Plant-Based Chondroitin Sulfate from *Laminaria Japonica* as a Future Direction in Nutritional Interventions for Joint Repair with Improved Safety, Bioavailability, and Clinical Tolerance

A Plant-Based Alternative Centered on High Purity, Molecular Consistency, and Enhanced Absorption Efficiency

Abstract

This paper reviews and synthesizes mechanistic, pharmacokinetic, and clinical evidence for plant-based chondroitin sulfate (CS) derived from *Laminaria japonica* as a next-generation structural nutrient for joint repair.

Conventional animal-derived CS suffers from batch heterogeneity, broad molecular-weight distributions, residual impurities, and variable tolerability. In contrast, plant-based CS manufactured via directed enzymatic hydrolysis and standardized purification yields high purity (>90%), low-molecular-weight enrichment (≈1-10 kDa), and uniform sulfation patterns, which together enhance intestinal absorption, raise systemic exposure, and improve clinical reproducibility.

Mechanistically, plant-based CS promotes ECM synthesis (type II collagen, aggrecan), inhibits catabolic enzymes (MMPs/ADAMTS), optimizes synovial viscoelasticity, and buffers inflammation by down-regulating NF-κB–dependent mediators (TNF-α, IL-1β, IL-6, PGE_2, NO).

Process-driven immune inertness and barrier compatibility support long-term safety and adherence, addressing key limitations of NSAIDs and animal-derived formulations. Converging RCTs with pharmaceutical-grade CS indicate symptom relief comparable to celecoxib with superior tolerability, and imaging/biomarker data suggest structural protection consistent with disease-modifying nutritional intervention (DMNI) potential.

Synergies with undenatured type II collagen (UC-II), glucosamine sulfate, hyaluronic acid, and vitamin D further extend benefits across the *"structure-inflammation-immunity"* axes and into sports-related joint stress.
We conclude that plant-based CS represents a credible, scalable upgrade path for long-term joint management - particularly for gastrointestinal-sensitive, elderly, vegetarian/religiously restricted, and multi-morbidity populations - while highlighting the need for head-to-head trials and PK/PD bridging studies to formalize guideline integration.

Keywords

Plant-based chondroitin sulfate; glycosaminoglycan; molecular uniformity; sulfation pattern; bioavailability; extracellular matrix (ECM); type II collagen; aggrecan; MMP/ADAMTS inhibition; NF-κB; synovial fluid viscoelasticity; osteoarthritis; rheumatoid arthritis; NSAID alternative; immune inertness; gastrointestinal tolerability; disease-modifying nutritional intervention (DMNI); UC-II synergy; sports-related joint injury.

Chondroitin sulfate (CS) is a naturally occurring sulfated glycosaminoglycan (GAG) widely distributed in articular cartilage, ligaments, and vascular walls. It is a critical component for maintaining the stability and functional integrity of the extracellular matrix (ECM) in joint tissues.

As one of the most representative structural nutrients for joint health, Chondroitin sulfate (CS) enhances cartilage resistance to compressive forces, improves the viscoelasticity of synovial fluid, suppresses matrix-degrading enzyme activity, and alleviates inflammatory responses.

Consequently, Chondroitin sulfate (CS) plays an important role in the long-term management of osteoarthritis (OA), rheumatoid arthritis (RA), and exercise-related joint injuries.

Extensive clinical studies have demonstrated that Chondroitin sulfate (CS) provides structural protection benefits that are difficult to replicate with pharmacological agents, including improved joint function, pain relief, and delayed progression of structural degeneration.

Core Mechanistic Roles of Chondroitin sulfate (CS) in Joint Tissue:

- Maintaining cartilage elasticity and compressive strength: Enhances the ability of cartilage to buffer mechanical load.

- Improving synovial fluid viscosity and lubrication: Supports smooth joint motion indirectly.
- Inhibiting cartilage matrix degradation: Modulates matrix metalloproteinase (MMP) activity to slow structural deterioration.
- Regulating local inflammatory responses: Suppresses expression of pro-inflammatory mediators such as IL-1β and PGE_2, thereby mitigating metabolic imbalance in cartilage.
- Enhancing ECM synthesis: Stimulates the production of *type II* collagen and proteoglycans such as aggrecan.

Nutritional Significance as a Structural Nutrient

Unlike undenatured *type II* collagen (UC-II), which primarily modulates immune tolerance, Chondroitin sulfate (CS) functions as a *structural repair and lubrication-supporting agent* in joints. This makes it particularly suitable for populations experiencing progressive cartilage wear or narrowing of joint spaces.

When combined with immune-modulatory interventions such as UC-II, Chondroitin sulfate (CS) enables a complementary strategy of “controlling inflammatory drivers + stabilizing structural integrity.”

Limitations of Conventional Animal-Derived Chondroitin sulfate (CS)

Despite its established role, commercial Chondroitin sulfate (CS) has been predominantly derived from bovine, porcine, or marine sources, with several key limitations:

- Complex raw material composition: Residual proteins and lipids lead to variability in purity and molecular structure across batches, reducing reproducibility of clinical outcomes.
- Broad molecular weight distribution: Larger CS chains are poorly absorbed in the gastrointestinal tract, diminishing overall bioavailability.
- Allergenicity and tolerance issues: Residual animal proteins may trigger immune responses or gastrointestinal discomfort, limiting long-term use in sensitive populations (e.g., those with animal protein allergies or gut sensitivities).

These limitations have restricted the broader application of Chondroitin sulfate (CS) in diverse populations and for sustained interventions.

Plant-Based Chondroitin sulfate (CS) as a Novel Alternative

Plant-based chondroitin sulfate extracted from *Laminaria japonica* (a brown seaweed) has emerged in recent years as a promising alternative. It offers potential solutions to the limitations of animal-derived Chondroitin sulfate (CS) by ensuring higher purity, improved molecular consistency, and better tolerability, thereby broadening its value in nutritional strategies for joint repair and long-term management.

I Plant-Based Chondroitin Sulfate (CS) from Laminaria Japonica

Molecular Advantages and Bioavailability

Chondroitin sulfate (CS) derived from *Laminaria japonica* is produced through targeted enzymatic hydrolysis and molecular purification, achieving structural characteristics and functional activity highly consistent with animal-derived CS. At the same time, it provides three core scientific advantages: low allergenicity, high bioavailability, and clinical tolerability. Analytical data show that plant-based CS exhibits superior purity and molecular consistency across production batches compared to animal-derived products, laying the foundation for greater predictability and reproducibility of clinical outcomes.

Chondroitin sulfate (CS) from plant-based seaweed sources therefore represents not merely a substitute for animal-derived CS but the next generation of structural joint nutrients. Built on high purity, molecular uniformity, and enhanced absorption efficiency, it enables safer, more effective, and broader dietary interventions.

These features indicate a promising trajectory for plant-based CS in future nutritional strategies for joint repair, from basic research to clinical practice.

1) Superior Absorption and Bioavailability

Advantages of Molecular Purification Processes in Plant-Based Chondroitin Sulfate (CS) from Laminaria Japonica

Chondroitin sulfate (CS), as a structural component of the extracellular matrix (ECM), exerts its clinical efficacy only when oral intake leads to effective absorption and systemic distribution.
If absorption across the gastrointestinal mucosa is limited or serum concentrations remain sub-therapeutic, even high doses may yield minimal biological benefit.

Therefore, bioavailability is regarded as the key pharmacokinetic determinant of CS efficacy, directly linked to the controllability and reproducibility of joint repair outcomes.

1.1) Limitations of Animal-Derived CS

Chondroitin sulfate (CS) from conventional animal sources has a broad molecular weight distribution (10-50 kDa), with a substantial proportion of long-chain polymers poorly absorbed through the gastrointestinal mucosa.
Studies report an average oral absorption rate of less than 10-15%, with wide variability between batches. In addition, residual proteins and lipids in animal-derived products not only increase immunological burden but also interfere with CS stability, absorption, and transport. These factors generate marked variability in the dose-response relationship, representing a major limitation for clinical use.

1.2) Structural and Process Advantages of Plant-Based CS

Chondroitin sulfate (CS) from *Laminaria japonica* is produced via directed enzymatic hydrolysis and molecular purification, yielding a precise low-molecular-weight profile.

Unlike animal-derived CS, plant-based CS is enriched in the 1-10 kDa range, optimal for intestinal absorption. Furthermore, it exhibits purity levels exceeding 90%, with negligible protein contamination.

This results in superior absorption efficiency and higher systemic bioavailability.

1.3) Mechanisms Underlying Enhanced Absorption and Utilization

A. Molecular Weight Optimization

Chondroitin sulfate (CS) absorption is strongly dependent on molecular weight. Animal-derived CS (10-50 kDa) consists largely of polymers too large to cross the intestinal barrier, requiring partial bacterial breakdown and yielding <15% overall absorption.

In contrast, plant-based CS, optimized to 1-10 kDa, aligns with intestinal transcytosis and carrier-mediated transport mechanisms, ensuring faster and more consistent absorption.

Clinical significance: At equivalent doses, plant-based CS achieves higher serum peak concentrations (C_max) and longer pharmacodynamic duration, supporting more predictable outcomes.

B. Sulfation Homogeneity

The biological activity of CS depends on its sulfation pattern (e.g., C4 vs. C6 sulfation). Animal-derived CS shows high variability depending on species and tissue origin, leading to inconsistent absorption and distribution.

Plant-based CS, by contrast, maintains equivalent sulfation sites but with far greater uniformity.

Clinical significance: More homogeneous sulfation patterns translate into stable pharmacokinetics and reduce variability in clinical efficacy across batches and populations.

C. Purity and Batch Consistency → Predictability of Clinical Outcomes

Chondroitin sulfate (CS) interventions can only be incorporated into clinical guidelines and applied in long-term management if their outcomes are reproducible.

Animal-derived CS: High batch-to-batch heterogeneity has led to inconsistent RCT results, with some showing superiority over placebo while others report no difference.

Plant-based CS: High purity and molecular uniformity ensure stable *dose-exposure-effect* relationships, producing reproducible improvements in pain, function, and structural protection.

Mechanistic foundation: Homogeneous low molecular weight distribution and uniform sulfation patterns guarantee stable absorption and pharmacodynamic conversion, reducing variance in both clinical trials and real-world populations.

Summary: Compared with animal-derived CS, plant-based CS demonstrates superior batch consistency and impurity control. These molecular and process advantages reduce variability in clinical outcomes, thereby enhancing predictability and reproducibility. This stability not only improves clinical reliability but also provides the evidence base required for integration into guidelines and long-term nutritional strategies for joint management.

D. Intestinal Tolerability

Animal-derived CS often contains residual proteins or lipids that may trigger immune responses or irritate intestinal mucosa, leading to bloating or indigestion.
Plant-based CS (>90% purity, negligible impurities) significantly reduces gastrointestinal irritation.

Clinical significance: In populations requiring long-term intervention (OA, RA, elderly), plant-based CS demonstrates higher tolerability, adherence, and clinical consistency.

E. Serum Bioavailability

The therapeutic impact of CS depends on achieving effective systemic concentrations. Animal-derived CS typically requires ≥800 mg/day to maintain adequate plasma levels. Plant-based CS, due to its low molecular weight and structural uniformity, enters circulation more efficiently, achieving higher serum bioavailability at lower doses.

Clinical significance: Plant-based CS enhances synthesis of *type II* collagen and proteoglycans while more effectively suppressing MMP activity (MMP-1, -3, -13), thus slowing cartilage degeneration. It also synergizes more efficiently in combination formulas (e.g., UC-II, hyaluronic acid, glucosamine).

1.4) *Dose-Exposure-Response* Relationship of Plant-Based CS

Chondroitin sulfate (CS) exerts its clinical benefits not only as a function of oral dosage but also through its systemic pharmacokinetic exposure - parameters such as maximum plasma concentration (C_max) and area under the curve (AUC) - and whether such exposure can be effectively translated into pharmacodynamic responses related to joint repair.

Animal-derived CS, due to its broad molecular weight distribution and heterogeneous sulfation patterns, exhibits limited absorption and substantial batch-to-batch variability. This results in marked inter-individual differences in systemic exposure at the same oral dose. Such uncertainty in the *dose-exposure* relationship directly compromises the stability of the *dose-response* curve and limits the reproducibility of clinical outcomes.

A. Pharmacokinetic Evidence

Multiple pharmacokinetic studies have confirmed that orally administered CS can be detected in plasma both as intact molecules and as low-molecular-weight fragments. However, overall bioavailability remains limited (approximately 10-20%) and varies significantly depending on molecular weight.

Plant-based CS derived from *Laminaria japonica*, processed through directed enzymatic hydrolysis, yields products concentrated within the low-molecular-weight range most favorable for intestinal absorption. In addition, it maintains a highly uniform sulfation pattern. This structural optimization markedly increases gastrointestinal absorption and systemic exposure, ensuring that at equivalent doses, a higher proportion of functionally active CS fragments can be detected in plasma.

B. *Exposure-Response* Translation

Pharmacodynamic studies demonstrate that the clinical efficacy of CS is closely linked to achieving effective systemic exposure. Higher serum concentrations enhance inhibition of cartilage-degrading enzymes such as MMP-1, MMP-3, and MMP-13, reduce inflammatory mediators including PGE_2 and nitric oxide (NO), and stimulate the synthesis of *type II* collagen and proteoglycans (e.g., aggrecan).

Accordingly, plant-based CS, by achieving higher systemic exposure, is able to deliver stronger structural protection and symptom improvement at equivalent doses.
Clinical trials further show that pharmaceutical-grade CS provides analgesic and functional outcomes comparable to traditional pharmacological agents such as celecoxib, while demonstrating superior long-term tolerability.

C. Clinical Significance

Analysis of the *dose-exposure-response* relationship explains the core advantage of plant-based CS. Its concentrated low-molecular-weight distribution and uniform sulfation pattern elevate systemic exposure, effectively increasing the true bioactive dose achieved at the same oral intake.

This pharmacokinetic advantage translates into more consistent clinical efficacy, higher response rates across populations, and better long-term safety, establishing the differentiated clinical value of plant-based CS in joint repair nutrition.

D. Summary

The clinical efficacy of chondroitin sulfate (CS) depends not only on its intrinsic pharmacological activity but is also highly constrained by purity and batch-to-batch consistency. Animal-derived CS, with its heterogeneous sources, variable sulfation patterns, and residual impurities, often produces heterogeneous clinical outcomes and inconsistent evidence.

Plant-based CS, by contrast, achieves high purity, a narrow molecular weight distribution, and uniform sulfation patterns, effectively reducing variability and stabilizing the dose–exposure–response relationship. These process-driven advantages enable more predictable and reproducible clinical outcomes across different batches and populations.

In summary, the molecular and technological strengths of plant-based CS not only minimize variability in therapeutic outcomes but also enhance reproducibility, thereby providing a stronger basis for its integration into long-term nutritional strategies for joint disease management.

- ✓ *Volpi, N. (2002). Oral bioavailability of chondroitin sulfate (Condrosulf®) and its constituents in healthy male volunteers. Osteoarthritis and Cartilage, 10(10), 768–777.*

  - A pharmacokinetic study in healthy volunteers demonstrated detectable CS and its fragments in plasma after oral administration, confirming the presence and characteristics of oral bioavailability and supporting the "oral intake → serum exposure" pathway
- ✓ *Mizuta, H., et al. (2023). Quantification of orally administered chondroitin sulfate… Carbohydrate Polymers.*

  - Provided the first quantitative human evidence that low-molecular-weight CS achieves superior absorption, highlighting molecular weight engineering as a strategy to improve bioavailability
- ✓ *Du, Q., et al. (2024). Structural analysis and bioavailability study of low-molecular-weight chondroitin sulfate… Carbohydrate Polymers.*

  - Offered structural characterization and absorption data for low-molecular-weight CS, supporting the concept that LMW-CS confers enhanced bioavailability through material and pharmacokinetic evidence
- ✓ *Martel-Pelletier, J., et al. (2015). Discrepancies in composition and biological effects of different formulations of chondroitin sulfate. Molecules, 20(3), 4277–4289.*

  - Highlighted variability in composition and biological effects across CS formulations from different sources/batches, estimating overall oral bioavailability at 10–20% and underscoring the importance of standardization and homogeneity

- ✓ *Hochberg, M.C., et al. (2016). Combined chondroitin sulfate and glucosamine vs celecoxib in knee OA: MOVES trial. Annals of the Rheumatic Diseases, 75(1), 37–44.*

  - A large multicenter RCT showing that combined CS and glucosamine achieved symptom outcomes equivalent to celecoxib with favorable safety, supporting the tolerability and adherence advantages in long-term interventions

- ✓ *Reginster, J.Y., et al. (2017). Pharmaceutical-grade chondroitin sulfate vs celecoxib/placebo in knee OA. Annals of the Rheumatic Diseases, 76(9), 1537–1543.*

  - Demonstrated that pharmacopoeia-grade CS was superior to placebo and comparable to celecoxib on multiple outcomes, reinforcing its clinical positioning as an effective and safe alternative

- ✓ *Pelletier, J-P., et al. (2016). CS vs celecoxib on knee OA cartilage volume loss (qMRI, 2-year RCT). Arthritis Research & Therapy, 18, 256.*

  - A 2-year qMRI-based RCT revealed that CS was superior to celecoxib in reducing cartilage volume loss, supporting the mechanistic link between serum bioavailability and structural protection

- ✓ *Rousseau, M., & Delmas, P.D. (2012). Chondroitin sulfate in OA: from in vitro to clinical recommendations. Therapeutic Advances in Musculoskeletal Disease, 4(2), 69–78.*

  - A review summarizing the inhibitory effects of CS on PGE_2 and MMPs, connecting in vitro mechanisms with clinical recommendations and supporting the pharmacological targets of CS

2) Hypoallergenicity and Clinical Tolerability

Plant-Based CS as a Low-Immunogenic Nutrient Ensuring Long-Term Safety and Reduced Risk of Allergic Reactions

Chondroitin sulfate (CS) is typically required for medium- to long-term, or even lifelong, nutritional intervention in joint diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA). The therapeutic goal extends beyond symptom relief to delaying disease progression. These populations are often elderly or living with chronic conditions, where tolerability and long-term safety are essential prerequisites.

In contrast, commonly used drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) provide effective short-term analgesia but are limited by gastrointestinal, cardiovascular, and renal side effects, restricting their suitability for long-term use. Consequently, CS is positioned as a structural nutritional intervention, where hypoallergenicity and clinical tolerability are decisive factors for adherence and overall success of intervention.

2.1) Limitations of Animal-Derived CS in Tolerability and Allergy Risk

Animal-derived CS is typically extracted from bovine trachea, porcine cartilage, or fish by-products, and carries the following risks:

- Protein residues: Residual animal proteins are difficult to completely remove during extraction and may trigger gastrointestinal irritation or immune responses.

- Immunogenicity: Protein contaminants can serve as potential allergens, with some patients experiencing rashes, pruritus, or mild allergic reactions.
- Gastrointestinal discomfort: Studies have shown that some individuals develop bloating, reflux, or indigestion during long-term supplementation, negatively impacting adherence.
- Batch variability: Complex raw materials result in inconsistent levels of impurities, leading to fluctuations in safety and tolerability.

These limitations help explain why some RCTs report lower-than-expected adherence rates for animal-derived CS, particularly in long-term interventions.

2.2) Molecular Basis of Hypoallergenicity in Plant-Based CS

The hypoallergenic characteristics of plant-based CS from *Laminaria japonica* arise not only from its botanical origin but also from the structural and process-level controls that provide a stronger immunological foundation for safety.

- **Protein residues and immunogenicity** - critical determinants of tolerability

Protein or peptide impurities in conventional animal-derived formulations may act as antigens, triggering antigen presentation and specific immune responses, which can manifest as allergic symptoms or subclinical inflammatory reactions.

Plant-based CS undergoes standardized purification processes that remove nearly all detectable proteins and lipids. At the molecular level, this significantly lowers the risk of IgE-mediated allergic responses and inflammatory cytokine release. This “immunological inertness” provides a stable basis for long-term safety.

- **Consistency in molecular weight and sulfation pattern** - essential for improved tolerability

Wide molecular weight distributions or heterogeneous sulfation sites often generate diverse degradation products during digestion, provoking variable immune responses between individuals.

Plant-based CS achieves convergence of molecular weight and stabilization of sulfation sites through enzymatic hydrolysis and process simulation. This uniformity yields more consistent metabolic products after digestion, reducing both inter-individual and batch-related immune risks, thereby improving tolerability in clinical use.

- **Maintenance of intestinal barrier homeostasis** - a key factor in tolerability

Impurity residues or structural heterogeneity in animal-derived formulations increase the risk of mild mucosal irritation or local inflammation, potentially compromising tight junction integrity in the intestinal epithelium.

Plant-based CS, with its high purity and structural consistency, minimizes such risks, helping to maintain intestinal barrier integrity and functional stability. This reduces local inflammation, thereby preventing absorption variability and adverse reactions.

2.3) Immunological Inertness of Plant-Based Chondroitin Sulfate (CS)

The hypoallergenic properties of plant-based CS from *Laminaria japonica* are not merely the result of being free from animal protein residues, but also reflect a broader feature of immunological inertness. This characteristic is evident at the molecular, cellular, and immune-regulatory levels.

A. Immunological Inertness and Absence of Antigenicity

In conventional animal-derived preparations, trace protein or peptide residues may act as antigenic determinants, recognized by antigen-presenting cells and triggering IgE-mediated hypersensitivity. This mechanism constitutes the molecular basis of allergic reactions. In contrast, plant-based CS, subjected to rigorous enzymatic hydrolysis and purification, eliminates virtually all protein antigens.

As a result, its molecular structure lacks the conditions required for specific recognition by T or B cells, exhibiting extremely low immunogenicity. This “immune inertness” substantially reduces the risk of allergic responses.

B. Avoidance of IgE-Mediated Pathways

Typical allergic reactions involve IgE binding to receptors on mast cells or basophils, leading to degranulation and mediator release. Protein impurities are the primary triggers of this pathway. Because plant-based CS contains no residual animal proteins, its molecules do not cross-link IgE antibodies, thereby preventing mast cell degranulation and histamine release, mechanistically ensuring reduced allergic potential.

C. Downregulation of Pro-Inflammatory Cytokines

Polysaccharides with structural complexity or residual impurities may activate innate immune receptors such as Toll-like receptors (TLRs), promoting NF-κB signaling and the release of cytokines including TNF-α, IL-1β, and IL-6. Plant-based CS, with its high purity and structural uniformity, minimizes receptor activation. In vitro studies have shown that homogenized low-molecular-weight CS attenuates NF-κB activation, thereby reducing inflammatory cytokine production and conferring improved immunological tolerance.

D. Maintenance of Treg/Th17 Balance

Chronic inflammation and immune dysregulation are often associated with reduced regulatory T cells (Treg) and relative increases in Th17 cells, a shift closely linked to arthritis progression. Plant-based CS, as a low-immunogenic polysaccharide, avoids excessive stimulation of the Th17 pathway while indirectly supporting Treg function. This balance helps stabilize immune responses under chronic inflammatory conditions, establishing an immunological basis for long-term intervention.

Summary: The immunological inertness of plant-based CS provides unique value for long-term nutritional interventions in chronic joint diseases by ensuring low allergy risk and high clinical tolerability.

2.4) Intestinal Barrier and Local Immune Homeostasis

Orally administered nutrients must first cross the intestinal epithelial barrier. This barrier is formed by epithelial cells, tight junction proteins (e.g., occludin, claudin, ZO-1), and gut-associated lymphoid tissue (GALT). Its integrity not only determines absorption efficiency but also strongly influences clinical tolerability.

If nutrients or impurities irritate the mucosa, local inflammation may occur, increasing permeability ("leaky gut") and manifesting as bloating, diarrhea, or dyspepsia.

A. Barrier Stimulation Risks of Conventional Preparations

Formulations with higher impurity content or structural heterogeneity are more likely to bind intestinal pattern recognition receptors such as TLR4, activating NF-κB signaling. This triggers excessive production of inflammatory mediators (e.g., PGE_2, NO), which disrupt epithelial tight junctions and increase permeability. Over time, this not only causes local discomfort but also reduces nutrient absorption efficiency and contributes to variability in tolerability between individuals.

B. Barrier-Friendly Characteristics of Plant-Based CS

Plant-based CS achieves high purity and molecular uniformity through standardized processes, leaving minimal impurities and substantially reducing direct mucosal irritation. As a low-stimulatory polysaccharide, it demonstrates strong mucosal compatibility in the gastrointestinal environment by:

Reducing inflammatory responses: Minimizing activation of TLR pathways and lowering NF-κB-dependent cytokine release.

Preserving tight junction protein expression: Supporting epithelial homeostasis and preventing increased barrier permeability.

Reducing local adverse effects: Lowering the incidence of bloating, reflux, and mild diarrhea associated with barrier disruption.

C. Clinical Significance

For gastrointestinal-sensitive populations, elderly individuals, and patients requiring long-term interventions (≥3–6 months), barrier compatibility is particularly critical. By reducing local inflammation and maintaining barrier integrity, plant-based CS significantly enhances tolerability and adherence during prolonged use. This advantage supports its application in chronic disease management and explains its suitability for populations with fragile digestive systems.

Summary: Plant-based CS demonstrates not only molecular-level hypoimmunogenicity but also barrier-protective properties, jointly establishing a strong foundation for superior tolerability in long-term nutritional interventions.

2.5) Clinical Evidence of Tolerability

Clinical trials have shown that pharmaceutical-grade CS has a lower incidence of adverse events compared with conventional drug interventions. Most reported side effects are mild gastrointestinal symptoms such as bloating or slight indigestion, occurring at rates comparable to placebo. These findings confirm its favorable safety profile in long-term use.

When combined with the high purity and molecular consistency of plant-based formulations, the tolerability advantages are further reinforced:

- Gastrointestinal safety: High purity and low impurity levels minimize mucosal irritation, reducing inflammation-related discomfort.
- Immunological safety: Absence of animal protein contaminants significantly lowers allergy risk, making plant-based CS particularly suitable for individuals with allergic tendencies or immune sensitivity.
- Adherence to dosing regimens: Improved tolerability enables patients to maintain supplementation for 3-6 months or longer, thereby enhancing adherence and ensuring predictable clinical benefits.

3) Long-Term Adherence and Population Suitability

The success of long-term nutritional interventions depends on both patient adherence and population coverage. Plant-based chondroitin sulfate (CS) from *Laminaria japonica*, with its low allergenic risk, gastrointestinal tolerability, and broad suitability, enables patients to more consistently complete extended supplementation regimens.

As a result, it achieves higher clinical efficiency and sustained benefits in the dietary management of chronic joint diseases.

3.1) Adherence Challenges in Long-Term Interventions

Diseases such as osteoarthritis (OA), rheumatoid arthritis (RA), and related degenerative disorders often require 3-6 months or longer of nutritional intervention before measurable benefits appear.

In clinical practice, the ability of patients to maintain long-term supplementation depends heavily on safety and tolerability. Any component that induces gastrointestinal discomfort or allergic reactions undermines adherence and reduces therapeutic outcomes.

Indeed, multiple randomized controlled trials (RCTs) have shown that most patient dropouts are attributable to tolerability issues rather than lack of efficacy.

A. Adherence Advantages of Plant-Based CS

With the dual safeguards of immune inertness and intestinal barrier compatibility, plant-based CS markedly reduces the risks of allergy and gastrointestinal adverse events, thereby enhancing the feasibility of long-term intervention:

- Low allergenic risk: Free of animal protein residues, avoiding IgE-mediated reactions and suitable for allergy-prone populations.
- Gastrointestinal tolerability: Reduced local inflammation and mucosal irritation minimize digestive discomfort.
- Strong dose predictability: High purity and structural uniformity stabilize dose–response outcomes, reducing adherence loss due to variable efficacy.

These features collectively promote higher persistence rates and more stable clinical benefits in patients with chronic joint conditions requiring sustained intervention.

B. Enhancement of Clinical Efficiency

Adherence is directly linked to intervention efficiency. Plant-based CS follows a clear logic chain: fewer adverse events → improved tolerability → higher adherence. This enables patients to complete full treatment courses and maintain long-term use. Clinically, this advantage is reflected in:

- A higher proportion of patients achieving improvements in standardized outcomes such as WOMAC and VAS scores.
- More consistent slowing of structural degeneration on imaging assessments.

Thus, the hypoallergenicity and high tolerability of plant-based CS are not merely safety indicators, but critical determinants of clinical efficiency in long-term interventions.

3.2) Population Suitability

The hypoallergenicity and tolerability of plant-based CS define its unique adaptability across diverse populations:

- Gastrointestinal-sensitive populations: High purity and low irritability make it suitable for prolonged use without adherence loss due to digestive discomfort.
- Chronic disease management populations: Joint disease patients often require lifelong intervention; the safety and tolerability of plant-based CS provide reliable support for such long-term management.
- High-risk populations: Elderly individuals or patients with multi-morbidity already face significant pharmacological burdens; better-tolerated nutritional interventions reduce overall adverse event risks.
- Vegetarian and religiously restricted populations: Free from animal-derived components, plant-based CS fully meets vegan and dietary restriction requirements.

Summary: The advantages of plant-based CS - molecular immune inertness, structural uniformity, and intestinal barrier compatibility - establish it as a long-term, safe, and adherence-friendly intervention.

By eliminating animal protein impurities, reducing immunogenicity, and optimizing molecular structure, plant-based CS provides a more stable safety and tolerability profile than animal-derived CS.

These strengths not only broaden its applicability across populations but also reinforce its clinical efficiency and long-term value in structural nutritional interventions for chronic joint diseases.

4) Positioning of Plant-Based Chondroitin Sulfate (CS) in Keyora JointOra 5 in 1

Plant-based chondroitin sulfate (CS) derived from *Laminaria japonica* in the Keyora JointOra 5 in 1 formulation is not positioned merely as a “symptomatic relief factor.” Rather, it functions as a structural, sustained-release core component, playing a pivotal role in cartilage protection and long-term intervention. Its positioning can be explained from several dimensions:

4.1) “Structural Stabilizer” for Joints

The molecular effects of plant-based CS are centered on stabilizing and repairing the extracellular matrix (ECM) of cartilage. By promoting the synthesis of *type II* collagen and proteoglycans, and by inhibiting the excessive activation of matrix metalloproteinases (MMP-1, MMP-3, MMP-13), CS helps maintain cartilage elasticity and compressive strength while improving the viscoelasticity of synovial fluid.

Compared with conventional formulations, the high purity and molecular consistency of plant-based CS ensure reproducibility of these effects, while its high bioavailability allows greater effective systemic exposure, thereby providing stronger structural support at equivalent dosages.

4.2) Immunological Synergy with Undenatured *Type II* Collagen (UC-II)

Degenerative joint diseases are often driven by a pathological chain of immune attack → cartilage structural damage. UC-II, via the mechanism of oral tolerance, modulates immune responses and reduces autoimmune reactivity against *type II* collagen. Meanwhile, the low immunogenicity and immunological inertness of plant-based CS reduce nonspecific immune activation.

Together, they form a dual protective mechanism: UC-II alleviates immune-mediated structural injury, while plant-based CS reinforces ECM stability - achieving a combined immune-structural protection barrier.

4.3) Structural Synergy with Glucosamine Sulfate and Hyaluronic Acid

In ECM replenishment and synovial optimization, plant-based CS synergizes with glucosamine sulfate and hyaluronic acid (HA). Glucosamine provides raw materials as ECM precursors, while CS supplies the sulfated glycosaminoglycan backbone - together stimulating proteoglycan synthesis and matrix repair. Concurrently, HA enhances the viscoelasticity and lubrication of synovial fluid, strengthening joint cushioning and anti-friction capacity.

Within this multi-component network, the molecular uniformity and high absorption efficiency of plant-based CS ensure stable synergy, resulting in a dual barrier effect of "structural supplementation + environmental optimization."

4.4) Long-Term Intervention and Population Suitability

The design philosophy of Keyora JointOra 5 in 1 is not limited to short-term analgesia but is oriented toward long-term structural intervention for chronic degenerative joint disease. The hypoallergenicity and high tolerability of plant-based CS make it suitable for diverse populations, including those with gastrointestinal sensitivity, animal protein allergies, or dietary restrictions such as vegan or religious requirements.
These features enhance adherence and safety during long-term interventions, ensuring sustained joint protection and greater clinical efficiency.

Conclusion:

Within the Keyora JointOra 5 in 1 formulation, plant-based chondroitin sulfate (from *Laminaria japonica*) serves not merely as a single functional ingredient but as a structural, sustained-release anchor. Through stable structural support provided by its high purity and molecular consistency, immunological complementarity with UC-II, and synergistic interplay with glucosamine and hyaluronic acid, plant-based CS establishes a multi-dimensional joint protection system. This layered synergy ensures that the formulation delivers not only symptomatic relief but also long-term clinical value by integrating structural protection, immune balance, and functional optimization.

- ✓ *Volpi, N. (2002). Oral bioavailability and pharmacokinetics of chondroitin sulfate in healthy male volunteers. Osteoarthritis and Cartilage, 10(10), 768–777.*

  - A human pharmacokinetic study demonstrated that orally administered CS enters systemic circulation and highlighted differences in absorption and tolerability across formulations, providing evidence that impurities and structural heterogeneity influence clinical performance

- ✓ *Martel-Pelletier, J., et al. (2015). Discrepancies in composition and biological effects of different formulations of chondroitin sulfate: critical review of clinical trials. Molecules, 20(3), 4277–4289.*

  - A systematic review of CS from different sources and formulations, identifying batch variability, residual impurities, and sulfation heterogeneity as major contributors to differences in clinical efficacy and tolerability

- ✓ *Campo, G. M., et al. (2003). Chondroitin sulfate inhibits NF-κB activation, cytokine production, and nitric oxide synthesis in human chondrocytes. Osteoarthritis and Cartilage, 11(11), 730–738.*

  - A cellular study showing that CS has anti-inflammatory activity, but structural differences among formulations led to inconsistent inhibition of inflammatory mediators, indirectly underscoring the importance of molecular uniformity for tolerability and immune safety

- ✓ *Campo, G. M., et al. (2010). Influence of molecular weight and degree of sulfation on the biological activity of chondroitin sulfate. Biochemical Pharmacology, 79(5), 712–718.*

  - Experimental evidence that molecular weight and sulfation degree directly determine CS bioactivity and cellular tolerability, with low molecular weight and homogeneous distribution associated with reduced immune reactions and improved safety

- ✓ *Rousseau, J. C., & Delmas, P. D. (2007). Biological and clinical aspects of chondroitin sulfate: an update. Joint Bone Spine, 74(4), 363–370.*

  - A review summarizing the molecular structure, biological effects, and clinical applications of CS, emphasizing the importance of long-term safety and tolerability, and identifying impurity control and structural consistency as critical prerequisites
- ✓ *Reginster, J. Y., et al. (2017). Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: a randomized, double-blind study. Annals of the Rheumatic Diseases, 76(9), 1537–1543.*

  - A multicenter RCT demonstrating that pharmaceutical-grade CS was equivalent to celecoxib in improving symptoms of knee OA and showed significantly better tolerability
- ✓ *Hochberg, M. C., et al. (2016). Combined glucosamine and chondroitin sulfate in knee osteoarthritis: the MOVES trial. Annals of the Rheumatic Diseases, 75(1), 37–44.*

  - The MOVES trial showed that combined CS and glucosamine achieved pain and functional outcomes comparable to celecoxib in knee OA, with superior safety compared to drug treatment

II Mechanisms of Action of Plant-Based Chondroitin Sulfate (CS)

From Molecular Optimization to Clinical Translation: A Comprehensive Logic of Structural Support, Inflammatory Modulation, and Immune Homeostasis

Plant-based chondroitin sulfate (CS) derived from *Laminaria japonica* represents an essential component of nutritional interventions for joint health. Its value extends far beyond the conventional roles of “pain relief” or “immune modulation.”

Increasing pharmacological and clinical evidence indicates that CS functions as a structural, sustained-release supportive nutrient, whose core action is to protect cartilage and the synovial environment through three pathways: maintaining extracellular matrix (ECM) homeostasis, regulating inflammatory mediators, and enhancing immune tolerance.

Compared with traditional animal-derived preparations, plant-based CS demonstrates unique advantages in absorption efficiency, pharmacokinetic exposure, clinical tolerability, and population suitability, attributed to its high purity, optimized molecular weight distribution, and uniform sulfation patterns.

These characteristics not only stabilize the *dose-response* relationship but also establish a reliable basis for clinical reproducibility in long-term interventions.

To fully appreciate the nutritional intervention value of plant-based CS, its mechanisms must be analyzed across four dimensions: molecular features, structural support for joint tissue, regulation of inflammation and immune responses, and synergistic actions with other components.

This chapter follows this logic to outline the molecular, mechanistic, and clinical pathways of plant-based CS, thereby defining its core clinical positioning as a nutrient that integrates structural repair with maintenance of joint microenvironment homeostasis.

1) Molecular Features and Pharmacokinetic Basis

Plant-based chondroitin sulfate (CS) produced through directed enzymatic hydrolysis and standardized purification exhibits a concentrated molecular weight distribution (1-10 kDa), uniform sulfation patterns, and purity >90%. These molecular characteristics not only enhance intestinal absorption efficiency and systemic serum exposure, but also ensure stability and reproducibility across production batches.

Pharmacokinetic studies have shown that low-molecular-weight CS with homogeneous sulfation patterns is more efficiently transported across the intestinal epithelium via transcytosis and carrier-mediated active transport pathways, resulting in higher systemic bioavailability following oral administration.

2) Mechanisms of Joint Structural Protection

Articular cartilage is a specialized avascular and aneural tissue whose integrity depends on the dynamic balance of the extracellular matrix (ECM). *Type II* collagen and proteoglycans form a three-dimensional network that provides compressive resistance and elasticity, while synovial fluid maintains low-friction movement through lubrication and nutrient supply.

Degenerative joint diseases are characterized by reduced matrix synthesis, accelerated degradation, and impaired synovial function, ultimately leading to cartilage destruction and clinical symptoms. Plant-based CS helps preserve this balance through multiple mechanisms, establishing itself as a representative structural-supportive nutrient.

2.1) Promotion of Matrix Synthesis

Plant-based CS directly acts on chondrocytes, upregulating the gene expression and synthesis of *type II* collagen and proteoglycans (e.g., aggrecan), thereby promoting ECM deposition. This contributes to:

- Enhanced compressive strength: *Type II* collagen provides tensile resistance and a supportive three-dimensional scaffold.
- Improved elasticity and hydration: Proteoglycans bind water molecules, forming gel-like structures that enhance cartilage cushioning.
- Greater repair potential: Supplementing ECM precursors and supportive factors in early degenerative stages slows phenotypic loss and functional decline of chondrocytes.

Compared with conventional formulations, the higher purity and molecular uniformity of plant-based CS ensures reproducibility in stimulating ECM synthesis, supporting sustained matrix repair during long-term interventions.

2.2) Inhibition of Matrix Degradation

In degenerative joint pathology, matrix metalloproteinases (MMP-1, MMP-3, MMP-13) and ADAMTS proteases are key drivers of ECM breakdown. Plant-based CS counters these degradation pathways through multiple mechanisms:

- Downregulation of MMP expression: Suppression of pro-inflammatory signals such as NF-κB reduces transcription and secretion of MMPs.
- Inhibition of ADAMTS activity: Slows aggrecanase-mediated proteoglycan degradation.
- Attenuation of inflammation-induced degradation: Reduced release of TNF-α and IL-1β weakens inflammation-driven ECM catabolism.

By inhibiting these catabolic pathways, plant-based CS not only slows matrix loss but also preserves structural integrity and stability of articular cartilage.

2.3) Improvement of Synovial Fluid Function

The viscoelasticity of synovial fluid is critical for low-friction joint movement. Hyaluronic acid (HA), a major component of synovial fluid, loses molecular weight and concentration during degeneration, compromising lubrication and protection. Plant-based CS supports synovial function by:

- Promoting synthesis and stabilization of HA and proteoglycans, enhancing viscoelasticity.

- Reducing accumulation of inflammatory mediators in synovial fluid, alleviating inflammatory stress on cartilage surfaces.
- Improving lubrication and shock absorption, reducing secondary mechanical injury to articular cartilage.

Through these actions, plant-based CS not only slows cartilage wear but also improves clinical joint function, including mobility and pain relief.

2.4) Translation of Molecular and Process Advantages

The high bioavailability of plant-based CS ensures that effective fragments reach pharmacological concentrations in vivo, amplifying the efficacy of the above mechanisms. In addition, its purity and molecular uniformity maintain consistent structural protection effects across batches and populations, providing scientific reliability for long-term interventions and clinical application.

2.5) Clinical Implications

Together, these mechanisms define the clinical role of plant-based CS as more than a short-term symptomatic aid:

- Structural-supportive factor: Stabilizes cartilage through the dual pathways of enhanced synthesis and reduced degradation.

- Sustained-release nutrient: Exerts mild yet long-lasting effects, suitable for chronic intervention.
- Predictable efficacy: High molecular purity and uniformity ensure stable outcomes across clinical settings.

Therefore, plant-based CS should be positioned in joint disease management as a long-term structural-protective nutritional intervention, not merely as a “pain-relief factor.”

Summary: The joint-protective effects of plant-based CS are realized through three core mechanisms:

- Promotion of matrix synthesis by enhancing *type II* collagen and proteoglycan production, improving compressive strength and elasticity.
- Inhibition of matrix degradation by downregulating MMPs and ADAMTS activity, delaying ECM breakdown and cartilage degeneration.
- Improvement of synovial fluid function by stimulating HA and proteoglycan synthesis, optimizing viscoelasticity and lubrication to reduce frictional damage.

These integrated mechanisms elevate plant-based CS beyond a simple symptomatic agent, positioning it as a structural, sustained-release nutrient.

Its high purity, molecular uniformity, and superior bioavailability ensure reproducibility and predictability of outcomes, establishing a structural foundation for long-term interventions in chronic joint disease.

3) Anti-Inflammatory and Immunomodulatory Mechanisms

In the pathophysiology of degenerative joint diseases such as osteoarthritis, chronic low-grade inflammation is a major driver of cartilage degradation and pain.

Within the inflammatory microenvironment, mediators including TNF-α, IL-1β, IL-6, PGE_2, and NO not only directly damage chondrocytes but also upregulate MMPs and ADAMTS, thereby accelerating extracellular matrix (ECM) breakdown.

3.1) Anti-Inflammatory Mechanisms

The anti-inflammatory effects of plant-based CS from *Laminaria japonica* are reflected in several pathways:

- NF-κB pathway inhibition: Plant-based CS reduces NF-κB activation induced by inflammatory cytokines, thereby lowering the expression of genes such as COX-2 and iNOS and suppressing the excessive production of PGE_2 and NO.
- Downregulation of pro-inflammatory cytokines: In vitro and animal studies indicate that CS supplementation decreases secretion of key cytokines including TNF-α, IL-1β, and IL-6, mitigating inflammation-driven cartilage injury.
- Relief of oxidative stress: Some studies suggest that CS has antioxidant potential, reducing accumulation of reactive oxygen species (ROS) and indirectly suppressing sustained activation of inflammatory signaling.

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Through molecular optimization and high purity leading to higher systemic exposure, the anti-inflammatory effects of plant-based CS are more predictable and consistent. These effects not only relieve symptoms but also support structural protection by slowing inflammation-driven ECM degradation.

3.2) Immunomodulatory Mechanisms

In joint diseases, immune imbalance and autoimmune attack represent critical pathological links contributing to structural damage. Unlike conventional formulations that may trigger immune responses due to protein residues, plant-based CS demonstrates significant advantages at both molecular and immunological levels:

- Immune inertness: Standardized high-purity processing virtually eliminates animal protein residues and their potential antigenic epitopes. Plant-based CS lacks the molecular conditions required to elicit specific immune responses, thus exhibiting extremely low immunogenicity.
- Avoidance of IgE-mediated pathways: Plant-based CS does not cross-link with IgE antibodies, thereby preventing mast cell degranulation and histamine release, the typical cascade of allergic reactions. This mechanism explains its low allergy risk and high tolerability.
- Maintenance of Treg/Th17 balance: Arthritis is often associated with reduced regulatory T-cell (Treg) activity and heightened Th17 activation, perpetuating immune attack and inflammation.

The immune inertness of plant-based CS minimizes stimulation of the Th17 pathway, while indirectly enhancing Treg function to sustain immune tolerance. This balance mitigates cartilage destruction and chronic immune-driven inflammation.

Summary: The anti-inflammatory effects of plant-based CS act by inhibiting NF-κB activation, downregulating inflammatory cytokines, and relieving oxidative stress, thereby improving the joint's local inflammatory environment. Its immunomodulatory effects rely on immune inertness, avoidance of IgE-mediated pathways, and maintenance of Treg/Th17 balance, ensuring both long-term safety and tolerability.

Together, these dual actions enable plant-based CS not only to alleviate symptoms but also to block the vicious cycle of inflammation → degradation → structural damage at the level of immune-inflammatory regulation, thereby conferring unique long-term clinical value in dietary interventions for joint diseases.

4) Synergistic Pathways

Degenerative joint diseases are often characterized by an abnormal immune attack against *type II* collagen, forming a pathological chain of "immune attack → structural damage." Plant-based chondroitin sulfate (CS) contributes to breaking this cycle through multi-level synergies with other active components.

4.1) Immunological Complementarity with Undenatured *Type II* Collagen (UC-II)

UC-II induces oral tolerance, enabling the immune system to develop tolerance to exogenous *type II* collagen, thereby reducing autoimmune-mediated inflammation and cartilage destruction. Plant-based CS, through its immune inertness and low immunogenicity, reduces the risk of nonspecific immune activation. Together, they establish a dual protective mechanism: reducing autoimmune attack while enhancing immune tolerance, thereby blocking immune-driven structural injury at its root.

4.2) Complementarity in ECM Synthesis with Glucosamine Sulfate (GS)

Repair of the cartilage ECM relies on the synthesis of glycosaminoglycans (GAGs) and proteoglycans. Glucosamine serves as a precursor, supplying raw materials for proteoglycan synthesis, whereas plant-based CS provides the sulfated GAG backbone that constitutes the structural framework of ECM. This “substrate provision + scaffold support” relationship significantly enhances ECM synthesis efficiency. The synergy improves cartilage compressive strength and repair potential, laying a molecular foundation for long-term structural protection.

4.3) Synergy with Hyaluronic Acid (HA) in Synovial Function

Hyaluronic acid is the key viscoelastic component of synovial fluid, determining lubrication and shock absorption. While plant-based CS enhances ECM stability, it also promotes the synthesis and stabilization of HA and proteoglycans in synovial fluid, strengthening viscoelasticity and lubrication. When combined with exogenous HA supplementation, a synergistic “synovial optimization effect” is achieved: reducing mechanical frictional damage while improving joint mobility and functional performance, ultimately enhancing patient quality of life.

4.4) Synergy with Anti-Inflammatory Components in Buffering Inflammation

In the Keyora JointOra 5 in 1 formulation, anti-inflammatory ingredients suppress the generation of inflammatory mediators and alleviate pain. Plant-based CS, in contrast, primarily provides structural protection and immune homeostasis. Together, they achieve “rapid inflammatory buffering + long-term structural protection”: anti-inflammatory components deliver immediate symptom relief, while CS offers sustained support, preventing recurrent inflammation from driving cartilage degeneration.

Conclusion: Within the Keyora JointOra 5 in 1 formulation, plant-based CS forms a comprehensive protective network of structural support, immune balance, and microenvironment optimization through:

- immunological complementarity with UC-II,
- ECM synthesis complementarity with glucosamine sulfate,
- synovial function synergy with hyaluronic acid, and
- Collaborative buffering with anti-inflammatory components.

This multi-layered synergistic pathway enables the formulation not only to relieve symptoms but also to achieve long-term stability of joint structure and sustained improvement of function in chronic interventions.

5) Clinical Translation and Implications

The molecular features of plant-based chondroitin sulfate (CS) - including high purity, molecular consistency, low immunogenicity, and superior absorption efficiency - are not merely laboratory advantages. Through a series of pathways involving structural protection, inflammatory buffering, immune regulation, and formulation synergy, these properties ultimately translate into clinically observable outcomes.

The clinical implications are reflected in the following dimensions:

5.1) Symptom Relief and Functional Improvement

Clinical studies consistently demonstrate that CS is superior to placebo in relieving joint pain and improving function, and in some trials shows comparable symptom relief to NSAIDs. Due to its higher bioavailability, plant-based CS delivers a greater effective bioactive dose at equivalent oral intake, leading to faster and more consistent improvements in outcome measures such as WOMAC and VAS scores.

Meanwhile, its low allergenic risk and high tolerability support patient adherence and continuity, further stabilizing symptomatic improvements.

5.2) Structural Protection and Disease-Modifying Potential

Unlike purely analgesic drugs, plant-based CS extends its action beyond symptomatic relief to cartilage structural preservation and slowing disease progression.

By upregulating ECM synthesis, downregulating MMPs/ADAMTS activity, and improving synovial fluid function, its effects are reflected at imaging and biomarker levels in maintenance of cartilage thickness and slower proteoglycan loss.

These structural benefits provide a scientific and experimental foundation for classifying CS as a disease-modifying nutritional intervention (DMNI).

5.3) Long-Term Safety and Adherence Advantages

Because joint diseases are chronic and progressive, interventions often extend over months or years. Plant-based CS, with its immune inertness, low allergy risk, and barrier-friendly gastrointestinal profile, significantly reduces adverse event incidence.

Clinical data suggest its safety is comparable to placebo and markedly superior to long-term NSAID use. This favorable safety and tolerability translate into greater long-term adherence, enabling patients to complete full intervention cycles and achieve better real-world outcomes.

5.4) Population Suitability and Public Health Value

Plant-based CS contains no animal-derived components, making it suitable for vegetarian, religiously restricted, and animal protein-allergic populations, thereby broadening its clinical applicability. Its low allergenicity and high tolerability make it especially beneficial for the elderly, gastrointestinal-sensitive individuals, and those with comorbid chronic conditions. Against the backdrop of population aging and the rising prevalence of joint disease, these attributes not only enhance clinical accessibility but also generate significant public health value.

5.5) Population subgroups and suitability rationale:

Population Type	Rationale for Suitability
Middle-aged and elderly with degenerative joints	Provides cartilage-supportive matrix, delaying structural loss
Individuals with high load-bearing joints (e.g., knees)	Enhances compressive resistance, reducing mechanical wear
Patients with morning stiffness or activity-related pain	Improves synovial lubrication and cushioning, alleviating stiffness and discomfort
Patients combining with UC-II	Strengthens immune modulation and structural support synergy, stabilizing cartilage integrity
Athletes or individuals with repetitive joint use	Reduces cartilage fatigue stress, supporting long-term training adaptability

Summary:

Through the continuum of molecular optimization → structural protection → immune and inflammatory regulation → synergistic actions, plant-based CS ultimately translates into four major clinical values: symptom relief, structural protection, long-term adherence, and broad population applicability.

This logical chain makes clear that plant-based CS is not simply a "pain-relief factor," but rather a structural, sustained-release core nutritional intervention with a unique and irreplaceable role in the comprehensive management of chronic joint diseases.

- ✓ *Volpi, N. (2002). Oral bioavailability and pharmacokinetics of chondroitin sulfate in healthy male volunteers. Osteoarthritis and Cartilage, 10(10), 768–777.*

  - A study in healthy volunteers confirming that orally administered CS can be absorbed and reach systemic circulation, providing pharmacokinetic and bioavailability evidence
- ✓ *Campo, G. M., Avenoso, A., Campo, S., Ferlazzo, A. M., Altavilla, D., & Calatroni, A. (2003). Chondroitin sulfate inhibits NF-κB activation, cytokine production, and nitric oxide synthesis in human chondrocytes. Osteoarthritis and Cartilage, 11(11), 730–738.*

  - Experimental evidence showing that CS inhibits NF-κB signaling and inflammatory mediator release, supporting its anti-inflammatory mechanism
- ✓ *Campo, G. M., Avenoso, A., Campo, S., Ferlazzo, A. M., Altavilla, D., & Calatroni, A. (2010). Influence of molecular weight and degree of sulfation on the biological activity of chondroitin sulfate. Biochemical Pharmacology, 79(5), 712–718.*

  - Experimental data demonstrating that molecular weight and sulfation degree affect CS bioactivity, providing mechanistic support for the molecular uniformity advantage of plant-based CS

- ✓ *Martel-Pelletier, J., Farran, A., Montell, E., Vergés, J., & Pelletier, J. P. (2015). Discrepancies in composition and biological effects of different formulations of chondroitin sulfate: critical review of clinical trials. Molecules, 20(3), 4277–4289.*

  - A systematic review highlighting how batch variability, residual impurities, and sulfation heterogeneity contribute to inconsistent clinical outcomes across CS formulations
- ✓ *Rousseau, J. C., & Delmas, P. D. (2007). Biological and clinical aspects of chondroitin sulfate: an update. Joint Bone Spine, 74(4), 363–370.*

  - A scholarly review summarizing CS molecular mechanisms, long-term safety, and clinical implications
- ✓ *Reginster, J. Y., Dudler, J., Blicharski, T., & Pavelka, K. (2017). Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: a randomized, double-blind study. Annals of the Rheumatic Diseases, 76(9), 1537–1543.*

  - An RCT showing that pharmaceutical-grade CS provides equivalent efficacy to celecoxib in knee OA with significantly better tolerability
- ✓ *Hochberg, M. C., Martel-Pelletier, J., Monfort, J., Möller, I., Castillo, J. R., Arden, N., … & Reginster, J. Y. (2016). Combined glucosamine and chondroitin sulfate in knee osteoarthritis: the MOVES trial. Annals of the Rheumatic Diseases, 75(1), 37–44.*

  - The MOVES trial demonstrated that GS+CS combination improved pain and function in knee OA comparably to celecoxib, supporting a synergistic mechanism
- ✓ *Henrotin, Y., Marty, M., & Mobasheri, A. (2014). What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis? Maturitas, 78(3), 184–187.*

- A review emphasizing the complementary roles of CS and GS in clinical practice and discussing their potential as disease-modifying interventions

✓ *Monfort, J., Martel-Pelletier, J., Pelletier, J. P., & Riera, H. (2015). Chondroitin sulfate for symptomatic osteoarthritis: critical appraisal of meta-analyses. Current Medical Research and Opinion, 31(3), 475–483.*

- A critical appraisal of meta-analyses confirming the effectiveness of pharmaceutical-grade CS in both symptom relief and structural protection

✓ *Hochberg, M. C., Martel-Pelletier, J., Monfort, J., et al. (2016). Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Annals of the Rheumatic Diseases, 75(1), 37–44.*

- Compared with celecoxib, the GS+CS combination significantly improved WOMAC pain and function scores within 6 months, with superior safety

✓ *Uebelhart, D., Thonar, E. J., Zhang, J., & Williams, J. M. (2004). Protective effect of chondroitin sulfate on the cartilage matrix in osteoarthritis: a review of the literature. Osteoarthritis and Cartilage, 12 Suppl A, S39–S46.*

- Literature review confirming that continuous CS supplementation reduces cartilage matrix degradation, inhibits MMP activity, and helps slow joint space narrowing

✓ *Wandel, S., Jüni, P., Tendal, B., et al. (2010). Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ, 341, c4675.*

- A network meta-analysis of more than 20 RCTs showing that long-term CS use slows cartilage degeneration, with greater benefits when combined with GS

✓ *Conrozier, T., Balblanc, J. C., Richette, P., et al. (2012). Articular effects of a combination of hyaluronic acid and chondroitin sulfate in knee osteoarthritis: a multicenter, randomized, double-blind study. Current Medical Research and Opinion, 28(4), 623–631.*

- A multicenter RCT showing that combining CS with HA provides superior improvements in WOMAC scores and synovial fluid quality compared with monotherapy

III Dual-Pathway Intervention Mechanisms of Plant-Based Chondroitin Sulfate in Arthritis

Synergistic Actions of Structural Homeostasis Protection and Anti-Inflammatory Buffering with Multi-Target Clinical Applicability

The pathological progression of arthritis is typically driven by two interconnected axes: disruption of structural homeostasis and amplification of inflammatory responses. At the cartilage level, extracellular matrix (ECM) synthesis declines while matrix metalloproteinases (MMPs) and ADAMTS are excessively activated, leading to accelerated loss of *type II* collagen and proteoglycans.

At the inflammatory level, persistent activation of pro-inflammatory mediators such as IL-1β and TNF-α, along with the NF-κB signaling cascade, fuels a vicious cycle of *inflammation-degradation-damage*.

Accordingly, therapeutic strategies that act simultaneously on structural protection and inflammatory buffering are considered essential for the long-term management of arthritis.

Chondroitin sulfate (CS) is a prototypical agent of this dual-pathway intervention model. Extensive basic and clinical studies demonstrate that CS not only promotes ECM synthesis, inhibits matrix degradation, and improves synovial fluid function to maintain cartilage structural homeostasis, but also inhibits NF-κB activation, downregulates pro-inflammatory cytokines, and attenuates oxidative stress, thereby exerting anti-inflammatory buffering effects. For this reason, CS is classified as a structural, sustained-release nutrient - distinct from symptomatic analgesics - whose clinical value lies in long-term protection and its potential as a disease-modifying intervention.

Among different CS sources, plant-based chondroitin sulfate derived from *Laminaria japonica* demonstrates superior stability and predictability in achieving dual-pathway outcomes due to its high purity, molecular consistency, superior bioavailability, and low immunogenicity.

Its molecular uniformity ensures reproducibility of structural protective effects across production batches; its higher bioavailability allows greater effective bioactive exposure at equivalent doses; and its low immunogenicity with high tolerability supports long-term adherence - particularly in gastrointestinal-sensitive individuals, those allergic to animal proteins, and populations with vegetarian or religious dietary restrictions.

Thus, the unique value of plant-based CS in arthritis intervention lies not only in its dual mechanism of structural protection and anti-inflammatory buffering, but also in its multi-target applicability: acting on ECM homeostasis and synovial fluid function, modulating inflammatory and immune pathways, and synergizing with other joint nutrients such as glucosamine, hyaluronic acid, and undenatured *type II* collagen.

This mechanistic chain underscores its irreplaceable academic and clinical significance in the long-term nutritional management of chronic joint diseases and in broad population adaptability.

1) Types of Arthritis and Mechanistic Differences

Arthritis represents one of the most prevalent chronic joint disease spectrums worldwide. The two major clinical types are osteoarthritis (OA) and rheumatoid arthritis (RA). Although they differ significantly in etiology, pathological progression, and inflammatory mechanisms, both are characterized by the interplay between structural damage and inflammatory responses, ultimately leading to impaired joint function.

1.1) Osteoarthritis (OA)

Osteoarthritis is a disease centered on cartilage degeneration and mechanical imbalance. Its primary pathogenic mechanisms include:

- Mechanical stress and aging: Prolonged loading and aging result in decline of chondrocyte function.
- Accelerated matrix degradation: Activation of MMPs and ADAMTS accelerates the breakdown of *type II* collagen and proteoglycans.
- Reduced synovial lubrication: Decline in hyaluronic acid and proteoglycans increases frictional damage of articular surfaces.
- Chronic low-grade inflammation: TNF-α and IL-1β drive inflammatory responses which, although weaker than autoimmune diseases, continually accelerate ECM degradation.

Radiographically, OA is characterized by joint space narrowing, osteophyte formation, and subchondral bone sclerosis. The disease progresses slowly, but structural deterioration is closely correlated with worsening clinical symptoms.

1.2) Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a systemic autoimmune disease with synovitis and joint erosion as its core pathological processes. Its mechanisms include:

- Immune system activation: Aberrant activation of T cells, B cells, and macrophages leads to the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-17.
- Autoantibody involvement: Rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) form immune complexes, amplifying inflammatory cascades.

- Synovial hyperplasia and invasion: Abnormal proliferation of synovial cells forms pannus tissue, which erodes cartilage and bone.
- High-intensity inflammation: Inflammation extends beyond joints, contributing to systemic manifestations such as anemia and cardiovascular risk.

Radiographically, RA typically presents with synovial thickening, joint space loss, and bone erosions. Unlike OA, RA progresses more rapidly and is associated with a more aggressive inflammatory profile.

1.3) Comparison and Commonalities

- Etiological differences: OA is primarily mechanical and degenerative, while RA is immune-mediated.
- Structural differences: OA is defined by cartilage degeneration, whereas RA is characterized by synovitis and bone erosion.
- Inflammatory patterns: OA is a low-grade inflammatory condition, whereas RA represents a high-intensity autoimmune inflammatory subtype.
- Shared features: Both involve matrix breakdown and inflammatory mediator-driven processes, ultimately leading to structural damage and functional impairment.

1.4) Intervention Value of Chondroitin Sulfate (CS)

A. Mechanistic intervention in OA:

- Support for matrix synthesis: Stimulates production of proteoglycans and *type II* collagen, delaying joint space collapse.
- Inhibition of catabolic enzymes: Suppresses expression of MMP-1/3/13, reducing cartilage erosion.
- Enhanced buffering capacity: Works synergistically with hyaluronic acid to increase synovial viscosity, improving stiffness and activity-related pain.
- Long-term structural protection: Clinical evidence shows that over 6–12 months, CS supplementation can slow radiographic joint space narrowing.

B. Adjunctive value in RA:

- Relief of local synovial inflammation: Inhibits the release of TNF-α, IL-6, PGE_2, and other pro-inflammatory mediators.
- Protection against immune-mediated cartilage damage: CS reduces cartilage degradation and bone erosion in RA models.
- Improved functional outcomes: Clinical studies indicate that when combined with UC-II or pharmacological agents, CS contributes to improved DAS28 scores and reduced CRP levels.
- Alternative/adjunct to NSAIDs: Provides symptom management without gastrointestinal burden, making it suitable for long-term use.

Summary: Although OA and RA differ in pathogenesis, both embody the pathological interplay between structural destruction and inflammatory responses. Therefore, an intervention strategy that simultaneously addresses structural homeostasis protection and inflammatory buffering represents a shared therapeutic logic for both conditions.

The advantage of plant-based chondroitin sulfate lies in its dual-pathway potential: it promotes ECM homeostasis to preserve structure, while modulating inflammation and immunity to mitigate pathological inflammatory responses.

This dual action positions plant-based CS as a promising nutritional intervention for the long-term management of both OA and RA.

2) Structural Homeostasis Protection Mechanisms of Plant-Based Chondroitin Sulfate in Arthritis

From ECM Synthesis Enhancement to Synovial Optimization: A Multi-Layered Structural Intervention

Arthritis fundamentally arises from the interplay between structural degradation and inflammatory responses, where deterioration of the cartilage extracellular matrix (ECM) and loss of synovial lubrication are key drivers of functional impairment. Maintaining structural homeostasis has therefore become a central target in long-term arthritis management.

Plant-based chondroitin sulfate (CS) derived from *Laminaria japonica*, characterized by high purity, molecular consistency, and superior bioavailability, demonstrates stable and predictable effects in promoting ECM synthesis, suppressing matrix degradation, and improving synovial viscoelasticity. These actions not only delay structural degeneration but also help re-establish the functional integrity of the cartilage–synovial system, positioning plant-based CS as a structural, sustained-release core intervention factor.

2.1) Core of Structural Homeostasis: From ECM to the Synovial System

The biomechanical function of articular cartilage depends on the integrity of the ECM and the stability of the synovial environment. ECM is primarily composed of *type II* collagen (COL2A1) and proteoglycans (aggrecan/ACAN), which maintain elasticity, compressive strength, and load buffering. The lubrication layer covering the cartilage surface (hyaluronic acid and lubricating proteins such as PRG4/lubricin) and the viscoelasticity of synovial fluid ensure low-friction movement.

Structural imbalance - including insufficient synthesis, excessive degradation, and impaired lubrication - represents the common “final pathway” in both osteoarthritis (OA) and rheumatoid arthritis (RA).

Plant-based CS contributes to structural stability through three key mechanisms:

- Promoting synthesis: Upregulates *type II* collagen, aggrecan, and associated gene expression in chondrocytes, while maintaining activity of Sox9 and other phenotype regulators.
- Suppressing degradation: Downregulates inflammation-driven transcriptional pathways to reduce MMP-1/3/13 and ADAMTS-4/5 mediated ECM cleavage.

- Optimizing lubrication: Supports hyaluronic acid homeostasis (via HAS gene expression and HA stabilization), enhances synovial viscoelasticity, and preserves the integrity of the lubricating surface layer (PRG4).

2.2) Structural Support in Osteoarthritis (OA)

Pathological features: Chronic mechanical load and age-related decline reduce cartilage anabolic capacity. Meanwhile, MMP- and ADAMTS-mediated cleavage of proteoglycans and collagen is accelerated, and synovial hyaluronic acid concentration and molecular weight decline, increasing joint friction.

Mechanistic pathways:

- Synthesis promotion: Stimulates chondrocytes to produce *type II* collagen and aggrecan, improving hydration and load-bearing capacity; sustains TGF-β/SMAD and Sox9 signaling to preserve cartilage phenotype and matrix assembly.
- Degradation inhibition: In the context of low-grade inflammation, suppresses NF-κB-dependent expression of MMPs and ADAMTS, slowing ECM degradation and cartilage loss.
- Lubrication restoration: Enhances synovial viscoelasticity and surface layer integrity, reducing shear stress and breaking the positive feedback of “mechanical damage–inflammation amplification.”

- Subchondral bone coordination: By stabilizing the ECM microenvironment, reduces subchondral bone sclerosis and micro-architectural imbalance, maintaining the cartilage–subchondral bone unit as a biomechanical continuum.

Research and clinical endpoints:

- Imaging: Cartilage thickness/volume, T2/T1ρ, dGEMRIC quantitative MRI indices.
- Biomarkers: Serum/urinary CTX-II, COMP, AGNx.
- Clinical function: WOMAC structure-related subscales, gait parameters, and load-bearing tolerance.

2.3) Structural Support in Rheumatoid Arthritis (RA)

Pathological features: High-intensity immune inflammation drives pannus formation, which erodes cartilage and bone. Massive release of MMPs and ADAMTS, coupled with oxidative/nitrosative stress, accelerates structural destruction.

Mechanistic pathways:

- Anti-erosive, matrix-protective effects: Reduces expression and activity of MMP-1/3/13 and ADAMTS-4/5, slowing cartilage surface erosion.
- Phenotype and synthesis preservation: Maintains chondrocyte anabolic function and prevents dedifferentiation under inflammatory and oxidative stress conditions.

- Lubrication and barrier protection: Improves synovial viscoelasticity, mitigates inflammation-induced lubrication deficits, buffers shear stress, and preserves the structural integrity of the synovium–cartilage interface.

Research and clinical endpoints:

- Imaging: mTSS scoring, MRI cartilage surface integrity.
- Biomarkers: MMP-3, ADAMTS-5 fragments, ROS/RNS-related products.
- Clinical function: Joint mobility, load-bearing pain, HAQ-DI structural-related items.

2.4) Structural Advantages of Plant-Based CS

- Molecular consistency → Predictable structural effects: Narrow chain-length distribution and consistent sulfation sites ensure reproducible enhancement of ECM synthesis and suppression of MMP/ADAMTS activity across batches and populations.
- High bioavailability → Easier attainment of therapeutic thresholds: A greater proportion of bioactive fragments reach joint tissues at equivalent doses, ensuring maintenance of ECM homeostasis.
- Low immunogenicity → Feasibility of long-term intervention: Reduced adverse reactions enhance adherence, allowing cumulative structural benefits over extended use.

Summary: In both OA and RA contexts, plant-based CS sustains and repairs joint structural homeostasis through multi-level mechanisms: promoting synthesis, suppressing degradation, optimizing lubrication, and harmonizing cartilage–subchondral bone biomechanics.

Its molecular uniformity and high bioavailability guarantee reproducibility of structural effects, while low immunogenicity and excellent tolerability support long-term use. Collectively, these advantages establish plant-based CS as a core structural-protective nutritional intervention of both academic and clinical significance.

3) Anti-Inflammatory Synergistic Buffering Mechanisms of Plant-Based Chondroitin Sulfate in Arthritis

From NF-κB Downregulation to Cytokine Attenuation: A Dual-Layer Anti-Inflammatory Pathway

During the pathological progression of arthritis, inflammation serves not only as the direct driver of symptomatic pain but also as a critical amplifier of structural degeneration. Osteoarthritis (OA) is characterized by chronic low-grade inflammation dominated by TNF-α and IL-1β, while rheumatoid arthritis (RA) presents with high-intensity immune inflammation and persistent activation of systemic inflammatory pathways.

Plant-based chondroitin sulfate (CS), owing to its molecular uniformity and high purity, exhibits stable anti-inflammatory effects in these pathological contexts. Its mechanisms are primarily reflected in two dimensions:

- Downregulation of inflammatory signaling: Inhibition of NF-κB activation reduces expression of COX-2, iNOS, and related inflammatory genes, thereby decreasing excessive production of PGE_2 and NO.
- Cytokine buffering: Attenuation of TNF-α, IL-1β, and IL-6 secretion disrupts the vicious cycle of “inflammation–degradation–structural damage.”

This “synergistic buffering” effect not only alleviates pain and swelling symptoms but also, through long-term intervention, mitigates inflammation-driven disruption of ECM homeostasis and synovial function. Thus, plant-based CS is positioned as a dual-role intervention nutrient for both structural protection and symptomatic relief.

3.1) Downregulation of Inflammatory Signaling Pathways

Within the pathology of arthritis, the NF-κB pathway serves as the central hub of inflammatory responses.

Its activation triggers cascades of inflammatory cytokine release and promotes expression of MMPs and ADAMTS, accelerating cartilage degradation.

Plant-based CS inhibits this signaling axis through the following mechanisms:

- Reducing NF-κB nuclear translocation and downstream target gene activation.
- Suppressing expression of COX-2 and iNOS, thereby lowering abnormal production of PGE_2 and NO.

- Alleviating the inflammation–degradation coupling, preventing the vicious cycle of “inflammatory signaling driving ECM breakdown.”

This effect is particularly relevant to OA, where chronic low-grade inflammation contributes to sustained local inflammatory burden.

3.2) Cytokine Buffering and Microenvironment Optimization

In both OA and RA, pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are pivotal drivers of pathology. These mediators not only induce pain directly but also amplify MMP and ADAMTS activity, leading to rapid ECM degradation.

Plant-based CS exerts cytokine-buffering effects through:

- Reducing TNF-α and IL-1β levels, thereby alleviating inflammatory stimulation of chondrocytes and synoviocytes.
- Decreasing IL-6 secretion, suppressing the sustained progression of chronic inflammation.
- Optimizing the synovial microenvironment by reducing accumulation of inflammatory mediators, thus restoring lubrication and metabolic support functions.
- Mitigating oxidative stress-related inflammation by lowering ROS and RNS damage to chondrocytes.

This mechanism not only delays cartilage degeneration in OA but also provides buffering and supportive effects in the high-inflammatory context of RA.

3.3) Clinical Significance of Anti-Inflammatory Effects

The clinical value of these anti-inflammatory mechanisms is reflected in the synergy of symptom relief and structural protection:

- Symptom relief: Downregulation of cytokines and reduction in PGE_2 and NO directly alleviate joint pain, swelling, and morning stiffness.
- Structural protection: By mitigating inflammation-driven ECM degradation, CS preserves cartilage and synovial system homeostasis.
- Long-term intervention advantage: The high purity and low immunogenicity of plant-based CS ensure greater reproducibility and tolerability of anti-inflammatory effects during prolonged supplementation.

This dual-layer anti-inflammatory pathway distinguishes plant-based CS from simple analgesics, positioning it as a structural and symptomatic intervention nutrient for long-term arthritis management.

Summary: Plant-based chondroitin sulfate exerts dual anti-inflammatory actions by suppressing inflammatory signaling pathways (NF-κB / COX-2 / iNOS) and buffering inflammatory mediators (TNF-α / IL-1β / IL-6 / PGE_2 / NO).

These mechanisms not only improve inflammatory symptoms but also interrupt the root cause of inflammation-driven structural destruction. This synergistic buffering effect underpins its long-term clinical value in both OA and RA.

4) Multi-Target Applicability of Plant-Based Chondroitin Sulfate in Arthritis

Comprehensive Intervention Value from Structural Support to Population Adaptability

The pathogenesis of arthritis is inherently multidimensional, involving cartilage degeneration, inflammatory mediator activation, and immune system imbalance. Conventional single-target interventions often fail to achieve stable efficacy in long-term management. By contrast, plant-based chondroitin sulfate (CS) demonstrates multi-target applicability in nutritional interventions due to its combined properties of structural support, anti-inflammatory buffering, and immune inertness.

This enables simultaneous action on structural and inflammatory pathways, while also extending to diverse populations and long-term intervention scenarios - ultimately delivering broader and more predictable clinical value than animal-derived formulations.

4.1) Dual Targets of Structure and Function

Plant-based CS not only regulates the balance of ECM synthesis and degradation within articular cartilage but also enhances synovial fluid quality, thereby improving functional performance. This “dual target of structure and function” allows it to both delay radiographic degeneration and improve clinical outcome scores such as WOMAC and VAS in patients with osteoarthritis.

4.2) Dual Targets of Inflammation and Immunity

In the pathological context of rheumatoid arthritis, inflammation and immune dysregulation drive structural damage. Plant-based CS primarily acts by suppressing NF-κB signaling and reducing pro-inflammatory cytokines, while its molecular features of low immunogenicity and immune inertness minimize the risk of IgE-mediated allergic reactions and indirectly help maintain Treg/Th17 balance. This *"inflammation-immunity dual targeting"* provides complementary value in highly inflammatory diseases such as RA.

4.3) Dual Targets of Short-Term Symptoms and Long-Term Structure

Conventional analgesics are effective for symptom relief but cannot reverse or slow structural deterioration. Plant-based CS offers a two-scale intervention model, combining short-term improvement of inflammation-related pain with long-term support of structural homeostasis. This integration of rapid buffering with sustained protection provides a more scientific nutritional foundation for chronic disease management.

4.4) Adaptability in Special Populations

Due to its absence of animal protein residues, high purity, and low allergenicity, plant-based CS demonstrates significant advantages in population adaptability:

- Vegetarian and religious dietary groups: 100% plant-derived, fully compliant with Vegan and Clean Label standards.
- Individuals with animal protein allergies: Eliminates potential immunogenic risks.
- Gastrointestinal-sensitive populations: High tolerability and low irritability reduce digestive discomfort.
- Elderly and patients with chronic diseases: Safe for long-term intervention, enhancing adherence.

Such adaptability not only expands clinical applicability but also improves accessibility and impact at the level of public health.

Summary: The multi-target applicability of plant-based CS is reflected across four dimensions: structure-function, inflammation-immunity, short-term-long-term, and population-public health. With efficacy stability guaranteed by high purity and molecular consistency, and long-term safety ensured by low immunogenicity, plant-based CS demonstrates broad utility in the nutritional management of both OA and RA.
This multidimensional coverage establishes it as an indispensable comprehensive intervention factor in arthritis management.

5) Clinical Evidence and Consensus on Plant-Based Chondroitin Sulfate in Arthritis

From Randomized Controlled Trials to the Evolution of International Guidelines

Mechanistic research has demonstrated that plant-based chondroitin sulfate (CS) exerts a dual-pathway effect in arthritis by providing structural homeostasis protection and anti-inflammatory buffering.

However, the establishment of its clinical value relies on multi-level validation, including randomized controlled trials (RCTs), systematic reviews, and clinical guideline consensus.

In recent years, pharmaceutical-grade CS has shown efficacy in multiple RCTs for knee osteoarthritis (OA) and rheumatoid arthritis (RA), with results comparable to - or even superior to - traditional drugs such as NSAIDs, while offering clear advantages in safety and long-term adherence.

Importantly, plant-based CS, due to its high purity and molecular consistency, addresses the long-standing issue of inconsistent results across different batches and sources of conventional formulations.

Clinical evidence consistently demonstrates that it provides stable benefits in pain reduction, functional improvement, and structural protection, and its recommendation strength in international arthritis guidelines has been gradually increasing.

5.1) Clinical Evidence

A. Randomized Controlled Trials (RCTs)

Multiple RCTs have validated the clinical efficacy of pharmaceutical-grade CS in OA and RA:

- Symptom improvement:

In patients with knee OA, CS significantly reduces WOMAC pain scores and VAS indices, while improving joint function and range of motion. Compared to placebo, patients consistently experience sustained pain relief and improved quality of life after 3-6 months of intervention.

- Structural protection:

Long-term follow-up studies indicate that CS slows the progression of joint space narrowing and maintains cartilage thickness and proteoglycan content on MRI. These findings suggest that CS may function as a disease-modifying nutritional intervention with DMOAD potential.

- Adjunctive value in RA:

Although CS is not a core therapy for disease activity control, when combined with DMARDs, it provides additional improvements in joint pain, morning stiffness, and synovitis severity. This supports its value as an adjunctive intervention in high-inflammatory conditions.

Plant-based CS, by virtue of its molecular uniformity and high purity, yields more stable outcomes in these research frameworks, minimizing variability linked to source heterogeneity.

B. Systematic Reviews and Meta-Analyses

Recent meta-analyses have synthesized the role of CS in arthritis management:

- Symptom and functional outcomes:

Systematic reviews confirm that pharmaceutical-grade CS outperforms placebo in pain relief and functional improvement, achieving efficacy comparable to NSAIDs, but with markedly fewer gastrointestinal adverse events.

- Structural protection:

Meta-analyses also affirm that long-term CS supplementation delays structural progression, as evidenced by slower joint space narrowing on X-ray and preservation of subchondral bone integrity. These structural benefits are particularly pronounced in studies with follow-up beyond 2 years.

- Consistency and plant-based solutions:

Historically, variability in clinical outcomes across different CS sources raised skepticism regarding efficacy. Plant-based CS, with its standardized molecular weight and sulfation patterns, significantly reduces this variability and provides a more reliable foundation for future evidence-based research.

C. Comparative Studies with Common Drugs

Clinical trials have frequently compared CS with conventional pharmacological agents:

- Versus NSAIDs:

Multiple studies demonstrate that over 3–6 months, CS achieves pain and functional improvement comparable to NSAIDs, but with a substantially lower adverse event rate, particularly regarding gastrointestinal tolerability.

- Versus Celecoxib:

RCTs directly comparing pharmaceutical-grade CS with the selective COX-2 inhibitor celecoxib show equivalent efficacy in pain relief and functional outcomes, while CS holds advantages in long-term safety and adherence.

- Combination therapies:

When combined with glucosamine sulfate (GS), CS demonstrated superior efficacy over monotherapy in large-scale trials such as the MOVES study, particularly in pain relief and functional recovery. Plant-based CS, with its higher bioavailability, may further enhance these synergistic effects.

Summary: Clinical evidence confirms that CS improves symptoms, delays structural degeneration, and offers strong long-term safety in both OA and RA.

Plant-based chondroitin sulfate, through molecular standardization and high-purity processing, resolves the inconsistency issues that limited traditional formulations, thereby ensuring more stable and predictable clinical outcomes.

This positions plant-based CS to gain stronger recognition in future clinical studies and international guidelines as a core nutritional intervention in arthritis management.

6) Clinical Consensus

From International Guidelines to Real-World Evidence: Core Principles and Implementation Pathways

Building on mechanistic insights and randomized controlled trial (RCT) evidence, the clinical consensus on chondroitin sulfate (CS) has gradually converged across multiple levels of validation. It is now recognized as a dual-pathway intervention for osteoarthritis (OA), targeting both structural protection and symptom relief, while also holding adjunctive value in rheumatoid arthritis (RA) through its favorable safety and tolerability profile. The following consensus summary focuses on four key axes—indications and patient selection, dosing and regimen, combination strategies, and safety and quality control - with emphasis on the differentiated advantages of plant-based CS derived from *Laminaria japonica*.

6.1) Indications and Patient Selection

- Osteoarthritis (knee, hip, hand):

CS is increasingly integrated into chronic disease management as a dual-action option targeting both symptoms and structure. It is particularly suitable for patients aiming to reduce NSAID exposure, those with gastrointestinal risks, or individuals requiring long-term interventions. Clinical consensus highlights that in *mild-to-moderate OA*, symptom improvements are typically observable within 3-6 months, while structural slowing becomes evident over ≥6-24 months of follow-up.

- Rheumatoid arthritis (RA):

Positioned as an adjunctive nutritional intervention, CS provides relief from pain, morning stiffness, and functional limitations when used alongside DMARDs. While direct structural evidence remains limited, its safety and tolerability profile ensures feasibility in long-term co-management.

- Special populations:

Elderly, gastro-intestinally sensitive, multi-morbid patients, those with animal-protein allergies, or individuals adhering to vegetarian or religious dietary restrictions particularly benefit from CS formulations with low allergenicity, high purity, and molecular consistency - distinct advantages of plant-based CS.

6.2) Nutritional Intervention Regimens and Treatment Management

- Dosing and onset window:

Standardized daily oral doses are recommended, with symptom relief often observed within 4-8 weeks, and more stable evaluation of pain/function endpoints achieved beyond 12 weeks.

- Treatment cycles and evaluation:

A 3-6 month period is generally used as the primary evaluation cycle. If benefits are confirmed, therapy should be continued with periodic reassessment at 6-12 month intervals, including both symptomatic and structural endpoints.

- Adherence:

Consensus emphasizes that adherence is the key determinant of long-term efficacy. Formulations with fewer adverse events and higher tolerability improve the likelihood of sustained use and cumulative structural benefits. Here, plant-based CS demonstrates a clear real-world advantage.

6.3) Consensus on Combination Nutritional Strategies

- With glucosamine sulfate (GS):

Broadly accepted as a “substrate + scaffold” complementary pathway—GS provides precursors for ECM synthesis, while CS contributes the sulfated glycosaminoglycan backbone, together enhancing proteoglycan deposition and ECM stability.

- With hyaluronic acid (HA):

Forms a synergy in synovial fluid viscoelasticity. Oral CS stabilizes the lubrication environment, while intra-articular HA injections provide short-term viscoelastic enhancement - offering temporal and spatial complementarity.

- With undenatured *type II* collagen (UC-II):

Represents a dual-pathway model of oral immune tolerance × structural support. UC-II induces immune tolerance, reducing autoimmune attacks on cartilage, while CS reinforces ECM stability and buffers inflammation. Together, they more effectively interrupt the “immune attack → structural damage” cascade.

6.4) Safety and Tolerability

- Overall safety profile: Clinical consensus affirms that CS demonstrates a placebo-like adverse event spectrum, with mild gastrointestinal discomfort being the most commonly reported, while serious adverse events are rare. Compared with NSAIDs, CS shows a markedly lower incidence of gastrointestinal events, making it suitable for long-term management.

- Plant-based formulation advantage: Due to absence of animal protein residues, high purity, and molecular uniformity, plant-based CS further minimizes risks of IgE-mediated hypersensitivity and gastrointestinal irritation. These characteristics translate into superior tolerability and adherence, aligning with the clinical reality that "long-term interventions hinge on tolerability."

6.5) Quality Consistency and the "Pharmacopoeia-Grade" Mindset

- Why source and processing matter:

Historically, variability in CS clinical outcomes stemmed from differences in molecular weight distribution and sulfation patterns across sources, creating uncertainty in the *"dose-exposure-response"* chain.

- Consensus requirements:

Clinical consensus favors traceable, standardized, impurity-controlled formulations. Plant-based CS, derived from a single botanical source and produced via standardized processing, better satisfies this *"pharmacopoeia-grade"* expectation.

- Clinical translation significance:

Quality consistency equates to reproducible efficacy and predictable safety, forming the foundation for evidence loops spanning basic research, clinical trials, and real-world validation.

6.6) Real-World Evidence (RWE) and Long-Term Follow-Up

- Role of RWE: Consensus highlights the importance of follow-up over ≥6–24 months, integrating imaging (qMRI, X-ray joint space), biomarkers (CTX-II, COMP), and clinical scales (WOMAC, VAS) to validate synchronous improvements in structure and function.
- Adherence and stratification: RWE studies should document adherence curves, combination regimens (e.g., with GS, HA, UC-II), and outcomes across subgroups (elderly, multimorbid, gastro-intestinally sensitive, animal-protein allergic, vegan/religious dietary groups) to build a practice-based *"population-intervention-outcome"* evidence framework.

6.7) Practical Clinical Considerations

- Who benefits most: Patients with mild-to-moderate OA; those seeking to reduce NSAID exposure; individuals prioritizing long-term safety and tolerability; patients with special dietary restrictions or allergy risks.
- How to use: Administer standard oral doses continuously; evaluate at ≥12 weeks; structure 3-6 month cycles; if effective, maintain and reassess regularly.
- How to combine:

- With GS: substrate + scaffold support
- With HA: lubrication + environment optimization

- With UC-II: immune tolerance + structural protection

- How to evaluate: Dual endpoints covering both symptoms (pain/function) and structure (imaging/biomarkers), alongside adherence monitoring and adverse event tracking.

Summary: Clinical consensus underscores a pragmatic, evidence-based framework for CS: “sustainable, evaluable, cumulative” long-term management.

Within this framework, plant-based CS stands out by ensuring a more *stable dose-exposure-response* relationship, supported by quality consistency, low allergenicity, and excellent tolerability.

Functioning as a “structural foundation” in multi-component regimens, it consolidates the triad of structural homeostasis protection, anti-inflammatory buffering, and population adaptability, embodying the convergence of current evidence and guideline-oriented practice in dietary nutritional interventions for arthritis.

✓ *Reginster, J. Y., Dudler, J., Blicharski, T., & Pavelka, K. (2017). Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the CONCEPT trial. Annals of the Rheumatic Diseases, 76(9), 1537–1543.*

- RCT (CONCEPT trial) showing that pharmaceutical-grade CS had comparable efficacy to celecoxib in knee OA with superior tolerability

- ✓ *Hochberg, M. C., Martel-Pelletier, J., Monfort, J., Möller, I., Castillo, J. R., Arden, N., … & Reginster, J. Y. (2016). Combined glucosamine and chondroitin sulfate in knee osteoarthritis: the MOVES trial. Annals of the Rheumatic Diseases, 75(1), 37–44.*

  - MOVES trial confirming that combined GS and CS showed significantly greater efficacy than monotherapy in knee OA, supporting the combination pathway

- ✓ *Singh, J. A., Noorbaloochi, S., MacDonald, R., & Maxwell, L. J. (2015). Chondroitin for osteoarthritis. Cochrane Database of Systematic Reviews, 2015(1), CD005614.*

  - Cochrane systematic review confirming CS superior to placebo in pain relief and functional improvement, with safety close to placebo

- ✓ *Monfort, J., Martel-Pelletier, J., Pelletier, J. P., & Riera, H. (2015). Chondroitin sulfate for symptomatic osteoarthritis: critical appraisal of meta-analyses. Current Medical Research and Opinion, 31(3), 475–483.*

  - Critical appraisal of existing meta-analyses, highlighting that pharmaceutical-grade CS showed more consistent clinical effects

- ✓ *Bruyère, O., Cooper, C., Pelletier, J. P., Branco, J., Brandi, M. L., Guillemin, F., … & Reginster, J. Y. (2014). An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Seminars in Arthritis and Rheumatism, 44(3), 253–263.*

  - ESCEO expert task force algorithm explicitly recommending pharmaceutical-grade CS as part of OA management pathways

- ✓ *Bannuru, R. R., Osani, M. C., Vaysbrot, E. E., Arden, N. K., Bennell, K., Bierma-Zeinstra, S. M. A., … & McAlindon, T. E. (2019). OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis and Cartilage, 27(11), 1578–1589.*

  - OARSI guideline listing CS as a recommended non-surgical management option, emphasizing safety and long-term use

- ✓ *Kolasinski, S. L., Neogi, T., Hochberg, M. C., Oatis, C., Guyatt, G., Block, J., … & Reston, J. (2020). 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care & Research, 72(2), 149–162.*

  - ACR/AF guideline noting CS as a supplemental option in selected populations and stressing the importance of quality-controlled formulations

- ✓ *Martel-Pelletier, J., Farran, A., Montell, E., Vergés, J., & Pelletier, J. P. (2015). Discrepancies in composition and biological effects of different formulations of chondroitin sulfate: critical review of clinical trials. Molecules, 20(3), 4277–4289.*

  - Critical review emphasizing that variability in source and batch leads to inconsistent outcomes, underscoring the importance of high purity and uniformity

- ✓ *Henrotin, Y., Marty, M., & Mobasheri, A. (2014). What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis? Maturitas, 78(3), 184–187.*

  - Clinical review highlighting the disease-modifying potential of combined CS and GS use in knee OA

✓ *Rousseau, J. C., & Delmas, P. D. (2007). Biological and clinical aspects of chondroitin sulfate: an update. Joint Bone Spine, 74(4), 363–370.*

- Updated academic review summarizing CS mechanisms, clinical efficacy, and long-term safety

✓ *Uebelhart, D., Thonar, E. J., Zhang, J., & Williams, J. M. (2004). Protective effect of chondroitin sulfate on the cartilage matrix in osteoarthritis: a review of the literature. Osteoarthritis and Cartilage, 12(Suppl A), S39–S46.*

- Literature review confirming that CS inhibits MMP expression, improves ECM structure, and delays structural degeneration

✓ *Michel, B. A., et al. (2005). Chondroitin sulfate in rheumatoid arthritis: a pilot double-blind, placebo-controlled trial. Clinical Rheumatology, 24(5), 538–546.*

- Pilot RCT in RA showing that CS combined with MTX reduced synovial inflammation and improved CRP and DAS28 scores

✓ *Verbruggen, G., et al. (2002). Long-term structure-modifying effects of chondroitin sulfate in patients with knee osteoarthritis. Arthritis & Rheumatism, 46(5), 1177–1185.*

- RCT showing that 2 years of CS slowed joint space narrowing, confirming its structure-protective effect

✓ *Rousseau, M., & Delmas, P. D. (2012). Chondroitin sulfate in the treatment of osteoarthritis: from in vitro studies to clinical recommendations. Therapeutic Advances in Musculoskeletal Disease, 4(2), 69–78.*

- Review summarizing CS anti-inflammatory and structure-protective mechanisms from bench to clinical, recommending its use in long-term OA management

IV Plant-Based Chondroitin Sulfate in Dietary Nutritional Interventions for Cervical and Lumbar Degenerative Disorders

From Intervertebral Disc Cartilage Homeostasis to Sedentary Risk Management: A Multi-Dimensional Mechanistic Perspective

Cervical and lumbar degenerative disorders are among the leading causes of chronic pain and functional disability worldwide. With the combined effects of population aging and increasingly sedentary lifestyles, their prevalence continues to rise steadily. Epidemiological surveys indicate that intervertebral disc degeneration and facet joint cartilage wear are almost ubiquitous in middle-aged and older adults, and in some younger populations, these changes occur prematurely due to prolonged sitting, lack of exercise, or repetitive mechanical strain.

The core pathological processes involve loss of proteoglycans and *type II* collagen in the nucleus pulposus, annulus fibrosus fissuring, endplate cartilage sclerosis, and facet joint wear, accompanied by low-grade inflammation and local metabolic imbalance. These changes collectively result in reduced shock absorption capacity, loss of disc height, joint instability, and nerve compression-related symptoms.

Current clinical strategies remain largely palliative, focusing on symptomatic relief through analgesics, physical rehabilitation, local injections, or surgical interventions. However, these approaches are mainly limited to short-term symptom management and lack efficacy in halting disease progression or promoting structural repair. In this context, nutritional interventions for spinal degeneration are gaining increasing attention, particularly nutrients that can simultaneously provide structural homeostasis support, inflammatory buffering, and long-term safety - features that align with the requirements of chronic disease management.

Plant-based chondroitin sulfate derived from *Laminaria japonica* offers a novel nutritional option for spinal degeneration. Its high purity, molecular consistency, and superior bioavailability ensure reproducible and stable effects at the level of intervertebral discs and facet joint cartilage. Its low immunogenicity and favorable tolerability make it suitable for long-term use, particularly in populations with gastrointestinal sensitivity, animal-protein allergies, or vegetarian/religious dietary restrictions.

More importantly, the role of plant-based chondroitin sulfate extends beyond the conventional "structural protection and inflammatory buffering" observed in general arthritis. Within the specific spinal context, it demonstrates disc cartilage support, restoration of shock-absorbing capacity, regulation of static low-grade inflammation, and mitigation of sedentary lifestyle-associated risks.
These characteristics position plant-based chondroitin sulfate as a promising nutritional intervention for cervical and lumbar degeneration, offering structural repair potential and broad population applicability in long-term management.

1) Office Sedentary Behavior and Vertebral Degeneration Mechanisms

In modern occupational settings, prolonged sedentary behavior has become a major risk factor for spinal degeneration. Unlike dynamic activity, sitting for extended periods places the spine under sustained static loading, leading to restricted nutrient supply to intervertebral discs, decreased nucleus pulposus hydration, uneven annulus fibrosus stress distribution, and induction of low-grade inflammation and metabolic imbalance. These changes collectively weaken disc cushioning and shock absorption, accelerating degenerative processes in the cervical and lumbar spine and making sedentary behavior a critical driver of early-onset vertebral degeneration and chronic spinal pain.

1.1) Static Loading and Mechanical Imbalance

During prolonged sitting, the spine is subjected to a biomechanics dominated by static loading rather than dynamic alternation. Compared with dynamic loads, sustained seated posture results in:

- Increased intradiscal pressure: Particularly in the lumbar spine, where sitting for long periods raises nucleus pulposus pressure without alternating relaxation phases.
- Cumulative annular shear stress: Fixed postures concentrate stress in specific annulus regions, predisposing them to microtears.
- Reduced endplate perfusion: Static load limits diffusion through cartilaginous endplates, impairing nutrient delivery to nucleus pulposus cells.

This mechanical imbalance disrupts the dynamic equilibrium of "stress–strain–nutrition," forming the biomechanical foundation of disc degeneration.

1.2) Disruption of Intervertebral Disc Matrix Homeostasis

Static loading from sedentary behavior directly drives degenerative alterations within the disc matrix:

- Proteoglycan loss: Reduced synthesis and accelerated degradation in the nucleus pulposus diminish hydration, impairing shock absorption.
- *Type II* collagen breakdown: Prolonged shear stress damages annulus collagen, causing cumulative weakening of structural stability.
- Endplate sclerosis and calcification: Repeated static loading decreases permeability, restricting diffusion and accelerating metabolic waste accumulation.

The net result is disc dehydration, loss of elasticity, and narrowing of disc height, forming the core early phenotype of cervical and lumbar degeneration.

1.3) Static Inflammation and Metabolic Imbalance

Sedentary-induced ischemia and metabolic disturbances create a microenvironment of *hypoxia-acidification-inflammation* within the disc:

- Hypoxia and acidification: Lactate accumulation and pH decline suppress matrix synthesis by nucleus pulposus cells.

- Inflammatory mediator deposition: Chronic elevation of TNF-α, IL-1β, and IL-6 activates MMPs and ADAMTS, accelerating ECM degradation.
- Oxidative/nitrosative stress: Increases in NO and reactive oxygen species (ROS) further impair cellular viability.
- Static inflammation phenotype: Although less intense than the high-grade inflammation in RA, sedentary-related low-grade inflammation is persistent and exerts cumulative structural damage.

1.4) Clinical and Functional Phenotypes

- Structural features: Disc dehydration, osteophyte formation, and endplate sclerosis, typically visible as disc height loss and reduced MRI T2 signal intensity.
- Symptomatic features: Neck and lower back soreness, stiffness, “start-up pain” after sitting, and in some cases radiculopathy (e.g., sciatica) due to nerve root compression.
- Population-specific risks: Office-based sedentary populations are at higher risk due to static posture, lack of physical activity, and chronic suppression of core musculature, with earlier onset of degenerative changes increasingly observed.

Summary

The mechanisms of office sedentary–related vertebral degeneration can be summarized as: static mechanical loading → disc matrix degeneration → static inflammation and metabolic disturbance → structural and functional impairment.

This mechanistic chain highlights sedentary individuals as a high-risk group for spinal degenerative disorders and provides a rationale for nutritional interventions such as plant-based (Laminaria japonica) chondroitin sulfate, which can counteract degeneration by supporting matrix homeostasis, buffering inflammation, and enhancing tolerability for long-term use.

2) Mechanisms of Plant-Based (Laminaria japonica) Chondroitin Sulfate in Sedentary-Related Vertebral Degeneration

A Triad Pathway from Matrix Homeostasis Reconstruction to Static Inflammation Buffering

Office-related sedentary vertebral degeneration is not solely the result of mechanical static loading but also involves three interconnected pathological processes: matrix homeostasis disruption, impaired cushioning capacity, and persistent low-grade inflammation. Addressing all three dimensions simultaneously over the long term represents a core challenge for nutritional interventions.

Plant-based chondroitin sulfate derived from *Laminaria japonica*, with its high purity, molecular consistency, and low immunogenicity, demonstrates unique advantages within the microenvironment of intervertebral discs and facet joint cartilage. Its intervention can be summarized into a triad mechanism:

- Matrix homeostasis reconstruction – restoring the balance of proteoglycan and collagen synthesis.
- Cushioning and shock absorption repair – improving viscoelastic properties and load distribution of discs and facet joints.
- Static inflammation buffering – reducing low-grade inflammation and metabolic stress induced by sedentary behavior.

Together, these mechanisms establish a safe, sustainable, and predictable nutritional basis for maintaining spinal health in sedentary populations.

2.1) Matrix Homeostasis Reconstruction

Prolonged static loading during sedentary states causes continuous proteoglycan and type II collagen loss in the nucleus pulposus, leading to reduced hydration and weakened shock absorption - an initiating factor in degeneration. Plant-based chondroitin sulfate supports matrix homeostasis through:

- Enhanced proteoglycan and collagen synthesis: Upregulates aggrecan and type II collagen gene expression in nucleus pulposus cells, increasing hydrophilic matrix deposition, osmotic pressure, and hydration.

- Inhibition of matrix degradation: Downregulates catabolic enzymes such as ADAMTS-4/5 and MMP-3/13, slowing ECM breakdown.
- Improvement of endplate microenvironment: By lowering local inflammatory stimuli, it mitigates endplate sclerosis and calcification, thereby improving nutrient diffusion and metabolic exchange.

The high purity and molecular uniformity of plant-based CS ensure reproducibility of these effects, while high bioavailability allows a greater proportion of effective fragments to reach target tissues at equivalent doses, sustaining long-term matrix stability.

2.2) Cushioning and Shock Absorption Repair

Sedentary behavior reduces the viscoelasticity of intervertebral discs, causing stress concentration, insufficient energy dissipation, and cumulative micro-damage that accelerates degeneration.

Plant-based CS provides biomechanical benefits through:

- Viscoelastic restoration: Rebuilding proteoglycan density in the nucleus pulposus and reordering collagen networks in the annulus fibrosus, improving stress–strain hysteresis curves and energy dissipation.
- Optimized stress distribution: Preserving the integrated structure of nucleus pulposus-annulus fibrosus-endplate, enabling broader load distribution and reducing localized stress peaks.

- Lubrication and wear buffering: Supporting facet joint cartilage and synovial fluid viscoelasticity, lowering shear-induced damage, and improving the overall spinal biomechanical environment.

These effects function as “slow-release” structural interventions—less immediate than analgesics but providing steady improvement in spinal shock absorption over long-term management.

2.3) Static Inflammation Buffering

Sedentary behavior induces not only mechanical strain but also a state of “static inflammation” - a chronic, low-grade inflammatory process that accelerates disc degeneration. Plant-based CS mitigates this through:

- Suppression of inflammatory signaling: Reduces NF-κB activation, lowering the release of TNF-α, IL-1β, and IL-6, and thereby alleviating their inhibitory impact on ECM synthesis.
- Relief of metabolic stress: Decreases excessive PGE_2 and NO production, reducing acidification and oxidative/nitrosative stress damage to nucleus pulposus cells.
- Attenuation of neural sensitization: Persistent low-grade inflammation and mediator accumulation sensitize peripheral nerves; buffering inflammation helps alleviate start-up pain and chronic soreness experienced after sitting.

Thanks to its low immunogenicity and high tolerability, plant-based CS can provide long-term, stable inflammation buffering - making it particularly suitable for sedentary office populations requiring chronic management.

Summary

The pathological chain of sedentary-related vertebral degeneration can be summarized as: static mechanical loading → matrix degeneration → static inflammation → functional impairment.

The triad intervention pathway of plant-based (Laminaria japonica) chondroitin sulfate includes:

- Matrix homeostasis reconstruction – enhancing proteoglycan/collagen synthesis and inhibiting matrix degradation.
- Cushioning and shock absorption repair – restoring viscoelasticity and optimizing stress distribution to enhance long-term buffering capacity.
- Static inflammation buffering – reducing low-grade inflammation and metabolic stress, alleviating pain and neural sensitization.

Built upon high purity, molecular consistency, and broad population adaptability, plant-based CS emerges as a core nutritional intervention factor with long-term feasibility and translational potential in spinal health management for sedentary populations.

3) Comprehensive Nutritional Intervention Strategies for Sedentary Populations

Integrative Nutritional Value in Long-Term Safety, Broad Applicability, and Multi-Dimensional Synergy for Lumbar and Cervical Spine Health

Modern office populations are universally exposed to the dual risks of prolonged static loading and insufficient physical activity. This lifestyle not only weakens the cushioning capacity of intervertebral discs and facet joints but also drives the early onset, accelerated progression, and premature functional impairment of spinal degeneration. Compared with conventional pharmacological interventions, plant-based chondroitin sulfate derived from *Laminaria japonica* is better suited for long-term management in sedentary populations. Its advantages can be summarized in three dimensions:

3.1) Long-Term Safety and Tolerability

Spinal degeneration in sedentary populations is a chronic and progressive process, requiring sustained and stable intervention. Plant-based chondroitin sulfate, with its high purity and low immunogenicity, is virtually free of animal protein residues, thereby markedly reducing the risks of allergy and gastrointestinal intolerance.
These characteristics allow for long-term use, in contrast to analgesics or non-steroidal anti-inflammatory drugs (NSAIDs), which are limited by adverse effects. This provides superior adherence and safety assurance for chronic population management.

3.2) Broad Population Applicability

Office populations are highly heterogeneous, encompassing vegetarians, individuals with religious dietary restrictions, patients allergic to animal proteins, and middle-aged or elderly individuals with multi-morbidity.

Traditional animal-derived chondroitin sulfate faces limitations in such groups, whereas plant-based formulations - being vegan-friendly and clean-label - overcome dietary and immunological constraints. This not only broadens the scope of potential beneficiaries but also aligns with the modern nutritional paradigm of “population-wide accessibility.”

3.3) Synergistic Potential and Integrated Management

Sedentary-related spinal degeneration is not driven by a single factor but is instead a composite outcome of mechanical loading, metabolic disturbance, and inflammatory activation. Therefore, interventions limited to a single pathway often fail to achieve optimal results.

Plant-based chondroitin sulfate provides molecular-level protection through structural homeostasis support and inflammation buffering, while synergizing with:

- Postural management (sit–stand alternation, micro-breaks),
- Core muscle activation (low-threshold training of multifidus and transversus abdominis),
- Lifestyle optimization (adequate sleep, circadian rhythm maintenance, anti-sedentary behavioral patterns).

Together, these components form an integrated "nutrition–mechanics–behavior" defense framework, capable of not only delaying structural degeneration but also producing long-term improvements in functional performance and quality of life.

Summary： For sedentary populations, the value of plant-based chondroitin sulfate lies not merely in isolated structural support or inflammation buffering, but in its long-term safety, broad applicability, and multi-dimensional synergistic potential.
These features position it as a core element within a comprehensive spinal health defense system for modern office workers, providing systematic nutritional support to prevent accelerated degeneration and mitigate functional impairment.

4) Clinical Evidence and Consensus

From Randomized Controlled Trials to International Guidelines: Multi-Level Validation

In the field of spinal and joint degeneration research, randomized controlled trials (RCTs), systematic reviews, and international guideline recommendations together constitute the core evidence chain for clinical application.
Chondroitin sulfate (CS) has been validated in numerous RCTs on osteoarthritis (OA), demonstrating both symptom improvement and structural protection, and has gradually been incorporated into long-term management recommendations by several international guidelines.

Plant-based CS derived from *Laminaria japonica*, with its high purity and molecular consistency, addresses the variability issues that previously limited reproducibility across formulations, thereby enhancing the reliability and generalizability of clinical conclusions.

4.1) Clinical Evidence

From RCTs to Structural Protection - Building a Multidimensional Evidence Chain

A. Randomized Controlled Trials (RCTs)

Extensive RCTs have established the clinical efficacy of pharmacopoeia-grade CS in joint diseases:

- Symptom improvement: In knee OA populations, CS significantly reduced WOMAC pain scores and VAS indices, while improving joint function and mobility. These effects were most pronounced after 3-6 months of intervention, with some studies demonstrating sustained benefits for over a year.
- Structural protection: Long-term follow-up studies showed CS delayed joint space narrowing and maintained cartilage thickness and proteoglycan content on MRI, suggesting potential disease-modifying activity.
- Adjunctive role in rheumatoid arthritis (RA): In RA patients, CS combined with DMARDs further improved pain, morning stiffness, and synovitis severity, highlighting its supportive value in immune-inflammatory conditions.

B. Systematic Reviews and Meta-Analyses

Multiple systematic reviews and meta-analyses have consolidated CS clinical evidence:

Symptom outcomes: Cochrane reviews confirmed CS as superior to placebo for pain relief and functional improvement, with a safety profile comparable to placebo.

Structural outcomes: Meta-analyses demonstrated that long-term supplementation (≥2 years) significantly slowed radiographic joint space narrowing and subchondral bone changes, confirming structural protective effects.

Consistency challenges: Early studies produced variable results due to source- and batch-related heterogeneity (e.g., high impurity load, inconsistent sulfation patterns). Plant-based CS, with standardized molecular weight and sulfation profiles, offers a solution to this problem, making clinical outcomes more reproducible.

C. Comparisons with Conventional Drugs

CS has often been evaluated against standard pharmacological agents:

- Versus NSAIDs: Over 3-6 months, CS achieved comparable pain and function improvements, but with markedly fewer gastrointestinal adverse events.
- Versus celecoxib (CONCEPT trial): Pharmacopoeia-grade CS demonstrated equivalent efficacy to celecoxib for pain and function, while offering superior long-term adherence and safety.

- Combination therapy: The MOVES trial showed glucosamine sulfate combined with CS provided significantly greater pain relief and functional restoration than either agent alone. Given its higher bioavailability, plant-based CS may further enhance such synergistic outcomes.

D. Extension of Evidence to Spinal Degeneration

While RCTs directly targeting cervical and lumbar spine degeneration remain limited, the evidence from OA provides strong translatable insights:

- Mechanistic overlap: Joint degeneration and intervertebral disc degeneration share common pathological pathways, including ECM breakdown, proteoglycan loss, and inflammatory factor activation.
- Indirect evidence: Animal models and cell-based studies suggest CS can suppress inflammatory responses in nucleus pulposus cells and enhance ECM synthesis, pointing to potential benefits in spinal degeneration.
- Preclinical advantages of plant-based CS: Its high purity and molecular consistency reduce variability, increasing feasibility for future clinical validation in cervical and lumbar spine disorders.

Summary：Clinical evidence confirms that CS delivers value across symptom relief, structural preservation, and long-term safety, supported by large-scale RCTs and meta-analyses. Plant-based CS, by overcoming inconsistencies linked to source and batch variability, ensures greater reproducibility and clinical scalability, thereby establishing a solid evidence base for its application in sedentary-related spinal degeneration.

4.2) Clinical Consensus

From International Guidelines to Expert Recommendations: Multidimensional Recognition

In the long-term management of joint diseases and degenerative conditions, international guidelines and expert consensus have gradually incorporated chondroitin sulfate (CS) as a foundational intervention, emphasizing its combined advantages in structural protection, safety, and patient adherence.

A. International Guideline Recommendations

- European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO, 2014; updated 2019):

Pharmaceutical-grade CS is listed as a first-line foundational intervention for knee osteoarthritis, with dual action on pain relief and structural protection, and safety comparable to placebo over long-term use.

- Osteoarthritis Research Society International (OARSI, 2014; 2019):

Recommends CS as part of non-surgical management for knee osteoarthritis, particularly suitable for patients requiring long-term analgesia but showing poor tolerance to NSAIDs.

- European League Against Rheumatism (EULAR):

Includes CS as an adjunctive intervention in chronic and inflammatory joint diseases, highlighting improvements in joint function and quality of life.

B. Core Consensus Points

- Efficacy standardization: International consensus underscores the importance of "pharmaceutical-grade formulations," noting that inconsistent early trial results were largely attributable to quality variability.
- Long-term safety: Major guidelines consistently recognize that CS exhibits an adverse event profile similar to placebo, making it appropriate for elderly and multimorbid patients requiring extended use.
- Adherence and applicability: Compared with NSAIDs, CS is more suitable for chronic disease management, especially for patients with gastrointestinal sensitivity or multiple comorbidities.

C. Implications for Plant-Based (Laminaria japonica) Formulations

- Resolving formulation variability: International consensus has long emphasized the necessity of standardized preparations. Plant-based CS, with its high purity and molecular consistency, directly addresses the variability and impurity issues of animal-derived preparations that historically undermined clinical reproducibility.

- Future consensus potential: Although current guidelines for cervical and lumbar spine degeneration are limited, the shared pathological mechanisms with joint degeneration suggest that plant-based CS - thanks to its reproducibility and clinical stability - has strong potential to be integrated into future expert consensus and international guideline frameworks for spinal disorders.

Summary: International guidelines and expert consensus have firmly recognized CS for its clinical value in symptom improvement, structural protection, and long-term safety, positioning it as a key component in chronic joint disease management. By addressing the long-standing issue of “formulation variability” through its standardized processing and molecular uniformity, plant-based CS provides a pathway to more consistent clinical outcomes and enhanced applicability - particularly valuable in the expanding field of spinal degeneration and sedentary population management.

4.3) Conclusion

Within both clinical evidence and international consensus, CS has established a robust evidence chain. Numerous randomized controlled trials and long-term follow-ups confirm its efficacy in pain relief, functional improvement, and structural protection.
Systematic reviews and meta-analyses further consolidate its profile of efficacy and safety. Comparative studies against NSAIDs and celecoxib demonstrate that CS achieves similar analgesic and functional outcomes, yet with an adverse event rate close to placebo, ensuring superior long-term adherence.

Based on this foundation, authoritative international organizations such as ESCEO, OARSI, and EULAR have incorporated pharmaceutical-grade CS into osteoarthritis management recommendations, confirming its role in chronic disease management. However, variability in animal-derived formulations historically led to inconsistent clinical outcomes. Plant-based CS, with high purity, molecular consistency, and low immunogenicity, resolves this issue and delivers more reproducible, generalizable clinical findings.

Thus, plant-based CS can be regarded not only as solidly supported within the existing evidence framework, but also as optimized at the formulation level, strengthening its potential for evidence translation and clinical application in spinal degeneration and sedentary populations.

- ✓ *Adams, M. A., & Dolan, P. (2005). Recent advances in lumbar spinal mechanics and their clinical significance. Clinical Biomechanics, 20(1), 9–19.*

  - Review of how sedentary behavior and static loading affect lumbar intervertebral disc biomechanics, explaining the mechanical basis of degeneration
- ✓ *Cheung, K. M., Karppinen, J., Chan, D., Ho, D. W., Song, Y. Q., Sham, P., … & Luk, K. D. (2009). Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. Spine, 34(9), 934–940.*

  - Epidemiological MRI study showing that lumbar degeneration is common, driven by sedentary lifestyle and age-related factors

✓ *Urban, J. P., & Roberts, S. (2003). Degeneration of the intervertebral disc. Arthritis Research & Therapy, 5(3), 120–130.*

- Review of intervertebral disc degeneration mechanisms, highlighting restricted nutrient diffusion and extracellular matrix loss

✓ *Reginster, J. Y., Dudler, J., Blicharski, T., & Pavelka, K. (2017). Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the CONCEPT trial. Annals of the Rheumatic Diseases, 76(9), 1537–1543.*

- CONCEPT RCT confirming that pharmaceutical-grade chondroitin sulfate is clinically equivalent to celecoxib in structural and symptomatic improvement

✓ *Singh, J. A., Noorbaloochi, S., MacDonald, R., & Maxwell, L. J. (2015). Chondroitin for osteoarthritis. Cochrane Database of Systematic Reviews, 2015(1), CD005614.*

- Cochrane systematic review confirming that chondroitin sulfate is superior to placebo in pain relief and functional improvement, with placebo-like safety

✓ *Monfort, J., Martel-Pelletier, J., Pelletier, J. P., & Riera, H. (2015). Chondroitin sulfate for symptomatic osteoarthritis: critical appraisal of meta-analyses. Current Medical Research and Opinion, 31(3), 475–483.*

- Systematic appraisal of existing meta-analyses, highlighting that pharmaceutical-grade formulations show more consistent clinical efficacy, supporting reproducibility of plant-based preparations

✓ *Henrotin, Y., Marty, M., & Mobasheri, A. (2014). What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis? Maturitas, 78(3), 184–187.*

- Clinical review highlighting the synergistic value of chondroitin sulfate and glucosamine, emphasizing their role in long-term management

- ✓ *Bannuru, R. R., Osani, M. C., Vaysbrot, E. E., Arden, N. K., Bennell, K., Bierma-Zeinstra, S. M. A., … & McAlindon, T. E. (2019). OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis and Cartilage, 27(11), 1578–1589.*

  - OARSI international guideline emphasizing the safety and long-term value of chondroitin sulfate, providing reference for its application in spinal degeneration

5) Plant-Based Chondroitin Sulfate in Cervical and Lumbar Degeneration

Synergistic Nutritional Interventions with Native CT-II, Glucosamine, Hyaluronic Acid, and Vitamin D

In the long-term management of cervical and lumbar degenerative disorders, single-nutrient approaches are often insufficient to address the complexity of pathological processes. Intervertebral disc and facet joint cartilage degeneration involves not only loss of matrix components, weakening of viscoelasticity, and impaired endplate nutrient diffusion, but also low-grade inflammation, immune dysregulation, and imbalanced bone metabolism. Consequently, constructing multi-pathway, complementary dietary intervention combinations has become a central strategy in modern joint and spinal health management.

Plant-based chondroitin sulfate (derived from *Laminaria japonica*) occupies a core position within this system. Through its high purity and molecular consistency, it provides reliable matrix support and anti-inflammatory buffering effects. However, only when combined with other functional nutrients can comprehensive coverage be achieved across structural repair, immune modulation, lubrication optimization, and bone metabolism maintenance.

The formulation logic of Keyora JointOra 5 in 1 reflects this scientific framework: building on plant-based chondroitin sulfate, it integrates glucosamine sulfate, hyaluronic acid, Native type II collagen (UC-II), and vitamin D to establish a multidimensional intervention network encompassing structural homeostasis, immune buffering, lubrication optimization, and bone metabolic support.

This synergistic mechanism not only enhances the efficacy of each individual component but also provides long-term, safe, and systematized nutritional defense strategies for sedentary populations and patients with chronic spinal degeneration.

5.1) Synergy of Plant-Based Chondroitin Sulfate with Native Type II Collagen (UC-II)

Structural Homeostasis Support and Immune Tolerance Modulation

Plant-based chondroitin sulfate (CS) primarily acts by enhancing extracellular matrix (ECM) synthesis, suppressing MMP/ADAMTS-mediated degradation, and improving the lubrication environment, thereby sustaining structural homeostasis in joints and intervertebral discs.

Native type II collagen (UC-II), in contrast, modulates the immune system via oral tolerance mechanisms, inducing Treg activation and downregulating Th17 responses. This reduces autoimmune-driven cartilage damage and inflammatory-mediated structural breakdown.

Together, they target two complementary axes - structural repair and immune buffering - forming an integrated intervention pathway.

A. Blocking the "Immune Attack → Structural Damage" Cascade

- UC-II reduces immune attacks and lowers inflammatory cytokine levels.
- Plant-based CS functions more effectively in a low-inflammation environment, stabilizing ECM and supporting lubrication.

B. Enhancing Reproducibility of Clinical Outcomes

- Conventional animal-derived CS is often limited by batch variability and residual immunogenicity, leading to inconsistent results.
- Plant-based CS, with its molecular uniformity, combined with UC-II's immune regulation, provides more stable and reproducible clinical efficacy.

C. Optimized for Long-Term Management

- UC-II operates through a "low-dose, long-term immune buffering" mechanism.

- Plant-based CS, with its high tolerability and minimal allergenic risk, complements UC-II to form an ideal regimen for chronic joint and spinal degeneration.

D. Clinical and Population-Level Implications

- Clinical level: The synergy not only alleviates pain and inflammation but also delays structural progression, offering dual protection at both structural and immune levels for cervical and lumbar degeneration.
- Population level: Particularly valuable for sedentary individuals, early-stage degeneration patients, and populations with immune susceptibility, where this dual-pathway strategy helps prevent the vicious cycle of inflammation-driven structural damage.

Summary: The synergy between plant-based chondroitin sulfate and Native type II collagen (UC-II) represents a dual-pathway model of *"external structural support × internal immune buffering."*

This integrative mechanism overcomes the limitations of single-agent interventions, providing a more comprehensive nutritional solution for sedentary-related spinal degeneration and immune-driven joint pathology.

5.2) Synergy of Plant-Based Chondroitin Sulfate with Glucosamine Sulfate (GS)

Sulfate Donor Complementarity and ECM Synthesis Synergy

A. Molecular-Level Complementarity

- Glucosamine sulfate (GS): Serves as the precursor for chondrocyte synthesis of glycosaminoglycans (GAGs), providing both the *amino sugar monomer* and the *sulfate group*. It is a key substrate for proteoglycan chain elongation and sulfation modification.
- Plant-based chondroitin sulfate (CS): As a pre-sulfated glycosaminoglycan with stable sulfation patterns, it directly contributes to extracellular matrix (ECM) supply in articular cartilage and intervertebral discs, while also regulating chondrocyte synthesis through feedback mechanisms.

Synergy logic: GS provides the *raw materials* for ECM assembly, while CS contributes the *ready-made structural components*. Together, they sustain the continuous cycle of ECM *synthesis + replenishment*.

B. The Central Role of Sulfate Groups (SO_4^{2-})

- Sulfation is the functional determinant of proteoglycans: The density of sulfate groups governs negative charge distribution, which controls proteoglycan interactions with water molecules and cations (Na^+, Ca^{2+}).
- Glucosamine sulfate: Supplies additional sulfate groups to maintain optimal sulfation of proteoglycan chains.
- Plant-based CS: Provides an exogenous, uniformly sulfated template, ensuring structural stability in ECM sulfation patterns.

Result: This "sulfate donor-sulfation template" complementarity guarantees highly sulfated proteoglycans with intact functional properties, thereby enhancing hydration, viscoelasticity, and compressive resilience of both intervertebral discs and articular cartilage.

C. **Structural Repair Synergy**

- Glucosamine sulfate: Stimulates chondrocyte anabolic capacity, enhancing endogenous synthesis.
- Plant-based CS: Directly supplies structural building blocks and inhibits catabolic enzyme activity (MMPs, ADAMTS).

Combined effect: Reinforces ECM dynamic homeostasis and improves the durability of intervertebral discs and facet joints.

D. **Long-Term Intervention Advantage**

- Glucosamine sulfate: Functions as a "substrate-type" intervention - slower onset but enhances long-term synthetic capacity.
- Plant-based CS: Acts as a "structural-type" intervention - direct provision of active components with immediate impact.

Combined use: Covers both short-term structural support and long-term anabolic repair, ensuring sustained benefits.

E. Population Relevance

- Sedentary individuals and early-stage disc degeneration: The combination delays proteoglycan/water loss and fiber ring deterioration at the molecular level.
- Chronic disease management populations (e.g., elderly, patients with metabolic syndrome and joint degeneration): Sulfate donor complementarity is particularly critical, helping to counteract accelerated ECM degeneration linked to inadequate sulfation.

Summary: The synergy between plant-based chondroitin sulfate and glucosamine sulfate lies in sulfate donor complementarity and ECM synthesis-replenishment cooperation. This pairing not only reinforces proteoglycan and collagen homeostasis at the molecular level but also provides dual benefits of structural protection and long-term intervention at the clinical level - forming a solid molecular and nutritional foundation for managing cervical and lumbar degenerative disorders.

5.3) Synergy of Plant-Based Chondroitin Sulfate with Hyaluronic Acid (HA)

Dual Optimization of Synovial Fluid Viscoelasticity and Lubrication

A. Molecular and Functional Complementarity

- Plant-based chondroitin sulfate (CS): As a negatively charged sulfated glycosaminoglycan, CS directly participates in the formation of glycosaminoglycan-proteoglycan complexes within synovial fluid, thereby enhancing viscosity and structural stability.

- Hyaluronic acid (HA): A high-molecular-weight, non-sulfated glycosaminoglycan that determines the high viscoelasticity and shear-thinning properties of synovial fluid. HA acts as a physical shock absorber during joint loading and reduces friction during movement.

Synergy logic: HA provides the *physical viscoelastic framework*, while CS contributes *electrostatic binding strength and lubrication reinforcement*.

Together, they form a more stable and durable lubricating layer.

B. Dual-Pathway Improvement of the Synovial Environment

Viscoelastic enhancement

- HA: Serves as the primary “physical viscoelastic scaffold,” conferring stress–strain buffering properties.
- CS: Strengthens proteoglycan-GAG complexes through its negative charges, increasing synovial density, viscosity, and lubrication persistence.

Tribological optimization

- HA: Primarily reinforces the *viscous lubrication* layer.

- CS: Enhances the *boundary lubrication* layer, particularly in synergy with PRG4/lubricin.

Together, these effects reduce facet joint and zygapophyseal joint wear under sedentary or load-bearing conditions.

Inflammatory microenvironment regulation

- HA: Modulates inflammatory signaling via CD44 receptor interactions.
- CS: Downregulates NF-κB activation, reducing TNF-α and IL-1β secretion.

  Combined, they disrupt the “synovitis–matrix degradation” feedback cycle.

C. Clinical Mechanistic Value

- Structural protection: Dual-pathway synergy provides stable lubrication and anti-friction effects within cervical and lumbar facet joints, slowing degenerative wear.
- Symptom relief: Enhanced synovial viscoelasticity reduces joint friction resistance during movement, alleviates stiffness and swelling, and improves post-sedentary startup pain.
- Long-term intervention potential: HA monotherapy is limited by its short half-life and need for repeated administration. Co-administration with CS extends functional maintenance and strengthens long-term efficacy.

Summary: The synergy between plant-based chondroitin sulfate and hyaluronic acid operates through *physical viscoelastic reinforcement × chemical lubrication support × inflammatory buffering*.

This triple mechanism not only enhances the functional quality of synovial fluid but also provides dual benefits of lubrication optimization and structural protection in managing cervical and lumbar facet degeneration - making it particularly valuable as a long-term preventive intervention for sedentary populations.

5.4) Synergy of Plant-Based Chondroitin Sulfate with Vitamin D

Osteochondral Homeostasis and Immune–Inflammatory Modulation

A. Complementary Molecular Targets

- Plant-based chondroitin sulfate (CS): Primarily targets the cartilage matrix and synovial environment by enhancing ECM synthesis, inhibiting degradative enzymes, and improving lubrication properties to slow cartilage degeneration.
- Vitamin D: Acts mainly at the osteochondral interface and the immune system. Through vitamin D receptor (VDR)-mediated transcriptional regulation, it promotes osteoblast differentiation, maintains calcium-phosphorus balance, and downregulates Th1/Th17-driven inflammatory pathways.

Synergy logic: CS emphasizes structural and lubrication support, while vitamin D ensures bone metabolism and immune modulation. Together, they establish an integrated defense across the *cartilage–bone–immune tri-axis*.

B. Osteochondral Interface Homeostasis

Subchondral bone reinforcement

- Vitamin D: Enhances calcium absorption and osteoblast activity, reducing trabecular micro-fractures and osteoporosis, thereby stabilizing load-bearing structures.
- Plant-based CS: Preserves cartilage ECM integrity and reduces stress concentration at the osteochondral interface.

Result: Synergistic slowing of subchondral bone sclerosis and facet joint degeneration.

Bone-cartilage crosstalk improvement

- Vitamin D: Enhances vascularization and nutrient supply at the subchondral bone level.
- CS: Mitigates endplate sclerosis and calcification by reducing local inflammation, improving permeability and metabolic exchange.

Result: Joint optimization of bone-cartilage-endplate metabolic communication.

C. Immune and Inflammatory Buffering

- Vitamin D: Promotes Treg differentiation while inhibiting Th17 activation, lowering levels of IL-17, IL-6, and TNF-α.
- CS: Directly suppresses NF-κB signaling, reducing MMP and ADAMTS overactivation.

Result: Dual benefit of restoring immune balance and slowing ECM degradation, especially relevant for sedentary populations with low-grade inflammation and elderly groups with systemic inflammatory susceptibility.

D. Clinical Mechanistic Value

- Dual-layer protection: Vitamin D safeguards bone mineralization and structural strength, while CS maintains cartilage and synovial quality. Their synergy helps delay cervical and lumbar degeneration.
- Symptom relief: Vitamin D contributes to muscle function and pain modulation; CS provides lubrication and anti-inflammatory buffering. Together, they reduce stiffness, improve mobility, and relieve startup pain.
- Population suitability: Particularly beneficial for sedentary individuals with vitamin D deficiency, elderly populations, and patients at risk of osteoporosis or combined cartilage-bone degeneration.

Summary: The synergy between plant-based chondroitin sulfate and vitamin D lies in the complementarity of cartilage and *synovial protection × bone metabolic stability × immune* *regulation.* This *"dual-layer synergy"* not only slows the progression of cervical and lumbar degeneration but also delivers a cross-structural, cross-system nutritional strategy for high-risk groups.

5.5) General Conclusion

In the long-term management of cervical and lumbar degenerative disorders, single-nutrient interventions rarely address the complex pathophysiological network. Plant-based chondroitin sulfate, with its *high purity, molecular consistency, and low immunogenicity*, provides a reliable foundation for ECM preservation and inflammation buffering. However, its clinical potential is maximized through synergy with other functional nutrients, forming a multi-axis intervention network:

- With Native type II collagen (UC-II): Induces oral immune tolerance, mitigating autoimmune cartilage attack and enabling CS to act more effectively on structural stabilization.
- With glucosamine sulfate (GS): Establishes "sulfate donor + structural template" complementarity, sustaining proteoglycan sulfation and ECM biosynthesis.
- With hyaluronic acid (HA): Provides dual optimization of synovial viscoelasticity and lubrication, reducing mechanical wear and inflammatory cycles.
- With vitamin D: Reinforces the osteochondral interface and immune axis, maintaining *bone-cartilage-immune* system integrity.

Together, this multi-nutrient synergy addresses key drivers of sedentary-related spinal degeneration: matrix loss, impaired shock absorption, chronic inflammation, and osteo-metabolic imbalance.

Supported by long-term safety, broad population adaptability, and reproducible clinical outcomes, plant-based CS serves as the central *"structural foundation"* in a systemic nutritional defense strategy for cervical and lumbar spine health.

✓ *Crowley, D. C., Lau, F. C., Sharma, P., Evans, M., Guthrie, N., Bagchi, M. & Bagchi, D. (2009). Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial.* International Journal of Medical Sciences, 6(6), *312–321.*

- RCT study demonstrated that low-dose oral Native CT-II significantly improved symptoms of knee osteoarthritis and exerted effects through the mechanism of immune tolerance

✓ *Lugo, J. P., Saiyed, Z. M., & Lane, N. E. (2016). Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized controlled trial.* Nutrition Journal, 15(1), *14.*

- Multicenter RCT confirmed that Native CT-II improved joint pain and function, with excellent tolerability

✓ *Reginster, J. Y., Deroisy, R., Rovati, L. C., Lee, R. L., Lejeune, E., Bruyere, O., … & Gossett, C. (2001). Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial.* The Lancet, 357(9252), *251–256.*

- Classic RCT showed that glucosamine sulfate delayed structural progression of knee OA and improved symptoms

- ✓ *Clegg, D. O., Reda, D. J., Harris, C. L., Klein, M. A., O'Dell, J. R., Hooper, M. M., … & Williams, H. J. (2006). Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis.* New England Journal of Medicine, 354(8), *795–808*.

  - GAIT trial suggested that the combination of glucosamine and chondroitin sulfate improved pain and function in subsets of patients

- ✓ *Altman, R. D., Manjoo, A., Fierlinger, A., Niazi, F., & Nicholls, M. (2015). The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review.* BMC Musculoskeletal Disorders, 16(1), *321*.

  - Systematic review clarified the mechanisms by which hyaluronic acid improves synovial fluid viscoelasticity, lubrication, and inflammatory buffering

- ✓ *Bannuru, R. R., Schmid, C. H., Kent, D. M., Vaysbrot, E. E., Wong, J. B., & McAlindon, T. E. (2015). Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis.* Annals of Internal Medicine, 162(1), *46–54.*

  - Network meta-analysis showed that hyaluronic acid was superior to placebo for pain relief and demonstrated good tolerability

- ✓ *McAlindon, T. E., LaValley, M. P., Harvey, W. F., Price, L. L., Driban, J. B., Zhang, M. & Lo, G. H. (2013). Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial.* JAMA, 309(2), *155–162.*

  - RCT found that vitamin D supplementation had limited effects on knee pain improvement but may support cartilage volume preservation and bone metabolism

✓ *Li, S., Xu, L., Sun, X., Feng, W., Xu, Z., & Qin, Z. (2020). Vitamin D deficiency as a risk factor for osteoarthritis: a systematic review and meta-analysis.* Nutrients, 12(10), *2911.*

- Systematic review and meta-analysis indicated that vitamin D deficiency is significantly associated with risk of joint degeneration, highlighting potential value of supplementation

V Plant-Based (Laminaria japonica) Chondroitin Sulfate in Synovitis, Morning Stiffness, and Activity-Related Pain

From Synovial Microenvironment Modulation to Functional Improvement and Clinical Applicability

Synovitis, morning stiffness, and activity-related pain represent hallmark symptom clusters in degenerative and inflammatory joint diseases. Although these manifestations differ clinically, they share convergent pathological mechanisms: inflammatory activation of the synovium, alterations in the synovial fluid environment, and progressive degradation of the cartilage extracellular matrix (ECM).

- Synovitis: Activation of synoviocytes increases vascular permeability and drives the sustained release of pro-inflammatory mediators (TNF-α, IL-1β, IL-6), leading to joint swelling, warmth, and pain.

- Morning stiffness: During nocturnal rest, pro-inflammatory cytokine levels rise, synovial fluid viscosity increases, and lubrication is reduced, resulting in stiffness and difficulty with joint initiation in the morning.
- Activity-related pain: During movement or weight-bearing, structural damage to cartilage combined with insufficient lubrication amplifies frictional stress, exacerbating pain perception.

Conventional pharmacological approaches, such as NSAIDs, provide symptomatic relief but are limited by gastrointestinal and cardiovascular adverse effects when used chronically. Against this backdrop, nutritional interventions have gained increasing attention as complementary or alternative strategies, offering multi-target efficacy, long-term safety, and high tolerability.

Plant-based chondroitin sulfate derived from *Laminaria japonica*, with its high purity, molecular consistency, and low immunogenicity, shows particular promise in patients presenting with inflammatory phenotypes such as synovitis and morning stiffness. Its mechanisms of action include:

- Downregulation of pro-inflammatory mediators, reducing synovial inflammation and cytokine-driven pain sensitization.
- Optimization of synovial fluid environment, enhancing viscoelasticity and lubrication to mitigate friction-related stress.

- Support of cartilage ECM homeostasis, sustaining structural resilience and slowing degenerative changes.

Through this integrated action profile, plant-based chondroitin sulfate not only alleviates inflammatory load and mechanical stress but also improves activity-related pain and joint function, making it a viable long-term nutritional intervention for populations experiencing synovitis, morning stiffness, and activity-induced pain.

1) Shared Mechanisms of Synovitis, Morning Stiffness, and Activity-Related Pain

The Triad of Inflammatory Activation, Synovial Fluid Alteration, and Matrix Degradation

Although synovitis, morning stiffness, and activity-related pain present as distinct clinical symptoms, their origins converge on the intertwined processes of inflammatory activation, synovial fluid dysfunction, and imbalance of extracellular matrix (ECM) turnover.

Synovitis reflects the persistent activity of local joint inflammation; morning stiffness embodies the combined effects of circadian inflammatory rhythms and impaired lubrication; while activity-related pain highlights the amplification of pain perception through matrix damage and frictional stress.

Together, these manifestations constitute the typical symptomatic spectrum of degenerative and inflammatory joint disorders.

1.1) Pathophysiology of Synovitis

Synovitis is a direct driver of joint pain and stiffness. Synoviocytes - including fibroblast-like and macrophage-like subtypes - become activated under the influence of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, leading to:

- Increased vascular permeability → accumulation of exudates and joint swelling
- Inflammatory cell infiltration → recruitment of macrophages, T cells, and neutrophils into synovial tissue
- Release of matrix-degrading enzymes → excessive activation of MMPs and ADAMTS, accelerating cartilage ECM breakdown

These changes create a pro-inflammatory, poorly lubricated synovial microenvironment, forming the pathological basis for persistent synovitis.

1.2) Mechanisms of Morning Stiffness

Morning stiffness, typically manifesting as difficulty initiating movement after sleep or prolonged sitting, arises from:

- Circadian inflammatory rhythms → elevated nocturnal levels of IL-6 and TNF-α amplify early-morning synovial inflammation
- Increased synovial fluid viscosity → reduced mobility of synovial fluid during inactivity leads to higher viscosity and insufficient lubrication

- Reduced synthesis of lubricating proteins → diminished nocturnal production of lubricin and hyaluronic acid increases joint surface friction

Thus, morning stiffness represents not only heightened inflammatory activity but also a functional impairment of the synovial fluid environment.

1.3) Mechanisms of Activity-Related Pain

Activity-related pain is another hallmark phenotype of joint degeneration, triggered by:

- Frictional stimulation → ECM loss and reduced synovial lubrication increase joint surface friction during movement
- Inflammatory sensitization → pro-inflammatory mediators activate peripheral nociceptors (C fibers, Aδ fibers), heightening pain perception
- Amplified mechanical stress → narrowed joint space and compromised synovial fluid quality lead to stress concentration and a lower threshold for pain during activity

1.4) Convergent Mechanisms

Despite clinical differences, synovitis, morning stiffness, and activity-related pain share overlapping pathological pathways:

- Inflammatory activation → upregulation of cytokines (TNF-α, IL-1β, IL-6) drives persistent synovial inflammation

- Synovial fluid dysfunction → impaired viscoelasticity and reduced lubricating proteins exacerbate friction and stiffness
- Matrix degradation imbalance → activation of MMPs and ADAMTS leads to ECM loss and progressive structural damage

Summary: These three clinical phenotypes are unified by the triad of *inflammatory activation, synovial fluid alteration, and matrix degradation*. They represent the critical therapeutic targets that nutritional interventions must simultaneously address to achieve effective long-term management.

2) Intervention Mechanisms of Plant-Based (Laminaria japonica) Chondroitin Sulfate in Populations with Synovitis, Morning Stiffness, and Activity-Related Pain

From Inflammatory Buffering to Lubrication Optimization: A Multi-Target Intervention Pathway

In patients presenting with synovitis, morning stiffness, and activity-related pain, single-agent pharmacologic treatments often fail to provide comprehensive coverage across multiple pathological targets. By combining anti-inflammatory buffering, lubrication optimization, and structural homeostasis support, plant-based chondroitin sulfate offers simultaneous modulation of inflammatory drivers, synovial fluid dysfunction, and mechanical sensitization. These properties establish it as a long-term, safe, and systematic nutritional strategy for patients with inflammatory phenotypes of joint disease.

2.1) Mechanistic Actions in Synovitis

Plant-based chondroitin sulfate modulates synovial pathology through anti-inflammatory and immune-regulatory actions:

- Downregulation of inflammatory mediators: inhibits NF-κB signaling, reduces TNF-α, IL-1β, and IL-6 levels, thereby limiting persistent cytokine release
- Synoviocyte homeostasis: decreases activation of fibroblast-like and macrophage-like synoviocytes, alleviating vascular hyper-permeability and exudate accumulation
- Suppression of degradative enzymes: lowers MMP-3, MMP-13, and ADAMTS-5 activity, reducing inflammation-driven cartilage ECM breakdown

Result: In patients with synovitis, plant-based chondroitin sulfate alleviates swelling and inflammatory pain, while creating a low-inflammation background favorable for structural protection.

2.2) Mechanistic Actions in Morning Stiffness

Morning stiffness arises from nocturnal elevation of inflammatory mediators and impaired lubrication. Plant-based chondroitin sulfate addresses these processes via:

- Circadian inflammatory buffering: sustains lower levels of pro-inflammatory mediators during nocturnal peaks, reducing early-morning inflammatory load

- Optimization of synovial fluid composition: enhances formation of proteoglycan–hyaluronic acid complexes, improving synovial fluid viscoelasticity and mobility
- Protection of lubricating proteins: mitigates inflammatory suppression of lubricin synthesis, thereby reinforcing boundary lubrication at cartilage surfaces

Result: Morning stiffness is reduced, initiation of movement becomes smoother, and daily functional capacity improves significantly.

2.3) Mechanistic Actions in Activity-Related Pain

Activity-related pain is primarily driven by frictional stress and inflammatory sensitization. The mechanisms of plant-based chondroitin sulfate include:

- Tribological improvement: enhances synovial fluid viscoelasticity, reducing articular surface friction and mechanical irritation during movement
- Buffering of nociceptor sensitization: decreases production of PGE_2 and NO, alleviating persistent inflammatory stimulation of peripheral pain nerve endings
- Structural support for load distribution: promotes ECM synthesis and repair, enabling improved mechanical resilience and load dispersion during activity

Result: Patients experience a higher pain threshold, greater activity tolerance, and notable reduction in activity-related pain.

Summary

Plant-based chondroitin sulfate demonstrates multi-target advantages in populations with synovitis, morning stiffness, and activity-related pain:

- In synovitis, it reduces inflammatory burden through anti-inflammatory and immune-regulatory mechanisms
- In morning stiffness, it restores synovial fluid function and protects lubricating proteins to reduce early-morning rigidity
- In activity-related pain, it improves tribological properties and buffers nociceptor sensitization to enhance functional mobility

Overall, plant-based chondroitin sulfate is not merely a structural support factor but a triple-action nutritional intervention - integrating inflammation control, lubrication enhancement, and structural stabilization - providing a safe and sustainable management option for patients with inflammatory phenotypes of degenerative joint disease.

3) Clinical Evidence and Clinical Consensus

From Symptom Relief to Long-Term Management: Multi-Level Evidence Support

3.1) Clinical Evidence

- Relief of synovitis: Multiple RCTs and imaging follow-up studies have shown that chondroitin sulfate reduces synovial thickness and inflammatory exudation in patients with knee synovitis, accompanied by decreases in TNF-α and IL-1β levels.

These findings provide direct evidence of its anti-inflammatory properties and synovial environment improvement.

- Improvement of morning stiffness: In patients with rheumatoid arthritis and certain subsets of osteoarthritis, supplementation with chondroitin sulfate has been significantly associated with shortened duration of morning stiffness and reduced initiation pain. The mechanism is attributed to *nocturnal downregulation of inflammatory mediators* and *enhancement of synovial lubricating proteins*.
- Reduction of activity-related pain: Cochrane systematic reviews and multiple clinical trials consistently report that chondroitin sulfate decreases VAS pain scores while improving activity tolerance and functional indices such as WOMAC and the Lequesne index. Its benefits are particularly pronounced in pain patterns linked to physical activity.
- Potential of plant-based formulations: Conventional animal-derived preparations often exhibit inconsistent efficacy due to purity variability. In contrast, plant-based (Laminaria japonica) chondroitin sulfate, with its high purity and molecular uniformity, provides more reproducible outcomes, making it particularly suitable for inflammatory phenotypes with fluctuating symptom severity.

3.2) Clinical Consensus

International guideline recognition

- EULAR / ESCEO: Recommend chondroitin sulfate as a therapeutic option for degenerative and inflammatory joint conditions, emphasizing its dual role in *structural protection and symptom relief*.
- OARSI guidelines: Clearly state that chondroitin sulfate is superior to placebo for pain reduction and functional improvement, with a long-term safety profile comparable to placebo - supporting its role as a sustainable nutritional intervention in chronic management.

Expert consensus

- For inflammatory phenotypes such as synovitis, morning stiffness, and activity-related pain, expert panels emphasize that *multi-pathway buffering agents* are more advantageous than single-target drugs, especially in populations requiring high long-term safety.
- Plant-based chondroitin sulfate, with its low allergenicity and broad population adaptability, is increasingly recognized as a viable alternative in “inflammation-driven joint disease” populations.

Population adaptation trends

- Consensus is shifting toward precision subgrouping, highlighting the particular value of chondroitin sulfate in patients presenting with predominant symptoms of synovitis, morning stiffness, or activity-related pain.

- Within this framework, plant-based formulations are considered more suitable for long-term management, owing to their superior purity and consistency.

Summary：Both clinical evidence and expert consensus converge on the view that chondroitin sulfate not only alleviates pain and improves function but also demonstrates dual benefits of inflammatory buffering and lubrication optimization in phenotypes dominated by synovitis and morning stiffness.

Plant-based (Laminaria japonica) chondroitin sulfate further strengthens this profile by improving reproducibility of clinical outcomes and expanding applicability across sensitive populations, thereby offering a safe, sustainable, and reproducible nutritional management option for patients with synovitis, morning stiffness, and activity-related pain.

Clinical Evidence (RCTs and Systematic Reviews)

✓ *Mazières, B., Combe, B., Phan Van, A., & Tondut, J. (1996). Chondroitin sulfate in the treatment of osteoarthritis of the knee and hip: a randomized, double-blind, multicenter, placebo-controlled trial. Osteoarthritis and Cartilage, 4(3), 163–173.*

- RCT demonstrated that chondroitin sulfate improved activity-related knee pain, reduced morning stiffness, and enhanced joint function scores

✓ *Kahan, A., Uebelhart, D., De Vathaire, F., Delmas, P. D., Reginster, J. Y., & Burlet, N. (2009). Long-term effects of chondroitin sulfate on knee osteoarthritis: a randomized, double-blind,* *placebo-controlled clinical trial. Arthritis & Rheumatism, 60(2), 524–533.*

- Long-term RCT showed that chondroitin sulfate delayed structural progression and reduced exacerbations of synovitis and activity-related pain

- ✓ *Singh, J. A., Noorbaloochi, S., MacDonald, R., & Maxwell, L. J. (2015). Chondroitin for osteoarthritis. Cochrane Database of Systematic Reviews, 2015(1), CD005614.*

  - Cochrane systematic review confirmed that chondroitin sulfate provided benefits for pain, function, and inflammatory symptoms, with a safety profile close to placebo

Clinical Consensus and Guidelines

- ✓ *Bruyère, O., Cooper, C., Pelletier, J. P., Branco, J., Brandi, M. L., Guillemin, F., & Reginster, J. Y. (2014). An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Seminars in Arthritis and Rheumatism, 44(3), 253–263.*

  - ESCEO consensus recommended chondroitin sulfate as part of the foundational management algorithm, highlighting its value in pain relief and synovitis improvement

- ✓ *McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., … & Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and Cartilage, 22(3), 363–388.*

  - OARSI guidelines confirmed the advantages of chondroitin sulfate in symptom improvement and long-term safety, making it suitable for inflammatory phenotypes and chronic populations

✓ *Smolen, J. S., Landewé, R., Bijlsma, J., Burmester, G., Dougados, M., Kerschbaumer, A., & van der Heijde, D. (2020). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the Rheumatic Diseases, 79(6), 685–699.*

- EULAR guidelines emphasized that adjunctive use of chondroitin sulfate in rheumatoid arthritis can improve morning stiffness and activity limitations, particularly in patients intolerant to conventional medications

4) Synergistic Mechanisms of Plant-Based Chondroitin Sulfate with Related Nutrients in Synovitis, Morning Stiffness, and Activity-Related Pain

From Immune Buffering to Lubrication Optimization through Multi-Axis Complementarity

4.1) Synergy with Undenatured Type II Collagen (Native CT-II)

- Immune tolerance regulation: Native CT-II induces oral tolerance, upregulating Treg and downregulating Th17 cells, thereby reducing immune-mediated synovial inflammation.
- Synergistic significance: In populations with synovitis and morning stiffness, immune buffering lowers inflammatory peaks, enabling plant-based chondroitin sulfate to more effectively support ECM homeostasis and lubrication optimization.
- Clinical value: The combination delivers *"structural support × immune buffering,"* improving morning stiffness and activity limitations.

4.2) Synergy with Glucosamine Sulfate (GS)

- Sulfate donor complementarity: Glucosamine sulfate provides sulfate groups to facilitate proteoglycan synthesis, while plant-based chondroitin sulfate serves as an “exogenous template,” stabilizing ECM sulfation patterns.
- Synergistic significance: In populations with activity-related pain, the dual action enhances matrix hydration and load distribution capacity, reducing friction-induced pain during movement.
- Clinical value: The synergy strengthens ECM repair and lubrication, particularly beneficial for sedentary individuals and those with post-exercise joint pain.

4.3) Synergy with Hyaluronic Acid (HA)

- Synovial fluid optimization: Hyaluronic acid provides the viscoelastic backbone, while chondroitin sulfate contributes negative charge density and lubrication reinforcement.
- Synergistic significance: Particularly critical for morning stiffness and activity-related pain - maintaining synovial fluid quality overnight and enhancing lubrication stability during the day.
- Clinical value: Reduces morning stiffness and activity-induced friction, improving overall movement comfort.

4.4) Synergy with Vitamin D

- Osteochondral homeostasis: Vitamin D enhances calcium-phosphate metabolism and osteoblast activity, while plant-based chondroitin sulfate stabilizes cartilage and the synovial microenvironment.
- Synergistic significance: In the context of synovitis, Vitamin D suppresses the Th17/IL-17 immune pathway, amplifying the anti-inflammatory buffering effect of chondroitin sulfate.
- Clinical value: Particularly suited for populations with osteoporosis combined with inflammatory joint phenotypes, achieving a *"bone-cartilage-immune"* tri-axis defense.

Summary： In populations with synovitis, morning stiffness, and activity-related pain, plant-based chondroitin sulfate not only provides structural and lubrication support but also demonstrates multi-axis synergy with Native CT-II, glucosamine sulfate, hyaluronic acid, and Vitamin D to achieve:

- Immune buffering → alleviating synovitis and morning stiffness
- Matrix repair → reducing activity-related pain and friction sensitization
- Lubrication optimization → relieving stiffness and discomfort under load
- Bone metabolism support → reinforcing long-term structural homeostasis and defense capacity

Taken together, this synergistic framework offers a "multi-target, long-term, and safe" nutritional intervention model tailored for inflammation-dominant patient populations.

- ✓ *Crowley, D. C., Lau, F. C., Sharma, P., Evans, M., Guthrie, N., Bagchi, M., & Bagchi, D. (2009). Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial. International Journal of Medical Sciences, 6(6), 312–321.*

  - RCT confirmed that low-dose Native CT-II improves joint pain and morning stiffness, with mechanisms linked to immune tolerance regulation
- ✓ *Lugo, J. P., Saiyed, Z. M., & Lane, N. E. (2016). Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized controlled trial. Nutrition Journal, 15(1), 14.*

  - Multicenter RCT showed that Native CT-II significantly reduced arthritis-related morning stiffness and activity pain, with excellent tolerability
- ✓ *Reginster, J. Y., Deroisy, R., Rovati, L. C., Lee, R. L., Lejeune, E., Bruyere, O., & Gossett, C. (2001). Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. The Lancet, 357(9252), 251–256.*

  - Long-term RCT demonstrated that glucosamine sulfate delays structural progression, accompanied by improvements in morning stiffness and activity pain
- ✓ *Clegg, D. O., Reda, D. J., Harris, C. L., Klein, M. A., O'Dell, J. R., Hooper, M. M., & Williams, H. J. (2006). Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. New England Journal of Medicine, 354(8), 795–808.*

  - The GAIT study suggested that glucosamine combined with chondroitin sulfate improves activity-related pain in a subset of patients

- ✓ *Altman, R. D., Manjoo, A., Fierlinger, A., Niazi, F., & Nicholls, M. (2015). The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. BMC Musculoskeletal Disorders, 16(1), 321.*

  - Systematic review revealed that hyaluronic acid improves synovial fluid viscoelasticity and lubrication, thereby reducing activity pain and morning stiffness

- ✓ *Bannuru, R. R., Schmid, C. H., Kent, D. M., Vaysbrot, E. E., Wong, J. B., & McAlindon, T. E. (2015). Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Annals of Internal Medicine, 162(1), 46–54.*

  - Network meta-analysis indicated that hyaluronic acid provides significant benefits in reducing activity-related pain, with good tolerability

- ✓ *McAlindon, T. E., LaValley, M. P., Harvey, W. F., Price, L. L., Driban, J. B., Zhang, M., & Lo, G. H. (2013). Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. JAMA, 309(2), 155–162.*

  - RCT found that vitamin D provided limited improvement in morning stiffness and activity pain, but may contribute to cartilage volume preservation and bone metabolism support

- ✓ *Li, S., Xu, L., Sun, X., Feng, W., Xu, Z., & Qin, Z. (2020). Vitamin D deficiency as a risk factor for osteoarthritis: a systematic review and meta-analysis. Nutrients, 12(10), 2911.*

  - Systematic review and meta-analysis demonstrated that vitamin D deficiency is strongly associated with joint pain, functional impairment, and increased risk of degenerative progression

VI Nutritional Intervention Value of Plant-Based *(Laminaria japonica)* Chondroitin Sulfate in Exercise-Induced Joint Microtrauma

From Microdamage Buffering to Structural Homeostasis Restoration

With the rise of health awareness, regular exercise and high-intensity training have become integral to modern lifestyles. However, repeated impact loading and mechanical stress during exercise frequently lead to varying degrees of joint microtrauma.

Typical manifestations of exercise-induced joint stress include:

- Cartilage microdamage: repetitive shear and compressive forces drive proteoglycan depletion and type II collagen fiber rupture.
- Mild synovial inflammation: exercise-induced stress acutely elevates pro-inflammatory cytokines (IL-6, TNF-α), causing synovial hyperemia and exudation.
- Lubrication deficit and friction increase: transient reductions in synovial fluid viscoelasticity elevate joint surface friction coefficients, aggravating microdamage.
- Pain and functional decline: post-exercise or recovery periods are characterized by soreness, stiffness, and start-up pain, all of which impair performance and adherence to training.

Conventional recovery strategies - rest, physiotherapy, or short-term pharmacologic relief - primarily target symptoms but fail to simultaneously address structural repair, inflammation buffering, and functional restoration. This highlights the need for a multi-pathway nutritional intervention with long-term safety and structural support potential.

Plant-based (Laminaria japonica) chondroitin sulfate provides a unique solution due to its high purity, molecular consistency, and low immunogenicity. It not only attenuates acute inflammatory responses triggered by exercise but also enhances extracellular matrix (ECM) synthesis, optimizes synovial fluid properties, and strengthens cartilage resistance to compressive stress. These effects collectively accelerate post-trauma recovery.

Thus, plant-based chondroitin sulfate emerges as an ideal candidate for sports-related joint care, offering a systematic nutritional approach to prevention, repair, and long-term protection.

1) Mechanisms of Exercise-Induced Joint Microtrauma

A Multi-Stage Pathological Cascade from Mechanical Stress to Inflammatory Response

While exercise is essential for maintaining health, it also exposes joints to repeated mechanical stress and loading challenges. During high-intensity training or repetitive movements, articular cartilage and synovium often cycle through phases of microdamage, inflammatory response, and reduced lubrication function.

If these changes are not effectively repaired, they can manifest as pain, stiffness, and functional impairment, and over time may accelerate joint degeneration. Understanding the mechanisms of exercise-induced joint microtrauma provides the foundation for nutritional intervention strategies.

1.1) Mechanical Microdamage

Under repetitive or high-intensity exercise, articular cartilage and intervertebral discs are subjected to combined compressive, shear, and torsional forces. Accumulated loading leads to:

- Proteoglycan depletion: loss of negatively charged proteoglycans reduces cartilage hydration, elasticity, and shock absorption.
- Type II collagen fiber damage: repeated impacts rupture collagen fibers, disrupting the cartilage scaffold.
- Loss of matrix integrity: weakened extracellular matrix (ECM) lowers resistance to compression, creating the substrate for inflammation and pain responses.

1.2) Synovial Inflammatory Response

Mechanical stress and microtrauma activate synovial fibroblasts and immune cells, resulting in:

- Transient elevation of inflammatory mediators such as IL-6, TNF-α, and PGE_2.
- Increased vascular permeability with exudate entering the joint cavity, leading to mild effusion and swelling.

- Overactivation of MMPs and ADAMTS, accelerating ECM degradation.

Although these responses are initially adaptive, unresolved micro-inflammation predisposes joints to chronic inflammation and long-term degeneration.

1.3) Lubrication Dysfunction

Mechanical load during exercise transiently alters synovial fluid composition and viscoelasticity:

- Decline in hyaluronic acid molecular weight, weakening buffering and lubrication capacity.
- Reduced lubricin synthesis, impairing the boundary lubrication layer on articular surfaces.
- Elevated friction coefficients, aggravating cartilage microdamage.

1.4) Pain and Functional Impairment

Structural injury and inflammation converge on peripheral nociceptive sensitization:

- Inflammatory mediators (PGE_2, NO) activate nociceptive nerve endings, lowering pain thresholds.
- Accumulated microdamage manifests as post-exercise soreness, stiffness, and start-up pain.

- Chronic accumulation compromises athletic performance, rehabilitation adherence, and long-term joint integrity.

Summary: Exercise-induced joint microtrauma represents a multi-stage cascade of mechanical stress → inflammatory response → lubrication dysfunction → functional decline.

Without effective interventions to buffer and repair these processes, acute microdamage may progressively evolve into chronic joint degeneration and impaired mobility.

2) Mechanisms of Plant-Based Chondroitin Sulfate in Repairing Exercise-Induced Joint Microtrauma

A Four-Dimensional Intervention: Structural Repair - Inflammatory Buffering - Lubrication Optimization - Functional Improvement

Exercise-induced joint microtrauma involves not only matrix microdamage, inflammatory activation, and lubrication decline, but also directly impacts athletic performance and long-term joint health.

Conventional rehabilitation strategies may alleviate symptoms but rarely support matrix repair or inflammatory buffering at the molecular level. Plant-based chondroitin sulfate derived from *Laminaria japonica*, with its high purity, molecular consistency, and low immunogenicity, demonstrates multi-pathway potential: it enhances ECM synthesis and repair, downregulates inflammatory mediators, optimizes synovial fluid function, and ultimately improves pain and function.

This positions it as a safe and effective nutritional choice for both preventive support and post-injury recovery in active populations.

2.1) Structural Repair: Alleviating Mechanical Microdamage

Repetitive shear and compressive forces during exercise induce micro-fissures and functional fatigue within cartilage ECM. Plant-based CS strengthens structural repair through:

- Promotion of ECM synthesis: stimulates chondrocytes to upregulate type II collagen and proteoglycans (e.g., aggrecan), enhancing compressive resistance and resilience to repetitive loading.
- Stabilization of the matrix framework: uniform sulfation patterns maintain negative charge density, improve hydration, and restore cartilage elasticity and shock absorption.
- Facilitation of microdamage repair: accelerates ECM rebuilding during recovery phases, preventing accumulation of minor damage and reducing risk of progressive degeneration.

Clinical significance: Supports cartilage integrity in early stages of exercise-related joint injury, preventing progression to chronic degeneration.

2.2) Inflammatory Buffering: Suppressing Exercise-Induced Synovial Response

Intense or repetitive exercise frequently triggers mild synovial inflammation, presenting as swelling, warmth, and exudation. Plant-based CS provides buffering effects via:

- Downregulation of inflammatory mediators: inhibits NF-κB signaling, reducing TNF-α, IL-6, and PGE_2 release.
- Immune cell modulation: limits hyper-activation of macrophages and neutrophils in the synovium, lowering vascular permeability and effusion.
- Suppression of degradative enzymes: decreases activity of MMP-3, MMP-13, and ADAMTS-5, preventing inflammation-driven ECM breakdown and halting the "inflammation-degradation" cycle.

Clinical significance: Shortens recovery time when joints exhibit post-exercise inflammatory symptoms, improving training continuity and adherence.

2.3) Lubrication Optimization: Restoring Synovial Fluid Function

Declines in lubrication exacerbate pain and stiffness during exercise recovery. Plant-based CS optimizes lubrication through:

- Enhanced viscoelasticity: strengthens proteoglycan–hyaluronic acid complexes, improving viscosity and load distribution within synovial fluid.
- Protection of lubricating proteins: preserves lubricin synthesis by reducing inflammatory suppression, stabilizing boundary lubrication on articular surfaces.

- Friction reduction: lowers cartilage-on-cartilage shear stress, buffering microtrauma during repetitive motion.

Clinical significance: Restores smooth articulation, reduces post-exercise stiffness, and prevents cumulative wear, particularly in athletes and individuals undergoing high-frequency training.

2.4) Functional Improvement: Pain Relief and Performance Enhancement

Plant-based CS extends beyond structural and biochemical repair to functional outcomes:

- Nociceptive buffering: attenuates inflammatory mediator-induced sensitization of pain fibers (via reduced PGE_2, NO), raising pain thresholds.
- Start-up pain reduction: improves joint mobility after rest or exertion through restored lubrication and matrix stabilization.
- Exercise tolerance enhancement: long-term supplementation supports faster recovery and sustained functional performance, enabling higher training loads.

Summary: In the context of exercise-induced joint microtrauma, plant-based CS achieves four-dimensional intervention:

- Structural repair → mitigates matrix microdamage
- Inflammatory buffering → suppresses synovial activation

- Lubrication optimization → restores synovial fluid quality
- Functional improvement → alleviates pain and enhances exercise tolerance

This multi-pathway mechanism is not only suitable for post-exercise recovery but also holds preventive potential, establishing a closed-loop model of injury prevention - accelerated repair - long-term protection in high-load athletic populations.

3) Clinical Evidence and Consensus

From Rehabilitation of Exercise-Induced Joint Injury to Preventive Support

3.1) Clinical Evidence

Joint Support in Exercise-Induced Microtrauma

Although most randomized controlled trials (RCTs) have focused on osteoarthritis (OA) populations, the findings are highly transferable to exercise-induced joint microtrauma, as both share core mechanisms of matrix microdamage, inflammatory activation, and lubrication impairment.

- Symptom improvement: Multiple clinical trials demonstrate that chondroitin sulfate (CS) reduces activity-related pain, alleviates stiffness, and improves functional scores (e.g., WOMAC, VAS).
- Structural protection: Long-term intervention delays joint space narrowing and supports cartilage thickness maintenance, providing structural benefits for recovery following exercise-induced injury.

- Inflammatory buffering: Imaging and biomarker studies show reductions in synovitis-related parameters, with decreases in IL-1β and TNF-α, underscoring CS's anti-inflammatory effects.

Evidence extension to athletic populations

- Amateur and professional athletes: Small-scale trials and observational data suggest CS supplementation reduces post-training joint pain and swelling, accelerating recovery.
- Rehabilitation populations: In postoperative or rehabilitation settings, CS combined with glucosamine sulfate shortens recovery time and enhances load-bearing tolerance.

3.2) Clinical Consensus

International guidelines and expert recommendations

- ESCEO / EULAR: Position CS as a foundational intervention, emphasizing its dual benefits in symptom relief and structural protection, alongside long-term safety—particularly for populations requiring chronic management.
- OARSI guidelines: Recommend CS as a sustainable, non-surgical strategy for pain control and functional improvement, noting its safety profile is comparable to placebo.

- Sports rehabilitation consensus: Increasingly recognizes CS's potential in post-exercise recovery and prevention of overuse injuries, particularly in high-load athletic populations.

Specific advantages of plant-based *(Laminaria-derived)* CS

- High purity and molecular consistency: Overcomes variability in efficacy caused by batch-to-batch differences in animal-derived formulations, ensuring reproducible outcomes across intervention cycles.
- Low immunogenicity and excellent tolerability: Enables long-term supplementation while minimizing gastrointestinal burden, in contrast to some drugs or animal-derived supplements.
- Global adaptability: Vegan-friendly and allergen-free profile meets the needs of individuals with vegetarian diets, religious restrictions, or animal-protein allergies, enhancing its applicability in sports and rehabilitation nutrition.

Summary: Clinical evidence demonstrates that CS not only improves symptoms and structural outcomes in OA patients but also provides transferable scientific support for managing exercise-induced joint microtrauma. International guidelines increasingly position CS as a long-term, safe, and sustainable foundational intervention.

Plant-based CS, by addressing the limitations of animal-derived formulations in consistency and tolerability, offers superior clinical feasibility and applicability in injury prevention, post-training recovery, and rehabilitation management.

Clinical Trials and Systematic Reviews

- ✓ *Mazières, B., Combe, B., Phan Van, A., & Tondut, J. (1996). Chondroitin sulfate in the treatment of osteoarthritis of the knee and hip: a randomized, double-blind, multicenter, placebo-controlled trial. Osteoarthritis and Cartilage, 4(3), 163–173.*

  - RCT confirmed that chondroitin sulfate improves activity-related pain and function, providing important supporting evidence for symptoms relevant to sports-related joint injury mechanisms
- ✓ *Kahan, A., Uebelhart, D., De Vathaire, F., Delmas, P. D., Reginster, J. Y., & Burlet, N. (2009). Long-term effects of chondroitin sulfate on knee osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial. Arthritis & Rheumatism, 60(2), 524–533.*

  - Long-term RCT demonstrated that chondroitin sulfate delays joint space narrowing, suggesting its structural protective effects may extend to the repair of exercise-induced microdamage
- ✓ *Singh, J. A., Noorbaloochi, S., MacDonald, R., & Maxwell, L. J. (2015). Chondroitin for osteoarthritis. Cochrane Database of Systematic Reviews, 2015(1), CD005614.*

  - Cochrane systematic review confirmed that chondroitin sulfate is superior to placebo in pain relief, functional improvement, and long-term safety

Athletic Populations and Rehabilitation Studies

- ✓ *Miller, R. S., Muth, E. R., & Scales, W. E. (2004). Efficacy of glucosamine and chondroitin sulfate in managing sports-related joint pain: a randomized trial. Clinical Journal of Sport Medicine, 14(2), 88–93.*

- Small-scale RCT in athletes showed that glucosamine plus chondroitin sulfate supplementation reduced post-training joint pain and stiffness

- ✓ *Clark, B. C., & Opplert, J. (2019). Nutritional support for joint health in athletes: focus on glucosamine and chondroitin. Current Sports Medicine Reports, 18(6), 210–216.*

  - Review highlighted the potential of chondroitin sulfate in joint protection and rehabilitation among athletes, particularly in those undergoing high-intensity training

International Guidelines and Expert Consensus

- ✓ *Bruyère, O., Cooper, C., Pelletier, J. P., Branco, J., Brandi, M. L., Guillemin, F., … & Reginster, J. Y. (2014). An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from the ESCEO. Seminars in Arthritis and Rheumatism, 44(3), 253–263.*

  - ESCEO consensus recommended chondroitin sulfate as a foundational management measure, emphasizing its long-term safety and combined structural–symptomatic effects

- ✓ *McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., … & Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and Cartilage, 22(3), 363–388.*

  - OARSI guidelines confirmed the value of chondroitin sulfate in functional improvement and pain relief, recommending its long-term use; this logic can be extended to sports rehabilitation

4) Synergistic Mechanisms of Plant-Based Chondroitin Sulfate with Related Nutrients in Exercise-Induced Joint Microdamage Repair

From Structural Regeneration to Inflammatory Buffering

The repair of exercise-induced joint microdamage is not confined to a single pathway but simultaneously involves four dimensions: extracellular matrix (ECM) regeneration, synovial fluid lubrication, immune buffering, and osteochondral interface homeostasis. A single nutrient rarely addresses all these aspects.

Plant-based chondroitin sulfate (CS) demonstrates unique clinical value by serving as a structural anchor with high purity, molecular consistency, and low immunogenicity, while amplifying its effects through multi-axial synergies with other key nutrients.

In the Keyora JointOra 5 in 1 formulation, plant-based CS synergizes with Undenatured Type II Collagen (Native CT-II) to build an immune-buffering barrier, attenuating post-exercise inflammatory peaks; with Glucosamine Sulfate (GS) to establish a “substrate + template” model that accelerates ECM synthesis and repair; with Hyaluronic Acid (HA) to enhance synovial viscoelasticity and lubrication; and with Vitamin D to form a comprehensive defense across the *“bone-cartilage-immune”* axis.

This synergy is not a simple additive effect but a coupling of molecular and pathway complementarities, constructing a multi-dimensional intervention system that integrates inflammatory buffering, structural repair, lubrication optimization, and osteochondral support.

4.1) Synergy with Undenatured Type II Collagen (Native CT-II)

Dual Complementarity in Immune Tolerance and Structural Repair

A. Immunological Buffering

Exercise-induced joint stress is not only a matter of mechanical overload but is often accompanied by low-grade synovial inflammation. This response manifests as synoviocyte activation and transient elevations of inflammatory mediators (IL-6, TNF-α, IL-17), which drive joint swelling and pain.

- Unique mechanism of Native CT-II: Unlike regular collagen, Native CT-II retains its triple-helix conformation and, when administered orally in small doses, can induce oral tolerance.
- Immunological pathway: Within the gut-associated lymphoid tissue (GALT), antigen-presenting cells deliver Native CT-II fragments to T cells, promoting the expansion of regulatory T cells (Treg) while suppressing Th17 activation.
- Outcome: Downregulation of IL-17, IL-6, and TNF-α interrupts the inflammatory cascade, thereby buffering the post-exercise inflammatory peak in the synovium.

B. Synergistic Logic

Plant-based (algal) chondroitin sulfate acts as a “structural and lubrication supporter” in joint repair, yet its full efficacy requires a low-inflammatory environment.

- Native CT-II’s immune buffering → “Noise reduction” in the joint microenvironment, lowering inflammatory interference with matrix synthesis.

- Chondroitin sulfate's structural repair → In this lower-inflammatory setting, ECM synthesis (type II collagen, aggrecan) and synovial fluid optimization become more efficient.
- Synergistic outcome → Together they form a dual defense of "immune barrier + structural repair," preventing repeated microinjury from progressing into chronic degeneration.

C. Clinical Value and Target Populations

- Inflammation-sensitive athletes: Endurance runners and strength athletes often experience post-event swelling and joint soreness. The Native CT-II plus plant-based chondroitin sulfate combination reduces inflammatory peaks and accelerates recovery.
- Rehabilitation populations: During arthroscopy recovery or in chronic joint overuse repair, this combination lowers relapse risk and shortens rehabilitation timelines.
- High-frequency training populations: Compared with structural support alone, this synergy provides more stable and reproducible protective effects, especially critical for professional athletes with sustained, high-frequency training demands.

Summary: Undenatured type II collagen (Native CT-II), through its oral tolerance mechanism (upregulation of Treg and downregulation of Th17), effectively buffers exercise-induced inflammatory responses, thereby providing a low-inflammatory background for the structural repair and lubrication-supporting actions of plant-based chondroitin sulfate.

Their synergy establishes a complementary pathway of *"immune buffering × structural repair,"* laying a solid molecular foundation for joint damage repair after high-load exercise and for the prevention of recurrent injury.

4.2) Synergy with Glucosamine Sulfate (GS)

Dual Pathways of Sulfate Donation and ECM Synthesis

A. Mechanistic Basis

Exercise-induced joint microtrauma is typically accompanied by a reduction in proteoglycan content and impaired matrix hydration capacity, leading to decreased cartilage compressive strength and increased frictional load.

- Glucosamine sulfate supplies amino sugar units and sulfate groups, serving as precursors for glycosaminoglycan and proteoglycan synthesis.
- Plant-based CS provides a pre-sulfated, structurally consistent GAG template that integrates directly into the ECM, maintaining charge density and hydration.

B. Complementary Logic

The combination of glucosamine sulfate and plant-based chondroitin sulfate establishes a *"substrate + template"* dual support system:

- Substrate supply (Glucosamine Sulfate): Provides raw materials and sulfate groups for chondrocytes to synthesize new proteoglycans.
- Template support (Plant-Based Chondroitin Sulfate): Directly incorporates into the ECM as a structural scaffold, ensuring proper alignment and functional stability of newly synthesized proteoglycans.

Outcome: This complementary relationship markedly accelerates ECM repair and enhances its functional integrity - improving matrix hydration, compressive elasticity, and reducing friction-induced damage.

C. Clinical Relevance

- High-impact athletes: In sports such as running, basketball, and football, where post-exercise ECM microdamage is pronounced, combined supplementation accelerates restoration of cushioning capacity and alleviates soreness and start-up pain.
- Endurance athletes: Under prolonged loading, gradual proteoglycan depletion occurs. Dual intervention helps maintain matrix homeostasis and delays fatigue-related cartilage damage.
- Rehabilitation populations: During post-surgical or injury recovery, the combination of glucosamine sulfate with plant-based chondroitin sulfate shortens repair cycles and improves rehabilitation efficiency.

Summary: Glucosamine sulfate provides the synthetic substrates and sulfate groups, while plant-based chondroitin sulfate offers the sulfated template and structural support. Together, they synergistically achieve a dual pathway of “matrix regeneration × hydration enhancement × functional homeostasis.” For physically active individuals, this synergy provides a more effective defense and repair mechanism against ECM microdamage caused by high-impact or repetitive exercise.

4.3) Synergy with Hyaluronic Acid (HA)

Dual Enhancement of Lubrication and Tribological Stability

A. Mechanistic Basis

Exercise-induced joint stress is often accompanied by dilution of synovial fluid components and a decline in viscoelasticity, resulting in insufficient lubrication, increased friction, and exacerbation of cartilage surface microdamage.

- Role of Hyaluronic Acid (HA): As the primary viscoelastic component of synovial fluid, HA provides fluid-based lubrication and shock absorption. However, under exercise-induced stress, HA molecular weight can decrease, weakening its lubricating capacity.
- Role of Plant-Based Chondroitin Sulfate: With its negatively charged polysaccharide chains, plant-based chondroitin sulfate can form complexes with HA, enhancing HA’s structural stability while reducing inflammation-mediated HA degradation.

B. Synergistic Logic

The combination of HA and plant-based chondroitin sulfate achieves both structural complementarity and functional enhancement within the synovial environment:

- Enhanced viscoelasticity: HA provides the foundational viscoelastic framework, while chondroitin sulfate reinforces its stability and rheological properties through ionic interactions and complex formation.
- Boundary lubrication protection: Chondroitin sulfate mitigates the inflammatory suppression of lubricin, while lubricin and HA together maintain the boundary lubrication layer on articular surfaces.
- Anti-inflammatory and anti-degradation effects: Whereas HA is vulnerable to degradation by hyaluronidase under inflammatory activation, chondroitin sulfate attenuates NF-κB–driven pathways, slowing this degradation process.

Outcome: The synergy of the two maintains synovial fluid quality and lubrication performance after exercise, reduces friction coefficients, and minimizes the risk of further microdamage.

C. Clinical Value and Target Populations

- Endurance athletes: In populations exposed to prolonged training, where synovial fluid viscoelasticity declines, the combination enhances joint comfort and accelerates recovery.

- High-intensity athletes: After high-frequency impact training or competition, HA and chondroitin sulfate together help relieve stiffness and pain caused by frictional stress.
- Rehabilitation patients: During injury repair or postoperative recovery, combined use helps maintain synovial function and prevent secondary damage.

Summary: Hyaluronic acid contributes the viscoelastic framework, while plant-based chondroitin sulfate provides reinforcement and boundary lubrication protection. Together they create a *"lubrication enhancement × tribological improvement"* dual safeguard. This synergy is highly relevant for post-exercise recovery, alleviation of joint friction, and prevention of repetitive stress injuries.

4.4) Synergy with Vitamin D

Dual Dimensions of Osteochondral Support and Immune Modulation

A. Mechanistic Basis

Exercise-related joint stress extends beyond the cartilage surface to involve microdamage of the subchondral bone and the osteochondral interface, regions that are subjected to additional pressure under long-term high-load training.

- Role of Vitamin D: By activating the vitamin D receptor (VDR), vitamin D regulates calcium–phosphate metabolism and osteoblast activity, enhancing bone matrix mineralization and bone density. In parallel, it downregulates Th17 cells and reduces IL-17 expression, thereby exerting an immune-modulatory effect.

- Role of Plant-Based Chondroitin Sulfate: It stabilizes the cartilage ECM, improves synovial fluid quality, and suppresses inflammation-driven MMP activation, preventing further cartilage degradation.

B. Synergistic Logic

Together, vitamin D and plant-based chondroitin sulfate act across the *"bone-cartilage-immune"* tri-axis through complementary mechanisms:

- Bone support × Cartilage protection: Vitamin D strengthens the subchondral bone's load-bearing capacity, while chondroitin sulfate preserves cartilage and synovial homeostasis - jointly enhancing overall structural stability.
- Immune-inflammatory buffering: Vitamin D suppresses the Th17/IL-17 axis, while chondroitin sulfate downregulates NF-κB and TNF-α signaling. This dual regulation reduces post-exercise inflammatory peaks.
- Long-term repair potential: During sustained training or rehabilitation, the combination mitigates the progression of subchondral micro-cracks and cartilage wear, thereby supporting integrated repair.

C. Clinical Value and Target Populations

- Vitamin D-deficient individuals: Indoor athletes or populations with limited sun exposure may benefit from combined supplementation to address osteochondral vulnerability.
- Older athletes: Those with declining bone density are more prone to microdamage after training; the combination helps reduce risks of osteochondral degeneration.
- Rehabilitation patients: In postoperative or chronic overuse recovery, vitamin D's role in bone reconstruction and chondroitin sulfate's cartilage support create a synergistic effect, accelerating functional restoration.

Summary：Vitamin D contributes through bone metabolism support and immune regulation, while plant-based chondroitin sulfate ensures cartilage homeostasis and inflammation buffering. Acting jointly on the *bone-cartilage-immune* tri-axis, they provide a robust safeguard for the repair and prevention of exercise-induced joint damage. This synergy not only alleviates short-term inflammation and microdamage recovery but also reduces long-term risks of degeneration and recurrence.

Conclusion

In the nutritional intervention of exercise-induced joint microtrauma, plant-based chondroitin sulfate is not only an independent structural support factor but also the central hub of multi-axis synergy. Its complementary interactions with key nutrients establish a systemic integrative intervention network:

- With undenatured type II collagen (Native CT-II): Creates an “immune buffering × structural repair” complementarity, reducing inflammatory peaks and stabilizing ECM recovery.
- With glucosamine sulfate: Builds a dual pathway of “substrate supply × sulfation template,” accelerating the regeneration of proteoglycans and collagen, and restoring matrix hydration and elasticity.
- With hyaluronic acid: Forms a “synovial skeleton × composite enhancement” lubrication network, markedly improving viscoelasticity and tribological stability.
- With vitamin D: Extends to the “bone–cartilage–immune” tri-axis, providing comprehensive support through subchondral matrix reinforcement and immune–inflammatory regulation.

Taken together, this synergistic system achieves four-dimensional coverage - inflammation buffering, structural repair, lubrication optimization, and osteochondral interface support.

Compared with single-agent nutritional interventions, the combined mechanism not only accelerates post-exercise recovery but also confers preventive protection and long-term homeostatic maintenance.

For high-intensity trainees, professional athletes, and rehabilitation populations, this multi-dimensional synergistic framework provides a sustainable dietary nutrition strategy for injury prevention, functional restoration, and long-term protection.

Synergy with Undenatured Type II Collagen (Native CT-II) → Immune Buffering

✓ *Bagchi, D., Misner, B., Bagchi, M., Kothari, S. C., Downs, B. W., Fafard, R. D., … & Preuss, H. G. (2002). Effects of orally administered undenatured type II collagen against arthritic inflammatory diseases: a mechanistic exploration. International Journal of Clinical Pharmacology Research, 22(3-4), 101–110.*

- Experimental study showing that Native CT-II, via oral immune tolerance, downregulates the Th17/IL-17 pathway and buffers inflammatory responses

✓ *Crowley, D. C., Lau, F. C., Sharma, P., Evans, M., Guthrie, N., Bagchi, M., … & Bagchi, D. (2009). Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial. International Journal of Medical Sciences, 6(6), 312–321.*

- Clinical trial demonstrating that low-dose Native CT-II improves morning stiffness and activity-related pain, supporting its immune-buffering role in exercise-induced joint microtrauma

Synergy with Glucosamine Sulfate → Matrix Synthesis and Sulfate Complementation

✓ *Matsuno, H., Nakamura, H., Katoh, S., Inoue, H., Kimura, T., & Tsuruha, J. (2009). Effects of glucosamine on the expression of cartilage matrix genes in cultured human chondrocytes. Osteoarthritis and Cartilage, 17(6), 754–762.*

- Experimental evidence that glucosamine promotes the expression of Aggrecan and COL2A1, thereby enhancing ECM synthesis

✓ *Reginster, J. Y., Deroisy, R., Rovati, L. C., Lee, R. L., Lejeune, E., Bruyere, O., & Gossett, C. (2001). Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized,* *placebo-controlled clinical trial. The Lancet, 357(9252), 251–256.*

- Long-term RCT confirming that glucosamine sulfate delays structural progression, indicating potential applicability in exercise-related ECM repair

Synergy with Hyaluronic Acid → Lubrication Optimization and Tribological Improvement

✓ *Balazs, E. A., & Denlinger, J. L. (1993). Viscosupplementation: a new concept in the treatment of osteoarthritis. Journal of Rheumatology Supplement, 39, 3–9.*

- Early research introducing the concept of “viscosupplementation,” highlighting HA’s central role in synovial lubrication and shock absorption

✓ *Altman, R. D., Manjoo, A., Fierlinger, A., Niazi, F., & Nicholls, M. (2015). The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. BMC Musculoskeletal Disorders, 16, 321.*

- Systematic review showing that HA enhances synovial fluid viscoelasticity and lubrication, reducing friction-related microdamage

Synergy with Vitamin D → Osteochondral Interface and Immune Regulation

✓ *Cantorna, M. T., Snyder, L., Lin, Y. D., & Yang, L. (2015). Vitamin Dand 1,25(OH)2D regulation of T cells. Nutrients, 7(4), 3011–3021.*

- Basic research demonstrating that vitamin D, via the VDR pathway, regulates the Treg/Th17 balance and exerts immune-modulatory effects

✓ *McAlindon, T. E., LaValley, M. P., Harvey, W. F., Price, L. L., Driban, J. B., Zhang, M., & Lo, G. H. (2013). Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. JAMA, 309(2), 155–162. - RCT showing that vitamin D supplementation had limited effects on pain relief but helped maintain cartilage volume and osteochondral interface stability*

VII Nutritional Value of Plant-Based (Laminaria japonica) Chondroitin Sulfate in NSAIDs Substitution and Gastrointestinal-Sensitive Populations

From Long-Term Safety to the Advantage of Low Immunogenicity

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the management of exercise-induced joint microtrauma and inflammatory symptoms of arthritis. However, their *"gastrointestinal side effects and limited long-term safety"* have become a major clinical concern. In particular, for patients with chronic joint strain, during rehabilitation training, or in elderly populations, issues such as gastric mucosal injury, risk of bleeding, and poor tolerability significantly restrict their long-term use.

By contrast, plant-based chondroitin sulfate, owing to its high purity, low immunogenicity, and multi-target mechanisms of action, provides a dual benefit of anti-inflammatory buffering and structural protection. Importantly, it demonstrates superior safety in long-term supplementation and among individuals with gastrointestinal sensitivity.

As a result, this nutrient is increasingly regarded in clinical nutrition as a potential alternative or complementary strategy to NSAIDs, offering a safer, sustainable option for managing joint symptoms in sensitive or chronic populations.

1) Background and Clinical Challenges

Non-steroidal anti-inflammatory drugs (NSAIDs) remain the most widely prescribed agents for exercise-induced joint strain, osteoarthritis, and inflammatory joint diseases. Their primary mechanism of action involves inhibition of cyclooxygenase (COX-1/COX-2), thereby blocking prostaglandin synthesis and achieving anti-inflammatory, analgesic, and antipyretic effects.

However, long-term clinical use has progressively revealed several critical limitations:

- Significant gastrointestinal side effects:

NSAIDs suppress COX-1–mediated protective prostaglandins, compromising the integrity of the gastric mucosal barrier. This predisposes to gastritis, gastric ulcers, bleeding, and even perforation. For individuals with pre-existing gastrointestinal conditions or heightened sensitivity, the risk is particularly pronounced.

- Insufficient long-term safety:

While NSAIDs provide rapid pain relief, they are symptom-oriented rather than structure-modifying. Prolonged use may accelerate joint structural degeneration. Furthermore, chronic NSAID exposure has been associated with cardiovascular risks (e.g., hypertension, myocardial infarction) and renal impairment.

- Poor tolerability in chronic populations:

Patients with rheumatoid arthritis, chronic sports-related joint strain, or age-related degenerative joint diseases often require sustained therapy. Yet long-term NSAID use is limited by tolerability issues, which frequently undermine patient adherence.

- Lack of structural protection:

The pharmacological effects of NSAIDs primarily target inflammatory mediator suppression, but provide no benefit for cartilage matrix synthesis, synovial fluid maintenance, or osteochondral homeostasis. This means NSAIDs can alleviate symptoms in the short term but do not halt the progression of joint damage.

Summary: NSAIDs still hold an irreplaceable role in acute symptom management. However, their gastrointestinal risks, lack of structural protection, and insufficient long-term safety pose significant limitations in the management of chronic joint disease, sports-related joint strain, and gastrointestinal-sensitive populations.

These shortcomings underscore the need for alternative interventions with superior safety, tolerability, and multi-target mechanisms from a clinical and nutritional perspective.

2) The Substitutive Potential of Plant-Based (Laminaria japonica) Chondroitin Sulfate

NSAIDs primarily rely on a single COX-inhibition pathway to alleviate pain and inflammation. In contrast, plant-based (Laminaria japonica) chondroitin sulfate exerts multi-targeted systemic effects, providing both symptom relief and structural support. These characteristics establish its clinical value in populations requiring long-term intervention or those with gastrointestinal sensitivity.

2.1) Superior Gastrointestinal Tolerability

- Plant-based formulations undergo rigorous purification, with chondroitin sulfate content ≥90% and virtually no protein or lipid impurities.
- This high-purity profile minimizes direct irritation of the gastrointestinal mucosa and avoids the protein-related immune reactions that may occur with animal-derived products.
- Clinically, its gastrointestinal adverse event rate is comparable to placebo and significantly lower than NSAIDs.

2.2) Long-Term Safety Advantages

- Chronic NSAID use is closely linked with gastrointestinal, cardiovascular, and renal risks. In contrast, the safety of chondroitin sulfate has been consistently validated in long-term RCTs and meta-analyses.

- Its adverse event incidence remains indistinguishable from placebo, with minimal burden on systemic organ function.
- This makes it suitable for rheumatoid arthritis, chronic sports-related joint strain, and elderly patients requiring long-term disease management.

2.3) Multi-Target Mechanisms of Action

- Anti-inflammatory buffering: Downregulates NF-κB, IL-1β, and TNF-α pathways, mitigating synovitis and post-exercise inflammatory peaks.
- Structural repair: Promotes synthesis of type II collagen and proteoglycans, while suppressing overactivation of MMPs and ADAMTS.
- Lubrication optimization: Synergizes with hyaluronic acid to enhance synovial fluid viscoelasticity, preserving tribological stability.
- Osteochondral interface support: Improves the subchondral bone–cartilage microenvironment, reducing long-term degenerative risk.

In contrast to NSAIDs, which only provide “pain relief and anti-inflammation”, plant-based chondroitin sulfate simultaneously achieves symptom control and structural protection.

Summary: With its high purity, low immunogenicity, multi-targeted actions, and validated long-term safety, plant-based (Laminaria japonica) chondroitin sulfate effectively addresses the gastrointestinal risks and lack of structural protection inherent to NSAIDs. For gastrointestinal-sensitive populations and chronic disease management settings, it represents not only a viable substitute for NSAIDs but also a superior nutritional intervention that balances safety with efficacy.

3) Population Suitability

The molecular characteristics and safety advantages of plant-based chondroitin sulfate make it uniquely suitable for populations with gastrointestinal sensitivity, those requiring long-term interventions, and individuals with specific dietary restrictions.
This broad spectrum of applicability represents a key clinical advantage that distinguishes it from NSAIDs and animal-derived chondroitin sulfate.

3.1) Gastrointestinal-Sensitive Populations

- Risk background:

NSAID users frequently develop gastritis, peptic ulcers, or gastrointestinal bleeding, with risks particularly elevated in elderly patients or those with a history of digestive tract disease.

- Advantage of plant-based formulations:

Produced through high-purity processes, they are virtually free of immunogenic proteins and lipid residues, minimizing irritation to the gastrointestinal mucosa.

- Clinical significance:

Provides a safe, long-term alternative for joint support in gastrointestinal-sensitive individuals, reducing the risk of treatment discontinuation due to drug-induced adverse effects.

3.2) Chronic Disease and Long-Term Intervention Populations

- Risk background: Patients with rheumatoid arthritis, degenerative joint disease, or chronic sports-related joint strain often require long-term and continuous management. NSAIDs are limited in this group due to safety and tolerability issues.
- Advantage of plant-based formulations: Long-term RCTs and systematic reviews consistently demonstrate that adverse event rates are comparable to placebo, with no added burden on cardiovascular, renal, or systemic safety.
- Clinical significance: Suitable as a foundational intervention for chronic disease management, contributing to inflammatory buffering, structural protection, and functional maintenance over time.

3.3) Populations with Allergies, Vegetarian Diets, or Religious Restrictions

- Risk background: Animal-derived chondroitin sulfate is unsuitable for vegetarians, individuals with religious dietary restrictions, or patients with animal protein allergies.
- Advantage of plant-based formulations: Derived from Laminaria japonica, naturally free from animal components, eliminating risks of immunogenicity and ethical concerns.

- Clinical significance: Facilitates international application and cross-cultural acceptance, while expanding accessibility to broader populations.

Summary: With its superior gastrointestinal tolerability, validated long-term safety, and compatibility with vegetarian, religious, and allergy-restricted diets, plant-based (Laminaria japonica) chondroitin sulfate demonstrates high adaptability across diverse populations.

In sharp contrast to the risk profile of NSAIDs, these features establish a solid foundation for its widespread application in both clinical practice and nutritional interventions.

Risks and Limitations of NSAIDs

- ✓ *Lanas, A., & Chan, F. K. (2017). Peptic ulcer disease. Lancet, 390(10094), 613–624.*

  - The systematic review pointed out that NSAIDs are a major risk factor for peptic ulcers and upper gastrointestinal bleeding, with significantly increased risk during long-term use
- ✓ *Sostres, C., Gargallo, C. J., & Lanas, A. (2010). Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Research & Therapy, 12(3), S2.*

  - The review showed that NSAIDs cause mucosal damage throughout the gastrointestinal tract, including the small intestine and colon, with risks correlated to dose and duration of use
- ✓ *Bhala, N., Emberson, J., Merhi, A., Abramson, S., Arber, N., Baron, J. A., … & Baigent, C. (2013). Vascular and upper gastrointestinal effects of NSAIDs: meta-analyses of individual participant data from randomised trials. Lancet, 382(9894), 769–779.*

- A large-scale meta-analysis confirmed that NSAIDs increase cardiovascular and gastrointestinal adverse events, limiting their long-term application

Safety and Tolerability of Chondroitin Sulfate

- ✓ *Singh, J. A., Noorbaloochi, S., MacDonald, R., & Maxwell, L. J. (2015). Chondroitin for osteoarthritis. Cochrane Database of Systematic Reviews, 2015(1), CD005614.*

  - The Cochrane systematic review showed that the long-term safety profile of chondroitin sulfate is close to placebo, with a low incidence of gastrointestinal adverse reactions
- ✓ *Kahan, A., Uebelhart, D., De Vathaire, F., Delmas, P. D., Reginster, J. Y., & Burlet, N. (2009). Long-term effects of chondroitin sulfate on knee osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial. Arthritis & Rheumatism, 60(2), 524–533.*

  - A long-term RCT (2 years) confirmed that chondroitin sulfate can improve symptoms and delay structural progression, with good tolerability

Advantages of Plant-Based/High-Purity Formulations

- ✓ *Houpt, J. B., McMillan, R., Wein, C., & Paget-Dellio, S. D. (1999). Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. Journal of Rheumatology, 26(11), 2423–2430.*

  - Early studies showed that glucosamine and chondroitin sulfate had better gastrointestinal tolerability than NSAIDs, with adverse event rates close to placebo

✓ *Bruyère, O., & Reginster, J. Y. (2007). Glucosamine and chondroitin sulfate as therapeutic agents for knee and hip osteoarthritis. Drugs & Aging, 24(7), 573–580.*

- The review highlighted that both agents have an excellent safety profile in joint degeneration populations, making them suitable for long-term interventions, especially for individuals with gastrointestinal sensitivity

VIII Conclusion

Plant-Based Chondroitin Sulfate derived from *Laminaria japonica* represents a significant advancement in the field of nutritional interventions for joint health. As a high-purity, low-immunogenic, and structurally consistent compound, it provides a breakthrough solution to the longstanding limitations of traditional animal-derived preparations, including residual impurities, molecular heterogeneity, and poor tolerability.

1) Molecular and pharmacokinetic advantages

Through targeted enzymatic hydrolysis and standardized purification, plant-based chondroitin sulfate achieves a defined low molecular weight distribution and uniform sulfation pattern. These features enhance intestinal absorption and systemic bioavailability while ensuring batch-to-batch clinical reproducibility, thereby establishing a more reliable *"dose-exposure-response"* relationship.

Mechanistic value chain

Its clinical efficacy is supported by a threefold mechanistic pathway:

- Structural homeostasis protection - Promotes the synthesis of type II collagen and proteoglycans, suppresses excessive MMP/ADAMTS activity, and improves synovial fluid quality
- Inflammation buffering and immune regulation - Inhibits NF-κB activation, downregulates pro-inflammatory cytokines, and restores Treg/Th17 balance, thereby breaking the cycle of *inflammation-degradation-damage*
- Tolerability and compliance advantage - Low immunogenicity and gut-friendly properties allow safe, sustained long-term use

2) Population adaptability

Owing to its low allergenicity and high tolerability, plant-based chondroitin sulfate is suitable for individuals with gastrointestinal sensitivity, patients requiring long-term management of chronic joint conditions, and populations restricted by vegetarian, religious, or anti-animal protein dietary preferences.

This broad adaptability underscores its public health relevance, particularly in the context of global aging and the rising prevalence of joint diseases.

3) Synergy within the Keyora JointOra 5 in 1 formula

Within the Keyora JointOra 5 in 1 formulation, plant-based chondroitin sulfate acts as a structural cornerstone synergizing with:

- Undenatured type II collagen (Native CT-II) – supporting oral immune tolerance
- Glucosamine sulfate – providing biosynthetic precursors
- Hyaluronic acid – enhancing synovial viscoelasticity

Together, these components form a comprehensive *“immune balance–structural repair–microenvironment optimization”* network, amplifying clinical outcomes beyond the capacity of any single nutrient.

4) Clinical translation and future perspectives

Multiple studies have confirmed that chondroitin sulfate improves joint pain, function, and structural integrity with efficacy comparable to NSAIDs, but with superior safety. This positions it as a candidate for Disease-Modifying Nutritional Interventions (DMNIs).

In the future, plant-based chondroitin sulfate is expected to play an increasingly important role in sports rehabilitation, chronic overuse syndromes, inflammatory joint conditions, and aging-related degeneration.

Final statement：Plant-based chondroitin sulfate should not be regarded merely as a substitute for animal-derived preparations. Instead, it represents the next-generation joint nutrient, defined by high purity, optimized bioavailability, and superior tolerability.

Through molecular refinement, multi-dimensional mechanisms, and broad population applicability, it redefines the clinical value and translational potential of nutritional strategies for joint diseases, offering a scientifically robust solution for long-term structural protection and functional improvement.