cosmetics

MDPI

Review

Extracellular Matrix Remodeling and Dermal Microenvironment Modulation in Regenerative Facial Aesthetics: A Critical Review of Collagen Biostimulators, Fibroblast Senescence, and Cutaneous Aging

Paola Tatiana Espinosa Cruel [1], Camila Pascoal Correia dos Santos [1], Daniela Vieira Buchaim [2,3,4], Silvia Yaoska Caldera González [5], Geraldo Marco Rosa Junior [4], Camila Aparecida Ribeiro [3], Carlos Henrique Bertoni Reis [6] and Rogerio Leone Buchaim [1,2,7,*]

1 Department of Biological Sciences, Bauru School of Dentistry (FOB/USP), University of Sao Paulo, Bauru 17012-901, Brazil; paolaespinosacruel@usp.br (P.T.E.C.); camila.pcs@usp.br (C.P.C.d.S.)
2 Graduate Program in Anatomy of Domestic and Wild Animals, Faculty of Veterinary Medicine and Animal Science, University of Sao Paulo (FMVZ/USP), Sao Paulo 05508-270, Brazil; danibuchaim@alumni.usp.br
3 Medical School, University Center of Adamantina (FAI), Adamantina 17800-000, Brazil; camilaribeiro@fai.com.br
4 Postgraduate Department, Dentistry School, Faculty of the Midwest Paulista (FACOP), Piratininga 17499-010, Brazil; geraldo.junior@facop.com.br
5 School of Medicine, Universidad Americana, Managua 663, Nicaragua; calderasilvia@hotmail.com
6 UNIMAR Beneficent Hospital (HBU), University of Marilia (UNIMAR), Marilia 17525-160, Brazil; dr.carloshenriquereis@usp.br
7 Center for the Study of Venoms and Venomous Animals (CEVAP), Sao Paulo State University (UNESP), Botucatu 18610-307, Brazil
* Correspondence: rogerio@fob.usp.br

Abstract

Skin aging is a complex biological process characterized by progressive alterations in the dermal microenvironment, including extracellular matrix (ECM) disorganization, fibroblast dysfunction, and changes in the biomechanical properties of the tissue. In this context, biomaterials used in regenerative aesthetic medicine have been widely employed with the aim of stimulating dermal remodeling processes. This review aimed to analyze the main biomaterials currently used in clinical practice, including calcium hydroxyapatite, poly-L-lactic acid, polycaprolactone, polynucleotides, polydeoxyribonucleotide, and nano-hydroxyapatite, focusing on their biological mechanisms and interactions with the cutaneous microenvironment. The available literature suggests that the effects of these materials are not limited to collagen induction, but also involve modulation of fibroblast activity, extracellular matrix reorganization, and progressive tissue remodeling processes. However, relevant limitations remain in the scientific literature, including methodological heterogeneity among studies and the scarcity of evidence directly clarifying the cellular mechanisms involved. Therefore, advances in this field depend on the integration of experimental research, histological analysis, and well-controlled clinical investigation, as well as a deeper understanding of cellular biology and extracellular matrix dynamics.

Keywords: skin aging; extracellular matrix; fibroblasts; tissue remodeling; dermal fillers; regenerative medicine; calcium hydroxyapatite; polynucleotides; orofacial harmonization

Check for updates

Academic Editor: Enzo Berardesca

Received: 15 April 2026
Revised: 26 May 2026
Accepted: 27 May 2026
Published: 1 June 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

There is a growing need to fill relevant gaps in the scientific literature on skin aging, not regarding its pathophysiological mechanisms, which have been widely described, but mainly about strategies capable of modulating or reversing this process in a biologically effective and clinically applicable way [1–5]. Current work on skin aging describes the cascade of events that occur so that aging is an intrinsic, progressive and inevitable phenomenon; the understanding of its cellular and molecular determinants has not yet fully translated into consistent regenerative approaches in clinical practice, especially in the context of orofacial harmonization [3,6,7].

In response to these limitations, technological advances have driven the development of increasingly safe and effective biomaterials, with tissue responses considered more natural [8,9]. In this scenario, collagen biostimulators have gained prominence for their ability to promote increased dermal thickness, neocollagenesis, and improved skin quality, and are procedures widely used in clinical practice [9–13]. However, most current approaches remain focused on macroscopic effects, often neglecting fundamental aspects of the biology of aging, such as cellular biochemistry, changes in the extracellular microenvironment, and phenomena associated with fibroblast senescence, factors directly involved in the progressive degradation of tissues [14–16].

From a biological point of view, biostimulation can be defined as the ability of certain polymers or biomaterials to induce a controlled inflammatory response, capable of triggering remodeling of the extracellular matrix [17,18]. After its application, there is gradual degradation of the material associated with the progressive deposition of collagen and other matrix components, allowing structural and functional changes in the skin tissue [19–21]. However, the effectiveness of this process depends directly on cell viability, the functional status of the fibroblasts and the balance of the tissue microenvironment in which these stimuli are inserted, especially in aged tissues, in which the presence of senescent fibroblasts and a pro-inflammatory and dysfunctional microenvironment significantly compromises the regenerative capacity and the response to biostimulatory stimuli [22,23].

Several biostimulators have been described in the literature, including platelet-rich plasma (PRP), injectable platelet-rich fibrin (i-PRF), poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), polycaprolactone (PCL), polydioxanone threads (PDO) and, more recently, hybrid fillers, each with unique physicochemical characteristics, as well as mechanisms of action [12,24,25]. Despite its wide clinical use, it is observed that many studies are limited to the evaluation of visible, macro and punctual histological results, without deepening the discussion on their effects on cellular aging, fibroblast senescence and modulation of the skin microenvironment, concepts that should be basic for a regenerative approach to aging skin [14,26,27].

Thus, the objective of this study is to perform a critical and integrative review of the main biomaterials used in regenerative facial aesthetics and orofacial harmonization, including established collagen biostimulators and emerging regenerative approaches, contextualizing their biological mechanisms in light of skin aging, fibroblast senescence, extracellular matrix remodeling, and changes in the dermal microenvironment, as well as discussing the gaps in the literature and the challenges for a truly regenerative approach to aging skin.

2. Dermal Microenvironment and the Extracellular Matrix

2.1. Dermal Microenvironment

In dermal tissue, the cutaneous microenvironment corresponds to a dynamic biological system formed by resident cells, components of the ECM, soluble mediators, and mechanical stimuli that, together, regulate the homeostasis and functionality of the skin

tissue [28,29]. This microenvironment acts as an integrated cellular communication platform, in which biochemical and biomechanical interactions modulate processes essential for maintaining the architecture and integrity of the skin [30,31] (Figure 1).

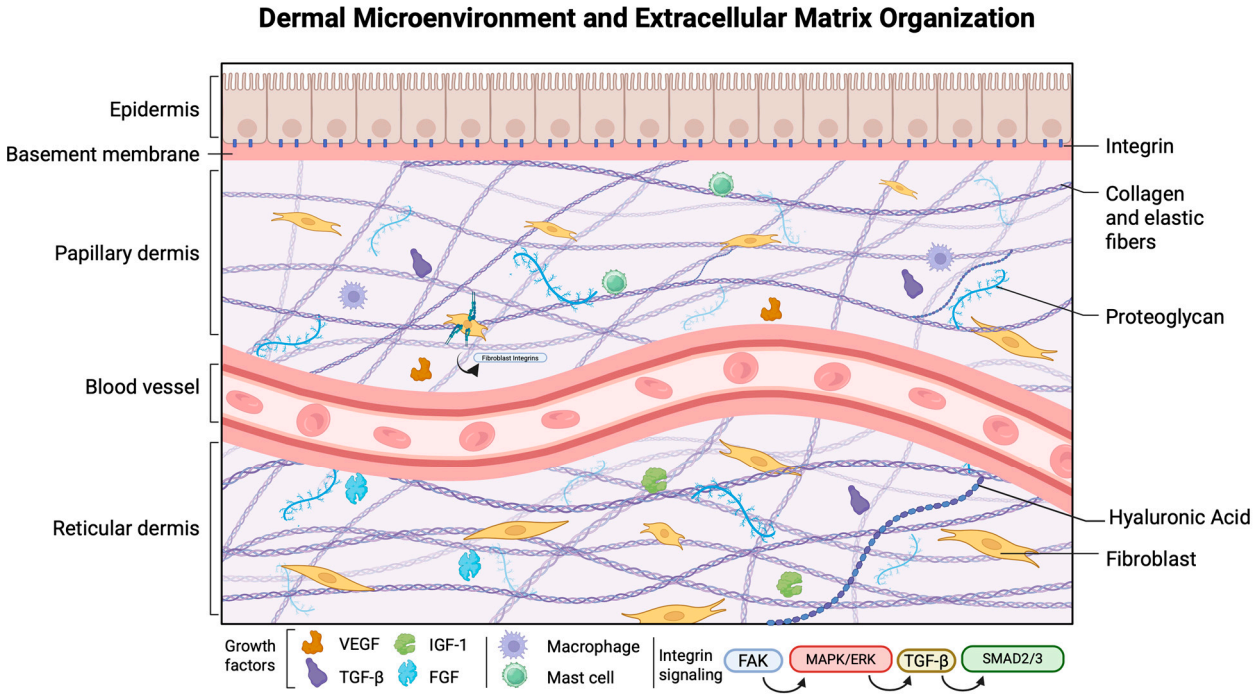


Figure 1. Schematic illustration of the dermal microenvironment showing extracellular matrix (ECM) components, resident cells, growth factors, and signaling pathways involved in dermal remodeling. Abbreviations: ECM, extracellular matrix; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor beta; IGF-1, insulin-like growth factor 1; FGF, fibroblast growth factor; FAK, focal adhesion kinase; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; SMAD2/3, SMAD family members 2 and 3. Illustration created in Biorender. Cruel, P. (2026) https://app.biorender.com/illustrations/69ac66af8c82ba0005ad67de.

From a biochemical perspective, the dermal microenvironment can be understood as an integrated system of molecular signaling in which several mediators regulate cellular activity and the interaction between cells and extracellular matrix, in which cytokines, growth factors, and inflammatory mediators act in a coordinated manner in the modulation of skin homeostasis and in the maintenance of the structural integrity of the tissue [32–34]. Among the main regulators involved in this process are transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), molecules that play a central role in the regulation of fibroblast proliferation, collagen synthesis, and dermal extracellular matrix remodeling mechanisms [35,36].

The continuous interaction between the resident cells of the dermis and the components of the extracellular matrix generates biomechanical and biochemical signals capable of modulating fundamental cellular processes, including migration, differentiation, and the synthesis of structural proteins that make up the dermal matrix, being mediated by mechanotransduction mechanisms and matrix-dependent signaling pathways, which regulate the cellular response to the tissue microenvironment [31,37].

Alterations in this microenvironment, such as those associated with skin aging or states of chronic inflammation, can significantly compromise the function of dermal fibroblasts, favoring the fragmentation of collagen in the extracellular matrix and reducing the regenerative capacity of the tissue. These processes contribute to the progressive loss of the structural integrity of the dermis and to changes in the homeostasis of the matrix [29,32,35].

2.2. Extracellular Matrix

The dermal ECM corresponds to a complex three-dimensional network of macromolecules that provides structural support to skin tissue and acts as an essential component in the regulation of interactions between cells and their microenvironment. This matrix is composed mainly of fibrillar proteins, adhesive glycoproteins, and proteoglycans, elements that act not only as structural components, but also as mediators of cellular communication and the functional organization of the dermis [28,38,39].

From a biochemical point of view, this matrix is mainly made up of adhesive glycoproteins, proteoglycans, collagen, and elastin. Collagen, particularly types I and III, represents the main structural protein of the dermis and is responsible for imparting mechanical strength and stability to the tissue, as well as providing support for cell organization and influencing the behavior of fibroblasts [29,40]. Elastin and elastic fibers, in turn, are responsible for the elasticity and recovery capacity of the tissue after mechanical deformations, allowing the skin to withstand external forces and return to its original configuration [41,42].

In addition to fibrillar proteins, the extracellular matrix contains adhesive glycoproteins, such as fibronectin and laminin, which play a key role in cell adhesion and the structural organization of the matrix [30]. These molecules interact with specific cellular receptors, particularly integrins, allowing the transmission of signals between the extracellular matrix and the cells and contributing to the regulation of cell migration, differentiation, and response to the tissue microenvironment [43–45].

Another essential group of components of the extracellular matrix is made up of proteoglycans and glycosaminoglycans (GAGs), among which hyaluronic acid stands out, a highly hydrophilic molecule that contributes to hydration, viscoelasticity and structural organization of the tissue microenvironment and the diffusion of nutrients and growth factors in the dermal microenvironment, contributing to tissue homeostasis [46–48] (Table 1).

Table 1. Selected structural components of the dermal extracellular matrix and their main structural and biological roles.

Component	Structural Role	Biological Role
Elastin	Elastic recoil and tissue elasticity	Adaptation to mechanical forces
Adhesive glycoproteins (fibronectin, laminin)	Cell adhesion and matrix organization	Integrin-mediated cell signaling
Glycosaminoglycans (GAGs) and proteoglycans	Hydration and matrix viscoelasticity	Diffusion of nutrients and growth factors

In an integrated way, these structural components not only maintain the architecture of the dermis but also modulate cellular behavior through mechanical and biochemical signals transmitted between the extracellular matrix and the resident cells. This dynamic interaction between matrix and cells forms the basis for mechanotransduction processes that regulate fibroblast function and dermal matrix remodeling [28,38,45].

2.3. Mechanotransduction and Integrins

Mechanotransduction corresponds to the process by which mechanical stimuli from the extracellular microenvironment are converted into intracellular biochemical signals capable of modulating cellular behavior [37]. In the skin, this mechanism allows cells to perceive and respond to the physical properties of the extracellular matrix, such as rigidity, tension, and structural organization, influencing fundamental processes such as proliferation, cell migration, and tissue remodeling [37,49].

In the dermis, the transmission of these mechanical forces occurs predominantly through integrins, transmembrane receptors that connect the components of the extracellular matrix to the cellular cytoskeleton; such molecules act as mechanical sensors capable of recognizing specific ligands of the matrix, such as collagen, fibronectin and laminin, converting physical stimuli from the microenvironment into intracellular signals that regulate cellular activity [43,50].

Structurally, integrins are heterodimers made up of α and β subunits that recognize specific ligands of the extracellular matrix, including collagen, fibronectin, and laminin [44]. After binding to their ligands, these proteins are organized into multiprotein complexes called focal adhesions, structures that connect the extracellular matrix to the cytoskeleton through adaptor proteins such as talin, vinculin, and paxillin. These molecular platforms act as signaling centers capable of integrating mechanical and biochemical stimuli into the cell's interior [45].

The formation of these structures allows the activation of intracellular pathways associated with the cellular mechanical response, including proteins such as focal adhesion kinase (FAK) and integrin-linked kinase (ILK) which regulate processes such as cell proliferation, fibroblast migration and synthesis of extracellular matrix components [51,52].

In addition, integrin-mediated signaling may interact with classical pathways involved in the regulation of dermal remodeling, particularly with the transforming growth factor beta (TGF-β) pathway [43]. The activation of this pathway promotes the phosphorylation of SMAD proteins and the modulation of the expression of genes involved in collagen synthesis and in the organization of the extracellular matrix, connecting mechanical stimuli from the microenvironment to the cellular responses responsible for dermal remodeling [53,54].

In this way, mechanotransduction mechanisms allow dermal fibroblasts to detect and respond to changes in the physical properties of the extracellular matrix, adjusting processes such as collagen synthesis, fiber organization, and dermal matrix remodeling [37,55]. This mechanical-biochemical communication system is essential for the maintenance of dermal homeostasis and for the adaptation of tissue to physiological or pathological changes in the cutaneous microenvironment [37,56].

2.4. Fibroblast–Matrix Crosstalk

The interaction between dermal fibroblasts and the extracellular matrix constitutes a dynamic system of bidirectional communication, often described as fibroblast–matrix crosstalk, in which cells and matrix mutually regulate their functions and structural organization [28,57].

In this system, fibroblasts play a central role in maintaining dermal homeostasis by synthesizing and organizing structural components of the extracellular matrix, including collagen, elastin, adhesive glycoproteins, and proteoglycans [40,46]. In parallel, the matrix components themselves exert control over fibroblast activity through interactions with cell surface receptors, especially integrins, which transmit biochemical and mechanical signals capable of modulating intracellular signaling pathways and gene expression patterns [43–45] (Figure 2).

Changes in the structural organization of the extracellular matrix can significantly impact this cellular communication system [30,58]. During skin aging, the progressive fragmentation of collagen fibers and changes in matrix architecture compromise the mechanical integrity of the dermal microenvironment, reducing the structural tension necessary for the maintenance of fibroblast function [35,59].

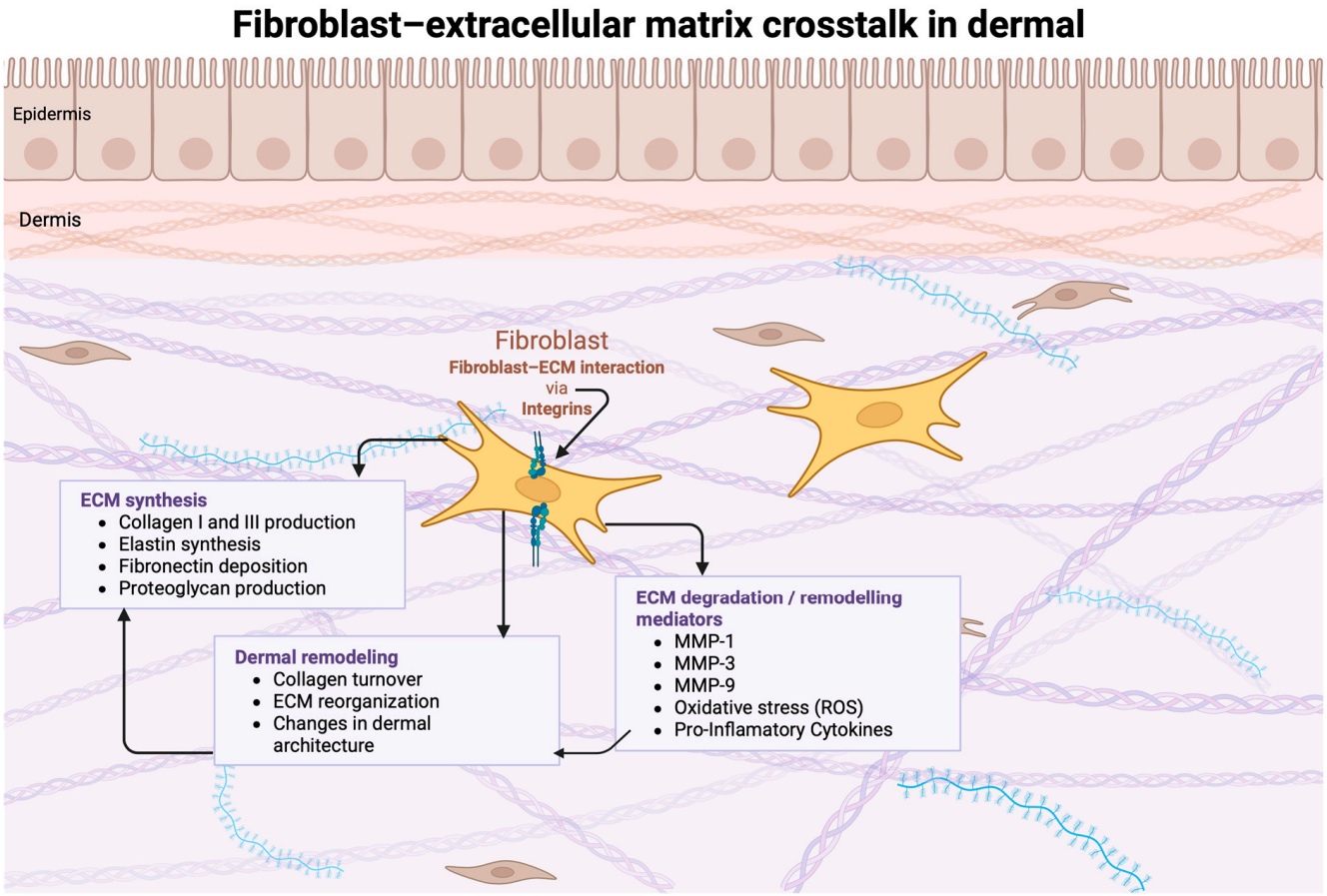


Figure 2. Schematic representation of the dermal microenvironment illustrating the interactions between fibroblasts and the extracellular matrix (ECM). Yellow cells represent fibroblasts; purple fibrillar structures represent collagen/ECM fibers; light-blue branched structures represent glycosaminoglycan/proteoglycan-rich matrix components; and brown cells represent other dermal stromal cells. The colors are used for illustrative differentiation and do not indicate quantitative differences or experimental conditions. Created in BioRender. Cruel, P. (2026) https://app.biorender.com/illustrations/69b29253dffec83a0cfcaa76.

The loss of this mechanical integrity alters matrix-derived signaling and promotes changes in the phenotype of dermal fibroblasts, characterized by a reduction in collagen synthesis and an increase in the expression of matrix metalloproteinases (MMPs), enzymes responsible for the degradation of matrix components [35,54]. This imbalance between synthesis and degradation contributes to the progressive disorganization of the dermal matrix and to the loss of structural integrity of the tissue [28,57].

In addition, collagen fragments generated during matrix degradation can act as biochemical signals capable of inducing phenotypic changes in fibroblasts, favoring the development of senescent cells [15,35]. These fibroblasts have reduced tissue regeneration capacity and start to secrete pro-inflammatory mediators and degradative enzymes associated with the so-called senescence-associated secretory phenotype (SASP), contributing to the alteration of the dermal microenvironment and to the progression of skin aging [60,61].

Together, these processes show that the balance between fibroblasts and extracellular matrix depends on an integrated system of cell signaling, matrix mechanical properties and continuous matrix remodeling [28,57]. The dysfunction of this crosstalk represents one of the main mechanisms involved in the loss of the regenerative capacity of the dermis observed during skin aging [15,35].

3. Skin Aging: An Integrated Perspective

3.1. Structural Changes in Skin Aging

Skin aging represents the peripheral manifestation of a progressive systemic biological process, in which intrinsic, genetic, hormonal, and metabolic factors interact with cumulative environmental exposures, particularly ultraviolet (UV) radiation, pollution, and smoking [62,63]. These factors result in progressive structural and functional changes in the skin tissue [64].

Unlike an alteration restricted to the epidermis, skin aging is a three-dimensional phenomenon that involves integrated modifications in the epidermis, dermis, hypodermis, and deep support structures, including adipose compartments, retention ligaments, and facial bone remodeling [28,45,62].

3.2. Epidermal Changes

Intrinsic aging is associated with a reduction in epidermal thickness due to a decrease in the proliferative activity of basal keratinocytes and the prolongation of the cell renewal cycle [65,66].

Histomorphometric studies show that with advancing age, there is a progressive flattening of the dermal-epidermal junction, with reduction of the interpapillary ridges, reducing the anchorage surface between epidermis and dermis [65]. This simplification of the interface between epidermis and dermis compromises the mechanical resistance and efficiency of metabolic exchanges, contributing to greater skin fragility at advanced ages [66].

In addition to these structural changes, epidermal aging is related to changes in the lipid composition of the stratum corneum of the skin barrier, particularly in the organization of ceramides, cholesterol and free fatty acids, as well as the reduction of sebaceous gland activity, which favors the development of xerosis and increased transepidermal water loss (TEWL), compromising the homeostasis of the skin barrier [67–69].

3.3. Dermal Alterations: Disorganization of the Extracellular Matrix

The most relevant structural changes associated with skin aging occur predominantly in the dermis, particularly in the ECM compartment, responsible for maintaining the mechanical and functional integrity of the skin tissue [29]. In young skin, the dermal matrix is composed mostly of type I collagen (approximately 80–85%) and type III collagen (about 10–15%), organized in densely packed fibrils that impart tensile strength and structural stability to the tissue. With advancing age, especially from the third decade of life, there is a progressive reduction in collagen synthesis, estimated at approximately 1% per year, accompanied by a relative increase in the activity of matrix metalloproteinases (MMPs), enzymes responsible for the degradation of matrix components [29,59,70].

The collagenic fragmentation observed in aging skin results primarily from the sustained increase in the expression of MMP-1, MMP-3, and MMP-9, whose activation of these enzymes is largely mediated by signaling pathways associated with oxidative stress, including the generation of reactive oxygen species (ROS) and the activation of transcription factor AP-1, which regulates the expression of genes involved in extracellular matrix degradation [71,72].

In parallel with collagen degradation, dermal aging involves alterations in the TGF-β/Smad pathway, often associated with reduced TβRII receptor expression in aging fibroblasts, which leads to decreased type I collagen synthesis [53]. The combination of lower biosynthetic capacity and greater degradation of the extracellular matrix contributes to dermal thinning, loss of mechanical resistance, and matrix disorganization [54].

The fragmentation of the extracellular matrix also directly alters the morphology and function of fibroblasts, a phenomenon known as "fibroblast collapse", characterized by the reduction of cytoskeletal tension and a further decrease in collagen production [22,29].

In addition to changes in fibrillar fraction, skin aging involves changes in the non-fibrillar components of ECM, particularly glycosaminoglycans (GAGs) and proteoglycans, which regulate hydration, viscoelasticity, and matrix organization [73]. Age-dependent changes have been described in proteoglycans such as decorin, which is important for collagen fibrillogenesis and dermal connective tissue architecture [74].

In vivo evidence further demonstrates that intrinsic aging is associated with measurable changes in the composition of GAGs and proteoglycans in human skin, indicating that dermal matrix deterioration is not limited to collagen fraction changes [75].

3.4. Hypodermis and Deep Structures

Facial aging involves selective and compartmentalized changes in subcutaneous adipose tissue, both in the superficial and deep compartments. Unlike homogeneous volumetric loss, these changes occur in a regional and predictable way, reflecting specific modifications in each adipose compartment [76] (Figure 3).



Figure 3. Comparison of the anatomical location of superficial and deep facial fat compartments in youth (yellow) versus aging (green). The illustration highlights how, with aging, previously cohesive fat pads undergo separation, volume loss, and inferomedial migration, contributing to contour changes and facial deflation. Illustration created in Biorender. Cruel, P. (2026) https://app.biorender.com/illustrations/6926f51e9b915c91ec73f5dd.

Anatomical evidence and imaging studies demonstrate that facial aging involves both selective atrophy of the adipose compartments and tissue displacement and rearrangement, associated with loss of support of the deep osteoligamentous framework [77]. At the same time, the progressive attenuation of the retaining ligaments reduces the mechanical containment of these compartments, favoring soft-tissue ptosis and the deepening of furrows and skinfolds in critical regions of the face [78]. Facial bone remodeling is also a fundamental component of structural aging, as it alters the support platform of the facial skeleton and directly influences the position and projection of the overlying soft tissues [79] (Figures 4 and 5).

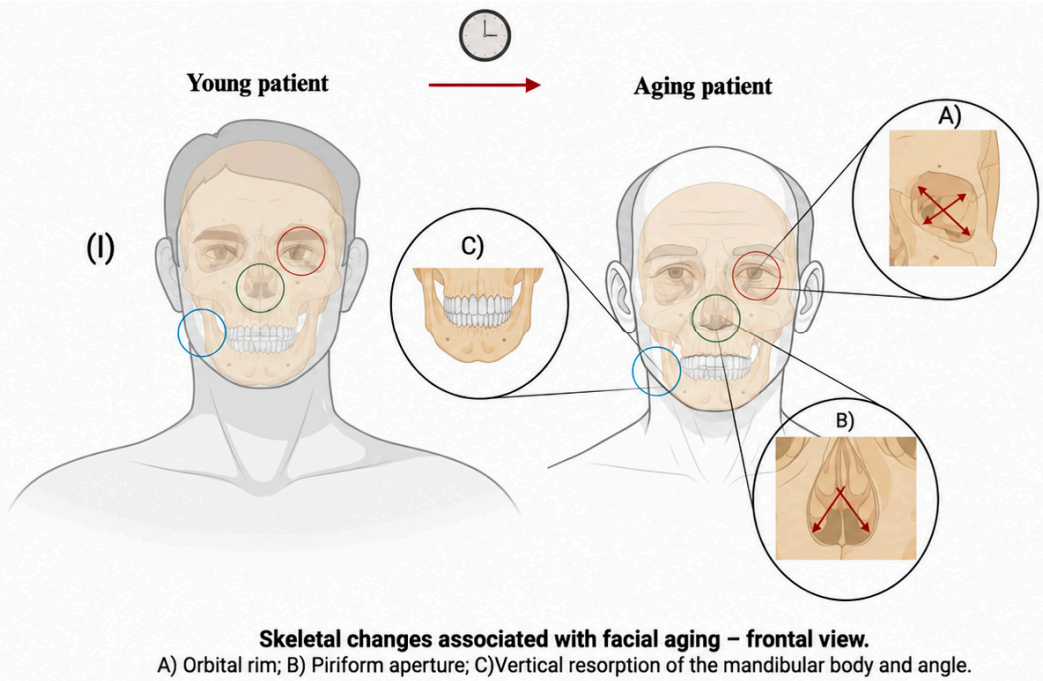


Figure 4. (I) Frontal view of skeletal remodeling associated with facial aging. The image compares a young patient and an aging patient and illustrates age-related skeletal modifications involving: (**A**) the orbital rim; (**B**) the piriform aperture; and (**C**) vertical resorptive changes in the mandibular body and angle. By reducing the underlying bony support for the facial soft tissues, these alterations may contribute to periorbital hollowing, midface flattening, changes in nasal base support, accentuation of facial folds, and progressive loss of definition in the lower facial contour. Figure 4 represents the frontal view of the same age-related skeletal remodeling process further illustrated in lateral view in Figure 5. Created in BioRender. Cruel, P. (2026) https://app.biorender.com/illustrations/690b50c95098e22e4b77b938?slideId=85f6558a-493f-4553-889c-c2ba659350a3.

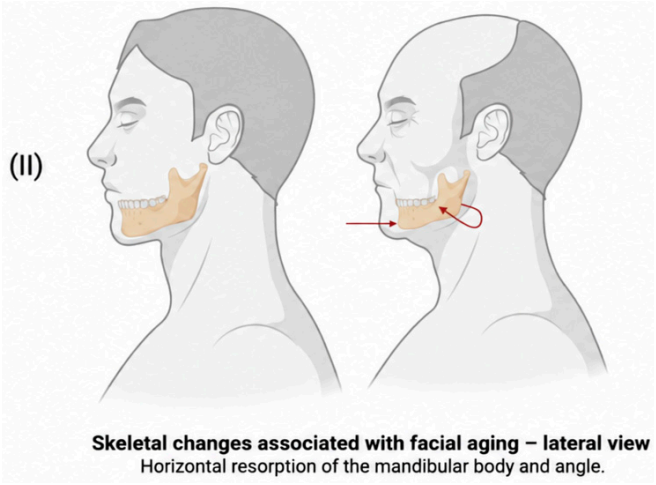


Figure 5. Lateral view of skeletal remodeling associated with facial aging. (II) Lateral representation of the same aging condition/process shown in Figure 4, highlighting mandibular remodeling and horizontal resorptive changes in the mandibular body and angle, with consequent impact on lower facial support. Illustration created in BioRender. Cruel, P. (2026) https://app.biorender.com/illustrations/690b50c95098e22e4b77b938?slideId=85f6558a-493f-4553-889c-c2ba659350a3.

Dentoalveolar structures may also influence aging of the lower face, as reduced dental and alveolar support can alter lip support, perioral folds, and mandibular definition, reinforcing the interpretation of facial aging as a multilayered process involving the skin, fat compartments, retaining ligaments, facial skeleton, and dentoalveolar support [77,79]. To-

gether, the interaction between compartmental changes in facial fat, progressive weakening of the ligamentous system, and bone remodeling triggers a cascade of three-dimensional changes that amplify clinical signs of aging, such as wrinkles, loss of facial contour, and irregularities in the skin envelope [76–79].

3.5. Extrinsic Aging and Photoaging

In addition to the intrinsic mechanisms associated with biological aging, environmental factors play an important role in the progressive deterioration of the skin. Among these factors, ultraviolet (UV) radiation represents the main determinant of extrinsic aging or photoaging, with more consistent environmental exposure associated with cumulative skin damage throughout life [35,62,80].

From a molecular point of view, repeated exposure to UV radiation promotes oxidative stress, with increased production of reactive oxygen species (ROS) and activation of intracellular signaling pathways such as MAPKs and pro-degradative transcription factors, particularly AP-1, resulting in increased expression of matrix metalloproteinases (MMPs) and relative reduction of dermal collagen synthesis [35,70,71,80].

Photoinduced damage is also associated with structural changes characteristic of the dermis, including solar elastosis, marked by the accumulation and disorganization of elastotic material in the superficial dermis, which compromises the biomechanical properties of the tissue [35,81,82].

In addition to UV radiation, environmental exposures such as air pollution, especially particulate matter (PM), polycyclic aromatic hydrocarbons (PAHs), and ozone, have been associated with worsening skin aging by mechanisms related to oxidative stress, inflammation, and activation of the AhR pathway, contributing to cellular senescence processes [62,80,83,84]. Table 2 provides a summary of the main histological and biological differences between chronological aging and photoaging.

Table 2. Histological and biological differences between chronological aging and photoaging.

Aspect	Chronological Aging	Photoaging
Main biological driver	Intrinsic, time-related biological changes influenced by genetic, hormonal, and metabolic factors [3,62,66,69].	Cumulative UV exposure associated with environmental stressors, including pollution, ozone, and particulate matter [35,62,80,84,85].
Epidermis	Reduced epidermal thickness, slower basal keratinocyte turnover, and flattening of the dermal–epidermal junction [65,66].	Irregular epidermal architecture, pigmentary changes, and cumulative UV-induced cellular damage [35,80,85].
Skin barrier	Decreased sebaceous activity and changes in stratum corneum lipids, contributing to xerosis and increased TEWL [67–69].	Barrier impairment may be intensified by oxidative stress, inflammation, and repeated environmental exposure [62,68,80,84].

Table 2. *Cont.*

Aspect	Chronological Aging	Photoaging
ECM and Collagen	Gradual reduction in collagen synthesis, decreased fibroblast activity, and progressive ECM disorganization [29,59,70].	Increased ROS production, MAPK/AP-1 activation, MMP upregulation, collagen fragmentation, and accelerated ECM degradation [35,70,71,81,85].
Fibroblast	Reduced mechanical stimulation, impaired fibroblast function, and lower matrix renewal capacity [29,59,70].	Oxidative and inflammatory signaling intensify fibroblast dysfunction and matrix-degrading activity [70,71,80,83,85]
Clinical Manifestation	Thin skin, fine wrinkles, dryness, reduced elasticity, and progressive laxity [3,66,69].	Pronounced wrinkles, rough texture, dyschromia, telangiectasia, and more visible damage in photo-exposed areas [3,35,80,82,85].

3.6. Regulatory Mechanisms Linking Fibroblast Senescence, Dermal Aging and ECM

Dermal aging should not be understood only as a reduction in collagen synthesis, but as a progressive alteration of the regulatory networks that maintain fibroblast activity, ECM organization, and tissue homeostasis [85–87]. In aged and photodamaged skin, cumulative oxidative stress, persistent low-grade inflammation, changes in mechanical signaling, and cellular damage may progressively impair fibroblast function and modify the dermal microenvironment [51,80,85].

In this context, senescent fibroblasts may acquire a senescence-associated secretory phenotype (SASP), characterized by the secretion of inflammatory mediators, growth factors, and matrix-remodeling enzymes, which can contribute to ECM disorganization and tissue dysfunction [87,88]. In parallel, changes in ECM architecture and stiffness may compromise fibroblast mechanosensing and mechanotransduction, influencing inflammatory signaling, matrix remodeling, and fibroblast behavior [51,87]. Thus, dermal aging can be interpreted as a self-sustaining biological process in which fibroblast senescence, ECM disorganization, inflammatory signaling, and impaired mechanotransduction interact progressively over time [51,86–88].

At the cellular level, fibroblast senescence results from the convergence of mechanisms related to genomic damage, activation of cell-cycle inhibitory pathways, inflammatory regulation, and metabolic imbalance. In this process, the p16INK4a/RB and p53/p21 axes play key roles in the induction and maintenance of the senescent state [5,14,60].

Other regulatory pathways, including NF-κB and mTOR signaling, have also been associated with the modulation of the SASP, contributing to the maintenance of a dermal microenvironment marked by persistent inflammation and matrix remodeling in aged tissues [14,60]. TGF-β signaling is also part of this regulatory network; however, its effects appear to depend on the biological context, since this pathway may be associated with ECM deposition, but also with fibroblast dysfunction or senescence according to the inflammatory, mechanical, and pathological conditions of the tissue [53,89].

These regulatory pathways are important for interpreting regenerative aesthetic interventions because dermal remodeling depends not only on the therapeutic stimulus

itself, but also on the biological condition of the recipient microenvironment [85,86]. In aged skin, fibroblast dysfunction, persistent inflammatory signaling, ECM disorganization, and altered mechanotransduction may influence both the intensity and the quality of the tissue remodeling response [51,86–88]. Therefore, collagen deposition after regenerative interventions should not be automatically interpreted as complete tissue regeneration, since current evidence still does not clarify whether these changes represent functional dermal repair, compensatory matrix remodeling, or biomaterial-induced fibrotic organization (Figure 6) [17,18,54,90].

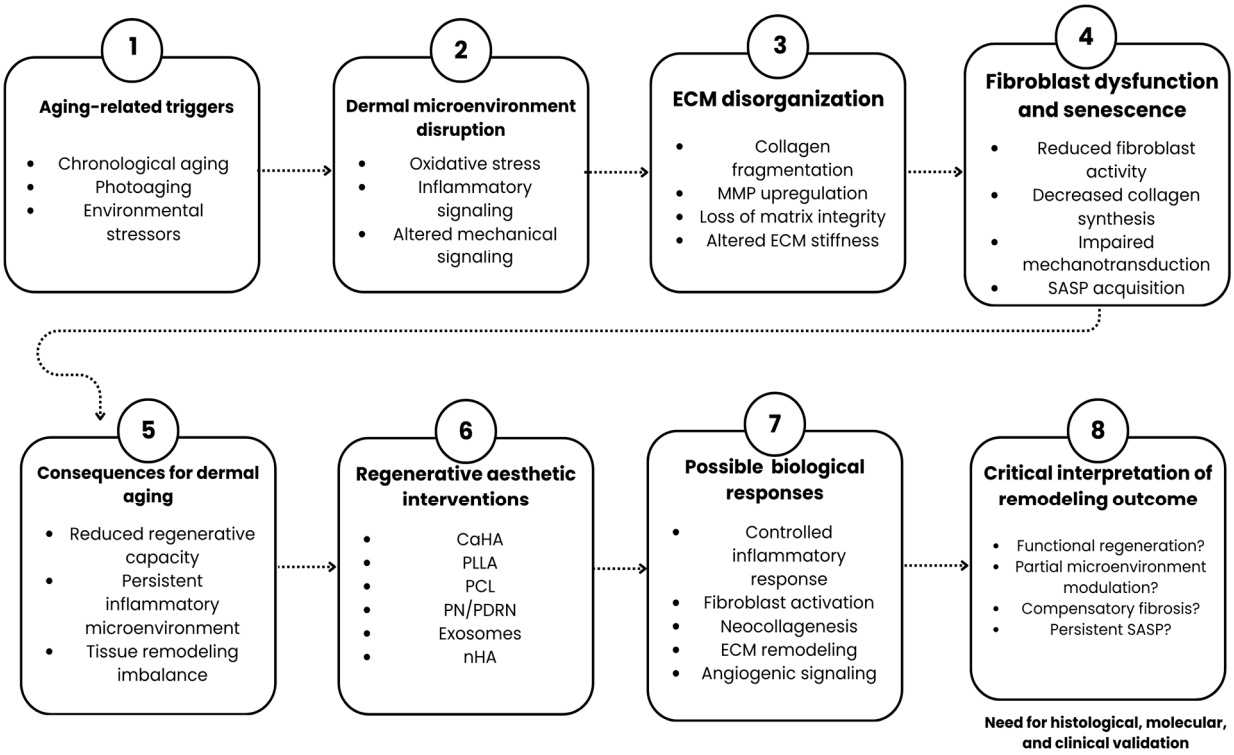


Figure 6. Integrated flow diagram of dermal aging and biostimulator-induced remodeling, showing the relationship between aging-related factors, dermal microenvironment imbalance, ECM disorganization, fibroblast dysfunction, senescence, and the potential responses induced by regenerative aesthetic interventions. Chronological aging, photoaging, and environmental stressors promote oxidative stress, inflammatory signaling, altered mechanotransduction, and loss of tissue homeostasis. These changes contribute to collagen fragmentation, impaired fibroblast activity, SASP acquisition, and reduced regenerative capacity. Although regenerative interventions may induce controlled inflammation, fibroblast activation, neocollagenesis, ECM remodeling, and angiogenic signaling, their final biological outcome may represent functional remodeling, partial microenvironment modulation, or compensatory fibrosis, highlighting the need for further histological, molecular, and clinical validation.

4. Collagen Biostimulators

Based on the biological mechanisms previously discussed, skin aging involves progressive changes in the dermal microenvironment that compromise extracellular matrix organization and fibroblast function, contributing to the structural deterioration of the dermis [29,85,86]. In this context, therapeutic approaches capable of modulating these processes have gained prominence in contemporary aesthetic medicine, especially those aimed at stimulating dermal remodeling rather than only providing immediate volumetric correction [12,90,91].

Among these approaches, collagen biostimulators correspond to biomaterials capable of inducing neocollagenesis and promoting progressive extracellular matrix reorganization,

differing from conventional fillers, whose main effect is related to immediate volumetric replacement [12,90].

Experimental studies suggest that injectable biomaterials may activate cellular pathways related to collagen synthesis and dermal matrix remodeling, including mechanisms associated with fibroblast activity and TGF-β/Smad signaling [53,92].

Thus, different biomaterials have been used with the objective of promoting dermal biostimulation in clinical practice. Among the main biostimulators used in aesthetic medicine are calcium hydroxyapatite (CaHA), poly-L-lactic acid (PLLA), and polycaprolactone (PCL), which have specific biodegradation profiles, clinical duration, and neocollagenesis-related mechanisms that influence their therapeutic indications and applications in facial rejuvenation [12,25,90].

4.1. Autologous Collagen Biostimulators

Autologous platelet concentrates are regenerative preparations obtained from the patient's own blood and contain different proportions of platelets, fibrin, leukocytes, and bioactive mediators involved in healing and tissue remodeling [93–97]. Among the main derivatives described are platelet-rich plasma (PRP), platelet-rich fibrin (PRF), injectable PRF (i-PRF), and plasma-derived gelled formulations, which differ in preparation method, biological composition, and growth factor release profile, aspects that influence their regenerative potential and clinical application [95–105].

4.1.1. PRP

PRP consists of an autologous preparation obtained by centrifugation of peripheral blood, generating a plasma fraction with platelet concentration above physiological values [93,97]. This product has been studied due to its content of growth factors, such as PDGF, TGF-β and VEGF, involved in processes such as cell proliferation, angiogenesis and extracellular matrix synthesis [95,97].

In the field of aesthetic dermatology, PRP has been evaluated as a complementary resource in skin rejuvenation, alopecia, and tissue repair [98,105]. Some studies report favorable effects on clinical and histological parameters of the skin, but these results should be interpreted with caution [98,105]. The available literature shows wide variability in the preparation protocols, in the final composition of the product, in the number of applications and in the evaluation methods, which makes it difficult to compare studies and limits the standardization of its clinical use [97,98,105].

4.1.2. PRF and i-PRF

PRF is an autologous platelet concentrate characterized by the formation of a fibrin matrix that incorporates platelets, leukocytes, and cytokines, without the need for anticoagulants during preparation [94,99]. i-PRF, in turn, is obtained by centrifugation protocols with lower relative force, which allows the preservation of a greater number of cells and biological mediators in the liquid fraction [96,100]. In the recent literature, these derivatives have been investigated as complementary therapies in tissue repair, alopecia, and facial rejuvenation procedures, with promising initial results [99,101,102]. However, the clinical evidence in aesthetics remains limited by the heterogeneity of the protocols and the small number of controlled studies available [101,102].

4.1.3. Gelled Formulations Derived from Plasma

Gelled formulations derived from platelet concentrates, described as plasma gel or plasma biofiller, have been proposed as autologous biomaterials with transient volumizing effect and bioactive potential [103,104]. Interest in these formulations in aesthetics stems

from the possibility of associating transient filling with regenerative properties derived from plasma and platelet components [104].

However, the available evidence for these formulations is still limited, with a predominance of small and methodologically heterogeneous studies, which restricts more robust conclusions about their efficacy and clinical standardization [103,105].

4.2. Biodegradable Synthetic Biostimulators

4.2.1. Calcium Hydroxyapatite (CaHA)

Calcium hydroxyapatite (CaHA) is a synthetic injectable biomaterial widely used in aesthetic medicine, described as combining an immediate plumping effect with a progressive biological response in dermal tissue [12,26]. In its classic formulation, CaHA is made up of uniform microspheres, ranging from 25 to 45 µm in diameter suspended in a carboxymethylcellulose (CMC) carrier gel that represents 70% of the total volume, this gel contributes to the initial volumetric effect after application, while the microspheres act as a temporary framework associated with the ECM remodeling processes [106]. Due to this combination of properties, CaHA has been used both for volume and contour replacement and, especially in diluted or hyperdiluted formulations, for gradual improvement of skin quality in different facial and body regions [106–108].

After the application of CaHA, the carrier gel is gradually reabsorbed in the first weeks, while the microspheres remain in the tissue for a longer period, favoring a sustained interaction between the biomaterial and the cells of the dermal microenvironment [26,109]. Histological studies suggest that this permanence of the particles is associated with a progressive increase in collagen deposition and remodeling of the extracellular matrix around the microspheres. In addition, the physical presence of the particles can temporarily modify the three-dimensional matrix organization and the mechanical properties of the tissue, factors known to influence fibroblast behavior and the synthesis of dermal matrix components, indicating a possible role of CaHA in the local modulation of the dermal microenvironment [21,30,110].

Due to this progressive behavior, CaHA is described in recent reviews as a biodegradable synthetic biostimulator, with clinical results generally reported between 12 and 18 months, although this duration may vary according to the indication, dilution, application plan, and treated area [107,108,111].

4.2.2. Poly-L-Lactic Acid—PLLA

PLLA is a biodegradable synthetic polymer of high molecular weight, belonging to the family of α-hydroxy acids and derived from lactic acid [112]. Unlike traditional volumizing fillers, its clinical effect is not predominantly based on immediate volume replacement, but on the progressive induction of structural changes in the dermal tissue after the deposition of the particles at the application site [112,113].

After injection, PLLA microparticles temporarily remain in the tissue and trigger a low-intensity local inflammatory response characterized by the recruitment of macrophages and other inflammatory cells [24]. With the progression of this cellular response, the formation of multinucleated giant cells around the particles is observed, characteristic of a controlled foreign body reaction. This process is associated with fibroblast activation and increased collagen deposition in the adjacent extracellular matrix, contributing to gradual changes in dermal matrix organization over time [113,114].

Histological studies demonstrate the presence of fibroblasts, macrophages and giant cells around the PLLA particles, accompanied by increased collagen density and reorganization of the extracellular matrix, findings compatible with a progressive process of dermal remodeling induced by the biomaterial [114]. In this context, the gradual increase

in collagen matrix deposition can result in dermal thickening and improved tissue support, a phenomenon often described as indirect volumization associated with dermal biostimulation, since the volume observed clinically results from the remodeling of the extracellular matrix and not from the permanence of the injected material [112,115].

However, some authors highlight that the tissue changes observed after the application of PLLA mainly reflect a controlled inflammatory response with the formation of fibrous tissue around the particles, a process compatible with biomaterial-induced fibrogenesis, and not necessarily a complete regenerative process of dermal tissue [113,114].

The biocompatibility and gradual biodegradation of PLLA also contribute to its use as a dermal biostimulator, since the polymer undergoes progressive hydrolytic degradation into lactic acid that is subsequently metabolized by physiological pathways, resulting in gradual reabsorption of the material over approximately 18 to 24 months [112,114].

4.2.3. Polycaprolactone

Polycaprolactone (PCL) is a biodegradable synthetic polymer belonging to the aliphatic polyester family, widely used in biomedical applications due to its biocompatibility and slow hydrolytic degradation [25]. In injectable formulations used in aesthetic medicine, the biomaterial consists of polycaprolactone microspheres suspended in an aqueous carboxymethylcellulose (CMC) carrier gel [116]. These microspheres have a smooth surface and a relatively uniform size, usually between 25 and 50 μm, characteristics described as important for reducing rapid phagocytosis of particles after application [116,117].

In contrast, PLLA particles have a more irregular morphology and rough surfaces, structural differences that can influence the interaction of the biomaterial with the cells of the recipient tissue [118]. The mechanism of action of polycaprolactone (PCL) is not limited to the immediate volumizing effect provided by the carrier gel, but also involves a progressive biological response associated with the temporary permanence of the microspheres in the tissue [119]. After application, these particles function as a local stimulus for remodeling the extracellular matrix, promoting gradual deposition of collagen around the microspheres and contributing to the maintenance of the volumetric effect over time [116,117].

Thus, the late clinical result seems to be related not only to the initial volume of the implant, but also to the neoformation of the dermal matrix induced by the interaction between the biomaterial and the recipient tissue [25]. In the initial phases after injection, a controlled local inflammatory response is initiated, considered part of the biological mechanism of the biomaterial and associated with the recruitment of inflammatory cells that participate in the tissue remodeling process [116].

From a clinical point of view, PCL has been used mainly for volume restoration and improvement of tissue support, with prolonged results compared to other resorbable biomaterials [25,116,117]. Clinical studies and long-term evaluations suggest maintenance of the volumizing effect for at least two years, a finding compatible with the progressive contribution of neocollagenesis to the clinical outcome [116,117] (Table 3).

Table 3. Overview of selected clinical and review studies investigating collagen biostimulators for facial rejuvenation, skin laxity, and dermal remodeling. The table summarizes study design, intervention, follow-up when available, and main objective or quantitative outcomes.

Author/Year	Type of Study	Objective	Intervention	Outcomes
Petrone et al., 2025 [10]	Prospective clinical study	To evaluate the efficacy and safety of a CaHA-based biostimulator in facial rejuvenation	CaHA injection in facial regions with 12-month follow-up	In 32 patients treated with diluted CaHA, 85% reported visible improvement at 120 days, ultrasound showed a 51% increase in dermal thickness in a subgroup, and 75% maintained aesthetic benefits at 360 days, with no serious adverse events.
Amiri et al., 2024 [91]	Systematic review	To assess clinical outcomes of CaHA in facial rejuvenation	Controlled Clinical Studies with CaHA Injection	Controlled studies reported CaHA-related improvement in GAIS scores, wrinkles, facial contour, nasolabial folds, and hand rejuvenation, although protocols and outcomes were heterogeneous.
Xu et al., 2024 [115]	Systematic review	Analyze clinical applications of PLLA in facial rejuvenation	Clinical studies involving the application of PLLA	Reported improvement in facial laxity, volume restoration, and collagen stimulation, although protocols and outcomes were heterogeneous.
Lin & Christen, 2020 [119]	Retrospective study	Evaluate complications associated with PCL	1111 treatments with polycaprolactone (Ellansé) in 780 patients	In 1111 PCL treatments, adverse events were uncommon and mainly included prolonged edema (4.5%), bruising (2.7%), malar edema (0.72%), palpable lumps (0.45%), and discoloration (0.18%), with no reported intravascular injection, nodules/granulomas, or infection.
Amiri et al., 2024 [120]	Systematic review	Investigate the regenerative mechanisms associated with CaHA	Experimental and clinical studies with calcium hydroxyapatite	Single-group studies reported CaHA-related aesthetic improvement in facial and nonfacial areas, including GAIS scores, wrinkle reduction, contour enhancement, nasolabial fold correction, and hand rejuvenation; however, outcome measures and protocols were heterogeneous.

Table 3. *Cont.*

Author/Year	Type of Study	Objective	Intervention	Outcomes
Signori et al., 2024 [121]	Systematic review	To evaluate efficacy and safety of PLLA in facial aesthetics	Clinical Studies with Poly-L-Lactic Acid Injection	PLLA was associated with long-lasting aesthetic improvement in facial indications, with most adverse effects described as mild to moderate and self-limited; however, the available evidence was mainly low quality and heterogeneous.
Ao et al., 2024 [122]	Narrative review	To review evidence on the use of PLLA in skin rejuvenation	Experimental and Clinical Studies with PLLA Injection	PLLA was associated with neocollagenesis, dermal remodeling, and skin quality improvement, although evidence was heterogeneous and mainly narrative.
Angelo-Khattar et al., 2025 [123]	Prospective clinical study	To evaluate volumetric and regenerative outcomes of PLLA in facial rejuvenation	PLLA injection into facial regions	3D volumetric assessment showed soft-tissue volume formation at 2 years, ranging from 0.75 to 6.4 cc per vial, with improved skin quality and no reported vascular compromise, nodules, or granulomas.
Ianhez et al., 2024 [124]	Retrospective case series	To describe complications associated with collagen biostimulators in Brazil	Clinical cases involving PLLA, CaHA and PCL	In 55 complication cases involving PLLA, CaHA, or PCL, nodules predominated (89.1%), mainly on the face (72.7%) and often with delayed onset (>1 month; 60.0%), supporting the need for ultrasound-based diagnosis and management.
Bravo et al., 2025 [125]	Prospective clinical study	To assess safety and satisfaction of patients treated with PLLA	Poly-L-lactic acid injection for facial rejuvenation	In 52 female patients treated with PLLA, GAIS scores remained stable from day 90 to day 150 (2.32 ± 1.0 vs. 2.32 ± 0.8; $p = 0.862$), with mild-to-moderate injection-site reactions and only one small painless nodule resolving without intervention.

Table 3. *Cont.*

Author/Year	Type of Study	Objective	Intervention	Outcomes
Bravo et al., 2025 [126]	Comparative prospective clinical study	Compare esthetic results of two CaHA-based fillers	CaHA injection (Radiesse®, manufacturer information not reported in the cited study; Rennova® Diamond Intense, manufacturer information not reported in the cited study)	In 30 patients, both CaHA fillers improved dermal thickness, skin elasticity, TEWL, and S-GAIS/P-GAIS outcomes up to 120 days; adverse events were mild and transient, resolving within 30 days.
Urdiales-Gálvez et al., 2026 [127]	Multicenter prospective clinical study	To evaluate clinical outcomes of PLLA (LASYNPRO) in facial rejuvenation	PLLA injections in different facial regions	PLLA-LASYNPRO improved wrinkles and volume, with 75% WSRS treatment success at month 4, increased P1CP at month 2, and no serious adverse events.

4.3. Emerging Therapies

4.3.1. Exosomes

Exosomes are extracellular vesicles of nanometric dimensions, usually ranging between approximately 30 and 150 nm in diameter, released by different cell types, including mesenchymal stem cells, fibroblasts, and keratinocytes [128–131]. These structures are delimited by a lipid bilayer and transport a variety of biologically active molecules, such as proteins, lipids, messenger RNAs and microRNAs. Through this molecular content, exosomes participate in intercellular communication processes, acting as mediators of signal transfer between cells and contributing to the modulation of different biological processes in tissues [129–131].

Unlike the biomaterials traditionally used in aesthetic medicine, exosomes do not act as volumizing agents, but as biological vesicles capable of mediating cell signaling processes and modulating the activity of receptor cells [129,132]. These nanovesicles can be obtained from different cellular sources, including autologous cells or cell cultures, and have characteristics such as high biocompatibility and biodegradability, properties that have contributed to the growing interest in their potential use in regenerative medicine [128,132].

After their application in dermal tissue, exosomes can be internalized by different cell types through mechanisms such as endocytosis, fusion with the plasma membrane, or interaction with cell surface receptors [129–131]. This process allows the transfer of their molecular content to target cells and may influence the activation of signaling pathways associated with tissue repair and regeneration, a phenomenon described mainly in experimental models of skin healing [128,133,134].

As a result, experimental studies have shown that exosomes derived from different cell types can stimulate the proliferation of dermal fibroblasts and increase the expression of extracellular matrix components, including collagen types I and III and elastin, fundamental elements for maintaining the structural integrity of the skin [133,134]. In addition, these extracellular vesicles can induce the release of mediators associated with angiogenesis, contributing to neovascularization processes and to the modulation of dermal microcirculation in experimental models of skin regeneration [128,133,134].

In the clinical context, the use of exosomes has been explored as an adjuvant approach in protocols aimed at improving skin quality, often associated with procedures such as

microneedling or energy-based technologies [132]. However, the clinical evidence remains limited and heterogeneous, being composed mainly of experimental studies and small-scale clinical series, which reinforces the need for controlled clinical trials that more robustly evaluate their efficacy and safety [128,132,135].

4.3.2. Polynucleotides

Polynucleotides (PN) are biopolymers made up of DNA-derived nucleotide chains, obtained by purification processes from genetic material of biological origin, often associated with marine species [136,137]. In aesthetic medicine, these compounds have been used as biomaterials in approaches aimed at skin revitalization and tissue regeneration. Recent reviews describe their application in aesthetic dermatology as a strategy aimed at improving parameters related to skin quality, although the available evidence is still predominantly based on small-scale clinical studies and narrative reviews [136,137].

From a structural point of view, polynucleotides correspond to polymers formed by nucleotide chains composed of nitrogenous bases, sugars and phosphate groups derived from DNA fragments [136,137]. In aesthetic medicine, these compounds are usually administered intradermally in protocols aimed at dermal biostimulation and skin revitalization [136,137]. In addition, experimental and clinical reviews suggest that DNA fragments may act as sources of available nucleotides for cellular metabolic processes associated with tissue repair and regeneration [138].

After their application to dermal tissue, polynucleotides can interact with cells in the cutaneous microenvironment, particularly fibroblasts, which play a central role in the maintenance and remodeling of the extracellular matrix [136,137]. Experimental evidence suggests that DNA-derived fragments can favor fibroblast proliferation and stimulate the synthesis of structural components of the extracellular matrix, including collagen types I and III, contributing to dermal tissue repair and reorganization processes [138]. In the clinical context, recent studies report improvement of skin parameters after intradermal application of polynucleotides, including reduction of erythema and improvement of characteristics related to skin quality, although many protocols involve therapeutic combinations and have limited clinical samples [139,140]. However, the available literature is still predominantly composed of small-scale clinical studies and heterogeneous protocols, which limits the comparison between results and reinforces the need for more robust controlled studies to better characterize their biological and clinical effects [137,139,140].

4.3.3. PDRN (Polydeoxyribonucleotides)

Polydeoxyribonucleotide (PDRN) is a set of low molecular weight DNA fragments obtained by extraction and purification processes from biological sources, often derived from marine material [138,141]. These fragments have high biocompatibility and can be metabolized by cells as a source of reusable nucleotides in biosynthetic pathways related to tissue maintenance and repair [138,141]. From a structural point of view, PDRN differs from the long-chain polynucleotides used in some dermal biostimulation formulations, since it consists of smaller fragments of DNA with greater metabolic availability for cellular processes involved in skin regeneration [138].

In addition to acting as a metabolic source of nucleotides, PDRN can modulate different cell signaling pathways associated with tissue regeneration [138,141–143]. Experimental studies have shown that PDRN-derived DNA fragments can influence the activity of fibroblasts and keratinocytes through the regulation of intracellular cascades related to ERK signaling, contributing to the modulation of cell proliferation and metabolic activity of these skin cells [144]. In parallel, recent investigations also suggest that specific forms of DNA derived from PDRN may exert biological effects on processes related to skin homeostasis

and cellular response to oxidative stress, indicating potential participation in mechanisms associated with the maintenance of skin integrity [142,143].

Biological effects associated with PDRN include modulation of mediators involved in tissue regeneration and reorganization of the extracellular matrix [138,141]. Experimental studies indicate that exposure to PDRN may favor processes related to angiogenesis and tissue repair, contributing to the restoration of microcirculation in tissues subjected to processes of damage or inflammation [138,141].

In addition, experimental models have shown that PDRN can influence fibroblast activity and the synthesis of structural components of the extracellular matrix, including collagen, favoring the reorganization of dermal tissue [138,141,144]. In the dermatological context, recent investigations have explored the use of PDRN in different approaches aimed at improving skin quality, including strategies aimed at modulating pigmentation, increasing skin elasticity, and overall improvement of parameters associated with skin aging [142,143].

Although frequently used interchangeably in the aesthetic literature, polynucleotides (PN) and polydeoxyribonucleotides (PDRN) have relevant structural and functional differences [145]. Polynucleotides correspond, in general, to nucleotide chains of higher molecular weight used in formulations aimed at dermal biostimulation and improved hydration and quality of the extracellular matrix [136,137,145]. In contrast, PDRN is made up of smaller fragments of DNA, whose biological activity has been associated primarily with modulation of cellular pathways related to tissue regeneration and purinergic signaling [138,141,145]. Experimental evidence indicates that these molecules can influence processes involved in tissue repair, including angiogenesis, fibroblast activity, and extracellular matrix remodeling [138,141,144]. In this context, recent reviews have emphasized that the conceptual differentiation between PN and PDRN is relevant for the proper interpretation of the biological mechanisms and clinical outcomes associated with these biomaterials in dermatological and aesthetic applications [145].

4.3.4. Nanohydroxyapatite

Nanohydroxyapatite (nHA) corresponds to the nanometric form of hydroxyapatite, a crystalline calcium phosphate with chemical similarity to the mineral phase naturally present in human bone tissue [146–149]. At the nanoscale, this material presents a greater specific surface area and distinct physicochemical properties compared with micrometric particles, which may influence its interaction with biological systems [146,147]. Due to these characteristics, nHA has been widely investigated as a biomaterial in tissue engineering and regenerative medicine strategies [148,149].

Calcium hydroxyapatite may present different structural configurations and particle dimensions, ranging from micrometric particles used in dermal fillers to nanometer-scale particles investigated in experimental regenerative applications. These structural variations can influence surface reactivity, biodegradation behavior, interaction with the biological microenvironment, and the type of cellular response induced in tissues [146,147].

In the experimental context, nanometer-scale hydroxyapatite and calcium phosphate-based particles have been investigated for their interaction with cells involved in tissue repair and skin regeneration. In vitro and preclinical models suggest that these particles may favor cell adhesion and modulate the activity of fibroblasts and keratinocytes, which are central to extracellular matrix maintenance and remodeling [150–152]. In addition, partial particle dissolution may release calcium and phosphate ions into the local microenvironment, potentially influencing signaling pathways associated with cell proliferation, migration, and matrix organization [146,147,153]. However, evidence supporting the use of nHA in dermal aesthetic applications remains mainly experimental, and its clinical relevance for facial rejuvenation

still requires specific validation. The main biostimulators used in aesthetic and regenerative medicine and their biological mechanisms are summarized in Table 4.

Table 4. Main biostimulators used in aesthetic and regenerative medicine and their biological mechanisms.

Biostimulator	Composition/ Particle size	Material Type	Main Mechanism of Action	Inflammatory Response	Average Duration of Effect	Main Clinical Indications
CaHA [12,21,26,106–111]	CaHA microspheres (25–45 µm) suspended in a carboxymethyl-cellulose	Synthetic biodegradable biomaterial	Fibroblast stimulation and collagen type I and III	Controlled foreign-body inflammatory response	12–18 months	Facial volume restoration, jawline contouring, nasolabial folds, hand rejuvenation
PLLA [11,24,112–115,121,122]	Synthetic polymer microparticles (40–63 µm)	Synthetic biodegradable polymer	Gradual collagen neosynthesis mediated by subclinical inflammatory response	Mild chronic inflammatory response with macrophage recruitment	18–24 months	Facial volume restoration, jawline contouring, nasolabial folds, hand rejuvenation
PCL [25,116,117,119]	PCL microspheres (25–50 µm) in a carrier gel	Synthetic biodegradable polymer	Long-term fibroblast stimulation and progressive extracellular matrix deposition	Mild-to-moderate foreign- body inflammatory response	24–36 months (depending on formulation)	Facial volume restoration and dermal bio-stimulation
EXOSOMES [128–135]	Extracellular vesicles (30–150 nm) containing proteins, lipids, and RNAs	Cell-derived biological vesicles	Intercellular signaling promoting tissue regeneration	Generally minimal or immunomodu-latory	Not yet clearly established; protocol-dependent	Skin quality improvement, experimental regenerative therapies, adjunctive procedures
PN [136,137,139, 140,145]	Long chains of nucleotides derived from purified DNA (commonly marine-derived)	Biological biodegradable biomaterial	Extracellular matrix hydration, fibroblast stimulation, and metabolic cellular support	Minimal inflammatory response	6–12 months (serial treatment protocols)	Skin revitalization, improvement of elasticity and dermal hydration
PDRN [138,141–145]	Low–molecular weight DNA fragments obtained from purified DNA	Biological biomaterial	Activation of adenosine A2A receptors and modulation of regenerative and angiogenic pathways	Immunomodulatory response	Variable depending on treatment protocol	Tissue repair, wound healing, improvement of skin quality
nHA [146–153]	Hydroxyapatite nanoparticles (<100 nm)	Inorganic nanostructured biomaterial	Interaction with dermal microenviron-ment cells and release of calcium and phosphate ions involved in cellular signaling	Not clearly established; evidence mainly experimental	Not established for dermal aesthetic use.	Experimental skin regeneration and tissue engineering applications

4.4. Safety Profile and Evidence Limitations

The clinical interpretation of regenerative aesthetic interventions should include safety considerations in addition to their proposed biological mechanisms, since adverse events and responses may vary according to the biomaterial, formulation, anatomical region, injection plane, dilution, dose, and injector technique [13,110,114,124]. For established injectable biostimulators, most reported adverse events are transient, including edema, erythema, ecchymosis, pain, and local tenderness [111,119,121,125,126]. Less frequent complications such as persistent nodules, granulomatous reactions, delayed inflammatory responses, vascular compromise, and tissue necrosis have also been described, reinforcing the importance of careful patient selection, anatomical knowledge, individualized treatment planning, and appropriate injection technique [13,119,124].

The level of safety evidence differs substantially among the interventions discussed in this review. CaHA, PLLA, and PCL have a broader clinical literature, although comparisons remain limited by heterogeneous protocols, follow-up periods, and adverse-event reporting [91,111,119–121,124–126]. Autologous platelet-derived products are generally considered biocompatible, but their reproducibility depends on preparation, centrifugation, activation, sterility, cellular composition, and handling methods [97,99,100,105].

Emerging approaches, including exosomes, polynucleotides, PDRN, and nanohydroxyapatite, require more cautious interpretation because formulation, regulatory status, follow-up, and long-term safety data remain insufficiently standardized [128,131,132,137,145,151]. Therefore, safety should be assessed according to the specific evidence base of each intervention rather than treated as a homogeneous attribute of regenerative aesthetic procedures [13,111,124,137,145,151]. Table 5 summarizes the main safety considerations and evidence limitations of the regenerative aesthetic interventions discussed in this review.

Table 5. Safety considerations and evidence limitations of regenerative aesthetic interventions.

Material	Main Safety Considerations	Limitations
CaHA [12,13,106–111,124,126]	Usually mild and transient reactions, with rare nodules, delayed inflammatory/granulomatous reactions, or vascular events depending on dilution, injection plane, anatomical site, and technique.	Safety data are more established than for emerging materials, but remain heterogeneous in protocols, indications, follow-up, and adverse-event reporting
PLLA [11,112–115,121,124,125,127]	Usually mild local reactions; delayed nodules, granulomatous/inflammatory responses, or overcorrection may occur when preparation, injection depth, intervals, or aftercare are inadequate.	Evidence is limited by heterogeneity in dilution, reconstitution time, number of sessions, massage recommendations, clinical endpoints, and follow-up duration.
PCL [25,116,117,119,124]	Usually transient reactions such as edema, ecchymosis, erythema, and pain; less frequent events include palpable product, nodules, delayed inflammatory/granulomatous reactions, and rare vascular complications.	Clinical safety data exist, but high-quality comparative studies remain limited compared with more established injectables.
PRP/PRF/i-PRF [97–102,105]	Generally biocompatible due to autologous origin; adverse events are usually local and transient, with infection risk mainly related to inadequate preparation or handling.	Reproducibility is limited by protocol variability, including centrifugation, cellular composition, activation, sterility, and growth-factor release.

Table 5. *Cont.*

Material	Main Safety Considerations	Limitations
Plasma gel/biofiller [103–105]	May cause transient swelling, bruising, irregularities, and unpredictable resorption; infection risk is mainly related to non-standardized preparation, heating, or handling.	Evidence is limited by small samples and non-standardized preparation protocols, restricting conclusions on efficacy, durability, and safety.
Exosomes [128,131,132,135]	Safety depends on source, isolation, characterization, sterility, dose, route, and regulatory control; concerns include contamination, immune reactions, product variability, and uncertain long-term effects.	Aesthetic use remains poorly standardized, with scarce long-term controlled safety data.
PN/PDRN [136,137,140,141,145]	Mostly local injection-site reactions, such as pain, erythema, swelling, and bruising; hypersensitivity or inflammatory responses may occur, while serious events remain poorly characterized in aesthetic use.	Evidence is limited by variability in composition, formulation, dose, combined therapies, treatment intervals, and follow-up duration.
nHA [146,147,150–152]	For dermal aesthetic use, safety remains insufficiently defined, with concerns about particle-related inflammation, biodistribution, and long-term tissue response.	Mainly experimental/preclinical evidence; dermal safety requires specific clinical validation.

5. Critical Perspective on Regenerative Approaches in Aesthetic Medicine

The traditional interpretation of skin aging often attributes the clinical signs observed to reduced collagen production or superficial structural changes in the skin. However, contemporary evidence indicates that this view represents an oversimplification of a highly complex biological process.

Skin aging involves progressive changes in the dermal microenvironment, including disorganization of the extracellular matrix, fibroblast dysfunction, changes in the biomechanical properties of tissue, and modifications in cell signaling pathways that regulate tissue homeostasis. In this context, fibroblasts should be understood not only as collagen-producing cells, but as dynamic regulators of dermal architecture, whose activity depends on continuous interaction with the components of the extracellular matrix and with biochemical and mechanical stimuli from the microenvironment.

This perspective has direct implications for the interpretation of the biological effects of biomaterials used in regenerative aesthetic medicine. Several injectable products used in clinical practice, such as calcium hydroxyapatite, poly-L-lactic acid, polycaprolactone, and nucleic acid derivatives, are often described in a simplified way as collagen biostimulators. However, restricting its effects to this mechanism may obscure the complexity of the interactions that occur in the dermal microenvironment after its application.

The biological response triggered by these biomaterials involves a sequence of interdependent cellular and molecular events, influenced not only by the chemical composition of the material, but also by factors such as particle morphology and morphometry, degradation kinetics, interaction with the recipient tissue, and intrinsic biological conditions of the skin microenvironment.

Another relevant aspect concerns the role of the biomechanical properties of the extracellular matrix in the regulation of cellular activity. During skin aging, changes in the organization and rigidity of the matrix can compromise the mechanotransduction mechanisms responsible for transmitting mechanical signals to resident cells. This process

can contribute to fibroblastic dysfunction and reduced remodeling capacity of the dermal matrix. In this scenario, therapeutic interventions aimed at the dermal microenvironment can act not only by stimulating collagen production, but also by modulating the interactions between cells and the extracellular matrix.

Despite the growing clinical use of these biomaterials, the scientific literature still has relevant limitations. Much of the available evidence derives from clinical series, observational studies, or heterogeneous experimental models, often with variations in dilution protocols, application techniques, and anatomical indications. These methodological differences make it difficult to directly compare the studies and limit the interpretation of clinical results.

In addition, although histological studies often demonstrate increased collagen density and reorganization of the extracellular matrix after the application of certain biostimulators, an important scientific question remains to what extent do these changes represent an effective regenerative process or predominantly reflect reparative or fibrotic responses associated with the presence of the biomaterial in the tissue. The distinction between true dermal regeneration and reparative remodeling induced by controlled inflammatory stimuli is not yet fully clarified.

Another aspect that has not yet been explored in the literature refers to the possible impact of these biomaterials on cellular processes associated with aging, such as fibroblast senescence and the modulation of the secretory phenotype associated with senescence. Considering that cellular senescence plays an important role in the pathophysiology of skin aging, understanding how regenerative therapies interact with these mechanisms represents a major gap in current knowledge.

Additionally, the study of the interactions between biomaterials and the dermal microenvironment still needs to be expanded beyond the isolated analysis of collagen synthesis. Skin tissue is a highly dynamic biological system, in which resident cells, extracellular matrix, vascular components, and inflammatory mediators interact continuously. Future investigations that integrate histological, molecular and biomechanical analyses may contribute to a deeper understanding of these processes.

Given this scenario, it becomes evident that the incorporation of new biomaterials and regenerative technologies in clinical practice requires a solid understanding of cell biology and the biochemistry of the extracellular matrix. The growing availability of therapies aimed at dermal biostimulation, polynucleotides, nanoparticles and other biomaterials reinforce the need for therapeutic decisions to be based not only on immediate clinical results, but also on a critical interpretation of the biological mechanisms involved.

In this sense, the objective of this review is not to establish hierarchies between different biomaterials or to promote certain therapeutic approaches. On the contrary, it is intended to highlight that the advancement of regenerative aesthetic medicine depends on the integration between basic knowledge in tissue biology and responsible clinical application. Only from this perspective will it be possible to develop therapeutic strategies capable of interacting more precisely with the dermal microenvironment, contributing not only to transient structural changes, but to interventions biologically based on the tissue remodeling process.

6. Conclusions

Skin aging results from progressive changes in the dermal microenvironment, including disorganization of the extracellular matrix, fibroblast dysfunction, and modifications in the biomechanical properties of the tissue. In this context, the biomaterials used in regenerative aesthetic medicine should be interpreted not only as collagen inducers, but as modulators of cellular and matrix processes involved in tissue remodeling.

Despite the growing clinical application of these materials, the literature still has important limitations, including methodological heterogeneity and scarcity of evidence capable of directly clarifying their biological mechanisms in human dermal tissue. Therefore, the advancement of this field depends on the integration between experimental investigation, histological analyses and well-controlled clinical studies. Thus, the development and application of regenerative therapies in aesthetic medicine must be grounded in a solid understanding of cell biology and extracellular matrix dynamics, allowing for progressively more evidence-based therapeutic approaches.

Author Contributions: Conceptualization, P.T.E.C. and C.P.C.d.S.; methodology, C.P.C.d.S., S.Y.C.G., G.M.R.J., C.A.R. and C.H.B.R.; validation, D.V.B. and R.L.B.; formal analysis, C.P.C.d.S., S.Y.C.G., G.M.R.J. and C.H.B.R.; investigation, C.P.C.d.S. and P.T.E.C.; resources, R.L.B.; data curation, C.P.C.d.S. and C.A.R.; writing—original draft preparation, C.P.C.d.S.; writing—review and editing, D.V.B. and R.L.B.; visualization, P.T.E.C., C.P.C.d.S., D.V.B., S.Y.C.G., G.M.R.J. and C.H.B.R.; supervision, R.L.B.; project administration, R.L.B. All authors have read and agreed to the published version of the manuscript.

Funding: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES)—Finance Code 001. R.L.B. is a CNPq (The National Council for Scientific and Technological Development/Conselho Nacional de Desenvolvimento Científico e Tecnológico) PQ1C research fellow (No. 302545/2025–5).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Ganceviciene, R.; Liakou, A.I.; Theodoridis, A.; Makrantonaki, E.; Zouboulis, C.C. Skin Anti-Aging Strategies. *Derm.-Endocrinol.* **2012**, *4*, 308–319. [CrossRef] [PubMed]
2. Fisher, G.J.; Kang, S.; Varani, J.; Bata-Csorgo, Z.; Wan, Y.; Datta, S.; Voorhees, J.J. Mechanisms of Photoaging and Chronological Skin Aging. *Arch. Dermatol.* **2002**, *138*, 1462–1470. [CrossRef] [PubMed]
3. Farage, M.A.; Miller, K.W.; Elsner, P.; Maibach, H.I. Intrinsic and Extrinsic Factors in Skin Ageing: A Review. *Int. J. Cosmet. Sci.* **2008**, *30*, 87–95. [CrossRef]
4. Naharro-Rodriguez, J.; Bacci, S.; Hernandez-Bule, M.L.; Perez-Gonzalez, A.; Fernandez-Guarino, M. Decoding Skin Aging: A Review of Mechanisms, Markers, and Modern Therapies. *Cosmetics* **2025**, *12*, 144. [CrossRef]
5. Wyles, S.P.; Carruthers, J.D.; Dashti, P.; Yu, G.; Yap, J.Q.; Gingery, A.; Tchkonia, T.; Kirkland, J. Cellular Senescence in Human Skin Aging: Leveraging Senotherapeutics. *Gerontology* **2024**, *70*, 7–14. [CrossRef]
6. López-Otín, C.; Blasco, M.A.; Partridge, L.; Serrano, M.; Kroemer, G. The Hallmarks of Aging. *Cell* **2013**, *153*, 1194. [CrossRef]
7. Fisher, G.J.; Wang, B.; Cui, Y.; Shi, M.; Zhao, Y.; Quan, T.; Voorhees, J.J. Skin Aging from the Perspective of Dermal Fibroblasts: The Interplay between the Adaptation to the Extracellular Matrix Microenvironment and Cell Autonomous Processes. *J. Cell Commun. Signal.* **2023**, *17*, 523–529. [CrossRef]
8. Nowag, B.; Schäfer, D.; Hengl, T.; Corduff, N.; Goldie, K. Biostimulating Fillers and Induction of Inflammatory Pathways: A Preclinical Investigation of Macrophage Response to Calcium Hydroxylapatite and Poly-L Lactic Acid. *J. Cosmet. Dermatol.* **2024**, *23*, 99–106. [CrossRef]
9. Cure, E.; Hernández, L.A.P.; Amado, A.M.; Cabrales, J.S.R.; Garcés, E.; Dicker, V.; Castelanich, D.; Schneider, C.; Salas, I.; Argueta, J.; et al. Optimizing Collagen Biostimulator Choice in LATAM: Expert Consensus on Patient Selection, Ethnic Skin Phenotypes, and Accessibility. *J. Cosmet. Dermatol.* **2025**, *24*, e70564. [CrossRef] [PubMed]
10. Petrone, G.; Leão, C.; Morais, D.; Ducati, E.; Kasai, M.; Viana, R. Clinical Evaluation of an Innovative CaHA Bio-Stimulator in Facial Rejuvenation: 1 Year Follow-Up. *J. Cosmet. Dermatol.* **2025**, *24*, e70210. [CrossRef]
11. Ouyang, R.; Su, X.; Liang, Y.; Lu, S.; Zhang, Z.; Wei, Q.; Hu, J. Advances in Poly-l-Lactic Acid Injections for Facial and Neck Rejuvenation. *Plast. Reconstr. Surg. Glob. Open* **2025**, *13*, e7029. [CrossRef]

12. Aguilera, S.B.; McCarthy, A.; Khalifian, S.; Lorenc, Z.P.; Goldie, K.; Chernoff, W.G. The Role of Calcium Hydroxylapatite (Radiesse) as a Regenerative Aesthetic Treatment: A Narrative Review. *Aesthet. Surg. J.* **2023**, *43*, 1063–1090. [CrossRef]
13. Liu, J.; Gao, M.; Hu, H.; Pang, H.; Liu, Y.; Zhang, P. Facial Injectable Fillers in Aesthetic Medicine: Clinical Applications and Safety Strategies. *Med. Sci. Monit.* **2025**, *31*, e949944. [CrossRef]
14. Nan, L.; Guo, P.; Hui, W.; Xia, F.; Yi, C. Recent Advances in Dermal Fibroblast Senescence and Skin Aging: Unraveling Mechanisms and Pioneering Therapeutic Strategies. *Front. Pharmacol.* **2025**, *16*, 1592596. [CrossRef] [PubMed]
15. Wlaschek, M.; Maity, P.; Makrantonaki, E.; Scharffetter-Kochanek, K. Connective Tissue and Fibroblast Senescence in Skin Aging. *J. Investig. Dermatol.* **2021**, *141*, 985–992. [CrossRef]
16. Zhang, J.; Yu, H.; Man, M.Q.; Hu, L. Aging in the Dermis: Fibroblast Senescence and Its Significance. *Aging Cell* **2024**, *23*, e14054. [CrossRef]
17. Anderson, J.M.; Rodriguez, A.; Chang, D.T. Foreign Body Reaction to Biomaterials. *Semin. Immunol.* **2008**, *20*, 86–100. [CrossRef]
18. Brown, B.N.; Ratner, B.D.; Goodman, S.B.; Amar, S.; Badylak, S.F. Macrophage Polarization: An Opportunity for Improved Outcomes in Biomaterials and Regenerative Medicine. *Biomaterials* **2012**, *33*, 3792–3802. [CrossRef] [PubMed]
19. Rice, J.J.; Martino, M.M.; De Laporte, L.; Tortelli, F.; Briquez, P.S.; Hubbell, J.A. Engineering the Regenerative Microenvironment with Biomaterials. *Adv. Healthc. Mater.* **2013**, *2*, 57–71. [CrossRef]
20. Miron, R.J.; Zhang, Y.F. Osteoinduction: A Review of Old Concepts with New Standards. *J. Dent. Res.* **2012**, *91*, 736–744. [CrossRef] [PubMed]
21. Berlin, A.L.; Hussain, M.; Goldberg, D.J. Calcium Hydroxylapatite Filler for Facial Rejuvenation: A Histologic and Immunohistochemical Analysis. *Dermatol. Surg.* **2008**, *34*, S64–S67. [CrossRef]
22. Fisher, G.J.; Varani, J.; Voorhees, J.J. Looking Older: Fibroblast Collapse and Therapeutic Implications. *Arch. Dermatol.* **2008**, *144*, 666–672. [CrossRef]
23. Campisi, J.; D'Adda Di Fagagna, F. Cellular Senescence: When Bad Things Happen to Good Cells. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 729–740. [CrossRef]
24. da Cunha, M.G.; Engracia, M.; de Souza, L.G.; Filho, C.D.A.M. Biostimulators and Their Mechanisms of Action. *Surg. Cosmet. Dermatol.* **2020**, *12*, 109–117. [CrossRef]
25. Christen, M.O.; Vercesi, F. Polycaprolactone: How a Well-Known and Futuristic Polymer Has Become an Innovative Collagen-Stimulator in Esthetics. *Clin. Cosmet. Investig. Dermatol.* **2020**, *13*, 31–48. [CrossRef]
26. De Almeida, A.T.; Figueredo, V.; Da Cunha, A.L.G.; Casabona, G.; Costa De Faria, J.R.; Alves, E.V.; Sato, M.; Branco, A.; Guarnieri, C.; Palermo, E. Consensus Recommendations for the Use of Hyperdiluted Calcium Hydroxyapatite (Radiesse) as a Face and Body Biostimulatory Agent. *Plast. Reconstr. Surg. Glob. Open* **2019**, *7*, e2160. [CrossRef] [PubMed]
27. Meçani, R.; Amiri, M.; Kadouch, J.; Sajic, D.; Lin, F.; Cheung, J.; Barrera, D.; Haroon, O.; Sil-Zavaleta, S.; Chao, Y.; et al. Combined and Hybrid Treatments of Hyaluronic Acid (HA) and Calcium Hydroxylapatite (CaHA): A Systematic Review of Mechanisms of Action, Aesthetic Effectiveness, Satisfaction, and Safety Profile. *Aesthetic Plast. Surg.* **2025**, *49*, 5292–5313. [CrossRef]
28. Theocharis, A.D.; Skandalis, S.S.; Gialeli, C.; Karamanos, N.K. Extracellular Matrix Structure. *Adv. Drug Deliv. Rev.* **2016**, *97*, 4–27. [CrossRef] [PubMed]
29. Quan, T.; Fisher, G.J. Role of Age-Associated Alterations of the Dermal Extracellular Matrix Microenvironment in Human Skin Aging: A Mini-Review. *Gerontology* **2015**, *61*, 427–434. [CrossRef]
30. Frantz, C.; Stewart, K.M.; Weaver, V.M. The Extracellular Matrix at a Glance. *J. Cell Sci.* **2010**, *123*, 4195–4200. [CrossRef]
31. Bonnans, C.; Chou, J.; Werb, Z. Remodelling the Extracellular Matrix in Development and Disease. *Nat. Rev. Mol. Cell Biol.* **2014**, *15*, 786–801. [CrossRef]
32. Tracy, L.E.; Minasian, R.A.; Caterson, E.J. Extracellular Matrix and Dermal Fibroblast Function in the Healing Wound. *Adv. Wound Care* **2016**, *5*, 119–136. [CrossRef]
33. Kalluri, R. The Biology and Function of Fibroblasts in Cancer. *Nat. Rev. Cancer* **2016**, *16*, 582–598. [CrossRef]
34. Eming, S.A.; Martin, P.; Tomic-Canic, M. Wound Repair and Regeneration: Mechanisms, Signaling, and Translation. *Sci. Transl. Med.* **2014**, *6*, 265sr6. [CrossRef] [PubMed]
35. Rittié, L.; Fisher, G.J. Natural and Sun-Induced Aging of Human Skin. *Cold Spring Harb. Perspect. Med.* **2015**, *5*, a015370. [CrossRef]
36. Barrientos, S.; Stojadinovic, O.; Golinko, M.S.; Brem, H.; Tomic-Canic, M. Growth Factors and Cytokines in Wound Healing. *Wound Repair Regen.* **2008**, *16*, 585–601. [CrossRef]
37. Humphrey, J.D.; Dufresne, E.R.; Schwartz, M.A. Mechanotransduction and Extracellular Matrix Homeostasis. *Nat. Rev. Mol. Cell Biol.* **2014**, *15*, 802–812. [CrossRef]
38. Hynes, R.O. The Extracellular Matrix: Not Just Pretty Fibrils. *Science* **2009**, *326*, 1216–1219. [CrossRef] [PubMed]
39. Daley, W.P.; Peters, S.B.; Larsen, M. Extracellular Matrix Dynamics in Development and Regenerative Medicine. *J. Cell Sci.* **2008**, *121*, 255–264. [CrossRef]
40. Ricard-Blum, S. The Collagen Family. *Cold Spring Harb. Perspect. Biol.* **2011**, *3*, a004978. [CrossRef]
41. Shoulders, M.D.; Raines, R.T. Collagen Structure and Stability. *Annu. Rev. Biochem.* **2009**, *78*, 929–958. [CrossRef]

42. Mithieux, S.M.; Weiss, A.S. Elastin. *Adv. Protein Chem.* **2005**, *70*, 437–461. [CrossRef]
43. Hynes, R.O. Integrins: Bidirectional, Allosteric Signaling Machines. *Cell* **2002**, *110*, 673–687. [CrossRef]
44. Humphries, J.D.; Byron, A.; Humphries, M.J. Integrin Ligands at a Glance. *J. Cell Sci.* **2006**, *119*, 3901–3903. [CrossRef]
45. Kleiser, S.; Nyström, A. Interplay between Cell-Surface Receptors and Extracellular Matrix in Skin. *Biomolecules* **2020**, *10*, 1170. [CrossRef] [PubMed]
46. Iozzo, R.V.; Schaefer, L. Proteoglycan Form and Function: A Comprehensive Nomenclature of Proteoglycans. *Matrix Biol.* **2015**, *42*, 11–55. [CrossRef]
47. Papakonstantinou, E.; Roth, M.; Karakiulakis, G. Hyaluronic Acid: A Key Molecule in Skin Aging. *Derm.-Endocrinol.* **2012**, *4*, 253–258. [CrossRef]
48. Cowman, M.K.; Lee, H.G.; Schwertfeger, K.L.; McCarthy, J.B.; Turley, E.A. The Content and Size of Hyaluronan in Biological Fluids and Tissues. *Front. Immunol.* **2015**, *6*, 261. [CrossRef]
49. Vogel, V.; Sheetz, M. Local Force and Geometry Sensing Regulate Cell Functions. *Nat. Rev. Mol. Cell Biol.* **2006**, *7*, 265–275. [CrossRef]
50. Sun, Z.; Guo, S.S.; Fässler, R. Integrin-Mediated Mechanotransduction. *J. Cell Biol.* **2016**, *215*, 445–456. [CrossRef] [PubMed]
51. Tiskratok, W.; Chuinsiri, N.; Limraksasin, P.; Kyawsoewin, M.; Jitprasertwong, P. Extracellular Matrix Stiffness: Mechanotransduction and Mechanobiological Response-Driven Strategies for Biomedical Applications Targeting Fibroblast Inflammation. *Polymers* **2025**, *17*, 822. [CrossRef] [PubMed]
52. Martino, F.; Perestrelo, A.R.; Vinarský, V.; Pagliari, S.; Forte, G. Cellular Mechanotransduction: From Tension to Function. *Front. Physiol.* **2018**, *9*, 824. [CrossRef]
53. Massagué, J. TGFβ Signalling in Context. *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 616–630. [CrossRef]
54. Xue, M.; Jackson, C.J. Extracellular Matrix Reorganization During Wound Healing and Its Impact on Abnormal Scarring. *Adv. Wound Care* **2015**, *4*, 119–136. [CrossRef]
55. Wells, R.G. The Role of Matrix Stiffness in Regulating Cell Behavior. *Hepatology* **2008**, *47*, 1394–1400. [CrossRef]
56. Jaalouk, D.E.; Lammerding, J. Mechanotransduction Gone Awry. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 63–73. [CrossRef]
57. Lu, P.; Takai, K.; Weaver, V.M.; Werb, Z. Extracellular Matrix Degradation and Remodeling in Development and Disease. *Cold Spring Harb. Perspect. Biol.* **2011**, *3*, a005058. [CrossRef]
58. Rozario, T.; DeSimone, D.W. The Extracellular Matrix in Development and Morphogenesis: A Dynamic View. *Dev. Biol.* **2010**, *341*, 126–140. [CrossRef]
59. Varani, J.; Dame, M.K.; Rittie, L.; Fligiel, S.E.G.; Kang, S.; Fisher, G.J.; Voorhees, J.J. Decreased Collagen Production in Chronologically Aged Skin: Roles of Age-Dependent Alteration in Fibroblast Function and Defective Mechanical Stimulation. *Am. J. Pathol.* **2006**, *168*, 1861–1868. [CrossRef] [PubMed]
60. Campisi, J. Aging, Cellular Senescence, and Cancer. *Annu. Rev. Physiol.* **2013**, *75*, 685–705. [CrossRef] [PubMed]
61. Zhu, L.; Liu, L.; Wang, A.; Liu, J.; Huang, X.; Zan, T. Positive Feedback Loops between Fibroblasts and the Mechanical Environment Contribute to Dermal Fibrosis. *Matrix Biol.* **2023**, *121*, 1–21. [CrossRef]
62. Krutmann, J.; Bouloc, A.; Sore, G.; Bernard, B.A.; Passeron, T. The Skin Aging Exposome. *J. Dermatol. Sci.* **2017**, *85*, 152–161. [CrossRef]
63. Vierkötter, A.; Krutmann, J. Environmental Influences on Skin Aging and Ethnic-Specific Manifestations. *Derm.-Endocrinol.* **2012**, *4*, 227–231. [CrossRef] [PubMed]
64. Gilchrest, B.A.; Krutmann, J. (Eds.) *Skin Aging*; Springer: Berlin/Heidelberg, Germany, 2006. [CrossRef]
65. Yaar, M.; Eller, M.S.; Gilchrest, B.A. Fifty Years of Skin Aging. *J. Investig. Dermatol. Symp. Proc.* **2002**, *7*, 51–58. [CrossRef]
66. Zouboulis, C.C.; Makrantonaki, E. Clinical Aspects and Molecular Diagnostics of Skin Aging. *Clin. Dermatol.* **2011**, *29*, 3–14. [CrossRef]
67. Elias, P.M. Stratum Corneum Defensive Functions: An Integrated View. *J. Investig. Dermatol.* **2005**, *125*, 183–200. [CrossRef]
68. Rinnerthaler, M.; Bischof, J.; Streubel, M.K.; Trost, A.; Richter, K. Oxidative Stress in Aging Human Skin. *Biomolecules* **2015**, *5*, 545–589. [CrossRef] [PubMed]
69. Makrantonaki, E.; Zouboulis, C.C. Characteristics and Pathomechanisms of Endogenously Aged Skin. *Dermatology* **2007**, *214*, 352–360. [CrossRef]
70. Shin, J.W.; Kwon, S.H.; Choi, J.Y.; Na, J.I.; Huh, C.H.; Choi, H.R.; Park, K.C. Molecular Mechanisms of Dermal Aging and Antiaging Approaches. *Int. J. Mol. Sci.* **2019**, *20*, 2126. [CrossRef]
71. Quan, T.; Qin, Z.; Xia, W.; Shao, Y.; Voorhees, J.J.; Fisher, G.J. Matrix-Degrading Metalloproteinases in Photoaging. *J. Investig. Dermatol. Symp. Proc.* **2009**, *14*, 20–24. [CrossRef] [PubMed]
72. Fisher, G.J.; Wang, Z.Q.; Datta, S.C.; Varani, J.; Kang, S.; Voorhees, J.J. Pathophysiology of Premature Skin Aging Induced by Ultraviolet Light. *N. Engl. J. Med.* **1997**, *337*, 1419–1428. [CrossRef]
73. Lee, D.H.; Oh, J.H.; Chung, J.H. Glycosaminoglycan and Proteoglycan in Skin Aging. *J. Dermatol. Sci.* **2016**, *83*, 174–181. [CrossRef]

74. Li, Y.; Liu, Y.; Xia, W.; Lei, D.; Voorhees, J.J.; Fisher, G.J. Age-Dependent Alterations of Decorin Glycosaminoglycans in Human Skin. *Sci. Rep.* **2013**, *3*, srep02422. [CrossRef]
75. Oh, J.H.; Kim, Y.K.; Jung, J.Y.; Shin, J.-E.; Chung, J.H. Changes in Glycosaminoglycans and Related Proteoglycans in Intrinsically Aged Human Skin in Vivo. *Exp. Dermatol.* **2011**, *20*, 454–456. [CrossRef]
76. Rohrich, R.J.; Pessa, J.E. The Fat Compartments of the Face: Anatomy and Clinical Implications for Cosmetic Surgery. *Plast. Reconstr. Surg.* **2007**, *119*, 2219–2227. [CrossRef]
77. Swift, A.; Liew, S.; Weinkle, S.; Garcia, J.K.; Silberberg, M.B. The Facial Aging Process from the "inside Out". *Aesthet. Surg. J.* **2021**, *41*, 1107–1119. [CrossRef]
78. Alghoul, M.; Codner, M.A. Retaining Ligaments of the Face: Review of Anatomy and Clinical Applications. *Aesthet. Surg. J.* **2013**, *33*, 769–782. [CrossRef]
79. Shaw, R.B.; Katzel, E.B.; Koltz, P.F.; Kahn, D.M.; Girotto, J.A.; Langstein, H.N. Aging of the Mandible and Its Aesthetic Implications. *Plast. Reconstr. Surg.* **2010**, *125*, 332–342. [CrossRef]
80. Parrado, C.; Mercado-Saenz, S.; Perez-Davo, A.; Gilaberte, Y.; Gonzalez, S.; Juarranz, A. Environmental Stressors on Skin Aging. Mechanistic Insights. *Front. Pharmacol.* **2019**, *10*, 759. [CrossRef]
81. Shao, Y.; Qin, Z.; Alexander Wilks, J.; Balimunkwe, R.M.; Fisher, G.J.; Voorhees, J.J.; Quan, T. Physical Properties of the Photodamaged Human Skin Dermis: Rougher Collagen Surface and Stiffer/Harder Mechanical Properties. *Exp. Dermatol.* **2019**, *28*, 914–921. [CrossRef]
82. Widgerow, A.D.; Napekoski, K. New Approaches to Skin Photodamage Histology—Differentiating "good" versus "Bad" Elastin. *J. Cosmet. Dermatol.* **2021**, *20*, 526–531. [CrossRef]
83. Martic, I.; Jansen-Dürr, P.; Cavinato, M. Effects of Air Pollution on Cellular Senescence and Skin Aging. *Cells* **2022**, *11*, 2220. [CrossRef]
84. Vierkötter, A.; Schikowski, T.; Ranft, U.; Sugiri, D.; Matsui, M.; Krämer, U.; Krutmann, J. Airborne Particle Exposure and Extrinsic Skin Aging. *J. Investig. Dermatol.* **2010**, *130*, 2719–2726. [CrossRef]
85. Zorina, A.; Zorin, V.; Kudlay, D.; Kopnin, P. Molecular Mechanisms of Changes in Homeostasis of the Dermal Extracellular Matrix: Both Involutional and Mediated by Ultraviolet Radiation. *Int. J. Mol. Sci.* **2022**, *23*, 6655. [CrossRef]
86. Boraldi, F.; Lofaro, F.D.; Bonacorsi, S.; Mazzilli, A.; Garcia-Fernandez, M.; Quaglino, D. The Role of Fibroblasts in Skin Homeostasis and Repair. *Biomedicines* **2024**, *12*, 1586. [CrossRef]
87. Mavrogonatou, E.; Papadopoulou, A.; Pratsinis, H.; Kletsas, D. Senescence-Associated Alterations in the Extracellular Matrix: Deciphering Their Role in the Regulation of Cellular Function. *Am. J. Physiol. Cell Physiol.* **2023**, *325*, C633–C647. [CrossRef]
88. Jipu, R.; Serban, I.L.; Goriuc, A.; Jipu, A.G.; Luchian, I.; Amititeloaie, C.; Tarniceriu, C.C.; Hurjui, I.; Butnaru, O.M.; Hurjui, L.L. Targeting Dermal Fibroblast Senescence: From Cellular Plasticity to Anti-Aging Therapies. *Biomedicines* **2025**, *13*, 1927. [CrossRef]
89. Zheng, Y.; Lei, J.; Zhang, A.; Cao, C.; Xu, A.; Zhou, M.; Lin, F. Regulatory Mechanisms of Transforming Growth Factor-β in Senescence of Fibroblast Associated with Refractory Skin Diseases. *Exp. Gerontol.* **2025**, *211*, 112900. [CrossRef]
90. Haddad, S.; Galadari, H.; Patil, A.; Goldust, M.; Al Salam, S.; Guida, S. Evaluation of the Biostimulatory Effects and the Level of Neocollagenesis of Dermal Fillers: A Review. *Int. J. Dermatol.* **2022**, *61*, 1284–1288. [CrossRef]
91. Amiri, M.; Meçani, R.; Llanaj, E.; Niehot, C.D.; Phillips, T.L.; Goldie, K.; Kolb, J.; Muka, T.; Daughtry, H. Calcium Hydroxylapatite (CaHA) and Aesthetic Outcomes: A Systematic Review of Controlled Clinical Trials. *J. Clin. Med.* **2024**, *13*, 1686. [CrossRef]
92. Fan, Y.; Choi, T.H.; Chung, J.H.; Jeon, Y.K.; Kim, S. Hyaluronic Acid-Cross-Linked Filler Stimulates Collagen Type 1 and Elastic Fiber Synthesis in Skin through the TGF-β/Smad Signaling Pathway in a Nude Mouse Model. *J. Plast. Reconstr. Aesthetic Surg.* **2019**, *72*, 1355–1362. [CrossRef] [PubMed]
93. Marx, R.E. Platelet-Rich Plasma: Evidence to Support Its Use. *J. Oral Maxillofac. Surg.* **2004**, *62*, 489–496. [CrossRef]
94. Dohan, D.M.; Choukroun, J.; Diss, A.; Dohan, S.L.; Dohan, A.J.J.; Mouhyi, J.; Gogly, B. Platelet-Rich Fibrin (PRF): A Second-Generation Platelet Concentrate. Part I: Technological Concepts and Evolution. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontol.* **2006**, *101*, e37–e44. [CrossRef]
95. Kobayashi, E.; Flückiger, L.; Fujioka-Kobayashi, M.; Sawada, K.; Sculean, A.; Schaller, B.; Miron, R.J. Comparative Release of Growth Factors from PRP, PRF, and Advanced-PRF. *Clin. Oral Investig.* **2016**, *20*, 2353–2360. [CrossRef]
96. Miron, R.J.; Fujioka-Kobayashi, M.; Hernandez, M.; Kandalam, U.; Zhang, Y.; Ghanaati, S.; Choukroun, J. Injectable Platelet Rich Fibrin (i-PRF): Opportunities in Regenerative Dentistry? *Clin. Oral Investig.* **2017**, *21*, 2619–2627. [CrossRef] [PubMed]
97. Alves, R.; Grimalt, R. A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. *Ski. Appendage Disord.* **2018**, *4*, 18–24. [CrossRef]
98. Asubiaro, J.; Avajah, F. Platelet-Rich Plasma in Aesthetic Dermatology: Current Evidence and Future Directions. *Cureus* **2024**, *16*, e66734. [CrossRef]
99. Dashore, S.; Chouhan, K.; Nanda, S.; Sharma, A. Platelet-Rich Fibrin, Preparation and Use in Dermatology. *Indian Dermatol. Online J.* **2021**, *12*, S55–S65. [CrossRef]

100. Wend, S.; Kubesch, A.; Orlowska, A.; Al-Maawi, S.; Zender, N.; Dias, A.; Miron, R.J.; Sader, R.; Booms, P.; Kirkpatrick, C.J.; et al. Reduction of the Relative Centrifugal Force Influences Cell Number and Growth Factor Release within Injectable PRF-Based Matrices. *J. Mater. Sci. Mater. Med.* **2017**, *28*, 188. [CrossRef]
101. Mohale, S.A.; Thakare, P.V.; Gaurkar, S.S.; Bharadia, D.G.; Acharya, S. Effectiveness of Injectable Platelet-Rich Fibrin Therapy in Alopecia and Facial Rejuvenation: A Systematic Review. *Cureus* **2024**, *16*, e62198. [CrossRef] [PubMed]
102. Hassan, H.; Quinlan, D.J.; Ghanem, A. Injectable Platelet-Rich Fibrin for Facial Rejuvenation: A Prospective, Single-Center Study. *J. Cosmet. Dermatol.* **2020**, *19*, 3213–3221. [CrossRef]
103. Gupta, S.; Bisht, P.B.; Kannan, C. Bio-Filler: An Effective Facial Rejuvenation Tool-Easy on Pocket. *J. Cutan. Aesthet. Surg.* **2020**, *13*, 243–246. [CrossRef]
104. Majewska, L. Autologous Plasma Gel as an Effective Method of Facial Volume Restoration and Skin Rejuvenation. *Dermatol. Ther.* **2023**, *2023*, 9989544. [CrossRef]
105. Nanda, S.; Chauhan, K.; Shetty, V.; Dashore, S.; Bhatia, S. Platelet-Rich Plasma in Aesthetics. *Indian Dermatol. Online J.* **2021**, *12*, S41–S54. [CrossRef]
106. Guida, S.; Galadari, H. A Systematic Review of Radiesse/Calcium Hydroxylapatite and Carboxymethylcellulose: Evidence and Recommendations for Treatment of the Face. *Int. J. Dermatol.* **2024**, *63*, 150–160. [CrossRef]
107. Van Loghem, J. Calcium Hydroxylapatite in Regenerative Aesthetics: Mechanistic Insights and Mode of Action. *Aesthet. Surg. J.* **2025**, *45*, 393–403. [CrossRef]
108. Galadari, H.; Guida, S. A Systematic Review of Radiesse® (Calcium Hydroxylapatite): Evidence and Recommendations for the Body. *Int. J. Dermatol.* **2024**, *63*, 881–889. [CrossRef]
109. Lorenc, Z.P.; Bass, L.M.; Fitzgerald, R.; Goldberg, D.J.; Graivier, M.H. Physiochemical Characteristics of Calcium Hydroxylapatite (CaHA). *Aesthet. Surg. J.* **2018**, *38*, S8–S12. [CrossRef]
110. Goldie, K.; Peeters, W.; Alghoul, M.; Butterwick, K.; Casabona, G.; Chao, Y.Y.Y.; Costa, J.; Eviatar, J.; Fabi, S.G.; Lupo, M.; et al. Global Consensus Guidelines for the Injection of Diluted and Hyperdiluted Calcium Hydroxylapatite for Skin Tightening. *Dermatol. Surg.* **2018**, *44*, S32–S41. [CrossRef]
111. Ferreira, A.C.M.; Silva, L.R.; Espasandin, I.; Sant'Anna, J.F.; Mourão, C.A.; Tedesco, A.D.; Vieira, M.G.; Colaço, A.R.A.; Varela, R.M.; de Paula Barbosa, A. Efficacy, Durability, and Safety of Collagen Biostimulators Based on Poly-L-Lactic Acid (PLLA) and Calcium Hydroxyapatite (CaHA) in the Face: A Systematic Review. *Aesthetic Plast. Surg.* **2025**, *50*, 1291–1300. [CrossRef]
112. Haddad, A.; Kadunc, B.V.; Guarnieri, C.; Noviello, J.S.; da Cunha, M.G.; Parada, M.B. Conceitos Atuais No Uso Do Ácido Poli-l-Láctico Para Rejuvenescimento Facial: Revisão e Aspectos Práticos. *Surg. Cosmet. Dermatol.* **2017**, *9*, 60–71.
113. Lam, S.M.; Azizzadeh, B.; Graivier, M. Injectable Poly-L-Lactic Acid (Sculptra): Technical Considerations in Soft-Tissue Contouring. *Plast. Reconstr. Surg.* **2006**, *118*, 55S–63S. [CrossRef]
114. Vleggaar, D.; Fitzgerald, R.; Paul Lorenc, Z.; Andrews, J.T.; Butterwick, K.; Comstock, J.; Hanke, C.W.; Gerald O'daniel, T.; Palm, M.D.; Roberts, W.E.; et al. Consensus Recommendations on the Use of Injectable Poly-L-Lactic Acid for Facial and Nonfacial Volumization. *J. Drugs Dermatol.* **2014**, *13*, s44–s51.
115. Xu, Q.; Sun, X.; Yang, W.; Bai, Y.; Tan, X. Comprehensive Systematic Review of Poly-L-Lactic Acid in Facial Clinical Application. *Aesthetic Plast. Surg.* **2024**, *48*, 5115–5135.
116. De Melo, F.; Nicolau, P.; Piovano, L.; Lin, S.L.; Baptista-Fernandes, T.; King, M.I.; Camporese, A.; Hong, K.; Khattar, M.M.; Christen, M.O. Recommendations for Volume Augmentation and Rejuvenation of the Face and Hands with the New Generation Polycaprolactone-Based Collagen Stimulator (Ellansé®). *Clin. Cosmet. Investig. Dermatol.* **2017**, *10*, 431–440. [CrossRef]
117. Moers-Carpi, M.M.; Sherwood, S. Polycaprolactone for the Correction of Nasolabial Folds: A 24-Month, Prospective, Randomized, Controlled Clinical Trial. *Dermatol. Surg.* **2013**, *39*, 457–463. [CrossRef]
118. Vleggaar, D. Soft-Tissue Augmentation and the Role of Poly-L-Lactic Acid. *Plast. Reconstr. Surg.* **2006**, *118*, 46S–54S. [CrossRef]
119. Lin, S.L.; Christen, M.O. Polycaprolactone-Based Dermal Filler Complications: A Retrospective Study of 1111 Treatments. *J. Cosmet. Dermatol.* **2020**, *19*, 1907–1914. [CrossRef]
120. Amiri, M.; Meçani, R.; Niehot, C.D.; Phillips, T.L.; Goldie, K.; Kolb, J.; Muka, T.; Daughtry, H. A Systematic Review and Meta-Analysis of Single-Group Studies Assessing the Role of Calcium Hydroxylapatite in Aesthetic Enhancements and Satisfaction. *Plast. Reconstr. Surg. Glob. Open* **2024**, *12*, e6400. [CrossRef]
121. Signori, R.; Barbosa, A.d.P.; Cezar-dos-Santos, F.; Carbone, A.C.; Ventura, S.; Nobre, B.B.d.S.; Neves, M.L.B.B.; Câmara-Souza, M.B.; Poluha, R.L.; De la Torre Canales, G. Efficacy and Safety of Poly-l-Lactic Acid in Facial Aesthetics: A Systematic Review. *Polymers* **2024**, *16*, 2564. [CrossRef]
122. Ao, Y.J.; Yi, Y.; Wu, G.H. Application of PLLA (Poly-L-Lactic Acid) for Rejuvenation and Reproduction of Facial Cutaneous Tissue in Aesthetics: A Review. *Medicine* **2024**, *103*, E37506. [CrossRef]
123. Angelo-Khattar, M. Poly-L-Lactic Acid in Facial Rejuvenation: Volumetric Data Supporting Regenerative Outcomes. *Clin. Cosmet. Investig. Dermatol.* **2025**, *18*, 3653–3666. [CrossRef]

124. Ianhez, M.; de Goés e Silva Freire, G.; Sigrist, R.M.S.; Colpas, P.T.; de Faria, I.A.; Parada, M.O.A.B.; Miot, H.A. Complications of Collagen Biostimulators in Brazil: Description of Products, Treatments, and Evolution of 55 Cases. *J. Cosmet. Dermatol.* **2024**, *23*, 2829–2835. [CrossRef]
125. Bravo, B.S.F.; Calvacante, T.; Nobre, C.S.; Bravo, L.G.; Zafra, M.C.; Elias, M.C. Exploring the Safety and Satisfaction of Patients Injected With Collagen Biostimulators—A Prospective Investigation Into Injectable Poly-l-Lactic Acid (PLLA). *J. Cosmet. Dermatol.* **2025**, *24*, e16723. [CrossRef]
126. Bravo, B.S.F.; Bravo, L.G.; Gouvea, B.F.; Neves, M.R.B.; Nobre, C.S.; Silva, C.d.S.; do Nascimento, C.M.O.L. Calcium Hydroxylapatite-Based Fillers in Facial Rejuvenation: A Prospective, Single-Center, Unblinded Comparative Outcome Study of Radiesse® vs. Rennova® Diamond Intense. *J. Clin. Med.* **2025**, *14*, 4072. [CrossRef]
127. Urdiales-Gálvez, F.; Benítez, P.A.; Díaz, I. Clinical Outcomes of an Innovative Poly-L-Lactic Acid (LASYNPRO) in Facial Rejuvenation: Prospective, Multicenter Spanish Study. *J. Cosmet. Dermatol.* **2026**, *25*, e70753. [CrossRef]
128. Tienda-Vázquez, M.A.; Hanel, J.M.; Márquez-Arteaga, E.M.; Salgado-Álvarez, A.P.; Scheckhuber, C.Q.; Alanis-Gómez, J.R.; Espinoza-Silva, J.I.; Ramos-Kuri, M.; Hernández-Rosas, F.; Melchor-Martínez, E.M.; et al. Exosomes: A Promising Strategy for Repair, Regeneration and Treatment of Skin Disorders. *Cells* **2023**, *12*, 1625. [CrossRef]
129. Kalluri, R.; LeBleu, V.S. The Biology, Function, and Biomedical Applications of Exosomes. *Science* **2020**, *367*, eaau6977. [CrossRef]
130. Raposo, G.; Stoorvogel, W. Extracellular Vesicles: Exosomes, Microvesicles, and Friends. *J. Cell Biol.* **2013**, *200*, 373–383. [CrossRef]
131. Théry, C.; Witwer, K.W.; Aikawa, E.; Alcaraz, M.J.; Anderson, J.D.; Andriantsitohaina, R.; Antoniou, A.; Arab, T.; Archer, F.; Atkin-Smith, G.K.; et al. Minimal Information for Studies of Extracellular Vesicles 2018 (MISEV2018): A Position Statement of the International Society for Extracellular Vesicles and Update of the MISEV2014 Guidelines. *J. Extracell. Vesicles* **2018**, *7*, 1535750. [CrossRef]
132. Xiong, M.; Zhang, Q.; Hu, W.; Zhao, C.; Lv, W.; Yi, Y.; Wang, Y.; Tang, H.; Wu, M.; Wu, Y. The Novel Mechanisms and Applications of Exosomes in Dermatology and Cutaneous Medical Aesthetics. *Pharmacol. Res.* **2021**, *166*, 105490. [CrossRef]
133. Hu, L.; Wang, J.; Zhou, X.; Xiong, Z.; Zhao, J.; Yu, R.; Huang, F.; Zhang, H.; Chen, L. Exosomes Derived from Human Adipose Mensenchymal Stem Cells Accelerates Cutaneous Wound Healing via Optimizing the Characteristics of Fibroblasts. *Sci. Rep.* **2016**, *6*, 32993, Correction in *Sci. Rep.* **2020**, *10*, 6693. [CrossRef]
134. Jo, C.B.; Choi, Y.J.; Lee, T.J. Therapeutic Potential of Stem Cell-Derived Exosomes in Skin Wound Healing. *Biomimetics* **2025**, *10*, 546. [CrossRef]
135. Wang, W.M.; Wu, C.; Jin, H.Z. Exosomes in Chronic Inflammatory Skin Diseases and Skin Tumors. *Exp. Dermatol.* **2019**, *28*, 213–218. [CrossRef]
136. Cavallini, M.; Bartoletti, E.; Maioli, L.; Massirone, A.; Pia Palmieri, I.; Papagni, M.; Priori, M.; Trocchi, G. Consensus Report on the Use of PN-HPT™ (Polynucleotides Highly Purified Technology) in Aesthetic Medicine. *J. Cosmet. Dermatol.* **2021**, *20*, 922–928. [CrossRef]
137. Lampridou, S.; Bassett, S.; Cavallini, M.; Christopoulos, G. The Effectiveness of Polynucleotides in Esthetic Medicine: A Systematic Review. *J. Cosmet. Dermatol.* **2025**, *24*, e16721. [CrossRef]
138. Colangelo, M.T.; Galli, C.; Guizzardi, S. The Effects of Polydeoxyribonucleotide on Wound Healing and Tissue Regeneration: A Systematic Review of the Literature. *Regen. Med.* **2020**, *15*, 1801–1821. [CrossRef]
139. Park, K.Y.; Seok, J.; Rho, N.K.; Kim, B.J.; Kim, M.N. Long-chain Polynucleotide Filler for Skin Rejuvenation: Efficacy and Complications in Five Patients. *Dermatol. Ther.* **2016**, *29*, 37–40. [CrossRef]
140. Lee, D.K.; Oh, M.; Kim, M.J.; Oh, S.M. Clinical Effects of Polynucleotide with Hyaluronic Acid Intradermal Injections on Facial Erythema: Effective Redness Treatment Using Polynucleotides. *Ski. Res. Technol.* **2024**, *30*, e70034. [CrossRef]
141. Galeano, M.; Pallio, G.; Irrera, N.; Mannino, F.; Bitto, A.; Altavilla, D.; Vaccaro, M.; Squadrito, G.; Arcoraci, V.; Colonna, M.R.; et al. Polydeoxyribonucleotide: A Promising Biological Platform to Accelerate Impaired Skin Wound Healing. *Pharmaceuticals* **2021**, *14*, 1103. [CrossRef]
142. Cavagnino, A.; Azadiguian, G.; Breton, L.; Baraibar, M.; Black, A.F. Modulating Skin Aging Molecular Targets and Longevity Drivers Through a Novel Natural Product: Rose-Derived Polydeoxyribonucleotide (Rose PDRN). *Curr. Issues Mol. Biol.* **2025**, *47*, 971. [CrossRef]
143. Lim, H.W.; Huang, Y.H.; Baek, H.S.; Kim, H.G.; Kim, K.E.; Lim, C.J. PDRN-like Marker DNA Shows Skin Beneficial Properties through Its Single-Stranded Form. *Biosci. Biotechnol. Biochem.* **2025**, *89*, 1168–1172. [CrossRef]
144. Shin, S.M.; Baek, E.J.; Kim, K.H.; Kim, K.J.; Park, E.J. Polydeoxyribonucleotide Exerts Opposing Effects on ERK Activity in Human Skin Keratinocytes and Fibroblasts. *Mol. Med. Rep.* **2023**, *28*, 13035. [CrossRef]
145. Marques, C.; Porcello, A.; Cerrano, M.; Hadjab, F.; Chemali, M.; Lourenço, K.; Hadjab, B.; Raffoul, W.; Applegate, L.A.; Laurent, A.E. From Polydeoxyribonucleotides (PDRNs) to Polynucleotides (PNs): Bridging the Gap Between Scientific Definitions, Molecular Insights, and Clinical Applications of Multifunctional Biomolecules. *Biomolecules* **2025**, *15*, 148. [CrossRef]
146. Uskoković, V.; Uskoković, D.P. Nanosized Hydroxyapatite and Other Calcium Phosphates: Chemistry of Formation and Application as Drug and Gene Delivery Agents. *J. Biomed. Mater. Res. B Appl. Biomater.* **2011**, *96B*, 152–191. [CrossRef]

147. Dorozhkin, S.V. Nanosized and Nanocrystalline Calcium Orthophosphates. *Acta Biomater.* **2010**, *6*, 715–734. [CrossRef]
148. Bose, S.; Roy, M.; Bandyopadhyay, A. Recent Advances in Bone Tissue Engineering Scaffolds. *Trends Biotechnol.* **2012**, *30*, 546–554. [CrossRef]
149. Dorozhkin, S.V. Calcium Orthophosphates in Nature, Biology and Medicine. *Materials* **2009**, *2*, 399–498. [CrossRef]
150. Wang, Y.; Shi, D. In Vitro and in Vivo Evaluations of Nanofibrous Nanocomposite Based on Carboxymethyl Cellulose/Polycaprolactone/Cobalt-Doped Hydroxyapatite as the Wound Dressing Materials. *Arab. J. Chem.* **2022**, *15*, 104270. [CrossRef]
151. Cruel, P.T.E.; dos Santos, C.P.C.; Cueto, T.M.; Avila, L.P.V.; Buchaim, D.V.; Buchaim, R.L. Calcium Hydroxyapatite in Its Different Forms in Skin Tissue Repair: A Literature Review. *Surgeries* **2024**, *5*, 640–659. [CrossRef]
152. Kawai, K.; Larson, B.J.; Ishise, H.; Carre, A.L.; Nishimoto, S.; Longaker, M.; Lorenz, H.P. Calcium-Based Nanoparticles Accelerate Skin Wound Healing. *PLoS ONE* **2011**, *6*, 0027106. [CrossRef]
153. Oyane, A.; Kim, H.M.; Furuya, T.; Kokubo, T.; Miyazaki, T.; Nakamura, T. Preparation and Assessment of Revised Simulated Body Fluids. *J. Biomed. Mater. Res. A* **2003**, *65A*, 188–195. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.