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Nanoskin®-ACT—The Impact of Natural Membrane & Soft with Chronic and Untreated Wounds

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Abstract

Bacterial cellulose (BC) is a versatile biomaterial with unique properties that make it promising for various biomedical applications, including wound healing. The extracellular matrix (ECM) plays a crucial role in wound healing, providing a structural scaffold and signaling cues for cell migration and proliferation. This study investigates the potential of BC as a scaffold for ECM production and its effect on *in vivo* wound healing. In this work, the bacterial cellulose fermentation process is modified by the addition of Green Propolis and Usnic acid to the culture medium and natural materials before the bacteria are inoculated. *In vivo* behaviour using natural membranes for regenerative medicine is presented and it is in edit. Overall, our findings demonstrate the potential of BC as a scaffold for ECM production and its beneficial effects on *in vivo* wound healing. BC-based dressings may offer a novel approach to promoting wound healing and tissue regeneration in clinical settings. Further studies are warranted to optimize BC-based therapies and explore their full potential in regenerative medicine.

Keywords

Bacterial Cellulose, Biomaterials, Nanomedicine, Wound Healing, Green Propolis and Usnic Acid

1. Introduction

In recent years, bacterial cellulose has emerged as a promising biomaterial in the field of tissue engineering and regenerative medicine. Unlike plant-derived cel-

lulose, bacterial cellulose is produced by certain species of bacteria, such as Acetobacter xylinum, in a pure and highly organized form, offering unique advantages for biomedical applications. [1] [2]

One of the key characteristics of bacterial cellulose is its remarkable structural and mechanical properties. It has a highly porous and interconnected network of nanofibers, similar to the extracellular matrix found in human tissues. This structure provides an ideal environment for cell attachment, proliferation, and differentiation, making it an excellent scaffold for tissue regeneration. [1] [2]

Moreover, bacterial cellulose is biocompatible, biodegradable, and non-toxic, minimizing the risk of adverse reactions in the body. Its high purity and lack of immunogenicity further enhance its suitability for use in regenerative medicine. Additionally, bacterial cellulose can be easily manipulated into various shapes and forms, allowing for the fabrication of complex tissue scaffolds tailored to specific applications. [3] [4]

In tissue engineering, bacterial cellulose has been explored for the regeneration of a wide range of tissues, including skin, bone, cartilage, and blood vessels. Its ability to support the growth and differentiation of different types of cells has shown promising results in preclinical studies and holds great potential for clinical translation.

Furthermore, bacterial cellulose has been investigated for its drug delivery capabilities. Its high water content and porous structure enable the loading and controlled release of bioactive molecules, such as growth factors and drugs, which can enhance tissue regeneration and wound healing processes. [3] [4]

Chronic wounds, characterized by their failure to proceed through the normal stages of healing in a timely and orderly manner, pose a significant challenge in healthcare. These wounds, often associated with conditions such as diabetes, vascular disease, or pressure ulcers, can lead to serious complications and impaired quality of life for patients. [1] [3]

The extracellular matrix (ECM), a complex network of molecules that provides structural support to tissues, plays a crucial role in the wound healing process. In chronic wounds, however, the ECM undergoes significant alterations, leading to a dysregulated healing response. Understanding the role of the ECM in chronic wounds is essential for developing effective therapeutic strategies to promote healing and reduce the burden of these challenging wounds. [1] [3]

The ECM serves as a scaffold for cells involved in wound healing, providing mechanical support and signaling cues that regulate cell behavior. It is composed of various proteins, such as collagen, fibronectin, and laminin, as well as proteoglycans and glycoproteins, which interact with cells through specific receptors to modulate cell adhesion, migration, proliferation, and differentiation. [1] [3]

In chronic wounds, changes in the composition, organization, and mechanical properties of the ECM can impair these cellular processes, leading to a prolonged inflammatory phase, delayed re-epithelialization, and impaired tissue

remodeling. Factors such as elevated levels of proteases, increased oxidative stress, and aberrant ECM deposition contribute to ECM dysfunction in chronic wounds. [5] [6]

Recent advancements in our understanding of the ECM have led to the development of novel therapies aimed at modulating the ECM to promote healing in chronic wounds. Strategies such as the use of ECM-derived scaffolds, growth factors, and stem cells show promise in restoring the balance of the ECM and promoting a more favorable wound healing environment. [5] [6]

In conclusion, the extracellular matrix (ECM) stands as a central player in the complex orchestration of wound healing processes. Its dynamic composition and structure provide the necessary framework for cellular activities crucial to successful tissue repair. However, in chronic wounds, this balance is disrupted, leading to impaired healing cascades and persistent inflammation. [7] [8]

Understanding the intricate interplay between ECM components and cellular responses is key to developing targeted therapies for chronic wounds. Recent advancements in biomaterials and regenerative medicine offer promising strategies to manipulate the ECM environment, promoting a more conducive milieu for healing. [9] [10]

Besides, Nanoskin® ACT natural membranes have green propolis and usnic acid which is effective antibacterial agent and immunogenic substance. When it is linked to skin surface, it decreases the rejection body response. Such natural membranes change ECM synthesis that is produced in patient skin. [9] [10]

This article highlights possible paths for the functionalization of BC, affecting all levels of its structural organization. The focus is on post-production treatment of BC, although selected studies referring to in situ modifications during the biosynthesis process are also emphasized.

2. Materials and Methods

2.1. Materials

The bacterial cellulose raw material was provided by Innovatec's (São Carlos SP, Brazil). Green Propolis and Usnic acid were bought by Sigma Aldrich International.

2.2. Methods

Synthesis of Bacterial Cellulose and Green Propolis and Usnic Acid Extract

The acetic fermentation process was achieved by using glucose as a carbohydrate source. Results of this process are vinegar and a nanobiocellulose biomass. Bacterial cellulose (BC) is produced by Gram-negative bacteria Gluconacetobacter xylinus, which can be obtained from the culture medium in the pure 3-D structure, consisting of an ultra fine network of cellulose nanofibers. The modifying process was based on the addition of Green Propolis and Usnic acid (1% w/w) to the culture medium before bacteria inoculation and after bacterial cellulose hydrogel is dried in an oven to produce bacterial cellulose mats. [9]-[15]

2.3. Characterization

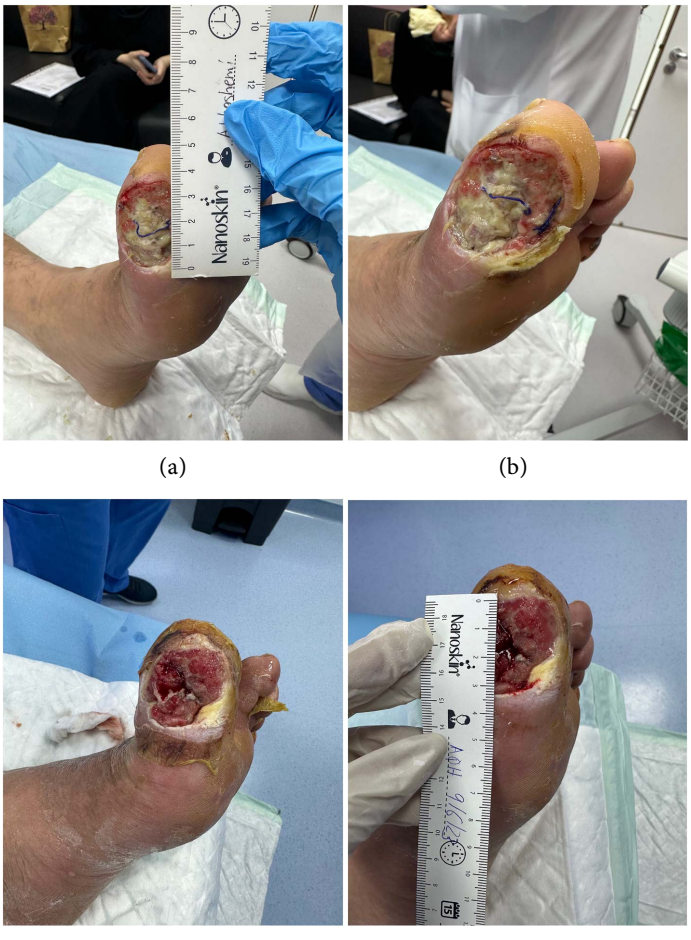
In vivo analysis—*In vivo* wound healing analysis of untreated and several chronic wounds.

3. Results and Discussion

***In Vivo* Analysis**

Case 1: Patient (H. H), Age: 68 Years, Gender: Male, Nationality: Algerian, Date of Admission: 11/05/2023.

History: Debridement of left big toe gangrenous patch. New patient, diabetic underwent incision and drainage of left big toe infection on 1/5/2023; PMH: Ischemic heart disease and hypertension: On Concor 5 mg, Clopidogrel, Lasix, Aspirin Diabetes: Sitagliptin/metformin, and glicazide; He underwent cardiac catheterization twice and has 3 stents Examination: there is a wound at the medial aspect of the left big toe with exposed tendon the wound is extending to plantar aspect of the toe, with slough present over exposed tendon and bone and discharge noted to have superficial ulcers between toes in all web spaces with evidence of fungal infection pulses felt; swab cultured reviewed and antibiotics started according to advise of infection control (Figure 1).



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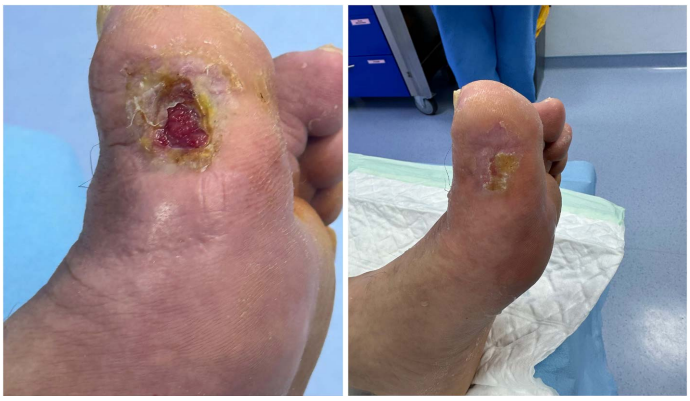


(e) (f)

Figure 1. Complete wound healing with untreat diabetic wounds using Nanoskin-ACT less than 3 treatment months (but only during 83 treatment days).

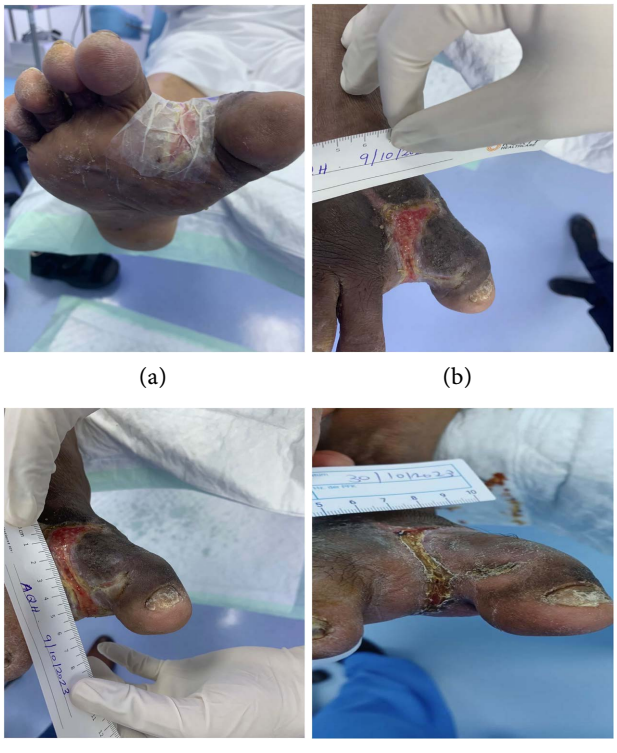
Case 2: A. R. Age: 61 Years Gender: Male. Nationality: UAE. FIRST VISIT: 10/08/2023.

History: RIGHT Diabetic FOOT WOUND

Post 4d tissue bioprinting done 27/9/2023

Doing well on Nanoskin ACT with Biogel

Start treatment with Nanoskin ACT DD 09/10/2023, Last Follow-Up on 30-10-2023 Wound is healed completely. (**Figure 2**)



(a) (b)

(c) (d)

Figure 2. Complete wound healing in site infection with Nanoskin-ACT during only 20 treatment days.

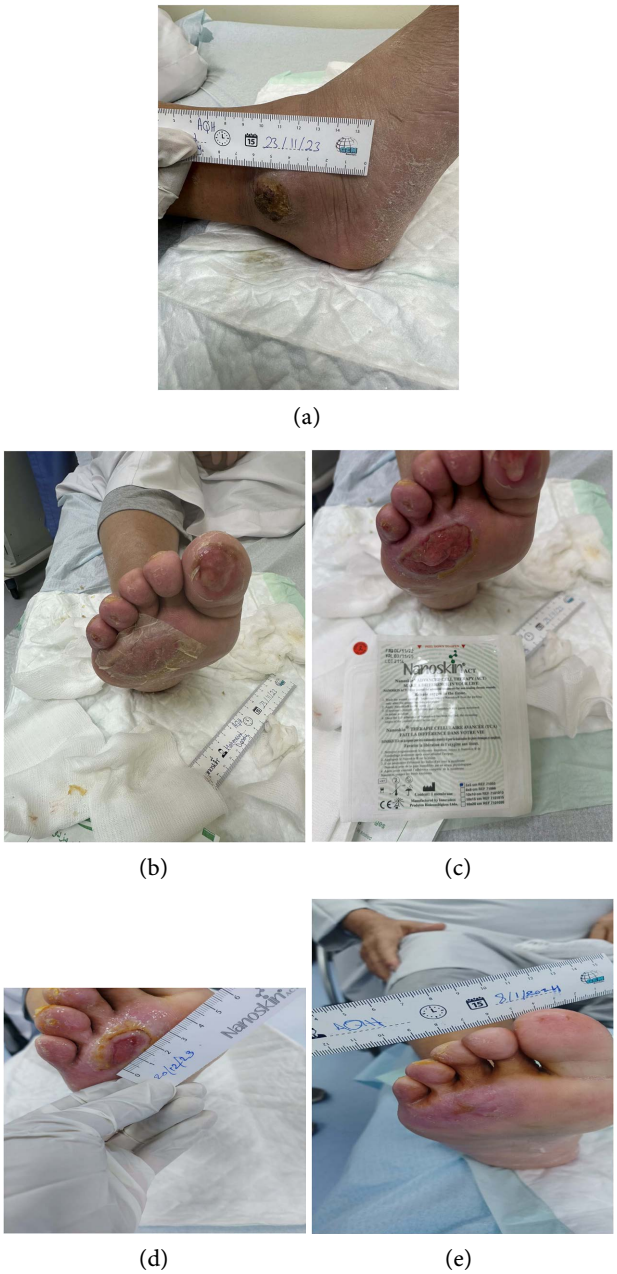
Case 3: M. D., Age: 67 Years, Gender: Male. Nationality: Syrian.

First Consultation with Surgical: 04/01/2023

History: Right diabetic foot ulcer, no offloading, 4 months duration

Superficial ulcer at plantar aspect of distal foot and the big toe; Raw area in the plantar aspect of the base of the toes on the right side. Unhealthy granulation. Blister noted on the plantar aspect of great toe on the same side.

Then First Visit in Wound Clinic DD 23/11/2023 & Start with Treatment Nanoskin ACT. Wound completely healed in 08/01/2024. (**Figure 3**)

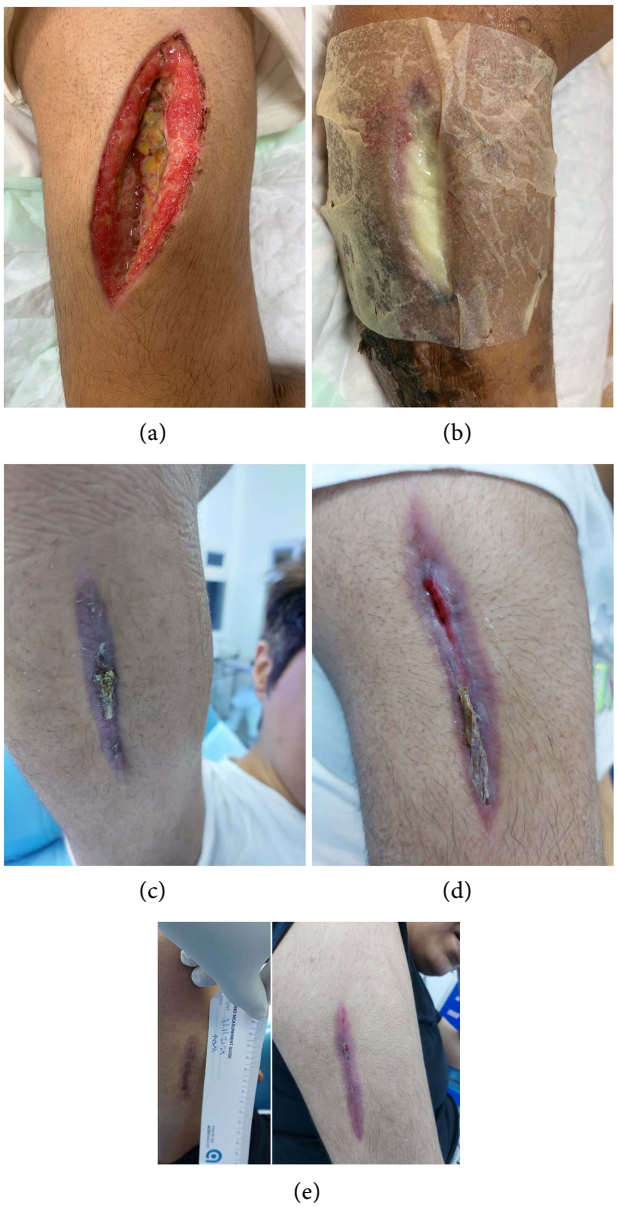


(a) (b) (c) (d) (e)

Figure 3. Complete wound healing in diabetic foot ulcer with Nanoskin-ACT during only less than 2 treatment months (but only during 46 treatment days).

Case 4: A. M., Age: 33 Years, Gender: Female, Nationality: UAE. Date of Admission: 10/11/2023 Treatment with Nanoskin ACT & Nanoskin ACT Soft began DD 27/11/2023 and Wounds completely healed 03-1-2024.

History: Right upper limb cellulitis with fasciotomy done on 15/11/2023. Diabetic with poor treatment History of lymphedema; Patient has 4 wounds at right arm and right forearm anterior and posterior aspect, Largest at posterior aspect of right arm with deemed sloughy wound. (Figure 4)



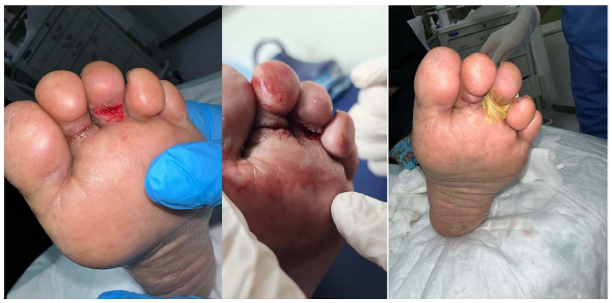
(a) (b) (c) (d) (e)

Figure 4. Complete wound healing in diabetic ulcer with Nanoskin-ACT during only less than 2 treatment months (but only during 37 treatment days).

Case 5: S. Q., Age: 67 Years, Gender: Female, Nationality: UAE. First Visit to OPD: 27/04/2023. Treatment with Nanoskin ACT & Biogel Activator began DD

27/04/2023 and Wounds completely healed 18-05-2023.

History: Diabetic patient, sustained trauma to left foot, she stepped at edge of the metal gate on Eid day with injury to plantar aspect of second and third toes, had significant bleeding at time of trauma. Examination: third toe has a small cavity with sloughs and evidence of hematoma. (Figure 5)



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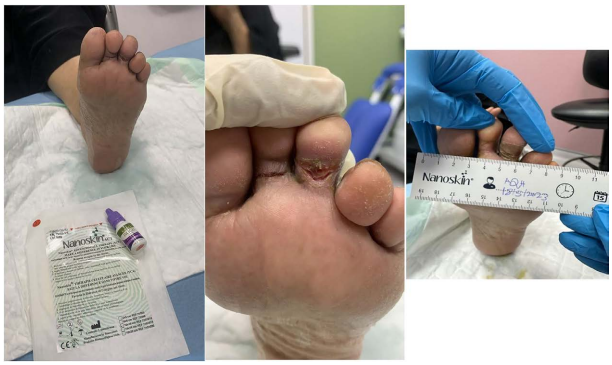


(b)

Figure 5. Complete wound healing in diabetic ulcer with Nanoskin-ACT during only less than 1 treatment month (but only during 22 treatment days).

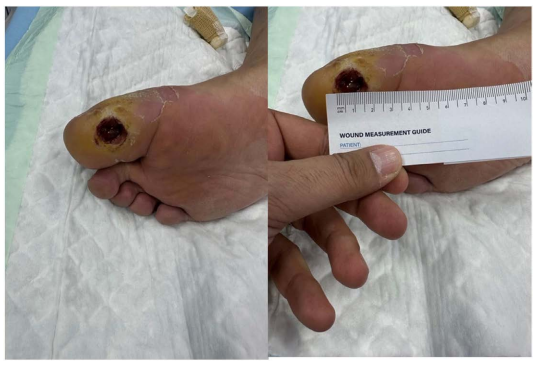
Case 6: M. A. R., Age: 46 Years, Gender: male, Nationality: Bahrain. First Visit to OPD: 15/05/2023 Treatment with Nanoskin ACT & Biogel Activator began DD 15/05/2023 and Wound completely healed 10-07-2023.

History: Recurrent right big toe ulcer; started on steroids for flare of ITP, not off loading properly

Type of Wound [right foot ulcer] [chronic]. Measurement The size of the wound measured in centimeters length 1 cm, width 0.5 cm, depth 0.2 cm the location and depth of any tunnelling or undermining.

Wound under right big toe Wound Bed clean tissue type [epithelial, granulation Coloring level of adherence using percentages 20% Wound Edges [wound's edges are defined, attached, rolled under, macerated, fibrotic, or callused]. Drainage The amount of drainage nill type of drainage include [serous, purulent. amount of drainage assessed IS MODERATE Odor [no odour]. Surrounding Tissue: pallor of the surrounding skin. signs of edema, Infection Wounds are of-

ten prone to infection, which can significantly disrupt the healing process. Any indicators of infection, including redness or localized pain [Pain no pain]. Surgery for L4-L5 disc prolapse 15 years ago. (Figure 6)



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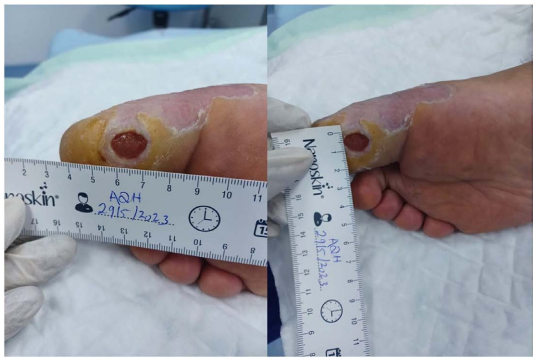

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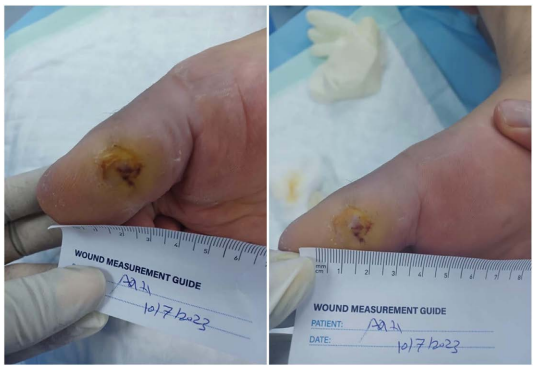


(c)

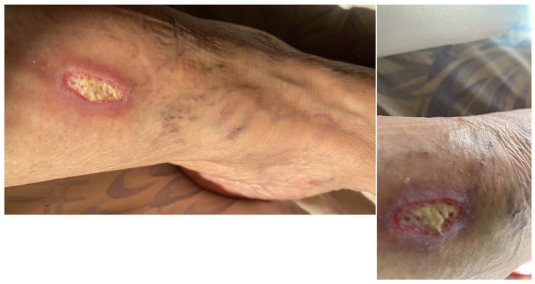
Figure 6. Complete wound healing in diabetic ulcer with Nanoskin-ACT during only less than 2 treatment months (but only during 57 treatment days).

Case 7: F. S., Age: 67 Years, Gender: Female, Nationality: UAE. First Visit to OPD: 15/05/2023 Treatment with Nanoskin ACT & Biogel Activator began DD 15/05/2023 and Wound completely healed 03-06-2023. (Figure 7)

History: Infected Acute wound

Rabbit bite; left lower leg

Wound size: (L 1.5 cm, W 0.5 cm, D 0.3 cm)
After one day and wound came clean
Last Application DD 03/06/2023 & wound got completely healed.



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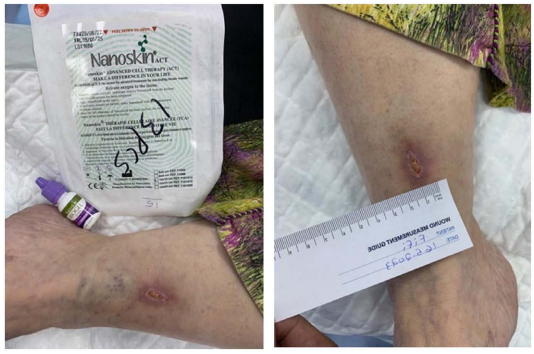

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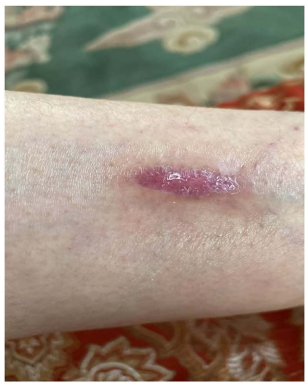

(c)

Figure 7. Complete wound healing in infected acute wiund with Nanoskin-ACT during only less than 1 treatment month (but only during 19 treatment days. (b) Oafter one day and wound coming clean; (c) Last Application DD 03/06/2023 & wound got completely healed.

4. Conclusions

In conclusion, bacterial cellulose (BC) emerges as a promising biomaterial for enhancing *in vivo* wound healing through its ability to support extracellular matrix (ECM) production. The unique properties of BC, including its high purity, biocompatibility, and structural similarity to native ECM, make it an excellent

scaffold for promoting tissue regeneration.

Studies have shown that BC can stimulate the deposition of key ECM components, such as collagen and fibronectin, in the wound bed.

The integration of BC-based dressings into wound care holds great potential for improving clinical outcomes in patients with chronic wounds. Future research should focus on optimizing BC-based therapies, exploring their mechanisms of action in ECM modulation, and conducting clinical trials to validate their efficacy and safety in human patients.

Overall, BC-based therapies represent a promising strategy for enhancing *in vivo* wound healing by leveraging the regenerative potential of the ECM. But, undoubtedly, natural-origin polymers or nature-inspired materials appear as the natural and desired choice for medical applications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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