Journal of Cosmetic Dermatology

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REVIEW ARTICLE OPEN ACCESS

Skin Boosters: 2026 Updated

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Received: 9 February 2026 | **Revised:** 23 March 2026 | **Accepted:** 6 April 2026

Keywords: hyaluronic acid | intradermal injections | platelet-rich plasma | skin aging | skin boosters | skin rejuvenation

ABSTRACT

Skin boosters are increasingly used to improve dermal quality through injectable and device-assisted approaches; however, definitions and clinical evidence remain heterogeneous.

Aims: To provide an updated overview and propose a practical classification of skin boosters, including mechanisms, delivery methods, clinical outcomes, and limitations.

Patients/Methods: A narrative review of recent literature on injectable and device-assisted skin boosters, including hyaluronic acid, biostimulatory polymers, calcium hydroxyapatite, polynucleotides, platelet-rich plasma, exosomes, and emerging agents.

Results: Skin boosters improve hydration, elasticity, texture, fine lines, erythema, and dyschromia with generally favorable safety profiles. Mechanisms include hydration, neocollagenesis, elastogenesis, angiogenesis, and anti-inflammatory effects. However, evidence remains limited by heterogeneity and lack of standardized protocols.

Conclusions: Skin boosters represent a promising modality for skin rejuvenation, but further standardized clinical studies are required.

1 | Introduction

The term “skin booster” has gained significant prominence in the field of aesthetic dermatology, evolving from its initial use in hyaluronic acid (HA) fillers, which were designed primarily for volume augmentation. These treatments have since broadened their scope, now focusing on enhancing skin quality by improving texture, elasticity, hydration, and addressing signs of aging. Skin boosters deliver key active ingredients directly into the dermal layer, targeting the extracellular matrix (ECM) to regenerate and rejuvenate the skin [1, 2].

Skin aging involves various intrinsic and extrinsic factors, such as the breakdown of collagen and elastin, the depletion of glycosaminoglycans (GAGs), and the increase in oxidative stress. These factors weaken the skin's structure and function, resulting in visible signs of aging like wrinkles, dehydration, and loss of elasticity. Skin boosters intervene in these processes by fortifying the dermal layer, improving hydration, enhancing elasticity, and promoting collagen production [2, 3]. The efficacy of skin boosters lies in their ability to restore the skin's natural regenerative processes, improving its overall condition over time. Key ingredients in skin boosters contribute to skin rejuvenation by promoting moisture retention, stimulating collagen synthesis, and providing antioxidant effects [1, 4–12].

As demand for non-invasive skin rejuvenation treatments continues to rise, skin boosters have become a game-changer in aesthetic dermatology. These treatments provide significant improvements in skin quality with minimal recovery time. Unlike traditional dermal fillers, which focus on restoring facial volume, skin boosters stimulate natural skin regeneration, promoting collagen production and enhancing dermal health [2]. Skin boosters offer a versatile solution for addressing a range of skin

concerns, such as fine lines, dehydration, and loss of elasticity, making them ideal for individuals seeking rejuvenation without resorting to more invasive procedures. The wide variety of skin boosters available ensures that these treatments can be tailored to meet the specific needs of each patient [4]. As the field of aesthetic dermatology continues to evolve, the role of skin boosters is expected to grow, offering a more holistic approach to skin rejuvenation and maintenance.

While the popularity of skin boosters continues to rise, there remains no universally accepted definition for the term. This review aims to provide clarity on what constitutes a skin booster, exploring the different types of ingredients involved, their mechanisms of action, and their role in modern dermatology. The effectiveness, safety, and benefits of these treatments are also examined.

An overview of the major skin booster classes, mechanisms, clinical efficacy, and limitations is summarized in Table 1.

1.1 | Editorial Restructuring Note

To improve readability, the reviewed materials are reorganized into four major categories. Within each subsection, the narrative emphasizes a consistent sequence of introduction, mechanism of action, clinical efficacy, and reported side effects/safety considerations.

2 | Classification of Skin Boosters

2.1 | Hydrating and Matrix-Support Boosters

2.1.1 | Hyaluronic Acid

Dermal fillers with varying physicochemical attributes—such as differences in particle size, lower degrees of cross-linking, and improved injection comfort—have been developed by multiple manufacturers and are extensively applied in clinical and commercial settings [13]. HA, a naturally occurring GAGs within the dermal matrix, is well recognized for its high water-binding capacity, role in maintaining skin hydration, and ability to stimulate the release of growth factors (GFs) in the skin's connective tissues [13–17].

In a randomized clinical trial conducted by Gao et al. [18], involving 129 female participants across a broad range of ages and skin types, the impact of oral HA supplementation on skin parameters was evaluated. The results demonstrated significant increases in skin hydration within 2–8 weeks in both younger and older cohorts, with subsequent improvements in skin tone observed after 4–8 weeks and enhanced epidermal thickness evident at 12 weeks of continuous HA intake. Collectively, these findings provide robust evidence supporting the efficacy of oral HA in improving skin health across diverse age groups and skin phenotypes [18].

Within the category of HA skin boosters, two main formulations are recognized: non–cross-linked and low–cross-linked HA (BYRYZN, Hugel Inc., Seoul, Korea). These products serve multiple functions, including dermal hydration, antioxidant activity, volumization of the dermal and subdermal compartments, and stimulation of dermal collagen synthesis. Owing to its capacity to bind up to 218 water molecules per HA molecule, HA prevents cutaneous dryness and contributes to volumetric enhancement in deeper skin layers. In a 2007 study, Wang et al. [19] used electron microscopy to examine skin biopsies from 11 elderly participants at 4 and 13 weeks after intradermal injection of cross-linked HA filler into the forearm. The results revealed fibroblast elongation and de novo collagen formation. HA introduced into the dermis absorbs water from the ECM, increasing its volume by approximately 500–1000 times its molecular size. This volumetric expansion promotes fibroblast elongation, which subsequently triggers the expression of connective tissue growth factor, transforming growth factor (TGF)-β1, and TGF-β2—critical mediators of collagen neogenesis—while also upregulating genes for tissue inhibitors of metalloproteinases such as TIMP-1, TIMP-2, and TIMP-3, thereby reducing collagen degradation [19].

As skin boosters, non–cross-linked HA fillers demonstrate lower volumizing capacity and shorter longevity than cross-linked formulations. Nevertheless, their superior diffusion into surrounding tissues minimizes the risk of surface irregularities following injection, making them particularly suitable for hydrating delicate and xerotic regions, such as the periorbital area. In contrast, cross-linked HA—owing to its greater volumizing potential and extended persistence—is better suited for use in anatomical sites other than the periorbital region.

HA filler products categorized as skin boosters are expected to strengthen their market position through ongoing technological advancements. However, certain inherent limitations remain. First, the duration of effect, while variably reported in the literature, generally averages approximately 6 months after three treatment sessions. Second, injection-related discomfort continues to be a notable drawback. Third, precise deposition of HA fillers into the intended anatomical site and skin layer remains technically challenging, with repeated concerns raised regarding the accuracy of intradermal delivery. Nonetheless, as more refined and accurate methods for dermal HA administration are developed, further improvements in clinical outcomes are anticipated [20].

The investigation by Chen et al. [21] evaluated the efficacy of a novel hyaluronan complex in mitigating intrinsic skin aging and elucidated its underlying mechanisms. Through immunohistochemical analysis and in vitro assays, the study demonstrated that the complex upregulated type I collagen expression while suppressing matrix metalloproteinase-1 (MMP-1) production in human fibroblasts. Furthermore, in skin equivalent models, the complex enhanced the expression of proteins associated with the dermal–epidermal junction. This proof-of-concept work indicates that the hyaluronan complex exerts anti-aging effects by downregulating MMP-1, promoting collagen deposition, and strengthening dermal–epidermal junction integrity, thereby offering new prospects for hyaluronan-based research [21].

Recent investigations suggest that HA combined with glycerol can provide durable improvements in hydration, elasticity, and surface texture, likely through synergistic water retention and

TABLE 1 | Overview of major skin booster classes, mechanisms, clinical efficacy signals, and reported side effects.

Material/class	Key feature	Mechanism of action	Clinical efficacy signal	Reported side effects/ limitations
Hyaluronic acid	Hydrator/viscoelastic filler	Water binding; fibroblast stretching; ECM support	Hydration, texture, fine lines; typical durability months	Bruising, edema, irregularity; limited longevity
PDLLA	Biostimulatory polymer	Fibroblast activation; neocollagenesis; remodeling	Rosacea, melasma, rejuvenation signals; medium-term durability	Nodules if technique is suboptimal; transient swelling
PLLA	Biostimulatory polymer	Collagen stimulation via controlled foreign-body response	Durable volume/ biostimulation; scar and laxity use	Delayed nodules/ granuloma concerns
PN/PDRN	Nucleotide-derived regenerative agent	A2A-related repair signaling; anti-inflammatory and regenerative effects	Pores, roughness, scars, erythema; good tolerability	Transient pain, edema, bruising
PRP	Autologous biologic	GF release; fibroblast proliferation; angiogenesis	Texture, elasticity, wrinkle and barrier improvement	Pain, erythema, edema, bruising; protocol heterogeneity
Growth factors	Biologic signaling mixture	Direct wound-healing and regenerative signaling	Adjunctive rejuvenation and pigment modulation	Variable efficacy in intact skin; formulation variability
Exosomes/secretomes	Cell-derived extracellular vesicles/soluble factors	Intercellular signaling; anti-inflammatory effects; collagen/elastin support	Post-procedure recovery, texture, photoaging signals	Standardization and source variability remain concerns
Chitosan	Polysaccharide regenerative scaffold	Stem-cell recruitment; liquid-to-gel scaffold; angiogenesis	Durability and collagen support in early studies	Limited clinical evidence
BoNT microdroplets	Neuromodulator	Sebum reduction; pore improvement; VEGF and fibroblast modulation	Pores, erythema/flushing, fine surface improvement	Transient weakness if overdosed or injected too deeply
CaHA	Biostimulatory ceramic	Scaffold effect; collagen stimulation; immediate support	Volume plus skin-quality improvement	Nodules possible; injection technique dependent
NAD+/metabolic support	Metabolic cofactor/precursor strategy	Mitochondrial support; sirtuin activation; oxidative-stress reduction	Early signals for texture and resilience	Evidence still preliminary

(Continues)

TABLE 1 | (Continued)

Material/class	Key feature	Mechanism of action	Clinical efficacy signal	Reported side effects/ limitations
GAG precursors	Matrix-supporting biochemical precursors	Barrier support; ECM modulation; MMP inhibition	Hydration and supportive anti-aging effects	Mainly topical evidence
Collagen	Structural protein/regenerative injectable	ECM reinforcement; fibroblast activation; neocollagenesis	Hydration, thickness, elasticity improvement	Source-related variability; generally favorable safety
Spicules	Transdermal micromechanical delivery system	Microinjury; enhanced penetration of actives	Periocular wrinkles, delivery enhancement	Transient irritation or discomfort
PDO	Biodegradable polymer	Controlled inflammation and TGF-beta mediated collagenesis	Fine lines, laxity, dermal thickness improvement	Transient edema, bruising
PCL	Long-acting biostimulatory polymer	3D scaffold; collagen I/ III stimulation	Fine lines and volumization with long duration	Nodules uncommon but possible
Succinic acid	Metabolic/biostimulatory small molecule	Mitochondrial and fibroblast senescence modulation	Early preclinical support for elasticity and resilience	Clinical evidence limited
hADM	Acellular ECM scaffold	Cell infiltration, angiogenesis, remodeling	Volume and skin-quality restoration	Usually transient edema/bruising
Ethosomes	Nanocarrier/delivery platform	Enhanced dermal penetration; photothermal synergy	Adjunctive delivery for pigmentation, acne, rejuvenation	Formulation and safety standardization needed
Tranexamic acid	Pigment-directed adjunct	Plasmin inhibition; reduced melanogenesis; VEGF suppression	Melasma and dyschromia improvement	Recurrence common after cessation; injection discomfort
Glutathione	Antioxidant adjunct	Tyrosinase inhibition; ROS reduction	Supportive brightening/ antioxidant role	Uncertain standalone efficacy
Ascorbic acid	Antioxidant/cofactor adjunct	Collagen synthesis; tyrosinase inhibition; ROS scavenging	Pigment and collagen support, especially in combinations	Irritation/instability at high concentrations

Abbreviations: CaHA, calcium hydroxyapatite; HA, hyaluronic acid; hADM, human acellular dermal matrix; PCL, polycaprolactone; PDLLA, poly-d,l-lactic acid; PDO, polydioxanone; PDRN, polydeoxyribonucleotide; PLLA, poly-L-lactic acid; PN, polynucleotide; PRP, platelet-rich plasma.

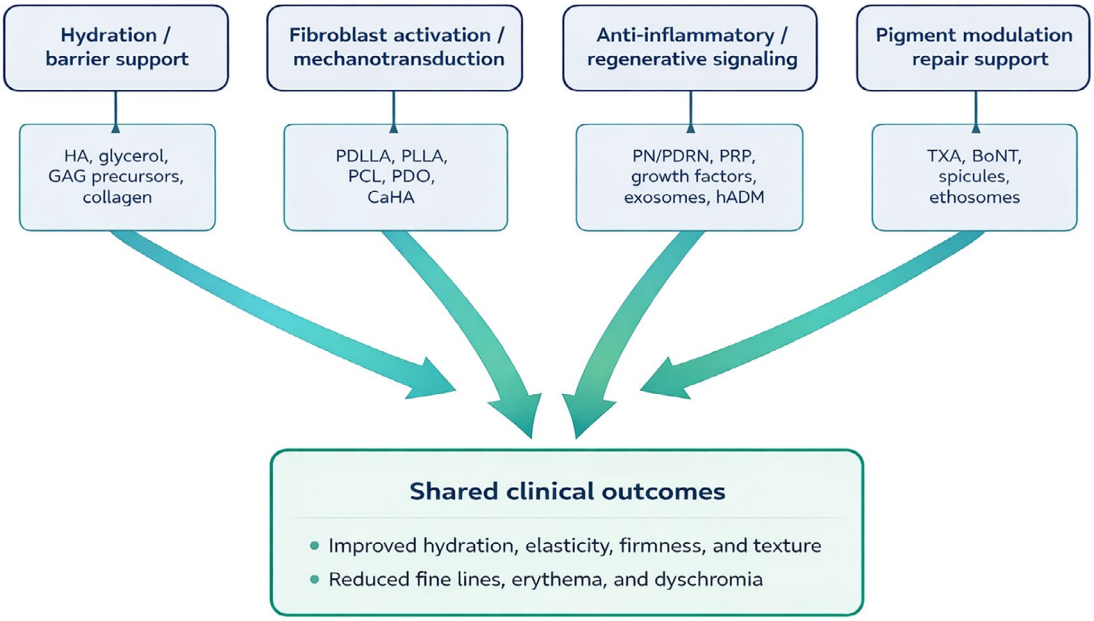

FIGURE 1 | Mechanistic framework for major skin booster classes. Skin boosters are organized according to their dominant biologic effects rather than commercial branding. Hydration/barrier support boosters (e.g., HA, glycerol, GAG precursors, and collagen) are distinguished from biostimulatory fillers (such as PDLLA, PLLA, PCL, PDO, and CaHA), regenerative signaling platforms (including PN/PDRN, PRP, growth factors, exosomes, and hADM), and pigment-modulating or repair-support strategies (e.g., tranexamic acid, intradermal botulinum toxin, spicules, and ethosomal systems). Although these categories overlap clinically, they converge on shared outcomes including improved hydration, elasticity, firmness, and texture with reduction of fine lines, erythema, and dyschromia.

extracellular matrix support. In this review, such formulations are discussed as hydrating and matrix-support boosters rather than as product-specific entities. Figure 1 summarizes the shared mechanistic framework used throughout this manuscript.

2.1.2 | Nicotinamide Adenine Dinucleotide

In aesthetic medicine, nicotinamide adenine dinucleotide (NAD^+) has attracted growing interest for its potential therapeutic applications, particularly as a functional component in skin booster formulations. This coenzyme is integral to sustaining cellular metabolic activity and mitochondrial performance—processes fundamental to preserving skin vitality and promoting rejuvenation. NAD^+ additionally facilitates the activation of sirtuins, a family of enzymes responsible for regulating cellular stress responses and DNA repair pathways, both of which are critical for maintaining skin elasticity and slowing age-related changes. Incorporating NAD^+ into skin treatments is intended to enhance the overall function of skin cells by increasing energy production and promoting the repair of DNA damage [22].

Evidence from multiple studies indicates that supplementation with NAD^+, particularly via its biochemical precursors such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), can enhance mitochondrial efficiency and mitigate oxidative stress—two processes fundamental to preserving youthful skin characteristics [23, 24]. These precursors have been shown to improve mitochondrial performance while reducing oxidative burden, both of which are essential for maintaining skin firmness and overall dermal health. Oxidative stress plays a pivotal role in skin aging by accelerating the degradation of collagen and elastin, resulting in the formation of wrinkles and the loss of skin turgor. By limiting oxidative injury, NAD^+ supplementation provides cellular protection and helps decelerate the visible manifestations of cutaneous aging [25].

Research has shown that precursors of NAD^+ can stimulate collagen synthesis, refine skin texture, and promote a luminous, healthy complexion by reestablishing the cellular energy balance within the skin [26]. Clinical evaluations of NAD^+ supplementation have reported encouraging outcomes, demonstrating improvements in skin condition and a reduction in visible signs of aging. NAD^+-enhancing agents, such as NR and NMN, have been incorporated into skin rejuvenation protocols, offering non-invasive means to enhance cellular repair mechanisms and restore skin vitality. Nonetheless, inconsistencies in treatment methodologies and variations in individual skin responses underscore the necessity for additional research to optimize NAD^+ application in dermatologic care [27]. Establishing standardized treatment parameters—including appropriate dosage and delivery systems—will be critical to achieving uniform therapeutic results across diverse patient populations.

Kang et al. recently reported an innovative strategy aimed at improving the therapeutic performance of exogenous NAD^+ in skin anti-aging applications. Their approach involved co-administration of NAD^+ with quercetin and enoxolone, which produced a synergistic suppression of CD38 expression, thereby increasing intracellular NAD^+ concentrations in human fibroblasts. This formulation enhanced mitochondrial efficiency, promoted autophagic activity, and activated sirtuins—enzymes linked to longevity regulation and cellular repair processes. As a

result, the amplified NAD^+ activity conferred protection against both intrinsic and extrinsic forms of skin aging, including damage induced by UV exposure, indicating that this combined regimen may represent a more potent modality for skin rejuvenation [28].

In summary, supplementation with NAD^+ holds considerable promise for improving skin health through the enhancement of mitochondrial performance, mitigation of oxidative stress, and regulation of inflammatory processes. Although early evidence supports its potential to improve skin texture, elasticity, and overall appearance, further investigation is required to identify optimal delivery strategies and to develop standardized treatment protocols for its application in dermatologic care [29]. As research advances, NAD^+ may emerge as a key component in skincare regimens aimed at maintaining youthful, healthy skin. Commercially, NAD^+-containing products include Sihler N (Sihler N, Sihler Inc., Seoul, Korea), reflecting growing interest in mitochondrial-targeted skin care.

2.1.3 | Glycosaminoglycan Precursors

GAGs are complex polysaccharides that play an essential role in maintaining skin homeostasis, particularly by supporting hydration, elasticity, and structural integrity. These linear molecules, characterized by their negative charge, are naturally found within the ECM of both the dermis and epidermis, where they help regulate collagen fiber organization and facilitate water retention. Among them, HA is the most abundant in the skin and is well known for its viscoelasticity and exceptional hydrating capacity, making it a fundamental component in a wide range of topical formulations and injectable treatments targeting skin aging [30].

Age-related reduction in GAG levels plays a substantial role in the manifestation of clinical signs of skin aging, such as increased dryness, diminished firmness, and the appearance of wrinkles. Non-invasive anti-aging approaches that target GAG-related pathways have gained growing attention, particularly in the form of topical treatments. Many cosmetic formulations now incorporate GAGs or their biochemical precursors—including N-acetyl glucosamine and dermatan sulfate—with the goal of restoring ECM content and improving dermal volume. Importantly, GAG-based interventions provide benefits beyond simple skin hydration by regulating ECM remodeling, stimulating fibroblast activity, and inhibiting MMPs, enzymes responsible for collagen degradation [30]. Commercial examples include Sihler G (Sihler G, Sihler inc.,Seoul, Korea), a GAG-focused topical designed to support ECM content and hydration.

Beyond their well-recognized hydrating capacity, GAGs possess anti-inflammatory, antioxidant, and cytoprotective properties, making them valuable candidates for multifunctional skincare formulations. Their capacity to regulate cytokine signaling and attenuate oxidative stress reinforces their role as potent bioactive agents in anti-aging cosmeceuticals. Additionally, specific GAGs—such as chondroitin sulfate and heparan sulfate—have been shown to enhance skin barrier integrity and facilitate wound healing, highlighting their versatility in applications that extend beyond purely aesthetic purposes [30].

With continued research elucidating the biological roles of GAGs in skin physiology, future advancements are expected to prioritize optimizing molecular weight, improving dermal penetration, and formulating combinations with complementary actives—such as peptides or antioxidants—to achieve synergistic anti-aging benefits. The rising interest in sugar-derived skin boosters mirrors a broader movement within dermatology toward leveraging endogenous biomolecules for regenerative purposes, thereby providing safer and more sustainable alternatives to invasive aesthetic interventions.

2.1.4 | Collagen

Collagen is the most prevalent protein in human connective tissues and is essential for preserving skin architecture, elasticity, and moisture balance. A gradual reduction in the body's natural collagen synthesis—driven by intrinsic aging processes and environmental stressors such as UV radiation—has stimulated the advancement of collagen-based injectables as minimally invasive options for aesthetic enhancement. Compared with traditional surgical procedures, injectable collagen products provide benefits such as shorter recovery times, a lower risk of complications, and greater patient acceptance [31]. Of particular interest, crosslinked and recombinant forms of human collagen types I and III are under active investigation for their excellent biocompatibility and their ability to facilitate dermal regeneration. Commercial examples include recombinant human collagen such as Sihler RH Collagen (a commercially available formulation), reflecting recombinant options now used for intradermal rejuvenation.

The pursuit of youthful and resilient skin has fueled increasing demand for minimally invasive interventions, with a particular emphasis on injectable therapies that promote dermal regeneration. Among these modalities, collagen-based injectables have gained notable recognition for their capacity to restore skin structure and elasticity, particularly in the context of age-related and UV-induced collagen depletion [31, 32]. Conventional approaches such as laser resurfacing, radiofrequency treatment, and chemical peeling often demonstrate limited efficacy, typically necessitating multiple sessions and yielding gradual results [32]. By contrast, intradermal injection techniques deliver active agents directly into the dermis, bypassing the epidermal barrier and enabling faster, more precisely targeted enhancement of skin architecture and hydration [2, 33].

Injectable collagen exerts its effects by strengthening the ECM, activating fibroblasts, and inducing neocollagenesis—particularly of collagen types I and III, which are the principal proteins responsible for dermal tensile strength and elasticity [25, 33]. Among available options, recombinant human collagen (Sihler C, Sihler Inc., Seoul, Korea) has shown superior bioavailability and reduced immunogenic potential compared with collagen derived from animal sources, while also improving photoaged skin through mechanisms involving collagen regeneration and modulation of immune responses [32]. In addition, the inherent biochemical compatibility

of collagen enables its gradual biodegradation and replacement with native ECM constituents, positioning it as a natural and safe option for regenerative therapy [2, 31].

Clinical evidence from both high-altitude and urban populations supports the rejuvenating benefits of collagen-based injectables. In one study, Yang et al. documented notable increases in skin thickness and enhanced hydration in high-altitude patients following six sessions of intradermal collagen administration, as confirmed by VISIA imaging analyses and patient-reported assessments [25]. Likewise, Liu et al. reported substantial aesthetic improvements and a reduced incidence of adverse events in individuals treated with a combination of collagen and HA for correction of tear trough deformities—indicating that collagen not only augments tissue volume but also lowers the risk of complications such as the Tyndall effect [33]. Collectively, these findings underscore the versatility of collagen injectables across diverse skin types and environmental conditions.

Contemporary skin booster therapies have evolved from solely providing volumetric enhancement to facilitating bioactive dermal restoration, incorporating collagen in combination with agents such as HA, polynucleotides, and exosomes [2, 34]. Although HA is highly effective in maintaining skin hydration, its rapid metabolic breakdown limits its durability. When paired with HA, collagen compensates for this limitation by delivering structural reinforcement and promoting prolonged ECM remodeling [2, 33]. This combined action enhances skin tone, elasticity, and barrier integrity, while simultaneously stimulating angiogenesis and diminishing pigmentation irregularities, thereby establishing collagen as an essential element in multifunctional injectable formulations.

With increasing patient interest in regenerative therapies that require minimal recovery time, collagen-based injectables have emerged as notable for their combined aesthetic and therapeutic benefits. Incorporating recombinant or purified collagen into skin booster regimens enables clinicians to deliver safer and more effective treatments customized to the patient's specific skin condition and ethnic background [31, 32]. Nevertheless, additional comparative research is necessary to determine optimal dosage parameters, treatment frequency, and long-term outcomes. Despite these needs, existing evidence highlights collagen's function beyond that of a conventional filler—acting as a regenerative agent capable of restoring skin function at the cellular level—and signifies a paradigm shift in the practice of anti-aging dermatology [2, 25].

2.2 | Biostimulatory Polymer and Ceramic Boosters

2.2.1 | Poly-d,l-Lactic Acid

Poly-d,l-lactic acid (PDLLA) is an amorphous stereoisomeric copolymer composed of randomly distributed D- and L-lactic units, a configuration that suppresses crystallinity and enables more uniform biodegradation compared with poly-L-lactic acid (PLLA) [35]. Commercial PDLLA products, such as Aesthefill and Juvelook (Juvelook, VAIM, Korea) (Figure 2), use microspheres that are typically spherical and porous (20–70 μm), a morphology that facilitates injection, prevents phagocytosis,

FIGURE 2 | Out of polymeric substance, the first skin booster used are Juvelook (VAIM, Korea).

and allows gradual degradation into lactic acid monomers. These physicochemical features support its biocompatibility and its role as a biostimulatory filler that activates fibroblasts, enhances ECM reinforcement, and promotes sustained neocollagenesis [35]. Importantly, compared with PLLA, PDLLA demonstrates faster degradation kinetics and more uniform particle morphology, which may provide a predictable clinical profile with reduced risk of late-onset granulomatous reactions [35].

Emerging clinical data have expanded the scope of PDLLA beyond volumization into disease-oriented skin rejuvenation. In a Korean case series, needle-free delivery of PDLLA using a laser-induced microjet achieved long-lasting improvements in erythema, flushing, and skin texture among patients with refractory rosacea, with benefits sustained up to 22 weeks and only mild, transient swelling or petechiae observed [36]. Similarly, subdermal PDLLA injections in women with moderate melasma led to MASI score reductions of 3.6–6.3 points at 12 weeks, accompanied by high patient satisfaction and minimal downtime [37]. These findings support the hypothesis that PDLLA's stimulation of angiogenesis, vascular stabilization, and dermal remodeling may extend its therapeutic potential into vascular and pigmentary conditions that are traditionally resistant to conventional therapies [36, 37].

Despite a generally favorable safety profile, localized adverse events can occur. A case report described firm, non-inflammatory nodules appearing 3 weeks after tear trough injections with a large-particle PDLLA formulation; however, complete resolution was achieved within 24 h following monopolar radiofrequency treatment (115 J, 28.75 J/cm^2) [38]. This rapid resolution was attributed to PDLLA's relatively low hydrated glass transition temperature (38°C–39°C), which allows for thermal degradation by energy-based devices [35, 38]. These findings underscore the importance of selecting appropriate formulations, injection planes, and dosages, while also highlighting the feasibility of integrating energy-based therapies into complication management strategies.

Overall, PDLLA occupies a unique niche between HA fillers (providing immediate hydration and volume) and PLLA

(long-lasting but less predictable biostimulation) [35–38]. Its distinct microstructure confers predictable degradation kinetics and compatibility with both needle-based and needle-free delivery, supporting applications that span skin rejuvenation, rosacea, and melasma [36, 37]. Moreover, its combined volumizing and collagen-stimulating properties, along with its potential synergy with adjunctive agents such as hyaluronic acid or polynucleotides, point to an expanding role in multimodal rejuvenation protocols [35]. Looking ahead, as more clinical evidence accumulates across diverse patient populations and aesthetic indications, PDLLA is expected to become an increasingly important biostimulatory platform in dermatologic practice. Larger randomized controlled trials and long-term follow-up are still warranted to validate comparative efficacy, refine injection protocols, and establish standardized approaches for complication management, but current data suggest a promising trajectory for this novel material [35–38].

2.2.2 | Poly-L-Lactic Acid

Polymer-based agents have recently been introduced as skin boosters. While HA fillers are valued for their biocompatibility and skin-enhancing effects, their primary limitation is the relatively short duration of volumetric correction, particularly in indications such as scar revision. This has generated clinical demand for skin booster fillers that provide durable volumetric retention while maintaining a favorable safety profile. PLLA, marketed as Sculptra (Galderma Laboratories, L.P., Fort Worth, TX, USA) and newer formulations such as MiraLine PLLA 28 (Lotos United LLC, Moscow, Russian Federation) has been utilized to address this need, initially demonstrating robust collagen-stimulatory activity, especially in individuals with rapid facial volume depletion, such as patients with acquired immunodeficiency syndrome. MiraLine PLLA 28 a poly-L-lactic acid formulation composed of spherical microparticles approximately 25–50 μm in size. Available experimental and clinical data indicate collagen-stimulating activity together with a favorable safety profile [39, 40]. Published studies also support the incorporation of PLLA into combination protocols, including HIFU- and hyaluronic acid-based approaches, with potential additive effects on dermal remodeling [41–44]. However, concerns have persisted regarding particle irregularity, size heterogeneity, surface unevenness, protrusions, and granuloma formation. Despite these advancements, physician apprehension regarding the intradermal application of polymer-based products remains, with long-term surveillance advised to monitor potential immune-mediated reactions involving multinucleated giant cells [45, 46], reminiscent of past PLLA-associated granuloma cases.

Additionally, certain skin booster strategies employ high-concentration solutions to induce localized tissue stimulation. One example is the use of hypertonic dextrose solution, a well-established proliferant in prolotherapy for pain management and rehabilitation. Sit et al. [47] reported that hypertonic dextrose is water-soluble and considered an ideal proliferative agent due to its safety, even when administered in large quantities across multiple anatomical sites containing body fluids. Nonetheless, its application in cosmetic dermatology has thus far been limited, with insufficient clinical evidence supporting its efficacy for aesthetic purposes.

2.2.3 | Calcium Hydroxyapatite

Within the field of tissue engineering, there is a growing demand for both natural and synthetic materials that simultaneously fulfill the requirements of biocompatibility, biodegradability, and adequate mechanical strength. Calcium hydroxyapatite (CaHA), classified as a bioactive ceramic, satisfies these conditions by facilitating cell adhesion, proliferation, and differentiation, while also contributing to wound repair through the release of calcium ions, which initiate blood clot formation and support tissue regeneration [48]. Clinically, CaHA fillers consist of laboratory-synthesized microspheres dispersed within a gel-based carrier. These microspheres typically exhibit a granular and polyhedral morphology under scanning electron microscopy, a structure that promotes integration with host tissue and stimulates collagen synthesis. CaHA particles form densely packed microsphere clusters at low magnification, while high-resolution imaging reveals their irregular, crystal-like surfaces. This combined architecture not only provides immediate volumetric correction but also functions as a scaffold for fibroblast adhesion, thereby facilitating progressive dermal remodeling [49, 50].

In clinical aesthetic applications, CaHA fillers consist of laboratory-synthesized microspheres dispersed within a gel-based carrier, providing immediate structural reinforcement while progressively inducing collagen synthesis. This biostimulatory action enhances the initial cosmetic outcome and contributes to sustained improvements in skin elasticity, surface texture, and volumetric integrity. Research conducted by Kadouch demonstrated that CaHA delivers prompt volumetric correction for facial folds and wrinkles, while its prolonged collagen-stimulating activity gradually refines skin texture and firmness [51]. In a separate investigation, Hong et al. reported that CaHA fillers achieve both persistent volume augmentation and notable skin-boosting benefits, evidenced by a reduction in Midface Volume Deficiency Scale (MFVDS) scores over a 24-week period, indicating lasting midface volume restoration. Furthermore, the study underscored that when properly administered, CaHA fillers yield durable results, high patient satisfaction rates, and a favorable safety profile [50]. Commercial CaHA fillers include Radiesse (Merz Aesthetics, Raleigh, NC, USA) and Facetem (CGBio, Seoul, Korea), which use CaHA microspheres suspended in a gel carrier to provide immediate support with subsequent collagen stimulation.

Beyond facial rejuvenation, CaHA has demonstrated efficacy in treating other anatomical regions, including the dorsal hands, cervical area, and décolletage. In clinical practice, CaHA is often used in a diluted form for skin-tightening procedures, where its biostimulatory properties alone enhance dermal elasticity and surface texture. Ladha reported that diluted CaHA functions as a collagen-stimulating agent, improving skin tone and firmness without contributing substantial volumetric change. This characteristic makes it an appealing non-invasive option for addressing skin laxity in areas such as the abdomen, thighs, and gluteal region. The capacity to adjust CaHA concentration according to

specific treatment goals highlights its adaptability and broad applicability within aesthetic medicine [52].

CaHA can be integrated with adjunctive agents to maximize therapeutic efficacy and improve patient comfort during aesthetic procedures. A common practice is to blend CaHA with lidocaine, which helps alleviate injection-related pain and enhances the overall treatment experience. Clinical observations indicate that incorporating lidocaine effectively reduces procedural discomfort, making the intervention more tolerable for patients [51]. In addition, CaHA is frequently combined with microneedling techniques or energy-based devices to augment skin rejuvenation outcomes. Such multimodal approaches may yield synergistic benefits, enabling a more comprehensive strategy for skin restoration, particularly in the management of facial aging. The adaptability of CaHA across diverse treatment modalities underscores its versatility as a non-invasive aesthetic tool, capable of delivering both immediate volumetric enhancement and prolonged improvements in skin quality [53].

Beyond its aesthetic advantages, CaHA has been the subject of extensive safety evaluations, confirming its appropriateness for long-term application in a variety of aesthetic interventions. In a study conducted by Driessen et al., CaHA was associated with a low rate of serious adverse events, with nodules reported as the most frequent complication; these typically resolved spontaneously without the need for medical intervention. The material's biocompatibility—attributable to its composition from a naturally occurring mineral found in human bone and dental structures—further supports its strong safety profile. Additionally, the gradual biodegradation of CaHA over time minimizes the likelihood of persistent complications, positioning it as a safer option compared with permanent filler materials. The combination of a well-established safety record and its proven ability to stimulate collagen production reinforces CaHA's status as a leading choice for non-surgical aesthetic enhancement [53].

2.2.4 | Polydioxanone

Polydioxanone (PDO)-based injectables have emerged as an effective, minimally invasive modality for promoting skin rejuvenation. PDO, a fully biodegradable synthetic polymer, induces collagen neogenesis within the dermal layer, thereby enhancing cutaneous texture, elasticity, and overall dermal quality [54]. Their rising popularity in aesthetic medicine stems from their capacity to improve skin condition while serving as a less invasive alternative to surgical lifting procedures such as rhytidectomy [2]. When introduced directly into the dermis, PDO stimulates fibroblast activation, which drives new collagen deposition and reinforces the ECM [55]. In current clinical practice, PDO is most widely used as threads, with injectable formats representing an emerging, complementary application.

Injectable PDO enhances collagen synthesis through the induction of a localized, controlled inflammatory response within the dermis. This process engages the TGF-β signaling cascade, which promotes fibroblast proliferation and subsequent neocollagenesis [54]. Upon administration, PDO filaments establish a temporary intradermal scaffold that supports tissue hydration, firmness, and elasticity, thereby offering a targeted therapeutic approach for cutaneous aging and fine wrinkles [55]. Owing to its biodegradable properties, PDO is gradually resorbed while the newly synthesized collagen remains integrated within the dermal matrix, sustaining long-term skin rejuvenation [2].

Injectable PDO is widely employed to address multiple manifestations of cutaneous aging, including fine wrinkles, dermal laxity, and diminished elasticity, with particular utility in anatomically delicate zones such as the periorbital region, malar area, and mandibular contour [2]. Beyond its lifting and firming capabilities, PDO has demonstrated clinical efficacy in refining skin texture, minimizing pilosebaceous unit ostia, and improving overall chromatic uniformity of the skin [55]. Evidence from controlled clinical investigations further supports its capacity to enhance dermal thickness and stimulate rejuvenative remodeling, establishing PDO as a preferred minimally invasive modality for patients seeking visible and durable aesthetic improvement [54].

Injectable PDO exhibits a favorable safety and tolerability profile, with transient, mild adverse events—such as localized edema or ecchymosis at the injection site—generally resolving spontaneously within several days [54, 55]. Longitudinal clinical investigations have reported no clinically significant delayed complications, further reinforcing its suitability for repeated use. The therapeutic capacity of PDO to induce neocollagenesis and enhance overall dermal quality has been substantiated in multiple controlled trials, underscoring its role as an effective modality for achieving sustained structural and aesthetic improvement of the skin [2].

PDO injectables are frequently evaluated alongside other biostimulatory agents such as PLLA and HA. While HA primarily confers rapid volumization and dermal hydration, PDO is distinguished by its capacity to induce sustained neocollagenesis, thereby supporting prolonged cutaneous rejuvenation [1]. Through its demonstrable enhancement of dermal texture and tensile strength, PDO has shown particular efficacy in mitigating fine wrinkles and early skin laxity. Relative to PLLA, PDO exhibits superior biodegradability and a more pronounced capacity to stimulate organized collagen deposition [54, 55].

2.2.5 | Polycaprolactone

Polycaprolactone (PCL) is an FDA-approved, biocompatible aliphatic polyester that undergoes slow hydrolytic degradation, typically persisting in vivo for 1–2 years depending on particle structure and molecular weight [56]. Conventional non-porous PCL fillers such as Ellansé (Sinclair, United Kingdom) are composed of smooth microspheres that provide long-lasting volumization but may exhibit limitations in dispersion stability and risk of palpable nodules. In contrast, LaFullen (Samyang, Korea) is characterized by uniformly sized porous microspheres. The porous configuration contributes to superior dispersion stability after dilution, enhanced usability as a skin booster, and safer biodegradation with a reduced incidence of nodular reactions [57, 58]. Once injected, these microspheres act as a three-dimensional scaffold, promoting fibroblast activation and stimulating collagen types I and III, thereby reinforcing dermal

ECM architecture and enabling progressive skin rejuvenation [56, 57].

The clinical efficacy of PCL fillers has been demonstrated in multiple studies. In a prospective, randomized controlled trial, Moers-Carpi and Sherwood showed that non-porous PCL fillers maintained significant correction of nasolabial folds for up to 24 months, confirming their long-lasting volumizing and biostimulatory effect [56]. Strawford further emphasized PCL's role as a next-generation collagen stimulator capable of sustained dermal remodeling [58]. More recently, porous PCL fillers have been evaluated for finer indications. In vitro degradation assays confirmed gradual polymer chain scission over 104 weeks, while in vivo rabbit studies showed that injected porous microspheres were largely degraded by 24 months and completely resorbed by 30 months [57]. Histological analyses revealed abundant collagen deposition around the microspheres with only mild inflammatory responses. In a UV-induced photoaging mouse model, LaFullen achieved nearly 48%–50% reduction in wrinkle roughness parameters (Rmax, Rt) at 12 weeks, outperforming non-porous PCL fillers [57]. Collectively, these data support PCL fillers as effective tools for both volumetric correction and fine-line skin rejuvenation.

PCL fillers are generally well tolerated, with most adverse events limited to transient swelling, bruising, or mild inflammatory responses that resolve spontaneously. The porous microarchitecture improves safety by reducing the likelihood of palpable nodules, a complication sometimes observed with other long-lasting stimulatory fillers. In preclinical studies, only grade 1 inflammatory reactions (occasional lymphocytes and giant cells) were observed, without evidence of granuloma formation. Furthermore, the predictable biodegradation kinetics of porous PCL contribute to its favorable safety profile. In clinical practice, the risk of nodules is further minimized through appropriate dilution, even injection planes, and post-treatment massage protocols [57, 58].

PCL fillers represent a unique class of biostimulatory injectables that bridge the gap between short-acting hyaluronic acid fillers and longer-acting PLLA stimulators. Their combination of immediate volumization, sustained collagen stimulation, and predictable biodegradability makes them attractive for both structural correction and regenerative skin treatments. With its porous microsphere technology, it offers improved dispersion stability, lower risk of nodules, and enhanced usability as a skin booster compared with earlier PCL formulations. While current evidence from animal and early clinical studies is promising, larger randomized controlled trials in diverse patient populations are warranted to confirm long-term efficacy, establish standardized protocols, and further consolidate the role of PCL fillers in aesthetic and regenerative dermatology.

2.2.6 | Succinic Acid

Succinic acid (SA) is a naturally occurring four-carbon dicarboxylic acid and a central intermediate of the tricarboxylic acid cycle, where it contributes to mitochondrial respiration and cellular energy metabolism [59]. Beyond this metabolic role, SA functions as a signaling molecule that influences pathways related to hypoxia, oxidative stress, and tissue remodeling. Recent studies have shown that SA can regulate fibroblast senescence and mitochondrial activity, highlighting its potential as a regenerative agent in dermatology. Although injectable SA formulations were introduced several years ago, their use in aesthetic practice has remained limited; nevertheless, emerging preclinical evidence suggests that SA may provide measurable benefits as a skin booster [60].

Laboratory and translational studies provide insight into SA's bioactive potential. Under hypoxic culture conditions, SA attenuated markers of fibroblast senescence (p16, DPP4) while enhancing expression of pluripotency-related genes such as SOX2, c-MYC, and OCT4, indicating partial rejuvenation of fibroblast phenotypes [60]. In senescent dermal fibroblasts and aged adipocytes, SA treatment upregulated extracellular matrix genes (COL1A1, CTGF, and FBN1) and TGF-β1, while downregulating inflammatory mediators including MMP1, CXCL10, IL-6, and IL-8. Moreover, SA promoted adipogenesis by increasing IGF1 expression and reducing TNFA, thereby restoring adipose homeostasis. Conditioned media from SA-treated adipocytes further enhanced fibroblast activity, upregulating COL3A1, FN1, and EGF, suggesting enhanced dermal–subcutaneous signaling [61]. Together, these findings support SA's dual action as both a dermal and subcutaneous biostimulator.

Preclinical evidence indicates that SA is well tolerated at physiologic concentrations (0.2–1.5 mM), with cytotoxic effects observed only at markedly higher levels [60, 61]. In vitro models consistently showed reduced inflammatory signaling following SA treatment, without evidence of increased cell death. Clinical experience with injectable SA formulations remains limited, but its endogenous role in energy metabolism supports a favorable safety profile.

Although succinic acid-based injectables have not yet achieved widespread clinical use, growing evidence highlights their ability to modulate fibroblast senescence, stimulate mitochondrial turnover, promote adipogenesis, and enhance dermal–subcutaneous communication. These effects provide a rationale for considering SA as a skin-boosting agent aimed at improving elasticity, texture, and metabolic resilience. Further translational and clinical studies are warranted to establish standardized protocols, validate efficacy, and confirm long-term safety. If supported by robust clinical data, SA may expand the current armamentarium of regenerative injectables in aesthetic dermatology.

2.3 | Polynucleotide, Autologous, and Cell-Derived Boosters

2.3.1 | Deoxyribonucleic Fragments (Polydeoxyribonucleotide and Polynucleotides)

Polynucleotides (PN) have garnered increasing global attention in aesthetic and cosmetic medicine owing to their excellent biocompatibility. Extracted from the gonads of chum salmon or trout, PN differs from other biostimulatory agents in that it is derived from natural sources rather than synthesized as polymer-based materials. Importantly, PN and polydeoxyribonucleotide

(PDRN) exhibit several key distinctions: PN is obtained from testicular tissue, whereas PDRN is sourced from sperm cells; PN also possesses longer nucleotide chains and a greater molecular weight, as demonstrated in recent studies. Furthermore, PN is characterized by a unique scaffold structure not observed in PDRN formulations. The first PN-based skin booster introduced in clinical practice was a polynucleotide-based formulation in 2014, Rejuran (DOT-PN; Pharmaresearch Inc., Korea).

In 1989, Bruroni et al. [62] introduced PDRN therapy in patients with cervical ectropion, followed by Perino et al. [63], who applied PDRN to promote re-epithelialization after cauterization. Muratore et al. [64], subsequently investigated human placental–derived PDRN using primary cultures of human knee skin fibroblasts. In 1999, Thellung et al. [65] published pivotal findings clarifying the involvement of A2A receptors in the mechanism of action of PDRN. Since then, additional studies have explored the therapeutic potential of PDRN in various domains, including enhancement of wound healing at skin graft donor sites [66, 67], stimulation of corneal fibroblasts in vitro, promotion of human osteoblast proliferation [68, 69], and facilitation of angiogenesis [70, 71].

A notable finding regarding PDRN is its capacity to promote cyclobutene pyrimidine dimer repair in dermal fibroblasts exposed to ultraviolet (UV)B radiation [72]. More recent studies have identified additional properties of PDRN, including antimelanogenic activity [73, 74], anti-allodynic effects [75], stimulation of mitochondrial biogenesis [73], and potential utility in inducing adipose tissue browning for anti-obesity applications [76]. In contrast, PN comprises longer nucleotide chains, yet there is comparatively less published research substantiating their biological effects. In 2016, Park et al. [77] demonstrated that PN improved multiple skin attributes—including pore size, dermal thickness, tone, melanin content, wrinkle depth, and skin laxity—in a clinical study involving five patients. Similarly, in 2018, Kim et al. [78] conducted a randomized, double-blinded, controlled trial in which 44 post-thyroidectomy patients exhibited significant scar improvement following PN treatment. These benefits were reflected in markedly enhanced Vancouver Scar Scale scores, three-dimensional scar height reduction, greater patient satisfaction, and decreased erythema index.

In 2022, Lee et al. [79] conducted a randomized, double-blind, split-face clinical trial involving 27 participants who received injections of PN on one side of the face and non–cross-linked HA filler on the other. The PN-treated areas demonstrated greater improvements in pore volume and skin roughness compared to the HA group; however, no statistically significant differences were observed between groups in terms of the global aesthetic improvement scale, visual analog scale, or dermal density. More recently, Kim et al. [80] reported two clinical cases in which PN was successfully applied for volumizing facial regions traditionally treated with other dermal filler types. In a separate survey of 557 Korean physicians, Lee et al. [81] found that a substantial majority used PN for managing various forms of facial erythema, with over 80% rating the treatment as "effective" or "highly effective." Two key points emerge from these studies: first, no serious adverse events were reported, supporting the favorable safety profile of PN. Second, although the precise mechanism of action remains unclear, it has been hypothesized that PN may act via pathways similar to those of PDRN due to their molecular resemblance. At present, however, this hypothesis lacks definitive scientific validation.

2.3.2 | Platelet-Rich Plasma

Platelet-rich plasma (PRP) refers to plasma containing a high concentration of platelets derived from autologous blood. The platelets within PRP harbor numerous bioactive constituents, including clotting factors, GFs, chemokines, and cytokines [82]. These molecules play key roles in promoting cellular proliferation and maintaining skin homeostasis, thereby contributing to tissue regeneration. When freshly prepared from whole blood, PRP remains in a non-coagulated state until platelet activation occurs, at which point the encapsulated growth factors are released for therapeutic use.

Platelets are anucleate cytoplasmic fragments derived from megakaryocytes, measuring approximately 2–3 μm in diameter and about 1.5 μm in thickness, with a lifespan of 8–10 days. Roughly one-third of the total platelet population is sequestered in the spleen, while the remaining two-thirds circulate within the peripheral bloodstream. PRP has emerged as a widely used skin booster in aesthetic medicine, supported by extensive evidence of its clinical efficacy. This therapeutic benefit is largely attributed to the diverse array of biologically active substances stored within platelet granules, which contribute to tissue repair and regeneration. Platelet storage granules are categorized into three main types: alpha granules, lysosomal granules, and dense granules. Among these, the alpha granules are particularly significant, as they contain a wide range of GFs [83].

Alpha granules encapsulate a diverse spectrum of bioactive molecules, including platelet-derived growth factor (PDGF), TGF-β, vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF). They also store von Willebrand factor, fibronectin, fibrinogen, vitronectin, clotting factors such as factor V and protein S, antifibrotic agents, chemokines, and various other regulatory proteins.

Lysosomal granules serve as reservoirs for a variety of digestive enzymes. Dense granules, on the other hand, contain bioactive substances such as serotonin, adenosine diphosphate (ADP), adenosine triphosphate (ATP), and multiple glycoproteins located on the platelet membrane, all of which play essential roles in the initiation of primary hemostasis.

PRP is composed of approximately 94% platelets, 5% red blood cells, and 1% white blood cells. For optimal clinical efficacy, PRP must meet a minimum platelet concentration threshold, generally recommended at no less than one million platelets per microliter, corresponding to approximately 4–7 times the platelet count found in normal peripheral blood.

The fundamental mechanism underlying PRP therapy involves the activation of its abundant cytokines and GFs through the addition of autologous thrombin or ionized calcium during the activation phase of highly concentrated PRP. Once released, these bioactive molecules promote wound healing and facilitate tissue regeneration.

PRP preparation techniques can be broadly categorized into the single-spin and double-spin centrifugation methods. In recent years, the single-spin method has gained prominence owing to the availability of user-friendly PRP preparation kits. One widely recognized example in the Republic of Korea is the NRP20 system, which incorporates a specialized centrifuge tube (a commercially available formulation) designed to efficiently separate PRP components.

A neutral schematic of platelet-rich plasma preparation and fraction isolation is provided in Figure 3.

Facial aging is characterized by a reduction in fibroblast numbers and a decline in the production of collagen and other ECM proteins, leading to the development of wrinkles, skin laxity, rough texture, and pigmentation irregularities [84]. PRP has the potential to promote ECM remodeling, stimulate fibroblast proliferation, and enhance collagen synthesis, thereby ameliorating the general signs of skin aging. Intradermal PRP injection induces a mild inflammatory response that activates the healing cascade, resulting in increased collagen deposition and subsequent skin tightening and strengthening [85]. Clinically, improvements in skin condition may be observed within 3 weeks, while complete collagen regeneration typically requires approximately 3 months [86, 87].

In one study, three sessions of intradermal PRP injections were administered to 12 female patients targeting the forehead, crow's feet, cheeks, and nasolabial folds [88]. Assessments using patient satisfaction questionnaires, clinical imaging, and investigator evaluations revealed enhanced skin texture, elasticity, barrier function, and wrinkle reduction, with no serious adverse effects reported. In a recent blinded split-face trial comparing PRP dermal injection to saline as a control, 19 participants were evaluated by two dermatologists. The PRP-treated side showed improvements in skin texture, wrinkle severity, pigmentation, and telangiectasia; however, fine lines, mottled pigmentation, roughness, and sallowness demonstrated no statistically significant differences [89].

Further histological evidence was provided by Abuaf et al. [90], who performed punch biopsies from the infra-auricular area at baseline, 28 days post-PRP injection, and 28 days post-saline injection. The PRP group exhibited increased collagen and elastic fiber density compared to control and saline groups. Interestingly, PRP efficacy did not correlate directly with concentration, as 5% PRP induced greater collagen synthesis and fibroblast proliferation than 10% PRP [91]. PRP as a skin booster is commonly delivered via microneedling or microinjection, with no significant difference in clinical outcomes between these methods [92].

Owing to its autologous origin, PRP therapy generally presents a lower risk of adverse effects compared to other skin rejuvenation modalities, with potential side effects limited to transient pain, infection, erythema, swelling, and bruising. Despite its simplicity, rapid preparation, and increasing popularity in aesthetic medicine, the efficacy and safety profile of PRP therapy remain subjects of ongoing debate.

2.3.3 | Growth Factors

Historically, GFs represent one of the earliest forms of skin boosters, recognized for their ability to stimulate a wide range

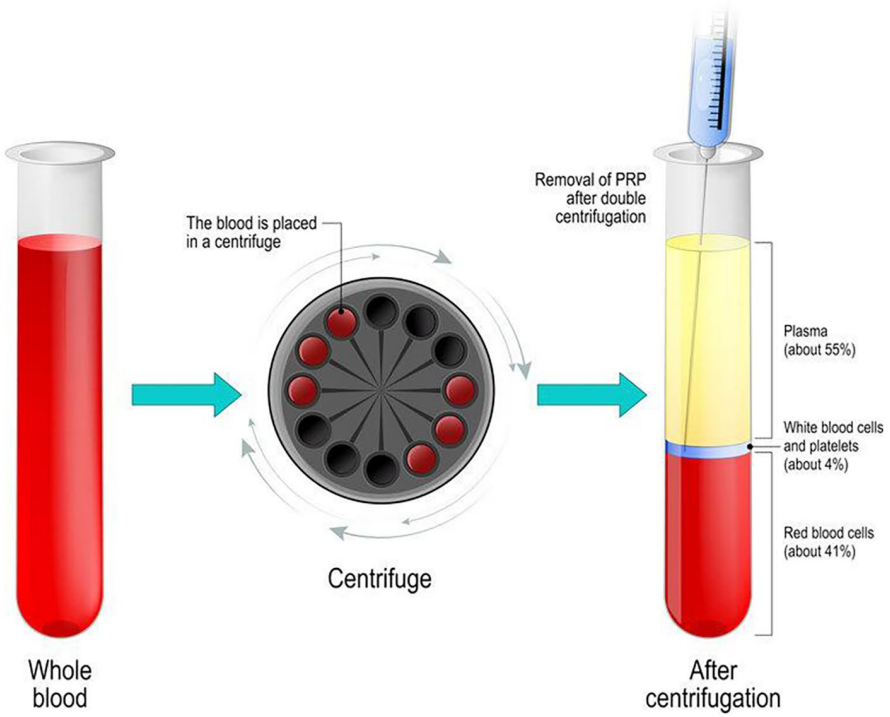

FIGURE 3 | Generic platelet-rich plasma preparation workflow. Neutral schematic illustrating a generic PRP preparation sequence using centrifugation-based separation of whole blood into plasma, platelet-rich fraction, and erythrocyte layers, followed by aspiration of the platelet-rich fraction. This figure is intentionally non-commercial and is included to clarify the principles of PRP isolation without depicting branded collection systems.

of cell types and facilitate wound healing. These bioactive proteins have been delivered intradermally through various methods, including PRP therapy. More recently, there has been an increasing trend toward incorporating GFs into cosmetic formulations, capitalizing on their well-documented skin-enhancing properties [93].

Furthermore, nearly all contemporary formulations are designed either to contain GFs directly or to promote their endogenous production [94]. However, the majority of cellular receptors for GFs are expressed predominantly by damaged cells rather than by healthy, intact cells[47] [95]. This raises the question of whether administering GFs to normal skin provides substantial benefit. It has been hypothesized that GF therapy may achieve greater efficacy in initiating wound-healing processes when combined with adjunctive stimuli, such as energy-based devices or microneedling. Additionally, the establishment of diverse GF receptors requires a certain period following the onset of tissue injury before they can be fully expressed and functionally active.

Since Cohen first elucidated the role of EGF in cell division in 1986, GFs have been recognized as essential mediators of cellular regeneration [96]. Multiple studies have demonstrated that different types of GFs are required at specific stages of the wound-healing process, making them among the most direct and effective biological agents in tissue repair.

In addition to GFs, various vitamins play critical roles in skin aging and regeneration. Vitamin C accelerates DNA synthesis, functions as a key antioxidant, and is indispensable for collagen production. Vitamin A regulates epidermal turnover and melanocyte activity while exerting antioxidant effects that, in combination with vitamin C, support the synthesis of collagen and other ECM components. Vitamin E contributes to the regulation of skin's physiological regenerative processes and aids in repairing damaged tissue. B vitamins are crucial for numerous cellular functions, acting as cofactors in the metabolism of carbohydrates, fats, and proteins, as well as in the synthesis of a variety of biomolecules.

Among minerals, calcium is a key regulator of cellular homeostasis, while phosphorus is essential for the formation of cell walls and various biological membranes. Magnesium plays a crucial role in sustaining numerous enzymatic reactions and is indispensable for maintaining normal cellular function. Amino acids support skin regeneration by promoting fibroblast proliferation, stimulating collagen synthesis, facilitating GF production, and reducing collagen degradation rates.

According to existing literature, with the exception of PDGF, most GF receptors require approximately 12–24 h to fully develop [97]. This underscores the importance of evaluating the potential benefits of GF administration in contexts where receptor integrity may be compromised [98]. Most GFs possess a positive charge, creating a challenge during transcutaneous delivery; however, once they reach the dermis, where resident cells carry a net negative charge, they are electrostatically attracted. Similarly, the epidermis of wounded skin also exhibits a negative charge, facilitating GF penetration. Consequently, relying solely on the passive absorption of GFs without the use of absorption-enhancing strategies may result in suboptimal efficacy.

In recent years, various GFs have been incorporated into skin pigmentation therapies. For example, EGF has been shown to suppress melanogenesis and reduce tyrosinase activity, making it a viable treatment for post-laser hyperpigmentation. Optimizing clinical outcomes requires careful selection and application of specific GFs for targeted purposes.

Representative growth factor-based skin boosters combine multiple peptide or fibroblast-derived signaling molecules with supportive excipients intended to enhance dermal repair. Because formulations vary substantially across manufacturers, this review emphasizes biologic rationale and published clinical outcomes rather than individual brand positioning.

2.3.4 | Exosomes

In recent years, dermatology and aesthetic medicine have witnessed a marked increase in the application of secretomes and exosomes, fueled by advances in the understanding of cellular communication and regenerative medicine. These biologically active entities are utilized to deliver targeted GFs, proteins, and genetic material directly to recipient cells, thereby enhancing tissue repair and regeneration. Skin boosters encompass various agents designed to improve the ECM of the dermis and enhance overall skin condition, with exosomes emerging as one of the most widely discussed innovations in this category.

While further research is needed to clarify their optimal source materials, efficacy, safety profile, and potential ancillary benefits, current evidence from several studies offers promising insights into their regenerative capabilities. Exosomes—classified as the smallest subtype of extracellular vesicles, typically measuring 30–110 nm—are enclosed by a lipid bilayer derived from the parent cell membrane and contain proteins, messenger RNA (mRNA), microRNA (miRNA), and lipids. These vesicles play a pivotal role in wound healing and skin rejuvenation. Despite their abundance in nature, their diminutive size and sensitivity to temperature, pressure, and pH variations pose significant challenges for extraction and stabilization. Although multiple isolation and purification techniques have been proposed, a universally accepted standard has yet to be established [99].

Functionally, exosomes are secreted by numerous cell types and represent a fundamental mechanism of intercellular communication and molecular transport. They mediate extensive signaling by transferring proteins, nucleic acids, miRNA, and diverse metabolites between cells [100].

Photoaging, primarily driven by environmental stressors such as UV radiation, exerts a profound negative effect on skin quality. Recent advances in regenerative medicine have highlighted the potential of mesenchymal stem cells (MSCs) and noncoding RNAs in combating photoaging, owing to their accessibility and broad physiological functions. Li et al. [101] reported significant clinical promise for MSCs and their derivatives—including exosomes and noncoding RNAs—in rejuvenating aged skin and mitigating photoaging-associated damage.

The topical or intradermal application of exosomes immediately following skin rejuvenation procedures—such as fractional laser

therapy, microneedling, radiofrequency microneedling, and microdermabrasion—has been shown to accelerate the healing process and reduce procedure-related erythema, edema, and discomfort [99]. Mechanistically, exosomes can hasten the transition from the inflammatory phase of wound repair to the remodeling phase by downregulating proinflammatory mediators. MSC–derived exosomes, in particular, have been found to modulate macrophage polarization via PKNOX1 targeting, thereby decreasing the expression of inflammatory factors such as interleukin-10 and tumor necrosis factor-alpha, ultimately aiding in inflammation control [4]. As a practical example, Exo-HL (edelweiss-derived exosome; Primoris International co. Ltd., Seoul, Korea) is marketed for adjunct use after such procedures. In a similar context, Creabello Exo (Lotos United LLC, Moscow, Russian Federation) has gained attention as an exosome-based formulation designed to enhance dermal regeneration and improve skin recovery following minimally invasive rejuvenation procedures.

Within the epidermis, exosomes serve as vital mediators of intercellular communication, significantly influencing keratinocyte behavior. By transferring proteins, lipids, and various RNA species between cells, they promote keratinocyte cohesion and stratification—processes essential for maintaining an effective and resilient skin barrier [102].

Exosomes exert a significant influence on keratinocytes, the predominant cell type within the epidermis. These extracellular vesicles regulate keratinocyte proliferation and differentiation—processes fundamental to preserving the structural integrity and functional capacity of the epidermis [103]. By delivering precise molecular signals, exosomes enable keratinocytes to mount appropriate responses to diverse environmental stimuli, thereby enhancing the skin's adaptability and resilience.

Within the dermis, exosomes function as critical signaling mediators, profoundly influencing fibroblasts—the primary cells responsible for synthesizing collagen and elastin, two structural proteins essential for skin elasticity and tensile strength [104]. By facilitating intercellular communication and enhancing fibroblast activity, exosomes promote collagen and elastin production, increase dermal adipose content, and thereby improve the skin's regenerative and restorative capacity. These effects translate into enhanced skin texture and a visible reduction in wrinkles and fine lines. Elastin production, in particular, is vital for maintaining youthful firmness and resilience in the skin. At the molecular level, exosomes mediate skin rejuvenation through multiple signaling pathways and growth factors, notably TGF-β, which regulates cellular growth, proliferation, and differentiation. By transporting TGF-β to target cells within the skin, exosomes initiate specific signaling cascades that improve dermal structure and function [104, 105].

Additionally, exosomes modulate the ECM—a complex network of proteins and biomolecules that provide structural and biochemical support to surrounding cells. This remodeling process is particularly critical in wound healing and scar prevention [106].

2.3.5 | Autologous Exosomes

Autologous exosomes are isolated from patient-derived sources, most commonly platelet-rich plasma or autologous stem-cell preparations such as adipose-derived stromal cells. This strategy is appealing because it offers personalized, cell-free delivery while potentially reducing immunologic concerns associated with heterologous materials.

Direct clinical trials using purified autologous exosomes remain limited, but translational evidence is encouraging. In a 2023 Japanese study, a single intradermal injection of autologous ADSCs yielded durable improvements in wrinkles, pore size, and eyelid contour for up to 12 months; in vitro assays from the same work implicated ADSC-derived exosomes in myoblast activation and dermal remodeling [107]. Complementary preclinical literature shows ADSC exosomes accelerating wound healing and modulating inflammatory pathways relevant to skin rejuvenation [108].

Overall, autologous exosomes represent a compelling skin booster strategy—combining personalized, cell-free delivery with growth factor synergy and reassuring safety profiles. Their patient-derived origin alleviates immunogenicity concerns, while emerging data support regenerative effects such as collagen remodeling, angiogenesis, and immune modulation. In particular, exosomes from PRP have been shown to enhance endothelial and fibroblast proliferation through growth factor–mediated signaling [109], and photoactivated PRP can sustain growth factor release together with ATP generation, providing prolonged regenerative cues [110]. The next step is a well-designed, assessor-blinded clinical trial with standardized isolation and potency assays to confirm their therapeutic potential.

2.3.6 | Secretomes

The secretome encompasses the full spectrum of soluble factors secreted by cells into their extracellular environment, including GFs, cytokines, and peptides, as well as insoluble components such as extracellular vesicles and exosomes. Dermal fibroblasts release a diverse repertoire of GFs, cytokines, and exosomes, acting as key mediators in intercellular communication to maintain and repair the ECM. Many products marketed as “growth factor formulations” are, in fact, secretome-based, containing exosomal components. Recent advances in biomedical research have underscored the pivotal role of extracellular vesicles—particularly exosomes—in orchestrating complex cell signaling events essential for numerous biological processes, including wound healing and skin regeneration [99, 111].

Secretomes can be obtained from a wide range of biological sources, including bone marrow, adipose tissue, neonatal tissues, skin tissue, and peripheral blood. These bioactive mixtures have been demonstrated to promote the migration and proliferation of multiple dermal cell types—such as fibroblasts, endothelial cells, and keratinocytes—while also supporting epidermal function [112]. Evidence from animal studies indicates that secretome administration can reduce wrinkle formation, enhance skin hydration, and stimulate collagen synthesis, as confirmed through Masson–trichrome staining analyses [113, 114].

The capacity of secretomes and exosomes to modulate fundamental cellular processes highlights their promise in advancing

skin care and dermatologic therapeutics. This emerging approach is reshaping the landscape of personalized skincare and noninvasive aesthetic procedures by providing more effective and targeted alternatives to conventional modalities. The integration of these biomolecular technologies marks a pivotal shift toward sophisticated, precision-based, and biologically inspired strategies in dermatologic treatments and aesthetic enhancement.

2.3.7 | Human Acellular Dermal Matrix

Human acellular dermal matrix (hADM) is derived from donated human skin that has undergone decellularization to remove cellular and antigenic components while preserving the ECM architecture composed of collagen, elastin, proteoglycans, and glycosaminoglycans [115]. This processing minimizes immunogenicity while maintaining mechanical integrity and biological cues for tissue integration. Once implanted, hADM serves as a biocompatible scaffold that facilitates fibroblast adhesion, cellular infiltration, angiogenesis, and ECM remodeling [115]. The most established brand, AlloDerm, was introduced in the 1990s and has been widely applied in breast reconstruction, abdominal wall reinforcement, periodontal surgery, and burn or wound coverage. Its long-standing clinical use underscores its safety, which derives from the removal of donor DNA and antigenic proteins, preservation of ECM structure, and rigorous donor screening and sterilization processes [115].

Initially developed for reconstructive surgery, hADM applications have recently expanded into the aesthetic domain. Adipose-derived acellular matrices (AAMs) have been introduced as off-the-shelf substitutes for fat grafting, overcoming the limitations of donor site morbidity and variable adipocyte survival [116]. In a randomized prospective trial, Kokai et al. demonstrated that injection of an allograft adipose matrix (Renuva) into the abdominal pannus of abdominoplasty patients resulted in progressive remodeling into perilipin-positive adipocytes, collagen deposition, and angiogenesis over 6 months, without severe adverse events. Similarly, a multicenter pilot study of an allograft adipose matrix for malar and prejowl volume restoration confirmed clinical improvements in contour and volume, with favorable tolerability [117]. More recently, Gold et al. reported real-world outcomes with an adipose-derived allograft matrix used for the face, hands, and body, showing sustained volumization, skin texture improvements, and high patient satisfaction, while maintaining a low complication rate [118]. Beyond adipose-derived products, dermis-derived hADM formulations have also emerged as injectable "skin boosters," targeting fine wrinkles, scars, and early skin laxity [117, 118].

The safety of hADM has been well established through decades of reconstructive use. Clinically, adverse events associated with hADM are typically limited to transient erythema, edema, or bruising, with no evidence of significant immunologic rejection or granuloma formation [116, 118]. Adipose-derived matrices are non-inflammatory and remodel gradually into host adipose tissue, further reducing risks of persistent nodules or irregularities [116]. Protocol optimization—including standardized dilution, depth of injection, and treatment intervals—further enhances safety in aesthetic practice.

hADM represents a biologically derived ECM scaffold that has transitioned from reconstructive surgery to aesthetic medicine as a versatile biostimulatory platform. In aesthetics, adipose-derived allograft matrices such as Renuva (MTF Biologics, USA) and dermis-derived injectables such as Elravie Re2O (Humedix, Korea), Reallo Inject Fine (CGBio, Korea) and Juveacell (VAIM, Korea) have been introduced as injectable boosters, complementing earlier reconstructive applications. These dermis- and adipose-derived products are being positioned not only for volumization but also for skin-quality enhancement, reflecting the broadening utility of hADM. With new brands and accumulating clinical evidence, further randomized trials and long-term outcomes are expected to refine algorithms and standardize protocols. Collectively, hADM is emerging as a next-generation skin booster that combines reconstructive reliability with aesthetic versatility.

2.4 | Adjunctive and Device-Enabled Boosters

2.4.1 | Chitosan

Chitosan is a polysaccharide derived from sources such as crab shells and certain fungi. Extensive research has explored its involvement in diverse cell signaling pathways within stem cells, platelets, and immune cells, as well as its potential applications in tissue regeneration [119–121]. The MALDI-TOF analysis from a prior study validates the key molecular attributes of ideal size chitosan (ISC) as produced by Arche (Doum Inc., Korea). The resulting spectrum shows a molecular weight profile mainly under roughly 200 Da, indicating a substantial proportion of low-molecular-weight chitosan. This is especially relevant, as low-molecular-weight chitosan is known for heightened biological activity, including superior anti-inflammatory, antioxidant, and tissue-regenerating effects. Importantly, its reduced molecular size enables greater absorption through the skin, allowing the chitosan to effectively cross the stratum corneum barrier and reach the deeper dermal and hypodermal layers when applied topically. As a result, Arche's ISC technology enhances the delivery of bioactive chitosan to deep tissue regions where collagen synthesis and extracellular matrix remodeling take place, thereby maximizing its therapeutic and cosmetic benefits (Figure 4) [122].

One of the principal regenerative mechanisms of chitosan involves promoting the proliferation and differentiation of stem cells. Notably, chitosan has been reported to enhance the expression of stromal-derived factor-1α, thereby facilitating stem cell homing and angiogenesis, which in turn contributes to improved tissue regeneration [123].

Charoenwongpaiboon et al. [124] reported that chitosan stimulates the proliferation and differentiation of human MSCs and demonstrated, in vitro, its capacity to enhance stem cell migration.

Liu et al. [125] investigated the angiogenic and regenerative potential of chitosan hydrogel. Using an ischemic myocardial infarction model, they compared its efficacy to that of adipose-derived stem cells and found that chitosan hydrogel promoted neovascularization and inhibited fibrosis to a degree comparable with adipose-derived stem cell treatment.

FIGURE 4 | The MALDI-TOF analysis from a prior study confirms that Arche's Ideal Size Chitosan (ISC, Doum Inc., Korea) exhibits a molecular weight predominantly below ~200 Da, indicating a high content of low-molecular-weight chitosan associated with enhanced anti-inflammatory, antioxidant, and tissue-regenerating properties. This reduced size facilitates superior percutaneous absorption past the stratum corneum to the dermis and hypodermis, allowing Arche's ISC technology to effectively deliver bioactive chitosan to deep tissue compartments where collagen synthesis and extracellular matrix remodeling occur, thereby maximizing therapeutic and aesthetic efficacy.

Building on the biological functions of chitosan, Kim et al. [126] developed a regenerative dermal filler by applying liquid-to-gel transformation technology. In this formulation, liquid chitosan transitions into a gel state within dermal tissue. The study reported that, when injected into the skin, this material demonstrated greater durability and enhanced collagen production compared to conventional HA fillers.

Injectable or liquid-to-gel chitosan formulations have been proposed as regenerative skin boosters because they may recruit mesenchymal stromal cells, improve local matrix organization, and support wound-healing cascades. In this review, chitosan is therefore discussed as a mechanistically defined platform rather than as a product-brand category.

2.4.2 | Botulinum Toxin

The hyper-dilution technique for intradermal delivery of botulinum toxin (BoNT), often termed "microbotox" or "babybotox," has been reported to enhance overall facial skin quality [127, 128]. Clinically used BoNT-A products for this approach include Letybo (Hugel Inc., Seoul, Korea), and Nabota (Daewoong Inc., Seoul, Korea). Clinical studies have demonstrated improvements in facial flushing and erythema following BoNT treatment [129–131], potentially mediated through the suppression of VEGF, a key proangiogenic mediator [132]. In a split-face controlled trial, Sayed et al. observed significant reductions in sebum production and pore size after intradermal BoNT administration, with results maintained for up to 4 months [133]. Evidence also supports BoNT's capacity to stimulate dermal remodeling. Chang et al. reported increased collagen deposition, confirmed by Masson trichrome staining, 2 months post-intradermal BoNT injection [134]. Mechanistically, BoNT may influence fibroblast collagen homeostasis by modulating interactions between acetylcholine and nicotinic acetylcholine receptors (α3 and α7 subtypes) [135, 136].

Emerging data suggest BoNT may positively influence skin pigmentation [137, 138]. Preclinical findings indicate that BoNT can inhibit UV-induced melanogenesis by reducing tyrosinase activity and suppressing melanocyte function [139]. Jung et al. further demonstrated BoNT uptake by cultured human melanocytes and keratinocytes, with both cell types exhibiting diminished melanin synthesis following exposure [139].

For optimal aesthetic outcomes, BoNT should be delivered intradermally in consistent microdroplet volumes [140]. Hyperdilution with minimal dosage is generally recommended; insufficient dosing may yield inadequate effects, whereas excessive dosing risks diffusion into deeper musculature with unintended functional consequences [140]. Standard technique employs a 30- or 32-gauge needle to deposit 0.03–0.05 mL of product per injection site, spaced 0.8–1.0 cm apart in a grid-like distribution, producing small wheals at each point [140]. The rejuvenating effects typically last 1–3 months. A notable advantage of BoNT skin rejuvenation is its compatibility with other injectable agents in so-called "mesococktail formulations," allowing synergistic enhancement without compromising the efficacy of individual components [140]. Overall, intradermal BoNT-A offers a cost-effective, low-risk intervention with a reasonable duration of action, and its versatility has led to widespread use across multiple aesthetic indications [140].

2.4.3 | Spicules

Spicules are microscopic, needle-shaped structures that occur naturally in marine sponges, functioning as skeletal components composed of either silica or calcium carbonate. Their rigid, pointed architecture enables them to provide structural reinforcement while serving as a natural defensive feature. In dermatologic practice, spicules have been adapted as a mechanical transdermal delivery system, leveraging their capacity to penetrate the stratum corneum with minimal discomfort or tissue injury [141]. This property makes them particularly effective for facilitating the penetration of active compounds in both medical and cosmetic treatments. Commercial spicule-based systems include Reedle Booster (Evov Therapeutics Inc., Korea), which leverages siliceous spicules to enhance transdermal delivery.

In the field of cosmetic dermatology, recent advancements have explored the use of spicules as delivery platforms for bioactive agents, including EGF and pectolinarin, to facilitate penetration into the deeper dermal layers. Kim et al. demonstrated that purified siliceous spicules can be incorporated with compounds and applied topically, achieving superior dermal uptake compared to traditional delivery techniques. Their findings indicated a notably high absorption rate of 73.4%, with release kinetics governed by principles consistent with Fick's law of diffusion and the Higuchi release model [142].

Clinical evidence further supports the therapeutic potential of spicules. In a split-face comparative trial, Ha et al. enrolled 20 participants presenting with periocular wrinkles to evaluate micro-spicules embedded with epidermal growth factor (MS-EGF) against a conventional EGF cream. The MS-EGF–treated areas demonstrated statistically significant enhancements in dermal thickness, tissue density, and wrinkle reduction, as assessed by high-resolution ultrasound imaging and digital skin analysis. These findings indicate that MS-EGF facilitates superior intradermal delivery of EGF, most likely through improved transdermal penetration and subsequent activation of fibroblast-mediated dermal remodeling [143].

Compared with conventional injectable skin boosters—including HA, PDRN, and PN—spicule-based therapies present a needle-free modality that nevertheless induces collagen synthesis and supports dermal regeneration. The application of spicules produces controlled micro-injury to the skin surface, thereby triggering wound-healing cascades and promoting ECM remodeling [1]. Furthermore, spicules can be co-formulated with other bioactive agents, such as HA, growth factors, and peptides, to achieve synergistic rejuvenation effects while avoiding the procedural risks typically associated with injection-based approaches [34].

In addition to facilitating transdermal penetration, spicules can function as microstructured scaffolds enabling the prolonged release of active agents. Their capacity to adsorb or polymer-encapsulated compounds, followed by their controlled diffusion across the skin barrier, opens new avenues for therapeutic application. The inherent physical and chemical stability of spicules, coupled with their favorable biocompatibility, underscores their potential as a versatile platform for sustained drug or cosmeceutical delivery within both aesthetic and dermatological practice [142].

In summary, the use of spicules—whether delivered via injection or applied topically—offers a novel, minimally invasive strategy for skin rejuvenation. This modality effectively narrows the divide between conventional, passive cosmetic treatments and fully invasive dermatologic interventions by concurrently facilitating transdermal delivery and activating intrinsic skin repair pathways. Continued advancements in research and formulation science are anticipated to refine their composition and expand their clinical utility, particularly in the management of age-associated cutaneous changes.

2.4.4 | Ethosome

Ethosomes are lipid-based nanocarriers first introduced in 2000 as a next-generation evolution of liposomes. They are primarily composed of phospholipids, water, and a high ethanol concentration (20%–45%), which disrupts the stratum corneum lipids and enhances vesicle deformability [144]. This unique structure allows ethosomes to encapsulate both hydrophilic and lipophilic agents and achieve superior penetration into deeper skin layers compared with conventional liposomes or creams. The ethanol component increases skin permeability by fluidizing the stratum corneum lipid bilayers, while phospholipids provide structural stability and facilitate fusion with cell membranes [144].

Ethosomes have been investigated for multiple cosmetic and dermatologic applications. In the cosmetic field, they have been explored as carriers for minoxidil and finasteride to enhance follicular penetration in androgenic alopecia, tretinoin and benzoyl peroxide for acne, and hydroquinone, kojic acid, and vitamin C for hyperpigmentation [144]. Formulation studies consistently demonstrated improved dermal deposition and enhanced bioavailability of these agents compared with traditional delivery vehicles.

A novel development is ethosome-based photothermal therapy (PTT), where ethosomes are engineered to encapsulate gold and platinum nanoparticles along with active cosmetic ingredients [145]. Upon near-infrared laser exposure, the metal nanoparticles generate localized heat via surface plasmon resonance, selectively ablating sebaceous glands and stimulating dermal collagen synthesis without scarring. Clinical pilot treatments combining ethosome-PTT with Q1064 lasers demonstrated reduction in acne lesions, improvements in skin texture, and decreased post-inflammatory hyperpigmentation [145]. A commercial implementation is marketed as Ethosome PTT (N-finders, Seoul, Korea), which incorporates gold and platinum within a multi-layered ethosomal vesicle and is promoted for use alongside Pico, Q-switched, and long-pulse lasers to enhance intradermal delivery of actives.

Ethosomes represent a versatile nanocarrier system capable of enhancing dermal delivery of cosmetic actives and expanding therapeutic strategies in aesthetic dermatology. Their ability to combine conventional active ingredients with nanotechnology and, more recently, integrate photothermal approaches underscores their potential to bridge topical skincare and procedural dermatology. Ongoing optimization of formulations, stability, and long-term safety will be crucial to translating ethosomal technologies into routine aesthetic practice. With continued innovation, ethosomes may emerge as both standalone boosters and multifunctional platforms synergizing with devices such as lasers and microneedling for comprehensive skin rejuvenation.

2.4.5 | Tranexamic Acid

Tranexamic acid (TA) is a synthetic lysine analogue that functions as a reversible plasmin inhibitor [146]. By occupying lysine binding sites on plasminogen, TA prevents its conversion to plasmin, thereby suppressing plasmin-induced release of arachidonic acid and subsequent inflammatory mediators. In dermatology, this antifibrinolytic action translates into reduced melanocyte tyrosinase activity, stabilization of the dermal–epidermal junction, and inhibition of VEGF release [147]. Collectively, these mechanisms contribute to its efficacy in downregulating

melanogenesis and improving hyperpigmentary disorders such as melasma. The therapeutic role of TA in melasma has been evaluated through oral, topical, microneedling-assisted, and intradermal delivery routes [147].

In a prospective pilot study, Lueangarun et al. assessed the long-term efficacy of intradermal TA injections (4 mg/mL every 2 weeks for seven sessions) in five women with Fitzpatrick skin types IV–V [148]. At 16 weeks, patients demonstrated a 33% reduction in modified Melasma Area and Severity Index (mMASI) scores and significant decreases in melanin index, accompanied by high satisfaction. However, by 48 weeks, melasma recurrence occurred in 60% of participants, although pigmentation severity remained below baseline. Importantly, no systemic side effects were observed, and local adverse reactions (erythema, swelling, injection pain) were mild and transient.

More recently, Hosfiar et al. conducted a randomized, double-blind, split-face trial in 32 women with melasma and Fitzpatrick skin types IV–V [149]. Patients received intradermal TA injections (10 mg/mL) or placebo on opposite facial halves, alongside daily hydroquinone and sunscreen. After 12 weeks, the TA-treated side showed significantly greater mMASI reduction compared with placebo (mean difference −0.82, $p = 0.009$). While melanin and erythema index reductions were observed bilaterally, differences were not statistically significant. Adverse events, including transient pain and small hematomas, were self-limited and no systemic complications were reported.

Tranexamic acid represents a safe and effective adjunctive therapy for melasma, particularly in patients with darker phototypes. Intradermal delivery provides localized pigment suppression while minimizing systemic exposure. Clinical studies consistently demonstrate significant short-term improvements, though recurrence following cessation is common [148, 149]. Future research should focus on optimizing dosage, treatment intervals, and multimodal combination strategies (e.g., with topical agents or energy-based devices) to improve durability of response. With robust clinical validation, TA may establish itself as a cornerstone injectable option for hyperpigmentation management in aesthetic dermatology. Commercial topical options also exist—for example, SkinCeuticals Discoloration Defense (SkinCeuticals, USA)—which is often used adjunctively in daily regimens. With robust clinical validation, TA may establish itself as a cornerstone injectable option for hyperpigmentation management in aesthetic dermatology.

2.4.6 | Glutathione

Glutathione is a tripeptide composed of glutamine, cysteine, and glycine, and serves as the body's principal intracellular antioxidant. Within dermatological contexts, Glutathione is recognized for its capability to inhibit tyrosinase by chelating copper ions at its active site and shifting melanin synthesis from eumelanin toward lighter pheomelanin, thereby contributing to skin lightening and brightening [150]. Beyond its role in pigmentation modulation, Glutathione protects dermal fibroblasts and keratinocytes against oxidative damage, indirectly supporting collagen integrity and epidermal health. Through its antioxidant properties, Glutathione helps to neutralize reactive oxygen species, reduce photoaging, and maintain skin barrier function, which together promote healthier and more resilient skin [8, 150]. Lorient Element, developed by Joonghun Pharmaceutical in Korea, is a dual-vial topical skin booster engineered to address post-procedure pigmentation, dullness, and skin barrier compromise. Vial 1 serves as a vehicle composed of non-crosslinked hyaluronic acid and acetylated hyaluronic acid, providing immediate hydration and facilitating optimal penetration of active ingredients. Vial 2 contains a precisely formulated pure element blend: glutathione 51%, ascorbic acid 28%, tranexamic acid 17%, and niacinamide 2%. This synergistic combination targets melanogenesis at multiple pathways—glutathione and ascorbic acid provide potent antioxidant and reducing effects, tranexamic acid interrupts plasmin-induced pigment activation, and niacinamide reinforces barrier function while inhibiting melanosome transfer. Designed for in-clinic application and post-procedure recovery, Lorient Element calms sensitised skin, improves hydration, and promotes brighter, clearer skin. It serves as a valuable adjunct to pigment-focused treatments such as laser, chemical peeling, or microneedling, helping clinics optimise outcomes, enhance patient satisfaction, and expand revenue opportunities through a non-invasive topical booster. In a 2025 survey of Korean board-certified dermatologists, Lorient Element was recognized for its efficacy in treating melasma, lentigo, and uneven skin tone, with practitioners frequently pairing it with fractional lasers, plasma-assisted delivery systems, or microneedle RF to enhance penetration and address post-inflammatory hyperpigmentation and background dyschromia that are otherwise difficult to manage with EBDs alone [151].

In clinical aesthetics, glutathione is rarely used as a standalone injectable because of formulation instability and variable clinical durability. It is more often incorporated into combination mesotherapy strategies or used adjunctively with energy-based procedures, although high-quality comparative evidence remains limited.

2.4.7 | Ascorbic Acid

Ascorbic acid, known as Vitamin C, is a water-soluble micronutrient that humans must obtain exogenously through diet or supplementation. It serves as a potent antioxidant and an essential cofactor in multiple enzymatic reactions throughout the body. In dermatology, ascorbic acid is valued for its unique ability to influence collagen metabolism, protect against oxidative stress, and modulate pigmentation pathways, making it an attractive component in aesthetic and regenerative treatments [152–155]. At the molecular level, ascorbic acid supports collagen biosynthesis by acting as a cofactor for prolyl- and lysyl-hydroxylases, enzymes required to hydroxylate proline and lysine residues in procollagen. This hydroxylation stabilizes the collagen triple helix, facilitating the assembly of mature collagen fibers within the dermis [152]. Furthermore, ascorbic acid regulates transcription factors involved in extracellular matrix turnover and enhances fibroblast proliferation, directly contributing to dermal remodeling and wrinkle reduction.

Ascorbic acid also plays a pivotal role in antioxidant defense and pigmentation control. By scavenging reactive oxygen species, it

protects dermal proteins from oxidative degradation and photoaging. In melanocytes, ascorbic acid reduces melanin synthesis by inhibiting tyrosinase activity and interfering with the oxidation of dopaquinone, thereby contributing to skin brightening [153]. In addition, it interacts with other antioxidants such as vitamin E and glutathione, regenerating their reduced forms and amplifying the skin's intrinsic defense network.

In aesthetic practice, ascorbic acid is rarely used as a standalone skin booster because of instability and irritancy at higher concentrations. It is more commonly delivered through mesotherapy cocktails, antioxidant combination regimens, or topical support protocols designed to complement collagen-stimulatory procedures.

Author Contributions

All authors have reviewed and approved the article for submission. Conceptualization: Kyu-Ho Yi and Hyunggyu Kang. Writing – original draft preparation: Kyu-Ho Yi, Hyunggyu Kang, Jong Keun Song, and Olena Sydorchuk. Writing – review and editing: Jeremy B. Green, Olena Sydorchuk, Hugues Cartier, Hyunggyu Kang, and Kyu-Ho Yi. Visualization: Benjamin Ascher, Roya Zarmehr Zamin, Hyunggyu Kang, and Kyu-Ho Yi. Supervision: Kyu-Ho Yi.

Funding

The authors have nothing to report.

Ethics Statement

This article is a review of previously published studies and does not involve any original research involving human participants or animals conducted by the authors. Therefore, ethical approval was not required.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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