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Plant-based hyaluronic acid for Osteoarthritis (OA)

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Abstract

Knee osteoarthritis is a degenerative joint disease that impairs quality of life. The burden and impact of Osteoarthritis (OA) in India are substantial and is increasing. Viscosupplementation (VS) with intra-articular hyaluronic acid (IA-HA) is a well-established treatment option in knee Osteoarthritis (OA). Hyaluronic acid (HA) injections are used to restore synovial fluid viscosity and improve joint function. Hyaluronic acid is a polysaccharide with various biological functions, widely used in medicine, cosmetics, and supplements. Hyaluronic acid (HA) injections, or viscosupplementation, inject gel-like fluid into joints to treat pain, stiffness, and improve mobility for mild-to-moderate osteoarthritis, primarily in the knee. Hyaluronic acid (HA) is also found as a component of synovial fluid, where it is the main regulator of fluid viscoelasticity and provides lubrication to the joint. Plant-based hyaluronic acid is categorized into three types: Food Grade, Cosmetic Grade, and Medical Grade. A specific high-molecular-weight hyaluronic acid derived from plant, known as **GreenIuronic®**, has been researched for its ability to cross the intestinal barrier, modulate molecular mechanisms to prevent and restore cartilage degradation in osteoarthritis (OA) models. Plant-derived HA (like GreenIuronic) helps by reducing joint inflammation, protecting and regenerating cartilage. and retaining moisture to lubricate joints. Transgenic *Nicotiana tabacum* hairy roots, engineered with the human hyaluronan synthase 2 gene, produced high concentrations of hyaluronic acid (HA), verified via SEM and ELISA. Additionally, hyaluronic acid can be found in some mollusks, yeasts, bacteria, and algal viruses. However, to date, hyaluronic acid has not been identified in fungi, plants, or insects.

Keywords: Arthritis; Osteoarthritis; Cartilage inflammation; GreenIuronic®; High molecular weight hyaluronic acid; Intestinal absorption; Chondrocytes

1. Introduction

Arthritis is a common health issue that affects billions of people throughout the world [1-20]. Patients suffering from arthritis struggle with severe joint pain and arthritis experience persistent pain [1,2-15]. The burden and impact of OA in India are substantial and is increasing [32, 33]. More than 100 types of arthritis have been identified [1-3-14]. Two of the most common types are osteoarthritis and rheumatoid arthritis [1,2-15-33-59]. Both osteoarthritis and rheumatoid arthritis impair joint structure and function but differ in symptoms, pathophysiology, and treatment. Osteoarthritis (OA), also known as degenerative joint disease, is the most common form of arthritis [1-4-25-49]. Osteoarthritis (OA) in India is a massive, growing public health concern, with cases nearly tripling from 23.46 million in 1990 to 62.35 million in 2019, and more than 100 million in 2025 [32, 33-59]. Prevalence is higher in women, older adults, and rural areas, driven by obesity, sedentary lifestyles, and daily habits like squatting or using Indian-style toilets [32, 33-59]. Adopting suitable control and preventive community measures to reduce modifiable risk factors (obesity, injuries, occupational stress) are needed to reduce the current and future burden of OA in India [32, 33-59]. Among the chronic rheumatic diseases, hip and knee osteoarthritis (OA) is the most prevalent and is a leading cause of pain and disability in most countries worldwide [32, 33]. Osteoarthritis (OA) is the most common age-related joint disease

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affecting more than 80% of people older than the age of 55 and one of the leading causes of elderly visits to hospital outpatient departments [32, 33-59]. Osteoarthritis is one of the major reasons for family physician visits and accounts for almost half of all non-steroidal anti-inflammatory drug (NSAID) prescriptions [32, 33-59]. Arthritis of the knee and hip in particular can compromise activities such as walking, climbing stairs, and self-care [32, 33]. Osteoarthritis especially of the hip and knee not only affects the quality of life of the individual physically but also emotionally and socially [32, 33-59-112]. India has a high share of population beyond 55 years of age, and as the population ages, the economic impact of OA is expected to increase proportionately [32, 33]. By 2050, India's 60 and older population is expected to encompass 523 million people, a number greater than the total US population in 2012 [32, 33-59]. Despite the prevalence and burden of OA in India, there is little published data on epidemiology and long-term treatment outcomes from the subcontinent [32, 33-59]. Its prevalence increases with age and generally affects women more frequently than men [32, 33-59]. OA is strongly associated with aging and heavy physical occupational activity, a required livelihood for many people living in rural communities in developing countries[32, 33-59-112].

Migliorini et al., (2025) [35] reported that HA injections lead to an initial worsening of symptoms. However, patients with early stage osteoarthritis, particularly older women, may experience significant long-term improvements [35-59]. Osteoarthritis (OA) affects more than 7.6% of the global population and poses a significant socioeconomic burdan[35-57-112]. Intra-articular hyaluronic acid (IAHA) has emerged as a pivotal non-surgical intervention for alleviating symptoms and delaying disease progression [1,2-59-112]. Hyaluronic acid is scientifically used to support and treat certain types of arthritis, particularly osteoarthritis, most commonly through intra-articular (joint) injections [1,2-59-112].

2. Osteoarthritis (OA)

Osteoarthritis (OA) is a chronic degenerative disorder of multi-factorial etiology characterized by the loss of articular cartilage, hypertrophy of bone at the margins, subchondral sclerosis, and range of biochemical and morphological alterations of the synovial membrane and joint capsule [1-32-59]. Osteoarthritis (OA) is a biomechanical and inflammatory disease influenced by several factors such as mechanical and oxidative stress, injury, age, obesity, and metabolic disease [1-5-23-33]. OA is characterized by joint cartilage degeneration, changes in the underlying bone, and synovitis [1-6-25-59]. Extracellular matrix breakdown can trigger the accumulation of innate immune cells that lead to inflammation and tissue destruction [1-7-25-59].

Migliore and Procopio (2015) [1] reviewed that osteoarthritis (OA) is a chronic degenerative joint disease characterized by pain and progressive functional limitation[1-30]. Viscosupplementation with intra-articular hyaluronic acid is a treatment option in knee [1]. OA that is included in the professional guidelines for treatment of this joint disease, but potentially should apply to all synovial joints in order to reduce pain and improve joint lubrication[1-59]. Exogenous HA can enhance chondrocyte HA synthesis, prevent the degradation of cartilage and promote its regeneration [1-26-59]. Viscosupplementation (VS) with intra-articular hyaluronic acid (IA-HA) is a well-established treatment option in knee OA [1-30-59]. Furthermore, it is included in the professional guidelines for treatment of the joint pain disease [1-30-59]. It is applied theoretically to all synovial joints in order to reduce pain, improve joint function and contrast joint damage [1-33]. Hyaluronic acid (HA), an integral component of both the synovial fluid and articular cartilage, has gained widespread usage in developing hydrogels that deliver cells and biomolecules to the OA [1-30-59-112]. The hyaluronic acid (HA) products market is dominated by single-cycle injection products as they are majorly used in **viscosupplementation** for osteoarthritis and other conditions [58-59]. They provide a simple, effective one-time treatment for enhancing joint function and reducing pain[1-30-59-112]. The primary benefit of single-cycle injections is that they are convenient. Patients are treated with a quick, easy solution without requiring multiple treatment sessions. This ease of use, in combination with immediate results, has made them be an attractive option to the group of people seeking quick relief from joint pain [1-30-59-112].

3. Knee Gel Injections

Hyaluronic acid (HA) injections, or viscosupplementation, inject gel-like fluid into joints to treat pain, stiffness, and improve mobility for mild-to-moderate osteoarthritis, primarily in the knee [1-30-59-97-112]. Hyaluronic acid (HA) lubricates joints and acts as a shock absorber, often providing relief for 3–6 months [1-30-59]. While generally safe, common, short-lived side effects include soreness and swelling [1-33-59-112]. HA injections can offer relief for up to six months, though studies showed mixed results, with some individuals seeing no improvement (30-40% of patients) [1-33-59-112].

HA is abundantly distributed in the human body as well as in other vertebrates. Additionally, it can be found in some mollusks, yeasts, bacteria, and algal viruses[59]. To date, it has not been identified in fungi, plants, or insects [59]. In the human body, HA acts as a passive structure on the basis of its physico-chemical properties, or as a signaling molecule by interacting with its binding proteins[59]. HA is also an important component of the skin in both the dermis and epidermis [59]. Due to its unique hygroscopic properties, it hydrates the skin and, together with collagen and elastin fibers, gives skin tissue its characteristic physical properties and thus helps it to fulfill its natural role [1-58,59]. HA also works as a lubricant and space filler in synovial fluids, reducing fractions and abrasions and absorbing pressure between articular cartilage [1-58, 59-97-112].

Hyaluronic acid (HA) is a complex sugar molecule that occurs naturally in the body, especially in the eyes, skin and joints [1-33-59-112]. The molecular weight of HA could play a critical role in its therapeutic efficacy [18–21-59]. HA products are categorized on the basis of their molecular weight into low, medium and high molecular weight preparations, each purported to have different biological effects and side effect profles [18–21-59-112]. Hyaluronic acid formulations are categorized as low (approximately 500–730 kDa), medium (800–2000 kDa) and high (>2000 kDa) molecular weights [35-59]. It attracts and retains moisture, making it an exceptional topical moisturizer for eyes and skin. HA serums are also important for healing wounds and regenerating scar tissue[1-30]. Furthermore, many people receive hyaluronic acid and other types of joint injections for arthritis pain [18–21-59]. Some of Common brands are, Synvisc®, Hyalgan®, Orthovisc®, Monovisc®, Supartz®, Euflexxa®, and Gel-One®[1-30]. HA injections are often considered when non-surgical treatment options have not worked or to delay joint replacement surgery [1-33-59]. They are not usually recommended for severe, late-stage osteoarthritis[1-30-112]. Costs can vary by brand, with some options being more affordable than others. Knee gel injections are a treatment for arthritis in knee joint [1-30-59]. Technically, they are hyaluronic acid injections. Hyaluronic acid is a natural lubricant found in many of body's tissues[1-30]. It is also the main ingredient in synovial fluid, which lubricates joints. It has a viscous quality — thick and gel-like[1-30-59-112]. Viscosupplementation injections are currently only FDA-approved to treat arthritis of the knee [1-30-59-112]. However, some healthcare providers do offer it as a treatment option, and some people do get gel injections in their other joints [1-30-59-112]. Treating knee arthritis requires a multi-pronged approach [1-30-112]. Healthcare providers usually recommend starting with first-line treatments for arthritis of the knee before moving on to injections [1-30]. When these treatments are not quite doing enough, knee injections can offer an extra boost of relief [1-30-112]. Hyaluronic acid is a lubricant for knee. Injections into the joint (intra-articular injections) can replace the synovial fluid, which have lost to help cushion knee joint [1-30-59-112]. Some studies have found that hyaluronic acid might also be chondroprotective, meaning it might slow down the progress of arthritis [1-30-59]. The most common side effect is mild pain and swelling at the injection site that goes away on its own[1-33]. About 1% of people have a more severe reaction called an injection flare. It causes fluid to accumulate in the joint, with significant swelling and pain [1-30-58-112].

Migliorini et al., (2025) [35] reviewed that the impact of molecular weight, patient demographics, disease severity and the use of different patient-reported outcome measures in patients who undergo intra-articular injections of hyaluronic acid (HA) for knee osteoarthritis is debated [35-59]. During the first 4 weeks following HA injections, patients with early-stage osteoarthritis eventually showed improvement, whereas patients with advanced osteoarthritis report worsening [35-59]. Patients who undergo intra-articular injections of hyaluronic acid in the knee with advanced osteoarthritis reported worsening [35-45]. Older women who undergo intra-articular injections of hyaluronic acid for knee osteoarthritis reported favorable outcomes in pain [35-112].

Migliorini et al., (2025) [35] reported that patients should be advised of findings suggesting a temporary PROM worsening during the first 4 weeks following HA injections [1-35-49]. However, PROM improvements are noted after this period in patients with early stage osteoarthritis; the effect of HA injections in those with advanced knee OA is more debatable[35-59]. Notably, older women demonstrated favorable results in VAS and WOMAC scores [35]. Despite the symptomatic relief provided by HA injections, the diversity in study designs and the lack of standardised treatment protocols significantly hinder the interpretation of these findings [35-112]. Furthermore, the predominance of studies with short-term follow-up contributes to the limitations in assessing long-term efficacy [35-59]. Higher molecular weight HA may be more beneficial for specific patient groups, yet evidence remains sparse [35-59]. The single-cycle injections are relatively more economical as compared to the multi-cycle, hence cost-effective to the patients and the healthcare providers [35-59]. This advantage in combination with a rise in consumer preference for non-invasive treatments has increased the demand for single-cycle HA products[35-112].

4. Hyaluronic acid (HA): Hydrogel

One of the potential reasons for the reported ineffectiveness of HA injection treatment is the short retention period of HA within the joint cavity, thus requiring repeated intraarticular injections to demonstrate its therapeutic efficacy [1-33]. Several research studies have thus focused on enhancing the retention of HA in the synovial fluid by delivering HA

as a component of a composite hydrogel [1-33-59]. The fabrication of such hydrogels most often involves modifying the backbone of HA with a reactive group, such as tyramine, vinyl sulfone, and hydrazide, and combining it with a second polymeric chain that will undergo either a non-covalent interaction or covalent cross-linking with the modified HA chain[1-33]. RegenoGel is an injectable, covalently conjugated HA–fibrinogen hydrogel that undergoes gelation within the joint by the interaction of thrombin on fibrinogen [1-33].

5. Hyaluronic Acid

Hyaluronic Acid (HA) polymer was first discovered in 1934 by Karl Meyer and John Palmer, who isolated it from the vitreous humor of bovine eyes [1-30-59-87-90]. Hyaluronic Acid (HA) was isolated from various biological sources, including pig skin, rooster comb, and human skin [1-34-59-85-112]. HA is a key constituent of the extracellular matrix in animal tissues, particularly notable in the dermis, ocular regions, articulations, and synovial fluid [58-87]. It plays critical roles in preserving tissue architecture, hydration, lubrication, promoting wound repair, and facilitating cellular signaling [1-24, 25-34-59-87-112]. Hyaluronic acid is a polysaccharide with various biological functions, widely used in medicine, cosmetics, and supplements[1-34-59-90]. Recently, hyaluronic acid has gained attention as a functional ingredient in food and dairy products due to its viscoelastic and health properties [1-34-59]. The global market for hyaluronic acid (HA) is anticipated to experience substantial growth, increasing from an estimated USD 8.3 billion in 2018 to USD 16.8 billion by 2030, with a predicted Compound Annual Growth Rate (CAGR) of 7.8% from 2024 to 2030 [1, 2-34-85]. The pharma-grade hyaluronic acid market is demonstrating robust growth, expanding from USD 1.71 billion in 2025 to USD 1.83 billion in 2026 and anticipated to reach USD 2.82 billion by 2032 at a CAGR of 7.36% [85].

Hyaluronic acid (HA) is a heteropolysaccharide with a linear molecule, consisting of repeating disaccharide units made up of N-acetyl-D-glucosamine (GlcNAc) and Dglucuronic acid (GlcA) [-3-GlcNAc-1-β-4-GlcA-1-β-]n. It was first isolated in 1934 by Karl Meyer and John Palmer from the bovine eye vitreous body. Its name is a conjugation of hyaloid (vitreous body) and uronic acid [59-85-90]. It is ubiquitously present in vertebrates, but it has also been identified in some mollusks, fungi, bacteria, and algal viruses[1-34-59]. In microorganisms, the production of HA is a virulence factor [1-59]. In vertebrates, including humans, HA fulfills a variety of functions [20-59]. It is a major compound of the extracellular matrix, eye vitreous humor, and cartilage joints and, as a signaling molecule, it plays a crucial role in an array of physiological and pathological processes, such as fertilization, embryogenesis, inflammation, wound healing, angiogenesis, and even carcinogenesis [59-87-90].

Hyaluronic Acid (HA) also historically known as hyaluronan, is a linear unbranched polysaccharide polymer composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine linked by β−1,3 and β−1,4 glycosidic bonds, which can reach a MW of up to 2 × 107 Da [1-21-31-59-87]. The molecular architecture of HA is characterized by the presence of hydrophilic groups, including hydroxyl, carboxyl, and acetamido functionalities, which confer its high solubility in water and significant hydrophilicity [1-21-31-59]. Moreover, HA's biological functions and bioactivity of HA are influenced by its molecular weight (MW), purity, structure, and partition coefficient [1-21-31-59-85]. Exceptional capacity of HA to bond with other substances (due to its chemical structure and different MWs), lack of toxicity, non-immunogenicity, biocompatibility, and biodegradability makes it an interesting candidate for research applications in a wide variety of fields [1-30-59]. HA has garnered significant attention in biomedical research due to its multifaceted biological functions. Its broad applicability spans diverse domains, including cosmetic dermatology, ophthalmology, rheumatology, tissue engineering, biosensors, drug and gene delivery, wound healing, and targeted cancer therapies [1-31–34-59-85]. While HA has an extensive history of use in the biomedical sector, it has recently garnered increased attention and acceptance as a dietary supplement attributed to its advantages in skin rejuvenation and joint health [1-21-31-59]. Furthermore, there has been a growing interest in the potential benefits of HA in food applications, driven by its functional physicochemical properties such as water binding, gel formation, emulsification, and its ability to bind with various organic and inorganic materials [1-18-33-85]. Consequently, research on the application of HA in the food industry and related domains has gained significant traction[1-34-59]. HA is also found as a component of synovial fluid, where it is the main regulator of fluid viscoelasticity and provides lubrication to the joint [1-23-59-85].

In cartilage and synovial fluid, HA is a widely distributed, high molecular weight material. It serves a number of purposes in the joint, such as lubricating, filling in gaps to maintain joint mobility, and controlling cellular processes like protein binding [1-44-59-85]. The endogenous HA in the joint breaks down from a high molecular weight (6500-10,900 kDa) to a lower molecular weight (2700-4500 kDa) as OA worsens [44-59-85]. As a result, the affected joint's synovial fluid has less mechanical and viscoelastic qualities [44-59]. It has been demonstrated that intra-articular HA injections enhance synovial fluid viscosity and joint lubrication, restore hyaluronan synthesis, prevent proteoglycan degradation, and provide analgesic and anti-inflammatory benefits when treating OA [44-59]. Intra-articular corticosteroids exert

anti-inflammatory effects by blocking the production of inflammatory cytokines [44-59]. However, their duration of effect is significantly shorter than the recommended interval between administration doses [44-59-87].

The global sales of hyaluronic acid products market is estimated to be worth USD 9.43 billion in 2025 and anticipated to reach a value of USD 15.94 billion by 2035. Sales are projected to rise at a CAGR of 5.4% over the forecast period between 2025 and 2035. The revenue generated by hyaluronic acid products market in 2024 was USD 8,878.3 million[1-34-59-87]. The industry is anticipated to exhibit a Y-o-Y growth of 5.5% in 2024. Hyaluronic acid is a formulation-based product that takes advantage of the natural molecule hyaluronic acid to trap moisture, acting in enhancing skin hydration[1-34-59]. They are used mainly for cosmetic applications: as injectable fillers in skin, to moisten cosmetics, and products against wrinkles, treatments involving joint lubrication in osteoarthritis; eye care; and management in the healing of wounds [1-58, 59-87].

6. Commercial Production of Hyaluronic acid

Streptococcus zooepidemicus is the primary bacteria used for industrial hyaluronic acid (HA) production, favored for its high yield and ability to produce high molecular weight HA [86,87-96]. Based on recent literature, *Streptococcus equi* subsp. *zooepidemicus* (SEZ) is a significant, opportunistic Gram-positive bacterium, primarily causing infections in horses, but increasingly recognized as a pathogen in pigs, dogs, and humans [86,87-96]. Other natural producers include pathogenic *Streptococcus* species (Group A and C) and *Pasteurella multocida*[86]. Modern research also utilizes genetically engineered GRAS (Generally Recognized As Safe) bacteria like *Bacillus subtilis* and *Lactococcus lactis* [86, 87-96]. HA polymer is also naturally produced by other pathogenic bacteria including *Streptococcus pyogenes, Streptococcus uberis, Pasteurella multocida* and *Cryptococcus neoformans*[86, 87-96].

7. Plant-based Hyaluronic acid

Plant-based hyaluronic acid is categorized into three types: Food Grade, Cosmetic Grade, and Medical Grade [1-23-34]. Food Grade is used in nutritional supplements and functional foods, driving demand for health-conscious consumers. Cosmetic Grade serves in skincare and beauty products, appealing to the growing market focus on natural ingredients for anti-aging and hydration[1-23-34]. Medical Grade is utilized in advanced therapeutic applications, such as injections and wound care, attracting healthcare sectors [1-21-34]. The diverse applications across these categories contribute to the overall growth in the plant-based hyaluronic acid market, fuelled by increasing consumer awareness and preference for sustainable, plant-derived solutions[1-23-34-59]. The future of plant-based hyaluronic acid appears promising, driven by advancements that are expected to significantly contribute to market expansion. Companies are increasingly prioritizing innovation and sustainability to align with consumer demands for eco-friendly and effective ingredients [1-23-34-45]. The growing awareness of the benefits associated with plant-derived products is fostering a shift in preferences, leading to heightened interest in natural alternatives[1-23-34]. This focus on sustainability not only enhances product appeal but also aligns with global trends towards healthier and environmentally conscious choices[1-23-34]. As a result, the market for plant-based hyaluronic acid is anticipated to experience strong growth potential through 2033, driven by ongoing research, product innovation, and a commitment to addressing consumer needs[1-23-34-49].

Plants do contain the precursor molecules required for the synthesis of hyaluronic acid (HA), namely UDP-glucuronic acid and UDP-N-acetylglucosamine. These precursors are produced in plants as part of normal metabolic processes, such as glycolysis and the pentose phosphate pathway. However, plants do not naturally produce hyaluronic acid themselves because they lack the necessary enzyme, hyaluronic acid synthase (HAS). Naturally, plants do not produce hyaluronic acid (HA), as they lack the necessary enzymes (hyaluronic acid synthase) to create it. However, "plant-based" or vegan HA in cosmetics is produced through the bio-fermentation of plant sugars (like corn or wheat) using bacteria. Research has enabled the engineering of transgenic plants (e.g., tobacco) to produce HA [1-34-59].

Plant-based hyaluronic acid is often extracted from *Tremella fuciformis*, the Chinese trembling mushroom [1-23-34]. More often, however, Indian senna (*Cassia angustifolia* or *Senna alexandrina*) is the source of plant-based hyaluronic acid. Research indicates that White Tremella (Silver Ear mushroom, *Tremella fuciformis*) is a plant-based source of hyaluronic acid (HA) that has been studied for its potential to improve joint pain in osteoarthritis (OA) [1-23-34]. A specific high-molecular-weight hyaluronic acid derived from this plant, known as GreenIuronic®, has been researched for its ability to cross the intestinal barrier and modulate molecular mechanisms to prevent and restore cartilage degradation in OA models [1-23-34]. It also forms a film that protects the skin from moisture loss. Hyaluronic acid is scientifically used to support and treat certain types of arthritis, particularly osteoarthritis, most commonly through intra-articular (joint) injections[1-34-59-112]. The rationale is based on hyaluronic acid's natural presence in synovial

fluid, where it acts as a lubricant and shock absorber for joints[1-23-34-59]. Research indicates that osteoarthritic joints have decreased quality and quantity of hyaluronic acid, leading to increased friction, pain, and inflammation [1-23-34-59]. Numerous randomized controlled trials and meta-analyses have evaluated the efficacy of hyaluronic acid injections (viscosupplementation) for knee osteoarthritis[1-23-34-59]. Some studies showed modest improvements in pain and joint function, especially in those who do not respond to first-line therapies like acetaminophen or NSAIDs[1-23-34-59]. However, the benefit appears to be moderate and may not be significantly better than placebo in all cases. Some suggest that hyaluronic acid injections may be considered for select patients, while others note that the clinical benefits are limited [1-23-34-112]. Overall, hyaluronic acid use for arthritis is scientifically justified, but its efficacy is moderate, and it is not recommended as a first-line treatment [1-23-34-59-112]. Recent research has identified plant-based sources of hyaluronic acid (HA) or compounds that stimulate its production, offering a potential natural remedy for managing osteoarthritis (OA) pain [1-23-34-59]. The primary plant-based source of high-molecular-weight HA is the fungus *Tremella fuciformis* (silver ear mushroom) [1-23-34-58]. Hyaluronic acid is a key component of synovial fluid that acts as a lubricant and shock absorber in joints [1-23-34]. In the osteoarthritis (OA), the concentration of HA decreases, leading to pain and cartilage damage[1-34-59]. Plant-derived HA (like GreenIuronic) helps by reducing joint inflammation, protecting and regenerating cartilage. and retaining moisture to lubricate joints[1-23-34-58].

Galla et al., (2022) [27] reviewed that hyaluronic acid (HA) has attracted great attention as a new treatment option for osteoarthritis [27-59]. Classical therapies are not able to stop the cartilage degeneration process nor do they favor tissue repair. Nowadays, it is accepted that high molecular weight HA can reduce inflammation by promoting tissue regeneration[27]. Galla et al., (2022) [27] reported that the efficacy of a new high molecular weight HA of plant origin (called GreenIuronic®) in maintaining joint homeostasis and preventing the harmful processes of osteoarthritis [27]. According to Galla et al., (2022) [27], the bioavailability of GreenIuronic® was investigated in a 3D intestinal barrier model that mimics human oral intake while excluding damage to the intestinal barrier [27]. Furthermore, the chemical significance and biological properties of GreenIuronic® were investigated in conditions that simulate osteoarthritis[27]. Galla et al., (2022) [27] demonstrated that GreenIuronic® crosses the intestinal barrier without side effects as it has a chemical–biological profile, which could be responsible for many specific chondrocyte functions [27]. Furthermore, in the osteoarthritis model, GreenIuronic® can modulate the molecular mechanism responsible for preventing and restoring the degradation of cartilage [27]. According Galla et al., (2022) [27], this new form of HA appears to be well absorbed and distributed to chondrocytes, preserving their biological activities[27]. Galla et al., (2022) [27] confirmed that, the oral administration of GreenIuronic® in humans can be considered a valid strategy to obtain beneficial therapeutic effects during osteoarthritis [27]. The results of study by Galla et al., (2022) [27] showed that this new form of plant HA is likely absorbed and distributed to the chondrocytes, while preserving its biological activities[1-27]. Although the *in vitro* data are very clear and promising, *in vivo* or even human studies would be needed to confirm these observations, before assuming an absolute efficacy of this HA extracted from plants [27]. Thus, despite the fact that data by Galla et al., (2022) [27] derived from an *in vitro* study, need further validation, the results of the present study about the effectiveness in improving chondrocyte function in conditions that mimic OA, may support the hypothesis that the oral administration of GreenIuronic® in humans can be considered a valid therapeutic strategy to obtain beneficial therapeutic effects during OA [27]. In particular, it can be hypothesized that these promising beneficial effects are relevant not only to the joint, but also to any OA-induced damage [27].

Thus far, HA has been extracted from animal waste, including bovine eyes and rooster combs [27-59]. Currently, this procedure is being replaced by production through bacterial fermentation [58]. These mentioned methods suffer from some major disadvantages, including possible contamination with the animal or bacterial toxins, expensive investment in scaling-up production systems, and the time-consuming processes of extraction and purification [58]. In recent years, there has been an increasing attempt to find an ideal bioreactor for HA production[58, 59].

HA is widely found in nature for instance in vertebrates, the capsular component of certain bacteria, the green algae Chlorella sp. affected by the Chlorovirus, yeasts, and mollusks [58]. However, it is not found in plants, insects, and fungi [58, 59]. Since the natural HA-producing organisms are mostly pathogenic, metabolic engineering currently represents an interesting opportunity to obtain HA from non-pathogenic, generally regarded as safe (GRAS) organisms[58]. The use of plant-based expression platforms offers some advantages for the production of recombinant human proteins compared to conventional expression systems such as bacterial, yeast, and animal cells[58]. The particular benefits of the plant-based systems are high scale-up capacity, low purification costs, lack of harmful substances or endotoxins, high stability of the engineered product, unique glycosylation patterns, and the capability of producing proteins with desired post-translational modifications [27-59].

Hyaluronic acid (HA), a unique polysaccharide with excellent physico-chemical properties, is broadly used in pharmaceutical, biomedical, and cosmetic fields [20-59]. It is widely present in all vertebrates, certain bacterial strains, and even viruses while it is not found in plants, fungi, and insects[58]. HA is naturally synthesized by a class of integral

membrane proteins called hyaluronic acid synthase (HAS) [12-58]. Thus far, industrial production of HA is carried out based on either extraction from animal sources or large-scale microbial fermentation[1-58]. The major drawbacks to using these systems are contamination with pathogens and microbial toxins[1-58]. Recently, the production of HA through recombinant systems has received considerable attention [58]. Plants are eco-friendly ideal expression systems for biopharmaceuticals production [58]. In one of the study by Nazeri et al., (2021) [58] reported the optimized human hyaluronic acid synthase2 (hHAS2) sequence was transformed into *Nicotiana tabacum* using *Agrobacterium rhizogenes* [58]. The highest rhHAS2 concentration of 65.72 ng/kg (wet weight) in transgenic tobacco hairy roots was measured by the human HAS2 ELISA kit [58]. The HA production in the transgenic hairy roots was verified by scanning electron microscope (SEM) and quantifed by the HA ELISA kit [58]. The DPPH radical scavenging activity of HA with the highest concentration of 0.56 g/kg (wet weight) showed a maximum activity of 46%[58]. Gel Permeation Chromatography (GPC) analyses revealed the high molecular weight HA (HMW-HA) with about > 0.8 MDa [58].

8. Plant-Based Sources and Boosters

- *Tremella fuciformis*: This fungus is used to create plant-based, high-molecular-weight hyaluronic acid that functions similarly to animal-derived HA for skin and joint health.
- GreenIuronic®: A new, high-molecular-weight, plant-derived HA that has shown promise in supporting joint homeostasis and treating cartilage degradation.
- Dietary Boosters: Leafy greens (spinach, kale), sweet potatoes, and soy-based foods (tofu, edamame) help the body naturally produce more HA through nutrients like magnesium.
- Herbal Agents: Plants do not directly containing HA, herbs such as *Boswellia serrata* and ginger are well-documented to help reduce arthritis pain and inflammation. *Boswellia* specifically known to attenuate inflammatory mediators. Vegetables: Food source which can boost natural hyaluronic acid in human body include spinach, kale, sweet potatoes, and soy. All of which helps to boost natural hyaluronic acid levels in the body for better skin hydration and joint health. Fruits: Citrus, avocado, and berries support hydration and skin health.

9. Hyaluronic acid (HA) in Food Industries

Sutariya et al., (2026) [23] reviewed that hyaluronic acid (HA) has been studied for various dairy ingredients and products, including milk, yogurt, cheese, whey proteins, and ice-cream [23]. Sutariya et al., (2026) [23] reported that hyaluronic acid (HA) is becoming popular as a food ingredient due to its health benefits, ability to bind water and modify viscosity [23]. Yogurt has been the most studied dairy product for examining the health and textural benefits of hyaluronic acid (HA) [23]. An additional advantage of incorporating hyaluronic acid (HA) in yogurt is the health benefits it offers compared to traditional texturizing ingredients [23]. Hyaluronic acid (HA) ability to hold on to moisture, maintain joint function, and provide anti-aging qualities can be advantageous in dairy products such as kefir [23]. Sutariya et al., (2026) [23] also confirmed that a randomized, double-blind, placebo-controlled trial with 40 healthy adults experiencing mild joint soreness found that consuming yogurt containing HA (MobileeTM) daily for 90 days significantly enhanced knee extensor muscle strength [23]. The yogurt containing sodium hyaluronate (0.005-0.01%) and collagen peptide (0.03–0.07%) developed to potentially reduce and prevent age spots and pigmentation, replenish body water, and enhance bone and joint functions in the consumers [23]. After yogurt, another dairy product recently getting researcher's attention to explore the benefits of HA is cheese, ice-cream, and milk protein ingredients [23]. Application of HA in cheese, has shown to improve the cheese's structural stability, water affinity, casein network, and enhancing stretchability [23]. HA also improved cheese whiteness, with low MW HA in cheese showed better shred fusion and less browning in pizza baking [23]. Overall, low MW HA significantly enhanced Mozzarella cheese's structure, texture, and functionality [23]. HA has a long history of application in the biomedical field owing to its viscoelastic properties and health benefits [23]. However, it has recently gained attention for its application in food formulations [23]. Research exploring the application of HA in foods such as sausage, tilapia protein isolate, milk, yogurt, cheese, and whey protein products has shown positive results with HA's significant water-binding, viscoelastic, and emulsification properties [23]. Sutariya et al., (2026) [23] are of the opinin that HA has shown great promise in the development of edible packaging and food flavor enhancers, HA's gelation and emulsification capabilities of HA are also helpful in food formulations containing nano-emulsion gels for flavonoids and other healthy compounds, which are otherwise difficult to incorporate in food because of their poor solubility, stability, and strong aroma[23]. Sutariya et al., (2026) [23] indicated that HA has great potential for application in food formulations with required gelation properties and health benefits, and it is just beginning to be led by the food industry in east Asia [23]

10. Hyaluronic acid (HA) in Osteoarthritis (OA)

Osteoarthritis (OA) is a slow progressive joint disorder that causes several disabilities in the adult population [1-34-59]. For a long time, OA was regarded as progressive wear of the joint cartilage alone. However, recent research has shown that it is an inflammatory disease of the entire synovial joint, which includes not only the mechanical degeneration of the articular cartilage, but also the concomitant structural and functional change of the entire joint, including the synovium, meniscus, periarticular ligaments, and subchondral bone [1, 2-34]. Today, the treatment modalities for OA include non-pharmacological (e.g., physiotherapy), pharmacological (e.g., steroidal and non-steroidal anti-inflammatory drugs), or intra-articular (e.g., injection of hyaluronic acid) therapies [1-4,5-34-59]. These classical therapies can reverse the symptoms only in a small number of cases, but they do not stop the degeneration process of the cartilage or promote the repair of the tissue[1-23-34].

Hyaluronic acid (HA) is a naturally occurring substance in the body that helps to lubricate and cushion the joints and keep the cells hydrated [1-23-33-59]. In some cases, hyaluronic acid (HA) injections may help to reduce the symptoms of osteoarthritis [1-23-34]. This treatment is most likely to be effective for individuals with mild to moderate osteoarthritis and may not work well for people with more severe symptoms[1-23-34]. However, there is less evidence to support this approach, and it is not a treatment that the Food and Drug Administration (FDA) has approved [1-23-34-59]. Hyaluronic acid (HA) is a substance that exists in the human body. It is a humectant, which means that it traps moisture inside cells, keeping them hydrated [1-23-34-59]. HA is part of the skin, eyes, and joints. Inside joints, HA is a key component of synovial fluid, which is responsible for cushioning and lubricating the bones as they move[1-23-34]. When a person has osteoarthritis, the joints are less able to glide smoothly due to cartilage degradation. The quality of the HA in the synovial fluid decreases, and inflammatory molecules become mixed into it. This can result in pain or swelling[1-23-34-59].

HA injections work by delivering HA directly to the joint, helping reduce friction and inflammation. In this way, they can decrease the symptoms of osteoarthritis for some people[1-23-34-59]. Research suggests that HA is an effective tool for managing osteoarthritis [1-23-34]. A person may require multiple HA injections before they notice an improvement in their symptoms. However, symptom relief from this treatment can last up to 6 months or possibly even 1 year in some cases[1-23-34].

Hyaluronic acid is a safe and effective treatment for many people with osteoarthritis[1-23-34-59]. It can reduce pain and help lubricate the joints. The effects of HA injections are temporary, so a person will need to have periodic courses of treatment to maintain the benefits. There may also be some mild pain or swelling at the injection site for a few days afterward. HA is not a cure for osteoarthritis[1-23-34-59]. It neither helps cartilage grow back nor improves the structure of the joints. Instead, it reduces inflammation. Therefore, the symptoms will eventually come back. A person will need to get HA injections periodically to maintain the effects[1-23-34]. People who may particularly benefit from HA injections include individuals who do not respond well to non-steroidal anti-inflammatory drugs (NSAIDs) and those with diabetes who wish to avoid taking corticosteroids. Corticosteroids are a class of drugs that can reduce inflammation, but they can also increase blood sugar levels[1-23-34].

HA is a non-sulfated glycosaminoglycan consisting of alternately repeating D-glucuronic acid and N-acetylglucosamine units[1-23-34-59]. HA exists naturally in various animal tissues, including rooster combs, shark skin, bovine eyeballs, bovine nasal cartilage, rabbit brain and heart and in various human tissues, including the umbilical cord, serum, vitreous body, dermis, epidermis, thoracic lymph, urine and synovial fluid (SF) [1-23-34]. However, the highest amounts of HA in the human body are found in the ECM of soft connective tissues [1-23-34]. In osteoarthritic joints synovial fluid contains a lower concentration of HA than in healthy joints, so intra-articular therapy with exogenous HA can restore its viscoelastic properties [1-23-34-59]. Indeed, exogenous HA can enhance chondrocyte synthesis of endogenous HA and proteoglycans, prevent the degradation of cartilage and promote its regeneration[1-23-34].

Moreover 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 and an excellent tolerability profile with a low incidence of complications at local level and absence of systemic effects [1-23-34]. A recent systematic review showed that Hylan GF-20 is a safe and effective treatment for decreasing pain and improving function in patients suffering from knee but also hip OA. Moreover new evidences are emerging for its use in other joints [1-23-34].

HA is a useful tool in OA treatment, with a potential structure-modifying activity. The structural effects of HA given as 5 weekly injections (20 mg/2 ml once a week for 5 weeks), were evaluated by microarthroscopy and morphological analysis of biopsy samples taken at baseline and after 6 months in an open clinical trial on 40 patients with knee osteoarthritis. At 6 months, compared to baseline, a statistically significant reconstitution of the superficial amorphous

layer of the cartilage, an improvement in the chondrocyte density and vitality, and a statistically significant reduction in synovial inflammation accompanied by a significant increase in the synovial repair process were observed [1-23-34]. Similar data were obtained in a prospective, controlled study of 1-year duration in which 36 patients with painful knee osteoarthritis were enrolled. After randomization, either conventional therapy or three cycles (every 3 months) of three intra-articular injections of Hyalgan (once a week) were given[1-23-34]. In another study, synovial membranes from patients with knee OA were examined by arthroscopy and by light and electron microscopy before and 6 months after local injection of HA (2 ml of 500–730.000 MW hyaluronan, 10 mg/ml in saline, one injection per week for 5 weeks) or MP (1 ml of methylprednisoloneacetate, 40 mg/ml, one injection per week for 3 weeks) [1-23-34]. Treatment with repeated cycles of IA-HA is suggested to delay surgical interventions in knee and hip osteoarthritis. Intra-articular hyaluronic acid is an useful therapeutic tool in the management of patients with osteoarthritis. Literature data seem to indicate its ability to reduce pain and improve joint function. Moreover, considering its high tolerability, its ability to contrast the structural joint damage and to delay the use of prosthetic surgery, it can be seen as a safe and effective long-term therapy. [1-23-34-59].

During the last decades, hyaluronic acid (HA) has attracted great attention as a new treatment option for knee OA pain [1-7–9-33]. Therefore, the native HA consists of 2000–25,000 disaccharide units, corresponding to 106–107 Da molecular weight; for that, a long chain contains more than 10,000 units, which is ~4000 kDa [9,11]. Applications of HA depend on its biological effects on cell differentiation and proliferation, and on its ability to lubricate, hydrate, and interact with various receptors present on the cell surface [1-23-34]. The safety, tolerability, and efficacy of HA-based formulations for the treatment of various types of joint diseases have been validated in several studies [1-10,15-33]. It is widely accepted that exogenous hyaluronic acid is incorporated into articular cartilage where it may have a direct biological effect on chondrocytes to improve joint lubrication as well described by clinical studies[1-23-34]. The concept of viscosupplementation is based upon the hypothesis that HA administration could improve the rheological properties of joints, and promote the endogenous synthesis of HMWHA and possibly more functional HA, thereby improving mobility, and articular function, and decreasing pain[1-23-34]. The growing use of HA in medical practice can be explained by its effectiveness and versatility as well as its favorable safety profile [16]. Nowadays, sodium HA seems to be the best choice available on market, since it exerts an analgesic effect by blocking pain receptors in synovial tissues and holding endogenous pain substances in its molecule [1-17]. Synovial inflammation and structural and molecular changes in the joint system should be the target of OA therapies[1-23-34-59].

11. Herbal medicine for Osteoarthritis (OA)

Osteoarthritis (OA) and rheumatoid arthritis (RA) are two major forms of arthritis associated with severe joint pain and reduced quality of life. Various pharmacological interventions may be utilized for arthritis treatment when non-pharmacological therapy is insufficient. However, pharmacological therapy can be associated with serious side effects and high costs[1-23-34]. Therefore, alternative therapies have been under investigation. Herbal medications have shown the potential for safe and effective management of arthritis. The herbs exhibited strong anti-inflammatory and anti-oxidant activities, contributing to a reduction in inflammation and tissue damage[1-23-34]. Several herbs elucidated new mechanisms for OA and RA treatment as well. Though these herbs have shown promise for OA and RA treatment, more studies and clinical trials are required for determining safety and efficacy, bioactivity, and optimal bioavailability[1-23-34]. Certain herbal medicines may be used as a complementary therapy to work with or reduce the need for pharmacological agents. Treatment with herbal medicines may also offer a safer alternative with equal or superior efficacy. The anti-arthritic mechanisms of herbs include inhibition of pro-inflammatory and pro-catabolic mediators such as cytokines, PGE2, MMPs, ROS, apoptotic proteins via signaling pathways (NF-κB, RANKL, and PI3K/Akt) [1-23-34]. These activities may contribute to improvement in OA and RA joint pain, inflammation, swelling, structure, and function, with minimal adverse effects[1-23-34]. A total of 23 clinical trials including 9 herbs: *Boswellia spp., Curcuma spp., Eremostachys laciniata, Eucommia ulmoides, Matricaria chamomillia L., Paeonia lactiflora, Tripterygium wilfordii Hook F, Withania somnifera, and Zingiber officinale* were reviewed[1-23-34].

- *Boswellia* spp : *Boswellia,* also known as frankincense, has been used for centuries in traditional Ayurvedic medicine. Boswellia is thought to exert its beneficial effects on arthritis by improving the knee joint gap, reducing osteophytes, and attenuating inflammatory mediators, such as C-reactive protein and hyaluronic acid, associated with knee OA [1-25,26-34]. The safety and efficacy of *Boswellia serrata* have been investigated in several studies.
- *Curcuma* spp: Roots of Curcuma are used as a spice commonly known as turmeric. Curcumin, a polyphenol extract of turmeric, is well known for its anti-inflammatory and antioxidant effects, and it has a long history of use in traditional Chinese and *Ayurvedic* medicine [1-28-34]. The anti-inflammatory activity of Curcuma may be attributed to multiple mechanisms [1-29-30].The short-term effects of highly-bioavailable curcumin (Theracurmin) on knee OA were investigated in a randomized, double-blind, placebo-controlled prospective

study [1-34]. A recent study reported that curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin, combined with diclofenac showed a greater improvement in pain and functional capacity with better tolerability in patients with knee OA [1-31].

- *Eremostachys laciniata*: Decoctions of the roots and flowers of the Iranian herb, *Eremostachys laciniata*, is usually given to alleviate inflammatory conditions, including arthritis [1-34]. One study has investigated the effects of topical *E. laciniata* application on arthritis pain and symptoms [2-34].
- *Eucommia ulmoides*: *Eucommia ulmoides* is an herb that has recently demonstrated potential for OA and RA reatment[1-23-34]. Furthermore, an aqueous extract of *E. ulmoides* was found to reduce serum MMP-1, MMP-3, and MMP-13 and protect the articular cartilage in a rat OA model [1-23-34].
- *Matricaria chamomilla* L: *Matricaria chamomilla*, also known as chamomile, has been used for centuries to treat joint pain [46,47]. The dried flower part of the plant has historically been used in the treatment of rheumatic pain and inflammation [1-23-34]. Now, chamomile is on the FDA's "generally recognized as safe" herbs list [46]. As a member of the *Asteraceae*; Compositae family, Chamomile has two common varieties, German chamomile, and Roman chamomile [1-23-34]. The most popular formulation of chamomile is herbal tea [58]. Chamomile contains several phenolic compounds such as apigenin, quercetin, patuletin, luteolin, and glucosides. These compounds showed anti-inflammatory action by reducing cytokines and PGE2, which play a role in the pathogenesis of arthritis [1-23-34]. Another trial found that daily consumption of 6 g of chamomile tea was associated with a reduction in tender joints and erythrocyte sedimentation rate compared placebo for RA patients [1-23-34].
- *Paeonia lactiflora* Radix Paeonia: The dried root of *P. lactiflora* Pallas, has a history of traditional use in Chinese medicine [1-23-34]. Decoctions of Radix Paeoniae have been used in the treatment of RA and other inflammatory/autoimmune disorders [1-23-34]. However, one study found that an ethyl acetate (EA) extract (at doses between 180 mg/day and 570 mg/day) and a polyglycoside preparation inhibited joint swelling and suppressed adjuvant arthritis with less adverse events in comparison to other preparations [1-23-34].
- *Withania somnifera*: *Withania somnifera* (Ashwagandha) is an *Ayurvedic* medicine known for its anti-inflammatory and analgesic effects [1-23-34]. *W. somnifera* extract has been found to inhibit the production of TNF-α, IL-1β, and IL-12 by diminishing the activation of NF-κB and activator protein 1 (AP-1) signaling pathways [1-23-34]. *W. somnifera* extract also slowed the degradation of bovine Achilles tendon type I collagen by inhibiting the activity of collagenase [1-23-34]. Treatment with *W. somnifera* decreased swelling, redness, deformity, and ankylosis in a collagen-induced arthritis rat model. A recent study has demonstrated its analgesic effects in patients with knee OA [1-23-34].
- *Zingiber officinale*: *Zingiber offcinale*, commonly known as ginger, is strongly associated with relieving inflammatory symptoms [1-23-34]. The anti-inflammatory activities of ginger have been widely investigated in patients as well as *in vitro* and *in vivo* models. Another study revealed that ginger extract was associated with reducing knee pain and WOMAC indices, although it was associated with gastrointestinal side effects [1-23-34].

12. Conclusion

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by progressive damage of articular cartilage and underlying bone. It is a common rheumatic disease that affects both genders and the majority of older people, but also younger subjects with consequent loss of workdays. As a chronic degenerative and inflammatory disease, OA affects the lives of hundreds of millions of people around the globe. HA injection is one of the most widely used methods to treat OA pain. Hyaluronic acid injections are majorly used in medical procedures for providing hydration, lubrication, and cushioning in an individual's body. They have ability to retain moisture and improve elasticity in tissues. These injections are widely used in aesthetic dermatology for dermal fillers to smoothen wrinkles, restore facial volume, and enhance skin rejuvenation. They also find their application in orthopedics for viscosupplementation in osteoarthritis patients as a reliever of articular pain, helping to restore mobility without any surgical interventions. However, its efficacy in altering disease progression has not been shown. During the last decades, hyaluronic acid (HA) has attracted great attention as a new treatment option for knee OA pain. HA injections work by delivering HA directly to the joint, helping reduce friction and inflammation. In this way, they can decrease the symptoms of osteoarthritis for some people. *Streptococcus zooepidemicus* is a primary industrial bacterium used for the high-yield fermentation of hyaluronic acid (HA), crucial for pharmaceuticals, cosmetics, and food. This Gram-positive bacterium produces high-molecular-weight HA, with optimized strains capable of producing up to 29.38 g/L.

The herbs exhibited strong anti-inflammatory and anti-oxidant activities, contributing to a reduction in inflammation and tissue damage. Hyaluronic acid (HA) is becoming popular as a food ingredient due to its health benefits, ability to bind water and modify viscosity. The HA production in the transgenic hairy roots was verified by scanning electron microscope (SEM) and quantifed by the HA ELISA kit. Yogurt has been the most studied dairy product for examining the

health and textural benefits of hyaluronic acid (HA). The efficacy of a new high molecular weight HA of plant origin (called GreenIuronic®) in maintaining joint homeostasis and preventing the harmful processes of osteoarthritis has been reported. The future of plant-based hyaluronic acid appears promising, driven by advancements that are expected to significantly contribute to market expansion. Companies are increasingly prioritizing innovation and sustainability to align with consumer demands for eco-friendly and effective ingredients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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