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Review Article

Hyaluronic Acid and its Potential Use in Various Medical Fields

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ABSTRACT

Hyaluronic acid is a naturally occurring glycosaminoglycan which is found throughout the tissues like connective tissue, epithelial tissue and the neural tissue .It has gained a significant attention due to its unique physicochemical and biological properties . It has a high biocompatibility, viscoelasticity and capacity to retain moisture makes it a versatile biomaterial across diverse medical fields. This review has information about the application of hyaluronic acid in medical field, including ophthalmology, orthopaedic, dentistry and tissue engineering. Hyaluronic acid has role in wound healing, drug delivery and regenerative medicine. Despite its widespread use challenges regarding the standardization ,long term safety and cost effectiveness are some disadvantages of hyaluronic acid-based therapies. Hyaluronic acid is a highly adaptable and valuable molecule across multiple disciplines. With more advancements a greater application in future particularly in the regenerative medicine and personalised therapies.

INTRODUCTION

Hyaluronic acid is a glycosaminoglycan widely distributed in the connective , epithelial and neural tissue of the human body. It has a simple ,unbranched structure of repeating disaccharide units , thus hyaluronic acid plays a vital role in maintaining tissue hydration, structural integrity and cellular communication .Unlike other glycosaminoglycans hyaluronic acid is not attached to a protein core ,making it unique in structure and function .It is biocompatible , hygroscopic in nature and viscoelasticity have made the molecule an indispensable molecule both physiologically and therapeutically. Over the years hyaluronic acid is been recognized as a biological lubricant to becoming a key component in a broad range of clinical, pharmaceutical and cosmetic applications. Hyaluronic acid is been used for wound healing and supporting joint health to enabling targeted drug delivery and also cosmetical.

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The intrinsic properties of hyaluronic acid that is biocompatibility, biodegradability and non-immunogenicity make it an attractive candidate for a wide range of scientific and industrial application. A crucial component in medical therapies such as wound healing by modulating inflammation and promoting tissue repair. Hyaluronic acid use is wide in various industries it is been used for various other purposes

Historical background :-

The discovery of hyaluronic acid took place back in year 1934 when Karl Meyer and John Plamer first isolated the substance from the vitreous body of bovine eyes at Columbia university. Initially it was named for its high uronic acid content and its presence in hyaloid tissue, hyaluronic acid soon captured scientific interest due to its unique properties. In 1950s the extraction of hyaluronic acid was done on a large scale form animal tissues, particularly from rooster combs for use in medical application such as ophthalmic surgery.[1] The 1970s and 1980s marked a shift as researchers developed a method for hyaluronic acid production from bacterial fermentation methods .This method significantly reduced the risk of reactions and contamination associated with animal derived hyaluronic acid sources. This biotechnological advancement lead to broader use of hyaluronic acid in cosmetic and pharmaceutical use. Today, hyaluronic acid is not only a Visco-supplementation therapied and dermal filler it is also used in drug delivery systems and regenerative medicine strategies.

Chemistry and structure :-

- Chemical structure of Hyaluronic acid

The chemical structure of hyaluronic acid has a repeating disaccharide unit comprising D-glucuronic acid and N-acetyl-D-glucosamine, connected by alternating β-1,4 and β-1,3 glycosidic linkages, forms the linear polymer .[4] The basic repeating unit can be represented as following-

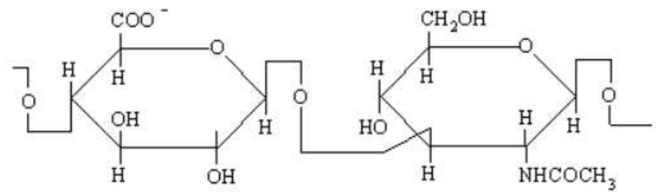


Figure 1-Chemical structure of hyaluronic acid

The polymer have molecular weight ranging from 10^4 to 10^7 Daltons and the weight depends on its source and method of production.

- Molecular weight variation

Hyaluronic acid molecular weight is a factor thar influence the physicochemical and biological properties[26] High molecular weight Hyaluronic acid(>1,000 kDa) -They typically exhibit anti-inflammatory and immunosuppressive effects. Low molecular weight hyaluronic acid (<500 kDa) – Hyaluronic acid of <500 kDa molecular weight can stimulate angiogenesis ,inflammation and cellular responses .

- **Physicochemical properties**

The highly hydrophilic nature of hyaluronic acid allow it to absorb and retain water up to 1,000 times of its weight. It is used in join lubrication and dermal filler because of its viscoelasticity property which provides both elasticity and viscosity depending on the applied force. Hyaluronic acid has polyelectrolyte behaviour that means it carries a negative charge under physiological pH influencing interactions with proteins, cells and other matrix molecules .

- **Synthesis**

The natural biosynthesis of hyaluronic acid in human body and other organisms is synthesized by a specific enzymes called as hyaluronan synthases (HAS) .The HAS is located on the inner side of plasma membrane .The main isoforms of HAS in humans are HAS1 , HAS2 , HAS 3 and each isoform produce hyaluronic acid of different lengths.[1][4] Traditionally hyaluronic acid was extracted from animal tissues such as rooster combs, umbilical cords ,synovial fluids. However this method were challenging because of reasons like risk of contamination with animal derived pathogens , batch to batch variability. To overcome this limitation microbial fermentation based synthesis is used for hyaluronic acid production .the main microorganisms used are *Streptococcus zooepidemicus* and some other genetically engineered non pathogenic bacteria .

- **Degradation and stability**

In vivo, hyaluronic acid is primarily degraded by the enzyme hyaluronidase and reactive oxygen species. Its natural half-life varies depending on its location — from 1–2 days in the skin and joints to minutes in the bloodstream. Chemical modifications like cross linking are often used to enhance HA's stability for longer-lasting biomedical and cosmetic applications.[1]

- **Mechanism of action**

Hyaluronic acid exerts its biological effects through both **physical** and **biochemical** mechanisms, depending on its molecular weight, concentration, and interaction with specific cellular receptors. Hyaluronic acid has an exceptional ability to attract and bind water molecule up to 1000 times of its own weight ,this property maintains tissue turgor, elasticity & volume particularly in skin ,eyes and cartilage. Viscoelastic property of under low stress or slow movements hyaluronic acid behaves like a viscous fluid for providing lubrication and under rapid movement it behaves elastically ny absorbing mechanical shocks . The interaction with cellular receptors to regulate cellular function .CD44 is a primary receptor for hyaluronic acid it is involved in cell adhesion, migration, proliferation and signalling pathways. RHAMM (receptor for HA mediated motility) regulates cell migration and tissue remodeling in case of wound healing and cancer metastasis. CAM-1 and LYVE-1 play a vital role in regulation of immune and lymphatic function [4] Hyaluronic acid has role in wound healing and tissue repair by modulating inflammation mostly low molecular weight hyaluronic acid fragments can stimulate response. Hyaluronic acid exhibit its anti-inflammatory action by inhibiting the pro inflammatory cytokine release also by supressing immune cell activation.

- **Pharmacokinetics**

The pharmacokinetics of hyaluronic acid including its absorption, distribution, metabolism, and excretion are influenced by factors such as molecular weight, route of administration, and degree of chemical modification.[4]

Absorption rate and plasma concentration

HA has limited absorption through the gastrointestinal tract due to its large molecular size. However, low-molecular-weight H fragments can be partially absorbed and are thought to exert systemic biological effects. Oral supplements primarily act by promoting endogenous HA synthesis or by exerting local effects in the gut lining.

After parenteral administration (e.g., intra-articular, intravenous, subcutaneous):

When injected directly into joints or tissues, HA remains localized at the site of administration for varying periods, depending on its molecular size and degree of crosslinking. It is slowly resorbed into systemic circulation. After *i.v.* injection of a bolus dose of Hyaluronic acid in rabbit the results were 98% of dose which was administered disappeared form systemic circulation within 6hrs after administration.

The topical administration: - Native HA has limited skin penetration due to its large size; therefore, low-molecular-weight derivatives or nanocarrier systems are used to enhance transdermal absorption.

Distribution

Hyaluronic acid is present in body tissue and fluids including the humour, synovial fluid, After absorption or injection, HA is primarily distributed in:

- The extracellular matrix of connective tissues (e.g., skin, joints, cartilage).
- The synovial fluid in joints.
- Eyes (especially the vitreous humor).

HA tends to accumulate at sites of inflammation or tissue remodeling, likely due to receptor-mediated mechanisms.

Metabolism

Endogenously, HA is continuously synthesized and degraded by Enzymatic degradation occurs primarily through hyaluronidases, which cleave HA into oligosaccharide fragments. Non-enzymatic degradation can also occur via reactive oxygen species (ROS), especially during inflammation or oxidative stress. Degradation typically occurs in:

- The lymphatic system,
- Liver (Kupffer cells and endothelial cells),
- Spleen and kidneys.

The half-life of HA depends on its location:

- Blood plasma: ~2–5 minutes,
- Skin: ~24 hours,
- Joints (synovial fluid): ~1–3 days,
- Vitreous humor: several weeks to months.

- **Excretion**

After enzymatic and non-enzymatic degradation into smaller fragments, hyaluronic acid and its breakdown products are eliminated primarily through the renal system [4] :

i. Renal Excretion:

Low-molecular-weight HA fragments (usually below 100 kDa) with the monosaccharides are filtered by the glomeruli in the kidneys and excreted in the urine. The kidney's filtration system is highly efficient at removing these small molecules, ensuring that degraded HA is rapidly cleared from the bloodstream. In humans, after intravenous administration, about 80–90% of HA degradation products are excreted through urine within 24 hours.

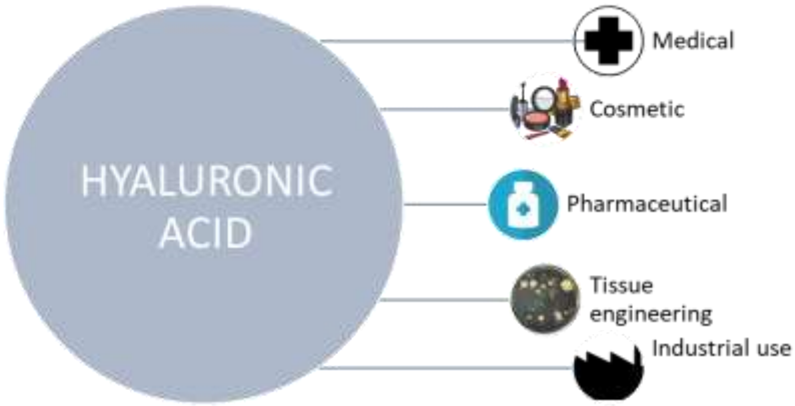
ii. Role of the Liver and Lymphatic System:

The liver, especially its Kupffer cells (specialized macrophages), plays a central role in clearing circulating HA by receptor-mediated endocytosis and lysosomal degradation. The hyaluronic acid fragments are drained by lymphatic system from the tissue to the systemic circulation .

Minor Routes:

A very small proportion of HA fragments may be metabolized by other tissues or eliminated through bile or feces, although this route is considered negligible compared to renal excretion.

Application of hyaluronic acid in various field -



A. Medical application

i) Hyaluronic acid in ophthalmology-

Hyaluronic acid plays a vital role in ophthalmology due to its presence in the eye and its unique viscoelastic ,lubricating and water retentive properties .Hyaluronic acid is a major component of the vitreous humour where it maintains gel like properties which is necessary for transmission of light and retinal support. It contributes in corneal hydration and supports the extracellular matrix of ocular tissues aiding in shock absorption and nutrient diffusion. Hyaluronic acid based viscoelastic solution are used widely in intraocular surgeries to maintain the shape of the anterior chamber. There are various eye drops available in market which acts for providing lubrication or as an adjuvant to eye tissue repair.

ii) Osteoarthritis treatment –

Osteoarthritis is joint disease which occurs by the breakdown of articular cartilage ,and leads to synovial inflammation or loss of joint function. Hyaluronic acid can be given as Visco supplementation which can restore the properties of synovial fluids by improving lubrication and shock absorption. Anti-inflammatory effects is inhibited by stopping the action of pro inflammatory cytokines and reduces the production of matrix metalloproteinases (MMPs) involved in cartilage breakdown. Hyaluronic acid also enhances the chondrocyte proliferation and inhibits the apoptosis of cartilage cells .

iii) Wound healing properties-

Topical formulation aid in wound management especially for burns, ulcers and surgical wounds. Hyaluronic acid promotes re-epithelization , angiogenesis and matrix remodeling while maintaining a moist wound environment.

B) Hyaluronic Acid in Biomaterials and Tissue Engineering –

Hyaluronic acid plays a pivotal role in as a major component of the extracellular matrix also it supports cellular functions such as adhesion, proliferation, and migration which makes it a suitable scaffold material for regenerating various tissue[34]

i. **Hydrogel scaffolds-** Used in cartilage regeneration thus helps chondrocyte function and matrix production. Skin tissue engineering- hyaluronic acid scaffolds promotes keratinocyte migration and wound closure. Neural tissue engineering they act by creating a supportive matrices for neural system cells and axon regeneration [13].
ii. **Composite Biomaterials-** Hyaluronic acid when combined with other biomaterials to

enhance the mechanical strength and biological performance

iii. **Injectable biomaterials** are developed for non invasive delivery into tissue defects.

iv. **Cartilage Repair:** Hyaluronic acid scaffolds provide chondrogenic support by maintaining chondrocyte phenotype and enhancing ECM synthesis. Hyaluronic acid based hydrogels are used in articular cartilage regeneration.

v. **Bone Tissue Engineering**: Hyaluronic acid is often combined with calcium phosphate or bioactive ceramics to create osteoinductive scaffolds that support osteoblast differentiation.

vi. **Skin and Wound Healing:** Hyaluronic acid based dressings enhance fibroblast activity, re-epithelialization, and angiogenesis. Its moisture retention and anti-inflammatory effects are beneficial in acute and chronic wound repair.

vii. **Neural Tissue Engineering:** HA hydrogels mimic brain ECM, supporting neural stem cell survival and differentiation. Injectable hyaluronic acid systems show promise for treating spinal cord injury and stroke.

viii. **Cardiac Tissue Repair [22]:** HA hydrogels have been explored as injectable matrices post-myocardial infarction to reduce scarring and support tissue regeneration.

C) Cosmetic use of Hyaluronic acid in aesthetic surgery

i. Dermal fillers [34] -

Hyaluronic acid based dermal fillers are used to restore the volume or smoothen the wrinkles and also enhance facial features. The dermal fillers are in form of injectable gels .The hyaluronic acid has hydrophilic nature and this attracts water . The hyaluronic acid has a short residence time and thus to improve the residence time the molecules are cross linked which leads to improvement of stability and viscoelasticity properties. Dermal fillers are widely used in aesthetic medicine for treating lip augmentation ,cheek contouring and tear trough correction. Some marketed Hyaluronic acid based filler brands are Juvederm®, Restylane®, and Belotero®.

ii. Breast surgery –

Hyaluronic acid has been trialled as a filler for the breast prostheses .Hyaluronic acid has been explored as a temporary soft tissue filler for minimal invasive breast augmentation. Macrolane® marketed by Q-Med is used for enhancing the breast volume during surgery.

D) Pharmaceutical application of hyaluronic acid –

Hyaluronic acid has a wide range of pharmaceutical application as it has a unique biological and physicochemical compatibility.[16]

i. Injectable drug delivery systems-

Intra-articular injections are used in treatment of osteoarthritis and hyaluronic has been approved for its treatment due to its ability to restore synovial fluid and relieve joint pain. There are various drug loaded hydrogels [15] where hyaluronic acid serves as a depot for controlled release of drugs such as corticosteroids, antibiotics and anticancer agents .

ii. Topical and transdermal delivery

Hyaluronic aid based creams ,gels and dressings also add up to epithelial regeneration, angiogenesis and collagen remodelling .Hyaluronic acid have been incorporated into microneedle ,patches and lipid based vesicles for enhancement of skin permeation of hydrophilic drug.[21]

iii. Ocular drug delivery [7]

Hyaluronic acid has the ability to retain moisture and thus it helps treating dry eye syndrome. As hyaluronic acid has a viscoelastic property thus used during surgeries & as a carrier for anti-inflammatory drugs.

iv. Mucoadhesive, buccal ,nasal and vaginal delivery

Buccal films or oral films hyaluronic acid based can be used for delivery of drugs like lidocaine or antifungals for local or systemic pain. In nasal spray they can be used to improve mucosal hydration and promoting the absorption of peptide ,hormones and vaccines

v. Oral drug delivery

Hyaluronic acid conjugates have shown improved solubility and targeted release

vi. Cancer targeted drug delivery

According to some articles it has bee found out that hyaluronic acid has affinity for CD44,RHAMM and LYVE-1 receptors [10] which are overexpressed on various tumour cells these cause active targeting of chemotherapeutics. Hyaluronic acid base liposomes or micelles, nanoparticles are used to deliver various drug to cancer site

vii. Gene and protein delivery

HA nanoparticles or complexes can encapsulate DNA, siRNA, or therapeutic proteins and deliver them to target cells, minimizing immune reactions and enhancing cellular uptake.

CHALLENGES AND LIMITATIONS

1. Rapid degradation of hyaluronic acid by hyaluronidase and free radicals in the body and hyaluronic acid has a short half life .
2. The cost for production of pharmaceutical grade hyaluronic acid is cost intensive.
3. Different regularity agencies may have a inconsistent standards for purity ,usage of hyaluronic acid. There is a lack of global standardization which makes the product development and approval complex
4. There might rise a problem associated with inflammatory reaction although hyaluronic acid is biocompatible but the chemically modified or contaminated with protein or endotoxins cause local inflammation ,foreign body reaction, rare hypersensitivity responses.

FUTURE PERSPECTIVE OF HYALURONIC ACID –

Hyaluronic acid continues to attract extensive interest in scientific and clinical communities due to its multifunctional properties and bio-integration potential. The future of HA lies not only in enhancing its current applications but also in leveraging cutting-edge technologies to create next-generation HA-based platforms for targeted, efficient, and personalized therapies.

i. Advanced Drug Delivery Systems

Research focusing on hyaluronic acid based targeted drug delivery systems in oncology, ophthalmology, and inflammatory diseases. HA's affinity for CD44 receptors, overexpressed in many tumor cells, makes it a promising candidate for ligand-targeted nanocarriers (e.g., HA-coated nanoparticles), stimuli-responsive systems that release drugs in response to pH, enzymes, or redox conditions, dual-delivery platforms combining HA with chemotherapeutics and gene therapies. These strategies aim to improve therapeutic efficacy while reducing systemic toxicity.

ii. Smart and Responsive Biomaterials

The development of "smart" HA-based materials that can respond to environmental stimuli (e.g., temperature, pH, light) will enable more precise control over drug release, cell behavior, or scaffold degradation. For example: Thermo-responsive HA hydrogels for minimally invasive injection and on-demand drug release and self-healing materials for tissue repair .These innovations hold great promise for regenerative medicine and chronic disease management.

iii. HA in Regenerative Medicine and Stem Cell Therapy

HA-based scaffolds are expected to become increasingly vital in stem cell therapy and 3D bioprinting as a bioink component in 3D bioprinting for fabricating tissue constructs (e.g., skin, cartilage, liver). As a stem cell delivery matrix, maintaining viability, promoting differentiation, and enhancing integration for cardiac, neural, and musculoskeletal tissue engineering, where HA mimics the extracellular matrix and supports cellular interactions.

iv. Integration with Artificial Intelligence and Personalized Medicine

Emerging integration of HA-based diagnostics and treatments with AI-driven platforms may enables the predictive modeling of HA behavior in tissues, personalized treatment regimens based on molecular profiling.Such innovations could accelerate the clinical translation of HA-based products in precision medicine.

v. Sustainability and Eco-friendly Production

There is growing emphasis on developing sustainable and animal-free sources of HA to minimize environmental impact and align with ethical practices. This includes fermentation using plant-based or microbial systems ,green chemistry approaches for HA modification and purification.

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