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Research Article

MANAGEMENT OF SKIN AGING AS A MODIFIABLE CONDITION THROUGH THE APPLICATION OF INNO TDS DNA PEPT HA FOR AN INTEGRATIVE APPROACH USING SONOPHORESIS. CADAVER ANALYSIS

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Abstract

The facial region presents a complex anatomical stratigraphy that organizes its structures in distinct planes, facilitating the application of treatments while presenting textural variations that require precise anatomical understanding. Skin aging is a multifactorial process manifested through structural and physiological modifications that affect not only aesthetics but overall health, leading to a loss of organized tissue integrity due to intrinsic and extrinsic factors. Acting synergistically, these factors promote the deterioration of the skin barrier and compromise its defensive function.

A quantitative observational study was conducted on a group of 50 female patients. The treatment cocktail used was **Inno TDS DNA PEPT-HA** (Innoaesthetics Laboratory, Spain), containing polynucleotide, glutathione, hyaluronic acid, palmitoyl tripeptide-5, tripeptide-1, and caprooyl tetrapeptide-3. Application was performed through **sonophoresis**, a non-invasive transdermal technique that enhances molecular penetration.

After 8 weeks of use, the treated side showed significantly lighter skin color and greater elasticity compared to the untreated side, while skin luminosity improved markedly after 4 and 8 weeks. No significant changes were observed in skin moisture ($P > .9999$) or TEWL ($P > .9999$) between treatment and control sides. The treatment was well tolerated, with only mild and transient side effects and no clinical repercussions.

These findings demonstrate that the I**nno TDS DNA PEPT-HA cocktail applied via sonophoresis** is an effective and safe strategy to improve key skin quality parameters in women with facial aging, without compromising the skin barrier function.

Keywords: Aging, sonophoresis, polynucleotides, glutathione, hyaluronic acid, peptides

Introduction

The skin, as the main interface between the body and the external environment, constitutes a functional barrier with unique anatomical and physiological characteristics that change with age [1]. Cutaneous aging is therefore understood as a natural, inevitable, and multifactorial process manifested through structural and physiological modifications that affect not only appearance but also overall health. These changes result in a loss of the organized integrity of the skin tissue due to intrinsic and extrinsic factors that, acting synergistically, promote the deterioration of the skin barrier and compromise its defensive function.

The facial region, particularly the face, exhibits an anatomical stratigraphy that clearly organizes its structures into defined layers, favoring treatment application. However, it also presents complex variations in texture that can become challenging without proper training and understanding of these anatomical elements, as shown in Figure 1.

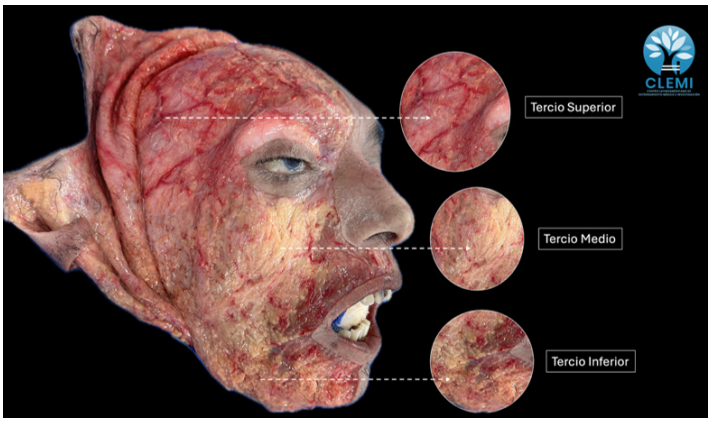

Figure 1. *Anatomical layers of the three facial thirds*. The upper third is fibrous due to its proximity to the orbital branch with specific adherence; the middle third shows fascicular disposition with visible separations de-

fining interseptal spaces; the lower third has a mixed musculo-adipose composition. Dissection performed at the Centro Latinoamericano de Entrenamiento Médico e Investigación (CLEMI), Bogotá, Colombia.

Facial soft tissues form a tridimensional laminar structure interconnected through a fibrous perpendicular system, extending either toward the dermis or the muscular and bone tissues (Figure 2). The skin, as the first layer, functions as a barrier between external and internal environments, where the epidermis, dermis, and hypodermis regulate distinct physiological functions. Over time, each of these layers manifests visible and functional signs of aging [4].

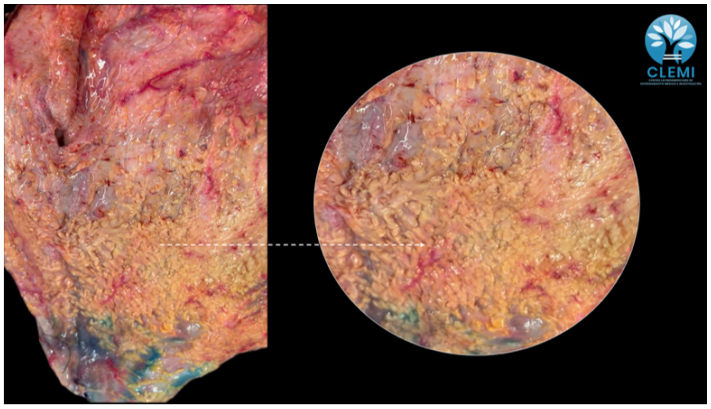

Figure 2. Facial soft tissues of the preauricular region forming a tridimensional laminar structure interconnected by a fibrous perpendicular system extending toward the dermis or the muscular/bone tissue. Dissection performed at CLEMI, Bogotá, Colombia.

The epidermis is a stratified squamous epithelium in constant renewal, typically over a 28–30-day cycle. It is avascular and composed mainly of keratinocytes responsible for keratin synthesis—insoluble structural proteins with high resistance to temperature and pH [5]. Other cellular types include melanocytes (responsible for skin pigmentation), Langerhans cells (linked to skin immune function), and Merkel cells (sensory receptors) [6].

According to [7], the epidermis is anchored to the dermis by hemidesmosomes forming the dermo-epidermal junction, which provides mechanical and structural support and acts as a protective barrier. Its integrity depends on the structural organization of the basement membrane, a complex network of extracellular matrix macromolecules connecting the outer epidermal layer with the underlying dermis.

Keratinocytes undergo transformation as they differentiate and migrate outward to replace cells shed from the body's surface [8]. Based on their morphology and location, the epidermis is divided into four main strata:

- **Basal or germinative layer:** The deepest layer, composed of undifferentiated basal keratinocytes situated above the basement membrane. These basal cells give rise to new keratinocytes through mitotic division. As they form, they migrate toward the next stratum, initiating the outward differentiation process [9]. Melanocytes are dispersed here, responsible for skin pigmentation and UV protection [10].
- **Spinous or prickle-cell layer:** The thickest layer, containing Langerhans cells (antigen-presenting cells). It consists of polyhedral keratinocytes connected through desmosomes. [11], report that this layer thins with age.
- **Granular layer:** The last layer containing living cells, composed of flattened cells parallel to the basal membrane containing keratohyalin granules. These granules, rich in glycoproteins, help retain moisture and form the skin's hydrophobic barrier. Their breakdown products (such as filaggrin and amino acids) maintain hydration of the stratum corneum [12].
- **Stratum corneum:** The outermost layer composed of flattened, dead cells (corneocytes) without nuclei or organelles. Their membranes contain involucrin and loricrin, along with lipids such as fatty acids, sterols, and ceramides, which maintain the barrier's impermeability [13]. The pH here ranges from 4 to 6.5, and any alteration can lead to bacterial or fungal infections [14]. Renewal occurs roughly every four weeks; however, in aged skin, keratinocyte turnover slows and the layer thickens with age [15].

The epidermis projects into the dermis through rete ridges, while the dermis projects upward through dermal papillae between these ridges, separated by the basement membrane [16].

Immediately beneath the epidermis lies the **dermis**, composed of fibroelastic connective tissue, loose in its superficial region, and vascularized [17]. It consists of collagen and elastic fibers, ground substance, and fibroblasts, mast cells, plasma cells, lymphocytes, dendritic cells, and histiocytes [18]. The dermis includes two strata: the papillary (loose connective tissue, fibroblasts, immune cells, capillary network) and the reticular (dense collagen and elastic fibers arranged horizontally).

This layer provides structural support to the skin due to its collagen and elastin content, maintaining strength and elasticity [19]. It also plays a role in wound healing and resistance to infection.

Below the dermis is the **hypodermis**, composed mainly of adipose tissue (Figure 3). Similar to the dermis, it originates from the mesoderm and contains mesenchymal stem cells capable of differentiating into fibroblasts. It provides volume and support; in the face, this tissue forms superficial and deep fat pads separated by fibrous septa that converge into retaining ligaments. Age-related redistribution of these fat compartments contributes to the characteristic morphology of the aged face [20].

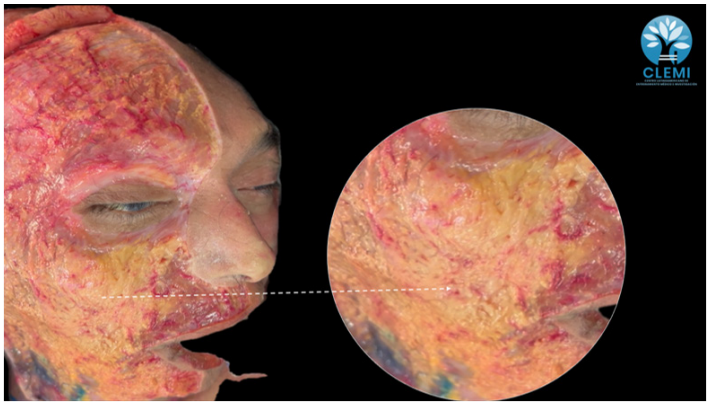

Figure 3. Superficial facial dissection showing adipose tissue or hypodermis below the dermal layer, with abundant vascularization and connective structures. CLEMI, Bogotá, Colombia.

Authors such as Bertossi [21] state that fat is classified as "structural," with a network of fibrous septa surrounding the fat cell lobules, which act as small pads with specific viscoelastic properties.

[22], state that three different types of facial adipose tissue can be identified, located either superficially (dermal white adipose tissue) or deeply (subcutaneous white adipose tissue): fibrous (perioral locations), structural (main parts of the middle third of the face), and deposit (buccal fat pad and deep temporal fat pad). These different types of fat differ in the size of the adipocytes and the collagen composition of their extracellular matrix and, therefore, in their mechanical properties.

In terms of facial structures, the aging process is most evident in the face because it is a sensitive area. The morphological changes that occur over time lead to the negative displacement of facial tissues due to gravity. This is caused by the degree of facial bone resorption, which leads to significant changes that affect the different soft tissues sequentially, including: Increased weakness of the facial support ligaments, alteration of muscle dynamics, and displacement and thinning of the fat compartments, causing structural changes in the skin and deepening dermal laxity [23].
As the skin ages, it undergoes changes such as loss of elasticity, slowing of cell regeneration, and a clear decrease in fibroblast function, which is reflected in the production of structural proteins such as collagen and elastin. Hence, most theories of facial aging include atrophy, deflation, ligament laxity, lipomatosis [24].

Studies affirm that this process, which involves changes at the cellular and molecular level [24,25], the skin's functions are affected due to the influence of intrinsic factors as a result of physiological changes that take place over time, at a variable and genetically determined rate with mutational implications, in addition to other causes such as age, cumulative DNA damage, free radical damage, and hormonal changes. Changes usually appear around the age of 30, when cell renewal slows down and hormone production undergoes changes that are directly reflected in the skin [26].
On the other hand, extrinsic factors known as exposomes, including lifestyle habits, pollution, chronic diseases, nutritional deficiencies, smoking, and unprotected exposure to solar radiation, affect the normal aging process of the skin.

Factors related to solar radiation cause skin photoaging, which damages skin structures, leading to skin atrophy and an increased risk of skin cancer. This type of natural light factor leads to the formation of free radicals, which destroy collagen and elastin, resulting in loss of hydration, changes in skin texture, and the appearance of fine wrinkles, rough and dry skin, telangiectasias, and pigmentary changes [27,28].

This shows that the synergistic effect of these extrinsic and intrinsic factors produces macromolecular and functional structural changes in the skin, which accelerates skin aging [29,30], and both mechanisms share a common pathway in which changes occur at the skin level, such as oxidative stress [31], which progressively weakens the substructure of the dermoepidermal junction and affects its functions, contributing to the gradual deterioration of the skin's overall physiology. Therefore, over time, it is necessary to protect against two independent processes that accelerate skin aging. In Figure 4, we can see the dermal structure susceptible to structural changes.

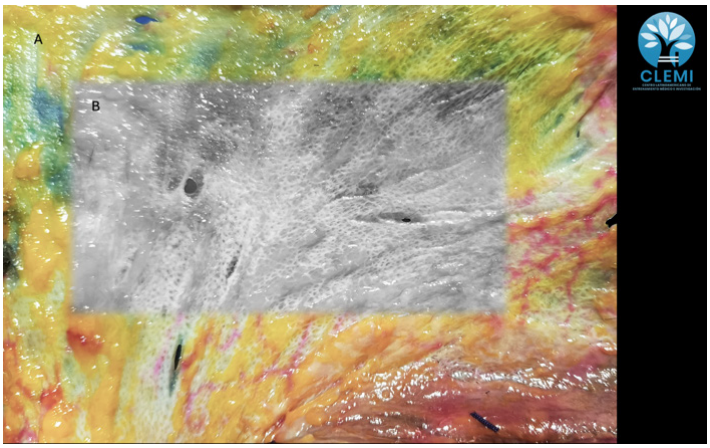

Figure 4. Superficial dissection of the face showing the dermal structure in a contrast photograph to observe the reticular dermal structure undergoing changes caused by photoaging and chronological aging. Dissection performed at the Latin American Center for Medical Training and Research (CLEMI) in Bogotá, Colombia.

Most changes involve a reduction in replacement or enzymatic alterations (superoxide dismutase, catalase, and glutathione peroxidase systems) or non-enzymatic alterations (compounds synthesized in vivo or obtained exogenously), which compromises the mechanical properties of the matrix components and cells [32,33].

Oxidative stress, resulting from an imbalance in the production of reactive oxygen species and the antioxidant defense system in living systems, leads to the disruption and damage of cellular function and, as a common pathway of skin aging, causes a decrease in barrier function at the epidermal level. It should be remembered that reactive oxygen species, as an inevitable consequence of aerobic metabolism in the mitochondrial electron transport chain, are one of the main causes of skin aging, as pointed out by [34].

According to authors such as [35], there is a progressive thinning of the epidermis along with cytological atypia in the epithelium, which in most cases destabilizes the skin barrier, slows down cell renewal, promoting dry and thin skin, low lipid production and pH changes directly affect the barrier function, exposing it to exposomic factors that disrupt its stability and facilitate transdermal water loss, leading to dehydration.

Similarly, as stated by [36], oxidative stress promotes aging in the dermis, driven by the activation of matrix metalloproteinases and the consequent degradation of extracellular matrix components, especially collagens and elastic fibers, as the number of dermal fibroblasts is reduced, leading to the appearance of fine wrinkles. The aging process in the skin is driven by reactive oxygen species to an extent not seen in any other organ.

At the level of this dermal layer, the ridges flatten due to the retraction of the epidermal papillae and the loss of projection of the basal cells in the dermis with loss of fundamental substance, making the dermis a less elastic, less resistant, and lax tissue, more prone to the development of wrinkles and elastolysis, where there is evidence of a decrease in the organization of collagen fibers. The classic signs of skin aging are sagging and wrinkles [37], which are related to the aging of skin cells and the decrease in collagen synthesis or the increase in its degradation and loss of tissue elasticity, affecting nutrient circulation and reducing its ability to repair itself. This results in a more fragile dermo-epidermal junction that is less resistant to shear forces [38].

The authors [39], conducted a histological and histochemical study of the skin of young adults (29 years old) with faces chronically exposed to the sun (SE) and abdomens not exposed to the sun (NSE), and relatively older skin (84 and 88 years old). Using hematoxylin and eosin (H&E) staining, epidermal thinning with loss of interpapillary ridges was observed in older skin, regardless of location or chronic UV exposure (Figure. 5).

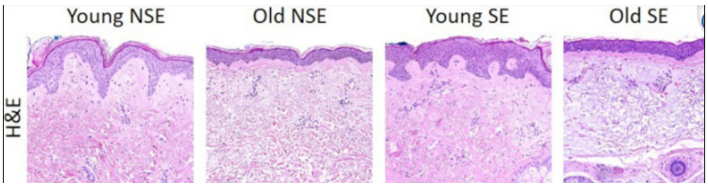

Figure 5. Histological and histochemical study of skin. Source: Adapted from[38].

Another study conducted by [40] speculates on what happens to skin stem cells during aging. Adult stem cells are located within specialized niches that allow for their self-renewal, proliferation, differentiation, and migration according to the body's needs. During skin aging, the self-renewal

capacity of stem cells decreases significantly, but increases actively during wound repair.

Furthermore, they state that resident stem cells are sheltered in niches, creating spatially differentiated microenvironments for their maintenance and function, and that in normal young skin with a stable epigenome, these keratinocyte stem cells are maintained in these niches at the tips of the dermal papillae, within a microenvironment nourished by dermal papillary microvessels surrounded by dermal mesenchymal stem cells (Figure. 6).

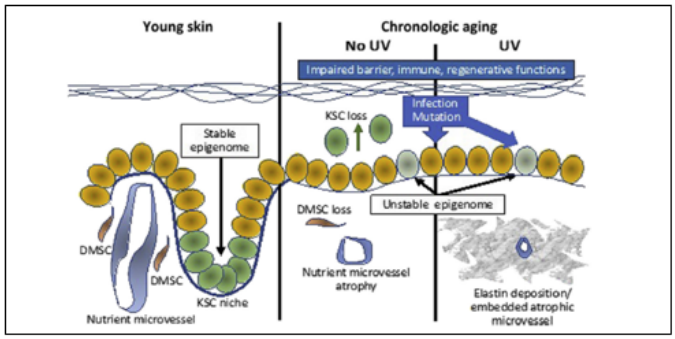

Figure 6. Schematic summary of the changes believed to occur in skin stem cells with aging. Source: [40,39].

Therefore, facial aging is the result of a combination of soft tissue decline and volumetric deflation, according to Lambros [41], so reversing this process is the clear objective of the various minimally invasive procedures applied. One of the key mechanisms of the anti-aging skin procedures and compounds used is the elimination of reactive oxygen species and the reduction of skin oxidation [42].

With a view to slowing down aging and increasing longevity, protocols are being designed every day based on active ingredients that seek to eliminate free oxygen radicals and improve antioxidant defenses.

Inno TDS DNA PEPT-HA (product pH: 6.5-7.5 and osmolarity: 260-340 mOsmol/kg) is a dermis reconstructor that improves dermal density and, therefore, skin texture, providing firmness and stability that reduces expression lines and wrinkles modulating skin aging through the synergistic effect of its active ingredients, such as polydeoxyribonucleotide, glutathione, peptide complex, and hyaluronic acid, which promote fibroblast proliferation and basal membrane repair, while also improving keratinocyte differentiation conditions.

The main objective of this research is to evaluate the clinical efficacy of Inno TDS PEPT-HA (Innoaesthetics Laboratory, Spain), considering the degree of hydration, skin sebum, and skin viscoelasticity measurements in volunteer patients with signs of aging and Fitzpatrick III or IV skin types, using sonophoresis as part of transdermal drug delivery systems through which the product penetrates the stratum corneum and diffuses through all layers of the skin for adequate efficacy [43].

Therefore, it is necessary to have a clear understanding of the anatomical, physiological, biochemical, and structural characteristics of the skin, as well as its functions, including its role as a skin barrier, which, if not stabilized, can affect the rate of diffusion of different drugs through the skin.

Sonophoresis involves the use of ultrasonic waves with an energy range between 20 kHz and 16 kHz, which is suitable for transporting drug molecules in transdermal drug delivery. The biomechanics of this transdermal therapy are based on increasing the skin temperature, which produces a controlled destabilization of the barrier function and allows molecules to penetrate the different layers of the skin to a depth of between 4 and 6 cm. Similarly, other authors such as [44], state that sonophoresis can be used to treat inflammatory conditions such as myositis and tendinitis, among others.

METHODOLOGY

A quantitative observational study was proposed in a group of 50 female patients with Fitzpatrick skin type III or IV, with a mean age of 47 years. Women who showed facial wrinkles, skin laxity, dry skin, or uneven skin tone were included in the study. Subjects were excluded if they were under the care of a physician or taking any medication that could interfere with the test results, were using nonsteroidal anti-inflammatory drugs, had a history of hypersensitivity to cosmetics, showed signs of skin infection or inflammation, or suffered from diseases that would increase the risk associated with participation or interfere with the results, excluding pregnant and breastfeeding women or those who intended to become pregnant during the study period. Other exclusion criteria related to skin treatments included the use of oral retinoids, dermal fillers, radiofrequency therapy, microfocused ultrasound therapy (in the previous year); botulinum toxin injections (within the previous 8 months); laser resurfacing (within the previous 6 weeks); or chemical peels or dermabrasion (within the previous 2 weeks). Subjects were asked to refrain from changing any facial skin products for at least 2 weeks prior to the study and nutritional supplements for at least 1 month prior to the study.

The treatment cocktail used was Inno TDS PEPT-HA, Laboratorio Innoaesthetics, Spain, which contains polynucleotide, glutathione, hyaluronic acid, palmitoyl tripeptide-5, tripeptide-1, and caprooyl tetrapeptide-3. Patients were instructed to use a cleanser (also from Inno Derma Soft Cleanser, Innoaesthetics Laboratory, Spain) and sunscreen (Inno Derma Sunscrem, Innoaesthetics Laboratory, Spain) as part of their general skin care routine. The product under study was applied using sonophoresis, which was performed every 7 days for a total of 6 sessions. The study was conducted on a hemifacial basis (split face), where one side of the face was treated with the product and the opposite side was treated with ultrasound and gel only.

Skin parameters were measured at baseline and after 4 and 8 weeks of use of the test product by the dermatologist in a simple blind manner. Subjects were required to thoroughly rinse their faces with a neutral lotion and acclimatize to the environment for at least 15 minutes prior to measurements. Patients at each session kept records of any undesirable effects.

In vivo skin parameters were evaluated using the following methods: Cutometer® dual MPA 580 Courage + Khazaka Electronic GmbH, to determine skin color using the Mexameter MX18® melanin index parameter, elasticity using the R2 Cutometer® parameter, luminosity using the Glossymeter GL200® DSC brightness value parameter, moisture using the Corneometer CM825®, and transepidermal water loss using the Tewameter TM300® on both upper cheeks at well-defined measurement sites.

Statistical analysis was performed using GraphPad Prism v8.3.0 and SPSS v26. The Shapiro-Wilk test was used to determine the normality of data distribution. Data processing was performed using repeated measures ANOVA with Bonferroni correction and Friedman's multiple comparison test to evaluate changes in normally distributed variables and non-normally distributed groups, respectively. Sample comparisons for TEWL were performed using the Kruskal-Wallis sum-of-ranks test, as the data could not be adjusted for multiple comparisons. Differences between treatment and no-treatment groups were considered biologically significant for P values of 0.05 or less.

RESULTS

The skin was observed to have a significantly lighter color and greater elasticity on the treated side compared to the untreated side after 8 weeks of product use, while skin luminosity improved significantly after 4 and 8 weeks of use. No significant changes were observed in skin moisture level (P > .9999) or TEWL (P > .9999) between the treatment and control sides. Skin luminosity improved significantly in the evaluations performed.

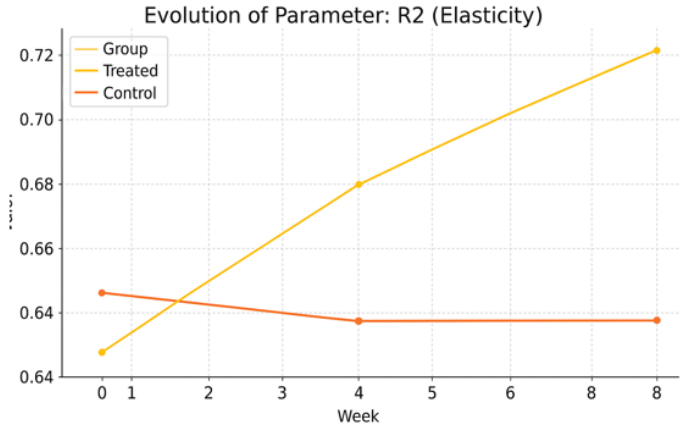

Figure 7. Graph representing elasticity over a range of time values.

In graph seven, we can see that as the time increased on the treated side, elasticity increased significantly, while on the side treated with ultrasound, there was a noticeable increase at the beginning, but then the values ceased to be representative.

Table 1. Results of the parameters measured on the skin.

Parámetros	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks	P1	P2
R2	0.63 ± 0.06	0.68± 0.07	0.72 ± 0.06	0.65 ± 0.10	0.64 ± 0.10	0.64 ± 0.10	.07	<.0001
Melanin index	226.7 ± 42.4	213.7 ± 39.4	209.3 ± 41.2	223.1 ±42.6	222.3 ±44.9	225.4 ± 46.6	.557	<.0001
Moisture level	73.04 ± 9.35	74.33 ± 8.46	73.77 ± 9.75	72.09 ± 9.29	73.77 ± 8.13	73.62 ± 10.06	>.9999	>.9999
TEWL (g/h/m2)	11.48 ± 2.38	12.45 ±2.05	11.79 ± 2.15	11.10 ± 2.04	12.87 ± 2.09	11.66 ± 2.45	>.9999	>.9999
Gloss DSC value	4.09 ± 1.52	4.90 ± 1.65	5.08 ± 1,61	4.41 ± 1.58	4.31 ± 1.49	4.41 ±1.71	.0221	.0201

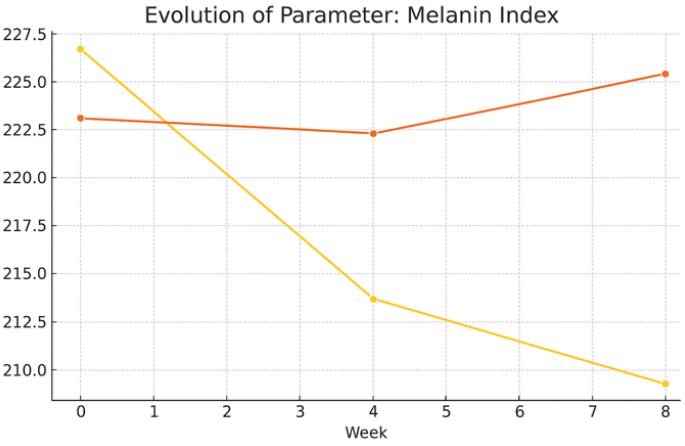

Figura 8. Gráfico que representa el índice de melanina en un rango tiempo valor.

Figure 8 shows a significant decrease in melanin on the treated side, which effectively explains the skin lightening experienced by the subjects. It is noteworthy that on the untreated side, we observed a range between 222.5 and week 4 of adaptive skin resilience without significant changes; however, from week 5 onwards, there was a significant increase. The product was well tolerated after application. No adverse reactions in the form of redness, swelling, dryness, flaking, itching, or burning were observed. Eight percent of subjects reported mild tightness (n = 4) in week 4, which decreased to 4% (n = 2) in week 8. Thirty-eight (76%) subjects experienced mild and transient tingling (mostly lasting less than one minute) in the fourth week, which decreased to twenty-five (50%) in the eighth week.

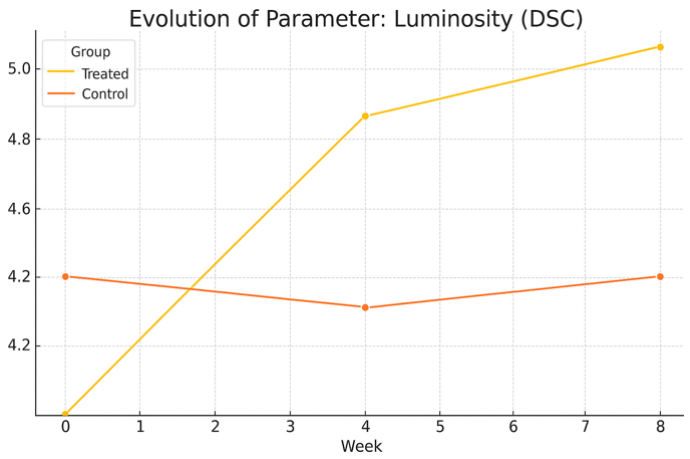

Figura 9. Gráfico que representa la luminosidad en un rango de tiempo valor

Analysis of the evolution graphs for each parameter measured in your study yields the following results:

- **Elasticity (R2):** shows a progressive and significant improvement on the treated side.

- **Melanin index:** a clear decrease is observed on the treated side, indicating an improvement in skin tone.
- **Luminousness (Gloss DSC):** sustained increase in brightness on the treated side from week 4 onwards.
- **Hydration and TEWL:** no significant differences, which supports the safety of the product in terms of barrier function.

DISCUSSION

Skin aging is a multifaceted and gradual process influenced by both internal and external factors, including environmental stressors that lead to a reduction in epidermal thickness and collagen content, loss of elasticity, hydration, and firmness, which clinically manifests as skin laxity, the appearance of wrinkles, and pigmentation [45].

With the advancement of technoscience, the introduction of instrumental measurements into dermatological and cosmetic research through equipment that allows for the quantitative evaluation of certain parameters related to skin functions has led to more accurate diagnosis.

In this study, biomechanical properties of the skin, such as elasticity and viscoelasticity, were determined as biomarkers of aging using a cutometer with the R2 parameter, coinciding with other studies [46,47] demonstrating a correlation between R2 (Ua/Uf) and the changes produced by aging, which facilitates the obtaining of absolute and relative elasticity values, as well as viscoelastic and distensibility properties related to skin firmness and thickness.

Another instrumental measurement used to determine skin color was the melanin index parameter (Mexameter MX18®), coinciding with its use and application to determine the intensity of melanin pigmentation before and after treatment, as in the study presented by [48].

Trans epidermal water loss (TEWL) was quantified using an instrumental measurement with the Tewameter TM300®, which provided accurate readings of skin hydration levels and trans epidermal water loss (TEWL) at well-defined measurement sites while maintaining barrier function stability, coinciding with. [49], who explored the relationship between skin surface hydration and transepidermal water loss (TEWL) when measured simultaneously, such that the greater the skin hydration, the lower the TEWL.

In relation to the pharmacological basis of Inno TDS PEPT-HA (Innoaesthetics Laboratory, Spain), reference is made to polydeoxyribonucleotides (also known as PDRN). These are double-stranded DNA fragments extracted from salmon (Oncorhynchus keta or mykiss) or trout sperm, purified to remove immunogenic proteins and preserve the nucleotide chains. It acts as a biological modulator capable of participating in cell repair pathways and new DNA synthesis in damaged tissues [50,51].

Polydeoxyribonucleotide (PDRN) is typically an A2A receptor agonist, which regulates various intracellular actions promoting tissue regeneration, since activation of this receptor increases collagen and elastin production in the skin, restoring skin structure, improving firmness and elasticity, and reducing the appearance of fine lines and wrinkles [52].

The results of the study by [53], indicated the effects of PDRN in mice with a second-degree deep dermal burn injury, demonstrating that the re-epithelialization of the burn wound improved and the time to final wound closure decreased. It has anti-inflammatory effects that manifest through the inhibition of inflammatory cytokines mediated by the activation of adenosine A2A receptors, which regulate the cytokine network [54].

PDRNs stimulate the production of vascular endothelial growth factor (VEGF) by activating the adenosine A2A receptor, thereby intervening in the skin repair process by significantly increasing the expression of VEGF, a key regulator of angiogenesis that acts as a mitogenic and angiogenic mediator and stimulates vascular permeability and angiogenesis [55].

Another active ingredient in Inno TDS DNA PEPT HA is glutathione (GSH: L-g-glutamyl-L-cysteinyl-glycine). This is a water-soluble tripeptide formed by the amino acids glutamic acid, cysteine, and glycine, which is present in the cytoplasm of all cells [56]. It has an antioxidant effect by acting on hydroxyl radicals and other free radicals. It plays a central role in defending tissues against oxidative stress [56]. It is a unique molecule with a fundamental role in cellular homeostasis, playing a significant role in defending against oxidative damage. Research indicates that there are two main forms of glutathione in the body [57,58].

Reduced glutathione (GSH): Active and capable of donating electrons to neutralize free radicals.

Oxidized glutathione (GSSG): Inactive form that can be recycled to become reduced glutathione again with the help of enzymes. It is mainly found in extracellular form.

Authors such as [49], note that it acts as a skin-whitening agent due to its antimelanogenic properties, inhibiting tyrosinase, eliminating free radicals, and diverting melanogenesis from darker eumelanin to lighter pheomelanin. The role of glutathione as a skin-lightening agent was an accidental discovery when it was noticed that skin lightening was a side effect of large doses of glutathione.

For their part, [60], conducted a literature search in the Clinical Key, Cochrane, Journal of the American Academy of Dermatology, Taylor and Francis Online, ScienceDirect, and PubMed databases to compare the efficacy and safety profiles of systemic glutathione as a skin-whitening agent in adults based on three (03) relevant randomized controlled trials (RCTs) and evaluated their validity, importance, and applicability. The results showed that one of the studies opposed glutathione as a skin-whitening agent, while the other two showed significant results only in some parts of the body or in certain age groups. They also demonstrated that glutathione produced other cosmetic benefits such as improving skin elasticity and reducing skin wrinkles. Another result confirmed that glutathione was well tolerated in oral preparations but not in parenteral preparations. In conclusion, these authors state that the majority of evidence showed that glutathione is not sufficiently beneficial as a skin-whitening agent, as it was only effective on certain parts of the body and did not produce lasting effects. However, its safety profiles in oral preparations were well tolerated. Nevertheless, in the team's opinion, further research is needed in this area.

When referring to the peptide complex (Tripeptide-1, Tripeptide-5, Tetrapeptide-3), peptides are defined as short chains of amino acids with varying effects depending on their formulation. A peptide begins with an alpha amino acid, a molecule containing amino and carboxyl functional groups attached to the same C1 atom.

They are produced naturally within the body by selective protein hydrolysis and, depending on which receptor they bind to, they determine a specific physiological effect or inhibit a specific glycation process of other proteins by modulating the permeation of the different channels of the cell membrane. Peptides have physiological properties, acting as antioxidants and anti-inflammatories, and are useful as anti-aging, anti-cellulite, and anti-stretch mark agents, among others [61].

They also stimulate the synthesis of extracellular matrix proteins such as type I collagen, type III collagen, elastin, fibronectin, and laminin, activating the action of certain growth factors such as TGF-β acting on fibroblasts to generate protein synthesis and decrease the activity of metalloproteinases [62].

The thinning and flattening of the dermoepidermal junction that occurs in aged skin results in compromised adhesion of the epidermis to the dermis, leading to a decrease in the mechanical stability and structural integrity of the skin. Based on this, [63], evaluated the anti-aging efficacy of the peptide complex through a clinical study in healthy volunteers, comprising a sample of 22 volunteers with a mean age (+/− standard deviation of 52.4 (+/− 6.2) (min. 40; max. 60). These researchers studied new peptide derivatives to determine their effects on the expression of basement membrane (BM) proteins in cultured human epidermal keratinocytes, and as a result, they obtained data revealing that the test peptide and peptide complex, once applied, stimulated the expression of collagen XVII, laminin, and nidogen proteins, which was confirmed in a subsequent ex vivo evaluation with excised human skin. Topical application of the peptide complex significantly increased the expression of dermal collagen, as well as collagen XVII and laminin (a protein derived from epidermal keratinocytes), noting that it was only detected in the upper layer of the dermis, suggesting a close binding of the laminin protein to the dermal side of the dermal junction. These results suggest that a peptide complex could improve the structural properties of the dermoepidermal junction.

Hyaluronic acid, the active ingredient in Inno TDS DNA PEPT HA, is an essential component of the extracellular matrix of all animal tissues. It is a glycosaminoglycan synthesized by fibroblasts that, when cross-linked with other proteins in the extracellular matrix such as collagen, contributes to the formation of macromolecules that increase tissue rigidity [64], playing a fundamental role in the reconstruction of skin tissue. It is also involved in the propagation and migration of keratinocytes, restoring hydration after the diffusion of nutritional supplies and eliminating waste from cellular metabolism.

This active ingredient interacts with proteins and also participates in inflammatory processes, immune responses, and the regeneration of damaged tissues [65]. The human body contains approximately 15 g of HA, 50% of which is found in the skin, mainly in the dermis. In its natural form, HA is highly soluble, non-immunogenic, and rapidly renewed through enzymatic degradation and free radicals [66].

HA is synthesized by membrane-bound synthases (HAS) on the inner surface of the plasma membrane of fibroblasts, and the chains are extruded through pore-like structures into the extracellular space by In vivo, HA can degrade fairly rapidly and is ultimately metabolized in the liver [67].

Rheological data can be used to understand the properties of a hyaluronic acid filler. One of the most important characteristics to consider when applying this active ingredient is its modulus of elasticity, which is expressed as G'. Basically, it is a measure that determines the gel's ability to withstand changes caused by external mechanical forces [68] and, when coupled with cohesiveness, reflects its resistance to mechanical degradation. This G' condition can be an indicator of a gel's lifting or stretching effect. Therefore, the stretching capacity increases as G' and cohesiveness increase [69].

Four studies with a total of 404 subjects were included in the meta-analysis conducted by [70]. Among them, 315 received HA-based fillers and 189 received non-HA-based fillers as controls. The random-effects meta-analysis demonstrated a higher hydration score in the HA filler group compared to the controls.

The various transdermal drug delivery systems offer advantages over other drug delivery systems due to their non-invasive nature, prolonged effects, high bioavailability, and fewer side effects. The route of drug penetration through the skin includes transcellular, intercellular, and transapendicular pathways, with the intercellular pathway being the most common for small uncharged molecules [71].

Limitations

The main limitations of this study include the **absence of long-term follow-up** and the **relatively small sample size**. While results at eight weeks were statistically significant, longer evaluation periods would be required to determine the persistence of effects and potential cumulative benefits.

Additionally, future research could incorporate **biophysical imaging** (confocal microscopy or high-frequency ultrasound) and **biomarker analysis** to quantify collagen and elastin remodeling more precisely.

Future Perspectives

Advances in **transdermal technology and bioactive compound development** will likely expand the therapeutic potential of non-invasive rejuvenation treatments. The integration of sonophoresis with polynucleotide-based cocktails may become a **standardized anti-aging protocol**, especially for patients seeking safe and effective alternatives to injections or ablative methods.

Further studies should explore **different molecular concentrations, combination protocols**, and **treatment frequencies** to optimize results and validate reproducibility across diverse populations.

CONCLUSIONS

The application of **Inno TDS DNA PEPT-HA** through **sonophoresis** demonstrated measurable and visible improvements in key parameters of skin quality—particularly in **luminosity** and **elasticity**—without altering the epidermal barrier's physiological function.

This integrative protocol represents a **non-invasive, effective, and safe approach** for the modulation of the facial aging process. Its efficacy derives from the synergistic action of bioactive components—polynucleotides, glutathione, hyaluronic acid, and peptides—that restore dermal homeostasis and stimulate tissue regeneration.

The histological and clinical findings confirm that **sonophoresis enhances molecular penetration** to a precise and biologically relevant depth, providing a viable alternative to injectable or ablative rejuvenation techniques.

In summary, the combination of **biochemical modulation (Inno TDS DNA PEPT-HA) and biophysical facilitation (sonophoresis)** offers an innovative therapeutic avenue for maintaining and restoring skin integrity, aligning with current trends toward integrative, evidence-based aesthetic medicine.

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