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# Review On Hyaluronic Acid (Hyaluronate, Sodium Hyaluronate): Uses, Side Effects

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**Abstract:**

Extrinsic and intrinsic aging are two separate and independent mechanisms that contribute to the multifactorial process of skin aging. Because youthful skin has a high water content, it maintains qualities like turgor, resilience, and pliability. Moisture loss results from everyday external damage in addition to aging naturally. Hyaluronic acid (HA) is the primary molecule responsible for skin hydration because of its exceptional ability to hold onto water. The intricacy of HA metabolism is reflected in the multiple locations for control over HA synthesis, deposition, cell and protein association, and degradation. The multigene families of enzymes that synthesize or catabolize HA and HA receptors, which are involved in numerous HA functions, exhibit unique tissue expression patterns. Knowing how HA is metabolized in It will be easier to regulate skin moisture in a sensible way because of the various layers of the skin and how HA interacts with other components of the skin.

**Keywords**: skin aging, CD44, RHAMM, hyaluronic acid, hyaluronic acid synthases, and hyaluronidases.

## Overview :

Composed of N-acetylglucosamine and D-glucuronic acid disaccharide units, hyaluronic acid (HA) is a polysaccharide that belongs to the glycosaminoglycans (Figure 1). It is a significant part of the extracellular matrix (ECM) and a constituent of the neural, connective, and epithelial tissues [1, 2, 3, 5, 6]. First identified in the vitreous humour of the eye in 1934, HA was synthesized in vitro in 1964 [7,8,9]. The molecular weights of HA vary greatly, from 2 × 105 to 107 Da [10,11,12,13]. The physico-chemical properties of HA can be influenced by its average molecular weight

Based on the application of cosmetic HA in varying concentrations, some studies identified by the experts panel of the Cosmetic Ingredient Review (CIR) revealed acute, short-term, or chronic toxicity [20]. Furthermore, following the application of a topical product containing hyaluronic acid (0.01%), hydroquinone (4%), and glycolic acid (10%) for the treatment of melasma, some acceptable side effects (such as scaling, erythema, and pruritus) were noted [4]. HA and NaHA can then be nebulized and utilized in aerosol-applying cosmetic products (like hair spray) [20]. The respiratory system can store the nebulized particles at different levels based on their concentration and size. This makes evaluating the safety of cosmetic aerosols a crucial matter. It was observed that HA had a protective effect on the respiratory system.

However, according to some studies [21], the propellant gas, vapors, and other soluble compounds that are linked to hyaluronan in cosmetic aerosols and cause respiratory sensitization effects like rhinitis, conjunctivitis, wheeze, dyspnea, or asthma include alkanes, alcohols, stabilization polymers, bentonite, aluminum chlorhydrate, perfume oils, cosmetic colorings, complexation agents, lanolin derivatives, plant extracts, etc. Furthermore, pulmonary overload brought on by insoluble aerosol particles may result in long-term toxicity (such as persistent inflammation, fibrosis, and lung tumors). The effects can be attributed to the particle size, duration of exposure, or concentration. For instance, it is advised to evaluate the inhalation toxicity of products containing insoluble particles smaller than 10 μm. Five minutes of exposure is recommended for these aerosols,

and it's also important to avoid to prevent being exposed to lipophilic substance fine droplets, which may cause "acute respiratory syndrome"

One of the most effective and secure ingredients that is commonly used in cosmetics is hyaluronic acid. Other bioactive components (e.g., plant extracts, vitamins, amino acids, peptides, proteins, minerals, saccharides, probiotics, etc.) can enhance the properties of HA. These days, several manufacturers sell a wide range of cosmetics that contain HA. These benefits of HA or bioactive ingredients are presented individually in the previously published papers. In this paper, we first discuss the biological effect of HA at the skin level. Next, we examine the product portfolios of a few well-known manufacturers, identify HA-containing commercial cosmetic brands, and assess the quality of the products based on their declared composition. Then, the other active ingredient's additional biologic effects and toxicological potential.

**Discovery of HA :**

Karl Meyer and his colleague John Palmer discovered HA in 1934 when they isolated a previously unknown material from the bovine vitreous body. They named this novel substance hyaluronic acid after discovering that it included two sugar molecules, one of which was uronic acid. The “hyal” portion came from the word hyaloid which refers to the vitreous body hence the combination was called hyaloid + uronic acid or hyaluronic acid [8,9]. This previously unknown substance would go on to become one of the most intriguing and extensively studied naturally occurring human polymers. HA was not used commercially until 1942, when Endre Balazs submitted a patent to replace egg whites with HA in baked goods [9,10]. However, it is not known if this patent was granted and the authors have not been able to find a reference to HA being used as a suitable alternative to egg white in baking. Subsequently, in the late 1950s, HA found its way into medical applications when it was used to replace the vitreous humour of the human eye.

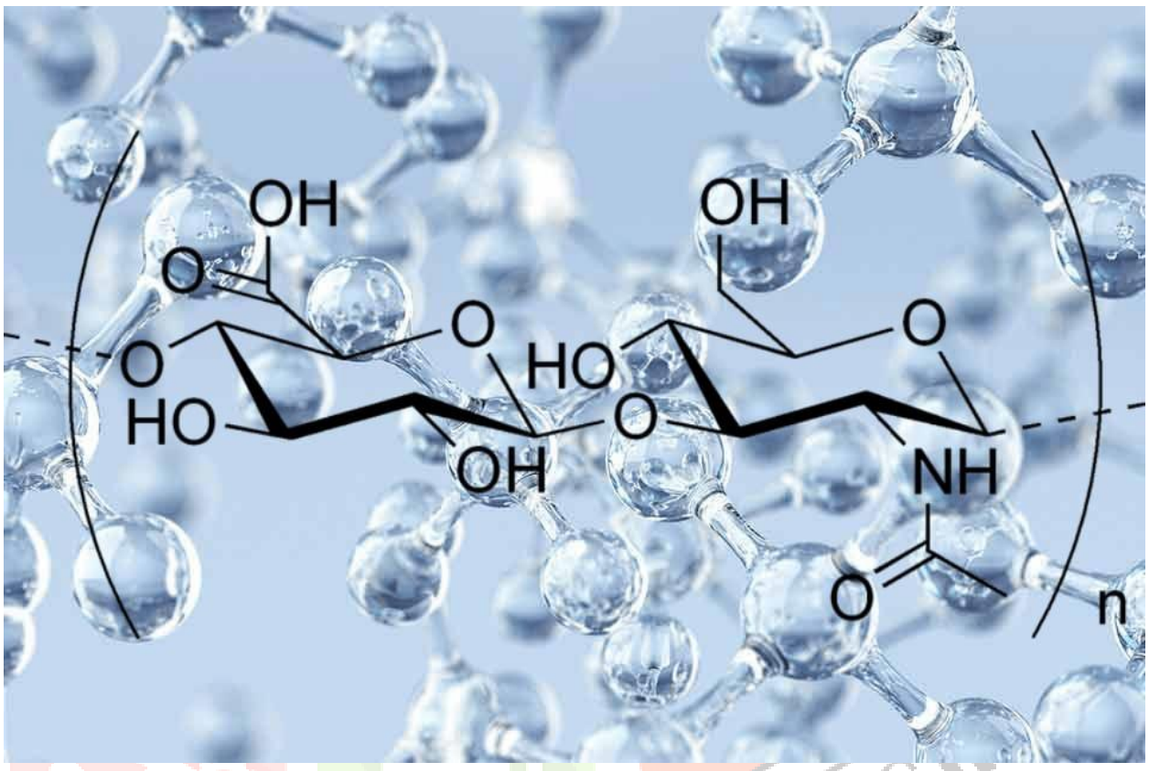
As a component of biomaterials, hyaluronic acid (HA), a naturally occurring glycosamino glycan, has several special benefits. For instance, hyaluronic acid is largely non-adhesive to cells and proteins, enzymatically degradable, and non-immunogenic [1]. Hyaluronic acid plays a physiological role in wound healing, angiogenesis, extracellular matrix, homeostasis, and the regulation of chronic inflammation. High molecular weight linear polysaccharide hyaluronic acid is manufactured commercially for a variety of applications, primarily as an adjunct to ophthalmic surgery. Hyaluronic acid is traditionally produced by extracting it from rooster combs [2].Every molecule of the polysaccharide has 500–50,000 monosaccharide residues. Its molecular weight therefore varies from 10. categorized chemically as a glycosamino glycan and made up of the

repeating disaccharide units of (1 - 3) N acetyl 2 - amino - 2 deoxy - β - D glycopyranosyl acid, and (1 - 4) β - D glycospyranosyl uronic acid. 107 Da to 4 Da [3, 4]. Soft connective tissue contains the highest concentration of hyaluronic acid, which is present in all living things. It is crucial to the body's transportation and mechanical functions. Applications for hyaluronic acid are numerous and include anti-aging periodontitis, comfort eye drops, osteoartitis, wound healing, and more. Historically, hyaluronic acid has been extracted from the vitreous humour of cows and cockscombs. Because it forms a complex with proteoglycans, high molecular weight

hyaluronic acid is difficult to economically isolate from these sources [5]. Unlike other sources, Streptococcus is an exclusive

**Chemical composition :**

D-glucuronic acid and d-N-acetyl- are the aminosugar and uronic acid in the disaccharide.glucose, and are connected to one another by beta-1,4 and beta-1,3 glycosidic bonds that alternate Refer to Figure 1. The two sugars are correlated spatially with glucose, which permits all in the beta configuration of its large groups (the carboxylate, the hydroxyls) the anomeric carbon on the nearby moiety and the sugar) in an equatorial position that is sterically favorabletions, and every single tiny hydrogen atom occupies the axial positions that are less sterically favorable. Consequently, The disaccharide's structure is energetically extremely steady.




**Hylaluronic Acid**

**Skin hyaluronic acid synthases :**

TGF-β1 differently upregulates the expression of HAS-1 and HAS-2 genes in the skin's dermis and epidermis, suggesting that the functions of HA in the dermis and epidermis are distinct and that HAS isoforms are independently controlled.16,98 Keratinocyte growth factor has the ability to increase the mRNA expression of HAS-2 and HAS-3. This, in turn, can activate keratinocyte migration and drive wound healing, resulting in the accumulation of intermediate-sized HA within keratinocytes and in the culture medium. The enhanced synthesis of HA stimulates the migratory response of keratinocytes during wound healing.Additionally, in fibroblasts100, TNFα and IL-1β stimulate HAS-2 mRNA, and in rat epidermal keratinocytes, epidermal growth factor does the same.101

**Streptococcus biosynthesis of hyaluronic acid** :

Anaerobes with strict dietary requirements, streptococci generate lactic acid as a byproduct of their metabolism of glucose. The mucoid capsule surrounding the cell, known as the hyaluronic acid capsule, is a biocompatibility factor that helps gram-positive bacteria evade host immune defenses and thus explains their high virulence level. Hyaluronic acid is produced by Streptococcus as a secondary metabolite, and its production is influenced by a number of factors, including nutritional and genetic factors. Hyaluronic acid is produced by Streptococcus in both aerobic and anaerobic environments [16]. At one point in their life cycle, some strains of Streptococcus produce hyaluronic acid. Later on in the organism's life cycle, the hyaluronidase enzyme is secreted, which breaks down the hyaluronic acid that was produced.Because of this, the strain chosen for the synthesis of hyaluronic acid had no hyaluronidase activity and was not pathogenic.

**Hydrotatation Impact of Hydrogen Acetate in Cosmetic Mixtures :**

Comparatively speaking, the epidermis produces a greater amount of hyaluronic acid than the dermis. For equal tissue amounts, it was shown that the epidermis synthesizes four times more hyaluronic acid than the dermis, despite the dermis being much thicker than the epidermis and containing four to nine times more HA. HA can be found in the basal and spinous layers of the epidermis during intercellular matrix formation. Hyaluronic acid's hygroscopic qualities play a significant role in hydrating the deep layers of the epidermis, just as they do in the dermis, but its role goes beyond simple hydration.

HA plays a significant role in cellular development, adhesion, and membrane receptor function. It can bind water up to 1000 times its volume. The primary physiologic function of HA in the intercellular matrix is to create the elastoviscous fluid matrix, which securely envelops the collagen and elastin fibers, and to reinforce the intercellular structures. HA retains moisture while also giving the skin strength and brightness [93,94]. Because of its extremely high molecular weight, which hinders it from passing through the SC, HA can be applied topically to promote hydration and skin regeneration.

**Effect of HA on Anti-Aging in Cosmetic Formulations :**

HA plays a significant part in the aging of the skin. As we age, our cells lose their capacity to make HA. Among other notable changes, the skin gets thinner, drier, and more loose, which causes wrinkles [97]. A reduction in skin moisture content is also linked to skin ageing. The special ability of hyaluronic acid (hyaluronan) to bind and hold onto water molecules [98]. As seen, hyaluronic acid is a naturally occurring substance found throughout the body. There are 15 g of hyaluronic acid in a 70 kg person, 5 g of which are replenished every day. Due to its quick deterioration, HA is naturally regenerated continually; but, as people age and are subject to outside aggression, its renewal begins to slow down. Consequently, it.

**Hyaluronic acid-based medication delivery applications in cancer :**

According to American Cancer Society estimates, the lifetime risk of having invasive cancer is fifty percent for men and thirty-three percent for women [123]. Chemotherapy is currently the most common cancer treatment, yet it has a number of disadvantages [124]. A cancer's resistance to a given medication may develop if the medicine is given intravenously on several occasions. Additionally cytotoxic, cancer medications cause the patient's cells to die off-target [95]. Targeted drug delivery research has therefore increased. Research has indicated that intravenous HA injections typically target the CD44 receptor, and scientists have been working on methods that might be able to take advantage of this process. M. B. Brown et al. compared the efficacy of HA and other glycosaminoglycans and polysaccharides in the delivery of diclofenac, a keratosis treatment drug, in 2001. The study concluded that HA is the most effective in dermal drug delivery and localization .

Drugs can be delivered to target cells by modifying hyaluronic acid. The properties that make hyaluronic acid an excellent hydrogel also apply to drug delivery. Hyaluronic acid, in addition to being biocompatible, can be taken into the cell via endocytosis triggered by CD44. CD44 is a receptor that is found on liver, kidney, and tumor cells. RHAMM and LYVE-1 are two other targetable receptors [102]. Endocytosis addresses the common issue of the novel drug's low intake.

**Engineering of skin tissue :**

Without a skin graft, skin loss greater than 4 cm in diameter cannot heal effectively [119]. Donor restrictions on the availability of skin grafts aggravate this problem even more [120]. Tissue engineering has thus been used in medicine to create substitute treatments for patients in need of skin grafts. Researchers sprayed poly-l-lysine films onto a HA scaffold as part of an in-vitro layer-by-layer assembly technique. This method produced an environment that was both cell-viable and adherent for the components of dermal and epidermal tissue. The main cell type in the epidermis, keratinocytes, was employed by the authors to test the structure [121]. The authors discovered through a cell viability assay that the keratinocytes Attached to the HA/polyllysine film, the bacteria formed colonies that grew in size over a three-day period. They also discovered that the keratinocytes did not infiltrate the HA scaffold.

**Applications in dermatology and wound healing :**

There is a high concentration of HA in nature. in the soft connective tissues and skin. Consequently, HA is a suitable option for a matrix to supportFor port dermal augmentation and regeneration. For instance, Prestwich and associates discovered that films of cross-linked HA hydrogel speed up the full-thickness wound healing, most likely By offering an extremely well-hydrated and non-immu-an atmosphere that is favorable to tissue restoration. In vitro cultured hyaff scaffolds with Fibroblasts and keratinocytes have been utilized to produce skin-like materials, comprising two distinct tissue layers that resemble dermis and epidermisers. Additionally, because of its capacity to form expanded matrices that are hydrated, HA has also been effectively employed in cosmetic applications, such as in soft tissue (Dechert et al., 2006; 2004).augmentation (Dechert et al., 2006; Leach and Schmidt, 2004).

**Adverse consequences :**

As long as users adhere to usage guidelines, hyaluronic acid injections, topical treatments, and supplements seem to be safe overall.

Hyaluronic acid, however, may cause allergic reactions and unfavorable side effects in certain individuals. When using a new skin care product, one should always perform a test patch.

The following adverse effects are possible with hyaluronic acid injections; these should go away in a weekTrusted Source:

ache, redness, itching

bruises and edema

It is more likely that the injection procedure will cause these side effects than the hyaluronic acid solution itself.

**RISK :**

Hyaluronic acid rarely causes severe side effects or allergic reactions because the body produces it naturally.

Hyaluronic acid users should exercise caution if they have a history of severe allergic reactions, such as anaphylaxis.

Women may wish to refrain from taking hyaluronic acid supplements during pregnancy and nursing as its effects are still unknown during these periods.

In general, before attempting a new supplement, individuals should consult a physician, particularly if they:

possess a chronic health condition, take prescription drugs, or are undergoing medical treatment for an illness

In order to determine whether hyaluronic acid is right for them, people can always consult a doctor.

**Uses :**

**1] Hyaluronic acid-containing eye drops appear to help with the symptoms of dry eyes.**

**2] weak blood circulation resulting in leg sores (venous leg ulcer). Hyaluronic acid-containing gauze appears to minimize sore size and accelerate healing.**

**CONCLUSION :**

In the human body, hyaluronic acid is a naturally occurring substance. The fluids in the joints and eyes contain the highest concentrations of it. Hyaluronic acid used in medicine is synthesized in a lab using bacteria or extracted from rooster combs. Hyaluronic acid is taken by people with osteoarthritis and other joint conditions. A medical practitioner may administer it orally or inject it into the injured joint. Hyaluronic acid has been given FDA approval for use in a number of eye surgeries, such as the removal of cataracts, corneal transplants, and repairs for detached retinas and other eye injuries. During the procedure, it is injected into the eye to help replenish natural fluids. Another use for hyaluronic acid is as a lip filler in the field of plastic surgery.

Hyaluronic acid is applied topically by some people as a moisturizer and to treat burns, wounds, and ulcers on the skin. Hyaluronic acid is also a popular choice for counteracting the signs of aging. Hyaluronic acid has actually been advertised as a "fountain of youth." But there's no proof to back up the assertion that taking it

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