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REVIEW

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Hyaluronic acid: comprehensive review of a multifunctional biopolymer

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Abstract

Background Hyaluronic acid (HA) has a broad range of cosmetic and therapeutic applications due to its unique physicochemical properties and involvement in various essential biological processes, including cell signaling, wound reparation, and tissue regeneration.

Main body In this review, we provide a comprehensive overview of HA, including its history, physicochemical properties, roles, molecular biology, and biochemistry (including occurrence, biosynthesis, and degradation), as well as its chemical modifications and conventional and emerging production methods. We also examine HA's medical, pharmaceutical, and cosmetic applications and its derivatives in arthrology, ophthalmology, wound healing, odontology, oncology, drug delivery, 3D bioprinting, and cosmetology. Finally, we discuss the potential role of HA in preventing Covid-19.

Conclusion Hyaluronic acid, a naturally found substance, has shown immense potential in the clinic. Thus, it is imperative to highlight its applications in the diverse fields impacting the lives of patients and healthy individuals.

Keywords Hyaluronic acid, Biomaterials, Cosmetics, Tissue: rejuvenation, Covid-19

Background

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan found in vertebrate connective, epithelial, and nervous tissues. This versatile substance has a broad range of applications in the medical and cosmetic industries, such as dermal fillers, osteoarthritis treatment, ophthalmology, and vesicoureteral reflux. In 2018, the global HA market was valued at USD 8.3 billion, with a projected Compound Annual Growth Rate (CAGR) of 7.8% during the forecast period [1–3]. HA was first discovered in cow's eyes in 1934 and later identified in humans and other animals. It is primarily found in the extracellular matrix of connective tissue, synovial fluid, and vital tissues such as the eye's vitreous, cartilage, fascia, and umbilical cord. In 1979, pharmaceutical-grade HA was produced by extracting and purifying the polymer from rooster combs and human umbilical cords [2]. HA is abundant in soft connective tissues, including skin, lungs, kidneys, brain, and muscles. Its unique viscoelastic properties, biocompatibility, and non-immunogenicity

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make it an ideal substance for clinical applications and cosmetic purposes [2, 4]. Due to changing beauty standards and rising health awareness, there has been a significant increase in nonsurgical cosmetic procedures, with hyaluronic acid injectables being the second most frequently performed procedure after Botox, with a total spending of more than USD 5 billion in America in 2015 [5, 6]. This review explores HA's potential benefits and limitations in various applications, such as tissue engineering, drug delivery, and wound healing, by examining this substance's positive and negative aspects to provide a comprehensive overview of its use in medicine and cosmetics.

Main text

Physiological functions of hyaluronic acid

Hyaluronic acid (HA) is a macromolecule that plays a vital role in the human body. It is a high molecular weight glycosaminoglycan composed of glucuronic acid and *N*-acetylglucosamine linked together via glycosidic bonds. In the body, it exists in sodium hyaluronate and is present in various soft connective tissues, including the skin, lungs, kidneys, brain, and muscle tissues [7]. HA's biological functions are diverse and significant. It plays a crucial role in regulating tissue hydration and water transport, maintaining the elasto-viscosity of connective tissues, and facilitating the supramolecular assembly of proteoglycans in the extracellular matrix. HA also engages in numerous receptor-mediated roles, such as cell detachment, mitosis, migration, tumor development and metastasis, and inflammation [8]. When bound to water molecules, HA forms a hydrated gel and acts as a water-binding agent that lubricates movable body parts, such as joints and muscles. HA's properties and functions have led to a broad range of applications in the medical field. For example, it is commonly used in dermal fillers for cosmetic purposes and is also used to treat osteoarthritis. The increasing demand for nonsurgical cosmetic procedures has led to a surge in using hyaluronic acid injectables [9] (Fig. 1).

Molecular biology and biochemistry

Hyaluronan is a linear glycosaminoglycan comprising approximately 10,000 disaccharide units of D-glucuronic acid and *N*-acetyl-D-glucosamine (Fig. 2A). The synthesis of HA is carried out by hyaluronan synthases, which are membrane-bound enzymes forming functional dimers with six transmembrane segments. The polymer chain is expelled through the plasma membrane during hyaluronan synthesis. The active form of the hyaluronan synthase enzyme was isolated from streptococci as a complex and characterized as a 42 kDa protein through immunological cross-reaction with the streptococcal enzyme and affinity labeling techniques [10]. Three mammalian genes are responsible for hyaluronan synthesis (HAS1, HAS2, and HAS3), each contributing to hyaluronan production with different molecular weights. The biological effects of hyaluronan are distinct from other biologically active molecules and are influenced by its molecular weight (Mw) [11, 12].

There is a total of 15 g of hyaluronan (HA) in the human body, and about 30% of it undergoes degradation through two distinct mechanisms (Fig. 3). One mechanism involves specific enzymatic degradation mediated by hyaluronidases, while the other mechanism is nonspecific and occurs due to oxidative damage caused by reactive oxygen species (ROS) [13–15]. ROS encompass hydrogen peroxide, peroxynitrite, nitric oxide, superoxide, and hypohalous acids. These ROS are generated during inflammatory responses in conditions like sepsis, tissue inflammation, and ischemia–reperfusion injury. They can degrade hyaluronan, a process that can occur due to ROS. The human genome contains six identified gene sequences related to hyaluronidase: HYAL-1, HYAL-2, HYAL-3 genes, HYAL-4 and PH20/SPAM1 genes, and HYAL-P1 pseudogene. These genes are associated with the production of hyaluronidase enzymes, which are involved in the degradation of hyaluronan [16, 17]. The degradation of HA occurs partially within the tissue itself, but a significant portion occurs in local lymph nodes and within the endothelial cells of the liver. The remaining 70% of HA undergoing systemic catabolism is transported by hyaluronan, primarily carried to the lymph nodes through the lymphatic system. Within the lymph nodes, hyaluronan is internalized and broken down by the endothelial cells of the lymphatic vessels. Additionally, a small fraction of HA enters the bloodstream and undergoes degradation by the endothelial cells in the liver [18–20]. Hyaluronidase-mediated degradation of HA plays a crucial role in various critical regulatory processes, including embryonic development and wound healing. The significance of HA degradation by hyaluronidases is evident in mucopolysaccharide hyaluronidase deficiency, a lysosomal storage disorder characterized by elevated levels of HA in the plasma due to a defect in hyaluronidase activity [21, 22]. HA exhibits one of the most rapid turnover rates among molecules in the mammalian body. It is estimated that approximately one-third of the 15 g of HA present in an average adult human is turned over daily (Fig. 4). The high turnover of HA in various tissues requires equally high rates of synthesis and degradation [23–25].

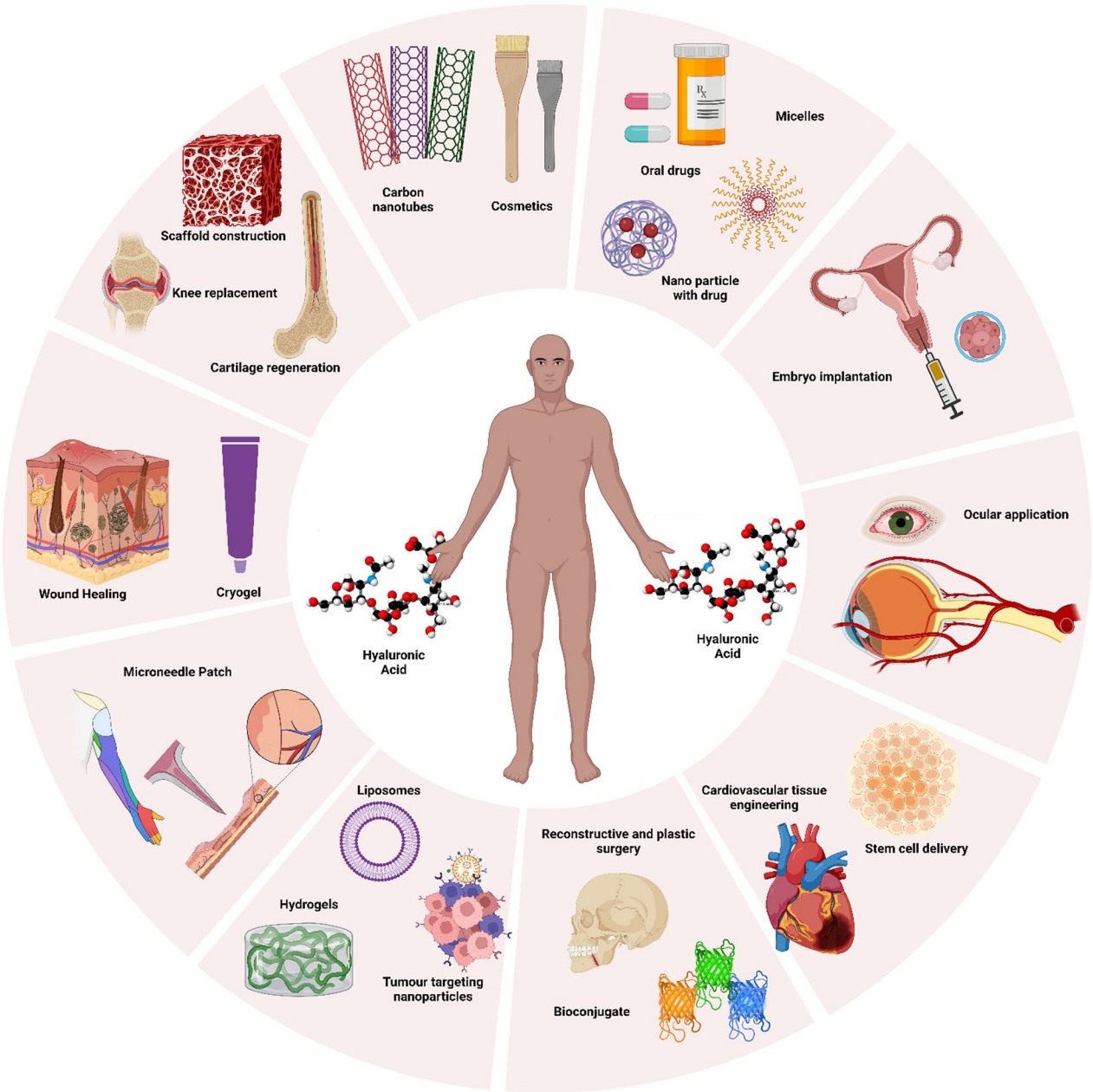

Fig. 1 Applications of hyaluronic acid (HA) in different fields. HA is a versatile biomaterial with various applications in various areas. This figure provides an overview of the diverse applications of HA, including drug delivery, tissue engineering, cosmetic procedures, and wound healing. The figure shows that HA can form nanoparticles for drug delivery, including oral drugs, micelles, and tumor-targeting nanoparticles. HA nanoparticles can also be used in ocular applications, enhancing drug delivery to the eye and improving ocular bioavailability. HA has also been used in tissue engineering, including cardiovascular tissue engineering, stem cell delivery, reconstructive and plastic surgery, and scaffold construction for knee replacement and cartilage regeneration. HA hydrogels, cryogels, and carbon nanotubes have enhanced tissue regeneration and repair. HA is commonly used as a filler for facial rejuvenation and volumization in cosmetic procedures. HA-based liposomes can also be used for targeted drug delivery in cosmetics. Other applications of HA include embryo implantation, wound healing, and microneedle patches. HA has been shown to improve embryo implantation rates and promote wound healing. Microneedle patches incorporating HA can enhance transdermal drug delivery and promote skin hydration [Figure generated using https://www.biorender.com/]

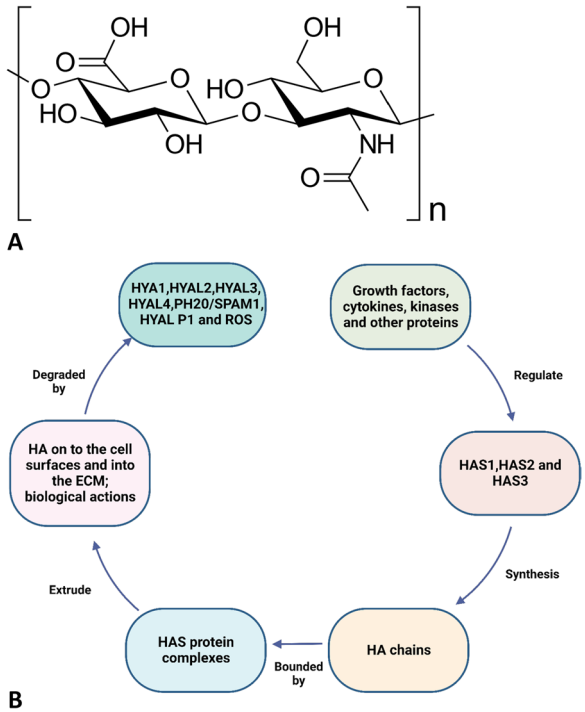

Fig. 2 **A** Structure of hyaluronic acid. **B** Schematic diagram illustrating the key steps involved in hyaluronic acid (HA) synthesis and degradation. The diagram shows that the synthesis of HA is regulated by various factors, such as growth factors, cytokines, kinases, and other proteins that modulate the activity of HA synthases (HAS1, HAS2, and HAS3). These enzymes are responsible for synthesizing HA chains, which are then bound by HAS protein complexes and extruded onto the cell surfaces and into the extracellular matrix (ECM). The biological actions of HA are tightly regulated by its degradation, which is carried out by several hyaluronidase enzymes, including HYAL-1, HYAL-2, HYAL-3, HYAL-4, PH20/SPAM1, HYAL-P1, and ROS. These enzymes cleave the HA chains into smaller fragments, which can be metabolized or eliminated from the body

Isolation from biological sources and manufacturing by biotechnology

HA is a glycosaminoglycan that serves vital functions in tissue hydration and cellular processes. Within the body, HA is synthesized by attaching sugar molecules to the reducing end of the polymer. This synthesis occurs within the plasma membrane of various cells, including fibroblasts. The resulting HA molecule extends into the pericellular space, contributing to its important physiological roles [26]. Historically, hyaluronic acid was extracted from animal tissues such as rooster combs, human umbilical cords, or other vertebrate tissue. However, this process was found to be relatively complex and expensive [27, 28]. In recent years, hyaluronic acid has been obtained through in vitro production or extraction from the cell walls of bacteria of streptococcal origin. Two types of hyaluronic acid can be produced depending on the method: isolation-origin HA and fermentation-origin HA. Isolation-origin HA is obtained through a series of steps that include the removal of epithelium from the rooster comb, followed by grinding of the comb. Subsequently, the ground material is treated with acetone, ethanol, and sodium chloride to extract and purify the hyaluronic acid [29]. In contrast, the production of fermentation-origin HA involves the continuous fermentation of Streptococcus in a controlled culture environment, such as a chemostat. However, it is essential to note that fermentation-origin HA often contains substantial amounts of endotoxins and elevated bacterial levels, necessitating the removal of these impurities through subsequent purification steps [30]. Therefore, additional purification steps are required to minimize the presence of bacterial proteins. Remarkably, hyaluronan has been discovered in the capsule of specific microbial pathogens, including Pasteurella multocida and certain strains of Streptococcus (Fig. 5). These microorganisms have developed enzymatic systems that resemble those found in vertebrate hosts to facilitate hyaluronan synthesis within their capsules [31, 32]. These microorganisms employ hyaluronan as a protective capsule around their cells, effectively evading the host's immune system and facilitating adhesion and colonization of the bacterial cells. This hyaluronan-based encapsulation serves as camouflage, allowing the microorganisms to bypass the animal defense mechanisms [21, 33]. Isolation-origin HA generated in biological systems is often associated with proteins and other glycosaminoglycans, necessitating thorough purification processes [34, 35]. Complex purification processes are essential to obtain a genuine product from traditional resources like rooster combs while minimizing the degradation of the molecular chains. However, even with sophisticated purification and sterilization methods, the final product's molecular weight will likely decrease, resulting in a lower molecular weight [36, 37]. Furthermore, the production of isolation-origin HA from traditional sources also poses a risk of viral contamination, necessitating complex purification procedures that can be costly [38–40].

Modification of HA

HA possesses various functional groups, such as carboxylic acids, *N*-acetyl groups, and alcohols, that can be modified to alter the properties of resulting materials for enhanced hydrophobicity and biological activity [41, 42]. These modifications are commonly carried out through chemical cross-linking or radical polymerization, leading to hydrogels known as hylans. Although HA is highly hydrophilic and soluble in water, it is often required to have limited solubility or insolubility for its use in medical devices. It can be achieved

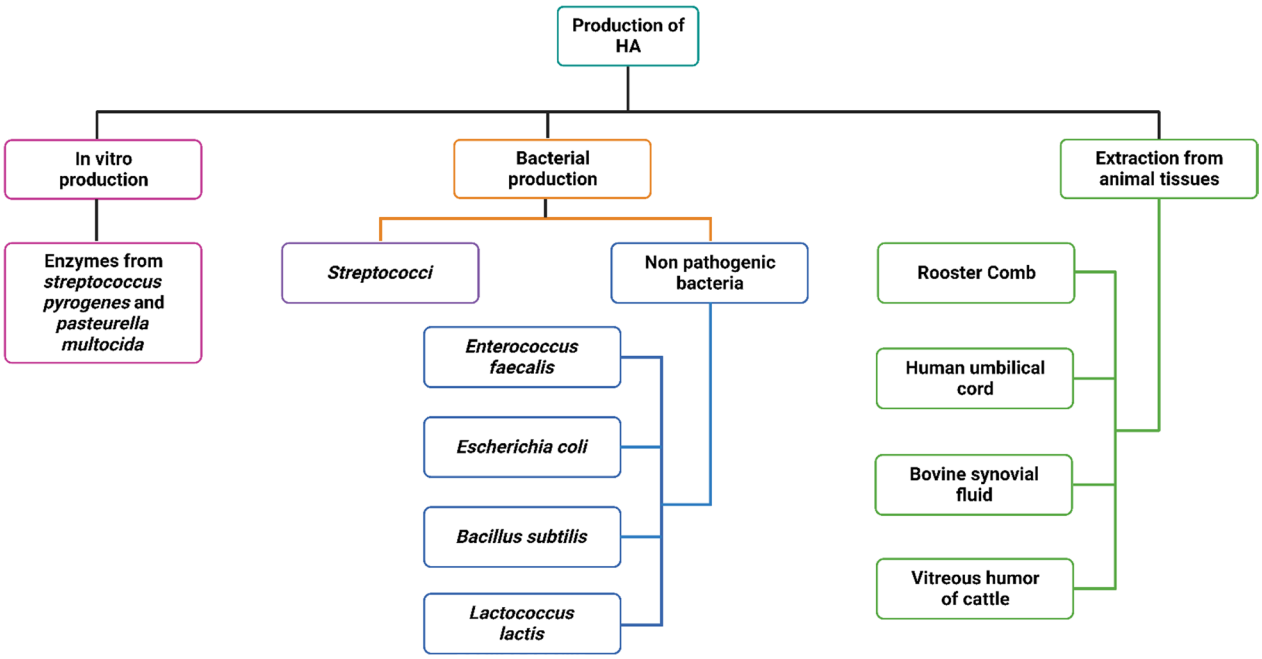

Fig. 3 Summary of the production of HA. This figure provides an overview of the methods used to produce HA, including in vitro production, bacterial production, and extraction from animal tissues. The first method described is in vitro production, which involves using enzymes derived from *Streptococcus pyogenes* and *Pasteurella multocida* to synthesize HA in a controlled laboratory setting. This method allows for the production of HA with precise molecular weight and purity, making it ideal for pharmaceutical and biomedical applications. The second method described is bacterial production, which involves using various strains of bacteria, including *Streptococci, Enterococcus faecalis, Escherichia coli, Bacillus subtilis,* and *Lactococcus lactis*, to produce HA. This method is relatively inexpensive and scalable, making it suitable for large-scale production of HA for commercial and industrial purposes. The third method described is an extraction from animal tissues, which involves isolating HA from various animal sources, including rooster comb, human umbilical cord, bovine synovial fluid, and vitreous humor of cattle. This method is less commonly used due to the challenges associated with obtaining HA from animal tissues, but it remains an essential source of HA for specific applications

by conjugating or cross-linking HA [43, 44]. Chemical modification of HA enables its transformation into diverse physical forms such as viscoelastic solutions, hydrogels with varying stiffness, electrospun fibers, flexible sheets, macroporous and fibrillar sponges, nonwoven meshes, and nanoparticulate fluids, which find applications in various clinical and preclinical settings [44–46]. This is achieved by targeting three functional groups: primary and secondary hydroxyl groups, carboxylic acid, glucuronic acid, and *N*-acetyl groups. Different approaches, such as addition/condensation chemistry or radical polymerization, can cross-link these groups [47]. However, the direct application of HA-based products in humans presents substantial challenges in their development (Fig. 6). The market for these products is expensive, and ongoing efforts are being made to create new formulations. The globalization of the industry has heightened the need for stringent quality controls to guarantee the safety of cosmetic products [47, 48]. Consequently, there is an immediate requirement to advance the development of cost-effective and efficient techniques for identifying and detecting toxic components present as contaminants or impurities.

Nanofibers and nanomicelles

Nanofiber scaffolds have a broad range of applications in fields such as tissue engineering, wound dressing, cosmetics, and drug delivery [49]. Biopolymers are ideal materials for these scaffolds due to their biodegradability and biocompatibility. However, the industrial development of such formulations is challenging due to modifying HA with toxic reagents during chemical processes, which are challenging to eliminate from the final product, making it unsuitable for pharmaceutical applications [50, 51]. Nanofibers based on photocurable ester derivatives of HA or its salt have been developed to overcome this issue. The skin barrier at the topmost layer, the stratum corneum, can prevent the penetration of drugs. However, nanosized colloidal systems, such as nanoparticles, liposomes, nanoemulsions, micelles, and polymeric suspensions, have demonstrated the ability to enhance drug penetration through this barrier [52, 53]. These systems have received significant attention for delivering cosmetic

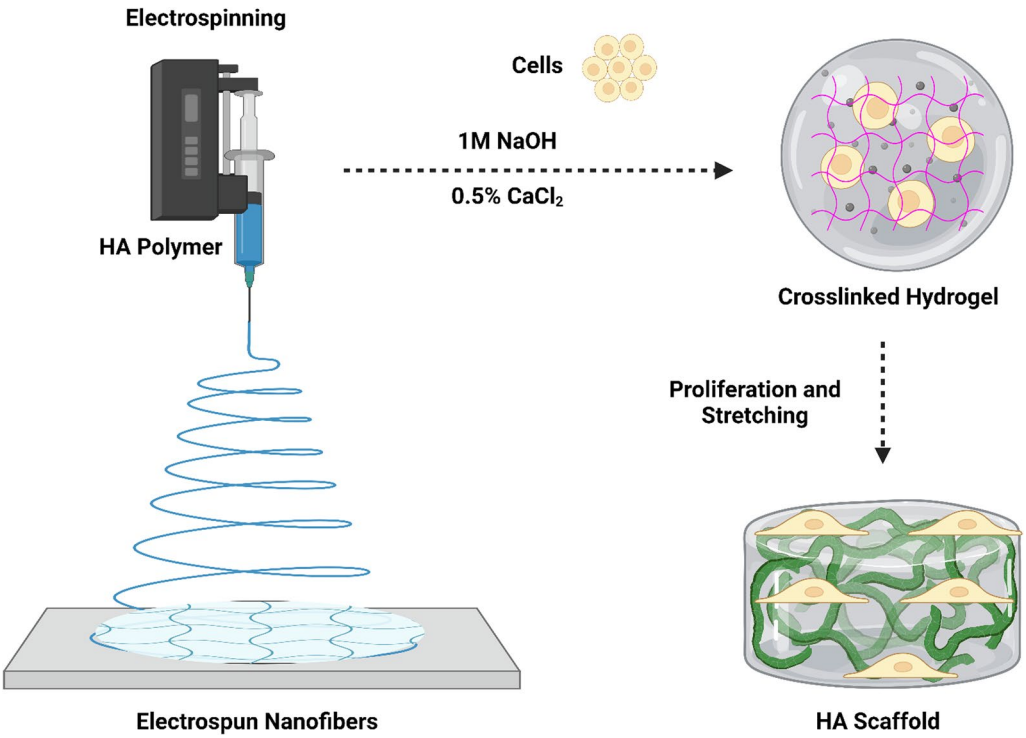

Fig. 4 Schematic diagram illustrating the electrospun nanofibers and hydrogel scaffold composite for tissue engineering applications. The figure shows that electrospinning is used to fabricate nanofibers from a hyaluronic acid (HA) polymer, which is then cross-linked with 1 M NaOH and 0.5% CaCl2 to form a hydrogel scaffold. The resulting composite material provides a suitable substrate for cell proliferation and stretching, which can lead to the formation of functional tissue structures. The electrospun nanofibers provide a high surface area-to-volume ratio, facilitating cell adhesion and migration, while the hydrogel scaffold offers mechanical support and promotes cell proliferation. The composite material can also be further functionalized with growth factors or other bioactive molecules to enhance tissue regeneration [Figure generated using https://www.biorender.com/]

and pharmaceutical compounds topically for local or systemic administration [54, 55]. Research on polymer-based drug delivery has aimed at developing biodegradable polymer systems to reduce the risk of accumulating non-biodegradable particles in the body [56]. HA is an intriguing material as a topical drug delivery agent since it is a substantial part of the skin's extracellular matrix and can be found in both the epidermis and dermis [57].

Hydrogels

Hydrogels are intricate polymeric networks characterized by a three-dimensional architecture that enables them to absorb substantial quantities of water while preserving their structural integrity [58]. Due to its very important physiological and biological roles in maintaining homeostasis in the human body, hydrogels made from HA have been developed for several biomedical applications such as, drug delivery, tissue engineering and regeneration, as well as diagnostics, etc. [59, 60]. Market for HA-based hydrogels is continuously expanding and HA hydrogels are already being used in medicine as viscosupplements, dermal fillers, would dressings, etc.

Although HA can form molecular networks in the presence of a solvent due to its conformation and molecular weight, it cannot form a physical gel alone which further warrants for further chemical modifications such as covalent cross-linking and use of gelling agents to prepare HA hydrogels. Chemical cross-linking, with some limitations, has been a versatile method to obtain HA hydrogel with excellent mechanical, chemical, and thermal stability [61]. HA-based hydrogels can be prepared by several methods, such as polymerization, enzymatic cross-linking, condensation reactions, and click chemistry. HA hydrogels can be directly cross-linked with the help of cross-linking agents such as glutaraldehyde, divinyl sulfone, bisepoxide, and carbodiimide. [62, 63]. Using Diels Alder-based click reaction, HA-based hydrogels with tunable properties were developed by reacting furan modified HA with peptide derivatized with bismaleimide in order to mimic extracellular matrix (ECM) for breast cancer cells invasion [64]. Furthermore, by avoiding the use of cytotoxic copper as a catalyst, HA-PEG hydrogels were synthesized by reacting cyclooctyne modified HA with azide functionalized PEG. This hydrogel showed

Fig. 5 Applications of hyaluronic acid (HA) and its derivatives in various fields. The figure shows that HA and its derivatives can be used as a drug delivery system, where they serve as carriers for different therapeutic agents, including small molecules, proteins, and nucleic acids. The biocompatibility and biodegradability of HA make it an ideal material for sustained drug release, enhancing the therapeutic efficacy of the delivered agent. In cancer therapy, HA and its derivatives have been used for targeted drug delivery, as well as for imaging and diagnosis. HA-based nanoparticles can selectively accumulate in tumor tissues, releasing the drug payload and effectively inhibiting tumor growth. HA, and its derivatives have also been used in soft tissue regeneration, including wound healing, cartilage repair, and bone regeneration. HA-based scaffolds and hydrogels can support cell adhesion, proliferation, and differentiation, forming functional tissue structures. HA and its derivatives are commonly used in skin care products in the cosmetic industry due to their moisturizing and anti-aging properties. HA-based fillers can also be used for facial rejuvenation and volumization. Other applications of HA and its derivatives include dietary supplements, urology, odontology, and wound treatment. HA-based materials can be used in urology for bladder augmentation and incontinence treatment. In odontology, HA-based materials can be used for tissue engineering and implantology. In wound treatment, HA-based dressings can promote healing and prevent infection [Figure generated using https://www.biorender.com/]

excellent mechanical properties, gelation time, and high stability [65, 66]. Recently, using another naturally occurring click chemistry between cyanobenzothiazole and cysteine, an in situ forming injectable HA hydrogel with encapsulated camptothecin nanocrystals was prepared for long-term treatment of inflammatory arthritis [66].

On the other hand, non-covalent bonds and supramolecular interactions have been researched to prepare physical hydrogels with tunable properties by applying various cues like pH, light, temperature, etc. [67, 68]. Taking advantage of inclusion complexation properties of cyclodextrins, self-assembled HA hydrogel was formed by reacting β-cyclodextrin with adamantane functionalized HA which displayed excellent shear thinning properties [69]. Interestingly, using gelling agents such as Pluronic F-127, thermosensitive HA hydrogel was prepared by mixing HA in water with Pluronic F-127. Due to the hydrophobic interactions of acetyl groups of HA and methyl groups of Pluronic F-127, stable and mechanically stronger hydrogel was formed which avoided the typical burst release of drugs when only Pluronic F-127 was used in hydrogel preparation [70].

Films

HA films have several advantages over conventional formulations like gels, ointments, and solution as films can be stable, long-lasting, and can enhance patient compliance. There have been continued research on HA-based films for the treatment of diverse diseases by overcoming the drug delivery barriers of drug molecules as well as delivery system itself [71, 72]. HA films have been found to have limited medical applications that require extended stability in aqueous environments due to their fast dissolution in water, poor mechanical stability, and rapid in vivo degradation. However, these limitations can be overcome by implementing physical and chemical cross-linking techniques [57, 73, 74]. To be suitable for biomedical applications, films must possess specific properties, such as self-supporting, adequate mechanical strength when hydrated, biocompatibility, biodegradability, non-cytotoxicity, and the ability to adjust in vivo stability [75, 76]. A new type of water-insoluble film composed of palmitoyl esters of hyaluronan (pHA) was developed in 2016 to overcome the solubility limitations of hyaluronan films [77]. A new method was formed in 2019 for creating free-standing films from lauroyl derivatives of HA without the need for cross-linking agents, plasticizers, toxic solvents, and activators. This method involves an artless single-step solution casting process. The resulting films were homogeneous, exhibited good mechanical strength, and were flexible. Hydrophobized or cross-linkable hyaluronan derivatives exhibit higher resistance to biodegradation. They can serve as scaffolds for cell culture and matrices for controlled drug-related augmentation of soft tissues via viscosupplementation [78]. Conjugation of hyaluronan with drugs also provides an exciting approach for targeted drug delivery [79]. Significant attention has been given to the preparation of hyaluronic acid derivatives that can undergo cross-linking reactions under mild physiological conditions to broaden their applications.

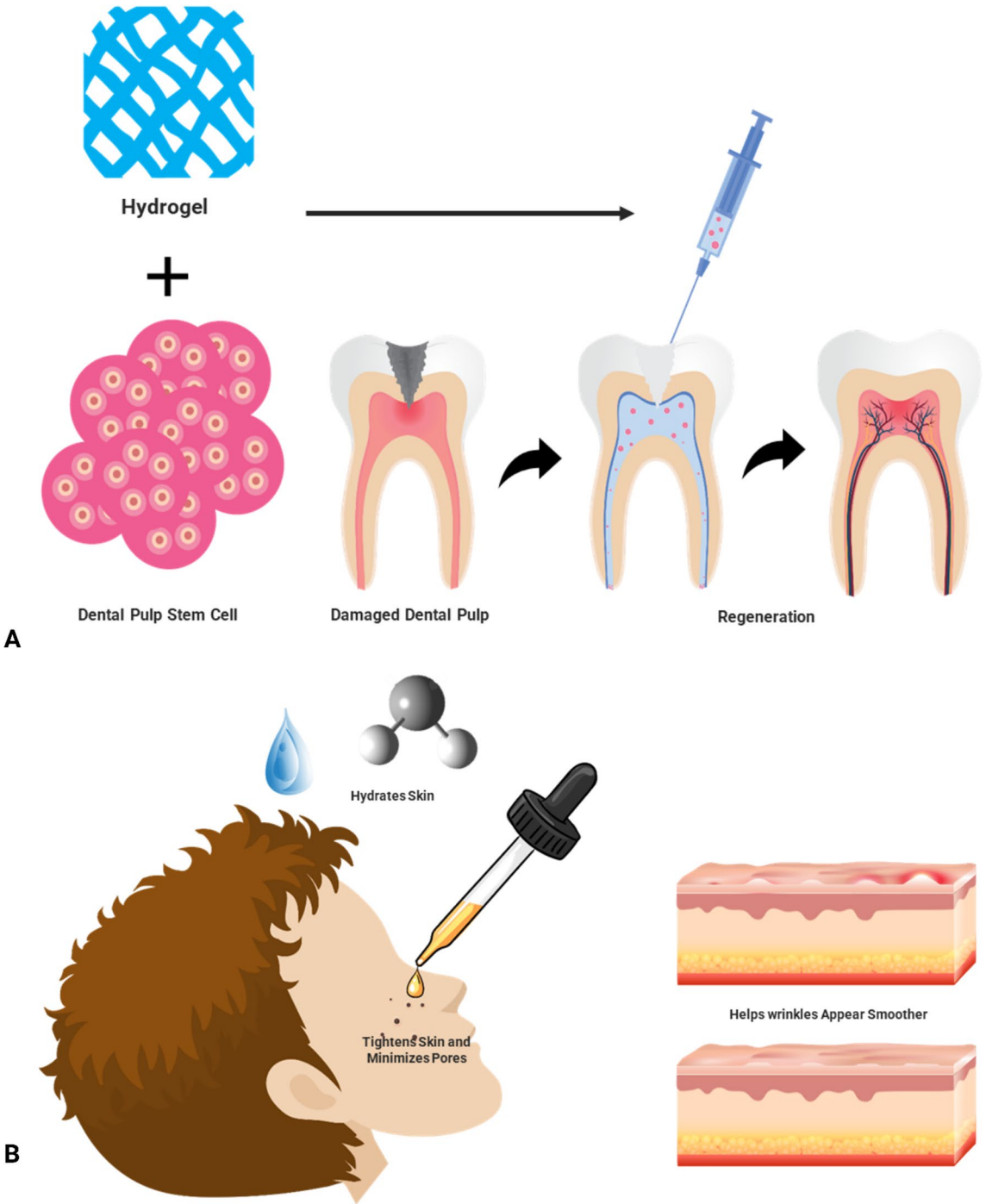

Fig. 6 Application of hyaluronic acid (HA) hydrogel in the regeneration of dental pulp and cosmeceuticals. **A** shows that HA hydrogel can regenerate damaged dental pulp. Dental pulp stem cells are mixed with the HA hydrogel and injected into the damaged pulp using a syringe. The HA hydrogel provides a suitable microenvironment for the proliferation and differentiation of dental pulp stem cells, leading to functional dental pulp tissue regeneration. In addition to dental pulp regeneration. **B** HA hydrogel can be incorporated into skincare products, such as creams and serums, to improve skin hydration and reduce the appearance of fine lines and wrinkles. HA hydrogel can also be used as a filler in facial rejuvenation procedures, providing immediate volumization and contouring [Figure generated using https://www.biorender.com/].

Applications of hyaluronan

HA is a biocompatible polysaccharide with distinctive physicochemical characteristics. These properties render it highly versatile and applicable in numerous medical domains [8]. In the human body, the total quantity of HA is estimated to be around 15 g in a 70-kg adult [80]. While HA is predominantly present in the skin, constituting approximately 50% of the overall HA content in the body, it is also distributed throughout various other tissues and fluids. HA can be found in the vitreous humor of the eye, the umbilical cord, and synovial fluid, as well as in all tissues and bodily fluids. This includes skeletal tissues, heart valves, the lungs, the aorta, the prostate gland, and specific structures of the penis, such as the tunica albuginea, corpora cavernosa, and corpus spongiosum [80–85].

HA in arthrology

Autograft reconstruction is a commonly employed surgical technique for treating severe ligament injuries. However, this approach has limitations, including the risk of donor site morbidity. Tissue engineering techniques that involve culturing isolated fibroblasts on scaffold materials offer a promising alternative to autografts [86, 87]. Successful regeneration in ligament and tendon tissues has been demonstrated through various scaffold materials. These scaffolds encompass both naturally occurring substances and synthetic materials. An effective strategy for ligament tissue engineering involves incorporating glycosaminoglycans (GAGs) or GAG-like materials as essential scaffold components [88]. The principal constituent of GAGs, integral components of extracellular matrices, has been proven to promote tissue healing in diverse tissue types. It is achieved through several mechanisms, including enhanced delivery of growth factors, improved cellular adhesion and proliferation, and the facilitation of anti-inflammatory response [89–91]. HA's biological effects could play a critical role in promoting the regeneration of ligament tissues. Moreover, the use of HA and hylans for intra-articular treatment has gained broader acceptance as a therapeutic approach for managing pain associated with osteoarthritis [92, 93]. HA plays a crucial role in maintaining the viscoelastic properties of synovial fluid in the knee. In osteoarthritic joints, HA concentration is typically lower than in healthy joints. Therapy aims to restore the lost viscoelastic properties of synovial fluid by introducing HA. This can help alleviate osteoarthritis pain by reducing nerve impulses and sensitivity associated with the condition [94–96].

HA for eye drops and ophthalmic surgery

Hyaluronan possesses distinctive characteristics, such as stabilization of the reduction of friction during blinking, tear film, and prevention of harmful substances from binding to the eye due to its various properties such as viscoelasticity and hydrophilicity, which greatly diminish the signs of dry eye [8, 97, 98]. Its viscoelasticity is mainly related to its cushioning and lubricating effect, as it is a component of the eye (aqueous humor) and synovial fluid. This unique rheological property is exploited in applying hyaluronan in ophthalmic surgery, where it is mainly used to establish and maintain a secure status to progress healing of the postsurgical area [30, 99]. The benefits of HA in ophthalmology extend to various aspects. HA aids in stabilizing the tear film, reducing healing time, minimizing adhesion risk, decreasing free radicals' formation, and normalizing intraocular pressure. The rheological properties of sodium hyaluronate have been examined for ophthalmic viscosurgical device (OVD) applications during cataract surgery. It has been concluded that the viscoelastic and flow properties of binary formulations consisting of sodium hyaluronate and HPMC (hydroxypropyl methylcellulose) are suitable for use as OVD. These formulations effectively maintain the ocular spaces and can be administered quickly [100, 101]. Furthermore, the adhesive properties of both sodium hyaluronate and HPMC in the binary formulation provide an additional advantage. These properties enable the formulation to effectively interact with the corneal endothelium, resulting in durable protection of ocular tissues. This interaction enhances the overall efficacy and safety of the formulation in maintaining ocular health during surgical procedures or therapeutic interventions [98, 102, 103].

HA in wound healing and tissue repair

CD44, the primary receptor for HA, is a versatile transmembrane glycoprotein expressed in various isoforms and found in nearly all human cell types. CD44 can interact with HA and various growth factors, cytokines, and extracellular proteins. This comprehensive interaction profile allows CD44 to participate in diverse cellular processes and signaling pathways involved in development, tissue homeostasis, inflammation, and cancer progression. The ability of CD44 to engage with multiple ligands highlights its significance as a critical regulator of cell adhesion, migration, proliferation, and signaling events within the extracellular microenvironment [104]. The interaction between HA and CD44 is implicated in many intracellular signaling pathways that govern various cell biological processes. These processes include receptor-mediated internalization and degradation of hyaluronan, angiogenesis (the formation of new blood vessels), cell migration, proliferation (cell growth and division), aggregation (cell clustering), and adhesion to extracellular matrix (ECM) components. The HA-CD44 interaction is a critical modulator of

these cellular activities, contributing to tissue development, wound healing, immune response, and other physiological and pathological processes [105, 106]. CD44 emerges as a pivotal player in inflammation and wound healing, encompassing intricate biological processes to restore damaged tissue. Throughout all phases of tissue repair, including cellular migration, inflammation, angiogenesis (formation of new blood vessels), remodeling, and scar formation, extracellular matrix components, including HA, exert significant regulatory influence. CD44, through its interaction with HA and other molecules, exerts precise control over these sequential events, orchestrating the complex interplay required for effective tissue repair and regeneration [107]. HA is a fundamental component of the ECM and possesses distinctive properties contributing to its crucial role in tissue regeneration. Besides its structural support, HA can also function as part of a feedback loop, promoting cell proliferation and migration in actively growing tissues. This interaction between HA and cells helps regulate critical tissue development, repair, and regeneration processes. HA contributes to the dynamic balance required for effective tissue growth and remodeling by influencing cell behavior [108]. Furthermore, the role of HA in maintaining water homeostasis can contribute to tissue hydration, which in turn has a beneficial impact on the healing process. During periods of rapid tissue proliferation, regeneration, and repair, there is an increase in HA levels. This heightened presence of HA helps retain moisture, providing a hydrated microenvironment that supports cellular activities and facilitates optimal conditions for tissue healing and recovery. The ability of HA to regulate water balance within tissues underscores its significance in promoting efficient healing processes [109, 110]. As HA is implied in every step of the wound healing procedure, exogenous application of HA can provide faster healing.

HA in odontology

In dentistry, biological materials such as HA have a broad range of applications, including regeneration and reconstruction of dentine, gingiva, dental pulp, cancellous bone, mucosal wound repair, and constructing a biophysical barrier between gingiva and jaw bones [111]. HA can act as a biocompatible scaffold or niche for mesenchymal stem cell (from apical papilla) differentiation, polarity, and a biophysical trigger or reservoir for the controlled release of various cytokines and chemokines for paracrine and autocrine signaling [112]. Additionally, HA can neutralize bacterial hyaluronate lyase enzymes, exerting a bacteriostatic effect.

Oral ulcer

Recurrent aphthous stomatitis (RAS), known as canker sores, is the most prevalent inflammatory ulcerative condition affecting the oral mucosa. However, the management of oral ulcers remains a challenge for clinicians. While topical corticosteroids, antibiotics, and antimicrobial agents are widely used, there are feeble proofs supporting the efficacy of any topical therapy. For these molecules to be effective, they should be easily applicable and preserved at the site of mucosal ulcer (MU) for an extended period [113]. Several studies have explored HA as a topical remedy for MU of the oral cavity. Notably, topical treatment of chronic aphthous MU with 0.2% HA gel for two weeks has promoted healing without side effects. Lee et al. demonstrated the effectiveness of topical 0.2% HA gel in treating oral MU in patients with RAS and Behçet's disease, suggesting improved symptoms [114, 115]. Hence, the primary activity of HA appears to be in tissue regeneration, performing a wide range of biological activities, including activating phlogistic responses, aiding cellular differentiation, proliferation, migration, and vasculogenesis, and reducing collagen deposition and scarring [116].

Gingivitis and periodontitis

Gingivitis is a highly prevalent disease that affects 82% of the population. Dental plaque has been identified as a crucial etiological factor in developing gingivitis and periodontitis [117]. Consequently, treating gingivitis and periodontitis aims to reduce dental plaque accumulation. In vitro studies have demonstrated that HA inhibits bacterial growth and interferes with bacterial morphology [118, 119]. Regarding clinical studies, it has been found that HA reduces plaque accumulation and inhibits gingival inflammation. A survey by Gizligoz et al. examined the plaque inhibitory impact of HA mouthwash compared to chlorhexidine. It was found that HA revealed an almost similar plaque inhibitory effect to chlorhexidine [120]. Jentsch et al. evaluated the effectiveness of the topical treatment of 0.2% HA. They concluded that it benefitted gingivitis by lowering the plaque indices and improving the papillary bleeding index (PBI) concerning gingival crevicular fluid (GCF) variables [121]. Similarly, Pistorius et al. proposed that the topical application of a HA reduced the PBI and sulcus bleeding index (SBI) [122]. Additionally, Sahayata et al. claimed that oral application of 0.2% HA gel in gingivitis, in addition to dental scaling and oral hygiene, offered a successful consequential response in the gingival index (GI) and PBI of placebo or control group (scaling plus placebo gel) and negative control group (scaling only) [123]. Dental scaling and root planning with topical HA are beneficial therapies

for controlling gingivitis and probing depths (PDs) in individuals with chronic gum disease. Annsofi Johannsen et al. explained the beneficial effects of HA-based formulations in treating periodontitis [124]. The adjunctive application of hyaluronan gel could benefit periodontal health. The hyaluronan-based scale and root planning (SRP) protocol resulted in statistically significantly more significant reductions in abnormal dental bleeding in SRP control. Additionally, Hyaluronan has also been proven to induce bacteriostatic effects in vitro [124].

Surgery

In a comparative analysis, the health status of peri-implant mucositis and peri-implantitis during the recovery period of functional implants using HA or CHX gels. Their results demonstrated a reduced bleeding index in the HA group compared to the control group managed with CHX. Therefore, treating peri-implant mucositis and per-implantitis patients with 0.2% HA gel may be beneficial. Ballini et al. proposed combining autologous bone graft with the esterified low-molecular HA formulation can accelerate bone regeneration in periodontal intrabone anomalies [125]. Additionally, the topical spray of 0.2% HA proved beneficial in managing inflammation and trismus during postoperative surgeries. Romeo et al. also demonstrated that the utility of essential amino acids with 1.33% HA solution could aid in secondary intention healing in laser-induced wounds during the total excisional biopsy of the gingiva and palate of the oral cavity [126]. Although it is not beneficial in pain perception, it can considerably expedite the repair processes [119].

HA in bioinks for 3D bioprinting

Manufacturing a three-dimensional (3D) object by layer-wise deposition or combination of materials, including plastics, metals, ceramics, powders, liquids, and living cells, is called 3D printing. When utilized in biomedical engineering and regenerative medicine to produce complex biological scaffolds or viable tissue structures that in vivo tissues and organs, 3D printing technology is referred to as 3D bioprinting; it holds immense potential for the fabrication, personalized prosthetics, precision implants, and histological models, and for pharmaceutical interventions such as controlled drug delivery, and microphysiological systems or organ-on-chip based drug discovery and development [127–129]. In 3D bioprinting, bioink is the main component, and different biomaterials are utilized as bioinks that are evaluated for crucial properties to ensure ease in the process [130]. It is imperative that bioinks possess high biocompatibility and physiological relevance to nurture viable cells, are mechanically sturdy after printing, and offer precise resolution during 3D printing. Therefore, biophysical characteristics, such as extrusion compatibility and mechanical properties, fluidic nature, viscosity, biodegradability, and cytotoxicity, must be evaluated [131]. Among the leading bioprinting materials used in 3D bioprinting to develop biological structures is HA, a natural ECM. HA is primarily employed because of its biological integrity, elasticity, mechanical and biodegradation properties, mimicking ECM composition, self-assembling ability, and yielding good resolution during printing [132]. To obtain increased stability and cell viability, HA can also be combined with different semi-synthetic or chemically defined polymers, such as hydrogel polymers, which exhibit stable rheology properties and excellent biocompatibility, resulting in gels that demonstrate printability in good shape. This development of biomaterials and cell biology has paved the way for bionic and regenerative medicine to become vital research fields with fast growth [133].

HA in cancer therapy

Cancer is a significant contributor to morbidity and mortality globally, with an estimated 18.1 million new cases and 9.6 million deaths reported in 2018 [140]. In recent decades, the progress of nanotechnology in medicine has offered new and promising solutions and insights for detecting, preventing, and treating cancer [143, 144]. HA plays a crucial role in various aspects of cancer cell behavior, primarily through its interactions with the stromal environment. The dysregulation of HA synthesis and the subsequent overproduction of HA often occur during the malignant transformation of cells. The impact of HA on tumor development can vary depending on the specific circumstances being evaluated, as it has the potential to either suppress or support tumor growth [146]. Extensive research has provided substantial evidence regarding the role of hyaluronan in promoting malignancies. It has been observed that increased invasion and dissemination of cancer cells can be attributed, at least in part, to the mesenchymal conversion facilitated by HA overexpression [147]. Experimental studies have demonstrated that various components of the hyaluronan signaling pathway, such as HA synthases, HA receptors, and HYAL-1 hyaluronidase, significantly promote tumor growth, metastasis, and angiogenesis. These findings highlight the potential of targeting each component as a therapeutic approach to cancer treatment [148]. The role of hyaluronan in cancer progression can vary depending on the expressed isoforms of HA synthases (HAS). Cancer cells at different stages may utilize the three HAS isoforms differently to enhance their survival. This suggests that the specific isoform of HAS expressed by cancer cells could influence their

behavior and response to treatment, highlighting the importance of considering the isoform-specific effects of HA in cancer research and therapy [149]. Multiple strategies have been devised to target different HA (hemagglutinin) family members. These strategies encompass small-molecule inhibitors, antibody-based therapies, and vaccine-based interventions [150]. These treatment approaches aim to block the intracellular signaling mediated by HA, which is critical in promoting tumor cell proliferation, motility, invasion, and the induction of endothelial cell functions. HA has been incorporated into nanoparticle formulations to achieve targeted delivery of chemotherapy drugs and other anticancer compounds to tumor cells. These preparations take advantage of the interaction between HA and cell-surface HA receptors, offering several advantages, such as being nontoxic, nonimmunogenic, and amenable to modifications for enhanced efficacy [148, 151]. The utilization of HA nanosystems shows great potential in facilitating the targeted and safe delivery of chemotherapeutic drugs and other anticancer compounds specifically to tumor cells. By leveraging the unique properties of HA and its interactions with cell-surface receptors, these nanosystems can enhance the specificity of drug delivery while minimizing potential adverse effects on healthy tissues. This targeted approach holds promise in improving the efficacy and safety of cancer treatments [152]. The utilization of HA nanoparticles offers several advantages in anticancer therapy. One such advantage is the ability to improve the half-life of anticancer agents and concentrate their delivery to cells that overexpress HA receptors. This targeted approach enables the potential for enhanced effectiveness at lower doses, leading to reduced drug-related toxicities. Many antineoplastic drugs have been successfully conjugated to hyaluronic acid, developing novel compounds with promising antitumor effects. For instance, HA-modified polycaprolactone nanoparticles encapsulating naringenin have demonstrated encouraging results. In vitro studies have shown enhanced drug uptake by cancer cells, indicating improved cellular internalization. Furthermore, in vivo experiments on rats with urethane-induced lung cancer revealed inhibited tumor growth following treatment with these nanoparticles. This highlights the potential of HA-based formulations to enhance therapeutic outcomes in cancer treatment [153]. Furthermore, it has been observed that HA-coated chitosan nanoparticles facilitate the delivery of 5-fluorouracil specifically to tumor cells that overexpress the CD44 receptor. The HA coating on chitosan nanoparticles enhances their affinity to CD44 receptors, enabling targeted drug delivery. This targeted approach improves the uptake of 5-fluorouracil by tumor cells and enhances its therapeutic efficacy against cancer. This finding underscores the potential of HA-coated chitosan nanoparticles as a promising strategy for improving drug delivery and enhancing the effectiveness of anticancer therapies [154, 155]. Paclitaxel, a widely studied compound, has demonstrated significant potential as an anticancer agent. However, its poor solubility in water has limited its therapeutic use. Recent research has focused on addressing this challenge by exploring novel approaches, such as utilizing unsaturated derivatives of HA and various HA-paclitaxel conjugates. These innovative strategies aim to enhance the aqueous solubility of paclitaxel and improve its delivery to target cancer cells. Researchers have sought to overcome its solubility limitations and enhance its therapeutic efficacy by conjugating paclitaxel to HA. Additionally, this approach can potentially reduce drug-related toxicities associated with conventional formulations. Furthermore, other anticancer agents are successfully linked to HA beyond paclitaxel, aiming to overcome toxicity and impart new physicochemical characteristics to the drug. These efforts seek to improve drug stability, enhance targeted delivery, and optimize therapeutic outcomes. These advancements in HA-based conjugates and derivatives showcase the potential of HA as a versatile platform for improving the delivery and efficacy of various anticancer agents. Such research holds promise for developing safer and more effective treatments for cancer patients [105, 156]. Eurand Pharmaceuticals implemented a similar strategy using methotrexate (MTX), an antimetabolite and folic acid analog commonly used as an antineoplastic drug. They developed an HA-MTX conjugate and conducted studies to evaluate its efficacy. The HA-MTX conjugate demonstrated significant activity in a liver metastasis tumor model, indicating its potential in treating metastatic liver tumors. Additionally, it exhibited activity in a mammary carcinoma model, demonstrating its effectiveness in combating breast cancer. These findings highlight the promising therapeutic potential of the HA-MTX conjugate in targeting and treating neoplastic conditions. By conjugating MTX with HA, the researchers aimed to enhance drug delivery, potentially improving the treatment outcomes and reducing adverse effects associated with conventional MTX formulations. This research demonstrates the valuable application of HA-based conjugates in expanding the therapeutic options for anticancer drugs like MTX, potentially offering more effective and targeted treatments for liver metastasis and mammary carcinoma [157]. Toxicology and

pharmacokinetics analyses have displayed an extended half-life and amplified area under the curve (AUC) worth concerning free MTX [158]. Recent work has highlighted the importance of hyaluronan in oncology and should be further researched.

HA for skin

The skin serves as a homeostatic indicator of overall physical and emotional well-being. Alterations in dermal characteristics such as temperature, tone, muscle tension, and hydration reflect somatic and emotional changes that occur in an individual, with the latter being beyond conscious control [134]. Skin aging is a complex, progressive, and irreversible process marked by biochemical, morphological, and biophysical changes in the body. With the global population aging and the increasing aesthetic demands of patients, the desire to appear youthful and healthy is gaining momentum. In the past, surgical interventions were the primary option for rejuvenation [135]. However, novel noninvasive outpatient techniques have revolutionized aesthetic dermatology. Injectable fillers, in particular, have garnered considerable attention due to their efficiency and safety [136]. Wrinkle filling remains a primary indication, but restoring volume and contours to achieve a natural, balanced look is equally vital in contemporary aesthetics. Additionally, advanced techniques have been developed to correct chin/nose deformities, and it is preferable to use biodegradable agents for aesthetic dermatology instead of permanent ones [137, 138]. Complications arising from using permanent agents in aesthetic dermatology can be particularly challenging to treat compared to those associated with biodegradable agents. Fortunately, a range of skin treatments, including injectable hyaluronic acid-based fillers (HAFs), are available to address age-related changes [139]. Fillers constitute an effective tool in skin rejuvenation, and while bovine collagen was previously the primary filler used for wrinkles and lip augmentation, since 1996, HA has become the preferred choice. Modern HA is produced through bacterial fermentation, eliminating the risk of animal-derived contamination, and because it is not species-specific, skin testing is not required [137, 140]. Recent statistics suggest that over 85% of dermal filler surgeries utilize HA derivatives. This figure will rise in the future, as no other potential filling agent is currently available to counter HA's popularity [141]. HA's efficacy, ease of administration, low toxicity, and high safety profile have made it the gold standard compound among fillers, and the list of cosmetic dermal fillers available continues to expand rapidly [142]. As the aging population seeks inexpensive and safe options to revise the signs of aging without major surgery, the popularity of HA-based fillers is only expected to increase [142].

The strength of HA to cross the biological barrier is primarily determined by its molecular weight (MW). High-MW HA, with a weight exceeding 600 KDa, has poor skin permeability and typically forms a very thin protective hydration veneer on the epidermis [45]. In contrast, low-MW HA can penetrate through the deeper layers of the skin and permeate up to the hypodermis level. Thus, using HA enables a comprehensive rejuvenation of the face, as thin HAs can be administrated by mesotherapy to rehydrate the skin's surface. In contrast, high-MW HAs have been used to address wrinkles, nasolabial folds, dark circles, under-eye hollows, and lip augmentation. High-MW HAs are also employed for tissue volume increase, highlighting the versatility of this approach [19]. Due to its unique viscoelasticity, biocompatibility, biodegradability, and non-immunogenicity, HA has been extensively applied in dermatology for its biomedical benefits, including skin anti-aging, anti-wrinkle, anti-nasolabial folds, skin rejuvenation, and dermal hydration properties [143]. HA can be administered through various routes, including ophthalmic, nasal, parenteral, topical, and intravenous, and in clinical, nutraceutical, nutritional, and cosmetic industries. Topical delivery systems offer several advantages over oral or parenteral delivery modes, such as overcoming the hepatic first-pass metabolism, improved prognosis, excellent dermal barrier permeability, and minimizing possible toxicity-related clinical adverse or side effects [45]. HA has been utilized to formulate microparticles for controlled dermal release of caffeine to medicate cellulite, topical hydrogels containing nonsteroidal anti-inflammatory drug diclofenac to manage actinic keratosis, and for manufacturing, HA-derived liposomes for healing dermal and subcutaneous wounds [45]. HA has also been extensively utilized for preparing transdermal formulations through various approaches, such as chemical tempering to create conjugates or physiochemical methods to create microneedles, including OVA-HA conjugates for noninvasive vaccination and HA-based microneedles for controlled release of insulin to treat Type I diabetes [144]. In current cosmetic trends, HA is commonly found in moisturizers, creams, gels, and serums due to its hydrating properties, lipid barrier enhancement, fine lines and wrinkles reduction, and skin tightening effects. Moreover, sunblock derived from hyaluronan may assist in preserving spry skin and shielding it against the detrimental impact of ultraviolet radiations attributed to HA's potential free radical scavenging effects. Overall, HA's diverse and promising applications in various fields of medicine and cosmetics

have established it as a highly desirable and versatile biomaterial.

Covid-19 and hyaluronic acid

In modern times, the coronavirus disease 2019 (COVID-19) pandemic posed a severe threat to international biosecurity and public health. The etiology of this respiratory illness is a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical investigations revealed that SARS-CoV-2 infection triggers a biphasic immune response. During the initial incubation period, a first-line defense-based protective phase is activated, which requires the activation of the adaptive immune system to intercept the virus replication and disease progression to severe stages. Therefore, strategies to enhance immune responses at this stage are paramount [145]. To establish an effective host immune response during the disease incubation period, the host must be in good physical condition, which can induce peculiar antiviral immunity. However, if the adaptive immune response is compromised, the infection will continue replicating, leading to massive tissue damage, particularly in tissues with high ACE2 expression [146]. This triggers an inflammation-driven damaging phase characterized by lung parenchymal tissue inflammation mediated primarily by alveolar macrophages and other granulocytes. Pneumonitis is the primary etiology of lethal upper and lower respiratory tract disorders during the severe stage of the disease. Hence, suppressing the proinflammatory system is critical to managing the clinical symptoms when severe damage to lung parenchyma occurs. SARS-CoV-2 infection is classified into three different stages: stage I is an incubation phase when the patient is usually asymptomatic and sometimes the virus cannot be detected in body specimens; stage II, a non-critical symptomatic phase with detectable viral immunogens; and stage III, an extreme respiratory or general symptomatic stage with elevated viral load in the body. Histopathological examinations of the tissues collected from COVID-19 patient atopies revealed edema and the presence of abnormal hyaline membrane pulmonary mesenchyme, forecasting the existence of acute respiratory distress syndrome (ARDS) [147].

Hyaluronan, a primary constituent of the lung extracellular matrix (ECM) in the lungs, is found in the pulmonary mesenchymal tissue. It is a key player in airway homeostasis by regulating cellular functions, growth factors, cytokine behavior, and biomechanical forces, among other aspects [148]. In various respiratory diseases, such as COPD, atypical asthma, idiopathic arterial pulmonary hypertension, and ARDS, airway hyaluronan levels are elevated and are associated with poor lung function [149, 150]. Furthermore, there is mounting evidence that hyaluronan and its degradation products are of critical significance in the pathophysiology of the respiratory tract. Aerosolized exogenous hyaluronan has been shown to exert beneficial effects against airway inflammation, protect against bronchial hyperreactivity and remodeling, and disrupt biofilms associated with chronic infections [151, 152]. Therefore, exogenous hyaluronan may serve as a novel therapeutic option in conjunction with conventional medical or surgical therapy for respiratory tract diseases involving inflammation, epithelial survival, remodeling, and the microbiome, such as rhinitis, asthma, COPD, cystic fibrosis, ARDS, and pulmonary hypertension, and should be considered for COVID-19 treatment [153, 154].

Hydroxychloroquine is currently one of the leading drugs being investigated worldwide for COVID-19 [155]. To mitigate its intrinsic toxicity, enhance its bioavailability, localization, and controlled release, and improve its efficacy, a proposal has been developed to conjugate it with HA to formulate a hyaluronic acid-hydroxychloroquine conjugate [156]. The ability of hyaluronic acid to form conjugates with pharmacologically active compounds offers an opportunity for this approach [157]. However, no clinically approved immunoglobulins or specific therapeutic drugs are available for COVID-19. Rigorous research is ongoing to screen potential therapeutic targets that may aid in developing effectual prevention and successful treatment strategies [158].

HA in drug delivery

Conjugating active ingredients to HA can create prodrugs with efficient physicochemical features, improved shelf life, stability, and therapeutic potency and safety compared to free drugs [2]. Since hyaluronan possesses multiple physiochemical properties, HA-drug conjugates can exert their biological activities as such. Moreover, therapeutic actions can also be achieved upon drug release when the chemical bonds linking active ingredients and HA are catalyzed in the biological system, ideally at the peculiar target sites [48, 159]. A diverse range of active ingredients can be compounded into HA for topical or intravenous application. HA is primarily utilized in controlled release or targeted drug delivery systems because of its excellent biocompatible gelation properties. One example is a polymer network created by gelating the adipic dihydrazide derivative of HA cross-linked with reagent poly (ethylene glycol)–propionaldehyde. This macromolecule gives rise to a hydrogel [72, 160]. Transdermal drug delivery using HA is possible, but the challenge lies in that HA, a high molecular weight compound, cannot cross the stratum corneum. To overcome this issue, nanoparticles of HA can be utilized, which can deliver the drug to the dermis. Moreover, bioavailability

has always been a limitation in ocular drug delivery due to various barriers [161, 162]. However, coating chitosan-based nanoparticles with HA can increase the cornea's retention time, thereby enhancing dexamethasone's bioavailability by almost two times. These nanoparticles are also suitable for gene delivery, as they are highly compatible with the mucous and ensure efficient transfer without loss of cell viability [163]. During eye-related surgeries, HA is employed to equilibrate the morphology of the frontal chamber. HA-based nanoparticles (NPs) in polymeric thin films can also serve as a hybrid therapeutic system for the controlled release of vitamin E to manage skin wounds [164]. HA formulations with phospholipids can develop surface-modified liposomes before or after liposome formulation [165]. HA-modified liposomes have shown great promise as drug carriers. They enhance drug stability in the dynamic blood flow, extend drug half-life, lower toxicity, improve tissue absorption and barrier permeability, sustain prolonged or controlled active ingredient release, and enhance therapeutic efficacy through synergistic actions [166]. HA and its derivatives have a strong affinity for CD44 receptors, specific receptors in cancerous tumors [167]. This makes HA an ideal candidate for targeted and effective delivery of anticancer drugs, given its high biocompatibility, non-immunogenicity, and non-toxicity [105]. Many approaches, like nanotheranostics and nanocarriers such as carbon tubes, quantum dots, and graphene, are used in conjugation with HA to achieve an efficient delivery system. In addition to anticancer drugs, HA is also used to deliver genes and proteins. HA-based microspheres and microparticles have been investigated as potential combinational compounds to enhance the bioadhesive properties, control drug delivery, and improve the ointments'

Table 1 Summarizing different types of HA forms available, their properties, and potential applications

Type of HA	Molecular weight	Properties	Potential application	Reference
Nanofibers	15–150 kDa	High porosity Mechanical strength Flexibility compared to microfibers Large surface area-to-volume ratio	Wound dressing Scaffolds for tissue engineering Drug release delivery systems Serums for cosmetics Nano masks Coatings for medical devices	[171–175]
Microfibers	100–700 kDa	Solubility is adjustable Different textile technologies can weave it Sterilizable	Tissue regeneration Pre- or postsurgical use Drug delivery or another active ingredient delivery Controlled release delivery system	[176–178]
Staple fibers	350 kDa–2.7 M	It can be loaded with growth factors or MRI contrast agents It can be combined with other HA forms for multilayer applications	Drug delivery and drug release materials Active layers for wound healing devices 3D structures Antiseptics Hemostatic Pads Scaffolds with GFs	[179–182]
Hydrogels	60–1000 kDa	Fully biocompatible and biodegradable Possible to incorporate cells, fibers, micro or nanoparticles, or active substances	Scaffolds Regenerative medicine Viscosupplementation Postsurgical adhesion Reservoir drug release Wound healing Cartilage tissue engineering Bioprinting Contact lenses preparation Super porous hydrogels in hygiene products	[73, 183–185]
Thin Films	15–1000 kDa	Swelling, degradation rates, and mechanical properties can be controlled by the type of modification and the degree of substitution	Prevention of postoperative adhesions Tissue engineering (cell sheets) Controlled release of active substances or growth factors Soluble or insoluble options Controlled dissolution materials Transparent or colored	[78, 180, 186, 187]
Micelles	10–20 kDa	Self-assembly into polymeric micelles with distinctive core–shell structures Non-covalent encapsulation of poorly water-soluble drugs HA in the shell can be used as a targeting molecule	Dermatology Topical applications and carrier system Enhancing penetration of encapsulated compounds into skin, hair, and nails Drug delivery systems—Parenteral applications	[52, 188–191]

physical quality. For instance, spray-dried HA-based microspheres have shown precision delivery of ofloxacin to the pulmonary tissues via nasal inhalation. This leads to better pharmacological impact than free ofloxacin and intravenous or oral routes of administration. HA and its derivatives have been utilized alone or in conjugates to formulate pro-drugs, surface-modified liposomes, NPs, microparticles, hydrogels, and other controlled drug delivery carriers [168, 169]. All these drug delivery systems are subject to intensive pharmaceutical optimization for harnessing the maximum benefits. This extensive biomedical and clinical reach is still in its infancy, as most of the findings are based on in vitro experiments, and there is a long way to go for the industrialization of HA-based pharmaceutical products [170].

Conclusion

This paper comprehensively overviews the natural biopolymer HA and its unique physicochemical characteristics, including biodegradability, biocompatibility, efficacy, safety, and immunogenicity (Table 1). HA has been generally utilized and proven successful in various biomedical applications, including controlled drug delivery and release, osteoarthritis treatment, open-wound healing, ocular surgery, odontology, cosmetology, regenerative medicine, and biomedical engineering. Extensive research from academia and the biomedical industry has been carried out to understand the various derivatives of HA and their applications. The game-changing potential of HA has been a driving force for this research. The application of HA for 3D bioprinting has also been discussed, along with its proposed use in combating the current COVID-19 crisis. Overall, the versatility and potential of HA make it a promising candidate for numerous future biomedical applications, and continued research in this field will undoubtedly yield more significant findings.

Future perspective

Looking ahead, the future perspective of HA and its formulations are propitious and diverse, with ongoing research indicating novel applications and opportunities in various fields. Genetic manipulation of the HAS synthase enzyme and isoenzymes in cancer therapy offers a new approach to combat cancer progression. At the same time, research into identifying cancer-associated HAS proteins presents new opportunities for cancer therapy. In regenerative medicine, HA derivatives have significant implications for immunomodulation, angiogenesis, nerve regeneration, and hybrid materials, suggesting new avenues for treating novel diseases such as COVID-19. In addition to cancer therapy and regenerative medicine, HA can potentially treat chronic inflammation, cardiovascular disease, and neurodegenerative disorders, with new and innovative applications emerging continually. For example, HA-based hydrogels are being explored for controlled drug delivery and drug release, biotechnology, and biosensors for detecting disease biomarkers. At the same time, HA is being investigated as an adjuvant in vaccines for infectious diseases.

Furthermore, 3D bioprinting using HA-based bioinks shows significant potential for tissue engineering and regenerative medicine. Advances in genetic engineering and biotechnology offer the production of tailored HA derivatives with enhanced properties and functionality, expanding the scope of its applications. Hyaluronic acid has also shown promising results in wound healing and skin regeneration, making it a popular ingredient in cosmetic products. At the same time, its potential in treating eye disorders and orthopedic applications is being actively researched. Its biocompatibility and ability to mimic natural ECM components make it an ideal candidate for bioengineering and implant coatings. At the same time, its presence and expression level can be correlated with disease severity and progression, making it a valuable tool for diagnosis and monitoring. As our understanding of HA and its properties continues to evolve, the possibilities for its applications and potential in biomedical research are vast. The future of HA and its derivatives looks bright, with continued research offering the potential for developing innovative therapies and treatments.

Abbreviations

HA	Hyaluronic acid
CAGR	Compound annual growth rate
ROS	Reactive oxygen species
pHA	Palmitoyl esters of hyaluronan
GAGs	Glycosaminoglycans
OVD	Ophthalmic viscosurgical device
ECM	Extracellular matrix
HAS	HA synthases
MTX	Methotrexate
AUC	Area under the curve
RAS	Recurrent aphthous stomatitis
MU	Mucosal ulcer
PBI	Papillary bleeding index
GCF	Gingival crevicular fluid
SBI	Sulcus bleeding index
PDs	Probing depths
SRP	Scale and root planning
3D	Three dimensional
NPs	Nanoparticles
COVID-19	Coronavirus disease 2019
ARDS	Acute respiratory distress syndrome

Author contributions

ARCS and HMUF were involved in data collection and analysis, manuscript writing. HA and PRK helped in manuscript writing, editing, coordination. SN assisted in supervision, manuscript editing. NM contributed to manuscript structure, conceptualization, administration, supervision. All authors have read and approved the manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
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