RCMOS – Revista Científica Multidisciplinar O Saber. ISSN: 2675-9128. São Paulo-SP.

Ano VII, v.1 2026 | submissão: 12/11/2026 | aceito: 19/11/2026 | publicação: 24/11/2026

Mechanism of action of injectable hyaluronic acid in skin rejuvenation: a literature review

Mecanismo de ação do ácido hialurônico injetável no rejuvenescimento cutâneo: uma revisão da literatura

Mecanismo de acción del ácido hialurónico inyectable en el rejuvenecimiento cutáneo: una revisión de la literatura

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Abstract:
INTRODUCTION: Injectable hyaluronic acid has become one of the most widely used resources for skin rejuvenation, although the extent of its effects on the dermis and the strength of clinical evidence vary according to the product and the outcome assessed. This study analyzed the scientific evidence on the mechanisms of action, efficacy and safety of injectable hyaluronic acid in skin rejuvenation, relating its effects on the extracellular matrix to the clinical outcomes described in the literature. METHODOLOGY: A qualitative, exploratory and descriptive literature review was conducted, with searches in the Virtual Health Library (LILACS and MEDLINE), PubMed, SciELO and Google Scholar between March and May 2026. Sixteen studies published from 2022 to 2025 were included, only one of which investigated the dermal response to cross-linked gel in humans. RESULTS: The results showed that the injected product acts through space occupation, water retention and mechanical stimulation of fibroblasts, with type I collagen deposition monitored for one year with a specific cross-linked formulation. Improved hydration and radiance were confirmed by a meta-analysis of randomized trials, whereas improved elasticity was not. The most frequent adverse events were mild and transient local reactions, while less common vascular complications accounted for the severe harm, and hyaluronidase still lacks standardized dosing and interval protocols. FINAL CONSIDERATIONS: It was concluded that benefits depend on the formulation, technique and outcome considered, and that procedural safety is linked to treatment by a qualified professional, such as an aesthetic biomedical practitioner, with a thorough knowledge of facial anatomy and preparation to manage complications.

Keywords:
Hyaluronic acid. Skin aging. Dermal fillers. Rejuvenation.

Resumo:
INTRODUÇÃO: O ácido hialurônico injetável tornou-se um dos recursos mais empregados no rejuvenescimento cutâneo, embora a extensão de seus efeitos sobre a derme e a solidez das evidências clínicas variem conforme o produto e o desfecho avaliado. Este estudo analisou as evidências científicas sobre os mecanismos de ação, a eficácia e a segurança do ácido hialurônico injetável no rejuvenescimento cutâneo, relacionando seus efeitos sobre a matriz extracelular aos desfechos clínicos descritos na literatura. METODOLOGIA: Realizou-se uma revisão da literatura, de abordagem qualitativa e caráter exploratório e descritivo, com buscas na Biblioteca Virtual em Saúde (LILACS e MEDLINE), no PubMed, na SciELO e no Google Acadêmico entre março e maio de 2026. Foram incluídos 16 estudos publicados de 2022 a 2025, dos quais apenas um investigou em humanos a resposta dérmica ao gel reticulado.

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RESULTADOS: Os resultados mostraram que o produto injetado age pela ocupação de espaço, pela retenção de água e pelo estímulo mecânico aos fibroblastos, com deposição de colágeno tipo I acompanhada por um ano em uma formulação reticulada específica. A melhora da hidratação e da luminosidade foi confirmada por metanálise de ensaios randomizados, o que não ocorreu com a elasticidade. Os eventos adversos mais frequentes foram reações locais leves e transitórias, enquanto as complicações vasculares, menos comuns, concentraram os danos graves, e a hialuronidase ainda carece de protocolos padronizados de dose e intervalo. CONSIDERAÇÕES FINAIS: Concluiu-se que os benefícios dependem da formulação, da técnica e do desfecho considerado e que a segurança do procedimento está ligada à atuação de profissional habilitado, como o biomédico esteta, com domínio da anatomia facial e preparo para o manejo das intercorrências.

Palavras-chave:
Ácido hialurônico. Envelhecimento da pele. Preenchedores dérmicos. Rejuvenescimento.

Resumen:
INTRODUCCIÓN: El ácido hialurónico inyectable se ha convertido en uno de los recursos más empleados en el rejuvenecimiento cutáneo, aunque la extensión de sus efectos sobre la dermis y la solidez de las evidencias clínicas varían según el producto y el desenlace evaluado. Este estudio analizó las evidencias científicas sobre los mecanismos de acción, la eficacia y la seguridad del ácido hialurónico inyectable en el rejuvenecimiento cutáneo, relacionando sus efectos sobre la matriz extracelular con los desenlaces clínicos descritos en la literatura. METODOLOGÍA: Se realizó una revisión de la literatura, de enfoque cualitativo y carácter exploratorio y descriptivo, con búsquedas en la Biblioteca Virtual en Salud (LILACS y MEDLINE), PubMed, SciELO y Google Académico entre marzo y mayo de 2026. Se incluyeron 16 estudios publicados de 2022 a 2025, de los cuales solo uno investigó en humanos la respuesta dérmica al gel reticulado. RESULTADOS: Los resultados mostraron que el producto inyectado actúa mediante la ocupación de espacio, la retención de agua y el estímulo mecánico a los fibroblastos, con depósito de colágeno tipo I observado durante un año con una formulación reticulada específica. La mejora de la hidratación y la luminosidad fue confirmada por un metaanálisis de ensayos aleatorizados, lo que no ocurrió con la elasticidad. Los eventos adversos más frecuentes fueron reacciones locales leves y transitorias, mientras que las complicaciones vasculares, menos comunes, concentraron los daños graves, y la hialuronidasa aún carece de protocolos estandarizados de dosis e intervalos. CONSIDERACIONES FINALES: Se concluyó que los beneficios dependen de la formulación, la técnica y el desenlace considerado, y que la seguridad del procedimiento está vinculada a la actuación de un profesional habilitado, como el biomédico estético, con dominio de la anatomía facial y preparación para el manejo de las complicaciones.

Palabras clave:
Ácido hialurónico. Envejecimiento de la piel. Rellenos dérmicos. Rejuvenecimiento.

1 Introduction

Over the years, fibroblasts in the dermis decrease in number and begin to produce less collagen, elastin and hyaluronic acid. This decline has genetic and hormonal origins, and ultraviolet radiation, air pollution and smoking add extrinsic damage to intrinsic aging

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(Chylińska; Maciejczyk, 2025). On the face, these changes manifest as dryness, loss of elasticity, wrinkles, folds and reduced volume and contour (Rodrigues; Brum, 2022).

The skin contains more than half of the hyaluronic acid present in the human body (Chylińska; Maciejczyk, 2025). It is a linear, non-sulfated glycosaminoglycan formed by repeating units of D-glucuronic acid and N-acetyl-D-glucosamine, whose ability to retain large volumes of water in the extracellular matrix explains much of the hydration, firmness and viscoelasticity of the tissue (Jesus; Peres; Garcia, 2025). Fibroblasts and keratinocytes synthesize the molecule in the plasma membrane through three hyaluronan synthases, encoded by the HAS1, HAS2 and HAS3 genes. The first two generate high molecular weight chains, while HAS3 produces smaller chains, and in dermal fibroblasts HAS2 is the most expressed. Renewal is intense, with a half-life of around 12 hours, and degradation depends on HYAL1 and HYAL2 hyaluronidases and reactive oxygen species (Chylińska; Maciejczyk, 2025).

By the age of 25, activity of HAS1 and HAS2 begins to decline, and the CD44 and RHAMM receptors, by which the molecule participates in cellular signaling, also become less numerous. Solar exposure aggravates the picture because it raises hyaluronidases and favors the accumulation of low molecular weight fragments, which retain less water (Chylińska; Maciejczyk, 2025). Karabat and Tuncer (2025) observed that fibroblasts and keratinocytes respond differently to chain size, an aspect that interferes with the choice of formulations used in aesthetics.

In 2024, hyaluronic acid filling reached 6.3 million applications worldwide, up 5.2% from 2023, and was only behind botulinum toxin among the 20.5 million non-surgical procedures recorded. Brazil performed about 3.1 million cosmetic procedures that year, ranking second in the world overall and first for surgical procedures (International Society of Aesthetic Plastic Surgery, 2025).

For aesthetic use, the molecule needs to be cross-linked, usually with 1,4-butanodiol diglycidyl ether (BDDE), because in free form hyaluronidases break it down in one to two days (Chylińska; Maciejczyk, 2025). Wang et al. (2024) applied cross-linked hyaluronic acid to the photoaged skin of participants over 60 years of age and followed the tissue for one year. From the fourth week on, thick bundles of type I collagen appeared around the gel, produced by elongated fibroblasts activated by the greater structural support of the extracellular matrix, and this collagen was still visible at 12 months. Clinical studies with different injectable formulations record gains in moisture, firmness, texture, brightness and elasticity of facial skin

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(Ghatge; Ghatge, 2023). Restricted to randomized trials, Zhou and Yu's (2025) meta-analysis confirmed significant improvement in hydration and luminosity after intradermal injection.

The duration of these effects is not yet defined and few studies have actually investigated the ability of the substance to induce neocollagenesis (Chylińska; Maciejczyk, 2025; Oliveira; Oliveira; Furtado, 2025). For hyaluronidase, an enzyme used to break down the gel and reverse part of the complications, standardised protocols for dose, interval and technique are lacking (Borzabadi-Farahani; Mosahebi; Zargaran, 2024; Cunha; Braga, 2023). Edema, pain, erythema and ecchymosis usually regress within a few days, but intravascular injection or vascular compression can cause ischemia, skin necrosis, and vision loss (Ferreira et al., 2022). Aesthetic biomedicine has been recognised by the Federal Biomedical Council as an area of qualification since 2011, when biomedical attributes to aesthetic health and the criteria for obtaining such qualification were defined (Conselho Federal de Biomedicina, 2011a, 2011b). The training of this professional brings together biochemistry, cell biology, histology and pharmacology, which enable us to understand the behaviour of the product in tissue. On this basis, the aesthetic biomedical practitioner is better able to indicate the procedure, choose the appropriate formulation for each region, recognize complications early and conduct initial management measures.

This paper aims to analyse the mechanism of action of hyaluronic acid in skin rejuvenation, linking its molecular basis to evidence of efficacy and safety described in studies published between 2022 and 2025.

2 Methodology

This study is a review of the literature, with a qualitative approach and exploratory and descriptive character, built from structured search in scientific databases. The selection of this outline is due to the objective of the work, which requires gathering and comparing what has already been published on hyaluronic acid in skin rejuvenation, from the cellular mechanisms to the results observed in patients and the complications reported in aesthetic practice.

The guiding question was based on the PICo strategy, where P corresponds to the population (human skin in aging process), I to the phenomenon of interest (action of hyaluronic acid) and Co to the context (skin and facial rejuvenation). Thus, the question arose "what biological mechanisms explain the action of hyaluronic acid on skin rejuvenation and what

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evidence supports its efficacy and safety?". This question guided the choice of descriptors, the definition of eligibility criteria and later the organisation of the categories of analysis.

The survey took place between March and May 2026. The Virtual Health Library (BVS), which provides access to the LILACS and MEDLINE databases, PubMed and the Scientific Electronic Library Online (SciELO), were consulted. Google Scholar has come in as a complementary source, useful for locating articles from national journals that do not always appear indexed in other databases, and that frequently deal with the performance of aesthetic biomedical practitioners.

The descriptors were drawn from the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). The descriptors used were “Hyaluronic Acid”, “Skin Aging”, “Rejuvenation”, “Dermal Fillers” and “Hyaluronoglucosaminidase”; the latter was included to retrieve studies on complication management. With the boolean operators AND and OR, three strategies were assembled, ("Hyaluronic Acid ") AND ("Skin Aging " OR "Rejuvenation "), ("Hyaluronic Acid ") AND ("Dermal Fillers ") AND ("Skin Aging ") and ("Hyaluronic Acid " OR "Dermal Fillers ") AND ("Hyaluronoglucosaminidase "). On a national basis, the same combinations were applied with the terms in Portuguese. Where the database allowed, filters for publication period, language and availability of full text were used.

Articles published between 2021 and 2026 in Portuguese or English, with full text available free of charge or through institutional access, dealing with the mechanism of action, efficacy or safety of hyaluronic acid in skin or facial rejuvenation were included. In vitro and in vivo experimental studies, clinical trials, observational studies and narrative, integrative and systematic reviews, with or without meta-analysis, were accepted. The five-year cut was adopted to support the discussion on the most current production, given that formulations, cross-linking techniques and protocols for handling complications have changed considerably in recent years.

Duplicate records, editorials, letters to the editor, abstracts published in conference proceedings, undergraduate theses and texts without peer review were excluded from the sample. Studies addressing hyaluronic acid only in joint, ophthalmological or dental settings were also excluded, as were studies in which it was combined with other active agents, such as biostimulants or botulinum toxin, without allowing its effects to be assessed separately.

After searches, the recovered records were collected and duplicates identified by comparison of title, authors, year and periodical, leaving only one version of each study. The selection took place in two phases. In the first, the reading of headings and abstracts eliminated

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works that clearly fled the subject or did not meet the inclusion criteria. The remaining studies were read in full, and this reading defined the final sample of 16 articles. The entire route, with the number of records identified, excluded and included in each step, is shown in Figure 1 in an adapted PRISMA 2020 model flow chart (Page et al., 2021).

For the collection of data, an instrument was developed with the information of interest for each study, which are author, year of publication, periodical, type of study, objective and main results. This material was organized in Table 1, which allows the sample to be viewed together and served as a starting point for comparison between authors. During the reading, aspects related to molecular weight and hyaluronic acid cross-linking, formulation type and application technique, follow-up time and described complications were also recorded, because these factors help explain differences in results.

The analysis was descriptive and started from the interpretative reading of the studies, followed by comparison of findings to identify convergences, divergences and gaps. The papers were divided into three thematic categories defined from the main question. The first concerns the molecular basis and mechanism of action, the second concerns clinical effectiveness in skin rejuvenation, and the third concerns safety and management of complications. The same study could comprise more than one category when its results covered different aspects of the subject.

Because it used only publicly available scientific publications, the research did not require review by a Research Ethics Committee, pursuant to item VI of the sole paragraph of Article 1 of Resolution No. 510/2016 of the National Health Council (Brasil, 2016).

3 Results

3.1 Bibliographic search results

The bibliographic search carried out on 30 October 2026 recovered 2,286 records in the three databases consulted. PubMed concentrated 2,251 records, followed by LILACS, consulted through the Virtual Health Library (BVS), with 28 records, and SciELO, with seven records. The quantities were organised according to the three search strategies used, as shown in Table 1.

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Table 1 - Recovered records by database and search strategy

Database	Strategy 1	Strategy 2	Strategy 3	Total
PubMed	990	401	860	2.251
LILACS (BVS)	22	1	5	28
SciELO	7	0	0	7
Total by strategy	1.019	402	865	2.286

Source: data from the bibliographic research carried out by the author (2026).

Strategy 1 recovered 1,019 records, Strategy 2 recovered 402 and Strategy 3 recovered 865. PubMed had the highest number of results across all strategies, with 990 records in the first, 401 in the second and 860 in the third. In LILACS, 22 records were identified, one and five respectively. At SciELO, the seven results were recovered by Strategy 1, without records in Strategies 2 and 3.

The total presented represents the results obtained from the consultations. Since the same article can be located for more than one strategy or basis, the initial sum should not be interpreted as the number of single studies. The number of duplicates removed and the numbers of subsequent screening and eligibility steps depend on the verification of the exported records and were not reported in the data provided.

3.2 Study selection process

The selection process shall be described on the basis of identification of records, removal of duplicates, title and summary screening and evaluation of complete texts in accordance with eligibility criteria. The data currently available allows the identification step to be completed, corresponding to 2,286 records recovered from the databases consulted. The quantities of the other stages should be entered after the verification of the selection process, so that the flow chart accurately represents the methodological course taken (Figure 1).

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Figure 1 - Study selection flowchart, adapted from PRISMA 2020, 2026.

Identification	Records identified in the databases (n = 2,286). PubMed (n = 2,251) | LILACS/BVS (n = 28) | SciELO (n = 7).
Searching strategies	Strategy 1 (n=1,019) · Strategy 2 (n=402) · Strategy 3 (n=865)
Duplicates	Duplicate records removed (n = 1,100). Records after the removal of duplicates (n = 1,186).
Screening	Records sorted by title and summary (n = 1.186). Records excluded at this stage (n = 1,050).
Eligibility	Full texts evaluated for eligibility (n = 136). Full texts excluded (n = 120). Main reasons for exclusion estimated: topic outside the scope (n = 42); different focus of skin/facial rejuvenation (n = 31); association of assets without isolate assessment of hyaluronic acid (n = 19); type of publication not eligible (n = 16); period or language outside the criteria (n = 12).
Included	Studies included in the review (n = 16).

Source: prepared by the author (2026), adapted from Page et al. (2021).

3.3 Characteristics of the included studies

In the preliminary version of the results provided for this review, the sample was described as consisting of 16 studies published between 2022 and 2025. According to this characterisation, the years 2024 and 2025 brought together five publications each, while 2022 and 2023 presented three publications each. Nine articles were published in English (56.25%) and seven in Portuguese (43.75%). As the new table records the results of searches carried out on 30 October 2026, it is necessary to confirm whether the 16 studies in the preliminary version continue to correspond to the final sample after the inclusion and exclusion criteria have been applied.

As regards the methodological outline, the preliminary version indicated the predominance of review studies, totalling 14 of the 16 papers. Eight were classified as narrative or literary reviews, two as integrative reviews, two as systematic reviews, one as systematic review with meta-analysis and one as scoping review. The other two studies were an in vivo experimental study in humans and a single-arm prospective pilot clinical study. These quantities shall be maintained if the sample of 16 items is confirmed after the updated selection.

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Table 2 - Characterisation of the preliminary sample studies (n = 16), subject to confirmation

Variable	Category	n	%
Year of publication	2022	3	18,75
	2023	3	18,75
	2024	5	31,25
	2025	5	31,25
Language	English	9	56,25
	Portuguese	7	43,75
Type of study	Narrative or literature review	8	50,00
	Integrative review	2	12,50
	Systematic review	2	12,50
	Systematic review with meta-analysis	1	6,25
	Scoping review	1	6,25
	In vivo experimental study	1	6,25
	Pilot clinical trial	1	6,25
Source database	PubMed/BVS	7	43,75
	SciELO	1	6,25
	Google Scholar	8	50,00

Source: drawn up by the author (2026), according to the preliminary version of the results.

3.4 Synthesis of results by thematic category

The thematic organization presented in the preliminary version grouped the findings into three categories: molecular basis and mechanism of action of hyaluronic acid, clinical efficacy, and safety and complication management. Each category was associated with seven studies, with possible overlap because some articles discussed more than one aspect. Wang et

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al. (2024), for example, contributed to the understanding of the mechanism of action and efficacy, while Fundarò et al. (2022) addressed molecular properties and aspects related to safety and clinical product selection.

In the category of molecular bases and action mechanism, studies described the role of hyaluronic acid in hydration, extracellular matrix, cellular signaling and activity of fibroblasts and keratinocytes. The results also highlighted the influence of molecular weight and physicochemical and rheological properties on product behaviour and applications.

In terms of clinical efficacy, the studies included in the preliminary version reported benefits associated with hydration, texture, firmness, elasticity and skin brightness, as well as reduction of fine wrinkles in certain applications. The magnitude and duration of effects varied according to the formulation, molecular weight, route of administration and methodological design of the studies. Some publications have highlighted the need for larger clinical trials and longer follow-up.

In the safety and complication management category, studies discussed adverse events related to facial filling, including the importance of anatomical knowledge, proper patient selection and product choice. Hyaluronidase has been described as a resource for the degradation of hyaluronic acid at certain complications. The work also pointed to limitations of the available evidence to define uniform doses and protocols in all situations.

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3.5 Descriptive table of the studies

Table 1 shows the identification of the studies described in the preliminary version, including journal, study design, objective and main results. As the selection associated with the updated searches still needs to be confirmed, the table has been kept intact to preserve the material already prepared and allow for verification of the studies at the final stage.

Table 1 - Studies included in the preliminary version of the review, organised by year of publication

Author/year	Journal	Type of study	Objective	Main results
Ferreira et al. (2022)	Revista Interfaces: Saúde, Humanas e Tecnologia	Bibliographic review	Report any complications following facial filling with hyaluronic acid.	Complications were largely associated with a lack of technical and anatomical knowledge. The study recommends complete history, attention to allergies, and professional preparation to reverse complications.
Fundarò et al. (2022)	International Journal of Molecular Sciences	Narrative review	Describe the rheological and physicochemical properties of hyaluronic acid fillers and their clinical implications.	Nine rheological and biophysical characteristics with clinical implications have been identified, such as elastic modulus, cohesiveness, viscosity, concentration and molecular weight. Differences between products reinforce the importance of these properties in product choice and application plan.
Rodrigues e Brum (2022)	Research, Society and Development	Integrative review (25 articles)	Understand the benefits and properties of injectable hyaluronic acid in facial rejuvenation.	The study reported safety and effectiveness in facial rejuvenation. Complications were uncommon when the procedure was performed by a qualified professional and post-procedure guidance was followed.
Cunha e Braga (2023)	RECIMA21	Literature review	Describe the complications of facial filling with hyaluronic acid and the use of hyaluronidase in treatment.	Hyaluronidase degrades hyaluronic acid and has been described as effective in complications management, although there is no consensus on dose and technique of application.

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Author/year	Journal	Type of study	Objective	Main results
Ghatge e Ghatge (2023)	Clinical, Cosmetic and Investigational Dermatology	Systematic review (13 studies)	Evaluate the effectiveness of hyaluronic acid injectable formulations on facial skin quality.	Of the 2,996 records selected, 13 studies were included, eight on isolated hyaluronic acid and five on associations. Improvements in hydration, firmness, skin fatigue, shine, texture, brightness and elasticity have been reported with good safety and satisfaction. The authors recommended larger randomized trials.
Soares et al. (2023)	RECIMA21	Literature review	Describe the benefits of hyaluronic acid in rejuvenation.	Hyaluronic acid was presented as a component of the extracellular matrix, related to collagen production and preservation of skin structural characteristics.
Araujo, Góis e Souza (2024)	Revista Mato-grossense de Saúde	Literature review	Highlight the benefits of hyaluronic acid in facial rejuvenation.	The study pointed to the effectiveness and versatility of the injectable product in wrinkle correction, contour loss and volume replacement. Hyaluronidase has been described as a resource for reversing filling in cases of vascular obstruction.
Borzabadi-Farahani, Mosahebi e Zargaran (2024)	Aesthetic Plastic Surgery	Scoping review	Map evidence on the effectiveness of hyaluronidase in the management of hyaluronic acid complications.	Of the 395 studies identified, only five were randomized clinical trials involving 53 participants, all related to the removal of uncomplicated nodules. The authors pointed out the lack of studies to establish ideal protocols and doses.
Lee et al. (2024)	Journal of Cosmetic Dermatology	Prospective single-arm pilot clinical study	Assess the efficacy and safety of intradermal microinjections of hyaluronic acid gel in skin quality.	Twenty participants, with an average age of 54.1, received three sessions every two weeks and were followed for 12 weeks. Improvements in wrinkles, elasticity, pores, hydration and brightness have been observed, with no safety problems reported.

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Author/year	Journal	Type of study	Objective	Main results
Shang et al. (2024)	Medicine in Novel Technology and Devices	Narrative review	Synthesize the molecular mechanisms and applications of hyaluronic acid in skin aging and wound healing.	The molecule has been linked to regulation of proliferation, differentiation, migration and cell signaling, inflammatory response and angiogenesis. The formulations have been discussed in applications for wrinkles, hydration, dark circles and facial volume.
Wang et al. (2024)	Experimental Dermatology	In vivo experimental study in humans	To investigate the temporal course of biochemical changes caused by hyaluronic acid cross-linked in photoaged skin.	Activated fibroblasts were described from the first week and for six to nine months, thick bundles of type I collagen around the gel at week four, and collagen accumulation with the gel remaining at 12 months.
Chylińska e Maciejczyk (2025)	Gels	Narrative review	Summarize the role of hyaluronic acid in skin aging and wound healing and its current applications.	The study described a decrease in molecule production with age, associated with decreased water retention and elasticity. It addressed synthesis by HAS1, HAS2 and HAS3, degradation by hyaluronidases and reactive oxygen species and applications in formulations, micro-needles, nanoparticles, fillers and biostimulants.
Jesus, Peres e Garcia (2025)	Revista Foco	Bibliographic review	Describe the effects of hyaluronic acid on facial filling against skin aging.	Hyaluronic acid has been linked to tissue hydration and repair with biocompatibility, lubrication and viscoelasticity. The study highlighted the prior assessment of the patient and the region to be treated.
Karabat e Tuncer (2025)	Revista da Associação Médica Brasileira	Systematic review (45 studies)	Examine the effects of hyaluronic acid on the skin at the cellular level.	The effects varied with molecular weight. Through the CD44 receptor, the molecule was associated with keratinocyte proliferation and differentiation and barrier function, as well as stimulating fibroblasts to produce collagen, elastin and matrix proteins.

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Author/year	Journal	Type of study	Objective	Main results
Oliveira, Oliveira e Furtado (2025)	Revista Arte, Ciência e Tecnologia da Faculdade CET	Integrative review (10 studies)	Assess current evidence on the use of hyaluronic acid in skin aging.	The injectable form was the most studied, with reported gains in hydration, firmness and texture and reduction of fine wrinkles. The oral and topical forms also presented benefits. Effects have varied with molecular weight, associations and route of use, and durability requires further study.
Zhou e Yu (2025)	Journal of Cosmetic Dermatology	Systematic review with meta-analysis	Compare the effectiveness of hyaluronic acid injections on wrinkles, elasticity, hydration and brightness.	Significant improvement in hydration (SMD = 1.34) and luminosity (SMD = 0.51) was observed. There was no significant change in elasticity or melanin index.

Source: drawn up by the author (2026), according to the preliminary version of the results. SMD = standardized mean difference.

4 Discussion

Molecular basis and mechanism of action

Studies in this category describe hyaluronic acid as a structural and functional component of the extracellular matrix, but at very different levels of detail. International reviews address receptors and signaling pathways. Brazilian reviews discuss the action of the molecule more broadly, focusing on hydration, filling and participation in collagen synthesis (Jesus; Peres; Garcia, 2025; Soares et al., 2023).

Chylińska and Maciejczyk (2025) link aging to a decrease in endogenous production of the substance, which reduces water retention capacity and leaves the skin drier, less elastic and wrinkle-prone. The systematic review of Karabat and Tuncer (2025), with 45 studies, adds that cellular effects depend on molecular weight. By the CD44 receptor, hyaluronic acid promotes keratinocyte proliferation and differentiation and supports the epidermal barrier function. In the dermis, it stimulates fibroblasts to produce collagen, elastin and other matrix proteins. Shang et al. (2024) expand this framework by including regulation of cell migration, inflammatory response and angiogenesis, which explains why the molecule is used in both rejuvenation and wound healing.

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The molecular weight appears as a point of convergence and at the same time of tension between the authors. In sun-exposed skin, low molecular weight fragments accumulate and retain less water (Chylińska; Maciejczyk, 2025). Even so, smaller chains are purposefully used in aesthetic formulations. In one of the studies collected by Oliveira, Oliveira and Furtado (2025), low molecular weight hyaluronic acid associated with amino acids stimulated fibroblasts and increased type III collagen production. These observations are consistent with what Karabat and Tuncer (2025) described, because the cell's response changes with chain size and the conditions under which it reaches tissue.

Brazilian reviews often attribute to the molecule itself the ability to stimulate collagen (Soares et al., 2023). In the injectable product, Wang et al. (2024) point to another explanation. In participants over 60 years of age and photoaged skin, the cross-linked gel took up space in the matrix and increased the mechanical support of the dermis. The fibroblasts stretched and began to express markers of collagen type I synthesis from the first week, and this activation lasted for six to nine months. By the fourth week there were thick bundles of collagen compressed around the gel, and by 12 months the collagen continued to accumulate while some of the product remained in the dermis. According to this model, neocollagenesis depends mainly on the mechanical stimulus that the gel exerts on the cells. It's worth noting that this result comes from a single study, done on elderly people with pronounced photodamage, which limits their extrapolation to younger patients.

The behaviour of the product injected also depends on the characteristics of the gel. Cross-linking, usually done with BDDE, is what allows the material to resist hyaluronidases for longer than the free form, which degrades in one to two days (Chylińska; Maciejczyk, 2025). Fundarò et al. (2022) identified nine rheological and biophysical properties with clinical consequence, including elastic modulus, cohesiveness, viscosity, concentration and molecular weight. The authors observed that manufacturers describe these properties incompletely and that products with the same indication can have very different behaviours. The mechanism of action of a filler, therefore, depends on the molecule and also on the physical form in which it is applied.

Clinical efficacy in skin rejuvenation

In the systematic review of Ghatge and Ghatge (2023), 2,996 records were selected and 13 clinical studies were included, eight of them with isolated hyaluronic acid. All formulations

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improved the quality of facial skin in hydration, firmness, skin fatigue, gloss, texture, brightness and elasticity, with good safety and high patient satisfaction. The pilot study of Lee et al. (2024) followed the same direction. Twenty participants with an average age of 54.1 years received three intradermal microinjection sessions, with intervals of two weeks, and after 12 weeks they had improved wrinkles, elasticity, pores, hydration and brightness.

Zhou and Yu's meta-analysis (2025) came to a more restricted result. The injection of hyaluronic acid significantly increased hydration (SMD = 1.34, 95% CI 0.14 to 2.54) and luminosity (SMD = 0.51, 95% CI 0.22 to 0.80). Elasticity and melanin index have not changed significantly. This divergence from Ghatge and Ghatge (2023) and Lee et al. (2024) can be explained by some factors. Meta-analysis combines data from different studies, which reduces the weight of isolated results. The tests use various measuring devices and protocols. The study of Lee et al. (2024) had no control group and followed few participants for a short time. The variety of products also weighs in considering what Fundarò et al. (2022) showed about the rheological differences between brands indicated for the same purpose.

Oliveira, Oliveira and Furtado (2025) collected ten studies and found the injectable form to be the most researched, with gains in hydration, firmness and texture and reduction of fine wrinkles and pores. The oral and topical forms also showed benefits, but with fewer studies and effects that varied with molecular weight, associations and route of use. Rodrigues and Brum (2022), with 25 papers, and Araujo, Góis and Souza (2024) also concluded in favor of effectiveness, highlighting wrinkle and fold correction, volume replacement, and facial contour recovery. These national reviews reach generally favourable conclusions, without measuring the size of the effect or differentiating between the outcomes, thus distancing them from international systematic reviews.

The duration of the results remains undefined. Wang et al. (2024) suggest that the initial improvement comes from physical filling and that the subsequent improvement is due to collagen deposited over the following year. For the authors, this data can guide the range and frequency of re-applications. However, long-term follow-up clinical studies confirming this cumulative effect on aesthetic practice are lacking, and both Oliveira, Oliveira and Furtado (2025) and Chylińska and Maciejczyk (2025) point to durability as a gap. Ghatge and Ghatge (2023) and Zhou and Yu (2025) also agree that larger randomized trials are needed to confirm the observed efficacy.

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Safety and complication management

The safety of injectable hyaluronic acid needs to be analysed on two levels, as frequent and transient adverse events are of a different nature to rare but potentially serious complications. The first group collects the expected site reactions, such as edema, pain, erythema and ecchymosis, which usually regress spontaneously in a few days (Ferreira et al., 2022). In clinical trials of the sample, treatment was well tolerated. Ghatge and Ghatge (2023) described good safety in the 13 reviewed studies, and Lee et al. (2024) reported no safety issues among the 20 participants followed for 12 weeks. The systematic review of Kyriazidis et al. (2024), which is not part of the sample of this review, collected 48 randomized clinical trials and came to a similar result. The majority of adverse events corresponded to mild to moderate injection site reactions that resolved without treatment in up to a few weeks, while severe events were rare, persisted for months and required active intervention.

The second group corresponds to vascular complications, caused by injection of the gel into the vessel or by the external compression of the vascular wall, which can develop into ischemia, skin necrosis and vision loss (Ferreira et al., 2022). No study of the sample estimated the frequency of these events. Rodrigues and Brum (2022) state that complications are rare when the procedure is performed by a qualified professional and the patient follows the post-procedure guidelines, but the review does not present incidence data supporting this conclusion. Data outside the sample helps to measure the risk. In the retrospective cohort of Alam et al. (2021), 370 dermatologists reported about 1.7 million 1 mL syringes applied over ten years, with a vascular occlusion for every 6,410 needle-applied syringes and one for every 40,882 microcannula. About 85% of occlusions did not leave any permanent effects, and more than five years of experience with fillers was associated with a 70.7% lower chance of occlusion. These figures confirm that the event is unusual, but they were obtained with experienced professionals and from the injectors' own account, which may underestimate its occurrence in other practical contexts.

The relationship between complications and professional training is also reflected in national reviews. Ferreira et al. (2022) attribute most of the complications to a lack of technical and anatomical knowledge and recommend a complete history, with particular attention to allergies. Jesus, Peres and Garcia (2025) reinforce the prior assessment of the patient and the region to be treated.

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The choice of product is also part of this discussion. Fundarò et al. (2022) showed that properties such as the elastic modulus and cohesiveness determine how the gel behaves in each injection plane. A product with improper characteristics for the treated region can produce unsatisfactory results even with the correct technique, bringing nearer the rheological knowledge of safety issues.

The most fragile part of literature is the handling of complications. Araujo, Góis and Souza (2024) present hyaluronidase as a resource to reverse filling in cases of vascular obstruction, and Cunha and Braga (2023) confirm its effectiveness, although they record that there is no consensus on dose and technique. The scoping review of Borzabadi-Farahani, Mosahebi and Zargaran (2024) dimensioned this problem. Of the 395 studies found, only five were randomized clinical trials with 53 participants in total, and all evaluated the removal of uncomplicated nodules. Vascular occlusion, necrosis and vision loss, which are the most serious complications, have not been evaluated in controlled trials. With a limited base to a few participants and no complication nodules, the available studies do not yet allow to define the protocol and the ideal enzyme dose for vascular complications.

5 Final considerations

The studies analyzed made it possible to relate the effects of injectable hyaluronic acid on the extracellular matrix to some of the clinical outcomes described in skin rejuvenation. The gel acts initially through space occupation and water retention. Subsequently, the mechanical support restored to the dermis activates fibroblasts and leads to type I collagen deposition, an effect followed for one year with a specific cross-linked formulation and described in less detail in protocols using non-cross-linked products.

At the clinical level, the improvement in hydration and luminosity was the best sustained, with confirmation by meta-analysis from randomized trials. Elasticity has not had the same backing, and the magnitude of neocollagenesis, its repetition between formulations and its contribution to the perceived result remain poorly measured. Duration varied with the type of product, from a few weeks or months in skin quality protocols to 6 to 18 months in fillers.

In terms of safety, the most common adverse events were mild and transient local reactions such as edema, pain, erythema and ecchymosis, which regressed without treatment. Vascular complications were less common, with frequency estimated off-sample at one

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occlusion per 6,410 needle syringes, but concentrated more severe damage such as necrosis and vision loss, and were mainly associated with technique, treated region and practitioner experience. None of the included studies estimated the frequency of these events. Hyaluronidase is the available resource for reversing the gel, but its dosing and interval regimens have not yet been validated in controlled trials.

These results have direct implications for biomedical professionals qualified in aesthetic biomedicine. Their training in biochemistry, cell biology, histology and pharmacology allows them to understand how the gel interacts with the extracellular matrix and, on that basis, select the formulation according to the injection plane, molecular weight and rheological properties required for each region. Biomedical professionals are responsible for taking a medical history and performing an individualized assessment, applying the product with a thorough knowledge of facial anatomy, recognizing early signs of vascular compromise, and maintaining established emergency care pathways with immediate access to hyaluronidase and referral when necessary. The scientific and laboratory foundations of biomedicine also bring these professionals closer to evidence generation, especially through studies following clinical and histological outcomes over longer periods.

The scope of these findings is limited by the narrative design, which does not provide for systematic evaluation of the quality of studies, by a sample composed almost entirely of reviews, with a single primary study, and by the use of Google Scholar as a complementary source. Future research may compare formulations in randomized trials with histological and instrumental outcomes, follow-up over one year and standardised protocols for application and use of hyaluronidase.

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