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Novel sponge formulation of mesenchymal stem cell secretome and hyaluronic acid: a safe and effective topical therapy for *Psoriasis vulgaris*

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Abstract

Background *Psoriasis vulgaris* is the most common form of psoriasis, yet current treatments often lead to significant side effects, resulting in a high rate of therapy desertion. Here, we explored a novel therapeutic approach using the secretome from Wharton Jelly-derived mesenchymal stem cells, biologically stabilized and enhanced with hyaluronic acid (HA), its presentation is an easy-to-apply topical sponge. This formulation had previously demonstrated efficacy in vitro and in experimental psoriasis mouse models.

Methods In vitro characterization studies included dynamic light scattering, nanoparticle tracking analysis, optical/electronic microscopy, microbiological experiments, and angiogenic capacity (HUVEC cells). In vivo studies included angiogenic capacity in chicken embryo chorioallantoic membrane (CAM), safety (hypersensitive and healthy volunteers), and efficacy (double-blinded and randomized patients).

Results We demonstrated the presence of spherical exosomes (164 ± 87 nm, PDI of 0.38, and 1.5×10^7 particles/mL) within the selected secretomes, which exhibited significant proangiogenic activity in HUVEC cells and in a CAM assay. The secretome-containing sponges displayed distinct physicochemical properties, such as the absence of nitrogen and reduced carbon and oxygen content, resulting in a more cross-linked material with thinner fibers. These characteristics extended the dispersion time in aqueous media. Microbiological testing confirmed sterility in the packed, ready-to-use secretome-HA sponges after 3 months of storage. To assess safety, we selected doses (based on total protein content) that were applied to three patients with atopic dermatitis (42 µg of protein, patch test, 5 days) and four healthy volunteers (210 µg, 15 days) with no observed adverse topical or systemic effects. In a 30-day

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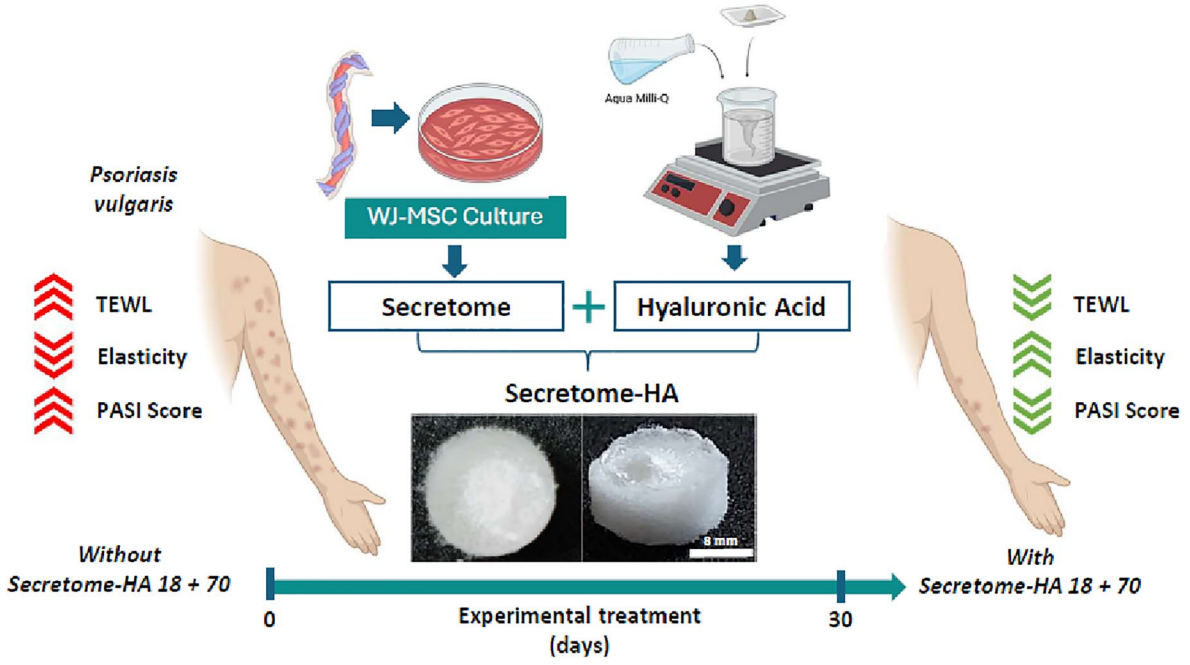
efficacy study, 12 patients with bilateral psoriasis exhibited up to a 33% reduction in mPASI scores and a 41% decrease in plaque size. Additionally, transepidermal water loss (TEWL) was reduced by up to 30%, while skin elasticity/flexibility improved by 43%.

Conclusions These findings suggest that the topical application of the secretome-HA sponge is a safe and effective therapeutic option for alleviating symptoms of *psoriasis vulgaris*.

Trial registration SSMN, SSMN047/2021. Registered 27 October 2021, https://www.ssmn.cl/comite_etica.php.

Graphical abstract



Keywords Mesenchymal stem cell, Secretome, Exosomes, hyaluronic acid, *Psoriasis vulgaris*, MSC-based therapy, cutometer

Introduction

Regenerative medicine has made significant strides in treating various diseases, including those associated with skin inflammation. Notably, efforts have been focused on rejuvenation, wound healing, and scar healing [1]. Our research introduces a promising therapeutic option for dermatologic conditions, such as psoriasis, offering a safe, effective, and easy-to-administer treatment for managing this chronic inflammatory disorder. Psoriasis, as a chronic inflammatory skin disorder, is characterized by excessive keratinocyte proliferation and differentiation, infiltration of multiple immune cells, and increased dermal vascularity, culminating in erythematous plaques with scales. Its prevalence ranges from 0.2 to 1.66% globally [2]. Beyond being a skin disorder, psoriasis is a systemic inflammatory disease linked to complications such as metabolic syndrome, hypertension, type 2 diabetes, cardiometabolic disease, psychological illnesses, and inflammatory bowel diseases [3, 4]. *Psoriasis vulgaris*, the most prevalent form, affects approximately 90% of psoriatic patients [5, 6].

To assess the severity of psoriasis, dermatologists rely on the "Psoriasis Area and Severity Index (PASI) score", which evaluates erythema (redness), desquamation (scaliness), and induration (thickness) of lesions on a scale from 0 (absent) to 4 (severe) [7, 8]. Additional parameters, such as Transepidermal Water Loss (TEWL), elasticity/flexibility, surface pH, hydration of the stratum corneum (SCH), temperature, melanin content, and erythema index, are also crucial for evaluating skin functionality [9–12]. In psoriatic patients, disruption in the skin barrier results in elevated TEWL and reduced elasticity [13].

A wide range of treatment options exist for psoriasis, including corticosteroids, phototherapy, and systemic or biological agents. While these interventions often improve symptoms, they are associated with significant side effects, and lesions frequently recur at previously

affected sites within months of remission, with a high-rate therapy desertion [14]. This highlights the urgent need for safer and more effective therapies or complementary treatments to enhance the efficacy of existing options.

Mesenchymal Stem/Stromal Cells (MSC) exhibit potent immunomodulatory and effector T-cell suppressive properties, making them attractive candidates for managing T-cell mediated disorders like psoriasis [15]. MSCs can be isolated from various sources, including human Wharton's Jelly-derived mesenchymal stem cells (hWJ-MSC), umbilical cord (UC-MSC), bone marrow (BM-MSC), and adipose tissue (AD-MSC). Each source offers distinct therapeutic benefits for inflammatory skin conditions [14]. Case studies have highlighted the potential use of MSCs in psoriasis treatment. Still, variability in cell source, culture methods, and donor type (autologous versus allogeneic) has posed challenges for consistent comparison across studies [16–18].

The conditioned medium, or secretome, from MSCs encompasses growth factors, cytokines, and extracellular exosomes; this secretome has shown promising preclinical efficacy in mitigating psoriasis-like skin lesions [14, 19, 20]. Despite these promising findings, challenges remain regarding the standardization of MSC culture protocols, optimal dosing, administration routes, and long-term safety assessments [21]. Another key limitation is the preservation and delivery of the secretome, as biological materials are prone to contamination and require specific storage conditions, such as freezing at -80 °C.

Polymeric sponges offer a practical solution for delivering secretomes, as they are stable, easy to handle, and transportable [22]. These materials also demonstrate substantial therapeutic potential [23–26]. Depending on the polymer used, the hydrated sponge forms a gel-like material with bioadhesive properties suitable for application to affected tissues [23, 27–31]. Another significant benefit for commercial applications is that these polymeric sponges can be produced using a simple mixture of safe components, dissolved or dispersed in an aqueous medium, and able to produce a dry product by lyophilization [32]. The above strategy minimizes the risk of toxicity or unexpected effects. However, when incorporating drugs into polymeric sponges, it is essential to conduct a case-by-case analysis of the compatibility of active components with the polymer matrix and their effects on sponge formation, as well as to carefully evaluate their influence on the sponge formation during the lyophilization process [32]. Our group has developed an innovative drug delivery system combining human conditioned media/secretome from hWJ-MSC (WJCM) with hyaluronic acid (HA) to create a lyophilized sponge formulation for psoriasis treatment [20]. This secretome-HA sponge allows topical self-administration while preserving the stability and properties of the active ingredients. Preclinical studies have demonstrated that this formulation significantly improves psoriasis signs, including reducing the PASI and alleviating aberrant angiogenesis. It also reduces the discomfort associated with psoriasis, ultimately leading to a complete recovery of body weight in a mice model [20].

In this study, we investigated critical aspects of the secretome-HA sponge, including the characterization of the exosomes in the secretome, and the concentration of the atoms within the sponge after enrichment with the secretome. Additionally, we studied the effects of secretome enrichment on the material's morphology and dispersion in an aqueous medium, which is the preferred environment for patient application. Microbiological safety assessments confirmed the absence of contaminants. Our clinical safety and efficacy design were evaluated using TEWL, skin elasticity/flexibility (R0) parameters, modified PASI (mPASI) score, and plaque size. These results validate the secretome-HA sponge as a potential therapeutic intervention for psoriasis, offering a safe, effective, and easy-to-administer treatment option for managing this chronic inflammatory condition.

Materials and methods

Cell culture, secretome obtention and Microbiological test

Nine umbilical cords were obtained by donation from healthy women thanks to a collaboration agreement with Dr. Luis Tisné Brousse Hospital. The medical background of donors was based on clinical criteria established by Prieto et al. 2017 [33]. Independent ethics committees from the University of Chile (2134-FCS-UCH), Dr. Luis Tisné Brousse Hospital (RES EX 5843), and Servicio de Salud Metropolitano Oriente (SSMO) approved the study (10/27/2021 CEI-SSM.NORTE). hWJ-MSC were isolated, cultured, and characterized according to previously established protocols [20, 34]. Cell isolation and culture were carried out following previously published protocols [33, 35]. Briefly, primary hWJ-MSC cultures were obtained by dissecting umbilical cords to remove blood vessels, cutting the tissue into 2 mm^2 pieces, and digesting with collagenase I (1 g/L; Gibco, Life Technologies, Carlsbad, CA, USA) in phosphate-buffered saline (PBS; in mM: NaCl 136, KCl 2.7, Na_2HPO_4 7.8, KH_2PO_4 1.5, pH 7.4) under gentle agitation at 37 °C for 16 h to disaggregate the tissue. The cell suspension was then centrifuged (2000 rpm, 10 min), and the resulting pellet was washed and seeded in DMEM (Life Technologies) supplemented with 10% fetal bovine serum (FBS; Hyclone, Logan, UT, USA) and antibiotics (100 U/mL penicillin/streptomycin; Thermo Scientific, Waltham, MA, USA). Cells were maintained at 37 °C in a 5% CO_2 atmosphere for 24 h. Adherent cells were cultured under the same conditions,

with medium changes every 2–3 days, and used between passages 2 and 5. Individual cell cultures were established from each umbilical cord to obtain the corresponding secretome. Subsequently, three distinct secretomes were pooled for the preparation of the sponge. A 48-hour derived-conditioned media/secretome (WJCM) from different donors was harvested and stored at -80 °C until use. To test the presence of *Mycoplasma spp*., all media, stem cell cultures, and secretomes were stained for DAPI and tested by DNA amplification encoding 16 S rRNA by PCR. Human umbilical vein endothelial cells (HUVEC) were obtained from full-term umbilical cords and cultured as previously described [34].

Analyses of the size, morphology, and concentration of exosomes isolated from the secretomes

The exosomes were isolated following a protocol adapted from Théry et al. (2006) [36] with some modifications. Briefly, the supernatant of hWJ-MSC conditioned medium was subjected to sequential centrifugation steps: 300 g for 10 min, 2,000 g for 10 min, 10,000 g for 30 min, and 100,000 g for 70 min. At each stage, the pellet was discarded, except for the final step, where the pellet containing the exosomes was retained. The final pellet was washed with PBS and centrifuged at 100,000 g for 70 min to purify the exosomes further. The exosomes' hydrodynamic diameter and polydispersity index (PdI) were determined using Dynamic light scattering (DLS; Malvern Instruments, UK). The morphology of the exosomes was assessed via scanning transmission electron microscopy (STEM, STEM, Inspect F-50, FEI, Netherlands). For STEM imaging, 20 µL of the sample was placed onto copper grids covered in a polymeric layer (Formvar®) and a carbon film. To enhance contrast, the grids were stained with a 1% phosphotungstic acid solution for one minute, then the excess was wiped off with filter paper and allowed to dry overnight. The determination of exosomes concentration was performed by Nanoparticle Tracking Analyses (NTA) in a NanoSight NS300 (Malvern Instruments, UK). Formulations were diluted in Milli-Q water to achieve an optimal concentration range of 10^7 – 10^9 exosomes (NPs/mL). At least five one-minute videos of the exosomes were recorded using the NanoSight (https://doi.org/10.1021/acs.molpharmaceut.9b00097). Exosom e size distribution and particle concentration were analyzed using NTA v 3.0 software (Malvern, UK).

Analysis of the angiogenic capacity of exosomes: tubules formation assay with HUVEC cells and chicken CAM assay

The angiogenic potential of the exosomes was evaluated using an in vitro tubule formation assay with HUVEC cells, following a protocol previously established in our laboratory [33]. This experiment aimed to confirm the angiogenic capacity of the exosomes present in the secretome of hWJ-MSC as a functional property. HUVEC (55,000 cells/well) were seeded onto Matrigel-coated 96-well plates, allowing the Matrigel to polymerize at 38 °C for 30 min. Subsequently, the HUVEC were resuspended in the presence of 500 µL of exosomes and plated over the Matrigel layer. After 4 h of incubation, tubule formation was quantified. The experimental conditions included positive control (Endothelial Cell Growth Medium 2: EGM-2), negative control (PBS), and exosomes at a 20 µg/mL concentration. The formation of endothelial tubules and branching points was analyzed using microscopy. The images were captured from five different fields per well, and tubule formation was evaluated and quantified using ImageJ software. Following established protocols, the in vivo CAM assay was conducted to further assess the angiogenic potential [35]. Briefly, fertilized chicken eggs (Rock iso, Agricola Chorombo, Chile) were incubated at 38.5 °C with 75% constant humidity. At embryonic day 1 (E1), 2 mL of albumin was extracted from each egg, and a 2 cm^2 round window was created on E4. On E8, the CAM vasculature was photographed before applying the experimental condition, using 10 eggs per condition. The CAM assay included testing 20 µL of the following treatments applied on the CAM: PBS (negative control), VEGF 50 ng/mL (positive control), and exosomes 20 µg/mL. The stimuli were positioned at the intersection of two major blood vessels, and a 12 mm coverslip was placed on top. On E12, the stimulated CAM regions were photographed using a 0.8 magnifying glass and an HD IC80 digital camera (Leica, Heidelberg, Germany). To enhance blood vessel visualization, we mixed 3 mL of a 1:1 solution of whipping cream and bidistilled water and injected under the CAM before imaging. All blood vessels intersecting the coverslip edges, and the total number of vessels within a 6 mm radius of the sponges at E12 were considered for quantification. The results were normalized relative to the number of vessels at E8.

Secretome-HA sponge

A 4.8 mg/mL hyaluronic acid (HA) solution (HYACARE, Evonik Industries, Germany) was prepared in Milli-Q water at room temperature. The solution included equal volumes (50% each) of high molecular weight (500–1000 kDa) and low molecular weight (50 kDa) HA. This HA solution was combined with a blended secretome suspension obtained from three different hWJ-MSC cultures. Protein concentration in the secretome suspension was determined using the BCA protein assay (DC™ Protein Assay; BioRad). The resulting mixture was aliquoted into 24-well plates (0,5 mL of solution per well), frozen at -80 °C for 24 h, and subsequently lyophilized. Freeze-drying was carried out for 6–8 h at a temperature of 16–24 °C to ensure complete sublimation (Model Given

One 5 K, Friologic, Chile). The lyophilized secretome-HA sponges were stored in individual, heat-sealed medical grade pouches to prevent contamination (Fig. 3a1). All procedures were conducted in biosafety class cabinets (model 1376 R, Thermo Scientific) to maintain sterility and prevent biological contamination. The application area for patients in the present study was estimated to be approximately 5–6 cm^2 and based on a previously established application dose for the sponge and considering that 12 $\mu g/cm^2$ is the protein/surface density of the material [20], a total of 70 µg of protein was determined to be suitable for this area (thus, representing the 100% of the dose). Notably, 70 µg was the maximum protein content that could be loaded into the sponge without compromising its structural properties. For this study, secretome-HA sponges were prepared with four different protein contents: 18 (secretome-HA 18), 42 (secretome-HA 42), and 70 µg (secretome-HA 70). When 210 µg of protein was administered (secretome-HA 210), three secretome-HA 70 sponges were used per application. Control sponges containing only HA, without secretome, were fabricated following the same protocol for comparative analyses.

Microbiological test control of hWJ-MSC cultures and secretomes

The sponges were stored in the dark until use. For testing, they were removed from their sterile pouches (Fig. 3a2) using sterile scissors and tweezers and placed into tubes containing 3 mL of CASO broth (Merck 105459). The samples were incubated at 35 °C for 48 h. To evaluate minimal contamination levels, the aliquots were inoculated into trypticase soybean agar supplemented with 5% lamb's blood (Biomérieux) and incubated at 35 °C for 24 h, following established protocols [37].

Characterization of sponges

To determine the surficial atomic composition of the sponges, scanning-transmission electron microscopy (STEM, Inspect F-50, FEI, Holland) coupled with energy-dispersive spectroscopy (EDS) was utilized. For morphological analysis, sponge samples were sputter-coated with gold using a Sputter Coater (Cressington TEDPELLA, model 108; coupled to a thickness controller, MTM 20 Cressington) prior to imaging. The pore size, fiber width, and other structural features observed in the images were quantified using ImageJ software.

To evaluate sponge dissolution times, 1/4 piece of the secretome-HA 70 was placed on a coverslip using tweezers and observed under an optical microscope (B-293PLi, Optika, Italy) equipped with a digital camera (B5 camera, Optika, Italy) at 4X magnification. A micropipette was used to deposit 75 µL of Milli-Q water onto the sponge, and the dissolution process was recorded via video for time analysis.

Studies with healthy volunteers and patients

Ethics approval and consent to participate

(1) Title of the approved project: Proyecto estatal concursable Fondef IdeAs 2022, Asesoría con estudio casos a caso y consentimiento informado para pacientes que padecen psoriasis vulgaris; (2) Name of the institutional approval committee or unit: Servicio de Salud Metropolitano Norte (SSMN); (3) Approval number: Nº 047/2021; (4) Date of approval: 10/27/2021. All patients provided written informed consents for the publication of images and clinical information and signed in the presence of an expert psoriasis dermatologist.

Analyses of skin mechanical characteristics

A non-invasive approach using the Cutometer Dual MPA 580® was selected to evaluate the mechanical properties of the skin. Two probes were used: (1) Cutometer® 580 to measure skin elasticity, and (2) Tewameter® TM Nano to assess water transepidermal water loss (TEWL) through humidity sensors.

Safety protocol 1

The safety of the secretome-HA sponge was evaluated using two protocols. In safety protocol 1, secretome-HA 42 was applied to individuals with hypersensitivity (atopic dermatitis). Three volunteers were exposed to the formulation for 96 h via a patch test. The test involved applying the sponges into metal chambers affixed to the forearm using medical tape [38, 39]. The metal chambers were designated as I, II, III, and IV, corresponding to: the HA sponge, secretome-HA 42, saline solution (control), and allergen-free control, respectively. After 96 h, the patches were removed, and the exposed areas were analyzed and photographed after 5–10 min. A follow-up visualization and photographic record were performed on the 5th day.

Safety protocol 2

In safety protocol 2, four healthy volunteers participated in a single-arm study. Baseline and post-treatment blood tests (complete blood count, liver, and renal function tests) were conducted to evaluate systemic toxicity. Each volunteer self-administered secretome-HA 210 sponge daily for 15 days by applying 0.5 mL of distilled water to the forearm with a Pasteur pipette before placing the sponge (materials were provided in individual kits). Clinical evaluations included the vital signs, weight, skin observations (irritation, edema, skin appearance), patient-reported symptoms (pain, itching, discomfort), and photographs of the treated area.

Efficacy protocol 1

The secondary objective of this study was to assess the therapeutic potential of the secretome-HA sponge. Therefore, we evaluated a 30-day trial with 12 patients diagnosed with *psoriasis vulgaris*. Participants were double-blinded, randomized, and divided into two groups. Group 1: Seven patients received secretome-HA 18 daily for 30 days. Group 2: Five patients received secretome-HA 18 for 15 days, followed by secretome-HA 70 for an additional 15 days. As a control, all groups applied plain HA sponges daily to a contralateral limb with symmetrical psoriasis lesions on areas such as arms, elbows, legs, abdomen, or back. As part of the protocol, participants refrained from using other antipsoriatic treatments and were provided with a moisturizing lotion for unaffected areas. Skin parameters such as elasticity/flexibility (R0), TEWL, mPASI, and lesion plate size were assessed before and after the 30-day treatment. A modified scoring system (mPASI) was adapted to score the PASI [40, 41]. At the beginning and end of the study (30 days), erythema and scaling were scored independently in one selected psoriatic plaque using a 4-point scale: 0, none; 1, slight; 2, moderate; 3, marked; 4, very marked. Skin thickness was measured using a caliper, and millimeter readings were converted to a scale value (on a scale from 0 to 4). Treatment success was assessed based on changes in thickness, which was included in the total mPASI score.

Data analysis

Statistical analyses were conducted utilizing GraphPad Prism Version 5.0 and R Software v2.12.2. The data are reported as the arithmetic means of the parameters of interest alongside their corresponding standard deviations (SD) or standard errors of the mean (SEM), as appropriate. Normal data distribution was analyzed using a one-way Analysis of Variance (ANOVA), setting the significance threshold at * $p < 0.05$ and ** $p < 0.01$, followed by post hoc Tukey HSD testing. For non-normal distributions, the Kruskal-Wallis test and/or the Mann–Whitney test were applied. Differences among groups were deemed statistically significant if they achieved a * $p < 0.1$; ** $p < 0.05$ and *** $p < 0.01$.

Results

Characterization of exosomes in the secretome and analysis of their angiogenic capacity in vitro (HUVEC cells) and in vivo (chicken CAM assay)

Exosomes within the secretome were characterized using multiple analytical techniques. Dynamic light scattering (DLS) analysis revealed nanometric exosomes with an average size of 164 ± 87 nm and a polydispersity index (PDI) of 0.38. Scanning transmission electron microscopy (STEM) at two magnifications confirmed the presence of spherical, homogeneous structures (Fig. 1a-b). Nanoparticle tracking analysis (NTA) further determined a peak size of 184.3 ± 3.4 nm, consistent with DLS results. The peak concentration of exosomes was estimated at 1.5×10^7 particles/mL (Fig. 1c). Additionally, NTA revealed that 36.4% of the exosomes were smaller than 150 nm, while 40% ranged between 150 and 200 nm in size (Fig. 1d). The angiogenic potential of the exosomes was evaluated using the HUVEC cell line. As shown in Fig. 2a1, 2, after 4 h of incubation, the presence of exosomes significantly increased the number of branch structures ($N = 93$) compared to the negative control/PBS ($N = 46$). In addition, exosomes also enhanced tubules formation, with 24 tubules observed in treated samples compared to 14 in the negative control (Fig. 2a1, 3). Similarly, as depicted in Fig. 2b1,2, exosomes significantly increased the number of blood vessels in vivo in the chicken CAM assay. Vessel density increased from 1.2 (PBS, negative control) to 1.53 ($p < 0.05$) following the application of isolated exosomes from the secretomes.

Microbiological tests in hWJ-MSC cell cultures and secretomes

Mycoplasma detection using indirect DNA staining on the three hWJ-MSC cultures used for this study confirmed the absence of microorganisms. Similarly, PCR analysis for pathogens in the hWJ-MSC cultures and their cell-derived secretome yielded 100% negative results. Microbiological analysis of the stored, ready-to-use secretome-HA sponge also confirmed the absence of microorganisms, even in sponges prepared three months prior. These comprehensive safety checks validate the feasibility of using both fresh and stored secretome-HA sponges in subsequent studies (Fig. 3a1-2).

Characterization of the sponges through EDS analysis

Energy-dispersive X-ray spectroscopy (EDS) analysis (Table 1) revealed significant differences in the surficial atomic composition between the secretome-HA 70 and the HA sponge. The HA sponge showed higher percentages of oxygen (54.9%) and carbon (35.3%), with nitrogen present at 8.6%. Trace amounts of zinc and chlorine were also detected (1 and 0.3%, respectively). In contrast, the secretome-HA 70 exhibited a lower oxygen content and a higher proportion of chlorine and carbon, with chlorine exceeding 20%. Sodium (14.9%) and calcium (2.2%) were present in reduced quantities, while potassium and sulfur were detected at concentrations below 1%. Notably, nitrogen was undetectable on the surface of the secretome-HA sponge fibers. This compositional variation highlights the impact of secretome enrichment on the surface properties of the HA sponge.

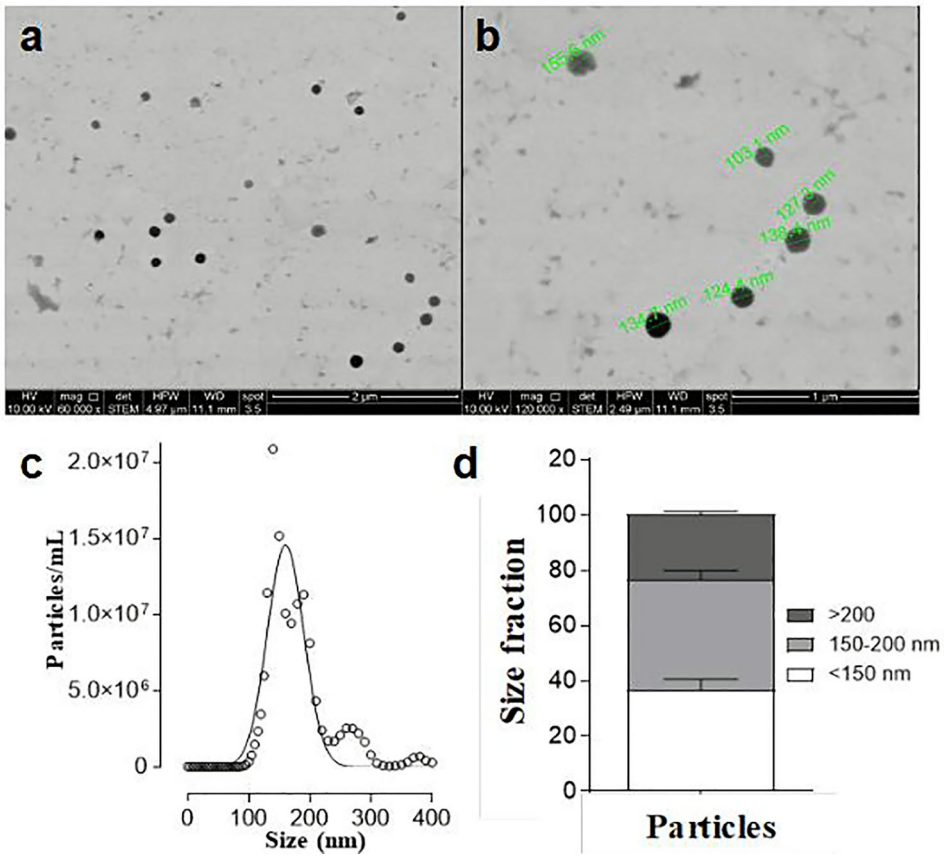


Fig. 1 Characterization of exosomes isolated from the secretomes. (**a**, **b**) STEM images of exosomes at 60,000X and 120,000X magnifications, respectively, showing morphological characteristics. (**c**) Hydrodynamic size and concentration of exosomes (particles/mL) analyzed using NTA. (**d**) Size distribution of the main exosome fractions identified ($n = 3$)

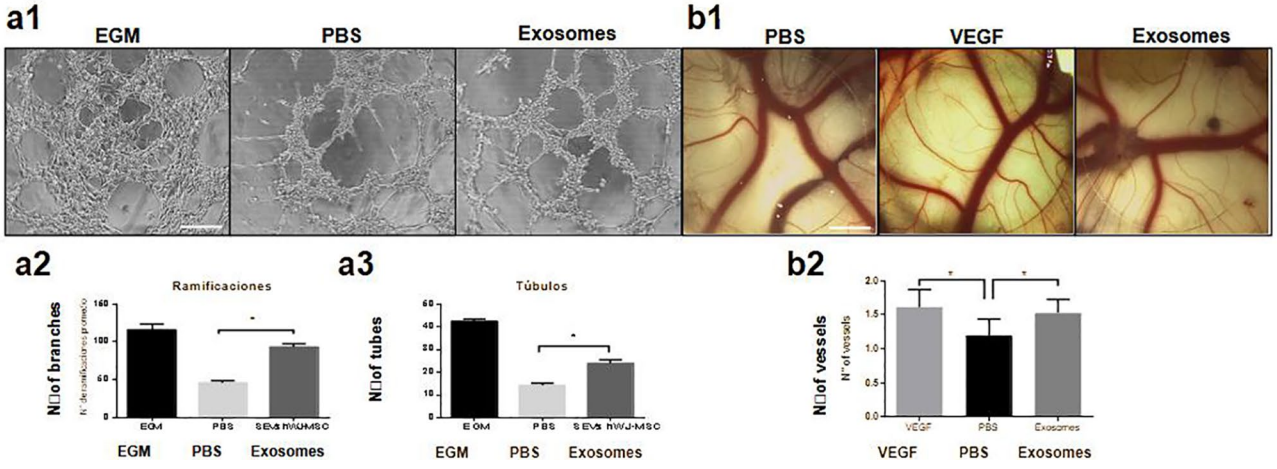


Fig. 2 Proangiogenic activity of hWJ-MSC-derived exosomes in vitro and in vivo. (a1) Microscopy images of the HUVEC tubule formation assay after 4 h of incubation with hWJ-MSC exosomes (bar = 6 mm). (a2) Quatification of branches, and (a3) tubule formation by HUVEC cells exposed to hWJ-MSC exosomes (*$p < 0.05$, permutation test). (2b1) Microscopy images of the blood vessel formation in the CAM assay after 12 days of incubation (bar = 3 mm). (2b2) Represent the quantification of the number of blood vessels for different conditions: VEGF 50 ng/mL (positive control), PBS (negative control), and exosomes 20 µg/mL (*$p < 0.05$, one-way ANOVA) ($n = 10$)

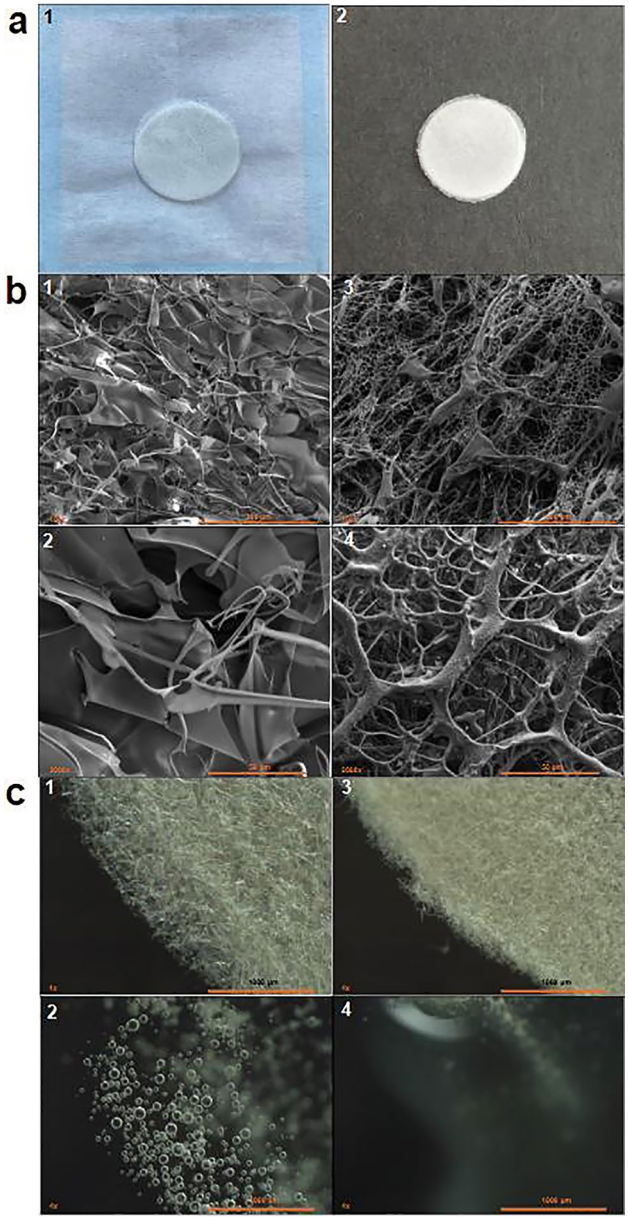


Fig. 3 Secretome-HA and HA sponge appearance (nude eye, electronic microscopy, and optical microscopy). **a1**) Secretome-HA 70 in individual packaging, **a2**) Unpackaged, ready-to-use secretome-HA 70. Scanning electron microscopy: **b1**) HA sponge at 400X magnification, (**b2**) HA sponge at 2000X magnification, (**b3**) Secretome-HA 70 at 400X magnification, (**b4**) Secretome-HA 70 at 2000X magnification. **c**) Optical microscopy of sponges: **c1**) HA sponge, **c2**) HA sponge with 75 µL of water until dissolution at 66 s, **c3**) Secretome-HA 70, **c4**) Secretome-HA 70 with 75 µL of water until dissolution at 200 s. ($n = 3$)

Morphological and dispersion properties of the sponges

The morphology of the sponges exhibited notable differences. SEM images revealed that the HA sponge was characterized by smooth, laminar, and interconnected structures (Fig. 3b1-2). In contrast, the secretome-HA 70 exhibited thinner, rougher, and highly cross-linked structures, likely resulting from incorporating the secretome into the formulation (Fig. 3b3-4). Quantitative analysis performed using ImageJ revealed significant differences in porosity and fiber diameter between the two sponges. The smooth laminar structures of the HA sponge had an average width of 97.3 µm in (SD ± 1.9). For the secretome-HA 70, the pore size ranged from 14.1 to 93.7 µm (SD ± 4.3), while the fiber width forming the interconnected networks averaged 6.6 µm (SD ± 0.2). The dispersion behavior of the sponges in an aqueous medium also differed markedly. Upon adding 75 µL of water, the HA sponge fully dispersed within 66 s (Fig. 3c1-2), whereas the secretome-HA 70 required 200 s for complete dispersion (Fig. 3c3-4). Videos illustrating this phenomenon are available in the supplementary material section (supplementary video S1-2).

Table 1 Surface atomic composition, expressed as percentages, of HA and secretome-HA 70 sponges analyzed by EDS

Element	Atom content (%)			
	HA sponge	SD	Secretome-HA 70	SD
C	35.4	0.37	21.5	7.75
N	8.6	0.97	-	-
O	54.9	0.96	35.1	8.29
Zn	1.0	0.15	-	-
Cl	0.3	0.18	23.8	12.74
Na	-	-	14.9	0.82
K	-	-	0.8	0.38
Ca	-	-	2.2	0.78
S	-	-	0.3	0.19

Safety protocol evaluation

Protocol 1: The first safety protocol, as outlined in Fig. 4, was conducted with three atopic dermatitis patients (ADP), who are typically sensitive to various physical stimuli. None of the patients experienced local side effects after applying the control patch test. Similarly, no skin reactions were observed after applying the secretome-HA 42. As shown in Fig. 4a, the patients did not exhibit eczema, erythema, or redness during the five-day protocol. In addition, none of the patients reported any physical discomfort attributable to the application of the sponges.

Protocol 2: In safety protocol 2, conducted with four healthy volunteers, blood analytical results after applying the secretome-HA 210 showed no significant differences compared to the baseline values (start of the study, $p < 0.05$), indicating no systemic effects even at the highest tested dose (see Supplementary material, Table S1). Furthermore, a visual evaluation of the volunteers' forearms treated with secretome-HA 210 for 15 days revealed no local adverse effects, such as redness, inflammation, erythema, or scaling (Fig. 4b). Volunteers also reported no physical discomfort attributable to the application of the sponges.

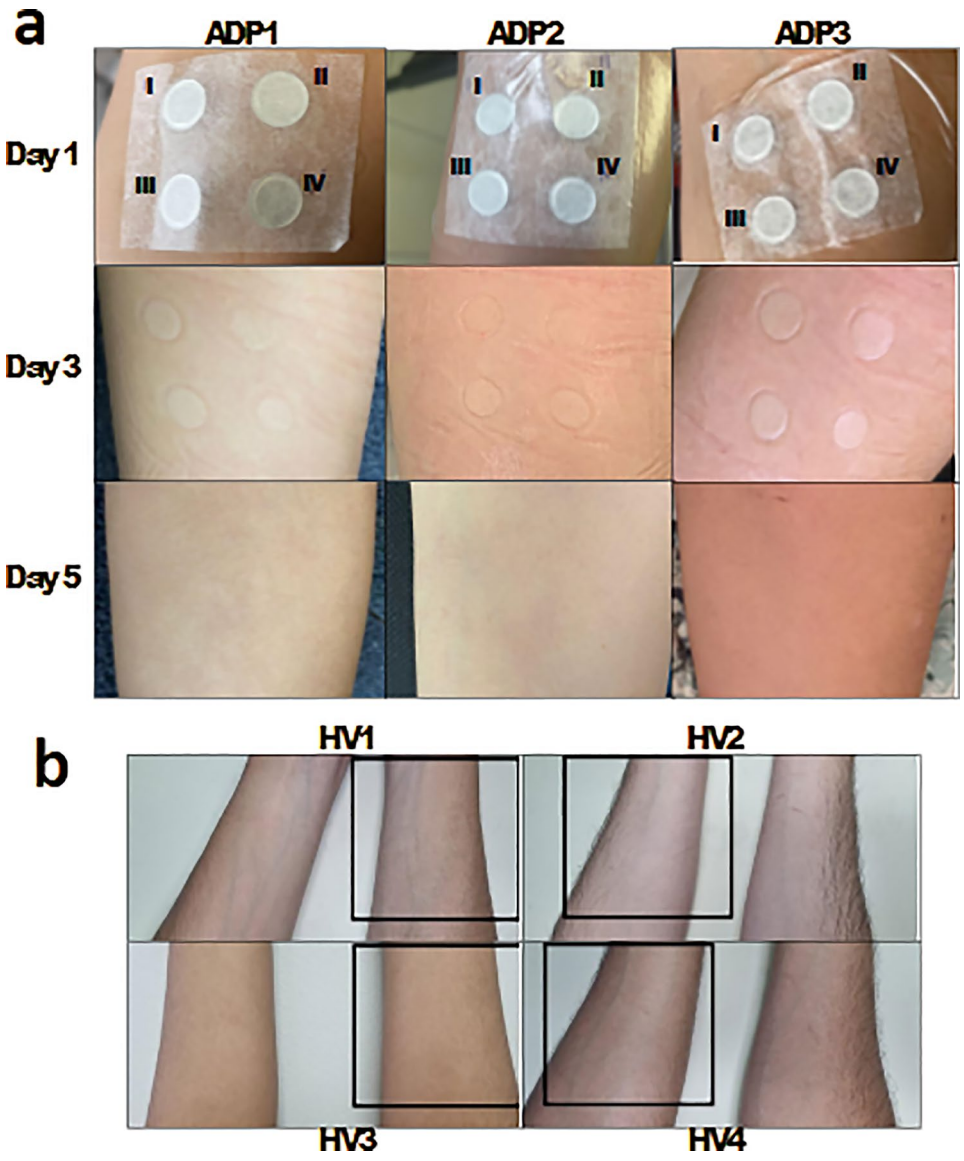


Fig. 4 Safety assessment of the Secretome-HA sponge. **a**) Protocol 1: Evaluation in three patients with atopic dermatitis (named as ADP1, 2 and 3, respectively) after 1, 2 and 5 days post- application of allergens/formulations. The application sites were: I: HA sponge; II: secretome-HA 42; III: physiological serum IV: control (no allergen). **b**) Protocol 2: Evaluation in four healthy volunteers (named as HV1, 2, 3, and 4, respectively) receiving daily application of the secretome-HA 210 sponge for 15 days. The framed area marks the treated site, which exhibits a similar appearance to the untreated opposite arm

Efficacy protocol

The patients were assessed over a 30-day period (Fig. 5a) to evaluate the long-term benefits of the treatment, where key parameters, including TEWL, skin elasticity, mPASI score, and plate size, were studied. Application of secretome-HA 18 alone resulted in a 30% reduction in TEWL. In comparison, a combined treatment of secretome-HA 18 (applied during the first 15 days) followed by secretome-HA 70 (applied from day 15 to 30) achieved a 38% reduction. The HA sponge reduced TEWL by only 2%, and a moisturizing lotion applied to non-psoriatic skin (adjacent to the evaluated lesion) decreased TEWL by 34% (Fig. 5b). The combined treatment of secretome-HA 18 and secretome-HA 70 significantly improved skin elasticity, increasing 43%. In contrast, the HA sponge alone provided a modest improvement of 18% (Fig. 5c).

Clinical evaluations revealed fewer lesions and a notable reduction in patients' desquamation, erythema, and infiltration after receiving the combined secretome-HA 18 + 70 treatment. The mPASI scores, which account for erythema, induration, and desquamation across bilateral areas, showed significant improvement, with a reduction of 33.0% (SEM ± 12.3) (Fig. 5d). Plaque size also decreased across all patient lesions, with the combined treatment (two weeks with secretome-HA 18 and two additional weeks with secretome-HA 70) achieving a

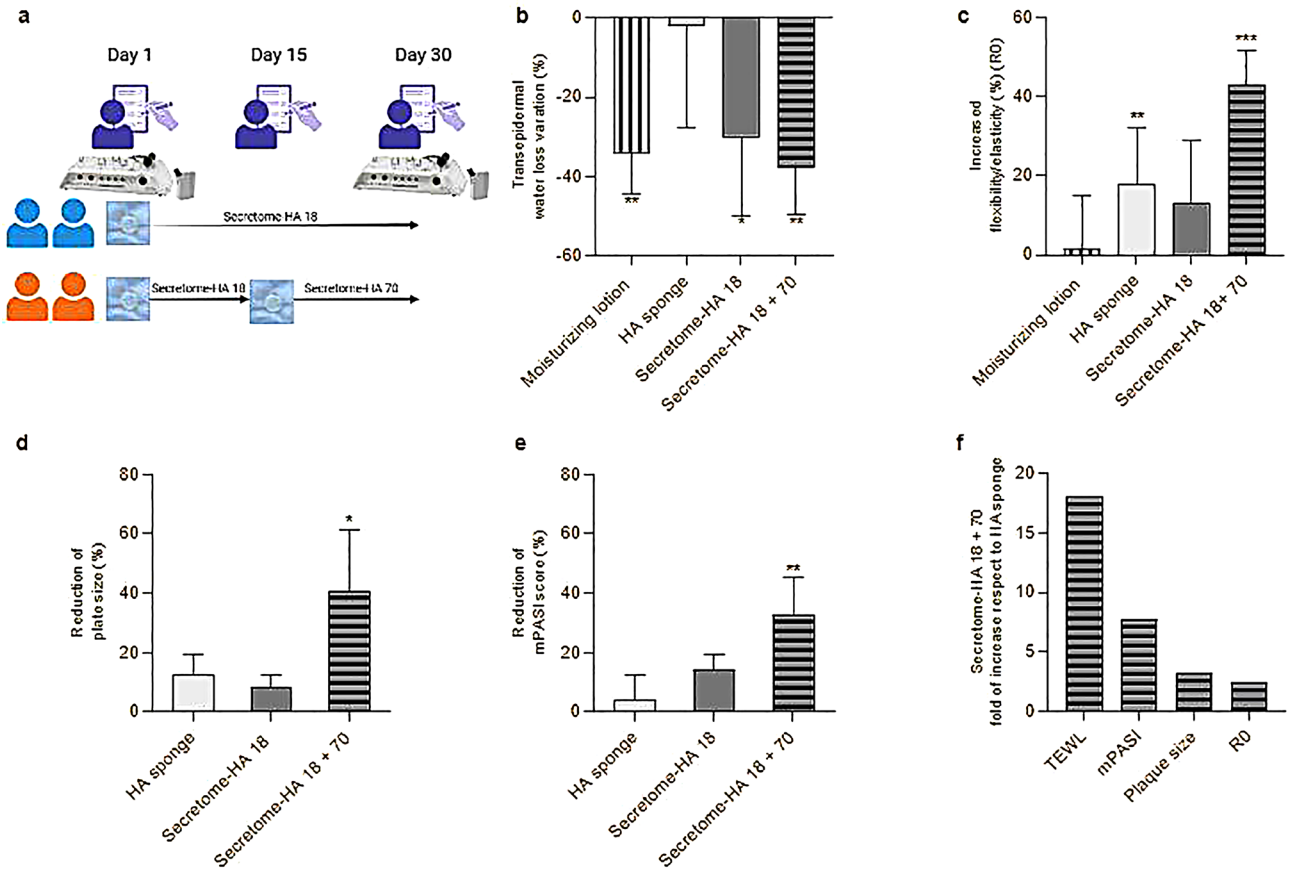


Fig. 5 Efficacy of the Secretome-HA sponge in psoriasis treatment. (**a**) Schematic representation of the 30-day efficacy protocol in patients with psoriasis. (**b**) TEWL variation following secretome-HA sponge treatment shows a similar trend to the healthy, non-lesioned skin (considering skin close to the lesion evaluated, in the same body region) treated with a standard moisturizing lotion. (**c**) The percentage of elasticity/flexibility variation (R0) is higher with the use of secretome-HA 18 + 70 and HA sponge. (**d**) Secretome-HA 18 + 70 effectively reduces mPASI. (**e**) The combination of secretome-HA 18 + 70 is effective in reducing the size of plaques ($n = 7$). The significant differences in a, b c, and d are given by the comparison of each parameter with the zero change condition (Kruskal Wallis test, $*p < 0.1$; $**p < 0.05$, $***p < 0{,}01$). (**f**) Relative increase in TEWL, mPASI, plaque size, and R0, expressed as the "secretome-HA 18 + 70 / HA sponge" ratio

substantial reduction of 41.0% (SEM ± 20.1, $p < 0.1$) versus 8.1% (SEM ± 4.3) for secretome-HA 18 alone, and 12.8% (SEM ± 6.5) for the HA sponge (Fig. 5e). To evaluate the relationship between the combined treatment and the HA sponge (control), the ratio of the values obtained for secretome-HA 18 + 70 and HA sponge was calculated for TEWL, R0, mPASI, and plaque size (Fig. 5f). As evidenced, TEWL showed the highest relative increase (18.1 times), followed by mPASI (7.8 times), plaque size (3.2 times), and R0 (2.4 times). Notably, two patients treated with the combined dose experienced a complete remission of psoriatic signs and symptoms, as reflected by both mPASI scores and plaque size measurements (Fig. 6).

Discussion

Psoriasis vulgaris is a chronic inflammatory skin disease affecting millions of people globally. Despite its widespread prevalence, effective and long-lasting treatments remain elusive due to factors such as low patient adherence, the discontinuation of topical therapy due to side effects, the lack of rapid improvement, and the high cost of the most effective treatments [42, 43]. Regenerative medicine provides a diverse range of therapeutic options for dermatologic conditions. Furthermore, the ongoing advancement of new techniques and the integration of various regenerative approaches hold considerable potential to enhance patient care in dermatology [1]. Moreover, stem cell therapy has emerged as a promising option for psoriasis treatment, with multiple studies demonstrating its potential efficacy in preclinical and clinical trials [21, 44]. Stem cell-based therapies, including regulatory T-cell therapy, hematopoietic stem cell transplantation, or MSC treatments, have shown promising results in restoring immune homeostasis, suppressing inflammation, and promoting tissue repair in psoriasis [21]. A case report highlighted the treatment of a 47-year-old man with a long history of psoriasis, which was refractory to conventional treatments. The patient

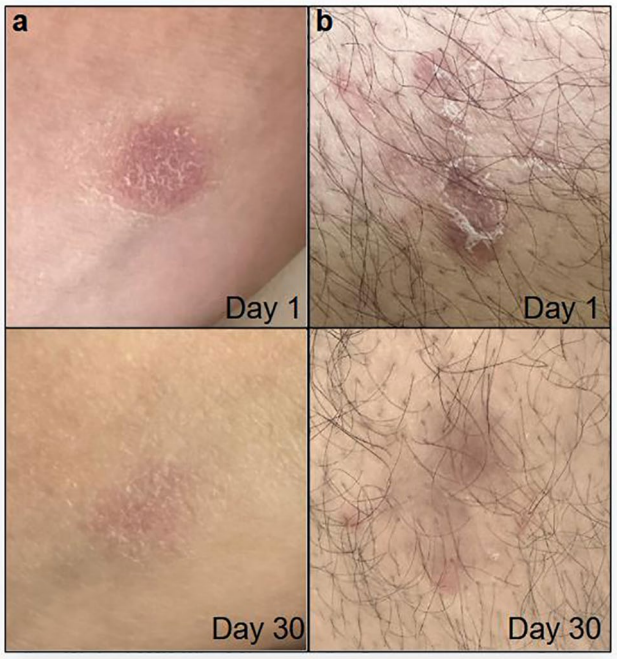


Fig. 6 Representative clinical outcomes of patients treated with secretome-HA. Images of two patients treated with secretome-HA 18 for 15 days followed by secretome-HA 70 for an additional 15 days. (**a**) Day 1: Psoriatic plaque on the instep, characterized by severe erythema, moderate to severe induration, and mild desquamation. Day 30: The plaque shows mild erythema and induration, with no visible desquamation. (**b**) Day 1: Psoriatic plaque on the thigh, with moderate erythema, induration and mild desquamation. Day 30: Induration and desquamation completely resolve. The remaining erythema is post-inflammatory and does not contribute to the mPASI

presented significant improvements after receiving a combined intravenous and local administration of UC-MSC (3×10^6 cells/mL) at 3-week intervals (three cycles). In the follow-up, the symptoms progressively decreased without adverse side effects [45]. In a clinical trial involving 17 patients who received intravenous UC-MSC infusion (a single dose of 1.5×10^6/kg every two weeks four times), significant reductions in psoriasis symptoms were observed, with a 40% improvement in the PASI score. No relapse or severe adverse effects were reported. Additionally, the allogeneic UC-MSC treatment led to increased frequencies of T- helper (Th) 17 and CD4 + memory T-cells, along with significant reductions in Th17 cells and IL-17 serum levels [17].

While MSC therapy shows considerable promise for treating psoriasis, it is essential to note that this treatment is still in the early stages of research and development. Additional clinical trials are necessary to confirm their safety and efficacy. Clinical reports on stem cell therapies for psoriasis are limited [17, 46–49], with only a few focusing on UC-derived stem cells [17]. This scarcity may be due to challenges and risks associated with systemic administration, such as undesired biodistribution, reduction in blood cells and platelets, tumor formation, and infections [50–53].

Regenerative medicine has shown minimal side effects on hypertrophic scars and keloids. It can also be combined with other therapeutic methods [54]. However, it is widely known that lack of treatment adherence is the primary cause of patients not receiving the full benefits of their medications. Despite this, we often overlook adherence as the main reason for therapeutic failure in daily clinical practice. Therefore, we aim to promote the topical use of our innovation to help patients avoid painful visits with injections. Moreover, topical treatment formulations whose active ingredients are dried/lyophilized offer advantages, including prolonged storage (helping to prevent microbiological contamination), ease of transport, and simple handling [55]. Recently, our group demonstrated the efficacy of WJCM contained in an HA sponge for topical treatment of psoriasis-like skin lesions in an imiquimod-induced mouse model [20]. In the present study, we observed the presence of spherical and nanometric exosomes in the secretomes, with a peak size between 160 and 180 nm and a concentration of 1.5×10^7 exosomes/mL (Fig. 1). Similarly, Chen et al. (2019) [56] identified exosomes in hWJ-MSC with sizes of ~200 nm. As shown in Fig. 2a, the administration of isolated exosomes to HUVEC cells significantly increased the number of branches and tubules formed compared to the negative control (PBS). These in vitro results were further validated in the in vivo CAM model, where exosome administration significantly increased vessel formation (Fig. 2b). These results are promising, as they suggest that the exosome-containing secretome could enhance angiogenesis, potentially supporting tissue repair when developed into a pharmaceutical formulation. Further research is warranted to explore its therapeutic applications and clinical viability.

The inclusion of the surficial atomic distribution in this study is based on scientific and technological considerations: (1) to achieve a more detailed characterization of the material and (2), if required, to compare the consistency across different batches. The surficial atomic composition (Table 1) and morphology of the secretome-HA sponge differ significantly from those of the plane HA sponge (Fig. 3b-c). This distinction can be attributed to incorporating the secretome in the formulation. In addition, the enrichment of the HA sponge with the secretome reduces the dissolution time of the formulation (Fig. 3c). As shown in video S1 (supplementary information), the secretome-HA sponge exhibits resistance to water penetration during dissolution, whereas the plain HA sponge dissolves more rapidly (video S2). This suggests that the secretome content may play a role in modulating the release of the active molecules from the formulation.

Previous studies have demonstrated the efficacy of the BM-MSC-derived secretome, indicating that the recovery of skin thickness was comparable to that achieved with fluocinolone acetonide (a potent corticosteroid) [57]. Additionally, Yang et al. (2020) [14] reported that a bi-daily injection of secretome derived from human amniotic epithelial cells for six days attenuates psoriasis-like skin lesions induced by imiquimod in mice. These results align with our preclinical results, where topical treatment with WJCM encapsulated in an HA sponge significantly improved a psoriasis-induced animal model. This included reducing the PASI score, correcting aberrant angiogenesis, alleviating disease-associated weight loss, and enhancing comfort [20]. These studies highlight the potential therapeutic role of MSC-derived paracrine factors in mitigating the symptoms and clinical manifestations of psoriasis.

Our clinical study supports these preclinical findings. The proposed secretome-HA sponge treatment represents a non-invasive, self-applying approach that enhances patient adherence while maintaining efficacy and avoiding adverse/collateral effects. One notable challenge (and limitation) during our study was the difficulty recruiting volunteers and patients, despite having access to an extensive patient database in Chile (CIEC in Chile). A significant number of individuals within this pool were reluctant to participate, a trend observed in other psoriasis-related stem cell clinical trials, which have reported low enrollment and randomization rates, with cohorts ranging from 5 to 17 participants [17, 49, 58]. Similarly, a clinical trial involving UC-derived stem cell injections for psoriasis patients noted a 90% completion rate [17]. In our study, we enrolled 14 patients, of whom 12 completed the treatment, resulting in a dropout rate of 24%. Several factors likely contributed to these withdrawals, including personal or familial circumstances. For this pilot study, the sample size was limited. Patient recruitment was carried out through social media and the International Center of Clinical Trials/Centro Internacional de Estudios Clinicos (CIEC). As known, for dermal studies of this nature, recruitment tends to be challenging, often due to patient hesitancy driven by fear, lack of awareness of the therapy, and reluctance to discontinue conventional treatments. Future studies could benefit from a more comprehensive examination of patients' perceptions regarding using stem cells versus acellular products derived from stem cells (such as the secretome from Wharton Jelly-derived mesenchymal stem cells used in this study). Educating the population on the risks and benefits of both therapeutic approaches is critical to fostering informed decision-making, increasing patients' recruitment, and advancing more extensive clinical trials.

In both safety protocols, no adverse events or abnormalities were observed in clinical analysis or biochemical indices (Figs. 4–6 and Supplementary material Table S1). In the safety protocol considering individuals with atopic dermatitis, due to the hypersensitivity of the volunteers, an approach considering a dose of 42 ug/sponge (secretome-HA 42) for 3 days was tested. Once the short-time safety was established in atopic dermatitis individuals, a 5 times higher dose was tested (secretome-HA 210) in healthy volunteers for a longer period (15 days).

For the efficacy protocol and to increase the range of doses and days of evaluation, the first group of patients receive secretome-HA 18 for 30 days without showing significant effects in safety and efficacy. Considering the above response and to discover potential therapeutic effects without adverse effects, we adopt a combined treatment of secretome-HA 18 × 15 days + secretome-HA 70 × 15 days. As could be presumed, the application of secretome-HA 70 could trigger a more significant therapeutic response. The efficacy protocol revealed a 33.0% reduction in mPASI with the secretome-HA 18 + 70 formulation (Fig. 5d). In addition, the sponges showed improvements in skin parameters, including a reduction in TEWL (Fig. 5b), increased skin elasticity (Fig. 5c), and a decreased plaque size (Fig. 5e). TEWL is a measurement of skin integrity, indicating the amount of water lost through the stratum corneum. This measure varies according to various factors, such as age, environmental conditions, and alterations in the skin barrier [59]. Lower levels of TEWL signify healthy skin, whereas psoriasis-affected skin often exhibits higher TEWL than the controls [59, 60]. Interestingly, Tagami and Yoshikuni (1985) [61] found that TEWL correlated with the clinical severity of the disease. The reduction in TEWL observed in our study is likely indicative of an improvement in the skin barrier. A 2019 study evaluated the TEWL of 50 individuals with psoriatic plaques, observing that TEWL was higher in plaques than in control areas (without lesions), indicating impaired water retention in the affected skin [60]. In our study, the secretome-HA sponge was shown to reduce TEWL value, suggesting skin barrier recovery. Hydration is often compromised in psoriasis patients, which can limit the penetration of antipsoriatic treatments [62]. Therefore, the topical application of a secretome-HA sponge, utilizing its water-based solvent, may effectively hydrate the skin. This hydration facilitates the optimal delivery of bioactive trophic factors contained within the secretome. These trophic factors play a crucial role in repairing psoriatic lesions. By creating a moist environment, the sponge enhances the skin's absorption capacity, ensuring the bioactive components reach deeper layers. As a result, this combination promotes tissue regeneration and mitigates the symptoms associated with psoriasis. Such a targeted approach underscores the potential of innovative therapeutic modalities in dermatological treatments.

A comparative analysis with the literature shows a 15.4% reduction in PASI following subcutaneous injection in plaques with AD-MSC (1×10^6 or 3×10^6 cells/cm^2, single dose) [63], a 46% decrease in PASI after 12 weeks of intravenous AD-MSC injections (0.5×10^6 cells/kg every month for 12 weeks) [49], and a reduction in the range of 40–90% in PASI scores after six months post-UC-MSC injections (a single dose of 1.5×10^6/kg every two weeks by 4 times) [17]. In contrast, our novel approach, which exclusively uses blended WJCM, offers a cell-free therapeutic alternative. This formulation is notable for its non-invasive nature and the ability to be administered without specialized medical personnel, making it more accessible and broadening treatment availability to a broader demographic. As a freeze-dried product, the secretome-HA sponge does not require special storage or transport conditions, ensuring its stability and ease of distribution across various regions. Overall, our results suggest that the combination of secretome-HA 18 + 70 significantly reduces transepidermal water loss, the clinical response (reflected by mPASI and plaque size), and elasticity (Fig. 5f).

In recent years, cell therapy studies, such as using MSCs, have shown an uprising. Systemic injection of MSCs and their derivatives has shown promising therapeutic effects in patients with inflammatory skin conditions such as vitiligo [64]. Despite these encouraging results, several challenges remain, particularly in standardizing treatment protocols to ensure long-term efficacy. Regenerative medicine offers significant potential to revolutionize the treatment of psoriasis and other pigmentary disorders [2–5]. Ongoing research and the development of innovative therapeutic strategies provide a valuable opportunity to enhance the quality of life for individuals affected by these dermatological conditions.

In this study, we demonstrate that the secretome-HA sponge offers key benefits, including safety, ease of self-application, and clinical efficacy, making it a viable treatment for *psoriasis vulgaris*. These findings pave the way for expanding this research into a larger prospective clinical trial.

Conclusion

In conclusion, *psoriasis vulgaris* remains a challenging chronic condition with limited effective and sustainable treatment options, often hindered by low patient adherence, side effects, and high costs. Advances in stem cell therapy, particularly through the application of MSCs and MSC-derived secretomes, have shown promising potential as novel approaches for restoring immune balance, reducing inflammation, and promoting tissue repair in psoriasis patients. The secretome-HA sponge formulation, developed as a topical and self-applicable therapy, has demonstrated efficacy in preclinical and clinical studies, with significant improvements in key skin health markers and psoriasis symptoms without any adverse effects. As a cell-free, freeze-dried product, it offers several advantages, including enhanced stability, improved accessibility, and ease of use, addressing many of the challenges associated with traditional treatments. While these results are promising, further research through larger clinical trials is essential to confirm this approach's long-term benefits and refine application protocols and dosages tailored to the severity of the disease. Our proposed formulation has potential for a wide range of applications. This innovative secretome-HA sponge effectively hydrates the skin while enhancing the delivery of bioactive trophic factors contained within the secretome. Approaches including a larger number of patients during more extended periods and/or integrating standard treatments with regenerative therapies, such as stem cell-based secretomes, could be valuable to understand the full potential of the developed formulation.

Abbreviations

AD-MSC	Adipose tissue-derived mesenchymal stem cells
BM-MSC	Bone marrow-derived mesenchymal stem cells
CBC	Count of Blood Cells
CIEC	International Center for Clinical Studies
HA	Hyaluronic acid
hWJ-MSC	Human Wharton's Jelly-derived mesenchymal stem cells
mPASI	Modified psoriasis area severity index
MSC	Mesenchymal Stem/Stromal Cells
PASI	Psoriasis area severity index
SCH	Stratum corneum hydration
TEWL	Transepidermal water loss
UC-MSC	Umbilical cord-derived mesenchymal stem cells
WJCM	human conditioned media/secretome from hWJ-MSC
EGM-2	Endothelial Cell Growth Medium 2

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Author contributions

Conceptualization: FV, DC, EE, FO, VP; Methodology: EE, DH, NE, DC, CPP, JL, CM, LV, BC, DP, FO, VP; Data Curation: EE, CPP, DC; Formal Analysis: EE, DH, NE, DC, FV, FO, VP; Resources: VP, FV, FO; Writing – original draft: EE, DH, FO, VP; Review and Editing: EE, CPP, DC, FV, FO, VP.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions.

Declarations

Ethical approval
The authors declare that they have not used AI-generated work in this manuscript.

Conflict of interest
The authors declare that they have no conflicts of interest in this publication.

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