



Review

Hyaluronic acid, a promising skin rejuvenating biomedicine: A review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects

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ABSTRACT

Hyaluronic acid (HA) plays multifaceted role in regulating the various biological processes such as skin repairment, diagnosis of cancer, wound healing, tissue regeneration, anti-inflammatory, and immunomodulation. Owing to its remarkable biomedical and tissue regeneration potential, HA has been numerously employed as one of the imperative components of the cosmetic and nutricosmetic products. The present review aims to summarize and critically appraise recent developments and clinical investigations on cosmetic and nutricosmetic efficacy of HA for skin rejuvenation. A thorough analysis of the literature revealed that HA based formulations (i.e., gels, creams, intra-dermal filler injections, dermal fillers, facial fillers, autologous fat gels, lotion, serum, and implants, etc.) exhibit remarkable anti-wrinkle, anti-nasolabial fold, anti-aging, space-filling, and face rejuvenating properties. This has been achieved via soft tissue augmentation, improved skin hydration, collagen and elastin stimulation, and face volume restoration. HA, alone or in combination with lidocaine and other co-agents, showed promising efficacy in skin tightness and elasticity, face rejuvenation, improving aesthetic scores, reducing the wrinkle scars, longevity, and tear trough rejuvenation. Our critical analysis evidenced that application/administration of HA exhibits outstanding nutricosmetic efficacy and thus is warranted to be used as a prime component of cosmetic products.

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1. Introduction

Hyaluronic acid (HA) (molecular formula $C_{28}H_{44}N_2O_{23}$) is a non-sulfated glycosaminoglycan that is composed of repeating polymeric disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine linked via glycoside bond in the arrangement of alternating β -(1 → 4) and β -(1 → 3) bonds (Fig. 1) [1]. The stability of HA structure confides in the stereochemistry of the disaccharides. Due to the natural abundance (animals and human bodies) of this biopolymer, its biodegradability, and biocompatibility appeals for its versatile uses as prognostic molecules and for treatment of a wide range of human and animal diseases. The structure of hyaluronic acid exhibits remarkable ability to hold/trap approximately 1000 times its weight of water. In human synovial fluid, the average molecular weight of HA is 3–

4 million Daltons. It may consist of 10,000 or more disaccharides repeating units in length in ~4 million Da molecular weight of HA [2].

HA has been utilized in various forms such as hydrogel, dermal filler, intradermal injection, scaffolds, creams, films, foams, and gels for treatment of different types of diseases. HA has shown wide range of pharmacological activities including anti-inflammatory [3], wound healing and tissue regenerating [4], immunomodulatory [5], anticancer and anti-proliferative [6], anti-diabetic [7], anti-aging [8], skin repairing [9], and cosmetic properties [10]. HA plays multifaceted role in regulating various the biological processes and maintaining homeostasis in the body.

HA has been found at the periphery and at interfaces of collagen and elastin fibers where it facilitates holding collagen and elastin in a proper configuration. In the aged skin, these connections with HA are particularly absent, which may contribute to the disorganization of collagen and elastin fibers might leads to the presence of skin fine line, wrinkle and nasolabial folds. HA has become one of the most crucial ingredients in the cosmetic as well as nutricosmetic products.

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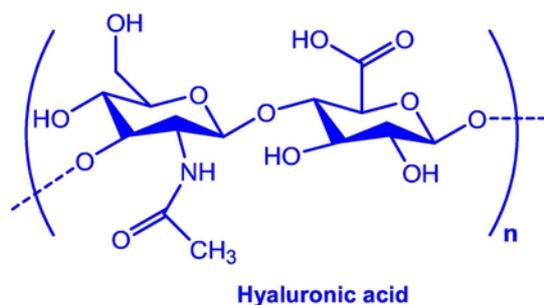


Fig. 1. Chemical structure of hyaluronic acid.

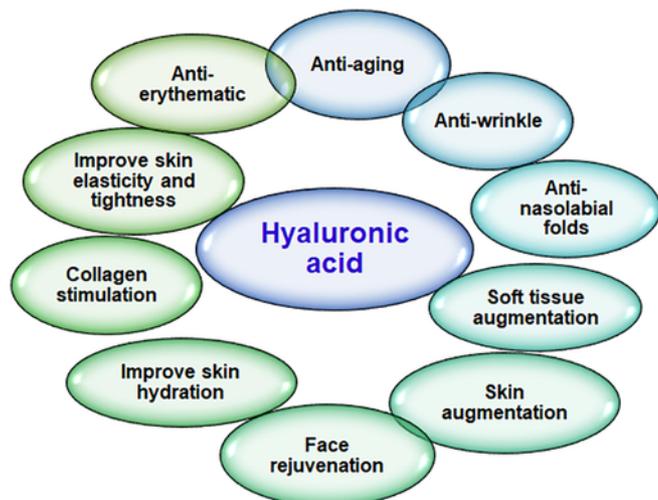


Fig. 2. Summary of cosmetic and nutraceutical effects of HA.

Almost all products having moisturizing, skin protective, and anti-aging properties consists of HA. It has been acknowledged for its ability to replenish moisture in the skin. The water holding ability of HA results in softer, smoother, and radiant skin. The hydration of the skin also leads to slow down the wrinkle formation and improves deep fine lines and already developed wrinkles which generally appear with age. The skin hydration and antioxidant effects of HA also promote cell regeneration and stimulate production of collagen due to its nutraceutical effects. There are various products of HA being used as dermal filler for cosmetic procedure. HA is non-toxic and non-sensitizing, therefore it is safely used for all types of skin with no risk of allergic reactions. This naturally-occurring biomolecule has commonly been used to inject into the dermis (as dermal filler) to restore skin volume and minimize the appearance of wrinkles as well as nasolabial folds. They are specifically injected into skin folds, deep wrinkles to lift and reshape the face due to its unique characteristics that mimic the natural materials found in our cells. Many studies been done to compare their effectiveness and safety as well as tolerability to the patients. Moreover, some researchers developed a new HA filler with the combination of other material such as lidocaine and carbon dioxide. There is also a combination of administration of HA filler with devices like radiofrequency and non-ablative infrared.

Plenteous researches have investigated the cosmetic and nutraceutical effects of HA for skin rejuvenation. However, there was lacking of critical appraisal of different formulations of HA for a particular type of skin defect and validation on safety and biocompatibility of HA based biomedicines for skin rejuvenation. The aim of the present review is to summarize and critically appraise recent develop-

ments in cosmetic and nutraceutical efficacy of HA based formulations including moisturizing effects, skin hydration, skin smoothing and rejuvenating, and skin regeneration efficacy. A thorough analysis of the literature revealed that HA based formulations (i.e., gels, creams, intra-dermal filler injections, dermal fillers, facial fillers, autologous fat gels, lotion, serum, and implants, etc.) have shown remarkable efficacy to treat a wide range of skin defects such as wrinkles, nasolabial folds, and skin aging. This has been achieved via soft tissue augmentation, improved skin hydration level, collagen stimulation, and face rejuvenation. The safety, tolerability, and efficacy of HA (as intra-dermal or facial filler injection) have also been well-documented for treatment of various types of skin problems. HA, alone or in combination with lidocaine and other agents, produce promising cosmeceutical and nutraceutical effects such as anti-aging, skin tightness and elasticity, face rejuvenation and improved aesthetic scores, reduced wrinkle scars, longevity of rejuvenating effects, and tear trough rejuvenation. The current critical appraisal and comparative analysis of various formulations of HA will enable scientists and researchers to understand pharmaceutical significance and therapeutic and clinical efficacy of HA-based formulations for skin rejuvenation.

2. Biomedical and pharmaceutical implications of HA

HA exhibits versatile algorithm of biomedical and pharmaceutical applications. HA in the form of hydrogel, scaffolds, films, creams, foams, and gels has shown wide ranges of pharmacological activities including anti-inflammatory [3], wound healing and tissue regenerating [4], immunomodulatory [5], anticancer and anti-proliferative [6], anti-diabetic [7], anti-aging [8], skin repairing [9], and cosmetic properties [10].

HA based hydrogels are also capable of rejuvenating injured cardiac tissues in myocardial infarction [11]. The temporal effect of HA hydrogels on left ventricle (LV) remodeling, infarct thinning and expansion, and infarct stiffness has been investigated in a porcine infarct model. HA based hydrogel treatment led to reduced LV volumes, increased wall thickness, and enhanced ejection fraction, when compared to the control groups [11]. HA has also been used in the prevention of urinary tract infections in fertile women. HA is an essential part of bladder surface glycosaminoglycans and encloses the urothelium which may help to prevent urinary tract infections. Breakage to this part has been hypothesized as a causal factor for the progression of recurrent urinary tract infections (RUTIs) [12]. In this study, 28 women who were diagnosed with RUTI, were underwent treatment with intra-vesicular instillations of chondroitin sulfate (CS) and HA. The effectiveness of treatment was evaluated in terms of symptom improvement, reduction of number of episodes of urinary tract infection, and quality of life. The evidence showed that patients treated with CS and HA combined therapy showed remarkable improvement in quality of life and reduction in RUTI episodes [12]. The efficacy of combination therapy with CS and HA has been validated by many researchers [13–15].

HA has also been used as a cosmeceutical to treat wide ranges of skin problems including wrinkles, nasolabial folds, anti-aging, skin augmentation, skin hydration, and collagen stimulator. Due to its strong water-binding potential, HA has been utilized as active ingredient in a large range of cosmetic formulations. HA used to help the skin to hold and maintain elasticity, turgor and moisture. A study was conducted on 76 female subjects (30–60 years age) having clinical signs of peri-ocular wrinkles. They were administered with HA cream formulation to the wrinkled area two time a day for 60 days [16]. A vehicle control cream was applied around the other eye. The skin hydration and elasticity were measured as evaluation parameters.

Table 1

A summary of clinical significance of HA for treatment of wrinkles: human clinical studies.

Cosmetic effect	HA formulation	Application	Experimental model/study design	Study parameters	Key findings	Ref.
Anti-wrinkle effect	Cream 0.1% (w/w) (50, 130, 300, 800 and 2000 kDa, respectively)	Twice daily at periorcular wrinkles for 60 days	76 female aged between 30 and 60 years with clinical signs of periorcular wrinkles	Skin hydration, skin elasticity, wrinkle depth	<ol style="list-style-type: none"> 1. Significant improvement in skin hydration level. 2. Remarkable improvement in skin elasticity. 3. Significant reduction of wrinkle depth due to better penetration abilities of low molecular weight (LMW) HA. 	[28]
	Topical (lotion, serum, and cream)	8 weeks of treatment using a DermaTOP, Corneometer, Cutometer and a Chroma Meter in the periorbital region	33 women with an average age of 45.2	Skin hydration, skin elasticity, skin roughness, wrinkle depth	<ol style="list-style-type: none"> 1. Significant improvement in moisturizing effect of the product range. 2. Significantly improved of the skin elasticity. 3. Remarkable improved in skin roughness. 	[29]
	Cream	3 month trial of the product for daily use.	20 patients assigned in four groups each with a different anti-wrinkle cream containing HA (Balea, Nivea, Lancôme, Chanel)	Wrinkle reduction, skin tightness and elasticity.	<ol style="list-style-type: none"> 1. Significant reduction in the depth of perioral and orbital wrinkles in all groups 2. All groups achieved remarkable increase in skin tightness. 3. Minimal significant changes in skin-elasticity could only be seen in individual groups. 	[30]
	Gel intradermal injection	Treated with either SGP-HA or LGP-HA for 2 weeks.	20 patients aged range 49–65 years with moderate-to-severe wrinkles.	Product safety and effectiveness	<ol style="list-style-type: none"> 1. Indication of aesthetic improvement by Global Aesthetic Improvement Scale (GAIS). 2. Both SGP-HA and LGP-HA were found to be safe and effective for the correction of perioral wrinkles and folds with no serious adverse event occurred. 	[31]
	Injection	6 months treatment of different types of HA E fillers.		The efficacy, patient satisfaction, and safety of new range of hyaluronic acid fillers (HA E) in perioral enhancement.	<ol style="list-style-type: none"> 1. Significant improvement in wrinkle assessment scale and lip fullness. 2. The products were indicated safe and well tolerated. 3. Perioral enhancement with HA E fillers led to sustained effects and high subjects' satisfaction. 	[32]

Table 1 (Continued)

Cosmetic effect	HA formulation	Application	Experimental model/study design	Study parameters	Key findings	Ref.
	Injectable filler	6 months treatment of different types of HA E filler.		The efficacy, patient satisfaction, and safety of the HA E filler range in periorbital rejuvenation	<ol style="list-style-type: none"> 1. HA E Touch effective for periorbital lines; HA E Classic and HA E Deep for the treatment of tear troughs. 2. Clinical improvement in wrinkle severity and aesthetic outcome of all treatments. 3. Treatments were safe and well-tolerated with high level of patients' satisfaction. 	[33]
	Injectable filler	6 months treatment with five different fillers from the same range (HA (E))	77 participants with a mean age of 54.5	The efficacy, patient satisfaction, and safety of the HA E filler range in full-face rejuvenation.	<ol style="list-style-type: none"> 1. Participants were satisfied with the durability of result. 2. Product was indicated effective and safe. 	[34]
	Injection filler	6 months treatment using BoNT-A and 5 HA fillers		Subject satisfaction, efficacy, and safety of BoNT-A and HA fillers for full-facial aesthetic rejuvenation.	<ol style="list-style-type: none"> 1. Full-face aesthetic outcome gives high satisfaction level of the patients. 2. Significant aesthetic improvement and product safety. 	[35]
	Implants injection			Facial wrinkles and scars	<ol style="list-style-type: none"> 1. HA is the most promising material for soft tissue augmentation. 2. The efficacy of HA is comparable to collagen. 	[36]
	Injectable gel	48 weeks follow-up	80 subjects	Wrinkle correction	<ol style="list-style-type: none"> 1. Significant improvement in the effectiveness for wrinkle correction after repeat treatment. 2. Remarkable improvement in NLF severity score. 	[37]
	Dermal fillers	Injection of finer viscosity follow up with thicker viscosity of HA. 0.5 mL Restylane and 0.5 mL Perlane were used per side, evaluate to 20 weeks	21 patients with mild to moderate tear trough deformities	Wrinkles severity improvement	<ol style="list-style-type: none"> 1. Clinically apparent improvement in wrinkle severity with the combination of two HA fillers with different viscosities. 2. Significant improvement in aesthetic scores with high patient satisfaction. 	[38]

A remarkable improvement in skin hydration and elasticity were observed in patients treated with HA based cream compared to the patients treated with placebo. The roughness index also showed a significant improvement in HA treated group after 60 days of treatment compared to the placebo group [16]. Several other researchers have also highlighted the significance of HA based formulation in the skin repairment [17–19].

HA has also been extensively used as a targeting ligand for targeted drug delivery systems [20–22]. HA based modifications of nanodelivery system enhance their penetrability across the biological membranes and improve the targeting efficiency and drug accumulation at target sites [20–22]. According to a recent review, HA based modifications improved tumor-specific delivery of anticancer agents, maximized anticancer efficacy, and mitigated tumor progression [6]. HA-based conjugation or surface modulation of anticancer drugs-encapsulated nanocarriers have shown promising efficacy against various types of carcinomas of liver, breast, colorectal, pancreatic, lung, skin, ovarian, cervical, head and neck and gastric. The success of this emerging platform is assessed in achieving the rapid internalization of anticancer payloads into the tumor cells, impeding cancer cells di-

vision and proliferation, induction of cancer-specific apoptosis and prevention of metastasis (tumor progression) [6].

3. Cosmetic and nutricosmetic efficacy of HA

Many researchers have investigated the cosmetic and nutricosmetic efficacies of HA based formulations for skin rejuvenation. Evidence based meta-analysis revealed that HA exhibits remarkable cosmetic and nutricosmetic efficacies in rectifying various skin defects such as wrinkles, nasolabial folds, and skin aging. To investigate cosmetic and nutricosmetic effects, HA has been utilized in various forms (i.e., gels, creams, intra-dermal filler injections, dermal fillers, facial fillers, autologous fat gels, lotion, serum, and implants, etc.). The cosmetic and nutricosmetic effects of HA have been associated with their ability to induce soft tissue augmentation, improve skin hydration, collagen stimulation, and face rejuvenation (Fig. 2).

3.1. Anti-wrinkle efficacy of HA

A wrinkle is a fold, ridge or crease in the skin, also known as a rhytide. The appearance of wrinkles is one of the typical signs of ag-

Table 2

A summary of clinical significance of hyaluronic acid for treatment of nasolabial folds: human clinical studies.

Cosmetic effect	HA formulation	Application	Experimental model/ study design	Study parameters	Key findings	Ref.
Nasolabial folds	Gel dermal filler	Hyaluronic acid gel implantation on one side of the face and hyaluronic acid gel followed by one of the nonablative laser/RF/IPL therapies on the contralateral side of the face.	33 patients with prominent nasolabial folds	Wrinkle severity, aesthetic scores	<ol style="list-style-type: none"> The use of hyaluronic acid gel implantation alone and hyaluronic acid gel with laser/RF/IPL treatment have the same efficacy and safe. No statistically significant differences between wrinkle severity and global aesthetic scores. 	[39]
	Gel dermal filler	One of three types of smooth-gel HA dermal filler (in one NLF) and cross-linked bovine collagen (in the other NLF) and were evaluated for ≤ 24 weeks.	439 subjects with moderate or severe nasolabial folds.	Longer lasting correction of NLF	<ol style="list-style-type: none"> Significant improvement with long lasting effect with HA dermal fillers. Majority of subjects preferred HA dermal filler over bovine collagen. 	[40]
	Gel dermal filler	Nonanimal stabilized hyaluronic acid gel (Perlane) and bovine collagen (Zyplast) on contralateral sides of the face for 6 months.	68 patients with prominent nasolabial folds	Effectiveness comparison.	<ol style="list-style-type: none"> Significant greater improvement of Perlane in cosmetic correction compared to Zyplast. Perlane is superior to Zyplast in wrinkle severity and aesthetic scores. Long-term safety and long-lasting improvement with Perlane. 	[41]
	Gel dermal filler	Hyaluronic acid gel and bovine collagen on contralateral sides of the face and evaluated up to 6 months after baseline.	138 patients with prominent nasolabial folds.	Efficacy and safety comparison.	<ol style="list-style-type: none"> HA gel was suggested to be more effective in maintaining cosmetic correction. HA gel was superior in the improvement of wrinkle severity and aesthetic scores. 	[42]
	Dermal filler	Further treatment with HA filler incorporating lidocaine	3566 patients had previously received facial fillers.	Skin comfort, improved aesthetic result.	<ol style="list-style-type: none"> Significant improvement of aesthetic result with HA filler incorporating lidocaine. Patients provided with more comfortable injection experience. 	[43]
	Facial filler	Hyaluronic acid facial filler containing pre-incorporated lidocaine (Juvederm ULTRA 3) and the established hyaluronic acid facial filler Restylane-Perlane randomly applied to the right or left naso-labial fold	Split-face, single blind study with 126 individuals	Skin comfort and ease of injection.	<ol style="list-style-type: none"> Total of 95% individual indicated more comfortable with Juvederm ULTRA 3 injection. Remarkable greater ease in injection with Juvederm ULTRA 3 than Restylane-Perlane. 	[44]
	Injectable gel dermal filler	Lidocaine filler in one NLF and the filler without lidocaine in the other NLF		Procedural pain.	<ol style="list-style-type: none"> Significant improvement NLF severity comparable for both products. Procedural pain reduction with dermal filler formulated with lidocaine 	[45]

Table 2 (Continued)

Cosmetic effect	HA formulation	Application	Experimental model/ study design	Study parameters	Key findings	Ref.
Dermal gel filler		Non-animal-derived hyaluronic acid based filler formulated with lidocaine (Prevelle SILK) was injected in one NLF, and without lidocaine (Captique) was injected in the contralateral NLF	Patient-blinded, prospective, randomized, split-face design trial with 45 patients with NLFs.	Pain evaluation at the injection site	<ol style="list-style-type: none"> 1. Significant reduced in pain associated with addition of lidocaine to HA filler. 2. No significant difference in outcome after 2 weeks for both products. 	[46]
Dermal gel filler		Injected into the deep layer of the dermis and/or subcutis of the NLF for 6 months.	Multicenter, randomized, patient and evaluator-blind, matched pairs, and active-controlled design clinical study with 66 subjects with moderate or severe wrinkle severity. 62 subjects	Efficacy and safety of both products.	<ol style="list-style-type: none"> 1. Both fillers were well tolerated and adverse reactions were mild and transient in most cases. 2. Remarkable equivalent efficacy and safety of both products. 	[47]
Dermal filler		HA IDF plus containing lidocaine was injected to one side of NLF, and HA IDF without lidocaine was injected to the other side.		Injection site pain	<ol style="list-style-type: none"> 1. Significant greater improvement in reduced pain with HA IDF plus compared to HA IDF. 2. No significant different in wrinkle correction and safety with both treatments. 	[48]
Injection filler		24 mg/mL hyaluronic acid with pre-incorporated lidocaine or without lidocaine and were followed-up for up to 76 weeks.	60 patients with moderate-severe bilateral nasolabial folds	Longevity of HA fillers.	<ol style="list-style-type: none"> 1. No significant effect on product longevity with addition of 0.3% lidocaine. 2. Significant improvement in HA gel with pre-incorporated lidocaine for physician assessment of injection pain. 	[49]
Dermal fillers		Injection of Neuramis or Perlane-L in the left or right side of the face for 24 weeks.	Randomized, multicenter, double-blind, intraindividual trial for 58 patients with moderate to severe nasolabial folds	Pain reduction, wrinkle severity and aesthetic scale	<ol style="list-style-type: none"> 1. Significant improvement efficacy in Wrinkle Severity Rating Scale and comparable aesthetic outcome with Neuramis. 2. No significant difference in pain reduction of both products. 	[50]
Dermal filler		Randomized injections with monophasic HA or biphasic HA on the left or right side of the face and evaluated up to 52 weeks.	72 Korean subjects with moderate to severe NLFs	Efficacy and safety of monophasic HA filler and biphasic HA filler.	<ol style="list-style-type: none"> 1. No significant difference in the efficacy between monophasic HA and biphasic HA filler. 2. Monophasic HA filler had lower elasticity and higher viscosity than biphasic HA filler. 	[51]
Dermal filler		Each subject was injected with Mesoglow® in one NLF and IAL System® in the other for 12 weeks.	40 subjects with visible nasolabial folds (NLFs)	Efficacy and safety of two non-cross-linked HA fillers.	<ol style="list-style-type: none"> 1. Mesoglow® and IAL System® were found to be equally effective in correction of NLFs. 2. No serious systemic adverse events occurred with both treatments. 	[52]

Table 2 (Continued)

Cosmetic effect	HA formulation	Application	Experimental model/ study design	Study parameters	Key findings	Ref.
	Gel dermal filler	6 months treatment.	88 subjects with moderate to severe NLF	Efficacy and safety of products.	<ol style="list-style-type: none"> 1. Significant improvement in wrinkle severity. 2. No significant difference in efficacy with Restylane and Bio-Hyalux. 	[53]
	Fillers	Injection of Emervel Classic or Restylane on their left or right side with 6 months follow up treatment.	Split-face, randomized and evaluator-blinded comparison study.	Efficacy and safety of dermal filler	<ol style="list-style-type: none"> 1. Significant improvement in wrinkle severity with Restylane and Emervel Classic are similar 2. Emervel Classic offer better tolerability compared to Restylane. 	[54]
	Filler	Injected with PP-501-B in one NLF and with Restylane Perlane (Q-med) in the contralateral NLF for 24 months.	81 patients	Long-term efficacy, durability and safety of PP-501-B	<ol style="list-style-type: none"> 1. Significant decreased in wrinkle severity score. 2. No severe complication after treatment of both products. 	[55]
	Gel dermal filler	Juvederm ULTRA in NLF and Restylane in the other NLF.	104 subjects	Product safety and effectiveness	<ol style="list-style-type: none"> 1. Significant improvement in NLF severity with Juvederm and Restylane. 2. Juvederm more preferable with fewer severe response. 	[56]
	Dermal filler	A single injection of Belotero® Basic and Restylane® in a split-face design in 4 weeks.	20 subjects with bilateral, symmetrical NLF	Effectiveness comparison.	<ol style="list-style-type: none"> 1. Belotero® Basic is significantly greater improvement compared to Restylane®. 2. Excellent tolerability of both treatments. 	[57]
	Injections	6 months evaluation	40 female patients	Cosmetic correction	<ol style="list-style-type: none"> 1. Significant greater cosmetic result with HA plus carbon dioxide. 2. Remarkable improvement in wrinkle severity. 	[58]
	Fillers	Retreatment of one nasolabial fold at 4.5 months and the contralateral fold at 9 months	75 patients with moderate to severe nasolabial folds	Skin wrinkle severity	<ol style="list-style-type: none"> 1. Significant improvement in wrinkle severity. 2. High patient satisfaction level. 	[59]
	Dermal filler	36 months follow-up	52 subjects	Skin wrinkle severity	<ol style="list-style-type: none"> 1. Significant improvement in wrinkle severity. 2. Remarkable improvement of NLFs correction. 	[60]
		5 subjects were treated with HA filler alone, the other five subjects were treated with intradermal RF prior to HA filler, follow up to 12–24 weeks	10 female volunteers with mild to severe NLFs	Wrinkle severity	<ol style="list-style-type: none"> 1. Significant greater improvement in wrinkle severity with the combination treatment. 2. RF treatment prior to HA filler provide synergistic and long-lasting effect. 	[61]

Table 2 (Continued)

Cosmetic effect	HA formulation	Application	Experimental model/ study design	Study parameters	Key findings	Ref.
	Gel	HA filler on both NLFs and with a nonablative IR device on the experimental side of the face for 2 months.	12 patients	Correction of facial wrinkles and folds.	<ol style="list-style-type: none"> 1. No significant difference of both HA gel alone and HA gel with nonablative IR device treatment. 2. Effectiveness in wrinkle remains the same. 	[62]
	Injection filler	Direct excision of the NLF followed by advancement of the nasolabial fat compartment into the nasolabial crease. Excised tissue samples were injected with HA fillers (Restylane, Perlane, or layered Restylane/Perlane), sectioned, and treated with histological stains.	Patients with deep NLF	Surgical correction of a prominent nasolabial fold (NLF) technique and the histology and localization of injected hyaluronic acid (HA) fillers.	<ol style="list-style-type: none"> 1. The surgical was a success for treatment patients with deep NLF. 2. Regardless of HA product applied, the localization appeared similar in the lower reticular dermis and subcutis which near the site of injection emphasized the importance of proper placement of HA fillers during soft tissue augmentation. 	[63]
	Dermal filler	PCL-based dermal filler in one of their NLFs, and a NASHA-based dermal filler on the contralateral side for 12 months	40 subjects	Safety, efficacy, and duration of cosmetic correction.	<ol style="list-style-type: none"> 1. Remarkable prove of safety of both products. 2. Significant greater improvement in wrinkle severity of PCL-based dermal filler than NASHA-based dermal filler. 	[64]
	Gel	Treatments of HA or fat in both NLFs for 12 months.	62 patients	NLF correction	<ol style="list-style-type: none"> 1. Significant improvement of both HA and fat in NLFs. 2. Similar in safe and efficacious in both products. 	[65]
	Gel	24 weeks follow-up	150 patients	NLF correction	<ol style="list-style-type: none"> 1. Remarkable safe for the correction of facial wrinkles in patients with skin of color. 2. Only mild to moderate adverse effect upon injection. 	[66]

ing processes [23]. Different causes which can enhance wrinkle formation include, habitual sleeping positions, loss of body mass, prolonged immersion in water, habitual facial expressions, aging, sun damage, smoking, and poor hydration. Wrinkles referred to the fine lines that appear on the skin, may become deep crevices or furrows in some people. Wrinkles are typically appeared around the eyes, mouth, forehead, hands, and neck. Aging is one of the primary factors which contribute to wrinkle formation as the skin loses its elasticity and fat contents, decrease collagen and elastin that causes skin thinner and less smooth appearance. Another undeniable fact is the morphological alterations which appear on the skin with ages as occurred in all other tissues and organs of the body. These morphologic changes associated with chronologically aged skin result in cutaneous laxity and fine wrinkling on the face. The progression loss of thickness in aging skin begins with a thinning of the epidermis and flattening of the dermoepidermal junction. Atrophy mainly occurs in the dermis as a consequence of these age-related morphological alterations in the skin [24]. With age, total number of fibroblasts and eosinophil also decreases [24]. The cutaneous tensile strength decreases as there is continuous reduction of elastic fibers and changes in collagen components [25]. Moreover, diminished dermal microvasculature and reduced sebaceous gland activity tenders to worse dryness of the skin [26]. The atrophy in subcutaneous tissues (fat, muscles, and bones) creates further prominence of skin folds with the overlying skin hanged from points of deep attachments. A clear grav-

itational line which represent the influence of atrophy and gravity on aged skin appear between the ages of 40 and 50 years, commonly occur through the face and neck [27]. Many researches have demonstrated the promising anti-wrinkle potential of HA based formulations (cream, gels, and injection).

Evidence-based analysis revealed that the anti-wrinkle efficacy of HA is molecular weight dependent which is expected to be due to differences in percutaneous absorption of different molecular weight HA across the stratum corneum [28]. Authors have conducted a clinical trial involving 76 female aged between 30 and 60 years having periorbital wrinkles. These patients were applied with 0.1% (w/w) cream formulation containing different molecular weights of HA (50, 130, 300, 800, 2000kDa) twice daily for a period of 60 days. They observed greater improvements in the skin hydration level, skin elasticity, and reduction in peri-ocular wrinkles in women applied with cream formulation containing low molecular weight HA [28]. In view of molecular weight dependent percutaneous absorption, researchers have tested ultra-small sized HA (nano-HA) containing topical formulations (lotion, serum, and cream) [29]. In this clinical trial, 33 women with an average age of 45.2 years having periorbital wrinkles were treated for eight weeks. The measurements were performed in the periorbital regions by investigating the three-dimensional structure using a DermaTOP for wrinkles, Corneometer for skin hydration, Cutometer for skin elasticity and Chroma Meter for erythema intensity. Standardized images were taken and evaluated by six se-

Table 3

A summary of clinical significance of hyaluronic acid as anti-aging biomedicine: human clinical studies.

Cosmetic effect	HA formulation	Application	Experimental model/study design	Study parameters	Key findings	Ref.
Anti-aging efficacy	Injection filler	HA is injected in the subgaleal glide plane between the brows at the mid procerus level between the supratrochlear vascular arcades.		Rejuvenation of upper face.	1. HA filler proved to be satisfying if proper patient selection and procedure are done.	[82]
	Injection of HA gel	Patients with bilateral volume loss of the cheeks.	A multi-center, six-month, open-label study	Subject satisfaction, efficacy, and safety	1. Significant aesthetic improvement in the cheeks. 2. The aesthetic outcome showed high satisfaction level.	[72]
	Injection	Voluma injected into the midface, follow up to 18 months.	102 patients (93 females, nine males; mean age: 51.27 years)	Facial volume restored, long lasting effect.	1. Significant improvement in aesthetic scores with Voluma. 2. Remarkable improvement of facial volume and long-lasting effect.	[73]
	Tear trough deformity filler	0.48 ml per eye	151 patients, female (86%), and middle-aged (mean age 48 years old).	Tear trough rejuvenation.	1. Significant cosmetic improvement in the treatment of tear trough rejuvenation. 2. High level of patients' satisfaction as well as tolerability of the treatment.	[74]
	Injection	0.1 ml was injected at each pass, follow up to 12 months.	25 patients with tears troughs	Correct tear trough deformity	1. Significant improvement in the treatment of tear trough deformity with HA gel filler. 2. Clinically effective and have high subject satisfaction.	[75]
	HA gel as tear trough filler	Mean volume of 0.59 ml per eye follow up to 5.1 months.	100 patients, female (87%), white (89%), and middle-aged (mean age=47.8 years)	Tear trough rejuvenation	1. Significantly effective in the treatment of tear trough rejuvenation. 2. High level of patient tolerability and satisfaction	[76]
	Injection	Application on one side of nasojugal groove	10 Korean women. A prospective randomized split face clinical controlled study.	Volume correction and skin tone of nasojugal groove.	3. Highly patients' satisfaction with minimal tissue trauma. 4. Restylane Vital® injector allows exact placement of hyaluronic and offer more predictable results.	[77]
	Injection	Two treatment with native HA at an interval of 14 days	20 patients with distinct to substantial signs of facial skin aging.	Skin elasticity and turgor.	1. Significant improvement in skin elasticity and turgor. 2. Remarkable method for extensive superficial treatment of skin.	[78]

Table 3 (Continued)

Cosmetic effect	HA formulation	Application	Experimental model/study design	Study parameters	Key findings	Ref.
	Intradermal injection	Received 2 treatments with natural HA	20 adults with flaccid facial skin	Skin elasticity and turgor	1. The mean elasticity values significantly increased 90 days later. 2. There is an improvement in the mean turgor values with no significant adverse events.	[79]
	Aqueous injection	6 to 8 ml of HA in 2–4 weeks.	10 women were no laser and HA fillers for 6 months.	Skin anti-aging.	1. Significant reduction of apparent aging face.	[80]
	O/W Cream 0.1%	Twice daily for 60 days	12 female aged between 30 and 60 years	Skin elasticity and hydration.	1. Reduced formation of intercellular tight junction in aged and photodamaged skin. 2. Remarkable reduction of wrinkles.	[81]

lected and trained rate for reduction of visible wrinkles, skin color uniformity and pigmentation. Results revealed a significant improvement in fines of skin in 2 weeks and improved skin elasticity in 2–8 weeks of treatment. The swift anti-wrinkle and skin rejuvenating effects of nano-HA containing topical formulations were expected to be due to superior percutaneous absorption of ultra-small HA molecules [29].

Anti-wrinkle efficacy of HA based topical cream formulation has also been investigated by other researchers [30]. Daily application of HA incorporated cream causes significant reduction in depth of wrinkles and improves skin elasticity and tightness. In this study, authors have tested four topical cream formulations (Balea, Nivea, Lancome, Chanel) containing HA on 20 women with periorbital wrinkles for 3 months. After treatment period, they observed significant improvement in skin elasticity and tightness by 13–30%, significant reduction in wrinkle depth by 10–20%, and improved hydration level in all treatment patients [30].

Besides topical application, the safety, tolerability, patient satisfaction, and efficacy of intradermal injection of HA (as fillers, gels, implants) in treating the facial wrinkles and skin rejuvenation have also been validated by many researchers [31–37]. Patients were assessed using Global Aesthetic Improvement Scale (GAIS). There were no serious adverse effects appeared in most of the patients; however, some patient showed mild sings of bruising, swelling, and tenderness which were resolved within seven days [31–33]. The tolerability and efficacy of injectable HA filler has also been validated for full face rejuvenation [34]. In this study, 77 human subjects with average age of 54.5 years were for treated for 6 months. At the end of treatment period, 92.1% subjects showed significant improvement in wrinkle depths; however, remaining participant showed complete satisfaction. There were no serious side effects reported during or after the end of the study. Full-face rejuvenation using HA proved to be effective, safe in participants with multiple indications [34]. The safety and efficacy of injectable HA filler has also been tested after combined with botulinum toxin Type A (BoNT-A) for full facial rejuvenation to reduce wrinkles [35]. In this multicenter, open-label clinical study, authors have tested five different HA fillers and BoNT-A to treat up to 13 facial zones. Resulting evidences showed that 96.5% subjects showed high level of satisfaction within 3 weeks of treatment and treatment was well-tolerated [35]. The anti-wrinkle and anti-scar ability of HA based injectable filler has also been compared with many other commonly utilized injectable implants such as injectable bovine collagen (Zyderm and Zyplast), gelatin matrix (Fibrel), and synthetic implants polytetrafluoroethylene (Gore-tex) for face rejuvenation [36].

Results revealed that HA based injectable filler showed the most promising efficacy for soft tissue augmentation which was equivalent to collagen [36]. These results were also validated by other researchers [37].

Combination of two HA fillers with different viscosities provide safe and effective mean of skin rejuvenation of the periorbital-cheek complex [38]. In this clinical trial, 21 patients with mild to moderate tear trough deformities were treated with concomitant injection of two dermal fillers (Restylane® and Perlane®). The result showed a statistically significant improvement in modified Wrinkle Severity Rating Scale scores at 20 weeks. Patients' self-reported overall mean improvement was 2.23, indicating moderate (26% to 50%) to good (51% to 75%) improvement. Overall, the combination filler procedure proves to produce clinically apparent improvement with high degree of patient satisfaction [38]. The therapeutic significance of hyaluronic acid formulations for the treatment of wrinkles including are shown in Table 1.

The molecular evidences revealed that skin rejuvenation and anti-wrinkle effects produced by the application/administration of HA is due to its ability to stimulate collagen synthesis via induction of fibroblasts in the dermis. The increased production of collagen makes skin smoother, reduce wrinkles, and improve skin elasticity and longevity.

3.2. HA based treatment of nasolabial folds

HA based dermal fillers have also shown promising ability to treat nasolabial folds. Nasolabial folds are the deep wrinkles or lines that form from the bottom of nose to the corners of the mouth. The appearance of the nasolabial folds are usually seen in the facial features as “smile lines” or “laugh lines”. It makes the distinctive look between the cheek and the upper lip. Literally, every person may develop with a slight trace of laugh lines. As a person ages, the fold becomes accessible. All wrinkles are a result of a combination of factors. One of the factors is the weakening of facial muscles as person's ages. It may also be due to the loss of foundation underneath mid-face known as the base of the face.

Common causes of nasolabial folds are aging, sun damage and smoking. When skin exposed to the skin regularly, ultraviolet (UV) rays may cause breakdown of collagen and elastin fibers that support structure integrity of the skin. Smoking can also lead to mouth wrinkles and hasten the process of aging by the chemicals contain in tobacco cigarettes by 20%. Significant weight gain or loss and the side sleeping habit also contribute in the presence of more pronounced na-

Table 4

A summary of other aesthetic improvements, cosmetic and nutricosmetic effects of HA.

Cosmetic effects	HA formulation	Application	Experimental model/ study design	Study parameters	Key findings	Ref.
Soft tissue augmentation	Gel intradermal injection.	Apply on wrinkles and folds, and for lip augmentation and/or recontouring with 8 months follow-up.	158 patients	Safety and efficacy of HA gel	<ol style="list-style-type: none"> 1. Remarkable improvement of dermal implantation in augmentation therapy. 2. No major evidence of side effect developed along the treatment. 	[83]
Skin augmentation	Gel	21 days treatment.	115 subjects	Cosmetic effect, mid-face volume enhancement.	<ol style="list-style-type: none"> 1. Significant improvement in the cosmetic effect with Juvéderm® VOLUMA® with Lidocaine. 2. High level of subjects' satisfaction and tolerability for face volume enhancement. 	[84]
Skin augmentation	Gel	Injection of in one or more of three facial subregions: (the zygomatic malar region, the anteromedial cheek and nasolabial folds)	60 adults aged 40–65 years with bilateral moderate to severe volume loss or contour deficiency for 6 months.	Face volume enhancement and contouring	<ol style="list-style-type: none"> 1. Significant improvement in aesthetic scores HA gel treatment. 2. Remarkable improved in volume loss and contour deficiency. 	[85]
Soft tissue augmentation	Injection		Retrospective review 144,000 patients (injection) 262,000 patients (gel)	Safety profile of non-animal stabilized hyaluronic acid gel	<ol style="list-style-type: none"> 1. The incidence of hypersensitivity appears to be declining after the introduction of a more purified hyaluronic acid raw material. 	[86]
Face rejuvenation	Injection			Wrinkles and volume.	<ol style="list-style-type: none"> 1. The use of different HAs for each area offers real possibilities to rejuvenate the skin without downtime. 2. Longevity of the correction depends on treated areas, HA used, and on the individual. 	[87]
Skin hydration	Injection	Pilot study	6 middle-aged male subjects.	Corneometer, TEWL, cutometer, measures of patient satisfaction, and the global aesthetic improvement scale (GAIS)	<ol style="list-style-type: none"> 1. There is significant improvement in the aesthetic score. 2. The patient satisfaction level greatly increases with the outcomes of treatment in terms of the enhancement of moisture, elasticity, and brightness. 	[88]
Collagen stimulator	Dermal filler injection	Filler injected into forearm skin and skin biopsy specimens taken 4 and 13 weeks later.	11 healthy volunteers (mean age, 74 years) with photodamaged forearm skin.	De novo synthesis of collagen	<ol style="list-style-type: none"> 1. Remarkable increase in collagen deposition around the filler. 2. There is an activation of dermal fibroblast demonstrated by mechanically stretched appearance around the injected skin. 	[89]

Table 4 (Continued)

Cosmetic effects	HA formulation	Application	Experimental model/ study design	Study parameters	Key findings	Ref.
Collagen stimulator	Dermal filler injection	Filler injected intradermally and skin biopsy specimens taken 1, 3, and 6 months	60 females were randomized who received a 0.5 mL injection of HA gel	De novo synthesis of collagen	<ol style="list-style-type: none"> 1. Significant increase in collagen synthesis. 2. Expression of procollagen, MMP and TIMP1 were also increased in subjects received HA dermal filler injection. 	[90]
Space filling properties	Dermal filler injection	Intradermal injection and evaluation were performed at 15 days and 6–18 months later	32 patients (aged 13–32 years) with congenital or acquired facial malformations	Space-filling, collagen and elastin synthesis	<ol style="list-style-type: none"> 1. Greater space filling efficacy of HA dermal filler was observed in all patients. 2. Significant improvement in collagen and elastin synthesis. 	[93]

solabial folds. Recent treatment of nasolabial folds is the use of skin-tightening treatment that includes fractional radiofrequency device, ultrasound, and fractional laser. Other than that, plastic surgery that involves facelift, cheek implants and nasolabial excision reduce the appearance of nasolabial folds and even other signs of aging.

Many researches have investigated the anti-nasolabial fold efficacy of HA dermal fillers, alone or in combination with other cosmetic procedures. The anti-nasolabial fold efficacy of HA based gel dermal filler alone is comparative with HA gel implantation in combination with nonablative laser/RF/IPL therapy [39]. In this clinical trial, 33 patients with prominent nasolabial folds were applied with HA gel implantation on one side and HA gel implantation in combination with nonablative laser/RF/IPL therapy on the contralateral side of the face. Results demonstrated significant improvement in wrinkles depth and anti-nasolabial fold depth and the efficacy was comparable on both sides of the faces of all patients [39].

The anti-nasolabial fold efficacy of dermal fillers containing non-animal originated HA showed better anti-nasolabial and anti-wrinkle efficacy compared to bovine collagen [40]. In this study, 439 subjects with moderate-to-severe nasolabial folds were enrolled. Resulting evidences and patients rating revealed that non-animal stabilized hyaluronic acid gel (Perlane) was found to be more effective and tolerable in maintaining the cosmetic correction compared to the bovine collagen (Zyplast) [40]. These results were in agreement with another clinical trial involving 68 patients with prominent nasolabial folds [41]. Result demonstrated that Perlane was found to be superior and efficacious in cosmetic corrections, reducing wrinkle severity, and longevity compared to Zyplast [41]. The efficacy of non-animal sourced HA (Restylane) compared to bovine collagen (Zyplast) has also been explored by Narins et al. [42]. In this randomized, placebo controlled trial, 138 patients were randomized to treat with Restylane on one side of the face and Zyplast on contralateral side of the face. It is also found that Zyplast were non-superior compared to Restylane. A high improvement was shown in effectiveness for maintaining cosmetic correction and wrinkle severity with the treatment of Restylane [42].

The quality of dermal HA filler has been improved to provide more comfortable injection by incorporating lidocaine (HAL) for the treatment of nasolabial folds [43]. Patients reported to experience less pain during the procedure and obtain a better aesthetic result compared to previous dermal filler. In this clinical trial, 3566 patients, 485 injectors across 16 countries participated. For comparative analysis, all the patients were recruited because they had previously received facial fillers. Hence, they received the new hyaluronic acid filler incorporating lidocaine (HAL). The comfort and aesthetic results obtained with HAL following the treatment of nasolabial folds

were evaluated by the injector and the patients. It was reported that the patients experiencing less pain during the procedure compared to previous dermal fillers. There is significant improvement in the aesthetic result and more comfortable injection experience for most of the patients with HAL than the previous dermal fillers [43]. The efficacy and tolerability of HAL dermal filler compared to HA dermal filler (Restylane-Perlane) has also been validated in another split-face, single blind study by involving 126 individuals [44]. Both products were randomly assigned to the right or left nasolabial fold and tolerability and anti-nasolabial fold efficacy was assessed. Injectors indicated that 92% of Juvederm ULTRA 3 injections were easily administered with higher patient compliance compared to 21% of Restylane-Perlane. Majority of individuals had preferred Juvederm ULTRA 3 which provides more comfortable and gentle experience during the procedure [44]. Nevertheless, Juvederm injectable gel with lidocaine (JUV+L) and commercially available Juvederm injectable gel without lidocaine (JUV) showed equivalent safety and efficacy in reducing severity of nasolabial folds; however, it was found that dermal filler formulated lidocaine is more effective in reducing procedural pain during correction of facial wrinkles and nasolabial folds compared to the filler without lidocaine [45]. These results were also in agreement with another study in which safety, efficacy, and effectiveness of HA based dermal filler formulated with lidocaine (Prevelle SILK) was compared with another dermal filler with same composition but without lidocaine (Captique) [46]. The safety, efficacy, and patient compliance were evaluated two weeks after dermal procedure in 45 human subjects. Results revealed that there was significant difference in safety and efficacy of both products in reducing severity of nasolabial folds; however, procedural pain was remarkably decreased in case Prevelle SILK compared to HA filler without lidocaine [46]. Similarly, a multicenter, randomized, patient and evaluator-blind, matched pairs, and active-controlled design clinical study to compare the efficacy and safety of PP-501-A-Lidocaine dermal filler with Restylane-Lidocaine® when injected into deep layer of the dermis and/or subcutis of the NLF was also conducted [47]. In this clinical trial, 66 subjects with moderate-to-severe wrinkle severity were involved. It was observed that PP-501-A-Lidocaine has the similar efficacy and safety after 6 months of follow-up compared to Restylane-Lidocaine®. Both fillers were well tolerated and adverse reactions were mild and transient in most cases [47].

One of the common problems to patients undergoing soft tissue augmentation is the pain at the injection-site. With the invention of lidocaine incorporated HA gel/matrix dermal filler, patient compliance to nasolabial folds related cosmetic procedures has been optimized [48]. A split-face study was conducted to compare procedural pain, efficacy, and safety of HA intradermal filler (IDF) containing lido-

caine with HA IDF without lidocaine in the correction of nasolabial folds (NLFs). Lidocaine incorporated HA IDF was injected to one side of NLF and HA IDF without lidocaine was injected to the other side in 62 subjects [48]. Upon follow-up visit, it was observed that the two fillers were not significantly different in safety profile or wrinkle correction; however, injection-related pain had been significantly reduced with lidocaine-incorporated HA IDF compared with HA IDF without lidocaine [48].

Besides improvement of patient compliance achieved after the inclusion of lidocaine in HA IDF, its effect on longevity of anti-nasolabial folds efficacy of dermal filler has also been investigated due to limited data available on this aspect [49]. In this clinical study, 60 human subjects with moderate-to-severe bilateral nasolabial folds received 24 mg/ml HA with pre-incorporated lidocaine or same product without lidocaine. The patients were followed up for up to 76 weeks. Upon patient follow-up, investigators observed that although there was significant improvement in injection-related pain at injection site; however, inclusion of 0.3% w/w lidocaine had no effect on filler longevity even after long-term follow-up. Researchers further suggested that despite full treatment, small volume required for 'touch-up' showed longevity along with high level of patient satisfaction [49].

In an attempt to manipulate release behaviour and physicochemical characteristics of intradermal filler, two different types of IDF have been designed; 1) monophasic, and 2) biphasic. Although, literature has suggested comparable efficacy and durability of both types of IDF; however, monophasic IDF are more cohesive due to homogeneous sizes of microspheres. A randomized, multicenter, double-blind, intra-individual trial was conducted to evaluate the effect of inclusion of lidocaine on the safety, efficacy, and durability of monophasic and biphasic IDF [50]. In this clinical trial, 58 patients with moderate-to-severe NLFs were treated with lidocaine-containing monophasic HA IDF (Neuramis Deep Lidocaine) on left side of the face and a lidocaine-containing biphasic HA IDF (Restylane Perlane-L) on right side of the face. Results revealed a significantly greater improvement in wrinkle severity and comparable aesthetic outcome with Neuramis Deep Lidocaine compared with Restylane Perlane-L. There was no significant difference in pain reduction between Neuramis and Perlane-L in the management of NLFs [50].

Rheological property is one of the primitive physicochemical characteristics of pharmaceutical formulations which affect the behaviour, efficacy, and safety of formulations. In a randomized clinical trial involving 72 Korean subjects with moderate to severe NLFs, rheological characteristics and clinical efficacies of monophasic HA IDF and biphasic HA IDF were compared [51]. Patients received intradermal injections with monophasic HA or biphasic HA on the left or right side of the face and were evaluated at 2, 10, 18, 26 and 52 weeks. The results reported that monophasic HA filler had lower elasticity and higher viscosity than biphasic HA filler. Both treatments were well tolerated and no significant difference in efficacy with only mild and transient adverse reactions [51]. The safety, efficacy, and tolerability of other HA based IDF have also been investigated by other researchers [52–57] and the major findings have been summarized in Table 3.

Durability and longevity of IDF is vital for soft tissue augmentation. Among various techniques to improve durability and longevity of HA IDF to maintain anti-nasolabial folds effects, the clinical efficacy of a combined therapy with HA IDF and subcutaneous injection of carbon dioxide was evaluated compared to HA IDF without carbon dioxide injection for cosmetic correction [58]. Results revealed that combination of subcutaneous injection of carbon dioxide with

HA filler significantly improved cosmetic corrections compared to IDF without carbon dioxide. Carbon dioxide has the ability to improve quality and elasticity of the dermis and increases the oxygen release to the tissue via enhancing Bohr's effect [58].

Non-animal-stabilized hyaluronic acid (NASHA) fillers are commonly used for cosmetic procedure; however unfortunately, their effects on the longevity of different retreatment procedures have yet to be discovered. A multicenter, randomized, evaluator-blinded study was conducted by involving 75 patients with moderate-to-severe NLFs to investigate the efficacy and perseverance of NASHA 100,000 gel particles/ml filler for two different retreatment schedule. With one retreatment, the filler persisted up to 18 months along with significant efficacy improvement [59]. On the other hand, 18-month small gel-particle HA persistence study continues to establish improvement of nasolabial folds up to 36 months after second retreatment [60]. There were 52 subjects involved in this study and the skin wrinkle severity is being measured. They found that, there was a significant improvement in wrinkle severity with remarkable improvement of NLFs correction [60].

Although HA IDF have shown significant promise and have been extensively used for skin rejuvenation, but their longevity is not established yet. To deal with this problem, some researchers investigated the effect of combination therapy of intradermal radiofrequency and HA filler on mild-to-severe NLFs [61]. Results revealed that combination treatment may provide synergistic and long-lasting effects for cosmetic correction of NLFs [61]. In contrast, another study was conducted to evaluate the efficacy of combined treatment using a nonablative infrared (IR) device and HA filler. Results revealed an equivalent efficacy of combined therapy with HA filler alone with no significant differences between wrinkle severities [62].

One study has been carried out to illustrate a technique for surgical correction a prominent nasolabial fold and use the excised fold to determine the histology and localization of injected hyaluronic acid (HA) fillers [63]. The excised tissue sample from the surgical correction by direct excision of the NLF were injected with HA fillers (Restylane, Perlane or layered Restylane/Perlane), sectioned and treated with histological stains. It was appeared that HA localized primarily in lower reticular dermis and subcutis of the excised NLF regardless of the HA product employed. Direct excision of the NLF with advancement of the nasolabial fat compartment is a successful treatment for patients with deep NLF. The injection of HA into the excised tissue near the site of injection shows the importance of proper placement of HA fillers during soft tissue augmentation. [63].

Nevertheless; NASHA-based dermal filler have been exclusively used for soft tissue augmentation; however, their efficacy was compared with bio-stimulatory polycaprolactone (PCL)-based dermal filler [64]. In this clinical trial, 40 subjects with mild-to-moderate NLFs were treated with NASHA-based dermal filler one side and PCL-based dermal filler on the contralateral side for a period of 12 months. At the end of treatment period, clinical observations revealed equivalent safety and tolerability of both products; however, a significantly greater improvement in wrinkle severity was achieved with PCL-based dermal filler compared with NASHA-based dermal filler [64]. The efficacy, durability, and safety of HA gel dermal filler has also been compared with autologous fat gel for cosmetic correction of NLFs [65]. This clinical trial involved 62 human subjects who were treated for 12 months. The result showed comparable efficacy of both products in treatment of NLFs and equivalent safety and tolerability in all patients [65]. The therapeutic significance of HA formulations for the treatment of nasolabial has been summarized in Table 2.

3.3. Anti-aging properties of HA

Aging is a natural process which declines/weakens biological functions and ability to adapt to the metabolic stresses. It is a progressive physiological change in an organism that leads to senescence or old age. As the age increases, tendons, blood vessels and skin lose its elasticity. This is due to the formation of cross-links between or within the molecules of collagen that alter the structure and shape of the enzyme molecules thus unable to carry out their functions in the cells.

Symptoms of aging include hearing loss [67], loss of muscle mass and mobility and impaired loss of vision. Aging causes skin to develop wrinkles especially at the sun-exposed areas, mainly at the face. The color of hair turns to grey [68] and cause hair loss rapidly. The reduction of skin elasticity makes skin become thin and more fragile with age and the fatty tissue underneath the skin decreases concurrently. The reduction in the production of natural oils causes skin to get dry, cracked, and thin.

In view of the importance of youthfulness in the life of every person, many scientists have discovered different anti-aging modalities. Anti-aging is one of the most beneficial elements in cosmetic application. A number of products including, diets and exercises, drugs and supplements are claimed to have anti-aging properties. Common antioxidants such as vitamin A, C, and E and coenzyme Q10 consumed to fight the release of free radicals called reactive oxygen species that contributes to aging process. But, there is little evidence shows the efficacy of the products instead many studies indicate that antioxidants do not slow the process of aging otherwise only slightly increase in the longevity [69–71]. Other treatments include laser therapy, wrinkle injections, peptide formulation and anti-aging sunscreens believed to delay aging process. In addition of these treatments, eating healthy food, having regular physical activity and avoid stress also promote in maintaining the youthful looking of aged person.

Among the various common signs and symptoms, facial volume loss is one of characteristic symptoms of aging process. The natural aging process and your genetics are the major causes of facial volume loss. However, certain medications, weight loss, stress and other lifestyle factors may contribute to exacerbated facial volume loss. Facial volume loss may appear as hollow temples, sunken-in eye sockets, flattened cheeks, or loose sagging skin around the jawline also known as jowls.

Numerous researchers have demonstrated that subcutaneous injection of HA E Volume gel improved the facial volume which is an important part of facial rejuvenation. A multicenter, six-month, open-label study was conducted with the application of HA E in the cheeks at baseline in patients with bilateral volume loss of the cheeks. After six months, a significant improvement (an optimal correction of 65.8%) has been achieved with high patient satisfaction of about 92.1% [72]. Similarly, another clinical trial involving 102 patients (93 females and 9 males) with the average age of 51.27 years received “Voluma”, a HA based sub-dermal facial filler injected into the midface [73]. Results revealed a significant improvement in maintaining increased facial volume for up to 18-month post-treatment with HA sub-dermal filler [73].

Despite facial volume loss, tear trough deformity is also one of the most common symptoms of aging process due to the volume loss and muscular hyperactivity. HA gel also acts as a tear trough deformity filler for patients for cosmetic improvement in periorbital rejuvenation. A clinical trial was conducted involving 151 patients with a total of 302 eyes which were administered with mean volume of

0.48 ml of semi-cross-linked HA gel per eye preperiosteally to achieve correction of tear trough deformity [74]. Most of the patients showed great satisfaction and tolerability with the treatment after experiencing remarkable improvement in the cosmetic effect with minimal complications [74]. Similarly, another group of researchers have also investigated the efficacy of periorbital filling with HA injection into preperiosteal tissues [75]. In this study, 25 human subjects were injected with 0.1 ml periorbital filling with HA at each preperiosteal tissues, follow up to 12 months. After 12 months, they measure the correct tear trough deformity in each patient. They found a significant improvement in the treatment of tear trough deformity with HA gel filler with clinically effective and have high subject satisfaction [75].

Despite injection of HA in periorbital tissues, the anti-aging effect of HA gel as tear trough filler have also been investigated [76]. In this clinical trial, 100 patients were recruited and were applied with mean volume of 0.59 ml of gel on each eye and followed up to 5.1 months. The resulting findings showed a significantly higher effectiveness of HA gel in the tear trough rejuvenation with high level of patient tolerability and satisfaction [76].

HA filler can also be used for reducing the nasojugal sulcus; however, it is associated with common adverse reactions such as irregular lumpiness and overcorrection. To overcome this, a prospective randomized split face controlled study was conducted to evaluate the effect of administering Restylane Vital® with its specialized injector on volume correction and skin tone of nasojugal groove [77]. The study enrolled 10 Korean women and randomly injected a stabilized HA-based gel of NAHSA injector, Restylane Vital®, Q-med on one side of nasojugal groove with the other side as control. The outcome duration of overall effect varied among the patients. The correction of the nasojugal groove with a Restylane Vital® injector provides a high degree of satisfaction to the patients with minimal tissue trauma and more specific injection site. It also has lower incidence of adverse reaction compared to more commonly used techniques. HA filler intradermal injection with special injector indicates to be safe and effective method for correction of nasojugal groove [77].

Skin elasticity, moisture and turgor are the best parameters to measure the effects of treatment with native HA. It has been shown that native HA has the positive effects in improving skin elasticity and turgor [78]. With regards to treatment of elastotic skin with native HA, one study using the product based on natural hyaluronic acid (Ial-System™) was assessed whether it is able to restore elasticity and turgor to the skin. Two treatments with native HA were given to 20 patients with distinct to substantial signs of the facial skin with mean age of 52 years old. The applications at an interval of 14 days found that there was significant improvement in the turgor and elasticity. Approximately 95% physicians and patients each judged the treatment results as very good or good [79].

To create more youthful appearance, the requirements of aesthetic treatments toward volume replacement were needed in multiple areas. One study shows positive effect of using multi-syringes of HA in the degree of perceived age reduction. Ten women with the criteria of 6 months for no laser and HA fillers or 1 year for no semi-permanent fillers, were treated with 6 to 8 ml of HA Multi-syringe injection of HA that has been applied to the aging face resulted in a reduction of apparent age from 6.1 to 9 years after several weeks [80]. This shows that full-face correction with HA is a promising remedy for anti-aging effects.

Besides the action of HA as dermal filler, in order to treat skin aging related problems, topical formulation of HA was introduced to treat aged skin in the parameters of skin roughness. An eight-week placebo controlled study with an oil-in-water cream containing 0.1% Na-salt of the HA derivatives were demonstrated to compare the ef-

fects of different low molecular weight HA molecules. Twelve female volunteers with age of 30–60 years were applied with topical cream twice daily for 60 days. It was reported that the better permeation of low molecular weight of HA has significantly reduced skin roughness as well as wrinkles. Although there was different penetration ability on variation molecular weight, the strong moisturizing properties of HA is undeniable [81]. Thus, by strengthening its penetration abilities based on decreasing molecular size, the effects of anti-aging and skin functioning could be achieved and improved. A summary of anti-aging potential of HA based formulations is appended in Table 3.

4. Other aesthetic improvements and cosmetic effects of HA

Besides anti-wrinkle, anti-aging, and anti-nasolabial folds, HA has also shown remarkable potential in soft tissue augmentation, skin augmentation, face rejuvenation, skin hydration, skin radiant, and as collagen stimulator. Duranti et al. [83] conducted a clinical trial involving 158 patients who were treated with facial intradermal implant of HA gel for face and lip augmentation/or recontouring. Results demonstrated a marked improvement and soft tissue augmentation after 8 months. Face rejuvenating potential (mid face augmentation) of HA-based injectable gel (Juvéderm® VOLUMA® with Lidocaine) has also been investigated by Philipp-Dormston et al. [84]. This prospective, observational, single-arm, open-label post-marketing study enrolled 115 healthy subjects. Results suggested that Juvéderm® VOLUMA® with Lidocaine was well accepted by all subjects and evaluators. HA based dermal filler has shown remarkable potential for treating facial volume loss and contour deficiency [85]. In this open label study, sixty adults (aged 40–60 years) with bilateral moderate-to-severe volume loss or contour deficiency were enrolled. At six months post-treatment, a significant improvement in FVLS (Facial Volume Loss Scale) scores and GAIS (Global Aesthetic Improvement Scale) was observed. These results were also in agreement with findings of other researchers [86,87]. Skin hydration is one of the prime factors that influence the skin health. The potential relationship between HA and skin hydration has been investigated by Seok et al. [88]. In this pilot study, six middle-aged male subjects were enrolled who were injected with 0.020 mL of HA filler at each injection point with a total of 100 points (2 mL of HA filler was injected to entire face at every treatment session) using an automatic intradermal injector. A total of three sessions were conducted for each subject in 2 weeks interval. Efficacy of HA filler was evaluated in terms of transepidermal water loss (TEWL), hydration level (corneometer), patient satisfaction, and the GAIS. Results demonstrated a considerable improvement in skin hydration and gradual decrease in TEWL at each treatment session. The satisfaction level of all patients was measured at “very much improved” or “much improved” according to GAIS scale. These results evidenced that HA dermal filler is a promising treatment to enhance skin hydration, brightness, and skin elasticity [88].

Another attractive feature associated with intradermal injection of HA filler is collagen production [89]. Collagen is the major structural protein of dermal extracellular matrix. To evaluate the efficacy of HA dermal filler injection on collagen biosynthesis, Wang et al. [89] conducted a clinical trial by enrolling eleven healthy subjects (average aged 74 years) with photodamaged forearm skin. The HA dermal filler was injected into forearm of each subject and nutricosmetic efficacy was evaluated in terms of de novo synthesis of collagen using immunohistochemical analysis, quantitative polymerase chain reaction, and electron microscopy. Results revealed that the subjects injected with HA cross-linked dermal filler showed greater increase in

collagen deposition around the filler compared to control groups (injected with normal saline). Fibroblasts in filler-injected skin demonstrated a mechanically stretched appearance and a biosynthetic phenotype. Resulting evidences validated that the intradermal injection of cross-linked HA stimulate collagen synthesis and partially restore dermal extracellular matrix components that are lost in photodamaged skin [89]. These results were also validated by another research group [90]. They conducted a clinical trial involving sixty female subjects who received dermal injection of 0.5 mL of HA gel and the skin biopsy samples were collected at 1, 3, and 6 months. The efficacy of collagen synthesis was evaluated in terms of protein and gene expression of procollagen, matrix metalloproteinases (MMP) and MMP tissue inhibitors (TIMP1) using ELISA and qPCR, respectively. A considerable improvement in collagen synthesis, procollagen expression, and increased levels of MMP and TIMP1 were evident at 1 month of post-receiving intradermal injection of HA gel [90]. A greater potential of HA based formulations to enhanced collagen synthesis to repair skin defects had also been validated by other researchers [91,92].

Besides improving skin hydration, restoring lost facial volume, collagen de novo synthesis stimulation, HA fillers have also shown greater space-filling properties in patients presented with congenital or acquired facial malformations [93]. In this study, three different commercially available HA fillers (15 mg/mL, 17.5 mg/mL, 20 mg/mL) were injected in 32 patients (aged 13–32 years) with congenital or acquired facial malformations and a total of 46 sessions were conducted. Clinical assessment was performed by patients and plastic surgeon, 15 days after injections and 6–18 months later. Post-treatment evaluation revealed a remarkable space-filling efficacy of HA filler, while having greater potential of enhancing skin elasticity and softness of scaring tissues. This observational study evidenced that intradermal injection of cross-linked HA stimulates production of several extra-cellular matrix components, including dermal collagen and elastin [93].

Mid-face volume deficit (MVD) is one of the most common signs of aging. Few et al. [94] conducted a clinical trial in which they enrolled 235 subjects with moderate-to-severe age-related MVD. All patients received Juvéderm Voluma XC for volumizing their MVD. At quarterly follow-up visits for 2 years, patients rated treatment outcomes on the GAIS, overall satisfaction with facial appearance, satisfaction with midfacial regions, achievement of treatment goal, Look and Feel of the Midface (LAFM), and Self-Perception of Age (SPA). Juvéderm Voluma XC for age-related MVD is effective and well-tolerated from the patient perspective, with results lasting up to 2 years [94]. The remarkable potential of HA dermal filler to correct age-related MVD has also been evidenced by other researchers [95–97]. In an attempt to elevate the supporting facial features, Bertucci et al. [98] conducted a 24-weeks open-label study in which they recruited 40 adults (aged 18 to 65) with bilateral moderate to substantial MVD or contour deficiency. They tested cosmetic efficacy of HA dermal filler with 0.3% lidocaine. They evidenced that MVD and contour deficiency is well-accepted treatment to repair skin defects and to restore MVD. These results were also in agreement with other researchers [99]. Besides restoring face contour deficiency, HA filler have also been attempted to restore lip contour and perioral area, thereby reducing age-related changes in lips [100]. In this study, the short-term aesthetic impact of HA dermal filler (Juvéderm® VOLBELLA®) with lidocaine was tested on 62 subjects for enhancement or correction of age-related asymmetry of the lips using a patient-centric approach. A patient satisfaction scale was at 83.6% immediately after injection at first visit which rated as “Extremely Satisfied, Very Satisfied or Satisfied”. In terms of improvement in the lips. The pa-

tient satisfaction level was increased to 94.1% and 93.0% of subjects with/without top-up treatment at follow-up, respectively [100]. These results were also in accordance with other study [101]. A summary of aesthetic improvements with HA dermal filler is presented in Table 4.

5. Summary

A thorough analysis of the literature revealed that HA exhibits remarkable cosmetic and nutricosmetic efficacy in treating the various skin defects such as wrinkles, nasolabial folds, and skin aging. HA has been utilized in various forms (i.e., gels, creams, intra-dermal filler injection, dermal filler, lotion, serum, and implants). The cosmetic and nutricosmetic effects of HA have been associated with their ability to stimulate collagen synthesis via induction of fibroblasts, improve skin hydration, and soft tissue augmentation. The anti-wrinkle efficacy of topically applied HA is molecular weight dependent which might be associated with differences in percutaneous absorption of different molecular weight HA across the stratum corneum. HA based dermal fillers have also shown promising ability to treat nasolabial folds. Many researches have investigated the anti-nasolabial fold efficacy of HA dermal fillers, alone or in combination with other cosmetic modalities such as non-ablative laser/RF/IPL therapy, lidocaine, and carbon dioxide. Comparative analysis of various anti-nasolabial folds formulations revealed that the anti-nasolabial fold efficacy of dermal fillers containing non-animal sourced HA showed better anti-wrinkle efficacy compared to bovine collagen. Nevertheless; NASHA-based dermal filler have been exclusively used for soft tissue augmentation; however, their efficacy was found to be significantly lower compared with bio-stimulatory polycaprolactone (PCL)-based dermal filler. One of the common problems to patients undergoing soft tissue augmentation is the pain at injection site. However, inclusion of lidocaine in HA dermal fillers significantly improve patient compliance and reduce severity of pain at injection site associated with intradermal injection. Though, inclusion of lidocaine with HA filler reduces injection related pain; however, it does not affect longevity, clinical efficacy, and durability of HA based dermal fillers. Moreover, many studies have also highlighted the clinical significance of HA based formulations (intradermal injection or topical application) to restore facial volume in periorbital tissues, face rejuvenation, lip contour, treatment of tear trough, treatment of mid-face volume deficit, nasojugal sulcus, restore moisture and turgor, and skin elasticity. These evidence based findings validated that application/administration of HA is a promising biomedicine and pharmacotherapy for the treatment of various skin related defects and slow down various physiological changes related to aging process. Having promising cosmetic and nutricosmetic efficacy, acceptable safety profile, biocompatibility, non-toxicity, and greater patient compliance, HA based formulations are warranted to be used for treatment of various skin defects and as anti-aging modality.

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Declaration of interest

The authors report no declaration of interest in the present work.

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