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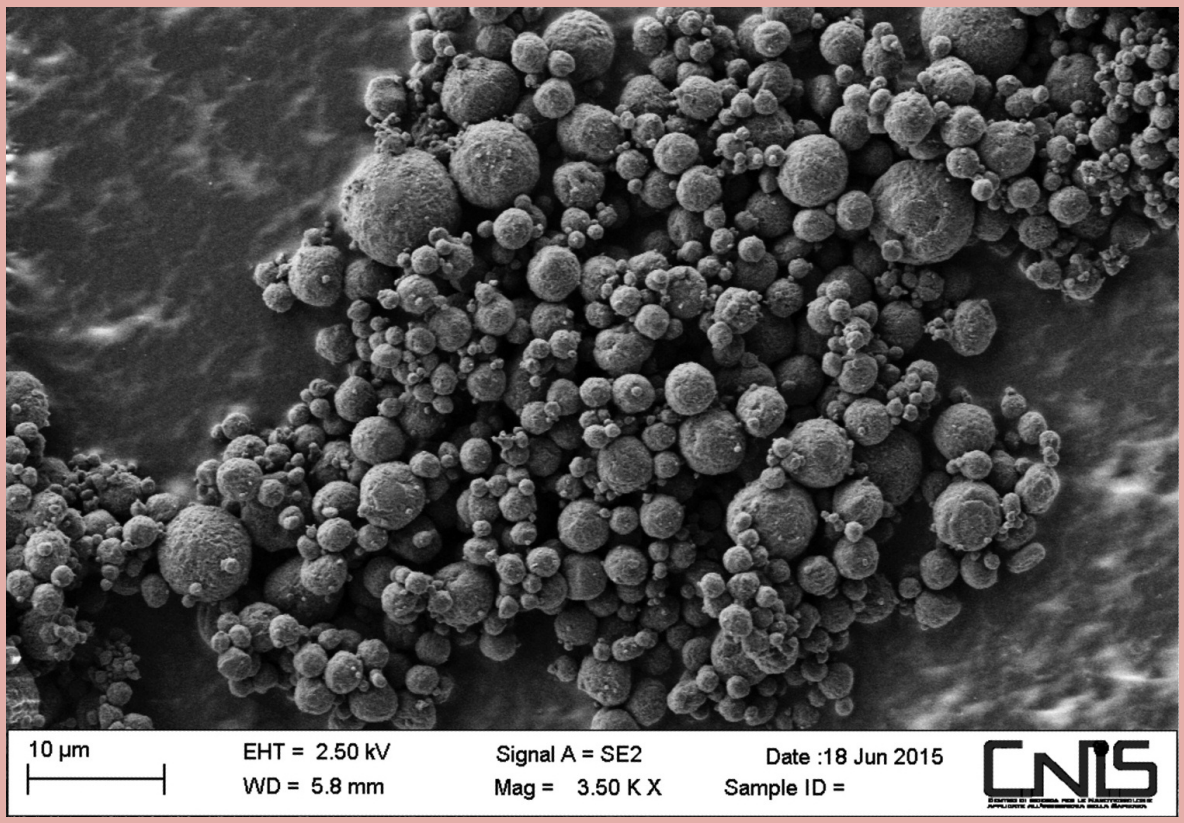

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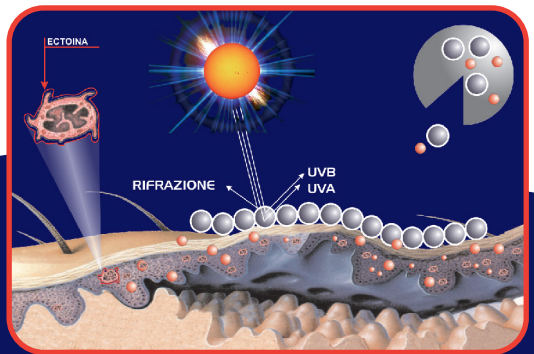

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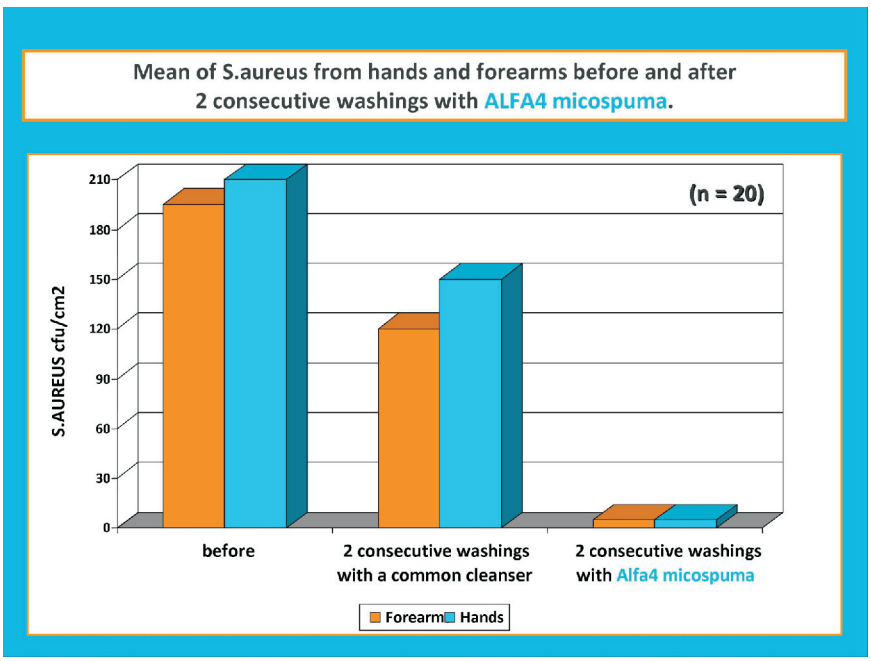

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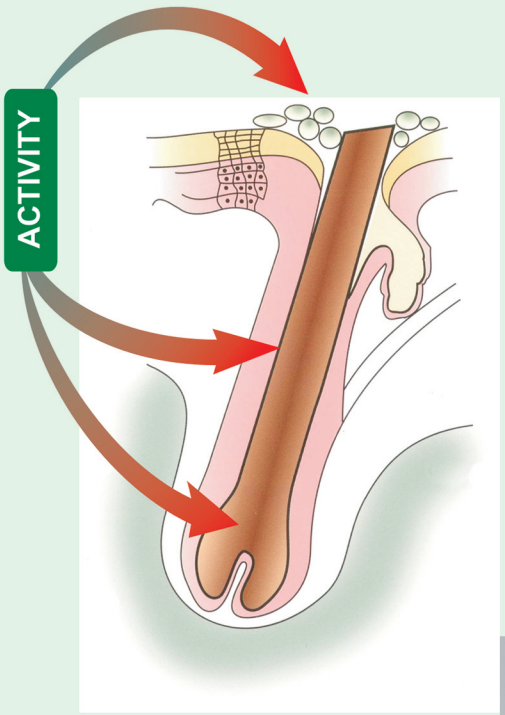

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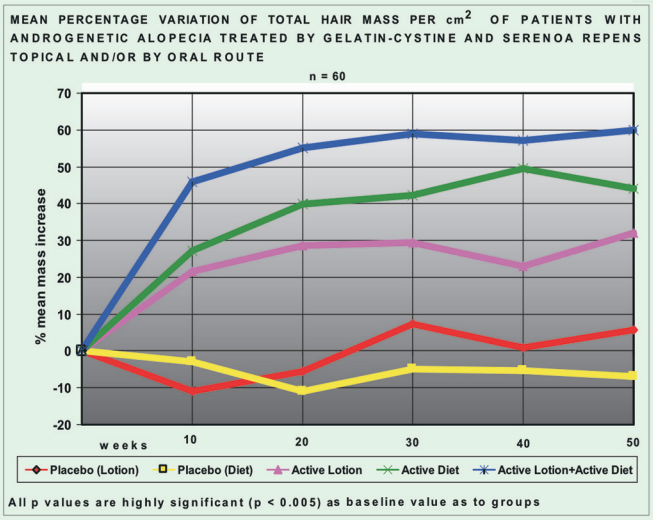

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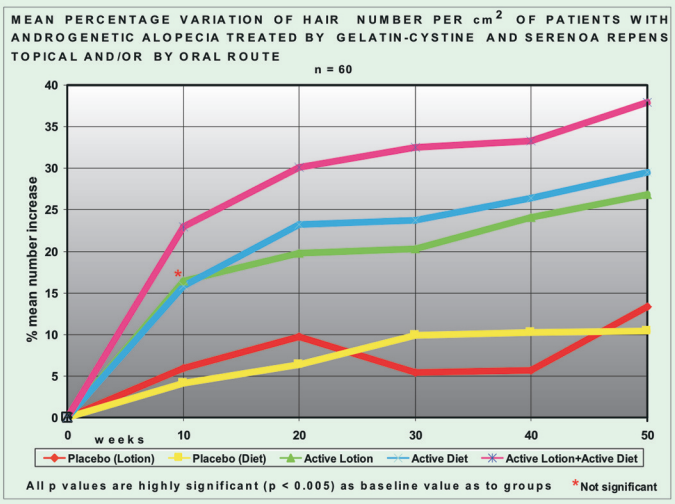

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3

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Trimestrale di Dermatologia Cosmetologica
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Contents

J. Appl. Cosmetol. **34,** 87-98 (July/December 2016)

Evaluation of Manuka Honey as an adjuvant antimicrobial preservative in a O/W emulsion

C. Juliano, E. Gavini, P. Giunchedi, G. A. Magrini
Dipartimento di Chimica e Farmacia, University of Sassari, Sassari, Italy

Received: *November, 2016*

Key words: *Manuka honey; Challenge test; Antimicrobial activity; Microbiology; Emulsions;*

Summary

Cosmetics and personal care products need to be protected against microorganism contamination to prevent microbial spoilage and consumers' health hazards. The use of parabens, the most common preservatives added to cosmetic products, is associated with allergies, and some studies suggested that they could cause hormone disruption; therefore, the need of efficient and safer alternatives to parabens is increasing. The present study investigates the preservative efficacy of Manuka honey, a New-Zealand honey well known for its pronounced antimicrobial activity, in a O/W emulsion, in comparison with the traditional preservative methylparaben. An emulsion containing 10% Manuka honey was tested against bacterial (Escherichia coli ATCC 8739, Staphylococcus aureus ATCC 6538, Pseudomonas aeruginosa ATCC 9027) and fungal strains (Candida albicans ATCC 10231, Aspergillus brasiliensis ATCC 16404) by a challenge test, a procedure in which the efficacy of a preservative system is challenged by contamination with specified bacterial and fungal strains, according to the European Pharmacopeia procedures. The unpreserved emulsion and the emulsion with 0.2% methylparaben were reference samples. Manuka honey showed a good ability to protect the emulsion from contamination with standard bacterial inocula; in particular, it has been proven more effective than methylparaben against Pseudomonas aeruginosa, and showed the same efficacy as methylparaben against E.coli. Conversely, there was no evidence of a protective effect activity of Manuka honey against fungal contamination in our experimental conditions. Manuka honey, if added to a formulation for its humectant and moisturizing activity, also exerts an antibacterial activity, and can therefore be considered as an effective candidate for alternative preservation systems intended for use in cosmetic and personal care products.

Riassunto

I conservanti devono essere presenti nei cosmetici per ridurre il rischio di contaminazioni microbiche, che potrebbero portare ad un deterioramento del prodotto e ad effetti negativi sulla salute dei consumatori. I parabeni, i conservanti antimicrobici per lungo tempo più frequentemente impiegati nei cosmetici, sono associati con manifestazioni allergiche ed alcuni studi, peraltro non confermati, li indicano come potenziali interferenti endocrini; benchè la loro sicurezza sia stata riconosciuta, i

consumatori si stanno sempre più orientando verso prodotti per la cura personale che non li contengano, e per questo motivo c'è una costante ricerca di conservanti alternativi ai parabeni che siano sicuri ed altrettanto efficaci.

Lo scopo del presente lavoro è stato quello di valutare l'efficacia conservante del miele di Manuka, un miele proveniente dalla Nuova Zelanda di cui è nota la spiccata attività antimicrobica, in una emulsione O/A, paragonandola con quella del tradizionale conservante metilparaben. A questo scopo un'emulsione contenente il 10% di miele di Manuka è stata sottoposta ad un challenge test, una procedura che consiste nel verificare l'efficacia di un conservante in una formulazione contaminata artificialmente con specifici ceppi di batteri (Escherichia coli ATCC 8739, Staphylococcus aureus ATCC 6538, Pseudomonas aeruginosa ATCC 9027) e miceti (Candida albicans ATCC 10231, Aspergillus brasiliensis ATCC 16404). Il miele di Manuka ha mostrato una buona efficacia nel proteggere l'emulsione dalla contaminazione batterica, risultando attivo quanto il metilparaben nei confronti di E.coli e addirittura più attivo nei confronti di P.aeruginosa. Nelle condizioni sperimentali adottate, invece, il miele di Manuka non si è rivelato utile nel proteggere la formulazione dalla contaminazione con i ceppi fungini. In base ai risultati ottenuti in questa indagine, si può concludere che il miele di Manuka, se aggiunto ad una formulazione topica per la sua azione umettante ed idratante, può anche esplicare un'apprezzabile azione antibatterica, e può quindi essere considerato come il possibile componente di sistemi preservanti alternativi destinati a cosmetici e prodotti per la cura personale.

INTRODUCTION

Cosmetic products do not need to be sterile, but they must be adequately protected from microbial contamination and spoilage. Microbial contamination of cosmetics can occur during manufacture processes or can be inadvertently caused by the consumer during use; microorganisms can be very versatile in their metabolism and can grow and reproduce inside the product. Microbial multiplication can cause product degradation, with visible growth, colour and odour changes and gas production; moreover, the presence of pathogenic and even nonpathogenic microorganisms in personal care products constitutes a threat to consumer safety, especially when cosmetic formulations are intended for use in areas of particular concern (e.g., the eye area) or when they are used by children or immunocompromised individuals (1). For these reasons, antimicrobial preservatives are needed in personal care product formulations to prevent both primary (during production) and secondary (after container opening) microbial contamination. The European Regulation (EC) N°1223/2009 on cosmetic products states that manufacturers can only use preservatives listed in the Annex V of the same Regulation (2). However, in recent years the safety of some of these preservatives has been called into question; several studies were published claiming a link between parabens and breast cancer (3-5), and, although these studies were subsequently rejected by a number of scientists and international health authorities (6-8), Regulation (EU) No 358/2014 recently amended Annex V of Regulation (EU) No 1223/2009 to prohibit the use of isopropylparaben, isobutylparaben, phenylparaben, benzylparaben and pentylparaben in cosmetics. Moreover, Regulations (EU) No 1003/2014 and 1004/2014 lowered the maximum concentration allowed for propylparaben and butylparaben, and prohibited their use in products for children. Because of the issues of traditional preservatives, the consumer perception of these ingredients is not very positive, and, as a consequence, cosmetic manufacturers are increasingly looking for alternative preservation systems.

There is a large number of compounds, included in skin care products for their beneficial effect, that may coincidentally contribute to the antimicrobial protection of cosmetic formulations; these compounds are not, strictly speaking, preservatives, since they are not listed in Annex V of the Regulation (EU) N° 1223/2009. The presence of these ingredients allows manufacturers to promote cosmetic and toiletry products with marketing claims such as “preservative free” or “contains no preservatives”, although these statements are sometimes considered misleading for consumers, and the term “self-preserving” would be more appropriate (9). Alternatives to traditional preservatives are, for example, multifunctional ingredients, approved for cosmetics without restrictions, which combine an antimicrobial action with other favourable functions (e.g., caprylyl glycol, phenethyl alcohol, ethyl hexylglycerin, pentylene glycol) (9). There are also a number of botanical extracts (grapefruit seeds, usnic acid, Japanese honeysuckle, rosemary) and essential oils (thyme, tea tree, neem seeds) with remarkable antimicrobial activity that can be used as a part of a preservative strategy of cosmetic formulations (10-11). A natural-based ingredient that can be brought to the attention of formulators is honey, used for centuries in ethnomedicine as a topical treatment of a wide range of burns and wounds, and currently revalued for its antiseptic and healing properties (12-13). These biological effects are essentially attributed to two factors: the presence in honey of hydrogen peroxide, which is produced by the bee-derived enzyme glucose oxidase, and hyperosmolarity, due to its very high sugar content (14). Processing with heat and filtration can

reduce peroxide-based antimicrobial activity of honey (15). Certain honey types present additional antimicrobial factors; in particular, Manuka honey, derived from Manuka tree (Leptospermum scoparium), a bush found throughout New Zealand, has been demonstrated to possess significant non-peroxide antimicrobial properties, attributed to its methylglyoxal (MGO) levels (16-18). On the other hand, honey is a cosmetic ingredient often present in personal care products, in which it is frequently present as a humectant and as a skin moisturizer (19-21). The purpose of this study was therefore to evaluate the preservative efficiency of Manuka honey in a simple O/W cream formulation and to compare it with methylparaben, chosen as a reference preservative.

MATERIALS & METHODS

Materials

Manuka honey with MGO® 400+ (certified to contain at least 400 mg/kg of methylglyoxal) was purchased via the Internet by Manuka Health Europe Ltd, Warrington, UK. Tryptone Soy Agar (TSA), Mueller Hinton Agar (MHA), Mueller Hinton Broth (MHB), Sabouraud Dextrose Agar (SDA), Sabouraud Liquid Medium (SLM), Peptone Water and phosphate-buffered saline tablets (PBS, Dulbecco A, pH 7.3) were purchased from Oxoid-Thermofisher Scientific (Rodano, Italy). Methyl parahydroxybenzoate (methylparaben) and all other chemicals were obtained by Sigma-Aldrich, Gallarate, Italy. Culture media, PBS and other solutions were prepared with MilliQ water. The test organisms used in this study were as follows: Escherichia coli (ATCC 8739) (Gram-negative bacillus), Staphylococcus aureus (ATCC 6538) (Gram-positive coccus), Pseudomonas aeruginosa (ATCC 9027) (Gram-negative bacillus), Candida albicans (ATCC 10231) (yeast), Aspergillus brasiliensis (niger) (ATCC 16404) (mold) (all purchased from Oxoid-Thermofisher Scientific, Rodano, Italy).

Cream formulation

The cream used in our experiments was "Macrogol cetostearileteres crema base (FUI XII)" (22), a white, odourless O/W hydrophilic base cream; it is for external application as an emollient and moisturizer, and for use as a diluent in medicinal external preparations. Cream emulsion formula was composed of two phases: a lipophilic phase, containing petroleum jelly (petrolatum) g 15, paraffinum liquidum (mineral oil) g 6, cetostearyl alcohol g 7.2, and a hydrophilic phase, containing Cetomacrogol 1000 (polyethylene glycol hexadecyl ether) g 1.8, purified water g 70.

To obtain the cream the components of the lipophilic phase were molten together at 70°C; separately, cetostearyl alcohol was dissolved in distilled, freshly boiled water cooled at 80°C. The aqueous phase was added to the oil phase and the mixture emulsified by using a mixer homogenizer (DS3 MultiGel, Sambuca-Tavarnelle, Firenze, Italy), stirring until it congealed. To prepare the cream containing methylparaben, this preservative was added at 0.2% to the boiling water; to prepare the cream containing Manuka honey (10%), honey was simply added to the aqueous phase (water amount was reduced to 60 g). The addition of 10% honey did not significantly affect the viscosity of the emulsion (data not shown). The concentrations of Manuka honey and methylparaben to be added to the creams were decided on the basis of the results of MIC evaluation (see next paragraph).

Determination of antimicrobial activity of Manuka honey and methylparaben

Preliminarily, antimicrobial activity of Manuka honey and methylparaben against our microbial

strains was determined as Minimum Inhibitory Concentration (MIC) by using an agar dilution test (23). Mother solution of Manuka honey was prepared by dissolving honey in sterile water to obtain a 50% wt/vol solution, which was sterilised by filtration; mother solution of methylparaben was obtained by dissolving it in DMSO at 5% wt/vol. Petri plates (5 mm diameter) containing increasing concentrations of Manuka honey (2.5%, 5%, 7.5%, 10%, 12.5% wt/vol) or methylparaben (two-fold serial concentrations from 0.025% to 0.2% wt/vol) were prepared by mixing appropriate volumes of mother solutions and molten (45°C) agar media (Mueller Hinton Agar for bacteria and Sabouraud Dextrose Agar for fungi; total volumes 10 mL). After solidification of the medium, the agar surface was inoculated with 2 μL of microbial suspensions containing about 10^4 c.f.u.; plates were inverted and incubated at 30-35°C for 18-24 hours (for bacteria), at 20-25°C for 48 hours (for Candida) and at 20-25°C for a week (for Aspergillus). After incubation, plates were visually checked for bacterial growth, and MICs were defined as the lowest concentrations at which no growth was observed. All test were conducted at least in triplicate; at the concentrations tested, DMSO had no inhibitory effect on microorganisms' growth. Results are reported in Table I.

TABLE I

Minimum inhibitory concentration (MIC) of Manuka honey and methylparaben against selected microbial strains.

	Manuka honey (wt/vol)	**Methyl paraben (wt/vol)**
Escherichia coli ATCC 8739	10%	0.2%
Pseudomonas aeruginosa ATCC 9027	>12.5%	0.2%
Staphylococcus aureus ATCC 6538	10%	0.2%
Candida albicans ATCC 10231	>12.5%	0.05%
Aspergillus niger ATCC	>12.5%	0.1%

Challenge test

In agreement with European Regulation, the microbiological stability of a cosmetic must be evaluated by a challenge test and its results must be included in the Cosmetic Product Safety Report; however, Regulation does not specify the protocol for this test. Among several protocols established to verify the antimicrobial protection of cosmetics (24), we decided to apply the challenge test described in European Pharmacopoeia 7 (25).

Briefly, the test consisted of artificially contaminating the preparations, in the final container, with a standard inoculum of suitable microorganisms. Inoculated formulations are stored at a prescribed temperature, and samples are withdrawn from the containers at specified inter-

vals of time, and surviving microorganisms counted on agar plates. Test was carried out on creams without any preservative, creams containing appropriate Manuka honey concentrations and, for comparison, creams containing methylparaben, a conventional pharmaceutical preservative widely used in cosmetics (26).

To prepare microorganisms inocula, bacterial strains were grown at 30-35°C for 18-24 hours on TSA plates, C. albicans at 20-25°C for 48 hours on SDA plates, and A. brasiliensis at 20-25°C for a week on SDA plates. To harvest the bacterial cultures, we used sterile saline solution, obtaining suspensions whose turbidity was adjusted to McFarland standard N° 4; these suspensions were further diluted 1:10 with saline to reduce the microbial counts to about $1x10^8$ microorganisms per milliliter. 400 μL of these final suspensions were added and thoroughly mixed to the formulation samples (50 g), contained in sterile plastic containers with screw cap, obtaining an inoculum of 10^5 to 10^6 microorganisms per gram of preparation. C. albicans inocula were prepared in the same way, but Candida number was determined performing a manual counting with a Nageotte chamber. Finally, to harvest A. brasiliensis spores, we used sterile saline containing 0.5 g/L of polysorbate 80 (Tween 80), and the spore enumeration was performed with a Nageotte chamber. Also in the case of Candida and Aspergillus the final inoculum was of 10^5 to 10^6 microorganisms per gram of the preparation.

Immediately after inoculation, 1 g of each cream was removed in sterile conditions and transferred into a sterile becher with a magnetic stirring bar, brought to a volume of 10 mL with Peptone Water and mixed on a magnetic stirrer at room temperature until a homogeneous suspension was obtained, and tenfold dilution were done in sterile saline. Any residual antimicrobial activity of the product was eliminated by dilution + the use of 0.5% Tween 80 (27). Triplicate plating of each dilution was performed by using appropriate media (Mueller Hinton Agar for bacteria, Sabouraud Dextrose Agar for Candida and Aspergillus) (zero hour count) and plates incubated at 37°C for 24 hours for bacteria and Candida and at 25°C for a week for Aspergillus. After incubation, the count of colony forming units (C.F.U.) per plate was counted and the number of surviving microorganisms per gram of tested cream was determined. After the first count, the inoculated formulations were maintained at 20-25°C protected from light, and, at appropriate time intervals, subjected to the enumeration of viable microorganisms as described above. Results are reported in Figures 1-5.

RESULTS

Antimicrobial activity of Manuka honey and methylparaben

Table I shows that, in our experimental conditions, Manuka honey is able to inhibit the growth of Gram-negative bacteria E.coli and S.aureus at a concentration of 10% wt/vol (concentration corresponding to 0.04% MGO, based on manufacturer's declarations); the growth of P. aeruginosa, C. albicans e A. brasiliensis was not inhibited at the highest honey concentration tested (12.5% wt/vol). Concentrations above 12.5% were not tested because the addition to the media of such amounts of honey made the agar excessively soft. MIC values obtained in our experimental conditions for Manuka honey tested are consistent with those reported by other Authors (28).

Methylparaben showed inhibitory activity against bacterial strains tested at 0.2% wt/vol and against A. brasiliensis at 0.1% wt/vol; it resulted more active against C. albicans (MIC 0.05% wt/vol). These values these values are in agreement with those reported in the literature (29).

Results of Challenge Test

A concentration of Manuka honey of 10%, although not inhibitory against all the strain tested, was added to creams, because higher quantities modify rheological properties of the formulation, making it too runny.

The challenge test is considered to pass the European Pharmacopoeia method if the following criteria (preparations for cutaneous application) are fulfilled: bacterial reduction = 99% (2 Log) reduction 2 days after inoculation and >99.9% (3 Log) reduction 7 days after inoculation; and fungal reduction = 90.0% (1 Log) reduction 7 days after inoculation and 99% (2 Log) reduction 14 days after inoculation.

The population of P. aeruginosa was effectively controlled by 10% Manuka honey, since bacteria number was reduced more than 99,9% (3 log) 7 days after inoculation and no longer increased; however, the test would have not fulfil the criteria fixed by the European Pharmacopoeia method, because bacteria count 2 days after inoculation was not reduced by 99% (2 log) (Fig. 1).

Anyhow it is noteworthy that 0.2% methylparaben in the same experimental conditions was not able to inhibit Pseudomonas, whose growth was comparable to the control for the whole duration of the experiment. Interestingly, honey concentration able to protect the emulsion against P. aeruginosa was not able to inhibit the growth of the same bacterium in the test for M.I.C evaluation. Manuka honey was also able to inactivate the inocula of E. coli at 7 days, with a reduction < 2 log after 2 days; similar inhibition was obtained with methylparaben (Fig. 2). Unpreserved formulations supported the growth of both Gram-negative bacteria during the test period (Fig. 1 and 2). Manuka honey and methylparaben exhibited similar inhibitory activity against S.aureus, as in both cases bacteria inocula were totally inactivated in 7 days; it is interesting that in the unpreserved formulation viable count of S.aureus decreased spontaneously, even though more slowly than in the preserved creams (Fig. 3). Finally, no appreciable protective activity against Candida and Aspergillus was found in our experimental conditions (Fig. 4 and 5).

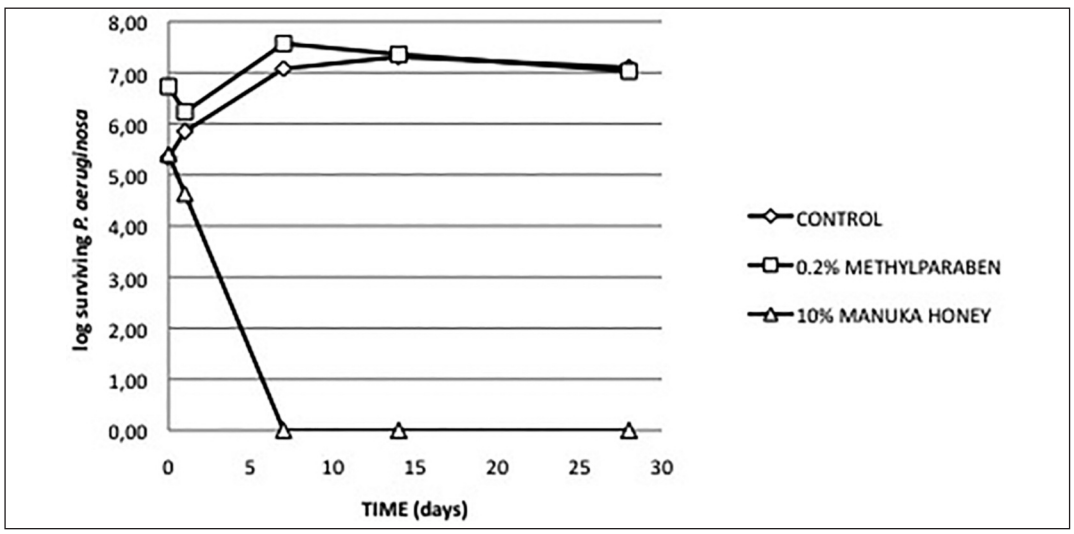

Fig. 1 *Survival of Pseudomonas aeruginosa ATCC 9027 in unpreserved emulsion and in emulsions containing 10% Manuka honey or 0.2% methylparaben. The results are mean of three experiments.*

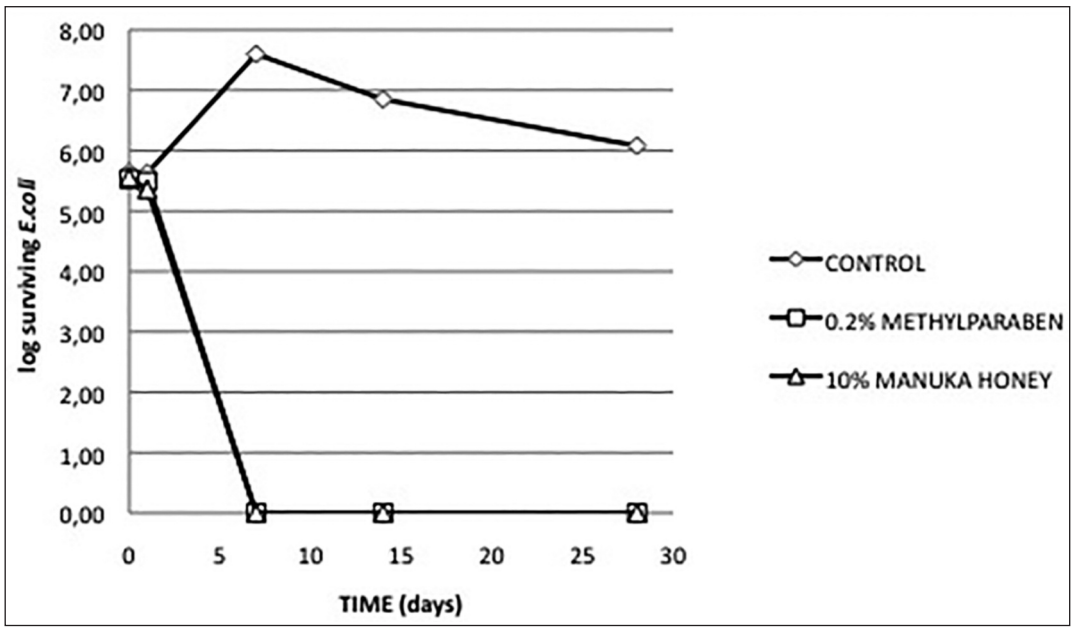

Fig. 2 *Survival of Escherichia coli ATCC 8739 in unpreserved emulsion and in emulsions containing 10% Manuka honey or 0.2% methylparaben. The results are mean of three experiments.*

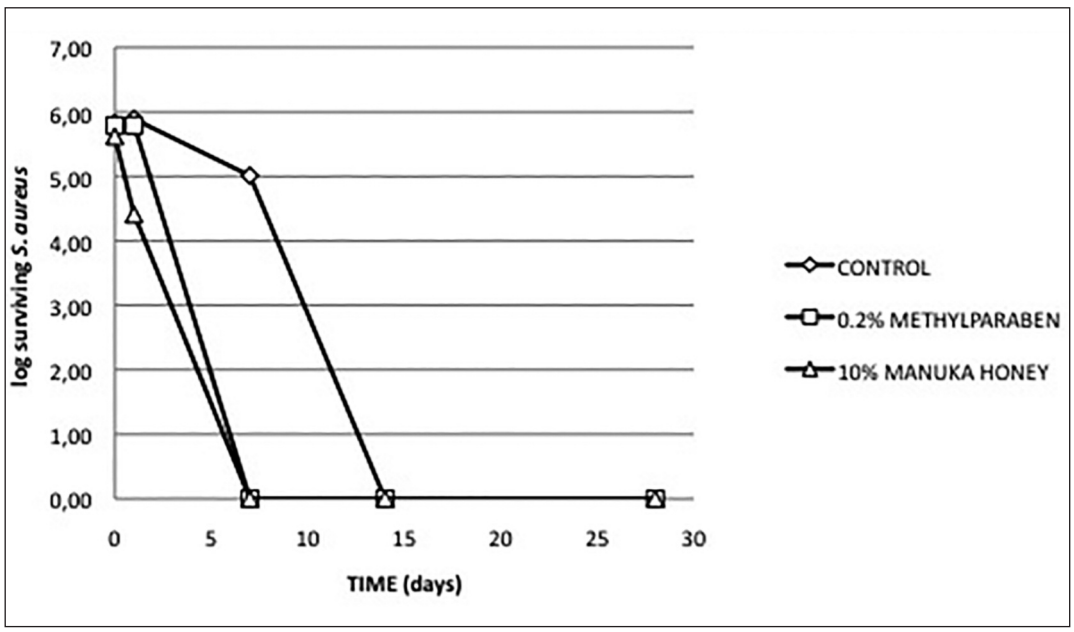

Fig. 3 *Survival of Staphylococcus aureus ATCC 6538 in unpreserved emulsion and in emulsions containing 10% Manuka honey or 0.2% methylparaben. The results are mean of three experiments.*

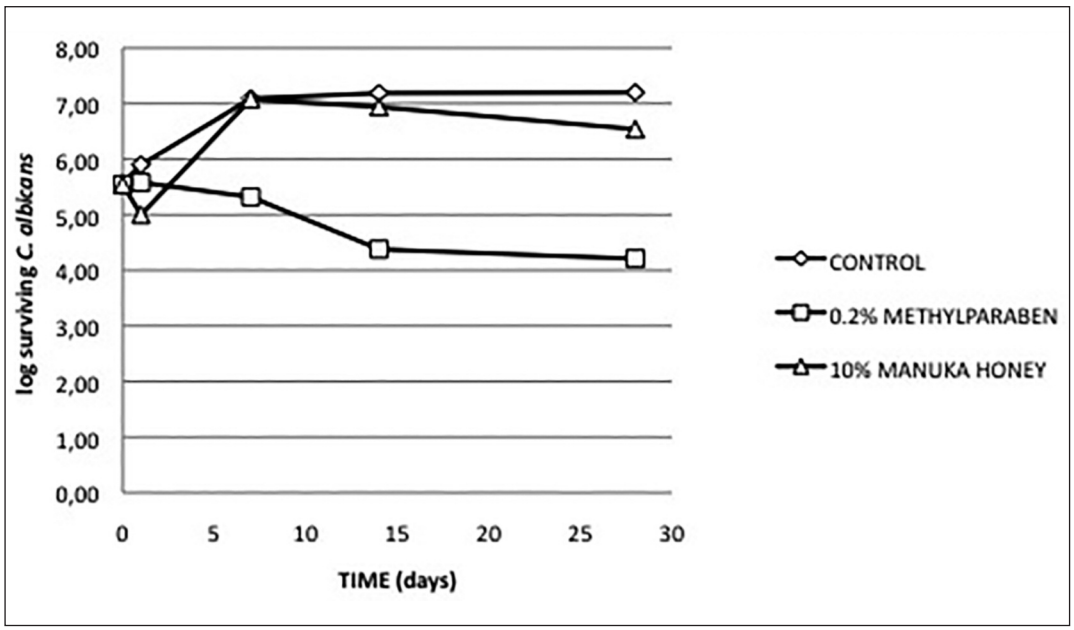

Fig. 4 *Survival of Candida albicans ATCC 10231 in unpreserved emulsion and in emulsions containing 10% Manuka honey or 0.2% methylparaben. The results are mean of three experiments.*

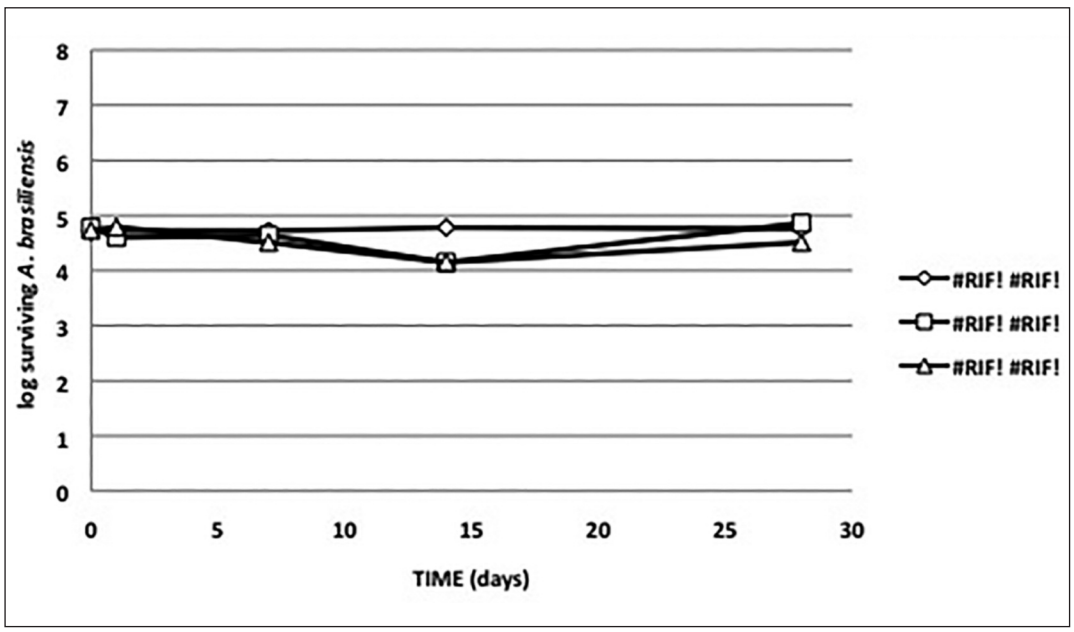

Fig. 5 *Survival of Aspergillus brasiliensis ATCC 16404 in unpreserved emulsion and in emulsions containing 10% Manuka honey or 0.2% methylparaben. The results are mean of three experiments.*

DISCUSSION

Particularly in leave-on cosmetic products, a blend of parabens is a standard preservative option; however, due to ongoing discussions regarding the safety of these compounds, cosmetic formulators are increasingly facing with the need to find reliable alternatives, possibly of natural origin, to protect microbiological quality of products during their use and storage.

The challenge tests performed on the cream preserved with 10% Manuka honey demonstrated that this product is able to protect the formulation against standard inocula of Gram-negative bacteria P. aeruginosa and E. coli equally or even better than methylparaben, although it does not fully meet the requirements of European Pharmacopoeia; a similar inhibition was obtained against S. aureus, while there was no evidence of an antifungal activity in our experimental conditions.

The antimicrobial activity of Manuka honey and methylparaben observed in the challenge test was substantially different from that found in *in vitro* conditions; in particular, although MIC of Manuka honey was >12,5%, a concentration of 10% in the emulsion has proven to be effective in reducing microbial load of 3 log after 7 days. These findings corroborate the results reported in previous papers (30-31) and confirm that physicochemical interaction with the ingredients of cosmetic formulations can enhance or reduce the efficacy of an antimicrobial preservative. Indeed parabens are effective against bacteria and fungi in standard microbiological tests (29), but when they are introduced in complex multi-phase products, such as creams or lotions, an appropriate antimicrobial efficacy may not be achievable, because they partition into the oil phase of the emulsions, requiring higher concentrations to remain active (32).

For this reason, the addition to cosmetic formulations of appropriate concentrations of Manuka honey (primarily intended as a moisturizer), featuring a documented antimicrobial activity and a remarkable water solubility, could help preserve cosmetics and consequently could allow to reduce the levels of traditional preservatives needed to avoid microbial spoilage, especially of cosmetics with high water content.

The use of a natural product as an ingredient of cosmetic formulations could pose some concerns related to microbial contamination and the reproducibility of its chemical composition. However, honey sample used in our experiments did not reveal any detectable microbial contamination when subjected to total viable counts (data not shown); in any case, even if a sterilization should be requested, some Authors have demonstrated that there was no significant changes in Manuka honey antibacterial activity when it was subjected to a commercial sterilization procedure using gamma-irradiation (33). As far as eventual variations in composition are concerned, it is possible to standardise accurately Manuka honeys as of their physicochemical and antimicrobial properties (34).

In conclusion, our results suggest that Manuka honey can be considered as a cosmetic ingredient, primarily usable for its humectant and skin conditioning effects, that presents the additional benefit of an antibacterial activity; it could be added to selected cosmetic formulations to reduce the concentration of conventional preservatives required, or as a component of alternative preservative combinations.

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Author Address:

Claudia Juliano
Dipartimento di Chimica e Farmacia
Via Muroni 23/A
07100, Sassari, Italy
Email: julianoc@uniss.it

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Chromium allergy. The new view

J. Arct, D. Kulik, K. Pytkowska
Academy of Cosmetics and Health Care, Faculty of Cosmetology, Warsaw, Poland.

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Summary

Chromium salts, the metal itself and its alloys are potent allergens and common cause of contact dermatitis. It was found that the toxicity have ions of trivalent chromium Cr^{3+}. This form of chromium barely penetrates the skin barrier as opposed to an easily accessible via the contact hexavalent chromium (chromate and dichromates). This last in the body is reduced to toxic Cr^{3+}. Chromium allergy, because of distribution of this metal, is considered a severe disease. The most common are allergy types V and VI. The aim of this study was to assess cosmetic raw materials potentially reducing the dermal bioavailability of chromium salts. We found that the most promising cosmetic ingredients that protect the skin against the penetration of salts of trivalent chromium appear to be hyaluronic acid and lactic acid.

Riassunto

II sali di cromo, il metallo stesso e tutti i suoi derivati sono dei potenti allergeni causa di dermatite da contatto.
È stato dimostrato da diversi studi come la tossicità sia intrinseca negli ioni di cromo trivalente Cr^{3+}. Questi ioni però penetrano con difficoltà attraverso la barriera cutanea che, al contrario, è facilmente aggredita dal cromo esavalente (cromati e bicromati) ridotto successivamente nell'organismo a cromo trivalente tossico Cr^{3+}.
Data la grande diffusione del cromo, le forme allergiche attribuibili a questo metallo sono considerate una vera e propria malattia. Le più comuni allergie collegate con il cromo sono di tipo V e VI.
Scopo di questo studio è stato di verificare quali materie prime fossero in grado di limitare la biodisponibilità cutanea dei sali di cromo. Abbiamo così dimostrato che l'acido ialuronico e l'acido lattico sembrano essere i due ingredienti più efficaci nell'impedire la penetrazione transcutanea dei sali trivalenti di cromo.

INTRODUCTION

Chromium is an element with potent allergenic potential, a frequent cause of allergies and contact dermatitis (ACD), which is one of the most common skin diseases. Repeated exposure to a contact allergen causes allergic contact dermatitis, which can be seen on the dorsal surface of the hands, interdigital spaces, bending wrists surfaces, spaces between fingers and bending wrists surfaces.

Chromium is an element ubiquitous in the environment, it belongs to the group of transition metals which have a high chemical reactivity and high biological activity. May be present in an oxidation state of 2 to 6, but the most common is on the state 0 (elementary), 3 and 6. Trivalent chromium is a naturally occurring form of chromium, which plays an important role in the biological processes occurring in the human body. It is an essential trace element, responsible for the transport of glucose into all cells in the body, is also present in the active centers of many enzymes. Affect the level of glucose and lipid synthesis which, in turn, facilitates the penetration of glucose from the blood into cells and reduces the need for insulin (2,15). Hexavalent chromium is the result of human activity and is a toxic and carcinogenic (3,9,20). The oxidation of trivalent to hexavalent chromium does not occur in the human body. In contrast, in the blood, chromate are reduced to chromium at the third oxidation state which penetrates the red cell membrane and is bound by the hemoglobin and other cell components; therefore they can no longer leave the cells. Coordination of trivalent chromium with biological ligands affect its solubility at physiological pH, and biological functions and potential for absorption in the intestine (3,18). The result of the reduction of Cr (VI) to Cr (III) in the blood is the formation of reactive intermediates, which in combination with oxidative stress and tissue damage may cause cytotoxicity, genotoxicity and carcinogenicity (19).

Trivalent form of chromium due to the strong affinity to the cells of the stratum corneum and living tissues, is considered to be virtually unable to penetrate the intact stratum corneum. In contrast, when we place the trivalent chromium compounds on damaged skin surface they penetrate and goes to the living layers of the skin. Hexavalent chromium as chromate, easily penetrates through the epidermal barrier and penetrates into the dermis and blood (3,8).

More and more often in everyday products we meet chromium and chromium salts. They are used to create anti-corrosion coatings, produce chromium steels, pigments, cement, leather and products for the wood protection. They are also known cases of allergies as a result of tattooing (in particular green color) There are many other, less obvious sources of this allergen, such as a matches or cigarette ashes (6,17).

Metallic chromium is biologically inactive, is not a hapten, however, influenced by free radicals, ROS, oxygen, and the compounds present in the plasma, sweat or saliva forms a trace amount of salts that have a high allergenic potential. This is a common problem of industrial hygiene. Published data indicate that the susceptibility to the chromium allergy may vary, apparently because of methodological differences in the tests carried out but not of the actual physiological state. It has been found that among workers occupationally exposed to chromium the rashes, sores and eczema are common. Type IV hypersensitivity to chromium is becoming increasingly common and represents a major health problem, and this is due to the increasing use of metal alloys. Hexavalent chromium, applied directly on the skin, during passage through the skin barrier is transformed into the trivalent form, which binds to thiol groups of the tissue proteins to form the complete antigen. Binding of the trivalent chromium ions to proteins at the site of penetration forms a kind of

depot, which is much larger in the affected skin (11). It is obvious that the rate of diffusion is affected by many factors such as the area of the skin, physicochemical properties of the substance, the concentration and the type of carrier or permeation enhancer (12).

Recent work (4) suggests that the Langerhans cells are not necessary in the initiation phase and causing the ACD. However, they may play a role in the development of immune tolerance to chromium. Keratinocytes play a role in all phases of the ACD.

Contact dermatitis, both clinically and histologically depends on the cell immune response, including the expression of cytokines, chemokines and adhesion molecules.

Visible swelling and hyperplasia of the spinous layer of the epidermis, hyperkeratosis and lymphocytic infiltration in both the skin and the epidermis are characteristic histology of contact hypersensitivity to chromium. Micropustules in the epidermis are due to swelling of the infiltrating mononuclear cells (21). A number of differentiated cells of the immune system is responsible for a development of type IVa and IVc allergic contact dermatitis.

Depending on the method of initiation of an immune response effector cell composition comprises Th1 cells, macrophages/monocytes, or lymphocytes Tc (CD8+), NK cells. Cytokines and inflammatory mediators include IFN-γ, IL-12, TNFα or perforin, granzyme B, FAS ligand (16).

In the delayed-type hypersensitivity to chromium, type IVa, there are two phases of the skin reaction: induction and effector phase. In the induction phase chromium ions penetrate through the stratum corneum and bind to proteins in the living layers of the epidermis and are then are absorbed by the Langerhans cells. These, in turn, move to the local lymph nodes, process the allergen, ripe, which results of increased expression of surface proteins. In the lymph nodes, Langerhans cells present antigen to the T cells, which then divide intensively and differentiate into effector cells, the surface of which are markers, allowing them to migrate to sites of inflammation. T-lymphocytes are transformed into Th1 cells and secrete cytokines IL-17, IFN-γ, which activate epidermal keratinocytes to secrete another type of cytokines. Cytokines and chemokines are produced by Th1 activated keratinocytes and other cells i.e. macrophages, monocytes and basophils. Their function is the secretion of inflammatory mediators directly involved in hypersensitivity reactions leading to allergic contact dermatitis (16). In the allergic reaction of type IVc antigen is connected to a cell, which directly stimulates the T-cells, which are converted into cytotoxic lymphocytes (Tc/CD8+). Further operation of immune cells leads to the formation of pustules (5).

Nonabsorbed chromium is removed from the body in urine and feces (7,20).

The penetration of chromium salts through the stratum corneum is affected by many factors, their allergenic potential can be limited by the use of cosmetics containing suitable complexing agents. Finding such raw materials among typical cosmetic materials would enable the development of cosmetics, to a certain degree protecting people, who are allergic, against contact allergies, both in work and in everyday life. The aim of this study was to assess cosmetic raw materials potentially reducing the dermal bioavailability of chromium salts. As an experimental method to predict the bioavailability we chose the determination of trivalent chromium ions penetration rate through membranes modelling human horny layer.

MATERIALS & METHODS

In the study side-by-side Flynn cells and sandwich-type synthetic membranes filled by s.c.

lipids mimicking mixture, modelling the stratum corneum were used (1,10,14). For quantification of chromium ions in the receiving solution colorimetric method with 1,5-diphenylcarbazide was used (13). As complexing agents common cosmetic raw materials were used: hyaluronic acid, chitosan, α-hydroxyacids: lactic acid and citric acid, and for comparison a known sequestrant - ethylenediaminetetraacetic acid (EDTA). As a donor solution acetate buffer of pH 5.5 with 0.45 mg/ml $CrCl_3$ was used. As the receiving solution acetate buffer of pH 7.2 was added, which reflects actual conditions in the living tissue.

RESULTS AND DISCUSSION

In order to determine the permeation rate of chromium ions through the model membrane a solution of chromium chloride (0.2 mmol/dm^3) in acetate buffer at pH 5.5 was prepared. Based on the results obtained in a constant flow conditions the rate of permeation was calculated. Each assay was performed three times and then the average values of permeation coefficients (Kp) were calculated.

Based on the experiments described above it was found that the chromium ions are able to pass through the model membrane, and may to some extent penetrate the intact stratum corneum (Kp= 0,012cm/h). In an analogous manner penetration coefficients of chromium ion in the presence of the above-mentioned complexing agents used in various concentrations were determined.

Results are presented in the Table I and figure 1. On the basis of the results obtained it can be concluded that all the tested complexing compounds inhibit significantly Cr^{3+} ions penetration through the epidermal barrier. This applies to the relatively low concentration of complexing agent (0.4 to 0.8 mmol/dm^3).

TABLE I

Penetration coefficient and ER of chromium ions in the presence of complexing agents.

Complexing agent	Concentration of complexing agent (mMol/dm^3)	Kp (cm/h)	ER (%)	No
None	---	0.0120	---	0
Hyaluronic acid	0.4	0.0068	33.4	1
	0.8	0.0038	62.75	2
Chitosan	0.4	0.0067	34.3	3
	0.8	0.0056	45.1	4
Lactic acid	0.8	0.0050	49.9	5
	4.0	0.0005	95.1	6
Citric acid	0.8	0.0060	50.0	7
	4.0	0.0019	90.2	8
EDTA	0.8	0.0001	99.02	9

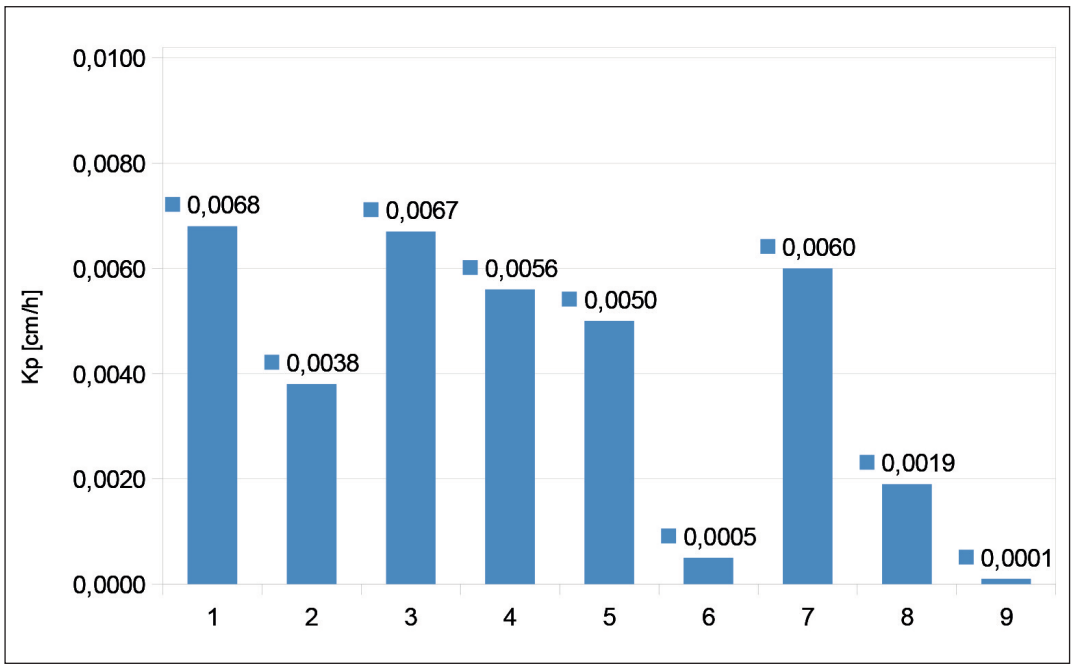

Fig. 1 *The influence of concentration and the type of complexing agents on chromium ions penetration coefficient.*

At a concentration of 0.4mmol/dm^3 hyaluronic acid and chitosan act equally (ER = approx. 35%), but even at twice increase of the concentration the obvious superiority of hyaluronic acid is visible. A similar relationship exists for the tested hydroxyacids - citric and lactic acid, at higher concentrations advantage of lactic acid is observed. At higher concentrations this compound matched EDTA.

The most promising cosmetic ingredients that protect the skin against the penetration of salts of trivalent chromium appear to be hyaluronic acid and lactic acid with a strong predominance of the latter. These issues will be the subject of further research.

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Author Address:

Katarzyna Pytkowska
Academy of Cosmetics and Health Care
Faculty of Cosmetology
Warsaw, Poland
Email: k.pytkowska@wszkipz.pl

Travelling all over China. Cultural heritages of two ancient civilities, Chinese and Italian, at the base of the progress. Part I

P. Morganti
Temporary Professor of Skin Pharmacology, Dermatology Institute, 2nd University of Naples, Italy
Visiting Professor, China Medical University, Shenyang
R&D Director, Nanoscience Centre, Mavi Sud, s.r.l, Italy

INTRODUCTION

China

By a surface square of 9.6 million of km^2, the China territory covers 6.5% of our Planet, being large quite as the entire Europe. Coasts and isles develop 18,000 km, while the Country orography is extremely variegated going from 8848 meters of Qomolangma (Everest) mountain (Fig. 1) to -154 depression of Turfan oasis in the Xinijiang (Fig. 2).

For its large surface with more than 2000 lakes and 50,000 rivers, Chinese define their land Zong Guo, i.e. Country in the Center.

Due to the very different language and culture, it is necessary to visit this wonderful country in tiptoe, with humility and a minimum of knowledge. This condition results indispensable for understanding and accepting the different Chineses' way of living, of relishing the poetry of a millenarian civility which fascinates, impresses, intrigues and seduces people who make the decision to know it more closely. It is also, interesting to remember that the population of about 1.5 billion of habitants is by 95% represented principally from the ethnic group Han and 5% of 56 minorities (Fig. 3), living into the peripheral regions of China.

The first strongest sensation arriving in China is the hypnosis caused from the mass of variegated people who walk smartly (Fig. 4). Buzz of the crowd absorbs the visitor into an atmosphere of bodies, merchandising, and every kind of sensations and objects into a great stage of the Chinese life, where all the activities are carried from the break of the day to the sunset, for continuing until and after midnight.

Fig. 1 *Everest (Qomolangma) mountain.*

Fig. 2 *Depression of Turfan in Xinijiang province.*

Fig. 3 *Some Chinese minorities in their traditional dress.*

Fig. 4 *Variegated people on the road in Beijing.*

The Patriarchal Family

The patriarchal family is influenced from the familiar structure of the antique civilities that, born both in East and West is based on more and more generations living all together as a single social, economical and religious unity, under the control of the patriarch, recognized as *Jiazhang* in ancient China and pater *familias* in ancient Rome. However, until now fundamentally the Chinese family remains principally based on six rules of the Confucianism, concretized by the relations established between wife and husband, parents and sons, among brothers, nephews, pro-nephews, and pro-pro-nephews.

Old people have proud of their nephews and are carefully to take photos with them in the right position, while nephews are happy to shout with joy with their grandparents. It is interesting to underline how elderly Chinese loves to socialize, playing by Chinese checkers (Fig. 5) or dominoes (Fig. 6), without never getting exuded and angry, as well as to bring by charges the birds in captivity (Fig. 7) in many public parks, for giving them the possibility to talk with their coetaneous in liberty, for learning to whistle.

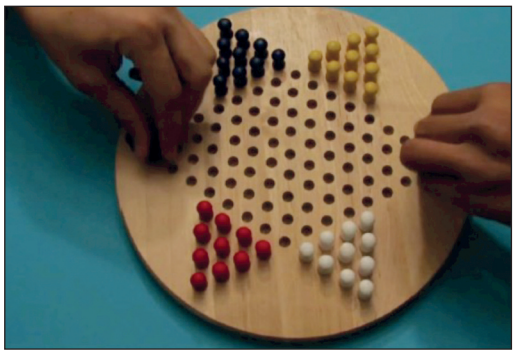

Fig. 5 *Playing the Chinese checker.*

This ancestral love for birds, sold in important locations such as the famous market in Shanghai (Fig. 8), is reported on many Chinese paintings since the antiquity (Fig. 9). And just by these friendly and caring behaviors, appears clear up today the Confucian ethics of the social order in the family, first and unquestionable in Chinese social nucleus.

Fig. 6 *An old Chinese man playing domino.*

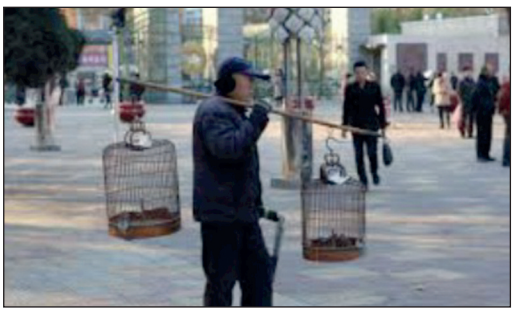

Fig. 7 *Transporting to a public park the birds in captivity.*

Fig. 8 *Birds in captivity in the famous Shanghai market.*

Fig. 9 *Painting the birds in China.*

CHINA and ITALY: family and heritages

In the same way, family was an important part of the ancient roman culture and society also. The *familia* in Rome included more than just the basic family of father, mother, children and nephews. It also included all the people who were part of the household, such as the slaves, servants, clients, and freedmen, so that the emperor's family often included thousands of members. Much of Roman law, therefore, was written around protecting the basic structure of the family Thus, as in ancient China, the Roman State derived its nature and existence from the family and not from the individual.

It is, however, to remember that cultural heritages and innovation represent the pillars of the progress. But it is to underline that the cultural heritages represent the pillars of the progress and are necessary to maintain a healthy body and environment-friendly, fundamental to obtain Wellness and Beauty.

To better understand this connection, it is necessary to show the evolution of the two different Chinese and Italian cultures, which representing the pillars of Eastern and Western civility and progress, may be underlined by two symbolic monuments passed over the centuries (Fig. 10).

Fig. 10 *On the left the Imperator, and right Colosseum, Rome.*

Fig. 11 *Antique road in Chinese (left) and Roman (right).*

Both the civilities were based on the construction of roads (Fig. 11), intelligent distribution of clean water (Fig. 12) and healthy food (Fig. 13), always respecting environment and culture, stimulating the studies of history and philosophy, (Fig. 14) to maintain a high level of knowledge by the use, for example of the theatre (Fig. 15). At this purpose, it is interesting to remember that since the ancient period in China the use of food and drugs was strictly connected with the Traditional Chinese Medicine (Fig. 16), as well as the antique Romans used the Thermal baths (Fig. 17) to maintain a *mens sana in corpore sano* (healthy brain in a healthy body), anticipating the modern way of living.

Fig. 12 *Distribution of water in ancient China (left) and Rome (right).*

Fig. 13 *Chinese noodles (left), and Italian spaghetti (right).*

Fig. 14 *Education of philosophy and history in ancient Chinese (left) and Roman (right) culture by an old painting and low relief.*

Fig. 15 *Chinese (left) and Roman (right) theatre.*

Fig. 16 *Traditional Chinese medicine (TCM).*

Fig. 17 *Roman thermal baths.*

For further knowledge it is also to remember that probably Chinese and Roman cultures had a contact during the period of the Roman imperator Marco Aurelio (161-180 after Christ) and the ChineseHan Dynasty (8-220 after Christ), as reported from an antique Chinese document of Han Shan (Fig. 18).

帝紀卷第四　范華　後漢書四

唐章懷太子賢　注

孝和皇帝

孝和皇帝諱肇

孝和皇帝諱肇

第四子也母梁貴人竇皇后所譖憂卒

竇后養帝以爲己子建初七年立爲皇太

子章和二年二月壬辰即皇帝位年十歲

尊皇后曰皇太后太后臨朝三月丁酉改

淮陽爲陳國　楚郡爲彭城國　平并州南郡　遣詔徙西平王羨爲

廬江郡　陳王六安王恭爲彭城王癸卯葬孝章皇

帝于敬陵　庚戌皇

太后詔曰先帝以明聖奉承祖宗至德要

道天下清靜庶事咸寧今皇帝以幼年嗣

統在孩　朕且佐

Fig. 18 *Ancient document reporting probably a contact between Chinese and Romans during the Marco Aurelio period.*

to be continued ...

Smart Pharmaceutical Nanocarriers

by Vladimir Torchilin

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Fax: +44(0)1235 465555
Email: enquiries@marston. co. uk

Drug delivery practices have undergone rapid advances largely due to parallel advances in the fields of nanotechnology and nano-medicine, as well as to the tremendous progress of our understanding of the fundamental human body biology. The efficacy of any product containing a functional ingredient, such a drug, is determined by two factors: the intrinsic activity of the active molecule as well as the delivery of this molecule to its site of action. Moreover, the active ingredient has to be delivered at the right concentration for a sufficient period of time to exert its biological or pharmacological activity. Which carrier is best for delivering the active ingredient?

This book, organized in 15 chapters try to give a reply to this enquire reporting the use of nanocarriers which have revolutionized the drug delivery practices in the past twenty years, thanks to the high advances in material chemistry. At this purpose *smart* nanopreparations have been designed capable not only to release their therapeutic cargoes at the right sites, but to offer also a spatial and temporal control over their properties linked to the right dosage. Thus, advance in biomedical nanotechnology have enabled the development of pharmaceutical nanocarriers with specialized features and tunable surface chemistries.

The use of nanoparticulate carriers, for example, can overcome many of the free therapeutic molecules' limitations since they may solubilize both hydrophilic and hydrophobic drugs, increase their stability and longevity *in vivo*, provide controllable drug delivery and drug release to specific organs, tissues, or cells, modifying also their pharmacokinetics. Moreover, the development of stimuli-responsive carriers, that can delivery different payloads from small molecules to complex biologics, such as DNA, RNA and proteins, have the ability to internalizing them into intracellular structures, responding to subtle changes of the redox potential between intra-and extracellular environments.

Additionally, developing engineer nanocarriers responsive to biochemical signals could improve the capability of these systems to minimize undesirable side effects and offer better control over their distribution and localization in the body. As an example, intracellular pH plays important roles in cellular functioning, where the pH detection is essential to understand the cellular processes. Thus the mechanism of pH-sensitive nanocomplexes, releasing proteins in a controllable manner, is often based on the change of electrical interaction between proteins and carriers by pH changes. pH differences in pathological regions, particularly in tumors and inflamed sites (pH ranges from 6.8 to 7.2) is, in fact, a natural and unique signal to induce the chemical reactions or changes in physicochemical properties. This is the reason why the pH-sensitive nanosystems seem to be able to penetrate deeply into the tumor tissue to meet the acidic regions (before they take advantage of acidity), discrimi-

nating pH values between 7.4 (physiological) and ~6. 8-7.2 (pathological).

These the topics reported and discussed on **chapter 1** *(Stimuli-Sensitive Nanopreparations: Overview)*, **chapter 2** *(pH-Sensitive Nanosystems)*, and **chapter 13** *(Smart Nanopreparations for Cancer)*.

Therapeutic or imaging molecules could be encapsulated into the inner layer or core of nanocarriers, or adsorbed on the surface or outer layer of nanocarriers, via physical forces or covalent bonds. Upon loading, the properties of the loaded molecules can be significantly altered in terms of their physicochemical properties as well as of their interaction with biological systems. Thus, compared to the conventional drug delivery systems, the metalloproteinase (MMP)-sensitive nanocarriers show a superior ability for the control and adjustment of both location and time of drug releasing and cell internalizating. In the same way PEGylation is a well-known technique that can enhance drug solubility and stability, prolonging the drug blood circulation time and preventing the drug's non-specific interaction with biological systems, via the so-called steric stabilization.

PEGylated carriers are characterized, in fact, by a slower uptake by some organs, showing a prolonged half-life in the body and thus an enhanced bioavailability. Hence, the frequency and amount of drug administration can be diminished, improving the quality of life of the patient and reducing clinical costs.

This the reason why a variety of stimulus-sensitive linkers have been incorporated between the PEG and nanocarriers to respond to local stimuli, including MMPs, and the shield PEG chains. However unlike pH and redox potential, the abnormal changes of certain proteins like MMPs are usually more significant and robust, probably because of their critical roles in many physiological processes. In any way, to ensure the success of MMP-sensitive nanocarrier, the *in vivo* distribution, expression level, and activity of designed MMPs, properties of designed MMP-sensitive substrates and their engineered nanocarriers, have to be thoroughly considered together with the pathological condition and the expected clinical outcomes. After drug-carrying, in fact, polymeric nanosystems that reach the target tissue need to be internalized into the cells releasing the encapsulated or complexed drugs. All these steps should take place sequentially and efficiently to maximize the therapeutic efficacy of delivered drugs, while minimizing the potential adverse effects. These particular delivery systems were discussed on **chapter 3** *(Matrix Metalloproteinase-Sensitive Nanocarriers)* and **chapter 4** *(Redox-Sensitive Nanosystems)*.

To modulate drug release, nanocarriers can be designed in such a way to take advantage of *physiological triggers* such as changes in pH, redox, hypoxia, or increased levels of certain enzymes that are characteristics of particular tissues, organelles, or pathologically altered areas. **Chapter 5** *(Temperature-Sensitive Pharmaceutical Nanocarriers)* is focused on drug delivery systems responsive to temperature changes, while **chapter 6** *(Ultrasound-Controlled Nanosystems)* refers to specialized nanosized active delivery vehicles that have the ability to respond to ultrasound pressure for the release of the active ingredients payload. Naturally, the success of temperature-sensitive drug depends not only on their careful design and particular properties, but also on the ability to homogenously heat the site of interest to a precise temperature, without damaging adjacent tissues.

On the other hand ultrasound-controlled nanosystems refer to specialized nanosized vehicles that have the ability to respond to ultrasound pressure, for releasing their payload active ingredients. Therefore, it is important to control in the right way each type of target tissue to determine the appropriate ultrasound parameters and the suitable therapeutic delivery agents for optimizing the ultra-

sound-based therapeutic delivery. At this purpose many examples are reported on these chapters for targeting the right goal.

Because of the high lethality and aggressiveness of some cancers together with their resistance to drugs and radiation, novel approaches have been developed to selectively amplify the efficacy of standard therapies and preserve the functionality of co-localized normal tissues for reducing treatment time and toxicity. This the topic focused on **chapter 7** *(Plasmonkc Nanobubble-Controlled on Demand Drug Delivery and Release with High Target Cell Specificity)*.

The reported approach employs two different strategies: 1) to use the mechanical, rather than chemical radiation, or thermal impact for cancer cell destruction and drug delivery, and 2) to selectively amplify chemo-and radiotherapy inside target cancer cells, by employing intracellular synergy of four standard components: gold nanoparticle (systemic), drug nanocarrier (systemic), low-energy short laser pulse (local), and X-rays (local), administered in a single three-step protocol. The therapeutic responses to this novel therapy are reported and discussed showing also that some mechanical and physical events can amplify the therapeutic effect of standard chemotherapy and chemo-radiation, only in cancer cells.

The use of light as an external stimulus has the potential to be used for controlling properties of materials, particularly in the delivery of drugs. Moreover, the ability to control wavelength, intensity, duration, and site of irradiation means that the quantity of drug released, its location, and the duration of release can be controlled. Combining photo-responsiveness with nanomaterials will lead to the generation of materials that are spatially and temporally specific, being biocompatible also. Light-sensitive systems, in fact, can be synthesized by incorporating photo-convertible or photo-labile groups into pendant groups of a polymer chain. Potential applications of these nanomaterials include ocular and dermal delivery, as both these tissues are easily light accessible, although other areas, particularly for cancer treatment, have been targeted. This is the interesting topic of **chapter 8**: *Light-Activated Nanopreparations*. The external stimulus can be provided by UV light, visible, or near-infrared, ultrasound, heat, or by an external magnetic field.

Chapter 9 is focused on magnetic field responsive nanocarriers (MFRNs) with their various applications, such as drug targeting, medical hyperthermia, imaging, and sophisticated theranostic and multifunctional nanocarrier platforms for drug delivery. The chapter reports a general introduction to magnetic nanoparticles (MNPs) with their properties and applications, the efficiency of which can be significantly improved by increasing their local accumulation in diseased tissues. Thus, active targeting of MNPs involves their surface modification by conjugation of targeting ligands that can identify and possess an enhanced affinity for unique molecular signatures, found on diseased cells and tissues. At this purpose novel applications of MNPs are reported, including those that combine diagnosis, treatment, and monitoring of therapy in a single carrier for *theranostic purpose*. However, also if these new nanocarriers can result very useful to solve many pathological problems, it is necessary to control their biocompatibility and safety. In any way the advantage of the theranostics system the dual functionality of diagnostics and therapy within one carrier- is mainly due to the goal that can be achieved with a single administration, potentially saving time and effort from multiple administrations. And this is the reason why the entire **chapter 15** *(Smart Theranostic Nanosystems)* has been dedicated to report the progress in the development of the last theranostic nanosystems.

The greatest challenge for pharmaceutical scientists, nowadays is finding novel formulation capable of improving the intraluminal solubility of poorly soluble drugs. Lipophilic drugs and many biolo-

gicals are, in fact, poorly water-soluble compounds and therefore soluble in lipids and non-polar solvents. Thus, lipophilicity reflects the *in vivo* partition of drugs from aqueous phases to cell membranes and protein binding sites, which are hydrophobic in nature. It is, therefore, one of the most important physicochemical properties in drug discovery and design, affecting its pharmacokinetic and pharmacodynamic profile.

The main biological functions of lipids are to store energy, conform cell membrane, and act as signalling molecules. At this purpose, the lipid-based drug delivery systems (LBDDSs) technology has emerged as the most promising formulation strategy for efficient delivery of poorly water-soluble compounds.

Chapter 10 describes smart lipidic formulations and lipid-structure changes of compounds used for systemic, oral, transdermal, ocular and intramuscular drug delivery, where the lipidic excipient assumes an active role in the enhancement of the therapeutic activity of incorporated drugs.

The major goal in polymer therapeutic design is to have the best efficacy, minimizing adverse side effects on healthy tissues. Thus, polymer-based intelligent systems has to be the goal of a modem nano-medicine, so that smart polymers find application in many biomedical and pharmaceutical fields, such as tissue engineering, cell-sheet engineering, hydrogel systems, and pharmaceuticals. Depending on the molecular and chemical structure characteristic of the polymers, they may self-assemble into micelles or polymer vesicles. Smart functionality can be easily incorporated into synthetic polymers by simply co-polymerization monomers with reactive functionality, pH-sensitive properties, or other stimuli-sensitive monomers. However, to be effective the polymer should incorporate biorecognizable functionalities, essential for reaching the target cells or tissues and releasing the drug, respectively. Characterization of the polymer therapeutic is also essential to understand the interactions of the polymer with cells, *in vitro* and with the host *in vivo*. Finally, polymers must be non-toxic and produce acceptable immunogenicity responses in their proposed administration route. *Smart Polymer-Based Nanomedicines* is the topic discussed on **chapter 11**.

One of major goals in drug delivery applications is to increase the efficacy of selective delivery into the site of interest by proper design of the delivery platform. The fate of inorganic nanoparticles (NPs) in biological environments is largely dependent on their physicochemical properties, such as hydrodynamic (HD) size and surface charge. NPs with positively charged surfaces are favoured for contact/adsorption on the membrane because cellular membranes largely consist of negatively charged domains, such as phospholipids with negatively charged head groups and polysulfated glycosaminoglycans. Understanding the role of surface charges in cellular adsorption versus internalization is one of the goals of the nanoparticles designed for delivery applications. Inorganic NPs with broad size ranges from a few to several hundred nanometers and can enter cells via a series of processes termed endocytosis, the efficiency of which is largely dependent on the NPs' HD size. HD size and surface charge also greatly influence delivery and distribution of NPs *in vivo*, because they affect the interactions with many bio molecules. It was shown, in fact, that positively charged NPs can be more adsorbed on the cell membranes, resulting in a higher level of internalizations when compared with negatively charged or neutral NPs. It seems that charged NPs can take advantage of electrostatic attractions with cellular membranes to enhance membrane adsorption and subsequent cellular internalization.

In addition, charged NPs can induce surface reconstruction at the points they adsorb on the lipid membrane bilayers; binding of negatively charges NPs causes local gelation in otherwise fluid

bilayers, while positively charged NPs induce fluidization of otherwise gelled bilayers. The structural charge into a more fluidic phase may disrupt bilayers integrity and cause direct cell penetration of positively charged NPs without being mediated by endocytotic pathways. On the other hand, neutral NPs show the least adsorption on the cell surfaces, which result in the lowest level of uptake. However, since the transport across the membrane hole is an energy-independent diffusive process, it should be more favourable than energy-dependent endocytotic pathways. In any way, the HD size and surface charge are the most important NP design parameters to be considered for efficient delivery of therapeutic agents in a target site because they can largely affect the cellular interaction, *in vivo* circulation, and tissue permeation. All these interesting observations are reported on **chapter 12**: *Inorganic Nanoparticle-Based Smart Drug Delivery Systems*.

Oral administration is a route that presents some advantages over other administration alternatives in drug delivery, because it is easy to manage and has a reduced cost. This the topic focused on **chapter 14**: *Advances in Smart Nanopreparations for Oral Drug Delivery*, where the use of biopolymers and compatible synthetic polymers become a new tool for the development of innovative nanosystems. Thus, when drugs are administered within a nanosystem that significantly enhances their poorly dissolution behaviour, the probability that they reach the systemic circulation in a non-free state is increased, and it is an alternative to overcome the drug concerns associated with solubility and stability. In this way the use of polymer nanocarriers can modulate the pharmacokinetics and bioavailability properties of the drug.

For example, the nanoparticles may remain for several days in the site making the drug delivery system properties very important, since reservoirs of these nanocarriers could be formed in damaged areas. At this purpose, PEG chains seem to impart stealth characteristics to the nanoparticles, improving bio-adhesion in the gastrointestinal tract, and providing surface hydrophilicity.

In conclusion, the smart nanosystems provide to improve drug dissolution and adsorption in physiological conditions, with a reduction of side effects. They, in fact, improve drug adsorption thanks to the high surface area to volume ratio; maintain drug stability, increasing the drug bioavailability in the target organ, contemporary enhancing its cell-penetration function by smart delivery systems that respond to different types of stimuli.

This interesting book written from well-known scientists represents a source of wide open window for dermatologists, plastic surgeons, cosmetic chemists, marketing managers and all academics and students who like to enter into the fascinating field of pharmaceutical and cosmetic nanocarriers.

Pierfrancesco Morganti
Editor-in-Chief

An Introduction to Interfaces and Colloids. The Bridge to Nanoscience

by John C. Berg

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Colloids refer to dispersion of one phase in another of small particles with a size ranging from 1 nanometer, (nm) to 10 micrometers, providing flexibility, for example, in the development of drug delivery. The particles may be either dissolved macromolecules or macromolecular structures formed from smaller structural units. They may also constitute a separate phase, as in aerosols, powders, pigment dispersions, emulsions, micro-foams and finely pigmented plastics. As carriers, they can be classified as self-assembled lipid systems, polymer systems, nanoparticle systems, and pro-colloidal systems. Thus, colloids have evolved to be used in the enhancement of solubility and protection of labile substances, to reductions, for example, in the toxicity of drugs and improving their therapeutic performances. For all these reasons, the colloidal properties have opened new frontiers in the delivery of active ingredients, and/or in chemical and nano-micro biotechnological products leading to an increased surge of interest as bridge to nanoscience. For colloid particles, the kinetic effects are still important and for their small size, when dispersed in a medium (gas or liquid) they move by a process known as Brownian motion. However, the delivery of colloidal active ingredients provides the formulation scientist with an alternative formulation approach that could enhance solubility; ensure improved dissolution; and provide options for controlling or sustaining the active ingredient release, tailoring its surface properties to modify its kinetics and dynamics. In any way, the foundation of all the advances in colloidal delivery science has based on the widespread and versatile use of surfactants and polymers. Surfactants are amphiphilic molecules with a polar, ionic hydrophilic part and a non-polar, hydrophobic part, that usually comprises a hydrocarbon or fluorocarbon chain. The strong dipole interactions between the hydrophilic part and water render them water soluble, and the balance between the dual properties of hydrophilicity and hydrophobicity endows them with a unique characteristic of surface-active properties in solution. Thus, the amount of surfactant adsorption at the interface depends on its structure and nature of the two phases forming the interface, while the degradation pathway mainly depends on the alkyl chain length, its linearity and degree of branching, and branch distribution in the main alkyl chain of the surfactant.

Like surfactants, the degradation of polymers depends not only on the composition of the individual monomer but also on the polymer architecture, polymer crystallinity, pH, and temperature, as well as the presence of other components like the active ingredients used in the delivery system.

The study of the fluid interfaces, the thermodynamic forces of interfacial systems, the physical interaction between liquids and solids, and the morphological, kinetic, phoretic and optical properties of colloids and nano-colloids are discussed on **chapter 1**, while the molecular mobility and thermody-

namic state of fluids are reported on **chapters 2** and **3** respectively, while the physical interaction solid-fluid is the topic of **chapter 4**, where the intermolecular forces between the molecules of the solid, liquid and gas are described and determined. Phenomenology and characterization of the colloidal systems are reported on **chapter 5**, where the differences between the properties of colloids and solutions of small-to-moderate molecular weight substances are listed and discussed. On the other hand the electrical properties of interfaces, which play an important role in the aggregation stability of aqueous colloids, are the topic of **chapter 6**, where their electrostatic characterization with the relative electro kinetic measurements of colloids are focused. When sufficiently close, colloid particles exert attractive forces on one another determining their fate with respect to aggregation. These forces also play a central role in the rate of the process, the structure of the aggregates formed and the ultimate structure of the colloidal system. The electrostatic and steric interaction phenomena between colloid particles is the topic of **chapter 7**, while the rheology of dispersions, that refers to the deformation and flow of materials in response to applied stresses, is discussed on **chapter 8** where all the viscosity laws are reported.

Chapter 9 is entirely dedicated to emulsions and foams which, as dispersions of one fluid or air phase in another, are stabilized by the presence of strong surfactant adsorption at the fluid interface. While emulsions refer to liquids dispersed in liquids, foams refer to gases dispersed in liquids. All the problems concerning foaming and emulsions formation, testing and stability are discussed and focused on this chapter, while on **chapter 10** the interfacial hydrodynamics, influenced by the boundary tension at fluid interfaces, are briefly reported, together with their variations with temperature, composition and surface charge density.

This interesting book, published for the first time in 2010, has been so interesting for many lecturers to be reprinted again in 2012, 2014 and 2015.It reports an update of knowledge and experience on the Interfacial and Colloidal Science applied from the industrial manufacturing to the use in biomedical research. It is important for researchers to understand the fundamental nature and role of surfactant interactions with the biological surface and bio-colloids which form the molecular base of the undesirable skin effects due, for example, to the use of household and personal care products. The compatibility between a biomaterial implant surface and constituents of the surrounding host environment, in fact, is based on cellular, molecular, and atomic interfacial reactions. Although the physical and chemical characteristics of bulk phase (colloids and surfactants) of commonly used biomaterials may be known, the same characteristics of their material surface may be significantly due to the rearrangement and relaxation of atomic and geometric structures. However, the fundamental principles of colloidal chemistry and theoretical physics may be applied to interactions between tissue and biomaterial surfaces. In conclusion this book may be of great interest not only for undergraduate and graduate students in science and engineering, but also for all the scientists of the medical and chemical community who wish to clearly understand the diverse functions in the living system on the basis of the complex network of interfaces and/or colloids activities. However, the reported description of all the interfacial phenomena characterizing colloidal and surface chemistry result also fundamental to better understand the biological processes of all the living organisms.

P. Morganti
Editor-in-Chief

Nanostructured Polymer Blends and Composites in Textiles

by M. Ciocoiu and S. Maamir

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The skin exerts an important protective function by the dynamic stratum corneum structure composed of lipids and corneocytes. Textiles and especially antimicrobial textiles may interfere with non-specific defence mechanisms like antimicrobial peptides of skin or the resident microbioma.
Therefore, the microorganisms of the skin can influence the skin itself, the textiles, as well as the interaction between skin and textiles. For all and other reasons, understanding polymer blends and composites used to make textiles together with their specific properties is fundamental for designing and engineering innovative and useful textiles. This book, organized in 11 chapters provides original, theoretical, and practical results on the use of novel applications and technologies to produce functional and smart textiles.
Chapter 1 - *Engineering nanotextiles: Design of Textile Products* - starts by review the textiles history, classifying them on the basis of their component fibers into animal, plant, mineral, and synthetic origin, reporting also the different production methods. On this chapter an important space has been dedicated to the use of nanotechnology by two different approaches: bottom-up and top-down. However, it is to underline that nanotechnology offers many advantages as compared to the conventional process in term of economy, energy saving, eco-friendliness, control release of substances, packaging, separating and storing materials on a microscopic scale for later use and release under control condition.
Materials reduced to the nanoscale, i.e. at molecular or atomic level, show different properties compared to what they exhibit on a macro scale. Textiles made from nanofibers, in fact, have high surface area and small pore size, making them ideal materials for use, for example, in protecting clothing. For these reasons nanoparticles can provide high durability for treated fabrics as they possess large surface area and high surface energy, that ensure better affinity for fabrics and led to an increase in durability of the desired textile function. The smaller particle size also plays a primary role in determining its adhesion to the fibers, because this dimension permits a deeper penetration and a stronger adhesion into the fabric matrix.
Thus, incorporating nanofibers into traditional textiles allow them to become multifunctional and produce fabrics with special functions, including antibacterial, UV-protection, easy-clean, water and stain repellent, and anti-odor. On one hand, pre-engineering TiO_2 and MgO nanoparticles adhere to textile substrates, and can break harmful and toxic chemicals and biological agents, due to the photocatalytic activity of these minerals. On the other hand, the UV-blocking property of the fabric may

be enhanced when a dye pigment, delustrant or ultraviolet absorber finish is present that absorbs ultraviolet radiation and blocks its transmission at level of the skin. Moreover, incorporating clay nanoparticles into a textile can result in a fabric with improved tensile strength, tensile modulus, flexural strength and fleural modulus.

On an aesthetic level, nanofiber textiles also exhibit extremely soft handling characteristics and have been proposed in the production of artificial leather and artificial cashmere. In biomedical applications the similarity between certain electro spun polymeric nanofibers and the naturally occurring nanofibrous structures of connective tissues, such as collagen and elastin, give rise to the opportunity to create artificial biomimicking wound dressings and tissue engineering scaffolds.

The bearing properties of nano-particles can be encapsulated to the textile materials, which can carry their properties. This the topic of **chapter 2** - *Modern Applications of Nanotechnology in Textiles*.

Advanced technology and innovative solutions are continuously explored with application of materials with electrical, chemical, mechanical, thermal and optical reaction. Thus, the production of the so-called *smart textiles*, are referred as products with additional value. These special fabrics have not only the common propertiy of textiles, but insure also additional functions, providing attractive solutions for a wide range of application fields.

In any way, functionalization of textiles may be processed at different levels, from fibers till fabric or even ready-made clothing. Modification of textiles via producing polymeric nano-composites and also surface modification with metallic and inorganic nanostructured materials, are developed due to their unique properties. Thus, by the concept of surface engineering and nano-textile hydrophobic fabric surfaces, capable of repelling liquids and resisting stains, have been made complementing the other desirable fabric attributes, such as breathability, softness, and comfort. Moreover, the main research efforts involving the use of nanoparticles of metal oxides have been focused, for example, on antimicrobial, self-decontaminating and UV-blocking applications for both military protection gears and civilian health products.

Another approach is to make nanocellular foam structures making use of their instability during the supercritical carbon dioxide extrusion. The reduced size of the obtained fibers can be used as high-performance composite fibers, as well as for sporting and aerospace materials. Additionally, the micro and nano-scale surface features of a fabric can be appreciably modified to achieve considerably grater abrasion resistance with UV resistance, electromagnetic and infrared protection properties.

Last but not least, electrically conductive textiles make it possible to produce electronic ones to be used for communication, entertainment, healthcare, safety, homeland security, computation, thermal purposes, protective clothing, wearable electronics and fashion. For example, in health and biophysical monitoring, these tissues can be used for monitoring cardiovascular and vital signs of infants, as well as clinical trials, health and fitness signs, home healthcare, hospitals, medical centers, assisted-living units, etc.

In conclusion, the smart textiles represent a new generation of fibers, yarns, fabrics and garments that are able to sense stimuli and changes in their environments, such as, thermal, chemical, electrical, magnetic, mechanical and optical changes, and respond to these changes in predetermined ways. The objective of this innovative textile is to absorb a series of active components, essentially without changing its characteristics of flexibility and comfort.

The study and realization of smart textiles involves, therefore, a multidisciplinary field of research in many sciences and technologies such as textile, physics, chemistry, medicine, electronics, polymer

biotechnology, telecommunications, information technology, microelectronics, wearable computers, nanotechnology and micro-electromechanical machines. Understanding the drivers, state-of-the-art and tendencies in smart textiles ensures further efficient development technology and its interaction with manufactures and consumers.

Membrane filtration is considered a very efficient and economical way of separating components that are suspended or dissolved in a liquid. This topic is focused on **chapter 3**, *Nanofiber Membranes: A Practical Guide*.

The membrane, that covers a wide range of processes (gas/gas, gas/liquid, liquid/liquid,gas/solid, and liquid/solid separations), is a physical barrier that allows certain components to pass through, depending on their physical and/or chemical properties. Nowadays, nanomaterials become the most interested topic in this field also because of their unique structural properties that cover their different efficient uses, such as ion exchange and separation, catalysis, biomolecular isolation and purification as, well as chemical sensing. One of the ways to enhance the functional properties is, in fact, to increase their specific surface area by creation of large number of nanostructured elements or by the synthesis of a highly porous material. Membranes, in fact, consist of a porous support layer with a thin dense layer on top that forms the true barrier, the components of which is determined by the selected materials used. These components involve several fundamental issues, such as polymer-chain rigidity, free volume so that their altered interface influence transport through the membrane. The membrane separation processes, based on a physical mechanism and compared to other conventional ones, are involved for the processing of food, beverage, and bio-products, where the products can be sensitive to temperature. The material used in their production determines their function and their driving forces i.e. their pressure across the membrane barrier. Thus, membranes became materials which form part of our daily lives.

As reported, nanofibers have yield potential application in areas such as filtration, recovery of metal ions, drug release, dentistry, tissue engineering, catalysts, enzyme carrier, etc. However, in both chemistry and biology, for example, the carrier for catalyst is used to preserve high catalysis activity, increase the stability, and simplify the reaction process. Nanotextile and tissue engineering from a *Biological Perspective* is the topic reported on **chapter 4**.

Catalysis is a molecular phenomenon and the reaction occurr on the active site, so that in chemistry and biology a carrier for catalyst is used to preserve high activity, increase the stability, and simplify the reaction process. While the only crucial step in catalysis is how to remove and recycle the catalyst after the reaction, chemical reactions using enzymes as catalysts have high selectivity, requiring mild reaction conditions. Thus, for example, heterogeneous photocatalysis system is an effective method for treating wastewater and photo-degrading organic pollutants as well as the combination of nanoscience/nanotechnology used in human biology to mimic and restore the structural and functional properties of tissues by the electrospinning method. However, in tissue engineering, the generated tissue should have similar properties to the native tissue in terms of biochemical activity, mechanical integrity and function. Thus, in regenerative medicine special scaffolds, made of porous structures, are used to support cells by filling up the space otherwise occupied by the natural extra cellular matrix (ECM).The material properties of the matrix as well as its architecture result fundamental to influence the cell binding, infiltration, orientation, differentiation, adherence and mobility. It is evident that the electrospun nanofibers, with their high surface area to volume ratio, combined with a microporous structure that provides a large surface area for the entrapment of enzymes, and

mimicking the ECM architecture also, offers great advantages for tissue engineering.
In daily life, the clothing acts as an important barrier for heat and vapour transfer between the skin and the environment, protecting the body against heat and cold, contemporary hampering the loss of superfluous heat during physical effort. Thus, the overall transfer in textile materials is the sum of contributions through the fiber and interstitial medium, which may involve multiple transfer mechanisms in terms of conduction, convention and radiation. Thanks to the porosity of the fabric, for example and, the interstices between fibers provide the space for moisture to flow away, as well as by its waterproof, the clothing can protect the body from wind and water.
This the topic focused on **chapter 5** - *Heat and Moisture Transfer in Clothing System* - where a mathematical model describing the physical mechanisms and concerning the heat and mass transfer *in vivo* worn facemasks during breathing cycles, has been developed.
Chapter 6 is entirely dedicated to *Electrospinning of Nanofibers and Porosity*. Electrospinning is a simple and convenient method to produce nanofibers. As previously reported, modifying nanofibers surface morphology, by introducing pores, their surface to volume ratio increases greatly so that nanofibers may be applied in chemical filtration, fuel cell membrane, as catalyst sensor and naturally in tissue engineering. Thus, nanofibers have the advantages of functionality due to their nanoscale structure and the ease of manipulation for their macroscopic length. Moreover, they provide good mechanical properties and good handling characteristics due to their three-dimensional network assembly. Electrospinning is a simple technique that has garnered much attention because of its capacity and feasibility in the generation of large quantity of nanofibers. This method consists of a spinneret with a metallic needle, a syringe pump, a high-voltage power supply, and a grounded collector. A polymer composite solution or melt is loaded into the syringe and this viscous liquid, driven to the needle tip by the pump, forms a droplet at the tip. When a voltage is applied to the metallic needle, the droplet is first stretched into a cone and then into an electrified jet. The jet is then elongated and whipped continuously by electrostatic repulsion until is deposited on the grounded collector. The electrospun nanofibers may be produced over a wide range of porosity values and their functionality are based on their nano scaled size, high specific surface area, and high molecular orientation ,and can be controlled by their fiber diameter surface chemistry and topology and internal structure of the nanofibers. Thus, electrospun nanofibers or membrane/tissues may be produced over a wide range of porosity values, from nearly non porous polymer coatings to very porous and delicate fibrous structures. The functionalities of the nanofibers or nanofibrous tissues, therefore, are based on their nanoscaled-size, high specific surface area, and high molecular orientation that may be easily controlled during the electrospinning process.
However, more study is needed to establish a better understanding of the size dependence in the nanometer scale. At this purpose nanocomposites and nanograined materials have been studied mainly for improved their physical and mechanical properties. Nanocomposites, as previously reported, refer to materials consisting of at least two phases with one erased in another that is called matrix and forms a three-dimensional network. On the other hand nanograined materials are multi-grained single phase polycrystalline materials. Naturally, in nanocomposites and nanograined polycrystalline materials, surface or grain boundaries play a much more significant role in determining the mechanical properties than in large grained bulk materials.
Chapters 7-10 are dedicated to an update regarding respectively the synthesis, reinforcement and characterization of nanocomposites and their polymerization techniques, reporting a special view on

the function of the biopolymers also. The performances of nature in this field, in fact, demand the polymer scientists to use more and more elaborated synthesis methods so that new discoveries result of great importance, involving different scientific and technical areas. The book ends with **chapter 11** - *A study on electrospun nanofiber mats* - focused on the study of ultrathin fibrillar biocompatible structures efficiently applicable in biomedicine and made by the electrospinning technology, reported previously.

This interesting volume is focused on the procedures necessary for selecting and designing innovative materials to be used for the textile applications. Moreover it reports not only the synthesis and fabrication of nanomaterials, but also includes their properties suggesting their applications. Additionally the different chapters of the book provide interesting scientific and practical information useful to professionals and researchers to enter in the fascinating field of polymer and textile materials. Finally, it may serve also as a general introduction to nanostructured polymers and nanocomposites for teaching and self-study purpose.

P. Morganti
Editor-in-Chief

Medicine and Biopharmaceuticals

by Masahide Takahashi

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World Scientific Co.Ltd
UK office, Coven Garden, London
e-mail: elaine@wspc.co.uk
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This book, reporting the Proceeding of the International Conference on Medicine and Biopharmaceuticals, held in Guilin, China, from August 15-16, 2015, provides an interesting source of the great quantity of studies organized from many Chinese universities and research institutes on this important topic.It,presenting many research results on related fields of medicine and Biopharmaceuticals, has divided into four sessions: Session 1 *Medical Science*; Session 2 *Biomedical Engineering and Biotechnology*; Session 3 *Biological Pharmaceutical*; and Session 4 *Food Hygiene, Environment and Human*. It is really difficult to report all the discussions focused on the about two hundred papers coming from the most famous 30 medical and technical universities and research institutes located in the vast territory of China. However the lecture of this book, gives the possibility to the reader to understand and evaluate the reason of the incredible increased scientific papers and patents published from Chinese scientists, especially in the last ten years.

Many are the papers regarding the tissue engineering that, involving material science and life science, tries to develop new tissue/organ substitutes to ameliorate the human wellbeing. These new tissue/organs, in fact, are composed of cells and biological materials capable to promote the restoration, for example, of burned or wounded skin, reporting the organ at the healthy state. Biomaterials, in fact, play a critical role in engineering of tissue constructs, working as an artificial extracellular matrix to support regeneration. Naturally the compatibility between cell and the biomaterials used is a key problem to construct engineered tissue and organs.

In order to achieve the function of the cell-scaffold, and cell carrier, it is necessary to ensure that the cells have good adhesion, growth and reproduction on this new tissue. At this purpose it is to remember that cell affinity is an adhesion mechanism mediated by proteins between cells and materials, to ensure a good cell adhesion properties, indispensable for influencing proliferation, differentiation and function of the cells into a tissue.

Additionally, nanomaterials research had a significant impact on the progress of drug delivery systems. Thus a vast number of active ingredients has been encapsulated as nanoparticles in order to improve their design and mechanism of action on the target site. At this purpose, it is well known that the physicochemical characteristics of each active ingredient determine its *in vivo* performance, conditioning its pharmacokinetic and pharmacodynamic properties also. These physicochemical features determine their solubility, polarity, absorption, form and time circulation, diffusion capacity, metabolization or excretion as well as intensity, duration and efficacy of their action.

Encapsulation and Nanodimension enable to overcome such problems and allow a controlled diffusion assuring not only homogeneity and avoiding toxicity, but providing also the substances protection and enhancing their stability.

The use of modern bioengineered methods and Traditional Chinese Medicine (TCM) is the life motif of many reported papers of this book. With the development of medicine and update of knowledge, breast cancer therapy has come into a diversified comprehensive treatment stage. In the world including Western countries, TCM has become well known for its significant role in preventing and treating cancer. Thus, it has been shown that Xiaozhengshugan recipe as an adjunctive therapy combined with western medicine can relieve the clinical Chinese medical symptoms of breast cancer patients, promote the scores of quality of life (QOL), decrease the bio marker level of cancer antigen 15-3(CA15-3) and cancer antigen 125(CA 125), also if it seems not sufficient in preventing and delaying recurrence and metastasis. Moreover, Ethyl gallate extracted from *Euphorbiae fischeriana Steud*, seems to affect the adhesion and migration of breast cancer, cells reducing the over-expression of ST3Gal I. Therefore these findings suggested that this compound may be a potential therapeutic agent for patient with breast cancer.

Osteoporosis and osteopenia has been rapidly increasing in China in people aged over 60, so that the risk of fracture is becoming more and higher. Many papers report new strategies and intervening measures to be adopted for helping to prevent bone loss, particularly for women, according to TCM and/or western medicine using, for example, bone morrow mesenchymal stem cells (BMSCS) considered as promising *sending cells* in tissue engineering and regeneration therapy. Additionally, after 1949, traditional Chinese doctors and workers who devoted themselves to combining TCM and western medicine, researched scientific measures to improve their ancient medicine and raised new manipulations called *New Eight Manipulations for Fracture*.

It becomes the basic method of modern clinical bone setting, specifically significant in bone injuries. Thus, bone setting operation in the "small splint fixation" belongs to China first, followed by many other countries. Palasy technique is, therefore, one of the great contributions of Traditional Chinese Medicine to the world of medicine.

Bronchial asthma belongs to the TCM asthma, *xiao*, and other categories. In the field of TCM, most important cause of bronchial asthma is phlegm, and individual factors, diet, mood and fatigue are predisposing factors.

In recent years, four diagnostics objectives and standards of TCM in the diagnosis of asthma had achieved good results. To reduce the influence of subjective factors, and to guarantee the information acquisition of clinical Chinese medicine interrogation in the process of collecting unified standards and conditions, some scholars have developed a preliminary scale and interrogation system, and through the reliability and validity test of the scale, good scientific and normative outcomes were achieved, constituting a collection of hardware and software platforms.

Hypertension, also, and stroke with a prevalence rate of 60% is another common disease causing elderly damages and death, usually complicated with cardiovascular and renal damages, so that its control, treatment and clinical diagnosis is a key factor controlled in China by the more modern technologies. With the further development of population aging in China, people aged over 60 to 2030 is expected to reach more than 300 million and the number of stroke survival will surely continue to increase with the therapies in progress, in both TCM and western medicine.

Together with the elderly problem, the result of Chinese sixth national population census have shown

that the children aged 0 years old to 14 years old has been more than 22 millions, which takes the 16.6% of the total population in China.

At this purpose, there is no doubt that the health status of children is related to the future of a state, so that Chinese government is posing great importance to the drug clinical application in children and development of paediatric pharmacy, providing a better medical and health service.

The learning of endocrinology courses is of great importance in the early stage of medical studies. Students are generally insufficient in learning passion due to strong profession, abstract content and varied diseases of endocrinology. The traditional teacher-centered LBL of medical theory is difficult to meet the requirements to cultivate high-level medicine talented persons, affecting the quality of education. Thus, it has been proposed to adopt the Target-based learning (TBL) teaching method in bilingual education, by which students are required to actively learn about the contents of courses first and then cooperating with other students in the team to solve relevant problems.

This new methodology refers to a discussion-based teaching method in which a proper grouping method is used to a class into several teams in the early clinical courses, so as to jointly learn about and accomplish the analysis on medical records on a team basis. Thus, the TBL teaching method, widely applied in physiology, hysto-embriology, medical chemistry and other basic courses, is also universally recognized in nursering, pharmacy, nutrition, public health and professional educations. Moreover, applied for the exploratory process of educational reform in China, it plays a positive role in improving the performance and learning initiative of students, enhancing their comprehensive quality. For these reasons, the improvement to English level of the students has become one of the more important goals for the reform of higher education in China. Therefore great importance is attached to bilingual education, serving as a kind of effective mean to master the latest specialized knowledge and follow cutting-edge information about science and technology.

On one hand, key points are highlighted, so as to guarantee that the contents of courses can be implemented, according to the teaching progress.

On the other hand, both Chinese and English languages are systematically used as teaching media. Thus, students are made to properly deal with the relationship between foreign language teaching and professional course teaching as much as possible in terms of specialized knowledge and competence of two languages.

Besides explanation in English, Chinese language is also used, especially to explain important concepts, contents and difficulties. Moreover, the method enhances the students' practical ability and collaborative spirit, and let's students possess social competitive capability. Finally, this Chinese cultural program lays a good foundation to realize the *internationalization of* higher education, necessary for cultivating versatile talents and accelerating the integration between research center/colleges/universities and the world. Towards this direction is going also the Clinical Pharmacy education, shifting from the current traditional mode of *chemical-drug* to a new mode of *biology-medicine-Pharmacy-society*. Thus, the concept of people-*oriented and service pharmacy* has been widely accepted.

The core of pharmacy services is, therefore, people-*oriented, which* requires that pharmacy workers should have strong self-learning ability and communication skill. It is to remember, in fact, that clinical pharmacy is a comprehensively applied discipline in combination of the pharmaceutical knowledge with the clinical practice. The patient-centered idea, the behaviour to face patients directly, the clinical drug treatment with research and practice, and the improvement of medication levels are

required by clinical pharmacy, so that the clinical practice of students is considered particularly important.

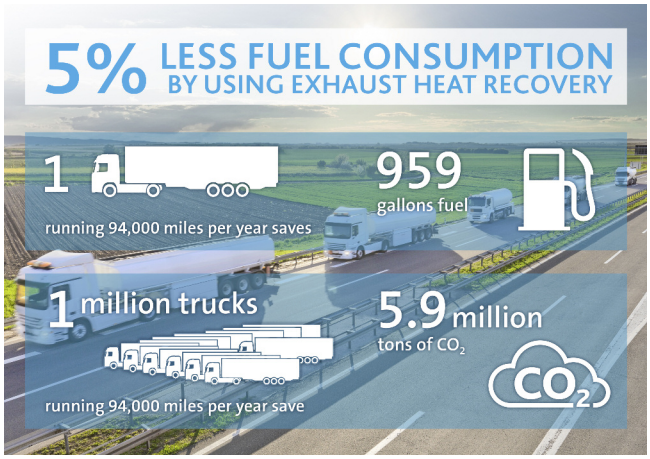
Currently, clinical pharmacy is facing the environment that has undergone tremendous changes in China, such as the great elevation in the proportion of hospitals pharmacy in the appraisal of Class 3 Hospitals by Ministry of Health.

It is difficult to focus and discuss all the interesting topics reported in this proceeding-book because many are the research results obtained in different technical fields: going from the tomographic imaging used for biomedical and biopharmaceutical applications to the metabonomics analysis for determining the endogenous cellular metabolic components, to the selection of the of ailments for ameliorating QOL or the use of natural drugs, recovered from plants in use since the ancient time from Chinese medicine.

In my opinion this book opens an interesting window to understand the great progress obtained in China in the last twenty years in the scientific, technological and economical fields, where all the universities and research centers have been involved to increase the progress of an entire people. For these reasons these proceedings could be of great interest for scientists who like to know and understand the so called Chinese miracle!

P. Morganti
Editor-in-Chief

WASTE HEAT IS PUT TO USE
Systems for waste heat recovery improve commercial vehicles' CO_2 balance sheet



Diesel engines in commercial vehicles today work extremely efficiently. For example, in long-haul trucks, it is possible to convert about 40 percent of the energy chemically bound up in the fuel into forward movement. A large portion of the currently-unusable energy escapes into the environment as exhaust heat. More and more manufacturers of commercial vehicles are working on new concepts, which convert some of the exhaust heat into kinetic energy. In this way, the fuel consumption of heavy trucks is expected to be cut by a minimum of 5 percent. Freudenberg Sealing Technologies supports such developments with innovative sealing solutions.

The transformation of heat into mechanical energy is possible with the help of a thermodynamic process known as the Organic Rankine Cycle (ORC), named after the Scottish physicist William Rankine (1820-1872). This circulation process, so far used solely in industrial plants, works like this: A working fluid is pumped from an accumulator into a heat exchanger along which hot exhaust gas is flowing. The fluid vaporizes over the course of the process. The steam is further heated, much as in a steam engine, to temperatures as high as 250°C (482°F).

At the same time, the pressure rises as high as 40 bar. In an expansion engine, the pressure sets either a piston or a turbine into motion. This mechanical work can be passed directly on to the truck's driveshaft. Or, alternatively, a generator can be driven to produce electricity. The steam is guided at reduced pressure into a condenser behind the expansion engine. The condenser cools the working medium to the point that it is again fluid. As a result, fluid is not wasted – on the contrary, it is intended to flow in the circuit, as much as possible without leaks or need for maintenance. The sole purpose of the pressure-controlled accumulator tank is to make sufficient fluid available under all operating conditions.

High-tech seals are necessary to apply such concepts in the harsh conditions of heavy duty transport. The manufacturers' minimum expectation for the system's lifespan is at least 1.6 million

kilometers (approx. 995,000 miles). It is essential to seal the pipe connections between the condenser and the vaporizer as precisely as the inner workings of the pump, the valves and the expansion engine.

The chemical composition of the working fluid represents a special challenge. There is no industry standard yet for the medium. But various scientific investigations by German Research Association for Combustion Engines (FVV) and other organizations, show that ethanol would be a suitable fluid. This monohydric alcohol has a relatively low boiling point of 78°C (173°C) in its favor, which means that it is possible to generate steam from exhaust heat without difficulty. At the same time, its freezing point, -115°C (-175°F), is so low that it is impossible for the tank to freeze. In addition, ethanol, which is used in many cosmetic products, is non-toxic to human skin. But ethanol poses a challenge to the elastomer seals that are traditionally used in vehicle manufacturing. That's because ethanol leads to the increased swelling of the material, which can lead to the system's inadequate leak-tightness if its design is flawed. There can even be a negative impact on mechanical properties such as elongation at break and tensile strength. Since biogenically produced ethanol is already contained in today's gasolines or has substituted it up to a 100 percent in the Brazilian market, among others, Freudenberg Sealing Technologies has already developed ethanol-resistant seals.

Seals made of fluoro rubber have already proven themselves in fuel-conducting components of the so-called flex-fuel engines. In systems with waste heat recovery, the material mixture must be adapted to the higher temperatures. Furthermore, systems that are designed to utilize hot air exhaust gases are installed near the engine in the tractor where the installation space is tight. So systems that simultaneously seal and make a mechanical connection with the piping could become a key approach to implementing assemblies technically. Freudenberg Sealing Technologies now has such a sealing solution: its "Plug & Seal" product. Yet another component of the ORC system is a pressure-regulated accumulator for the working fluid. Freudenberg Sealing Technologies has already successfully developed these accumulators in high volumes for various industrial applications.

"Exhaust heat recovery systems based on the Organic Rankine Cycle are still in the pre-development stage," said Oswaldo Anaya of Freudenberg Sealing Technologies. "Series applications in the coming decade are becoming increasingly likely due to stricter CO_2 regulations and high cost pressures in the transportation sector." Due to expanding freight transport volume, fuel savings of five percent would mean a substantial reduction in CO_2 emissions. This would yield per-vehicle savings of 2,250 liters (595 gal.) of diesel for an annual mileage of 150,000 km (94,000 miles) at an average of fuel consumption of 30 liters per 100 km driven.

According to estimates, the system would pay for itself within two years due to the fuel savings. If a million newly registered heavy-duty commercial vehicles were equipped with such a system, the result would be overall savings of 2.25 billion liters, which corresponds to the elimination of 5.9 million tons of carbon dioxide per year.

The use of heat recovery systems is not exclusively limited to heavy-duty commercial vehicles. The direct mechanical energy gain from the organic Rankin cycle is also suited to ship engines, for example, where they are already in series use. Car manufacturers are now doing research on thermoelectric generators (TEG), which are designed to generate electric current from exhaust heat. The use of TEG technology is expected to reduce fuel consumption by two to three per-

cent. This works with the help of the Seebeck effect, named for the German physicist Thomas Seebeck (1770-1831): Electrical voltage results if two electrical conductors exhibiting a temperature difference are connected. Whether the effect is great enough to be utilized technologically for a supply of onboard electrical current largely depends on the molecular structure of the conducting material. Most of the materials now being investigated only function within a specified temperature window. If the temperature of the exhaust gases exceeds the maximum permissible value, the flow of electricity comes to a halt. "It is therefore obvious that thermoelectric systems must be connected to their own cooling circuit," said Anaya. "Seals play a crucial role for the sustainably reliable functioning of every cooling system." That is why Freudenberg Sealing Technologies is supporting research into systems of this kind.
In the future, whether in cars or heavy commercial vehicles, waste heat losses will not be a combustion waste product that at most helps to heat the interior. Instead, it will be a source of valuable mechanical or electrical energy.

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Your contact
Ulrike Reich
Head of Media Relations
Tel: +49 (6201) 80-5713
E-Mail: ulrike.reich@fst.com

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How to trap Sun for the skin treatment of Vitiligo and Psoriasis. A new cream

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

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Key words: *Vitiligo; Mexameter; Psoralea corylifolia; Photosensitizing;*

Summary

By this preliminary study the effect of topical preparation of *Psoralea corylifolia* cream in enhancing the benefits of sun was studied using mexameter. Due to the poor number of subjects involved in this study, it has not been possible to organize a statistical analysis on the obtained results.
The findings are presented in the paper with the intention to go on with another study to verify the reliability of the obtained results.

Riassunto

Con questo primo studio riportiamo alcuni dati a supporto dell'attività protettiva nei confronti dei raggi ultravioletti esercitata da una emulsione cosmetica contenente un estratto di *Psoralea corylifolia* su un gruppo di 9 volontari.
Data l'esiguità del gruppo non è stato possibile effettuare una indagine statistica sui risultati ottenuti che verranno ulteriormente controllati su un numero maggiore di volontari con uno studio successivo.

INTRODUCTION

For the treatment of several skin diseases, sun exposure is widely used since time immemorial. Incurable diseases like Vitiligo, Psoriasis etc., come under the above category of diseases where the sun exposure is one of the much sought after methods of treatment followed globally (1).

The UV A and UV B rays in the sun are likely to trigger both the inflammatory responses and genetic memory of melanocytes to produce melanin as skin protectant. The inflammatory responses also would result in hyperpigmentation due to inflammatory events triggering hyper melanogenesis. This is how the benefit of sun is exploited for the treatment of vitiligo (2).

The UV B would affect the cell division. So that augmenting the benefits of sun would be effective in reducing the cell proliferation, essential step in the treatment of psoriasis (3).

However, prolonged exposure to sun may also results in serious side effects. Therefore enhancing the solar effect in short duration is a relatively necessary and safe approach for treating the above diseases.

To achieve the above benefit, use of certain photosensitizing agents are opted. Psoralen is the chemical constituent, which present in the plant *Psoralea corylifolia* is widely used for the above purpose (4).

It requires the oral usage of psoralen at least two hours prior to UV/Sun exposure to ensure the dermal absorption of psoralen to maximize the effect of sun. However the oral use of psoralen is known to produce several unpalatable side effects (6, 7). Therefore topical preparation of natural psoralen is desired.

The present study shows the usefulness of *Psoralea corylifolia* herbal extracts, in trapping the UV light increasing the skin pigmentation (5).

Further the usefulness of this herbal extract in the treatment of vitiligo and psoriasis is discussed. The pigmentary changes of the skin was measured by Mexameter.

MATERIALS & METHODS

Preparation of Psoralea corylifolia extract

A known quantity of shade dried and coarsely powdered seeds of *Psoralea corylifolia* was taken, boiled in coconut oil for 10 minutes and then filtered. 2 % of this filtered oil was incorporated into the cream base.

Evaluation

Two concentrations of the cream viz., 5 mg/ cm^2 and 10 mg/cm^2 were applied separately on the volar forearm region of nine volunteers (5 male and 4 female). All the volunteers were involved in indoor acivities.

The skin site adjacent to cream application (without cream application) was used as control. The difference in melanogenesis in cream treated and untreated control site were measured.

We have used 2% extract of *Psoralea corylifolia* which is known to be safe. The synthetic Psoralen is quite phototoxic agent and known to cause skin sensitization.

After 10 minutes, the cream applied regions and pre identified control sites were exposed to sun for 3 minutes. After sun exposure, the pigmentary changes in both cream applied on the treated areas and control region were read by Mexameter.

The above procedure was repeated for seven days and the pigmentary changes on day seven was recorded to control the effect of melanogenesis of the mela-pro cream.

RESULTS

Seven days continuous usage of mela pro cream with the extract of *Psoralea corylifolia* and regular exposure to sun for 3 minutes over a period of seven days has resulted in 2.1 and 3.3 percentage increase in melanogeneis for 5 and 10 mg/cm^2 respectively.

On the contrary the extent of melanogeneis in the control site was 0.9 Table I.

Seven days continuous usage of mela pro cream without the extract of *Psoralea corylifolia* and regular exposure to sun for 3 minutes over a period of seven days of usage has resulted in 0.3 and 2.3 percentage decrease in melanogeneis for 5 and 10 mg/cm^2 respectively.

On the contrary the extent of melanogeneis in the control site was 0.7 Table II.

TABLE I

The effect of Mela pro cream with Psoralea corylifolia extract on skin pigmentation.

VOLUNTEER code	Reading after 7 days usage								
	CONTROL			5 mg/cm^2			10 mg/cm^2		
	BF	AF	% diff	BF	AF	% diff	BF	AF	% diff
1	485	487	-0.4	510	520	-2.0	546	560	-2.6
2	438	440	-0.5	457	468	-2.4	526	545	-3.6
3	420	421	-0.2	444	451	-1.6	494	510	-3.2
4	545	550	-0.9	573	585	-2.1	592	610	-3.0
5	488	490	-0.4	466	475	-1.9	393	405	-3.1
6	266	268	-0.8	265	269	-1.5	249	262	-5.2
7	336	345	-2.7	350	363	-3.7	380	394	-3.7
8	484	490	-1.2	444	452	-1.8	485	499	-2.9
9	481	485	-0.8	490	500	-2.0	489	502	-2.7
Avg	438.1	441.8	-0.9	444.3	453.7	-2.1	461.6	476.3	-3.3

TABLE II

The effect of Mela pro cream without Psoralea corylifolia extract (vehicle) on skin pigmentation.

VOLUNTEER code	Reading after 7 days usage								
	CONTROL			5 mg/cm²			10 mg/cm²		
	BF	AF	% diff	BF	AF	% diff	BF	AF	% diff
1	470	471	-0.2	515	512	0.6	485	470	3.1
2	420	425	-1.2	460	459	0.2	480	475	1.0
3	419	422	-0.7	434	420	3.2	500	499	0.2
4	552	555	-0.5	560	550	1.8	575	570	0.9
5	475	476	-0.2	450	435	3.3	400	395	1.3
6	270	273	-1.1	266	270	-1.5	235	215	8.5
7	340	345	-1.5	345	351	-1.7	370	365	1.4
8	490	491	-0.2	410	412	-0.5	482	475	1.5
9	485	488	-0.6	444	458	-3.2	464	450	3.0
Avg	435.7	438.4	-0.7	431.6	429.7	0.3	443.4	434.9	2.3

DISCUSSION

The present study has revealed that melapro cream seems effective in trapping both UVA and UVB rays from sunlight. The extent of melanogenesis in mela pro cream with *Psoralea corylifolia* extract was significantly higher than that of control. Further the effect was dose dependent.

When we tested the melapro cream without the active i.e., *Psoralea corylifolia* extract, instead of upregulation of melanogenesis we have observed mild sun protection resulting in reduced melanogenesis.

The above finding strongly indicate that the cream base may be offering weak sun protection hence the pigmentation was less despite sun exposure.

Based on the various research findings, *Psoralea corylifolia* does not have any direct effect on either tyrosinase activity or melanogenesis except DOPA oxidation (9).

In the light of the above findings we presume that increased melanogenesis observed when mela pro cream with *Psoralea corylifolia* extract was used may be due to its photo trapping mechanism. When the effect of sun is increased, naturally the genetic memory of melanocytes are likely to get upregulated to produce melanin to protect the skin (2, 8).

As expected, we found the same biochemical events occurring in the skin when mela pro cream with *Psoralea corylifolia* was used.

We have tested the photo trap mechanism of mela pro cream in normal individuals and hence the same level of result may not occur in vitiligo patients. However the direction is clear although it may take more time to see hyper melanogenesis in the case of vitiligo patients.

In our previous experiment (Data on file) we observed that mela pro cream indeed increase the erythema value as well. This specific effect of mela pro cream in increasing the inflammato-

ry changes in the skin suggests its possible usefulness in the treatment of psoriasis as well.

The oral psoralen preparation is known to produce several side effects (6, 7). Further at least two hours prior to sun exposure or UV therapy, the oral psoralen is to be taken. Whereas in the case of mela procream such systemic side effects are less and within a few minutes of application, sun exposure or UV exposure can be followed. Further the cream base also has weak sun protection effect to protect the skin.

The findings of the study seems to prove the usefulness of mela pro cream in the treatment of vitiligo and psoriasis as 'pro drug'.

We are studying the effect of mela pro cream in trapping in magnifying both narrow and broadband UVA and UVB rays.

However, due to the poor number of subjects involved in this study, which gave no possibilities of a serious statistical control on the obtained results, our aim is to go on and repeat the experience by the use of a more significant number of volunteers to confirm this first study.

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Author Address:

Aruna V.
Dr JRK's Siddha Research and Pharmaceuticals Pvt., Ltd.
No 18 & 19, Perumal Koil Street, Kunrathur
Chennai- 600 069, India
Email: aruna_v@jrksiddha.com

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Chitin Nanofibril: a natural eco-friendly and immunoadjuvant active carrier for medical use

P. Morganti[1], Hong-Duo Chen[2], Xing-Hua Gao[2]

[1] Prof., Skin Pharmacology, Dermatology Institute, 2nd University of Naples, Italy
Visiting Professor, Dermatology Depart., China Medical University, Shenyang, China
R&D Director, Centre of Nanoscience, Mavi Sud, Aprilia (LT), Italy

[2] Department of Dermatology, No.1 Hospital of China Medical University, Shenyang, P.R. China

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Key words: *Chitin nanofibrils; Chitin; Chitinases; Chitotriosidase; Electrospinning; Nanocomposite; Advanced medications; Aesthetic- Medical procedures;*

Summary

Chitin, second polysaccharide in nature, occurs as a polymer based on the N-acetyl glucosamine monomer. This sugar-like compound in its small size dimension has the interesting capacity to enhance the immune response, being non toxic, skin-friendly and environmentally-friendly. Moreover, being it capable to make nanofibrous structure that mimic the ECM of the skin, it may find many applications in the medical field.

By many interesting studies it has been shown how the small size and nano size crystal chitin has the capacity to modulate the skin inflammatory processes, releasing anti-inflammatory cytokines by the activation of the macrophage function.

For the interesting physico-chemical, ecological and biological characteristics of this natural polymer, it may be used to make innovative products for the medical and cosmetic market. This paper reports some market data on the worldwide aesthetic and medical field of cosmetics and advanced medications together with the different possibility to use chitin nanofibrils

Riassunto

La chitina, che rappresenta il secondo più abbondante polisaccaride riscontrabile in natura, è un polimero formato da più molecole di N-acetil-glucosammina. Questo derivato, simile allo zucchero, pos-

siede interessanti capacità immunostimolanti legate soprattutto alle sue dimensioni e caratteristiche chimico-fisiche che lo rendono amico della pelle e dell'ambiente. Può trovare, quindi, molte applicazioni nel campo medico, data la sua struttura nanofibrosa che mima la struttura della matrice extracellulare cutanea (ECM).

Molti studi hanno posto in evidenza come la chitina abbia la capacità di regolare i processi infiammatori, mediante l'attivazione dei macrofagi e la relativa secrezione di citochine, soprattutto quando utilizzata come polimero cristallina puro e di dimensione micro-nano. Questo polimero naturale può trovare impiego per realizzare prodotti innovative per il mercato cosmetico come per quello medico, date le sue interessanti caratteristiche chimico-fisiche e biologiche.

In questo lavoro verranno riportati dati di mercato che riguardano sia il mercato mondiale delle medicazioni avanzate che dei prodotti cosmetici, assieme alle diverse possibilità d'uso delle nanofibrille di chitina.

INTRODUCTION

Chitin is a natural and linear nitrogen-containing polysaccharide monomers of which occur with glycosidically linked components beta 1,4 (1). Organized as a polymer, it is the second abundant polysaccharide in nature and occurs as ordered macrofibrils based on the N-acetyl-glucosamine monomer. However, chitin serves as indispensable structural component in a variety of organisms, such as fungi and arthropods (Fig. 1), resembling human keratin in its structural function. In any way this natural polymer, that differs from keratin for its structure, has a great potentiality of use in the medical field.

It has, in fact, interesting haemostatic activities and capability to enhance the immune response and wound healing functions (2-4). Differently from the synthetically substituted cellulose compounds, the biocompatibility, biodegradability and adsorption properties of chitin and its derivatives are considerably higher and more eco and skin friendly (5). Moreover, the three-dimensional (3D) structural organization of this natural polymer (Fig. 2) results essential to initiate appropriate cell-cell interactions when used as support for tissue engineered scaffolds. In addition, the human body generates enzymes that degrade chitin, thereby making this polysaccharide useful for in vivo medical applications also (6-8). Finally, being easily metabolized by endogenous human enzymes and possessing eco and bio compatible characteristics, chitin can be used as a safe product free of toxic side effects. Compared to proteins, in fact, this polysaccharide is more stable, providing biomaterials with the required mechanical properties, processability into various forms, and possessing also the right aqueous stability, with abundant availability at low cost (9). At this purpose chitin, that represents the more abundant raw material after cellulose, may be used to make nanofibrous structures, which mimicking the skin extracellular matrix (ECM), has also the same backbone of hyaluronic acid (Fig. 3).

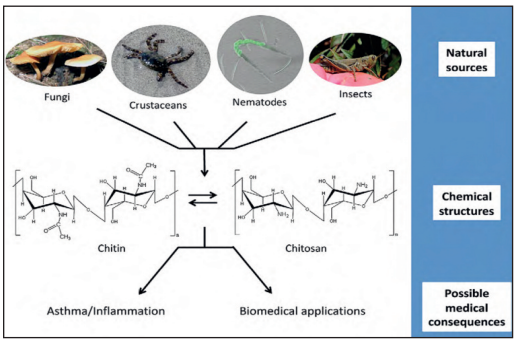

Fig. 1 *Chitin is an indispensable structural component of fungi and arthropods.*

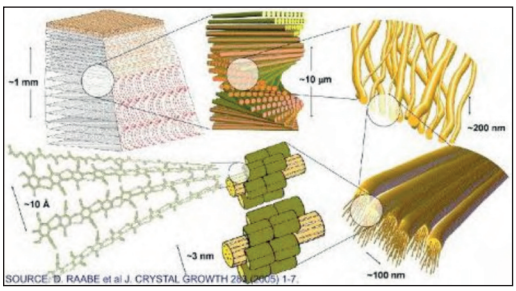

Fig. 2 *Natural structural organization of chitin.*

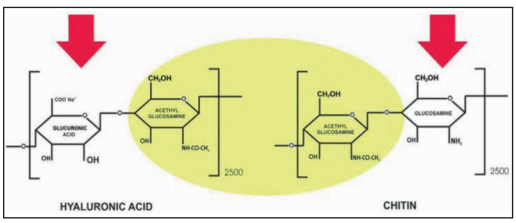

Fig. 3 *Chitin has the same backbone of hyaluronic acid.*

Chitin nanofibrils

Chitin nanofibrils (CN_s) with a mean dimension of 240x7x5 nm, has been separated from their amorfous part by an industrialized patented process (10), and produced in the purest and crystalline structure for optimizing its performances. These nanocrystals have been used, therefore, as active ingredient delivery system and as natural

carrier for improving the efficacy of bioactive molecules (11-13). This polymer, formed by alpha chitin nanocrystals, is made by chains arranged in anti parallel fashion which favours strong hydrogen bonding. Thus, the degradation kinetics, length of the chains, and the random and homogeneous distribution of the acetyl groups, seem to be inversely related to the degree of crystallinity which is controlled mainly by the degree of de-acetylation of the adopted purification process (10). Accordingly, its application may go from the generation of innovative emulsions effective as anti-aging (14) or whitening cosmetics (15) to the production of non-woven tissue matrices (Fig. 4) for making innovative beauty masks (16) or advanced medications (17). By water degradation of these innovative non-woven tissues, beneficial ingredients for both aged or diseases skin are released (16, 17). Another important characteristic of the CN-matrices, made as non-woven tissues or films, is their biocompatibility, which is related with the acceptance and the timely degradation of the material by human tissues. It is interesting to underline, in fact, that CN and its related matrices are completely degraded by the environmental chitinases and human chitotriosidases (Fig. 5) (8) to glucosamine/acetyl glucosamine for the synthesis of glycan (Fig. 6), or to glucose, used as energy by the mitochondrial activity (Fig. 7). Glycans, in fact, play many critical roles in/or the normal function of both healthy and abnormal cells, providing them a protective extracellular matrix. Additionally, they are implicated in many cell signalling pathways, such as protein trafficking and immune system activity.

Thus, the CN catabolities are easily and completely utilized as active ingredients from the skin cells life. Moreover, to respect the principle of green chemistry (Fig. 8), the solvent processing to make these non-woven tissues and films, has been based on water, while all the entrapped active ingredients were of natural origin. Therefore, by this new technology based on the use of CN-derived matrices (scaffolds), no toxic by-products and contaminants have been produced and none of the carrier-tissues caused skin hypersensitive reactions. The rate of degradation of CN-scaffold seems to mirror and respect necessities and rate of the new skin regeneration and to be adequate for the controlled release of bioactive ingredients (11-17). Thus the innovative CN-non-woven tissues and films, together with the active molecules, included into these renewable polymeric matrices, have been not only controlled in advance for their physicochemical features but have been also considered for their possible allergy and sensibility action provoked by their use. (data not reported). However, it has been verified that, both this natural polymer and the scaffolds produced have shown to combine several advantageous properties both physicochemical and clinical.

Among the former high stability and hydrophilicity can be mentioned, and among the latter low toxicity, good biocompatibility, and biodegradability both *in vitro* and *in vivo* can be evidenced (18-20). In our opinion, the non-woven tissues based on the use of natural polymers such as chitin nanofibrils and chitin-derived compounds, could have a great application as innovative cosmetic carriers to be used, for example, during the aesthetic procedures in Medical Offices and/or in Beauty Centers. More people, in fact, perceive cosmetic enhancements and medical procedures as essential. To preserve a young look, is considered a commodity and for this reason people are investing in themselves to maintain a younger and healthier appearance. At this purpose, social media play an important role in encouraging or inspiring a person to enhance his/her body by the use of cosmetics and/or medical procedures. This is the reason why just over the past five years medical procedures have increased more than 30% in the US.

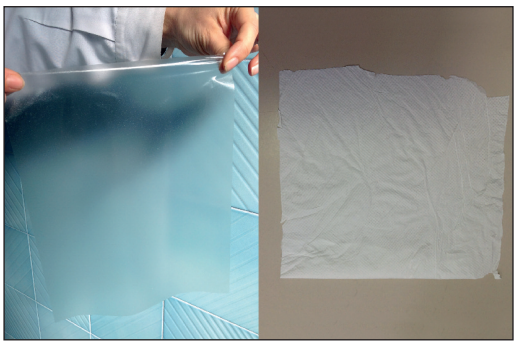

Fig. 4 *Matrices made by the use of chitin nanofibrils. On the right non-woven tissue and on the left film.*

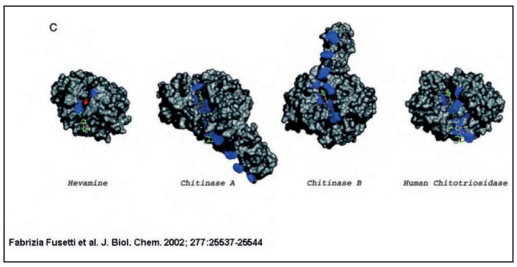

Fig. 5 *Molecular structure of chitinases and chitotriosidases.*

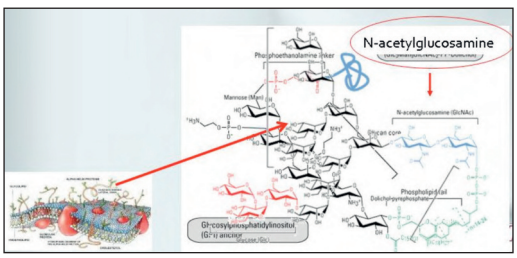

Fig. 6 *Acetyl glucosamine as part of the glycan structure.*

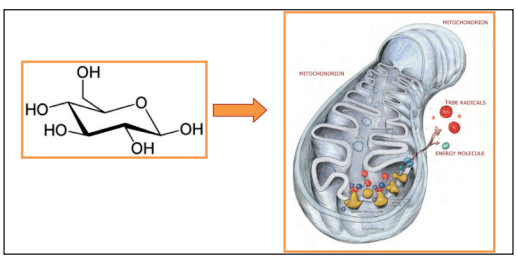

Fig. 7 *Glucose used by mitochondries to produce energy.*

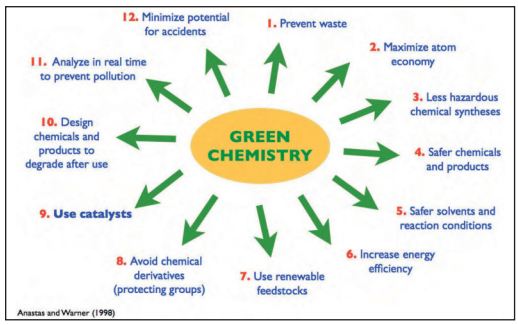

Fig. 8 *The principles of green economy.*

The aesthetic medical market

According to the American Society for Aesthetic Plastic Surgery (ASAPS) (21), Americans spent in 2015 more than $13.5 billion on combined (surgical and non-surgical) aesthetic procedures, reflecting a $ 1.5 billion increase from 2014. Of these procedure surgical accounted for 58% and non-surgical for 48%; $ 3.5 billion of non surgical aesthetic procedures were determined by: botulinum toxin (4,267,038 procedures with a total expenditures of $ 1,354,742, 009); hyaluronic acid (2,148,326 procedures with a total expenditures of $ 1,269,519,548); hair removal by laser or pulsed light (1,136,834 procedures with a total expenditures of $ 289, 006, 022); and chemical peel (603, 305 procedures with a total expenditures of $ 379,050,763). Moreover, on one hand the global market for advanced drug delivery systems has been valued at $ 151.3 billion in 2013, forecasted to reach nearly $ 173.8 in 2018 and $ 330.70 billion by 2025 with an annual growth of 7.8% (22), while the advanced wound care segment is the fastest area with a yearly double-digit growth of more than 10%, driven by an aging population. The number of aged people, in fact, has increased from a global share of 9.2% in 1990, to 11.7% in 2013 and is expected to reach 21.1% by the end of 2050 (Fig. 9). Additionally and according to WHO (23), 300,000 deaths per year are attributed to fire-

related burn injuries, while 6.5 million individuals suffer from chronic ulcers (24). For obvious reasons, all these patients need advanced and effective medications.

On the other hand, the global cosmetic market has been of $ 460 billion in 2014 and it is estimated to reach $ 675 billion by 2020 (23). It is interesting therefore to underline that the same non-woven tissues realized may be used to make both Beauty Masks for slowing down the aging processes, as well as to produce advanced medications necessary for increasing the quick re-epithelialisation of a wounded or burned skin. The only difference between the two tissues used for beauty purposes or as medications, is due to the active ingredients entrapped into the CN-matrices.

About the market EU and USA countries are expected to maintain dominance in the global market of both cosmetic and medications, while Asian market is expected to witness the highest growth, in the years to come (25, 26).

For all these reasons and to keep up with the demand of the market, it could be necessary to use innovative tools and products.

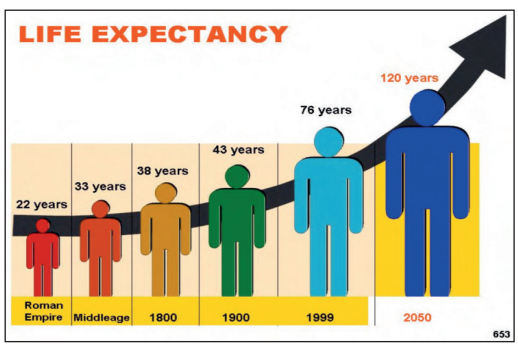

Fig. 9 *The aged people is estimated to reach 21.1% by 2050.*

Medical science and biotechnology

Medical science and biotechnology are playing a great role to improve and maintain normal physiological properties of skin affected by the aging process or degraded by burns and wounds. Thus the increased demand of natural and biodegradable materials -as the biopolymer CN- to be used for formulating innovative Clinical Correct Cosmetics® and making new products for medical aesthetic procedures (27). At this purpose, the potential applications of chitin and its main derivatives, in fact, are estimated to be more than 200 (28). Naturally all the biopolymers have to possess specific properties like, biocompatibility, high bio-activity, low antigenicity, appropriate mechanical properties and processability and, of course, to support cell growth and proliferation, and being biodegraded to non-toxic end-products also. In addition, when used to make non-woven tissues or films, these biopolymers have to possess an optimal surface-area-to-volume ratio, crystallinity, adequate pore size, and porosity for enabling easily diffusion of the active ingredients through human tissues (29) and/or mucous membranes. CN and chitosan used as carrier, could act as permeation enhancer (30) showing also interesting muco-adhesive properties, based on the interaction of their positive charges with the negative charges of skin and mucous membranes (31). They seem capable to reorganize the tight junction-associated proteins, localized between epidermis and dermis (32), and interacting by electrostatic forces with mucin, which serves to protect mucous membranes in mammals (33). Moreover, chitin and its derivative compounds could accelerate natural blood clothing by activating platelets and stimulating proliferation of fibroblasts, and the cytokine production through macrophage activation and angiogenesis regulation (2,11-13). In addition, they show antimicrobial activity against bacteria, yeast and fungi by different mechanisms by preventing or chelating the transport of essential nutrients through their cell surface and/or inhibiting the RNA and protein synthesis

(30, 34). Due to this interesting activities, CN has been used by casting solution or electrospinning technology with other natural polymers and active ingredients to produce innovative films or non-woven tissues for aged, wounded, and burned skin (17-20). The paucity of cellular and molecular signals, essential for wound healing, makes difficult the skin heal. The electospun nano fibrous scaffolds, providing similar architecture to the ECM, lead to enhancement of cell adhesion, proliferation, migration and new tissue formation. For these reasons, silver bound to CN and collagen of marine origin, used together for making fibrous scaffolds non-woven tissues by electrospinning, have balanced and modulated the cellular behaviour wound healing and skin regeneration (35). The effective re-epithelialisation of the burned skin (Fig. 10) shown by these innovative films and non-woven tissues is probably due to the activity of both keratinocytes and fibroblasts. These specialized cells, utilizing more easily some of the amino acids of the marine-collagen, have positively interfered with the skin cell network, offering to the neo-tissue growth the right tensile strength (36). Moreover, the nano-sized silver bound to the CN carrier at a very low concentration (20 ppm) and used with chitosan (CS) for the nano-composites production, has been useful to maintain the normal level of free-floating microorganisms, eliminating the formation of the pathogenic bacterial biofilm also (Fig. 11) (36).

In conclusion, it has been shown that probably these innovative CN-nano-composites could involve formation of new cells helping the secretion of ECM by fibroblasts followed by the keratinocytes formation and proliferation. All these steps, fundamental for restoring, maintaining and improving the tissue function, it results necessary to regenerate the outmost layer of the epidermis altered by aging processes or by wounds and burns. Over and above the biological activity of micro and nanoparticles are continuously investigated as carrier and drug delivery systems (37). These polysaccharides, in fact, possess new pharmacological properties, such as special route internalization, selectivity, segmentation and slow release. But what the forecast activity of chitin and chitin-derived compounds?

Chitin and chitinases in mammals

As previously reported, the chitin catabolites, such as acetyl glucosamine, glucosamine and glucose are covalently bound to various proteins and lipids, involved in the complex synthesis of the glycoconjugates populating the surface of mammalian cells (38). At this purpose, these surfaces may contain as 10 million N- or O-linked glycans attached to proteins which are also present in all mammalian body fluids (39). In addition, it is estimated that the human genome encodes over 900 proteins involved in glycan assembly or recognition (40). Thus, glycomics is now being used with, epigenomics, proteomic, lipidomics and metabolomics to better understand the cellular functions in healthy and diseases state (38, 41).

Moreover, mammals produce chitinases that, amplified during many infections (42), is associated with pathological conditions such as fibrosis (43), allergy (44), and asthma (45). These enzymes with chitinolytic activity are thought to play a role in the innate immune and adaptive type 2 immune response to fungal and parasitic infections (46). In any way, mammalian cells do not contain chitin, but they produce several forms of chitinases, including chitotriosidases (CHT1), acidic mammalian chitinase (AMCase), and other chitinases. Given the importance of chitin for a variety of pathogens, it makes sense that humans have evolved mechanisms to recognize and respond to chitin exposures. Thus, the connection of chitin not to the cell, but to the host response and inflammation, has been recognized (47). Recent data, in fact, sug-

gest that fungi may play a larger role, particularly in the contest of severe diseases, highlighting the expanding awareness of fungi in asthma, recognized from World Health Organization (WHO) as a major public health concern (48). According to the Global Asthma Network, asthma may affect almost 334 million people! (49). However, it is interesting to underline that different chitin preparations, of different sizes, have shown different effects, activating inflammation via different mechanisms (50). While large chitin fragments were inert, intermediate-sized ones (49-70μm) had an inflammatory activity stimulating the of IL-17 and TNF-alpha production, and the small chitin (<40 um) induced an anti-inflammatory activity by the production of IL-10, as it seems to happen in asthma disease also (Fig. 12).

These data support the results obtained from our group who has shown the anti-inflammatory activity of chitin nanofibrils by *in vitro* and *in vivo* studies (11-20). Thus on one hand, the purified polysaccharide CN for its high crystallinity degree, colloidal behaviour, and nanosized dimension, has probably the ability to stimulate macrophages to produce anti-inflammatory cytokines and other compounds which, significantly down-regulate and depress the development of adaptive type 2 allergic responses. On the other hand, the nanosized chitin could augment the evolution of adaptive immunity responses by the formation of chitin-containing antigens, being chitotriosidase the major chitinase enzyme in human respiratory tissues (51, 52).

Moreover, despite its ubiquity, this natural polymer does not accumulate in the environment because chitinolytic bacteria or saprophytes efficiently recycle most of the chitin in nature (53).

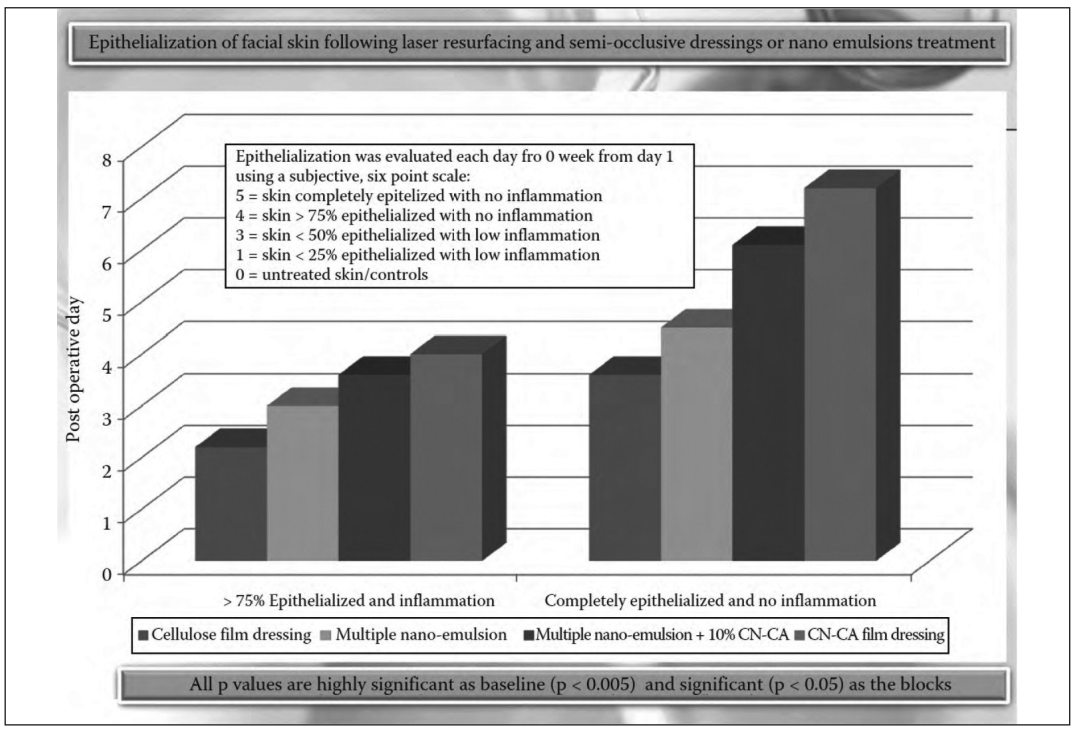

Fig. 10 *The re-epithelialization of the skin after laser treatment.*

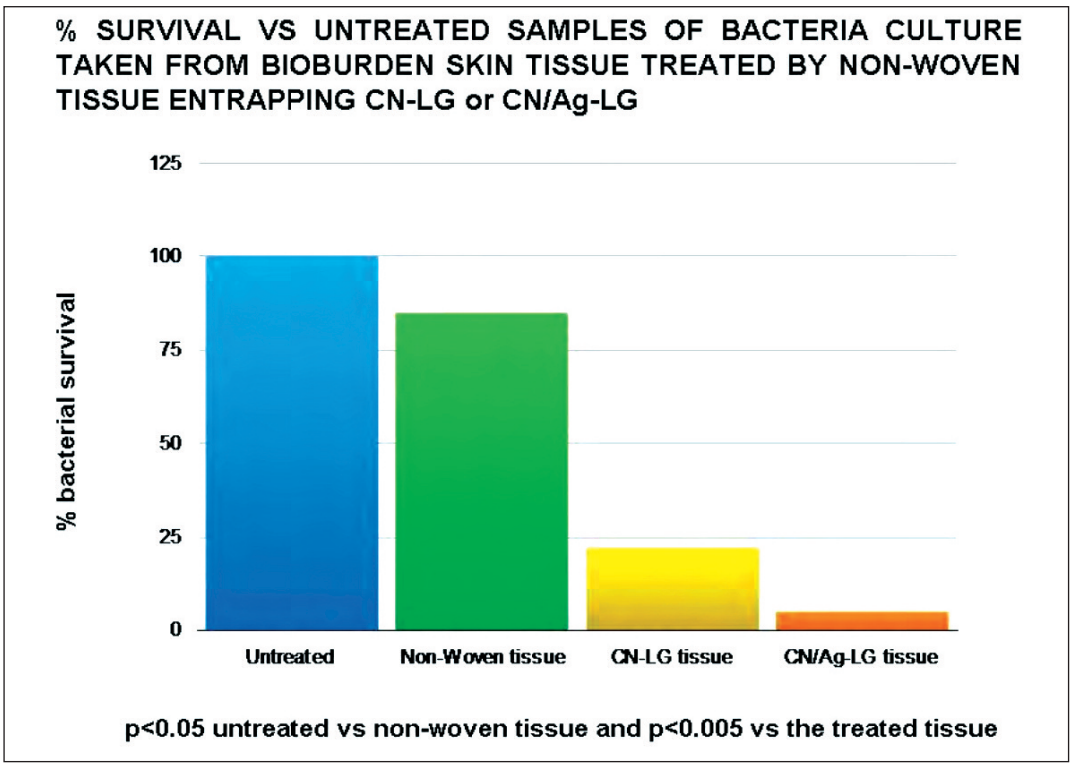

Fig. 11 *Slowdown of microbial skin growth after treatment by a CN-Ag-non-woven tissue.*

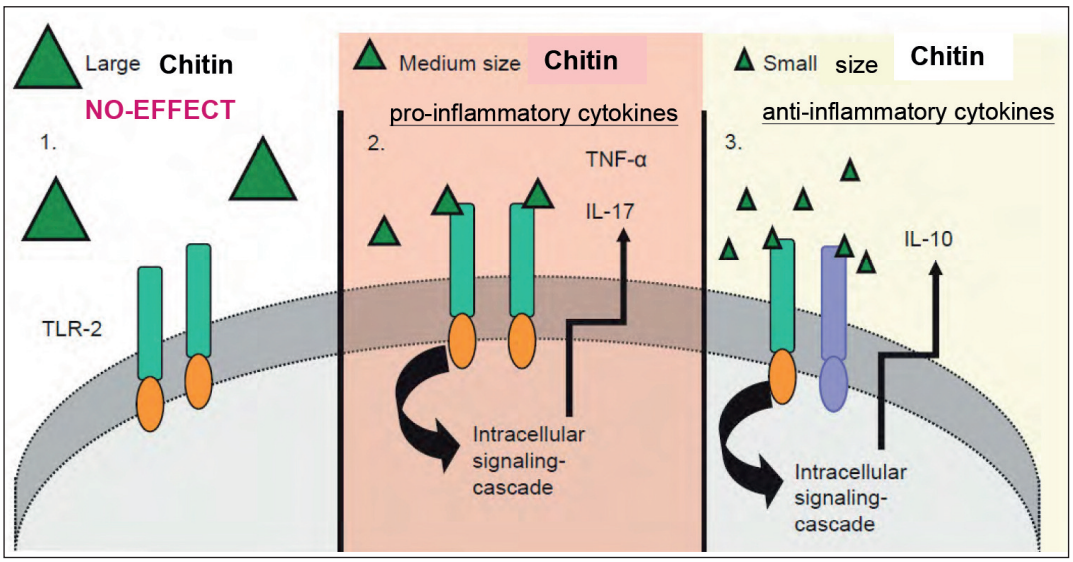

Fig. 12 *Antiinflammatory activity of different sizes of chitin.*

CONCLUSIONS

Chitin nanofibril, for its natural origin and for its bio-friendly /biodegradation characteristics, may find many applications in the medical field, such as vehicle for a controlled delivery of drugs, cosmetics, food and other different biological molecules, or as active ingredient to fastening the wound healing activity and/or as biological polymer to realize hard and soft tissue engineering applications. By this polymer, in fact, it is possible to produce porous scaffolds that, mimicking the natural ECM, can facilitate the appropriate cell infiltration, proliferation and differentiation.

Additionally, due to the possibility of obtaining varying degrees of porosity, the CN-scaffolds could be used as excellent carrier to supply nutrients and oxygen for the cells, being also a source of active ingredients when metabolized from chitotriosidases.

Finally, the right manipulation and engineerization of its molecular structure could open emerging biomedical applications ranging from high-throughput cell culture platforms for innovative natural biomedical devices or innovative carriers useful to solve, for example, the great problem of asthma and other allergic diseases. Moreover, the development of bio-smart surfaces, nanocomposites and nanoparticles with the function of controllable capturing and releasing of biochemicals could be also produced and used to make innovative fast theragnostics (54). The realization of these innovative products could have a strong influence for the medical science, representing a worldwide challenge for all scientists and people involved in the research field.

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Author Address:

Pierfrancesco Morganti Ph.D.
R&D Director Nanoscience Center
Mavi sud S.r.l.
Viale dell'Industria 1
04011 Aprilia (LT) - ITALY
Email: pierfrancesco.morganti@mavicosmetics.it

Green Organic Chemistry and its interdisciplinary Applications

By Vera M. Kolb

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According to the US Environmental Protection Agency and the US Pollution Prevention Act of 1990, the *Green Chemistry* is the "design of chemical products and processes that aims to reduce or eliminate the generation of hazardous substances".

This innovative chemistry is based on 12 principles developed by Anastas and Warner in 1998, i.e. 1) preventing waste; 2) maximizing the incorporation of all materials into the final product by the so called *atom economy*; 3) organizing less hazardous chemical synthesis; 4) Designing safer chemicals with the minimum toxicity possible; 5) using safer solvents and auxiliaries; 6) increasing energy efficiency; 7) utilizing renewable feed stocks; 8) reducing the production of unnecessary derivatives; 9) substituting stoichiometric reagents with the more selective enzymatic catalysts; 10) designing products that break down into innocuous degradable ingredients; 11) analyzing and preventing in real-time the air/water pollution; 12) minimizing the potential of chemical accidents.

Thus, the green chemistry aims to design and produce cost-competitive chemical products and processes that attain the highest level of the pollution-prevention by reducing pollution at its source.

To reduce waste and environmental contaminants, it is necessary to modify equipments, technologies, and processes, redesigning the products and substituting the natural materials with by-products obtained from industrial and agricultural biomass. This the topic of the book that, in **13 chapters**, underlines how the *green chemistry*, considered for creative thinking, became a necessity to reduce and eliminate the hazardous pollution invading our planet. Several major environmental disasters, in fact, have been caused by the release of toxic ingredients into the environment due to the production, for example, of pharmaceuticals, agricultural chemicals, and different plastics obtained by organic synthesis that involve toxic starting materials, reagents, catalysts, solvent, and by-products.

On one hand, rapid advance in chemistry brought numerous benefits to the society, alleviating many diseases by the discovery of new effective drugs, rendering more productive agriculture, or revolutionizing the production of automobiles, furniture, and household products with the introduction of plastics. On the other hand, toxic materials have been released on the air or dumped into rivers, lakes and oceans, thinking that their dilution would not be hazardous anymore. Thus the necessity to use benign chemicals instead of the toxic one, developing benign chemical processes and redesigning the old chemical processes for making them more safe. At this purpose, the green chemistry became a new paradigm in which chemistry has been reinvented and putted into practice, with an emphasis

on the new synthetic methods, reaction conditions, catalysts, analytical tools, and industrial processes, that are all nonhazardous and environmental and human friendly.

This is the reason why green chemistry requires creative work or has to invent and put into practice new chemical reactions and processes to realize its principal tenet of being a benign chemistry. However, a large number of chemical reactions and processes, that are not green, are still in place and require innovative green-thinking to reduce waste. "It is better to prevent waste than to treat or clean up waste after it is formed" according to the principle formulated by Anastas and Warner. If chemical waste is hazardous, in fact, its separation from the desired product(s) and its final disposal may require special handling and protective expensive equipment.

In conclusion, hazardous waste is generally costly to dispose of, so that to design non toxic chemicals it will be necessary to learn as possible about the reasons why some chemicals are toxic and some others not. Additionally, it should be necessary to predict in advance if the chemical to make would be toxic and /or have toxic effects on humans or not. At this purpose it should be useful to know the structure-activity relationship, correlating selected parts of the designed chemical structure to a particular biological function by innovative methodologies. Innovation, in fact, refers to the implementation and application of novel ideas and methods, whereas invention produces new or improved strategies, products, services, or processes for trying to solve unsolved problems. Innovation, at the base of green chemistry, uses in fact critical thinking to identify and examine the reasoning errors and re-evaluate the accepted paradigms, creating sufficient conditions for a new creativity.

Because chemists believed that organic solvents increase mobility of the reactants' molecules, the organic reactions were always done in solvents without questioning this practice.

With the birth of the green chemistry movement, the negatives about the use of organic solvents, as a reaction medium, came to light. Many organic solvents are toxic to humans and after life, may be hazardous to the environment. In addition, they may be flammable or explosive. Thus, the in-water and on-water reactions were implemented by green chemistry together with the use of green engineering, focused on how to achieve sustainability through science and technology. As a consequence of this principles the products have to be designed to be durable, i.e. biodegradable, rather than immortal and therefore, persistent in the environment, such as plastics.

Green chemistry and green economy state that material and energy inputs should be renewable rather than depleting. The ultimate goal is sustainability that has economic, social, and environmental aspects. Sustainability, in fact, is a broad term that meets the needs of the present without compromising the ability of future generations to meet their own needs. For example, fossil fuels, such as petroleum, natural gas, and coal, are not renewable and their continues use is not sustainable. In contrast solar, wind, and hydro energy sources are renewable and, therefore, sustainable. Thus, because petroleum and gas are non-renewable resources, the greening of chemical industry needs to involve steps of replacing these raw materials with renewable ones.

In conclusion, the green economy is based on the production of eco-friendly chemicals designed "so that at the end of their function they do not persist in the environment and breakdown into innocuous degradation products".

In addition, environmental chemistry is concerned with the ways chemical pollutants affect living organisms and ecosystems, and the way the negative impact of these pollutants can be neutralized and reversed by natural means that are available to the ecosystems.

All and other news on the green chemistry and its applications in pharmaceutical, food, analytical and environmental chemistry are reported and clearly discussed in this interesting book useful not only for students but for scientists of both the chemical and medical community that like to know and learn the significance of this new brunch of organic chemistry, which is expanding worldwide day by day.

P. Morganti
Editor-in-Chief

Essential Oils. Contact Allergy and Chemical Composition

by Anton C. de Groot and Erich Schmid

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The essential oils, which the plant releases affect our nervous system and just for their potential aroma therapists use them as relaxation aids in the form of massage oils and vaporizers. Although there is something mysterious about the sense of smell, it is a simple process in which the highly sensitive nerves in the membranes lining, perceive volatile compounds in the air by the nostrils. They, in fact, stimulate the nerves in the olfactory organs, which are linked directly to the parts of the brain that control the emotions. Additionally they stimulate the nerve endings on the skin surface, and it seems that their effect passes back along the nerves until it eventually reaches the pituitary gland. This gland, in fact, controls all the body's other glands, including the adrenals, which, in turn, regulate our stress by a relaxation response. However, most of us find the fragrance of lavender or roses pleasing, but few of us realize that the emotional uplift these essential oils provide is due to more than their scent or beauty, to the direct activity on our nervous system. Thus, growing plants in and around the home remind us how close and important our relationship with the world of plants can be, and how essential this relationship is to our well-being.

Today that the scientists have discovered the full extent of the damage to our health that can result also from chemical toxins and allergy ingredients in products as air fresheners and skin cleansers, the time is ripe for a renaissance of the knowledge and use of natural products as the essential oils.

The gentle, right, and balanced action of essential oils and herbs may be healthier not only for our bodies but also for the environment, and allows us to bypass products that contain harmful chemicals, and those that have been made or packaged with scant regard to the earth's resources. The essential oils that are used in beauty and skin-care and for home-care products are the ones that are most enjoyable to grow and have around the home. Many of them are fragrant, like lemon balm, rosemary, and the different species of rose. Others have properties that benefit the skin nourishing, soothing, and healing blemishes, such as the healing oils in lavender, the soothing as melissa and bergamot in helping the body to fight infections.

This book, organized in **6 chapters**, reports many scientific information presented in different sections, evidencing also the negative effects associated with the essential oils use. However, the concept of the innate wisdom of body mind, and spirit has not been forgotten. Natural healing, in fact, is founded on the basic principle that the human organism possesses the inherent ability to protect regulate, adjust, and heal itself. This innate wisdom has been often termed the vital force, not only from the Chinese philosophic way of living, but also from antique Romans with their *Vic medicatrix naturae*.

In any way, the ability to maintain a steady internal state, despite the onslaught of powerful external influences which threaten to upset our equilibrium, is known as the body homeostasis.
The goal of the book has been not only to introduce dermatologists and cosmetic chemists to the essential oils cause of contact allergy or allergic contact dermatitis, but also to give them their chemical compositions. This reason of the two specialized authors: the dermatologist Anton C. de Groot and the chemist Erich Schmidt.
By the use of this book dermatologists can adequately diagnosing their patient with suspected contact allergy from essential oils counselling them the right therapy. They, in fact, may be facilitated in diagnosing a probable allergic contact dermatitis by a more deep knowledge of the essential oils composition. Thus the patients may avoid contact with those fragrances and fragranced products containing the chemical compounds recovered by the patch tests. In this way, every patient who wants to continue having contact with certain essential oils, may be informed which oils are safe to use and which should be avoided.
While **chapter 1** provides general data on chemical composition of essential oils, **chapter 2** reports their general aspects, **chapter 3** is focused on contact allergy caused by these oils, **chapter** 4 reports chemicals identified in essential oils which have caused contact allergy, **chapter 5** describes the chemical composition of and contact allergy to essential oils, and **chapter 6** presents an alphabetic list of all chemicals which have been identified in the 91 essential oils and two jasmine absolutes reported.
However, it is to remember that essential oils can be obtained from around 30,000 plant species, 600 of which are or have been used in the past. Today, the number of essential oils produced is limited to about 150, of which 70-80 are high-volume products, so that in 2009 the world production was over 120,000 metric tons. They, in fact, have many applications in foods, beverages, cosmetics and perfumes, but are also widely employed as pharmacological agents in medicine i.e., traditional medicine, folk medicine, Ayurveda and aromatherapy.
Aromatherapy, in particular, has considered the therapeutic application of essential oils and aromatic plant extracts in a holistic contest to maintain or improve physical, emotional and menfolk well-being.
At this purpose, it is important to remember that essential oils are multi-component mixtures each component of which may contain up to 400 chemicals or even more, when sophisticated analytical equipments and methods are used. However, the largest group of chemicals, found in essential oils, consists of terpenes and the most important ones are the monoterpenes and the sesquiterpenes which, by their volatility, create the perceived typical odour. Chemical modification of these terpenes produces compounds termed terpenoids by the creation, for example, of subgroups like alcohols, aldehydes, phenols ethers and ketones. In any way, it is to underline that the composition of essential, oils can vary considerably from country to country from producer to producer, and even from year to year for the same producer and crop.
Important parameters, in fact, are related to the plant (species, cultivar, variety), to the environment (climatic and soil conditions, water, fertilization) to harvest and post-harvest conditions (mode and duration of storage, pre-distillation conditions, etc), the mode of production and other factors, such as the analytical procedures adopted. At this purpose, for example it is also to remember that when the essential oils are stored under the wrong conditions (i.e. too warm, exposure to light and oxygen) a chemical process called aging occurs. As a result of reduction and/or oxidation of chemicals, the composition of the oil changes.
The main problem of the aging process may be the formation of peroxides and hydroperoxides acting as strong allergens. It is well known, for example that important essential oils ingredients, such as

linalool, limonene, geraniol and citronellol are weak contact allergens, and that their auto-oxidation products have far stronger sensitizing capacities.

While in literature search the authors of this book have found 79 essential oils which have caused contact allergy or allergic contact dermatitis, in chapter 4 they have presented 110 chemicals cause of allergic reactions. Some are well-known allergens, others have been cause of allergic reactions infrequently, rarely, or even only once. This is because a number of chemicals reported to be present in essential oils, may have been identified incorrectly; some have apparently not be found in nature so far and are known to be synthetic compounds. Nevertheless, as it is impossible to definitely exclude their presence in nature, the authors have opted to include these chemicals in the list. Just to identify correctly the chemicals reported, they have been presented by the name of the compound, as number, availability as commercial test preparation, important synonyms together with some additional information and one or more relevant literature references.

The main part of the book is represented by chapter 5, comprosed of 878 pages. In this chapter, literature data on contact allergy to and chemical composition of essential oils are presented. It is organized by 91 subchapters of individual essential oils and 2 of jasmine absolute, selected on the sole criterion of having caused contact allergy. All the subchapters, which have the commonly used oil name as title, have a standardized format and present the following sections: definition, which include the common name, ISO name (International Organization for Standardization), the source species' botanical name and the plant part(s) used for obtaining the essential oil; INCI name (International Nomenclature Cosmetic Ingredients), used in the European Union and USA systems; CAS (Chemical Abstract Service) number; EINECS number (European Inventory of Existing Chemical Substances). Moreover, the plant, the oil and their uses are reported, providing general information on the oil's source plant, its origin and cultivar.

Finally chemical composition is reported together with the case reports on contact Allergy/Allergic Contact Dermatitis recovered in literature. As previously reported, on chapter 6 the alphabetical list of all the chemicals identified in 91 essential oils and two jasmine absolutes are discussed and reported with their CAS Numbers by 117 pages.

This interesting book, written by two well-known scientists, results a fundamental tool to be kept in the library as consultant mean useful not only for all students of the chemical and medical community, but also for dermatologists and cosmetic chemists, who wish to know the chemical composition of the more known essential oils and understand their capacity to cause possible contact allergy. The review of the book has been important for me also because I had the occasion to meet personally and live friendly with dr de Groot many years ago on the occasion of the 2nd International meeting on Cosmetic Dermatology, held in Rome on May 19-22,1987, during which he takes a speech on the risk of sensitization of the cosmetic preservative Kathon C.G.!

In the same years he edited the first and successful book in the Unwanted Effects of Cosmetics and Drugs used in Dermatology.

I think that also this book will represent a milestone for Dermatologists and Cosmetic Chemists. This is my hope.

P. Morganti
Editor-in-Chief

Handbook of Sustainable Polymers Processing and Applications

by V.K. Thakur and M. K.Thakur

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Email: t&fcredit.control@informa.com

Sustainability deals with design and management procedures that, coinciding with natural processes, minimizes waste production and safeguards the natural systems. Consequently, the sustainable business meets the needs of the present world, without compromising the ability of the future generations to meet their own needs.

Air and water pollution released from industrial, agricultural, and household wastes, in fact, has contaminated our environment to such an extent that it definitely requires a rescue plan to save our planet. Thus, the design of eco-friendly chemical/products needs to be informed by the findings of environmental chemistry. Products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation compounds.

The bio-accumulation of toxicants is the reason why the World Health Organization states that 2.4 million people die each year from causes directly attributable to air pollution, with 1.5 million of these deaths attributable to indoor air pollution. At this purpose, synthetic polymers have been used in great quantity for the past decades for a number of applications, becoming an important commodity to enhance comfort and quality of life. As a consequence, the most of these plastic materials, derived from fossil sources, have contributed to many of the environmental issues since plastics are generally labelled *unsustainable*. These polymers, in fact, are durable and degrade very slowly, and the molecular bonds that make plastic so durable make it equally resistant to natural processes of degradation.

Despite these shortcomings, it is hard to imagine our modern society without polymers. In the process of solving these problems scientists, such as biotechnologists, play a vital role in providing arrays of solutions to reduce pollution creating new and innovative products. Because petroleum is a non renewable resource, greening of chemical industry needs to involve a critical step of replacing petroleum with renewable resources. Thus, the necessity to produce natural and more environmentally-friendly polymers, synthesized by biological systems through *green* technologies, such as for example, by the use of enzymes as catalysts.

While on one hand researchers have been working to find methods to degrade the existing plastic; on the other hand, they are also working on the development of biodegradable plastic. This book, comprising **25 chapters**, reports the new processes and applications recovered for the more used and sustainable green polymers.

The polymers family comprises the largest output of the chemical industry, about 80%, also creating about one-third of the revenue in the basic chemicals category, classified in five major groups: plastics, fibers, rubbers, adhesives, and coatings. But what a polymer is? Polymer is a high-molecular-weight molecule made up of a small repeating subunits termed as monomers which, as low-molecular-weight compounds, can be connected together to give a polymer. These compounds in fact, are macromolecules characterized by the presence of repeating blocks of covalently linked monomers which give them different functional properties and applications. Basically, there are two families of polymers: synthetic macromolecules, produced by normal man-made chemical processes by polymerization of chemical monomers, or natural macromolecules synthesized by some biological systems through specific metabolic pathways by polymerization of biological building-block monomer groups, obtained from the inexpensive waste. However, in biological systems, synthesis of these polymer macromolecules, such as DNA and RNA, is a highly complicated and precisely regulated process not easy to be reproduced. Thus, all the chapters report definition classification, synthesis, mechanical performance, mechanisms of biodegradability and applications of many synthetic and natural polymers to be used as an alternative to plastic.

Among the many applications, innovative textile processing have been reported as well as the use of eco-friendly polymers as super adsorbent compounds for agricultural applications or for their important role in the medical field as drug carrier to ameliorate, for example, the transdermal drug delivery, wound closure or vascular grafts. It is however to underline that with the rapid development of modern industry and living standard, the problem of environmental pollution became more serious, as municipal wastewater, dying, printing, textile, domestic sewage etc. This is the reason why plastics have gathered a rather bad reputation as they are able to resist degradation and therefore accumulate in the environment.

The introduction of oil-based polymers such as polyethylene, polypropylene for the industrial packaging, for example, has truly revolutionized the market. Thus, contamination of air, soil, and surface water with organic and inorganic pollutants is recognized as a problem of growing importance.

These polymers, in fact, are typically divided into *commodity plastics*, which are high volume and low cost, such as packaging films, flooring, and carpeting, and *engineering plastics*, which are lower volume and higher cost, such as aircrafts, computers, and automobiles. Thus, despite the advances in polymer synthesis and processing, their end of life still poses a great problem.

The first choice for processing plastic waste is reuse, but only some plastics can be reused after proper processing. Many of those are difficult to recycle, so that, for example, it is estimated that of the 57 Mtonne of EU plastic waste, only 26.3% gets recycled!

For this reason polymers derived from renewable resources, also known as green polymers, are gaining increasing attention, also if they account today only for 1% of the global market of synthetic plastics. However, the market for degradable and sustainable plastics grows about 20-30% each year, being considerably higher than the total market growth. At this purpose, two are the strategies to overcome the negative view on plastics.

The first strategy is focused on the sustainability, realized with the selection of naturally occurring polymers, by polymerising monomers derived from the natural biomass and the use of environmentally-friendly synthesis routes.

A second strategy is focused on minimizing the environmental impact of plastics by applying more efficient sorting and recycling methodologies. In any way, materials and polymers used should: (1)

be non-toxic and generate non-toxic degradation products; (2) possess suitable properties for specific applications; (3) be economically viable, (4) show tunable degradation kinetics via polymer modification; (5) be processable via standard technique, reducing or eliminating the use or generation of feedstocks, products, by-products, solvents, reagents, etc., that are or could be hazardous to human health or the environment.

In conclusion, the increasing concerns about the environmental degradation caused by conventional polymers have directed worldwide research toward renewable resources. As a consequence, the use of bio-based materials, composite materials and nano-sized materials are receiving wide attention together with the chemical routes for incorporating them into innovative polymers. Thus, innovative technologies and competitive industrial products are reducing both the dependence on petrol-derived polymers and increasing the production of sustainable and biodegradable polymers, consequently reducing waste of land and oceans.

This interesting book, written by highly recognized scientists, cover all the topics regarding production and use of innovative and sustainable polymers in different fields such as drug delivery, air and water cleaning, optical functions, textile production, etc. It may be of great interest not only for both the chemical and medical community interested to know and understand all the processes and applications regarding the biodegradable polymers, but also for scientists and students that like to discover all the methodologies used to day for producing the so called biopolymers by the use of by-products obtained from industrial and agricultural waste.

P. Morganti
Editor-in-Chief

Carbohydrate Chemistry. State of the art and Challenges for Drug Development

by Laura Cipolla

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Glycobiology is the study of the structure, function and biology of carbohydrates, also called glycans, which are widely distributed in nature. They are saccharides that can be attached to a wide variety of biological molecules through an enzymatic process called glycosilation necessary to augment their function. These natural compounds consisting of carbon, hydrogen, and oxygen atoms have several roles in living organisms including energy transportation, as well as being the main structural support for plants and arthropods. When combined together to form polymers, in fact, they can function as long-term food storage molecules, protective membranes for organisms and cells, and as the main structural support for plants.

Despite the important functions of the four fundamental building blocks of life, proteins, carbohydrates, lipids, and nucleic acids, glycans have received the least attention from researchers also if, glycobiology is a rapidly growing field with relevance to biomedicine biotechnology and basic research. However, these important polysaccharides, conjugated to lipids or proteins, cover the extracellular side of most cell membranes and are involved in the majority of biological processes at the cellular level, including host defense, cell development and differentiation. Thus, the glycan composition membrane, being species-and tissue-specific, is used as a cellular post code in cell-cell and cell-pathogen recognition.

The book tries to give an overview of the key aspects of carbohydrate biology and chemistry by **19 chapters divided in 4 parts.**

Structure and Biological Function of Glycoconjugates is the topic reported of **Part 1** by the **chapters 1-3**. Glycoproteins characterized for containing one or more covalently linked glycan chains, play important biological roles. Existing widely in eukaryotic systems and in some bacteria and archea, they can serve as structural cell wall components, lubrificants, protective agents, transport molecules, inhibitors, hormones, and enzymes. For these reasons glycoproteins represent the major therapeutic proteins to produce humanized therapeutics with improved functions and homogenous forms at industrial scale. Thus, plant have been established as alternative hosts to mammalian cell lines for glycoprotein production, and recently the yeasts are successfully genetically engineered to produce human-like glycans. Chemoenzymatic glycosilation of natural and recombinant glycoproteins *in vitro* provides, in fact, an attractive approach to produce glycan-defined glycoforms. Among them gangliosphingolipids, also called gangliosides and characterized by the presence of one of several sialic acid residues in their carbohydrate moieties, are important compounds of the cell membranes. The lipid moiety of vertebrate glycosphingolipids (GSLs), for example, consists of either a sphingoid

or ceramide which is a sphingoid base linked to a fatty acid through an amide bond. According to the most common way to classify them neutral, GSLs are glycolipids containing only uncharged sugars, such as glucose, galactose, or fucose as substituents on the ceramide moiety, while the acidic mojeties of GSLs (gangliosides) are those that contain ionized functional groups attached to neutral sugars, or ionizable sugar residues, such as sialic acid.

These complex compounds support different functions in tissue and cells and may change under physio-pathological conditions through a differential hydroxylation or saturation that may occur at level of the alkane chain. On one hand, most of the structural variability of gangliosides and glycosphingolipids are connected to the carbohydrate domain that exhibits a staggering structural diversity. On the other hand, lipid rafts are highly dynamic structures containing specific lipids and proteins and can be seen as critical signalling platforms for many cellular functions, such as adhesion, growth, and migration. Moreover, gangliosides serve as receptors for a large set of pathogens, including viruses, bacteria, and toxins and are involved in cell mitochondrial damage and apoptosis, and overexpressed on several types of cancer including melanoma, brain tumors, small cell lung carcinoma and breast cancer.

As part of living systems, Lipopolysaccharides (LPSs), consisting of carbohydrates and lipids, are endotoxins which activate the immune system and represent the major component of the outer membrane (OM) of almost Gram-negative bacteria and some Cyanobacteria. These endotoxins, in fact, play a key role during severe Gram-negative infection, sepsis, and septic shock.

LPSs are heat-stable amphiphilic molecules indispensable for the viability and survival of Gram-negative bacteria, contributing to the structural integrity of their outer membrane and to the protection of the bacterial envelope. The ordered structure and low fluidity of the LPS monolayers, stabilized by electrostatic interactions between divalent Ca/Mg cations and negatively charged groups present on LPS molecules, are responsible not only for the increased permeability of hydrophobic compounds and to higher molecular weight of hydrophilic compounds, but also for the bacterial resistance to external stress factors. Moreover, LPSs have been shown to be the most potent immunostimulant molecules, playing a key role in the pathogenesis of Gram- negative infections, triggering the immune system from insects to humans.

Part 2, *Towards Glycomics: Methodologies and Techniques for the Determination of the Structure and Activity Relationship*, reports the modern technologies used to elucidate and investigate the biological role of carbohydrates by the **Chapters 4-7**. The 3D structure of carbohydrates, in fact, play a pivotal role in their recognition by receptors. Thus, knowledge at the maximum resolution possible of this complex structure together with the characterization of its recognition by different entities, such as lectins, enzymes, viruses, and antibodies, is essential for a thorough understanding of many vital processes and opening the possibility of their modulation.

On one hand, NMR spectroscopy, assisted in many cases with molecular modelling protocols, provides scientists with the possibility to study in solution and atomic scale, the structure of carbohydrates and the mechanisms that govern their recognition by receptors. Thus, advances in different biophysical and spectroscopic techniques, such as X-Ray crystallography and nuclear magnetic resonance (NMR), complemented by quantitative data obtained through isothermal titration microcolorimetry (ITC), allowed for gathering information on protein-carbohydrate complexes at atomic resolution, permitting speculations on the forces involved in their interactions. On the other hand glycan, isolated from natural materials as a component of the entire glycome, became an important source for microarray preparation. However, rather than being a diagnostic device, glycan arrays can also

be a valuable aid in finding antigens of diagnostic value for the subsequent production of monoclonal diagnostic antibodies used for enzyme-linked immunosorbent assay tests. Unfortunately, the rate of data production in glycomics has been rather limited, in comparison to proteomic and genomic research, but if genomic is perceived as a starting point, glycomics could be considered the end.

Part 3, *Synthetic Challenges: Towards Drug Development* reports, by **chapters 8-10**, reports some outlines on the synthetic methodologies developed to produce new oligosaccharides and glycoconjugates. The creation of the corresponding building blocks is the most time-consuming part for the complete synthesis of oligosaccharides. The first step is, in fact, the retrosynthetic analysis and the choice of the appropriate building blocks that have to be built up, before the glycosilation reactions necessary to connect the different monosaccharidic subunits. Thus, the need for simple and efficient methodologies to access structurally defined oligosaccharides, polysaccharides, and glycoconjugates. For the chemical assembly of these blocks, in fact, a repetitive series of glycosilation and tedious protection/deprotection steps result necessary.

In contrast to the complex chemical synthesis, enzymatic glycosilation offers many advantages, since enzymes provide selectivity and perfect control of the sugar substrate configuration, without the need of protecting groups. For these reasons, the enzymatic strategies are an open field of research in glycosciences and industrial biotechnology, so that new enzymes and protein engineering for novel specificities and improved performance are the today fast developing topics. In any way, to keep pace with the exploding area of glycobiology, it is critical to make complex carbohydrates more accessible to the general chemical, biochemical, and industrial audience. Expeditious strategies for oligosaccharide assembly in solution require, in fact, specialist knowledge of all the aspects of carbohydrate chemistry, fine-tuning of the reaction conditions and reactivity levels, and sophisticated and expensive synthesizers.

Part 4, *Carbohydrate-Based Compounds for Medical Chemistry Applications*, by **chapters 11-18**, reports relevant cases and opportunities for the development of therapeutics, based on carbohydrate structures. Glycosidases are involved in many important biological, processes, such as intestinal digestion, post-translational processing of the sugar chain of glycoproteins, cell-cell and cell-virus recognition, etc. Therefore, glycoside inhibitors could have great potential for the treatment of diabetes, viral infection, lysosomal storage disorders, and metastatic cancer. However in the last decade, it has become clear that sugar mimetics can be not only glycosidases inhibitors for biological effects, but can also act as immune modulators and pharmaceutical chaperones of misfolded proteins, without inhibiting glycosidases. Thus iminosugars, sugar-analogs with a nitrogen in place of the corresponding oxygen in the ring, become one of the most interesting discoveries in the fields of natural product chemistry.

The initial pharmaceutical interest in iminosugars was related to their properties as glycosidase inhibitors, while now they have been re-evaluated for the new and unexpected therapeutic applications due to their structural similarity with the corresponding sugars.

Despite the advent of antibiotics, implementation of national vaccination campaigns, and intensive care support, bacterial meningitis continues to be an important cause of morbidity and mortality among high risk groups With the exception of hygienic water, therefore, nothing has probably been more important in the history of infectious diseases and medicine than vaccines. Carbohydrates, in the form of oligosaccharides and glycoconjugates, are associated, in fact, with protein stabilization, cancer metastasis, viral host interactions, bacterial pathogenicity, and signal transduction, for their metabolic role. As matter of fact, the most common feature of the organisms, causing most of the

bacterial meningitis, is a carbohydrate capsule with different oligosaccharide patterns that act as both a virulence determinant and target protective antibody. Specific antibodies acting against the bacterial surface polysaccharides may, therefore, enhance the elimination of pathogenic bacteria. Thus, the significant and recent progress in immunology, resulted in the development of several sophisticated vaccines, polysaccharide-based, which can be used against invasive bacteria and other human pathogens, for their efficacy and safeness.

Another recent progress has been the design of sophisticated antitumoral vaccines made with the aim to stimulate more specific and efficient immune responses against tumours. These synthetic vaccines are principally composed of tumor-associated carbohydrate antigens (TACAs) that are over expressed at the surface of a large variety of tumors, where they play crucial roles in invasion and metastasis processes.

In any way, glycans are not only an important source of metabolic energy, but as previously reported, are also widely expressed as glycoconjugares on the surface of cells, forming the glycocalix (dense coat of carbohydrates) that plays a key role in many biological processes. One of its key role is to recognize and translate the chemical information encoded in the sugar structures. At this purpose, lectins are the protein that recognize glycans with high specificity, so that the carbohydrate-lectin interactions are implicated in several key biological events, such as cell-cell self-recognition processes, cell-extracellular matrix interactions, cell growth, differentiation, signaling, adhesion, migration, etc. However, most lectins are multimeric so that polyvalent presentations of saccharides, acting as binding determinants for a given lectin, are used in nature to establish multivalent interactions. Thus the necessity to make glycomimetic molecules and scaffolds, capable to antagonize these lectins and improve drug-like properties, comparable to natural sugars.

According to the conclusion, reported on **Part 5** by **chapter 19** *Carbohydrate-Based Drugs on the Market: Overview and Future Directions*, the renaissance in glycobiology has led to an increasing interest towards the pathophysiological mechanisms in which carbohydrates take part, with the ultimate aim of discovering novel spots for therapeutic intervention.

Carbohydrates are providing to be promising drug, leading to cover several therapeutic niches and challenging discoveries by the creation of new structures with an incredible biological and innovative therapeutic potential. By an increased knowledge of the carbohydrate chemistry and the cell biochemistry, therefore, will be possible to industrializing new potent carbohydrate-based drugs and vaccines characterized by a high effectiveness and very low toxic side effects.

In conclusion, this interesting book, written from leading experts addresses the state of the art for drug development by the use of carbohydrate compounds. Moreover, it provides also a greater understanding of their involvement in human physiological and pathological states. Each chapter, highlighting the more recent research and development conducted in the field of chemistry, biology and therapeutic potentialities of carbohydrates, can be of help for all academic and industrial researchers, working in the faculty of chemistry or medicine, as well as students and marketing managers who wish to enter into the fascinating field of glycobiology.

P. Morganti
Editor-in-Chief

Biopolymers for Medical Applications

by J.M. Ruso and P.V. Messina

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Skin wounds are today a major social and financial burden. WHO has estimated that annually over 300,000 deaths are attributed to burn injuries and 6.5 million individuals suffer from chronic skin ulcers caused by venous status and diabetes mellitus. Thus, the necessity for more suitable wound dressings to promote the skin regeneration by tissue-engineered scaffolds. Moreover, current research has integrated the concept of engineering skin scaffolds, to promote and create a favourable cellular micro environment at clinical level. These scaffolds, made by synthetic or natural non-woven tissues, have to serve as a platform for cellular localization, adhesion, and differentiation, as well as to guide the development of new functional tissues. At this purpose, biomaterial play a pivotal role to provide three-dimensional templates and synthetic extracellular-matrix environments for tissue regeneration. It includes novel processing technologies and innovative composites capable to emulate and interact with the extracellular matrix.

This book, organized by **14 chapters**, provides a comprehensive overview of the main polymeric systems used to made products, tools and advanced medications for medical application.

Science and technology play a key role in the extended life expectancy, so that the recovery of new delivery systems for improving the efficacy of bioactive molecules, represents an essential strategy for achieving treatments against many diseases. Thus, the convergence of synthetic and natural macromolecules, such as polysaccharides, inherently leads to biomedical applications, as the ability to control polymer structure leads to the ability to manipulate functionality.

On one hand, the specificity of biopolymer block in terms of bio activity, biocompatibility, and biodegradability allows specific application over the bio-medical fields. On the other hand, bio-printers can automate the complex manipulation of biopolymers-from the macromolecular to the living cell level- to produce tissue and organ substitutes that mimic their natural counterparts.

Studies and production of biopolymer nano-composites constitute, therefore, a great area of interest to realize implant and devices for the tissue engineering, so that they are widely considered and used for hard and soft tissue reconstruction. Among them polysaccharides, produced by from microorganisms, animals, and plants, represent a renewable resource of biodegradable raw materials and are regarded as economical and environmentally favourable resource. In addition, they can be modified in their chemical structures to improve, enhance or avoid any molecular feature necessary to reach the ultimate objective.

Compared to proteins polysaccharides are more stable and provide biomaterials with the required mechanical properties and aqueous stability. Moreover, these natural polymers are more readily avai-

lable than proteins, can better withstand processing conditions, and can be more easily made into various shapes and sizes. Naturally, the main objective is to create biodegradable nanocomposites that can match the mechanic and biological properties of the replaced biological tissue. These constructs have to elicit the specific and desired cellular responses, such as cell adhesion, proliferation and differentiation, and exhibit chemical breakdown into non-toxic degradation products. It is, in fact, possible to mimic the extra cellular matrix (ECM) environment, activating, for example and at molecular level, the specific gene expression response of cells .The result may be obtained by the construction of three-dimensional porous scaffolds into which immobilize specific bio molecules, such as signalling molecules or cell-specific proteins.

These are the topics reported on **chapters 1-3**, where different polysaccharides and blending with other biopolymers are focused on view of their possible medical applications.

Chapter 4 is entirely dedicated to problem and solutions regarding the dental erosion. This topic has and will have a major economic impact on all the dental services, being associated not only to aesthetic and functional complications of the dental erosion, but also to the sensitivity and pain of the patient. Moreover, being the aetiology of erosion multi factorial, it is difficult both it's diagnosing in early stage and treatment. At this purpose the topically applied biopolymers could be adsorbed on teeth, increasing their acid-resistance. The erosiveness of acidic beverage, for example, can be lowered if modified with biopolymers. Dental erosion, in fact, that continues to escalate in time, is basically induced by acids of non-bacterial origin, being the main factor responsible for tooth-wear. This chapter is, therefore, focused on the strategies necessary to find novel and improved anti-erosive formulations, based on the use of the new biopolymers described. However, it has been underlined the necessity to organize *in vivo* clinical trials in order to prove the efficacy of the biopolymers used as protectants of teeth erosion.

Biopolymer, biomedical science and bio fabrication technologies are reported on **chapters 5-9** where the different typology of polysaccharides used in medicine are focused and discussed. However, one of the integral components of biofabrication, and tissue engineering is represented from biomaterials, such as gelatin, alginate, hyaluronan, fibrin, and silk.

The production of a successful tissue construct is, therefore, based on the delicate orchestration of the cell, as well as on the physicochemical materials and aspects involved in its realization. Thus, with advanced biotechnologies the development of devices, such as chip system, have shown to play a significant role in cell metabolism, and based on the bioavailability of oxygen. The metabolomics-on-a-chip, for example, demonstrated that the microfluidic environment provide more access to oxygen compared to Petri dish cultures, opening new ways for the *in vitro* studies. However, up today no single biomaterial or biofabrication techniques as shown to be perfect, but, the creation of materials exploiting molecules from renewable resources and the green processing routes remain the more important steps towards a sustainable society. Thus, the use of polysaccharides, derived from by-products/waste materials obtained from agricultural or fishery activities, is a must of our society to preserve the natural raw materials of our planet for the incoming generations.

At this purpose, nanocarriers such as liposomes, polymeric micelles, and dendrimers are extensively utilized as targeted drug carrier systems because of their ability to encapsulate drugs, proteins, gene and other therapeutic molecules. On the other hand, the present need to realize high porosity and effective network structures necessary to create favourable interactions between the biomaterial and the cells of the body. Moreover biomaterials, that can tolerate high mechanical strains, are very

important for example, for bone and cartilage tissue engineering. Nanocellulosa, nanochitin, and nanochitosan seem to be ideal natural candidate in this respect. All these polysaccharides have shown to possess a better tissue regeneration and a faster and better healing effect and a lower inflammatory response on epithelial tissues, when compared to the control group.

Chapters 10-4, focused on the computer simulation of biological systems by mathematical and theoretical models, discuss the atomistic basis of the interaction occurring during the imprinting process between the biopolymers and all the other species included in the in study. These simulations collect information about the biological system under study by a building computational model, which helps to analyze and find an accurate representation of its complexity.

The relative mathematical model results very useful in studying, for example, the gene expression. Thus, for a given computational model of a complex biological system, it is possible to define the structural properties, to estimate the system normal behaviour, and its response in abnormal conditions. As a consequence, the medical applications of informatic have gained prominence as essential science in nanobiotechnology research, becoming particularly suitable in generating the appropriate research design frameworks. Modelling and simulation play, therefore, an important role in modern research whether it is pure or applied science, making them to be a tool of choice for studying biological systems, especially in medical applications.

The book is principally focused on the physicochemical and biological characteristics of the main natural biopolymers, clearly introducing the lecturer to their versatility of use and safeness. Polysaccharides, in fact, as the main group reported, may be easily engineered for being used for specific medical applications, such as drug delivery or the reconstruction of tissues and organs of our body. Thus, amply reported, all the chapters are of high interest not only for specialized people, such as dermatologists, plastic surgeons, pharmacologists, and cosmetic chemists, and also for student of the medical and chemical community and marketing experts wishing to know in a deeper way or enter for the first time into the fascinating field of the bio polymeric systems used to produce advanced medications. Additionally, it could be of utility for all scientists and students of the chemical, biological, medical, social and political community who have some odd ideas about biodegradability and compostability of bio-based or fossil fuel-based polymeric materials.

P. Morganti
Editor-in-Chief

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Okayama University research: Prevention of RNA viruse replication

(Okayama, 29 November 2016) Researchers at Okayama University have successfully cleaved influenza viral RNA to prevent its replication using novel artificial RNA restriction enzymes in laboratory cell cultures. While further improvements are needed, the findings show great promise and could lead to anti-viral drug development in future. The findings are published in *Biochemical and Biophysical Research Communications, October 2016*.

Introduction

Developing technologies that can inactivate viruses and prevent them from infecting humans could transform the way in which we tackle various diseases. Several methods aiming at inactivating viruses have been tried, including preventing the binding of viral proteins and using artificial enzymes to 'cleave', or split, molecules in viral genomes.

By splitting a chosen molecular strand, such as DNA or RNA, essential bonds are broken and the molecule can no longer function correctly. In the case of viruses, integrating DNA or RNA cleaving ability into anti-viral drugs could prevent viral replication and infection within a host. Following recent success cleaving DNA in the human papillomavirus, Takashi Sera and coworkers at Okayama University have now used the same technique to cleave RNA in influenza cell cultures.

Firstly, the team developed artificial RNA restriction enzymes. These enzymes incorporate an artificial RNA binding protein, whose job is to target the correct virus, and an RNA cleaving enzyme that targets a specific domain in the viral RNA in order to create the split. Enzymes created for previous studies targeted the viral PIN domain but with limited success, and so Sera's team created new RNA restriction enzymes targeting the staphylococcal nuclease (SNase) domain instead.

The researchers compared the ability of the SNase-based enzymes to cleave influenza RNA with PIN-fusion enzymes. They found that the SNase enzymes recognized and completely cleaved their target RNA in five minutes in cultures in the lab; in fact, the SNase enzymes had higher cleavage rates in one minute than the PIN-fusion enzymes had in two hours.

With improvements to the enzymes for use in animal (and eventually human) cells, the SNase restriction enzyme technique could one day prove to be a very powerful tool in the development of anti-viral drugs.

Background

DNA and RNA viruses

Viruses have either DNA or RNA as their genomes. Examples of DNA viruses include herpes, chickenpox and smallpox – they replicate in nuclei after infiltrating host cells. RNA viruses, on the other hand, inject their RNA into host cell cytoplasm where it is then used to synthesize proteins and form replica viruses. RNA viruses include influenza, HIV and Ebola, to name but a few.

Scientists are keen to find ways of preventing both DNA and RNA viral infection and replication inside the body. Such technology could transform the way in which we tackle various diseases. One feasible way of stopping viral replication is to target the genetic machinery involved in the process – namely by cleaving, or splitting, the DNA or RNA strands so that they can no longer function correctly.

The techniques developed by Takashi Sera and his team at Okayama University involves the creation of artificial restriction enzymes – carefully-designed molecules incorporating proteins and enzymes that can home in on, and cleave, specific RNA or DNA targets. Their previous studies have been successful in cleaving DNA in human papillomavirus, and now they have used the same technique to cleave RNA in influenza cell cultures.

Implications of the current study

Following further work on the RNA restriction enzymes to ensure they are effective and safe for use in animal (and eventually human) cells, the team hope that their technique could lead to future development of anti-viral drug. Their findings represent a significant step forward in realising this goal.

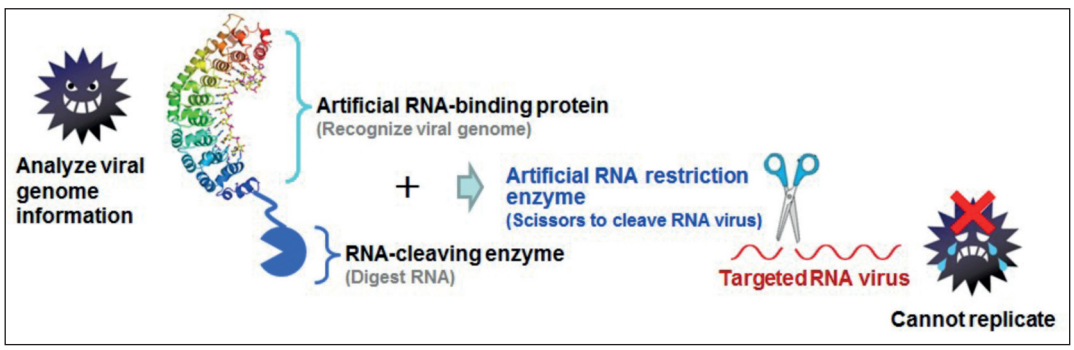

Figure. Analyse virus gene information and create an artificial RNA restriction enzyme. Viruses cannot replicate as their gene information is cleaved (which means virus cannot cause diseases). This technique can be applied to all kinds of RNA viruses both for animals and plants.

Reference

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Correspondence to

Professor Takashi Sera, Ph.D.
Department of Applied Chemistry and Biotechnology, Graduate School of Natural Science and Technology, Okayama University,
3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan
e-mail : sera@cc.okayama-u.ac.jp

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