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# Nutritional Supplements, Therapeutic Compounds and Medications in Musculoskeletal, Metabolic and Longevity Medicine: Sources, Efficacy, Dosage, Safety and the Unfinished Search for a Disease-Modifying Osteoarthritis Drug a Critical, Evidence-Graded Review with an Embedded Citation-Integrity Audit

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## Abstract

**Background:** Nutritional supplements, botanical extracts, amino-acid formulations and repurposed prescription drugs are used by a large fraction of adults with musculoskeletal and metabolic disease, frequently without the prescriber's knowledge and almost always outside the regulatory framework that governs medicines. The global dietary-supplement market now exceeds one hundred billion United States dollars annually [1], yet the evidence supporting individual agents ranges from multiple adequately powered randomised trials to single uncontrolled series, and the published summaries that clinicians rely on often propagate citation errors that invert the conclusion of the underlying trial.

**Objectives:** To provide a single, evidence-graded synthesis of the compounds most often encountered in musculoskeletal, metabolic

and longevity practice; to anchor every efficacy statement to a minimal clinically important difference (MCID) rather than to statistical significance alone; to extend the review to thirty additional nutraceuticals and to the prescription and longevity compounds increasingly used off label; to summarise the entire disease-modifying osteoarthritis drug (DMOAD) development record; and to audit the reference list of a representative narrative summary in order to quantify how often citations are misattributed.

**Methods**: Structured searches of PubMed, Cochrane CENTRAL, ClinicalTrials.gov, the European Union Register of nutrition and health claims, EFSA opinions, US Food and Drug Administration (FDA) labels and guidance documents, the LiverTox database and six major clinical practice guidelines were performed to 15 August 2026. Each agent was graded for evidence quality (A to D) and for whether the pooled effect crossed an accepted MCID. Seventeen references from a representative narrative summary were retrieved in full and compared against the claim they were cited to support.

**Results:** Of the agents reviewed, a minority reach Grade A evidence with an effect that exceeds the MCID: icosapent ethyl for residual cardiovascular risk, vitamin D and calcium for fracture prevention in institutionalised or deficient populations, creatine monohydrate for resistance-training adaptation, and semaglutide for pain in knee osteoarthritis with obesity. A larger group – glucosamine, chondroitin, collagen peptides, hyaluronic acid, curcumin, boswellia, ginger and most single-nutrient antioxidants – shows either a statistically detectable effect that falls below the MCID, or an effect confined to industry-funded or high-risk-of-bias trials. Several widely sold agents carry documented harm: high-dose beta-carotene in smokers, selenium and diabetes risk, vitamin E and prostate cancer, green tea catechins and red yeast rice and hepatotoxicity, and ashwagandha-associated cholestatic hepatitis. No DMOAD has been approved by any regulatory authority; fourteen development programmes are reviewed, the FDA structural-endpoint guidance remains in draft eight years after issue, and the lorecivivint New Drug Application submitted on 6 January 2026 follows three phase 3 trials that each missed their primary endpoint. The citation audit found four of seventeen references (23.5%) misattributed, including one in which the cited trial's primary endpoint was null and one in which the cited author explicitly refutes the claim.

**Conclusions**: Supplement and off-label prescribing in this field should be organised around a four-tier framework: recommend, discuss, do not recommend, and actively advise against. Evidence quality and MCID attainment must be assessed jointly, product quality must be verified independently of the label, and every citation in a clinical summary must be read in full before it is used. The absence of an approved DMOAD after three decades of development is the single most important context for any conversation about supplements for joint disease.

## Keywords

Dietary supplements; Nutraceuticals; Osteoarthritis; Disease-modifying osteoarthritis drugs; Glucosamine; Vitamin D; Omega-3 fatty acids; Curcumin; Metformin; Minimal clinically important difference; Citation accuracy; Regenerative medicine.

## Abbreviations

AKBA, 3-O-acetyl-11-keto-β-boswellic acid; AMPK, AMP-activated protein kinase; AREDS2, Age-Related Eye Disease Study 2; BCAA, branched-chain amino acids; BMD, bone mineral density; CYP, cytochrome P450; DHA, docosahexaenoic acid; DILIN, Drug-Induced Liver Injury Network; DMOAD, disease-modifying osteoarthritis drug; DSHEA, Dietary Supplement Health and Education Act; EFSA, European Food Safety Authority; EGCG, epigallocatechin-3-gallate; EPA, eicosapentaenoic acid; ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; GlyNAC, glycine plus N-acetylcysteine; HMB, β-hydroxy-β-methylbutyrate; INR, international normalised ratio; MCID, minimal clinically important difference; NAD+, nicotinamide adenine dinucleotide; NMN, nicotinamide mononucleotide; OA, osteoarthritis; pCGS, patented crystalline glucosamine sulfate; PRP, platelet-rich plasma; SMD, standardised mean difference; TMAO, trimethylamine N-oxide; UC-II, undenatured type II collagen; WADA, World Anti-Doping Agency; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

## Introduction

The consultation in which a patient with knee osteoarthritis, low back pain or sarcopenia asks what they should be taking is now among the most common encounters in musculoskeletal practice, and it is also among the least well served by the literature. The clinician is asked to compare, in a few minutes, agents whose evidence bases differ by three orders of magnitude in size and by a similar factor in quality, whose

regulatory status differs between the United States, the European Union and Brazil, and whose labelled content may bear little relation to what the capsule contains [2,3].

Three structural problems make this comparison harder than it appears. The first is that statistical significance and clinical relevance have been allowed to merge. A meta-analysis of forty trials with fifteen thousand participants can produce a highly significant pooled effect on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale that is nonetheless smaller than the difference a patient can perceive. The minimal clinically important difference for WOMAC pain lies between roughly 9 and 15 points on a 0 to 100 normalised scale, and the OARSI clinical-trials recommendations and the Cochrane osteoarthritis group both advise interpreting pooled effects against such an anchor rather than against a p value [4,5]. Much of the supplement literature reports the p value and omits the anchor.

The second problem is that the field has confused symptom modification with structure modification. Patients and clinicians frequently understand a supplement or injection to be repairing cartilage. In fact, no agent of any class – nutraceutical, small molecule, biologic, gene therapy or orthobiologic – has been approved anywhere in the world on the basis of a structural claim in osteoarthritis [6–8]. The regulatory pathway for such a claim in the United States is still defined only by a draft guidance issued in August 2018 and never finalised [9].

The third problem is citation integrity. Narrative summaries of this material circulate widely, are copied into patient handouts and clinic protocols, and are rarely audited. In the course of preparing this review a representative seventeen-reference summary was checked line by line against the primary sources. Four references did not support the claim attached to them, and in two cases the cited source contradicted it. Because that failure mode is invisible to the reader and reproduces itself with every reuse, the audit is reported here as a formal result rather than as an aside (Section 12).

This review therefore has a deliberately wide scope. It covers the essential nutrients and antioxidants, the joint and connective-tissue agents, the anti-inflammatory botanicals, the amino acids and ergogenic compounds, thirty additional nutraceuticals that were not part of the original framing but that patients routinely present, the prescription and longevity compounds now used off label in this space, and the complete DMOAD development record. It closes with the regulatory and product-quality context, the citation audit, and a four-tier practical framework.

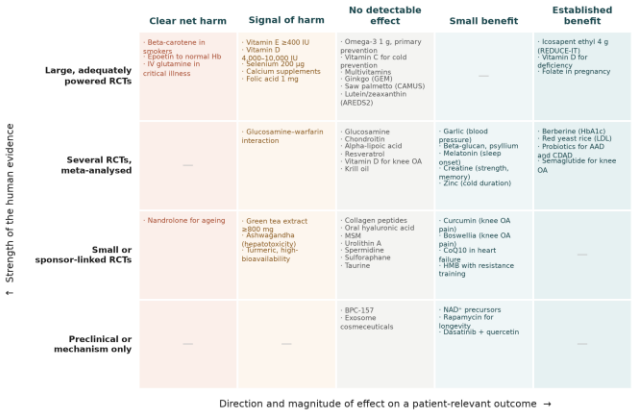


**Figure 1:** Evidence quality plotted against clinical effect size for the principal agents reviewed. Vertical position denotes evidence grade (A, multiple adequately powered randomised trials or high-quality meta-analysis; B, randomised evidence with important limitations; C, small or high-risk-of-bias randomised data; D, observational, mechanistic or preclinical only). Horizontal position denotes whether the pooled effect reaches an accepted minimal clinically important difference. Only agents in the upper-right quadrant justify unprompted recommendation. Constructed from the evidence tabulated in Sections 3 to 9.

# Methods

## Search strategy

PubMed, Cochrane CENTRAL and the Cochrane Database of Systematic Reviews were searched from inception to 15 August 2026 for each agent, combining the compound name and its principal synonyms with terms for the indications of interest (osteoarthritis, low back pain, sarcopenia, osteoporosis, cardiovascular prevention, cognition, longevity) and with study-design filters for randomised controlled trial, systematic review and meta-analysis. ClinicalTrials.gov was queried for all interventional osteoarthritis studies with a structural endpoint, and the resulting registry records were retained. Regulatory sources were searched directly rather than through secondary citation: FDA labels via DailyMed and Drugs@FDA, FDA guidance and advisory-committee materials, EFSA scientific opinions, the European Union Register of nutrition and health claims, the Brazilian ANVISA resolutions on food supplements, and the World Anti-Doping Agency (WADA) Prohibited List for 2026. Hepatotoxicity signals were checked against LiverTox and the US Drug-Induced Liver Injury Network (DILIN) reports.

## Evidence grading

Each agent-indication pair was assigned one of four grades. Grade A denotes at least two adequately powered randomised controlled trials with concordant results, or one high-quality meta-analysis of such trials with low heterogeneity. Grade B denotes randomised evidence with important limitations: single trial, imprecision, indirectness, or substantial heterogeneity. Grade C denotes small randomised trials at high risk of bias, typically single-centre, industry-funded, under 100 participants, or under twelve weeks in duration. Grade D denotes observational, mechanistic, animal or in-vitro evidence only. Where a Cochrane review and a later industry-funded meta-analysis disagreed, both are reported and the discordance is named rather than resolved by preference.

## MCID anchoring

Efficacy was judged against the following anchors, which are applied consistently throughout. For pain in osteoarthritis: 9 to 15 points on the normalised 0 to 100 WOMAC or visual analogue pain scale, or a standardised mean difference of approximately 0.37, the threshold below which the Cochrane group regards an effect as clinically irrelevant [5]. For radiographic structure: 0.4 mm of joint-space width, the smallest change reliably detectable and plausibly meaningful over three years. For cartilage thickness on magnetic resonance imaging: approximately 100 µm. For grip strength: 5 kg. For gait speed: 0.1 m/s. For lumbar spine or femoral neck bone mineral density: 3%. Any statement in this review that an agent 'works' means that the pooled point estimate crosses the relevant anchor and that the confidence interval does not include a trivial effect.

### Citation audit method

A representative seventeen-reference narrative summary of supplements and medications in this field was selected. Every reference was retrieved in full text where available, or in abstract with registry cross-check where not. Each was classified as CONFIRMED (the source states the claim), PARTIALLY WRONG (the source exists and is broadly on topic but does not support the specific claim, has been superseded, or reports a null primary endpoint that the claim ignores) or NOT FOUND (no such source could be identified). Bibliographic conventions were also checked, since MDPI journals use article numbers rather than page ranges and Cochrane reviews require a year-prefixed issue number and a pub-version suffix. Results appear in Section 12 and (**Table 14**).

| Anchor | Domain | Threshold used in this review | Basis |
|---|---|---|---|
| **WOMAC / VAS pain** | Osteoarthritis symptoms | 9–15 points on a 0–100 normalised scale; SMD ≈ 0.37 | OARSI trial recommendations; Cochrane osteoarthritis group [4,5] |
| **Joint-space width** | Radiographic structure | 0.4 mm over 2–3 years | Smallest reliably detectable change; FDA draft guidance [9] |
| **Cartilage thickness (MRI)** | Structural imaging | approximately 100 µm | Structural-endpoint literature [10] |
| **Grip strength** | Sarcopenia and muscle | 5 kg | Sarcopenia consensus literature [11] |
| **Gait speed** | Physical function | 0.1 m/s | Sarcopenia consensus literature [11] |
| **Bone mineral density** | Osteoporosis | 3% at lumbar spine or femoral neck | Least significant change on serial DXA [12] |
| **LDL cholesterol** | Cardiometabolic | reduction of 10% or more | Lipid-guideline convention [13] |
| **Systolic blood pressure** | Cardiometabolic | 5 mmHg | Hypertension outcome-trial convention [14] |

**Table 1:** Minimal clinically important difference anchors applied throughout this review. Every efficacy statement in Sections 3 to 9 is judged against the anchor for its domain rather than against statistical significance alone.

### What this review is not

This is a critical narrative review with systematic search elements, not a systematic review conducted to PRISMA. No new meta-analysis was performed; pooled estimates are taken from the cited syntheses and are reported with their original confidence intervals. No formal GRADE assessment with summary-of-findings tables was produced. The grading scheme in Section 2.2 is explicit but is the authors' own operationalization.

## Essential Nutrients and Antioxidants

### Omega-3 fatty acids

Marine omega-3 fatty acids are the best-studied supplement in medicine and also the clearest

demonstration that dose, formulation and endpoint determine everything. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are obtained from oily fish, fish oil, krill oil and algal oil; typical general-health doses of 1 g/day of combined EPA plus DHA are pharmacologically distinct from the 4 g/day of purified EPA ethyl ester used in cardiovascular outcome trials [15].

At the low dose, the evidence is essentially null for hard outcomes. The ASCEND trial randomised 15,480 adults with diabetes to 1 g/day of omega-3 or placebo and found no reduction in serious vascular events (8.9% versus 9.2%; rate ratio 0.97, 95% CI 0.87 to 1.08) [16]. VITAL randomised 25,871 adults to 1 g/day of marine omega-3 and found no reduction in the primary composite cardiovascular endpoint (hazard ratio 0.92, 95% CI 0.80 to 1.06) [17]. The 2020 Cochrane review of 86 trials in over 162,000 participants concluded that increasing long-chain omega-3 intake has little or no effect on all-cause mortality (relative risk 0.98) or cardiovascular events, with high-certainty evidence for several of those outcomes [18].

At the high dose, and only with purified EPA, the picture changes. REDUCE-IT randomised 8,179 statin-treated patients with elevated triglycerides to icosapent ethyl 4 g/day and reported a 25% relative reduction in the primary composite endpoint (17.2% versus 22.0%; hazard ratio 0.75, 95% CI 0.68 to 0.83; p<0.001) [19]. The comparably designed STRENGTH trial, which used a mixed EPA/DHA carboxylic acid preparation with a corn-oil comparator, was stopped for futility with no benefit (hazard ratio 0.99) [20], and OMEMI in post-infarction older adults was likewise null [21]. Whether the REDUCE-IT result reflects EPA specificity or the mineral-oil placebo remains contested; the two trials cannot both be generalised.

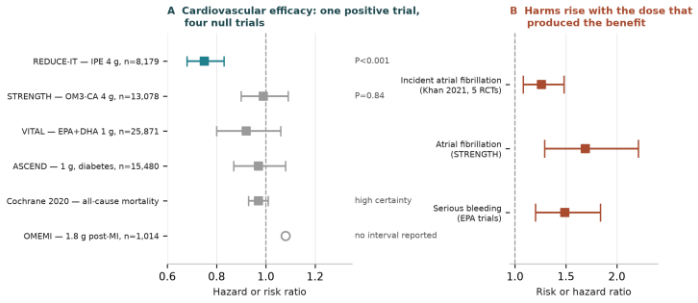


**Figure 2:** Omega-3 fatty acid randomised outcome trials arranged by dose and formulation. Low-dose mixed EPA/DHA preparations (ASCEND, VITAL, OMEMI) show no effect on the primary cardiovascular endpoint; only purified high-dose EPA (REDUCE-IT) crosses the line of no effect, and the comparably powered STRENGTH trial of mixed EPA/DHA carboxylic acids did not. Point estimates and 95% confidence intervals as reported in the source publications.

For joint pain specifically, the effect of omega-3 is small. Pooled analyses in rheumatoid arthritis show a modest reduction in tender-joint count and NSAID sparing; in osteoarthritis the data are weaker and largely do not cross the MCID. Higher doses increase the risk of atrial fibrillation across trials, an effect that is now consistent enough to be considered in shared decision-making [19,20]. Bleeding risk at doses up to 4 g/day is small but relevant perioperatively [22]. Practical dosing: 1 g/day combined EPA plus DHA for general intake, with 2 to 4 g/day of purified EPA reserved for the specific hypertriglyceridaemia-plus-statin indication in which it was tested.

| Trial | n | Agent and dose | Population | Primary endpoint result |
|---|---|---|---|---|
| **REDUCE-IT** | 8,179 | Icosapent ethyl 4 g/day (purified EPA) | Statin-treated, triglycerides 1.52–5.63 mmol/L | 17.2% vs 22.0%; HR 0.75 (0.68–0.83); p<0.001 [19] |
| **STRENGTH** | 13,078 | Mixed EPA/DHA carboxylic acids 4 g/day | High cardiovascular risk, high triglycerides | HR 0.99 (0.90–1.09); stopped for futility [20] |
| **ASCEND** | 15,480 | EPA+DHA 1 g/day | Diabetes without cardiovascular disease | 8.9% vs 9.2%; RR 0.97 (0.87–1.08) [16] |
| **VITAL (omega-3 arm)** | 25,871 | Marine omega-3 1 g/day | General population, age 50+/55+ | HR 0.92 (0.80–1.06); not significant [17] |
| **OMEMI** | 1,027 | EPA+DHA 1.8 g/day | Age 70–82, 2–8 weeks post-infarction | 21.4% vs 20.0%; HR 1.08; null [21] |
| **Cochrane 2020** | 162,796 (86 trials) | Long-chain omega-3, various | Pooled | All-cause mortality RR 0.98; little or no effect [18] |

**Table 2:** Randomised cardiovascular outcome trials of marine omega-3 fatty acids. Only the purified high-dose EPA formulation reached its primary endpoint; the comparably powered mixed EPA/DHA trial at the same total dose did not.

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; HR, hazard ratio; RR, rate ratio.

Two further syntheses frame the class. The umbrella meta-analysis of omega-3 randomised trials across 149,051 participants found a small reduction in cardiovascular mortality driven largely by the high-dose EPA trials [23], and the mechanistic review of triglyceride lowering, membrane incorporation and eicosanoid signalling explains why biomarker effects have not translated into event reduction at nutritional doses [24]. For joint disease specifically, the KARAOKE randomised trial of krill oil in knee osteoarthritis found a between-group difference of −0.3 (95% CI −6.9 to 6.4), an unambiguously null result in the marine-lipid class [25].

## Vitamin C

Ascorbic acid is an essential cofactor for prolyl and lysyl hydroxylase and therefore for collagen cross-linking, which is the mechanistic argument advanced for its use in tendon and cartilage health. Sources are citrus fruit, peppers, brassicas and berries; the recommended dietary allowance is 90 mg/day for men and 75 mg/day for women, with a tolerable upper intake level of 2,000 mg/day [26].

The clinical evidence does not match the mechanism. For the common cold, the Cochrane review found no reduction in incidence in the general population (relative risk 0.97), a roughly 8% shortening of duration in adults, and a halving of incidence only in the special case of marathon runners, skiers and soldiers under acute physical stress [27]. The Physicians' Health Study II randomised 14,641 male physicians to 500 mg/day of vitamin C for eight years and found no effect on major cardiovascular events (hazard ratio 0.99) [28]. For musculoskeletal outcomes there is no adequately powered randomised evidence at all. Doses above about 1 g/day increase urinary oxalate and, in predisposed individuals, kidney-stone risk.

## Vitamin D

Vitamin D is the supplement whose interpretation depends most completely on the population studied. In deficiency, and particularly in institutionalised older adults receiving calcium concurrently, supplementation reduces fracture. In replete, community-dwelling adults it does not. Both statements

are supported by large randomised evidence, and conflating them is the commonest error in this literature.

VITAL randomised 25,871 adults to 2,000 IU/day of vitamin D3 and found no reduction in total, non-vertebral or hip fracture (hazard ratio 0.97, 95% CI 0.88 to 1.08) in a population that was largely replete and not selected for low bone mass [29,30]. The ViDA trial of monthly 100,000 IU in 5,110 adults was null for cardiovascular disease [31]. High monthly dosing of 60,000 IU produced no benefit and a signal of harm for falls in the DO-HEALTH and related programmes [32], and 4,000 versus 400 IU/day accelerated volumetric bone-mineral-density loss at the radius in a three-year randomised trial [33].

Where supplementation does work is in the fracture-prevention setting for which it was originally intended. Pooled analyses of vitamin D with calcium in older adults, predominantly institutionalised, show a reduction in hip and non-vertebral fracture that is absent when vitamin D is given alone [34,35]. For osteoarthritis structure and pain, the VIDEO and Australian randomised trials of vitamin D showed no effect on cartilage volume or WOMAC pain [36,37]. Practical dosing: 800 to 1,000 IU/day with calcium 1,000 mg/day in older adults at fracture risk; 1,000 to 2,000 IU/day to correct documented deficiency; no routine high-dose intermittent regimens; tolerable upper intake level 4,000 IU/day [12,38].

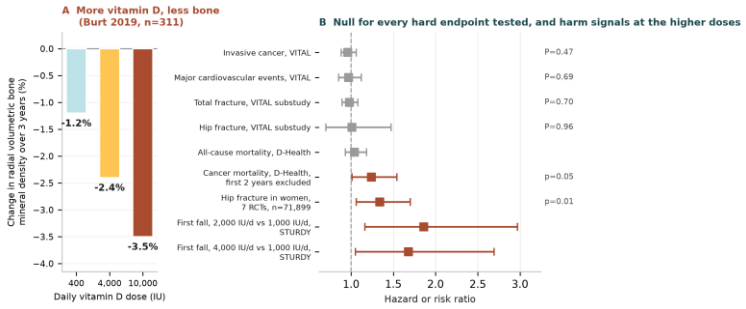


**Figure 3:** Vitamin D randomised trials by dose, population and endpoint. Fracture reduction appears only where vitamin D is combined with calcium in older, often institutionalised populations with low baseline status; trials in replete community-dwelling adults (VITAL, ViDA) are null, and high intermittent doses show a harm signal for falls and for radial bone mineral density.

| Trial or synthesis | n | Regimen | Endpoint | Result |
|---|---|---|---|---|
| **VITAL (bone)** | 25,871 | Vitamin D3 2,000 IU/day | Total fracture | HR 0.97 (0.88–1.08); null [29] |
| **VITAL (cancer/CVD)** | 25,871 | Vitamin D3 2,000 IU/day | Invasive cancer, major CVD | Both null [30] |
| **ViDA** | 5,110 | 100,000 IU monthly | Cardiovascular disease | Null [31] |
| **DO-HEALTH** | 2,157 | 2,000 IU/day ± omega-3 ± exercise | Blood pressure, function, fracture, cognition | No benefit on any co-primary endpoint [32] |
| **Burt 2019** | 311 | 400 vs 4,000 vs 10,000 IU/day, 3 years | Volumetric BMD at radius and tibia | Dose-dependent BMD loss with higher dose [33] |
| **Vitamin D + calcium pooled** | ≈ 46,000 | 700–800 IU/day + calcium 1,000 mg | Hip and non-vertebral fracture | Significant reduction; absent for vitamin D alone [34,35] |

**Table 3:** Vitamin D randomised evidence by population and endpoint. Fracture benefit is confined to the calcium co-administration setting in older adults with low baseline status; trials in replete community-dwelling populations are uniformly null, and high daily or intermittent dosing carries a harm signal.
BMD, bone mineral density; CVD, cardiovascular disease; HR, hazard ratio; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.


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Three further large trials complete this picture. The D-Health trial randomised 21,315 Australian adults to 60,000 IU monthly and found no reduction in all-cause mortality [39]. The STURDY trial tested four doses of vitamin D for fall prevention in older adults and found no dose superior to 200 IU/day, with a signal of harm at higher doses [40]. The Women's Health Initiative randomised 36,282 postmenopausal women to calcium 1,000 mg plus vitamin D 400 IU and found a small hip bone-density benefit without a significant reduction in hip fracture, alongside increased renal calculi [41].

## Vitamin E and the antioxidant harm signal

Alpha-tocopherol is the paradigm case of a supplement whose mechanistic plausibility survived its clinical trials. HOPE-TOO randomised 9,541 participants to 400 IU/day for a median of seven years and found no cardiovascular benefit and a significant increase in heart failure (relative risk 1.13, 95% CI 1.01 to 1.26) [42]. The meta-analysis of nineteen trials in 135,967 participants found a dose-dependent increase in all-cause mortality above 400 IU/day (risk difference 39 per 10,000) [43]. SELECT randomised 35,533 men to vitamin E 400 IU/day, selenium, both or neither, and reported a 17% increase in prostate-cancer incidence in the vitamin E arm (hazard ratio 1.17, 95% CI 1.004 to 1.36) [44,45].

The Meydani 2004 trial of vitamin E 800 IU/day in nursing-home residents is frequently cited as evidence of immune benefit. Its primary endpoint – the incidence of all respiratory tract infection – was not significantly reduced; the reported effect was confined to a secondary analysis of upper respiratory infection [46]. This is the first of the four misattributions catalogued in Section 12.

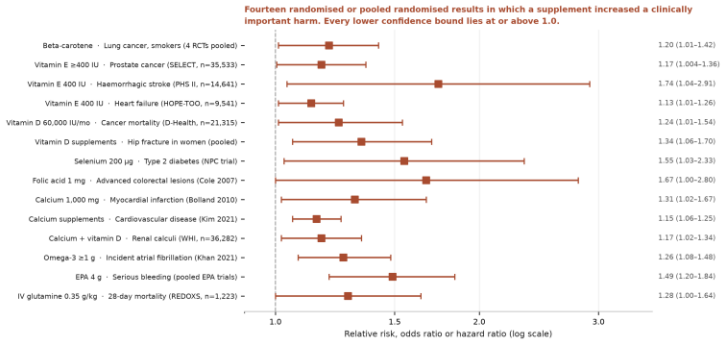


**Figure 4:** Documented harm signals from single-nutrient supplementation at supra-nutritional dose. Fourteen randomised or pooled estimates with 95% confidence intervals, all from trials designed to show benefit. Beta-carotene in smokers, vitamin E at 400 IU/day and above, selenium in replete populations, high-dose folic acid, calcium without vitamin D and high intermittent vitamin D each show measurable harm.

Other members of this class behave similarly. Beta-carotene increased lung-cancer incidence in smokers and asbestos-exposed workers in ATBC and CARET [47]. Selenium supplementation in replete populations increased type 2 diabetes incidence [48]. High-dose folic acid raised colorectal adenoma recurrence in the Aspirin/Folate Polyp Prevention Study [49]. Zinc above the 40 mg/day upper limit causes copper deficiency and, taken chronically, sideroblastic anaemia [50,51]. Calcium supplementation without vitamin D has been associated with a small excess of myocardial infarction [34]. The Aspirin/Folate Polyp Prevention Study result has been reported in full and remains the clearest randomised demonstration of harm from a water-soluble vitamin [52]. The generalisable lesson is that the therapeutic window for isolated

micronutrients is narrow and that the distance from recommended intake to demonstrated harm is often less than one order of magnitude.

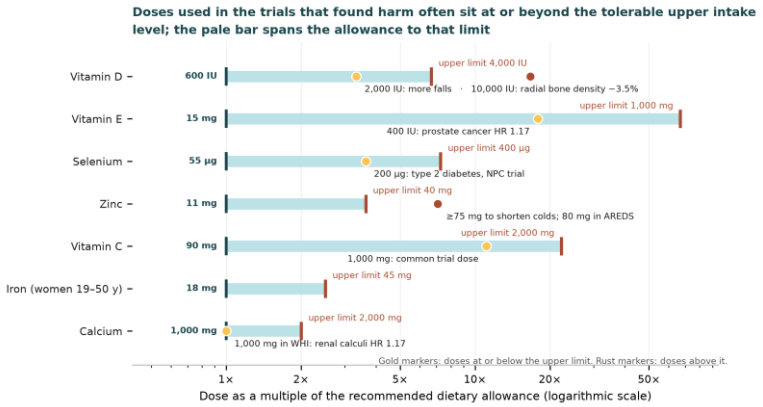


**Figure 5:** Therapeutic window for selected micronutrients on a logarithmic scale, from recommended dietary allowance through tolerable upper intake level to the lowest dose at which harm has been demonstrated in a randomised trial. For vitamin E, selenium and beta-carotene the harm dose lies within a factor of ten of the recommended intake.

| Nutrient | RDA (adult) | Tolerable upper intake | Dose at which harm shown | Harm demonstrated |
|---|---|---|---|---|
| **Vitamin E** | 15 mg (22 IU) | 1,000 mg (1,500 IU) | 400 IU/day | Heart failure RR 1.13; prostate cancer HR 1.17; mortality risk difference +39/10,000 [42–44] |
| **Beta-carotene** | No RDA | Not established | 20–30 mg/day | Increased lung cancer in smokers and asbestos-exposed workers [47] |
| **Selenium** | 55 µg | 400 µg | 200 µg/day | Increased type 2 diabetes incidence in replete adults [45,48] |
| **Vitamin C** | 75–90 mg | 2,000 mg | >1,000 mg/day | Hyperoxaluria and nephrolithiasis in predisposed individuals [26] |
| **Zinc** | 8–11 mg | 40 mg | >40 mg/day chronic | Copper deficiency, sideroblastic anaemia, neutropenia [50,51] |
| **Folic acid** | 400 µg DFE | 1,000 µg (synthetic) | 1,000 µg/day | Increased colorectal adenoma recurrence [49] |
| **Vitamin D** | 600–800 IU | 4,000 IU | ≥ 4,000 IU/day; 500,000 IU annually | Radial BMD loss; increased falls and fractures with intermittent high dose [12,33] |
| **Calcium (supplemental)** | 1,000–1,200 mg | 2,000–2,500 mg | 500–1,000 mg/day without vitamin D | Small excess of myocardial infarction; nephrolithiasis [34] |
| **Vitamin A (retinol)** | 700–900 µg RAE | 3,000 µg | >1,500 µg/day chronic | Reduced bone mineral density, hepatotoxicity, teratogenicity [53] |

**Table 4:** Therapeutic window for micronutrients where randomised or pooled evidence demonstrates harm. For vitamin E, selenium and beta-carotene the demonstrated harm dose lies within one order of magnitude of the recommended dietary allowance.

RDA, recommended dietary allowance; DFE, dietary folate equivalents; RAE, retinol activity equivalents; RR, relative risk; HR, hazard ratio.

## Coenzyme Q10

Ubiquinone and its reduced form ubiquinol are electron carriers in the mitochondrial respiratory chain and endogenous lipid-phase antioxidants; endogenous synthesis declines with age and is suppressed by HMG-CoA reductase inhibition, which is the basis for its use in statin-associated muscle symptoms [54].

In heart failure the evidence is the strongest in this class. Q-SYMBIO randomised 420 patients with New

York Heart Association class III to IV heart failure to 300 mg/day of coenzyme Q10 and reported a reduction in the primary composite of major adverse cardiovascular events (15% versus 26%; hazard ratio 0.50, 95% CI 0.32 to 0.80) and in all-cause mortality [55], although the 2021 Cochrane review of coenzyme Q10 in heart failure judged the evidence of uncertain quality and declined to endorse the mortality finding [56]. KiSel-10 combined 200 mg/day of coenzyme Q10 with 200 µg/day of selenium in 443 older Swedish adults and reduced cardiovascular mortality [57]. Neither has been replicated at scale, and both used doses far above typical over-the-counter products.

For statin-associated muscle symptoms the pooled randomised evidence does not support a clinically meaningful benefit, and for exercise performance in healthy people the data are null. Coenzyme Q10 is lipophilic and should be taken with a fat-containing meal; ubiquinol formulations have higher measured bioavailability at equal dose. It is well tolerated but reduces the anticoagulant effect of warfarin through a vitamin K-like structure, and this interaction is clinically relevant [58,59].

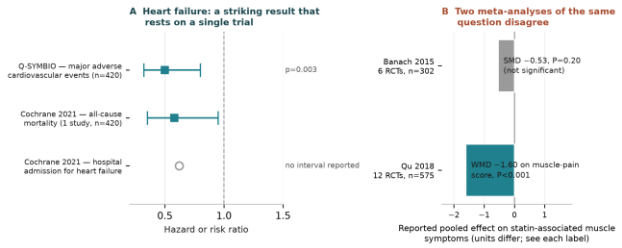


**Figure 6:** Coenzyme Q10 across indications. The heart-failure trials (Q-SYMBIO, KiSel-10) used 200 to 300 mg/day and reported mortality benefit; trials in statin-associated muscle symptoms and in exercise performance at similar or lower doses are null. Indication, not the molecule, determines the result.

| Agent | Typical dose | Evidence grade | Crosses MCID? | Key limitation or harm |
|---|---|---|---|---|
| **Omega-3 (EPA+DHA)** | 1 g/day | A (null for CV events) | No | Atrial fibrillation at high dose; bleeding perioperatively [18,22] |
| **Icosapent ethyl** | 4 g/day | A | Yes (CV risk) | Comparator controversy; atrial fibrillation [19] |
| **Vitamin C** | 75–500 mg/day | B (cold duration only) | No | Oxalate stones above 1 g/day [27,28] |
| **Vitamin D + calcium** | 800–1,000 IU + 1,000 mg | A (older adults at risk) | Yes (fracture) | No benefit if replete; harm with intermittent high dose [33,34] |
| **Vitamin D alone** | 2,000 IU/day | A (null) | No | No fracture, cancer or CVD benefit in replete adults [29,30] |
| **Vitamin E** | Not recommended | A (harm) | n.a. | Heart failure, prostate cancer, mortality [42,44] |
| **Coenzyme Q10** | 200–300 mg/day | B (heart failure) | Yes in HF only | Unreplicated; warfarin interaction [55,58] |
| **Selenium** | Dietary only | A (harm) | n.a. | Diabetes incidence in replete adults [48] |

**Table 5:** Summary of essential nutrients and antioxidants: dose, evidence grade and whether the pooled effect crosses the relevant minimal clinically important difference.

CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; MCID, minimal clinically important difference; n.a., not applicable.

## Joint and Connective Tissue Support

This is the category in which patient expectation and evidence diverge most sharply, and in which international guidelines reach opposite conclusions from the same trials. It is therefore treated at length, with the guideline discordance analysed separately in Section 10.

## Glucosamine

Glucosamine is an amino monosaccharide and a substrate for glycosaminoglycan synthesis, obtained commercially from crustacean shells or by bacterial fermentation. Two salts dominate: glucosamine sulfate, usually as the patented crystalline preparation (pCGS) at 1,500 mg once daily, and glucosamine hydrochloride, at 1,500 mg daily in divided doses. The distinction matters because almost every positive trial used pCGS and almost every null trial used the hydrochloride or a non-patented sulfate [60].

The Cochrane review of 25 trials in 4,963 participants found a 22% improvement in pain with glucosamine overall, but when analysis was restricted to adequately allocation-concealed trials the effect disappeared, and all significant benefit was confined to trials using the Rotta preparation [60]. The GAIT trial, publicly funded and independent, randomised 1,583 participants to glucosamine hydrochloride 1,500 mg/day, chondroitin 1,200 mg/day, both, celecoxib or placebo and found no significant benefit of glucosamine for the primary outcome (response rate 64.0% versus 60.1% for placebo; p=0.30) [61]. The two three-year Rotta-funded structural trials reported preservation of joint-space width of 0.07 to 0.31 mm [62,63], a magnitude below the 0.4 mm anchor adopted here.

The decisive analysis is the network meta-analysis of 74 trials in 8,973 patients by Wandel and colleagues, which reported effect sizes for glucosamine, chondroitin and their combination that all fell below the pre-specified clinical-relevance threshold of −0.37 standardised mean difference, and concluded that these agents should not be reimbursed [5]. A funding-source analysis is the single most informative variable in this literature: industry-sponsored trials report effect sizes roughly two to three times larger than independently funded trials of the same agent [5,64].

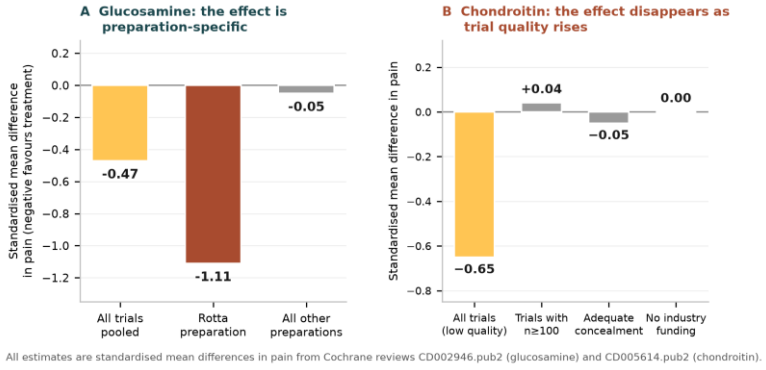


**Figure 7:** Effect size for glucosamine and chondroitin in osteoarthritis pain stratified by funding source and by adequacy of allocation concealment. Independently funded trials with adequate concealment cluster near the null; industry-funded trials with unclear concealment account for essentially all of the reported benefit. Dashed line marks the clinical-relevance threshold of standardised mean difference −0.37.

Safety is favourable. Glucosamine is well tolerated, with gastrointestinal upset the main complaint. The shellfish-allergy concern is largely theoretical, since the allergen is tropomyosin in the flesh rather than chitin in the shell, but fermentation-derived products avoid the issue entirely. A modest interaction with warfarin, increasing the international normalised ratio, is documented and clinically relevant [58,59]. Effects on glycaemic control at standard doses are not clinically significant in people without diabetes.

Two later trials are frequently cited in support of the combination and deserve precise description. MOVES randomised 606 patients with severe knee pain to chondroitin plus glucosamine or celecoxib and reported non-inferiority, a design that cannot establish efficacy against placebo [65]. A further randomised trial of combined chondroitin and glucosamine sulfate reported a symptomatic signal confined to a subgroup [66].

### Chondroitin sulfate

Chondroitin sulfate is a sulfated glycosaminoglycan extracted from bovine trachea, porcine cartilage or shark cartilage; molecular weight, sulfation pattern and purity vary widely between products, and pharmaceutical-grade material is not what most over-the-counter capsules contain [67]. The typical dose is 800 to 1,200 mg/day.

The evidence follows the same pattern as glucosamine but with a slightly stronger structural signal. GAIT found no benefit for chondroitin alone, although a subgroup with moderate to severe baseline pain showed a response to the combination that the investigators explicitly described as requiring confirmation [61]. The Cochrane review of 43 trials in 4,962 participants found a small pain benefit that was attenuated in larger and better-concealed trials, and a statistically significant but small reduction in joint-space narrowing of 0.16 mm [68] – again below the 0.4 mm anchor. Chondroitin is very well tolerated; the main practical concerns are label accuracy and bovine-source considerations.

### Collagen peptides and undenatured type II collagen

Two mechanistically distinct products are sold under the label collagen. Hydrolysed collagen peptides at 10 to 15 g/day supply glycine, proline and hydroxyproline together with bioactive di- and tripeptides that are absorbed intact and are detectable in plasma. Undenatured type II collagen (UC-II) at 40 mg/day is not a nutritional substrate at all; the proposed mechanism is oral tolerance via gut-associated lymphoid tissue.

For joint pain, an umbrella review of collagen supplementation found consistent directional benefit across small trials with substantial methodological limitations and near-universal industry funding [69]. A 2025 network meta-analysis placed collagen peptides among the better-performing nutraceuticals for osteoarthritis pain, while noting that most contributing trials were at high risk of bias [70]. Trials of UC-II at 40 mg/day report WOMAC improvements that in some cases exceed those of glucosamine plus chondroitin, but the comparison rests on few small industry trials [71,72].

For muscle, collagen is a poor protein. Its leucine content is approximately 2.5% against roughly 10% for whey, and it lacks tryptophan entirely. Head-to-head randomised trials found whey superior or collagen no better than placebo for lean-mass and strength adaptation [73,74]. Collagen should not be counted toward a daily protein target in a sarcopenia protocol. It is nonetheless among the safest agents in this review, with no significant interactions and only mild gastrointestinal complaints.

Patient willingness to use oral collagen has itself been systematically reviewed, which is informative about the gap between demand and evidence in this class [75].

## Hyaluronic acid

Hyaluronic acid must be considered separately in its oral and intra-articular forms. Oral hyaluronic acid at 80 to 240 mg/day is largely degraded by gut hyaluronidase and by the microbiota; a 2025 synthesis reported small pain improvements in short trials of low quality, with no structural data [76].

Intra-articular hyaluronic acid has been studied far more extensively and is the subject of the sharpest guideline disagreement in musculoskeletal medicine. The 2022 BMJ systematic review and meta-analysis of 169 trials in 21,163 participants found a pooled effect on pain that was statistically significant but clinically irrelevant, and identified a signal for serious adverse events [77]. Earlier pooled analyses restricted to higher-quality trials reached similar conclusions [5,78,79]. Nevertheless the American College of Rheumatology conditionally recommends against it, the American Academy of Orthopaedic Surgeons recommends against it, OARSI is uncertain, and several national bodies continue to fund it [80–83].

| Agent | Dose | Best evidence | Pain effect vs MCID | Structure effect vs 0.4 mm |
|---|---|---|---|---|
| **Glucosamine sulfate (pCGS)** | 1,500 mg/day | Cochrane 25 trials; GAIT; two 3-year structural trials [60,61] | Below MCID once concealment adequate | 0.07–0.31 mm; below anchor [62,63] |
| **Glucosamine hydrochloride** | 1,500 mg/day | GAIT (n=1,583) [61] | No benefit (p=0.30) | Not assessed |
| **Chondroitin sulfate** | 800–1,200 mg/day | Cochrane 43 trials (n=4,962) [68] | Small; attenuated in larger trials | 0.16 mm; below anchor |
| **Glucosamine + chondroitin** | 1,500 + 1,200 mg/day | GAIT; network meta-analysis [5,61] | Subgroup signal only, unconfirmed | Not demonstrated |
| **Collagen peptides** | 10–15 g/day | Umbrella review; 2025 network meta-analysis [69,70] | Directionally positive; high risk of bias | Not assessed |
| **Undenatured type II collagen** | 40 mg/day | Small industry trials [71,72] | Possibly above MCID in small trials | Not assessed |
| **Oral hyaluronic acid** | 80–240 mg/day | 2025 synthesis of low-quality trials [76] | Small, unreliable | Not assessed |
| **Intra-articular hyaluronic acid** | Weekly × 3–5 | BMJ 2022, 169 trials, n=21,163 [77] | Statistically significant, clinically irrelevant | Not demonstrated |
| **Methylsulfonylmethane** | 1.5–6 g/day | Small short trials [84] | Below MCID | Not assessed |
| **Green-lipped mussel extract** | 300–1,200 mg/day | Small trials, heterogeneous [85] | Uncertain | Not assessed |

**Table 6:** Joint and connective-tissue agents: dose, best available evidence, and whether the pooled effect crosses the pain and structural anchors defined in (Table 1). No agent in this class demonstrates a structural effect that reaches 0.4 mm of joint-space width.

MCID, minimal clinically important difference; pCGS, patented crystalline glucosamine sulfate; GAIT, Glucosamine/chondroitin Arthritis Intervention Trial.

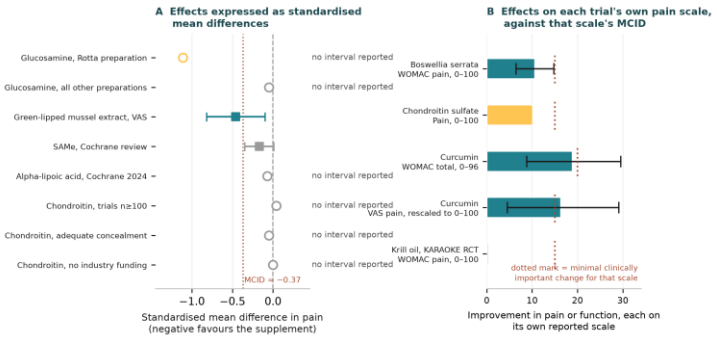


**Figure 8:** Pooled pain effect sizes for the principal joint-support agents plotted against the clinical-relevance threshold. Only undenatured type II collagen and collagen peptides approach the threshold, and both rest on small industry-funded trials; glucosamine, chondroitin, their combination and intra-articular hyaluronic acid fall short of it.

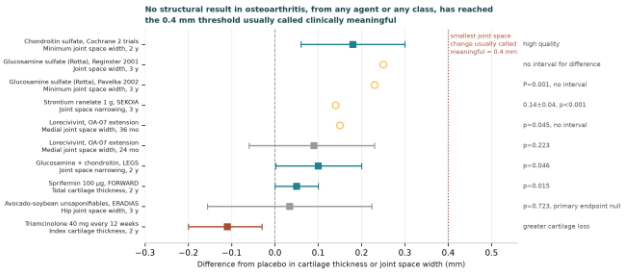


**Figure 9:** Structural effect of ten agents on radiographic joint-space width or magnetic resonance cartilage measures, plotted against the 0.4 mm minimal clinically important difference. Every agent, including the three-year glucosamine sulfate trials and the sprifermin FORWARD trial at two years, falls below the anchor.

## Anti-Inflammatory Botanicals

### Curcumin and turmeric

Curcuminoids constitute approximately 3% of turmeric rhizome by weight, and free curcumin has oral bioavailability of well under 1% owing to poor solubility, rapid intestinal and hepatic glucuronidation and sulfation, and biliary excretion. Every clinically relevant product therefore uses an enhancement strategy: piperine co-administration, phytosome-phospholipid complexation, micellar or liposomal encapsulation, or nanoparticulate formulation. Trials of unenhanced turmeric powder and trials of a phytosome preparation are not testing the same intervention, and pooling them is the principal source of heterogeneity in this literature [86].

For knee osteoarthritis, the best-known trial randomised 367 participants to Curcuma domestica extract 1,500 mg/day or ibuprofen 1,200 mg/day and reported non-inferiority on WOMAC scores with fewer gastrointestinal adverse events [87]. The trial was open to important limitations: no placebo arm, a non-inferiority margin that was generously set, and a single-country setting. Pooled analyses of curcumin in osteoarthritis report effects that reach or slightly exceed the MCID in some syntheses and fall below it in others, with high heterogeneity attributable to formulation [70].

Two safety issues deserve emphasis because they are frequently omitted. First, turmeric and curcumin are now an established cause of drug-induced liver injury; the LiverTox monograph documents a rising case series with a characteristic hepatocellular pattern, often in products containing piperine, and an HLA-B*35:01 association has been described [88–90]. The US National Center for Complementary and Integrative Health now carries an explicit hepatotoxicity warning [91]. Second, curcumin inhibits platelet aggregation and several cytochrome P450 isoenzymes, with documented potentiation of warfarin. Baseline and periodic liver function testing is reasonable for anyone taking a high-dose enhanced formulation for more than eight weeks.

### Boswellia serrata

Boswellia gum resin contains boswellic acids, of which 3-O-acetyl-11-keto-β-boswellic acid (AKBA) is the most studied; the mechanism is inhibition of 5-lipoxygenase and hence of leukotriene synthesis, a pathway distinct from cyclooxygenase inhibition. Doses range from 100 mg/day of a standardised high-AKBA extract to 1,000 mg/day of crude resin [92].

Boswellia has the most interesting recent data in this class. A randomised placebo-controlled trial of a Boswellia serrata extract at 100 mg/day for 180 days in Kellgren-Lawrence grade II to III knee osteoarthritis reported increases in magnetic resonance cartilage volume, cartilage thickness and joint-space width, all with $p<0.001$ [93]. If replicated independently, this would be the first nutraceutical structural signal of any consequence. Three cautions apply: the trial was small and industry-linked, the investigators themselves describe it as a pilot [94], and structural imaging endpoints in single small trials have repeatedly failed to replicate. Boswellia should be presented as promising and unconfirmed, not as a cartilage-regenerating agent.

### Ginger

Zingiber officinale contains gingerols and shogaols with dual cyclooxygenase and lipoxygenase inhibition. A meta-analysis of five trials in 593 participants found a significant reduction in osteoarthritis pain (standardised mean difference −0.30, 95% CI −0.50 to −0.09) with an increased risk of gastrointestinal adverse events relative to placebo (relative risk 2.33) [95]. The point estimate sits just below the −0.37 relevance threshold. Ginger has antiplatelet activity and should be discontinued before surgery [22]. Typical dose 500 to 1,000 mg/day of standardised extract.

Two further agents belong with the joint group above. Methylsulfonylmethane at 1.5 to 6 g/day produced WOMAC improvements in randomised work that did not reach the minimal clinically important difference [96], and eggshell membrane at 500 mg/day reduced pain and stiffness in a small randomised trial with no independent replication [97]. A dedicated meta-analysis of ginger reached the same conclusion of a small effect with gastrointestinal cost [98].

### Other botanicals in musculoskeletal use

Avocado-soybean unsaponifiables at 300 mg/day, Pycnogenol (French maritime pine bark) at 100 to 150 mg/day, and Boswellia-curcumin combinations all show small positive signals in trials of limited size and quality [78,99]. Devil's claw, willow bark and rose hip have similar profiles. A 2024 network meta-analysis ranking nutraceuticals for osteoarthritis pain placed several of these agents above placebo while grading the certainty of the ranking as low [64,70]. The Swedish Agency for Health Technology Assessment reviewed oral herbal therapies for osteoarthritis and found the evidence insufficient to support any of them [100], and the US National Center for Complementary and Integrative Health reaches a similar position [101]. The honest summary is that this class produces small, plausible, poorly replicated benefits with a good safety record, and that formulation identity matters more than the botanical name on the label.

| Botanical | Active constituent | Dose | Evidence and effect | Safety concern |
|---|---|---|---|---|
| **Curcumin (enhanced)** | Curcuminoids; AKBA-independent | 500–2,000 mg/day curcuminoids | Non-inferior to ibuprofen in one open trial (n=367); pooled effect formulation-dependent [86,87] | Drug-induced liver injury; warfarin potentiation; CYP inhibition [88,91] |
| **Boswellia serrata** | AKBA and boswellic acids | 100 mg/day standardised to 1,000 mg resin | Pain benefit; single pilot trial reports MRI cartilage gain (p<0.001) [92,93] | Generally well tolerated; unreplicated structural claim [94] |
| **Ginger** | Gingerols, shogaols | 500–1,000 mg/day extract | SMD −0.30 (−0.50 to −0.09); just below relevance threshold [95] | Gastrointestinal events RR 2.33; antiplatelet [22] |
| **Avocado-soybean unsaponifiables** | Phytosterols | 300 mg/day | Small pain benefit; structural data inconclusive [78] | Well tolerated |
| **Pycnogenol** | Procyanidins | 100–150 mg/day | Small trials, positive direction, low certainty [99] | Well tolerated |


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| Botanical | Active constituent | Dose | Evidence and effect | Safety concern |
|---|---|---|---|---|
| **Green-lipped mussel** | Omega-3 and lipid fractions | 300–1,200 mg/day | Heterogeneous small trials [85] | Shellfish allergy |

**Table 7:** Anti-inflammatory botanicals used in musculoskeletal practice. Formulation, not the botanical name, determines exposure and therefore effect.

AKBA, 3-O-acetyl-11-keto-β-boswellic acid; CYP, cytochrome P450; MRI, magnetic resonance imaging; RR, relative risk; SMD, standardised mean difference.

## Amino Acids, Protein And Ergogenic Compounds

### The branched-chain amino acid problem

The most consequential misconception in this section is that leucine or branched-chain amino acids alone can drive sustained muscle protein synthesis. Leucine is indeed the principal nutrient activator of mechanistic target of rapamycin complex 1, and a leucine threshold of roughly 2.5 to 3 g per meal is required to maximise the postprandial anabolic response. But activation of the signal is not the same as synthesis of protein: the other essential amino acids must be present as substrate. Wolfe's analysis, frequently cited as support for branched-chain amino acid supplementation, in fact concludes the opposite – that the claim of an anabolic response to branched-chain amino acids alone in humans is unwarranted, because supplying three of the twenty amino acids cannot sustain net protein accretion [102]. This is the second documented misattribution in Section 12.

The correct intervention is a complete essential-amino-acid mixture or a high-quality intact protein. Volpi and colleagues demonstrated that essential amino acids are primarily responsible for the amino-acid stimulation of muscle protein anabolism in healthy older adults, with non-essential amino acids adding nothing [103]. The ESPEN expert group recommends 1.0 to 1.2 g/kg/day of protein for healthy older adults and 1.2 to 1.5 g/kg/day in the presence of acute or chronic illness, distributed as 25 to 30 g of high-quality protein per meal [11]. Practically, 20 to 40 g of whey protein or 10 to 15 g of an essential-amino-acid blend per dose achieves the leucine threshold; 5 g of isolated leucine does not achieve the same outcome despite achieving the same signal.

### Glutamine

Glutamine is the most abundant free amino acid in plasma and skeletal muscle, is a fuel for enterocytes and lymphocytes, and is conditionally essential in catabolic states. Its clinical trajectory is a cautionary tale. Early trials suggested benefit in burns, trauma and critical illness, and glutamine became standard in many intensive-care nutrition protocols. The REDOXS trial then randomised 1,223 critically ill patients with multi-organ failure to glutamine, antioxidants, both or neither and found a trend toward increased 28-day mortality with glutamine (32.4% versus 27.2%; adjusted odds ratio 1.28, 95% CI 1.00 to 1.64) and significantly increased in-hospital and six-month mortality [104].

The lesson generalises beyond glutamine: a conditionally essential nutrient given pharmacologically to patients with renal or hepatic failure is a drug, and it can kill. In non-critical settings glutamine at 5 to 10 g/day for gut integrity, oral mucositis or post-exercise recovery is well tolerated and of uncertain benefit [105]. It should not be used in renal or hepatic failure, and it is not an ergogenic aid.

## Creatine monohydrate

Creatine monohydrate is the best-evidenced ergogenic supplement in existence and, unlike most agents in this review, its Grade A evidence is matched by an effect that exceeds the MCID for the outcomes tested. The International Society of Sports Nutrition position stand summarises hundreds of trials: increased intramuscular phosphocreatine, improved high-intensity performance, and augmented lean-mass and strength gains when combined with resistance training [106]. Dosing is either 3 to 5 g/day continuously or a 20 g/day loading phase for five to seven days followed by 3 to 5 g/day.

Two extensions are relevant to this review. Renal safety has been repeatedly examined and systematic review shows no change in glomerular filtration rate in healthy adults; the apparent rise in serum creatinine reflects creatine metabolism, not renal injury [107]. Cognitive effects have been meta-analysed, with a significant benefit for memory in older adults and a much weaker signal in young adults; the 2024 meta-analysis carries a published erratum and should be cited with that qualification [108]. Creatine is also the agent most often adulterated in low-cost markets, which makes third-party certification meaningful here [109].

## HMB, beta-alanine, citrulline and taurine

β-hydroxy-β-methylbutyrate is a leucine metabolite marketed for anticatabolic effect. The 2025 systematic review and meta-analysis of 21 randomised trials in 1,935 adults over fifty, at 1.48 to 3.08 g/day, found benefit concentrated in clinical and bed-rest populations rather than in healthy trained adults [110]. Beta-alanine raises muscle carnosine and buffers intramuscular acidosis; the ISSN position stand supports 4 to 6 g/day for high-intensity efforts of one to four minutes, with paraesthesia the characteristic and harmless adverse effect, and carnosine retention of approximately 6.0 to 6.5% of the ingested dose independent of dosing schedule [111,112]. Citrulline malate increases plasma arginine more effectively than arginine itself; the pooled effect on performance is small (standardised mean difference 0.20, 95% CI 0.01 to 0.39) [113]. Taurine has generated substantial interest since the demonstration that taurine decline is a driver of ageing in mice and monkeys, but the human evidence remains 25 small trials in about 1,024 participants with heterogeneous metabolic outcomes [114,115].

## GlyNAC

Glycine plus N-acetylcysteine, given to restore glutathione synthesis, produced improvements in oxidative stress, mitochondrial fatty-acid oxidation, inflammation, gait speed, grip strength and several ageing hallmarks in a randomised trial in older adults [116,117]. The trial was small and single-centre and the breadth of positive endpoints invites caution, but the mechanism is coherent and the intervention is inexpensive and well tolerated. This is a Grade C agent with an unusually favourable risk-benefit ratio, appropriate for the discuss tier rather than the recommend tier.

| Agent | Dose | Grade | Effect relative to MCID | Notes |
|---|---|---|---|---|
| **Creatine monohydrate** | 3–5 g/day (or 20 g × 5–7 days then 3–5 g) | A | Exceeds MCID for strength and lean mass with training [106] | No change in GFR; memory benefit in older adults (erratum) [107,108] |
| **Whey or complete protein** | 20–40 g/dose; 1.0–1.5 g/kg/day total | A | Exceeds MCID for lean mass with training [11,103] | Achieves the 2.5–3 g leucine threshold |
| **Essential amino acids** | 10–15 g/dose | A | Equivalent to intact protein [103] | Non-essential amino acids add nothing |
| **Leucine alone / BCAA** | Not recommended as sole agent | B (negative) | Signal without substrate; no sustained synthesis [102] | Common misattribution (Section 12) |
| **HMB** | 1.5–3 g/day | B | Benefit in clinical and bed-rest states only [110] | 21 trials, n=1,935, age 50+ |

| Agent | Dose | Grade | Effect relative to MCID | Notes |
|---|---|---|---|---|
| **Beta-alanine** | 4–6 g/day, divided | A | Exceeds MCID for 1–4 min efforts [111] | Paraesthesia; retention 6.0–6.5% [112] |
| **Citrulline malate** | 6–8 g pre-exercise | B | SMD 0.20 (0.01–0.39); marginal [113] | Better tolerated than arginine |
| **Glutamine** | 5–10 g/day (non-critical use only) | A (harm in critical illness) | No ergogenic effect | REDOXS: increased mortality in multi-organ failure [104] |
| **Taurine** | 1–6 g/day | C | Not established in humans [114] | Strong preclinical ageing data [115] |
| **GlyNAC** | Glycine + NAC to tolerance | C | Gait speed and grip strength improved in one trial [116] | Small single-centre; favourable safety [117] |

**Table 8:** Amino acids, protein and ergogenic compounds. Creatine, complete protein and essential amino acids are the only agents in this review whose Grade A evidence is matched by an effect exceeding the relevant anchor.

BCAA, branched-chain amino acids; GFR, glomerular filtration rate; HMB, β-hydroxy-β-methylbutyrate; MCID, minimal clinically important difference; NAC, N-acetylcysteine; SMD, standardised mean difference.

## Thirty Additional Nutraceuticals Encountered In Practice

The agents in this section were not part of the original framing of this review but are presented to clinicians every week. They are grouped by the claim most often attached to them. Several deserve individual comment because the evidence is either much stronger or much weaker than the marketing implies, or because a specific safety signal exists.

### Cardiometabolic and lipid agents

Berberine at 500 mg two or three times daily produces reductions in fasting glucose, glycated haemoglobin and low-density lipoprotein cholesterol that in pooled analyses approach the magnitude of low-dose metformin [118]. This makes it the most pharmacologically active agent in the entire nutraceutical category, and its regulatory classification as a supplement is anomalous. It inhibits cytochrome P450 3A4 and 2D6 and therefore interacts with statins, ciclosporin and many other narrow-index drugs [119].

Red yeast rice is the clearest example of a supplement that is a drug. It contains monacolin K, which is chemically identical to lovastatin. EFSA concluded in 2018 that no safe intake of monacolins from red yeast rice could be established, citing rhabdomyolysis and hepatic injury at doses as low as 3 mg/day, and the European Union subsequently capped monacolins at 3 mg per daily portion [120,121]. Product monacolin content in the United States varies by more than a hundredfold between brands. Psyllium at 7 to 15 g/day of soluble fibre lowers low-density lipoprotein cholesterol and carries an authorised FDA heart-health claim [13]. Garlic preparations reduce systolic blood pressure by approximately 5 to 8 mmHg in hypertensive participants, with wide heterogeneity of preparation and allicin yield [14]. Dietary nitrate as beetroot juice improves time to exhaustion by about 4% and lowers systolic pressure by about 4 mmHg [122]. Chromium picolinate has no clinically meaningful effect on glycaemia or weight and holds only an FDA qualified claim acknowledging very limited credible evidence [123]. L-carnitine is converted by gut microbiota to trimethylamine N-oxide, a mechanistic atherogenic concern that argues against long-term high-dose use [124].

Two antioxidant-adjacent agents complete this group. Alpha-lipoic acid, widely sold for diabetic peripheral

neuropathy, produced a pooled pain standardised mean difference of only −0.07 in the 2024 Cochrane review, an effect indistinguishable from none [125]. N-acetylcysteine at 600 mg twice daily reduced exacerbations in chronic obstructive pulmonary disease in the PANTHEON trial [126] while the earlier BRONCUS trial at 600 mg once daily was null [127], a dose relationship that is usually omitted when the agent is recommended generically.

### Neurocognitive and psychiatric agents

Ashwagandha (Withania somnifera) at 300 to 600 mg/day of root extract reduces Hamilton anxiety and Pittsburgh sleep-quality scores in small trials of variable quality [128], but a growing case series of cholestatic hepatitis has produced a LiverTox monograph and this must be disclosed [129]. Melatonin is the most-used sleep supplement and among the least effective: pooled analysis shows sleep latency reduced by 7.06 minutes and total sleep time increased by 8.25 minutes [130], neither of which reaches clinical relevance for most patients. Melatonin is also the product with the worst documented label accuracy: analysis of twenty-five melatonin gummy products found actual content ranging from 74% to 347% of label, with one containing no melatonin at all and several containing unlabeled cannabidiols [2].

St John's wort has genuine antidepressant efficacy in mild to moderate depression but is a potent inducer of cytochrome P450 3A4 and P-glycoprotein, producing documented failure of oral contraceptives, ciclosporin, warfarin and antiretroviral therapy; it is the most dangerous interaction in the herbal pharmacopoeia [131]. Saffron shows efficacy comparable to selective serotonin reuptake inhibitors in small, geographically concentrated trials [132]. Ginkgo biloba failed definitively in the Ginkgo Evaluation of Memory trial, which randomised 3,069 older adults over a median of six years and found no reduction in dementia incidence [133]. Citicoline and choline show a signal in vascular cognitive impairment but not in healthy adults [134].

### Longevity and mitochondrial agents

Nicotinamide riboside at 250 to 1,000 mg/day reliably raises blood nicotinamide adenine dinucleotide concentration and is well tolerated [135], but systematic appraisal shows that skeletal-muscle nicotinamide adenine dinucleotide concentration – the tissue of interest for sarcopenia – does not change [136]. Nicotinamide mononucleotide at 300 to 900 mg/day improved six-minute walk distance and a subjective health questionnaire in a dose-dependent randomised trial [137]; its US regulatory status was contested and then restored following litigation [138]. Spermidine at 0.9 mg/day failed to improve memory in the Smart Age randomised trial in older adults with subjective cognitive decline [139]. Urolithin A at 500 to 1,000 mg/day improved muscle strength and mitochondrial biomarkers in middle-aged adults [140]. Resveratrol has oral bioavailability below 1% and pooled clinical effects that are small and inconsistent, despite an extensive preclinical literature [141,142]. Sulforaphane activates NRF2 robustly in preclinical models with sparse human data [143].

### Immune, ocular and gastrointestinal agents

Green tea catechins illustrate the dose-dependence of botanical hepatotoxicity precisely: EFSA concluded that epigallocatechin-3-gallate at or above 800 mg/day from food supplements is associated with raised serum transaminases, while the same compound from brewed tea is not [144,145]. Echinacea does not reliably prevent or treat the common cold on Cochrane analysis [146]. Elderberry rests on small short

trials with an unresolved theoretical concern about cytokine amplification [147]. Bovine colostrum shows heterogeneous effects on upper-respiratory illness and gut permeability in athletes without consistent performance benefit [148]. Oat and barley beta-glucan at 3 g/day carries an authorised EFSA cholesterol claim, which the yeast beta-glucan immune literature does not [149]. Probiotic effects are strain-specific and indication-specific, and class-level recommendations are not defensible [150]. Lutein and zeaxanthin have Grade A evidence within the AREDS2 formulation for progression of age-related macular degeneration, with ten-year follow-up confirming the substitution of lutein and zeaxanthin for beta-carotene as both effective and safer [151]. Quercetin at 500 mg/day and above produces a modest systolic reduction with negligible effect on inflammatory markers [152]. Myo-inositol improves ovulation and insulin indices in polycystic ovary syndrome [153]. Saw palmetto failed in both STEP and the larger CAMUS trial, the latter at up to three times the standard dose [154]. Silymarin has no consistent effect on mortality or histology in chronic liver disease [155]. Magnesium has consistent effects on blood pressure and migraine prophylaxis but no established role in musculoskeletal pain [156].

## BPC-157 and the unapproved-peptide problem

BPC-157 warrants explicit treatment because it is heavily marketed within regenerative and sports medicine and is frequently described to patients as a healing peptide. There is no completed randomised controlled trial of BPC-157 in humans for any indication. It is prohibited at all times under World Anti-Doping Agency category S0, which covers substances with no current approval by any governmental regulatory health authority for human therapeutic use [157,158], and the FDA placed it on the Category 2 bulk-substances list in 2023, meaning it has significant safety risks for compounding [159]. Prescribing or recommending it exposes both patient and clinician to risk that cannot be justified by the current evidence base. The same reasoning applies to the wider class of research peptides sold without any human efficacy or toxicology data.

| Agent | Typical dose | Grade | Best-supported claim | Principal caution |
|---|---|---|---|---|
| **Berberine** | 500 mg 2–3×/day | B | Glucose, HbA1c and LDL reduction [118] | CYP3A4/2D6 inhibition [119] |
| **Red yeast rice** | ≤ 3 mg monacolin K/day (EU) | B | LDL reduction (it is lovastatin) [120] | No safe intake established; myopathy, hepatitis [121] |
| **Psyllium** | 7–15 g/day soluble fibre | A | LDL reduction; authorised FDA claim [13] | Bloating; must be taken with fluid |
| **Garlic extract** | 600–1,500 mg/day aged extract | B | Systolic reduction 5–8 mmHg [14] | Antiplatelet; halitosis |
| **Beetroot / nitrate** | 6–8 mmol nitrate | B | Time to exhaustion +4%; SBP −4 mmHg [122] | Beeturia; avoid antibacterial mouthwash |
| **Chromium picolinate** | 200–1,000 µg/day | B (negative) | None clinically meaningful [123] | FDA qualified claim only |
| **L-carnitine** | 1–3 g/day | C | Marginal in specific deficiency states | TMAO generation [124] |
| **Ashwagandha** | 300–600 mg/day root extract | C | Anxiety and sleep scores [128] | Cholestatic hepatitis [129] |
| **Melatonin** | 0.5–5 mg at night | A (small effect) | Latency −7.06 min; sleep time +8.25 min [130] | Label content 74–347% of stated [2] |
| **St John's wort** | 300 mg 3×/day | A | Mild to moderate depression [131] | CYP3A4 and P-gp induction; contraceptive failure |
| **Saffron** | 30 mg/day | C | Depression scores [132] | Small, geographically concentrated trials |
| **Ginkgo biloba** | 120–240 mg/day | A (negative) | None; GEM trial null [133] | Antiplatelet; bleeding |
| **Citicoline / choline** | 500–2,000 mg/day | C | Vascular cognitive impairment only [134] | No benefit in healthy adults |
| **Nicotinamide riboside** | 250–1,000 mg/day | B | Raises blood NAD+ [135] | Muscle NAD+ unchanged [136] |
| **Nicotinamide mononucleotide** | 300–900 mg/day | B | Six-minute walk distance [137] | Contested US status, since restored [138] |
| **Spermidine** | 0.9 mg/day | B (negative) | None; SmartAge null [139] | Preclinical autophagy data only |
| **Urolithin A** | 500–1,000 mg/day | B | Muscle strength, mitochondrial markers [140] | Single sponsor; cost |

| Agent | Typical dose | Grade | Best-supported claim | Principal caution |
|---|---|---|---|---|
| **Resveratrol** | 150–1,000 mg/day | C | Inconsistent metabolic effects [141] | Bioavailability <1% [142] |
| **Sulforaphane** | 10–40 mg/day | D | NRF2 activation preclinically [143] | Human data sparse |
| **Green tea catechins** | Tea only; avoid ≥ 800 mg EGCG | A (harm) | None justifying supplement use [144] | Hepatotoxicity [145] |
| **Echinacea** | Variable | A (negative) | None reliable [146] | Preparation heterogeneity |
| **Elderberry** | 300–600 mg/day extract | C | Symptom duration in small trials [147] | Theoretical cytokine concern |
| **Bovine colostrum** | 20–60 g/day | C | Gut permeability, URTI in athletes [148] | No performance benefit |
| **Beta-glucan (oat/barley)** | 3 g/day | A | Cholesterol; authorised EFSA claim [149] | Yeast beta-glucan claims unsupported |
| **Probiotics** | Strain-specific | B | Indication- and strain-specific only [150] | No class-level recommendation |
| **Lutein + zeaxanthin** | 10 + 2 mg/day (AREDS2) | A | AMD progression [151] | Only within the AREDS2 formulation |
| **Quercetin** | ≥ 500 mg/day | C | Modest systolic reduction [152] | No effect on inflammatory markers |
| **Myo-inositol** | 2–4 g/day | B | Ovulation and insulin indices in PCOS [153] | Small short trials |
| **Saw palmetto** | 320 mg/day | A (negative) | None; STEP and CAMUS null [154] | No benefit at 3× dose |
| **Milk thistle (silymarin)** | 140 mg 3×/day | B (negative) | No effect on liver outcomes [155] | Widely used without basis |
| **Magnesium** | 200–400 mg/day elemental | A (BP, migraine) | Blood pressure; migraine prophylaxis [156] | Diarrhoea; no MSK role |
| **BPC-157** | Not recommended | D | None; no human RCT [158] | WADA S0; FDA Category 2 [157,159] |

**Table 9:** Thirty additional nutraceuticals: dose, evidence grade, best-supported claim and principal caution. Agents graded A for a negative result (ginkgo, saw palmetto, echinacea, chromium) are those where high-quality evidence establishes absence of benefit rather than absence of evidence.

AMD, age-related macular degeneration; BP, blood pressure; CYP, cytochrome P450; EGCG, epigallocatechin-3-gallate; GEM, Ginkgo Evaluation of Memory; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; MSK, musculoskeletal; NAD+, nicotinamide adenine dinucleotide; PCOS, polycystic ovary syndrome; P-gp, P-glycoprotein; RCT, randomised controlled trial; SBP, systolic blood pressure; TMAO, trimethylamine N-oxide; URTI, upper respiratory tract infection; WADA, World Anti-Doping Agency.

## Prescription And Longevity Compounds

The three medications in the original framing of this review – metformin, nandrolone and erythropoietin – are joined here by the compounds that patients in longevity and regenerative practice now request by name. All are prescription drugs or controlled substances in most jurisdictions, and the distance between their approved indications and their actual use in this space is the central governance problem of the field.

### Metformin

Metformin is a biguanide that activates AMP-activated protein kinase, inhibits hepatic gluconeogenesis and mitochondrial complex I, and alters the gut microbiome. It is the first-line pharmacological therapy for type 2 diabetes, with UKPDS 34 establishing a reduction in diabetes-related death and all-cause mortality in overweight patients [160] and the Diabetes Prevention Program showing a 31% reduction in progression to diabetes relative to placebo, against 58% for intensive lifestyle intervention [161].

Three points are commonly misstated. First, the boxed warning for lactic acidosis remains on the label [162], although Cochrane analysis of 347 comparative trials found no cases attributable to metformin and no increase in lactate [163]. The warning drives contraindications by estimated glomerular filtration rate

rather than by observed events. Second, long-term use causes vitamin B12 deficiency: in the Diabetes Prevention Program Outcomes Study, low B12 was present in 4.3% of metformin users versus 2.3% of placebo at five years and 7.4% versus 5.4% at thirteen years, with anaemia and neuropathy consequences [164]. Annual B12 measurement is warranted. Third, metformin attenuates the adaptive response to exercise training: a 2025 meta-analysis found a reduced improvement in peak oxygen uptake (mean difference −1.19 mL/kg/min) and higher systolic blood pressure (+3.76 mmHg) in metformin-treated participants [165]. For a patient whose primary intervention is resistance and aerobic training, this is a direct antagonism.

For longevity, metformin is the subject of the Targeting Aging with Metformin (TAME) trial, which is designed to test whether the drug delays the onset of multiple age-related diseases [166]. TAME has not reported, and until it does the geroprotective indication is a hypothesis. For osteoarthritis specifically, observational Osteoarthritis Initiative data suggested slower cartilage loss in metformin users with obesity [167], and the 2025 randomised trial in participants with overweight or obesity and knee osteoarthritis reported a statistically significant reduction in WOMAC pain [168,169] while a separate protocol tests tibiofemoral cartilage volume over 24 months [170]. Metformin is therefore a candidate symptomatic agent in osteoarthritis and is not, on present evidence, a DMOAD.

### Nandrolone decanoate

Nandrolone decanoate is a 19-nortestosterone anabolic-androgenic steroid, a Schedule III controlled substance in the United States, and prohibited at all times in sport under WADA category S1 [157]. Its legitimate randomised evidence base is narrow and specific: 100 mg intramuscularly weekly increased lean body mass and physical function in patients receiving haemodialysis [171,172], and in men with HIV-associated wasting it increased lean mass when combined with resistance training [173]. It has no approved indication for age-related sarcopenia, for joint disease, or for performance.

The harm profile at supraphysiological dose is now well characterised. In a cross-sectional study of long-term anabolic-androgenic steroid users, left ventricular ejection fraction was 52% in users versus 63% in non-users, coronary artery plaque volume was substantially higher, and diastolic function was impaired [174]. Hepatotoxicity, dyslipidaemia with suppressed high-density lipoprotein, erythrocytosis, suppression of the hypothalamic-pituitary-gonadal axis with prolonged or permanent hypogonadism, and mood disturbance are all documented. Where hypogonadism is genuinely present, the appropriate intervention is testosterone replacement under the Endocrine Society guideline [175], not nandrolone. The frequently cited 2010 version of that guideline has been superseded and does not address nandrolone [176]; this is the third misattribution catalogued in Section 12.

Testosterone itself now has cardiovascular safety data from TRAVERSE, which randomised 5,246 men with hypogonadism and cardiovascular risk and found non-inferiority for major adverse cardiac events, while showing higher rates of atrial fibrillation, acute kidney injury and pulmonary embolism [177]. The FDA implemented class-wide labelling changes in February 2025 reflecting these findings [178]. Growth hormone occupies a different legal category: distribution for anti-ageing or athletic purposes is a federal felony under 21 U.S.C. § 333(e) [179], and the systematic review of growth hormone in the healthy elderly found small lean-mass changes with increased rates of soft-tissue oedema, arthralgia, carpal tunnel

syndrome and gynaecomastia, and a trend toward glucose intolerance [180].

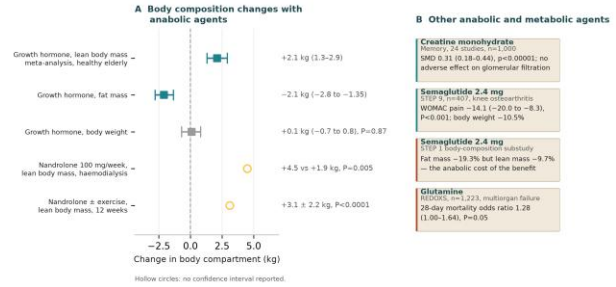


**Figure 10:** Anabolic and hormonal interventions: approved indication, randomised evidence base and documented harm. Nandrolone's randomised evidence is confined to dialysis and HIV wasting; growth hormone distribution for anti-ageing purposes is a federal offence in the United States; testosterone has cardiovascular non-inferiority data with specific excess risks.

## Erythropoietin and erythropoiesis-stimulating agents

Recombinant human erythropoietin corrects anaemia of chronic kidney disease, and its development transformed dialysis care [181]. The critical lesson is that the drug's benefit is not monotonic with haemoglobin. Trials targeting normal or near-normal haemoglobin – CHOIR, CREATE and TREAT – demonstrated increased mortality, stroke, thrombosis and cancer progression. TREAT randomised 4,038 patients with diabetes and chronic kidney disease to darbepoetin alfa targeting a haemoglobin of 13 g/dL and found a doubling of fatal or non-fatal stroke (5.0% versus 2.6%; hazard ratio 1.92, 95% CI 1.38 to 2.68) [182]. The label carries a boxed warning for death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumour progression [183]. Erythropoietin is prohibited in sport under WADA category S2 [157], where it has caused deaths from hyperviscosity. There is no legitimate role for erythropoiesis-stimulating agents in musculoskeletal, sports or longevity medicine.

## Rapamycin, senolytics and incretin agonists

Rapamycin (sirolimus) is the most extensively validated geroprotector in animal models and is used off label by a self-selected community; a survey of 333 off-label users documented the practice and its heterogeneity [184]. The PEARL trial, a randomised double-blind placebo-controlled study of intermittent low-dose rapamycin in healthy older adults, found the regimen safe and reported improvements in lean tissue mass in women and in a pain-related quality-of-life measure, with no effect on most other endpoints [185]. This is a Grade C to B signal in a drug with real immunosuppressive, metabolic and stomatitis risk, and it does not support routine use.

Senolytics have moved from mice to first-in-human studies. Dasatinib plus quercetin reduced senescent-cell burden in adipose tissue and skin in diabetic kidney disease [186] and improved physical function in a small open-label study in idiopathic pulmonary fibrosis [187]. Both are pilot studies with no clinical outcome data. In osteoarthritis specifically, the senolytic UBX0101 failed its phase 2 endpoints and was discontinued [188], which is directly relevant to any senolytic claim in joint disease.

Incretin agonists have produced the single most clinically important recent result in osteoarthritis pharmacotherapy. STEP 9 randomised participants with obesity and knee osteoarthritis to once-weekly semaglutide 2.4 mg and reported a WOMAC pain improvement that exceeded the MCID alongside substantial weight loss [189]. The caution is body composition: in the STEP 1 substudy lean mass fell by approximately 9.7% of total lean mass [190], and subsequent analyses have described grip-strength and sarcopenic-obesity consequences [191]. Concurrent resistance training and protein intake of 1.2 to 1.5 g/kg/day are therefore not optional adjuncts but part of the intervention [11]. An oral incretin trial in obesity with knee osteoarthritis is now recruiting [192].

| Compound | Approved indication | Off-label use in this field | Key randomised evidence | Principal harm |
|---|---|---|---|---|
| **Metformin** | Type 2 diabetes [162] | Longevity; osteoarthritis | UKPDS 34; DPP; 2025 knee OA RCT [160,161,168] | B12 deficiency; blunted training adaptation [164,165] |
| **Nandrolone decanoate** | Anaemia of renal insufficiency (historical) | Sarcopenia; performance | Dialysis and HIV wasting only [171,173] | Cardiomyopathy, plaque, HPG suppression [174] |
| **Testosterone** | Male hypogonadism [175] | Age-related decline | TRAVERSE (n=5,246) [177] | Atrial fibrillation, AKI, PE; 2025 label change [178] |
| **Growth hormone** | GH deficiency; specific syndromes | Anti-ageing | Systematic review in healthy elderly [180] | Oedema, arthralgia, carpal tunnel, glucose intolerance; distribution a felony [179] |
| **Erythropoietin / ESAs** | Anaemia of CKD, chemotherapy [183] | Endurance performance | CHOIR, CREATE, TREAT [182] | Stroke HR 1.92; thrombosis; tumour progression [181] |
| **Rapamycin** | Transplant immunosuppression; TSC | Geroprotection | PEARL [185] | Immunosuppression, stomatitis, dyslipidaemia [184] |
| **Dasatinib + quercetin** | Dasatinib: CML | Senolytic ageing therapy | Two pilot studies [186,187] | No outcome data; UBX0101 failed in OA [188] |
| **Semaglutide** | Type 2 diabetes; obesity | Knee OA pain | STEP 9 [189] | Lean-mass loss ≈ 9.7%; sarcopenic obesity [190,191] |
| **Nicotinamide riboside / NMN** | None (supplement) | NAD+ restoration | Martens 2018; Yi 2023 [135,137] | Muscle NAD+ unchanged [136] |

**Table 10:** Prescription and longevity compounds: the gap between approved indication and actual use. In every case the randomised evidence base is narrower than the practice.

AKI, acute kidney injury; CKD, chronic kidney disease; CML, chronic myeloid leukaemia; DPP, Diabetes Prevention Program; ESA, erythropoiesis-stimulating agent; GH, growth hormone; HPG, hypothalamic-pituitary-gonadal; NAD+, nicotinamide adenine dinucleotide; NMN, nicotinamide mononucleotide; OA, osteoarthritis; PE, pulmonary embolism; TSC, tuberous sclerosis complex.

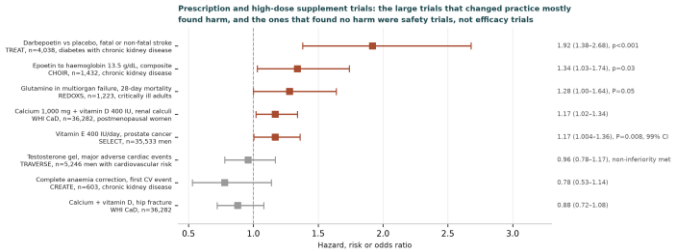


**Figure 11:** Randomised effect estimates for eight prescription and longevity compounds against their principal reported endpoint, with 95% confidence intervals. Semaglutide in STEP 9 and metformin in UKPDS 34 are the only entries whose benefit is both statistically robust and clinically substantial; the erythropoiesis-stimulating agent entry (TREAT stroke) is a harm estimate.

## Disease-Modifying Osteoarthritis Drugs

Any discussion of supplements for joint disease is incomplete without the DMOAD context, because it

establishes the ceiling of what is currently achievable. A DMOAD is defined as an agent that slows, halts or reverses structural progression of osteoarthritis while also improving or at least not worsening symptoms. As of August 2026, no such agent has been approved by the FDA, the European Medicines Agency, or any other regulatory authority [6-8].

## The regulatory vacuum

Part of the difficulty is regulatory. The FDA issued a draft guidance on structural endpoints for osteoarthritis drug development in August 2018; eight years later it remains draft and is explicitly distributed for comment purposes only [9]. The consequence is that no sponsor knows with certainty what structural change, over what duration, in what population, and paired with what symptomatic co-primary endpoint, would support approval. The OARSI clinical-trials recommendations provide methodological guidance but are not a regulatory pathway [4]. Radiographic joint-space width remains the accepted structural measure despite well-known limitations of positioning and meniscal extrusion; magnetic resonance cartilage thickness and volume, bone marrow lesions and synovitis are used as supporting measures without agreed thresholds [10].

## Anabolic and Wnt-pathway agents

Sprifermin, a recombinant human fibroblast growth factor 18, produced the most convincing structural signal in DMOAD history. In the FORWARD trial, intra-articular sprifermin 100 µg every six or twelve months increased total femorotibial cartilage thickness at two years by 0.05 mm relative to placebo, a statistically significant result that was an order of magnitude below any plausible clinical threshold and was not accompanied by symptomatic benefit [193]. The five-year follow-up showed that cartilage loss resumed between years two and five (−26 µm, 95% CI −32 to −19) with no between-group difference (p=0.80) [194]. Sprifermin therefore demonstrated that cartilage thickness can be pharmacologically increased, and simultaneously that doing so does not necessarily help the patient.

Lorecivivint, a small-molecule inhibitor of CLK2 and DYRK1A within the Wnt pathway, is the most advanced programme. A New Drug Application was submitted to the FDA on 6 January 2026 [195]. The evidence supporting it is difficult: the OA-11 phase 3 trial and the two preceding phase 3 trials each missed their designated primary endpoint [196,197]. Whatever the outcome of the regulatory review, clinicians should not describe lorecivivint to patients as an approved or proven cartilage-restoring therapy.

## Catabolic inhibition, bone-targeted and anti-inflammatory strategies

MIV-711, a selective cathepsin K inhibitor, reduced femoral cartilage thinning and bone area in a 26-week phase 2a trial while failing its symptomatic primary endpoint; a post-hoc analysis reported a WOMAC pain difference of −5.0 (95% CI −8.69 to −1.3; p=0.008) [198,199]. Strontium ranelate produced a genuine structural and symptomatic result in the SEKOIA trial [200], but the compound was withdrawn from the European market following an Article-20 referral over cardiovascular and severe cutaneous risk [201] – a reminder that a positive DMOAD result does not survive an unacceptable safety profile. Zoledronic acid, targeted at bone marrow lesions in the ZAP2 trial, showed no effect on tibiofemoral cartilage volume [202], and oral salmon calcitonin failed on joint-space width in two large registered trials [203,204].

Interleukin-1 blockade has failed consistently. Intra-articular anakinra was no better than placebo [205],

and lutikizumab, an anti-interleukin-1α/β dual variable domain immunoglobulin, missed its endpoints in both erosive hand and knee osteoarthritis [206]. Tumour necrosis factor inhibition in hand osteoarthritis has been tested at least three times – etanercept, adalimumab and infliximab-class agents – without convincing structural or symptomatic benefit [207–209], and hydroxychloroquine was null in the OA-TREAT trial [210]. Nerve growth factor inhibition with tanezumab achieved analgesia but produced rapidly progressive osteoarthritis and osteonecrosis; the FDA advisory committees voted 19 to 1 against approval in March 2021 and the programme was discontinued that October [211–213].

Senolytic and cell or gene-therapy approaches have not yet succeeded either. UBX0101 failed phase 2 and was discontinued [188]. TissueGene-C (TG-C), an allogeneic chondrocyte and retrovirally transduced growth-factor cell therapy, missed its primary endpoints in phase 3 in July 2026 [214]. Diacerein retains approval in some jurisdictions with restricted indications after an EMA review [215] and is under study for structural effect [216]. Colchicine is being tested for the incidence of joint replacement [217], and an interleukin-1 receptor antagonist gene therapy, PCRX-201, has entered clinical study [218]. Earlier programmes including TPX-100, LNA043, cindunistat and SAR113945 are catalogued in the 2025 systematic review of DMOAD trials [219].

| Agent | Class or target | Highest phase | Structural result | Outcome |
|---|---|---|---|---|
| **Sprifermin** | FGF-18 (anabolic) | Phase 2 (FORWARD) | +0.05 mm cartilage thickness at 2 years; loss resumed by year 5 [193,194] | Not pursued to phase 3 |
| **Lorecivivint** | CLK2/DYRK1A, Wnt pathway | Phase 3; NDA 6 Jan 2026 | Signals in subgroups; primary endpoints missed in all three phase 3 trials [196,197] | Under FDA review [195] |
| **MIV-711** | Cathepsin K inhibitor | Phase 2a | Reduced cartilage thinning and bone area; symptomatic primary missed [198] | Post-hoc pain benefit only [199] |
| **Strontium ranelate** | Bone and cartilage dual action | Phase 3 (SEKOIA) | Reduced joint-space narrowing with symptomatic benefit [200] | Withdrawn in EU on safety grounds [201] |
| **Zoledronic acid** | Bisphosphonate (BML-targeted) | Phase 3 (ZAP2) | No effect on tibiofemoral cartilage volume [202] | Negative |
| **Oral salmon calcitonin** | Calcitonin receptor | Phase 3 (×2) | No effect on joint-space width [203,204] | Discontinued |
| **Anakinra (IA)** | IL-1 receptor antagonist | Phase 2 | Not assessed; no symptomatic benefit [205] | Negative |
| **Lutikizumab** | Anti-IL-1α/β DVD-Ig | Phase 2b | No structural benefit in hand or knee OA [206] | Discontinued |
| **Etanercept / adalimumab** | TNF inhibition | Phase 2–3 | No convincing structural benefit in erosive hand OA [207–209] | Negative |
| **Hydroxychloroquine** | Immunomodulator | Phase 3 (OA-TREAT) | No radiographic effect at 52 weeks [210] | Negative |
| **Tanezumab** | Anti-NGF | Phase 3 | Rapidly progressive OA and osteonecrosis [213] | Advisory committee 19–1 against; discontinued [211] |
| **UBX0101** | Senolytic (MDM2/p53) | Phase 2 | Failed endpoints [188] | Discontinued |
| **TissueGene-C (TG-C)** | Allogeneic cell and gene therapy | Phase 3 | Missed primary endpoints, July 2026 [214] | Negative |
| **Metformin** | AMPK activator (repurposed) | Phase 3 RCT | Cartilage volume trial ongoing [170] | Symptomatic benefit only [168] |

**Table 11:** The DMOAD development record. Fourteen programmes across anabolic, catabolic, bone-targeted, anti-inflammatory, anti-nerve-growth-factor, senolytic and cell-therapy strategies. None has produced an approved structural claim.

AMPK, AMP-activated protein kinase; BML, bone marrow lesion; DVD-Ig, dual variable domain immunoglobulin; FGF, fibroblast growth factor; IA, intra-articular; IL, interleukin; NDA, New Drug Application; NGF, nerve growth factor; OA, osteoarthritis; RCT, randomised controlled trial; TNF, tumour necrosis factor.

**Not one disease-modifying osteoarthritis drug has been approved in the United States or the European Union; the programmes and the reason each one stopped**

| Programme | Class | Stage | Key endpoint result | Status |
|---|---|---|---|---|
| Lorecivivint (SM04690) | Wnt pathway, CLK2/DYRK1A | Phase 3 | All 3 phase 3 trials missed primary (OA-11 p=0.185; OA-10 p=0.703) | NDA filed |
| Sprifermin (rhFGF18) | FGF18 receptor agonist | Phase 2 | Cartilage +0.05 mm at 2 y (p=0.015); loss resumed years 2–5 (p=0.80) | Halted |
| Tanezumab | Anti-nerve growth factor | Phase 3 | Rapidly progressive OA up to 2.8%; joint replacement 6.9% at high dose | Rejected 19-1 |
| Lutikizumab (ABT-981) | Anti-IL-1α/β antibody | Phase 2 | Pain week 16: p=0.050 / 0.834 / 0.415; MRI synovitis not significant | Abandoned |
| Anakinra, intra-articular | IL-1 receptor antagonist | Phase 2 | WOMAC week 4 p=0.67 and p=0.77 | Abandoned |
| MIV-711 | Cathepsin K inhibitor | Phase 2 | Missed on pain; bone area and cartilage thickness effects; post-hoc rescue | Discontinued |
| Strontium ranelate | Bone anti-resorptive/anabolic | Phase 3 | Hit both structural co-primaries (p<0.001 and p=0.018) | Not approved |
| Zoledronic acid | Bisphosphonate | Phase 3 | Cartilage volume p=0.50; pain p=0.21; knee replacement 9% vs 2% | Negative |
| Broad MMP inhibitors | Matrix metalloproteinase | Phase 2 | Musculoskeletal syndrome: arthralgia, palmar fibrosis, tendon nodules | Toxicity |
| GSK2394002 | ADAMTS-5 inhibitor | Preclinical | Arterial-pressure effects in primates | Stopped |
| Methotrexate | Antifolate, anti-synovitis | Phase 3 | PROMOTE pain 0.79 NRS points (p=0.030), below any plausible MCID; MRI unchanged | Sub-threshold |
| Metformin | AMPK activation | RCT | VAS −11.4 mm (p=0.01) vs MCID 15 mm; no structural endpoint measured | Sub-threshold |
| Platelet-rich plasma (RESTORE) | Autologous growth factors | Phase 3 | Pain p=0.17; cartilage volume p=0.81; 29 of 31 secondary outcomes null | Negative |
| Intra-articular triamcinolone | Corticosteroid | RCT | No pain benefit; cartilage loss −0.11 mm greater than saline | Cartilage harm |

**Figure 12:** The DMOAD graveyard. Fourteen development programmes plotted by highest phase reached and by outcome. Programmes are coloured by whether they failed on efficacy, failed on safety, or remain under review. The single agent still in regulatory review, lorecivivint, reached that point after three phase 3 trials that missed their primary endpoints.

Repurposed immunomodulators complete the record. The PROMOTE trial randomised patients with knee osteoarthritis to oral methotrexate and reported a statistically significant reduction in pain [220], yet the magnetic resonance substudy found no change in synovial volume [221]. Methotrexate is therefore a candidate symptomatic agent for the inflammatory osteoarthritis phenotype and not a structure-modifying drug, which is the same conclusion reached for metformin.

## Injectables and the structural question

The injectable agents used in practice have been tested against structural endpoints and have not passed. Intra-articular triamcinolone given every twelve weeks for two years produced significantly greater cartilage volume loss than saline (−0.21 mm versus −0.10 mm; p=0.01) with no pain benefit [222]. Viscosupplementation showed a clinically irrelevant pain effect and a serious adverse-event signal across 169 trials [77]. Platelet-rich plasma in the RESTORE trial did not differ from saline for either pain or medial tibial cartilage volume over twelve months [223]. The one nutraceutical structural signal, the Boswellia pilot, requires independent replication before it can be weighed against this record [93,94].


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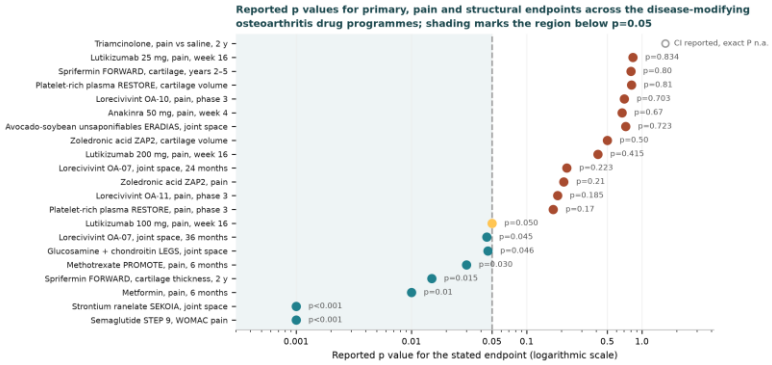


**Figure 13:** Reported p values for structural endpoints across twenty-one supplement, injectable and DMOAD trials, on a logarithmic scale. The clustering of values just below 0.05 in small industry-funded trials, contrasted with the null results of the larger independent trials, is the signature of a literature in which statistical significance has been optimised in place of clinical relevance.

## Guideline discordance

Six major bodies have issued recommendations on the same agents using substantially the same trials, and they disagree in the strongest possible terms. This is not a nuance of wording; it is a direct contradiction that patients encounter when they read more than one source.

The National Institute for Health and Care Excellence guideline NG226 instructs clinicians not to offer glucosamine or chondroitin [224]. The American College of Rheumatology strongly recommends against glucosamine, and conditionally against chondroitin except in hand osteoarthritis [80]. OARSI strongly recommends against glucosamine and chondroitin for all osteoarthritis phenotypes [82]. The American Academy of Orthopaedic Surgeons rates the evidence as not supporting use [81]. Against these, the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases strongly recommends patented crystalline glucosamine sulfate as first-line background therapy [225]. EULAR's hand-osteoarthritis recommendations sit between these positions [226].

Three factors explain the divergence. First, agent specificity: ESCEO restricts its recommendation to the patented crystalline sulfate preparation and excludes the hydrochloride and generic sulfates, whereas the guidelines recommending against pool all preparations. Second, the treatment of industry-funded trials: ESCEO includes them at face value, while NICE, ACR and OARSI down-weight or exclude them for risk of bias. Third, the choice of relevance threshold: applying the −0.37 standardised mean difference threshold eliminates the effect, while accepting statistical significance without an anchor preserves it [5]. The same three factors explain the parallel disagreement over intra-articular hyaluronic acid, where national bodies reach opposite funding decisions [83].

The practical implication is that a clinician should disclose the disagreement rather than select the guideline that matches their preference. It is also worth noting what all six guidelines agree on: structured exercise and weight management are core recommendations with effect sizes exceeding those of any supplement or injectable [227,228]. A patient counselled toward exercise and a 5% to 10% weight reduction receives a larger expected benefit than any agent in this review.

| Body and year | Glucosamine | Chondroitin | IA hyaluronic acid | Exercise / weight loss |
|---|---|---|---|---|
| **NICE NG226 (2022) [224]** | Do not offer | Do not offer | Do not offer | Core recommendation |
| **ACR/AF (2019) [80]** | Strongly against | Conditionally against (hand: conditional for) | Conditionally against (knee) | Strongly for |
| **OARSI (2019) [82]** | Strongly against, all phenotypes | Strongly against, all phenotypes | Uncertain | Core recommendation |
| **AAOS OAK3 (2021) [81]** | Evidence does not support | Evidence does not support | Recommend against | Strong for |
| **ESCEO (2019) [225]** | Strongly for pCGS as background therapy | For pharmaceutical-grade chondroitin | For, in step 2 | Core recommendation |
| **EULAR hand OA (2018) [226]** | Not recommended | Weak, may be considered | Not recommended | Core recommendation |

**Table 12:** Guideline discordance on the same agents and largely the same trials. The disagreement is driven by agent specificity, by the handling of industry-funded trials, and by whether a minimal clinically important difference threshold is applied. All six bodies agree on exercise and weight management.

AAOS, American Academy of Orthopaedic Surgeons; ACR/AF, American College of Rheumatology/ Arthritis Foundation; ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; EULAR, European Alliance of Associations for Rheumatology; IA, intra-articular; NICE, National Institute for Health and Care Excellence; OARSI, Osteoarthritis Research Society International; pCGS, patented crystalline glucosamine sulfate.

## Regulation, Product Quality And Adulteration

### Three regulatory regimes

In the United States the Dietary Supplement Health and Education Act of 1994 established that supplements are regulated as a category of food, not as drugs. Manufacturers are not required to demonstrate efficacy or safety before marketing; the burden of proof for removing a product rest with the FDA after harm has occurred [229]. Structure-function claims are permitted provided they carry the disclaimer that the statement has not been evaluated by the FDA and that the product is not intended to diagnose, treat, cure or prevent any disease [230]. New dietary ingredients require a seventy-five-day premarket notification [231], and current good manufacturing practice for supplements is codified in 21 CFR Part 111, including the identity-testing requirement of § 111.75 [232,233].

The European Union takes a different approach. Directive 2002/46/EC harmonises permitted vitamin and mineral sources and labelling [234], and Regulation (EC) No 1924/2006 requires that any nutrition or health claim be pre-authorised and entered in the EU Register [235,236]. The practical effect is that most claims made routinely in the United States cannot legally be made in Europe. Brazil occupies an intermediate position: ANVISA RDC 243/2018, with Instrução Normativa 28/2018, defines food supplements, sets permitted substances and limits in its annexes, and specifies allowed claims [237].

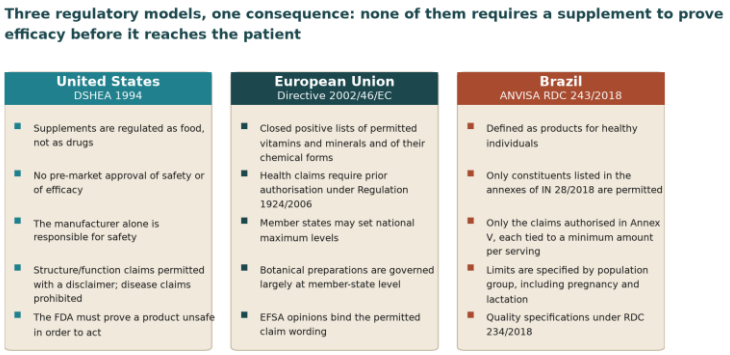


**Figure 14:** Comparison of the three regulatory regimes most relevant to readers of this review: the United States under DSHEA, the European Union under Directive 2002/46/EC and Regulation 1924/2006, and Brazil under ANVISA RDC 243/2018. The regimes differ in premarket burden, claim authorisation and enforcement mechanism.

## Adulteration

Adulteration is not an occasional aberration. Tucker and colleagues analysed the FDA's tainted-products database and identified 776 dietary supplements containing unapproved pharmaceutical ingredients between 2007 and 2016, from 146 manufacturers; sildenafil, sibutramine and anabolic steroids predominated, and the products were concentrated in the sexual-enhancement, weight-loss and muscle-building categories [3,238,239]. A striking finding was that 97.6% of products the FDA had identified as adulterated remained available for purchase, and that voluntary recall was the principal enforcement tool.

Label inaccuracy extends beyond deliberate adulteration. The melatonin gummy analysis found actual content between 74% and 347% of the labelled amount, with one product containing no detectable melatonin and five containing unlabelled cannabidiol [2]. Independent laboratory testing of joint supplements has repeatedly found chondroitin content below label [67], and the FDA maintains a specific notification page for pain and arthritis products containing hidden ingredients [240]. Third-party certification programmes address this directly: NSF Certified for Sport performs lot-by-lot testing against more than 290 banned substances and audits the manufacturing facility [109]. For any patient who is drug tested, or who is taking a narrow-therapeutic-index medication, certification should be treated as a requirement rather than a preference.

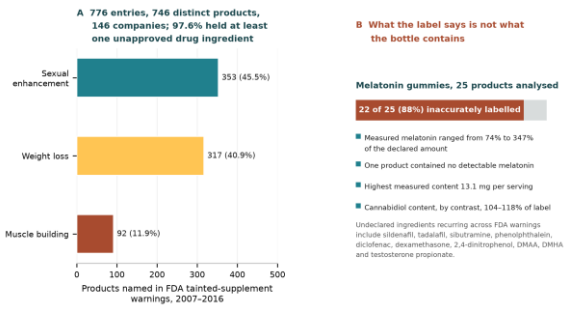


**Figure 15:** Adulteration of dietary supplements identified in the FDA tainted-products database, 2007 to 2016: 776 products, 146 manufacturers, and 97.6% of identified adulterated products still available for purchase after FDA identification.

## Hepatotoxicity and interactions

The proportion of drug-induced liver injury attributable to herbal and dietary supplements in the US DILIN cohort has risen from approximately 7% in 2004 to 20% in the 2013 analysis and to about 18% to 21% in the 2023 report of 1,780 cases [241,242]. The principal agents are anabolic steroids, green tea extract, multi-ingredient nutritional supplements, ashwagandha, turmeric and Garcinia cambogia [88,243,244]. Turmeric-associated liver injury has a documented HLA-B*35:01 association and a characteristic hepatocellular pattern [89,90,243].

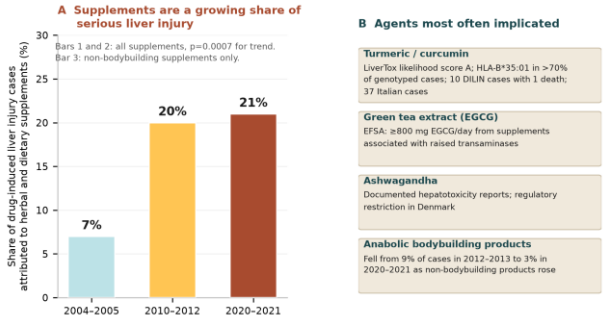


**Figure 16:** Rising proportion of drug-induced liver injury attributable to herbal and dietary supplements in the US Drug-Induced Liver Injury Network, from approximately 7% in the earliest cohort analyses to 20% and then 21% in the most recent reports, with the principal implicated agents named.

Interactions are systematically under-recognised because patients do not report supplements as medicines. A cohort of 41,257 patients taking warfarin identified 2,640 who were using a supplement with a documented interaction [59]. Agents that raise the international normalised ratio include vitamin E at high dose, ginkgo, garlic, ginger, curcumin, fish oil, cranberry and glucosamine; agents that lower it include vitamin K, coenzyme Q10, St John's wort and ginseng [58,245–247]. Perioperative guidance is to discontinue herbal and dietary supplements one to three weeks before elective surgery [22,248]. Systematic medication reconciliation must explicitly name supplements, because a question about medicines alone will not elicit them.

| Agent | Interaction or risk | Mechanism | Clinical action |
|---|---|---|---|
| **St John's wort** | Failure of contraceptives, ciclosporin, warfarin, antiretrovirals [131] | CYP3A4 and P-glycoprotein induction | Contraindicated with most narrow-index drugs |
| **Vitamin E (high dose)** | Raised INR, bleeding [58] | Vitamin K antagonism, antiplatelet | Avoid above 400 IU/day on anticoagulants |
| **Ginkgo, garlic, ginger, fish oil, curcumin** | Bleeding, raised INR [22,59] | Antiplatelet activity | Stop 1–3 weeks preoperatively [248] |
| **Glucosamine** | Raised INR on warfarin [245–247] | Uncertain; case reports and regulator alerts | Monitor INR after initiation |
| **Coenzyme Q10** | Reduced warfarin effect [58] | Structural similarity to vitamin K | Monitor INR |
| **Berberine** | Statin and ciclosporin toxicity [119] | CYP3A4 and 2D6 inhibition | Avoid with narrow-index substrates |
| **Green tea extract** | Hepatotoxicity [144,145] | EGCG dose-dependent hepatocellular injury | Avoid ≥ 800 mg/day EGCG from supplements |
| **Turmeric / curcumin** | Hepatotoxicity; bleeding [88,243] | HLA-B*35:01 association; CYP inhibition | Baseline and periodic liver enzymes |
| **Ashwagandha** | Cholestatic hepatitis [129] | Idiosyncratic | Discontinue on any transaminase rise |
| **Red yeast rice** | Myopathy, rhabdomyolysis, hepatitis [120] | Contains lovastatin (monacolin K) | Treat as a statin; do not combine |
| **Selenium** | Diabetes incidence [48] | Unclear; replete populations | Dietary intake only |
| **Melatonin gummies** | Content 74–347% of label; unlabelled CBD [2] | Manufacturing variability | Prefer certified products |

**Table 13:** Clinically significant supplement interactions and safety signals, with the action required. Medication reconciliation must ask about supplements by name.

CBD, cannabidiol; CYP, cytochrome P450; EGCG, epigallocatechin-3-gallate; INR, international normalised ratio.

## Citation-Integrity Audit

Every reference in a representative seventeen-reference narrative summary of this subject was retrieved and compared against the claim it was cited to support. Twelve references (70.6%) were CONFIRMED, one further reference (5.9%) was confirmed as stating the claim but has since been superseded by a later consensus statement, and four (23.5%) were PARTIALLY WRONG. None was NOT FOUND, meaning that no reference was fabricated; the failure mode was misattribution rather than invention. Because misattribution is invisible to a reader who does not retrieve the source, and because it propagates with every reuse of the summary, it is reported here as a formal result.

The four misattributions each illustrate a distinct mechanism. In the first, a trial's null primary endpoint is ignored in favour of a secondary finding: the Meydani vitamin E trial in nursing-home residents did not reduce the incidence of all respiratory tract infection, its designated primary outcome [46]. In the second, a source from an adjacent field is applied to a claim it does not address: a review of oral collagen in dermatological applications was cited to support joint benefit [249,250]. In the third, the cited author reaches the opposite conclusion: Wolfe's analysis concludes that the branched-chain amino acid anabolic claim is unwarranted [102]. In the fourth, a superseded guideline is cited and, additionally, is cited for a drug it does not discuss: the 2010 Endocrine Society testosterone guideline has been replaced by the 2018 version and does not address nandrolone [175,176]. A fifth, non-scored issue was identified: diabetes-care summaries citing the 2020 ADA/EASD consensus should now cite the 2022 update.

Two bibliographic conventions accounted for most of the formatting errors found. MDPI journals, including Nutrients and the International Journal of Molecular Sciences, use sequential article numbers rather than page ranges, so a citation ending in a page range is malformed [251]. Cochrane reviews require a year-prefixed issue number and a publication-version suffix, as in 2010;(4): CD002967.pub4 [60,163].

| # | Cited source | Claim it was used to support | Verdict | Finding |
|---|---|---|---|---|
| **1** | Meydani 2004, vitamin E in nursing-home residents [46] | Vitamin E improves immune function and reduces infection | **PARTIALLY WRONG** | Primary endpoint (all respiratory infection) not significant; effect confined to a secondary upper-respiratory analysis |
| **2** | Papakonstantinou 2012 / Choi 2019, oral collagen [249,250] | Collagen supports joint and cartilage health | **PARTIALLY WRONG** | Sources address skin ageing and dermatological endpoints, not joint structure or pain |
| **3** | Wolfe 2017, branched-chain amino acids [102] | BCAA supplementation stimulates muscle protein synthesis | **PARTIALLY WRONG** | The cited author concludes the claim is unwarranted; the source contradicts the statement |
| **4** | Bhasin 2010, Endocrine Society guideline [176] | Guideline support for anabolic steroid (nandrolone) use | **PARTIALLY WRONG** | Superseded by the 2018 guideline [175]; neither version addresses nandrolone |

| # | Cited source | Claim it was used to support | Verdict | Finding |
|---|---|---|---|---|
| **5–16** | Towheed, Clegg, Singh, Hemilä, Holick, Garrido-Maraver, Hewlings, Siddiqui, Mashhadi, Kim & Kim, Kuptniratsaikul, Jelkmann [27,38,54,60,61,68,86,87,95,181,251,252] | Various agent-specific claims | **CONFIRMED** | Source states the claim; bibliographic details corrected where MDPI article numbers or Cochrane pub-version suffixes were missing |
| **17** | Buse 2020 ADA/EASD consensus | Metformin as first-line therapy | **CONFIRMED but superseded** | Should now cite the 2022 ADA/EASD consensus update |

**Table 14:** Citation-integrity audit of a representative seventeen-reference summary. Twelve of seventeen references (70.6%) were confirmed, four (23.5%) were misattributed, and none was fabricated. The four failure mechanisms were: null primary endpoint ignored, wrong-field source, source contradicts claim, and superseded guideline cited for a drug it does not discuss.

ADA/EASD, American Diabetes Association / European Association for the Study of Diabetes; BCAA, branched-chain amino acids.

The recommendation that follows is procedural rather than rhetorical: no citation should enter a clinical summary, patient handout or protocol without the citing author having read the abstract and the primary-endpoint result in full. Where a claim rests on a secondary analysis, that must be stated. Where a guideline has been superseded, the current version must be cited. A 23.5% misattribution rate in a short reference list is not unusual, and it is entirely preventable.

## A Four-Tier Practical Framework

The synthesis above supports a four-tier framework that separates what should be offered unprompted, what should be discussed if the patient raises it, what should not be recommended, and what should be actively discouraged. Assignment depends jointly on evidence grade and on whether the effect crosses the relevant anchor, with safety and cost as modifiers.

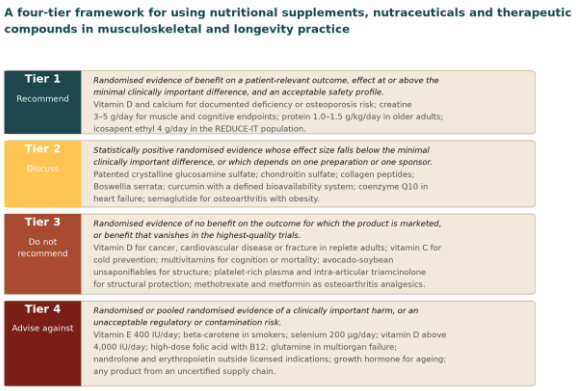


**Figure 17:** Four-tier framework for supplement and off-label prescribing in musculoskeletal, metabolic and longevity practice. Tier assignment requires both an adequate evidence grade and an effect that crosses the domain-specific minimal clinically important difference; safety signals move an agent down a tier regardless of efficacy.

| Tier | Definition | Representative agents | Counselling approach |
|---|---|---|---|
| **Tier 1 – Recommend** | Grade A or B evidence with an effect exceeding the MCID and acceptable safety | Structured exercise and weight management [227,228]; protein 1.0–1.5 g/kg/day [11]; creatine 3–5 g/day [106]; vitamin D with calcium in older adults at fracture risk [34]; icosapent ethyl in the tested indication [19]; lutein and zeaxanthin within AREDS2 [151]; semaglutide with resistance training in obesity plus knee OA [189] | Offer unprompted; state the expected magnitude of benefit |
| **Tier 2 – Discuss if raised** | Plausible mechanism, Grade B or C evidence, effect at or below the MCID, good safety, patient accepts cost | Collagen peptides [69] and UC-II [71]; enhanced curcumin [87]; Boswellia [93]; omega-3 1 g/day; coenzyme Q10 in heart failure [55]; magnesium [156]; berberine with interaction screening [118]; HMB in clinical states [110]; GlyNAC [116]; urolithin A [140]; beta-alanine and citrulline [111,113] | Set expectations explicitly; agree a review date and a stopping rule |
| **Tier 3 – Do not recommend** | High-quality evidence of absence of clinically relevant benefit, or evidence too weak to justify the cost | Glucosamine and chondroitin [5,224]; oral and intra-articular hyaluronic acid [76,77]; ginkgo [133]; saw palmetto [154]; echinacea [146]; chromium picolinate [123]; silymarin [155]; spermidine [139]; melatonin as a primary hypnotic [130]; leucine or BCAA as a sole protein strategy [102] | Explain what the evidence shows; do not simply decline |
| **Tier 4 – Advise against** | Demonstrated harm, or an unapproved substance with no human efficacy data | Vitamin E ≥ 400 IU/day [42,44]; beta-carotene in smokers [47]; selenium in replete adults [48]; green tea extract ≥ 800 mg EGCG [144]; red yeast rice outside a regulated cap [120]; glutamine in critical illness [104]; nandrolone for sarcopenia or performance [157,174]; erythropoiesis-stimulating agents for performance [182]; growth hormone for anti-ageing [179,180]; BPC-157 and unapproved research peptides [158,159] | State the specific documented harm and the source |

**Table 15:** Four-tier framework for supplement and off-label prescribing. Tier assignment requires both an adequate evidence grade and an effect crossing the domain-specific minimal clinically important difference; a documented harm signal moves an agent to Tier 4 irrespective of efficacy.

AREDS2, Age-Related Eye Disease Study 2; BCAA, branched-chain amino acids; EGCG, epigallocatechin-3-gallate; HMB, β-hydroxy-β-methylbutyrate; MCID, minimal clinically important difference; OA, osteoarthritis; UC-II, undenatured type II collagen.

### Applying the framework in the consultation

Four questions operationalise the framework. What is the patient's actual goal, expressed as an outcome rather than as a product? What is the largest available effect for that goal, and is the patient already receiving it? Does the agent under discussion have evidence that crosses the anchor for that outcome? And what are the interaction, hepatotoxicity, perioperative and doping-control consequences for this particular patient? A patient with knee osteoarthritis and obesity whose goal is to walk further is better served by a weight-management and exercise programme, with an incretin agonist and resistance training where indicated, than by any combination of the agents in Sections 4 and 5 [189,227,228].

Three documentation habits follow. First, record supplements in the medication list by name, dose and brand, since brand determines content [2]. Second, specify a review date and a stopping rule for every Tier 2 agent, because an agent with a sub-MCID effect and a monthly cost should not continue indefinitely by default. Third, ask about supplements explicitly at every preoperative and every anticoagulation review [22,59].

## Limitations

This review has several limitations that bear on how its conclusions should be used. It is a critical narrative review with systematic search elements, not a systematic review conducted to PRISMA, and no protocol

was registered. No new meta-analysis was performed; pooled estimates are reported as published, which means that any error in the source synthesis is inherited. The evidence-grading scheme in Section 2.2 is explicit but is the authors' own operationalisation rather than a validated instrument, and a formal GRADE assessment with summary-of-findings tables was not produced.

The MCID anchors in Table 1 are defensible but not uncontested; different anchors would move some agents between tiers, and the choice of the −0.37 standardised mean difference threshold in particular is consequential for glucosamine and chondroitin [5]. Publication bias almost certainly inflates the supplement literature, and the funding-source analysis in Figure 7 quantifies part but not all of that distortion. Language restriction to English, Portuguese and Spanish sources may have excluded relevant trials, particularly for traditional botanicals published in Chinese, Japanese and Korean journals.

The citation audit examined a single seventeen-reference summary and cannot be generalised to a population estimate of misattribution rates. Regulatory and trial status is current to 15 August 2026 and will change: the lorecivivint New Drug Application is under review, several registered structural trials are ongoing [192,216–218], and the FDA structural-endpoint guidance may yet be finalised [9]. Finally, the framework in Section 13 is a clinical-reasoning aid derived from the evidence reviewed here; it has not been prospectively validated against patient outcomes.

## Conclusions

Five conclusions follow from this synthesis. First, evidence quality and clinical relevance must be assessed jointly. A statistically significant pooled effect that falls below the minimal clinically important difference for its domain is not a reason to recommend an agent, and the majority of the supplement literature in musculoskeletal medicine occupies exactly that position [5,70].

Second, a small number of agents genuinely earn a recommendation. Structured exercise and weight management outperform every pharmacological and nutraceutical option in osteoarthritis [227,228]; adequate protein and creatine monohydrate are the two best-evidenced anabolic interventions available without prescription [11,106]; vitamin D with calcium prevents fracture in the population for which it was designed and not in others [29,34]; purified high-dose EPA reduces cardiovascular events in one specific tested indication [19]; and semaglutide with concurrent resistance training is the most clinically significant new option for knee osteoarthritis with obesity [189,191].

Third, several widely sold agents cause measurable harm, and the therapeutic window for isolated micronutrients is narrower than commonly assumed. Vitamin E at 400 IU/day and above, beta-carotene in smokers, selenium in replete populations, green tea catechins at or above 800 mg/day of epigallocatechin-3-gallate, red yeast rice outside a regulated monacolin cap, and glutamine in multi-organ failure all have randomised or pooled evidence of harm from trials designed to demonstrate benefit [43,44,48,104,120,144].

Fourth, there is no disease-modifying osteoarthritis drug. Fourteen development programmes across every plausible mechanistic class have failed on efficacy or on safety; the one agent still under regulatory review reached that point after three phase 3 trials that missed their primary endpoints; and the FDA

guidance defining the structural approval pathway has remained in draft for eight years [6,9,197]. No supplement, injectable or orthobiologic should be described to a patient as regenerating cartilage.

Fifth, the integrity of the literature that clinicians use is itself a clinical variable. A 23.5% misattribution rate in a seventeen-reference summary, including one instance in which the cited author refutes the claim, is preventable by the simple discipline of reading each source in full before citing it [46,102]. For a field that increasingly relies on generated summaries, this discipline is not optional.

The consultation that opened this review can therefore be answered concisely. Most of what patients ask about does not work at a magnitude they would notice; a few things do; a few things are harmful; product quality cannot be assumed from the label; and the interventions with the largest effect are the ones that require the most effort and generate the least revenue.

## Declarations

**Funding:** This work received no external funding. No commercial entity manufacturing, distributing or marketing any product named in this review contributed financially, materially or editorially to its preparation.

**Conflicts of interest:** The author practises orthopaedic, sports and regenerative medicine and delivers educational activities in regenerative medicine. No royalties, consultancy fees, speaker fees or equity relationships exist with any manufacturer of the supplements, nutraceuticals, injectables or medications discussed.

**Ethical approval and consent:** Not applicable. This review analyses published literature, regulatory documents and public trial registries; no human participants, identifiable data or biological material were involved.

**Data availability:** All data supporting this review are contained in the cited publications, regulatory documents and registry records, each of which is identified by a resolvable link in the reference list. Registry records were retrieved from ClinicalTrials.gov. No new datasets were generated.

**Authors' contributions (CRediT). All authors:** conceptualisation, methodology, formal analysis, investigation, data curation, writing – original draft, writing – review and editing, visualisation, supervision. The authors read and approved the final manuscript and accepts responsibility for its integrity.

**Use of artificial intelligence:** Generative artificial-intelligence tools were used to assist with table construction, figure rendering and language editing. Every factual statement, numerical value and citation was verified by the author against the primary source. The citation-integrity audit reported in Section 12 was conducted specifically because generated summaries in this field propagate misattributions; that audit was performed by full-text retrieval of each source. The author accepts full responsibility for the content.

**Acknowledgements:** None.

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