

The Effectiveness of Injectable Hyaluronic Acid in the Improvement of the Facial Skin Quality: A Systematic Review

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Background: Several studies have evaluated the role of various injectable formulations of hyaluronic acid (HA) in the improvement of the quality of facial skin. It is important to systematically summarize the available evidence in this regard.

Methods: Relevant databases were searched for clinical studies that evaluated the therapeutic role of any injectable formulation of HA in improving the quality of facial skin in adult humans until 31 December 2022. The available studies were critically analyzed and the data were extracted.

Results: A total of 2996 articles were screened and 13 studies were finally included. Eight studies evaluated the effect of various formulations of HA alone, while five evaluated the effect of various formulations of HA along with other active ingredients (cocktails) on the quality of facial skin. All types of HA formulations cause a significant improvement in facial skin quality, in terms of hydration, firmness, skin-tiring effect/fatigue, brightness, texture, radiance, and elasticity. The effect of HA monotherapy was more pronounced than that of the cocktail ingredients. HA treatment was quite safe and the patient satisfaction level was high.

Conclusion: The clinical evidence on the use of injectable HA alone in the improvement of the quality of facial skin, in terms of hydration, firmness, skin-tiring effect/fatigue, brightness, texture, radiance, and elasticity, is quite promising. Large randomized controlled trials are required in this regard.

Keywords: face, hyaluronic acid, HA, skin booster, skin quality

Introduction

The dermis, a layer of skin beneath the surface, is made up of three main components: collagen, elastin, and ground substance. These components, which are largely produced by fibroblasts, are essential for maintaining the normal structure and function of the skin.¹ Each component plays a unique role in maintaining the normal structure and function of human skin.¹ They help keep the skin healthy by performing various physiological functions and biosynthetic activities.²

Skin aging is a complex process that is influenced by both inherited genetic factors and external environmental factors. Recent research has shown that skin aging is not simply a result of the passage of time, but rather it is also influenced by a wide range of external factors known as the “exposome”. The exposome refers to all of the environmental exposures that a person experiences throughout their lifetime, such as UV radiation, pollution, and diet, which can contribute to the aging of the skin. Understanding the various factors that contribute to skin aging can help individuals make informed decisions about how to care for their skin and may potentially help to slow the aging process.³ There are many external factors that can contribute to the aging of the skin, such as environmental exposures, lifestyle habits, and chronic diseases. These factors can accelerate the aging process and should be taken into consideration by dermatologists and other healthcare providers when assessing an individual’s skin aging concerns and determining strategies for minimizing or delaying it. It is important for individuals to be

aware of these factors and to take steps to protect their skin from harmful exposures, maintain a healthy lifestyle, and manage any underlying health conditions in order to support healthy, youthful-looking skin.⁴

Hyaluronic acid (HA) is a chemical that plays a key role in maintaining normal skin moisture levels.⁵ HA first gained attention in the medical field in the 1970s and 1980s when it was used in ophthalmic surgery. Since then, its use in dermatology has grown significantly due to its ability to retain moisture, improve skin texture and elasticity, and provide a variety of other benefits. HA is now commonly used in a variety of skin care products, including filler injections and cosmeceuticals, to help improve the overall quality of the skin.^{6,7} Clinical studies in dermatology have often focused on evaluating the elasticity and hydration of the skin in order to assess overall skin quality, particularly in relation to aging skin.⁸

HA injectable formulations have been used in recent years as a means of improving skin quality in addition to their traditional use for filling wrinkles and adding volume to the face. These treatments work by injecting HA into the dermis, the layer of skin beneath the surface. HA helps to hydrate the skin and create a stable extracellular matrix, which is a supportive structure that is essential for the normal function of the fibroblasts in the dermis. This can help to improve the overall quality of the skin, including its elasticity, hydration, and texture. The procedure is relatively quick and non-invasive and can be used to address a range of skin concerns related to aging and other factors.⁹ There are a number of ways to improve the structural integrity and appearance of aging skin, and injectable formulations of HA are one option that has been studied extensively. These treatments work by injecting HA into the dermis, the layer of skin beneath the surface, where it helps to hydrate the skin and support the normal function of the fibroblasts, the cells responsible for producing collagen and elastin. This can help to improve the overall quality of the skin. There have been several studies that have evaluated the effectiveness of various injectable HA formulations in improving skin quality, and it is important to review and summarize this evidence in order to understand the potential benefits and risks of these treatments.

Materials and Methods

Study Design

We aimed to include published original clinical research studies that evaluated the therapeutic role of any injectable formulation of HA in improving the quality of facial skin in adult humans. Pre-clinical studies, case reports, case series, reviews, commentaries, view points, or opinions were excluded. Studies that evaluated the therapeutic role of HA on augmentation of the facial contour (eg nasolabial fold augmentation, malar augmentation, lip augmentation, temple hollowness, upper orbital hollowness, deflated earlobes, etc.), those which used topical formulations of HA alone or in combination, those which had evaluated the effect of HA on the quality of skin apart from the face, and those which used an ex vivo explant model were excluded. The primary outcome of this study was the effect of various formulations of HA on facial skin quality. The secondary outcome was the safety of these formulations.

Search Strategy

PubMed, Embase, ClinicalTrials.gov, World Health Organization - International Clinical Trials Registry Platform, Cochrane Library databases [Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Methodology Register], and two pre-print servers (medRxiv.org and Research Square) were searched from inception until 31Dec 2022. The search terms used in various combinations were: “cheek”, “face”, “mid-face”, “malar”, “filler”, “hyaluronic acid”, “HA”, “hyaluronan”, “cosmetics”, “cosmeceuticals”, “cosmetology”, “Skin aging”, “aging treatment”, “skinboosters”, “skin boosting”, “boosters”, “exosome”, “Juvederm”, “Restylane”, “Perlane”, and “Belotero”. These search terms were adapted for use with different bibliographic databases in combination with database-specific filters for studies, if available. The search strategy was used to obtain the titles and the abstracts of the relevant studies in the English language, and they were independently screened by two authors, who subsequently retrieved abstracts, and if necessary, the full text of articles to determine the suitability.

Analysis of the Selected Articles

Two authors independently extracted data using a standardized data extraction spreadsheet. The extracted data included the general characteristics of the articles, population, intervention, and outcome of interest (according to the study

objectives). During data extraction, no simplifications or assumptions were made. All the studies were critically analyzed. The risks of bias of each study were analyzed by the Cochrane risk of bias tool¹⁰ for the randomized controlled trials and the Newcastle-Ottawa scale¹¹ for the observational studies. Data related to the key efficacy and safety outcomes related to the use of HA from the included studies were noted. Two authors independently validated the assessment, and discrepancies or disagreements were resolved in consultation with a third author.

Results

A total of 2996 articles were screened and 15 studies^{12–26} met our eligibility criteria and were finally included (Figure 1). There was one randomized controlled trial,¹⁵ one non-randomized observational study,²⁵ and 13 observational studies.^{12–14,16–24,26} Eight studies^{12–19} evaluated the effect of various formulations of HA alone, while five^{22–26} evaluated the effect of various formulations of HA along with other active ingredients (cocktails) on the facial skin quality. The summary of all the included

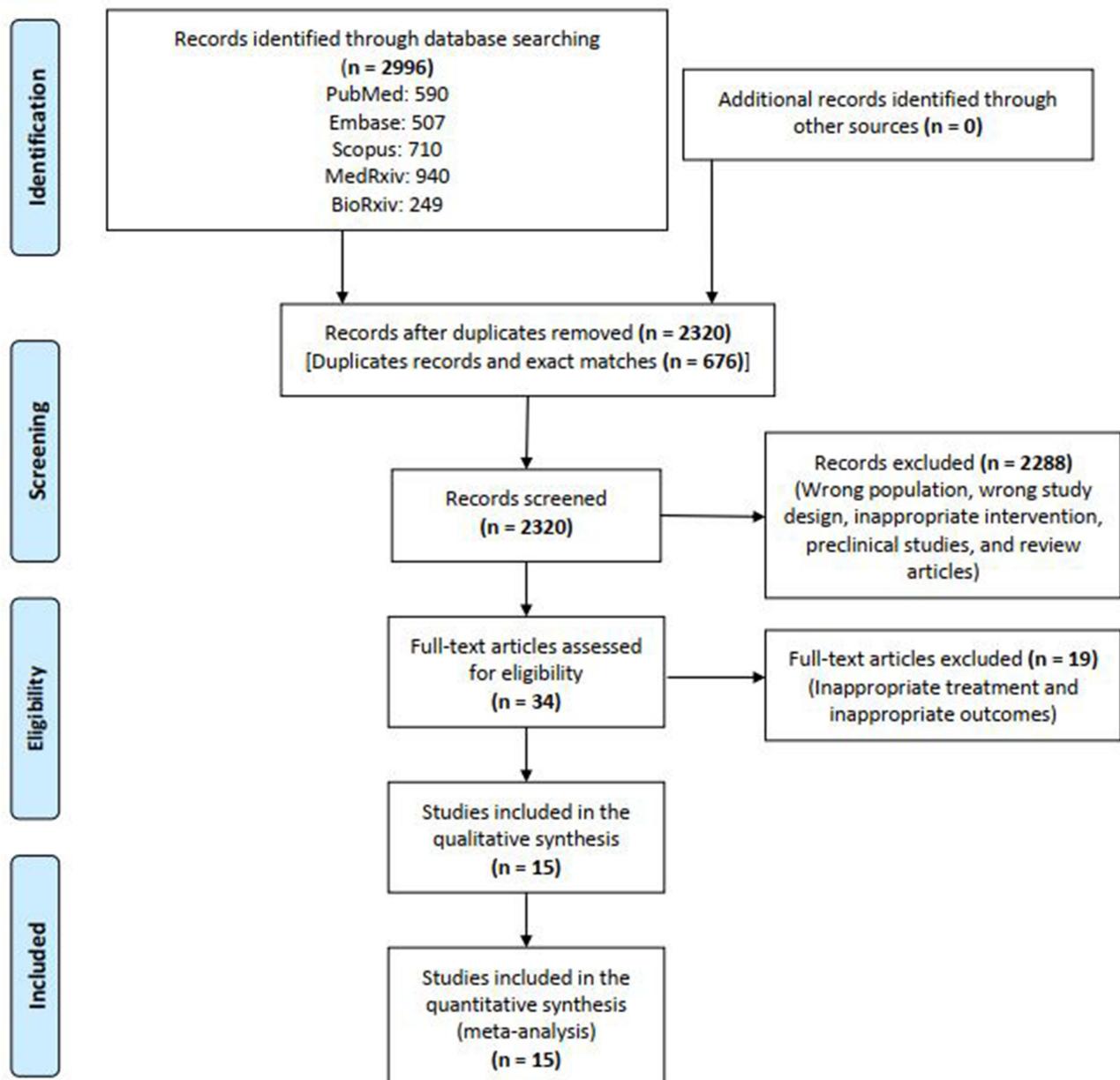


Figure 1 Study flow chart depicting the steps of the synthesis of evidence from the literature.

studies is enumerated in [Table 1](#) and [Table 2](#). The risk of bias in the included studies is depicted in [Tables s1](#) and [s2](#) ([Supplementary Material](#)). Most of the studies had a moderate risk of bias.

Most of the studies used subjective endpoints, such as Global Aesthetic Scale, Subject Global Impression of Change Scale, Wrinkle Severity Rating Scale, Allergan Skin Roughness Scale, Allergan Fine Lines Scale scores, etc. Some of the

Table 1 Characteristics of the Studies Using Various Formulations of Hyaluronic Acid (HA) Alone for Improving Facial Skin Quality

Author, Year	Country	Hyaluronic Acid Formulations Used	Mode of Administration	Treatment Protocol	n	Age (Years)	Key Findings
Kerscher et al 2008 ¹²	Germany	Stabilized HA-based gel of non-animal origin	Mid-dermal placement	Three treatment sessions 4 weeks apart	19	54±10	Skin elasticity and surface roughness improved significantly, and patient feedback was positive
Reuther et al 2010 ¹³	Germany	Stabilized HA-based gel of non-animal origin	Micropuncture injections	Three treatment sessions four 4 apart	19	54±10	Significantly increased skin firmness and improved viscoelastic recovery capacities
Streker et al 2013 ¹⁴	UK	Stabilized HA-based gel of non-animal origin	Micropuncture injector device	Three treatment sessions 4 weeks apart	30	40–65	Overall skin quality was improved throughout the study and significant aesthetic improvements were observed
Sundaram et al 2018 ^{15*}	USA	Cross-linked HA	Multiple injections	Four sessions at 15-day intervals	24	35–55	Statistically significant improvements in skin surface topography and hydration in terms of moisture, tone/complexion, radiance, texture, uniformity, and global appearance
Hertz-Kleptow et al 2019 ¹⁶	Germany	Cohesive polydensified matrix HA	Multiple injections	Three injections 4 weeks apart	25	36±5	Effective and safe for skin revitalization
Niforos et al 2019 ¹⁷	France	Cross-linked HA gel	Intradermal injection	30 days and optional repeat treatment after 9 months	131	32–72	Safely and effectively improved skin smoothness and hydration
Ayatollahi et al 2020 ¹⁸	Iran	Small particles of HA	Multiple injections	Three injections 3 weeks apart	20	40.15 ±6.63	Skin hydration increased, skin firmness was reduced, skin-tiring effect/fatigue was reduced, and skin elasticity increased
Kleine-Börger et al 2022 ¹⁹	Germany	Small particles of HA	Microinjections	Microinjections 4 weeks apart	15	25–45	Significantly improved biomechanical viscoelastic skin properties
Nikolis et al 2018 ²⁰	Canada	Small particles of HA	Microinjections	Three injections 4 weeks apart	20	30–75	Significantly improved hydration
Hsieh et al 2022 ²¹	China	Cross-linked HA	Microinjections	Three injections 4 weeks apart	8	35–50	Stimulated the production of collagen and other extracellular collagen components and restored the structural integrity of dermal microenvironment

Note: *Randomized controlled trials. All other studies were observational studies.

Abbreviations: HA, hyaluronic acid; UK, United Kingdom; USA, United States of America.

Table 2 Characteristics of the Studies Using Various Formulations of Hyaluronic Acid (HA) Along with Other Active Ingredients (Cocktail) for Improving Facial Skin Quality

Author, Year	Country	Hyaluronic Acid Formulations Used	Mode of Administration	Treatment Protocol	n	Age (Years)	Key Findings
Amin et al 2006 ²²	USA	HA and multivitamin solution	Multiple injections	Injections at 4 monthly intervals	10	–	No significant clinical or histologic changes
Taieb et al 2012 ²³	France	Uncross-linked HA and mannitol	Depot and picotage injection technique	Single dose	34	29.5–59.9	Aesthetic parameters were improved and subjects were delighted with the treatment
El-Domyati et al 2013 ²⁴	Egypt	Non-cross-linked high-viscosity HA and multivitamin solution	Multiple injections	Three-month (six sessions at two-week intervals)	6	37–49	No significant clinical or histologic changes
Savoia et al 2013 ^{25*}	Italy	HA, vitamins, amino acids, minerals, coenzymes, and antioxidants	Multiple injections	Four sessions at 15-day intervals	50	35–65	Significant clinical improvement in terms of brightness, texture, and firmness; biopsies showed decreased inflammatory markers
Draeos et al 2016 ²⁶	USA	Recombinant epidermal growth factor with a filler grade HA	Multiple injections	Three injections 4 weeks apart	60	–	Significantly improved skin smoothness, firmness, radiance, and overall appearance; transepidermal water loss was reduced

Note: *Non-randomized interventional study. All other studies were observational studies.

Abbreviation: USA, United States of America.

studies used histology and immunohistochemistry. Some studies have used biophysical evaluations, such as noninvasive suction skin elasticity meter or cutometer (to measure elasticity), corneometer (to measure skin hydration), spectrophotometer (to measure skin pigmentation), high-resolution camera (to measure skin surface morphology), and ultrasound scanner (to measure skin thickness and density).

Regarding the use of HA monotherapy, stabilized HA-based gel of non-animal origin, cross-linked HA, and small particles of HA were most commonly used. The sample size of the studies ranged from 15 to 131 and the age of the patients ranged from 25 to 65 years. More than 80% of the study population was female. All studies showed significant improvement in facial skin quality in terms of skin hydration, skin firmness, skin-tiring effect/fatigue, and skin elasticity. More than 95% of the patients were quite satisfied with the treatment outcomes.

Regarding the use of HA monotherapy along with other active ingredients (cocktail), multivitamins were commonly used along with HA. The sample size of the studies ranged from 6 to 60 and the age of the patients ranged from 29.5 to 75 years. More than 85% of the study population was female. Three studies showed significant improvement in facial skin quality in terms of brightness, texture, radiance, and firmness, while two studies showed no significant clinical or histologic changes in facial skin quality. Patient satisfaction varied. However, two studies^{22,24} showed negative results.

All HA formulations were very well tolerated and no major safety issues were noted in any studies. The most common adverse events included bruising, swelling, and tenderness, which typically lasted for less than two weeks.

Discussion

In this study, we found that facial skin boosting using HA alone could significantly improve skin quality. HA along with other active ingredients also showed beneficial effects and the treatment was found to be quite safe. A majority of the

patients, particularly those who received HA monotherapy, were highly satisfied with their results following HA treatment. This reinforces the fact that HA injections are an integral part of facial aesthetics. HA products are similar but not interchangeable.²⁷ Individual patient assessment and an understanding of facial aging are necessary for optimal results with HA injections.

HA is a common ingredient in many cosmetic products due to its ability to retain moisture and improve the texture and elasticity of the skin. It is known for its excellent hygroscopic, rheological, and viscoelastic properties, which make it an effective choice for a range of skin care products. Some research has suggested that HA may have beneficial effects when used topically in dermatological practice, although more studies are needed to fully understand its potential effects.²⁸ There is a growing body of evidence suggesting that HA is well-tolerated and effective when used in combination with various facial rejuvenation procedures, such as botulinum toxin type A, photodynamic therapy, fractional CO₂ laser skin resurfacing, fillers, microneedling, and chemical peeling. Clinical studies have generally found that HA-based cosmeceuticals, which are skin care products that contain HA and other active ingredients, can help to improve skin hydration, rejuvenation, and healing. In addition to advising patients about healthy lifestyle habits and skin protection, dermatologists can recommend the use of HA-based cosmeceuticals as a way to counterbalance the negative impact of external factors on the skin (exposome). These products may be useful for helping to maintain healthy, youthful-looking skin and may be suitable for people of all skin types and concerns.^{28,29}

HA has been shown to be effective in improving the quality of facial skin, particularly when used in consecutive treatments spaced a few weeks apart. This may be due to the viscoelastic properties of HA, which help to improve skin elasticity and firmness. It is generally recommended that patients with mild loss of skin elasticity and firmness receive a single treatment, while those with more pronounced changes in skin quality may benefit from three consecutive treatments in order to gradually improve skin fatigue and firmness.¹⁹ Some studies have shown negative results when using a cocktail regimen of HA, which may be due to differences in the concentration and particle size of the HA used. Overall, HA appears to be a promising option for improving skin quality and addressing a range of skin concerns related to aging and other factors.

HA is thought to play a role in skin rejuvenation due to its viscoelastic properties. When applied to the skin, HA forms a condensed network within the connective tissue that helps to attract water into its matrix. This can improve skin turgor, or firmness, and stimulate the production of collagen fibers, which are important for maintaining the structure and elasticity of the skin. Additionally, HA may help to modulate the elongation of collagen fibers, which can help to improve the overall quality and appearance of the skin.³⁰ It is well-established that collagen fibers in the extracellular matrix, which is a supportive structure in the skin, have a faster turnover rate than elastin fibers. This means that collagen is more quickly replaced in the skin than elastin, which is a protein that helps to give the skin its elastic properties.¹⁹ HA products with larger particles and higher densities are typically injected into the upper subcutaneous layer of the skin, while those with smaller particles and lower densities are typically injected into the dermis. The subcutaneous layer is the layer of tissue beneath the skin that contains fat cells and blood vessels, while the dermis is the layer of skin beneath the surface that contains collagen, elastin, and other supporting structures. In general, smaller HA particles are able to attract and hold more water in the skin, without adding volume, compared to larger particles.¹³

Skin boosting with small HA particles is a new method of skin rejuvenation. There are several studies and case reports proving the skin boosting idea as a novel treatment for skin improvement using injectable cross-linked HA.^{31,32} “Skin boosting”, has been shown to have a number of potential benefits for the skin. By increasing the hydration of the skin, skin boosting with HA may help to delay or reverse the aging process, reduce the appearance of aging indicators such as wrinkles and sagging skin, and improve the overall quality of the skin.

There are several commercial products available that contain small particles of HA and are designed to be injected into the dermis to boost skin hydration. These products typically have a concentration of HA ranging from 13.5 to 20 mg/mL and are administered in small aliquots using a series of punctures in order to distribute the product evenly over the treated area. Once injected, the HA attracts water into the skin matrix, which can help to improve skin turgor, add extra volume, and refine the skin structure.³²

The goal of using small particle HA injections, or “microinjections”, as a skin treatment is not just to increase hydration, but also to stimulate the activity of fibroblasts, the cells responsible for producing collagen and elastin. The

skin's mechanical behavior is not purely elastic, but rather it is viscoelastic, meaning that it exhibits both elastic and viscous behavior. This is due to the presence of collagen and elastin fibers in the skin, which respond to mechanical stresses in different ways. By injecting cross-linked HA into the dermis, it is thought that the extracellular dermal scaffold, which is the supportive structure in the skin, may be restored more diffusely and uniformly, compared to more localized injections used for correcting wrinkles or adding volume. This may help to improve the overall quality and appearance of the skin, including its elasticity, hydration, and texture.¹² According to a review of the available evidence, skin boosting with small particle HA injections may have a number of beneficial effects on the skin, including improving hydration, elasticity, anisotropy, roughness, and radiance.¹² To achieve these effects, it is generally recommended that patients receive a series of monthly treatments in order to adequately stimulate and restore the extracellular matrix, which is the supportive structure in the skin. The specific number and frequency of treatments will depend on the individual's skin concerns and goals and may vary from person to person. Skin boosting with HA injections may be suitable for people of all skin types and concerns and may be used as a standalone treatment or in combination with other skin care procedures.

Regarding the safety aspect, HA treatment in the face was generally mild and self-limiting.³³ While generally safe and well-tolerated, skin boosting with HA injections can carry the risk of certain complications, such as lumpiness, nodules, and extrusion of the filler material. The incidence of these complications may vary depending on the type of HA product used and the individual's specific skin concerns and goals. Some research suggests that the risk of nodule formation may be lower with HA compared to other skin boosters, such as poly-L-lactic acid, although more research is needed to confirm this.³⁴ The formation of nodules after skin boosting with HA injections may be due to a number of factors, including a delayed inflammatory reaction, an infectious biofilm process, the location of the injection, and the volume of the injection. To reduce the risk of nodule formation, it is important to thoroughly clean the skin with an antiseptic prior to injecting the HA.³⁵ Furthermore, placing injections deep into the muscle in the upper cheeks and the deep subcutaneous in the lower cheeks may prevent nodule formation.³⁶

There were a few limitations to the included studies. Some of the studies enrolled very few patients and these studies could have a high fragility index. Most of the studies were not randomized controlled trials, the risk of bias in some of the studies was high, and hence, the quality of evidence generated was low. Most of the studies did not use any hard endpoint. The long-term treatment outcomes were not reported in any study. There were a few limitations to our review process as well. Data for all outcomes of interest were unavailable, and hence, either could not be included in the review. Notwithstanding these limitations, to the best of our knowledge, this is the first systematic review to demonstrate the effectiveness of HA as skin booster in the improvement of the quality of facial skin.

Conclusion

Skin aging is a complex biological process affected by both genetic and extrinsic factors. HA has nowadays been used extensively in dermatology due to its hygroscopic, rheological, and viscoelastic properties. The clinical evidence on the use of various injectable formulations of HA alone in the improvement of the quality of facial skin, in terms of hydration, firmness, skin-tiring effect/fatigue, brightness, texture, radiance, and elasticity, is quite promising. The effect of HA monotherapy was more pronounced than that of the cocktail ingredients. However, the results need to be confirmed in robust and large randomized controlled trials.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Disclosure

The authors declare that they have no conflict of interest.

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