

**IMPACT OF
IMMUNOSENESCENCE ON
THE EFFICACY OF
COLLAGEN
BIOSTIMULATORS:
IMPLICATIONS FOR THE
INFLAMMATORY RESPONSE
AND NEOCOLLAGENESIS**

**IMPACTO DA IMUNOSSENESCÊNCIA NA EFICÁCIA DOS
BIOESTIMULADORES DE COLÁGENO: IMPLICAÇÕES NA RESPOSTA
INFLAMATÓRIA E NA NEOCOLAGÊNESE**

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Laura de Carvalho Silva

Leandra Alves Teixeira

Samyra Giarola Cecílio

Daniele Sapede Alvarenga Medaglia

Martinelle Ferreira da Rocha Taranto

ABSTRACT

Skin aging is associated with a decline in the efficiency of the skin's immune system, a process known as immunosenescence. In this context, collagen biostimulators are therapeutic agents that promote collagen synthesis by inducing localized inflammatory and immune responses, triggering cellular processes that lead to neocollagenesis. Therefore, this study aims to analyze the efficacy of collagen biostimulators in patients experiencing immunosenescence through an integrative literature review. The studies analyzed indicated that the immune response plays a fundamental role in the mechanisms of action of these agents, involving the recruitment and activation of inflammatory cells, the release of mediators and growth factors, and the subsequent activation of fibroblasts and collagen deposition. In parallel, studies on immunosenescence have demonstrated quantitative and functional alterations in immune cells, as well as the persistence of a state of chronic low-grade inflammation. These changes can modify the cutaneous microenvironment and cellular responses to reparative stimuli. However, limited clinical evidence directly establishes whether immunosenescence-related changes reduce the efficacy of collagen biostimulators, highlighting the need for further research on this topic. This review is expected to clarify the relationship between aging and the immune system, contribute to the development of more individualized therapeutic protocols, and encourage further research in this relatively underexplored area of the scientific literature.

Keywords: Immune system; Skin stimulation; Collagen synthesis; Skin aging.

RESUMO

O envelhecimento cutâneo está relacionado ao processo de

diminuição da eficiência do sistema imunológico da pele, conhecido por imunossenescência. Nesse contexto, os bioestimuladores de colágeno destacam-se como estratégias terapêuticas que atuam através da ativação dos agentes imunológicos, desencadeando respostas celulares que culminaram na neocolagênese. Dessa forma, o objetivo desse estudo é analisar a eficácia do bioestimulador de colágeno em pacientes cujo sistema imunológico esteja passando pelo processo de imunossenescência, através de uma revisão integrativa. Os estudos analisados evidenciaram que a resposta imunológica desempenha papel fundamental no mecanismo de ação dos bioestimuladores, envolvendo o recrutamento e a ativação de células inflamatórias, a liberação de mediadores e fatores de crescimento e, posteriormente, a ativação de fibroblastos e a deposição de colágeno. Paralelamente, os estudos sobre imunossenescência demonstraram alterações quantitativas e funcionais de células do sistema imune, além da manutenção de um estado inflamatório crônico de baixo grau, características que podem modificar o microambiente cutâneo e a resposta celular ao estímulo reparador. Entretanto, foram identificadas poucas evidências clínicas que estabeleçam diretamente uma redução da eficácia dos bioestimuladores de colágeno em indivíduos com alterações relacionadas à imunossenescência, ressaltando a necessidade de novos estudos acerca do tema proposto. Assim, espera-se elucidar a correlação entre envelhecimento e sistema imunológico, e contribuir para a melhor elaboração de protocolos terapêuticos individualizados, além de incentivar o desenvolvimento de novos estudos nessa área ainda pouco explorada na literatura.

Palavras-chave: Sistema imunológico; Estimulação cutânea; Síntese de colágeno; Envelhecimento cutâneo.

1. INTRODUCTION

Human longevity is currently understood as a multifactorial phenomenon influenced by social, biological, and behavioral factors and directly associated with quality of life. This concept extends beyond a mere increase in life expectancy, encompassing the ability to live with autonomy, health, and well-being. Aging is a natural, dynamic, and progressive process involving a series of biological events that lead to significant changes in biochemical, physiological, psychological, and immunological mechanisms. These changes vary among individuals, resulting in different biological responses (Souza *et al.*, 2017; Rodrigues; Dala-Paula, 2023).

Skin aging is a natural and progressive process associated with reduced collagen synthesis by dermal fibroblasts. Studies indicate that collagen production declines with age, with estimates suggesting an approximately 1.0% to 1.5% annual decrease in skin collagen content (Reilly; Lozano, 2021). Over time, collagen fibers undergo structural disorganization, becoming thinner and more fragmented, thereby compromising skin firmness and elasticity. These changes manifest clinically as wrinkles and skin laxity and are associated with alterations in type I and type III collagen, the predominant collagen types in the dermis, accounting for approximately 85%–90% and 8%–11% of total dermal collagen, respectively (Proksch *et al.*, 2014; Prestes *et al.*, 2013).

Fibroblasts play a central role in wound healing, and one of their primary functions is to maintain connective tissue integrity, particularly through the synthesis of extracellular matrix components, including collagen, elastin, glycoproteins, and proteoglycans (Junqueira & Carneiro, 2004). During tissue repair, these cells are stimulated to synthesize and deposit extracellular matrix components. In the skin, this activity is essential for tissue

repair and remodeling and supports the restoration of the injured area, including reepithelialization (Amadeu *et al.*, 2003).

Fibroblasts are mesenchymal cells characterized by considerable functional diversity and play fundamental roles in tissue homeostasis and the development of various pathological conditions. These cells actively participate in the production and organization of the extracellular matrix and contribute to the formation of signaling niches through biochemical and biophysical cues (Plikus *et al.*, 2021).

Furthermore, fibroblasts respond to the mechanical forces to which tissues are subjected under both physiological and pathological conditions (Hildebrand *et al.*, 2005). These mechanical interactions influence collagen fiber organization and are associated with the formation and development of granulation tissue. In addition to producing collagen, fibroblasts synthesize other important extracellular matrix components, such as elastin, fibronectin, and glycosaminoglycans. They also produce proteases that participate in physiological tissue debridement and remodeling processes (Lund *et al.*, 2012).

At the molecular level, aging is also associated with changes in gene expression and progressive telomere shortening, both of which are related to cellular senescence and age-associated tissue dysfunction (Borson; Romano, 2020). Telomere shortening is associated with a progressive reduction in cellular replicative capacity. When telomeres reach a critically short length, cells can undergo replicative senescence, thereby limiting further cell division (Teixeira; Guariento, 2010). Oxidative stress can induce molecular damage, including lipid peroxidation and oxidative damage to DNA and

proteins, and can also contribute to telomere attrition (Borson; Romano, 2020).

Age-associated cellular changes can include alterations in nuclear and Golgi apparatus morphology, as well as mitochondrial dysfunction. Over the course of aging, the accumulation of cellular damage and mitochondrial dysfunction can impair cellular respiration and reduce ATP production, affecting energy-dependent cellular processes (Silva *et al.*, 2011). These factors can contribute to the establishment of cellular senescence, a state characterized by a stable, generally irreversible arrest of cell proliferation (Colavitti & Finkel, 2005).

Cellular senescence is characterized by the cessation of cell division, which can impair tissue renewal and contribute to the development of characteristic features of skin aging (Silva *et al.*, 2011). As aging progresses, the physiological functions of several systems, including the immune system, undergo age-associated changes that can compromise immune regulation and increase susceptibility to chronic diseases, including cancer, diabetes, cardiovascular diseases, neurodegenerative disorders, and autoimmune diseases (Lv *et al.*, 2024).

Immunosenescence affects both innate and adaptive immunity, impairing the ability to mount rapid and effective responses to pathogens (Chen *et al.*, 2022). Furthermore, it contributes to the development of a state of chronic low-grade inflammation known as *inflammaging*, which can promote the degradation of dermal collagen fibers (Leal *et al.*, 2022). These age-related changes can contribute to wrinkle formation, loss of skin firmness and elasticity,

and increased susceptibility to skin disorders, including dermatitis and skin tumors (Matias, 2025).

With the substantial growth of the older adult population in recent decades, aesthetic procedures have become increasingly popular as strategies to improve appearance and mitigate the visible signs of aging, potentially supporting self-esteem and psychological well-being. In this context, the demand for approaches that provide natural-looking rejuvenation and long-lasting results has driven the use of technologies aimed at improving skin laxity and overall skin quality (Matias, 2025).

Among these approaches, collagen biostimulators have gained prominence in dermatology and aesthetic medicine because of their ability to stimulate the production of structural components that decline or become altered with skin aging. These agents promote the synthesis of collagen, elastin, and other extracellular matrix components, which are essential for maintaining skin firmness, elasticity, and structural integrity (Matias, 2025).

Therefore, expanding scientific knowledge of the influence of immunosenescence on the mechanisms of action of collagen biostimulators can help improve evidence-based treatments by accounting for age-related changes and their potential implications for therapeutic responses. Despite advances in aesthetic medicine, important knowledge gaps remain regarding the relationship between immunological aging and the tissue responses induced by these agents.

In this context, understanding the factors associated with age-related changes in immune function is essential for developing safer

and more effective approaches, as well as individualized therapeutic protocols that account for each patient's specific characteristics.

2. METHODOLOGY

Study Design

An integrative literature review was conducted to synthesize existing knowledge and support the application of findings from relevant studies to practice (Souza *et al.*, 2010).

Search Strategy

An integrative literature review was conducted using the following electronic databases and search platforms: the Virtual Health Library (VHL), PubMed, Google Scholar, SciELO, and EBSCO. Publications from 2015 to 2026 were considered. The Boolean operators “AND” and “OR” were used to combine search terms related to immunosenescence and collagen biostimulators, thereby broadening the search results across the selected databases and platforms.

Study Selection and Analysis

Following the initial screening of titles and abstracts, the articles were carefully assessed to exclude publications that were not relevant to the research topic. The selected articles were then critically appraised to develop a descriptive synthesis. The full texts of the selected articles were analyzed to extract information on the relationship between immune system aging and the mechanisms of action of collagen biostimulators.

Original research articles and review articles published within the previous ten years, in English, Portuguese, or Spanish, were eligible for inclusion if they were available in full text and addressed the relationship between immunosenescence, skin aging, and collagen biostimulators. Studies investigating cellular and molecular mechanisms, including fibroblast activity, inflammatory processes, and collagen production, were also considered. Duplicate and incomplete studies, as well as publications that were not directly relevant to the research topic, were excluded.

3. RESULTS AND DISCUSSION

Collagen is the main structural protein in the skin's extracellular matrix and plays a fundamental role in maintaining skin firmness and elasticity. Its production is closely associated with the activity of dermal fibroblasts, which are influenced by various chemical and cellular stimuli (Kisiel *et al.*, 2019; Soroushanova *et al.*, 2019).

Given the lack of studies directly establishing a relationship between immunosenescence and the response to collagen biostimulators, a comparative analysis of the main mechanisms involved in these processes was conducted based on evidence reported independently in the literature. Table 1 presents key aspects of immunosenescence and the mechanisms of action of collagen biostimulators, highlighting potentially convergent cellular and tissue-level mechanisms, particularly those involving inflammatory responses, fibroblast activity, and extracellular matrix remodeling. This comparison does not establish a causal relationship between these phenomena but helps identify potential mechanistic intersections that can contribute to understanding responses to collagen biostimulators in the context of skin aging.

Table 1. Comparison of mechanisms associated with immunosenescence and the effects of collagen biostimulators on skin aging.

Aspect	Immunosenescence	Collagen biostimulators
Inflammation	Reduced levels of mediators associated with tissue remodeling, including IL-4, IL-13, and TGF- β , potentially resulting in decreased M2 macrophage polarization, fibroblast activation, and collagen synthesis (Oh <i>et al.</i> , 2023).	Neocollagenesis is stimulated by a localized inflammatory response triggered by the recognition of biostimulator particles as foreign material by the host tissue (Matos <i>et al.</i> , 2023).
Aspect	Immunosenescence	Collagen biostimulators
Extracellular matrix remodeling	Increased expression of matrix metalloproteinases (MMPs), potentially promoting collagen and elastin degradation, together with reduced collagen synthesis (Lee <i>et al.</i> , 2021; Pilkington <i>et al.</i> , 2021).	TGF- β 1 promotes fibroblast activity and extracellular matrix synthesis, supporting collagen deposition around poly-L-lactic acid (PLLA) particles (Stein <i>et al.</i> , 2015; Lotaif, 2021).
Inflammatory response	A shift toward a pro-inflammatory macrophage phenotype (M1) and alterations in the M2 phenotype can contribute to chronic inflammation and impaired tissue repair (da Cunha <i>et al.</i> , 2022).	Biostimulators induce changes in extracellular matrix composition and organization, potentially promoting collagen production and improving skin support and firmness (Oliveira <i>et al.</i> , 2025).
Immune response	Reduced density and altered function of Langerhans cells, together with changes in T lymphocytes, can contribute to impaired cutaneous	The response to biostimulation is influenced by interactions between the biomaterial and the host

	immune surveillance and altered adaptive immune responses (Vukmanovic-Stejic <i>et al.</i> , 2017; Mancheno, Ramón, & Odeh, 2026).	immune system, which can affect the quantity and quality of newly synthesized collagen (Nicolau, 2007).
Fibroblast activity	Senescent fibroblasts exhibit reduced collagen and elastin production and increased MMP expression, potentially compromising extracellular matrix integrity (Chambers <i>et al.</i> , 2021; Plikus <i>et al.</i> , 2017).	Inflammatory mediators, including TGF- β 1, stimulate fibroblast activity and promote the synthesis and deposition of extracellular matrix components (Stein <i>et al.</i> , 2015).

Source: Prepared by the authors.

Skin aging is characterized by alterations in the dermal–epidermal junction, dermal atrophy, a reduction in fibroblast number and activity, changes in collagen hydration and organization, and elastin degeneration. Collagen is the most abundant structural protein in the skin and provides essential support to connective tissue. Collagen loss is one of the major contributors to visible signs of skin aging, including roughness, deep skin folds, and wrinkles. Other changes, such as subcutaneous fat loss in the hypodermis and bone resorption, can also affect facial appearance (Moreto, 2022).

Collagen loss can begin in early adulthood, with reported rates varying according to age, anatomical site, and the methods used to assess collagen content. Some sources report that collagen loss becomes more pronounced after the age of 40, potentially reaching approximately 1% per year. A reported reduction of 75% in collagen production by the age of 80, compared with that in young adults, requires careful interpretation and verification against the original source, as collagen content and collagen synthesis are distinct

measures (Ferreira *et al.*, 2020). Age-related collagen loss contributes to visible skin changes and can negatively affect body image and self-perception (Lotaif, 2021).

Collagen biostimulation is an aesthetic treatment in which biocompatible and biodegradable materials are injected into the skin to stimulate collagen synthesis. Depending on the product and injection technique, these materials can be delivered into the dermis or deeper tissue planes. By stimulating fibroblast activity and extracellular matrix remodeling, collagen biostimulators can improve skin texture, quality, and firmness and, in selected applications, provide a lifting effect (Lima, 2020; Palma, 2023). Commonly used agents include poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL) (Lima, 2020).

Poly-L-lactic acid (PLLA) is a biodegradable polymer that induces a localized tissue response and stimulates collagen synthesis over several weeks to months. This gradual process is associated with increased type I collagen deposition and can produce long-lasting aesthetic results (Santos *et al.*, 2025).

Calcium hydroxyapatite (CaHA) consists of microspheres suspended in a carrier gel. The gel and the physical properties of the microspheres contribute to the initial volumizing effect after injection. CaHA also induces a localized tissue response and can stimulate neocollagenesis, including the production of type I and type III collagen. Changes in extracellular matrix remodeling can contribute to improvements in skin quality, elasticity, and firmness. Angiogenesis, defined as the formation of new blood vessels from preexisting vessels, has also been discussed in relation to tissue remodeling; however, its extent and clinical relevance should be

supported by evidence specific to CaHA (Oliveira *et al.*, 2025; Naka *et al.*, 2024).

Polycaprolactone (PCL) is a biodegradable polymer-based biostimulator containing microspheres that can persist in tissue for an extended period. Depending on the formulation, its effects can last approximately 18–24 months, during which it can stimulate fibroblast activity and type I collagen production (Rodrigues, 2023; Ianhez *et al.*, 2024). Its persistence in tissue requires careful patient selection and precise injection technique. Although PCL-based products can provide long-lasting results, outcomes depend on the formulation, treatment technique, and individual patient characteristics (Lins *et al.*, 2025).

Collagen biostimulators induce neocollagenesis through a localized tissue response to the injected material. The recognition of the biomaterial by the host tissue initiates a sequence of inflammatory and reparative processes that contribute to extracellular matrix remodeling (Matos *et al.*, 2023). Early responses involve the recruitment and activation of immune cells, particularly macrophages, alongside the participation of fibroblasts. Depending on the material's properties and particle characteristics, macrophages can be unable to completely engulf individual particles. In such circumstances, macrophage fusion can lead to the formation of multinucleated foreign body giant cells (Schierle & Casas, 2011).

Fibroblasts produce and deposit extracellular matrix components. Their activation can be influenced by mediators released during the tissue response, including transforming growth factor beta 1 (TGF- β 1), which is associated with fibroblast activity and extracellular

matrix synthesis (Stein *et al.*, 2015). In response to PLLA, fibroblasts and myofibroblasts can accumulate around the particles, contributing to fibrous encapsulation and collagen deposition (Lotaif, 2021). This capsule consists of connective tissue formed as part of the host response to the implanted material; it is not a structure produced directly by macrophages alone (Stein *et al.*, 2015).

During this process, type III collagen has been described in proximity to PLLA particles, whereas type I collagen has been observed predominantly in the peripheral regions of the fibrous capsules (Fitzgerald *et al.*, 2018). As PLLA particles gradually degrade, the surrounding tissue undergoes extracellular matrix remodeling and continued collagen deposition (Stein *et al.*, 2015).

Thus, the effects of collagen biostimulators extend beyond increasing collagen abundance and involve changes in extracellular matrix composition and organization that can improve skin support, firmness, and structural quality (Oliveira *et al.*, 2025). The response to biostimulation depends on individual biological characteristics and on interactions between the biomaterial and the host immune system, which can influence the amount and properties of newly synthesized collagen. Factors such as age, sex, lifestyle, general health, comorbidities, and medication use can also affect treatment responses (Nicolau, 2007).

In this context, aging is associated with changes in immune cell function and the cutaneous microenvironment that can modify the host response to biomaterials. The involvement of the immune system in the response to collagen biostimulators makes this relationship particularly relevant, as interactions between biomaterials and immune cells can influence fibroblast activation

and extracellular matrix remodeling. Experimental findings reported by Oh *et al.* (2023) support the relevance of this interaction. The authors investigated the effects of PLLA on collagen synthesis in models of aged skin and reported that PLLA modulated macrophage polarization toward an M2-like phenotype, increased the expression of IL-4, IL-13, and TGF- β , and promoted fibroblast proliferation and the expression of type I and type III collagen. These markers were reduced in aged tissue and were partially restored following PLLA treatment (Oh *et al.*, 2023). These findings suggest that the tissue response to collagen biostimulation is influenced by interactions between the biomaterial and the local immune and cellular microenvironment, which undergoes changes during aging.

Given the relationship between aging and immune responses, immunosenescence is of particular relevance. It is defined as a set of progressive and multifaceted changes in immune function associated with aging, including changes in cutaneous immunity (Štrbo *et al.*, 2025). During this process, quantitative and qualitative alterations occur in several cell populations of the innate and adaptive immune systems and can affect skin homeostasis and dermal organization. Age-related changes include reductions in the density and functional capacity of Langerhans cells, which contribute to the initiation of adaptive immune responses, as well as quantitative and functional alterations in memory T-cell populations and changes in CD4⁺ and CD8⁺ T-cell responses (Vukmanovic-Stejic *et al.*, 2017; Mancheno, Ramón, & Odeh, 2026).

Macrophage activity also changes with age. Studies have reported alterations in the balance between pro-inflammatory M1-like and anti-inflammatory M2-like macrophage phenotypes, including a relative increase in M1-like activity and a reduction in M2-like activity

in certain contexts. These changes can contribute to persistent inflammation and interfere with tissue repair processes (Cunha *et al.*, 2022). This phenomenon is associated with inflammaging, a state of chronic low-grade inflammation that can affect several aspects of cutaneous homeostasis, including epidermal barrier function, epidermal renewal, angiogenesis, and responses to tissue damage (Guimarães *et al.*, 2021; Horiba *et al.*, 2022).

Macrophages can also exhibit functional alterations, including increased production of pro-inflammatory cytokines such as IL-6, IL-1 β , TNF- α , and IL-8 in the circulation and the cutaneous microenvironment of older individuals (Pilkington *et al.*, 2021). These mediators can contribute to extracellular matrix degradation, inhibit collagen synthesis, impair epidermal barrier function, and alter keratinocyte differentiation (Papa *et al.*, 2023). Phagocytic capacity can also decline with age, potentially compromising tissue repair (Guimarães *et al.*, 2021).

In addition to macrophages, other skin-resident cells can undergo age-related changes. Mast cells, for example, can exhibit alterations in their distribution and functional activity, including changes in degranulation and the release of inflammatory mediators (Pilkington *et al.*, 2019).

Fibroblasts can acquire a senescence-associated secretory phenotype (SASP), characterized by increased secretion of pro-inflammatory cytokines, including IL-6, IL-1 β , IL-8, and TNF- α ; chemokines, such as CCL2, CXCL1, and CXCL8; growth factors, including VEGF and TGF- β ; and matrix metalloproteinases (MMPs) (Boismal *et al.*, 2020). The release of these mediators contributes to the maintenance of an inflammatory microenvironment and can

disrupt tissue homeostasis and function (Lee *et al.*, 2021; Mancheno, Ramón, & Odeh, 2026).

Among the mediators produced by senescent fibroblasts, the chemokine CCL2 is particularly relevant because it can promote the recruitment of inflammatory monocytes, thereby contributing to the persistence of inflammatory responses in the cutaneous microenvironment (Quan; Fisher, 2015). Thus, fibroblast senescence can not only directly alter the extracellular matrix but also influence interactions between tissue-resident cells and immune cells (Chambers *et al.*, 2021). Furthermore, senescent fibroblasts exhibit impaired extracellular matrix synthesis and maintenance, including reduced production of structural components such as collagen and elastin, together with increased expression of matrix metalloproteinases (MMPs) (Plikus *et al.*, 2017). This imbalance can promote extracellular matrix degradation and contribute to the structural changes characteristic of skin aging (Lee *et al.*, 2021).

The chronic inflammatory microenvironment associated with inflammaging is also linked to remodeling of the dermal extracellular matrix. Increased production of matrix metalloproteinases, particularly MMP-1, MMP-3, and MMP-9, by senescent fibroblasts and inflammatory cells can promote the degradation of structural dermal components, including collagen and elastin (Lee *et al.*, 2021). At the same time, new collagen synthesis is impaired in senescent tissue, resulting in an imbalance between extracellular matrix synthesis and degradation. This process can contribute to reduced dermal thickness, disorganized collagen architecture, loss of elasticity, and wrinkle formation associated with skin aging (Pilkington *et al.*, 2021).

Mitochondrial dysfunction is considered one of the mechanisms involved in the persistence of inflammaging. With age, mitochondrial DNA damage can accumulate, respiratory chain efficiency can decline, and the production of reactive oxygen species (ROS) can increase, creating conditions that favor chronic oxidative stress (Ferrucci, 2018). Mitochondrial dysfunction is not merely a consequence of aging; it can also contribute to the persistence of chronic inflammation. Increased ROS production can act as an endogenous danger signal, activating inflammatory pathways such as nuclear factor kappa B (NF- κ B) and promoting the release of pro-inflammatory cytokines, including interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α) (Baechle *et al.*, 2023). In addition, mitochondrial DNA fragments released into the cytosol can function as damage-associated molecular patterns (DAMPs), activating inflammasome-related pathways and contributing to sterile inflammation (De Azevedo Rabelo *et al.*, 2026).

The sources of inflammatory mediators are not limited to immune cells; adipose and muscle tissue cells can also contribute to inflammaging. During aging, circulating inflammatory mediators, including IL-6, can increase. However, immunosenescence is also associated with impaired functions of the innate immune system, including reduced phagocytic capacity. Accordingly, immunosenescence should be understood as a dynamic process involving ongoing adaptation to age-related changes in the organism (Bauer *et al.*, 2022).

Biostimulators are increasingly used to address tissue volume loss by stimulating the production of endogenous collagen. Therefore, understanding the immune pathways triggered by each specific biomaterial is essential (Corduff *et al.*, 2025). In this context, assessing

a patient's immune status can help inform the development of more effective and individualized treatment protocols (Matias, 2025).

4. CONCLUSION

The analysis of the selected studies revealed an association between skin aging, immunological changes related to immunosenescence, and the mechanisms of action of collagen biostimulators. Overall, the response to these agents depends on interactions among the biomaterial, immune cells, and dermal fibroblasts, which trigger a localized and controlled inflammatory response and stimulate extracellular matrix remodeling and collagen production.

Regarding their mechanisms of action, poly-L-lactic acid (PLLA), calcium hydroxyapatite (CaHA), and polycaprolactone (PCL) induce tissue responses capable of stimulating fibroblast activity and extracellular matrix remodeling. PLLA application, in particular, triggers a localized inflammatory response involving macrophages, multinucleated giant cells, and fibroblasts. Mediators involved in this response, including transforming growth factor beta 1 (TGF- β 1), contribute to fibroblast activation and the progressive deposition of collagen around the biomaterial particles.

Studies on immunosenescence have shown that aging is associated with quantitative and functional changes in several immune cell populations, including Langerhans cells, memory T cells, and CD4⁺ and CD8⁺ T cells, as well as changes in macrophage activity and the production and regulation of inflammatory mediators. These alterations are associated with the development of inflammaging, a state of chronic low-grade inflammation involving pro-inflammatory cytokines such as interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), and

tumor necrosis factor alpha (TNF- α), which can compromise tissue homeostasis and repair capacity.

In senescent skin, alterations in fibroblast activity have also been observed. Fibroblast senescence is associated with reduced proliferative and functional capacity and the acquisition of the senescence-associated secretory phenotype (SASP), characterized by the release of various mediators, including pro-inflammatory cytokines and matrix metalloproteinases (MMPs). These changes can promote an imbalance between extracellular matrix synthesis and degradation, contributing to reduced collagen content and skin elasticity.

Taken together, the findings indicate a biologically plausible relationship between immunosenescence and the response to collagen biostimulators. Age-related changes in macrophage activity, Langerhans cells, T lymphocytes, and fibroblasts can modify the cutaneous microenvironment and, consequently, influence processes involved in the inflammatory response, extracellular matrix remodeling, and new collagen production. However, few clinical studies have directly investigated the influence of immunosenescence on the response to collagen biostimulators.

The findings therefore suggest that age-related immunological and cellular changes can be among the factors contributing to variability in treatment responses, potentially through changes in inflammatory responses, fibroblast activity, and tissue remodeling capacity. Nevertheless, the available evidence remains insufficient to establish directly the extent to which immunosenescence can alter or compromise the efficacy of collagen biostimulators, highlighting an important gap in the scientific literature.

In this context, collagen biostimulators remain a relevant option for addressing changes associated with skin aging, contributing to dermal remodeling and improvements in skin firmness and quality. However, the findings underscore the importance of considering individual biological characteristics when evaluating treatment responses. Further clinical studies, particularly those directly investigating the relationships among immunosenescence, immune responses, fibroblast activity, and clinical outcomes following collagen biostimulator treatment, can improve understanding of these processes and contribute to the development of more individualized, safe, and evidence-based approaches.

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