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ADVANCED MEDICATIONS MADE BY GREEN NANOCOMPOSITES

Giovanna Donnarumma[*1], Alessandra Fusco[1], Pierfrancesco Morganti[2], Marco Palombo[3], Tommaso Anniboletti[3], Paola Del Ciotto[4] , Adone Baroni[5] and Angelo Chianese[6]

[1*]Department of Experimental Medicine, Second University of Naples, Naples, Italy.

[2]Dermatology Department, 2nd University of Naples, Italy, R and D Director, Nanoscience Centre Mavi, Aprilia (LT), Italy.

[3] Plastic, Reconstructive and Aesthetic Surgery Department, CTO Hospital, Rome, Italy.

[4]R and D, Nanoscience Centre MAVI, Aprilia (LT), Italy.

[5]Department of Dermatology and Venereology, Second University of Naples, Naples, Italy.

[6]Chemical Materials Environmental Engineering, Department, University "La Sapienza", Italy.

ABSTRACT

Nanoscience and nanotechnology, involving the ability to control and manipulate the material at level of individual atoms and molecules, make possible to realize a personalized medicine towards a new therapeutic approach. At this purpose, new non-woven tissues have been realized by the use of bio renewable natural polymers, such as chitin nanofibrils and lignin, obtained from crustacean waste and plant biomass respectively. The aim of the study was to control effectiveness and safeness on burned skin of advanced medications made prevalently by the complex chitin nanofibrils (CN) nano-lignin (LG) bonded with nano silver, in comparison with in commerce medications. The non-woven tissues, prevalently made by CN, were electro spun by the NS Lab 500 on a bed of polypropylene of pharmaceutical grade. The engineered CN-LG nanoparticles, electro spun fibres and tissues, together with their physicochemical characteristics, such as diameter and uniformity, as well as the right strength end elasticity, pore size and density, were controlled. According to the declaration of Helsinky, the *in vivo* effectiveness was verified on 30 selected patients (group A) affected by second degree burns, that utilized non-woven tissues of 15x30 cm in dimension, posed on a bed of polypropylene of pharmaceutical grade, put into a sealed aluminium envelope and sterilized by gamma-rays. They compare Group A with 30 patients that were treated with standard dressing for the same wound characteristic (Group B). The *in vivo* results have evidenced that the realized advanced medications are able not only to rapidly repair and regenerate the skin, but also to prevent the bacterial infections. It was possible, in fact, to obtain a fast process of wound healing in a week, avoiding the need to remove the medication with an economical advantage for the hospital and the patient. The CN-non-woven tissue, made by natural raw materials obtained from biomass, has shown to be skin-friendly and 100% biodegradable and therefore useful for medical purposes and to decrease the dependence from fossil fuel resources, in agreement to the and EU program of a green economy.

KEYWORDS

Complex chitin nanofibrils, Nano-lignin and Natural biodegradable non-woven tissues.

Author for Correspondence:
Giovanna Donnarumma,
Department of Experimental Medicine,
Second University of Naples, Via Costantinopoli,
Naples, Italy.
Email: giovanna.donnarumma@unina2.it

INTRODUCTION

Despite the recent questions, the skin is considered the largest organ system that protects our body from the environmental aggressions[1]. Normally, wounds in the skin trigger a rapid and effective healing process. But major injuries, that span great skin

areas, may occurs in burns or in patients with compromised conditions, complicating the skin would healing. For the treatment of skin lesions several strategies are currently available, such as the application of auto grafts or synthetic and/or natural wound dressings[2]. At this purpose, it has been programmed to try to use a natural tissue-engineered nanocomposite as a promising therapy for treatments of burns.

Nanoscience and nanotechnology, in fact, involving the ability to see, control and manipulate the material at level of individual atoms and molecules, make possible to realize a personalized medicine towards a new theranostic (therapy + diagnosis) approach, also[3]. Nanotechnology in medicine, involves applications of nanoparticles to make repairs skin more efficiently and deliver the active ingredients at the cellular level[4]. By this new technology it is possible the manipulation of the body's own mechanisms to successfully repair diseases or damaged tissues. For these reasons scientists are making fibres, materials and nanocomposites at the nanoscale to take the advantage of their enhanced properties, such as higher strength, lighter weight, increased control of light spectrum, greater surface-to-weight ratio, and chemical reactivity[5,6]. Composite materials, in fact, are the most advanced and adaptable engineering materials made by a matrix with a filler compound incorporated to improve its own properties. Among nanofillers, polysaccharides such as chitin and chitin-derived biopolymers are considered useful for green label, also because attractive to health-conscious consumers[7]. It is to remember that these biopolymers are group of natural macromolecules collectively recognized as polymer because composed of linked, repeating chains of sugar-like molecules. By these natural polymers it is also possible to make biodegradable scaffolds, which mimic the behavior of native tissue, resulting useful to guide and promote controlled cellular growth and differentiation in order to generate new tissue. Sustainability is another important driver for a greener development to produce innovative products by the use of sustainable and biodegradable molecules derived from renewable raw materials[8]. Thus, bio renewable polymers, such as chitin-derived compounds coming from fishery's waste, and lignin obtained from plant biomass, are considered as great sources of sustainable material in the world[9]. At this purpose, chitin nanofibrils (CN) and nanolignin (LG) have been also used to make non-woven tissues for producing innovative and effective beauty facial masks of natural origin[10]. This is the reason why the concept of sustainability and the creation of healthy product is giving a second wind also to the global advanced medication industry, which had a selling turnover of US$ 30 billion in 2012 and it is estimated to reach about US$ 70 billion by 2020[9,11].

The aim of this study has been the use of natural biodegradable non-woven tissues made by nanolignin and Chitin Nanofibrils pre-linked to nanostructured silver ions, for producing advanced medications by the electro spinning technology. These advanced medications have been used to obtain a more fast re-epithelialization and recovery of the skin affected by burns of 1st and 2nd grade in a shorter period of time.

At this purpose, our group has developed advanced medications made by non woven-tissue based on green nanocomposites of Chitin Nanofibrils (CN) pre-bonded to nano silver and electro spun with bio-Lignin, chitosan, poly (ethylene) oxide (PEOX) and natural polypeptides. The purpose has been to produce advanced medications (classified as medical devices) made by innovative nanocomposites respective of the skin and the environment. Chitin is, in fact, one of the most available natural polymer, safe and non toxic, while chitin nanocrystal or nanofiber represents its purest form[11-13], and the presence of nanostructured silver at very low quantity reduces sensibly the toxicity of this metal. The main aim of this work is to show the possibility to produce advanced medications made by non-woven tissue, skin friendly and environmentally-friendly, verifying, *in vivo*, their functionality, their effectiveness and safeness.

MATERIALS AND METHODS

Materials

Chitin Nanofibrils in the form of 2% water suspension and nanostructured silver were kindly supplied by MAVI Sud Srl (Italy), bio-lignin by CIMV (France), PEOX was purchased from Amerchol (Dow Italia, Italy), polypeptides were purchased from Rousselot Sas (France) and chitosan from Giusto Faravelli Spa (Italy). As solvent was used only distilled water.

Preparation of non-woven tissues

The non-woven tissues, prevalently made by CN, were electro spun by the NS Lab 500 on a bed of polypropylene of pharmaceutical grade. The engineered CN-LG nanoparticles, electro spun fibres and tissues, together with their physicochemical characteristics, such as diameter and uniformity, as well as the right strength end elasticity, pore size and density, were controlled at the Engineering Department of *La Sapienza* University of Rome, while the safeness and effectiveness, was previously controlled *in vitro* by culture of cheratinocytes at the Department of Experimental Medicine, Second University of Naples.

Chitin Nanofibrils-Ag/ bio-lignin, chitosan/ polypeptides/ and PEOX bio composite non-woven tissues, used elsewhere with different active ingredients to produce innovative Beauty Masks[14] were electro spun by the NS Lab 500 (Elmarco, Chezch Republic) on a bed of polypropylene of pharmaceutical grade. Before going on with the tissue production by the electro spinning, CN-bio lignin aggregated polymeric nanoparticles were produced by using the spray-dryer DF 500 B9 (JCF, Italy). These nanoparticles were dissolved into water to obtain a gel-mixture, which was then used as starting material for an electro spun material. The sol-gel mixture prepared for the electro spinning tests was obtained mixing the CN-bio-lignin complex with deionized water at temperature of 15°C for few minutes. Then PEOX was added to the solution, under stirring until completely dissolved. This last step took 24 hours to obtain a homogeneous gel without agglomerations.

Electro Spinning

Electro spinning represents the most commonly used way to fabricate fibrous matrices by an easy and low costing approach for biomedical and bio technological applications[15,16]. The electro spinning process was performed by using the pilot scale machine Elmarco Nanospider NS LAB 500 based on the nozzle-less technology (S. Petrik, M. Maly, "Production Nozzle-Less Electro spinning Nanofiber Technology", (Elmarco S. R. L.). In a typical electro spinning process, an electrical field is used to stretch a viscoelastic polymer solution jet, which solidifies into nanofibers that may mimic the fibrous network of native ECM (Extra cellular matrix). The obtained natural tissue, collected as a non-woven tissue, can be used for wound repair[17,18]. The thin layer of solution is carried out on the drum surface and exposed to a high voltage electric field. If the voltage exceeds the critical value, a number of electro spinning jets are generated. The jets are distributed over the electrode surface with periodicity. This is one of the main advantages of nozzle-less electro spinning, the number and location of the jets is set up naturally in their optimal positions. The setting parameters are reported elsewhere[11].

Morphological Characterization of nanoparticles and non-woven tissues

In the scaffold-based tissue engineering, the functionality is related to its porosity, pore and nanoparticle size together with the interconnectivity of all the fibres. The final structure of the tissue, which should possess a structure ECM-like, should allow the diffusion of nutrients and cell migration, thus promoting optimal tissue in growth *in vivo*[17]. Thus, the necessity to control morphology and structure of both nanoparticles and non-woven tissue. The surface morphology of electro spun nanofibres was characterized by a field emission electron microscope - FESEM Auriga Zeiss, including microanalysis EDS 123 Mn-Ka eV (Bruker) and EBL -7 nm resolution (Raith). Samples cut from the electro spun material mounted on aluminium stubs were coated by an ultrathin layer of platinum for better conductivity during imaging. The samples were observed at

magnifications between 100 and 40,000 times their original sizes to visually evaluate the electrospinnability and existence of beads.

Fiber diameters were also determined using Image-J image processing software. For each electro spun material, at least 100 fibers were considered from three different images to calculate the average diameter. Mean size and electrical charge of the nanoparticles were measured by The Dynamic Light Scattering (DLS) and Surface Zeta Potential, using the Zetasizer Nano ZSP (Malvern Instrument Limited, Worcestershire, UK).

***In vivo* Evaluation of the effectiveness and safeness of the advanced medications**

The non-Woven tissues (NWT) were cut at the dimension of 15x20 cm, put into aluminum sealed envelope and sterilized by gamma rays. According to the declaration of Helsinky, The *in vivo* effectiveness was verified by a clinical randomized study on 30 patients affected by second degree burns and selected from a plastic surgery team in the S Eugenio Hospital in Rome, Italy. The exclusion criteria were: admitted patients; full-thickness burns; operated patients that came to the ambulatory facility for postoperative follow up. The inclusion criteria were out-patient treatments selected according to the American Burn Association classification: second degree burn with TBSA less that 15% in adults (10% in children), burns not involving eyes, ears, face, feet or perineum, burns not derived from electrical injuries, not associated with inhalation, not in poor-risk patients. A prospective randomized clinical study was performed on 60 burnt patients with second superficial degree burns to investigate the effectiveness, safety and tolerability of MAVI dressings. NWT dressing was applied on a group of 30 patients (GROUP A), treating the coverage of a superficial second degree burns in 15 patients (GROUP A1) and treating the coverage of the split-thickness skin graft donor sites in the remnant 15 patients (GROUP A2). Patients of GROUP A1 and A2 were than compare to patients of group B (30 patients) that were treated with standard dressing for the same wound characteristic: superficial second degree burn wound in 15 patients (GROUP B1) and split-thickness skin graft donor sites in the remnant 15 patients (GROUP B2). NWT dressing was applied on superficial second degree burns and split-thickness skin graft donor sites in patients aged between 7 and 71 years old, average age 43, 6. Burn depth was clinically assessed. And no systemic antibiotics were used. Burns were diagnosed as completely healed up when re-epithelisation was complete in all affected areas. For each patient, we collected the age, sex, cause of burn (scald or flame), type of dressing used and the days required for complete healing (healing time). The cause of burn was scald in 83% of cases and fire in the remaining 17%. The study was organized in a period of 30 days (June-August 2014), according to the principles of the declaration of Helsinki revised in Seoul. Each patient provides written informed consent and received a unique identification number. Both patients and investigators were blinded through the study as to treatments assigned. Skin regeneration of the burned skin, characterized by skin irritation phenomena, regardless of different skin layers, and possible presence of serum, has been evaluated by an expert dermatologist, according to an analogic visual score following the reported parameters: 10=no reparative phenomena and presence of uniform erythema; 5=satisfactory reparative phenomena and visible reduction of inflammation; 0=Total injury reparation and reconstruction of the normal skin. The evaluation of the perceived effectiveness of the in study medications has been evaluated enquiring the patients about their perceived painful, itch and discomfort according to the Following scores: 10=not satisfactory (no perceived effectiveness); 5=little satisfactory; 0=completely satisfactory.

Statistical analysis

Each experiment was performed at least three times. The results are expressed as mean ± standard deviation (SD). Student's t test was used to determine statistical differences between the means, and statistical analysis was done using a one-way ANOVA. $p<0.001$ was considered statistically significant.

RESULTS AND DISCUSSION

Morphology of the CN-bio-Lignin nanoparticles and the bionanocomposite non-woven tissues

On one hand, the SEM analysis of the block co-polymeric nanoparticles of CN-bio-Lignin displayed a nanometer scale textured surface consisting of a tender and regular granular morphology where bio-Lignin is intimately incorporated and linked to the CN nanocrystal to form prevalently nano balls of a mean size of 61.90nm covered by positive charges (Figure No.1, Figure No.2). On the other hand the bionanocomposite non-woven tissue, shows a morphology consisting of randomly assembled nanofibers characterized by a disposition resembling the human Extra Cellular Matrix (ECM) (Figure No.3),while the electropositive charges of the CN-fibers seems to favor the bactericidal activity of the silver-entrapped. Thus, the interaction between the positively charged CN/Ag and negatively charged microbial cell membranes could lead to the disruption of microbial membrane, and sequentially the leakage of proteinaceous and other intercellular constituents, can alter the cell permeability.

Effectiveness *in vitro* and *in vivo* of the advanced medications made by CN-biolignin

The particular morphology and composition of the tissue, made prevalently of nanochitin and bio-lignin, fibers randomly assembled, have shown a great cell-affinity by *in vitro* studies on human keratinocytes as reported elsewhere[4], while the interesting reparative effectiveness was achieved in vivo on the burned skin. It is to remember, in fact, that nanochitin, as polymer made of glucosamine and acetyl glucosamine with the same backbone of hyaluronic acid, on one hand has the capability to bond a great quantity of water, necessary for all the cell activities[19] and to optimize the re-epithelialization of the skin. On the other hand it is easily metabolized from the many family of chitotriosidases present into the human body to form glucosamine, acetyl glucosamine and glucose[20]. Moreover, the bio-lignin, as interesting macromolecule made of many polyphenol units, has shown to have a useful antioxidant activity[21,22].

Thus, as previously reported by *in vitro* studies on human keratinocytes (HaCat cells), the non-woven tissue has the capability to stimulate the release of beta-defensin-2 with its protective and antibacterial activity, decreasing also the cytokine expression, of IL-1α, IL-8 and TNF-α and increasing the expression of metalloproteinase 2 and 9, as previously shown by our group[4].

In this respect it has to remember that IL-1α plays a central role in the regulation of immune and inflammatory responses to infections and insults, while IL-8 induces phagocytosis, being also a potent promoter of angiogenesis and wound repair[23-25]. TNF-α, involved in systemic inflammation as one of the cytokines that make up the acute phase reaction, is able to induce fever, apoptotic cell death, cachexia, inflammation and to inhibit viral replication[26]. Moreover, beta-defensin-2 is a dynamic component of the local epithelial defense system of the skin, stimulating angiogenesis[27] and exhibiting a potent antimicrobial activity against gram-negative bacteria, *Candida and Malassezia*[28].

Clinical results

The donor sites and the superficial second degree burn wounds were assessed for all groups on postoperative days 1, 5, 14, 21 and long term for infection, hyperemia, pruritus, pain, exudate level, and adherence to the wound bed. At the follow-up visits, the donor sites and the superficial second degree burn wounds were assessed again for pruritus and pain, patient comfort and convenience for the doctor. Touch-pressure, thermal and pain sensibility tests were performed preoperatively and on postoperative follow-up together with the assessment of color and texture of the re-epithelialization areas. In all patients of group A, re-epithelialization was completed between 5 and 10 days (mean 7 days) after the application of NWT dressing while was completed between 6 and 13 (mean 9,5 days) for patients of group B. There were no significant differences between donor sites and the superficial second degree burn wounds with regard to pain, hyperemia, pruritus, exudate, and final appearance (color and texture). The areas dressed with NWT dressing completely healed

within 5-13 days in a significant higher proportion than the traditional dressings, showing during the whole study less incidence of exudates and of perilesional erythema and the absence of infection that there was instead in 3 patients of group B. The aesthetic outcome of the treated lesions after healing was significantly better for NWT. The interval time between dressing changes in Group A was significant reduced compare to group B and it reduced the number of medications (in 12 patients of group A1 and 11 patients of group A2 there was not need to change the medication), patient suffering, overall costs and human resources.

After the application of NWT dressing we observed the complete re-epithelialization of the split-thickness skin graft donor sites (group A2) in 13 patients and an healing delay due to exudate in 2 patient; the complete superficial second degree burns healing (group A1) in 13 patients and healing delay due to exudate in 1 patient and due to other reasons in 1 patient.

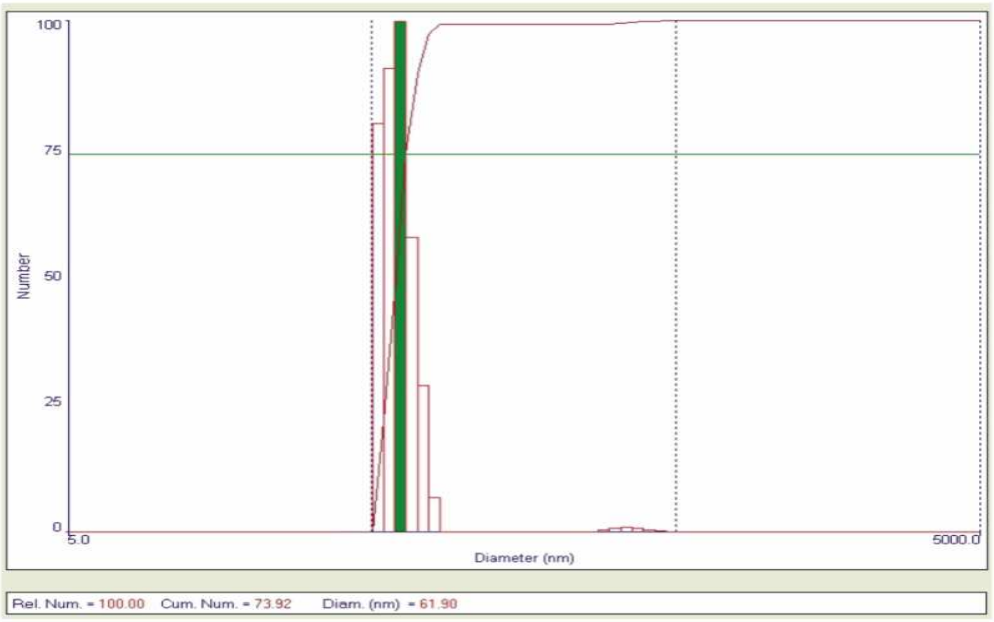


Figure No.1: Mean size of CN-Lignin nanoparticles

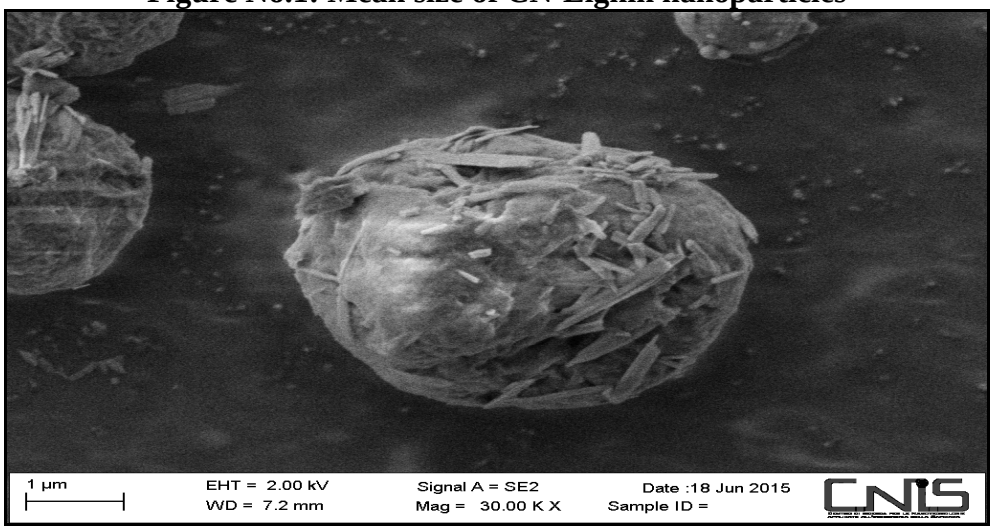


Figure No.2: Mean size of the greatest Chitin Nanofibril-Lignin ball at SEM

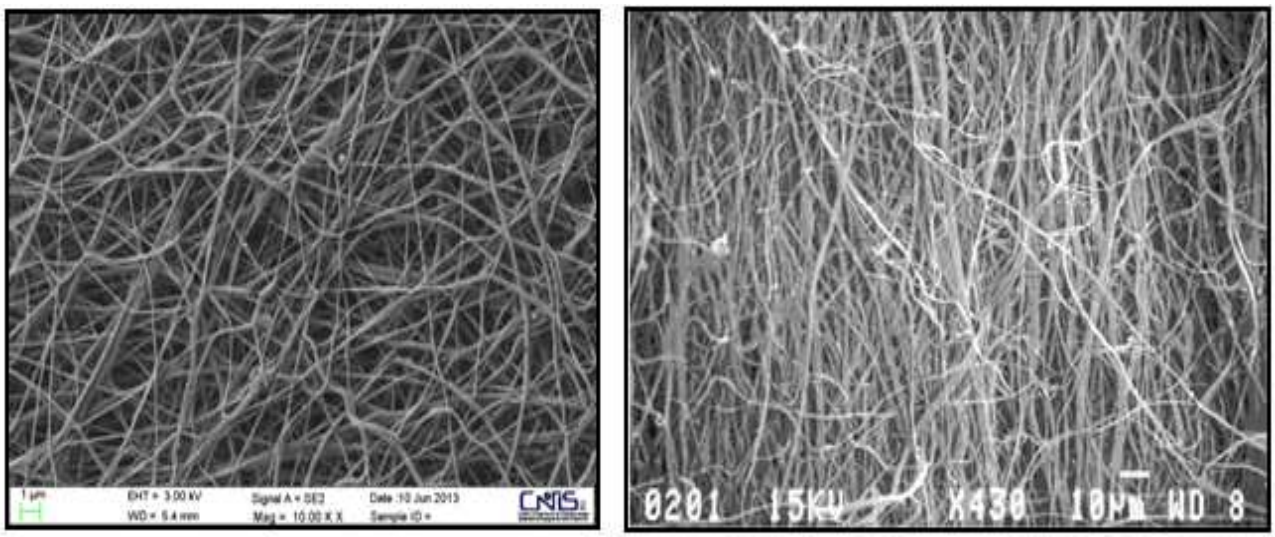
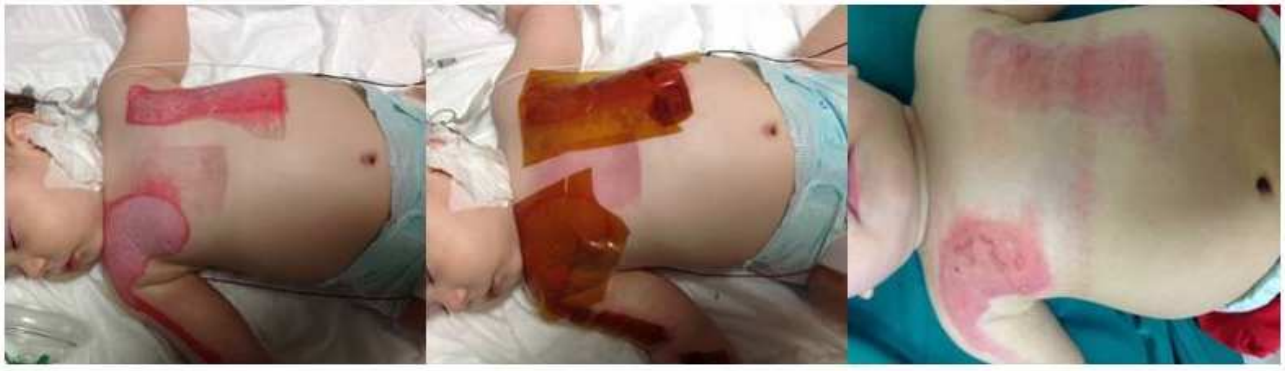


Figure No.3: On the left, ECM-like porous structure of a non-woven tissues based on the use of CN. At scanning electron microscope (SEM), on the right the human ECM

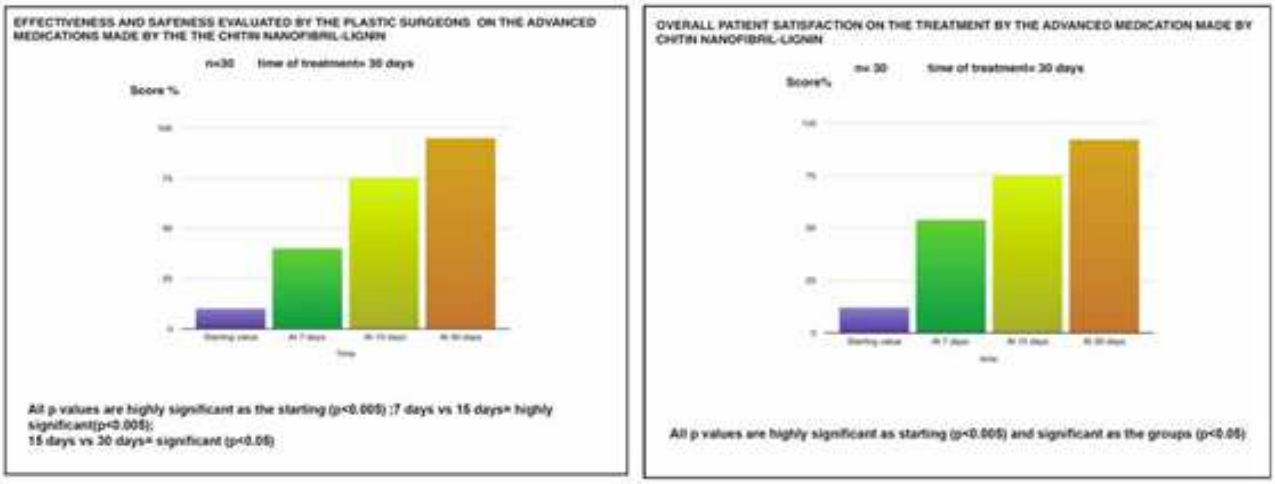
A **B** **C**

Figure No.4: Clinical case n°1 of group A1: A: superficial second degree burn on the back of the right hand, B: Application of dressing CN-Lignin, C: Complete re-epithelialization after five days post burn



A **B** **C**

Figure No.5: Clinical case n°2 of group A1: A: Second degree burn of the chest and right shoulder, B: Application of dressing CN-Lignin, C: Complete re-epithelialization after six days post burn



A **B**

Figure No.6: Effectiveness and safeness evaluated from the plastic surgeons and perceived from the patients

CONCLUSION

The in *vivo* results, obtained on burned skin as reported in Figures No.4,5, have shown that the realized advanced medications are able not only to rapidly repair and regenerate the skin, but also to prevent the bacterial infections. It was possible, in fact, to obtain an accelerated process of wound healing in a week in almost all patients, avoiding the need to remove the medication (in 23 patients out of 30) with an economical advantage for the hospital and the patient. In addition, the effectiveness and safeness, evaluated from the plastic surgeons and perceived from the patients also, were considered more effective in comparison with commercial classic medications, according to the results reported on Figure No.6.

Natural nanofibers as CN and bio-lignin have found applications especially to develop non-woven tissues for biomedical use and drug delivery device. They are preferred because of its easy biodegradability that avoids the post-removal process after application of the nanofibers into biological systems. CN-bio-lignin, and in particular the described electro spun tissues have shown to be able to carry cargos, such as nanosilver and other selective active ingredients, necessary to prevent infection while skin repair and regeneration occurs. Moreover CN-bio-lignin has evidenced to be bioresorbable at level of skin tissues, effective as re-ephitelialization agent and non toxic compound, because of its hierarchical structure identical to the macromolecules present in the extra cellular matrix (ECM), being easily electro spun by an economical method also. Additionally, early studies highlighted the immunoadiuvant and anti-inflammatory activities of low-sized chitin in humans, due to the presence in mammalian cells of chitinases which, with their chitinolytic activity, play a supposed role in the innate immune response to fungal and parasitic infections[29-31]. Finally the realized CN-bio-lignin non-woven tissue, made by natural raw materials obtained from biomass, has shown to be environmentally-friendly, skin-friendly and 100% biodegradable and, therefore, useful to decrease the dependence from fossil fuel resources, in agreement to the EU and UNEP programmes on bioeconomy[32,33]. These, the reason why nanomaterial has brought an important economic potential with an exponential increase of number of patents and market growth[34], and push us to go on with new researches to better understand the known and not jet discovered activities of both the fascinating nanochitin and nanolignin.

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CONFLICT OF INTEREST

All authors declare that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We declare that Pierfrancesco Morganti and Paola Del Ciotto work at the R and D Department of Mavi Nanoscience Center. The authors have no conflict of interest to declare.

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