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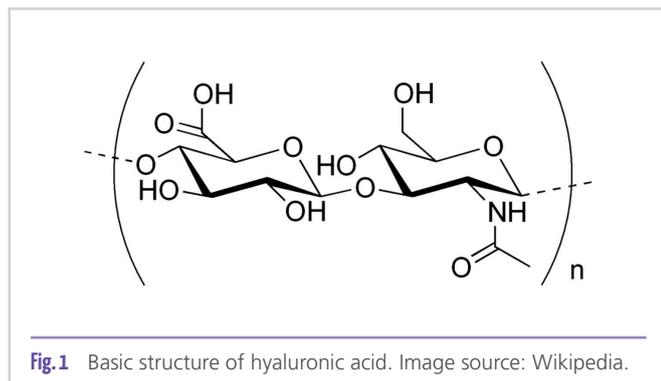
Hyaluronic acid (synonym: Hyaluronan, HA) is an important component of the human skin. It is synthesized with the help of the enzyme hyaluronate synthase (HAS) by fibroblasts of the dermis and epidermis. As the main component of the extracellular matrix it also occurs in other types of the human connective tissue.

Chemically speaking, hyaluronic acid (HA) is a glycosaminoglycan (**Fig. 1**). Its basic structure is a disaccharide of about 400 Dalton which is composed of D-glucuronic acid and N-acetylglucosamine linked together through alternating beta-1,4- and beta-1,3 glycosylic bonds. The specific basic structure and high packing densities are responsible for the fact that HA has a gel-like consistency in water.

Functions of Hyaluronic Acid in the Skin

Due to its anionic character, HA is able to bind a high number of water molecules. Thus, it contributes to the shaping of the skin and also acts as a pressure-compensating “shock absorber”. HA mediates the interaction of the skin cells with each other and with the extracellular matrix. It also helps maintaining the integrity of the tissue. HA is able to regulate the association with adjacent cells, thus influencing the proliferation of epidermis cells such as keratinocytes and their differentiation in corneocytes.

HA makes tissues more permeable for the transport and migration of substances through the extracellular matrix. It is involved in numerous cell processes. For example, the transport of molecules for cell nutrition and the removal of substances in degradation processes are influenced by HA. In addition, HA mediates inflammatory processes and other regulatory mechanisms.



HA can interact with certain receptors triggering intracellular signal cascades. For example, the receptor CD44 mediates cell-cell contacts and contacts to collagen and other extracellular matrix proteins. CD44 is responsible for the interaction of HA with lipid membranes, allowing HA to permeate through the membranes and to accumulate in the cells.

Due to the features mentioned above and due to the fact that HA and related polysaccharides are depolymerized by free radicals, HA can also function as an antioxidant. Thus, it can protect the skin from premature ageing and damaging caused by UV radiation [11].

Hyaluronic Acid in Anti-Aging Products

The cosmetics industry has long since discovered hyaluronic acid and uses it in a wide range of skin care products, which promise a reduced wrinkle depth and a younger look. There are a large number of scientific studies which prove the improvement of the skin by HA [3,8,11].

A challenge in the external application of HA is the skin barrier. Basically, the larger the molecules, the less deep they can penetrate into the skin: A study from 2016 shows with the help of Raman spectroscopy, that 20-300 k Da HA molecules can penetrate through the stratum corneum into the skin, whereas larger HA molecules remain on the skin surface [3].

Positive Effect of a HA Gel Mix on Skin Hydration, Elasticity and Wrinkle Depth

In order to examine the influence of the molecular masses of HA molecules on the skin in more detail and to test the effect of a mixture of HA molecules of different chain lengths (Raya Hyaluoran Gel 2.5), we carried out a study cooperation with the company Dermatest (Münster): Firstly, we investigated the water content of the cornea cornometrically. Furthermore, we measured the skin roughness and elasticity (cutometric assessment). The tests were carried out with probands (n = 10) aged between 40 and 60 years after they had applied the HA gel for four weeks. The results are shown in figures 2.1-2.3. We were able to show that all parameters examined had improved after the application, namely by 20.7 % (skin hydration), 16.3 % (skin elasticity) and 22.2 % (reduction of the wrinkle depth).

With these values, Raya Hyaluron Gel 2.5 showed greater skin improvement than documented for an 800 k Da HA gel and a 50 k Da HA gel [8]. In general, the positive effects appear to be higher for shorter-chain HA, presumably because these can penetrate deeper into the skin [1-4, 11]. The particular improvement in skin we found in our mixture of HA molecules of different sizes is attributed to several positive effects that add up: Small molecules (below 50 k Da) may penetrate the stratum corneum, permeate deeply into the epidermis and unfold their positive effects there. Medium-sized molecules (200-400 k Da) can act in less deep skin layers and large molecules form a gel-like film on the surface of the skin where they may have a bolstering effect. (Fig. 2)

Raya Hyaluron Gel 2.5 in Ultrasound Treatment and Mesotherapy

Due to its unique combination of HA molecules, the 2.5% HA mixture Raya Hyaluron Gel 2.5 is well-suited as a cosmetic ingredient for the classical topical application. Furthermore, it can be used for ultrasound treatment and mesotherapy. Ultrasound provides for a local warming of the skin, which can accelerate the material transport into the skin. In addition, HA polymers with high molecular mass are broken down into fragments by ultrasonic, so that they can penetrate even better into the skin. A small part of the larger hyaluronic acid molecules remains on the skin surface and helps to retain moisture there. By combining different molecular sizes, Raya Hyaluron Gel 2.5 is able to enhance the beneficial effects of ultrasound treatment in skin care.

In mesotherapy (needling), vital substances are introduced into the skin surface of the face, the neck or back of the hand with fine needles. The gentle needling in presence of HA promotes blood circulation and stimulates

the formation of collagen and elastin. Fine wrinkles are smoothed and skin damages are repaired. Here, too, the effect achieved with HA can be optimized by using a HA gel mixture.

Hyaluronic Acid in Wound Healing

Since HA has a whole range of biochemical properties that affect skin and connective tissue in multiple ways, the application potential of HA in cosmetics and aesthetic medicine is far beyond anti-aging.

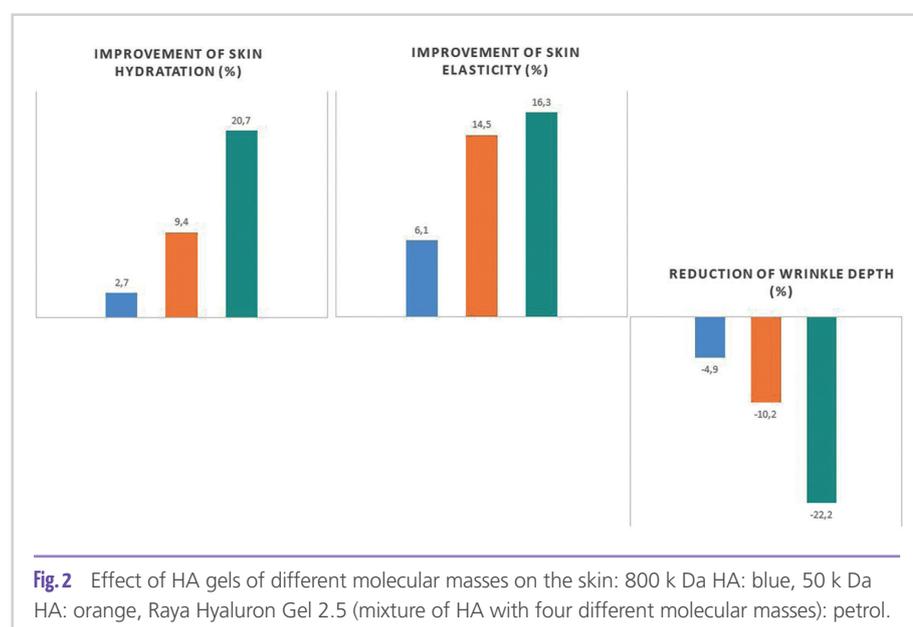
A well-documented effect of HA is wound healing, for example in the case of burns and acne [4]. As the main component of the extracellular matrix, HA plays a key role in wound healing and is involved in a whole series of inflammatory and regeneration processes: It activates and regulates inflammatory reactions and promotes cell proliferation and angiogenesis in the granulation tissue. In addition, in the remodeling process of wound healing, HA-rich extracellular matrix prevents the accumulation of collagen, helping to reduce the risk of scarring [4,5,9].

A controlled double blind study proves the wound healing stimulation effect of HA in patients with superficial or deep burns of second degree. In patients who received HA in addition to the antiseptic silver sulfadiazine, significantly higher wound healing rates were achieved [4].

A scientific study by *Shakir et al.* [9] investigated the effect of HA on scar formation in 36 acne patients. All patients received an ablative CO₂ laser treatment, with specific patients being applied a HA gel to the skin prior to laser treatment. It was found that in patients who used HA, visible scars formed back more than in patients who did not apply HA.

Hyaluronic Acid – a Multi-Talent

Its biochemical properties make HA a true multi-talent. In addition to the application possibilities as an anti-aging agent in cosmetics and wound care products, HA has been successfully used as an active ingredient in joint diseases for decades [5,6]. In ophthalmology, HA is used as an “artificial tear” to moisten the eyes [10]. HA is also suitable as a carrier molecule (“drug delivery system”) [5]. Furthermore, it has proven to be an effective nutritional supplement. Its benefits to patients with osteoarthritis has already been shown [12] and the favorable effect of orally taken HA on the skin has also been described [13]. Hyaluran Cosmetics GmbH produc-



es the vital substance hyaluronic acid according to the needs of their customers. Raya Hyaluron gel 2.5 comes without preservatives. Thanks to its innovative and patented packaging, it is ensured that the gel remains free of bacteria and fungi even after the first use. Storage in the refrigerator – as required by other products in the market – is not necessary. The gel mix is available under the name Hyaluran sensitive in 30 ml and 50 ml airless packaging. Raya Hyaluron Gel 2.5 can also be delivered as a variant for natural cosmetics with the name Hyaluran nature (30 ml in airless dispenser).

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