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

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## 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).

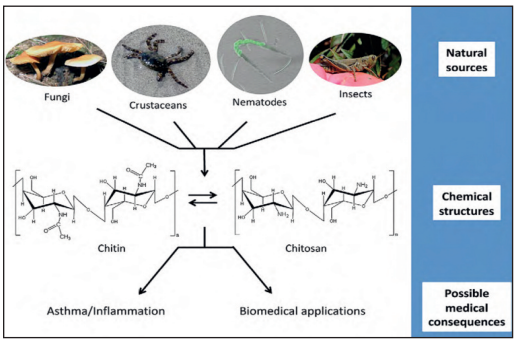


***Fig. 1*** *Chitin is an indispensable structural component of fungi and arthropods.*

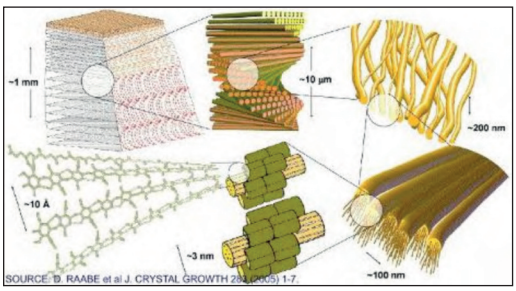


***Fig. 2*** *Natural structural organization of chitin.*

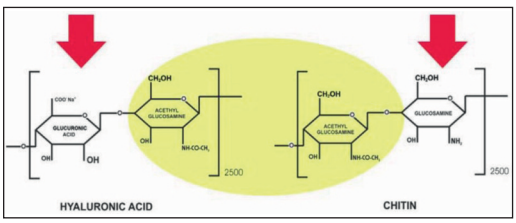


***Fig. 3*** *Chitin has the same backbone of hyaluronic acid.*

## *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.

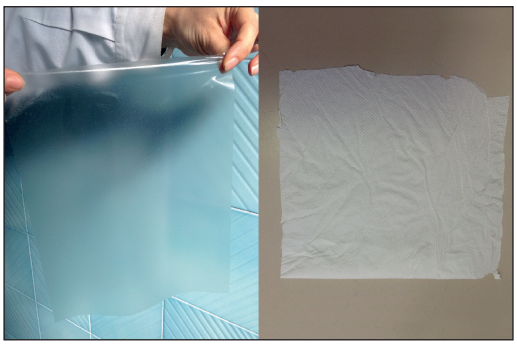

***Fig. 4*** *Matrices made by the use of chitin nanofibrils. On the right non-woven tissue and on the left film.*

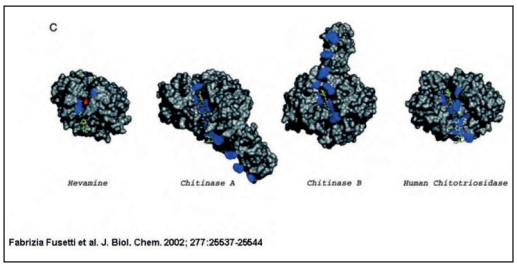


***Fig. 5*** *Molecular structure of chitinases and chitotriosidases.*

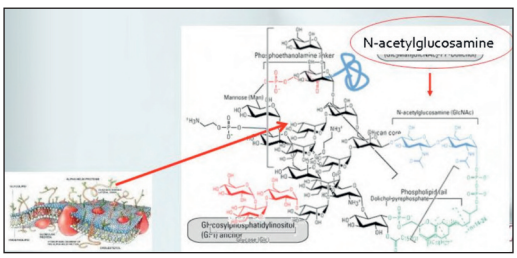


***Fig. 6*** *Acetyl glucosamine as part of the glycan structure.*

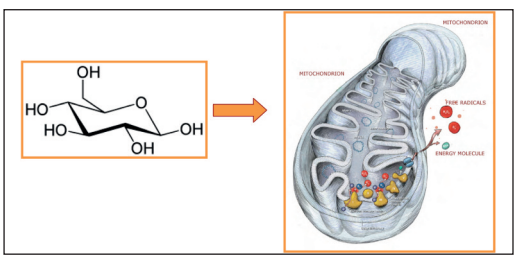


***Fig. 7*** *Glucose used by mitochondries to produce energy.*

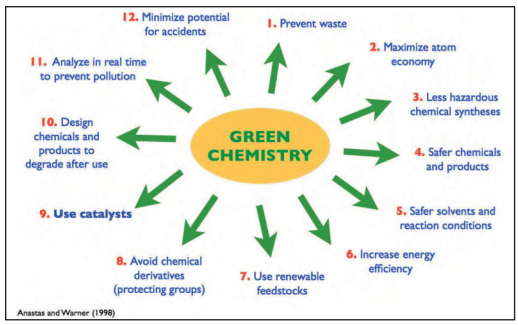


***Fig. 8*** *The principles of green economy.*

## 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.

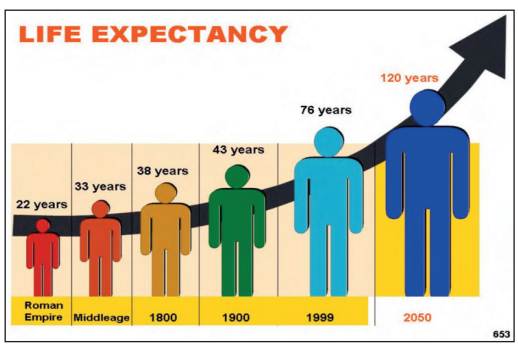


***Fig. 9*** *The aged people is estimated to reach 21.1% by 2050.*

## *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).

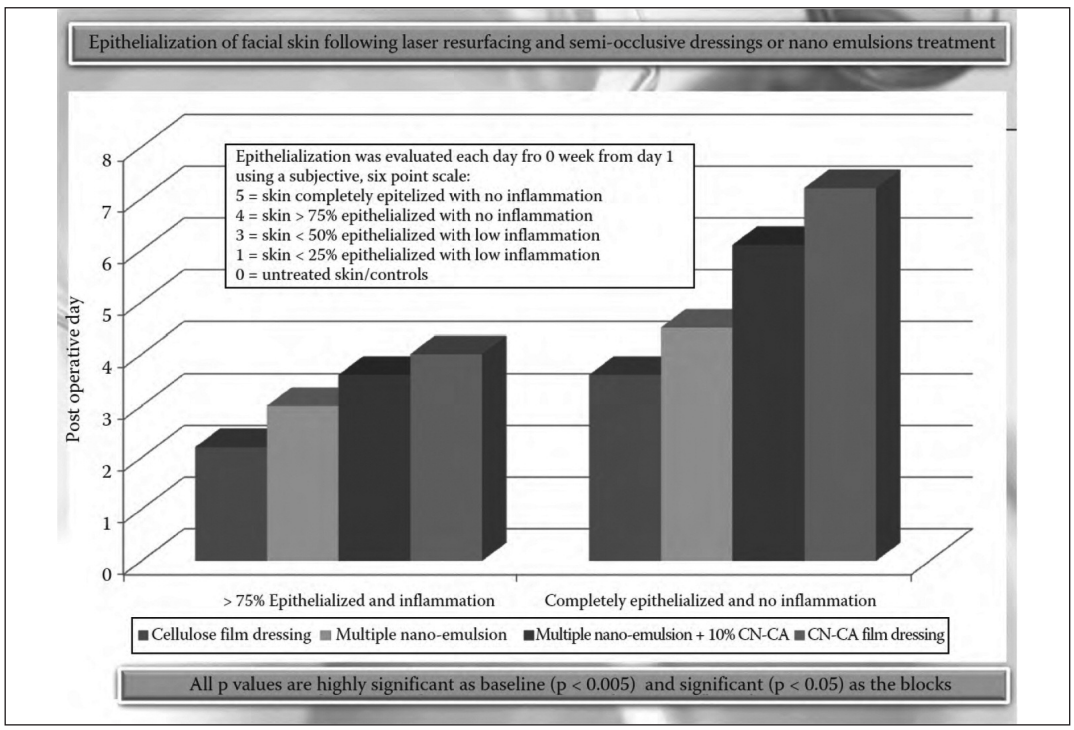


***Fig. 10*** *The re-epithelialization of the skin after laser treatment.*

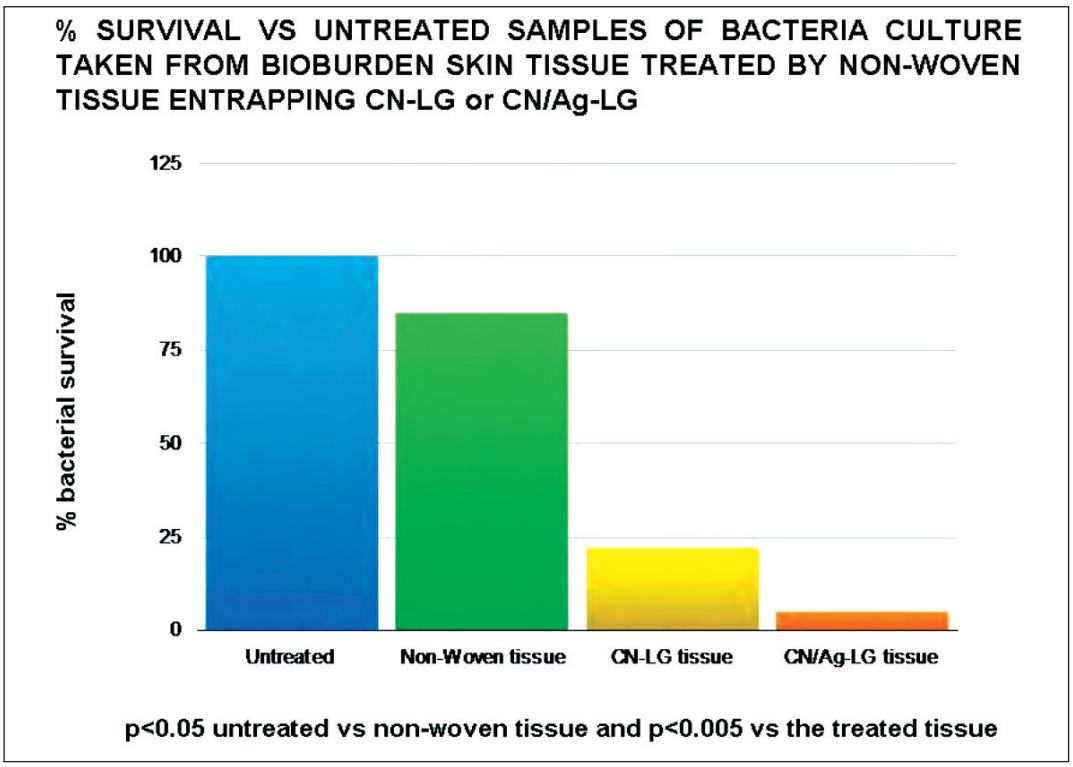


***Fig. 11*** *Slowdown of microbial skin growth after treatment by a CN-Ag-non-woven tissue.*

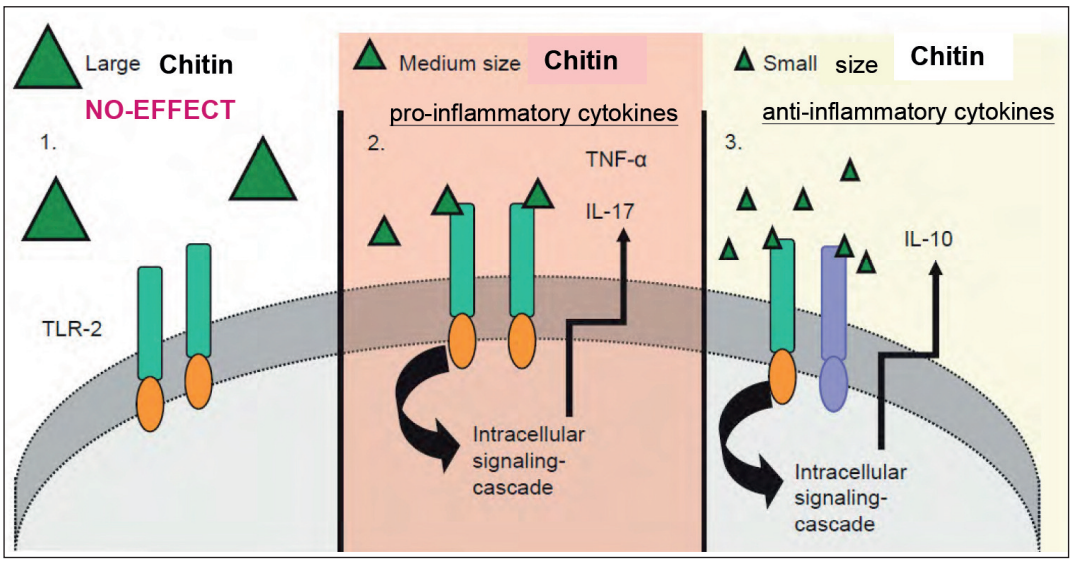


***Fig. 12*** *Antiinflammatory activity of different sizes of chitin.*

## 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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