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Hyaluronic acid: Innovations and prospects in biology and medicine

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Hyaluronic acid (HA) is a natural glycosaminoglycan found in all tissues and body fluids of vertebrates, including those of humans. Its biological functions vary with molecular weight. As the main component of the extracellular matrix, HA, owing to its high water-binding capacity, plays a critical role in maintaining tissue hydration, osmotic balance, lubrication, and cellular activity. It influences cell proliferation, differentiation and migration, inflammation, immunomodulation, angiogenesis, and other biological processes. This article reviews recent advances in HA applications across regenerative medicine, orthopedics, dermatology, neurology, dentistry, cosmetology, cryobiology, drug delivery, oncology, and the food industry. Effectiveness of HA in wound healing depends largely on its molecular weight: high molecular weight HA exhibits immunosuppressive and anti-inflammatory effects, whereas low molecular weight HA promotes immunostimulation and amplifies inflammation. Hydrogels based on HA and its derivatives have gained prominence as potential treatments for bone diseases. Advances in 3D printing enable precise control of scaffold architecture and porosity, which is essential for mimicking native bone tissue, and allow integration of HA-based hydrogels with other materials to generate composite scaffolds with enhanced performance. In dentistry, HA is commonly used for diverse procedures, including papilla regeneration injections, implant coating, topical treatment of oral ulcers, supplementation to platelet-rich fibrin, plasma and growth factors, use as a matrix for encapsulation of stem cells and signalling molecules and as a nanocarrier of drugs, and therapy of denture- or surgery-induced stomatitis and irritation. In ophthalmology, HA is used in eye drops to relieve eye dryness and to improve contact lens tolerance. Due to its viscosity, HA is useful in various ophthalmic procedures, including cataract surgery, vitreoretinal surgery and glaucoma treatment. In cryobiology, HA is being explored as part of complex cryoprotectant formulations. For example, HA is known to be able to neutralize free radicals and to protect cells from reactive oxygen species generated by cryoprotectants. The article also highlights prospects for the rising use of innovative HA-based products to advance current medical practices and biotechnologies.

Keywords: molecular weight; regeneration; wound healing; hydrogel; cryopreservation.

Introduction

Hyaluronic acid (HA) is a natural non-sulfated linear polysaccharide with a molecular weight ranging 500 kDa to 4,000–5,000 kDa (Petit et al., 2025; Wang et al., 2025). It belongs to the class of glycosaminoglycans. Its molecule is repeating disaccharide residues consisting of D-glucuronic acid and N-acetyl-D-glucosamine, which are linked together by β-1,3- and β-1,4-glycosidic bonds (Jiang et al., 2025; Wang et al., 2025).

This biologically active compound is an important structural component of extracellular matrix (ECM) and plays a key role in main-taining the structural integrity and mechanical stability of various tissues, in particular the ECMs of skin, brain and cartilage, ensuring their shape and elasticity. In the adult body, the total HA content is approximately 12–15 grams, with the highest concentrations detected in skin, connective tissue, ECM, vitreous humor, synovial fluid of joints, and embryonic structures (in particular, in the umbilical cord) during intrauterine development (Petit et al., 2025; Rodella et al., 2025).

Exceptional hydrophilicity and ability to significantly increase in volume when interacting with water are important features of glycosaminoglycans. HA, due to its anionic structure and high osmotic activity, can bind significant amounts of water. The polymeric structure of HA simultaneously gives it excellent viscoelastic properties (Musiał, 2021; Rodella et al., 2025). At the same time, HA has a number of unique differences from other glycosaminoglycans:

– it is the only non-sulfated representative of this class (Fallacara et al., 2018);

– it is the only glycosaminoglycan that does not form covalent bonds with protein molecules (Fallacara et al., 2018);

– it is capable of non-covalent interactions with proteoglycans, forming large proteoglycan aggregates, which fill extracellular matrix spaces with an amorphous gel (Fallacara et al., 2018);

– it is noticeable for a special mechanism of biosynthesis: it is synthesized directly on the plasma membrane of cells, not in the Golgi apparatus, with subsequent immediate release into extracellular matrix (Rodella et al., 2025);

– it has a relatively low density of negative charge, since it contains only one carboxyl group (Fallacara et al., 2018; Kolaříková et al., 2024).

Three hyaluronan synthase isoenzymes (HAS1-3) are responsible for HA synthesis. These isoenzymes use uridine diphosphate-glucuronic acid and uridine diphosphate-N-acetylglucosamine as substrates, and their enzymatic activities directly affect the molecular weight of a synthesized HA molecule. Each HAS isoenzyme exhibits specificity in the synthesis of polymers of a certain molecular range: HAS1 and HAS2 produce longer chains (from 200 to 2,000 kDa and heavier), while HAS3 predominantly synthesizes shorter chains (from 100 to 200 kDa) (Rodella et al., 2025).

HA concentration in tissues is determined by dynamic balance between HA synthesis and degradation. HA catabolism can occur both by nonspecific and enzymatic mechanisms, which depends on molecule localization in the body (Buckley et al., 2022; Rodella et al., 2025). For example, the half-life of HA in the vitreous body of the eye is 70 days, while in skin this period is much shorter – about 24 hours. Nonspecific degradation involves spontaneous hydrolysis under the influence of reactive oxygen species (ROS), which is mainly observed in skin and skeletal muscles (Kotla et al., 2021). In humans, six subtypes of these enzymes have been identified, which can be localized both in cell membranes and in lysosomes, and their activity depends on the pH of the environment. It is important to note that hyaluronidases are actively involved in pathological processes, in particular in tumor growth, angiogenesis and metastasis in the development of such oncological diseases as brain, lung, bladder and metastatic breast cancers.

HA degradation results in the formation of polymers with different molecular weights, determining a wide range of their functional properties. The molecular weight of HA remains a key factor determining the diversity of physicochemical characteristics and biological activities of this substance (Fallacara et al., 2018; Wang et al., 2025). It has been proven that the higher the molecular weight of HA , the better its viscoelastic properties (Quartey et al., 2024; Wang et al., 2025). In humans, natural HA has a molecular weight of 100–10,000 kDa, with this figure varying significantly in different tissues. For example, in synovial fluid, the molecular weight of HA is 6,000–7,000 kDa, while in joint fluid, it is 3,000–5,000 kDa.

Although there is no universal classification of HAs by molecular weight in scientific literature, it is generally accepted to divide them into high molecular weight (HMW)-HA with a weight of >1,000 kDa, medium molecular weight (MMW)-HA with a weight of 250–1,000 kDa, and low molecular weight (LMW)-HA with a weight of <250 kDa. The size of a HA molecule is a critically important factor determining its biological activity. Numerous studies demonstrated that (HMW)-HAs exhibited anti-inflammatory effects, while (LMW)-HAs could have pro-inflammatory properties. Mechanisms of these differences remain unclear, but there are hypotheses that explain this phenomenon by changes in receptor clustering and interaction, peculiarities of cellular uptake, differences in intracellular and extracellular signaling, specificity of interactions with HA ligands, and spatial organization of the molecule during receptor binding (Quartey et al., 2024; Wang et al., 2025). These findings highlight the key role of molecular weight in determining the biological effects of HA in physiological and pathological processes.

(HMW)-HA possesses unique physicochemical properties due to the presence of carboxyl groups in each glucuronic acid unit, which gives the molecule a net negative charge. This feature allows the polymer to interact intensively with water molecules, absorb them in large quantities (up to 1,000 times its own weight) and form volumetric spiral-like structures in physiological solutions (Petit et al., 2025; Wang et al., 2025). Aqueous solutions of (HMW)-HA (>1,000 kDa) are characterized by extremely high viscosity and elasticity: 1% solution acquires a jelly-like consistency due to abundant hydrogen bonds, hydrophilic interactions and intramolecular bonds. These rheological properties determine the wide application of (HMW)-HA in biomedical products: injectable fillers, dermatological creams, ophthalmic gels, and eye drops.

The biological significance of (HMW)-HA is attributed to its localization in specific cell populations: vascular endothelium, cumulus cells of oocytes, and perichondrocyte matrix, where it confers structural integrity and mechanical protection of cartilage tissue. As a key structural component of ECM, (HMW)-HA dominates in connective tissue, the dermal layer of skin, articular cartilage, and synovial fluid (Kobayashi et al., 2020). At the molecular level, (HMW)-HA exhibits pronounced anti-inflammatory activity by suppressing the expression of cyclooxygenase-2 and matrix metalloproteinases, inhibiting the activation of mitogen-activated protein kinases and nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB) (Campo et al., 2008). This polymer also protects mitochondrial DNA from oxidative damage caused by pro-inflammatory cytokines (Altman et al., 2019; Buckley et al., 2022), which explains its therapeutic potential in rheumatoid arthritis, osteoarthritis, and eardrum regeneration.

(LMW)-HA, unlike (HMW)-HA, is characterized by significantly lower viscosity and increased solubility in water. These fragments demonstrate a fundamentally different biological activity: they are able to modulate functions of tumor and immunocompetent cells via induction of pro-inflammatory cascades. (LMW)-HA takes an active part in the regulation of cell migration and proliferation, tissue morphogenesis, and reparative processes in wounds (Rodella et al., 2025; Zhang et al., 2025). The pathogenetic significance of (LMW)-HA is well illustrated in joint inflammation, where its formation is the consequence of oxidative cleavage of (HMW)-HA through exposure to ROS, leading to the loss of lubricating properties of synovial fluid. It is a vivid example of the structural-functional interdependence between HA molecular forms (Kobayashi et al., 2020).

In addition to the structural function, HA exhibits significant biological activity, modulating different physiological processes. This is achieved through interactions with cellular receptors such as CD44 and receptors for HA-mediated motility, which regulate cell proliferation and migration as well as inflammatory responses (Quartey et al., 2024; Al Jayoush et al., 2025).

Due to all the above-mentioned properties, HA has found wide application in clinical practice as a biomaterial, which is successfully used in many medical procedures and manipulations. These clinical applications confirm the excellent safety profile, versatility and therapeutic potential of HA, which can be further expanded by state-of-the-art methods of chemical modification.

Wound healing

Wound healing is a key example of using HA according to its biological function. Initial tissue damage leads to an imbalance between HA synthesis and degradation and its accumulation in the lesion (Zhang et al., 2025). In the early stages, (HMW)-HA plays a crucial role by binding to fibrinogen and promoting clot formation to stop bleeding. In parallel, (HMW)-HA is secreted by cells in the form of specific structures, elongated cables and fibrils, which effectively capture neutrophils and pro-inflammatory mediators, such as TNFα, IL-1β and IL-8. This mechanism allows inflammatory mediators to be maintained in an inactivated state, creating a protective barrier to preserve the integrity of the surrounding tissues (Lierova et al., 2022; Zhang et al., 2025).

During the inflammatory phase, neutrophils, as the first line of defense, activate the production of myeloperoxidase, leading to ROS generation (Lierova et al., 2022). These reactive compounds not only help destruct pathogens but also initiate (HMW)-HA degradation, converting it into low-molecular-weight forms, i.e. (LMW)-HA (Kobayashi et al., 2020). This transformation is of key importance for the subsequent healing process, as (LMW)-HA acquires new biological properties. Chemokines and cytokines that were released from damaged tissues and immune cells create a chemical gradient that attracts monocytes and leukocytes to the injury site. Interactions of these cells with (LMW)-HA activate them and stimulate production of inflammatory cytokines, such as TNFα and IL-8, which is an important step for further wound cleansing and initiation of regeneration processes. Thus, the sequential change in the molecular profile of HA from HMW to LMW forms reflects its key role in coordinating the complex processes of wound healing.

The effectiveness of HA in wound healing depends largely on its molecular weight (Collins & Birkinshaw, 2013; Monteiro et al., 2015): (HMW)-HA has immunosuppressive and anti-inflammatory properties, while (LMW)-HA stimulated immune response and enhances inflammatory processes. In the innate immune system, (HMW)-HA reduces the expression of TLR2, TLR4, thereby promoting healing, but the absence of TLR4 can delay epithelialization. Macrophages, mast cells, and dendritic cells are also involved in healing processes through HA-dependent mechanisms. In the adaptive immune system, B cells produce antibodies, and T cells regulate immune responses through cytokines such as IL-2, IL-10, and growth factors such as TGF-β. Subsets of T cells, such as (γδ) T lymphocytes, occupy an intermediate position between the innate and adaptive systems, displaying properties of both (Kaul et al., 2021; Sudhakar et al., 2022). HA is catabolized in two ways: (a) by hyaluronidases or radical fragmentation and subsequent elimination through the lymphatic system; (b) by enzymatic degradation followed by HA transportation to lysosomes or endosomes. Different receptors, such as CD44, RHAMM, TLR2 and TLR4, interact with HA of different molecular weights and regulate healing through several intracellular signaling pathways. Wound healing proceeds through four phases (Sudhakar et al., 2022):

1. Hemostasis and coagulation: Platelets in wounds produce significant amounts of (HMW)-HA. Edema is formed when HA binds to fibrinogen (blood clotting factor I), facilitating effective clot formation, and when HA becomes saturated with fluid and expands around wound sites. It also enables immune cells to access wounds

and furnishes temporary scaffolding (Frost & Weigel, 1990; Nagy et al., 2019).

2. Inflammation: In inflammation sites, (HMW)-HA is converted to (LMW)-HA. (LMW)-HA activates an immune response and angiogenesis by interacting with TLR2 and TLR4 in the wound area. Cytokines and chemokines induced by (LMW)-HA promote activation, infiltration, and maturation of immune cells. However, prolonged inflammation can transform acute wounds into chronic ones. During inflammation, (LMW)-HA is converted to oligomeric HA (OHA), which suppresses inflammatory response and enhances cell proliferation (Slevin et al., 2007).

3. Proliferation and migration: In this phase, OHA reduces inflammation, promotes re-epithelialization, stimulates angiogenesis, and accelerates granulation tissue development. OHA interacts with CD44 and RHAMM to activate keratinocytes, endothelial cells, and fibroblasts. In addition, OHA increases the type III collagen-producing and -deposing activities of endothelial cells and fibroblasts at wound sites, leading to the formation of a new collagen matrix (Knudson et al., 2019).

4. Maturation and remodeling: Interactions of OHA with CD44 and RHAMM stimulate collagen I production. Extracellular matrix remodeling requires increased activities of matrix metalloproteinases and transforming growth factor, which stimulate differentiation of fibroblasts into myofibroblasts, completing the tissue remodeling process (Yang et al., 2021; Sudhakar et al., 2022).

Scar formation is the final phase of dermal wound healing and associated with significant problems, affecting over 100 million people annually. Scars reduce the biomechanical strength of skin, increase healthcare costs, and cause psychosocial problems. Interleukin-10 (IL-10) is a key mediator that converts the pro-inflammatory process into an anti-inflammatory one, counteracting collagen deposition in scars. HA interacts with IL-10 to block pro-inflammatory signals and attenuate fibrosis. High concentrations of IL-10 and HA in skin facilitate scar-free healing. There is a possibility of autoregulation of the IL-10/HA axis, which regulates the activation of CD4+ T lymphocytes and T regulatory cells to reduce scarring (Singampalli et al., 2020).

Prolonged inflammation caused by unregulated macrophage activation impairs chronic wound healing (Parmal et al., 2025; Zhang et al., 2025). Hyaluronan/collagen (HA-AC/coll) hydrogels with highly sulfated hyaluronan (sHA) can modulate inflammatory macrophage activity (Hauck et al., 2021). It was shown that sHA decreased the inflammatory activity of macrophages in vitro and in a murine model of acute inflammation, abating inflammation and altering macrophage activation. sHA-releasing HA-AC/coll hydrogels improve wound healing, reduce inflammation, and promote vascularization and new tissue formation. In diabetic mice (db/db line), these hydrogels significantly improved healing, making sHA a promising agent for therapy of chronic wounds (Hauck et al., 2021). In addition, skin loss greater than 4 cm in diameter is known to complicate healing without skin grafts, and limited availability of donor materials exacerbates the problem. To address this, an in vitro layer-by-layer assembly technique was developed; in this technique, poly-lysine films were applied on a HA scaffold, creating a favorable environment for dermal and epidermal components. Analysis demonstrated that keratinocytes attached to a HA/poly-lysine film formed colonies as early as after three days and these colonies continued to grow (Bui et al., 2023).

Nanotechnology in wound healing and other spheres

To cure wound infections, HA-based nanocomposites containing silver, gold, or zinc oxide (ZnO) nanoparticles have been developed; such nanocomposites destroy bacterial cell walls or generate ROS. The choice of material depends on healing phases, therapeutic effect duration, dosage, wound depth, and mechanism of action (Barroso et al., 2020; Tallapaneni et al., 2021). Nanomaterials offer a moist environment and have antimicrobial properties. Various natural and synthetic materials, alone or in combinations, are used for individualized wound healing approaches (Tottoli et al., 2020). Nanomaterials stimulate self-healing by mimicking regeneration (Li et al., 2020). These nanocomposite dressings deliver sustained release of antibacterial agents, which improves healing both in vitro and in vivo, making them promising for medical dressings (Sudhakar et al., 2022; Parmal et al., 2025). In a study (Cho et al., 2022), HA was successfully immobilized on electrospun nanofibrils (NFs), which allowed the development of a cell/NF complex. Thermogravimetric and colorimetric analyses demonstrated that immobilization degree could be regulated by changing photocrosslinking time. As photocrosslinking time was increased, the swelling ratio rose and the surface charge of NFs decreased. Tests with NIH3T3 cells showed that enhanced HA immobilization improved cell viability and proliferation compared to NFs without HA. HA was effectively fixed on aminolyzed NFs under UV irradiation, which affected thermograms, microstructure and physicochemical properties of the material. In addition, the HA/NF complex stimulated fibroblast self-assembly and cell plate formation, and immobilization degree was directly correlated with cell proliferation (Cho et al., 2022).

Development of bioinks for 3D bioprinting of stem cells is an expecially important area. Such bioink should have optimal gelation kinetics, viscoelasticity, and thixotropy to foster tissue maturation. Recently, a bioink based on ECM with double crosslinking of cysteine- and aldehyde-modified HA has been developed. This bioink forms stable hydrogels. Such crosslinking includes disulfide and thiazolidine bonds, which improve hydrogel stability, uphold high cell survival, and elevate stemness markers such as OCT3/4 and NANOG. Disulfide bonds enable cell self-renewal and migration, while thiazolidine bonds promote faster gelation and structural stability, opening new opportunities for cell therapy and regenerative medicine (Tavakoli et al., 2023).

Application of HA for bone and cartilage regeneration

Bone tissue engineering. Hydrogels based on HA and its derivatives have become popular as potential treatments for bone-related diseases. They are intensively studied and modeled to mimic natural bone matrix and to form an appropriate microenvironment for cell support and tissue regeneration (Jiang et al., 2025; Petit et al., 2025). Physical and chemical properties of HA can be modified to improve mechanical strength, biocompatibility, biodegradability, viability, and osteogenic potential (Hwang & Lee, 2023). HA can also be used to deliver various growth factors, drugs, mineralized components, or cells, which helps accelerate bone formation. HA-based hydrogels and microparticles are covalently bound to the surface of metal implants, improving osteogenesis and osseointegration. This in turn is extensively used in craniofacial and dental medicine for bone regeneration, including maxillary augmentation and therapies of craniofacial injuries (Zhai et al., 2020).

HA hydrogels were revealed to reduce the need for re-surgery in patients with brain traumas (Cui et al., 2015). When exposed brain tissue is covered with cross-linked HA hydrogels encapsulated in devitalized tissue, the hydrogel and devitalized tissue slowly regenerate bone tissue, eliminating the need for re-surgery. This idea was investigated using pentanoate-functionalized HA (PHA) and HA as a hydrogel as well as demineralized bone matrix, devitalized cartilage, devitalized meniscus, or devitalized tendon (DVT) as encapsulated tissues. It was found that PHA made bones stronger, while addition of devitalized tissue significantly increased the yield strength, except for PHA-DVT. The PHA-DVT and PHA groups had the greatest effectiveness in bone regeneration (Townsend et al., 2018).

3D printing allows precise control of scaffold design and pore structure, which are important for mimicking natural bone tissue. It also allows combining different materials, including HA-based hydrogels, to create composite scaffolds with improved properties (Sun et al., 2021). Kim et al. (2021) used 3D printing to fabricate a porous HA scaffold that enables in vitro proliferation and osteogenic differentiation of human mesenchymal stem cells (MSCs). Patel et al. (2020) developed a composite hydrogel scaffold of methacrylated HA and electrospun nanofibers, which exhibits appropriate mechanical properties and reinforces osteogenic differentiation of stem cells. Hwang & Lee (2023) also reported a 3D-printed scaffold based on HA, chitosan, and graphene oxide. The scaffold conferred controlled porosity and mechanical properties, supporting in vitro adhesion and proliferation of murine osteoblasts and their osteogenic differentiation.

Due to low cell density and absence of blood vessels in cartilage, treatment of severe bone injuries requires additional methods. Tissue engineering uses 3D printing and freeze-drying, and addition of TiO_2 to antibacterial nanocomposite scaffolds increases their strength, hardness, and wetting ability without by-products (Sun et al., 2021).

Cartilage tissue engineering. Due to its biocompatibility and ability to promote cartilage regeneration, HA is extensively used in cartilage tissue engineering (Jiang et al., 2025). HA is an important component of hydrogels, which can contain bioactive factors. HA-based functionalized hydrogels were demonstrated to be promising in cartilage regeneration. Wang et al. (2022) noted that multifunctional hydrogels with high biomimetic properties were of great importance in this field. Zhai et al. (2020) implanted a HA-based hydrogel into rabbits to investigate its efficacy for MSC delivery and cartilage repair. The outcomes showed that the combination of hydrogel and MSCs ensured the best cartilage repair, with faster hyaline cartilage formation and better tissue integration. Matsiko et al. (2012) showed that glycosaminoglycans added to a collagen scaffold improved MSC infiltration and proliferation as well as early gene expression, promoting ECM production.

HA also has significant lubricating properties, which has prompted research into its clinical application. HA-loaded polymers reduce joint friction and retain HA for up to 72 hours. HA is used for intraarticular injections to improve the viscoelastic properties of synovial fluid. A combination of HA with diclofenac was demonstrated to improve rheological properties, reduce friction, and enhance antioxidant activity and biocompatibility (Laradji et al., 2021).

HA- and dopamine-containing biomimetic lubricants have been developed for osteoarthritis therapy; they reduce friction and counteract ROS, promoting cartilage regeneration. Studies confirmed their biocompatibility and efficacy (Yuan et al., 2024). The drug Hyruan-Plus showed promising outcomes, reducing inflammation and improving the expression of type II collagen and aggrecan in chondrocytes by decreasing levels of pro-inflammatory cytokines (Kuppa et al., 2024).

Vascular tissue engineering

Cardiovascular diseases are the leading cause of death in many countries (Heron, 2019). Nör et al. (2001) showed that vascular regeneration could help in correction of such diseases. An in vitro study of HA hydrogels with endothelial colony-forming cells confirmed that HA hydrogels could promote microvessel development.

Endothelial cell incorporation has been considered to improve biocompatibility of materials used for treatment of vascular diseases. Endothelial cells can form monolayers on the surface of biomaterials for more effective tissue integration (Hanjaya-Putra et al., 2011). Researchers used a composite scaffold with a 10:1 ratio of collagen to HA. Based on the obtained data, it was concluded that the hydrogel scaffold had mechanical properties similar to those of native vascular tissue and enabled excellent cell viability. In addition, endothelial cells were able to proliferate and spread on the scaffold, thus forming a desired monolayer on the hydrogel surface (Zhu et al., 2014).

Ophthalmology

HA is currently used in eye drops such as DropStar and Lubristil to treat dry eye syndrome and improve contact lens comfort. Its viscous properties make HA useful in various ophthalmic procedures, including cataract surgery, vitreoretinal surgery, and glaucoma therapy. It was shown that HA could be used to replace vitreous humor after vitrectomy (Fallacara et al., 2018).

HA in eye drops mitigates oxidative stress, stabilizes the tear film, and promotes healing (Scheuer et al., 2016). HA- and arabino-galactan-containing artificial drops reduce uric acid and ROS levels (Silvani et al., 2020). HA also protects the cornea from oxidative damage, promotes healing of the ocular surface (Wu et al., 2017), and reduces the rate of water evaporation from contact lenses, displaying a potential for clinical applications. Use of (LMW)-HA-conjugated gold nanoparticles improves stability and penetration through ocular tissues (Apaolaza et al., 2020). Recently developed redox-sensitive HA-based nanogels deliver drugs to the retina, resulting in promising outcomes, i.e. improving photoreceptor function (Laradji et al., 2021).

Dentistry

HA has a wide range of applications in dentistry due to its biological properties.

– Injections of HA for papilla regeneration allow for restoration of the aesthetic appearance of patients' gums (Sánchez et al., 2017; Patil et al., 2020).

– Coating of dental implants with HA promotes osseointegration, improving fusion of implants with bone (Al-Khateeb & Olszewska-Czyz, 2020).

– Topical application of HA to treat oral ulcers helps accelerate tissue healing and abate discomfort (Iviglia et al., 2019; Canciani et al., 2021).

– Addition of HA to platelet-rich fibrin, plasma and growth factors improves overall tissue regeneration outcomes (Iviglia et al., 2019).

– Use of HA as a matrix for encapsulation of stem cells and signaling molecules is a promising approach for reconstruction of different structures in dentistry, including the temporomandibular joint, salivary glands, dental pulp, dental bone, enamel, root canals, and mucous membrane (Iviglia et al., 2019; Patil et al., 2020).

– Use of HA as a nanocarrier of drugs allows for effective delivery of drugs to affected tissues (Iviglia et al., 2019).

– Use of HA to treat stomatitis and irritation caused by dentures or surgical manipulations reduces inflammation and promotes tissue healing (Iviglia et al., 2019).

HA is extensively used in periodontal regenerative procedures. Its ability to stimulate bone and soft tissue cells makes it an excellent biological material for surgical soft tissue augmentation and bone regeneration around implants and the periodontium (Mansour et al., 2024). Addition of HA and chitosan to polyelectrolyte complexes improves transport properties and controlled release of drugs, making such systems more effective for treatment of periodontitis due to better release of ampicillin (Arısoy et al., 2024).

HA in oncology

HA plays a central role in the complex relationships between cancer cells and the immune system. Hyperexpression of CD44 receptors on the surface of cancer cells, along with increased HA production, creates a unique mechanism that promotes tumor progression. These molecular features are directly related to increased aggressiveness of tumor growth, active angiogenesis and metastatic spread (Al Jayoush et al., 2025; Rodella et al., 2025).

HA participates in complex interactions with different types of immune cells, including macrophages, dendritic cells, lymphocytes, neutrophils, and natural killer (NK) cells. It should be noted that interactions of HA with cancer stem cells directly promotes their proliferation and boosts tumor growth. HA plays a key role in the formation of the tumor microenvironment, where it actively modulates functions of various stromal cells, including fibroblasts, immunocompetent cells, and vascular endothelium. Of particular interest is the effect of HA on tumor-associated macrophages (TAMs), which are critical participants in tumor progression (Bhattacharyya et al., 2023; Rodella et al., 2025). Clinical observations confirm a close relationship between HA level in tumor and the number of TAMs, although the molecular weight of HA is usually not taken into account. A striking example is a study on 278 female patients with breast cancer, where a clear correlation was found between HA and CD44 high levels and increased numbers of M2-like (anti-inflammatory) TAMs, which was associated with poor prognosis. These findings suggest that HA–CD44 interaction can activate specific populations of TAMs in tumor stroma, suppressing the antitumor immune response and enhancing malignant transformation. Moreover, HA-activated TAMs are able to stimulate proliferation of cancer stem cells and maintain their stem-like properties, thereby further elevating tumor aggressiveness (Rodella et al., 2025).

Low-molecular-weight HA fractions (below 5 kDa) are able to stimulate proliferation of colorectal cancer cells, to reduce their apoptosis and to increase resistance to radiation through activation of TLR4 receptors. Similar mechanisms were detected in glioblastoma, where (LMW)-HA of 15–40 kDa, through interaction with TLR4, activated the NF-κB signaling cascade, which fosters proliferation of cancer stem cells and blocks their final differentiation. Additionally, it was found that (LMW)-HA promoted the development of lymphatic vessels in tumor, activating proliferation and migration of lymphatic endothelial cells (Rodella et al., 2025).

ECM, where HA is the major component, plays a crucial role in regulation of intercellular interactions, helping specific ligands to bind to receptors, signaling molecules to spread and immune cells to migrate (Caon et al., 2020; Al Jayoush et al., 2025). Although the exact mechanisms of HA effects on the immune response in cancer require further research, experimental data indicate that high HA content in the tumor microenvironment creates a barrier to penetration of immunocompetent cells and decreases the effectiveness of chemotherapy. A striking example is a study by Singha et al. (2015), who showed that the use of PEG-modified hyaluronidase for HA degradation significantly improved NK cell infiltration into tumor and enhanced the cytotoxic effect of antibodies.

Of particular interest are interactions between ECM HA and CD44 receptors on cancer stem cells, which lead to release of TGF-β, a key immunosuppressive cytokine that is significantly elevated in the tumor microenvironment. TGF-β stimulates tumor progression by increasing populations of cancer stem cells and suppressing the immune response, which occurs through recruitment of immunosuppressive cells (TAMs, Tregs, MDSCs) and inhibition of functions of dendritic cells, T lymphocytes, B cells, and NK cells (Yang et al., 2020; Rodella et al., 2025).

HA performs a complex and multifaceted function in the immune system and oncological processes through interactions with various hyaluronan-binding receptors. These molecular interactions are crucial for regulation of immune cell functions and affect key aspects of carcinogenesis. It is important to note that (LMW)-HA predominantly activates pro-inflammatory processes, whereas (HMW)-HA exhibits protective and antitumor properties (Collins & Birkinshaw, 2013).

HA plays a key role in regulation of tissue repair and metastatic cancer progression through its involvement in signaling pathways that drive inflammation and fibrosis. HA, as the major component of ECM, both stimulates and inhibits these processes, determining its function in wound repair. However, tumor cells use these mechanisms to invade and evade immune detection. Two HA receptors, CD44 and the receptor for hyaluronic acid-mediated motility (RHAMM), are critical for the regulation of these processes. RHAMM, a cell surface receptor that is important for cell migration and microtubule stability, is involved in cellular responses to stress and cell cycle progression. Tumor cells use RHAMM for metastatic spread and malignant progression, and its overexpression is often a negative prognostic factor for different cancers, such as breast and prostate cancers. Pharmacological or genetic inhibition of RHAMM can decrease tumor invasiveness and metastatic spread, making RHAMM a promising therapeutic target, although its subcellular distribution complicates development of targeted therapies (Tolg et al., 2021; Hinneh et al., 2022). CD44, another key receptor, is abundant in liver, kidney, and tumor cells. HA tends to aggregate around tumor cells, and elevated expression of CD44 promotes endocytosis, making HA an effective vector for delivery of anticancer drugs (Fallacara et al., 2018; Valachová & Šoltés, 2021).

The tumor microenvironment is a key modulatory factor in cancer progression and has emerged as a novel target for therapy. Accumulation and metabolism of HA are often increased upon tumor progression and are associated with aggressive malignancy, therapy resistance, and poor prognosis. The major sources of HA are wound healing-associated myofibroblasts and activated cancer-associated fibroblasts (CAFs). Both cell types can synthesize new matrix components and reorganize ECM. It was revealed that CAFs were insensitive to transforming growth factor beta-1 (TGF-β1) in terms of cell proliferation and matrix remodeling compared with normal human fibroblasts (NHFBs). However, both cell types can produce matrix-bound HA; however, activated CAFs exhibit higher HA production. The average molecular weight of produced HA is approximately 480 kDa for both TGF-β1-treated NHFBs and CAFs (Sapudom et al., 2020).

Tumor cells hijack HA production and fragmentation, which are normally tightly regulated in wound healing processes, and these HA functions aid stimulation and maintenance of malignant progression. Increased production of (HMW)-HA without fragmentation may be associated with resistance to cancer. (LMW)-HA enhances tumor cell proliferation and migration, whereas (HMW)-HA reduces tumorigenicity and confers resistance to cancer by limiting proliferation, inflammation, neoangiogenesis, and, possibly, DNA damage. A deeper understanding of size-dependent mechanisms of HA action is critical to unlocking its therapeutic potentials and developing new strategies to limit tumorigenesis (Liu et al., 2019; Sapudom et al., 2020).

Chemotherapy, particularly gemcitabine (GEM), is commonly used to treat cholangiocarcinoma. Gemcitabine inhibits proliferation, migration, and invasion of cancer cells. However, its efficacy is limited by systemic toxicity and lack of targeting. To overcome these drawbacks, GEM@ZIF-67-GA nanoparticles, where HA grants tumor cell targeting due to overexpression of CD44 receptors on cholangiocarcinoma cells, were developed (Long et al., 2024).

Neurology

Strokes have serious social and economic consequences. Although there are some therapeutic approaches, effective treatments are still few. Current platforms focus on neuroprotection, reperfusion, and neuroregeneration. HA shows promising outcomes as a new therapeutic candidate for stroke treatment due to its effects on stroke-related processes (Shahi et al., 2020).

HA-based tissue-engineered constructs are effective for tissue regeneration due to their effects on cell signaling and tuning ECM properties. Hydrogels, particularly those based on ECM-mimicking biopolymers, offer a 3D environment to mimic neural tissue and address tissue engineering challenges such as sequestration of cytotoxic agents and local drug delivery. Fibrin and HA hydrogels are used to treat neural tissue injuries. ECM-mimicking biopolymer hydrogels will be further developed to improve treatments of nervous system injuries (Jensen et al., 2020).

Applications in cryobiology

Addition of L-carnitine, HA, and sucrose, as well as their combinations to diluents, was shown to have a positive effect on the quality of Gaga rooster sperm after freezing-thawing. Cryopreservation is known to impair the integrity of plasma membranes and acrosomes and to reduce mitochondrial activity in rooster sperm (Khaeruddin et al., 2022). HA plays an important role in maintaining membrane functions and acrosome integrity, as it is able to form a glassy protective layer on the membrane of a damaged spermatozoid during freezing, thereby abating cryopreservation-caused physical trauma (Qian et al., 2016; Khaeruddin et al., 2022). LMW)-HA was also shown to potently inhibit lipid peroxidation and scavenge hydroxyl radicals. HA neutralizes free radicals, and all reactions between ROS and HA lead to fragmentation of HA chains (Dovedytis et al., 2020; Khaeruddin et al., 2022). Regarding kinematic parameters, addition of HA, L-carnitine or HA+L-carnitine combination, increased the speed and distance of curvilinear movements of spermatozoa. Therefore, supplementation of the “Ringer-acetate-egg yolk” diluent with HA, L-carnitine or their combination can improve the sperm quality of Gaga roosters after freezing-thawing (Khaeruddin et al., 2022).

In a study related to development of a therapeutic product for repair of intervertebral discs using nucleus pulposus cells (NPCs), an attempt was made to mitigate intracellular ROS-induced cytotoxicity caused by dimethyl sulfoxide (DMSO). HA was demonstrated to protect chondrocytes from ROS. HA treatment suppresses DMSO-induced ROS. These findings highlight the ability of HA to sustain functions of NPCs, suggesting that addition of HA during transplantation may be useful upon development of finished NPC products (Munesada et al., 2023).

Drug delivery

The American Cancer Society estimates that men have a 50% chance of developing invasive cancer and women a 33% chance (Arısoy et al., 2024). Chemotherapy, being the primary treatment for cancer, has drawbacks such as drug resistance and cytotoxicity (Scheuer et al., 2016; Kuppa et al., 2024). HA was proven to be an effective agent for transdermal delivery of drugs due to binding to the CD44 receptor (Senbanjo & Chellaiah et al., 2017). In addition, HA facilitates drug delivery through CD44-mediated endocytosis (Fallacara et al., 2018).

HA-based nanomaterials (HANPs) are promising carriers for therapeutics, but existing methods for their synthesis have limited reproducibility and a wide size distribution. Recent studies have improved production of HANPs of 80–135 nm with low polydispersity, making them suitable for drug delivery across mucosal barriers to the respiratory tract (Lierova et al., 2020). HA nanofibers are effective for rapid drug release in a humid environment and can be used as coatings or carriers for cytotoxic drugs, modulating inflammatory processes (Rao et al., 2020; Kang et al., 2021). HANPs are also useful for pre-radiation therapy as a lung protectant (Lie-rova et al., 2020).

Antimicrobial activity of HANPs loaded with antibiotics is effective against infections caused by *Staphylococcus aureus* (Liu et al., 2021). HANPs can be modified to improve targeted delivery and prevent uptake by reticuloendothelial cells. Thus, HANPs have a great potential for precise targeted cancer therapy and control of bacterial infections (Lei et al., 2021; Curcio et al., 2022).

Cosmetology

HA has found wide application in current medical and cosmetology practices and become a basis for many cosmetics, which has been confirmed by numerous clinical studies (Kaul et al., 2021; Iaconisi et al., 2023). HA does not require skin testing before injections due to its biodegradability in the body. Scientific data indicate high safety and clearly manifested effectiveness of HA in improving skin hydration and correcting age-related changes. In current cosmetology, HA has become one of the most sought-after components, which is part of both surface cosmetics and injectable drugs for contouring. HA-based tissue fillers have become particularly popular, effectively restoring tissue volume lost because of aging (Al-Halaseh et al., 2022; Chylińska et al., 2025). HA is used to fill in the volume, moisturize and rejuvenate skin by injection into the superficial layers of dermis and epidermis. Injections of HA fillers help smooth out facial wrinkles, stimulate collagen synthesis and prevent its breakdown (Chylińska & Maciejczyk et al., 2025).

Cross-linking of HA molecules improves their stability in tissues. Combinations of HA with other matrix proteins, such as collagen, allows formation of complex supramolecular structures, which improve HA effectiveness as a dermal filler (Chylińska & Maciejczyk et al., 2025). Mixtures of HA fillers with calcium hydroxylapatite are used to maintain volume and ensure long-term results. Such mixtures can compensate for early volume loss and provide high satisfaction with outcomes (Chang et al., 2020).

Recently, the scientific community has paid special attention to potential benefits of oral administration of HA for improving skin condition. It was demonstrated that systemic use of HA could improve skin quality and appearance, opening up new prospects in anti-aging therapies (Fallacara et al., 2018; Chylińska & Maciejczyk et al., 2025). These data confirm the important role of HA not only as a local cosmetic agent but also as a systemic component of anti-aging regimens.

Food industry

The food industry globalization and growth of international trade in fresh produce raise issues of quality and safety during long-term transportation. To reduce losses and extend shelf life, it is important to use effective packaging methods. Edible coatings made from natural sources have significant advantages. HA in combination with chitosan and gelatin is a leader among such edible coatings. They reduce weight loss, regulate pH, decrease lipid oxidation, control respiration, improve antioxidant properties due to phenols and ascorbic acid (which was confirmed by DPPH test), and preserve colors and textures of original products (Al-Hilifi et al., 2024).

Conclusion

HA is a unique biomolecule in structure and diverse properties, which determines its wide use both in scientific research and for practical applications in different industries. It has a natural origin, is present in the human body and plays key roles in many vital processes.

The HA functions depend largely on its molecular weight.

To fully use the HA potential, it is necessary to further deepen research into molecular mechanisms of HA action and to optimize methods of HA use, taking into account the needs of each specific industry.

Innovative solutions on use of HA-based products will significantly improve the quality of medical practices and state-of-the-art biotechnologies.

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