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REVIEWS

HYALURONIC ACID: BIOCHEMICAL PROPERTIES AND MEDICAL APPLICATIONS

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This literature review examines the biological properties of hyaluronic acid (HA), its various chemical modifications with carboxyl, hydroxyl, and acetamide groups, applicable in drug and genetic material delivery systems. Special attention is paid to the use of HA in complexes with metal nanoparticles, other biopolymers, and biomolecules. HA molecules of different molar masses exhibit different effects on cellular processes. Therefore, HA fractions with strictly defined molecular masses are used to achieve various goals. Unique properties of HA such as high bioavailability, biocompatibility, antioxidant properties, and high affinity for a number of cellular receptors make HA a promising means for use in targeted therapy. The use of HA in regenerative medicine has been also discussed.

Keywords: hyaluronic acid; drug delivery systems; metal nanoparticles; antioxidant properties; aging; geroprotective properties

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INTRODUCTION

Hyaluronic acid (HA) is one of the most important natural biopolymers, found in connective, epithelial, and nervous tissues. HA is a major component of the extracellular matrix; it is found in biological fluids (e.g., synovial fluid and the extracellular matrix), skin, ligaments, joints, and the vitreous humor of the eye [1]. HA acts as a barrier against the spread of infectious agents and toxic macromolecules. It plays a role in regulating plasma protein distribution, water homeostasis, extracellular matrix stabilization and regulation of cellular activity through interaction with receptor proteins on the cell surface [2]. Serum HA concentrations increase in joint and liver diseases, as well as in cancer, uremia, septicemia, Hutchinson-Gilford progeria syndrome, Werner syndrome, myelofibrosis, and systemic scleroderma [2, 3].

The unique physicochemical properties of HA include high viscosity due to the unique rheological properties of the viscoelastic gel of this polymer, a specific ability to bind water (for example, one molecule of sodium hyaluronate can bind up to 1000 water molecules) and proteins, forming proteoglycan complexes [1–6]. HA is involved in cell proliferation and migration; it interacts with cell surface receptors, especially the CD44 receptor, which plays an important role in intercellular interactions, cell adhesion, and migration [3, 4].

HA is widely used in the creation of synovial fluid endoprostheses, as an “ink” in 3D bioprinting, in cosmetic surgery, as a surgical medium for ophthalmological procedures, and in the production of cosmetics as a component of creams, lotions, and many other products that prevent skin aging. The HA application is not limited to the creation of endoprostheses and the use as a component of cosmetic products. Due to its unique properties, it has found application in nanomedicine for the creation of next-generation healing agents, drug delivery systems, and genetic material [3–5] (Fig. 1).

The purpose of this review is to summarize and analyze information about unique properties of HA and potential areas of its biomedical application.

1. STRUCTURE AND BIOLOGICAL PROPERTIES OF HA

HA is a negatively charged polymer consisting of D-glucuronic acid and N-acetyl-D-glucosamine residues linked alternately by β-1,4- and β-1,3-glycosidic bonds (Fig. 2). A HA molecule can contain up to 50,000 such units. In nature, its molecular weight varies from 5,000 Da to 20,000,000 Da; in human synovial fluid, the molecular weight of HA averages 3,140,000 amu (Da) [5]. At physiological pH, HA is a linear polysaccharide chain. In the human body, HA exists as sodium hyaluronate. Changes in pH

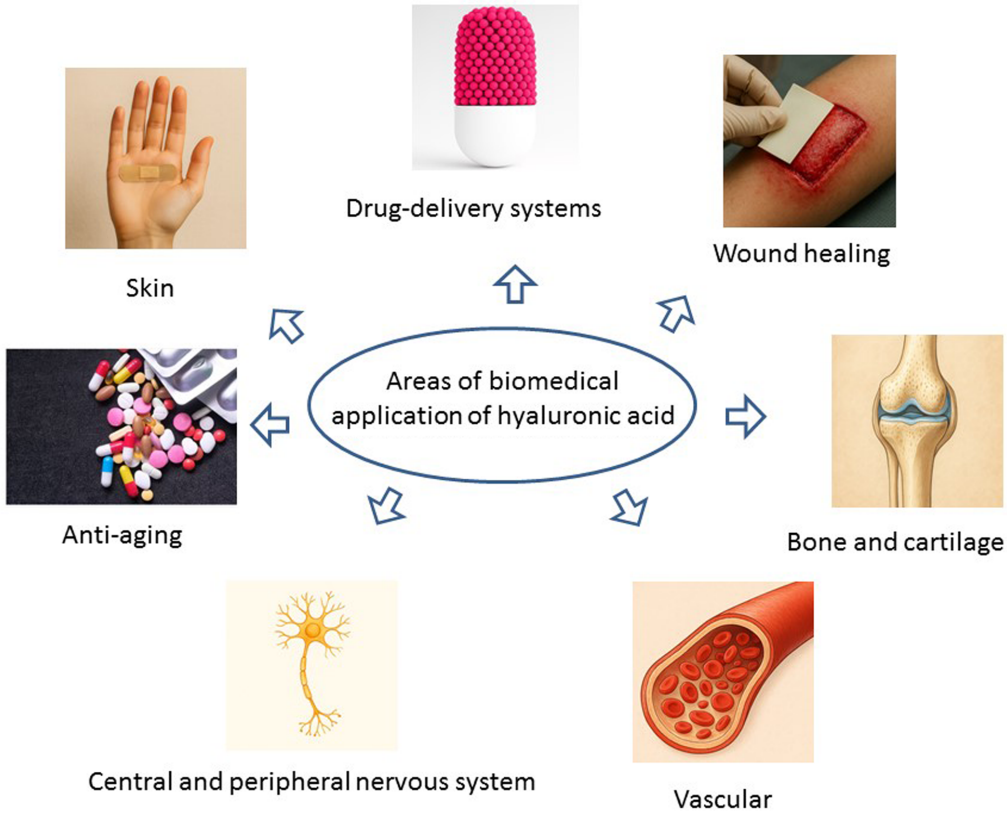


Figure 1. Areas of biomedical application of HA.

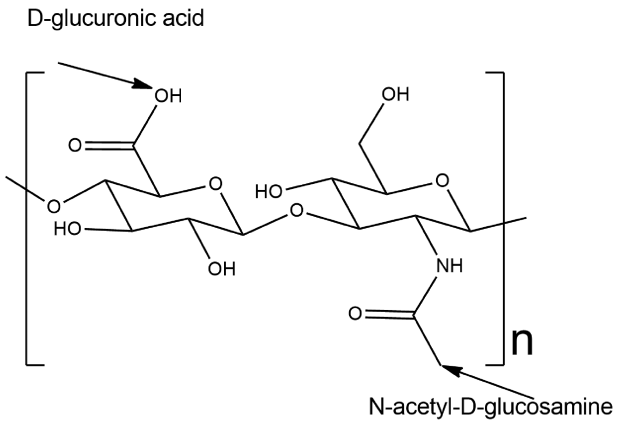


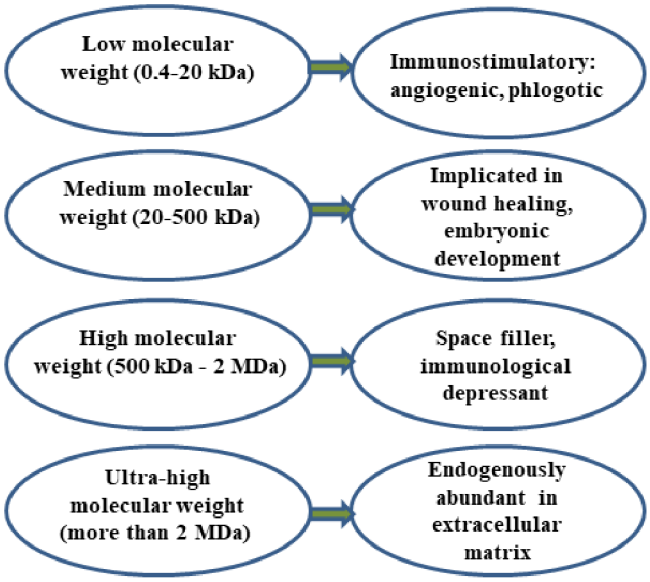
Figure 2. Chemical structure of HA.

cause changes in the structure and conformation of the polymer. This is due to the fact that the carboxyl groups of HA are completely ionized at pH 7, and at physiological pH the carboxyl group of each D-glucuronic acid unit typically dissociates, resulting in the formation of a negatively charged biomolecule. HA can form left-handed single and double helices, various multi-stranded flat structures, and supercoiled structures that form a dense molecular network. This is due to the formation of hydrogen bonds, binding with alkali metal cations, and hydrophobic interactions. At pH 2.5, approximately 75% of the carboxyl groups of HA are protonated; this limits electrostatic repulsion between chains and ensures double hydrogen bonds between carboxylic acids, amines, and the remaining carboxylate anions. These interactions promote denser packing of HA chains, leading to a relative increase in the viscoelasticity of the solution and the formation of gel-like solutions [6].

HA is highly hydrophilic due to the presence of hydroxyl and carboxyl groups. Its stabilization is ensured by the stereochemistry of its constituent polysaccharides.

HA naturally present in the body (endogenous HA) is a glycosaminoglycan that does not contain sulfate bonds. The chemical structure of $C_{14}H_{21}NO_{11}$ per subunit, containing hydroxyl and carboxyl groups, as well as one amide functional group, enables HA to undergo numerous chemical reactions to modify its structure. Its water binding capacity provides support for the extracellular matrix. It should be noted that the physicochemical properties and biological functions of endogenous HA (Fig. 3) vary depending on its molecular weight [6].

HA biosynthesis by hyaluronate synthases (HAS) occurs on the inner surface of the plasma membrane. There are three types of these enzymes in vertebrate organisms: HAS1, HAS2 (the most common), and HAS3. They elongate the HA molecule by alternately adding glucuronic acid and N-acetylglucosamine to the polysaccharide and pushing the polymer through the cell membrane into the intercellular space.



Molecular weight (kDa)	Chain contour length (nm)	Molecular size of polymer chains (nm)	Intrinsic viscosity (ml g^{-1})
100	250	52	290
500	1,250	140	1,100
1,000	2,500	210	1,800
3,000	7,500	400	4,400
6,000	15,000	600	7,700

Figure 3. Biological functions and physical properties according to HA molecular weight.

The HAS1 and HAS2 proteins are involved in the synthesis of high-molecular-weight HA. When HAS2 function is blocked in human chondrocytes, extracellular matrix assembly is disrupted and proteoglycans are lost from the pericellular space, while cell viability is not impaired. HAS3 synthesizes shorter HA molecules. HA biodegradation occurs by hyaluronidase (HYAL) enzymes [5–8]. In the presence of hyaluronidases HYAL1 and HYAL2, β-glucuronidase, and hexosaminidase, linear HA is cleaved with formation of low-molecular-weight HA. Hyaluronidase activity increases during inflammation, causing further degradation of low-molecular-weight HA into oligomers that act as "danger signals" for cells [6].

HA can regulate the cell life cycle, cell migration, and the inflammatory state of the extracellular matrix, as it is one of its main components. The properties of HA vary depending on its molecular weight. High-molecular-weight HA (> 10^3 kDa) can promote cell proliferation and migration and inhibition of apoptosis [5–10]. High-molecular-weight HA molecules stimulate anti-inflammatory responses, while low-molecular-weight molecules, conversely, can induce inflammation [5–9]. HA with a molecular weight of approximately 200 kDa inhibits dendritic cells maturation, but enhances their apoptosis and endocytosis [10].

HA with a molecular weight of 1000 kDa is used in ophthalmology, cosmetology, and also as a dressing material. Macromolecular HA (from 1000 kDa to 1400 kDa) remains on the skin thus creating a protective film that prevents water evaporation. HA with a molecular weight ranged from 10 kDa to 1000 kDa is used for tissue engineering and wound dressings. Medium molecular weight HA (100 kDa to 300 kDa) actively moisturizes the outer layer of the epidermis. HA with a molecular weight ≤ 10 kDa is important for inducing angiogenesis, fibroblast proliferation, and for cosmetic purposes. Thus, small HA molecules (from 5 kDa to 20 kDa) have the ability to penetrate deeper layers of the skin and are therefore suitable for repairing damage and moisturizing the skin [1, 3].

In contrast to high-molecular-weight HA, low-molecular-weight HA (< 10^3 kDa) is a marker of inflammatory processes in the body. It induces inflammation by regulating the expression of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β. The effect of HA on the release of these cytokines is mainly due to the interaction of the N-acetyl fragments of HA and the TLR4 (toll-like receptor-4). Deacetylation of HA leads to inhibition of inflammation, while reacetylation restores this effect. In addition, N-acylated HA inhibits the release of pro-inflammatory cytokines due to competitive binding to TLR4 of human macrophages; this explains why the use of N-acylated HA has a positive impact on skin healing processes [11, 12]. Oligomeric HA, on the contrary, can increase inflammation [13].

Acylated HA exhibits altered rheological properties, such as lower viscosity, compared to unmodified HA with a molecular weight of 1500–1800 kDa, due to the cleavage of bonds in the HA chain through deacetylation/acetylation, which leads to a decrease in molecular weight to 30–214 kDa [11]. In addition, acylated HA has a block structure. Acylated HA stimulated cultured human macrophages (THP-1 cells) and increased interleukin IL-1 secretion [11]. The proinflammatory cytokine activity of acylated HA is largely due to its block structure, which appears to facilitate receptor binding [11].

HA binds to a number of specialized receptor proteins, acting as a signaling molecule regulating cellular proliferation, migration, and differentiation. Hyaluronan-binding proteins, or hyaladherins, are located on the surface and in the cytoplasm of several cell types. The primary functions of hyaladherins include cell adhesion, structural support of the extracellular matrix, and cell signaling [11–13]. HA specifically binds to eight cell surface receptors throughout the body [6, 13]. Table 1 summarizes the properties and functions of these cellular receptors responding to the action of low-molecular-weight and high-molecular-weight HA.

These receptors induce a wide range of cell-specific responses, including endocytosis and degradation of HA in endothelial cells, regulation of cell migration and adhesion in fibroblasts and immune cells, angiogenesis in endothelial and smooth muscle cells, and modulation of inflammatory signals in nociceptors and dendritic cells [6].

Among these interactions, the interaction of HA with CD44 is particularly interesting in the context of drug delivery system development, because this receptor is overexpressed on the surface of many types of cancer cells, as well as on the surface of cells associated with the occurrence of inflammatory processes [13]. Besides cancer cells, CD44 is also highly expressed on the surface of other cells, such as chondrocytes; this may represent a basis for the use of HA in joint diseases, tissue engineering and other biomedical fields [14]. HA is used in the treatment of osteoarthritis and rheumatoid arthritis, in particular in the knee joint to replenish synovial fluid, and to improve viscosity, cushioning and joint mobility while relieving pain [6]. Normal synovial fluid contains ultra-high molecular weight HA (≈3–7 MDa) at a concentration of ~2–4 mg/ml, which provides lubrication and cushioning. In joints affected by osteoarthritis, a decrease in the size and concentration of HA is observed; this may be compensated for by intra-articular administration of HA (injection directly into the joint space, administered once a week for 5 weeks) [6]. HA binding to CD44 receptors and toll-like receptors (TLR2 and TLR4) suppresses production of pro-inflammatory mediators, including IL-1β and IL-6 [6]. The anti-inflammatory activity of HA is realized due to its binding to CD44 receptors on the surface of chondrocytes and is manifested by a decrease in IL-1β secretion. This leads to a decrease in the production of catabolic enzymes (metalloproteinases) [6].

The HA interaction with the receptor for HA-mediated motility (RHAMM) promotes the migration of both myoblasts and fibroblasts, while the HA interaction with CD44 promotes only fibroblast migration.

Endogenous HA binding to the TLR4 receptor stimulates the proliferation of colorectal cancer cells. However, agents that block this binding (e.g., the 12-membered PEP1 peptide, H_2N-GAHWQFNALTVR-OH) can be used as adjuvants in cancer therapy [9].

2. ANTIOXIDANT PROPERTIES OF HA

HA has an antioxidant effect and low-molecular-weight HA (45 kDa) exhibits more pronounced antioxidant properties than high-molecular-weight HA (145 kDa) due to the neutralization of free radicals (Fig. 4) [3, 13, 17, 18]. Free radicals are highly reactive molecules determined by the presence of unpaired electrons. They can attack various cellular structures, causing irreversible damage and DNA mutations, which can lead to cancer [13]. Reactive oxygen species (ROS) cause the symptoms of aging and the development of osteoarthritis in elderly patients, which leads to cartilage wear in joints [13, 17–21]. This cartilage damage may be associated with HA cleavage in the extracellular matrix by ROS (Fig. 4A). Therefore, osteoarthritis therapy involves the transplantation of autologous chondrocytes or chondrospheroids [22].

Regenerative medicine is one of the most studied areas of HA application. A common approach to tissue regeneration is the scaffold implantation into the area where tissue formation is required [13, 17–22]. Regeneration of vascular networks may contribute to the improvement of cardiovascular diseases [23, 24]. An *in vitro* study of HA hydrogels with incorporated embedded human endothelial colony-forming cells (ECFCs) has demonstrated that HA hydrogels can be used to develop a microvascular network [24].

Skin lesions greater than 4 cm in diameter cannot be effectively repaired without skin grafting. A layer-by-layer assembly *in vitro*, in which poly-L-lysine films were sprayed onto a HA matrix, enabled the formation of the adhesive and viable environment for both dermal and epidermal tissue components. The structure was tested using keratinocytes, the main cell type of the epidermis [22–24].

The quality of tissue-engineered constructs such as chondrocytes or chondrospheroids (chondrospheres) used in regenerative medicine, depends on the composition of the extracellular matrix, including HA. HA is the main structural component of the cartilage proteoglycan complex; it envelops each chondrocyte and provides tensile strength to cartilage tissue [23, 24]. To monitor the quality of chondrospheres and perform comparative quantitative analysis of extracellular matrix components, a method for electroanalysis of these structures has been developed [25]. Comparative

Table 1. Properties and functions of cellular receptors that specifically bind HA

Receptors	Features	Functions	Receptor affinity to HA	HA Mw
• CD44	cluster of differentiation 44, transmembrane glycoprotein	• is involved in uptake and degradation of HA • stimulates migration of circulating lymphocytes in lymphoid tissue • promotes fibroblast adhesion wound healing and extracellular matrix restoration	25000	HMW
• Stabilin-2	HARE (Hyaluronan Receptor for Endocytosis) is a class H scavenger receptor	• cycles between the plasma membrane and lysosomes, thus confirming its role as a scavenger receptor • the main receptor for the removal of circulating HA through cellular internalization and lysosomal degradation • induces mitogen-activated protein kinase (MAPK) responsible for cellular reactions such as transcription, survival, migration, cytoskeletal remodeling, differentiation, and cell cycle progression during proliferation	7	HMW
• RHAMM	receptor for HA-mediated motility, cluster of differentiation 168, CD 168	• regulates growth and migration of cells; blocking the HA binding site on the RHAMM receptor induces apoptosis and necrosis, inhibits the viability and invasiveness of tumor cells • promotes HA associated healing • RHAMM can be distributed on the cell surface or intracellularly in the cytoplasm or nucleus	2	LMW
• LYVE1	HA receptor of lymphatic vascular endothelium, integral membrane glycoprotein type I	• binds to soluble and immobilized hyaluronan • LYVE-1 receptor dimers demonstrate higher affinity to hyaloronan, than CD44 monomers, and preferentially interact with HMW HA • LYVE1 may be involved in hyaluronan transport in the lymphatic system and play a role in tumor metastasis	125000 (monomer) 8000 (dimer)	LMW HMW
• Layilin	a C-type transmembrane lectin receptor that serves as a bridge between extracellular matrix sensing and intracellular signaling	• is involved in many cellular functions, including adhesion and cell signaling • Layilin binds the cytoskeleton intracellularly, while HA binds extracellularly. In contrast to the low-affinity binding of CD44-HA, Layilin binds HA with high affinity	100	LMW
• TLR2	Toll-like receptor 2, a transmembrane protein, CD282	• plays a key role in activating innate immunity, including in the fight against bacterial infections	unknown	LMW
• TLR4	Toll-like receptor 4, a transmembrane protein, CD284	• plays an important role in mechanisms of inflammation • binds to LMW HA fractions with the participation of the cofactor MD-2, and through the TIR domains the signal is transduced into the cell	unknown	LMW
• ICAM-1	intercellular adhesion molecule type 1, a transmembrane protein	• in combination with RHAMM and CD44, it is able to regulate inflammation and healing processes by influencing the migration and adhesion of proinflammatory cells	unknown	LMW

Compiled from data reported in [6, 13]. HA Mw – molecular weight of HA, LMW – low molecular weight HA, HMW – high molecular weight HA.

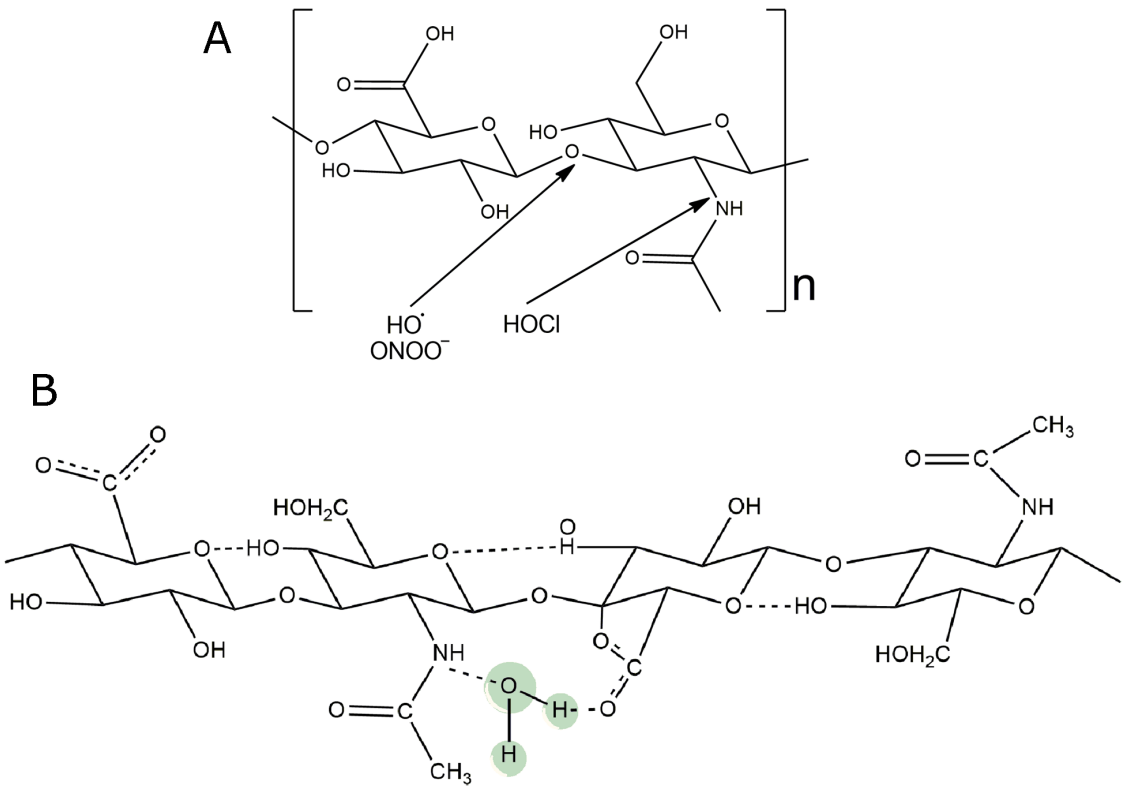


Figure 4. Chemical properties of HA: **A**) interaction of HA with ROS causing cleavage of glycosidic bonds; **B**) binding of water to carboxyl and acetamide functional groups of the HA molecule.

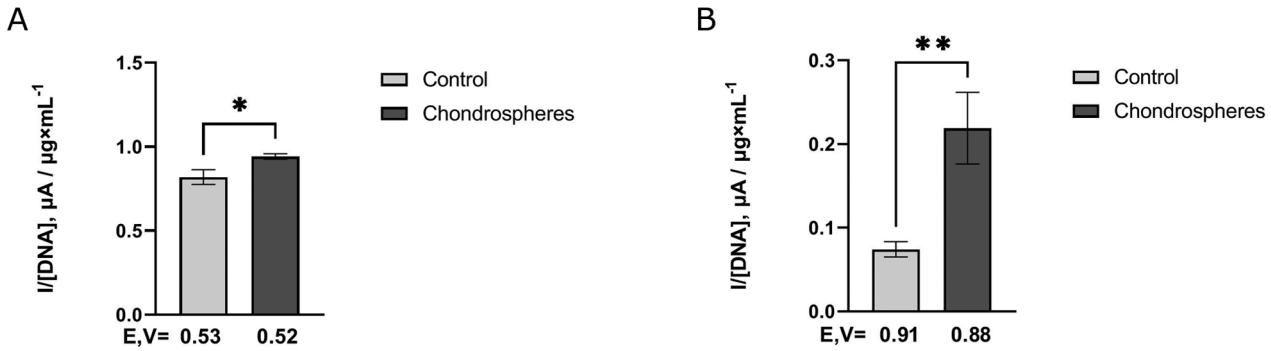


Figure 5. Diagrams corresponding to the maximum amplitudes of electrooxidation currents of control (grey columns) and differentiated (black columns) chondrospheres. The oxidation current values: **A**) the first peak, 0.52±0.01 V, and **B**) the second peak, 0.88±0.03 V, are normalized to the concentration of dsDNA isolated from the cells. Statistically significant differences were designated as * $p \leq 0.05$, ** $p \leq 0.01$. Prepared using data reported in [25].

electrochemical profiling was performed between control spheroids cultured without TGF-β1 addition and 3D chondrospheres differentiated for 21 days with TGF-β1. During induced chondrocyte differentiation for 21 days with TGF-β1, accumulation of extracellular matrix was observed as evidenced by an increase in the maximum amplitudes of electrochemical oxidation currents of differentiated chondrospheres compared to control spheroids (Fig. 5).

Human skin, with its large surface area, plays a vital role as a barrier protecting the body from external aggressive factors. Despite its elasticity, skin remains highly susceptible to aging, a complex process influenced by both intrinsic factors, such as chronological aging, and extrinsic factors, including exposure to ultraviolet (UV) radiation and environmental pollutants [1, 3, 26]. These stressors stimulate excessive production of ROS, which accelerate the breakdown of skin structure and impair its physiological functions [26–31]. Oxidative stress, resulting from an imbalance between ROS levels and the skin's antioxidant defenses, is a major contributor to skin aging [27].

Vitamin C, vitamin E, and polyphenols are often used in skincare products as antioxidants; however, their clinical efficacy is reduced by low stability, limited absorption by the skin, and degradation upon exposure to atmospheric oxygen

or UV radiation. HA is a biocompatible biopolymer. Due to the abundance of hydroxyl, carboxyl, and N-acetyl functional groups in its structure (Fig. 2), HA exhibits exceptional water-binding capacity and biological activity (Fig. 4A,B). It serves as a structural component of the extracellular matrix, which promotes cell proliferation and migration. In addition, due to its high viscosity and elasticity HA can be used as a lubricant in dermatological hydrogels [25–31]. These functional properties make HA-based hydrogels effective means for biomedical and cosmetic applications, especially in formulations aimed at combating skin aging and oxidative stress [1, 3, 25–31]. The antioxidant properties of HA are widely used in cosmetology [28–30]. The rejuvenating effect of a gel based on stabilized HA of non-animal origin on the aging process of facial skin has been confirmed. Films (masks) with HA are used as skin care products. The action of such films is based on the moisturizing and moisture-retaining properties of HA (Fig. 4B). Moreover, they are positioned as a means of promoting the growth of new cells for healthier skin, since cosmetic films also contain other substances, such as vitamins and antioxidants [27–31].

3. CHEMICAL MODIFICATIONS OF HA

The HA molecule contains four active sites: hydroxyl and carboxyl groups, acetamide groups, and reduced end groups, accessible for cross-linking between HA molecules themselves or between HA and other polymers (Fig. 2). Therefore, HA can be modified with various functional reagents to alter its biological activity and introduce new functions [32–39] (Fig. 6).

Chemical modifications of HA at carboxyl and hydroxyl groups are carried out using hydrazide, methacrylate, and by introducing mercapto groups and tyramine. In addition, aldehyde groups can be obtained by oxidizing HA with sodium periodate [38].

3.1. Introduction of Dihydrazide

Dihydrazide is introduced at the carboxyl group of HA using adipic acid dihydrazide. The original carboxyl groups and hydrazide groups after HA modification are used to create covalent bonds with chemotherapeutic drugs or probes [38].

3.2. Introduction of Methacrylate

The introduction of a carbon-carbon double bond into HA typically occurs through the reaction of secondary hydroxyl groups with methacrylic anhydride or 2-aminoethyl methacrylate. This modification is primarily used to create cross-linked hydrogels.

3.3. Thiol Introduction

HA binds to S-trityl-L-cysteine or cystamine, followed by cleavage of the disulfide bond to form thiol groups. HA containing SH groups is used in the preparation of hydrogels and to stabilize gold nanoparticles [38].

3.4. Tyramine Introduction

HA can be modified with tyramine to produce phenolic groups, which in turn can be oxidized with a catalyst (horseradish peroxidase — HRP) to produce phenoxyl radicals used for further cross-linking of aromatic rings at C–C or C–O bonds. Hydrogels based on tyramine-modified HA exhibit a higher degree of cross-linking, which is explained by a higher level of cellular adhesion. On the other hand, the use of this modification is quite difficult, as the presence of the HRP enzyme is required [38].

3.5. Aldehyde Group Introduction

The hydroxyl groups of HA in the *cis*-position can be oxidized with sodium periodate to form dialdehyde. Using this modification of HA it is possible to form acid-labile hydrazone bonds or amide bonds via a Schiff base reaction between HA and therapeutic agents or other polymers. Antibodies or enzymes can be attached to dialdehyde HA via imide bonds under mild conditions to maintain their biological activity.

Thus, hydrazide-modified HA is capable of forming bonds with therapeutic drugs, probes, and various polymers. Thiol, tyramine, and methacrylate modifications are used to create cross-linked hydrogels. Thiol-modified HA can be used as shells or ligands for delivery systems and for coupling to gold nanoparticles. Tyramine modification enables self-cross-linking through transformations of the phenolic group. Methacrylic-modified HA can be cross-linked with a wide range of cross-linking agents with different properties. Dialdehyde HA can be used to create pH-sensitive conjugates and hydrogels. This modification is preferably used for protein delivery under mild conditions via the Schiff base reaction [40].

HA PEGylation is a covalent modification with polyethylene glycol fragments. This results in a copolymer that is resistant to hyaluronidases [39, 41]. Such HA PEGylated derivatives are used in cosmetology, ophthalmology, and for drug delivery [42]. HA-based membranes modified with carboxymethylcellulose are used as an adhesion preventer [39]. Modification of HA with chitosan modified with quaternary amines (quaternization) results in the formation of copolymers used for articular cartilage regeneration [43].

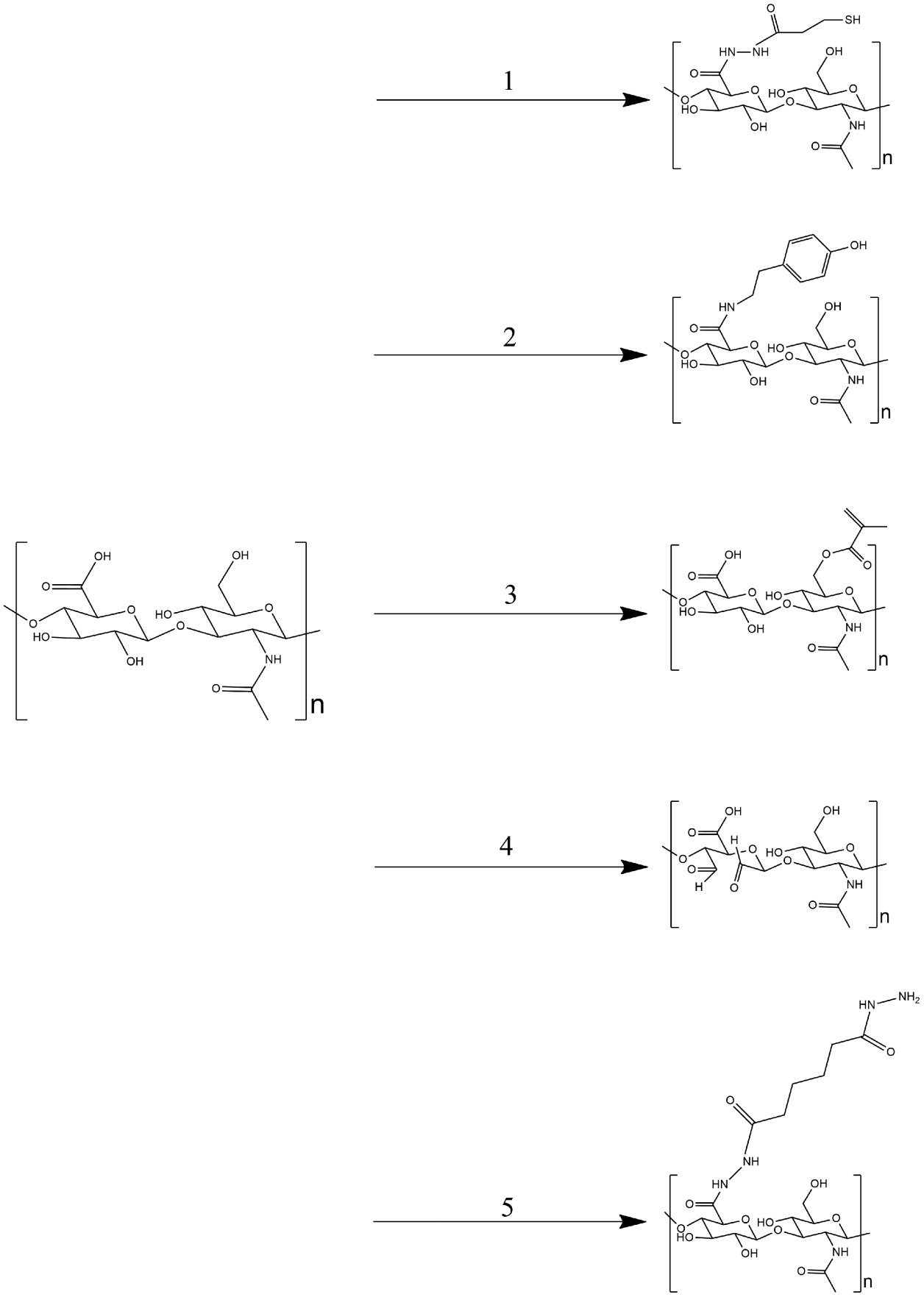


Figure 6. Chemical modifications of HA: *1* – sulfation, *2* – tyramine modification, *3* – methacrylate modification, *4* – oxidation, *5* – hydrazide modification [38].

To obtain crosslinks and incorporate additional functional groups into the polymer structure of HA, a wide range of crosslinking reagents (crosslinkers) are used. These include 1,4-butanediol diglycedyl ether, divinyl sulfonone, dimethyl urea, 1,2,3,4-diepoxybutane, dimethylol ethylene urea, ethylene oxide, polyaziridine or polyisocyanate, bishalides; homobifunctional crosslinking agents such as bis-sulfosuccinimidyl suberate, 3,3′-dithiobis-sulfosuccinimidyl propionate, dimethyl suberimidate dihydrochloride, and ethylene glycol bis-sulfosuccinimidyl succinate and water-soluble carbodiimides [39]. The chemical structures, conditions and mechanisms of reactions occurring during crosslinking using crosslinkers containing various functional groups are described in detail in the review [39].

Based on the fact that HA can be modified with various functional groups, the production of HA-based drug delivery systems that respond to various stimuli significantly increased. Furthermore, these systems enable the development of drug delivery systems that specifically bind to the CD44 receptor and are biodegradable by hyaluronidases and ROS [33, 38].

4. HA APPLICATION IN THERAPY. USE OF HA IN DRUG DELIVERY SYSTEMS

Currently, chitosan, a natural biopolymer with intrinsic anti-inflammatory activity and strong binding to nucleic acids (Fig. 7), is widely used in therapy and in the development of drug and genetic material delivery systems. However, since chitosan imparts a positive charge to the complexes by protonating amino groups, this can lead to negative consequences, such as aggregation of the complexes in the bloodstream and nonspecific interactions with cells [32–35].

Despite the obvious advantages of chitosan, such as protection of the biomaterial from biodegradation and the interaction of positively charged chitosan and negatively charged DNA, these very advantages come with negative effects, such as a low degree of transfection of genetic material. To improve the stability and transgene expression of chitosan complexes with plasmid DNA

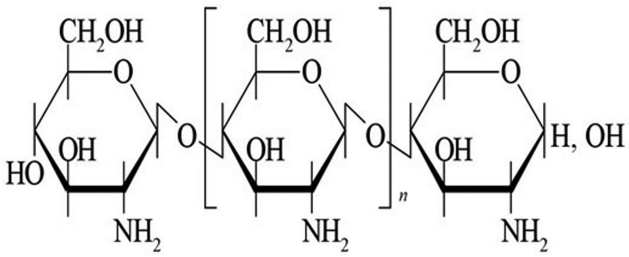


Figure 7. Structural formula of chitosan, a natural biopolymer.

(pDNA/chitosan), it has been proposed to modify them with polysaccharides; in this context the most promising is HA and its use results in pDNA/chitosan/HA system formation [36, 37]. The molecular weight of HA plays an important role in the design of drug delivery systems. Samples with molecular weights of 400 kDa, 600 kDa, and 1300 kDa were studied. The results of the study showed that complexes with 1300 kDa HA exhibited the highest degree of delivery of genetic material in gene therapy and the greatest stability [36].

HA is used as a drug delivery vehicle [38, 40]. The anionic nature of the HA molecule allows for prolonged presence of the HA-modified drug delivery system in the bloodstream without additional surface modifications of the molecules; it also facilitates their accumulation due to the EPR effect (enhanced permeation and retention effect). After the molecules of the HA-modified drug delivery system accumulate on the surface of the tumor cell, their ability to target the CD44 receptor on the surface of these cells and CD44-mediated endocytosis facilitate drug uptake by the cells [40]. Drug release can be initiated following HA degradation by hyaluronidases and ROS at the affected site. Thus, HA is a promising material for the development of drug delivery systems for antitumor therapy [40].

The combined use of albumin and HA as nanocarriers offers several advantages, including effective targeting, controlled particle size, biocompatibility, the ability to combine various drugs, and non-immunogenicity.

Drug delivery systems are actively developed for the treatment of cancer. A wide variety of approaches to developing these systems exist; these include incorporation of pH-, redox-, and enzyme-sensitive linkers, which are tailored to the specific conditions and microenvironment of a particular tumor [38, 40]. Important characteristics of linkers include water solubility, biocompatibility, biodegradability, and the ability to bind to the CD44 receptor, a specific tumor antigen, which is overexpressed on the surface of many types of cancer cells, as well as cells involved in inflammatory processes. The combined use of albumin and HA as nanocarriers has the above-mentioned advantages; in addition it also includes controlled particle size, the ability to combine various drugs, and non-immunogenicity [14]. HA is highly soluble in water, economical, effective, and has a wide range of target tumor cells; albumin contains a large number of functional groups and hydrophobic binding sites that can be used for binding to ligands and drugs.

3D bioprinting is widely used in tissue engineering and clinical applications [44]. HA is used as a bioink for the formation of 3D bioactive tissue with

a given geometry, where the bioink is a biomaterial encapsulated by living cells. Bioprinting enables the rapid creation of large-scale structures with high resolution, which opens up vast possibilities for tissue engineering.

HA is one of the most promising objects for creation and modification of drug delivery systems [40, 44–53]. The presence of carboxyl and hydroxyl functional groups in HA can be used for the aldehyde group production by oxidation of HA and amino groups during interaction with adipine dihydrazide (Figs. 2 and 6). Using introduction of aldehyde groups and additional amino groups it is possible to modify HA with various molecules, including antibodies, drugs, lipophilic fragments, and specific linkers that interact with receptors [44–51].

Drug delivery systems can have various structures, the most common micelles, liposomes, and hydrogels [54, 55]. Due to its hydrophilic properties, HA can interact with hydrophobic fragments of drugs, polymers, and small molecules thus forming amphiphilic polymers, which can then spontaneously form micelles. In addition, HA can combine with β-cyclodextrin to complex hydrophobic drugs, which can then transform into micelles. One important application of HA in the fabrication of drug delivery systems is its use as a coating. The anionic nature of HA allows to attach it to cationic surfaces of delivery systems, such as liposomes, via electrostatic interaction. Furthermore, HA can combine with hydrophobic molecules, such as 3-(diethylamino)-propylamine, to introduce hydrophobic regions into the lipid bilayer of liposomes [52]. In the production of HA-based hydrogels, the gelation process refers to the self-crosslinking of modified HA. Hydrophilic polymers, such as PEG and chitosan, are also used for crosslinking with HA to produce hydrogels [1, 56–59].

A short half-life and uncontrolled drug release into the tumor are one of the main problems in treating cancer with chemotherapy, which causes negative side effects. The use of drug delivery systems not only increases half-life, reduces toxicity, and increases bioavailability, but also allows for controlled drug release so that it reaches the tumor in uniform and constant dosages.

To produce a controlled HA-modified drug delivery system, crosslinking of hydrogels isolated from HA is used to create a “compressed” dense structure. In this case, the drug release rate is proportional to the degradation rate of this structure. The rate of decomposition of the compressed structure, in turn, can be regulated by various factors: the degree of crosslinking, the degree of swelling, and the concentration of the hydrogel [31].

Micelles and liposomes are the most common carriers for chemotherapeutic drug molecules. One of the advantages of liposomes is the ability to control the release of drugs by regulating the rate of liposome degradation. In this case, HA is used as a coating layer to create liposomes to improve bioavailability through CD44-mediated endocytosis, since the negatively charged HA is able to bind to the cationic components of liposomes through electrostatic interactions. For example, HA-coated liposomes containing paclitaxel demonstrated enhanced growth inhibition in T47D human breast cancer cells compared to the free drug or paclitaxel-loaded liposomes without a HA coating [54].

Another advantage of HA is its ability to control the density of HA attachment by conjugating HA to liposomes. The rate of endocytosis of HA-liposomes can be controlled by the density of HA fragments attached to the liposomes. To improve the stability of nanoparticles, it is proposed to use dendrimers in the creation of drug delivery systems. Dendrimers are spherical 3D-nanoparticles with unique characteristics [60]. The availability of numerous functional groups allows the surface of dendrimers to be modified with therapeutic agents, diagnostic groups, and targeted substances. For example, a system using docetaxel (DTX) as an antitumor drug, HA-DTX (docetaxel)-dendron (HADD), showed a higher level of accumulation in tumors and a higher antitumor effect compared to the linear structure. Thus, modification of the HA-modified drug delivery system with dendrimers or dendrons enhances its therapeutic properties [61]. Drug delivery systems based on HA can be used not only in chemotherapy, but also in such fields as photodynamic therapy, photothermal therapy, immunotherapy, combination therapy, and genetic material delivery [62].

Small interfering RNAs (miRNAs) and plasmid DNAs (pDNAs) are often delivered to target cells to silence or introduce specific genes. Cationic drug delivery systems (DDSs) are typically used for this purpose, as they can interact electrostatically with the anionic phosphate groups of DNA or RNA. However, such delivery systems, including polyethyleneimine (PEI) and poly(hexamethylene biguanide), are cytotoxic due to the positive charge excess of the DDS/pDNA or DDS/miRNA complex [63]. HA can act as a negatively charged building block neutralizing the excess positive charges of these complexes during circulation; HA is then cleaved by hyaluronidases in the extracellular tumor microenvironment, releasing the positively charged complexes for internalization and endosomal exit. Since DDSs/pDNA or DDSs/miRNA complexes are protected by a HA layer, the systemic toxicity of cationic drug delivery systems can be significantly reduced. Furthermore, these HA-DDSs for pDNA or miRNA delivery

are capable of targeting CD44 receptors on the surface of tumor cells, thereby enhancing delivery efficiency through the interaction of HA with the CD44 receptor. It was found that after cationic nanoparticles obtained from PEI modified with hydrophobic lithocholic acid by self-assembly were complexed with pDNA (DDS/pDNA) coated with a HA layer, this reduced the positive charges of the complex and also protected pDNA from degradation during circulation in the blood [63].

Other commonly used carriers for miRNA delivery include protamine, containing at least 60% arginine residues, and cell-penetrating peptides (CPPs), which consist only of arginine residues. HA can bind to the cationic guanidine group of arginine via electrostatic interaction, thereby preventing the degradation of protamine and CPPs by enzymes and the cleavage of miRNA by ribonuclease. Highly biocompatible cationic polymers, such as chitosan, are also widely used for miRNA delivery. For example, a product of miRNA and thiolated chitosan self-crosslinked into nanoparticles was loaded into transfersomes (artificial vesicles with cell-like characteristics known as vesicular drug delivery systems used to improve drug penetration through the skin) derived from amphiphilic HA derivatives. This HA-DDS provided effective protection for miRNA and also promoted cytoplasmic distribution, which could be explained by CD44-mediated endocytosis. After nanocomplexes formed from HA, miRNA, and protamine were loaded inside the liposomes, the liposomes were coated with other receptor-targeting ligands to give DDSs additional precision [64–67].

Low molecular weight and very low molecular weight HA, which promote wound healing, stimulate the proinflammatory cytokine production and play a crucial role in accelerating the re-epithelialization process, thereby preventing new recurrent mucosal infections [68–70]. The inclusion of low molecular weight and very low molecular weight HA in complex therapy including epigallocatechin gallate (EGCG epigallocatechin gallate) (200 mg), folic acid (400 μg), vitamin B12 (1 mg), and HA (50 mg) (PervistopR, Lo.Li. Pharma, Italy) has shown efficacy during oral administration in the treatment of human papillomavirus infection [70].

Lipid nanoparticles containing doxorubicin and oligomeric HA functionalized with an iRGD peptide targeting integrins (iRGD-DOX-oHA-PLN) have been proposed for the treatment of breast cancer to prevent immunosuppression, DNA repair, and metastasis [71].

Nanoparticles used for targeted therapy provide precise drug delivery with increased efficacy and reduced side effects during prostate cancer treatment. HA-coated PLGA nanoparticles loaded with shikonin were successfully used for the targeted therapy of LNCAP prostate cancer cells expressing the CD44 receptor. CD44+LNCAP cells showed increased uptake of HA-coated nanoparticles due to the HA affinity for the CD44 receptor, overexpressed on many cancer cells, including LNCAP prostate cancer cells. Cytotoxicity studies revealed a decrease in the IC_{50} values to 70.02 μg/ml (24 h) and 48.78 μg/ml (48 h), compared to 111.54 μg/ml and 54.02 μg/ml for HA uncoated nanoparticles. Apoptosis assay revealed 68.37% late apoptosis with HA-coated nanoparticles compared to 45.87% for uncoated nanoparticles. Spheroid analysis revealed a 17.69% reduction in tumor size at 96 h, compared to 15.75% and 9.8% for uncoated nanoparticles and pure shikonin, respectively. These results demonstrated the potential of shikonin-containing and HA-coated nanoparticles to enhance the efficacy of targeted therapy for prostate cancer [72].

5. BACTERICIDAL PROPERTIES OF HA IN HA-METAL NANOPARTICLES COMPLEXES

HA exhibits bacteriostatic properties, so it is used to create antimicrobial materials. Despite these advantages, HA-based hydrogels typically exhibit weak tissue adhesion, which limits their ability to effectively seal wounds. Their low adhesive capacity to some extent limits their clinical application. Therefore, various modifications are currently developed to overcome these drawbacks and maintain bacteriostatic properties [73, 74].

The antimicrobial activity of metal nanoparticles, particularly gold, silver, and copper, has been well studied [75, 76]. Such nanoparticles were shown to be potential alternative drugs for the treatment of wounds infected with antimicrobial-resistant bacteria [77].

Gold nanoparticles are inert and do not exhibit toxic effects on human cells. Secretion of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) was not detected in a study with macrophage cells [77]. These results indicate that gold nanoparticles are not cytotoxic or immunogenic but are biocompatible, confirming their potential for use in nanoimmunology, nanobiotechnology and nanomedicine [77]. At the same time, their high antibacterial activity against various pathogenic bacteria has been demonstrated [77]. In contrast to gold nanoparticles, silver nanoparticles exhibit toxicity due to their genotoxicity and cytotoxicity [78]. Silver nanoparticles can inhibit antioxidant defense mechanisms through glutathione reduction, superoxide dismutase inactivation and lipid peroxidation stimulation. Thus, ROS accumulation and oxidative stress can cause many physiological and cellular disorders, including stress, mitochondrial destruction,

apoptosis, inflammation, and DNA damage. Mitochondria are particularly sensitive to silver nanoparticle-induced toxicity [79]. In addition to DNA and mitochondrial damage, exposure to silver nanoparticles, unlike gold nanoparticles, induces the release of a number of proinflammatory markers, primarily TNF-α, pulmonary intravascular macrophages, and granulocyte colony-stimulating factor. Furthermore, silver nanoparticles release Ag^+ ions into aqueous solution due to oxidative processes (the presence of silver ions significantly increases the nanoparticle toxicity) [80].

Nanoparticles of copper or copper oxides exhibit even a more toxic effect on pathogenic microorganisms, and this effect is directly related to the particle size [81]. As in the case of other metals, the presence of excess copper is toxic to organisms in general to some degree. This is because, in the presence of water and oxygen, copper releases positive ions and forms hydroxyl radicals, which are highly toxic. In addition, electrons generated by oxidation reactions interact with water molecules, forming further hydroxyl radicals [81].

Copper toxicity is manifested by inhibition or alteration of protein synthesis; alteration of cell membrane permeability caused by lipid peroxidation, leading to oxidative damage. This results in an imbalance in the transport of ions (particularly sodium and potassium), which are necessary for normal cellular function, and destruction or alteration of the secondary structure of nucleic acids (DNA), impairing the cell's reproduction ability [82].

A study that assessed the *in vitro* toxicity of copper nanoparticles in mouse embryonic fibroblasts showed that copper nanoparticles, like silver nanoparticles, exhibited less toxicity than copper ions Cu^{2+} [80, 83].

The formation of complexes of metal nanoparticles with HA (Mw ~35 kDa) as a stabilizing support offers the safety and capacity for its use in the preparation of medical dressings that accelerate skin healing and have an antibacterial effect, without a toxic effect on body cells [76]. Complexes of HA with nanoparticles of gold, copper, silver, and palladium-silver alloy were investigated using high-resolution transmission electron microscopy, IR spectroscopy, thermogravimetric analysis, and bacteriological studies [84]. The average sizes of nanoclusters were determined: HA-Au = 17.88 nm; HA-Ag = 50.41 nm; HA-Cu = 13.33 nm; HA-AgPd = 33.22 nm. The toxicity of the complexes was studied on laboratory mice. Based on the experimental results obtained, it was concluded that the use of HA as a stabilizing support ensured the safety and productivity required for its use in the preparation of medical dressings with metal nanoparticles and did not cause adverse reactions; the complexes were completely biocompatible and promote tissue regeneration [76]. The HA complexes with silver, copper, and palladium-silver alloy nanoparticles showed antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* bacteria. However, a complex of gold nanoparticles with HA did not exhibit an antibacterial effect [76]. Analysis of the toxic effect of metal nanoparticle complexes with HA revealed that the use of HA as a stabilizer reduced the toxicity of complexes with copper, silver, and palladium-silver alloy nanoparticles (gold nanoparticles, unlike the above complexes, were not toxic). These conclusions were based on the fact that alanine aminotransferase, gamma-glutamyl transpeptidase, and bilirubin levels in the blood of mice, measured on day 14 of the study after two injections (on days 1 and day 7) of 0.5 ml of 0.5% metal nanoparticle solutions with HA, were normal. No hepatotoxicity was observed with these complexes after a two-week study, and albumin and bilirubin levels were also within normal limits. Solutions of metal nanoparticle complexes with HA did not affect liver and kidney tissue after 14 days of the study. Thus, it can be concluded that HA complexes with metal nanoparticles do not exhibit significant toxicity [82–84].

6. ANTI-AGING PROPERTIES OF HA

The search for ways to slow down aging is one of the most important issues related to improving the quality of life as a factor in longevity and its active prolongation [1, 3, 85]. There is a constantly growing trend in the development of new materials and drugs with anti-aging properties. Biomaterials are actively studied in the context of delayed aging. Since HA is the main element of basal keratinocytes in the extracellular matrix, it is considered a major component of the epidermis, possessing both structural and functional properties [85]. Increased HA content in the skin can significantly protect it from the harmful effects of radiation, wrinkles, and aging. Over the past few years, various anti-wrinkle products have been developed, such as microneedle patches with HA and acetyl hexapeptide-8, which are suitable for improving skin elasticity, its integrity, and collagen production [86]. A combination of anti-aging skin firming materials such as tripeptide and carnosine has been developed to induce HA synthesis in dermal fibroblasts and keratinocytes [87]. Niosomes are vesicles composed of non-ionic surfactants containing cholesterol as an excipient. Niosomes are used for drug delivery. Niosomes modified with HA and containing asiaticoside were developed as an anti-aging drug delivery system [87]. This system had enhanced transdermal internalization and rapid action and

was used against dry and flaky skin [87]. HA-based materials can be used in the production of skin lotions as well as dermal fillers in plastic surgery. HA maintains the integrity of the extracellular matrix and serves as a free radical scavenger, stimulating keratinocyte proliferation and migration.

CONCLUSIONS

HA is a natural biopolymer widely used in biomedicine, with clinical applications including ophthalmology, orthopedics, general and plastic surgery, dentistry, otolaryngology, neurology, obstetrics and gynecology, urology, and radiology [6]. The lack of toxicity of HA, its selective binding to cellular receptors, and the ability to create modifications with various functional groups offers its use in the creation of drug and genetic material delivery systems. HA doped with metal nanoparticles possesses antibacterial and wound-healing properties. The most important advantages of HA over other biopolymers are its high bioavailability and biocompatibility, as well as its anionic nature, which allows it to be used to create drug delivery systems with controlled release, anti-aging agents, and as bioink in 3D bioprinting for the formation of bioactive tissue with a given geometry.

HA molecules of different molar masses exert different effects on cellular behavior. Short HA chains stimulate angiogenesis (Mw 400–10,000), cell migration, and proliferation (Mw 50,000–100,000), while high-molecular-weight HA (Mw > 500,000) has the opposite effect, suppressing angiogenesis and inhibiting cell migration and proliferation (Fig. 3). Therefore, HA fractions with precisely defined molecular masses are used to achieve various goals.

Thus, HA represents a versatile therapeutic platform based on understanding the action of HA in various tissue microenvironments and then applying this knowledge to refine and optimize this highly flexible biomaterial for its use in wound healing, regeneration, and functional restoration. The role of endogenous HA in both physiological processes and pathological conditions demonstrates the potential of exogenous HA to address complex issues associated with tissue damage, diseases, or defects in a completely new way.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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ГИАЛУРОНОВАЯ КИСЛОТА: БИОХИМИЧЕСКИЕ СВОЙСТВА И ПРИМЕНЕНИЕ В МЕДИЦИНЕ

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В данном обзоре литературы рассмотрены биологические свойства гиалуроновой кислоты (ГК), её различные химические модификации по карбоксильным, гидроксильным и ацетамидным группам, их применение в системах доставки лекарств и генетического материала. Рассмотрено использование ГК в комплексах с наночастицами металлов, с другими биополимерами и биомолекулами. Молекулы ГК разной молярной массы оказывают различное действие на клеточные процессы. Поэтому для достижения различных целей используются фракции ГК со строго определённой молекулярной массой. Обсуждаются уникальные свойства ГК, такие как высокая биодоступность, биосовместимость, антиоксидантные свойства, а также высокая аффинность к ряду клеточных рецепторов, что перспективно для использования ГК как средства в таргетной терапии. Рассмотрено применение ГК в регенеративной медицине.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: гиалуроновая кислота; системы доставки лекарств; наночастицы металлов; антиоксидантные свойства; старение; геропротекторные свойства

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