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A review of the cosmetic use and potentially therapeutic importance of hyaluronic acid

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ABSTRACT

Hyaluronic acid (HA) is an endogenous substance detected and isolated from various tissues and biological fluids. Owing to its physicochemical properties, HA contributes to many biological processes at intra- and extracellular levels, such as skin hydration, joints lubrication, and wound healing, besides its anti-inflammatory and antioxidant effects. The current review highlights the employment of exogenous HA in many aesthetic and dermatological aspects. Also, it aims to clarify the skin rejuvenating activity by compensating for the biological loss of HA with advanced age. Other positive impacts of HA on hair, nail, and overall health status were also revised. Cosmetics and cosmeceuticals that contain HA, among other active ingredients, are commercially available in different dosage forms such as gels, creams, intradermal injections, and fillers. Aesthetic enhancement is achieved via soft tissue augmentation, skin hydration level increasing, grooves refilling, and collagen and elastin biosynthesis stimulation. HA contributes to various therapeutic approaches such as gingivitis, stomatitis, ulceration, and osteoarthritis. Additionally, it has beneficial uses in dentistry due to its antioxidant and anti-inflammatory properties. The recent implication of HA following the claims that it has a rejuvenating power for the skin and many therapeutic benefits has to be thoroughly investigated and delivered by a trained expert to avoid undesirable effects.

INTRODUCTION

Hyaluronic acid (HA) or hyaluronan is chemically derived from the mucopolysaccharides glycosaminoglycans (Vasvani *et al*., 2020). HA is a natural component detected in the intra- and the extracellular matrixes in the skin, articular cartilage, synovial fluid, vitreous humor, and mammalian bone marrow (Hascall *et al*., 2004). The physicochemical properties of HA are responsible for its vital biological and physiological functions. The properties of biological importance include high viscoelasticity, biocompatibility, hygroscopicity, and moisture retention abilities (Gupta *et al*., 2019; Hascall *et al*., 2004). Skin hydration ability, lubrication, and diminishing aging symptoms are among the physiological functions of our interest.

Since the late 50s, when the first therapeutic application of HA in eye surgery was introduced, HA and its derivatives have been incorporated wi dely into many health aspects, including the medical, pharmaceutical, dietary, aesthetic, and cosmetic fields (Necas *et al*., 2008). Moreover, the drug delivery system has used HA to optimize and enhance drug particles activities (Arshad *et al*., 2021).

Regarding skincare products, HA has a clinically approved efficacy in fighting aging symptoms and counteracting the negative impact of skin chronic exposure to exposomes,

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external environmental challenges, such as sunrays, tobacco smoking, and pollution (Gueniche *et al*., 2022).

Nowadays, HA and derivatives are the most popular cosmetic agents with promising aesthetic results. Delivering HA in variable routes of administrations such as topical, internal, and injectable showed confirmed antiwrinkles properties, skin hydration, aging marks reversal, and grooves filling. Additionally, there are clinical pieces of evidence on its ability to reduce hallow marks, boost nail strength, and rejuvenate hair fibers, among many other therapeutic aspects (Fagien *et al*., 2012; Monheit and Coleman, 2006; Peng *et al*., 2022 ; Schwartz and Park, 2012).

MECHANISM OF ACTION

Clinical studies demonstrate several physiological effects of exogenous HA. Studies on osteoarthritic cartilage using *in vitro* articular chondrocytes in a hydrogel culture system revealed its significant stimulatory effect on the metabolic activity of chondrocytes which explains its longer term protective effect on articular cartilage (Liu *et al*., 2022). This effect is associated with inhibition of immune complex adherence to polymorphonuclear cells, scavenging of free radicals, and inhibition of leucocyte and macrophage migration and regulation of fibroblast proliferation (Akmal *et al*., 2005). Moreover, it was found that combinational treatment of HA and platelet-rich plasma (PRP) in intra-articular injection exerts a synergistic effect in both regenerative and anti-inflammatory potentials on osteoarthritis compared to either HA or PRP alone (Whitmire *et al*., 2012).

Topically, HA is well known for its hydrophilic nature. The high water-binding capacity is attributed to the high density of negative charges from the carboxyl groups in its structure, which causes the osmotic pressure and draws the water molecules into the tissues (Valachová *et al*., 2022). The exact moisturizing mechanism varies with HA molecular weight. For this reason, the choice of HA fragment for cosmetic formulation should be carefully considered in context with the intended reason of use and application. Generally, the larger the molecular weight, the more predominant the physicochemical properties, while biological properties will be overcome in the case of smaller-molecular-weight fragments (Smejkalova *et al*., 2015; Snetkov *et al*., 2020). The biological activity of HA was conducted through its interaction with several receptors, such as CD44 and the receptor for hyaluronic acid-mediated motility (RHAMM), as shown in Figure 1 (Jensen *et al*., 2020).

DERIVATIZATION OF HYALURONAN FOR COSMETOLOGY

As mentioned earlier, HA is highly susceptible to degradation by the hyaluronidases, which means a high rate of *in vivo* turnover. Thus, chemical modifications are required for cosmetic or pharmaceutical applications. These modifications are either chemical attachment of groups to decrease HA hydrophilicity, so it can be easily blended with the hydrophobic ingredients typically found in cosmetics, or cross-linking to form insoluble HA derivatives or hydrogels (Smejkalova *et al*., 2015).

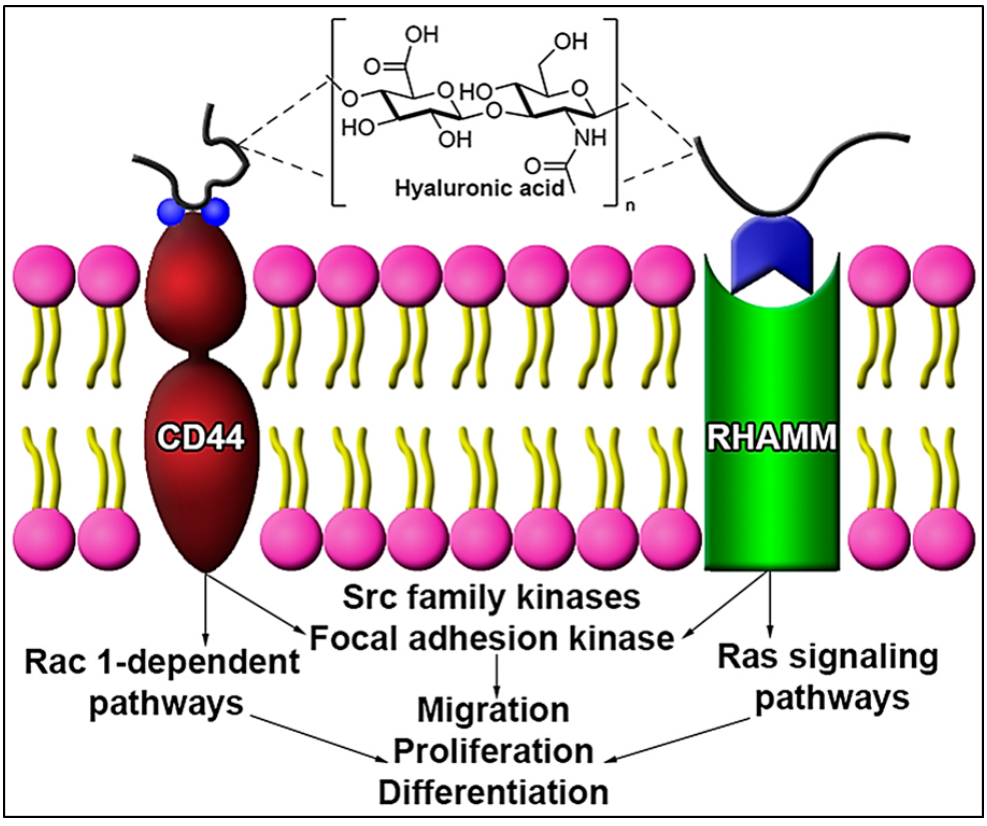

Figure 1. The interaction between HA and CD44 receptor and RHAMM receptor. Each acts differently to elicit cell behavior (Jensen *et al*., 2020).

THE USE OF HYALURONAN IN COSMETOLOGY

In skincare products

Skin moisturizing is one of the primary goals of commercially available skincare products. HA possesses an exceptional capacity to bind and retain water molecules and, hence, contribute to skin moisturization, elasticity improvement, skin hydration, collagen and elastin stimulation, and face volume restoration showing promising results in skin tightness and wrinkles reduction (Juncan *et al*., 2021; Papakonstantinou *et al*., 2014).

Sunscreen products

Sunscreen products containing HA can maintain firmer skin besides their UV-radiation protection activity. The sun protection activity refers to its antioxidant properties. Additionally, adding HA to sunscreens provides extra protection against type B ultraviolet (UVB) radiation by prohibiting mutation in the HA synthase, decreasing the release of proinflammatory mediators. Accordingly, the anti-inflammatory effect is an added value (Hašová *et al*., 2011).

Dermal fillers

Injectable dermal fillers containing cross-linked HA have become a desirable aesthetic procedure. Patients are looking to rejuvenate the skin and compensate for the age-related loss and, overall, diminish age-related symptoms. This procedure is not invasive and needs to be performed by an expert specialist (Aziz *et al*., 2019).

After Food and Drug Administration approval, the cosmetic industry field commenced HA use in various cosmetic products, including dermal fillers. The high safety profile and promising aesthetic enhancement properties make it the component of choice in cosmeceuticals. Adding HA to dermal fillers aims to increase the augmentation of the soft tissue and to hydrate skin compartments. Hydrating skin takes part by attracting water molecules to compensate for the loss of natural components at the cellular level. Therapy supports the collagen and elastin fibers that diminish and lose their function partially by advanced age. Due to the noninvasive method of treatment and the quick observed results, injecting HA into the dermis would minimize the hallmarks of aging and boost the skin volume and elasticity (Kontis and Rivkin, 2009; Rohrich *et al*., 2019; Zerbinati *et al*., 2018).

Haircare products

Recently, manufacturers of cosmetic haircare products have tended to incorporate HA into their formulas for its claimed efficacy in the revitalization of hair follicles. Researchers interested in hair cosmetology confirmed the efficacy of the compound of our interest combined with a range of amino acids in promoting the anabolic process of the dermal papilla cells. These biological processes include the synthesis of needed proteins and the production of intracellular matrix components (Matarasso *et al*., 2006). Moreover, HA contributes to counteracting the oxidative stress of the hair follicles triggered by various internal and external factors. The main external trigger is exposure to type A ultraviolet (UVA) and UVB radiation. Formulas enriched with HA participate in reducing the inflammatory responses by decreasing the inflammatory marker IL-8 and the keratinocytes' vascular growth factors. This biological activity was confirmed after *in vitro* testing using a human follicle dermal papilla cell line (Zerbinati *et al*., 2021a).

Nail care products

Nails are considered one of the cosmetologist and manufacturer target tissues. Nail cosmetic products and cosmeceuticals are designed either to beautify the nails or for therapeutic purposes. Fragile periungual tissues could result from environmental factors or excessive cuticle removal. Nail care products have incorporated HA derivatives to add strength to brittle nails. According to the results obtained by Leah and Schmidt, an aqueous solution containing a mixture of mastic tree extract, *Pistacia lentiscus*, and HA has shown an improvement in nail plate strength after 6 months of regular topical application. Softening rough nail plates and minimizing distal breakage would positively influence wholescale nail resistance and appearance. Because HA has a good surface adherence property, it would enhance the deep moisturizing of nail compartments (Zerbinati *et al*., 2021b). The adhesion property refers to the ionic interaction between the positively charged acid and the nail surface. This characteristic allows a desirable spreading of the formula, extends the contact time, and delivers the active ingredient more efficiently (Piraccini *et al*., 2020).

Nutraceuticals and other food supplements containing HA have clinically significant positive effects on the health of nails, hair, and skin after regular intake for 8 weeks. Other adjuvant components include peptides, fatty acids, and collagen (Uyttendaele *et al*., 2003).

THE THERAPEUTIC ACTIVITY OF HA IN DERMATOLOGICAL CONDITIONS

Dry skin

Several internal and external factors contribute to dry skin conditions. These include UV radiation, nutrition, heredity, and aging. Due to aging, the amount of natural moisturizing factors stored in the phospholipids' envelopes of the stratum corneum decreases. This reduction disturbs the skin barrier mechanism and limits its resistance to external stimuli (Engelke *et al*., 1997; Rogers *et al*., 1996; Sunwoo *et al*., 2006; Yagoda and Gan, 2014).

Applying topical moisturizers is recommended to avoid dry skin complications such as bruising and open cuts. Unfortunately, topical application is not convenient for all patients, especially those of advanced age and who live alone. On the other side, a dietary supplement containing HA, at a minimum daily dose of 120 g, would help moisturize the skin and reduce the complications of chronic rough skin cases (Di Cerbo *et al*., 2015; Sato *et al*., 2002).

Dry skin is also associated with atopic dermatitis and xerosis; these dermatological conditions also benefit from HA consumption. Treatment reduces pruritus accompanied by a dry skin condition (Kawada *et al*., 2014).

Oily skin

Overactivity of the skin sebaceous gland leads to a condition known as oily skin. The experimental and clinical studies outputs found that HA has an essential role in reducing lipid synthesis, therefore decreasing secretion from the sebaceous

gland (Jung *et al*., 2017). Intradermal injection of the acid reduces the size of the sebaceous gland and limits lipid production. At the molecular level, downregulation of the HA binding receptors (CD44) occurs which affect the lipid and sebum biosynthesis as well. In general, formulas with HA would effectively address oily skin (Kawada *et al*., 2014).

Alcoholic-skin damage

Skincare formulas contain alcohol for its disinfectant properties or as a vehicle to dissolve other ingredients. Unfortunately, alcohol, in particular, ethanol, harms skin health and induces skin cytotoxicity and inflammatory responses (Lachenmeier, 2008; Neuman *et al*., 2011; Pershing *et al*., 1990; Rotter *et al*., 1998). Cutaneous erythema, for example, is among the most common allergic reactions after topical ethanol application (Haddock and Wilkin, 1982).

Neuman *et al*. (2010) confirmed that HA at a concentration range of 2%–4% could repair skin damage induced by ethanol (Neuman *et al*., 2010).

Antiaging effect

HA is a natural skin component, its biosynthesis and production diminishing with advanced age. A lower concentration is associated with wrinkle formation and dryer, thinner skin (Lee *et al*., 2016). Because hyaluronan can preserve water content in skin cells, the decrease in its concentration would ultimately dehydrate the skin (Prasathkumar and Sadhasivam, 2021). In normal healthy skin, HA is continuously renewed after its degradation. Unfortunately, the rate of renewal tends to decrease with age. The decrease would be greater if combined with other external factors such as exposure to UV radiation. The optical concentration of HA at the cellular level is essential to retard aging symptoms (Bucay, 2021; Fraser *et al*., 1997; Olejnik *et al*., 2012). Not only does HA has an ability to retain moisture, but it also influences the keratinocytes' growth rate; besides, HA confers antioxidant properties due to the attached units of *d*-glucuronic acid (Fallacara *et al*., 2018; Haeusler., 2015; Manuskiatti and Maibach, 1996; Pavicic *et al*., 2011; Witting *et al*., 2015).

THERAPEUTIC USES OF HA

Oral ulcers and aphthous stomatitis

Our acid of interest and its salt, sodium hyaluronate, are effective after topical administration to address oral mucosa ulceration. The active component works by applying a protective coat around the cavity, promoting hydration, and eventually accelerating the healing process (Nolan *et al*., 2006). The gel dosage form containing 0.2% of HA showed a good response and alleviates oral ulcers after topical administration in clinical studies (Lee *et al*., 2008). Mucosal protection effects result from the physical barrier formed over the ulceration after gel application (Abo-shady *et al*., 2020; Casale *et al*., 2017). Repeated administration is recommended to keep the infected area covered and to obtain better healing activity (Casale *et al*., 2017; Koray *et al*., 2016).

Dentistry

Hyaluronan has been incorporated into dentistry as a potential remedy for minor oral diseases. It can accelerate periodontal tissue healing, attenuate gingivitis symptoms, and promote wound healing (Al-Khateeb and Olszewska-Czyz, 2020). An HA derivative could have a synergistic effect with other topical medicines in minor oral operations such as implants, sinus lifts, and surgical extraction. Other potential benefits include delivering a high concentration of the chemical drugs topically and promoting tissue regeneration (Casale *et al*., 2016).

Osteoarthritis

External HA provides viscoelasticity to the joints because it compensates for the loss in the endogenous HA in the synovial fluid. Due to its anti-inflammatory activities, HA contributes to the relief of arthritic conditions. The anti-inflammatory mechanisms involve cytokines suppression and multiple effects on other inflammatory mediators (Yang *et al*., 2012). The anti-inflammatory activity of the HA derivatives largely depends on their molecular weight, oligosaccharide chain length, and affinity toward the CDD4 receptors (Campo *et al*., 2010; Higman *et al*., 2014; Termeer *et al*., 2002; Wolny *et al*., 2010). HA for treating arthritis is delivered via an intra-articular route either as a single component or combined with other drugs such as steroids or nonsteroidal anti-inflammatory drugs (Euppayo *et al*., 2017; Gomes *et al*., 2022).

Intra-articular injection of corticosteroids has short-term effects (about 4 weeks) while injecting HA via the same route has an elongated effect for up to 26 weeks (Bannuru *et al*., 2009).

Rosacea

Rosacea is a common dermatological condition characterized by erythema, flushing, and papules. The disease pathogenesis is mainly affected by genetic factors which are exacerbated by reverse environmental conditions. Recently, dermatologists confirmed the positive effect of treating rosacea with HA. By reinforcing the skin's natural antioxidant capability, HA was found to minimize the severity of rosacea symptoms. For example, improvement in erythema and increased skin tightness was observed in addition to a total decrease in the basal sensitivity scores (Berardesca *et al*., 2020; Schlesinger and Powell, 2013). The implications of HA and its derivatives in medicines and cosmetics are summarized in Figure 2.

SAFETY PROFILE AND LIMITATION OF USE

Generally, HA is considered safe to use as it is a natural component of the skin. After oral ingestion of the acid and derivatives, no clinical observation was noticed according to published data. Also, no food interaction or clinical or pathological effects were found (Kawada *et al*., 2014; Lee *et al*., 2017).

This is not always the case with filler injection containing HA or derivatives. Unfortunately, Lee *et al*. (2018) reported a case of blepharoptosis, skin necrosis, and a decrease in visual acuity after injection with hyaluronidase in the filler component. These serious adverse effects were due to accidental injection of the acid into the blood vessels. Physicians refer the complications to the high vascularity around the nose area combined with a large filler injection volume (Lee *et al*., 2017). Caution has to be taken when injecting fillers containing HA and derivatives, and it should be done by a trained specialist. Examples of reported cases of undesirable side effects following HA administration either for aesthetic purposes or for therapeutic efficacy are summarized in Table 1.

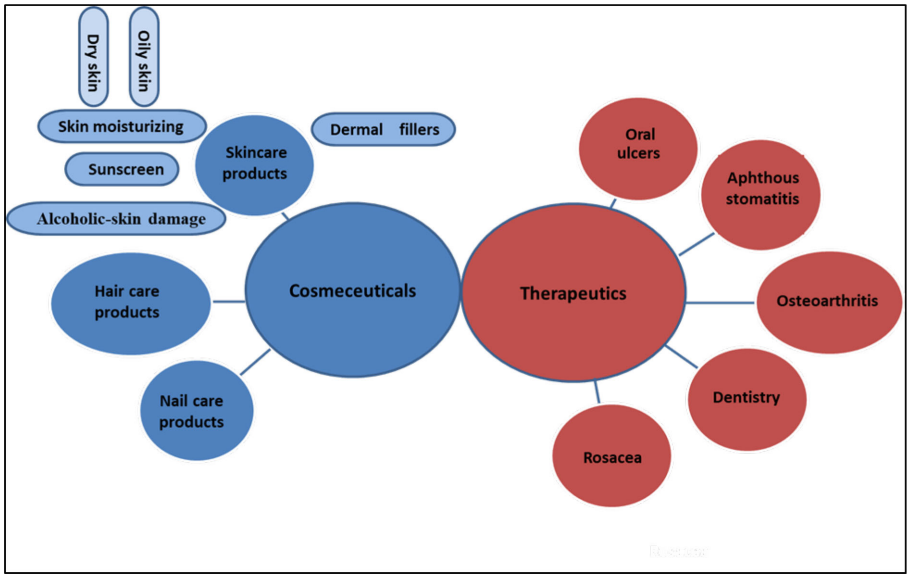

Figure 2. The implications of HA and its derivatives in medicines and cosmetics.

Table 1. Reported cases of undesirable effects after HA administration.

HA route of administration	Reason of use	Reported case	Reference
Injection	Aesthetic	Facial granulomatous nodules and fungal/ bacterial infection	Horriat *et al*. (2020)
Injection	Aesthetic	Blepharochalasis: dermatochalasis of the upper eyelids, rigid mass after HA injections	Maione *et al*. (2021)
Intra-articular injection	Therapeutic: for ankle osteoarthritis	Cutaneous necrosis of ankle and foot.	Aaron *et al*. (2021)
Injection	Aesthetic	Acute and chronic infections	Becker *et al*. (2021)
Injection	Aesthetic	Delayed inflammatory reaction following COVID-19 vaccination	Michon, (2021); Luciena *et al*. (2022)
Injection: breast augmentation	Aesthetic	Migration of Macrolane (stabilized HA of nonanimal origin) in an axillary lymph node	Trignano *et al*. (2020)
Injection	Aesthetic	Orbit mass secondary to migration to lumps, allergic skin reactions, edema, migration, scarring, skin necrosis, retinal artery occlusion, paralysis in the face, skin discoloration, and xanthelasma-like reaction	Mosleh *et al*. (2019)

CONCLUSION

Innovative formulas for aesthetic appearance and diminishing aging symptoms have become the main interest of manufacturers, the cosmetic sector, and even pharmaceutical companies. Recently, HA and its derivatives have become trendy compounds in cosmeceuticals for their claimed effects of beautifying, hydrating, regenerating, and compensating the natural loss by advanced age. The efficacy of HA, and its derivatives, is confirmed due to its antioxidant and anti-inflammatory activities. Moreover, these compounds have desirable physicochemical properties. Accordingly, in-depth investigation to introduce HA in the treatment protocols of age-related deformations is much encouraged.

Enhancing the bioavailability and efficacy after noninvasive routes of administration is recommended to attain customers' compliance and to avoid undesirable consequences of the injectable routes.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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