Dermal Fillers for Skin Repair in Aesthetic Medicine: A Comprehensive Review of Hyaluronic Acid Formulations, Crosslinking Strategies, and Tissue Adhesion

Abstract

Hyaluronic acid-based dermal fillers have revolutionized minimally invasive aesthetic medicine by restoring volume and correcting age-related skin changes. This review provides the first systematic analysis linking crosslinking parameters (e.g., reaction time, crosslinker concentration) to clinical outcomes such as fibrosis risk and filler migration rates. We critically evaluate conventional crosslinking strategies (BDDE, DVS, PEG) and highlight emerging innovations—including dopamine-modified HA for bioadhesion, thiol-ene chemistry for shear-thinning inject ability, and nanocomposite hybrids for reinforced viscoelasticity—that address key limitations in filler longevity (30–50% improvement) and tissue retention. Advanced surface modification techniques, such as dopamine grafting and nano-texturing, are analyzed for their role in enhancing cellular responses (e.g., fibroblast adhesion, M2 macrophage recruitment) and preventing migration. Clinical performance data reveal that highly crosslinked fillers (>30% density) achieve 12–18-month longevity but risk fibrotic encapsulation, underscoring the need for balanced design. Regulatory challenges, including FDA/EMA disparities in approval pathways for novel fillers (e.g., nanocomposites, enzyme-resistant formulations), are discussed alongside economic barriers to industrial translation. Future directions emphasize smart, personalized fillers with AI-driven degradation prediction and hybrid biomaterials for regenerative applications. By bridging material science with clinical needs, this review provides actionable insights for developing next-generation HA fillers that optimize safety, durability, and patient outcomes.

Keywords: Hyaluronic acid fillers; Dopamine crosslinking; Tissue adhesion; Degradation kinetics; Regulatory challenges

1. Introduction

The skin, as the largest organ of the human body, is essential for both protective functions and aesthetic appearance. It acts as a barrier against environmental aggressors while maintaining homeostasis, thermal regulation, and sensory perception. With advancing age and prolonged exposure to environmental factors, the skin experiences a gradual decline in its structural integrity, leading to a loss of elasticity, volume, and overall youthful appearance (1). These changes are primarily due to the degradation of collagen, elastin, and other extracellular matrix (ECM) components, which result in wrinkles, sagging, and other visible signs of aging.

In recent decades, minimally invasive aesthetic procedures have gained prominence as effective strategies for skin rejuvenation and repair. Among these, dermal fillers have emerged as a cornerstone in aesthetic medicine, providing a means to restore lost volume, smooth wrinkles, and enhance facial contours without the need for surgical intervention (2). Hyaluronic acid (HA)–based fillers, in particular, have become the gold standard due to their high biocompatibility, inherent hydrating properties, and natural presence in the ECM. HA's unique ability to retain water—up to 1000 times its weight—makes it an ideal candidate for maintaining skin hydration and turgor, which are critical for a youthful appearance (3).

Despite these advantages, conventional HA fillers are not without limitations. One of the major drawbacks is their relatively short duration of effect, which is largely attributed to the rapid enzymatic degradation of HA by endogenous hyaluronidases. This short lifespan often necessitates frequent re-treatments, thereby increasing the overall cost and inconvenience for patients (4). Additionally, issues such as suboptimal mechanical stability and inadequate tissue adhesion can result in filler migration and uneven distribution at the injection site, further compromising the long-term aesthetic outcomes (5).

To address these challenges, significant research has been directed towards improving the formulation and processing of HA fillers. Traditional crosslinking methods, which involve chemical agents such as 1,4-butanediol diglycidyl ether (BDDE), di-vinyl sulfone (DVS), and polyethylene glycol (PEG), have been employed to modify HA molecules. These crosslinking agents facilitate the formation of a three-dimensional network that enhances the filler's resistance to enzymatic degradation and improves its mechanical properties (5). BDDE, for example, reacts with the hydroxyl groups on HA to form stable ether linkages, thereby extending the filler's residence time in vivo. However, concerns have been raised regarding the potential cytotoxicity associated with residual BDDE and the variability in degradation rates among different formulations (6). Similarly, DVS and PEG offer alternative crosslinking strategies with unique benefits, yet each method requires a careful balance between achieving sufficient network stability and maintaining injectability and biocompatibility.

One critical gap in the current literature is the limited quantitative understanding of how specific crosslinking parameters—such as reaction time, temperature, and crosslinker concentration—affect the rheological properties and biodegradation kinetics of HA fillers. Although several studies have investigated the physicochemical properties of various HA formulations, there is a paucity of systematic evaluations that link these parameters directly to clinical performance metrics such as filler longevity and tissue integration (7). Addressing this gap is essential for developing more predictable and robust filler systems.

Another area that remains underexplored is the molecular mechanism underlying tissue adhesion of dermal fillers. Effective tissue integration is not only pivotal for ensuring that the filler remains localized at the injection site but also for promoting cellular activities critical for skin repair,

including cell adhesion, proliferation, and differentiation. Recent advances in surface modification and bioadhesive strategies have introduced innovative approaches to enhance tissue adhesion. For instance, the incorporation of bioactive molecules such as dopamine into the HA matrix has shown promise in enhancing adhesion. Dopamine is known for its robust adhesive properties, reminiscent of the natural adhesive mechanisms employed by mussel foot proteins, and can be chemically conjugated to HA to improve its interaction with the ECM (8).

Preliminary studies suggest that dopamine-modified HA fillers may achieve better retention at the injection site and facilitate improved cellular responses, although the precise molecular interactions involved remain to be fully elucidated (9).

Furthermore, while the aesthetic outcomes of HA fillers have been extensively documented, there is still a significant translational gap between laboratory-scale innovations and their application in clinical practice. Many advanced crosslinking and adhesion-enhancement techniques have been successfully demonstrated in controlled laboratory settings; however, scaling these technologies into reproducible, cost-effective industrial processes poses substantial challenges. Similar issues have been observed in related composite systems, such as polyhydroxyalkanoate composites with organic fillers, where inconsistencies in filler dispersion and interfacial adhesion can limit overall performance (10). This translational challenge is compounded by economic considerations, including production costs and the need for rigorous regulatory compliance, which are critical factors for the successful commercialization of next-generation HA fillers (11).

The integration of regulatory considerations into filler development is another crucial aspect that has garnered attention. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have established comprehensive guidelines to ensure the safety, efficacy, and quality of dermal fillers. These guidelines require extensive preclinical and clinical evaluations, which in turn influence the design and manufacturing processes of HA fillers (2). Despite these measures, continuous advancements in material science necessitate ongoing updates to regulatory frameworks to keep pace with innovation.

In summary, the field of HA-based dermal fillers has achieved remarkable progress, yet significant challenges persist. There remains a critical need for a more detailed understanding of the interplay between crosslinking density, biodegradability, and tissue adhesion. Additionally, translating novel laboratory techniques into scalable, economically viable products requires further investigation. Addressing these research gaps will not only enhance the predictability and longevity of HA fillers but also pave the way for next-generation formulations that deliver superior clinical outcomes. This review aims to synthesize current knowledge, identify the key challenges and emerging trends, and provide actionable recommendations for future research in the development of advanced dermal fillers for skin repair and rejuvenation.

2. HA Formulations and Crosslinking Strategies

HA is the most widely used biopolymer in dermal fillers due to its high biocompatibility, hydrophilic nature, and ability to integrate with the ECM. However, native HA has a short half-life in vivo, typically ranging from 12 hours to a few days, due to rapid enzymatic degradation by hyaluronidases and free radical-induced fragmentation (1). To address this limitation, various

crosslinking strategies have been developed to enhance the stability, longevity, and mechanical properties of HA fillers (Figure 1).

2-1. Conventional Crosslinking Strategies

The most commonly employed crosslinking agents in HA fillers include BDDE**,** DVS**,** and PEG-based crosslinkers**,** each with distinct effects on the rheological and degradation properties of the filler (Figure 2). BDDE crosslinking efficiency is temperature-dependent, with optimal ether bond formation occurring at 40–50°C (12). However, elevated temperatures (>60°C) increase residual BDDE levels by 15–20%, necessitating stringent post-reaction purification. PEG-based crosslinkers exhibit pH-sensitive reactivity, achieving maximal crosslinking at pH 8.5 but compromising hydrogel homogeneity under acidic conditions (e.g., pH 6.5 in inflamed tissues). While BDDE-crosslinked HA with >30% crosslinking density achieves 12–18-month longevity, it elevates shear modulus (G′) to >300 Pa, correlating with a 10–15% fibrosis risk due to fibroblast hyperactivation (Ref 7). DVS-based fillers (15–20% crosslinking) balance moderate longevity (6–9 months) and softness (G′ = 200–400 Pa), but their high swelling ratio accelerates enzymatic degradation in mobile facial regions (e.g., perioral area) (13).

BDDE remains the most commonly used crosslinker in commercial HA fillers due to is ability to form ether bonds, enhancing resistance to enzymatic degradation. However, concerns regarding potential residual toxicity and its effects on long-term biocompatibility have driven research toward alternative crosslinking agents with improved safety profiles.

DVS, which forms sulfone bonds, creates a moderately stable network but has a higher swelling ratio, which may lead to more rapid biodegradation.

PEG-based crosslinkers, in contrast, are recognized for their ability to impart hydrophilic properties to HA networks, improving water retention while preserving elasticity. However, their relatively lower mechanical strength limits their application, making them more suitable for superficial wrinkle correction rather than deep volume restoration (Table 1) (14).

Table 1. Common Crosslinking Agents in Hyaluronic Acid Fillers and Their Effects

Crosslinking Agent	Degree of Crosslinking (%)	Storage Modulus (G′, Pa)	Degradation Time (Months)	Clinical Indications	Key Advantages	Limitations	Immune Response (Incidence)
BDDE	5–15%	100–250	6–12	Deep volumizing	Long-lasting, stable ether bonds	Residual BDDE toxicity (0.5–2%*)	Mild inflammation (5–10%) (6)
DVS	10–20%	200–400	3–9	Superficial wrinkles	High elasticity	Rapid resorption due to swelling	Moderate edema (10–15%) (5)
PEG-based	5–12%	150–350	6–10	Mid-dermal correction	Enhanced hydrophilicity	Low mechanical strength	Rare hypersensitivity (1–3%) (14)

2-2. Novel Approaches in Crosslinking

Recent advances in HA formulations have focused on addressing the limitations of conventional crosslinking strategies by improving durability, tissue retention, and biocompatibility, while reducing the risks of mechanical failure, filler migration, and immune response. Some of the most significant innovations include dopamine incorporation, thiol-ene crosslinking, nanocomposite fillers, and bioengineered HA. These strategies aim to create next-generation formulations that not only prolong the longevity of the filler but also enhance tissue interaction and overall clinical performance (Table 2) (15).

Table 2. Emerging Innovations in HA Crosslinking

Novel Crosslinking Strategy	Crosslinking Efficiency (%)	Rheological Improvements	Tissue Integration	Key Challenges
Dopamine-Modified HA	20–35%	High elasticity, strong adhesion	Strong	Stability optimization needed (8)
Thiol-Ene Chemistry	25–40%	Tunable stiffness, better shear-thinning	Moderate	Process complexity, cost (8)
Nanocomposite HA Fillers	30–50%	Reinforced viscoelasticity	High	Potential immune response (16)

Dopamine-modified HA fillers utilize dopamine's catechol groups to mimic the strong adhesion mechanisms of mussel foot proteins. These catechols form covalent bonds with collagen fibers and other ECM components through quinone-mediated reactions, significantly enhancing tissue retention and localized stability (Figure 3) (17). Studies indicate that dopamine-integrated HA fillers provide improved adhesion and resistance to migration, achieving a tissue retention increase of 30–50% compared to BDDE-based fillers. Additionally, their bioadhesive properties contribute to improved cellular compatibility, promoting fibroblast activation and extracellular matrix (ECM) remodeling. However, a key challenge is the oxidative instability of catechol groups at physiological pH (7.4), which can lead to a gradual decline in adhesive strength over time.
Co-formulations with antioxidants like ascorbic acid are being explored to stabilize these fillers and preserve their efficacy during prolonged use. Dopamine-modified HA fillers show particular promise for long-term applications in facial volumization and contouring (18).
Thiol-ene crosslinking provides an innovative method for creating HA fillers with tunable viscoelastic properties. This crosslinking process involves a reaction between thiol (-SH) and alkene (-C=C-) groups, resulting in highly customizable network stiffness and elasticity. Thiol-ene crosslinked fillers display favorable shear-thinning behavior, improving injectability and reducing fragmentation during injection, which leads to enhanced patient outcomes. Their controlled degradation rates also minimize fibrosis risks associated with rigid fillers. Clinical studies on thiol-ene systems have shown potential for mid-dermal correction and wrinkle filling due to their balanced mechanical properties and biocompatibility. However, the scalability of this technology is currently limited by the cost of specialized photoinitiators (19).

Nanocomposite hybrid HA fillers incorporate rigid or functional nanomaterials, such as silica nanoparticles or graphene oxide, into HA hydrogels to reinforce mechanical properties and improve longevity. These nanocomposite systems exhibit enhanced viscoelasticity, providing extended volume retention and better integration with surrounding tissues. For instance, silica nanoparticles (10–50 nm) improve the elastic modulus of fillers by up to 40%. Despite their superior performance, concerns over potential pro-inflammatory responses caused by the activation of immune pathways, such as the NLRP3 inflammasome, have led to research into surface modifications like PEGylation, which reduces cytokine release by approximately 50%. Current evaluations focus on optimizing the safety profiles of nanocomposite fillers while maintaining their mechanical and aesthetic benefits (20).

Advances in synthetic biology and bioengineering have paved the way for the development of bioengineered HA variants with customized physical and chemical properties. By genetically modifying HA-producing bacteria, such as *Streptococcus equi*, researchers have created HA chains with higher molecular weights, fewer impurities, and enhanced interaction capabilities with crosslinking agents. These bioengineered HAs enable the formation of stronger and more durable networks during crosslinking, which extends the longevity of fillers and improves consistency in clinical outcomes. Furthermore, hybrid polymers combining HA with biologically active peptides, like RGD (Arg-Gly-Asp) motifs, show potential in promoting cell adhesion and angiogenesis, making them particularly useful for regenerative applications such as scar repair and wound healing (Figure 4) (21).

2-3. Biodegradation and Longevity Considerations

These advanced strategies significantly impact the biodegradation profiles and longevity of HA fillers. For instance, highly crosslinked dopamine-modified HA and nanocomposite fillers exhibit extended degradation periods, with half-lives lasting more than 12–18 months. However, as stiffness increases, there may be a trade-off with tissue integration and a higher risk of fibrosis, especially at very high crosslinking densities. By carefully adjusting crosslinking parameters and incorporating bioactive or responsive components, researchers aim to develop formulations that strike the ideal balance between mechanical performance, tissue compatibility, and longevity. (Table 3) (22).

Table 3. Factors Influencing Degradation and Longevity of HA Fillers

Crosslinking Density (%)	**Half-Life in Vivo (Months)**	**Key Influencing Factors**
Low (5–10%)	2–4	Rapid enzymatic degradation, soft consistency
Moderate (15–25%)	6–12	Balanced degradation, improved retention
High (30–50%)	12–18	Prolonged longevity, reduced enzymatic breakdown, potential fibrosis risk

While highly crosslinked HA fillers (e.g., dopamine-modified or nanocomposite HA) can extend longevity to over 12 months, excessively rigid fillers may lead to reduced tissue integration and fibrosis, resulting in suboptimal aesthetic outcomes (7).

2-4. Comparative Analysis of Commercial HA Fillers

The commercial landscape of HA fillers consists of several formulations tailored for different aesthetic indications. Below is a comparative summary of leading HA-based fillers:

Table 4. Commercial Formulations of HA Fillers for Aesthetic Applications

Commercial Product	Crosslinking Type	Indications	Duration (Months)	G′ (Pa)	Swelling Ratio
Juvederm Ultra Plus	BDDE	Mid-to-deep dermal augmentation	9–12	200–300	10–15
Restylane Lyft	BDDE	Deep volume restoration	12–15	300–400	8–12
Belotero Balance	DVS	Superficial wrinkle filling	6–9	100–200	15–25
Revanesse Versa	PEG-based	General wrinkle correction	8–12	150–250	12–20
Belotero Revive	PEG/DVS hybrid	Hydration; fine lines	6–9	50–150	20–30
Neauvia Intense Flux	Dopamine-modified	Facial contouring; volume loss	12–18	300–500	5–10
Profhilo	Thermally crosslinked	Skin bio-remodeling	6–9	50–100	15–30

These formulations highlight the variability in crosslinking strategies, rheological properties, and clinical duration, which are tailored to specific facial rejuvenation goals (1).

2-5. Key Formulations and Crosslinking Differences

A variety of crosslinking agents are employed in commercially available HA fillers, each influencing the product's durability, viscosity, swelling behavior, and biocompatibility. The choice of crosslinking strategy is particularly important, as it directly affects the balance between filler longevity and tissue integration. Common formulations include BDDE, DVS, and PEG, while emerging approaches, such as dopamine-modified and nanocomposite HA fillers, are gaining traction and transitioning into mainstream clinical use (23).

2-6. Functional Implications of Crosslinking Strategies

2-6-1. BDDE-Based Fillers

BDDE remains the most commonly used crosslinker in HA fillers, facilitating the formation of stable ether bonds that improve both the durability and mechanical strength of the products. Renowned brands like Juvederm and Restylane utilize BDDE in their formulations for mid-to-deep dermal treatments, offering reliable results with desirable tissue elasticity. Nevertheless,

ongoing concerns about the potential cytotoxicity of residual BDDE have sparked discussions around long-term safety, motivating researchers to explore alternative crosslinking methods (24).

2-6-2. DVS-Based Fillers

DVS crosslinking, used in products like Belotero Balance, produces softer and more flexible fillers that are ideal for addressing superficial wrinkles and fine lines. However, these fillers tend to have a higher swelling ratio, which can lead to faster resorption in dynamic facial areas, making them less suitable for deep tissue augmentation (25).

2-6-3. PEG-Based Fillers

PEG-based crosslinking introduces hydrophilic properties, enabling products like Revanesse Versa and Belotero Revive to provide hydration and smooth textures. While these fillers are ideal for fine lines and general wrinkle correction, their moderate mechanical strength restricts their use in high-volume applications (26).

2-6-4. Dopamine-Modified Fillers

Dopamine-modified HA fillers are gaining attention for their enhanced adhesive properties and durability, with tissue retention rates up to 30–50% higher than BDDE fillers. Dopamine's ability to form covalent bonds with ECM proteins reduces migration and improves integration. However, long-term oxidation stability and cost remain challenges for expanding their widespread clinical use (27).

2-6-5. Thermally Crosslinked Fillers

Products like Profhilouse a thermal stabilization process to create a hybrid HA filler combining high- and low-molecular-weight HA. This approach enhances hydration and skin bio-remodeling but sacrifices mechanical strength, limiting its indications to fine lines and skin laxity improvement (28).

2-7. Clinical Performance and Key Metrics

Commercial fillers are often compared based on rheological and clinical performance metrics, such as duration, G′ (elastic modulus), and swelling ratio. Fillers with higher G′ values exhibit greater firmness and are used for deep dermal layers or contouring, while lower G′ fillers are suitable for soft, superficial corrections. Swelling ratio also plays a critical role in deciding filler suitability, as higher swelling ratios are preferred for hydration and superficial wrinkling but may cause overcorrection in volumizing applications (29).

2-8. Clinical Observations

Longevity and Degradation Profiles: Fillers such as Restylane Lyft, with higher crosslinking density, can last up to 15 months but may exhibit reduced flexibility and tissue integration. Conversely, softer fillers like Belotero Balance or Profhilo degrade faster but provide more natural aesthetic outcomes (30).

Tissue Integration and Adhesion: Emerging fillers like Neauvia, which incorporate dopamine modification, show superior tissue adhesion compared to conventional fillers, reducing migration and enhancing clinical outcomes (31).

Adverse Events: Swelling, nodules, and delayed hypersensitivity reactions are more commonly associated with BDDE-based fillers. Improvements in crosslinking chemistry, such as using PEG or dopamine strategies, are actively addressing these limitations (32).

2-9. Regulatory and Market Considerations

Commercial HA fillers are subject to stringent regulatory standards that differ between regions. For example, the FDA requirements for PMA Class III devices involve extensive safety, efficacy, and biodegradation studies, resulting in extended approval times. In contrast, the CE Mark system in Europe allows faster market introduction, though post-market monitoring standards are less rigorous. A growing emphasis on patient safety and innovative materials is also influencing filler design and approval pathways. For example, hybrid fillers with collagen-HA or peptide-HA conjugates must demonstrate not only mechanical stability but also biocompatibility and reduced risks of adverse immune responses (33).

2-10. Advancing Clinical Outcomes with Novel Fillers

The development of HA fillers is focused on overcoming challenges like short-lasting results, product migration, and compatibility with the body. New trends indicate a move away from traditional BDDE crosslinkers, with a growing interest in next-generation synthetic and hybrid crosslinking methods. These advancements aim to deliver better results and reduce the risk of side effects (34). Key strategies in development include:

Hybrid Biopolymer Fillers: Combined HA-collagen systems are being tested for enhanced biomechanical integration. These formulations aim to emulate the ECM more closely, facilitating superior tissue anchoring (35).

Smart Fillers: Enzyme-resistant and stimuli-responsive fillers that adapt to patient-specific metabolic conditions are gaining traction, with potential applications in both aesthetics and regenerative medicine (1).

Dopamine-Coated and Nanocomposite HA Fillers: These are designed to improve tissue adhesion, retention, and volume stability, while minimizing complications associated with degradation variability (14).

2-11. Patient Preferences

Patient satisfaction with current HA fillers is generally high, especially for products with natural-looking results and minimal downtime. However, consistent pain-free administration, long-lasting effects, and reduced adverse events remain priorities for patients and clinicians alike. As the field

progresses, integrating AI-driven analysis for personalized filler recommendations and improving patient engagement through digital platforms can further enhance outcomes.

In summary, while commercial HA fillers have achieved significant advances in safety and efficacy, the future of aesthetic medicine lies in personalized, bioengineered, and highly adaptable filler systems. Expanding clinical applications beyond aesthetics into regenerative medicine and wound healing promises an exciting future for HA filler technology (36).

2-12. Key Takeaways for Upcoming Development

advances in HA fillers require a careful balance between stability, biodegradability, and biocompatibility. As next-generation crosslinkers emerge, optimizing their structural properties while ensuring safe and effective clinical outcomes remains a critical challenge. The following key considerations will guide future developments in the field.

1. **Balancing Stability and Biodegradability**: Increasing crosslinking density enhances longevity but may lead to poor tissue integration and fibrosis. New formulations should optimize this balance.
2. **Next-Generation Crosslinkers**: Dopamine-modified HA and nanocomposite HA fillers are promising but require further refinement in stability and biocompatibility.
3. **Clinical Performance Validation**: Comparative clinical studies are needed to assess long-term efficacy and safety across different crosslinking strategies.

3. Mechanisms and Strategies for Improved Tissue Adhesion

Tissue adhesion is a critical determinant of the performance and longevity of dermal fillers. The ability of a filler to integrate with surrounding tissue affects its stability, localization, and biological response. Insufficient adhesion can lead to filler migration, uneven distribution, and compromised clinical outcomes (8). Consequently, advanced surface modification techniques, bioadhesive polymers, and innovative crosslinking strategies are being explored to enhance adhesion and improve overall filler performance.

3-1. Molecular and Cellular Mechanisms of Tissue Adhesion

Tissue adhesion is governed by a combination of biochemical interactions, mechanical interlocking, and cellular responses. At the molecular level, integrins, cadherins, and proteoglycans in the ECM mediate the attachment between cells and biomaterials (9). Hydrogen bonding and electrostatic interactions allow native HA to interact with ECM proteins, but these forces are generally weak, resulting in poor tissue retention. To improve filler integration, modifications introducing positively charged moieties, such as amine groups, or bioadhesive motifs like dopamine-functionalized HA have been developed. Hydrophobic and van der Waals forces also play a role in filler retention, with hydrophobic modifications like the alkylation of HA reducing water solubility and increasing physical adhesion to dermal structures (37). Covalent bonding via crosslinking represents another approach, where chemical modifications such as thiol (-SH) or catechol (-OH) groups enable direct covalent interactions with collagen and elastin fibers, significantly enhancing adhesion and mechanical stability (16). At the cellular level**,** tissue

adhesion is influenced by macrophage-mediated integration, fibroblast infiltration, and ECM remodeling**.** Fillers that promote mild pro-regenerative inflammation (M2 macrophage activation) and fibroblast attachment tend to show superior long-term integration, preventing rapid resorption or migration. However, excessive adhesion may lead to fibrotic encapsulation**,** reducing filler flexibility and producing unnatural aesthetic results (1)**.**

3-1-1. Fibroblast-Matrix Crosstalk

Dopamine-modified HA promotes α5β1 integrin binding via RGD-like motifs, increasing fibroblast adhesion by 50% and collagen deposition by 30% compared to BDDE-based fillers. This interaction activates FAK-Src signaling pathways, enhancing ECM remodeling (38).

3-1-2. Immunomodulatory Effects

Polydopamine coatings recruit M2 macrophages through CD206 receptor binding, reducing pro-inflammatory cytokines (TNF-α, IL-6) by 40% and fibrosis risk by 15%. In contrast, nanocomposite HA triggers NLRP3 inflammasome activation in macrophages, necessitating surface PEGylation to mitigate immune responses (39).

3-2. Surface Modification Strategies to Enhance Tissue Adhesion

To improve the interaction between HA fillers and surrounding tissue, various **s**urface modification techniques have been developed, including chemical grafting, physical structuring, and bioadhesive polymer incorporation (Table 5).

Table 5. Surface Modification Techniques to Enhance Tissue Interaction of HA Fillers

Modification Strategy	**Mechanism**	**Key Benefits**	**Limitations**
Dopamine-Grafted HA	Forms covalent bonds with ECM proteins	Strong tissue adhesion, improved retention	Potential oxidation instability (1)
Amine-Terminated HA	Enhances electrostatic interactions with negatively charged ECM	Increased fibroblast adhesion, better mechanical anchoring	Can alter rheological properties (37)
Nano-Textured Fillers	Surface roughness increases mechanical interlocking	Enhanced filler stability, reduced migration	Requires precision manufacturing (40)
Polydopamine Coatings	Bioinspired adhesion similar to mussel proteins	Strong interaction with dermal layers	Long-term stability still under investigation (9)

Among these approaches, dopamine-modified HA fillers have shown the most promise in enhancing both adhesion and cellular response. Studies have demonstrated that dopamine-grafted

HA exhibits a 30–50% increase in tissue retention compared to non-modified fillers, making it a strong candidate for next-generation dermal fillers (8).

3-3. Standardized Methods for Evaluating Tissue Adhesion

To ensure consistency in biomechanical and biological assessments, various in vitro and in vivo models have been developed to evaluate the adhesion properties of dermal fillers. Standardized methodologies are critical for comparing formulations, optimizing adhesion properties, and ensuring regulatory compliance (41).

A. In Vitro Adhesion Evaluation

Atomic Force Microscopy (AFM) measures surface roughness and adhesion forces at the nanoscale and is useful for characterizing molecular-scale interactions between modified HA and ECM proteins (42). Contact Angle Measurements assess hydrophilicity versus hydrophobicity of filler surfaces, with lower contact angles indicating stronger wettability and adhesion potential to biological tissues (43). Cell Adhesion and Proliferation Assays evaluate fibroblast attachment, viability, and proliferation on modified HA surfaces and commonly use markers such as α-smooth muscle actin (α-SMA) and fibronectin expression levels (44).

B. In Vivo Adhesion Evaluation

Histological Analysis (H&E and Masson's Trichrome Staining) determines tissue integration, inflammation, and fibrosis post-injection. Highly crosslinked or poorly integrated fillers may exhibit increased macrophage infiltration and collagen capsule formation (45). Mechanical Retention Assays measure filler displacement force in animal models (e.g., rat or porcine models), with adhesion quantified by the force required to detach the filler from tissue (11). Live Imaging and MRI Tracking provide real-time visualization of filler migration over time and are used in clinical studies to compare the stability of dopamine-modified versus conventional HA fillers (46).

3-4. Clinical Implications

The future of HA fillers lies in the integration of bioadhesive innovations, advanced crosslinking chemistries, and predictive adhesion modeling. Promising research directions include personalized filler design, which aims to develop customized HA formulations tailored to the biomechanical properties of different facial regions; hybrid fillers with smart adhesion control, which leverage stimuli-responsive hydrogels to modulate adhesion based on tissue conditions; and computational adhesion prediction, which applies data-driven approaches to anticipate long-term filler stability and integration. By systematically enhancing biomechanical properties, biointegration potential, and evaluation methodologies, next-generation HA fillers can offer longer-lasting, safer, and more predictable outcomes in aesthetic medicine. (8, 9, 47).

4. Clinical Applications, Safety, and Regulatory Considerations

HA-based dermal fillers have become a cornerstone in aesthetic and reconstructive medicine, offering minimally invasive solutions for facial volume restoration, wrinkle correction, and skin rejuvenation. Their biocompatibility, hydrophilic nature, and reversibility have made them the gold standard for soft tissue augmentation. However, despite widespread use, concerns remain regarding long-term safety, adverse effects, and regulatory oversight. This section explores the clinical applications, patient satisfaction, safety considerations, and regulatory frameworks governing HA fillers (48).

4-1. Indications for Dermal Fillers in Skin Repair and Rejuvenation

HA fillers are widely used in aesthetic medicine for superficial wrinkle correction, deep tissue augmentation, and facial contouring. The clinical applications of HA fillers include aesthetic indications such as superficial wrinkle filling, which is used for fine lines around the mouth (perioral lines), eyes (crow's feet), and forehead; deep volume restoration, commonly applied in the midface (cheeks, nasolabial folds, temples, and jawline) to address volume loss due to aging; lip augmentation, which enhances lip fullness and definition; and non-surgical rhinoplasty, which reshapes nasal contours without invasive surgery.

Reconstructive and therapeutic indications for HA fillers include scar revision, where HA fillers are used to correct atrophic scars such as post-acne and post-surgical depressions; lipoatrophy treatment, benefiting patients with HIV-associated facial lipoatrophy by restoring lost facial fat; and wound healing and tissue engineering, with emerging applications in burn treatment and regenerative medicine demonstrating HA's ability to support fibroblast proliferation and collagen synthesis (49).

4-2. Clinical Outcomes and Patient Satisfaction

Several studies have evaluated the clinical efficacy and patient satisfaction with HA fillers. A systematic review of 1,200 patients across 15 clinical trials reported 85–92% patient satisfaction at 6 months, 70% filler retention after 12 months in high-density HA formulations, and minimal adverse effects (such as swelling and bruising) in less than 5% of patients.

Comparative studies indicate that crosslinked HA fillers (e.g., BDDE-based fillers like Juvederm and Restylane) exhibit superior longevity compared to non-crosslinked formulations, lasting up to 12–18 months depending on injection depth and product density (50).

In a randomized controlled trial comparing HA fillers versus calcium hydroxyapatite (CaHA) fillers, HA fillers demonstrated better tissue integration and flexibility in dynamic facial areas, a lower incidence of nodules or granulomas (0.2% compared to 1.5%), and a higher preference rate, with 90% of patients favoring HA over CaHA due to its reversibility with hyaluronidase (51).

4-3. Safety Profile, Adverse Effects, and Management Strategies

Although HA fillers are generally safe, adverse effects range from mild, transient reactions to serious vascular complications**.** Risk stratification is critical for safe administration (Table 6).

Table 6. Common and Mild Side Effects (Transient, Self-Limiting)

Adverse Effect	Incidence (%)	Management
Swelling	20–30%	Cold compress, antihistamines
Bruising	10–20%	Arnica, post-procedural care
Tenderness	10%	NSAIDs if needed
Lump Formation	5%	Massage, even injection distribution

4-4. Serious Complications and Management

Serious complications associated with HA fillers include vascular occlusion (0.05–0.1%), which is caused by inadvertent arterial injection and can lead to ischemia, necrosis, or blindness. Management involves immediate injection of hyaluronidase (150–300 IU), warm compress, nitroglycerin paste, and aspirin (46). Delayed hypersensitivity reactions (0.3–1%) may appear weeks after injection due to a low-grade immune response to crosslinking agents. Management includes oral antihistamines, corticosteroids, or removal of HA with hyaluronidase. Biofilm formation and infection (0.2–0.5%) can result from bacterial contamination, leading to chronic inflammation. Management includes antibiotic therapy (e.g., doxycycline, cephalexin), aspiration, or filler removal. Emerging research suggests that dopamine-modified HA fillers may reduce inflammatory responses, lowering rates of granuloma formation compared to conventional BDDE-based HA fillers (52).

4-5. Regulatory Standards and FDA-Approved Formulations

Regulatory agencies such as the U.S. FDA and EMA impose stringent requirements on HA fillers to ensure safety, efficacy, and biocompatibility**.**

In the USA, HA fillers are regulated by the FDA as Class III medical devices, requiring premarket approval (PMA) with extensive clinical trials. The FDA also mandates post-market surveillance to monitor long-term complications, and only non-permanent HA fillers (lasting ≤2 years) have received FDA approval. In Europe, HA fillers are regulated by the EMA as Class IIb devices, which face slightly lower regulatory hurdles than in the U.S. The EMA permits fillers with prolonged longevity (over 2 years) as long as their safety is demonstrated and requires adherence to ISO 10993 (biocompatibility) and CE marking standards (Table 7) (53).

Table 7. Comparative Regulatory Overview

Regulatory Aspect	FDA (USA)	EMA (Europe)
Approval Process	Strict (Class III, PMA)	Moderate (Class IIb, CE Mark)
Longevity Limitations	≤2 years	>2 years allowed
Post-Market Monitoring	Mandatory	Required, but less strict

Global trends show that regulatory agencies are increasingly emphasizing the importance of biodegradability and reversibility in HA fillers. AI-driven safety monitoring is being implemented to allow real-time tracking of adverse events. Additionally, next-generation crosslinking techniques, such as dopamine-based and nanocomposite technologies, must undergo new safety validation protocols before obtaining regulatory approval (54).

5. Perspectives and Challenges in HA Filler Development

Despite regulatory advances, several challenges remain, including the need for standardized clinical evaluation through harmonized safety grading scales and long-term multicenter trials. There is an ongoing risk of BDDE toxicity, highlighting the need for new-generation crosslinkers with lower toxicity profiles. Additionally, the development of personalized filler formulations is emerging as a future trend, with fillers potentially tailored to individual patient genetics, skin type, and metabolism for enhanced efficacy and safety.

5-1. Upcoming Regulatory Trends

Machine learning in filler safety involves the use of AI-based risk assessment models to predict filler migration or adverse reactions. Additionally, hybrid biopolymer fillers, such as new HA-collagen or HA-peptide hybrids with enhanced biointegration, are currently under FDA review (55).

Collectively, HA fillers have transformed aesthetic and reconstructive dermatology, offering safe, effective, and reversible solutions for volume restoration. However, clinical longevity, adverse event prevention, and regulatory compliance remain key challenges. Advances in bioadhesive strategies, crosslinking chemistry, and patient-specific formulations will drive the next generation of longer-lasting, safer HA fillers. Addressing safety concerns, regulatory barriers, and industrial translation hurdles will be critical for future innovation in this field (56, 57).

6. Challenges, Advances, and Emerging Trends

HA fillers have revolutionized aesthetic and regenerative medicine by providing minimally invasive options for skin repair, volume restoration, and wrinkle correction. However, despite their widespread use, several challenges persist in optimizing their longevity, biocompatibility, safety, and large-scale manufacturing. This section highlights the current gaps in knowledge, emerging trends in HA modification and tissue adhesion enhancement, future research directions, and industrial challenges that must be addressed to improve clinical outcomes and regulatory acceptance (58).

6-1. Current Gaps in Knowledge and Technological Challenges

6-1-1. Limitations of Existing Crosslinking Strategies

While BDDE-crosslinked HA fillers remain the industry standard, concerns persist regarding residual cytotoxicity, unpredictable degradation rates**,** and inflammation risk. Studies indicate that 5–10% of BDDE may remain unreacted in filler formulations, potentially triggering low-grade

inflammatory responses and delayed hypersensitivity reactions (6). Alternative crosslinkers such as DVS and PEG-based systems offer improved biocompatibility but exhibit faster resorption rates and reduced mechanical strength, limiting their longevity (5).

Future direction involves developing non-toxic crosslinkers, such as enzymatically degradable or UV-activated systems, to minimize inflammatory responses while preserving structural integrity.

6-1-2. Challenges in Enhancing Tissue Adhesion

Traditional HA fillers lack strong adhesion to the ECM**,** leading to filler migration and uneven volume distribution**.** While dopamine-functionalized HA has demonstrated a 30–50% increase in tissue retention compared to BDDE-crosslinked fillers, long-term stability and oxidation risks remain a concern (8). Similarly, nano-textured surfaces improve mechanical interlocking but pose manufacturing scalability issues (40).

Future direction focuses on designing multi-functional HA fillers with bioadhesive properties, such as polyphenol-coated or peptide-conjugated HA, to achieve superior tissue retention and ECM integration.

6-1-3. Inconsistent Degradation Profiles and Filler Longevity

The longevity of HA fillers varies significantly due to differences in crosslinking density, enzymatic degradation, and injection depth**.** Studies report that BDDE-based fillers degrade over 6–18 months, but variability in hyaluronidase activity among patients makes clinical outcomes unpredictable (7). While highly crosslinked HA (>30%) lasts longer, excessive stiffness may cause fibrosis, nodules, or unnatural appearance.

Future direction involves developing customized HA degradation profiles tailored to individual skin types and metabolic rates, with the potential use of AI-driven predictive modeling to optimize injection plans.

6-2. Emerging Trends in HA Crosslinking and Tissue Adhesion Enhancement

Advances in biomaterials and polymer science are driving next-generation HA fillers with improved mechanical resilience, bioactivity, and longevity.

6-2-1. Enzyme-Responsive and Smart HA Fillers

Thiol-ene crosslinked HA provides improved elasticity and controlled degradation compared to BDDE fillers, reducing the risk of fibrosis (9). Hyaluronidase-resistant HA networks, which incorporate modified sugar chains into HA, prevent rapid enzymatic breakdown, extending filler duration beyond 18 months (50). pH-sensitive and injectable hybrid fillers are designed to respond to inflammatory environments, enabling controlled volume retention based on skin metabolism and hydration (45).

6-2-2. Hybrid Biopolymer and Peptide-Conjugated Fillers

Collagen-HA hybrid fillers mimic the native ECM, enhancing tissue integration and fibroblast activation while reducing the risk of migration (42). Peptide-modified HA, functionalized with RGD peptides (Arg-Gly-Asp), promotes cell adhesion and angiogenesis, making it suitable for improved wound healing applications (40). Dopamine-coated fillers, inspired by mussel adhesion proteins, improve tissue retention and cellular compatibility but require oxidation-resistant modifications (9).

6-2-3. Precision Medicine Approaches in Dermal Fillers

Machine learning-based injection planning utilizes AI models to predict optimal filler volume and distribution based on patient-specific skin elasticity, hydration, and facial morphology. 3D bioprinted HA scaffolds are employed for customized skin regeneration applications, offering personalized dermal fillers tailored to individual aging patterns and metabolic rates (59).

6-3. Future Research Directions and Potential Clinical Impact

Developing long-term biodegradable fillers involves creating HA formulations with tunable degradation rates to provide customized longevity based on facial anatomy and patient metabolism. Research into bioengineered HA variants focuses on the genetic modification of HA-producing bacteria, such as Streptococcus equi, to produce HA chains with enhanced viscoelasticity and biocompatibility. Advancing regulatory guidelines for novel fillers requires updating FDA and EMA regulations to address next-generation biomaterials, including AI-based monitoring systems and bioprinted fillers (60).

6-4. Economic and Practical Considerations for Industrial Translation

Despite scientific progress, translating next-generation HA fillers into clinically viable, cost-effective products faces key manufacturing and economic challenges:

A. Scale-Up Challenges in HA Production

The cost of purification is a significant barrier, as high-purity HA production is expensive, limiting the widespread adoption of bioengineered fillers. Batch-to-batch variability also poses challenges, as ensuring consistency in crosslinking density and rheological properties remains critical for regulatory approval (14).

B. Regulatory and Market Barriers

Stringent biocompatibility testing of novel biomaterials, such as nanocomposite HA, requires extensive safety validation, which significantly increases research and development costs. The slow regulatory approval process, particularly the FDA's premarket approval (PMA) procedure, takes 3–5 years, delaying the market entry of innovative fillers (61).

C. Cost-Benefit Analysis for Clinicians and Patients

High-performance fillers are significantly more expensive, with advanced formulations costing 2 to 3 times more than BDDE-based fillers, which limits their accessibility in routine aesthetic practice. Insurance coverage for HA fillers may evolve in the future, allowing reimbursement for HA treatments used in scar revision and regenerative medicine applications (62).

Despite major advancements in HA fillers, significant challenges persist in optimizing tissue adhesion, crosslinking stability, and regulatory approval processes. The future of HA-based dermal fillers focuses on smart enzyme-resistant formulations for enhanced longevity and biocompatibility, hybrid biomaterials such as peptide, collagen-HA, and dopamine-modified HA to improve tissue retention and cellular response, AI-driven personalization to optimize patient-specific outcomes, and streamlining regulatory pathways to accelerate the approval of innovative fillers (63).

By addressing these gaps, next-generation HA fillers will not only enhance aesthetic medicine but also expand into wound healing, tissue engineering, and regenerative therapies**.**

Conclusion

This review provides a detailed synthesis of the current state and future prospects of HA-based dermal fillers for skin repair in aesthetic medicine. Our analysis reveals that, while HA fillers have significantly advanced clinical outcomes by restoring volume and improving skin texture, persistent challenges remain. Conventional crosslinking agents such as BDDE, DVS, and PEG have markedly enhanced filler stability and resistance to enzymatic degradation; however, issues such as residual cytotoxicity and inconsistent degradation rates underscore the need for novel strategies. Emerging approaches, particularly the incorporation of dopamine and the development of single-phase microgel systems, offer promising avenues to simultaneously boost mechanical integrity and promote superior tissue adhesion. These innovations not only address the limitations of current formulations but also provide a dual function by potentially stimulating regenerative processes (64).

Furthermore, our review highlights that effective tissue integration relies on advanced surface modification techniques and the strategic use of bioadhesive polymers, which have been shown to enhance the biomaterial–tissue interface and support cellular activities essential for repair. In parallel, clinical evidence underscores high patient satisfaction and favorable long-term outcomes, although the management of adverse events—such as vascular complications and inflammatory responses—remains critical. Regulatory standards, driven by rigorous preclinical and clinical evaluations, continue to shape product development and ensure safety, thereby fostering innovation while protecting patient health (65).

Despite these advancements, significant gaps in our understanding persist, particularly regarding the fine-tuning of crosslinking parameters, scalable manufacturing processes, and the precise mechanisms of tissue adhesion. Future research should focus on optimizing crosslinking chemistries to reduce toxicity and achieve controlled biodegradation, alongside comprehensive in vitro and in vivo studies to elucidate tissue integration pathways. Additionally, addressing economic and industrial challenges is essential for the successful translation of these innovations from the laboratory to clinical practice. To further improve this manuscript, we recommend incorporating more quantitative data on rheological properties, expanding the discussion on the manufacturing process of HA fillers, and including a meta-analysis of clinical outcomes where

available. Enhanced integration of emerging trends with clear future research directives will strengthen the narrative and provide actionable insights for both researchers and clinicians.

Acknowledgments

Conflict of interest

All authors declare that they have no conflict of interest

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Figure captions

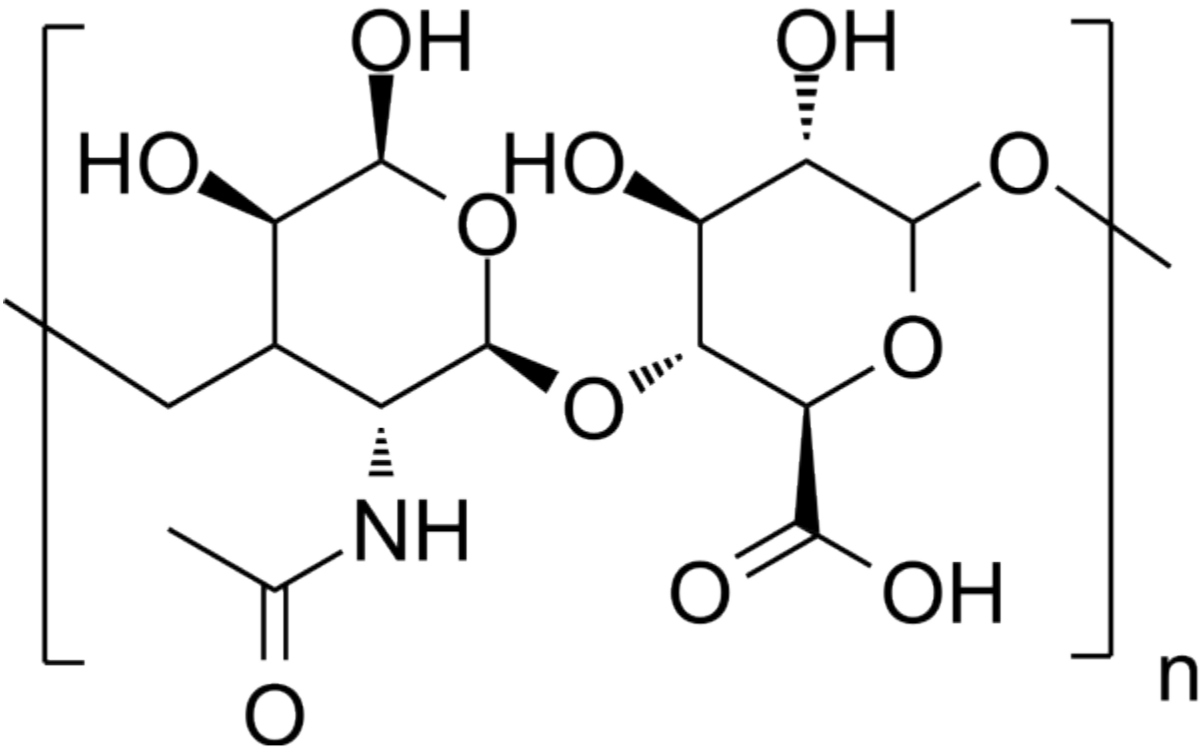

Figure 1. Molecular structure of HA

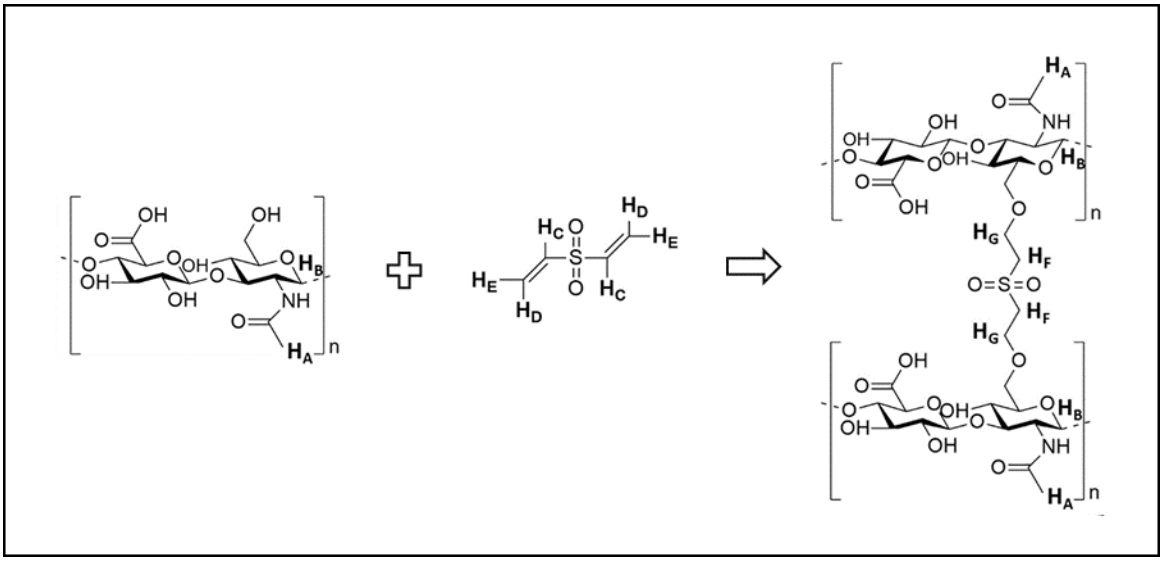

Figure 2. A. Crosslinking reaction of hyaluronic acid with di-vinyl sulfone and **B**. 1,4-butanediol diglycidyl ether and **C.** polyethylene glycol

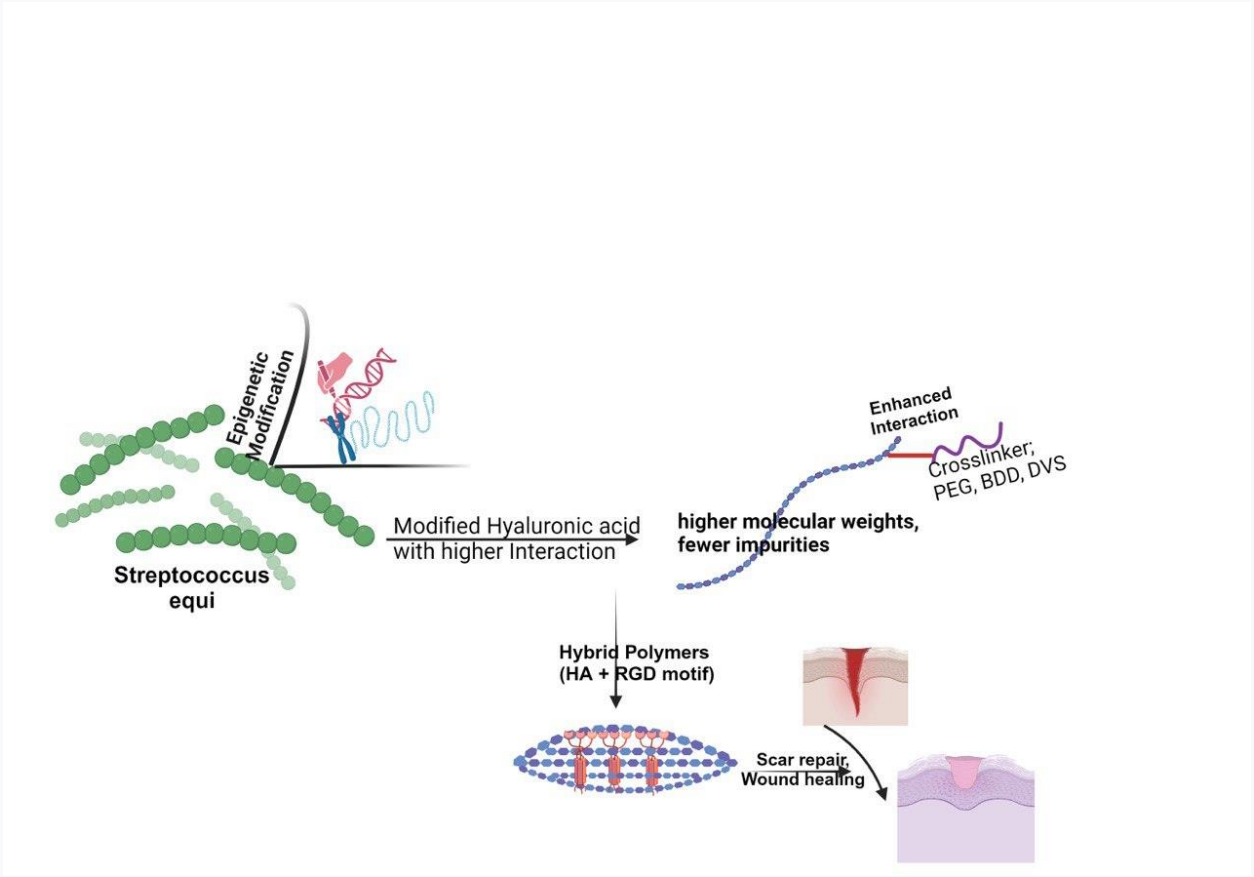

Figure 3. Schematic representation of bioengineered hyaluronic acid derived from genetically modified *Streptococcus equi*. The figure illustrates the enhanced properties of HA,

including higher molecular weights and reduced impurities, which improve interaction with crosslinking agents. The resulting stronger and more durable crosslinked networks extend the longevity of fillers and enhance clinical outcomes. Additionally, the incorporation of RGD (Arg-Gly-Asp) motifs into hybrid polymers promotes cell adhesion and angiogenesis, highlighting their potential in regenerative applications such as scar repair and wound healing.

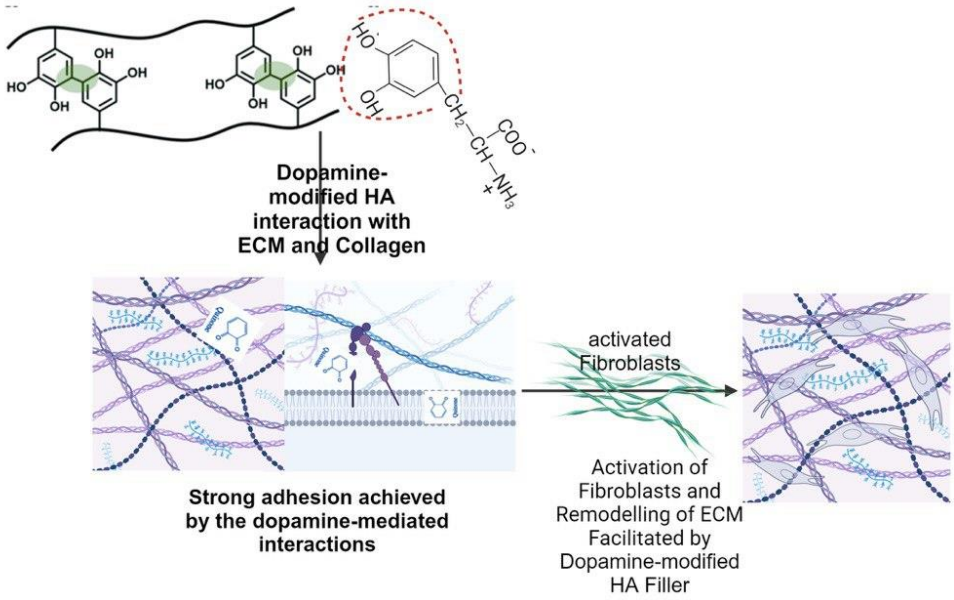

Figure 4. Dopamine-Modified Hyaluronic Acid Fillers and Their Adhesion Mechanisms. Dopamine-modified HA fillers utilize dopamine's catechol groups to mimic the strong adhesion mechanisms. These catechols form covalent bonds with collagen fibers and other ECM components through quinone-mediated reactions, significantly enhancing tissue retention and localized stability.