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NAD$^+$, Resveratrol, Omega-3 Fatty Acids, Vitamin D and Orthobiologics: A Critical Synthesis of the Human Evidence for a Synergistic Approach to Lifespan Extension, Tissue Repair and Wellness

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Abstract

Background: Nicotinamide adenine dinucleotide (NAD$^+$) precursors, resveratrol, marine omega-3 fatty acids, vitamin D and autologous orthobiologics are increasingly bundled into commercial longevity and regenerative programmes on the argument that they act on complementary hallmarks of ageing and therefore act synergistically. The argument is mechanistically attractive and, at the level of human outcomes, almost entirely untested.

Objective: To assemble the randomised human evidence for each agent, to state precisely what has and has not been demonstrated, and to test the synergy hypothesis against the only human factorial data that exist.

Findings. NAD⁺ precursors reliably raise blood NAD⁺ in a dose-dependent manner — nicotinamide riboside 1000 mg/day increases whole-blood NAD⁺ by 142 ± 14% over eight weeks [1] — but the only reproducible downstream human signal is a reduction in circulating inflammatory markers [2]; muscle NAD⁺ did not change significantly in aged men [3], the pooled effect on physical performance is null (SMD 0.24, 95% CI −0.03 to 0.50, p = 0.074) [4], and nicotinamide riboside did not extend lifespan in either sex in the genetically heterogeneous mice of the Interventions Testing Program [5]. Resveratrol fails on pharmacokinetics before it fails on efficacy: oral bioavailability is "considerably less than 1%" [6] and a 5 g dose reaches a plasma Cmax of 2.4 µmol/L [7], below the ≥ 5 µmol/L needed for the cell-based effects on which the entire rationale rests; the largest neurological trial reported greater brain volume loss on active drug [8]. Omega-3 fatty acids and vitamin D are the two agents with genuinely positive randomised signals, and both are narrow. In DO-HEALTH, a 2×2×2 factorial trial of 2157 adults aged 70 and over, all six co-primary endpoints were null [9], yet omega-3 shifted three epigenetic clocks by roughly three to four months of biological age over three years [10]. Vitamin D shows a genuine but non-monotonic dose-response: 800–1000 IU/day reduces fractures and falls, while ≥ 1000 IU/day increased serious falls in STURDY [11] and 4000–10 000 IU/day reduced radial volumetric bone density in a dose-dependent fashion [12]. For orthobiologics, the largest placebo-controlled knee trial was null [13], a 2026 network meta-analysis of 24 trials found no orthobiologic exceeding the minimal clinically important difference [14], and contextual effects account for roughly 63% of the observed benefit [15].

The synergy gap: We could identify no randomised trial that combines a geroprotective nutraceutical with platelet-rich plasma, bone marrow aspirate concentrates or a mesenchymal stromal cell product and reports a clinical outcome. No orthobiologic trial stratifies participants by 25-hydroxyvitamin D status, despite a 39.4% prevalence of deficiency in arthroplasty candidates [16] and 70.9% in knee osteoarthritis [17]. The only human factorial evidence of additivity among any of these agents is the DO-HEALTH methylation-clock analysis, worth roughly three months of clock age [10].

Conclusions: The honest position is that these agents are individually modest, jointly untested, and marketed far ahead of their evidence. We propose a three-tier clinical framework separating correction of a measured deficiency from reasonable but unproven adjuncts and from research-only agents, a peri-procedural schedule for supplement handling around an orthobiologic injection, and a 2×2×2 factorial trial (N = 480) that would, for the first time, test the synergy claim directly.

Keywords

Nicotinamide riboside; Resveratrol; Omega-3 fatty acids; Vitamin D; Platelet-rich plasma; Bone marrow aspirate concentrate; Mesenchymal stromal cells; Epigenetic clocks; Healthspan.

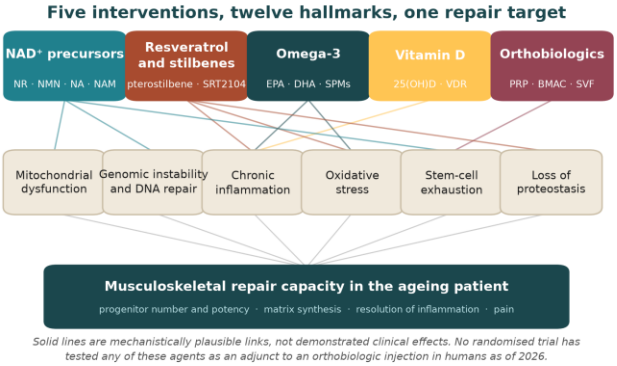

Figure 1: The architecture of this review. Five agent classes are mapped onto the endpoints at which each has been tested in humans. Green denotes a reproducible randomised signal, amber a mixed or underpowered literature, and red a null or adverse randomised result. The right-hand column shows the single question this review was written to answer: whether any of these agents changes the outcome of an orthobiologic injection.

Introduction

The hallmarks of ageing framework organised a fragmented biology into nine, and later twelve, interlocking processes [18,19]. It was descriptive, not prescriptive, but it was rapidly read as a shopping list: if genomic instability, that mitochondrial dysfunction, cellular senescence and chronic inflammation are separable, then a compound address each of them should, in combination, address ageing. That inference is the intellectual engine behind the modern longevity clinic, and it is the inference this review

examines.

Four agents dominate the commercial and clinical conversation. NAD^+ precursors are offered on the argument that NAD^+ falls with age and can be restored. Resveratrol is offered as a sirtuin activator and calorie restriction mimetic. Marine omega-3 fatty acids are offered as anti-inflammatory and pro-resolving agents. Vitamin D is offered as a pleiotropic hormone with receptors in muscle, bone and immune tissue. Increasingly, these four are bundled with autologous orthobiologics — platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC) and adipose-derived stromal vascular fraction — on the further argument that a metabolically optimised patient will respond better to an injected cell or growth factor product [20,21].

Each step of that argument is plausible. Almost none of it has been tested in the form in which it is sold. This review was written because the gap between the mechanistic literature and the randomised literature has become wide enough to constitute a clinical governance problem. Patients are being charged for combinations whose components are individually modest and whose combination has never been randomised.

We therefore take an unusual stance for a review of this kind. We do not attempt to make the case for the combination. We attempt to state, agent by agent and endpoint by endpoint, exactly what the randomised human data support, where the pharmacokinetics preclude the proposed mechanism, and where a widely cited number turns out to rest on a single small study. We then set out what would have to be done to convert the synergy hypothesis from a marketing claim into a finding.

What this review adds

- A pharmacokinetic reckoning for resveratrol that places the achievable human plasma concentration against the concentration required in the cell-based experiments that generated the hypothesis (Figure 5).
- A separation of the NAD^+ literature into biomarker effects, which are robust, and functional effects, which are not (Tables 4–6, Figures 2–3).
- An explicit treatment of the two agents with real randomised signals — omega-3 and vitamin D — including the non-monotonic vitamin D dose-response that most reviews omit (Figures 8–9).
- A systematic search for any trial combining a geroprotector with an orthobiologic, and the documentation of its absence (Section 9, Table 21).
- A three-tier clinical framework, a peri-procedural supplement schedule, and a fully specified factorial trial (Figures 14–16, Tables 24–25).

Methods of this Critical Review

This is a narrative critical review with systematic evidence tabulation. It is not a systematic review and makes no claim to exhaustive retrieval; it prioritises randomised evidence, meta-analyses of randomised evidence, and the primary reports of the trials most frequently cited in support of the agents under discussion.

Element	Specification
Databases	PubMed/MEDLINE, ClinicalTrials.gov, EU Clinical Trials Register, and the reference lists of included trials and guidelines
Date range	Inception to July 2026
Agent search terms	nicotinamide riboside; nicotinamide mononucleotide; NAD+ precursor; resveratrol; pterostilbene; omega-3; EPA; DHA; icosapent ethyl; cholecalciferol; 25-hydroxyvitamin D; urolithin A; spermidine; alpha-ketoglutarate; taurine; GlyNAC; creatine; curcumin; dasatinib AND quercetin; fisetin
Orthobiologic terms	platelet-rich plasma; bone marrow aspirate concentrate; mesenchymal stromal cell; stromal vascular fraction; adipose-derived; microfragmented adipose tissue
Interface search	each agent term AND each orthobiologic term, plus a ClinicalTrials.gov interventional search for any registered trial listing both an orthobiologic and a nutraceutical co-intervention
Prioritised designs	randomised placebo- or vehicle-controlled trials; meta-analyses of randomised trials; factorial trials; the Interventions Testing Program for lifespan
Explicitly downweighted	uncontrolled before-after series; retrospective methylation-age cohorts; single-arm registry data; in vitro results at concentrations not achievable in human plasma
Effect reporting rule	point estimates are reported with the interval as published. Where a source reports no interval, the text states "no interval reported" rather than supplying one
Judgement rule	an agent is called "reasonably supported" for an endpoint only where at least one adequately powered randomised trial, or a meta-analysis with a confidence interval excluding the null and acceptable heterogeneity, supports it

Table 1: Search strategy, inclusion priorities and reporting rules.

Three conventions deserve emphasis because they change the conclusions. First, we distinguish biomarker endpoints from functional endpoints throughout; raising blood NAD^+ is not the same as improving muscle function, and the literature routinely conflates the two. Second, we treat the concentration achievable in human plasma as a hard constraint on any proposed mechanism; a pathway demonstrated at 50 µmol/L in culture is not available to a patient whose Cmax is 2.4 µmol/L. Third, where a widely repeated figure derives from a single cohort, we say so and give the sample size.

Hallmark of ageing	NAD^+ precursors	Resveratrol	Omega-3	Vitamin D	Orthobiologics
Genomic instability	PARP substrate supply (preclinical)	—	—	—	—
Epigenetic alteration	No methylation change in humans	—	PhenoAge, GrimAge2, DunedinPACE shifted	No clock effect	Not measured
Mitochondrial dysfunction	Central claim; muscle NAD^+ unchanged	PDE→cAMP→AMPK	Membrane remodelling	—	—
Cellular senescence	—	Preclinical only	—	—	Donor-age dependent
Chronic inflammation	Only reproducible human effect	IL-6 null in meta-analysis	CRP −18.1%; SPM synthesis	No overall effect; only in dysglycaemia	Leucocyte content dependent
Stem cell exhaustion	Preclinical rescue of aged BMSC	—	—	Osteogenic gene expression	The intervention itself
Altered intercellular communication	—	—	Resolvins, protectins, maresins	VDR transcription	Growth factor delivery

Table 2: Which hallmark each agent is claimed to address, and what human evidence exists for that claim. Cells marked "—" indicate no meaningful human data. Note that for four of the five agents the majority of hallmark-level claims rest on preclinical work.

Nad^+ and Cellular Rejuvenation

Does NAD^+ actually decline with age?

The claim that NAD^+ falls by roughly 50% between young adulthood and old age is the foundation of a multi-billion-dollars supplement category. It derives principally from a single human skin cohort of 49 participants [22]. A magnetic resonance study of brain NAD^+ found a correlation with age of $r = -0.75$ in 17 participants [23]. A more careful survey of the available human tissue data reported a cerebrospinal fluid decline of about 14%, brain declines of 10 to 25% and a liver decline of around 30%, and emphasised that plasma NAD^+ is nanomolar and is not a proxy for tissue NAD^+ [24]. A systematic appraisal concluded that the evidence for a universal, cross-tissue age-related decline is "very limited" [25].

This matters for two reasons. First, the magnitude of the deficit that supplementation is supposed to

correct is uncertain by a factor of three or more depending on tissue. Second, whole-blood NAD^+ — the endpoint on which essentially every commercial claim rests — is not the compartment in which the pathology is proposed to reside.

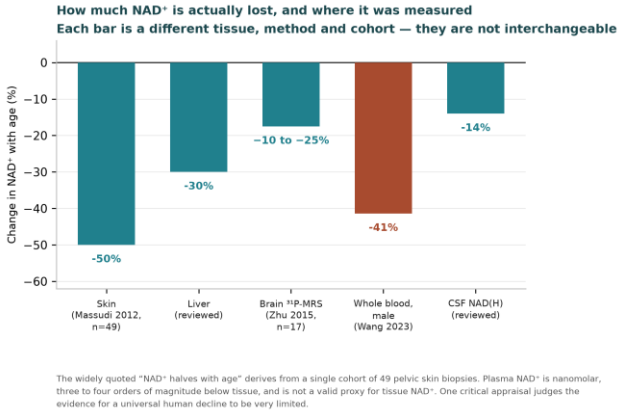

Figure 2: Reported age-related NAD^+ decline by tissue, with sample size. Each bar is annotated with the number of participants in the study that generated it. The frequently quoted 50% figure comes from a single skin cohort of 49 people; the brain correlation rests on 17. Plasma NAD^+, the compartment measured in almost all supplement trials, is nanomolar and does not track tissue content.

Tissue	Reported change with age	n	Source
Skin	≈ 50% lower in older adults	49	Massudi 2012 [22]
Brain (in vivo MRS)	r = −0.75 with age	17	Zhu 2015 [23]
Cerebrospinal fluid	− 14%	not stated in summary	McReynolds 2020 [24]
Brain (post-mortem series)	− 10 to − 25%	varies	McReynolds 2020 [24]
Liver	≈ − 30%	varies	McReynolds 2020 [24]
Plasma	Nanomolar; not a tissue proxy	—	McReynolds 2020 [24]
Overall appraisal	Evidence for universal decline "very limited"	—	Peluso 2021 [25]

Table 3: Human evidence for age-related NAD^+ decline, by tissue. The dispersion in these estimates, and the small samples underlying the largest of them, should be weighed against the confidence with which the 50% figure is repeated.

Nicotinamide riboside: the biomarker works, the function does not

Nicotinamide riboside raises whole-blood NAD^+ reliably and in a dose-dependent manner. In 140 overweight adults, 1000 mg/day increased whole-blood NAD^+ by 142 ± 14% over eight weeks with a clear dose gradient [1]. In heart failure with reduced ejection fraction, whole-blood NAD^+ rose by 30.0 ± 20.0 µmol/L in 30 patients [26]. In older adults with mild cognitive impairment, NAD^+ rose from 23.4 to 48.5 µmol/L ($p < 0.001$) — and cognition did not change [27].

The tissue story is different. In aged men, muscle NAD^+ was 210 versus 197 pmol/mg on nicotinamide riboside versus placebo, $p = 0.22$ [3] — that is, the compartment the therapy is meant to rescue did not change significantly. A comprehensive appraisal of the human nicotinamide riboside literature concluded that the only reproducible downstream effect is a reduction in circulating inflammatory markers [2]. The frequently cited blood pressure result — a 10 mmHg fall in systolic pressure, $p = 0.03$ — comes from a subgroup of 13 participants with elevated baseline pressure [28].

Trial	Population, n	Dose and duration	NAD⁺ effect	Functional effect
Conze 2019 [1]	Overweight adults, 140	100/300/1000 mg/day, 8 wk	**+142 ± 14% at 1000 mg; dose-dependent**	Safety and tolerability endpoints only
Elhassan 2019 [3]	Aged men, 12 (crossover)	1000 mg/day, 21 d	Muscle 210 vs 197 pmol/mg, p = 0.22	Anti-inflammatory transcriptomic signature
Martens 2018 [28]	Healthy middle-aged/older, 30	1000 mg/day, 6 wk	Blood NAD⁺ roughly doubled	SBP −10 mmHg in a subgroup of 13, p = 0.03
Wang 2022 [26]	HFrEF, 30	Up to 2000 mg/day, 12 wk	+30.0 ± 20.0 µmol/L	Safety; no efficacy claim
Martens 2025 [27]	Mild cognitive impairment	NR, randomised	23.4 → 48.5 µmol/L, p < 0.001	**Cognition null**
NR-SAFE [29]	Parkinson disease	3000 mg/day	Elevated	Safety trial; high dose tolerated

Table 4: Randomised trials of nicotinamide riboside: biomarker versus function. The pattern is consistent across trials. The blood biomarker responds; the tissue biomarker and the functional endpoints largely do not.

Nicotinamide mononucleotide

The nicotinamide mononucleotide literature is smaller and more discordant. A dose-ranging trial in middle-aged adults reported a six-minute walk distance increase from 323 to 480 m at 900 mg/day ($p < 0.001$) [30], a magnitude that is difficult to reconcile with the rest of the field. A trial in older Japanese men found a gait speed effect at $p = 0.033$ [31]. A multicentre trial of a commercial product found all efficacy endpoints null [32]. In prediabetic women, muscle insulin sensitivity improved, but the authors explicitly reported that "a change in NAD⁺ content was not detected" [33] — which, if taken at face value, severs the effect from the proposed mechanism. A proposed dedicated NMN transporter, Slc12a8, was rebutted shortly after publication [34].

Trial	Population, n	Dose	Primary result
Yi 2022 [30]	Healthy middle-aged, multicentre	300/600/900 mg/day, 60 d	**6MWD 323 → 480 m at 900 mg, p < 0.001**
Igarashi 2022 [31]	Older men	250 mg/day, 6–12 wk	Gait speed improved, p = 0.033
Huang 2022 [32]	Healthy middle-aged	300 mg/day	**All efficacy endpoints null**
Yoshino 2021 [33]	Prediabetic women, 25	250 mg/day, 10 wk	Muscle insulin sensitivity improved; "a change in NAD⁺ content was not detected"

Table 5: Randomised trials of nicotinamide mononucleotide. The dispersion between Yi 2022 and Huang 2022 at comparable doses in comparable populations has not been resolved.

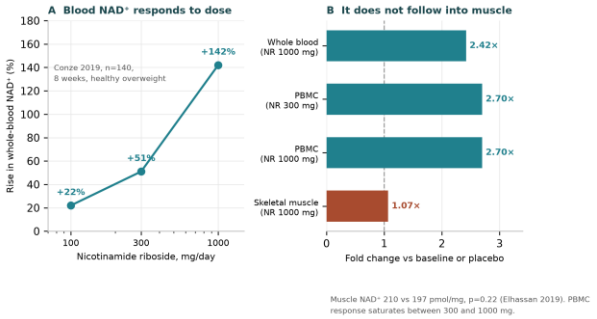

Figure 3: Blood NAD⁺ response to precursor dose across randomised trials. The biomarker response is orderly and dose-dependent. The functional response, shown in the lower panel as the pooled effect on physical performance, is not distinguishable from zero.

What the meta-analyses show

Pooling clarifies. Body mass index falls by 0.19 kg/m² (95% CI −0.29 to −0.09) with low heterogeneity ($I^2 = 5.1\%$) [35] — a real but clinically trivial effect. Physical performance shows a standardised mean difference of 0.24 (95% CI −0.03 to 0.50, $p = 0.074$) [4] — not significant. Glycaemic indices moved in the

adverse direction: fasting glucose +2.17 mg/dL and HbA1c +0.11% [36].

Endpoint	Pooled estimate (95% CI)	Heterogeneity	Interpretation
Body mass index	−0.19 kg/m² (−0.29 to −0.09)	I^2 = 5.1%	Statistically robust, clinically trivial
Physical performance	SMD 0.24 (−0.03 to 0.50), p = 0.074	Not stated in summary	**Null**
Fasting glucose	+2.17 mg/dL	Not stated in summary	**Adverse direction**
HbA1c	+0.11%	Not stated in summary	**Adverse direction**

Table 6: Meta-analyses of NAD⁺ precursor supplementation. Sources: body composition [35]; performance [4]; glycaemia [36].

Safety, and one decisive negative

Nicotinamide riboside at 3000 mg/day was tolerated in a dedicated safety trial [29]. Methyl-donor consumption is real — the methylated metabolite Me2PY rose 8.4-fold [37] — but no change in blood DNA methylation was detected [38]. Theoretical concerns about NAD⁺ and tumour metabolism remain weakly supported [39].

The most informative result in the whole NAD⁺ literature is not a human trial. In the Interventions Testing Program — the most rigorous lifespan platform in rodent biology, run in parallel at three independent sites in genetically heterogeneous mice — nicotinamide riboside produced a 0% change in female median lifespan (p = 0.612) and −3% in males (p = 0.252), with a site range from +10% at Jackson to −7% at Michigan [5]. In the same programme, rapamycin plus metformin produced +23%, 17-α-estradiol +19% in males, and canagliflozin +14% in males. Resveratrol had no effect (p between 0.3 and 0.9). If NAD⁺ repletion was a general geroprotector, this is the platform on which it should have shown.

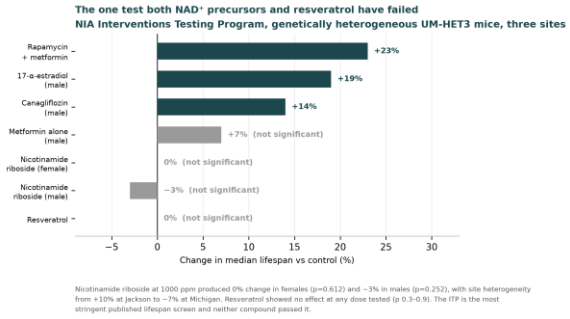

Figure 4: Interventions Testing Program: median lifespan effects of candidate geroprotectors. Nicotinamide riboside and resveratrol are indistinguishable from control, while rapamycin-based regimens are clearly positive. The site range for nicotinamide riboside (+10% to −7%) is wider than its point estimate, which is itself the argument for multi-site lifespan testing.

The contrast with the agents that do work in that platform shows how a geroprotective claim should be built. Rapamycin's rodent result has been followed into a participant-blinded randomised human trial [40], and metformin's into a proposed pragmatic outcome trial [41]. Neither NAD⁺ precursors nor stilbenes have that trajectory, because neither has the rodent lifespan result that would justify starting it.

Regulatory status has moved recently and in opposite directions on the two sides of the Atlantic. The United States Food and Drug Administration reversed its exclusion of nicotinamide mononucleotide from the dietary supplement definition on 29 September 2025 [42], while the European Food Safety Authority completed a favourable safety assessment of one nicotinamide mononucleotide preparation on 11 May

2026 at a maximum of 300 mg/day [43]. Neither action constitutes a finding of efficacy.

Resveratrol and the Sirtuin-Adjacent Polyphenols

The founding result was an assay artefact

Resveratrol entered longevity medicine as a direct allosteric activator of SIRT1. That finding was obtained in assays using a fluorophore-conjugated peptide substrate. When the fluorophore was removed, the activation disappeared: resveratrol did not activate SIRT1 against native substrates [44,45]. A subsequent reinterpretation argued that the fluorophore mimicked a hydrophobic motif present natively in PGC-1α and FOXO3a, and identified Glu230 in the SIRT1 N-terminal domain as critical for activation [46]. That rescue is persuasive for synthetic sirtuin-activating compounds; it does not establish that dietary-range resveratrol activates SIRT1 in a human being.

The best-supported proximal mechanism is different altogether. Resveratrol competitively inhibits cAMP phosphodiesterases, raising cAMP and activating AMPK through Epac1, phospholipase Cε, ryanodine-receptor calcium release and CamKKβ; NAD^+ and sirtuin activity rise downstream as a consequence, not a cause. Decisively, the PDE4-selective inhibitor rolipram reproduced every metabolic benefit of resveratrol, including mitochondrial biogenesis and protection from diet-induced obesity [47].

Human confirmation is inconsistent even for the downstream marker. At 75 mg/day, resveratrol did not change SIRT1, NAMPT, PGC-1α, UCP-3 or AMPK phosphorylation in muscle or adipose tissue [48]; at 150 mg/day, SIRT1 protein rose in muscle in an eleven-participant crossover [49].

The pharmacokinetic ceiling

Even if the mechanism were correct, the exposure is not achievable. Resveratrol is well absorbed — about 70% of an oral dose — but first-pass sulfation and glucuronidation reduce oral bioavailability to "considerably less than 1%" [6,50]. A 5 g oral dose produces a peak plasma concentration of approximately 2.4 µmol/L [7]. The cell-based experiments underlying the sirtuin, AMPK and senescence claims are conducted at concentrations of 5 to 50 µmol/L. The gap is not marginal; it spans the entire therapeutic hypothesis.

Micronisation narrows it but does not close it: micronised resveratrol (SRT501) at 5 g/day for 14 days achieved mean plasma resveratrol of 1942 ± 1422 ng/mL, 3.6-fold higher than the equivalent non-micronised dose, with hepatic tissue concentrations up to 2287 ng/g and a 39% increase in cleaved caspase-3 in malignant hepatic tissue [51]. That trial also demonstrates the cost of forcing exposure: in 24 patients with myeloma given 5 g/day of the same formulation, six serious renal events occurred and the trial was terminated [52,53].

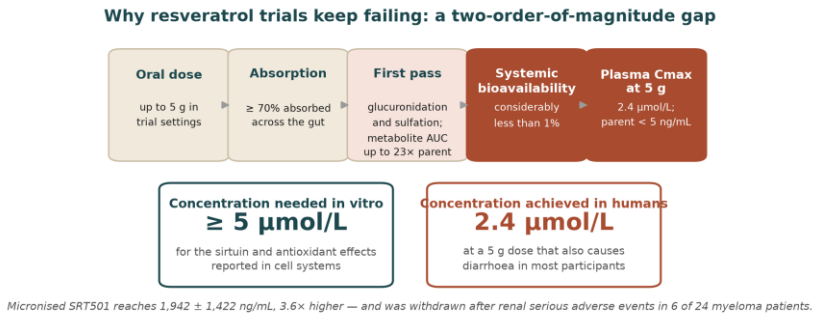

Figure 5: The resveratrol pharmacokinetic gap. Achievable human plasma concentrations, plotted on a logarithmic axis against the concentrations used in the cell-based experiments that generate the mechanistic claims. The shaded band is the in vitro active range. No orally tolerable dose reaches it; the one formulation that approaches it produced dose-limiting renal toxicity.

Parameter	Value	Source
Oral absorption	≈ 70% of dose absorbed	Walle 2004 [50]
Oral bioavailability	**"Considerably less than 1%"**	Walle 2011 [6]
Cmax after 5 g oral	**2.4 µmol/L**	Boocock 2007 [7]
Cmax after 5 g/day micronised × 14 d	1942 ± 1422 ng/mL (3.6× non-micronised)	Howells 2011 [51]
Concentration required in vitro	**5–50 µmol/L**	See Section 4.1
Dose-limiting toxicity	6 serious renal events in 24 patients at 5 g/day; trial terminated	NCT00920556 [52]; Popat 2013 [53]
Drug interaction	Plasma dihydroresveratrol correlated with metformin dose (R = 0.66, P = 0.005)	Timmers 2016 [54]

Table 7: Human pharmacokinetics of resveratrol against the in vitro requirement. The pharmacokinetic argument is prior to the efficacy argument: the concentration at which resveratrol works in a dish is not attainable in a patient at a tolerated dose.

The randomised trials

The pivotal metabolic trials were null. High-dose resveratrol 1500 mg/day in 24 obese men produced no effect on insulin sensitivity by hyperinsulinaemic-euglycaemic clamp, blood pressure, resting energy expenditure, lipid oxidation, ectopic or visceral fat, or biomarkers [55]. In non-obese postmenopausal women, 75 mg/day for 12 weeks changed neither insulin sensitivity nor any of the proposed molecular targets [48]. In well-controlled type 2 diabetes, 150 mg/day did not improve hepatic or peripheral insulin sensitivity, and intramyocellular lipid actually increased in type 2 fibres ($p = 0.03$) [54]. In 192 patients with type 2 diabetes, high-sensitivity C-reactive protein fell 15.9% at 500 mg/day, not significantly, while total cholesterol and triglycerides slightly increased [56].

The reproducible positive signal is narrow and largely confined to postmenopausal women: cerebrovascular responsiveness to hypercapnia improved 17% ($p = 0.010$) with concomitant gains in verbal memory ($p = 0.041$) [57]; lumbar spine bone mineral density rose 0.016 ± 0.003 g/cm^2 over 12 months with a 7.24% fall in C-terminal telopeptide [58]; and word retention improved in overweight older adults ($p = 0.038$) [59], although the primary memory endpoint was null in mild cognitive impairment [60].

The longest trial, RESHAW, ran 24 months in a crossover design and reported improved pain perception, menopausal symptoms and overall well-being [61]; its cognitive gain, however, was Cohen's $d = 0.170$ — detectable and of doubtful clinical relevance. That is the honest ceiling of the positive resveratrol literature.

The largest and most consequential negative is neurological. In 119 patients with mild to moderate Alzheimer disease escalated to 1000 mg twice daily for 52 weeks, cerebrospinal fluid and plasma Aβ40

declined more on placebo, and brain volume loss was greater with resveratrol [8]. A compound proposed as neuroprotective was associated with more atrophy than placebo.

Trial	n	Dose	Population	Primary result
Timmers 2011 [49]	11	150 mg/day, 30 d crossover	Obese men	Positive: metabolic and mitochondrial profile improved
Poulsen 2013 [55]	24	1500 mg/day, 4 wk	Obese men	**Null on clamp insulin sensitivity and all secondary endpoints**
Yoshino 2012 [48]	30	75 mg/day, 12 wk	Postmenopausal women	**Null; no change in SIRT1, NAMPT, PGC-1α, UCP-3 or AMPK**
Witte 2014 [59]	46	200 mg/day, 26 wk	Overweight 50–75 y	Positive: word retention p = 0.038; hippocampal connectivity increased
Bo 2016 [56]	192	40 or 500 mg/day, 6 mo	Type 2 diabetes	**Null on hs-CRP; cholesterol and triglycerides slightly increased**
Timmers 2016 [54]	17	150 mg/day, 30 d crossover	Well-controlled type 2 diabetes	**Null; intramyocellular lipid increased in type 2 fibres, p = 0.03**
Kobe 2017 [60]	40	200 mg/day, 26 wk	Mild cognitive impairment	**Primary memory endpoint null**
Evans 2017 [57]	80	150 mg/day, 14 wk	Postmenopausal women	Positive: cerebrovascular responsiveness +17%, p = 0.010
Turner 2015 [8]	119	up to 2000 mg/day, 52 wk	Alzheimer disease	**Null with greater brain volume loss on active drug**
Wong 2020 (RESHAW) [58]	125	150 mg/day, 12 mo	Postmenopausal women	Positive: lumbar BMD +0.016 ± 0.003 g/cm²; CTX −7.24%
Hussain 2018 [62]	110	500 mg/day + meloxicam, 90 d	Knee osteoarthritis	Positive on WOMAC and VAS; single centre, single trial

Table 8: Randomised controlled trials of resveratrol. Six of eleven trials failed their primary endpoint. The positives cluster in postmenopausal cerebrovascular and bone outcomes at 150 mg/day — not at the high doses used in metabolic and neurological trials.

Meta-analysis	Scope	Result
Marx 2018 [63]	Cognition and mood, 10 studies	Delayed recognition SMD 0.39 (0.08–0.70), I^2 = 0%, P = 0.01, 3 studies n = 166; negative mood SMD −0.18 (−0.31 to −0.05), P = 0.006
Farzaei 2018 [64]	Cognition, 4 RCTs, n = 226	**Null for memory and cognition; only vigour and fatigue improved**
Koushki 2018 [65]	Inflammation, 17 RCTs, n = 736	TNF-α WMD −0.44 (−0.71 to −0.164), P = 0.002, I^2 = 49.1%; hs-CRP WMD −0.27 (−0.50 to −0.02), P = 0.033; IL-6 not significant (P = 0.38, I^2 = 72.3%)
Zhu 2017 [66]	Metabolic endpoints	Small effects on glycaemic indices; heterogeneity high

Table 9: Meta-analyses of resveratrol. Two pooled analyses of the same domain — cognition — reach opposite conclusions on evidence bases of three and four trials respectively. That is the signature of an underpowered literature, not of a robust effect.

Hormesis, and why more is not better

Resveratrol's dose-response is non-monotonic. Cerebrovascular responsiveness improved 13.8% at 75 mg, 8.9% at 150 mg and 13.7% at 300 mg; in the posterior cerebral artery only the 75 mg dose worked [67]. The adverse signals track the ascending doses: gastrointestinal toxicity at 2.5 to 5 g, accelerated brain volume loss at up to 2 g/day [8], renal failure at 5 g/day micronised [52], and adverse lipid movement at 500 mg/day in diabetes [56]. This is the classic hormetic pattern described for antioxidant interventions generally [68,69], and it has a direct clinical corollary: the high-dose consumer products sold for longevity sit on the descending limb.

The related stilbene pterostilbene is not a clean substitute. At 250 mg/day, blood pressure fell by 7.8/7.3 mmHg but low-density lipoprotein cholesterol rose by 17.1 mg/dL (P = 0.001) on monotherapy [70].

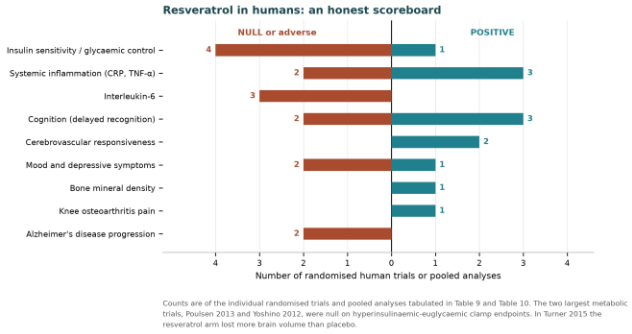

Figure 6: Resveratrol scored against its own claims. Each proposed mechanism or outcome is rated by the strength of the human evidence supporting it. The two claims that anchor the commercial case — direct sirtuin activation and calorie-restriction mimicry — score lowest.

Omega-3 Fatty Acids: The one Agent with a Clock Signal

DO-HEALTH: a null trial with an interesting secondary

DO-HEALTH randomised 2157 adults aged 70 and over in a 2×2×2 factorial design to vitamin D3 2000 IU/day, marine omega-3 1 g/day, and a home strength-training programme, for three years. All six co-primary endpoints were null [9]. This must be stated plainly, because DO-HEALTH is routinely cited as supportive of both agents.

Co-primary endpoint	Vitamin D 2000 IU	Omega-3 1 g/day	Exercise
Systolic BP (mmHg)	−0.8 (99% CI −2.1 to 0.5); P = .13	−0.8 (−2.1 to 0.5); P = .11	0.5 (−0.8 to 1.9); P = .30
Diastolic BP (mmHg)	0 (−0.7 to 0.8); P = .88	−0.5 (−1.2 to 0.2); P = .06	0.3 (−0.4 to 1.0); P = .32
SPPB (points)	−0.1 (−0.3 to 0.1); P = .26	−0.0 (−0.2 to 0.2); P = .76	−0.1 (−0.3 to 0.1); P = .25
MoCA (points)	−0.1 (−0.4 to 0.1); P = .11	−0.1 (−0.3 to 0.2); P = .52	0.0 (−0.2 to 0.2); P = .96
Non-vertebral fracture (IRR)	1.03 (0.75–1.43); P = .79	1.18 (0.85–1.63); P = .19	1.06 (0.77–1.47); P = .62
Infection rate (IRR)	0.95 (0.84–1.08); P = .33	0.89 (0.78–1.01); P = .02	1.04 (0.92–1.18); P = .38

Table 10: DO-HEALTH co-primary endpoints, all null. N = 2157 adults aged ≥ 70 y, three years, significance threshold P < .01 with 99% confidence intervals [9]. Every positive DO-HEALTH result in circulation is secondary or post hoc.

DO-HEALTH's secondary and post hoc analyses are the source of almost everything positive attributed to the trial: signals on falls [71], on pre-frailty prevention [72], and on cancer risk in the combined-intervention group [73]. These are hypothesis-generating analyses inside a trial that missed all six co-primary endpoints, and they should be described that way rather than as trial results.

The secondary analysis that matters for this review is the DNA-methylation-clock substudy. Omega-3 slowed PhenoAge by −0.16 (−0.30 to −0.02), roughly 2.9 months over three years; GrimAge2 by −0.32 (−0.59 to −0.06), roughly 3.8 months; and DunedinPACE by −0.17 (−0.31 to −0.04), roughly a 1% slower pace of ageing. GrimAge, Horvath and Hannum clocks showed no effect [10]. Combining all three interventions was additive for PhenoAge only.

This is, to our knowledge, the only human randomised evidence of additivity among any of the agents in this review. It is worth about three months of clock age over three years, on a surrogate endpoint, in a trial that was null on everything it was designed to measure. It is a legitimate finding and it is a thin foundation for a clinical programme.

Clock	Omega-3 effect (95% CI)	Equivalent
PhenoAge	−0.16 (−0.30 to −0.02)	≈ 2.9 months
GrimAge2	−0.32 (−0.59 to −0.06)	≈ 3.8 months
DunedinPACE	−0.17 (−0.31 to −0.04)	≈ 1% slower pace
GrimAge, Horvath, Hannum	No effect	—
All three interventions combined	Additive on PhenoAge only; d −0.24 to −0.32	2.9–3.8 months

Table 11: DO-HEALTH epigenetic clock substudy. Source: DO-HEALTH methylation analysis [10]. Vitamin D showed no clock effect in this analysis.

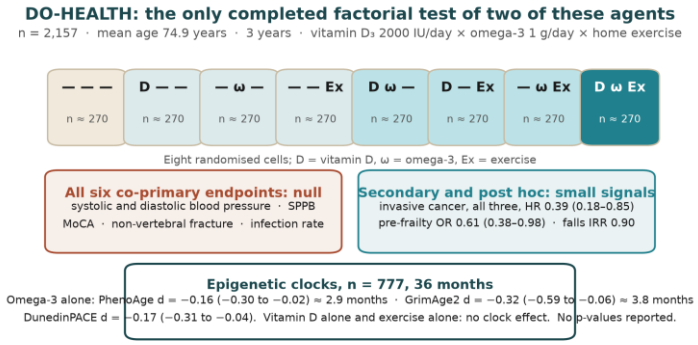

Figure 7: DO-HEALTH: six null co-primaries and one positive clock substudy. The upper panel plots the six co-primary endpoints with their 99% confidence intervals, all crossing the null. The lower panel shows the methylation-clock secondary analysis, the only positive factorial signal in the trial.

Cardiovascular outcomes: dose and molecule both matter

The cardiovascular literature is not ambiguous once dose and molecule are separated. Low-dose EPA plus DHA at about 1 g/day does not reduce major cardiovascular events: VITAL was null, and ASCEND in 15 480 people with diabetes gave a rate ratio of 0.97 (0.87 – 1.08; P = 0.55) [74,75]. High-dose purified EPA does: REDUCE-IT, in 8179 patients on 4 g/day icosapent ethyl, gave a hazard ratio of 0.75 (0.68 – 0.83; P < 0.001), an absolute risk reduction of 4.8 percentage points and a number needed to treat of 21 [76]. High-dose EPA plus DHA does not: STRENGTH, 13 078 patients on 4 g/day omega-3 carboxylic acids, gave 0.99 (0.90 – 1.09; P = .84) and was halted early [77].

Both comparators are contested. The REDUCE-IT mineral-oil arm showed a 33% rise in median high-sensitivity C-reactive protein by year two, though the Food and Drug Administration concluded that mineral oil is unlikely to account fully for the benefit; achieved plasma EPA at 12 months was 144.0 µg/mL in REDUCE-IT against 89.6 µg/mL in STRENGTH, a pharmacological rather than a purely methodological explanation for the divergence [78].

Any longevity framing must disclose the atrial fibrillation hazard. A meta-analysis of five randomised trials found an incidence rate ratio of 1.37 (1.22–1.54; P < 0.001), and 1.29 (1.13 – 1.48) in the sensitivity analysis including VITAL-Rhythm [79]. Within REDUCE-IT, hospitalisation for atrial fibrillation or flutter was 3.1% versus 2.1% (P = 0.004) [76].

Trial	n	Intervention	Comparator	Primary result
REDUCE-IT [76]	8179	Icosapent ethyl 4 g/day	Mineral oil	**HR 0.75 (0.68–0.83); P < 0.001; ARR 4.8 pp; NNT 21**
STRENGTH [77]	13 078	Omega-3 carboxylic acids 4 g/day	Corn oil	**HR 0.99 (0.90–1.09); P = .84; halted early**
ASCEND [74]	15 480	840 mg/day EPA+DHA	Olive oil	**Rate ratio 0.97 (0.87–1.08); P = 0.55**
VITAL [75]	25 871	840 mg/day EPA+DHA	Placebo	**Null on the primary cardiovascular composite**
AF meta-analysis [79]	5 RCTs	Marine omega-3	—	**IRR 1.37 (1.22–1.54); P < 0.001 for atrial fibrillation**

Table 12: Cardiovascular outcome trials of marine omega-3. The determinants of benefit are dose and molecule: only 4 g/day of purified EPA has produced a positive primary endpoint, and it carries an arrhythmia signal.

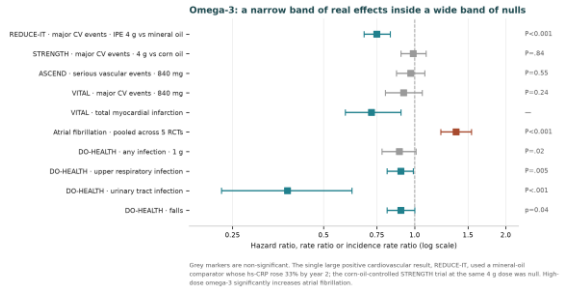

Figure 8: Omega-3 randomised outcomes. Forest plot of cardiovascular, arrhythmia, muscle and pain endpoints. Only high-dose purified EPA achieves a cardiovascular hazard ratio below unity; the atrial fibrillation estimate sits clearly above it.

Muscle, pain and the resolution pathway

The musculoskeletal case is more relevant to an orthobiologic practice. Omega-3 augmented the muscle protein synthetic response to hyperaminoacidaemia and hyperinsulinaemia in older adults [80], and over six months increased handgrip strength by 2.3 kg (0.8 to 3.7) and one-repetition maximum strength by 4.0% (0.8 to 7.3), both $p < 0.05$ [81]. Pooled, the picture is weaker: lean mass shows a small reproducible effect around SMD 0.33, grip strength pools to SMD 0.53 (−0.64 to 1.69, $p = 0.37$), and the most consistent functional signal is on the Timed Up-and-Go [82]. Doses above 2 g/day and durations of at least six months appear necessary.

Mechanistically, the pathway of most interest is not simple anti-inflammation but active resolution. EPA and DHA are the substrates for resolvins, protectins and maresins, which terminate inflammation rather than suppress it [83] — a distinction that matters greatly at the interface with platelet-rich plasma, where suppression of the early inflammatory phase may be counterproductive but its timely resolution may not.

Two further findings sharpen the dosing question. In knee osteoarthritis, a randomised comparison of low-dose against high-dose fish oil found the low dose superior [84], the same non-monotonic pattern seen with resveratrol and vitamin D. Pooled across 41 randomised trials, omega-3 has a measurable effect on chronic pain [85], and marine omega-3 lowers C-reactive protein, interleukin-6 and tumour necrosis factor-α in meta-analysis [86]. The erythrocyte omega-3 index, rather than the administered dose, is the exposure measure that tracks outcome [87] — an argument for measuring status rather than prescribing a dose. Efficacy is also indication-specific: omega-3 has a treatment effect in established depression [88] but did not slow cognitive decline in Alzheimer disease [89].

Vitamin D: A Genuine Effect with a Genuine Ceiling

The large trials in replete populations are null

VITAL randomised 25 871 adults to vitamin D3 2000 IU/day and was null on its cancer and cardiovascular

co-primaries [90], on total fracture (HR 0.98, 0.89 – 1.08; P = 0.70), non-vertebral fracture and hip fracture [91], and on incident depression (HR 0.99, 0.87 – 1.13) [92]. All-cause mortality was unchanged (HR 0.99, 0.87 – 1.12) [93]. The one positive VITAL result of relevance was a reduction in incident autoimmune disease [94], and a secondary analysis found telomere preservation with vitamin D and none with omega-3 [95] — the mirror image of DO-HEALTH's clock findings, which is itself a reason for caution about both.

The dose-response is not monotonic

Two independent randomised lines of evidence show harm above roughly 1000 IU/day in replete adults. In a three-year dose-ranging trial of 400, 4000 and 10 000 IU/day, radial volumetric bone density fell in a dose-dependent manner: −3.9% (−6.5 to −1.3) for 4000 versus 400 IU, with a group-by-time interaction of P < .001 at both radius and tibia, and a significant dose-response for hypercalciuria (P = .006) [12]. In STURDY, a randomised dose-finding fall-prevention trial, event rates were higher for 2000 IU (HR 1.86, 1.16–2.97) and 4000 IU (HR 1.68, 1.05–2.69) than for the 1000 IU dose that was selected as best [11].

The fracture analysis of the same trial found no benefit from the higher doses [96], and the inflammatory picture is not favourable either: pooled across randomised trials, vitamin D did not reduce inflammatory markers overall [97], with an effect detectable only in participants with dysglycaemia [98] — again pointing to correction of an abnormality rather than supplementation of the replete.

The clinical instruction is therefore precise and unfashionable: correct deficiency, then stop. Meta-analytic support for fracture and fall reduction sits at 800 to 1000 IU/day [99]. The Institute of Medicine tolerable upper limit is 4000 IU/day [100]; the Endocrine Society committee proposed 10 000 IU/day [101] — a threshold the Burt data do not support for bone. Cholecalciferol is preferred to ergocalciferol on the basis of superior 25-hydroxyvitamin D raising [102].

Dose (IU/day)	Bone density	Falls and fractures	Verdict
< 400	Insufficient to correct deficiency	No effect	Under-dosed
800–1000	Adequate for repletion	**Fracture and fall reduction in meta-analysis [99]**	**Target range**
2000	No added benefit	Serious falls HR 1.86 (1.16–2.97) [11]	No advantage; possible harm
4000	Radial vBMD −3.9% (−6.5 to −1.3) [12]	Falls HR 1.68 (1.05–2.69) [11]	**Harm signal; at the IOM UL**
10 000	Further dose-dependent vBMD loss [12]	Not tested for falls	**Not supported**

Table 13: Vitamin D dose-response for skeletal outcomes. The curve is not monotonic. Higher doses are not neutral; they are associated with lower radial volumetric bone density and more falls.

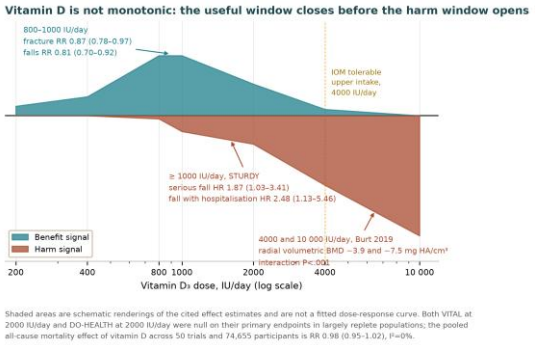

Figure 9: The non-monotonic vitamin D dose-response. Radial volumetric bone density and fall hazard plotted against daily dose. Both curves turn unfavourable above approximately 1000 IU/day, converging on a therapeutic window rather than a

threshold.

Vitamin D and orthopaedic outcomes: the observational case

This is where vitamin D becomes directly relevant to an orthobiologic practice, and where the evidence is observational rather than randomised. Deficiency is common in the exact populations receiving injections: 39.4% of arthroplasty candidates [16] and 70.9% of patients with knee osteoarthritis [17]. Deficiency is associated with more severe early post-operative pain after rotator cuff repair [103] and with higher revision rates in pooled analysis [104]; unplanned reoperation after arthroplasty was 13% versus 5.3% ($p < 0.001$) in hypovitaminosis D [16]. Post-operative WOMAC pooled to 4.32 (−1.85 to 8.70; $p = 0.07$) — a trend, not a finding.

The mechanistic bridge is plausible: vitamin D response elements regulate osteogenic gene expression in mesenchymal stromal cells [105] and vitamin D receptors are present in myotubes [106]. The critical caveat is that no randomised trial has tested whether correcting deficiency before an orthobiologic procedure changes the procedure's outcome. The authoritative review of the arthroplasty literature concluded that the evidence is insufficient to establish the association and that whether pre-operative correction helps remains undetermined [16].

Outcome	Finding	Design
Prevalence, arthroplasty candidates	39.4% deficient [16]	Cohort
Prevalence, knee osteoarthritis	70.9% deficient [17]	Cohort
Unplanned reoperation after arthroplasty	13% vs 5.3%; $p < 0.001$ [16]	Retrospective
Early pain after rotator cuff repair	More severe in deficient patients; $P < .05$ [103]	Cohort
Rotator cuff revision	Higher rate with deficiency [104]	Meta-analysis of observational studies
Post-operative WOMAC	4.32 (−1.85 to 8.70); $p = 0.07$, $I^2 = 58\%$ [16]	**Pooled; not significant**
ACL reconstruction	Association reported [107]	Cohort
Effect of correcting deficiency pre-procedure	**No randomised evidence**	**Gap**

Table 14: Vitamin D status and orthopaedic outcomes. Every row above the last is observational. The last row is the study that has not been done and that the field most needs.

The Expanded Nutraceutical Field

A review confined to the four agents named in the title would misrepresent current practice, in which longevity protocols routinely contain eight to fifteen compounds. We therefore summarise the human evidence for the most commonly added agents, applying the same standard used above: what has been randomised, in whom, and at what endpoint.

Urolithin A

Urolithin A is a gut-microbial metabolite of ellagitannins that induces mitophagy. It has the strongest randomised evidence of any second-tier agent in this list. A trial in middle-aged adults reported improvements in muscle strength, exercise performance and biomarkers of mitochondrial health [108], and a separate randomised trial examined muscle endurance and mitochondrial health in older adults [109]. The limitations are that both trials are small, both were conducted with manufacturer involvement, and neither reports a hard clinical endpoint. It is the most promising of the extended agents and it is not yet a treatment.

Spermidine

Spermidine is an autophagy inducer with strong preclinical support. The SmartAge randomised trial tested spermidine supplementation for cognition and biomarkers in older adults with subjective cognitive decline [110]. As with urolithin A, the human evidence base consists of a small number of surrogate-endpoint trials. There is no randomised human evidence bearing on tissue repair.

Calcium alpha-ketoglutarate

The frequently cited claim that calcium alpha-ketoglutarate produces an eight-year reduction in biological age comes from an open-label, uncontrolled series using a commercial methylation test [111]. Uncontrolled methylation-age series are particularly vulnerable to regression to the mean and to assay noise (Section 11). This claim should not be presented to patients as a trial result.

Taurine, GlyNAC, creatine, curcumin and senolytics

Taurine depletion was proposed as a driver of ageing on the basis of cross-species data and rodent supplementation experiments [112]; there is no adequately powered human outcome trial. Creatine, by contrast, is the best-supported musculoskeletal supplement in this list, with an updated meta-analysis of creatine plus resistance training in older adults [113] — notably, it is almost never marketed as a longevity agent. A bioavailable curcumin formulation was tested over 18 months for memory and amyloid and tau imaging endpoints in non-demented adults [114]. Senolytic dasatinib plus quercetin has been tested only in small open-label pilots, in idiopathic pulmonary fibrosis [115] and diabetic kidney disease [116], where it reduced senescent cell burden. Pterostilbene combined with nicotinamide riboside raises NAD^+ sustainably [117] but inherits the lipid signal noted in Section 4.4 [70].

Agent	Proposed mechanism	Best human evidence	Verdict for clinical use
Urolithin A	Mitophagy induction	Two randomised trials on muscle performance and mitochondrial biomarkers [108,109]	Most promising second-tier agent; surrogate endpoints only
Spermidine	Autophagy induction	SmartAge randomised trial in subjective cognitive decline [110]	Research agent; no repair data
Ca-alpha-ketoglutarate	Epigenetic and metabolic	**Open-label uncontrolled methylation series only [111]**	**Not supported; claim is not trial-derived**
Taurine	Multiple hallmark pathways	Cross-species and rodent data [112]	**No human outcome trial**
Creatine monohydrate	Phosphocreatine buffering, lean mass	Meta-analysis with resistance training in older adults [113]	**Best-supported musculoskeletal agent in this table**
Curcumin (bioavailable)	NF-κB inhibition	18-month trial with memory and amyloid/tau imaging [114]	Adjunct at best; formulation-dependent
Dasatinib + quercetin	Senolysis	Small open-label pilots [115,116]	**Research only; not for office use**
Pterostilbene	Stilbene, SIRT-adjacent	Raises NAD^+ with NR [117]; LDL +17.1 mg/dL as monotherapy [70]	**Lipid monitoring mandatory if used**

Table 15: The expanded nutraceutical field: what is actually randomised. No agent in this table has been tested against a clinical endpoint in combination with an orthobiologic. Verdicts reflect the evidence for the endpoint stated, not for lifespan.

Orthobiologics: The Current Evidence and the Ageing Donor

The rigorous trials are null; the pooled estimates are heterogeneous

RESTORE remains the most methodologically demanding placebo-controlled trial in the field: 288 patients randomised to three weekly intra-articular leukocyte-poor platelet-rich plasma injections or saline, with a structural co-primary endpoint. Twelve-month knee pain changed −2.1 with platelet-rich plasma versus −1.8 with saline, a between-group difference of −0.4 (95% CI −0.9 to 0.2, P = .17) against a minimal clinically important difference of 1.8; medial tibial cartilage volume changed −1.4% versus −1.2%, difference −0.2% (−1.9 to 1.5, P = .81) [13].

Pooled analyses look considerably more favourable, and are dominated by heterogeneity. One pooled estimate gives a WOMAC mean difference of −20.69 (−24.50 to −16.89) with $I^2 = 94\%$, and a visual analogue scale difference of −1.50 (−1.61 to −1.38) with $I^2 = 90\%$ [118]. A bone marrow aspirate concentrate pooled WOMAC estimate was 0.80 (−1.07 to 2.67; $p = 0.40$) with $I^2 = 99\%$ [119]. Heterogeneity of that magnitude means the pooled point estimate describes no real population.

The most decisive recent synthesis is a network meta-analysis of 24 studies and 2960 patients. Pain mean differences against hyaluronic acid were −0.7 to −1.1 for stromal vascular fraction and bone marrow aspirate concentrate and −0.3 to −0.7 for umbilical-cord mesenchymal stromal cells and platelet-rich plasma; function differences were −0.6 to −1.4. None exceeded the minimal clinically important difference [14]. Separately, contextual factors accounted for approximately 63% of pain reduction and 61% of functional improvement at six months, with $I^2 \leq 8\%$ [15].

Study	Design	Result
RESTORE [13]	288 patients, PRP vs saline, structural co-primary	**Pain difference −0.4 (−0.9 to 0.2), P = .17 (MCID 1.8); cartilage volume difference −0.2% (−1.9 to 1.5), P = .81**
Wu 2020 [118]	Pooled RCTs of PRP	WOMAC MD −20.69 (−24.50 to −16.89), $I^2 = 94\%$; VAS −1.50 (−1.61 to −1.38), $I^2 = 90\%$
Nie 2021 [120]	Meta-analysis of PRP RCTs in knee OA	Favours PRP on function; heterogeneity and bias high
BMAC pooled [119]	Pooled WOMAC	**SMD 0.80 (−1.07 to 2.67), p = 0.40, $I^2 = 99\%$**
Han 2026 [14]	Network meta-analysis, 24 studies, 2960 patients	**No orthobiologic exceeded MCID; SUCRA ranking SVF > BMAC > UC-MSC > PRP > HA**
Yin 2025 [15]	8 RCTs, 467 patients, contextual-effect analysis	**≈ 63% of pain reduction and 61% of function gain attributable to contextual factors at 6 months, $I^2 \leq 8\%$**

Table 16: Orthobiologics for knee osteoarthritis: the most rigorous evidence. The pattern is that the more rigorous the design and the more conservative the synthesis, the smaller the effect. This is the space in which an adjunctive host-optimisation strategy could plausibly matter — and in which it has never been tested.

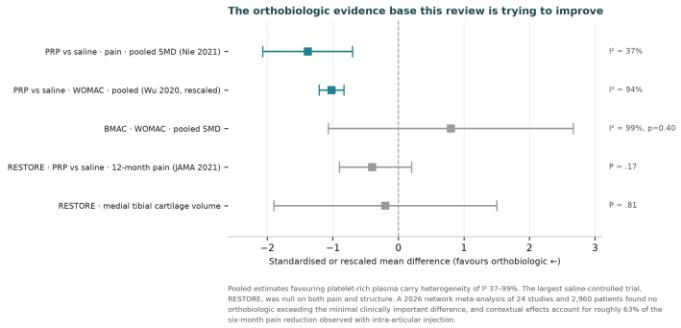

Figure 10: Orthobiologic effect sizes against the minimal clinically important difference. Point estimates from the network meta-analysis and the principal randomised trials are plotted against the MCID threshold. The dashed vertical line is the MCID; no product crosses it.

Guideline bodies have converged on conditional or negative recommendations. The American Academy of Orthopaedic Surgeons knee guideline [121] and its 2026 ankle guideline [122], the ESSKA-ICRS consensus [123], the 2026 American Academy of Physical Medicine and Rehabilitation consensus [124] and the GRIIP consensus [125] all place orthobiologics as second-line, conditional or research interventions. None of these documents mentions nutraceutical co-therapy at all — which is itself a finding about the state of the field.

Reporting quality compounds the problem. Adherence to the Minimum Information for Studies Evaluating Biologics in Orthopaedics standard remains poor [126], and the DEPA classification demonstrated that commercially available devices differ so much in platelet dose and purity that trials of "PRP" are frequently not trials of the same product [127]. A 2026 analysis of patient-level modifiers of response found that host factors influence outcome [128] — the empirical opening for the hypothesis this review examines.

The ageing donor: the strongest biological argument for adjunctive therapy

If a host-optimisation strategy has a rationale, it is here. Autologous orthobiologics harvest cells from the same aged marrow that the therapy is meant to compensate for, and the age effect is measured, not hypothetical.

Parameter	Young donors	Older donors	Source
CFU-F/ALP⁺ colony frequency per 10^6 cells	66.2 ± 9.6 (age 3–36 y)	**14.7 ± 2.6 (age 41–70 y)**	D'Ippolito 1999 [129]
Maximal replicative lifespan (population doublings)	41 ± 10 (18–29 y)	**24 ± 11 (68–81 y), P < 0.05**	Stenderup 2003 [130]
Proliferation rate (PD/day)	0.09 ± 0.02	0.05 ± 0.02, P < 0.05	Stenderup 2003 [130]
Senescence-associated β-galactosidase accumulation	0.4% per PD	**4% per PD**	Stenderup 2003 [130]
Nucleated cells per iliac aspirate	Mean 64 million overall	Declines with age, P = 0.002	Muschler 2001 [131]
CFU-AP prevalence	Mean 55 per million nucleated cells	Declines with age in women (P = 0.02), not men (P = 0.3)	Muschler 2001 [131]
Telomere cost of ex vivo expansion	—	**Expansion consumes ≈ half of total replicative lifespan**	Baxter 2004 [132]

Table 17: Measured effects of donor age on marrow-derived progenitors. A four-fold fall in progenitor colony frequency and a ten-fold increase in the rate of senescence accumulation are the quantitative basis for asking whether the host can be optimised before harvest.

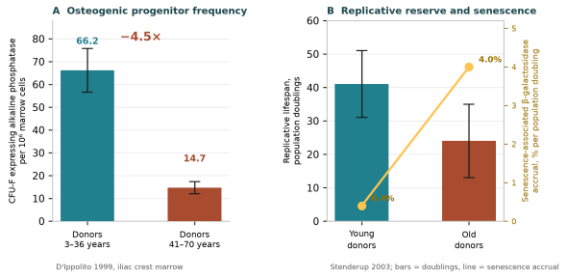

Figure 11: Donor age and progenitor quality. Colony-forming unit frequency, replicative lifespan and senescence accumulation rate plotted against donor age band. The magnitude of these differences is larger than the difference between any two orthobiologic products in the network meta-analysis.

The Synergy Hypothesis and the Trials That Do Not Exist

What synergy would require

The claim that nutraceuticals and orthobiologics act synergistically is usually made without specifying what would count as evidence. Three distinct claims are conflated. Additivity requires only that two interventions each produce benefit and that the benefits do not cancel; this is testable in a factorial trial and, for omega-3 with vitamin D and exercise on PhenoAge, has been demonstrated once [10]. Potentiation requires that one agent increases the effect of the other beyond additivity, which requires an interaction term. Permissiveness — the most clinically plausible version — requires that a deficiency limits response and that correcting it restores response; this requires stratification by baseline status,

which no orthobiologic trial performs.

The preclinical interface

The preclinical evidence at the interface is real and consistent in direction. A NAD^+-replenishing nanoplatform in senescent bone marrow stromal cells raised the NAD^+/NADH ratio 11.2-fold and adenosine triphosphate 3.25-fold, reduced the senescent fraction to 21.2% at day seven, and increased bone volume fraction by 119% at four weeks in a defect model [133]. Nicotinamide riboside improved bone microarchitecture in diabetic mice through oxidative phosphorylation and a Sirt1/FOXO/ β-catenin axis in osteoblast progenitors [134]. Intra-articular resveratrol at 10 µmol/kg reduced cartilage destruction ($p = 0.04$), proteoglycan loss ($p = 0.03$) and synovial inflammation ($p = 0.01$) in rabbit inflammatory arthritis [135].

Every one of these is an animal or cell experiment, and two of the three use delivery routes or concentrations not achievable by oral supplementation in a human being. The preclinical interface justifies a trial. It does not justify a protocol.

Study	Model	Result	Translational limit
Xie 2026 [133]	NAD^+ nanoplatform in senescent BMSCs; bone defect	NAD^+/NADH +11.2-fold; ATP +3.25-fold; senescent fraction 21.2% at day 7; BV/TV +119% at 4 wk	**Engineered local delivery, not oral supplementation**
Gao 2025 [134]	NR in type-2 diabetic mice	Improved bone microarchitecture and quality; OXPHOS and Sirt1/FOXO/β-catenin	Species and disease model
Elmali 2007 [135]	Rabbit LPS inflammatory arthritis	Less cartilage destruction ($p = 0.04$), proteoglycan loss ($p = 0.03$), synovitis ($p = 0.01$)	**Intra-articular 10 µmol/kg; unachievable orally (Table 7)**

Table 18: Preclinical evidence at the geroprotector–orthobiologic interface. Direction of effect is consistent and encouraging. Route and concentration are not translatable.

The central finding of this review: the trials do not exist

We searched for any randomised trial combining a nutraceutical or geroprotector with platelet-rich plasma, bone marrow aspirate concentrates or a mesenchymal stromal cell product and reporting a clinical outcome. We found none, published or registered, as of the search date. The closest entries are a small registered combination study [136] and a supplement-only study in a regenerative medicine practice, unpublished [137].

The corollary gaps are equally striking. No orthobiologic trial stratifies by baseline 25-hydroxyvitamin D despite deficiency prevalences of 39.4% and 70.9% in the relevant populations [16,17]. No study reports HbA1c thresholds against orthobiologic outcome, although dysglycaemia predicts therapeutic failure after platelet-rich plasma for tendinopathy, with a mean VISA increase of 8.92 ± 0.67 ($p = 0.003$) but a higher risk of failure by minimal clinically important difference analysis [138]. No study tests whether antioxidant supplementation blunts the early inflammatory phase after an orthobiologic injection, despite the established hormetic precedent from exercise physiology [68,69].

Question	Status
Any RCT of NAD^+ precursor, resveratrol, omega-3 or vitamin D as adjunct to PRP/BMAC/MSC with a clinical endpoint?	**None found, published or registered**
Any orthobiologic trial stratified by baseline 25(OH)D?	**None found**
Any study relating HbA1c thresholds to orthobiologic outcome?	**None found**
Any study testing whether antioxidants blunt post-injection healing?	**None found**

Question	Status
Any orthobiologic guideline or consensus mentioning nutraceutical co-therapy?	**None of AAOS, ESSKA-ICRS, AAPM&R or GRIIP [121,123–125]**
Does dysglycaemia predict PRP failure?	Yes, in tendinopathy: higher failure risk by MCID analysis [138]
Do NSAIDs compromise PRP?	Yes: impaired platelet aggregation in PRP from NSAID-exposed patients [139]

Table 19: The interface evidence gap, stated as answered and unanswered questions. Five of seven rows are empty. This is the principal finding of this review and the justification for the trial proposed in Section 13.

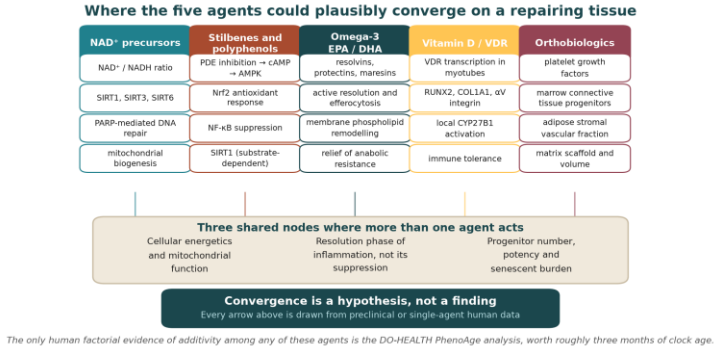

Figure 12: Where the agents converge mechanistically, and where the human evidence stops. Arrows denote proposed mechanistic interactions with an injected orthobiologic product. Solid arrows are supported by at least preclinical experiment; dashed arrows are asserted in commercial protocols with no supporting experiment. No arrow in this diagram is supported by a randomised human trial.

Safety and Interaction at the Procedural Interface

Platelet function

This is the one interaction with direct procedural consequence. trans-Resveratrol produces dose-dependent inhibition of both thrombin- and adenosine-diphosphate-induced platelet aggregation in vitro, with corresponding inhibition of thromboxane B_2 synthesis [140]. The picture is more reassuring at achievable exposures: resveratrol-enriched grape juice did not alter aggregation ex vivo in 24 healthy men [141], and resveratrol at 3.125 µM alone did not affect thrombin-induced aggregation, although it significantly augmented the inhibitory effect of ethanol [142]. The practical inference is that resveratrol alone is unlikely to compromise a platelet-rich plasma preparation at dietary or supplemental doses, but that the combination of resveratrol with alcohol — common in patients who take resveratrol for its wine association — has a demonstrated additive antiplatelet effect and should be avoided before harvest.

The established interaction is with non-steroidal anti-inflammatory drugs. Platelet-rich plasma prepared from patients taking non-steroidal anti-inflammatory drugs showed significantly impaired aggregation on light-transmission aggregometry despite normal platelet counts, irrespective of the drug used; the authors recommended that these drugs be administered only after blood collection [139]. Platelet count, the parameter that most clinics report as their quality metric, was normal in those samples — which means a count-based release specification will not detect this problem.

Omega-3 raises a theoretical bleeding concern that randomised data do not support: in the OPERA trial, perioperative fish oil was not associated with increased bleeding [143].

Agent	Direction of effect on platelets or healing	Evidence	Peri-procedural action
NSAIDs	**Impaired PRP platelet aggregation at normal count**	Ex vivo aggregometry in patients [139]	**Stop ≈ 7 d before harvest; resume only after injection**
Resveratrol alone	Inhibits aggregation in vitro; no effect at 3.125 µM	[140] [142]	Hold 7 d before harvest as a precaution
Resveratrol + ethanol	**Augmented inhibition of aggregation**	In vitro [142]	**Avoid alcohol with resveratrol for 7 d before harvest**
Omega-3	No increase in perioperative bleeding	OPERA randomised trial [143]	May continue
High-dose antioxidants	Theoretical blunting of the healing inflammatory phase	Exercise-adaptation hormesis [68,69]; no orthobiologic study	Hold from 3 d before to 14 d after injection
Vitamin D	No platelet effect; deficiency associated with worse outcome	Observational [16]	Measure and correct before scheduling
Corticosteroids	Not an agent in this review, but frequently co-administered	See guideline documents [125]	Avoid intra-articular steroid within 3 months of an orthobiologic injection

Table 20: Peri-procedural handling of supplements and co-medications around an orthobiologic injection. Only the NSAID row rests on direct experimental evidence in PRP. The remainder are precautionary positions derived from mechanism, and should be presented to patients as such.

Agent-specific safety summary

Agent	Established safety concern	Monitoring
Nicotinamide riboside / NMN	Well tolerated to 3000 mg/day [29]; methyl-donor consumption with Me2PY × 8.4 [37]; glycaemic indices drift adversely in meta-analysis [36]	Fasting glucose and HbA1c at 3 months
Resveratrol	**GI toxicity at 2.5–5 g; 6 serious renal events in 24 patients at 5 g/day micronised [52,53]; greater brain volume loss in Alzheimer disease [8]**	**Do not exceed 150–500 mg/day; renal function if higher**
Pterostilbene	**LDL +17.1 mg/dL as monotherapy (P = 0.001) [70]**	**Lipid panel at 3 months**
Omega-3	**Atrial fibrillation IRR 1.37 (1.22–1.54) at high dose [79]; no perioperative bleeding excess [143]**	Palpitation history; ECG if symptomatic
Vitamin D	**Dose-dependent radial vBMD loss and hypercalciuria at 4000–10 000 IU/day [12]; more serious falls at ≥ 1000 IU/day [11]**	**25(OH)D and serum calcium; do not chase high levels**
Senolytics	**Small open-label experience only [115,116]**	**Research setting only**

Table 21: Agent-specific safety and monitoring. Three of six agents have a documented dose-dependent harm signal. None of them is a benign vitamin at high dose.

Endpoints: What Should Be Measured, And What a Clock Can Bear

The commercial longevity field has largely adopted DNA-methylation age as its outcome measure. This is a defensible research choice and an indefensible clinical one, for a reason that is technical rather than philosophical: first-generation clocks have poor test-retest reliability, such that a reported change of a few years can be entirely assay noise. Principal-component reconstruction of the clocks was developed precisely to make longitudinal tracking feasible [144].

Second-generation and pace-of-ageing measures are better suited to trials. DunedinPACE was constructed to estimate the rate rather than the level of biological ageing [145], and the epigenetic clock literature is explicit about the difference between a biomarker that correlates with age and one that responds to intervention [146]. The benchmark for what a genuine intervention produces is CALERIE, in which sustained caloric restriction slowed DunedinPACE [147], and DO-HEALTH, in which omega-3 shifted PhenoAge by about 2.9 months over three years [10]. Against those benchmarks, an open-label report of an eight-year reduction in methylation age after seven months [111] is not a larger effect; it is a measurement artefact.

Measure	What it estimates	Suitability for a trial	Caveat
Horvath, Hannum (1st gen)	Chronological age correlation	**Poor — low test-retest reliability [144]**	Null in DO-HEALTH [10]
PhenoAge, GrimAge2 (2nd gen)	Mortality-trained biological age	Acceptable with principal-component versions	Omega-3 effect ≈ 2.9–3.8 months [10]
DunedinPACE	Pace of ageing [145]	**Best current choice for intervention trials**	Slowed by caloric restriction in CALERIE [147]
Leukocyte telomere length	Replicative history	Weak — high measurement variance	Preserved by vitamin D in VITAL [95]

Measure	What it estimates	Suitability for a trial	Caveat
SPPB, gait speed, grip strength	Physical function	**Strong — clinically interpretable**	Null in DO-HEALTH [9]
WOMAC, KOOS, VAS with MCID	Symptom and function in joint disease	**Required for any orthobiologic claim**	MCID must be pre-specified [13,14]
Commercial "biological age" reports	Unvalidated composite	**Not acceptable as an endpoint**	Vulnerable to regression to the mean

Table 22: Endpoint selection for trials at this interface. A trial that reports only a methylation clock and no functional endpoint cannot support a clinical claim, and a trial that reports a first-generation clock may not be measuring anything at all.

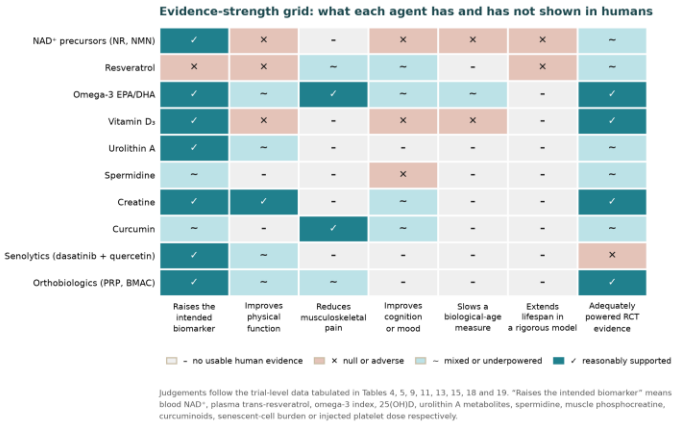

Figure 13: Evidence-strength grid. Each agent is scored against each endpoint class by the strength of randomised human evidence. Read vertically, the grid shows that inflammatory biomarkers are the only endpoint on which several agents converge; read horizontally, it shows that no agent has evidence across more than two endpoint classes.

A Tiered Framework for Clinical Practice

The practical question a clinician faces is not whether these agents extend lifespan but what to do on Monday morning with a 62-year-old who has knee osteoarthritis, a request for a bone marrow injection, and a bag of supplements. The framework below separates three categories that the commercial field deliberately blurs.

Tier	Definition	Agents	Consent language
Tier 1 — Correct a measured deficiency	A laboratory abnormality is documented and correction has independent evidence of benefit	Vitamin D3 800–2000 IU/day if 25(OH)D < 30 ng/mL, retested at 3 months; protein and creatine if intake or lean mass is inadequate [99,113]	**"We are correcting a deficiency that is independently worth correcting. We do not know whether it improves your injection result."**
Tier 2 — Reasonable adjunct, unproven at this interface	Randomised evidence exists for a relevant endpoint, but not in combination with an orthobiologic	Omega-3 EPA+DHA 1–2 g/day (clock and muscle signals) [10,81]; urolithin A [108]; curcumin in a bioavailable formulation [114]	**"There is randomised evidence for this agent on other endpoints. There is none for its effect on this procedure. It is optional."**
Tier 3 — Research only	No adequate randomised human evidence for any relevant endpoint, or a documented harm signal at effective doses	NAD^+ precursors [4]; resveratrol above 500 mg/day [8,52]; spermidine [110]; Ca-AKG [111]; senolytics [116]; taurine [112]	**"This is not established therapy. If you wish to take it, that is your decision; it is not part of the treatment I am recommending or charging for."**

Table 23: A three-tier framework for nutraceutical use alongside orthobiologic therapy. The tier assignment is by strength of randomised evidence for a relevant endpoint, not by mechanistic plausibility. Note that vitamin D is Tier 1 only when a deficiency is measured; in a replete patient it is Tier 3.

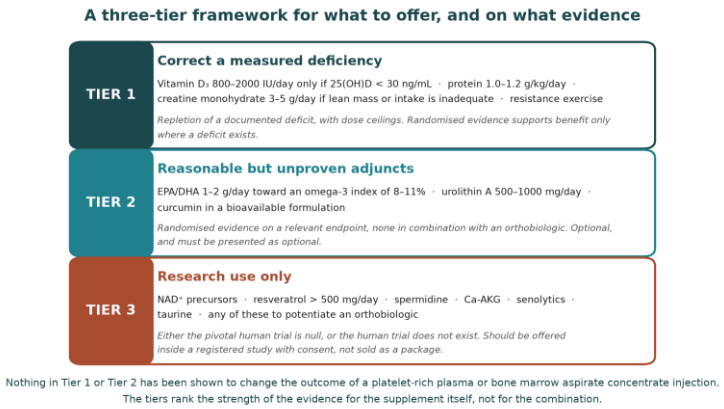

Figure 14: The three-tier framework as a clinical decision path. The decision turns on a single question asked first: has a deficiency been measured? Everything downstream of a negative answer is optional and must be presented as such.

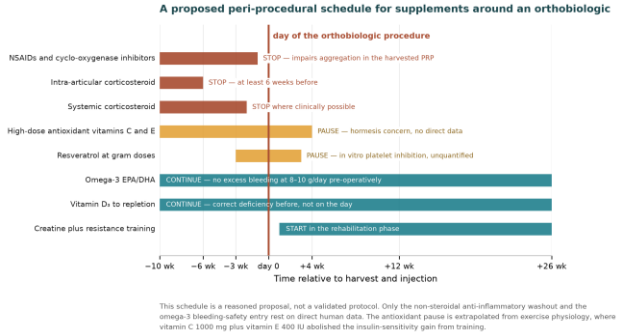

Figure 15: Proposed peri-procedural supplement schedule. A 21-day window around an orthobiologic injection. Only the NSAID hold is supported by direct experimental evidence in platelet-rich plasma (Schippinger 2015); the antioxidant hold and the resveratrol hold are precautionary and derived from mechanism.

Timepoint	Action	Basis
−30 to −7 days	Measure 25(OH)D, HbA1c, full blood count, ferritin; correct deficiency	Deficiency prevalence 39.4–70.9% [16,17]
−7 days	**Stop NSAIDs**	**Impaired PRP aggregation demonstrated [139]**
−7 days	Hold resveratrol and pterostilbene; avoid alcohol	Additive antiplatelet effect in vitro [142]
−3 days	Hold high-dose isolated antioxidants	Hormesis precedent [68,69]; no orthobiologic data
Day 0	Harvest and inject; record product characterisation to MIBO	Reporting standard [126,127]
Day 0 to +14	Continue the antioxidant and NSAID hold; paracetamol for analgesia	Precautionary; inflammatory phase of repair
+14 days	Resume Tier 1 and Tier 2 agents	Precautionary
+3 months	Retest 25(OH)D; record WOMAC or KOOS against pre-specified MCID	Endpoint discipline [13,14]

Table 24: Peri-procedural schedule. One row of eight rests on direct experimental evidence. This schedule is a defensible default, not a validated protocol, and should be described to patients in those terms.

A Trial That Would Settle the Question

The synergy hypothesis is testable, and cheaply, because the factorial design used in DO-HEALTH and VITAL transfers directly to this setting. We specify one below so that the proposal is concrete rather than a call for further research.

Element	Specification
Design	2×2×2 factorial, randomised, double-blind, placebo-controlled, single or multi-centre; 12-month primary follow-up with 24-month extension

Element	Specification
Population	Adults 45–75 y with symptomatic Kellgren–Lawrence grade 2–3 knee osteoarthritis, WOMAC pain ≥ 4/10, failed ≥ 3 months of conservative care
Factor A	Bone marrow aspirate concentrate injection versus saline injection (both under identical ultrasound-guided technique, opaque syringe shields)
Factor B	Omega-3 EPA+DHA 2 g/day versus matched placebo, started 8 weeks before injection and continued 12 months
Factor C	Vitamin D3 titrated to 25(OH)D 30–50 ng/mL versus placebo, in participants with baseline 25(OH)D < 30 ng/mL (stratification variable)
Primary endpoint	WOMAC pain change at 12 months, with responder analysis against a pre-specified MCID of 1.8 points on a 0–10 NRS [13]
Key secondary endpoints	KOOS subscales; quantitative MRI cartilage volume and T2; DunedinPACE and PhenoAge; hs-CRP, IL-6, TNF-α; SPPB and gait speed
Product characterisation	Mandatory: total nucleated cell count, CFU-F, platelet dose, leucocyte content, reported to MIBO and DEPA [126,127]
Interaction analysis	Pre-specified BMAC × omega-3 and BMAC × vitamin D interaction terms, powered as secondary; the factorial main-effect analysis is primary per the CONSORT factorial extension
Sample size	N = 480 (60 per cell) gives 90% power at α = 0.05 two-sided to detect a 1.8-point WOMAC pain difference assuming SD 2.4, allowing 15% attrition; the interaction terms are powered to detect only large interactions and are explicitly hypothesis-generating
Blinding integrity	Saline sham with identical harvest theatre for Factor A is not feasible; use an injection-only sham with blinded outcome assessment and report a blinding index, as contextual effects account for ≈ 63% of observed benefit [15]
Registration and reporting	Prospective registration; SPIRIT-compliant protocol; CONSORT 2010 factorial extension for the report

Table 25: Specification for a 2×2×2 factorial trial of a geroprotector-optimised orthobiologic. The design deliberately mirrors DO-HEALTH so that the clock outcomes are comparable, and deliberately uses the RESTORE MCID so that the symptomatic outcome is interpretable against the field's most rigorous negative trial.

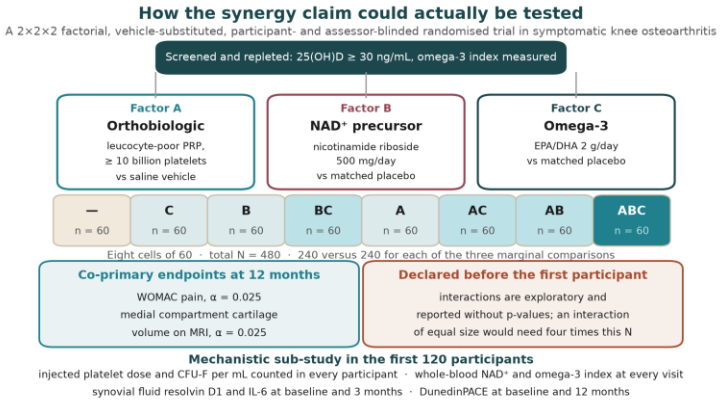

Figure 16: The proposed 2×2×2 factorial design. Eight cells of 60 participants. The main effects answer whether each agent works; the interaction terms are the first direct test of the synergy claim that this entire class of protocols rests on.

Why this trial, and not a larger one

A pragmatic objection is that the interaction terms are underpowered. That is true and it is deliberate. A trial powered to detect a modest interaction would require several thousand participants and would not be funded. The argument for the design above is that it delivers three interpretable main effects, an honest test for a large interaction, and the first product-characterised, clock-instrumented dataset at this interface. If the main effects are null, as the existing literature suggests they may be, the field will have learned something worth more than another uncontrolled series.

Research Agenda

Priority	Question	Design	Feasibility
1	Does correcting vitamin D deficiency before an orthobiologic injection improve outcome?	Randomised, deficiency-stratified, correction versus delayed correction	**High — cheap, ethical, immediately actionable**
2	Does omega-3 pre-loading alter the composition or potency of the harvested product?	Randomised pre-treatment with harvest-product characterisation as primary endpoint	**High — mechanistic, small n, fast**

Priority	Question	Design	Feasibility
3	Do high-dose antioxidants blunt the post-injection repair response?	Randomised, antioxidant versus placebo after standardised PRP, with biomarker and imaging endpoints	Moderate
4	Does donor-age-related progenitor decline predict clinical response?	Prospective cohort with mandatory CFU-F counting and 12-month outcome	**High — requires only that clinics count what they inject**
5	Does any NAD^+ precursor change a functional endpoint in a population selected for low baseline NAD^+?	Randomised, biomarker-enriched enrolment	Moderate — requires validated tissue assay
6	Is the DO-HEALTH omega-3 clock effect reproducible and does it track function?	Replication in an independent factorial cohort with paired functional endpoints	Moderate
7	Does the full commercial stack outperform its best single component?	Randomised stack versus best-component versus placebo	Low — but this is the question patients are actually paying to have answered

Table 26: Prioritized research agenda. Priorities 1, 2 and 4 are achievable within existing clinical practice at negligible additional cost, and would transform the interpretability of the field.

Limitations

- This is a narrative critical review with systematic tabulation, not a systematic review. We did not register a protocol, did not conduct dual independent screening, and did not perform formal risk-of-bias scoring of every included trial. Selection bias in favour of the most-cited trials is possible.
- We did not perform a new meta-analysis. Where we report pooled estimates, they are as published, with their published heterogeneity.
- Our conclusion that no trial combines a geroprotector with an orthobiologic is a negative search result. Negative search results are weaker than positive ones: an unregistered or non-English trial could exist.
- We treat achievable plasma concentration as a constraint on mechanism. This is reasonable for systemically acting compounds but may be unfair to agents with active metabolites, tissue accumulation, or intracellular concentration that plasma does not reflect.
- The tiered framework and peri-procedural schedule are expert proposals derived from indirect evidence. They have not been validated prospectively and should not be cited as guideline recommendations.
- The proposed trial's interaction terms are underpowered by design, as stated in Section 13.1.

Conclusion

Five agents, one review, and a short list of things that are actually known. NAD^+ precursors raise a blood biomarker reliably and change almost nothing else that has been measured in a human; they did not extend lifespan in the most rigorous rodent platform available. Resveratrol fails on pharmacokinetics before it fails on efficacy, and its founding mechanism was an assay artefact. Omega-3 fatty acids are the only agent in this review with a positive randomised signal on a biological-age measure, worth about three months over three years, in a trial that was null on all six of its co-primary endpoints. Vitamin D works when it corrects a deficiency and causes harm when it does not. Orthobiologics do not exceed the minimal clinically important difference in the most conservative synthesis of their own literature, and roughly 63% of what patients experience is contextual.

Against that background, the synergy hypothesis is not refuted. It is untested. No randomised trial has combined any of these agents with any orthobiologic and measured a clinical outcome. No orthobiologic trial stratifies by the one deficiency that is present in a majority of its patients. No orthobiologic consensus

document mentions nutraceuticals. The gap between what is sold and what is known is the largest single finding of this review.

The clinical position that follows is narrow and defensible: measure, correct what is deficient, offer the rest as optional and unproven, hold anti-inflammatory and antiplatelet agents around the procedure, count and report what you inject, and measure outcomes against a pre-specified minimal clinically important difference. The research position that follows is a 2×2×2 factorial trial of 480 patients. Both are considerably less exciting than the marketing, and both are considerably more likely to help a patient.

Declarations

Ethics approval and consent to participate. Not applicable; this is a review of published literature.

Consent for publication: Not applicable.

Availability of data and materials: All data discussed are available in the cited publications and trial registry records.

Competing interests: Each author to declare all financial and non-financial interests, including any relationship with manufacturers of nutraceuticals, orthobiologic devices or laboratory services, and any clinical practice income derived from the therapies discussed. Given the subject matter, reviewers and readers will expect this section to be explicit.

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Use of artificial intelligence: AI tools were used in figure generation and language editing, per journal policy. The authors are responsible for all content.

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