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Hyaluronic Acid (Hyaluronan): A Review on Pharmacokinetics and its Application

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Abstract:- Karl Meyer and his assistant John Palmer first found hyaluronic acid (HA), a biopolysaccharide with a high molecular weight, in the vitreous of cows' eyes in 1934. In addition to humans, microorganisms have major biological uses for hyaluronic acid. This review discusses hyaluronic acid's clinical applications, basic pharmacological properties, various physiological and pathological activities, and metabolisms. In addition to being present in most connective tissues, it is notably concentrated in umbilical cords, chicken combs, synovial fluid, and the vitreous fluid of the eye. Hyaluronan synthases, a type of integral membrane proteins, produce it in nature, while hyaluronidases are the enzymes that break it down.

Keywords:- *History, Metabolism, Toxicity, Properties, Structure, Application.*

I. INTRODUCTION

All living things naturally contain hyaluronic acid (HA), a mucopolysaccharide and a type of saccharide. It may consist of thousands of sugars. When unattached to other molecules, it forms a stiff, viscous substance that resembles "Jello" when it binds with water. Hyaluronan (HA), a polysaccharide, is a linear polyanion with the disaccharide structure [(13)—dGlcNAc-(14)—d-GlcA-]. Although it has been demonstrated that HA can occur intracellularly, it is most commonly found in the extracellularmatrix and pericellular matrix.Although it has been demonstrated that HA can occur intracellularly, it is mainly found in the extracellular matrix and pericellular matrix. The biological tasks of HA include regulating tissue hydration and water transport, supramolecular assembly of proteoglycans in the extracellular matrix, and a variety of receptor-mediated involvement in cell detachment, mitosis, relocation, tumor growth, among others.Its role in the body is to combine with water and lubricate movable body parts including joints and muscles, among other things. It works well as a moisturizer in cosmetic goods due to its homogeneity and tissue-friendliness. One of the most hydrophilic compounds found in nature, hyaluronic acid is sometimes referred to as "nature's moisturizer." As a result of HA's special viscoelastic properties, biocompatibility, and lack of immunogenicity, it is used in a variety of clinical procedures, such as the supplementation of joint fluid in cases of arthritis [5-8], as a surgical aid in cases of eye surgery, and to speed up the healing and regeneration of surgical wounds.In more recent times, HA has been researched as a drug delivery agent for many routes of administration, including topical, parenteral, pulmonary, nasal, and ocular [9].

II. HISTORY

In 1934, Karl Meyer and his coworker John Palmer extracted a chemical compound from the vitreous body of cows' eyes. They discovered that there were two sugar molecules in the material, one of which was uronic acid. They suggested the name "hyaluronic acid" for beneficial use. The common name is a combination of the Greek words "hyalos," which means glass, and "uronicacid" [10]. They had no idea that the chemical they had found would turn out to be one of the most fascinating and practical natural macromolecules at the time. When EndreBalazs submitted a patent application in 1942 to use HA as an alternative to egg white in bakery goods, that was the beginning of HA's commercial use. Hyaluronan was used as a vitreous substitute or replacement during eye surgery in the late 1950s, which was the first time it had been used medically on people. In the 1950s, Karl Mayer and his collaborators largely solved the chemical structure of haluronan. Although it was initially separated as an acid, it behaved like a salt when exposed to physiological circumstances (sodium hyaluronate). Endre Balazs [1] is credited with coining the term "hyaluronan," which was first used in 1986 to comply with the international nomenclature of polysaccharides and to cover the various forms the molecule can take, including the acid form, hyaluronic acid, and the salts, such as sodium hyaluronate, which form at physiological pH [11]. Later, HA was isolated from various additional sources, and numerous laboratories examined its physicochemical structure, biological function, and characteristics [12]. A recent review and a Ciba Foundation Symposium both provided summaries of this study [11-13].

III. PHYSICOCHEMICAL AND STRUCTURAL PROPERTIES

Hyaluronan, an extracellular matrix component, is a high molecular weight glycosaminoglycan throughout all mammals, suggesting that HA is a biomolecule of considerable importance (Chen and composed of disaccharide repeats of N-acetylglucosamine and glucuronic acid[14].

A. Chemical structure

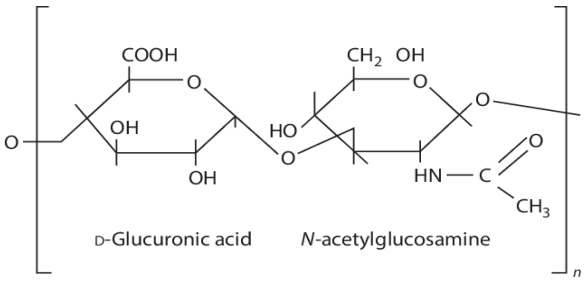
The disaccharide's uronic acid and aminosugar, d-glucuronic acid and d-N-acetylglucosamine, are joined by alternate beta-1,4 and beta-1,3 glycosidic linkages (see Figure 1). Both sugars are positioned next to glucose, which, in the beta configuration, places all of its bulky groups—the hydroxyls, the carboxylate moiety, and the anomeric carbon on the neighbouring sugar—in sterically advantageous equatorial positions while placing all of the small hydrogen atoms in less favourable axial positions. As a result, the

disaccharide's structure is relatively stable in terms of energy.

B. Solution structure

The chemical makeup of the disaccharide, internal hydrogen bonds, and interactions with the solvent all work together to stiffen the backbone of a hyaluronan molecule in a physiological solution. A twisting ribbon structure is produced by the axial hydrogen atoms, which form a non-polar, generally hydrophobic face, and the equatorial side chains, which form a more polar, generally hydrophilic face. Hyaluronan solutions have extremely unique rheological characteristics, are extremely lubricious, and are very hydrophilic. The hyaluronan polymer chain assumes the shape of an extended, random coil in solution. The remarkable rheological features of these chains may be a result of the fact that they entangle with one another at incredibly low concentrations. Solutions have a very high but shear-dependent viscosity at higher concentrations. A 1% solution feels like jelly but moves freely under pressure and can be injected with a small-bore needle. As a result, it has been referred to as a "pseudo-plastic" material. Hyaluronan solutions are excellent lubricants because of their exceptional rheological characteristics. There is proof that most tissue surfaces that move past one another are separated by hyaluronan. Meanwhile, it has been demonstrated that the exceptionally lubricious qualities of hyaluronan prevent the development of postoperative adhesions after abdominal and orthopedic surgery. As previously established, the presence of hydrogen bonds between the hydroxyl groups throughout the chain is what causes the polymer to take on a stiffened helical structure in solution. The outcome is the formation of a coil structure that traps around 1000 times its weight in water[15].

C. Synthesis



The production of HA within cells is a distinct and tightly regulated process. The Golgi networks of the cell are where glycosaminoglycans are primarily produced. The class of integral membrane proteins known as hyaluronan synthases, of which vertebrates have three types: HAS1, HAS2, and HAS3[16], naturally produces HA. Homology modelling and secondary structure predictions suggest an integral membrane protein (IMP). A protein molecule (or protein assembly) that crosses the biological membrane with which it is associated (particularly the plasma membrane) or is sufficiently embedded in the membrane to remain with it during the earliest stages of biochemical purification is referred to as an integral membrane protein (in contrast to peripheral membrane proteins).

D. Biosynthesis

- *Synthesis of UDP-glucuronic acid*

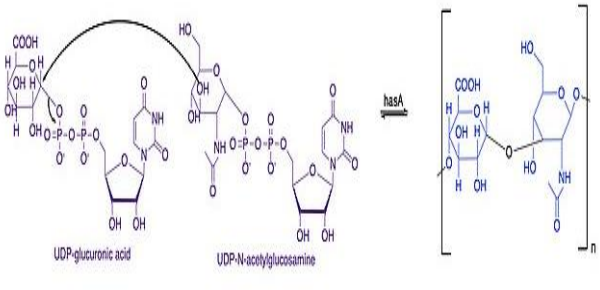
UDP-glucuronic acid is formed from *hasC* (UDP-glucose pyrophosphorylase) converting glucose-1-P into UDP-glucose, which then reacts with *hasB* (UDP-glucose dehydrogenase) to form UDP-glucuronic acid[17].

- *Synthesis of N-acetyl glucosamine*

The path forward from fructose-6-P utilizes glmS (amidotransferase) to form glucosamine-6-P. Then, glmM (Mutase) reacts with this product to form glucosamine-1-P. hasD (acetyltransferase) converts this into n-acetylglucosamine-1-P, and finally, hasD (pyrophosphorylase) converts this product into UDP-n-acetylglucosamine [18].

- *Final step: Two disaccharides form hyaluronic acid*

UDP-glucuronic acid and UDP-n-acetylglucosamine get bound together to form HA via hasA (HA synthase) [18].



E. Degradation

Three different types of enzymes—hyaluronidase (hyase), b-d-glucuronidase, and -N acetyl-hexosaminidase—work together to break down HA in mammals. These enzymes are distributed throughout the body in a variety of intracellular and serum forms. High molecular weight HA is often broken down into smaller oligosaccharides by hyase, and then the oligosaccharide fragments are further broken down by -d-glucuronidase and -N-acetylhexosaminidase by eliminating nonreducing terminal sugars [19].

IV. MECHANISM OF ACTION

Although the primary mechanism of HA is unknown, in vivo, in vitro, and clinical studies have shown that exogenous HA has a variety of physiological consequences. Many protective physiochemical properties of hyaluronic acid may contribute to further chondroprotective effects in vivo and help to explain its longer-term effects on articular cartilage. Hyaluronic acid can lessen the pain-related nerve sensitivity and impulses. This glycosaminoglycan exerts protective effects on cartilage in experimental osteoarthritis [20].

High hygroscopicity of hyaluronan is thought to be crucial for controlling tissue hydration and osmotic equilibrium [21]. Hyaluronan not only serves as a passive structural molecule but also as a signaling molecule, controlling cell division, migration, and differentiation through interactions with cell surface receptors. Hyaluronan

is crucial for embryogenesis and probably has a role in the development of tumors [22–23].

Several hyaluronan functions exist. Hyaluronan has a substantial impact on the extracellular matrix's hydration and physical characteristics because of its hygroscopic qualities. Hyaluronan can also interact with a variety of receptors, activating signaling cascades that affect gene expression, cell migration, and proliferation [3] [24].

V. PHARMACOKINETICS

Many species, including man, have well-established normal systemic kinetics of HA. With a half-life of 2–6 min and an average daily turnover of 10–100 mg in an adult human, the elimination of HA from the circulation is quite effective. The liver endothelial cells are responsible for the majority of blood absorption. Yet, there is mounting evidence that the kidneys play a part in the removal of HA.

Recently published data suggest that the elimination kinetics of HA from the systemic circulation may be influenced by a number of factors, such as saturation of the elimination caused by an increased lymphatic input of HA to the circulation, alteration of the blood flow over the eliminating organ and competition with other macromolecular substances such as chondroitin sulphate or proteoglycans. Many of these factors may be operative during different disease states, and may therefore partly explain the observed differences between normal and pathological HA kinetics. The normal and pathological turnover of hyaluronan from the circulation has been determined in many different species, including man by many different authors using different techniques [25-27].

A. Absorption rate and concentration

In plasma After i.v. injection of a bolus dose of [14C]-HA in rabbits, it was shown that 98% of the administered dose had disappeared from the systemic circulation within 6 h after the administration. Similar results were also obtained in man, where 55% and 85% of the acetyl content after i.v. injection of [3H]HA, was completely oxidized after 3 h and 24 h, respectively [13]. It is known that the major part of the elimination of HA from the blood circulation takes place in the liver [27]. via receptor-mediated endocytosis in the sinusoidal liver endothelial cells [28-29].

B. Distribution

HA is a common component of the tissue cement or ground substance that surrounds cells and is widely distributed in bodily tissues and intracellular fluids, such as the aqueous and vitreous humour and synovial fluid [30–31]. The distribution of sodium hyaluronate into breast milk is unknown.

C. Excretion (elimination)

- *Renal excretions*

The kidneys filter around 1% of the daily average amount of HA from the systemic circulation in humans, according to a direct measurement of HA in urine. Studies on humans [26] and research on rabbits [27] both produced similar findings. Using the approach of measuring directly over the organ, it was recently reported that the extraction ratio and clearance over the kidney in pigs were 14% and 41 ml per min, respectively. Moreover, it was discovered in this investigation that renal clearance was around three times greater than urine clearance [28].

- *Hepatic elimination*

Direct measurement of the difference of the endogenous concentration over a specific organ and knowledge of the blood flow enables calculation of the extraction ratio or clearance directly over a specific organ. By use of this method Bentsen et al. (1989) deter-mined the hepatosplanchnic extraction ratio and clearance of hyaluronan in man to be 33% and 250 ml/min, respectively. The hepatic extraction ratio and clearance have also been determined in pigs by measurement directly over the organ and were found to be 23% and 150 ml/min, respectively [28]. In a similar study on pigs, using the same method of direct determination, the extraction ratio and clearance over the liver were determined to be 49% and 332 ml/min, respectively. The reason for the discrepancies between these two studies is not known [26].

- *Pulmonary excretion*

Within 100 h, 63% and 20% of the administered dose was excreted and recovered in the respiratory gas (as $14CO_2$) [26].

- *GIT excretion*

The total amount of excretion into bile within 24 h was reported to be very low, 0.7% of the ad-ministered dose. Similarly, the total amount of excretion into feces, within 100 h of administration, was also very small, about 0.5% of the administered dose [26].

VI. TOXICITY

A. Cytotoxicity

A conduit made of hyaluronan was tested for biocompatibility, degradation, and any potential cytotoxic effects by Jansen et al. in 2004. The findings demonstrate that a conduit made of hyaluronan is not cytotoxic and exhibits good biocompatibility. Due to its strong structural homology across species and low interaction with blood components, hyaluronan is highly non-antigenic and non-immunogenic [32].

B. Neurotoxicity

It was thought that HA delivered epidurally during spinal adhesiolysis treatments could improve the condition of patients with chronic lower back pain since HA has an anti-inflammatory impact and prevents and/or lowers tissue adhesion. Due to this, the following clinical trial evaluated the neurotoxicity of HA delivered epidurally in rabbits using light microscopy (LM) and electron microscopy (EM). The normal saline (NS) group (n = 10) and the HA group (n = 10) were each given a set of 20 rabbits. The same volume of HA and saline (0.2 ml/kg of 0.9% solution) were injected into the spinal space. With the exception of one rabbit in the NS group who displayed decreased hunger, activity, and weight loss over the course of the three weeks, no rabbits displayed any sensory-motor or behavioural alterations. Two rabbits in the NS group had aberrant results by LM; these

were assumed to be the result of injury and infection brought on by epidural catheterization. No substantial neurotoxic findings were seen in either group according to EM results. In conclusion, HA delivered epidurally to rabbits did not result in neurotoxicity [33].

C. Carcinogenicity

Cell development, differentiation, and migration are only a few of the tasks that HA performs in the extracellular matrix [34–35].

D. Mutagenicity

Assay for Sister Chromatid Interchange. The sodium hyaluronate Orthovisc® solution (High Molecular Weight Hyaluronan) was not deemed mutagenic to Chinese Hamster Ovary cells under the assay's parameters [36].

Assay for Chromosomal Aberration. The Orthovisc® solution was not thought to be mutagenic to Chinese Hamster Ovary cells under the assay's parameters [36].

Mammalian Microsome Mutagenicity Assay for Salmonella. The Orthovisc® solution was not thought to be mutagenic to tester strains of Salmonella typhimurium under the assay conditions [36].

VII. EFFICACY AND APPLICATIONS

A. Chondro protective effect

Although HA's physical characteristics are significant, there is evidence that it may also have favourable physiochemical and pharmacological effects. The glycoprotein CD44 is expressed on the cell surfaces of chondrocytes. This has the potential to serve as a HA receptor and may interact biochemically with chondrocytes. By interactions with CD44, a HA injection may have a mediated impact [19].

B. Chondroprotective effect in vitro

The chondroprotective effects of hyaluronic acid, e.g., that it stimulates the production of tissue inhibitors of matrix metalloproteinases (TIMP-1) by chondrocytes, inhibits neutrophil-mediated cartilage degradation and attenuates IL-1 induced matrix degeneration and chondrocyte cytotoxicity have been observed *in vitro* [36]. Articular chondrocytes cultured in the presence of HA have a significantly greater rate of DNA proliferation and extracellular matrix production, compared with chondrocytes cultured without HA [19].

C. Chondroprotective effect in vivo

HA has been experimentally studied as a potential agent of therapeutic intervention in osteoarthrosis (OA). Hyaluronic acid has been applied to the therapy of experimental OA. Investigations have shown that intra-articular injection of HA reduces arthritic lesions in experimental animal models of articular cartilage injury [5] [18] [37-42].

D. Orthopedic applications

The growth of cartilage, the preservation of synovial fluid, and the regeneration of tendons are all critically dependent on HA [43]. All mature joint tissues, including the synovial fluid and the outer layer of cartilage, exhibit high levels of HA in the ECM [18]. The way HA behaves in the joint as a lubricant and shock absorber is in part due to its viscoelastic properties and capacity to generate highly hydrated matrices.

The idea of visco supplementation was inspired by the pathologic alterations to hyaluronic acid in synovial fluid, including its decreased molecular weight and concentration.

Currently, the positions of specialist groups are divided as to the use of hyaluronic acid in the treatment of OA. According to some societies, HA is not recommended as a reliable method of treating degenerative joint changes. AAOS (American Academy of Orthopedic Surgeons) in recommendations does not recommend the use of hyaluronic acids in the treatment of knee degenerative changes [76]. ACR (American College of Rheumatology) also does not recommend the use of hyaluronic acid in the treatment of knee and hip degenerative disease [77]. However, the international organization Cochrane states that there is evidence of positive effects of hyaluronic acid in degenerative changes in the knee joints [78].

- *Viscosupplimentation*

Viscosupplementation is a brand-new, secure, and perhaps beneficial method of treating osteoarthritis locally [7]. By enhancing the shock absorption and lubricating qualities of osteoarthritic synovial fluid, viscosupplementation with HA products helps to improve the physiological environment in an osteoarthritic joint. The purpose of viscosupplementation is to reduce discomfort and enhance mobility while restoring the protective viscoelasticity of synovial hyaluronan. Pain alleviation is one of viscosupplementation's early advantages. The return of joint mobility through the restoration of trans synovial flow and, ultimately, the metabolic and rheologic equilibrium of the joint are thought to have longer-term advantages [44].

Viscosupplementation was first used in clinical settings in 1987 in Japan and Italy, 1992 in Canada, 1995 in Europe, and 1997 in the US. Currently, the United States offers two hyaluronic acid products: synthetic hylan G-F 20 and naturally occurring hyaluronan (Hyalgan) (Synvisc). Hylans are hyaluronic acids that have been cross-linked, giving them a larger molecular weight and more elastoviscous characteristics. Due to hylan's improved elastoviscous characteristics and longer persistence in the joint area, its larger molecular weight may make it more effective than hyaluronic acid [45].

E. Antiadhesion applications

HA is a polymer that works well for applications needing little cellular adherence since it is very hydrophilic. Postoperative adhesions, which develop between adjacent tissue layers after surgery, prevent wound healing and frequently need further surgeries to be completely healed. Such adhesions can be efficiently avoided by using barriers constructed of cross-linked HA. Esterified HA has also been utilised to inhibit bacterial adhesion to dental implants, intraocular lenses, and catheters [18]. Moreover, the attachment of bacteria to biomaterials can result in infections and pose a significant risk to the patient.

F. Opthalmology

HA, a naturally occurring element of the vitreous fluid of the eye, has been used successfully in numerous ophthalmologic surgical procedures. An intraocular injection of HA is utilised during surgery to maintain the shape of the anterior chamber because HA is particularly useful as a space-filling matrix in the eye. Moreover, HA solutions function as an adjuvant to ocular tissue restoration as well as a component that increases the viscosity of eye drops.

Aqueous humour, trabecular meshwork, and vitreous body are just a few of the ocular tissues that contain HA. HA can easily connect to cell membranes via the glycoprotein CD44 on the cell surface [67]. Furthermore, HA hydrates the eye, boosts biocompatibility, and extends drug residence duration to improve drug delivery [68–70]. These characteristics make HA suitable for use in tissue engineering, artificial tears, eye drops, intravitreal injections, in situ hydrogel formation, modified nanoparticles, and tissue engineering.

A frequent ocular condition called dry eye syndrome (DES) can be brought on by factors like age, gender, nutrition, environment, illness, surgery, or a drug's negative effects [71–73]. Artificial tears can be given HA to improve and prolong moisture retention, which will lessen the symptoms of DES.

G. Dermatology and wound healing applications

The skin and soft connective tissues have significant levels of HA naturally. The adoption of HA as a matrix to facilitate skin regeneration and augmentation is thus acceptable. Prestwich and colleagues discovered, for instance, that cross-linked HA hydrogel films hasten the healing of full-thickness wounds. This is probably because they offer a highly hydrated and nonimmunogenic environment that is helpful for tissue repair. Hyaff scaffolds have been used to produce skin-like materials, including two separate layers of tissue that resemble the epidermis and dermis, in vitro. Moreover, HA has been employed successfully in cosmetic applications such soft tissue augmentation due to its capacity to generate hydrated, expanded matrices [18] [20]. The highest concentrations of HA are found in connective tissues, and most HA (about 56%) is found in the skin. The estimated total amount of HA in human skin has been reported to be 5 g [50].HA is present in the dermis (approximately 0.5 mg/g wet tissue) and the epidermis (approximately 0.1 mg/g wet tissue [55]. The use of biotinylated HA-binding peptide [51] has enabled the visualization of HA in the epidermis, mainly in the extracellular matrix of the upper spinous and granular layers, whereas in the basal layer HA is predominantly intracellular [52]. The stratum granulosum is primarily responsible for maintaining skin moisture, while the dermis and the crucial portion of the epidermis are significantly important for skin hydration [53]. Along with the lymphatic and vascular systems, the HA of the dermis controls water balance, osmotic pressure, and ion flow. It also serves as a sieve, excluding some molecules, enhancing the extracellular domain of cell surfaces, and stabilising skin structures through electrostatic interactions [54].

- *Soft tissue augmentation*

Treatment for the ageing face has undergone a revolution thanks to soft tissue augmentation. Because to its durability, simplicity of application, and minimal immunogenicity, HA dermal fillers have been utilised regularly over the past ten years to enhance the soft tissues of the face [56]. Stabilized HA gels' ability to promote collagen production and prevent collagen deterioration may further contribute to their protracted benefits [57]. HA also has a low chance of causing previously documented hypersensitivity reactions due to its nonanimal source [58–60]. Injectable fillers, which cover and reinforce the static rhytides, are the most effective treatment for facial wrinkles brought on by the volume loss associated with ageing [61]. HA fillers from different manufacturers differ in characteristics such as total HA concentration, modulus, particle size, degree of crosslinking, percentage of crosslinked HA, amount of unmodified HA present, and extrusion force [62].

- *Skin rejuvanation*

In today's culture, maintaining a young and attractive facial look has an impact on many patients' quality of life. The process of facial ageing is dynamic and complex. Because of the imbalance, discord, and disproportion of the ageing process between the covering soft tissue and the underlying bony structures, every person ages differently. Although though the exact causes of skin ageing are still unknown, it is clear that as people age, their epidermis loses the main molecule that keeps and binds water molecules. This causes a loss of skin moisture and is responsible for some of the most obvious changes in ageing skin, such as wrinkles, reduced suppleness, and loss of face volumes, particularly in relation to the cheekbones and lips [63].

H. Cardiovascular applications

In a manner related to its antiadhesive properties, HA has also proven to be effective for increasing the blood compatibilities of cardiovascular implants such as vascular grafts and stents. For example, biomaterial surfaces treated with cross-linked HA have been associated with reduced platelet adhesion and thrombus formation [18]. Furthermore, sulfated HA derivatives can act as heparin mimics [48]; in fact, HA derivatives with higher degrees of sulfation are associated with increased abilities to prevent blood coagulation (as measured by longer times required for whole blood clotting [47].The non-sulfate glycosaminoglycan hyaluronic acid (HA) is made up of repeated disaccharide

groups, D-glucuronic acid, and N-acetyl-D-glucosamine. Hepatic stellate cells and fibroblasts, endothelial cells, and smooth muscle cells of the artery wall produce it [64]. Its functions include preserving the osmotic balance, controlling cellular processes like migration, adhesion, and proliferation, and retaining tissue water. Modification of the tissue, inflammation, and morphogenesis are all influenced by HA's interaction with cell membrane receptors [65]. High molecular weight HA (106Da) inhibits angiogenesis, whereas HA molecules of 3–25 disaccharide units increase it. Varying length HA molecules have varied effects. HA plays a significant role in the interaction between vascular tissue and blood components, along with other glycosaminoglycans (GAGs). GAGs reduce the interaction between endothelial cells and leukocytes [66], contributing to the regulation of redox state; they are crucially involved in the mediation of shear-induced nitric oxide release as well as physiologic anticoagulation.

I. Tissue engineering

In the year of 1988, tissue engineering was developed [79]. It was used as the replacement of engineering materials of tissue or specific organ. There are millions of patients suffering from loss or failure of organ caused by diseases or accidents every year. As per reports, more than eight million surgeries are performed in U.S. to treat these patients [80].To be around about there was 400$ billion per year cost of this issue estimated in the U.S. economy. Transplantation of organs and tissue are usually conventional therapies, but they're limited by contributor shortages [81]."Hydrogels" are used as scaffolds for growth, differentiation, cell loading, and delivery in tissue engineering. Space-filling agents and mucoadhesive materials can be included in hyaluronic acid hydrogels, which can offer a new formulation for tissue engineering [82]. In order to release more cytokines for the flexible design of tissue engineering, hyaluronic acid hydrogels have the capacity to alter the three-dimensional architectures of the natural ECM [83]. By blocking cell attachment, the group of HA hydrogels act as biological glue to bulk up the matrix or scaffold and increase its therapeutic efficiency while also improving anti-aging goals. The transplantation of cells into the body for tissue repair and regeneration, including cartilage, bone, and smooth muscles, is another use for hyaluronic acid hydrogels [84].

VIII. CONCLUSION

For the past 20 years, hyaluronic acid has been found in numerous goods all around the world. HA has been thoroughly studied in drug-delivery applications due to its biocompatibility, biodegradability, and easily changed chemical structure. For the purpose of drug delivery, numerous commercially accessible formulations of HA derivatives and cross-linked HA materials have been developed; these materials come in a range of shapes, including films, microspheres, fibres, hydrogels, and liposomes. HA has achieved success in an incredibly wide range of biomedical applications thanks to multidisciplinary discoveries concerning the structure, characteristics, biological activity, and chemical modification of this special polymer. A deeper comprehension of the effects of HA molecular weight and concentration and how this biomolecule particularly interacts with cells and ECM components in the body is crucial for developing future clinical therapies using HA-derived materials. When these materials are used more frequently, interactions between HA and its surroundings will need to be precisely regulated and under control. Work is being done in these fields; sticky peptide sequences, for instance, have been covalently attached to HA materials. Moreover, HA has been used to create materials that are environmentally friendly. These substances can be made to enlarge or break down in response to heat, electrical stimulation, and inflammation.

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