Development of natural dermaceuticals based on a novel atelocollagen complex for oncological wound healing

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INTRODUCTION

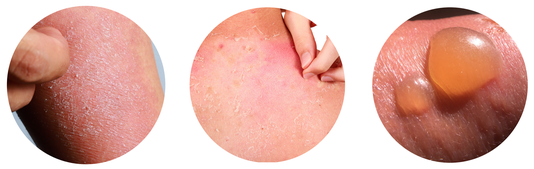
Current treatments are resulting in higher survival rates and improved quality of life for oncology patients, however dermatological toxicities are still a major concern.

Skin side effects often lead to patients' noncompliance with receiving treatment and available options for skin care management are still limited and not effective.

The current study supports the development of natural topical products based on a novel water-soluble atelocollagen complex specially formulated to penetrate through skin layers, alleviate skin issues and promote wound healing.

Common skin conditions during oncology treatment

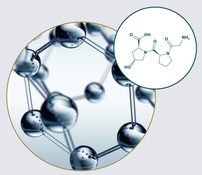
Skin inflammation, Brittle nails and cracking cuticles, Stomatitis, Malignant wounds



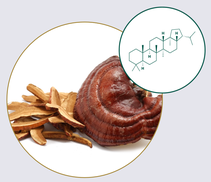
Atopic dermatitis, Radiation dermatitis, Chemotherapy extravasation

Key ingredients in our products

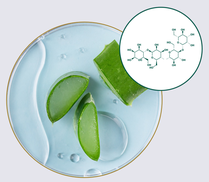
Gynura procumbens



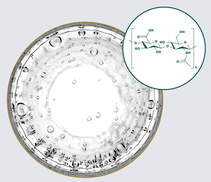
Collagen peptides



Ganoderma lucidum

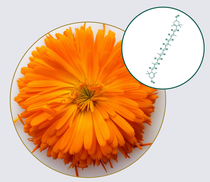


Aloe vera



Hyaluronic acid

Balsam oil

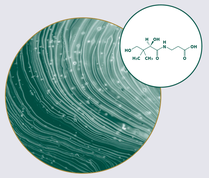


Calendula officinalis

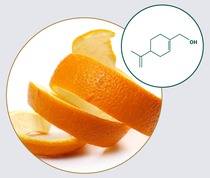
Shea butter

Cannabis seed oil

Grapeseed oil



Panthenol



Sweet orange peel oil

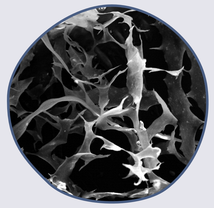
Cucumber extract

Chamomile extract

Lavender essential oil

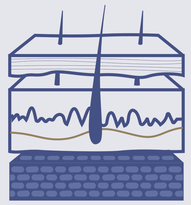
OUR PROPOSED SOLUTION

NOVELTY OF THE PROJECT



Novel medical-grade atelocollagen developed
by Promed Bioscience and tested by CUT

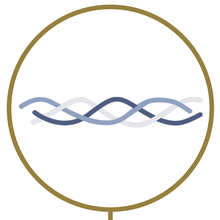
Blending of natural products with molecularly engineered materials
developed by RSL Revolutionary Labs



***In vitro* efficacy and toxicity testing in 3D skin models**
by Theramir

Clinical trials and assessment of patients' quality of life
by GOC and CUT

MATERIALS & METHODS

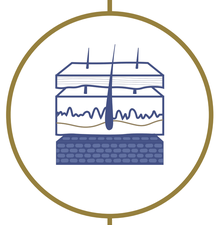


New collagen development
Triple-helix atelocollagen was developed from porcine tendons via enzymatic and thermal modifications resulting in a protein complex of three distinct MW (up to 20, 60 and 120kDa).

Characterization of biomaterial
Atelocollagen was modified to a water-soluble state and characterized using SDS-PAGE, Amino Acid Analysis, and Scanning Electron Microscopy.

Mechanical testing
Mechanical testing of the biomaterial was performed by swelling, viscosity, solubility and contact angle assays.

Formulation compatibility
Formulation blending using natural extracts of aloe vera, ganoderma, balsam oil, grape seed oil, gynura, cannabis seed oil, panthenoic acid and hyaluronic acid was performed at different phases and concentrations.



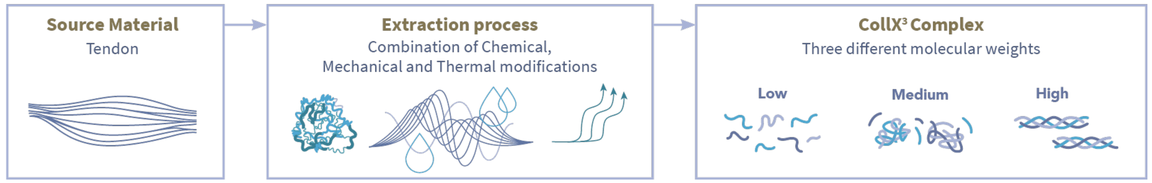
In vitro biocompatibility
3D-skin assays and ex vivo blood and skin assessment
The final topical formula was tested for in vitro biocompatibility, irritation, toxicity and efficacy using cell monolayers, 3D-skin assays and ex vivo blood and skin assessment.

Multicenter clinical trial
(NCT05588973) Now recruiting

CHARACTERIZATION OF NOVEL ATELOCOLLAGEN COMPLEX

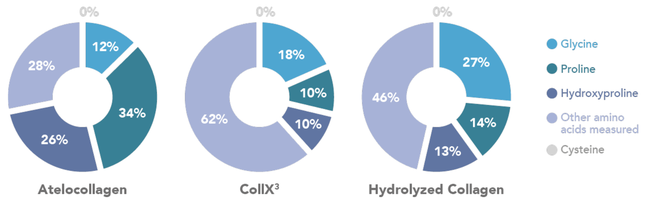
Unique Method of Production

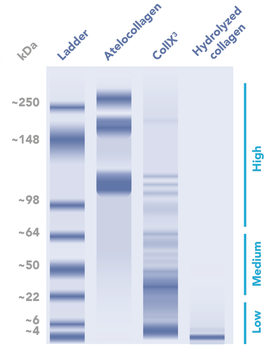
The protein complex is created through a series of chemical, thermal, and mechanical modifications that yield collagen of three distinct molecular weights, with reduced antigenicity and enhanced biocompatibility.



Key Characteristics of a High-Quality Collagen Formulation

CollX³ boasts an amino acid profile that closely resembles the natural collagen molecule. Glycine, the most abundant single amino acid in collagen, is also present in significant quantities. It is also rich in Hydroxyproline, Alanine, Glutamic acid, Proline, and Hydroxyl residues, which contribute to its unique composition. Notably, Cysteine content in CollX³ is negligible.

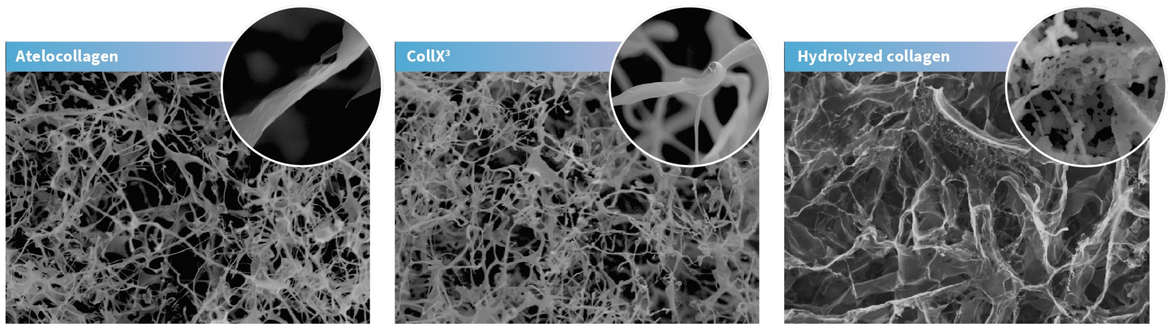




SDS-PAGE protein analysis of CollX3 confirms the presence of three distinctive ranges of molecular weight, characteristic of collagen.

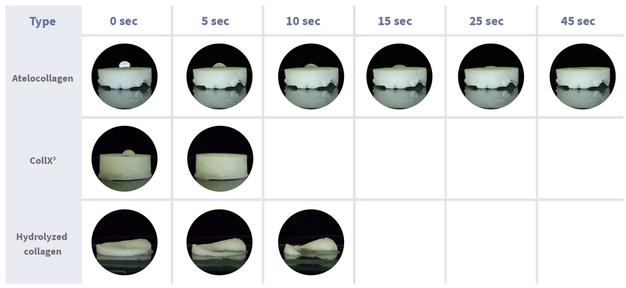
Microstructural Characteristics of CollX³

Unlike commonly used hydrolyzed collagen peptides, CollX³ maintains the fibrillar and porous structure of full-length atelocollagen. This unique property of CollX³ enables improved incorporation into the microenvironment of cells and tissues, making it a superior choice for skin regeneration applications.

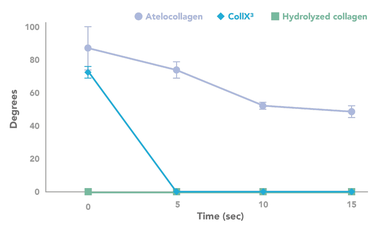


CollX³ – Hydrophilic Collagen Innovation

CollX³ exhibits superior hydrophilic properties as water droplets rapidly dissolve upon contact with its surface. CollX³'s remarkable wettability characteristics enhance its biocompatibility and highlight its versatility as a biomaterial for skin regeneration applications.



The graph highlights the contact angle measurements of CollX³ with deionized water for up to 15 seconds. This data demonstrates the hydrophilic nature of CollX³ and its superior wettability characteristics.

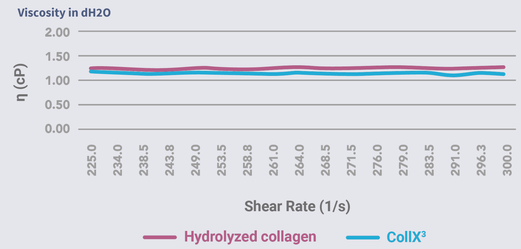


FORMULATION BLENDING OF PROTOTYPING CREAM

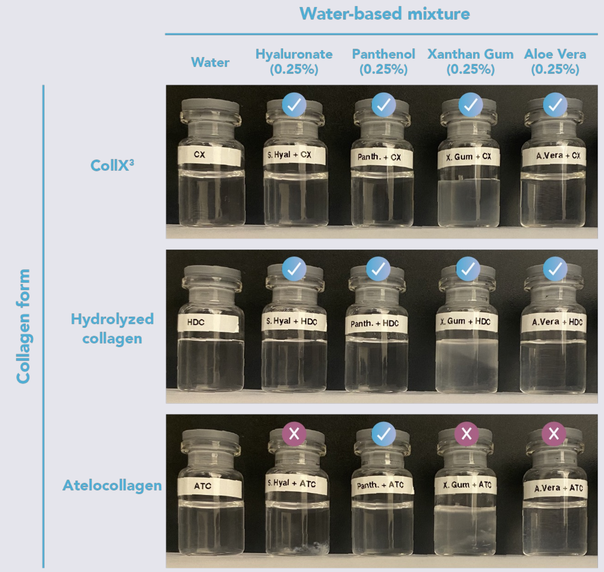
Optimal Blending Characteristics

CollX³ exhibits excellent compatibility with commonly used cosmetic raw materials, leading to the formation of a uniform solution. This renders it an ideal choice that is equally suitable as standard hydrolyzed collagen for cosmetic product formulations.

Additionally, CollX³ demonstrates remarkable stability in various mixtures over a 30-day period at room temperature, making it a reliable choice for cosmetic product blending.



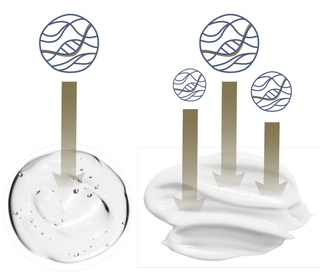
The viscosity and rheological properties of CollX³ closely resemble those of hydrolyzed collagen, exhibiting constant shear rate behavior when diluted in water. This makes CollX³ an ideal choice for formulations where consistent flow characteristics are desired.



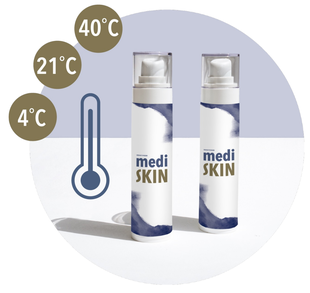
Diluent	Sample	Mean value (cP)	Fluid characterization
H2O	PRO-2003	Not possible to be measured	–
	Hydrolyzed collagen	1.27	Newtonian
	Complex	1.18	Newtonian

Optimal Blending Characteristics

Testing for optimal blending characteristics of a new raw material in a topical cream requires a systematic and comprehensive approach that takes into account the physical properties, compatibility, and performance of the cream. Optimal blending characteristics of a new raw material in a topical cream involves several steps: Initial physical testing such as visual inspection and basic rheology, to determine the basic properties of the cream. Compatibility testing including stability testing, which assesses the shelf-life of the cream, as well as sensory testing, which evaluates the texture and appearance of the cream. Optimization by adjusting the formulation as necessary to optimize the blending characteristics of the new raw material in the cream. Final validation such as microbiological testing, to ensure that it meets regulatory and quality standards.



Physical and chemical characterization

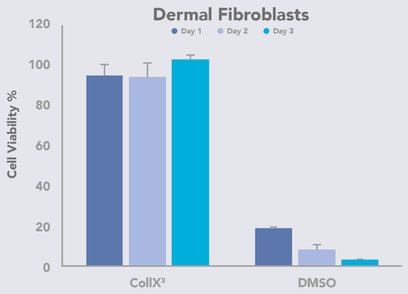


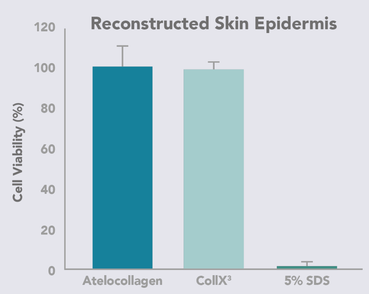
Stability testing during a variety of conditions

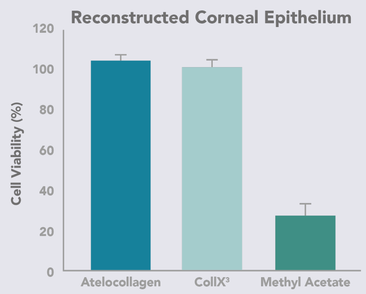
Microbiological assessment and conservation level

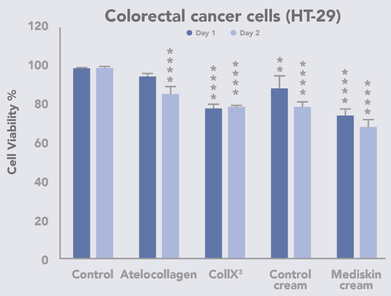
Biocompatibility Assessment of novel cream formulation

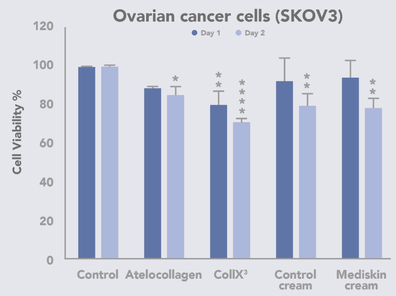
In vitro evaluation of CollX³ reveals outstanding biocompatibility, with no observed toxicity and no induction of cell death in human dermal fibroblast cells. Moreover, in vitro skin irritation test of CollX³ shows no signs of irritant activity or change in cell viability in reconstructed human skin epidermis and corneal epithelium[6]. Additionally, tumorigenicity assessment demonstrates that CollX³ is non-carcinogenic, rendering it safe for dermaceutical applications.









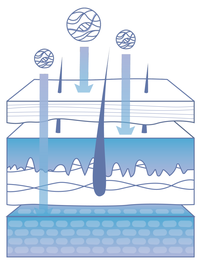


Non irritant
(does not affect cell viability)

Non toxic
(does not cause cell death)

Safe to use
(non-tumorigenic)

Advanced Skin Penetration and Cellular Benefits of CollX³



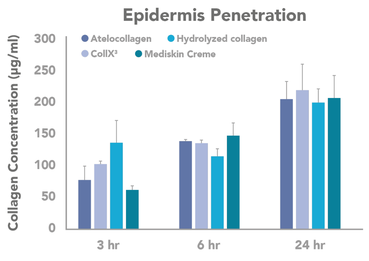
***de novo* PRODUCTION**

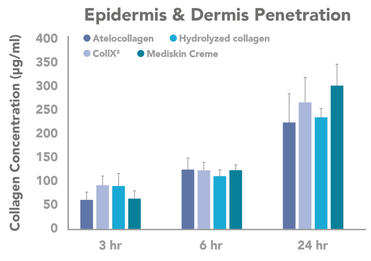
Elastin

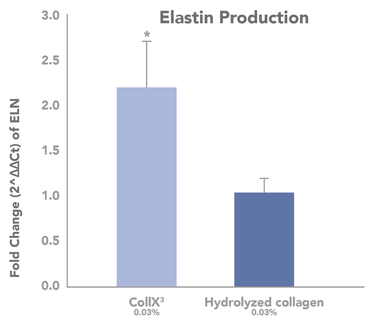
Type I collagen

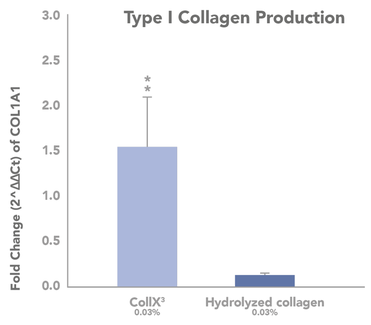
In ex vivo experiments on human skin tissues, CollX³ demonstrates enhanced permeability through both the single layer (epidermis) and double layers (epidermis & dermis) of the skin.

Moreover, CollX³ stimulates the expression of Type I collagen and elastin in dermal fibroblast human skin cells (assessed by qPCR analysis), highlighting its potential to positively impact skin health and function.





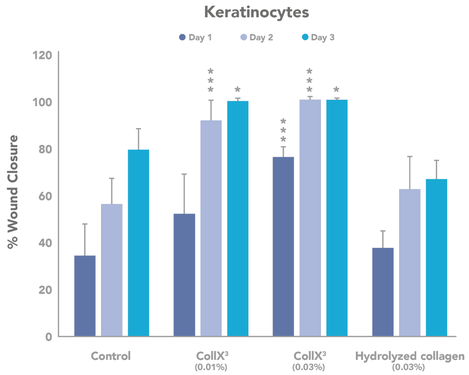


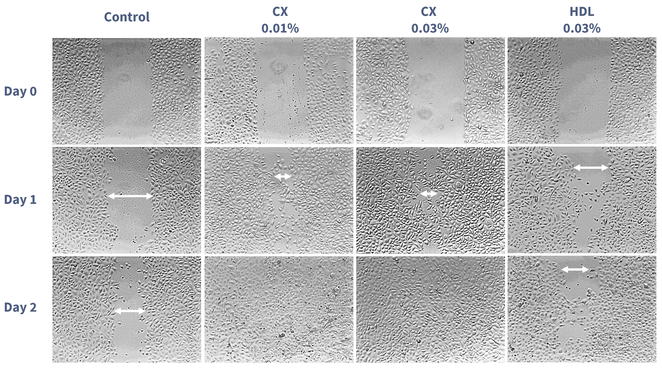


Assessing healing efficacy

In vitro wound healing assessment

Investigation into the effect of CollX³ on wound healing demonstrates accelerated wound closure compared to negative control (no treatment), as well as compared to treatment with hydrolyzed collagen peptides, which are commonly used in many topical formulations. This highlights the superior wound healing efficacy of our novel atelocollagen complex.

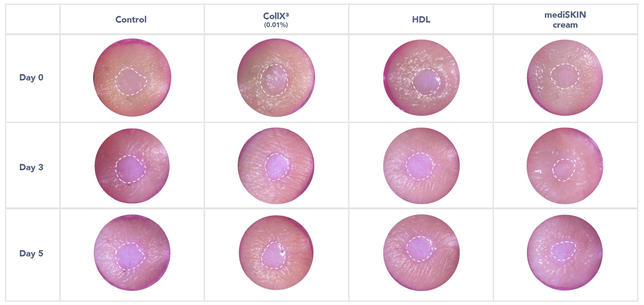


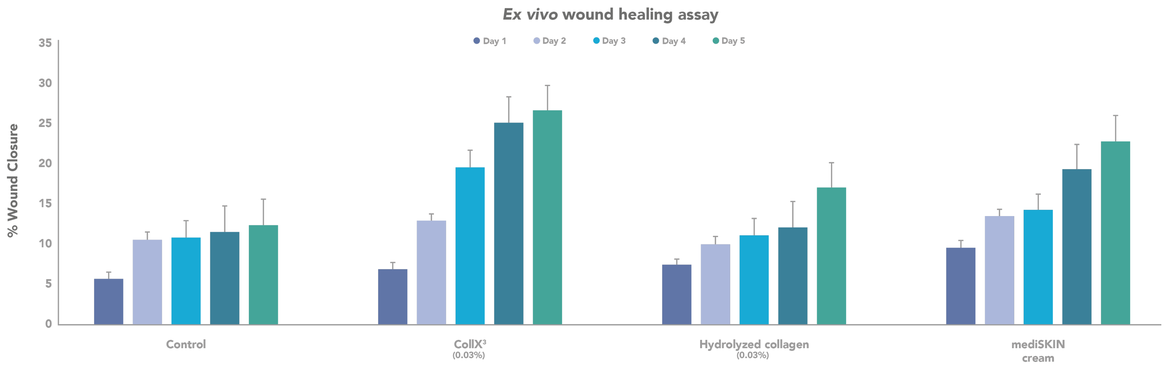


Ex vivo wound healing assessment

Wound healing efficacy of novel CollX³ and mediSKIN formulation was evaluated in an *ex vivo* skin wound model. Treatment with both newly developed formulas accelerated wound healing dynamics compared to control and hydrolyzed collagen. The observed acceleration confirms the efficacy of mediSKIN for tissue regeneration.

In this study, full thickness 8 mm skin biopsies were wounded in the centre with 4 mm biopsies, and then introduced into well chamber inserts and maintained with supplemented growth media. Various treatments, were topically applied to the wound. Images were captured every 24 hrs for 5 days and the percentage of wound closure was calculated.





Discussion

The present investigation provides evidence to support the advancement of natural topical agents that employ a new water-soluble atelocollagen complex, specifically designed to permeate the layers of the skin, ameliorate dermatological conditions, and stimulate tissue repair. The development of mediSKIN cream involved meticulous testing and optimization procedures.

This topical formulation has been granted approval as a cosmetic-grade product by the Cyprus Pharmaceutical services of the Ministry of Health ((File no 21.14.10 No of Cert: 07/2022 and European CPNP Portal notification number: 4091379). A multicenter clinical trial is currently underway to assess the efficacy of mediSKIN and CollX3 in wound healing. The trial is actively recruiting participants in Cyprus and Greece (NCT05588973).

Clinical trials patients in Cyprus under radiotherapy treatment

Breast cancer 80

Head & neck cancer 40

Clinical trials patients in Greece under radiotherapy and chemotherapy treatments

Breast cancer 100

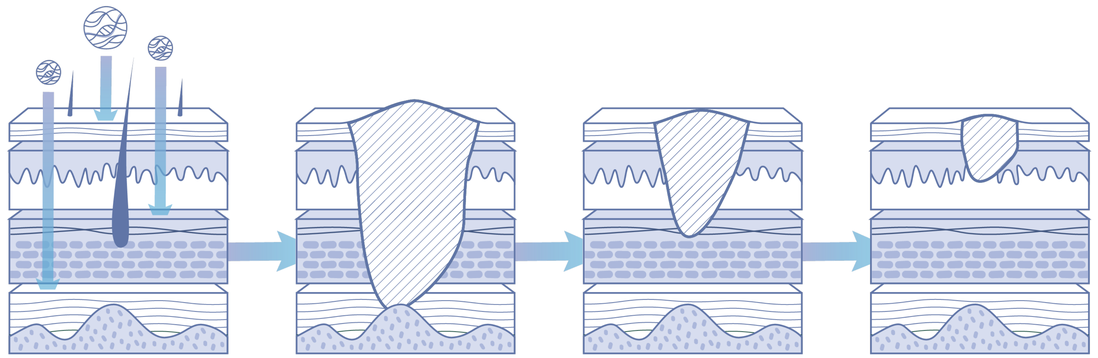
Lung cancer 100

Conclusion

In conclusion, the development of a novel water-soluble triple-helix atelocollagen presents a promising solution for oncological wound healing applications.

The retention of triple helices is a critical factor in collagen binding with wound exudating growth factors and cytokines, thereby ensuring mechanical stability in the hydrated state of the injury.

These findings offer potential avenues for the advancement of wound healing therapies that employ this innovative atelocollagen complex.



SEED/0719/0200 mediSKIN

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RESEARCH & INNOVATION FOUNDATION

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[1] ClinicalTrials.gov, NCT05588973, Prevention of Radiodermatitis in Breast and Head and Neck Cancer Patients in Cyprus and Greece. [2] Yousef H, Alhajj M, Sharma S. Anatomy, Skin (Integument), *Epidermis.* [Updated 2022 Nov 14]. [3] Mh Busra, F, Rajab, NF, Tabata, Y, Saim, AB, B.H. Idrus, R, Chowdhury, SR. Rapid treatment of full-thickness skin loss using ovine tendon collagen type I scaffold with skin cells. *J Tissue Eng Regen Med.* 2019; 13: 874– 891. [4] Anne L. Plant, Kiran Bhadriraju, Tighe A. Spurlin, John T. Elliott, Cell response to matrix mechanics: Focus on collagen. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research,* 2009; 1793:5. [5] Meilang Xue and Christopher J. Jackson. Extracellular Matrix Reorganization During Wound Healing and Its Impact on Abnormal Scarring. *Advances in Wound Care.* Mar 2015.119-136.
[6] EU Test Method Regulation (440/2008/EC).