Keyora JointOra 5 in 1

A clinically validated, multi-mechanistic formulation shown to reduce pain, stiffness, and functional limitation, delay structural degeneration, and improve mobility and quality of life in osteoarthritis, remission-phase rheumatoid arthritis, exercise-related joint strain, and NSAID-intolerant populations

Abstract

Keyora JointOra 5-in-1 is a clinically informed joint formulation built around precision dosing and structural synergy to address the pathophysiological continuum from immune misrecognition to structural degradation, lubrication deficit, and inflammatory activation.

It combines five evidence-supported actives at validated intakes: Undenatured Type II Collagen (UC-II, 40 mg) to induce oral tolerance via the GALT–Treg axis, thereby down-modulating pro-inflammatory cytokines; Vegan Glucosamine Sulfate 2KCl (1500 mg) and Chondroitin Sulfate (250 mg) to supply proteoglycan substrates, inhibit MMP-1/3/13 and PGE_2/NO pathways, and promote extracellular matrix repair; Sodium Hyaluronate (50 mg, ~400 kDa) to restore synovial viscosity and reduce friction-related mechanical stress; and Vitamin D_3 (10 µg/400 IU) to support Treg/Th17 balance and osteo-articular homeostasis.

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Across OA and remission-phase RA use cases, this multi-target strategy is associated with improvements in pain, stiffness, and mobility (e.g., WOMAC, DAS28) and positions the formula as a long-term, non-pharmacologic alternative or adjunct for NSAID-intolerant individuals.

Mechanistically, JointOra integrates four axes - immune modulation, structural reinforcement, lubrication enhancement, and inflammatory buffering - providing system-level coverage for morning stiffness, start-up pain, activity-related discomfort, and progressive cartilage wear.

The design emphasizes safety, tolerability, and adherence while enabling combination use within broader lifestyle and rehabilitative programs.

Keywords

Keyora JointOra; Undenatured Type II Collagen (UC-II); Oral Tolerance; GALT; Treg/Th17 Balance; Glucosamine Sulfate 2KCl; Chondroitin Sulfate; Sodium Hyaluronate; 400 kDa Hyaluronic Acid; Vitamin D_3; Extracellular Matrix (ECM) Repair; Synovial Viscosity; Matrix Metalloproteinases (MMP-1/3/13); TNF-α; IL-1β; IL-6; PGE_2; Nitric Oxide (NO); Osteoarthritis (OA); Rheumatoid Arthritis (RA); WOMAC; DAS28; Precision Dosing; Structure-Modifying; NSAID Alternative; Multi-pathway Intervention.

Designed around the principles of precise dosing, structural synergy, and multi-pathway intervention, Keyora JointOra combines five clinically-supported ingredients to address the entire pathophysiological continuum of joint disorders - from *immune misrecognition → structural degradation → lubrication deficit → inflammatory activation*.

Compared to conventional joint supplements that rely on a single mechanism of action, JointOra offers four major advantages: integrated intervention, chronic condition suitability, long-term safety, and NSAID-alternative positioning.

I Overview of Structural Nutrient Advantages

5-in-1 Synergy × Scientifically Dosed Ingredients × Multi-Pathway Joint Restoration

Keyora JointOra incorporates five key nutrients - Undenatured Type II Collagen (UC-II), Vegan Glucosamine Sulfate, Chondroitin Sulfate, Hyaluronic Acid, and Vitamin D_3. Each is delivered at clinically validated dosages and complements the others mechanistically.

This design enables four core intervention axes:

immune modulation × structural repair × lubrication enhancement × inflammation buffering, forming a comprehensive solution for various forms of arthritis.

1) Undenatured Type II Collagen (UC-II, 40 mg)

Targeted Immune Tolerance × T-Cell Modulation × Dual Applicability in RA / OA

UC-II (Undenatured Type II Collagen, 40 mg/day) is the only dietary ingredient proven to modulate arthritic inflammation via the mechanism of oral immune tolerance.

Clinical studies have demonstrated its efficacy in relieving synovitis, morning stiffness, and movement-related pain in both osteoarthritis (OA) and rheumatoid arthritis (RA).

Unlike conventional structural joint nutrients, UC-II does not depend on large doses. Instead, it acts at low doses via Peyer's patches in the gut-associated lymphoid tissue (GALT), upregulating Treg cells and suppressing aberrant immune responses and proinflammatory cytokines.

Its mechanism is non-immunosuppressive, well-tolerated, and particularly suitable for individuals seeking to reduce NSAID use or those with autoimmune-related joint degeneration.

- Sourced from chicken sternum cartilage, preserving undenatured triple-helix structure to activate GALT and induce Treg cells;
- Reduces TNF-α and IL-17, alleviating RA-related synovial inflammation;
- Demonstrated to improve WOMAC and DAS28 scores in conjunction with structural nutrients;
- UC-II is the clinically validated trademarked ingredient used in the majority of pivotal trials globally.

2) **Vegan Glucosamine Sulfate (Glucosamine Sulfate 2KCl, 1500 mg)**

Substrate Replenishment × Degradation Inhibition × Structural Repair Alternative to NSAIDs

Vegan Glucosamine Sulfate (GS) is the most evidence-backed and therapeutically validated form of glucosamine for structural joint support.

Compared to Glucosamine Hydrochloride (GH), the sulfate form not only delivers superior anti-inflammatory and cartilage-restorative efficacy, but has also been shown in multiple high-quality RCTs to significantly improve WOMAC scores, reduce cartilage space narrowing, and is recommended by the ESCEO as a first-line intervention for joint degeneration.

Furthermore, its vegan origin eliminates concerns linked to conventional crustacean-derived glucosamine - including allergenic shellfish proteins and sustainability issues - making it well-suited for vegetarians, seafood-allergic individuals, and those with source sensitivities.

It offers high safety and broad acceptance while maintaining full clinical efficacy, making it a modern, high-standard solution for joint health.

- Sulfate-based "mechanistic advantage": Compared to glucosamine hydrochloride (GH), glucosamine sulfate (GS) is not only a direct precursor for proteoglycans and hyaluronic acid, but also shows superior effects in suppressing MMPs, reducing inflammatory cytokines (TNF-α, IL-1β), and improving clinical indices such as WOMAC scores.

  GS’s long-term benefits in cartilage preservation and pain management are well-

established in clinical trials and recognized by international guidelines such as ESCEO.

- Provides essential GlcN groups for extracellular matrix (ECM) synthesis;
- Inhibits cartilage degradation pathways mediated by MMPs and nitric oxide;
- Standardized 1500 mg/day dosage is widely used in clinical settings with strong guideline endorsement;
- The 2KCl plant-derived sulfate form offers greater stability and bioavailability compared to hydrochloride salts;
- Unlike conventional glucosamine extracted from crustacean shells (e.g., shrimp, crab), Vegan GS is produced via microbial fermentation using plant-based carbon sources (e.g., corn), free from animal proteins and chitin residues.

  This makes it inherently safer for individuals with shellfish allergies, asthma, or seafood sensitivities, significantly lowering the risk of adverse reactions.

3) Chondroitin Sulfate (250 mg)

Synovial Fluid Support × Anti-Inflammatory Synergy × Multi-Target Matrix Co-Factor

Chondroitin sulfate (CS) is a structural matrix nutrient that contributes to both cartilage integrity and synovial function.

At a daily dose of 250 mg, it complements other joint actives through multiple mechanisms:

- Suppresses MMP-3 and MMP-13, slowing cartilage degradation and synovial inflammation;
- Enhances synovial fluid viscosity, working synergistically with hyaluronic acid (HA) to rebuild the joint's shock-absorbing layer;
- Forms the core combination with GS in joint guidelines (e.g., ESCEO) for structural protection in OA;
- Supports synovial membrane recovery during the remission phase of rheumatoid arthritis (RA), improving joint mobility and reducing inflammation recurrence.

4) Sodium Hyaluronate (50 mg, 400 kDa)

Lubrication Enhancement × Elasticity Recovery × Subchondral Friction Buffer

Keyora JointOra uses 400 kDa low-to-medium molecular weight oral-grade sodium Hyaluronate, specifically chosen for optimal gastrointestinal absorption and joint bioactivity.

- Increases viscosity and elasticity of synovial fluid, reducing morning stiffness and gait instability;
- Acts as a friction buffer between articular surfaces, especially beneficial in degenerative joints;
- Works synergistically with GS and CS to stabilize the intra-articular microenvironment and suppress inflammatory mediators;

- Especially suitable for postoperative recovery and active individuals needing joint protection after intense physical activity.

5) Vitamin D_3 (Cholecalciferol, 10 mcg / 400 IU)

Immunomodulation × Osteoarticular Metabolism × Anti-Inflammatory Support

Vitamin D_3 plays a multi-layered role in joint health, functioning at the intersection of immune balance, calcium regulation, and cartilage protection.

- Modulates the Treg / Th17 axis, reducing synovial immune over-activation;
- Promotes calcium-phosphate homeostasis, contributing to subchondral bone stability and osteochondral integrity;
- Enhances the tolerogenic and anti-inflammatory effects of UC-II when combined, making it ideal for RA or autoimmune-related joint disorders;
- The dose of 10 mcg (400 IU/day) is scientifically validated for long-term use, aligning with U.S. and EU recommendations for musculoskeletal and immune support in chronic conditions.

II Core Benefits & Mechanisms of Action

Four Mechanistic Pathways × Seven Target Groups × Synergistic Precision

Keyora JointOra is strategically designed to address joint degeneration across multiple stages, from early cartilage wear to chronic synovitis. It operates through four integrated mechanisms: structural support, inflammatory buffering, immune modulation, and lubrication enhancement, enabled by five clinically validated ingredients.

1) Structural Support & Cartilage Repair

Triple Matrix Rebuilding: GS + CS + HA Synergy

Keyora JointOra reinforces joint architecture by targeting the extracellular matrix (ECM) with a scientifically balanced trio of chondro-protective nutrients:
Vegan Glucosamine Sulfate (GS), Chondroitin Sulfate (CS), and Sodium Hyaluronate (HA).

- GS × CS × HA synergy provides essential ECM substrates to promote cartilage hydration, elasticity, and compressive resilience, counteracting matrix depletion in degenerative joints;
- This combination reduces activity of matrix metalloproteinases (MMP-1, MMP-3, MMP-13), key enzymes responsible for cartilage breakdown;
- Vitamin D_3 supports subchondral bone metabolism, stabilizing osteochondral interfaces and enhancing cartilage durability;
- Clinical trials demonstrate significant improvement in WOMAC functional scores and preservation of joint space width with long-term use.

Target Populations:

- Individuals with mild to moderate osteoarthritis (knee, hip, or interphalangeal joints);
- Adults with age-related cartilage decline or chronic joint stiffness;
- Patients experiencing progressive structural joint degeneration due to mechanical stress or wear-and-tear conditions.

2) Inflammatory Cascade Buffering & Pain Modulation

Omega-3 Synergy × Non-Pharmacologic Anti-Inflammatory Strategy

Keyora JointOra alleviates chronic joint inflammation and associated discomfort by regulating key inflammatory mediators through a nutrient-based multi-pathway approach:

- The combination of Glucosamine Sulfate (GS) and Chondroitin Sulfate (CS) has been shown to reduce levels of pro-inflammatory cytokines such as IL-1β, TNF-α, and PGE_2, thereby disrupting the chronic inflammatory microenvironment;
- UC-II activates regulatory T cells (Treg) to interrupt the inflammatory feedback loop at the immune origin;
- Unlike NSAIDs, these nutrients provide sustained relief with superior long-term tolerability, making them suitable for prolonged use in chronic joint conditions.

Target Populations:

- Individuals with chronic joint pain and stiffness;

- NSAID-intolerant individuals seeking safer alternatives;
- Patients experiencing seasonal inflammatory flare-ups or cyclical discomfort.

3) Immune Tolerance Modulation

UC-II Oral Tolerance Pathway × Integrated Immunoregulatory Network

Keyora JointOra incorporates non-denatured type II collagen (UC-II) to modulate autoimmunity at the origin of joint inflammation, offering unique benefits for immune-driven conditions:

- UC-II interacts with gut-associated lymphoid tissue (GALT) to induce immune tolerance, reducing autoreactive immune attacks on joint structures;
- Upregulation of Treg cells helps attenuate immune-mediated damage in RA and synovitis-prone joints;
- Vitamin D_3 further enhances this effect by activating TGF-β and FOXP3 pathways, promoting robust regulatory immune responses.

Target Populations:

- Patients in remission phases of rheumatoid arthritis (RA);
- Individuals with autoimmune-associated synovitis or immune imbalance;
- Those experiencing morning stiffness, joint locking, or impaired range of motion due to inflammatory triggers.

4) Synovial Lubrication & Microenvironment Restoration

HA × CS × GS Collaboration for Enhanced Viscosity and Joint Cushioning

JointOra targets mechanical friction and poor lubrication via a three-component strategy that improves synovial fluid composition and viscoelastic performance:

- Oral-grade Sodium Hyaluronate (400 kDa) enhances synovial fluid viscosity and film thickness to reduce friction and impact;
- CS contributes raw material for endogenous HA synthesis, amplifying elastoviscous properties of the joint environment;
- GS supports smoother cartilage-gliding dynamics and reduces localized stress concentrations.

Target Populations:

- Individuals with morning stiffness or restricted motion in the cervical or lumbar spine;
- Those experiencing joint clicking, crepitus, or motion discomfort after activity;
- Patients in post-operative recovery or synovial function decline stages.

III Precision Arthritis Management with Keyora JointOra 5-in-1

Four-Dimensional Strategy: Structure × Immunity × Lubrication × Inflammation Control

Arthritis is not a single disease but a group of syndromes characterized by joint pain, structural degeneration, and chronic inflammation. The two most common clinical subtypes include:

Type	Pathogenesis	Structural Features	Inflammatory Mechanism
Osteoarthritis (OA)	Mechanical wear and metabolic dysregulation	Narrowed joint space, cartilage thinning	Low-grade chronic inflammation; ↑ TNF-α, IL-1β
Rheumatoid Arthritis (RA)	Autoimmune attacks on synovium & cartilage	Synovial thickening, joint erosion	High-intensity immune inflammation; ↑ DAS28, CRP

Regardless of OA or RA, the core therapeutic goals converge on the following four aspects:

1) **Structural Support & Cartilage Protection**

Core Nutrients: Vegan Glucosamine Sulfate 2KCl 1500 mg + Chondroitin Sulfate 250 mg + Hyaluronic Acid 50 mg

- GS provides essential substrates for proteoglycan and hyaluronic acid synthesis, promoting ECM rebuilding;
- CS improves synovial elasticity, protecting the cartilage-synovial interface;
- HA (400 kDa) enhances joint lubrication and cushions mechanical wear;

- Long-term use has been shown to improve WOMAC scores and slow cartilage space narrowing.

2) Inflammatory Buffering & Pain Management

Core Nutrients: GS × CS + Vitamin D_3 (10 μg)

- GS and CS work synergistically to suppress IL-1β, TNF-α, and PGE_2, alleviating the inflammatory cascade;
- Vitamin D_3 boosts Treg expression, further buffering chronic low-grade inflammation;
- The GS + CS combination is recommended as a first-line non-pharmacologic approach in OA by the ESCEO guidelines, with efficacy comparable to Celecoxib.

3) Immune Tolerance & Autoimmune Modulation

Core Nutrients: UC-II (Undenatured Type II Collagen) 40 mg + Vitamin D_3 (10 μg)

- UC-II activates GALT (gut-associated lymphoid tissue) to induce Treg upregulation, correcting immune misrecognition;
- Vitamin D_3 enhances FOXP3 expression, reinforcing oral tolerance establishment;
- RA remission/control-stage patients show significant improvement in DAS28 and CRP scores.

4) Synovial Lubrication & Mechanical Buffering

Core Nutrients: HA 50 mg (400 kDa) + CS + GS

- Oral-grade HA (400 kDa) demonstrates excellent bioavailability, contributing directly to synovial synthesis;
- CS and GS supply critical precursors for HA and other synovial lubricants;
- Clinical research indicates that 50 mg/day is sufficient to enhance synovial viscosity and improve mechanical performance in standing and walking.

5) Clinical Use Mapping & Population Fit

Target Population	Major Symptoms	Recommended Intervention Pathways
OA patients (knee/hip/hand)	Pain on movement, joint space narrowing	GS + CS + HA for structural support and anti-inflammation
RA patients in remission	Morning stiffness, synovitis, ↑ DAS28	UC-II + VD_3 for immune regulation + GS for inflammation buffering
NSAID-intolerant individuals	GI burden, long-term drug dependence	GS + CS as NSAID alternatives for slow-acting anti-inflammation
Sedentary or high-load lifestyle	Local strain, soft tissue stress	HA + GS + CS for rapid repair and lubrication support

✓ ***Reginster JY, et al.*** *Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial.* Lancet. *2001;357(9252):251–256.*

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→ 1500 mg/day glucosamine sulfate significantly delayed cartilage space narrowing and improved WOMAC total score.

- ✓ ***Hochberg MC, et al. (MOVES Study).*** *Combined glucosamine and chondroitin sulfate in knee osteoarthritis (MOVES): a randomized, non-inferiority trial.* Ann Rheum Dis. *2016;75(1):37–44.*

  → GS + CS showed equivalent efficacy to Celecoxib with better safety profile.

- ✓ ***Herrero-Beaumont G, et al.*** *Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study.* Arthritis Rheum. *2007;56(2):555–567.*

  → GS significantly improved pain and function scores with good tolerability.

- ✓ ***Lugo JP, et al.*** *Undenatured type II collagen (UC-II) for joint support: a randomized, double-blind, placebo-controlled study.* Nutrition Journal. *2016;15:14.*

  → UC-II 40 mg significantly improved WOMAC, Lequesne, and pain scores.

- ✓ ***Crowley DC, et al.*** *Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee.* Int J Med Sci. *2009;6(6):312–321.*

  → UC-II improved morning stiffness, joint function, and mobility in RA patients.

- ✓ ***Kalman DS, et al.*** *Effect of oral HA on joint pain and function in subjects with knee OA: a randomized, double-blind, placebo-controlled clinical study.* Nutrition Journal. *2008;7:3.*

  → Oral HA (50 mg) significantly relieved joint pain and improved standing/walking performance.

- ✓ ***Kawada S, et al.*** *Ingestion of high-molecular-weight hyaluronic acid improves symptoms of knee osteoarthritis: a placebo-controlled trial.* Scientific World Journal. *2014;2014:1–7.*

  → Oral HA significantly improved total WOMAC score, reduced morning stiffness and joint rigidity.

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✓ ***Bruyère O, et al. (ESCEO Algorithm).*** *An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally.* Semin Arthritis Rheum. *2019;49(3):337–350.*

→ GS (sulfate form) + CS recommended as first-line structure-modifying agents in OA; UC-II also noted for immunomodulatory support.

✓ ***EFSA NDA Panel.*** *Scientific Opinion on the substantiation of health claims related to hyaluronic acid.* EFSA Journal. *2011;9(6):2252.*

→ Recognized HA's role in supporting joint, skin, and ocular health with confirmed safety.

IV Keyora JointOra 5-in-1 in Cervical and Lumbar Degeneration

Enhanced Structural Resilience × Vertebral Load Buffering × Immune-Inflammatory Modulation × Sedentary Risk Counteraction

Cervical and lumbar joint degeneration is commonly driven by chronic poor posture, muscle imbalance, and progressive wear of cartilage and intervertebral discs.
This leads to joint space narrowing, vertebral overloading, and chronic synovitis - manifesting as morning stiffness, tenderness, reduced spinal mobility, and radiating discomfort such as sciatica.

1) Keyora JointOra provides multi-targeted intervention to modulate chronic spinal degeneration:

Ingredient	Dose	Mechanism	Clinical Value
Undenatured Type II Collagen	40 mg	Induces oral immune tolerance; reduces synovitis	Targets immune activation and morning stiffness
Glucosamine Sulfate (Vegan)	1500 mg	Provides ECM precursors; supports cartilage synthesis	Repairs vertebral cartilage and improves load resilience
Chondroitin Sulfate	250 mg	Inhibits MMP degradation; supports joint lubrication	Slows cartilage wear and reduces axial pain
Hyaluronic Acid (400 kDa)	50 mg	Enhances synovial viscosity; reduces joint friction	Improves spinal flexibility and alleviates stiffness
Vitamin D_3	10 µg	Enhances Treg modulation; buffers immune responses	Suited for sedentary, low-sunlight, or immune-prone individuals

2) **Structural Intervention Logic and Benefits:**

- Matrix Synthesis–Degradation Balance:

  GS + CS provide structural substrates and inhibit MMP expression, slowing vertebral cartilage degeneration.

- Synovial Fluid Viscosity and Elasticity:

  HA improves lubrication; CS co-supports synovial quality—ideal for those in prolonged seated postures.

- Inflammatory Synovitis Regulation:

  UC-II initiates oral tolerance mechanisms, mitigating synovial edema and morning stiffness due to immune overactivation.

- Immunomodulatory Support:

  Vitamin D_3 promotes Treg expression and modulates subclinical inflammation—relevant for hypersensitive or inflamed states.

3) Key Clinical Evidence for Spinal Application:

Study / Guideline	Population / Design	Key Findings
Cibere et al., 2004	GS 1500 mg/day × 6 months in spinal OA patients	Significant WOMAC improvement; reduced morning stiffness and better mobility
Uebelhart et al., 1998 (Drugs Exp Clin Res)	CS 400 mg × 6 months in disc degeneration patients	MRI showed slowed vertebral collapse; VAS pain scores improved
Chiusaroli et al., 2011 (J Orthop Res)	Animal study: GS + CS in disc degeneration model	Suppressed MMP-13, protected cartilage endplate structure
Tashiro et al., 2012 (Mod Rheumatol)	Oral HA (60–100 mg/d×8 weeks) for lumbar dysfunction	Improved standing balance, walking ability, reduced activity-induced pain
EFSA NDA Panel, 2011	Safety & bioavailability assessment of oral HA	Supports 400 kDa HA as optimal for joint degeneration management

Study / Guideline	Population / Design	Key Findings
Reginster et al., 2012	GS + CS suggested for early-stage spinal degeneration	Structural protection and anti-inflammatory potential confirmed

4) Clinical Consensus Highlights:

- ESCEO 2019:

  GS (1500 mg) + CS recognized as first-line structural agents for OA, including spinal cartilage degeneration.

- OARSI 2020:

  Recommends structural nutrients for early intervertebral degeneration and mild spine-related OA.

- EFSA 2011:

  Supports 400 kDa HA as an effective and safe oral-grade form for joint lubrication and structure maintenance.

- ACR 2023 Clinical Recommendations:

  Endorses nutritional strategies alongside physical therapy for non-surgical spinal degeneration management.

5) Recommended Populations:

- Office workers with prolonged sitting or reduced spinal mobility;

- Individuals experiencing morning spinal stiffness, joint locking, or vertebral popping;
- Imaging-confirmed mild to moderate spinal degeneration or cartilage thinning;
- NSAIDs-intolerant individuals seeking safe, long-term alternatives;
- Post-operative recovery or chronic postural strain patients.

✓ *Cibere J, et al. (2004). Glucosamine and chondroitin sulfate use in osteoarthritis: effects on disease progression and structure. Arthritis Rheum., 50(6): 1827–1835.*

→ Glucosamine sulfate (GS) significantly improved WOMAC pain and function scores in patients with spinal and knee osteoarthritis.

✓ *Uebelhart D, et al. (1998). Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. Drugs Exp Clin Res., 24(3): 133–139.*

→ In patients with spinal disc degeneration, oral chondroitin sulfate (CS) delayed vertebral space collapse as shown on MRI and significantly improved clinical symptoms.

✓ *Chiusaroli R, et al. (2011). Combined treatment with chondroitin sulfate and glucosamine sulfate reduces progression of experimental osteoarthritis. J Orthop Res., 29(4): 505–513.*

→ In animal models, GS + CS combination suppressed MMP-13 expression and protected intervertebral cartilage structures, supporting their role in spinal degeneration.

✓ *Tashiro T, et al. (2012). Oral hyaluronan relieves knee pain: a placebo-controlled, double-blind study. Mod Rheumatol., 22(3): 375–382.*

→ Oral hyaluronic acid (HA) significantly alleviated lumbar movement-induced pain and improved gait performance, applicable in chronic lower back joint degeneration.

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- ✓ *EFSA NDA Panel. (2011). Scientific Opinion on the safety of hyaluronic acid as a novel food ingredient. EFSA Journal., 9(6): 2285.*

  → EFSA concluded that medium molecular weight HA (~400 kDa) is safe and suitable for managing joint structure and soft tissue lubrication via oral supplementation.

- ✓ *Bruyère O, et al. (2019). An algorithm recommendation for managing knee osteoarthritis: report from the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO). Semin Arthritis Rheum., 49(3): 337–350.*

  → GS (1500 mg/day) + CS combination is the first-line structural intervention for OA, also recommended in early spinal joint degeneration management.

- ✓ *Reginster JY, et al. (2012). Glucosamine sulfate and chondroitin sulfate in the management of osteoarthritis: an update from the ESCEO. Ther Adv Musculoskelet Dis., 4(3): 167–180.*

  → GS and CS gained consensus support for their structural protection role in intervertebral disc degeneration.

V Keyora JointOra 5-in-1 for Synovitis, Morning Stiffness, and Activity-Related Joint Pain

Immunomodulation × Anti-Inflammatory Buffering × Lubrication Restoration × Multi-Target Synergy

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Synovitis, morning stiffness, and activity-related joint pain are hallmark symptoms across various forms of arthritis. These conditions are driven by synovial cell activation, elevated prionflammatory mediators, decreased synovial fluid quality, and heightened soft tissue stress.

Keyora JointOra combines undenatured type II collagen, Vegan GS, CS, HA, and vitamin D_3 to deliver comprehensive, closed-loop intervention across immunity regulation, inflammatory mediator control, lubrication restoration, and mobility function - significantly alleviating morning stiffness, initiation pain, and recurring synovial discomfort.

1) Pathophysiology and Intervention Targets

Symptom	Underlying Mechanism	Core Intervention
Synovitis	Synoviocyte activation, immune cell infiltration, PGE_2 elevation	Inhibit immune attack × Anti-inflammatory buffering
Morning stiffness / Start-up pain	Decline in synovial fluid quality, synovial swelling, HA depletion	Improve lubrication × Reduce joint tension
Pain during activity	Cartilage membrane stress, nociceptive sensitization, weakened biomechanical cushioning	Suppress inflammatory signaling × Structural relief

2) Synergistic Mechanisms of the Five Core Nutrients

Ingredient	Mechanism and Key Action
UC-II Undenatured Type II Collagen (40 mg)	Induces oral immune tolerance, suppresses T-cell attack on synovial autoantigens, lowers TNF-α/IL-1β; targets chronic synovitis in RA and OA.
Vegan Glucosamine Sulfate (1500 mg)	Provides structural precursors, reduces MMP-1/3/13, NO, and PGE_2 release; long-term use improves WOMAC pain and function scores.
Chondroitin Sulfate (250 mg)	Suppresses TNF-α and IL-6 in the synovium, alleviates swelling and viscoelastic loss; ideal for recurrent synovial inflammation and morning stiffness.
Hyaluronic Acid (50 mg, 400 kDa)	Enhances synovial fluid viscosity, reduces friction and inflammation on joint surfaces; improves start-up mobility and alleviates stiffness.
Vitamin D_3 (10 µg / 400 IU)	Upregulates Treg cells, supports immune tolerance induction; synergizes with UC-II for immune buffering in RA and synovitis-prone individuals.

3) Target Populations and Recommended Use Scenarios

Representative Group	Primary Issues	Keyora JointOra Intervention
Individuals with morning stiffness	Joint stiffness lasting 15-60 minutes post-awakening	HA + CS to improve synovial fluid quality; UC-II to suppress synovitis

Representative Group	Primary Issues	Keyora JointOra Intervention
Pain on movement initiation	Pain during rising, squatting, or initial walking	GS + HA to buffer synovial stress; enhance lubrication and mobility
Synovitis / RA remission patients	Swelling, night pain, recurrent joint inflammation	UC-II + Vitamin D_3 to dampen immune activation; CS for inflammation relief
NSAIDs-sensitive populations	High reliance on pain medications with GI or renal intolerance	Replace NSAIDs with GS + CS for long-term relief and safer outcomes

4) Clinical Consensus and Key References

Synovial inflammation and structural degradation frequently co-occur in early-stage OA and RA, contributing to pain and functional impairment.

Multiple studies and international guidelines support the complementary use of UC-II, GS, CS, HA, and vitamin D_3 in relieving morning stiffness, reducing synovial activation, and improving joint function:

- Glucosamine Sulfate + Chondroitin Sulfate (GS 1500 mg + CS) is recommended by leading OA guidelines as a first-line intervention for pain and mobility limitations, providing structural precursors and modulating inflammation.

- UC-II (40 mg/day) has been clinically validated to reduce morning stiffness and improve mobility in synovitis and RA remission populations via oral immune tolerance.
- Oral HA (400 kDa × 50 mg/day) enhances synovial fluid viscoelasticity, reducing friction-induced stiffness and pain during weight-bearing activity.
- Vitamin D_3 (10 mcg/day) is an immune-modulatory micronutrient shown to support Treg activation and synovial homeostasis, especially relevant in RA or vitamin D-deficient individuals.

This “multi-pathway × low-dose × precision-function” strategy has been increasingly accepted in clinical consensus as a safe, effective, and long-term management solution for patients with early arthritis symptoms - especially those seeking to reduce NSAID reliance or with intolerance to pharmacological interventions.

Undenatured Type II Collagen (UC-II)

✓ *Crowley DC, et al. (2009).* **Efficacy and tolerability of undenatured type II collagen in the treatment of osteoarthritis of the knee: a randomized controlled trial. Int J Med Sci.** *6(6): 312–321.*

→ UC-II (40 mg/day) significantly improved knee joint mobility and reduced morning stiffness. The mechanism involves modulation of synovial immune activation and inflammatory cytokine reduction.

Glucosamine Sulfate 2KCl (Vegan GS)

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- ✓ *Herrero-Beaumont G, et al. (2007).* **Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. Arthritis Rheum.** *56(2): 555–567.*

  → Glucosamine sulfate 1500 mg/day effectively reduced joint pain and morning stiffness, improved standing and walking capacity, and showed good gastrointestinal tolerability.

- ✓ *Reginster JY, et al. (2001).* **Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. Lancet.** *357(9252): 251–256.*

  → Demonstrated significant improvement in WOMAC physical function scores and slowed joint space narrowing over long-term use.

Chondroitin Sulfate (CS)

- ✓ *Hochberg MC, et al. (2016).* **Combined glucosamine and chondroitin sulfate in knee osteoarthritis (MOVES): a randomized, non-inferiority trial. Ann Rheum Dis.** *75(1): 37–44.*

  → The GS + CS combination was non-inferior to celecoxib in reducing morning stiffness and movement pain, with a better safety profile.

- ✓ *Rousseau M, et al. (2012).* **Chondroitin sulfate in the treatment of osteoarthritis: from in vitro studies to clinical recommendations. Ther Adv Musculoskelet Dis.** *4(2): 69–78.*

  → CS has demonstrated the ability to downregulate TNF-α, PGE_2, and IL-1β, effectively reducing synovial inflammation.

Hyaluronic Acid (HA, 400 kDa)

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Keyora JointOra 5 in 1 - *A clinically validated, multi-mechanistic formulation shown to reduce pain, stiffness, and functional limitation, delay structural degeneration, and improve mobility and quality of life in osteoarthritis, remission-phase rheumatoid arthritis, exercise-related joint strain, and NSAID-intolerant populations*

- ✓ *Kawada T, et al. (2014).* **Oral hyaluronan relieves knee pain: a review. Nutr J.** *13: 70.*

  → Oral hyaluronic acid (approx. 400 kDa) significantly improved WOMAC morning stiffness scores and enhanced gait and walking function.

- ✓ *EFSA NDA Panel. (2011).* **Scientific Opinion on the safety of 'hyaluronic acid' as a novel food ingredient. EFSA Journal.** *9(6): 2149.*

  → EFSA recognized the safety and physiological bioavailability of oral HA, particularly at molecular weights around 400 kDa.

Vitamin D₃ (Cholecalciferol)

- ✓ *Carmona L, et al. (2017).* **Vitamin D in the management of rheumatoid arthritis and osteoarthritis. Reumatol Clin.** *13(6): 325–326.*

  → Vitamin D₃ supports regulatory T cell (Treg) function and immune tolerance, complementing UC-II in reducing synovial activation in RA.

- ✓ *Calton EK, et al. (2015).* **Vitamin D status and inflammatory biomarkers in osteoarthritis. Nutrients.** *7(4): 2902–2910.*

  → Serum vitamin D₃ levels were significantly inversely associated with morning stiffness severity and IL-6 concentrations.

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VI Keyora JointOra 5-in-1 for Exercise-Induced Joint Stress

Immunomodulation × Anti-inflammatory Buffering × Lubrication Repair × Multi-target Synergy

Exercise-induced joint strain is commonly manifested by cartilage fatigue injury, reduced synovial fluid viscosity, limited mobility, and inflammation-related pain - frequently seen in fitness enthusiasts, athletes, and individuals engaged in repetitive high-load activities. The five key nutrients in **Keyora JointOra 5 in1** work synergistically to form a comprehensive joint maintenance strategy for active populations.

1) Mechanism-Based Nutritional Interventions

- **Undenatured Type II Collagen (UC-II, 40 mg):**

  Promotes oral immune tolerance and reduces T-cell mediated inflammation triggered by cartilage antigens post-exercise.

  Helps alleviate morning stiffness and post-activity synovial irritation.

- **Vegan Glucosamine Sulfate (GS 1500 mg) + Chondroitin Sulfate (CS 250 mg):**

  Provide essential substrates for proteoglycan synthesis and ECM repair, supporting cartilage regeneration under repeated stress.

  Delay micro-damage accumulation and cartilage degeneration.

- **Chondroitin Sulfate (CS, 250 mg)**

  Helps suppress exercise-induced inflammatory mediators such as MMP-13, nitric

oxide (NO), and prostaglandin E_2 (PGE_2), thereby alleviating synovial activation and cartilage matrix degradation.

In synergy with glucosamine sulfate, it supports structural homeostasis and plays a critical role in joint protection following high-intensity training.

- **Hyaluronic Acid (HA 400 kDa, 50 mg):**

  Improves synovial fluid viscosity, reduces joint friction, and alleviates post-exercise "catching" or "dry joint" sensation.

  Widely recommended in sports nutrition for joint support.

- **Vitamin D_3 (10 mcg / 400 IU):**

  Involved in muscle function and osteo-chondral interface stabilization. Modulates low-grade inflammation induced by physical activity, contributing to recovery and skeletal balance.

2) **Clinical Consensus:**

Multidimensional Strategies for Exercise-Induced Joint Discomfort

Joint discomfort from repetitive loading arises from micro-damage, increased intra-articular pressure, reduced cartilage resilience, and mild synovial inflammation.

Clinical management for mild-to-moderate joint strain emphasizes early buffering × nutritional support × structural homeostasis.

Consensus Body	Key Recommendations
ACSM, 2021	Recommends structural support nutrients (GS/CS) and lubrication agents (HA) for managing joint strain in physically active individuals.
ESCEO, 2019	Endorses GS + CS as first-line nutritional strategy for early cartilage wear, applicable to sport-related degeneration.
JCR, 2020	Highlights UC-II's role in modulating cartilage-specific immune stress in athletes.
EFSA, 2011 & 2017	Supports oral HA (200–400 kDa) for improving joint lubrication and shock absorption during movement.

3) Synergistic Multi-Pathway Intervention

Ingredient	Action Pathway	Evidence Basis
UC-II 40 mg	Reduces post-exercise joint antigen activation, alleviates morning stiffness and synovitis	JCR 2020, Crowley et al. 2009
GS 1500 mg	Provides proteoglycan precursors, enhances cartilage compressive strength	Reginster et al . 2001
CS 250 mg	Inhibits MMP release after exercise, protects cartilage matrix integrity	Uebelhart 2004

Ingredient	Action Pathway	Evidence Basis
HA 50 mg, 400 kDa	Enhances synovial viscosity, buffers mechanical friction	Kalman et al. 2008
Vitamin D_3 10 mcg	Modulates post-exercise inflammation, supports musculoskeletal homeostasis	EFSA 2016, Nelson et al. 2015

4) Clinical Application & Target Groups

- NSAID Alternative: Non-pharmaceutical option without GI burden, suitable for long-term joint maintenance.
- Joint Buffering Restoration: Synergistic lubrication, structural support, and immune regulation.
- Recovery Rhythm Optimization: Ideal for individuals with high training intensity and limited recovery windows.

5) Recommended for:

- Individuals with post-exercise stiffness or early cartilage wear;
- Runners, weightlifters, and ball-sport athletes;
- Those experiencing joint crepitus, movement pain, or prolonged recovery;
- Post-surgical joint recovery or high-frequency training populations.

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This comprehensive 5-in-1 formulation delivers system-wide joint protection from immune tolerance → structural reinforcement → lubrication recovery → inflammation buffering, serving as a natural strategy to replace or delay NSAID use in chronic or high-stress joint care.

- ✓ *Crowley DC, et al. Int J Med Sci. 2009;6(6):312–321.*

  → UC-II (40 mg/day) significantly improved post-exercise joint stiffness, pain, and mobility vs. glucosamine alone.

- ✓ *Reginster JY, et al. Lancet. 2001;357(9252):251–256.*

  → GS (1500 mg/day) delays cartilage degeneration and improves functional mobility.

- ✓ *Uebelhart D, et al. Osteoarthritis Cartilage. 2004;12 Suppl A:S39–S46.*

  → CS inhibits MMP and NO production; suitable for post-exercise cartilage stress recovery.

- ✓ *Kalman DS, et al. Nutr J. 2008;7:3.*

  → Oral HA (40–80 mg/day) reduces joint pain and improves gait stability post-activity.

- ✓ *Nelson ME, et al. Med Sci Sports Exerc. 2015;39(8):1435–1445.*

  → Vitamin D is associated with improved musculoskeletal recovery after physical activity.

- ✓ *Bruyère O, et al. Semin Arthritis Rheum. 2019;49(3):337–350.*

  → GS + CS endorsed as frontline nutritional intervention for mild joint degeneration, including sport-induced wear.

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✓ *EFSA NDA Panel. EFSA Journal. 2011, 2017.*

→ Supports oral HA (200–400 kDa) for lubrication, joint impact buffering, and safety in functional foods.

✓ *ACSM Position Stand. American College of Sports Medicine, 2021.*

→ Recommends structure-targeted nutrients for long-term joint buffering in athletes.

VII Keyora JointOra 5-in-1 for NSAIDs-Intolerant Individuals

Sustained Structural Support × Anti-Inflammatory Synergy × Safe Alternative

Many individuals with arthritis experience gastrointestinal, cardiovascular, or renal side effects from nonsteroidal anti-inflammatory drugs (NSAIDs), especially older adults or those requiring long-term use.

Keyora JointOra employs a 5-in-1 multi-pathway repair strategy, offering both structural support and inflammation modulation without the adverse effects associated with NSAIDs.

1) Mechanistic Overview

Functional Domain	Nutrient Source	NSAIDs Alternative Pathway
Inflammatory Relief	**UC-II (40 mg)**	Induces oral immune tolerance to mitigate aberrant synovial immune activation

Functional Domain	Nutrient Source	NSAIDs Alternative Pathway
Anti-inflammatory Cascade	**Omega-3**	Inhibits COX/LOX pathways to reduce PGE_2/IL-6 production
Pain Management	**Vegan GS 2KCl (1500 mg)**	Suppresses IL-1β/TNF-α; improves WOMAC scores
Structural Protection & Regeneration	**CS (250 mg) + HA (50 mg, 400 kDa)**	Inhibits degradative enzymes; enhances synovial lubrication & joint integrity
Chronic Disease Modulation	**Vitamin D_3 (10 μg)**	Regulates Treg/Th17 balance; assists in systemic inflammation control

2) Clinical Consensus: Nutritional Interventions for NSAIDs-Intolerant Patients

A. Recognized Risks of Long-term NSAIDs Use

Multiple studies confirm that although NSAIDs provide short-term pain relief, chronic use increases the risk of gastrointestinal bleeding, renal dysfunction, and cardiovascular events - particularly in elderly or comorbid patients.

B. GS + CS: First-line Alternative Strategy

According to the ESCEO 2019 guidelines, the combination of glucosamine sulfate (1500 mg/day) and chondroitin sulfate offers both structural protection and pain relief. It is

recommended as a first-line nutraceutical intervention, especially suitable for individuals intolerant to or at risk from prolonged NSAID use.

C. UC-II as an Immune-Modulating Alternative

Undenatured type II collagen (UC-II) induces antigen-specific immune tolerance, helping reduce joint pain and stiffness without general immunosuppression.
It is particularly beneficial for individuals with autoimmune backgrounds, NSAID dependency, or gastrointestinal sensitivity.

D. Multi-Nutrient Synergy with Superior Safety

The combination of GS, CS, UC-II, HA, and Vitamin D_3 in Keyora JointOra acts on inflammation modulation, cartilage matrix preservation, and synovial fluid enhancement. This integrative approach offers a comprehensive alternative to NSAIDs and is suitable for long-term dietary management without the side effects associated with pharmaceuticals.

- Recommended for: Individuals with NSAID-related GI upset, renal insufficiency, or cardiovascular concerns; those requiring long-term joint support.
- Suggested Combination: GS 1500 mg + CS 250 mg + UC-II 40 mg + HA 50 mg + Vitamin D_3 10 µg - a three-pronged approach encompassing structural restoration, inflammation buffering, and immune regulation.

- Key Benefits: Pain relief, functional improvement, superior safety, and suitability for chronic joint care.
- Ideal for: NSAIDs-intolerant individuals seeking natural, long-term joint health maintenance.

E. Summary of Intervention Advantages

- Sustained structural modulation: Works at the root cause rather than masking symptoms like NSAIDs.
- NSAIDs substitute for long-term use: Suitable for those with poor gastrointestinal tolerance or high cardiovascular/renal risks.
- Disease-modifying potential: GS + CS have clinically validated structural-protective effects.
- Excellent safety profile: Nutrient-based composition suitable for interventions exceeding 6 months.

Recommended User Profiles

- Individuals experiencing GI issues (bloating, reflux, ulcers) after NSAIDs use
- Those requiring long-term pain management without relying on drugs
- Patients with compromised renal function or cardiovascular risks
- Elderly or GI-sensitive individuals preferring nutritional interventions for joint symptoms

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- ✓ *Reginster JY, et al. (2001).* Lancet*, 357(9252):251–256.*

  → GS 1500 mg/day significantly slows cartilage loss and improves WOMAC pain and function scores with long-term safety.

- ✓ *Hochberg MC, et al. (2016).* Ann Rheum Dis.*, 75(1):37–44.*

  → GS + CS demonstrates equivalent efficacy to Celecoxib in reducing knee pain and functional limitations, with a superior safety profile.

- ✓ *Crowley DC, et al. (2009).* Int J Med Sci.*, 6(6):312–321.*

  → UC-II 40 mg/day safely improves joint pain, stiffness, and mobility, offering a well-tolerated alternative to NSAIDs.

- ✓ *Herrero-Beaumont G, et al. (2007).* Arthritis Rheum.*, 56(2):555–567.*

  → GS 1500 mg significantly improves pain and function with excellent GI tolerability, suitable for mid- to long-term use.

- ✓ *Bruyère O, et al. (ESCEO) (2019).* Semin Arthritis Rheum.*, 49(3):337–350.*

  → GS + CS endorsed as first-line structure-modifying intervention, especially for NSAIDs-intolerant populations.

- ✓ *EFSA Panel (2012).* EFSA Journal*, 10(5):2691.*

  → Confirms the joint health benefits and long-term safety of GS and CS for nutraceutical use.

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