structural biochemistry of the lignified cell wall is to determine the nature and proportion of building units and interunit linkages in native lignin structures. Thus Chemical and spectral structural studies are reported from **Chapter 2** to **7**.

Lignins are essentially composed of C_6C_3 units, namely p-hydroxyphenyl (H), guaiacyl (G), and syringyl(S) units, in various proportions, according to botanical, physiological, and cytological criteria. These units are interconnected by a series of carbon-oxygen(ether) and carbon-carbon linkages in various bonding patterns. Moreover, there is a universal consensus for the predominance of the labile Beta-O-4 ether linkages in native lignins, as well as the occurrence of the more resistant Beta-5, 5-5, Beta-Beta, 5-O-4, and Beta-1 interunit linkages, and the advent of sophisticated nuclear magnetic resonance (NMR) techniques has greatly aided the understanding of lignin structure.

The real unsolved problem is to obtain lignin samples not significantly altered by their isolation from the other plant components, also if the chemical degradation methods will continue to have an important role in lignin research. Thus, the electronic spectra of lignin and lignin model compounds can be adequately understood by examining the substituent effects on the three bands of benzene. On one hand improvements in instrument design and the wide availability of microcomputers studies have confirmed the importance of quinone structures to the colour of wood and pulps, clarifying their response to the common bleaching agents. On the other hand , the transient spectroscopy and emission spectroscopy have clarified the spectra and chemistry of the excited electronic states of lignin.

Another important tool in modern chemistry is vibrational spectroscopy evidenced by three important methods: Raman spectroscopy, infrared spectroscopy (IR), near-infrared spectroscopy (NIR). In organic molecules, in fact, vibrational spectra arise from two different types of energy exchanges between the molecules under study and the electromagnetic radiation. In infrared spectroscopy, a vibrational transition that involves a change in dipole moment results in absorption of an infrared photon. The energy of the absorbed photon is equal to the different energy occurring between the two vibrational states of the molecule. It is therefore possible to correlate the well-defined frequencies at which certain bond types of carbon, hydrogen, and oxygen are expected to absorb or scatter.

Thus, it is important to consider the types of functional groups that occur in lignin, together with their structural variations, correlating the characteristic absorption of each single bond with the collective properties of the clusters' bonds of the aromatic centers by the use of these techniques.

However, NMR has enormously facilitated the investigations into of lignin structural aspects, playing the major role in the qualitative and quantitative understanding of its structure, because of the high resolution and the high dispersion of its chemical shifts. In any way the selective and quan-

titative tagging of lignin, followed by quantitative NMR data acquisition, has the potential to provide some truly unique insights toward understanding the complex and variable reactions of lignin under conditions of natural or commercial transformations, also if its true quantification remains difficult because of the signal overlap and other factors. The best quantitative method remains, therefore, the relatively tedious inverse-gated technique, along with an internal standard substance. But with molecules like lignins there are few guidelines and there are no absolutes, so that any value obtained from a nonquantitative technique must be compared to a corresponding value obtained from an inverse-gated experiment to determine its quantitative validity.

Lignin/lignan reactions are reported in **Chapters** from **9** to **15**. The complex and variable structure of lignin in wood and pulp, combined with the morphology of wood-derived fibers, have stimulated research in the areas of pulping and blenching, amply reported and discussed in these chapters according to their different and challenging aspects. The mechanical and chemical processes remain, however, the most widely used in today's pulp and paper industry being actually the less expensive. Nevertheless, there has been an increase of new engineered productive bioprocesses competing with the conventional chemical and mechanical methodologies, due to the rapid advances in biotechnology and molecular biology, the dramatic improvements in computational chemical methods, the marked increase in the understanding of the mechanisms of fungal and enzymic pulping and biobleaching, and the rapidly growing of database of fungal genomes.

Mechanical pulping, in fact, needs much energy and also does not preserve the quality of the product, while biological pulping by use of lignin-decomposing fungi such as *Phanerochaete chrysosporium, Pholiota mutabilis, Tremetes versicolor, and Phlebia spp* is a finding application in the paper industry because of the better results for the quality obtained.

In contrast with cellulose and hemicellulose, lignin is the only polymeric component of the plant fiber that absorbs both visible and near-UV light, because of the presence of quinones and catechols in its molecule. During the productive process of pulping, the photooxidation of lignin causes depolymerization through cleavage of interunit bonds and yellowing through the oxidation of the aromatic groups.

Chapter 6 describes the results of researches elucidating the detailed reaction pathways leading to photodegradation and chromophore formation. Lignin, in fact, undergoes photooxidative degradation through two mechanisms. One involves excitation followed by abstraction oh hydrogen, which is followed by addition of ground-state triplet oxygen to carbon-based radicals to form hydroperoxides. The other mechanism is sensitizing the formation of singlet oxygen that undergoes electrophilic addition to the aromatic rings. Both free radicals and singlet oxygen produced inside the fiber wall degrade the macromolecule lignin.

By far, the principal use of lignin is as fuel in the production of pulp used for paper and corrugated board, due to its high calorie content, which make it excellent for this purpose.

Moreover, for its carbohydrate component some plants are now being processed for ethanol fuel production also. However, the many pharmacological properties of lignans have not been forgotten from the authors of this interesting book.

This is the interesting topic of **Chapter 17**. Lignans and neolignans are natural products derived from the same phenylpropane units that make the lignin polymer; many of them, isolated from medicinal plants and identified, have shown a variety of biological activities having, for example, antiinflammatory, antioxidant, antibacterial or hypolipidemic activity, as well as antiallergy, analgesic or

hypotensive effect etc. These and many other pharmacological activities are amply reported and discussed in this final chapter.

As previously reported, plant biomass is a renewable resource that causes problems when not used. The challenge, therefore, is to convert biomass as a resource for energy and other productive uses, identifying and assess environmentally-sound technologies and goods. Overall the necessity to raise awareness on the waste raw material use globally, especially in the developing countries, enable the implementation of technologies to reduce *greenhouse gas* emissions from the use of fossil fuels, and augment material resources for a variety of products. One purpose of this book is to give the necessary chemical information to decision-makers and end-users in selecting plant biomass conversion by knowledge and technologies. Hence, the development of efficient and cost-effective processes for the synthesis of biopolymers or renewable goods is a key requirement for the gradual replacement of petroleum-based chemicals and materials.

This will require a deep knowledge on the chemical composition of lignin and lignans together with flexible plant designs that can adapt to varying needs and demands. In addition, the pre-treatment method, amply described on this book, is a crucial factor governing the quality of cellulose, hemicellulose and lignin fractions from the bio-refinery processes, and therefore the potential value-added bio- products that can be produced.

Continuing knowledge and investments in academic and private research efforts for the development of a mature bio-products industry. Widespread societal adoption of bio-energy and bio-based products will require education of the general public, as well as environmental and economic policies, encouraging the transition from fossil to renewable resources, such as lignin and lignans.

This is the reason why this book has to be in the library of scientists working in academic and industrial research laboratories, interested not only on the field of Organic chemistry, Analytical chemistry, Engineering chemistry, Biochemistry, and Pharmacology, but also for people interested in Cosmetic Dermatology, Industrial processes and Environmental problems.

P. Morganti
Editor-in-Chief

LITHIUM IN THE BRAIN

Neutrons show accumulation of antidepressant in brain

Experiments with neutrons at the Technische Universität München (TUM) show that the antidepressant lithium accumulates more strongly in white matter of the brain than in grey matter. This leads to the conclusion that it works differently from synthetic psychotropic drugs. The tissue samples were examined at the Research Neutron Source Heinz Maier-Leibnitz (FRM II) with the aim of developing a better understanding of the effects this substance has on the human psyche.
At present lithium is most popular for its use in rechargeable batteries. But for decades now, lithium has also been used to treat various psychological diseases such as depressions, manias and bipolar disorders. But, the exact biological mode of action in certain brain regions has hardly been understood. It is well known that lithium lightens moods and reduces aggression potential.
Because it is so hard to dose, doctors have been reluctant to prescribe this "universal drug". Nonetheless, a number of international studies have shown that a higher natural lithium content in drinking water leads to a lower suicide rate in the general population. Lithium accumulates in the brains of untreated people, too. This means that lithium, which has so far been regarded as unimportant, could be an essential trace element for humans.

Lithium detection with neutrons

This is what Josef Lichtinger is studying in his doctoral thesis at the Chair for Hadron and Nuclear Physics (E12) at the Technische Universität München. From the Institute for Forensic Medicine at the Ludwig-Maximilians-Universität Munich (LMU) he received tissue samples taken from patients treated with lithium, untreated patients and healthy test persons. The physicist exposed these to a focused cold neutron beam of greatest intensity at the measuring station for prompt gamma activation analysis at FRM II.
Lithium reacts with neutrons in a very specific manner and decays to a helium and a tritium atom. Using a special detector developed by Josef Lichtinger, traces as low as 0.45 nanograms of lithium per gram of tissue can be measured. "It is impossible to make measurements as precise as those using the neutrons with any other method," says Jutta Schöpfer, forensic scientist at the LMU in charge of several research projects on lithium distribution in the human body.

Lithium wirkt auf die Nervenbahnen

Lichtinger's results are surprising: Only in the samples of a depressive patient treated with lithium did he observe a higher accumulation of lithium in the so-called white matter. This is the area in the brain where nerve tracts run. The lithium content in the neighboring grey matter was 3 to 4 times lower. Lithium accumulation in white matter was not observed in a number of untreated depressive patients. This points to the fact that lithium does not work in the space between nerve cells, like other psychotropic drugs, but within the nerve tracts themselves.
In a next step Josef Lichtinger plans to examine further tissue samples at TUM's Research Neutron Source in order to confirm and expand his results. The goal is a space-resolved map showing lithium accumulation in the brain of a healthy and a depressive patient. This would allow the universal drug lithium to be prescribed for psychological disorders with greater precision and control. The project is funded by the German Research Foundation (DFG).

http://mediatum.ub.tum.de/?cfold=1174328&dir=1174328&id=1174328#1174328

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Technische Universitaet Muenchen (TUM) is one of Europe's leading universities. It has roughly 500 professors, 9,000 academic and non-academic staff, and 32,000 students. It focuses on the engineering sciences, natural sciences, life sciences, medicine, and economic sciences. After winning numerous awards, it was selected as an "Excellence University" in 2006 and 2012 by the Science Council (Wissenschaftsrat) and the German Research Foundation (DFG). In both international and national rankings, TUM is rated as one of Germany's top universities. TUM is dedicated to the ideal of a top-level research-oriented entrepreneurial university. The university's global presence includes offices in Beijing (China), Brussels (Belgium), Cairo (Egypt) and Sao Paulo (Brazil). The German Institute of Science and Technology (GIST), founded in 2002 in Singapore, is the first research campus of a German university abroad. www.tum.de

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Trimestrale di Dermatologia Cosmetologica
Quarterly Review of Cosmetic Dermatology

Contents

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Fucoidan: Versatile Cosmetic Ingredient. An Overview

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Key words: *Fucoidan; Photo-aging; UV radiation; Skin gloss; Hair gloss; Wound repair;*

Summary

The growing demand for new cosmetic agents continues to be a significant challenge as well as driving force for good revenue returns to the cosmetic industries. In the present review, we describe fucoidan (a sulfate polysaccharide derived from marine source) and its cosmetic applications. The effects of fucoidan have been shown to protect the skin and hair which includes the reduction of wrinkles, scavenging free radicals, reduction in inflammation and a decrease in allergy and sensitive reaction of the skin. Furthermore, the fucoidan have been reported to improve the skin elasticity, skin elasticity retentive, skin glosses & skin firmness and as well as hair cleaning, hair conditioning, hair protecting: hair glosses, hair stiffness and hair growth. Even, effects of fucoidan have been shown to protect the skin against Ultraviolet (UV) radiation- induced skin damage. Thus the fucoidan has found potential applications in cosmetic industries.

Riassunto

La crescente domanda di nuovi principi attivi cosmetici rappresenta una importante sfida per l'industria cosmetica anche per il significativo ritorno economico che comporta.

Con il presente articolo si è voluto riportare e descrivere l'attività svolta dal fucoidan quale principio attivo di uso cosmetico secondo i dati riportati in letteratura questo polisaccaride di origine marina, svolgerebbe un effetto protettivo nei confronti sia della pelle che dei capelli includendo un'attività anti radicali liberi, una riduzione dei processi infiammatori e dell'attività allergica e sensibilizzante oltre ad una possibilità di ridurre l'apparenza delle rughe.

È stato riportato, inoltre, che il fucoidan migliorerebbe l'elasticità e la compattezza della cute oltre a dare lucentezza e maggiore resistenza ai capelli. Infine svolgerebbe un'attività fotoprotettiva riparando che il danni cutanei provocati da un'eccessiva esposizione ai raggi solari.

Per tutti i motivi riportati questo interessante polisaccaride può trovare molte applicazioni nell'industria cosmetica.

INTRODUCTION

Fucoidan refers to a type of typical polysaccharide which contains substantial percentage of L-fucose and sulfate ester groups being mainly derived from brown seaweed or algae from marine source. The polysaccharide was named as "fucoidin" after it was first isolated from marine brown algae by Kylin in 1913. Now it is named as "fucoidan" according to International Union of Pure and Applied Chemistry (IUPAC) naming nomenclature, but some also called it as fucan, fucosan or sulfated fucan as shown in the Fig. 1.

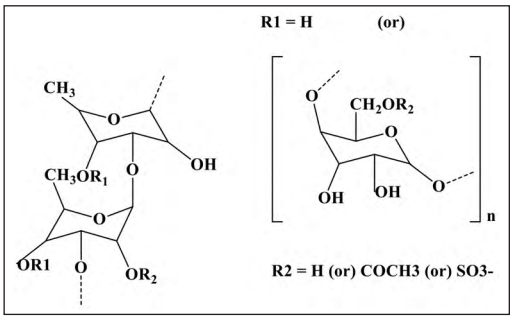

Fig. 1 *Structure of fucoidan.*

For the past more than six decades fucoidan has been extensively studied for its numerous interesting biological activities as shown in the Fig. 2. Recently, the search for new marine drugs has raised huge interest in fucoidans. In the past few years, several fucoidans' structures have been reported, world-wide and many of their biological activities have also been elucidated. Anticoagulant and antithrombotic, antivirus, anti-tumor and immuno-modulator, anti-inflammatory, blood lipids reducing agent, anti-oxidant and anti-complementary properties, activity against hepatopathy, uropathy and renalpathy, gastric protective effects and therapeutic potential in surgery are some of the available literature on biological activities of fucoidan (1).

With regard to Cosmetics, it seems to play a major role in human-being.

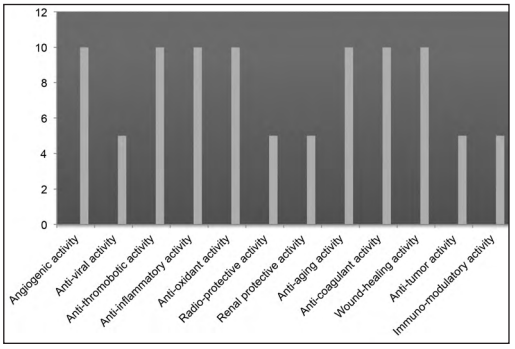

Fig. 2 *Various biological activities of fucoidan reported so far.*

Today, cosmetics have to meet the technical safety, effectiveness and application standards required by our society for the busy modern man or woman. They have not only to be care for their physical appearance as fundamental, but also safeguarding their physical well-being as instructed by regulatory authorities world-wide. This is the today prime priority differently from the 1980-1990 period, principally dominated by fashion and personnel image. Recent search is for physical authenticity and the explorations of new poly-sensorial experiences, promoting not only a sense of well-being but stimulating also the desire to express a personal individual creativity.

These statements well agree with the Morganti report on "Beauty and Wellness at 360°", where the author highlighted that Global beauty and well-being obtainable with the use of appropriate cosmetics, combined with a healthy and balanced diet (2).

Similarly Tranggono and Adityarini highlighted the need for Asians to use cosmeceuticals for a total ultraviolet (UV) protection (include UV A and UV B protection), being UV radiation causes of sunburn, free radicals, and skin cancers formation, and suppression of the immune system and skin aging, especially to tropical countries (3). On the other hand (4) highlighted the same need to protect the skin from prematu-

re aging by using tools able to counteract both the action of the proteases on the dermis and the disappearance of the antioxidant defenses from the skin.

Keeping in mind all these above aspects/reports, the paper summarizes the fucoidan (Marine active ingredient) and its applications in cosmetic industry.

Emulsifying effect of Fucoidan

Kim et al. reported that fucoidan (an anionic sulfated polysaccharide) along with bovine serum albumin (BSA), effectively stabilized the Oil-in Water (O/W) emulsion under any pH conditions (5). This adds one more credit or value to fucoidan as emulsifying agent in the cosmetic industry.

Anti-inflammatory effect of Fucoidan

Park et al. reported *in vitro* model the inhibitory effects of fucoidan on production of lipopolysaccharide(LPS) – induced pro-inflammatory mediators in BV2 microglia cell line (Gila cells are typical cells that are resident macrophages of the brain and spinal cord). These results suggest that fucoidan could be considered a potential therapeutic agent for inflammatory and neurodegenerative disorders, as well as a cosmetic agent, for inflammed and/or photo-aged skin (6).

Anti-oxidant effect of Fucoidan

Kim et al. reported the antioxidant activities of fucoidan against peroxyl radicals, peroxynitrites and hydroxyl radicals as shown in the Fig.3. These results suggest that fucoidan should have direct oxy-radical scavenging capacity, again related with its anti-inflammatory effect (7). Similarly, Barahona et al. (2011) reported that fucoidan, from *Lessonia vadosa* (brown sea weed), exhibited a very high antioxidant capacity (via the ORAC (Oxygen Radical Absorbance Capacity) method). Both the anti-inflammatory and anti-oxidant activities add new value for the use of this polysaccharide as functional cosmetic agent, especially used to protect a photo-aged skin (8).

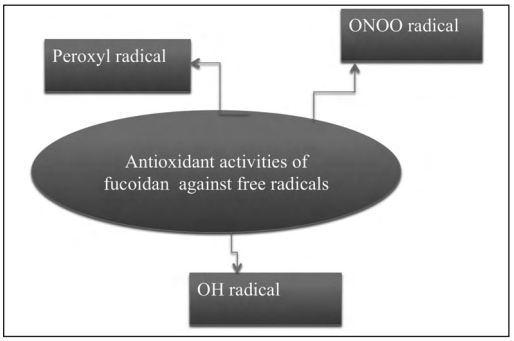

Fig. 3 *Antioxidant activities of fucoidan against free radicals.*

Effect of Fucoidan in inhibiting body lipid accumulation

Min-Kyoung Park et al. reported that fucoidan showed high inhibition of lipid synthesis at 200 µg/mL concentration. This report further suggests that this ingredient can be useful for the prevention or treatment of obesity or as a body sliming agent (9), due to its stimulatory activity on lipolysis.

Effect of Fucoidan on wound repair

O'Leary et al. reported that cells treated by fucoidan showed increased wound healing rate compare to the control. This report suggests its beneficial properties in the treatment of wound healing (10). Similarly, Ali Demir Sezer et al. (2008) underlined that in combination with chitosan for hydrogels formulations fucoidan has shown properties, especially beneficial in the treatment of wound healing (11).

Effect of Fucoidan on melanin synthesis and tyrosinase activity

Sook Hee Jung et al. reported that melanin synthesis by tyrosinase activity in $B_{16}F_{10}$ melanoma cells was decreased in a dose-dependent manner by the use of fucoidan as shown in Fig. 4. Moreover the α-melanocyte stimulating hormone (α-MSH) was also inhibited by fucoidan with a dose-dependent manner compared to the control. This report indicates that fucoidan, which inhibit melanin synthesis and tyrosinase activity, could serve as effective skin-whitening or lightening agent (12).

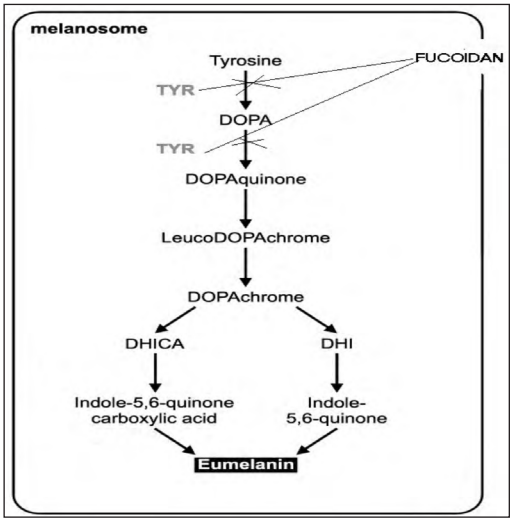

Fig. 4 *Level of fucoidal activity.*

Effect of Fucoidan on photo-aging

Hee Jung Moon et al. reported that cell pretreatment with fucoidan inhibited UVB-induced matrix metalloproteinase-1(MMP-1) expression in a dose-dependent manner, probably inhibiting the extracellular signal regulated kinase (ERK) pathway. Therefore, it might be used as a potential agent for the prevention and treatment of skin photo-aging (13), as shown in Fig. 5.

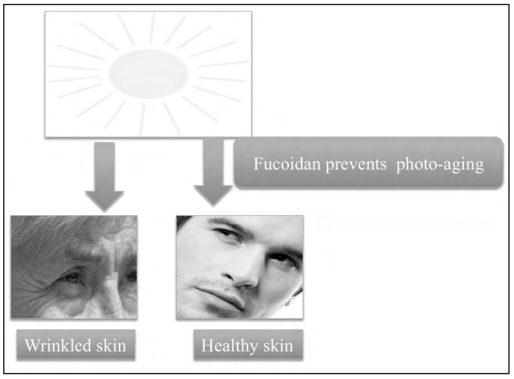

Fig. 5 *Supposed effect of fucoidan on photo-aging.*

Effect of Fucoidan on matrix metalloproteinase-2 & 9 (MMP-2 & 9) activities

Ye et al. reported that enzyme-digested fucoidan significantly inhibits the human fibrosarcoma (HT_{1080}) cell's invasion via suppressing MMP-2 and MMP-9 activities. This matrix metalloproteinase inhibition may have a great potential of use in clinical as well as in cosmetic applications as an anti-aging agent (14).

Effect of Fucoidan as a modulator of extracellular matrix (ECM) (or) connective tissue proteolysis

Senni et al. reported that fucoidan inhibits geltainase A or MMP-2 secretion and inhibiting also inhibits human leukocyte elastase activity, results in the protection of human skin elastic fiber network provoked by the enzymatic proteolysis of its serine proteinase. For this activity this polysaccharide could be used for treating some inflammatory pathology (even in photo-aging) in which uncontrolled extracellular matrix degradation takes place (15).

Patents pertaining to Fucoidan and its cosmetic applications

Table 1 provides a comprehensive summary of the intellectual properties, especially patents pertaining to Fucoidan and its cosmetic applications. And, this restricted to Korea and Japan countries, as they are major contributors of fucoidan research. According to McLellan and Jurd, in fact, the brown seaweeds has to be considered a staple of both Korean and Japanese diets and has also been documented as being used in traditional Chinese's medicine for over 1000 years (28).

TABLE I

Patents pertaining to fucoidan and its cosmetic applications.

S.no	Country	Patent no	Year	Important claim	Ref.
1	Japan	305011	1989	Crude fucoidan improves skin moisture retention property	[16]
2	Japan	021247	1999	Crude fucoidan inhibits release of histamine and thus acts as allergy inhibitor	[17]
3	Japan	155218	2003	Fucoidan in combination with other ingredients, enhances the hair growth	[18]
4	Japan	313131	2003	Fucoidan, serves as anti-wrinkle agent, skin elasticity improver, as well as skin elasticity retentive agent	[19]
5	Worldwide	093175	2006	High molecular weight fucoidan acts as cosmetic agent	[20]
6	Japan	008599	2006	Crude fucoidan containing formulation improves skin smoothing, hair protecting and hair growth agent	[21]
7	Japan	298916	2006	Fucoidan in combination with other ingredients, improves the hair cleaning and conditioning property	[22]
8	Japan	044913	2008	Fucoidan inhibits hyaluronidase and serves as therapeutic agent of the atopic-dermatitis	[23]
9	Japan	059065	2010	Fucoidan along with cellulite, improves swelling and slimming action	[24]
10	Japan	168296	2010	Fucoidan in combination with other ingredients, improves the skin gloss and firmness and also improves the hair gloss and stiffness	[25]
11	Korea	0023261	2011	Fucoidan acts as cosmetic agent especially for curing sensitive skins	[26]
12	Korea	0059394	2011	Fucoidan in combination with other ingredients serves as antibiotic agent	[27]

CONCLUSION

Being a constant need and requirement for new ingredients in the cosmetics field, fucoidan may represent an old ingredient of interesting new uses. Naturally, in our opinion further clinical studies could be necessary to evaluate the formulation stability, together with its safety, biological activity, and effectiveness of all the new products designed by the use of fucoidan.

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Role of a Caffeine Shampoo in Cosmetic Management of Telogen Effluvium

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Summary

Telogen effluvium (TE) is the most common hair-loss condition, that presents with a complaint of increased shedding over normal levels and associated diffuse alopecia. No specific medical treatment exists for TE. Recently, caffeine have shown to have beneficial effects in patients suffering from hair loss. We studied, in 30 women with TE induced by stress, the skin compatibility of a shampoo containing caffeine and assessed its anti hair loss efficacy and its cosmetic qualities.
The product in study has been shown to have a very good skin compatibility and a good cosmetic efficacy in the treatment of female TE. However, further studies need to be done to confirm and establish the role of caffeine in management of TE.

Riassunto

Il telogen effluvium (TE) è la più comune condizione di perdita dei capelli, che si manifesta con un aumento del diradamento rispetto ai livelli normali ed alopecia diffusa. Non esiste alcun trattamento medico specifico per il TE. Di recente, la caffeina ha mostrato effetti benefici nei pazienti con caduta di capelli. Abbiamo studiato, in 30 donne con TE indotta da stress, la compatibilità cutanea di uno shampoo che contiene caffeina e valutato la sua efficacia contro la caduta dei capelli e le sue qualità cosmetiche. Il prodotto studiato ha dimostrato di avere una tollerabilità cutanea molto buona e una buona efficacia nel trattamento cosmetico del TE femminile. Tuttavia, sono auspicabili ulteriori studi per confermare e stabilire il ruolo della caffeina nella gestione del TE.

INTRODUCTION

Telogen effluvium (TE) is the most common hair-loss condition that presents to the dermatologist and it is seen in all races and ethnic groups. Patients present with a complaint of increased shedding over normal levels and associated diffuse alopecia. The excessive shedding is the result of alterations of the hair-growth cycle with premature conversion of anagen follicles to telogen follicles, which represents a shift of 7–25% of anagen follicles to telogen. Clinically TE has been described as having at least three different clinical scenarios. It presents as acute (<4 months), chronic (>4 months), and chronic-repetitive. In chronic TE, the anagen cycle gradually shortens and the hair fibers become thinner and shorter. In acute and repetitive TE, follicular regeneration is common. Since TE is a medical sign rather than ultimate diagnosis, it is important to explore the possible triggers. An important trigger is the TE seen with the onset of androgenetic alopecia (AGA). Other triggers include hormonal fluctuations or abnormalities, endocrine disorders, postpartum, physiological, and metabolic stress, drugs, weight loss, nutritional deficiencies, systemic acute and chronic illnesses, surgeries, and scalp inflammation.

The diagnosis of TE is based on the clinical presentation and the confirmation of excess of shedding of telogen hair. The specific time of onset is important to establish. TE can begin 2 weeks after a trigger but peaks between 6–8 weeks and then tapers off in about 6–8 weeks if the trigger is removed or treated. Regrowth is not appreciated for several months, usually 4–6 months. Frequently, patients have multiple triggers that occur concomitantly, sequentially, chronic-repetitive, or chronic. Repetitive, multiple concomitant or sequential triggers, can prolong the TE and be mistaken for chronic TE. Prolonged or repetitive TE can also lead to diminished regrowth and a chronic diffuse alopecia. The differential diagnosis of diffuse alopecia includes AGA, diffuse alopecia areata, and an inflammatory alopecia such as central centrifugal cicatricial alopecia and lichen planopilaris, especially when the primary loss involves the central scalp. Since the diagnosis of TE is dependent on demonstrating increased telogen hair loss (greater than 7%), the pull-test allows to roughly evaluate the intensity of the hair loss. On hair unwashed since 2 days, neither brushed nor combed within the 2 hours before examination, 3 areas of the scalp (fronto-temporal, parietal and occipital) are chosen. A clump of about 50 hair per area is taken between the thumb and thefore finger and slightly pulled. A loss equal or higher than 15 on the 3 areas is considered as abnormal.

To determine the true trigger of telogen hair loss, the relationship between the trigger and the hair loss must be reproducible, with improvement of the hair shedding following correction of or removal of the trigger, and deterioration on rechallenge (1).

No specific medical treatment exists for TE, but use of antiseborrheic and antiandrogen shampoos, such as ketoconazole or pyrithione zinc; topical corticosteroids, minoxidil; nutrient/hormonal support and antiandrogens have been invoked. Caffeine is a methylxanthine, a well-known substance, but its effect on human hair follicle growth is not yet defined. Recently, certain newer advances have shown caffeine to have beneficial effects in patients suffering from AGA (2,3,4,5). We studied, in a panel of healthy women with TE induced by stress, the skin compatibility of a shampoo containing caffeine[1] and assessed its anti hair loss efficacy and its cosmetic qualities, after application under the normal conditions of use.

MATERIALS AND METHODS

The study has been performed in 30 female sub-

[1] *TRADEMARK: PLANTUR21 NUTRI CAFFEINE SHAMPOO.*

jects. The mean age was 31. The informed consent form was personal and previous to the start of the study.

Inclusion criteria were: age from 18 to 40, female, phototype (Fitzpatrick) from I to IV, copious hair loss started in the past 2 months, presence of TE induced by stress, absence of clinical signs of AGA or other forms of alopecia, no significant skin disease located on scalp, able to compromise the evaluation of skin tolerance of the investigational product or being possibly aggravated by the application of the investigational product (dermographism, recurrent herpes, pityriasis versicolor, psoriasis, important pigmentary disorders), UV light induced dermatitis, urticaria, no history of organ removal (kidney, lung, spleen, axillary lymph node) or organ transplant, no current treatment able to interfere with the interpretation of the study results (immunosuppressive drugs, anti-inflammatory products, antihistamine products, antibiotics).

Exclusion criteria were: different causes of alopecia [AGA, alopecia areata, trichotillomania, hair loss due to medication (immunologics, chemo-therapy, etc.)], unhealthy condition of the scalp (highly expressed eczema, high grade of dandruff), regular use of hair dye, bleaching products or products for permanent wave, present or past history of hypo/hyperthyroidism or iron deficiency (at the present or in the past), known allergies to the same type of products as the investigational products (cosmetic hygiene and care products) or other products (drugs, food), personal history of atopy, treatment, prior to the study, able to interfere with the interpretation of the study results (topical or systemic medication with anti-inflammatory or antihistamine products within the 6 months, antibiotics within the 4 weeks, medication for malignancy).

Investigational products was a hair hygiene product containing caffeine.

The constraints for the test subjects during the study were no application of any other hair products than the tested one, no intensive sun or UVA exposure (UV lamps), no colouring, hair bleaching, permanent wave during the study, no additional vitamin supply (vitamins B or H) or products which could have an effect on hair, no hair loss treatment by oral route, no medical treatments likely to induce an alopecia (antimitotics, anticoagulants, antithyroid, antidepressive agents, anticonvulsants, beta-blockers, hypocholesterolemic drugs, retinoids), no application of hair lacquer or gel, no violent brushing and repeated massage of the scalp, no change of diet.

The shampoo has been applied at home by the test subjects, once day for 6 months, on wet hair. The product has been left in contact with the scalp for 2 minutes, massaged with the fingers into the scalp and rinsed off accurately.

Checking of the skin compatibility (local tolerance) based on: skin examination of the scalp, at baseline, after 3 and 6 consecutive months of treatment, by the investigator; the analysis of the sensations of discomfort reported directly by the test subjects to the investigator, during the study or in the daily logs.

Assessment of the cosmetic qualities and efficacy based on:pull-test performed at baseline, after 3 and 6 consecutive months of treatment, to evaluate the resistance of the hairs to traction; proband and dermatological questionnaire after 3 and 6 consecutive months of treatment.

Statistics

For the data of the pull test and the questionnaire information, descriptive statistical indicators (mean, standard deviation, 25%, 50% [median] and 75% percentiles as well as frequencies and percentages (where applicable) have been calculated.

In order to check whether the number of the hairs pulled (Pull test) changed after application of the investigational product, the exact, non-parametric Wilcoxon signed-ranks test has been conducted.

The questionnaire data have been also evaluated using the Wilcoxon test. One-tailed and two-tailed p-values has been reported, and the exact, two-tailed p-values have been used in each case.

RESULTS

After 3 and 6 consecutive months of product use at home, no intolerance reaction has been noted by the investigator and no sensation of discomfort has been described by the volunteers.

After 6 months of application of the shampoo, the number of hairs pulled was slightly, but significantly lower compared to the baseline [19.2 ± 3.9 vs. 21.2 ± 3.3; p=0.003, two-sided, exact Wilcoxon test], while after 3 months of application, the number of hairs pulled was only marginally lower (20.3 ± 3.6 vs. 21.2 ± 3.3; p=0.095, two-sided, exact Wilcoxon test).

In 17 (56.7%) subjects a decrease of hairs pulled has been observed after 3 months as well as after 6 months of application of the shampoo, whereas in 11 (36.6%) subjects and 8 (26.6%) the number of hairs pulled increased after 3 months and 6 months, respectively (Tables I, II).

The results of the pull tests are shown in Figure 1.

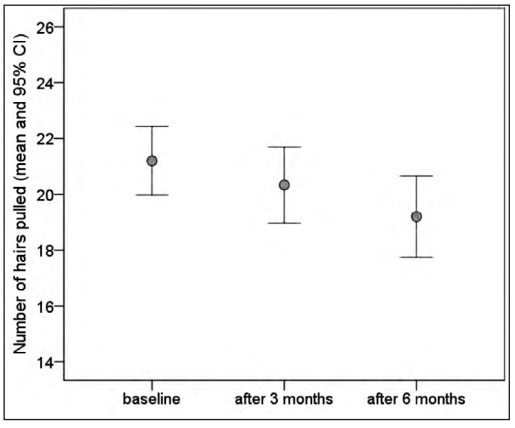

Fig. 1 *Number of hairs pulled (pull test) at baseline, after 3 and after 6 months of application of Plantur21 Nutri Caffeine Shampoo (means and their 95% confidence intervals are shown).*

The efficacy of investigational product has been assessed by the test subjects using the proband questionnaire at baseline, after 3 and 6 months of product application.

The following efficacy variables have been evaluated: intensity of hair loss, decrease or normalization of hair loss, number of hairs during daily combing, strength and thickness of hair.

After 6 months, as well as after 3 months, the intensity of hair loss significantly improved, compared to the baseline ($p<0.001$). Furthermore after 6 months, the majority of the test subjects agreed that their hair loss decreased or normalized.

After 3 months and 6 months of product application, the number of hairs during daily combing significantly decreased, compared to the baseline ($p<0.001$) and the strength of the hair significantly improved compared to the baseline ($p=0.031$ and $p<0.001$). Especially after 6 months of application, the contentment of the test subjects with the investigational product was high. The majority of the test subjects would like to continue with the shampoo and recommended it.

The scalp conditions have been assessed by the test subjects, evaluating itching and tension/dryness at baseline, after 3 and 6 months of product application.

After 3 and 6 months itching was slightly, but did not significantly improved, compared to the baseline ($p=0.312$ and $p=0.188$), while after 6 months tension/dryness improved compared to the baseline; this was not the case after 3 months ($p=0.016$ and $p=0.250$).

The efficacy of the investigational product has been assessed by the investigator using the dermatological questionnaire at baseline, after 3 and 6 months of product application. The following efficacy variables have been evaluated: strength of the hair, extent of the out falling hairs, progression of the thinning hair.

After 6 months, the strength of the hair significantly improved, compared to the baseline; this

was not the case after 3 months of application (p=0.002 and p=0.50). Similar results have been documented as regards the extent of out falling hairs (p<0.001 and p=0.125) and the progression of balding (p=0.001 and p=0.100), significantly decreased after 6 months, but not after 3 months of application.

After 6 months of product application, a reduction of balding/premature hair loss, an improved structure of hair or improved scalp conditions have been observed in the majority of the test subjects.

For the majority of the test subjects the shampoo has been recommended as a daily treatment of hereditary hair loss to reduce the number of out falling hairs.

The scalp conditions have been assessed by the investigator, evaluating redness and scaling/dandruff at baseline, after 3 and 6 months of product application. Redness was absent in the vast majority of the test subjects. Therefore, after 3 and 6 months of product application, redness did not significantly improved compared to the baseline (p=1.00 and p=0.50). Instead, after 6 months of product application, scaling / dandruff significantly improved, compared to the baseline; this was not the same after 3 months (p=0.016 and p=0.250).

TABLE I

Number of hairs pulled - Descriptive statistics

Number of hairs pulled (pull test)	N	Mean	Standard deviation	Min.	Max.	Percentiles		
						25th	50th (Median)	75th
at baseline	30	21,20	3,295	15	28	18,75	21,00	23,25
after 3 months of treatment	30	20,33	3,642	13	29	17,00	20,00	22,25
after 6 months of treatment	30	19,20	3,890	12	29	16,75	18,50	22,00

TABLE II

Number of hairs pulled – Results of exact Wilcoxon test

Test Statistics[b]		
	3 months vs. baseline	6 months vs. baseline
Z	-1,674[a]	-2,863[a]
Asymp. Sig. (2-tailed)	,094	,004
Exact Sig. (2-tailed)	,095	,003
Exact Sig. (1-tailed)	,048	,002

DISCUSSION

The most common type of diffuse shedding is TE, in which anagen-phase hair follicles prematurely transition to the telogen phase, resulting in a noticeable increase in hair shedding at the end of the telogen phase 2 to 3 months later.

TE mainly affects women. Primary or idiopathic chronic TE almost exclusively involves women between 30 and 50 years of age (6). Hair loss, as it occurs with TE, provokes anxieties and distress more profound than its objective severity would appear to justify. This reflects the profound symbolic and psychosocial importance of hair. Stress has long been implicated as one of the causal factors involved in hair loss (7).

No specific pharmacological intervention is currently available to manage stress-induced hair loss.

The beneficial effects of topical application of caffeine in hair loss can be attributed to inhibition of phosphodiesterase, improvement in barrier function, follicular penetration, stimulation and promotion of hair growth (8). Thus it appears to be a useful adjuvant in the management of TE.

According to the experimental conditions adopted in this study, the shampoo in study has been shown to have a very good skin compatibility, after application under normal conditions of use.

Moreover, the product has been shown to have a good cosmetic efficacy in the treatment of female TE. Precisely, the pull-test results documented an increase of the resistance to the traction strain of the hair and a decrease of hair loss in 56,7% of the volunteers after 3 as well as after 6 months of treatment.

Also the Investigator confirmed the good cosmetic efficacy of the product, noting a significantly improvement in the strength of the hair, a significantly decrease in the extent of the out falling hairs and in the progression of the balding.

After 6 months of treatment 66,7% of the volunteers have been satisfied with the product. Particularly, they referred a significantly improvement in the intensity of the hair loss, a significantly decrease in the number of hairs during daily combing and a significantly improvement of the strength of the hair.

Moreover, 66,7% of the volunteers agreed that their hair loss decreased or normalized with the treatment.

In other respects, the product was also well appreciated for its cosmetic qualities.

However, further studies need to be done to confirm and establish the role of caffeine in management of TE.

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Dual Skin-care Activity of Selected Herbs. Promising 'do-good' Ingredients in Skin Care Formulations?

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Summary

The use of natural ingredients have become increasingly popular in the cosmetics. One of the approaches in development of natural skin care/personal care products is the utilization of consortium of herbal extracts that have multiple functional benefits such as antimicrobial, anti-tyrosinase and antioxidant activities for their cognition-enhancing effects in skin care formulations.

This study reports the unique attributes of four plants viz. Tridax procumbens, Lantana camara, Thevetia peruviana and Euphorbia hirta with regard to the dual properties of antioxidant and anti-tyrosinase activities and their possible exploitation in skincare products.

The results indicate that there is a high positive correlation between anti-tyrosinase activity and antioxidant activity of the extracts of the study plants.

Riassunto

L'uso di ingredienti naturali nei prodotti cosmetici è diventato sempre più popolare.

L'approccio più seguito è basato sull'utilizzazione di diversi principi attivi estratti dalle piante in grado di svolgere diverse azioni utili per la cute, quali l'attività antibatterica, antiossidante, e quella depigmentante svolta al livello della tirosinasi.

Questo studio riporta i risultati ottenuti sull'attività antiossidante e anti tirosinasica di quattro piante: Tridax procumbens, Lantana camara, Thevetia peruviana and Euphorbia hirta.

In conclusione l'azione di questi quattro estratti vegetali inseriti in formulazioni cosmetiche ha posto in evidenza la loro interessante attività "sbiancante".

INTRODUCTION

Phytochemicals are produced by plants as plant secondary metabolites which are non-nutritive compounds that possess protective or disease preventive properties (1). Each of the phytochemical has a unique medicinal property that has found its application in preparation of various cosmetics and personal care products. Phenols are one of the major groups of phytochemicals that are ubiquitous in plants. In the previous decade, experimental studies have revealed pharmacological properties of phenol compounds such as anti-inflammatory activity, antiviral and cytotoxic activity. It is a well-documented fact that most of the medicinal plants which are rich in phenolic compounds have excellent antioxidant properties (2,3). Hence the relationship between total phenolic content and anti-oxidant properties has been reported by many researchers (4-7). The presence of antioxidant compounds may also enhances the reduction of melanin pigments by blocking the oxidative-phosphorylation reaction. A few reports suggest that a relationship between antioxidant and anti-tyrosinase activities may exist. (8,9). This study reports the unique attributes of four plants viz. *Tridax procumbens, Lantana camara, Thevetia peruviana* and *Euphorbia hirta* with regard to the dual properties of antioxidant and anti-tyrosinase activities and their possible exploitation in skincare cosmetics.

MATERIALS AND METHODS

Plant extraction

Collected leaves of *Tridax procumbens, Lantana camara, Thevetia peruviana* and aerial parts of *Euphorbia hirta* were shade dried for 3 weeks and coarsely powdered. The powdered plant samples were macerated with solvents such as petroleum ether, acetone and methanol in sequence from non-polar solvent to polar solvent in a ratio of 1:6. The supernatant was removed from the retentate using Whatman filter paper No. 1 and concentrated using a rotary evaporator at a temperature less than the boiling point of the solvent.

Phytochemical screening

There are three major classes of phytochemicals namely alkaloids, terpenoids and phenolics. Qualitative analysis of the three classes of phytochemicals was carried out in order to find out the presence and absence of phytochemicals in the selected plants. Following the qualitative phytochemical analysis, quantitative analysis of phenolics was done with an aim to quantify the amount of phenolics present in the selected plants.

Test for alkaloids

The presence of alkaloids in the different solvent extracts was tested using Dragendorff's reagent (10). Stock solution was prepared by dissolving 100 mg of petroleum ether, acetone and methanol plant extracts in 5 ml of respective solvents. To 2.5 ml of aliquots drawn from stock solution, few drops of Dragendorff's reagent were added. Presence of alkaloid was confirmed with the formation of reddish brown precipitate.

Test for terpenoids

Stock solution of 100 mg of individual solvent plant extracts in 5 ml of respective solvents was prepared. From the stock solution, 2.5 ml of plant extracts were mixed with 2 ml of chloroform and acidified with 1.5 ml of concentrated sulphuric acid along the sides of the test tubes dropwise. While gently adding sulphuric acid, the solution inside the test tube was observed for the formation of reddish brown colouration to

confirm the presence of terpenoids (11). No colouration indicates absence of terpenoids in the plant extract.

Test for phenols

Phenols were identified using the method described by Chitravadivu *et al.;* (12). From the prepared stock solution containing 100 mg of plant extract in 5 ml of solvent, 2 ml of plant extract was taken and mixed with 2 ml of 95% alcohol. To the mixture, few drops of ferric chloride solution were added. Formation of brown, blue or black colour of the solution showed the presence of phenols.

Test for total phenolic content

Total phenolic content was determined as described by Stanjovic *et al.,* (13) with gallic acid as a positive control. Phenols in the sample react with the phosphomolibdic acid in Follin-Ciocalteau reagent and undergo a complex redox reaction which causes blue colouration of the solution. Six concentrations of gallic acid such as 0, 100, 200, 300, 400, 500 μg /ml were prepared in the volumetric flasks. To each of the volumetric flasks 10 ml of 10% Follin-Ciocalteau's reagent and 10 ml of 7% sodium carbonate solution were added and the volume was made up to 25 ml with distilled water. The volumetric flasks were incubated for 90 minutes in dark at room temperature and the absorbance values were recorded at 750 nm using a spectrophotometer. The experiment was conducted in triplicates and the results are reported in terms of gallic acid equivalents (GAE).

Test for anti-oxidant activity

The effect of anti-oxidant activity was estimated using DPPH assay (14). Plant extracts at 1.0, 2.5, 5.0, 10.0, 15.0 and 25.0 mg/ml concentrations were diluted in respective solvents. Experiment was carried out in triplicates to compensate experimental variation. To 50 μl of test extracts, 5 ml of 0.004% DPPH in methanol was added and the mixture was incubated in dark for 30 minutes. The absorbance was measured at 517 nm using a spectrophotometer and percentage of DPPH scavenging was calculated using the formula given below.

Test for anti-tyrosinase activity

The mushroom tyrosinase inhibition method (15) using DOPA as substrate was employed to determine the anti-tyrosinase activity of plant extracts with slight modifications. Stock solution of plant extracts at 2, 0.2, 0.02, 0.002 and 0.0002 mg/ml concentration were prepared. The microtitre plate was filled with 140 μl of Phosphate buffer (pH 6.8), 20 μl of 1000 u/ml tyrosinase, 20 μl of plant extract and 20 μl of 0.85 mM L-DOPA. Kojic acid was used as the positive control. The negative control was prepared by replacing tyrosinase with phosphate buffer. The microplate was incubated for 10 minutes at room temperature and absorbance was recorded at 475 nm using a microplate reader. These absorbance values correspond to the amount of dopachrome produced. Experiment was carried out in triplicates and the percentage of tyrosinase inhibition was calculated using the following formula.

$$\text{DPPH scavenging activity (\%)} = ((A_o - A_1)/A_o) \times 100$$

Here, A_o is the absorbance of the control DPPH and A_1 is the absorbance of individual test plant extracts

$$\% \text{ Tyrosinase inhibition} = \frac{(A-B) - (C-D)}{(A-B)} \times 100$$

Here,
A = absorbance of blank solution with enzyme
B = absorbance of blank solution without enzyme
C = absorbance of sample solution with enzyme
D = absorbance of sample solution without enzyme

Correlation analysis

Pearson's correlation was carried out to correlate the total phenolic content with anti-tyrosinase and anti-oxidant activities that were worked out using Microsoft® Excel 2007 programme.

Statistical analysis

Data obtained were reported as mean ± standard error of three replicate determinations and analysed by SPSS (version 13.0). One way analysis of variance (ANOVA) and Turkey's multiple comparison tests were used to determine the differences among the means. P values < 0.05 were regarded as significant.

RESULT

Phytochemical screening

Alkaloids can dissolve well in non-polar solvents. Being a non-polar solvent, only petroleum ether was able to solubilise the alkaloids and hence, petroleum ether extracts showed the presence of alkaloids. In the case of terpenoids, it is clear that petroleum ether extracts of all the four plant samples showed terpenoids as seen in Table 1. While there were no terpenoids seen in methanol extracts, some amount of terpenoids were noticed in acetone extracts. This could be because acetone falls in the intermediate category of solvent polarity called polar aprotic solvents. Phenols are known to be extracted using polar solvents. Hence, the presence of phenols in methanol extracts was not surprising. Nevertheless, acetone extracts also showed a fair amount of phenols due to its polar aprotic property as mentioned earlier.

Test for total phenolic content

Total phenolic content in the plant extracts, as shown in table 2 was calculated as gallic acid equivalents (GAE). Standard curve of gallic acid showed high accuracy of fitness with R^2 = 0.9190 (Petroleum ether extracts); R^2 = 0.9418 (Acetone extracts) and R^2 = 0.9598 (Methanol extracts). Acetone extracts of *Lantana camara* and *Euphorbia hirta* showed higher total phenolic content when compared to the rest of the plant extracts. Methanol extracts also showed notable total phenolic content than petroleum ether extracts. Also, this has to be seen in the light of the fact that the difference in the total phenolic content extracted with different solvents is due to its varying polarity index that has specific solubility for phenolic compounds as stated by Ghasemzadeh, *et al.;* (16). Eventually, this matches with the results of qualitative test of this study.

TABLE I

Qualitative profile of phytochemicals found in selected four plants

Plant name	Petroleum ether extract			Acetone extract			Methanol extract		
	A	T	P	A	T	P	A	T	P
Tridax procumbens	+	+	-	-	+	+	-	-	+
Lantana camara	+	+	-	-	+	+	-	-	+
Euphorbia hirta	+	+	-	-	+	+	-	-	+
Thevetia peruviana	+	+	-	-	+	+	-	-	+

A – Alkaloids; T – Terpenoids; P – Phenols

TABLE II

Total phenolic content in selected four plants - GAE (μg/ml)

Plant name	Petroleum ether extract	Acetone extract	Methanol extract
Tridax procumbens	0.03 ± 0.002	2.37 ± 0.159	0.88 ± 0.082
Lantana camara	0.06 ± 0.005	2.50 ± 0.182	1.42 ± 0.091
Euphorbia hirta	0.31 ± 0.032	2.50 ± 0.128	1.25 ± 0.098
Thevetia peruviana	0.03 ± 0.003	1.62 ± 0.057	0.51 ± 0.048

Test for anti-oxidant activity

The antioxidant capacity of the plant extracts as determined by DPPH assay are compared with standard curve of the positive control, BHT (Petroleum ether - R^2 = 0.9696; Acetone – R^2 = 0.9443; Methanol – R^2 = 0.9937). Higher the percentage of anti-oxidant activity, higher is the free radical scavenging capability of the plant extracts. Based on the absorbance readings and the formula, percentage of DPPH scavenging was determined. One way ANOVA analysis showed that means of individual plant extracts were significantly different at alpha subset = 0.05 level. On comparing the test samples with the positive control (BHT) it is deducible that the percentage of DPPH scavenging expressed by the petroleum ether extracts are very low. Whereas, acetone and methanol extracts of plant sample are considerably higher than petroleum ether extracts. These findings can also be ascertained by the findings of Zhou (17), who states that the solvent ability to dissolve special group of antioxidant compounds can vary with the polarity of the solvents. Therefore, this signifies that more polar solvent favours the extraction of free radical scavenging compounds.

Test for anti-tyrosinase activity

The anti-tyrosinase activity of each plant extract was expressed in terms of KAE. One way ANOVA analysis showed that the KAE average values of individual plant extracts were significantly different at alpha subset = 0.05 level. Tyrosinase inhibition by plant extracts increased

in the following order: acetone extracts > methanol extracts > petroleum ether extracts. Acetone extracts of Euphorbia hirta shows highest tyrosinase inhibiting property amongst all tested plant samples. Petroleum ether extract of Tridax procumbens showed less anti-tyrosinase activity of all the plant extracts.

TABLE III

Percentage of DPPH scavenging ability in selected four plants

Plant name		Petroleum ether extract	Acetone extract	Methanol extract
Tridax procumbens		10.07 ± 0.36 ^{d}	28.40 ± 0.61 ^{c}	50.50 ± 0.29 ^{a}
Lantana camara		19.64 ± 0.15 ^{c}	76.42 ± 0.41 ^{a}	62.16 ± 0.70 ^{c}
Euphorbia hirta		34.15 ± 0.14 ^{b}	69.93 ± 0.73 ^{b}	87.61 ± 0.38 ^{a}
Thevetia peruviana		9.51 ± 0.12 ^{d}	17.83 ± 0.17 ^{d}	32.76 ± 0.14 ^{d}
Control	BHT	75.82 ± 0.27 ^{a}	76.11 ± 0.61 ^{a}	68.79 ± 1.40 ^{b}

$^{a,b,c,d:}$ Values in same column containing same superscript are not significant (P>0.05).

$^{a,b,c,d:}$ Values in same column containing different superscripts are significant (P>0.05).

TABLE IV

Anti-tyrosinase activity in selected four plants – KAE (mg/ml)

Plant name	Petroleum ether extract	Acetone extract	Methanol extract
Tridax procumbens	0.31 ± 0.01 ^{b}	0.56 ± 0.12 ^{d}	0.53 ± 0.00 ^{b}
Lantana camara	0.38 ± 0.01 ^{a}	0.72 ± 0.14 ^{c}	0.63 ± 0.02 ^{a}
Euphorbia hirta	0.36 ± 0.11 ^{a}	0.91 ± 0.01 ^{a}	0.62 ± 0.01 ^{a}
Thevetia peruviana	0.39 ± 0.01 ^{a}	0.81 ± 0.01 ^{b}	0.60 ± 0.01 ^{a}

$^{a,b,c,d:}$ Values in same column containing same superscript are not significant (P>0.05).

$^{a,b,c,d:}$ Values in same column containing different superscripts are significant (P>0.05).

TABLE V

Correlation between Total phenolic content, anti-oxidant activity and anti-tyrosinase activity

Parameter	Total phenolic content	Anti-tyrosinase activity	Anti-oxidant activity
Phenols	1	0.587*	0.647*
Anti-tyrosinase activity	0.587*	1	0.420*
Anti-oxidant activity	0.647*	0.420*	1

*. Correlation is significant at the 0.01 level

Correlation analysis

High anti-tyrosinase activity has been reported in plants that showed high phenolic content (18). Similarly, high anti-oxidant activity has been reported in plants that contain high phenolic content (19). Hence, Pearson correlation analysis was carried out. Correlation gets stronger in the following order: anti-oxidant and anti-tyrosinase activity < Phenols and anti-tyrosinase activity < Phenols and anti-oxidant activity. From the output (Table 5) obtained using SPSS, high positive correlation between the phytochemical, phenolics with anti-tyrosinase (0.587) and anti-oxidant properties (0.647) could be observed. Also, the relationship between anti-tyrosinase activity and anti-oxidant activity (0.420) were found to be directly proportional. The close relationship of the phytochemical, phenolics with anti-oxidant activity and anti-tyrosinase activity matches well with the research findings of Yoon *et al.;* (9).

DISCUSSION

In conclusion, the current study indicates that the plant extracts obtained from the leaves of *Tridax procumbens*, Lantana *camara*, *Thevetia peruviana* and aerial parts of *Euphorbia hirta* have significant anti-oxidant and anti-tyrosinase activities. On comparison with the total phenolic content, data indicates a positive correlation that exists between anti-oxidant and anti-tyrosinase activities. Though there are literature references of the toxic nature of seeds of *Thevetia*, the leaves with proper processing procedures are used in cosmetic applications. Earlier workers have suggested use of Thevetia leaf extract in wash off skincare products like soap (20). All the plants used in the study however may need to undergo proper toxicology studies. Further study on characterization of individual phenolic compounds of the plant extracts is also essential in order to segregate various phenolic compounds based on their anti-oxidant mechanisms. Since cosmetic and personal care preparations of the current era use extracts of medicinal plants/ herbs for various skin benefits including skin lightening effect and anti-aging effect, the herbs used in our study can be used individually or in poly-herbal combination for the dual benefits as they are found to enclose anti-tyrosinase and anti-oxidant activities.

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Biotechnology Fundamentals

by Firdos Alam Khan

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Biotechnology, being a field involving the use of biological systems or living organisms to manufacture or develop processes useful to benefit humans, may be represented by different classes: animal, agricultural, medical, industrial, and environmental. In addition to these major classes, other fields are directly or indirectly associated with biotechnology, such as nanobiotechnology, bioinformatics, pharmacogenomics, regenerative medicine, and therapeutic proteins. However, modern biotechnology deals more with the treatment of ailments and alteration of organisms, including prevention, diagnosis and cure of diseases, all necessary to bettering the quality of human life. Through human genetics, biotechnology has found applications in genetic counselling, antenatal diagnosis, and gene therapy, while in forensic medicine it is extensively used for identification of individuals who could be criminal.

These are the reasons why as per estimate, biotechnology is a € 30 billion a year industry that has produced approximately 160 drugs and vaccines, while more then 270 biotechnology drugs and vaccines are currently in clinical trials, targeting more then 200 diseases, including various cancers, Alzheimer's disease, hearth disease, diabetes, multiple sclerosis, AIDS, and arthritis. Moreover, many consumers are already enjoying biotechnology foods such as papaya, soybeans, and corn, while hundreds of biopesticides and other agricultural products are also being used to improve human food supply and to reduce the actual dependence on conventional chemical pesticides.

At the moment, the United States of America is the world leader in the research, development, and commercialization of biotechnology products with 1437 biotechnology companies, of which 314 are publicly held, having spent $17.9 billion on R&D in 2003 with an average of $104,000 per employee. It is important to underline that R&D, in general, has a special economic significance apart from conventional association with scientific and technological development, generally reflecting government or organization willingness to forgo current operations or profit to improve future performance or returns.

With this philosophy in mind, the world's four largest spenders on R&D were for 2006 USA (US$ 343 billion), EU (US$ 231 billion), China (US$136 billion), and Japan (US$ 130 billion). However compared with their GDP, the order of these spenders was: China, Japan, USA and the EU, with approximate percentage of 4.3, 3.2, 2.6, and 1.8 respectively, while the top 10 countries in terms of percentage of GDP were Israel, China, Sweden, Finland, Japan, South Korea, Switzerland, Iceland, USA, and Germany.

With the arrays of opportunities and challenges given from biotechnology, there is a dramatic increase in the number of institutes and universities around the world that offer graduate, postgraduate,

doctoral, and postdoctoral research in various specialized fields of this new branch of science.
In the world, USA and Canada have the largest number of biotechnology institutes and universities, but Europe has shown a great interest also, so that Germany, UK, and Switzerland have the largest number of biotechnology institutes and universities. Moreover, over the past decade, there has been a dramatic increase in the number of biotechnology institutes and universities in Asia and India, that have shown interest in both education and research activities. Particularly in China, where the R&D funding has been increasing continuously during the last 20 years, the government pays a great deal of attention to the development of modern life science, prioritizing the development of the agricultural aspect of biotechnology.
On one hand, with more than 400 universities, research institutes, and companies, and a total of over 20,000 scientists and researchers involved in biotechnology, the number of published scientific papers is increasing rapidly in China. On the other hand, the total sales of biotechnological products increased 50-fold during the last 10 years, surging from approximately US $ 1.6 billion in 1997 to more than US$ 2.5 billion in 2000.
Like China, India has an agricultural-based economy also concentrates on agricultural-based education and research, so that it has emerging as a key player in biotechnology-related activities and investments in this specific field.
Currently, although its biotechnology market contribute a mere 2% share in the global market, it is on the threshold of colossal growth in the coming decade. Thus, Indian government has evolved biosafety guidelines and has helped to lay down patent rules, so that biotechnological products sale has increased from Indian Rupees (INR) 404 million in 1987-1988 to INR 1138 million in 1997-1998 and to INR 2356 million in 2202-2003. However, India is the second largest food producer after China, and thus offers a huge market for biotechnology products such as transgenic rice, brassica, moonbean, pigeon pea, cotton and tomato, while its nutraceuticals market is valued at US$ 532-638 million. In any way, R&D represents a critical component of the biotechnological industry and is critical for all the industrial revolutions.
Without research it is impossible to discover, make, develop or bettering new products and biotechnology is the most exciting sector with the higher potential to discover and develop innovative products. This is the reason why the field offers promising jobs in universities, R&D centers, and corporate organization such as drug, cosmetics and agricultural products manufacturing and marketing companies.
For the same reasons there is an increased demand for clinical trial managers, clinical professionals, environmental, health and safety specialists, plant breeders, product development and manufacturing engineers, regulatory affairs specialists, and outsourcing managers, as well as for finance and administration personnel.
Biotechnology and nanotechnology are, in fact, multi-disciplinary fields including, but not limited to, materials, mechanical and biomedical engineering, clinical medicine, molecular cell biology, histology, bioethics, regulatory affairs, business administration, and commercialization transition. Therefore, to go on in biotechnology fundamentals, it is necessary an interactive approach, as one can contribute to the others, and vice versa.
The bio-revolution resulting from advances in molecular bioscience and biotechnology has already outstripped the advances of the *Green Revolution*. The next decade will see significant advances in medicine, agriculture, and animal health directly attributable to biotechnology, not confined to bio-

based industries only. Genetically engineered microbes may become more widely used, for example, to extract oil from the ground and valuable metals from factory wastes, as well as the plant biomass and the fishery' by-products, may be totally used to produce goods and bio-energy. However, one of the greatest challenges of modern biotechnology will be to face the ethical, social, and regulatory issues, safeguarding the production of innovative goods to ameliorate the quality of life, maintaining the environmental equilibrium and the biodiversity of the earth. These some sentences and data reported on *Biotechnology Fundamentals*, useful to briefly understand the actual and future importance represented from Biotechnology and Nano-technology.

This interesting book, comprised of **15 Chapters**, gives the readers all the necessary news for understanding the complexity of this new field, covering topics ranging from introduction to biotechnology, genes and genomics, proteins and proteomics, recombined DNA technology, microbial biotechnology, agricultural biotechnology, animal biotechnology, environmental biotechnology, medical biotechnology, nano-biotechnology, product development in biotechnology, industrial biotechnology, ethics in biotechnology, careers in biotechnology, and laboratory tutorials.

The interesting descriptions and discussions reported for all the treated topics as well as the references enriching each chapter, result useful not only for all the students who want to pursue a career in the field of biotechnology, but may be of great interest for researchers and scientists of the chemical and medical communities interested to understand where this new brunch of science is going to.

In conclusion and in my opinion *Biotechnology Fundamentals* has to find a place in every scientific library.

P. Morganti
Editor-in-Chief

Marine Biomaterials: Characterization, Isolation and Applications

by Se-Kwon Kim

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After the 2011 publication *Chitin, Chitosan, Oligosaccharides and Their Derivatives*, and the 2012 *Marine Cosmeceutical*, both edited by professor Se-Kwon Kim this third book, completes the series on the topic of chitins and other raw materials obtainable from the sea.

As well known chitin is a natural polymer obtained from the fishery' waste material, easily metabolized from the human chitotriosidases and the environment chitinases and, therefore, considered safe and grass ingredient. It is interesting to underline how the major use of industrial by-products, as the plant biomass and the fishery' waste, is becoming a fundamental necessity to save the environmental pollution and slow down the greenhouse gas emissions. At this purpose this book represents another precious source of ideas useful for increasing the knowledge on chitins and the other interesting raw materials obtainable from the sea, contemporary stimulating their industrial use, necessary to safeguard both the equilibrium of the earth environment and the maintenance of its biodiversity. Our life depends from an intricate net of correlations and all together plants, animals and microorganisms regulate the entire biosphere, maintaining the condition for our living.

According to Fritjof Capra "the survival of humanity will depend from our ecological knowledge, the capacity of understanding the fundamentals of ecology and to live accordingly with them". Thus the necessity of a sustainable economy based on a lower use of energy and water and a major utilization of the great quantity of the industrial green by-products poorly utilized, such as the fishery' waste and the marine biomaterials.

The book, organized by **Four Parts** and **40 Chapters**, provides an up-to-date coverage of marine biomaterials from their isolation to the relative characterization and applications.

Marine environment consists of several polymers, such as chitin, chitosan, collagen, carrageenan, fucoidan, and alginate, playing predominant role in biological and medical applications. Among these, *chitin is* the second abundant natural polymer after *cellulose*, so that the fishery' waste and the plant biomass represent indispensable by-products necessary to produce these *green* raw materials. On the other hand, different polysaccharides, bioactive peptides, and PUFA compounds may be derived from marine algae. **The first 14 Chapters** are dedicated to isolation and characterization techniques of these marine compounds.

Thunnus obesus, occupies 12% of the total amount of fish production in Korea, so that from its waste material it has been isolated the hydroxyapatite (HAp), amply used in bone tissue engineering for nutrient supplementation and cell attachment. Isolation and characterization of pure HAp from fish

bone and scales, algae and corals are the topic of **Chapters 2** and **3**.
Commercially, chitins and chitosans are produced from biowastes obtained from aquatic organisms, in which the physicochemical characteristics of chitosan batch-to-batch present variability due to seasonality of raw materials, freshness and quality of the shell, difficulty in process control, climate, etc. The success of the applications of chitin and chitosan, therefore, depends on their properties. Chitin nanofibrils (CN), for example, when well characterized as nano-crystals, present an interesting cicatrizing character or an anti-aging activity when and if used by the right carrier and dose, as well as a low-molecular-weight chitosan for plant growth stimulation is required. In any way, there is a need to develop a nomenclature system to represent each type of chitin and chitosan, establishing also international official standard methods to determine their degree of
deacetylation and molecular weight, as reported in **Chapter 4**.
Marine polysaccharides from algae, such as carrageenans, with a yearly global production of 45, 000 tons, have wide application in cosmetic, pharmaceutical and especially in food industry. Carragenan has a repeating disaccharides unit of Bets-D-galactose and Alpha-D-galactose and its double helix structure has been solved by x-ray diffraction, and controlled by NMR. Due to its interesting biological activities, such as its capacity to stimulate macrophages, to release the immunostimulatory agent interleukin 1 (IL-1) and the supposed antiviral property, inhibiting the replication of hepatitis A viruses, many study have been done on this sugar-like compound as reported on **Chapter 5**.
The Bay of Bengal is rich of fish, containing high level of polyunsaturated fatty acids (PUFA) particularly of the n-3 series that, capable to modulate the blood lipid profiles, result beneficial in combating many diseases. The extraction of PUFA from these fishes, the analysis of the different fatty acids composition end the large-scale preparation of EPA-/DHA-fraction, are discussed on **Chapter 6**, while the production of toxins from marine animals and the small peptides isolated from marine cone snails (conotoxins) are the respective topic of **Chapters 7** and **8**. In fact, among the potential new molecules provided from the marine environment, toxins obtainable from vertebrates and invertebrates living in the sea are finding broad applications in development of innovative drugs, because of their origin and complex nature. On the other hand the small marine peptides, for their diversity and the very high selectivity in targeting specific sites of neuronal system, are opening a wide horizon for designing new drugs for treatment of many severe diseases, such as pain and hearth stroke.
Natural products are organic, complex molecules often with multiple chiral centres characterized by specific biological functions, derived from plants, animals, or microorganisms. The opportunity to discover new species and, therefore, new types of natural molecules has increased through the application of new tools to explore the marine environment. Living systems produce, in fact, a vast and diverse range of organic and small molecules that can be classified as either primary or secondary metabolites. Whole primary metabolites, such as phytosterols, vitamins, and amino acids, are necessary to sustain the life of living system, the secondary metabolites are not involved in the normal growth and development of an organism, but have an ecological role, providing a survival vantage, such as defence against predators, competition for space, and antimicrobial activity. However, secondary metabolites have found to be more important as drugs for their pharmacological activities, including anti-tumour, anti-fungal, antiviral, and antibacterial properties. Thus, marine habitats provide unique conditions for microbial growth and secondary metabolite expression that are not found in terrestrial ecosystems. The co-evolution of many marine microorganisms with microbes has led to the development of very close associations or symbiotic relationships between the hot organism

and a specific microbe.

As the microbiota world displays the greatest biodiversity, it has a potential to be the most important source of natural products that can be utilized to generate novel therapeutic compounds. Bacteria maintain, in fact, a broad array of genetic, metabolic, and physiological capabilities that allow for a high degree of adaptability and metabolic diversification into numerous niches and habitats. And the marine ecosystems are presumed more heterogeneous than the soil ecosystems at the bacterial level. Apart the drugs, marine-fouling invertebrates (e.g. Mussel, barnacle, hydroid, etc) form a strong attachment to the marine substratum against mechanical stresses, using their special physical and chemical underwater adhesives. These compounds possess a strong adhesion to various material substrates, water displacement, biocompatibility, and controlled biodegradability. Therefore, by the use of the fundamental biochemical, physical and mechanical study-researches obtained studying the mussel adhesion, many attempts have been made for translating this knowledge to the biomedical materials production.

The structural characteristics, the environmental and human impact of many bioactive marine natural products are reported and discussed on **Chapters 9-14 Part I**: *Isolation, Characterization of Marine Biomaterials*.

Owing to the unique physicochemical properties of the marine-derived compounds, enormous potential biological applications as anticoagulant, antiinflammation, antiviral, and anticancer agents have been shown. Thus, the production and invention of new drugs became essential to approach these problems that could be partially solved by the use of many untapped natural compounds of the sea covering over 70%of the earth surface. At this purpose, many novel ingredients isolated from diverse marine macro- and microorganisms have been reported as capable to exert anticancer activity by the activation of P53 anti-proliferative gene, inducing, for example, apoptosis, or inhibiting angiogenesis. Modulating apoptotic pathways by chemical agents are, in fact, promising approaches for cancer therapy.

Biological Activities of Marine Biomaterials are the topics treated on **Part II**, by 10 **Chapters** from **15** to **24**. At this purpose, the formation of cancer cells in human body can be directly induced by free radicals and natural anticancer antioxidant drugs as chemopreventive agents have gained a positive popularity in treatment of cancer. Hence, radical scavenging compounds, as polysaccharides (SPs) obtained from seaweeds can be used to reduce cancer formation. SPs, with a wide range of important biological activities such as antioxidant, anticoagulant, anticancer, antiviral, and antiinflammation, include a complex group of macromolecules found in three major groups of marine algae, red, brown, and green.

The major SPs of red algae are *galactans*, (agar and carrageenan), those of brown algae are *fucans* (fucoidan, sargassan, ascophyllan, and glucuronoxyfucan), while green algae contain *sulphated heteropolysaccharides* (galactose, xylose, arabinose, mannose, glucuronic acid, and glucose). In any way, due to their valuable biological functions with health beneficial effects, SPs have much potential as active agents for preparation of nutraceutical products. These the topics discussed on **Chapters 15** and **16**.

Marine organisms therefore, comprising approximately a half of the global biodiversity, represent rich sources of structurally diverse compounds with different biological activities. Thus, marine alkaloids constitute an extraordinary source of new bioactive compounds for therapeutic purpose, while marine-derived bioactive peptides have shown to possess many physiological functions, inclu-

ding antihypertensive, antioxidant, and antimicrobial activities. Moreover, such of these peptides possess nutraceutical potentials for human health promotion and disease risk reduction, by lowering plasma cholesterol level, slowing down the cell proliferation on human breast cancer cell lines, showing also antiviral and anti-inflammatory activities. In addition, many studies proved that structurally diverse compound of marine origin could express better activity and understanding their mechanism of action, they may be used, for example, as antidiabetic and antiobesity products.

Apart from fishes, also marine algae are interesting sources of bioactive novel compounds rich in sulphated polysaccharides (SPs) and phlorotannins with a potent anticoagulant effect. The major amount of these compounds differ according to the three major divisions of marine algae, *Chlorophyta* (green algae), *Rhodophyta* (red algae), and *Phaeophyta* (brown algae). Among brown algae, *Ecklonia* cava is the richest source of phenolic compounds as phlorotannins, used from the plant as defensive mean against stress conditions and herbivores. These the topics reported on **Chapters 17-23**.

Coral reefs comprise a complex array of communities, including many types of coelenterates such as cnidarians (corals, sea pens, sea anemones, etc) as well as ascidians and sponges.

Ortocorallia is estimated to include about 3000 species which defend themselves by production of terpenoids, diterpenes and sesquiterpenes, the activity of which together with their chemical structural features are reported on **Chapter 25 Part III**: *Biomedical Application of Marine Biomaterials*.

Tissue engineering for *regenerative* medicine is designed to repair injured body part and restore their functions by using laboratory-grown tissues, materials, and artificial implants. At this purpose, bone tissue engineering aims to mimic the natural process of bone formation by delivering a source of cells and/or growth factors in a scaffold matrix, which can induce cellular attachment, migration, proliferation, and osteoblastic differentiation. Scaffolds are, in fact, temporary structures that provide adhesive matrix for cell infiltration and growth, acting also as controlled devices to the tissues' physiological need. Porous architecture, biodegradability, biocompatibility, surface characteristics, and mechanical strength are some vital features for a successful scaffold to be used as an implant for bone tissue engineering. However, the main critical factor affecting bone formation is the contemporary presence of *macropores* that promote vascularisation and transportation of nutrients and waste products, and micropores that favour capillary formation. Therefore, the bone engineering involves the use of scaffold matrices through which bone marrow stromal cells can be delivered to the defect site using different vehicles. Ideal scaffolds should have an internal structure designed with a predetermined density, pore shape, and size, with appropriate interconnection pathways. Thus, high porosity levels are necessary to support migration and proliferation of osteoblasts and mesenchymal cells, bone tissue ingrowths, vascular invasion, nutrient delivery, and matrix deposition in empty spaces. The adsorption of proteins, as collagen, onto the scaffolds is also important to influence the cell adhesion.

Biomedical engineers are continually striving to improve and update therapeutic medical treatments to reduce pain, inflammation, surgery time, and invasiveness of surgery using drug and protein delivery vehicles. Irrespective of animal or human being, wound healing is a complicated and well-orchestrated process involving multiple biological pathways and signalling. In any way the wounds need to be repaired. The aim of skin tissue engineering is to produce a construct that offers the complete regeneration of functional skin and allow it to fulfill normal functions like barrier formation, pigmentary defence against UV irradiation, thermoregulation, and mechanical and aesthetic func-

tions. Skin substitutes promote wound healing by simulating the host to produce various cytokines, which in turn play an important role in preventing dehydration and increasing inflammation, promoting also the formation of granulation tissue in wound healing processes. Therefore, the emerging challenge of engineered tissues is to rely on producing scaffolds with an informational function. The strategy is to mimic the extra cellular matrix (ECM) and provide the necessary information or signaling for cell attachment, proliferation, and differentiation to meet the requirements of dynamic reciprocity for tissue engineering. At this purpose electrospun materials, such as chitin nanofibrils, chitosan, collagen, etc offer a broad range of non-woven tissues with dimensions and organization analogous to ECM matrices, providing equivalent physicochemical properties. The fibers, in fact, can be tailored with specific surface compounds alike to native ECM, to encourage cell adhesion. However, to control cellular activities, the physical and chemical surroundings pay a pivotal role in the quality of tissue organization, formation, and quantity, hence the focus on material design and synthesis. In conclusion tissue engineering is a multidisciplinary venture aimed at reproducing healthy, living human tissue and organs at laboratory level. Engineering natural tissue requires scaffolding to anchor and support it in precise anatomical arrangement, particularly affected by the use of nanobiotechnological materials. In any way, the biodiversity that characterizes the marine environment represents an enormous potential for the acquisition of new microstructures that display a complex and hierarchical organization similar to the ones required or present in the human body.
These and others are the interesting topics focused and discussed on **Chapters 26-36**, while **Part IV** *Industrial Application of Marine-Derived Biomaterials*, provides information about the important step of commercialization of these innovative raw materials by other 4 Chapters treating wastewater engineering and treatment, agricultural applications, and paper technology, by the use oligosaccharides of marine origin.
As previously reported, by this book and the other two publications it is possible to have an almost complete knowledge on the scientific and industrial possibility the marine biomaterials have to be used for producing different goods safeguarding the environment from the increasing pollution.
The ever-expanding aged population and market of pharmaceutical, cosmeceutical and nutricosmetic products give the possibility to innovate the relative ingredients by the use of marine biomaterials and the affording the opportunity for customized treatments that combine the utility of pharmaceutically based dermatologic formulations and the activity of cosmetics and diet supplements, with a supposed worldwide cosmetic market growth to over US$ 350 billion by 2018.
For all the data reported on isolation, characterization, control and production of marine and marine-derived biomaterials for biological and biomedical applications and for the richness of the bibliographic references, this book results interesting not only for novice and students interested to better know the field of the ocean resources, but also for expert of biological, chemical and medical communities interested and working on biomedical, agricultural, and environmental engineering sciences.
Finally it has to be of interest for all peoples and scientific communities who want to reduce production and use of petrol-based ingredients, favouring the utilization of innovative natural goods made from fishery' waste and plant biomass by a lower use of energy and water.

P. Morganti
Editor-in-Chief

Dermatological Diseases and Cumulative Life Course Impairment

by M.D. Linder and A.B. Kimball

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This book, volume 44 of the series *Current Problems in Dermatology*, consisting in **4 Parts** and **15 Chapters**, represents the life course perspective to arrive at a better understanding and more effective treatment of skin dermatological diseases. Thus, it is important to find and treat people while they are still young rather than during the middle age or when they are elderly. Delayed treatment can cause other problems to accumulate such as obesity, depression, and loneliness, not all endogenous to the individual but influenced from the outside environment.

Distinctive life course outcomes are, in fact, shaped by the stage of life when a significant event occurs, such as changing of the family socioeconomic status or exposure to historical events as war and depression, leading to a deprived or non-deprived childhood.

However, chronic diseases of elderly people can severely impair patients' quality of life (QoL) but little information is available about the long-term impact of this kind of disease. The chronic nature of a disease, in fact, may decrease patients' psychosocial well-being, changing their attitude towards life goals and influencing major life-changing decisions.

QoL refers to a complex, multifaceted concept, encompassing psychological, social, even philosophical aspects and, often, it is a simply synonymous with beauty and happiness. Thus, it is measured in a given moment of patients' lives and its concept is cross-sectional and depicts the symptomatic, emotional, and social impact of a disease on a patient in a given time point. Therefore, nowadays measuring QoL with a beauty appearance is considered as essential for a complete evaluation of the status of dermatological patients.

The *what is beautiful is good* stereotype extends, in fact, not only into the older age group, but also into diseased patients so that unattractive individuals are perceived significantly less favorably. When evaluating the attractiveness of individuals within a population elderly, or affected by acne, atopic dermatitis the unattractive tend to be viewed in terms associated with old age; viz, deteriorated appearance, worn out, ugly. By contrast persons who have preserved their appearance are associated with youthfulness, and personable qualities of being young, happy, and healthy.

Thus, the concept of cumulative life course impairment (CLCI) and health-related QoL are analyzed, in order to find shared and divergent aspects and its concept includes the patients' perception of their health and their personal experiences concerning the psychosocial impact of the disease on their life. CLCI aims to investigate the impact of a chronic disease on the milestones of life, such as education,

work, relationships, children, social life, and how the disease may influence the possibility of patients of living their life up to its potential. Thus, QoL is a cross-sectional measure, while CLCI takes into account the lifetime. However, it is clear that the possibility of reaching one's full life potential and QoL at a certain time are correlated.

Approaching diseases (chronic) within a *life course* framework provides, therefore, primary answers to two main questions: What are long-term effects on health of life events and of previous exposures to risk factors during sensitive periods (childhood, adolescence) of life? What are the effects of the onset of a chronic disease on all other variables (social and economic pathway, marital status, etc.) that define a life trajectory and how can this influence be modulated by medical and social interventions?

In order to tackle such questions it will be necessary to represent life course trajectories by formal means within the mathematical model in order to render the trajectories classifiable and measurable, as proposed by this book. In any way chronic diseases can have a different impact on QoL depending on patients' cultures and medical systems.

A cumulative life course approach to chronic dermatologic diseases assesses the long-term consequences of disease burden on economic, social, psychological and behavioral aspects of an individual's life. On the other hand, both cumulative and current cultural, social, ethnic and financial aspects may influence health status. CLCI measures should be designed to assess more thoroughly the impact of diseases on quality of life measurements over time. Thus, the components of CLCI interact to varying extents in patients with acne, psoriasis, vitiligo, epidermolysis bullosa, chronic wounds, and melanoma and nonmelanoma cancer, as reported by different chapters. Evidence also exists that the patients' personality, coping style, social support, and access to efficacious medical treatment and psychological support can modulate the burden of these illnesses. For a person with skin problems as acne or vitiligo products that mask pathologic alterations can strikingly improve appearance and thus benefit the patient psychologically. Often Physicians treat the lesion or the spot very well but do not sense how important it is to improve appearance at the same time.

Thus for example, adding cosmetics to dermatological treatment programs can improve the therapeutic result: a person can enjoy the psychological benefits of looking better while receiving medical care.

Daily use of normal skin care cosmetics can also encourage self care and engender feelings of nurturance, relaxation and general wellbeing, preventing the development of the vicious cycle of self-abandonment and self-destructiveness that can occur in the elderly or in subjects affected by vitiligo, and rather serve as a vehicle to help them to increase their self - and social acceptance. This is the reason why cosmetic therapy for the emotionally ill should be incorporated into the therapeutic program as an adjunct to pure psychotherapy.

According to the bio-psycho-social model, psychosocial and biological factors interact in a number of ways influencing onset of course of medical disease. Such factors may elicit different effects on health depending on their accumulation mechanisms and timing of exposure over the life course. These aspects have become particularly relevant in the field of chronic diseases such as chronic dermatological conditions, where complete healing is unlikely to occur. Moreover, the concept of allostatic load may represent the link between the cumulative effect of various challenging situations and the disease onset through the progressive *wear and tear* induced by chronic exposure to fluctuating allostatic responses. In addition, the concept of allostatic overload emphasizes that the cumulative

interaction of stressors and psychological symptoms may constitute a danger to health.
On the other hand, the concept of CLCI underlines the fact that illness is only one of the many recordable parameters, which determine ultimately, through their mutual interaction, the *life trajectory of individuals*.
In conclusion, cumulative life course results very important in the evaluation of chronic diseases and their long term physical, psychological, cognitive and social consequence.
It impacts the QoL depending on patients' cultures and medical systems. Thus, individuals with same diseases and disease severities, but with diverse cultural backgrounds and medical systems, may value health differently and this has to be taken into account when performing multinational studies of cumulative life course impairment.
These and other topics are reported and discussed in this interesting book written by scientists particularly expert to treat different dermatological diseases by a life course approach to ameliorate the QoL and the patient' self-esteem.
Dermatological Diseases and Cumulative Life Course Impairment, is an original and unusual book that has to be read and remain into the library of anyone of the Medical community, such as Dermatologists, Allergologists, Gynaecologists, Psychologists, Pediatricians and General practitioners who wish to cure the patients not only by the use of drugs, but also taking care of their psychological distresses. Moreover it may be of help for students as well as Researchers in Medical Sociology, Cosmetic Chemists, and Opinion leaders in Public Health.

P. Morganti
Editor-in-Chief

Index to Volume 31, 2013

Contents:

Book Reviews

Original Laboratory Studies

General Articles

Introduction

Press Release

Author Index

Subject Index

In copertina / Front cover

Block co-polimero formato da Nanofibrille di Chitina (CN) e Acido Ialuronico (HA).

Foto al microscopio elettronico a scansione (SEM). Archivio privato MAVI SUD S.r.l.
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Block co-polymer of Chitin Nanofibrils (CN) and Hyaluronic Acid (HA).

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