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HYALURONIC ACID USED IN COSMETICS AND COSMECEUTICALS: A REVIEW

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Abstract: Hyaluronic acid is commonly known as hyaluronan or hyaluronate. Karl Mayer and John Palmer discovered hyaluronic acid in synovial fluid, the vitreous fluid of the eyes, the rooster's comb, the umbilical cord, and arterial walls. It is found in the bacterial cell walls of certain bacteria, like Streptococci and Staphylococci. They are the main commercial source of hyaluronic acid. It is naturally synthesis in 1934. Hyaluronic acid is found in connective tissue, synthesized by the protein named hyaluronan synthases, and it is destroyed by the enzyme named hyaluronidases. It plays a major role in different fields of medicine like, tissue engineering, cancer therapy, ophthalmology, osteoarthritis, and nerve reconstruction. It is used in skin regeneration, with an anti-ageing and moisturizing effect. Its applications are found in the pharmaceutical, cosmetic, and medical fields. Hyaluronic acid penetrates the skin due to its high molecular weight. The current study describes the main characteristics related to its use in cosmetology.

Key Word:- Hyaluronic acid, , Opthalmology, Osteoarthritis, Wound healing, Hair.

Introduction

Hyaluronic acid (HA), it is also called as hyaluronan having (molecular formula C28H44N2O23),it is a glucosaminoglycan which is composed of D-glucuronic acid and N- acetyl-D-glucosamine disaccharide units linked by glycosides. bond in an alternating -(1 4) and -(1 3) bond arrangement.[1] Initially, it is extracted from the vitreous of the bovine eyes and eventually found in different connective tissues and fluids**.[**2**]** Nowadays, Hyaluronic acid can be obtained from a variety of sources, including microbial fermentation (F-HA) and extraction from mammalian and marine animals (E- HA).The extraction phase and the purification phase are the two main stages in the process of obtaining hyaluronic acid. F-HA is extracted from bacterial strain culture medium (e.g., Streptococci, Bacilli, and Escherichia coli).[3] Several microorganisms, including Streptococcus zoo epidemicus, Bacillus subtilis, and Escherichia coli, have been used in fermentation to produce hyaluronic acid. Another microorganism that has been used to produce hyaluronic acid is Bacillus subtilis. It is a Gram-positive bacterium that is non-pathogenic and known for its ability to produce high yields of hyaluronic acid. Hyaluronic acid with a lower molecular weight produced by Bacillus is appropriate for cosmetic uses such moisturizing lotions and serums.On the other hand, the low-molecular-weight hyaluronic acid produced by Bacillus bacteria has great potential in the cosmetics industry, and the demand for hyaluronic acid-based cosmetics continues to grow.[18]

There are two primary ways that hyaluronic acid is broken down: enzymatically by a group of enzymes known as hyaluronidases (HYALS) non-enzymatically, such as through the action of free radicals.[19] The primary enzymes that break down hyaluronic acid are called HYALS: Generally speaking, these enzymes break B-N-acetyl-D- glucosamide links of polymer chains at random, resulting in smaller oligosaccharides and low-molecular weight HAs with pro-angiogenic characteristics.[20] The concentration of hyaluronic acid naturally present in the skin decreases with age, affecting wrinkles, skin elasticity and dryness. Therefore, hyaluronic acid can be used in cosmetics to provide anti-aging and anti-wrinkle benefits increase**.**

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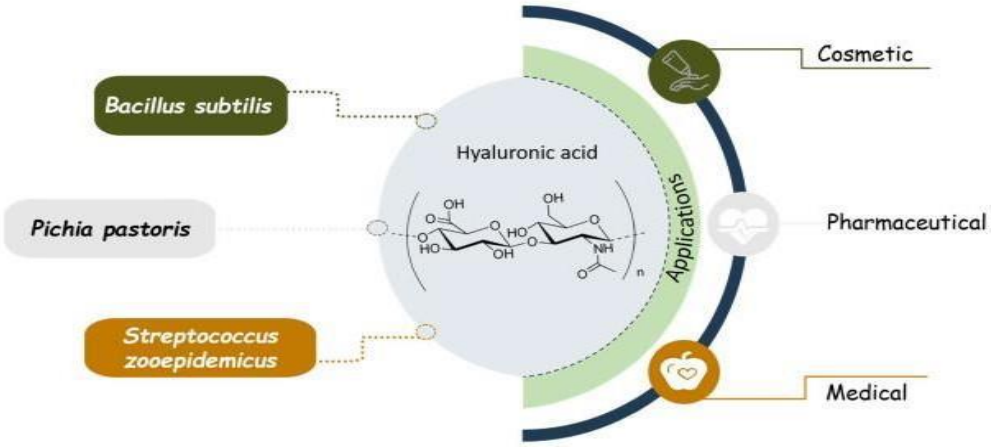

Fig 1: Production of Hyaluronic Acid

Karl Meyer and John Palmer isolated a new polysaccharide containing amino sugars and uronic acid from bovine vitreous and named it hyaluronic acid from 'hyaloid' (glass) and' uronic acid'[5] From a cosmetic point of view, hyaluronic acid supports the synthesis of collagen and elastin, which declines with age, leading to the breakdown of collagen and elastin. Hyaluronic acid is used to make gels, lotions, scaffolds, hydrogels, intradermal injections, dermal fillers, and other products.This phenomenon leads to the formation of wrinkles, fine lines and smile lines. Because of its moisturizing retention ability, viscoelasticity, resistance to mechanical damage, and lack of immunogenicity and toxicity, hyaluronic acid is an appealing biomaterial for a variety of applications. It serves as a lubricant (joints), structure stabilizer, organ space filler (skin), and shock absorber (cartilage) in many cases. Several pieces of evidence in recent years have indicated that administering hyaluronic acid also orally can achieve relevant results in counteracting skin ageing, thus improving its diffusion in nutricosmetics applications[6] One of the most effective and safe ingredients frequently used in cosmetics is hyaluronic acid. Other bioactive ingredients, such as plant extracts, vitamins, amino acids, peptides, proteins, minerals, saccharides, and probiotics, can enhance the properties of HA. Numerous cosmetics containing HA are currently available from various manufacturers [7] In 1979, there was an initial production of a cosmetic product based on HA. In 1942, HA was sold as a foodstuff; therefore, it was It was used as food for a long time before the use of medicines, cosmetics [8]

Fig 2: Hyaluronic Acid

STRUCTURE AND PHYSICO CHEIMCAL PROPERTIES OF HYALURONIC ACID:

Hyaluronic acid, also known as (HA) is a non-protein, naturally occurring non- sulfated glycosaminoglycan (GAG) having peculiar physicochemical features of repeating - 1,4-D-glucuronic acid[9].Depending on its molecular weight, the physical characteristics and physiological functions of HA vary. With regard to cosmetics, From a broad range of possibilities was chosen the appropriate molecular weight of hyaluronic acid. MW, from hundreds of thousands to millions of them, was determined by the type of cosmetic product.[8] A glucosaminoglycan (GAG) with an unbranched polysaccharide chain of repeated disaccharide units linked by glycosidic bonds is hyaluronic acid. However, Hyaluronic acid is distinguished from other GAGs by a few unique properties, the quantity of rehashing disaccharides in hyaluronic corrosive can arrive at 10,000 or much more, bringing about sub- atomic loads of 4x106 Da[10] Dermatan sulfate, heparin, heparan sulfate, keratan sulfate, and chondroitin 4– and chondroitin 6–sulfates are all glycosaminoglycans that are found physiologically in the dermis. Hyaluronic acid is one of these glycosaminoglycans. Basically, hyaluronic acid is addressed by an extended chain of rehashing non sulfated disaccharides (glucuronic corrosive, N-acetyl glucosamine. It is known that hyaluronic acid binds to water and gives the dermis volume, helps sodium and water homeostasis, and protects the dermis from being compressed.[11] Hyaluronic acid possesses great visco-elasticity, high moisture retention capacity, high biocompatibility, and hygroscopic characteristics.[12] The high density of negative charges from the carboxyl groups in its structure is responsible for the strong water-binding ability. This generates osmotic pressure and causes water molecules to be drawn into the tissues.[13] The specific saturating instrument differs with hyaluronic acid sub-atomic weight. Consequently, the selection of an hyaluronic acid fragment for cosmetic formulation should be carefully considered in light of the intended purpose and application. For the most part, the bigger the sub-atomic weight, the more prevalent the physicochemical properties.[14] Due to its enormously high water-binding capacity, HA is known to play a significant role in tissue hydration and water transport in connective, epithelial, and neural tissues. It is a major component of the extracellular matrix. The high density of fixed negative charges from carboxyl groups in HA chains, which creates the osmotic pressure and pulls water molecules into tissues containing HA, is responsible for the high water-binding capacity of HA.[15]

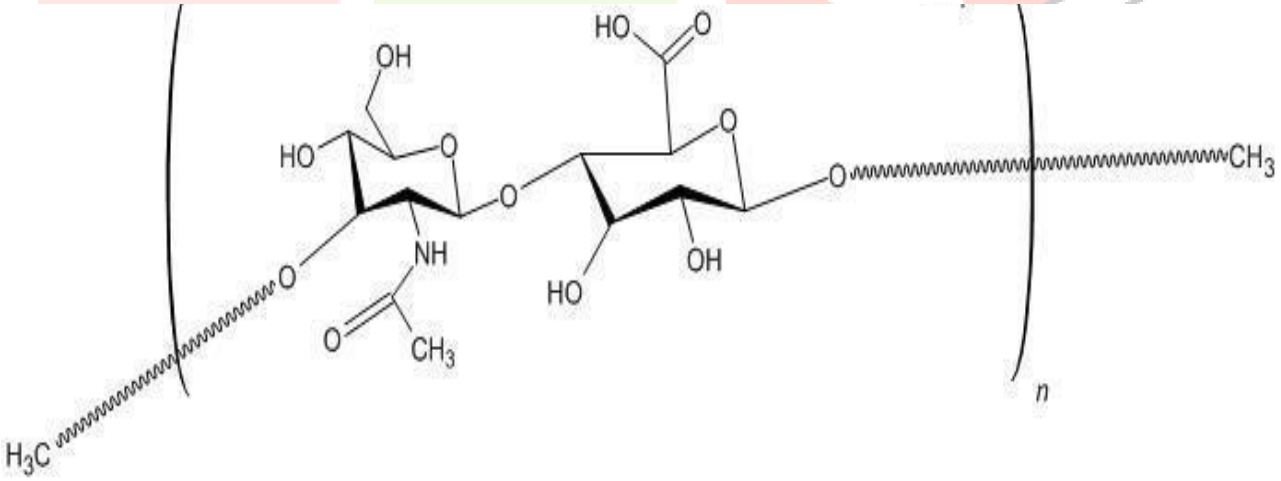

Fig 3: Chemical structure of Hyaluronic Acid

A.	**ORGANOLEPTIC CHARACTERISTICS:-**	
1.	Appearance	Transparent, viscous fluid or white powder
2.	Color	White
B.	**PHYSICAL & CHEMICAL CHARACTERISTICS:-**	
1.	pH	6.5-0.7
2.	Water solubility	Soluble
3.	Organic solvent solubility	Insoluble
4.	Average molecular weight	20-200 kDa

MECHANISM OF ACTION OF HYALURONIC ACID:

Human tissues including the skin, eyes, connective tissue, and synovium all contain hyaluronic acid, which is a major component of the extracellular matrix. Hyaluronic acid may attract water to swell, produce volume, and offer structural support because of its highly anionic properties. Hyaluronic acid and collagen synthesis in the skin decline with ageing. Overlying wrinkles develop as the skin loses its visco-elastic characteristics.[16] The hydrophilic properties of HA are widely recognized on the topic. The high density of negative charges from the carboxyl groups in its structure, which creates the osmotic pressure and pulls the water molecules into the tissues, is responsible for the high water-binding capacity. The precise moisturizing process varies according on the molecular weight of HA. As a result, the selection of HA fragment for cosmetic formulation should be carefully studied in relation to the desired usage and application. Generally, the larger the molecular weight, the more predominant the physicochemical properties, while biological properties will be overcome in the case of smaller-molecular weight fragment.[17]

COSMETOLOGICAL DERIVATIZATION OF HYALURONIC ACID:

A high rate of in vivo turnover results from HA's high susceptibility to hyaluronidase breakdown, as was previously described. Therefore, chemical alterations are necessary for applications in the pharmaceutical or cosmetic industries. These alterations are either chemical attachment of groups to lower HA hydrophilicity, so it may be readily mixed with the hydrophobic ingredients commonly found in cosmetics, or cross-linking to generate insoluble HA derivatives or hydrogels.[14]

USE OF HYALURONIC ACID IN COSMETICS

A) **FOR SKIN:** It is obvious that hyaluronic acid is one of the key components for healthy skin, and that it is also a good predictor of an individual's health.[21] Due to its hydrophilic nature, it can be employed as a moisturizing component in skin care products. Utilizing, cosmetics containing HA, such as creams or lotions, helps to hydrate the skin and increase elasticity, reducing the depth of wrinkles. It is believed that when applied to the skin's surface, HA solutions create an occlusive barrier, absorb moisture, hydrate the skin, and automatically fill in wrinkles.

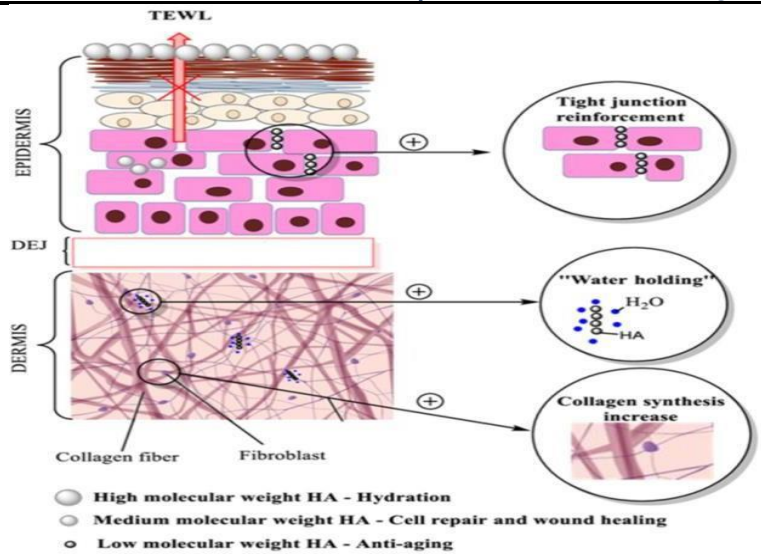

Fig 4: Effect of molecular weight of HA (Transepidermal Water Loss TWEL)

Low molecular weight Hyaluronic acid (LMW-HA) has the power to increase the skin's moisture content and speed up regeneration. When applied to the skin, high molecular weight hyaluronic acid (HMW-HA) creates a viscoelastic layer that moisturises. The HMW-HA polymer's primary function is film formation, which lowers skin water loss and has an occlusive effect. Additionally, the hygroscopic characteristics of HMW-HA, Medium Molecular Weight (MMW-HA), and LMW-HA support the capacity to maintain skin moisture.[22]

HYALURONIC ACID'S THERAPEUTIC ACTIVITY IN DERMATOLOGICAL CONDITIONS:
Table no.2

Sr.no	Skin type	Purpose of Hyaluronic acid
1.	Dry Skin	hyaluronic acid helps dry skin by boosting the skin's moisture content. Patients with atopic dermatitis and senile xerosis experience itching due to dry skin. Consuming hyaluronic acid thereby moisturises the skin and lessens the itchiness brought on by dry skin[8] Applying effective creams, gels, lotion are prescribed to stay away from dry skin complexities like swelling and open cuts. HA in a minimum daily dose of 120 g, which would help to moisturize the skin and lessen the complications.[23]
2.	Oily skin	The results of the experimental and clinical studies revealed that HA plays a crucial role in reducing lipid synthesis, thereby reducing sebaceous gland secretion.[24] The acid is injected intradermally, shrinking the sebaceous gland and limiting lipid production. At the sub-atomic level, down regulation of the HA restricting receptors (CD44) happens which influence the lipid and sebum biosynthesis as well. In general, HA-based formulations can effectively treat oily skin.[25]
3.	Alcoholic skin Deterioration	The present study aimed to appraise physiological levels of ethanol-induced damage in skin cells in vitro and the possible repair by hyaluronic acid (HA).[26]
4.	Antiaging effect	Hyaluronic acid (HA) is important, safe, and effective for treating patients' faces' aging skin. The connective tissues of the skin naturally contain HA, but its concentration decreases with age.[26] Hyaluronic acid fillers are glycosaminoglycan complex sugars that are increasingly utilized in nonsurgical treatments for facial rejuvenation. These fillers have

		alternating units of D-glucuronic acid and N-acetyl-D-glucosamine.[27]
5.	UV protection	the addition of HA to sunscreens provides further protection against type B ultraviolet (UVB) radiation by preventing mutation in the HA synthase, which reduces the release of proinflammatory mediators. As a result, the anti-inflammatory action provides an extra benefit.[28]

PRODUCT	COMPANY NAME	BENEFITS
Lotions	Cetaphil	Provide hydration, lock moisture, prevent acne
Gel	St. Botanica	Maintain skin elasticity, moisture retention,
Moisturizing cream	Home health	Prevent dryness, maintain
Microneedle Pathces	Biomiracle	Maximize elasticity, deliver active ingredients into the skin, gives plumping effect
HA powder	Bliss of Earth	Helps in tissue regeneration, wound healing
Injections	Hyfil (sterile injection)	Reduces wrinkles, fine lines

Table.3. Skin Care Products of Hyaluronic Acid

A) FOR HAIR: Because of its alleged effectiveness in rejuvenating hair follicles, HA has become increasingly used by producers of cosmetic haircare products. The effectiveness of the substance of our interest mixed with a variety of amino acids in enhancing the anabolic process of the dermal papilla cells was proven by researchers with an interest in hair cosmetology.[29] Additionally, HA helps to mitigate the oxidative stress that different internal and external causes cause in the hair follicles. Exposure to type A ultraviolet (UVA) and UVB radiation is the primary external trigger. By lowering the inflammatory marker IL-8 and the keratinocytes' vascular growth factors, HA-enriched formulas help to reduce inflammatory reactions.[30]

PRODUCT	COMPANY NAME	BENEFITS
Shampoo	Loreal paris	Replumps hair, provide long lasting hydration for dry hair
Conditioner	Suave	Detangle, nourishes hair, retain natural moisture
Serum	Haironic Hair Science	Reduce frizziness, improve shine

Table.4. Hair Care Products of Hyaluronic Acid

B) **FOR NAILS:** Hyaluronic acid increases hydration capacity, which is essential since dehydration causes brittle nails, which emerge when the water content of the nails drops to less than 16%.[31]The patented formulation of the hyaluronic acid contained in watersoluble nail strengthener has very strong adhesion characteristics, which allow it to retain its skin and nails for a longer duration because of these favourable charges.[32]

HYALURONIC ACID USED IN COSMECEUTICALS:

A) OSTEOARTHRITIS

HA is found in both synovial fluid and as a component of the cartilage ECM in joints, and it has been shown to have a variety of therapeutic benefits in the treatment of OA. In order to restore the degraded visco-elastic properties of synovial fluid, one of the most important roles played by HA is its physicochemical role in supporting joint lubrication, which has led to the development of various injectable. HA based therapeutic products [33], several clinical trials have shown that HA is more active than saline in reducing arthritic pain in osteoarthritis of the knee with significant improvements in pain and physical function**.** [34][35]
For treating knee OA, the following hyaluronic acid injection are approved:[36]

- Euflexxa
- Hyalgan
- Orthovisc
- Monovisc
- Supartz
- Synvisc

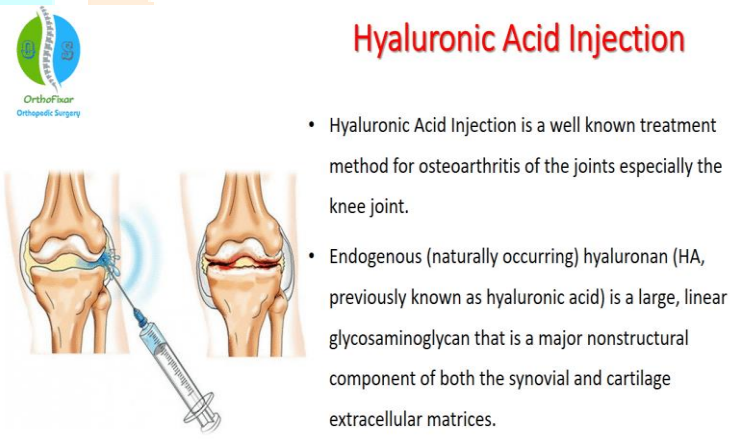

Fig 5 : Hyaluronic acid used in osteoarthritis

C) WOUND HEALING

The biology of wound healing is an entirely natural science. Generally speaking, normal wound healing is based on three key stages: inflammation, proliferation and remodeling with each stage showing a cluster of interconnected cell processes . These cellular processes are mediated by cytokines, which allow wound healing cells to produce the necessary structural proteins and polymers for wound healing. HA polymers are varied in length, and each molecular size plays a unique function during the healing phase of wounds.[37] A rapid increase in synthesis of HA is observed at the inflammation stage of wound healing. In short, large HA molecules are space-filling molecules with regulatory structural functions, whereas small HA fragments are involved in angiogeneis, inflammation and immunostimulation.63 In the treatment of wounds using different HA based wound dressing, antioxidant and free radical scavenging properties were used. [38] HA is widely applied in wound dressing applications, according to various morphologies such as films and hydrogels, fibers and fabrics and foams that are not knitted.[39]

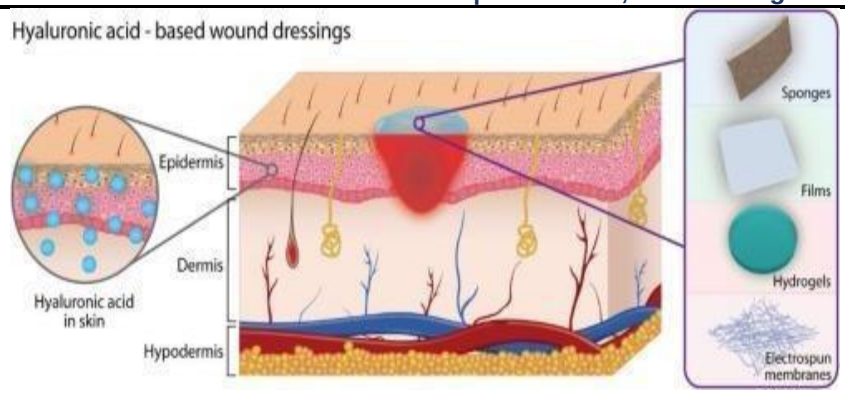

Fig 6: Hyaluronic acid for wound dressing

D) CANCER THERAPY

Numerous tumour cells, particularly tumor-initiating cells, over express HA. In medication delivery systems, HA-based nano particles play an important role. HA is employed in a variety of nano material formulations, including micelle, polymer some, hydrogel, and inorganic nano particle formulations. Many investigations suggest that HA-based nano materials can be used as a platform for targeted chemotherapy, gene therapy, immunotherapy, and combination therapy, with promising future biological applications in cancer treatment.[40] It is well known that many cancer cells over express HA-binding receptors, including CD44, LYVE-1 receptors, and RHAMM.[41] In experimental research, HA is frequently utilised in the creation of nano particles (NP).[40] HA has multiple functional groups that have applications in various conjugations and modifications. Because of these qualities, HA is an important component of multifunctional NPs used to administer effective cancer therapy. [42]

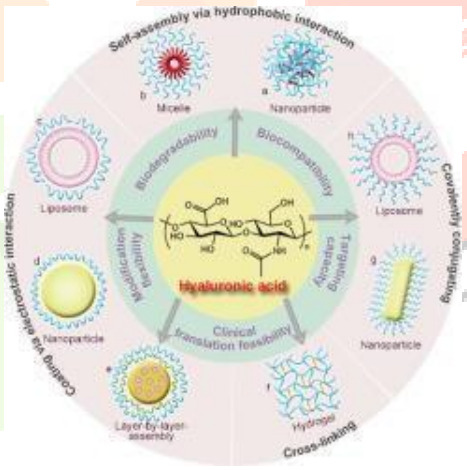

Fig7: Hyaluronic acid based nanomedicine in cancer therapy

E) CHRONIC AIRWAY DISEASES

An essential component of the extracellular matrix of the lungs is hyaluronic acid (HA). Due to HA's special ability to hold water, it plays a crucial part in controlling the fluid balance in the lung interstitium. it has also been suggested for the treatment of several lung diseases, including airway diseases. Hyaluronic acid aerosol inhibits broncho constriction in people with asthma, lessens the severity of elastase-induced emphysema in mouse models, and improves several functional indices in people with chronic obstructive pulmonary disease (COPD) Inhaled HA would increase the amount of airway surface liquid due to its hydration capabilities, which would result in mucus hydration, enhanced mucous transport, and decreased mucus clogging of the airways.[43] Different studies demonstrate that low-molecular weight HA shields the airway epithelium against the harm brought on by bacterial infections by wetting its surface. These studies employ in vitro models of airway mucus transport and the epithelial barrier.[44] Asthma is characterised, among others, as a chronic inflammation and remodelling of the airways .The importance of HA to the pathogenesis of asthma has been recognised recently in studies demonstrating an increased number of short fragments causing inflammation and respiratory hyper arrhythmias.[45] Inhalation of HA by aerosol or inhalation acts to reduce inflammation, protect the airways against hyperactivity and bronchial parenchyma

remodelling. The role of HA and degradation products in the respiratory system physiopathology was highlighted by a number of studies. HA is effective in reducing inflammation, protecting airway against hyperactivity and remodelling of bronchial parenchyma by aerosol or nasal instillation.[43]

F) CENTRAL NERVOUS SYSTEM

HA has a significant role to play in maintaining homeostasis of neuronal tissues, by influencing cell migration, proliferation, differentiation and other cellular behaviour as an important component of the brain ECM. [46] Although HA is an important factor in tissue regeneration and healing, some CNS disorders are observed to progress through the presence of HA and its interactions with cell receptors. An experimental autoimmune encephalomyelitis (EAE) mouse model shows that HA accumulates within demyelinated lesions.[47] The study and treatment of central nervous system disorders have been greatly facilitated by the use of HA based materials. Configurable and flexible scaffolds for CNS Tissue Engineering and Regenerative Medicine have been developed based on HA's biological activity, as well as its ease of chemical modification and manufacture. As a naturally derived polymer, HA materials will continue to play an important role in tissue regeneration as they serve as personal platforms enhancing the inherent regenerative processes within the CNS. [48]

G) **OPHTHALMOLOGY:**

Hyaluronic acid is used in the treatment of dry eye syndrome. Hyaluronic acid is used in the treatment of dry eye syndrome.41 HA has been detected in many tissues of the eye such as aqueous humor, corneal meshwork or vitreous body; through cell surface glycoprotein CD44, it can be readily binding with a cellular membrane. To improve the delivery of drugs, HA is also helping to moisturise the eyes, increases biocompatibility and prolongs time for drug administration by 37, 57, 58, 59, 60 minutes. These properties enable HAU to be used for the manufacture of artificial tears, eye drops, in vitro developed hydrogels, modification nanoparticles, intra vitreally injected and Tissue Engineering.[49] Hyaluronic acid has numerous ophthalmology-related applications, including intravitreal injection, dry eye therapy, and contact lenses, because of its biological safety and water retention qualities. In order to enhance the delivery of medicinal products, HA has also been found to moisturise eyes, increase biocompatibility and extend drug stay longer than expected. These properties make it possible to use HA for human tears, eye drops, in situ hydrogel formation, reconstituted nanoparticles, intravitreal injections and tissue engineering. [50]

I. HYALURONIC ACID USED IN EYE DROPS & ARTIFICIAL TEARS:

In order to increase and prolong the time of moisture retention, HA can be used in artificial tears which is also capable of reducing DES. [51] In eye drops, a high concentration of HA stabilizes the tear film and increases the goblet cells of the conjunctiva.[52] The core function of Dry Eye is heavily influenced by tear film instability . Dry eye disease, as a function of (Visual Display Terminal) VDT treatment, tears are more prone to evaporate because the blinking frequency is reduced and lacrimal dysfunction causes decreased secretion of tears. In addition, increased friction on the surfaces of the eyes and ocular surface damage leads to reduced expression of secretory mucin MUC5AC and membrane mucin resulting in tear film instability. Based on two factors, it is believed that high molecular weight hyaluronic acid (HMWHA) has a therapeutic effect in the treatment of Dry Eye. Due to its molecular biological effects, it has anti inflammatory and water retention properties. As regards treating dry eye disease, Fig.8 summarizes the recommended mechanism of ocular HMWHA drops. [53]

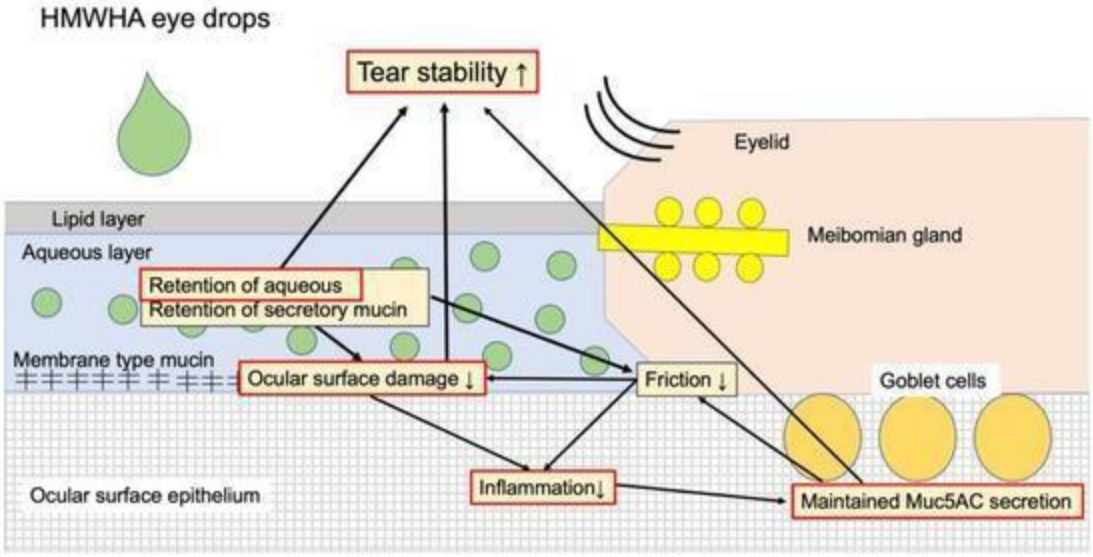

Fig 8: Recommended mechanisms of HMWHA Eye Drops in the treatment of dry eye disease

II. HYALURONIC ACID USED IN CONTACT LENSES:

The addition of hyaluronic acid to contact lenses works as a wetting agent in addition to helping with dry eye therapy. The most important molecule for treating dry eye with contact lenses is hyaluronic acid. Although a higher concentration of HA has relatively high initial release rate, an increase in HA concentration does not prolong the release time. [54] HA is biocompatible and effective at keeping contact lenses wet. HA has been used in the contact lens industry for almost 20 years, and its uses include lens integration, surface modification, multipurpose fluid augmentation, eye medicine stabilisation, and drug release sustainment.[50] Contact lenses with HA modifications retain more surface water. [55] In order to improve their biocompatibility with human corneal epithelial cells, contact lenses include HA coatings on their surfaces. Contact lenses containing HA integrate and release more of the medicine, particularly hydrophobic drugs for 6 days. [56] [57] HA can be created as a film to cover contact lenses and temporarily bind to cells, preserving their viability to heal corneal injury. [58] HA is bonded to the surface of the contact lens. In addition, HA bound by HABpep significantly reduced the water loss of the modified contact lenses. [55]

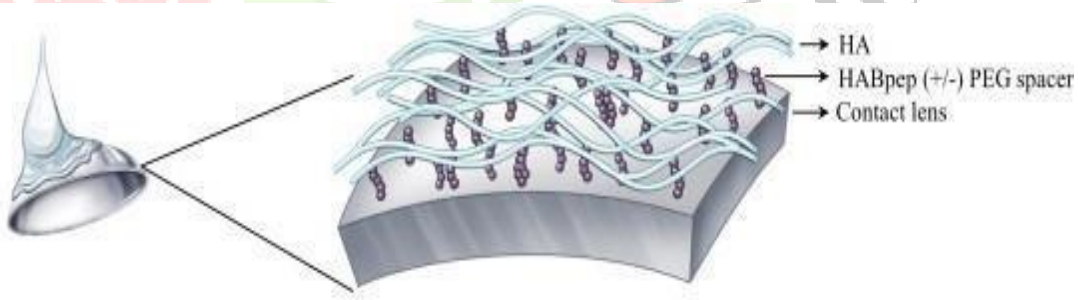

Fig 9: Surface-bound HA with HABpep improved the water retention of the modified contact lenses.

CONCLUSION:

Overall, hyaluronic acid is a promising ingredient that shows potential benefits in both cosmetics and pharmaceuticals. Further research is needed to fully understand its mechanisms of action and optimize its use in different applications.

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