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From Cartilage Protection to Functional Recovery: Palm-Oil-Derived Tocotrienols at the Interface of Musculoskeletal Regeneration and Rehabilitation—A Review

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Abstract

Musculoskeletal disorders are major contributors to chronic pain, disability, mobility restriction, and loss of independence worldwide. Although rehabilitation remains central to functional recovery, its effectiveness occurs within a biological environment that may be compromised by chronic inflammation, oxidative stress, cartilage degeneration, abnormal bone remodelling, mitochondrial dysfunction, and skeletal-muscle loss. Palm-oil-derived tocotrienols, particularly the tocotrienol-rich fraction (TRF), have attracted attention because of their antioxidant, anti-inflammatory, chondroprotective, osteogenic, and emerging muscle-protective properties. This qualitative literature review critically synthesizes contemporary evidence published predominantly from 2020 onward concerning the potential role of palm-derived tocotrienols in musculoskeletal regeneration and rehabilitation. The literature was purposively identified and interpreted through critical thematic narrative synthesis rather than systematic-review methodology. Seven interconnected themes emerged: regulation of the oxidative-inflammatory environment; chondrocyte and cartilage protection; subchondral bone and osteogenic signalling; skeletal-muscle preservation; relationships with pain and joint function; potential enhancement of rehabilitation capacity; and the persistent preclinical-to-clinical translation gap. The evidence is strongest at molecular and preclinical levels, whereas direct evidence demonstrating cartilage regeneration or improved rehabilitation outcomes in humans remains limited. Recent human findings, including a randomised trial in rheumatoid arthritis, nevertheless strengthen the rationale for clinical translation. Palm-derived tocotrienols should therefore be viewed as promising biological adjuncts for regenerative rehabilitation research rather than established regenerative therapies. Future trials should integrate standardised tocotrienol formulations with structured rehabilitation and simultaneously measure molecular, structural, functional, and patient-centred outcomes.

Keywords: Palm Oil, Tocotrienols, Tocotrienol-Rich Fraction, Musculoskeletal Regeneration, Rehabilitation, Osteoarthritis, Cartilage, Bone Regeneration, Skeletal Muscle, Functional Recovery.

Introduction

Musculoskeletal disorders constitute a major and expanding source of disability worldwide. Osteoarthritis (OA), osteoporosis, age-related skeletal-muscle deterioration, joint injury, and inflammatory musculoskeletal disorders collectively affect mobility, participation, quality of life, and the ability of individuals to remain economically and socially active. OA is particularly important because it illustrates how structural degeneration, pain, inflammation, muscle weakness, ageing, obesity, and behavioural constraints can interact to produce persistent functional limitation. The Global Burden of Disease 2021 analysis estimated approximately 595 million people living with OA in 2020, equivalent to about 7.6% of the global population, and projected substantial increases in OA cases toward 2050 as populations age and obesity prevalence remains high [1-3]. Contemporary understanding of OA has shifted decisively away from a simple model of age-related mechanical "wear and tear". OA is increasingly understood as a whole-joint disorder involving

articular cartilage, subchondral bone, synovium, ligaments, menisci, periarticular muscles, inflammatory mediators, metabolic dysregulation, and nociceptive mechanisms. These components interact dynamically, which helps explain why radiographic damage, pain severity, muscular impairment, and functional disability do not always progress in parallel [4-7]. Such complexity also implies that successful management cannot rely solely on the pharmacological suppression of pain or on a single tissue-specific intervention.

Rehabilitation therefore remains fundamental to musculoskeletal care. Therapeutic exercise, progressive loading, resistance training, aerobic conditioning, neuromuscular training, education, weight management, and behavioural support can reduce symptoms and improve function in OA and many other musculoskeletal conditions. Current rehabilitation recommendations emphasize individualised exercise, physical activity, adherence, education, and person-centred management rather than passive treatment alone (Holden et al., 2023; Hinman et al., 2023; Pers et al., 2024). Exercise interventions can improve pain and physical function, although the magnitude and persistence of benefit vary according to programme design, baseline impairment, adherence, and disease characteristics [8]. Nevertheless, rehabilitation occurs within a biological substrate. Mechanical loading can stimulate beneficial musculoskeletal adaptation, but persistent inflammation, oxidative stress, abnormal cartilage metabolism, subchondral bone dysfunction, mitochondrial impairment, and muscle catabolism may constrain adaptive capacity. This interaction has contributed to the emerging concept of regenerative rehabilitation, in which regenerative biology and rehabilitation science are considered complementary rather than independent therapeutic domains. Regenerative interventions seek to restore or preserve tissue integrity, whereas rehabilitation supplies biomechanical and neuromuscular stimuli needed to translate tissue-level improvement into movement, activity, and participation [9-13].

This framework is relevant to palm-oil-derived tocotrienols. Tocotrienols are members of the vitamin E family and occur as α-, β-, γ-, and δ-tocotrienol isoforms. Palm oil represents one of the important natural sources of tocotrienols, frequently delivered experimentally or clinically as a palm tocotrienol-rich fraction containing several vitamin E isoforms. Tocotrienols differ structurally from tocopherols by possessing an unsaturated isoprenoid side chain, a characteristic associated with differences in membrane behaviour, distribution, biological signalling, and potentially pharmacological effects. Contemporary literature attributes to tocotrienols biological activities extending beyond conventional free-radical scavenging, including regulation of inflammatory pathways, cellular survival, mitochondrial homeostasis, bone metabolism, and other signalling systems relevant to chronic degenerative disease [14, 15]. Musculoskeletal interest in tocotrienols has grown because oxidative stress and chronic inflammation contribute to cartilage degradation, osteoblast dysfunction, excessive bone resorption, skeletal-muscle catabolism, and age-associated impairment. Experimental studies have reported effects of tocotrienols on nuclear factor kappa B (NF-κB) signalling, osteoblast migration and differentiation, Wnt/β-catenin pathways, cartilage preservation, oxidative damage, mitochondrial function, and muscle-atrophy pathways [16-19]. These findings create a plausible biological connection between palm-derived tocotrienols and musculoskeletal tissue preservation.

However, an important conceptual problem remains. Evidence that a compound reduces oxidative stress does not prove that it regenerates cartilage. Evidence of osteoblast activity does not automatically translate into improved mobility. Cartilage preservation does not necessarily produce pain reduction, while lower pain does not necessarily demonstrate structural restoration. Similarly, muscle preservation in an experimental model cannot be equated directly with improved gait, rehabilitation tolerance, participation, or long-term functional recovery in humans. Recent reviews of tocotrienols in arthritis and musculoskeletal ageing consistently indicate that promising evidence is dominated by experimental or preclinical research, with a comparatively small human musculoskeletal evidence base [20]. A recent randomised, double-blind, placebo-controlled trial in individuals with active rheumatoid arthritis is therefore noteworthy. Tocotrienol-rich fraction at 400 mg/day for six months, used alongside conventional disease-modifying antirheumatic therapy, was associated with improvements in disease activity, stiffness, discomfort, knee pain, and physical function compared with placebo. These findings strengthen the human translational case, yet they demonstrate neither cartilage regeneration nor a direct rehabilitation-enhancing effect and should not be extrapolated beyond the population and outcomes studied [21].

Against this background, the present qualitative literature review addresses three questions. First, through which biological mechanisms may palm-oil-derived tocotrienols contribute to cartilage protection, bone remodelling, skeletal-muscle preservation, and other processes relevant to musculoskeletal regeneration? Second, how far does the evidence support translation from tissue-level protection toward pain reduction, better physical function, enhanced rehabilitation capacity, and functional recovery? Third, what biological, pharmacokinetic, methodological, and clinical evidence gaps must be resolved before palm-derived tocotrienols can reasonably be considered an adjunct to regenerative rehabilitation? The purpose is therefore not to establish tocotrienols as a treatment recommendation, but to critically evaluate a translational continuum extending from molecular mechanisms through tissues to patient function. In doing so, the review proposes a cartilage–bone–muscle framework within which palm-derived tocotrienols may be understood as potential biological modifiers of the environment in which rehabilitation occurs.

Literature Review: Conceptual and Theoretical Foundations

Palm-Derived Tocotrienols as Bioactive Vitamin E Compounds

Vitamin E consists of eight majors naturally occurring compounds: four tocopherols and four tocotrienols, each represented by α-, β-, γ-, and δ-isoforms. Whereas tocopherols contain a saturated phytyl side chain, tocotrienols contain three double bonds in an unsaturated side chain. This structural distinction can influence mobility within lipid membranes and may partly explain differences between tocotrienols and tocopherols in biological activity. Importantly, however, the term “tocotrienol” should not be treated as describing a homogeneous intervention because biological effects may vary by isoform, dose, source, formulation, accompanying tocopherols, and delivery technol-

ogy. Palm-derived TRF commonly contains α-, γ-, and δ-tocotrienols together with α-tocopherol in proportions determined by processing and formulation. Consequently, evidence from purified γ-tocotrienol, δ-tocotrienol, palm TRF, and tocotrienols obtained from non-palm sources should not automatically be pooled conceptually as though the exposures were identical. This distinction is especially important when interpreting bone and muscle experiments, because studies identifying a signalling effect of a purified isoform provide mechanistic evidence but do not automatically establish equivalent effects for a commercial palm TRF preparation.

Bioavailability represents another translational constraint. Tocotrienols are lipophilic molecules with absorption influenced by food intake, digestive processes, formulation, competition within vitamin E transport systems, dose, and delivery technology. Human pharmacokinetic studies have shown substantial heterogeneity in systemic exposure among formulations and tocotrienol isoforms. Self-emulsifying delivery systems and related technologies have consequently been investigated as means of improving solubility and oral bioavailability [22]. A recent synthesis of randomised palm-TRF trials likewise demonstrated substantial variation in participant characteristics, dosing regimens, trial duration, and intervention composition [23]. These pharmacokinetic issues have major implications for musculoskeletal translation. A cellular concentration capable of activating an osteogenic pathway in vitro may not be reproduced consistently in cartilage, subchondral bone, synovium, or muscle after oral supplementation. The pathway from ingestion to tissue-level effect therefore contains several stages—absorption, distribution, metabolism, tissue exposure, receptor or signalling engagement, and sustained biological response—that need to be considered before clinical conclusions are drawn.

Oxidative Stress, Inflammation and Musculoskeletal Degeneration

Oxidative stress and inflammation constitute overlapping biological processes in many musculoskeletal disorders. In OA, excessive reactive oxygen species can interfere with extracellular-matrix metabolism, mitochondrial function, chondrocyte survival, cellular senescence, and inflammatory signalling. Oxidative damage can stimulate catabolic responses while inflammatory mediators such as IL-1β, IL-6 and TNF-α further amplify tissue stress, creating a self-reinforcing degenerative environment [24, 25]. Mitochondrial dysfunction is increasingly recognised as a component of OA pathophysiology. Mitochondrial abnormalities can alter cellular energy production, ROS generation, apoptosis, autophagy, and stress responses, while dysfunctional mitophagy may contribute to the persistence of damaged organelles. These processes are relevant not only to chondrocytes but also to skeletal muscle, where mitochondrial quality is closely associated with endurance, fatigue resistance, and adaptation to exercise [26-28].

Tocotrienols are potentially relevant to this redox-inflammatory axis because their effects extend beyond direct antioxidant chemistry. Experimental literature has implicated modulation of NF-κB and associated inflammatory mediators, although the magnitude and consistency of such effects differ by experimental context. Importantly, clinical evidence is less uniform than laboratory evidence. A meta-analysis of randomised trials examining inflammatory and oxidative-stress biomarkers found that tocotrienol supplementation did not produce uniformly significant improvements across all markers and populations, highlighting the difference between mechanistic potential and clinically reproducible systemic effects [29]. Thus, oxidative-stress regulation should be viewed as one component of a multi-pathway model rather than as sufficient evidence of tissue regeneration. A more defensible proposition is that tocotrienol-mediated redox and inflammatory regulation may help create a less hostile cellular environment in which cartilage, bone, and muscle maintenance processes can operate.

Cartilage and the Problem of Limited Regeneration

Articular cartilage has a highly specialised extracellular matrix dominated by type II collagen, proteoglycans, water, and relatively sparse chondrocytes. It is avascular and has limited access to reparative cell populations. These features make major cartilage defects difficult to repair spontaneously, particularly in established OA where cellular senescence, inflammatory signalling, matrix fragmentation, abnormal loading, and subchondral pathology coexist. Modern regenerative medicine has consequently explored biomaterials, stem cells, biologics, engineered scaffolds, and other approaches, yet reliably restoring durable native-like articular cartilage remains challenging [30, 31]. Recent advances in cartilage regeneration reinforce an important semantic distinction. Interventions may slow catabolism, preserve viable chondrocytes, improve extracellular-matrix homeostasis, stimulate endogenous repair, or generate new cartilage-like tissue, but these effects are not interchangeable. Reviews of tissue engineering and regenerative therapies emphasize that structural regeneration requires more demanding evidence than biochemical or histological protection alone [32, 33]. Therefore, the tocotrienol literature should generally use the terms chondroprotective, cartilage-preserving, or supporting chondrocyte repair unless direct evidence demonstrates generation of functional new cartilage.

Subchondral Bone as a Regenerative Target

The subchondral bone is not simply a passive support for cartilage. It participates in mechanical load transmission, biochemical crosstalk, vascular changes, remodelling, and pain-related processes. OA can involve altered osteoblast and osteoclast activity, abnormal bone turnover, sclerosis, microstructural changes, angiogenesis, and communication between subchondral bone and articular cartilage [34]. These observations have encouraged a whole-joint perspective in which cartilage and bone are treated as biologically interconnected compartments. Tocotrienols have demonstrated particularly interesting effects within osteogenic pathways. Palm-derived δ-tocotrienol has been shown experimentally to enhance migration of osteoblast-like cells and bone-marrow-derived mesenchymal cells through pathways involving Akt and Wnt/β-catenin signalling. γ-Tocotrienol has similarly been reported to stimulate proliferation and osteogenic differentiation in MC3T3-E1 osteoblasts through Wnt/β-catenin signalling. More recent work indicates that palm tocotrienol can preserve osteogenic signalling and promote bone-forming activity in dexamethasone-exposed osteoblast models. This literature complements broader evidence suggesting effects of tocotrienols on osteoblastogenesis, osteoclastogenesis, oxidative damage, and pathways such as RANK/RANKL/OPG and Wnt signalling [35]. Animal evidence also continues to devel-

op, including studies of osteocyte and trabecular-bone indices in oestrogen-deficient models [36]. These findings provide a biologically coherent argument for bone protection, but clinical evidence demonstrating fracture prevention, accelerated fracture rehabilitation, or improved mobility specifically attributable to palm-derived tocotrienols remains insufficient.

Skeletal Muscle as the Functional Bridge

Skeletal muscle provides a particularly important connection between tissue biology and rehabilitation because muscle strength directly affects walking, joint stability, balance, exercise tolerance, and independence. Age-related loss of muscle mass and strength can worsen the functional consequences of OA, while pain-driven inactivity can further promote muscle deconditioning. Sarcopenia is therefore both a biological and rehabilitation problem. Recent rehabilitation evidence also reinforces the clinical importance of quadriceps strengthening for reducing pain and improving function in knee OA [37]. Exercise is one of the best-supported interventions for sarcopenic impairment. Meta-analytic evidence indicates that resistance and multicomponent exercise can improve muscle strength and physical performance, with benefits influenced by intervention design and baseline characteristics [38]. Rehabilitation-focused work further shows that improvements in strength and performance are possible in older adults with sarcopenia, although setting, intensity, adherence, and multimorbidity influence outcomes [39].

Tocotrienol research provides an emerging biological complement to this rehabilitation literature. Metabolomic analysis of muscle from young, adult, and old rats supplemented with TRF suggested alterations in pathways associated with energy and amino-acid metabolism, providing a basis for hypotheses about muscle renewal and ageing. More recently, γ-tocotrienol was reported to attenuate inflammation-induced skeletal-muscle atrophy, preserve myotube size and muscle strength, reduce oxidative stress, and protect mitochondrial function in experimental systems. The muscle evidence remains predominantly preclinical, but its functional relevance is substantial. If future human trials reproduce meaningful effects on muscle strength, fatigue resistance, or training adaptation, skeletal muscle could become the most direct pathway through which tocotrienol biology interacts with rehabilitation outcomes.

Regenerative Rehabilitation as an Integrative Framework

Traditional regenerative medicine often focuses on restoring tissue structure, whereas conventional rehabilitation focuses on function, movement, participation, and adaptation. Regenerative rehabilitation attempts to connect these domains by recognizing that biological repair and mechanical loading interact. Tissue that is biologically capable of adaptation still requires appropriate mechanical and neuromuscular stimulation, while rehabilitation may be limited when the underlying biological environment remains highly catabolic or inflammatory. Mechanobiological approaches further suggest that controlled physical loading can influence cell behaviour, extracellular-matrix organisation, tissue maturation, and functional integration of regenerating tissues.

Consequently, the most appropriate theoretical role for tocotrienols is not as replacements for rehabilitation but as potential biological adjuncts that could reduce tissue stress or improve regenerative permissiveness while rehabilitation provides the mechanical and behavioural stimulus required for functional adaptation.

Method

Review Design

This study adopted a qualitative literature review using critical thematic narrative synthesis. It was intentionally designed as a qualitative and interpretive review rather than a systematic literature review. Narrative reviews are particularly suitable when an inquiry requires integration of heterogeneous mechanistic, preclinical, clinical, and conceptual evidence and when the goal is to construct explanatory relationships rather than estimate a pooled intervention effect [40]. Accordingly, the review did not employ PRISMA as its governing methodology, did not claim exhaustive retrieval of all potentially eligible studies, did not calculate pooled effect sizes, and did not undertake a formal study-by-study systematic risk-of-bias assessment. Instead, evidence was purposively assembled and critically interpreted to clarify how palm-derived tocotrienol biology may connect with musculoskeletal regeneration and rehabilitation.

Literature Identification

Contemporary peer-reviewed literature was identified iteratively through major academic databases and publisher platforms, principally PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, SpringerLink, Wiley Online Library, and citation chaining. The principal temporal emphasis was January 2020 to August 2026 in order to capture recent understanding of OA biology, regenerative rehabilitation, tocotrienol pharmacology, cartilage and bone biology, skeletal-muscle ageing, and clinical translation. Search concepts were combined iteratively and included “palm tocotrienol”, “tocotrienol-rich fraction”, “tocotrienol AND osteoarthritis”, “tocotrienol AND arthritis”, “tocotrienol AND cartilage”, “tocotrienol AND chondrocyte”, “tocotrienol AND osteoblast”, “tocotrienol AND osteoclast”, “tocotrienol AND Wnt beta-catenin”, “tocotrienol AND skeletal muscle”, “tocotrienol AND sarcopenia”, “tocotrienol AND muscle atrophy”, “tocotrienol AND mitochondrial function”, “tocotrienol AND inflammation”, “tocotrienol AND rehabilitation”, and related conceptual terms. These combinations served as navigation devices rather than a fixed systematic-search protocol.

Purposive Selection and Interpretation

Priority was assigned to peer-reviewed studies published since 2020 that materially contributed to one or more of five evidence domains: molecular mechanisms, cellular responses, animal models, human biomarkers or clinical outcomes, and rehabilitation-relevant outcomes. Contemporary reviews were used to map the field and identify influential mechanistic studies, while primary studies were prioritised when they directly informed important translational claims. Evidence was not treated as equivalent across study types. The analytical hierarchy moved conceptually from cellular mechanisms to animal models, then to human biological outcomes, clinical symptoms and function, and finally rehabilitation-specific outcomes. This hierarchy was not used to create a formal numerical quality score; rather, it functioned as a safeguard against translating preclinical findings prematurely into therapeutic recommendations.

Thematic Synthesis

The literature was coded conceptually around oxidative stress, inflammation, NF-κB signalling, chondrocyte survival, cartilage matrix, subchondral bone, osteoblasts, osteoclasts, Wnt/β-catenin signalling, skeletal muscle, mitochondrial function, pain, mobility, physical function, and rehabilitation. Similar concepts were grouped into broader interpretive themes. Qualitative synthesis was used to examine convergence, contradiction, explanatory mechanisms, and evidence gaps, consistent with principles of transparent qualitative evidence synthesis [41]. Seven themes were ultimately developed: (1) regulation of the redox-inflammatory environment; (2) chondrocyte and cartilage protection; (3) subchondral bone and osteogenic signalling; (4) skeletal-muscle preservation; (5) translation to pain and joint function; (6) rehabilitation capacity; and (7) the preclinical-to-clinical translation gap. Together, these themes provided the analytical structure for tracing the evidence from molecular mechanisms to rehabilitation-relevant outcomes.

Results: Thematic Findings

Theme 1: Tocotrienols as Regulators of the Redox–Inflammatory Environment

The first and most recurrent theme concerns oxidative stress and inflammatory regulation. Across degenerative musculoskeletal conditions, excessive ROS can damage lipids, proteins, DNA, mitochondria, and extracellular-matrix regulatory systems. In chondrocytes, oxidative stress can contribute to catabolic signalling, cellular senescence, apoptosis, and impaired matrix maintenance. In bone, oxidative stress may interfere with osteoblast survival and differentiation while favouring resorptive processes. In skeletal muscle, chronic inflammation and mitochondrial oxidative damage can promote proteolysis and reduced contractile capacity. Tocotrienols appear capable of influencing several components of this environment. NF-κB is particularly important because it integrates inflammatory and stress signals and controls transcription of multiple inflammatory mediators. The contemporary evidence reviewed by Abdul Nasir, Sadikan and Agarwal (2021) indicates that tocotrienols can modulate NF-κB-related signalling across experimental models. Palm-derived tocotrienol research has also linked redox regulation with protection in chronic disease settings.

Nevertheless, human clinical evidence introduces necessary caution. The systematic review and meta-analysis by Khor et al. (2021) did not find uniform reductions across inflammatory and oxidative-stress biomarkers following tocotrienol supplementation. Differences in baseline disease, dose, formulation, intervention duration, and biomarker selection may contribute to inconsistent findings. Therefore, the most defensible interpretation is that tocotrienols possess context-dependent redox-inflammatory regulatory potential, rather than a universally demonstrated systemic anti-inflammatory effect.

This distinction matters for regenerative rehabilitation. Reduced oxidative-inflammatory stress could theoretically improve cellular responsiveness to exercise and loading, but no direct evidence currently demonstrates that tocotrienol-mediated biomarker changes increase human rehabilitation responsiveness. The redox-inflammatory pathway should therefore be interpreted as a biological foundation for hypothesis generation. The translational logic emerging from the literature is summarized in Figure 1, which places molecular and tissue effects upstream of the clinically meaningful endpoint of functional recovery. The figure also makes explicit that the evidential chain becomes progressively less direct as it approaches rehabilitation-specific outcomes.

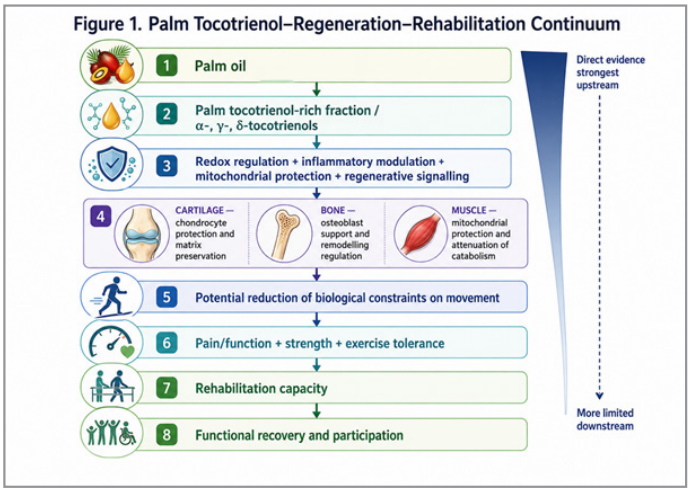

Figure 1: illustrates a conceptual continuum linking palm-derived tocotrienols to musculoskeletal tissue biology and rehabilitation. The strength of direct evidence generally decreases from molecular and preclinical mechanisms toward rehabilitation-specific functional outcomes.

The figure intentionally depicts a narrowing evidence base as the pathway moves from molecular biology toward patient-centred function. Tocotrienol effects on oxidative stress, inflammation, bone signalling, and experimental muscle biology have a growing evidence base, whereas the arrows connecting these effects with exercise tolerance, adherence, rehabilitation responsiveness, and long-term functional recovery remain predominantly hypotheses requiring prospective testing.

Theme 2: Chondrocyte Protection and Cartilage Preservation

A second major theme concerns cartilage biology. Tocotrienol

studies summarized in recent arthritis reviews suggest that vitamin E isoforms may protect cartilage partly through antioxidant and anti-inflammatory mechanisms and through preservation of chondrocyte viability and matrix homeostasis. Experimental evidence has supported beneficial effects in OA-related models, although study numbers remain limited. This evidence should be interpreted against the intrinsically poor regenerative capacity of adult articular cartilage. Contemporary regenerative-medicine literature demonstrates that cartilage repair requires coordinated control of cell phenotype, extracellular matrix, inflammatory signals, biomechanical loading, and integration with subchondral tissue [42]. Even sophisticated biomaterial- and cell-based approaches face difficulties in generating stable tissue with the structure and mechanical characteristics of native hyaline cartilage.

For this reason, the term cartilage regeneration must be used cautiously when discussing tocotrienols. Evidence that a compound reduces cartilage degradation or preserves chondrocyte viability supports chondroprotection. Evidence of improved histological appearance can suggest structural preservation. True regeneration, however, implies formation or restoration of functional tissue rather than simply reduced deterioration. The recent tocotrienol literature does not yet provide sufficient human evidence to state that oral palm-derived tocotrienols regenerate articular cartilage. The more plausible conceptual contribution is regenerative permissiveness: by lowering oxidative and inflammatory injury, tocotrienols may help maintain viable cells and matrix processes, potentially creating conditions more favourable for endogenous repair or mechanically stimulated adaptation. Whether this biological advantage becomes clinically meaningful depends on disease stage, exposure, mechanical environment, metabolic phenotype, and other therapies.

The combined postmenopausal–OA model examined by Ekeuku et al. (2024) is relevant because it evaluated emulsified and non-emulsified palm tocotrienol preparations in ovariectomised rats with experimentally induced OA. Besides contributing to the joint-health evidence base, the study illustrates how formulation and host biological context can alter interpretation of tocotrienol efficacy. Animal findings, however, remain insufficient to infer cartilage regeneration in humans.

Theme 3: Subchondral Bone, Osteoblasts and Osteogenic Signalling

The third theme concerns bone biology. The cartilage–bone interface is now regarded as integral to OA pathophysiology because subchondral bone remodelling can alter joint mechanics, cartilage nutrition and signalling, vascular invasion, and pain mechanisms. A therapeutic intervention affecting bone may therefore have consequences extending beyond bone mineral density. Several tocotrienol studies identify plausible osteogenic pathways. Casati et al. (2020) demonstrated that δ-tocotrienol could influence migration of osteoblast-like and bone-marrow-derived mesenchymal cells. Cellular migration is relevant to repair because regenerative responses require recruitment of cells to damaged or remodelling tissue. Xu et al. (2022) subsequently reported that γ-tocotrienol stimulated proliferation and differentiation of MC3T3-E1 cells through Wnt/β-catenin signalling, a major pathway involved in osteoblastogenesis.

Evidence has also been generated in glucocorticoid-related models. Glucocorticoids can impair bone formation partly by inducing oxidative stress and disturbing osteoblast biology. Reviews have proposed that tocotrienols may counter several of these mechanisms. More recent experiments with palm tocotrienol demonstrated activation of Wnt3a/β-catenin-associated osteogenic signalling and protection of osteoblasts exposed to dexamethasone [43]. Osteocyte-focused work has further suggested effects on trabecular osteocyte indices in ovariectomised models. These studies support an osteoprotective and potentially pro-osteogenic interpretation. They do not yet demonstrate that supplementation accelerates human fracture healing or improves post-fracture rehabilitation. Nonetheless, the bone literature is important because it expands tocotrienol research beyond generalized antioxidant effects toward pathways directly implicated in tissue formation and remodelling. The evidence suggests that tocotrienols may act across several musculoskeletal tissues simultaneously rather than through a single “cartilage pathway”. This multi-tissue model is depicted in

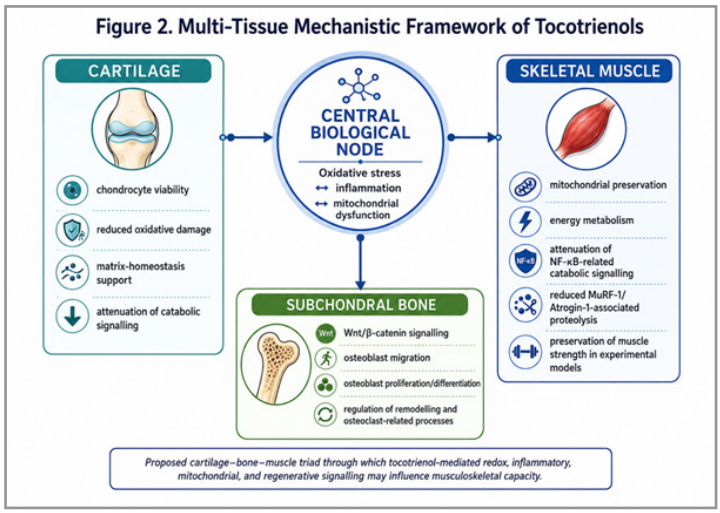

Figure 2: emphasizes that functional musculoskeletal health is produced by coordinated tissues. A structurally preserved joint may remain dysfunctional when periarticular muscle is weak, while stronger muscle cannot fully overcome severe articular damage. The conceptual value of palm-derived tocotrienols may therefore reside in their potential multi-tissue actions, although the clinical importance of such simultaneous effects remains to be established.

Theme 4: Skeletal-Muscle Preservation and Functional Reserve

The fourth theme is skeletal muscle, which may provide the most direct conceptual bridge to rehabilitation. Muscle strength is strongly related to mobility, balance, joint stabilization, exercise capacity, and independence. In OA, periarticular muscle weakness can increase functional limitations and reduce the capacity to participate in therapeutic exercise. In older adults, concurrent sarcopenia can compound these problems. Contemporary rehabilitation evidence consistently supports exercise as a major treatment for muscle impairment. Resistance and multicomponent training can improve strength and physical performance in older adults with sarcopenia, although heterogeneity remains regarding dose, programme duration, and responder characteristics [44]. Rehabilitation settings can also influence outcomes; centre-based geriatric rehabilitation may produce advantages for lower-limb strength and Timed Up and Go performance compared with some home-based approaches, although individualised circumstances remain important.

Tocotrienol research introduces a possible biological adjunct to such exercise-based interventions. Saud Gany et al. (2022) identified TRF-associated differences in muscle metabolites across the lifespan in rats, including pathways related to energy and amino-acid metabolism. Their subsequent synthesis positioned tocotrienols as potential modifiers of age-related musculoskeletal deterioration. The 2025 work by Chong et al. provides stronger mechanistic support for a muscle-centred interpretation. γ-Tocotrienol attenuated inflammation-induced muscle atrophy and was associated experimentally with reduced oxidative stress, preservation of mitochondrial function, maintenance of myotube size, and preservation of muscle strength. Such mechanisms are relevant to rehabilitation because exercise-induced adaptation depends substantially on mitochondrial competence, protein turnover, and the ability of muscle to tolerate repeated loading. Yet an essential evidence gap remains: these mechanisms have not been shown to increase training responsiveness in human rehabilitation populations. A future tocotrienol–exercise trial would therefore need to demonstrate more than biochemical changes. It should show that supplementation produces an incremental benefit above structured rehabilitation in outcomes such as quadriceps strength, gait speed, chair-rise capacity, fatigue, exercise adherence, or participation.

Theme 5: From Tissue Biology to Pain and Joint Function

Pain is the principal reason many people with OA seek treatment, but pain cannot be inferred directly from cartilage structure. OA pain may originate from synovium, subchondral bone, periarticular tissues, sensitization, mechanical factors, and psychosocial processes. Consequently, a compound that preserves cartilage could theoretically have no substantial analgesic effect, whereas an anti-inflammatory intervention could improve pain without regenerating cartilage. Contemporary reviews further emphasize that OA pain is multifactorial and can reflect inflammatory, neurovascular, subchondral, and peripheral nociceptive mechanisms rather than cartilage loss alone [45].

This distinction becomes important when interpreting the emerging clinical tocotrienol literature. The scoping review by Tejpal Singh et al. (2023) identified a limited number of studies directly addressing tocotrienols in arthritis and found that most evidence remained experimental. Human OA evidence was therefore insufficient for strong treatment conclusions. The recent rheumatoid arthritis RCT reported by Zainal et al. (2025) provides a meaningful advance because physical function was measured alongside disease activity and symptoms. Participants receiving 400 mg/day TRF for six months in addition to conventional disease-modifying therapy showed improvements in several clinical outcomes compared with placebo. The result demonstrates that tocotrienol supplementation can be investigated using meaningful patient-level outcomes rather than biomarkers alone. However, rheumatoid arthritis differs biologically from OA, the supplementation was adjunctive to established pharmacological therapy, and the findings cannot be interpreted as evidence of structural joint regeneration. Accordingly, the human evidence should be described as encouraging but preliminary. A clinically persuasive musculoskeletal programme would require convergence between biological changes, structural measures, symptoms, objective physical performance, and patient-centred outcomes.

Theme 6: Tocotrienols as a Potential Modifier of Rehabilitation Capacity

Rehabilitation capacity may be understood as a patient's ability to engage with, tolerate, and adapt to a therapeutic programme. Pain, inflammation, fatigue, muscle weakness, poor cardiometabolic status, low confidence, fear of movement, and structural disease can all reduce this capacity. Rehabilitation recommendations therefore emphasize personalisation and progressive adaptation rather than uniform exercise prescription [46, 47]. Exercise itself has substantial therapeutic value. Reviews have reported improvements in OA pain and function relative to placebo or minimal-intervention comparators, while current recommendations position exercise and physical activity among the pillars of non-pharmacological care [48]. Outcome frameworks increasingly emphasize not only pain but physical function, participation, health behaviour, and quality of life [49].

Tocotrienols could theoretically improve the biological environment in which exercise operates. For example, attenuation of excessive muscle oxidative stress could allow better muscle adaptation; preservation of cartilage might permit more comfortable joint loading; and improved inflammatory control might reduce symptoms that interfere with exercise. Such effects could produce an indirect pathway: Conceptually, this sequence can be expressed as biological protection leading to greater tolerance of loading, better rehabilitation adherence or progression, and ultimately improved physical performance. This pathway remains hypothetical until tested prospectively in human rehabilitation populations. No current evidence, however, establishes this sequence in humans. The term tocotrienol-enhanced rehabilitation should consequently be treated as a research hypothesis rather than a therapeutic claim.

This distinction aligns with regenerative rehabilitation theory. The objective is not to replace exercise with a biological agent but to determine whether a biological intervention can modify the tissue environment sufficiently to amplify adaptation to rehabilitation. Regenerative rehabilitation therefore provides a more appropriate conceptual home for tocotrienol research than conventional nutraceutical discourse because it requires explicit connection between biology and function.

Theme 7: The Preclinical-to-Clinical Translation Gap

The final theme concerns translation. Across the evidence base, the strength of findings declines as the outcome becomes more clinically meaningful. Cellular studies provide detailed mechanisms, animal models permit evaluation of integrated tissue responses, and human trials provide clinical relevance—but each transition introduces uncertainty. Formulation is one source of uncertainty. Purified γ-tocotrienol, δ-tocotrienol, palm TRF, emulsified preparations, and other formulations differ substantially. Pharmacokinetic evidence indicates that oral exposure and bioavailability vary, while delivery technologies can alter absorption [50]. Human palm-TRF trials also vary widely in dose and duration. Consequently, a biological effect observed with one tocotrienol preparation should not automatically be attributed to all tocotrienol products.

A second problem concerns disease heterogeneity. OA associated with ageing, obesity, trauma, metabolic dysfunction, inflammation, or postmenopausal bone changes may not respond identically to the same intervention. Similar considerations apply to sarcopenia and rheumatoid arthritis. Even within OA, different joints have distinctive anatomical, biomechanical, and clinical profiles, reinforcing the need for careful phenotyping rather than treating OA as one uniform disease. A third issue is outcome selection. Many nutritional-intervention studies prioritise circulating biomarkers, while rehabilitation studies prioritise pain, strength, mobility, activity, and quality of life. Regenerative studies may focus on imaging or histological endpoints. These different traditions need to converge if the tocotrienol–rehabilitation hypothesis is to be tested convincingly. The central evidence problem is summarized by the translation ladder in Figure 3, which differentiates established mechanistic evidence from increasingly uncertain clinical inference. Its purpose is to prevent mechanistic plausibility from being interpreted as equivalent to demonstrated clinical efficacy.

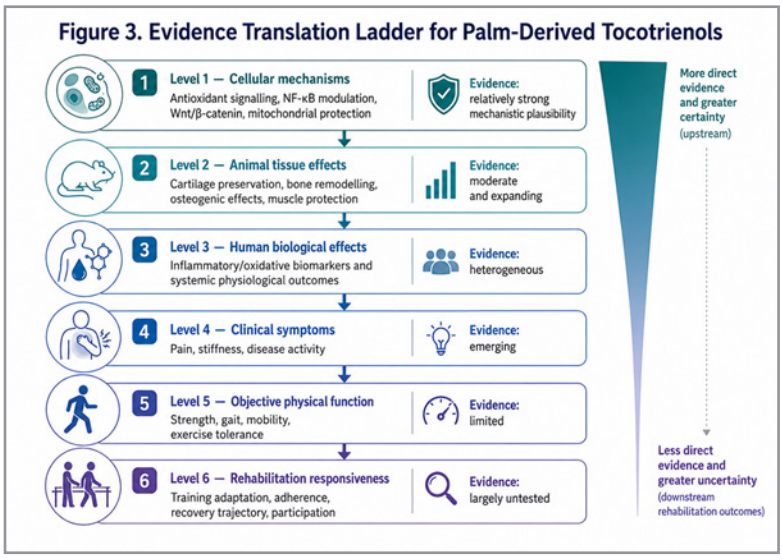

Figure 3: presents a translational evidence hierarchy in which direct evidence progressively decreases as tocotrienol research moves from molecular mechanisms toward rehabilitation-specific outcomes. This visual distinction underscores the need for clinical studies that connect biological effects with objective physical function and rehabilitation responsiveness.

The ladder clarifies why mechanistic enthusiasm must not be equated with clinical certainty. A credible research programme should aim to move evidence upward by designing trials that connect the levels rather than examining each in isolation.

Discussion and Analysis

An Integrated Cartilage–Bone–Muscle Interpretation

The principal contribution of this qualitative synthesis is the identification of a plausible multi-tissue model linking palm-derived tocotrienols with musculoskeletal regenerative rehabilitation. Existing tocotrienol literature has often been organized around separate domains—arthritis, osteoporosis, oxidative stress, ageing, or muscle metabolism. When these bodies of evidence are integrated, three primary tissue compartments emerge: cartilage, subchondral bone, and skeletal muscle. The cartilage evidence suggests predominantly protective rather than proven regenerative actions. Tocotrienols may reduce oxidative-inflammatory stress and preserve chondrocyte viability, thereby potentially slowing the shift from matrix homeostasis toward catabolism. This is meaningful because cartilage regeneration remains intrinsically difficult, even using advanced tissue-engineering approaches [51]. Tocotrienols therefore appear more plausible as biological modifiers of the cartilage environment than as direct cartilage-regenerating agents.

The bone evidence is mechanistically stronger in certain respects. Tocotrienol effects involving osteoblast migration, Wnt/β-catenin signalling, osteogenic differentiation, glucocorticoid-related oxidative injury, and bone-remodelling processes point toward direct regulation of pathways involved in bone formation and turnover. This raises potential future applications in populations where bone health and rehabilitation interact, such as older adults with osteoporosis, individuals receiving glucocorticoids, or patients undergoing fracture rehabilitation [52]. Skeletal muscle supplies the most immediate connection to function. Unlike subtle cartilage or bone changes, muscle strength has direct implications for rising from a chair, walking, stair negotiation, balance, joint stability, and exercise tolerance. Experimental protection of mitochondrial function and muscle strength by γ-tocotrienol is therefore especially relevant to the rehabilitation hypothesis.

Nevertheless, replication in older adults and musculoskeletal patient populations is essential before clinical significance can be assigned [53].

Figure 2's cartilage–bone–muscle triad consequently provides a more complete framework than a cartilage-centred model. Musculoskeletal recovery depends on the interaction among load-bearing tissues and the neuromuscular system. An intervention capable of modestly influencing several biological compartments may, in principle, be more relevant to functional recovery than one that modifies a single biomarker strongly without affecting performance [54].

Protection, Repair and Regeneration Must Be Distinguished

One of the most important interpretive issues is terminology. Regenerative medicine frequently uses terms such as regeneration, repair, restoration, preservation, and disease modification, but these refer to different biological outcomes. Preservation means maintaining existing structure or function. Repair can produce replacement tissue without fully restoring native architecture. Regeneration implies restoration toward functional native tissue. Disease modification generally requires evidence that the natural course of disease has been altered [55]. The tocotrienol literature currently supports protection more strongly than regeneration. A reduction in oxidative damage or preservation of cartilage morphology in an animal model is important but does not demonstrate regeneration. Similarly, osteoblast proliferation is relevant to regenerative processes but does not establish increased bone strength or fracture healing in humans. The article's title therefore uses the phrase "from cartilage protection to functional recovery" as a translational continuum rather than as a declaration that each step has already been clinically demonstrated [56]. This distinction is especially important for preventing nutraceutical overstatement. Tocotrienols are naturally derived compounds, but "natural" does not remove requirements for dose optimisation, pharmacokinetic characterisation, safety evaluation, identification of responders, interaction testing, and rigorous clinical efficacy trials. The appropriate scientific position is neither dismissal nor premature therapeutic endorsement [57].

A Proposed Concept of Biological Readiness for Rehabilitation

The synthesis supports the development of a testable concept termed biological readiness for rehabilitation. This refers to the extent to which tissue and systemic biological conditions permit effective adaptation to therapeutic loading and physical activity [58]. For example, a patient with severe knee pain, active synovitis, oxidative stress, quadriceps weakness, and poor mitochondrial function may have limited capacity to progress through strengthening exercises. If a biological intervention safely reduces one or more of these constraints, rehabilitation progression could become easier. Conversely, a biological intervention that improves biomarkers without influencing pain, strength, fatigue, or exercise tolerance would probably provide little rehabilitation benefit [59]. This framework transforms the research question. Rather than asking whether tocotrienols "treat OA", investigators could ask whether tocotrienols increase the response to a standardised rehabilitation programme. That question is experimentally testable and directly relevant to rehabilitation medicine. A trial designed around biological readiness should measure both mediators and outcomes. Potential mediators include inflammatory biomarkers, oxidative-stress markers, muscle mitochondrial-related measures, cartilage-degradation biomarkers, and bone-turnover indices. Outcomes should include pain, muscle strength, gait speed, functional tests, exercise progression, adherence, physical activity, participation, and quality of life. This multilevel design would reveal whether biological effects actually mediate functional benefits [60].

Why Exercise Must Remain the Therapeutic Foundation

Any interpretation of tocotrienols within rehabilitation should recognise that exercise and physical activity already possess a substantial clinical evidence base. Contemporary international recommendations identify therapeutic exercise as a core component of OA management. Exercise also has benefits for sarcopenic muscle strength and physical performance [61]. Therefore, a future tocotrienol intervention should normally be evaluated on top of rehabilitation, rather than against rehabilitation. A supplementation-only arm would answer whether tocotrienols have clinical effects, but it would not answer the more relevant regenerative-rehabilitation question of whether they enhance adaptation to evidence-based therapy [62]. The most clinically useful hypothesis is that standardised rehabilitation combined with an optimised palm-derived tocotrienol formulation will produce greater biological and functional benefits than standardised rehabilitation combined with placebo. This hypothesis is deliberately comparative because it tests whether tocotrienols add value to evidence-based rehabilitation rather than replace it [63]. Importantly, even if this hypothesis were confirmed, tocotrienols should still be understood as an adjunct rather than a substitute for exercise, physical activity, education, weight management, appropriate pharmacotherapy, or surgery where indicated. Any future clinical recommendation would therefore need to remain embedded within multimodal, guideline-concordant musculoskeletal care [64].

Reconciling Promising Preclinical Evidence with Limited Human Evidence

The gap between preclinical and human evidence is not unusual in regenerative medicine. Cell and animal models offer experimental control but simplify heterogeneous human disease. Human OA develops over years, interacts with obesity, metabolic disease, behavioural factors and central pain mechanisms, and occurs in tissues exposed to complex mechanical loading. A compound may therefore produce clear effects in experimental models but modest or inconsistent clinical outcomes [65]. The available human tocotrienol literature illustrates this problem. Broader randomised trials of palm TRF demonstrate that tocotrienols can be administered to humans and can influence selected biological outcomes, yet results vary across populations and biomarkers. Clinical evidence for direct musculoskeletal benefit remains far smaller than evidence for general cardiometabolic or antioxidant outcomes. The 2025 rheumatoid arthritis trial represents an important development because it connects TRF administration with patient-level musculoskeletal outcomes. However, several interpretive boundaries remain. Rheumatoid arthritis is primarily an immune-mediated inflammatory disease, whereas OA involves a more heterogeneous interplay between degeneration, mechanical loading, ageing, metabolic dysfunction, inflammation, and repair. Furthermore, improvement in pain or physical function is not direct evidence that tocotrienols

regenerated cartilage or restored bone. Nevertheless, the trial demonstrates that prospective musculoskeletal trials with meaningful functional endpoints are feasible [66].

Pharmacokinetics and Formulation as Central Translational Variables

A major lesson from the literature is that pharmacokinetics should not be relegated to a technical footnote. Tocotrienols have complex oral bioavailability, and differences between formulations can substantially influence systemic exposure. Strategies such as self-emulsifying delivery systems have been developed specifically because the lipophilic nature of tocotrienols can limit predictable absorption.

This issue is particularly relevant to musculoskeletal tissues, which may require sustained exposure rather than short systemic peaks. Future trials should therefore specify the complete composition of TRF, concentrations of each tocotrienol isoform, α-tocopherol content, delivery technology, timing relative to meals, dose, and adherence. When possible, pharmacokinetic or circulating tocotrienol measures should be obtained in a subsample.

The distinction between palm TRF and isolated isoforms must also be preserved. A mechanism demonstrated with purified γ-tocotrienol should be described as evidence about γ-tocotrienol, not automatically as evidence for all palm-oil-derived products. Conversely, clinical evidence obtained using mixed palm TRF cannot reveal with certainty which individual isoform is responsible for an observed response. This compositional complexity creates an opportunity for future comparative-effectiveness research.

Candidate Populations for Future Translational Research

Knee OA accompanied by quadriceps weakness may be the most logical first population for a tocotrienol–rehabilitation trial. The condition is common, exercise rehabilitation is well established, objective measures are available, and the cartilage–bone–muscle triad is clinically relevant. Participants could be stratified by inflammatory phenotype, obesity, age, baseline vitamin E status, and radiographic severity. Older adults with sarcopenia represent a second candidate population.

The rationale here would focus less on cartilage and more on mitochondrial function, muscle catabolism, oxidative stress, strength, and physical performance. Such a study could test whether TRF enhances the response to progressive resistance training.

A third population could include individuals receiving long-term glucocorticoids who are at elevated risk of bone deterioration and muscle weakness. Existing osteoblast and osteoporosis-related tocotrienol research provides mechanistic justification, although safety and interactions with underlying disease treatments would require careful consideration. Post-fracture rehabilitation is another future possibility, but this application is further from current evidence. Before clinical testing, stronger translational evidence would be needed that tocotrienol-related osteogenic mechanisms improve actual bone-healing quality and mechanical strength rather than only cellular markers.

Proposed Future Clinical Trial Framework

A robust clinical trial should use a randomised, double-blind, placebo-controlled design in which all participants receive standardised rehabilitation. The experimental group would receive a fully characterised palm-derived TRF formulation, while the comparison group would receive matched placebo. Duration should be sufficient for both biological and functional adaptation, potentially 24–52 weeks depending on population and structural endpoints. Rehabilitation should be progressive and reproducible, with resistance, aerobic, neuromuscular, and functional components adapted to disease severity. Outcome assessment should operate across four complementary levels so that biological change can be related to clinically meaningful recovery.

Molecular outcomes could include inflammatory and oxidative-stress markers, cartilage-turnover biomarkers, bone-turnover markers, and selected metabolic indicators; structural outcomes could include MRI cartilage measures, subchondral bone parameters, muscle cross-sectional area, or body-composition indices where feasible. Objective functional outcomes should include quadriceps strength, gait speed, Timed Up and Go, chair-rise testing, six-minute walking distance, balance, and objectively monitored physical activity.

Patient-centred outcomes should include WOMAC or KOOS domains, pain, fatigue, activities of daily living, participation, self-efficacy, rehabilitation adherence, and health-related quality of life. Mediation analysis could then examine whether biological changes explain part of the functional response. Such a design would directly test the conceptual model proposed in this article.

A trial capable of moving the field beyond mechanistic inference should combine a standardised tocotrienol exposure with standardised rehabilitation while simultaneously measuring biological, structural and functional outcomes, as proposed in Figure 4. Such a design would allow investigators to determine whether biomarker or tissue-level changes are accompanied by benefits that are meaningful to patients.

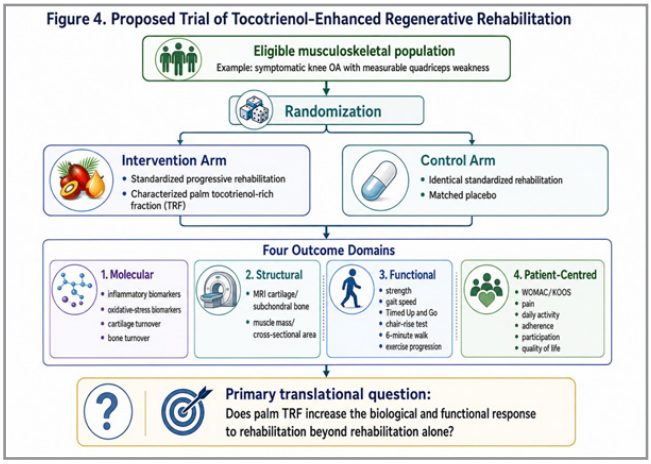

Figure 4: illustrates a proposed randomised trial framework for determining whether palm-oil-derived tocotrienols function as an adjunct to regenerative rehabilitation. The parallel-arm design keeps rehabilitation constant across groups so that any incremental effect can be attributed more confidently to the characterised palm TRF intervention.

The defining feature of this design is that improvement in a biomarker would not by itself constitute success. The strongest evidence would require a consistent pathway in which supplementation modifies biological processes and produces an incremental, clinically meaningful improvement in physical function or rehabilitation outcomes.

Implications for Regenerative Medicine and Rehabilitation Science

The proposed framework has implications beyond tocotrienols. Regenerative medicine frequently evaluates products at molecular or tissue levels, whereas rehabilitation science evaluates activity and participation. Integration requires a shared outcome hierarchy. Tocotrienols provide a useful case study because their biological plausibility is sufficiently developed to justify translation but not sufficiently established to bypass clinical testing. The concept also discourages false dichotomies between "biological" and "physical" therapies. Mechanical loading is itself biological: exercise changes muscle-protein synthesis, mitochondrial function, inflammatory signalling, neural recruitment, bone remodelling, and tissue mechanics. A nutritional or pharmacological compound similarly operates within systems modified by loading, diet, ageing, disease and behaviour. Regenerative rehabilitation therefore asks whether these interventions interact. For palm-derived tocotrienols, the crucial future question is not whether one can identify another antioxidant pathway. It is whether modulation of those pathways produces outcomes that matter to patients: less pain, stronger muscles, safer movement, greater walking capacity, greater independence, and sustained participation. Only such evidence would justify moving from biological promise to rehabilitation relevance.

Strengths and Limitations of the Present Review

The main strength of this qualitative review is its integration of several previously separated literatures. Rather than interpreting tocotrienols solely through antioxidant or nutritional perspectives, it places cartilage, subchondral bone, skeletal muscle, pain, and rehabilitation within a single translational framework. It also deliberately distinguishes mechanistic plausibility from clinical efficacy and treats negative or heterogeneous human evidence as scientifically informative rather than inconvenient. The review also focuses primarily on literature published since 2020, thereby incorporating recent developments in OA pathophysiology, regenerative rehabilitation, tocotrienol pharmacology, skeletal-muscle biology, and clinical evidence. The inclusion of the recent rheumatoid arthritis randomised controlled trial further updates the human translational context and provides an important, although still limited, human functional evidence layer. Several limitations should nevertheless be recognised. First, the review is qualitative and narrative rather than systematic; consequently, it does not claim exhaustive identification of every relevant publication. Second, the heterogeneity of tocotrienol preparations makes cross-study interpretation difficult. Third, much of the direct musculoskeletal evidence remains preclinical. Fourth, rehabilitation-specific tocotrienol trials are largely absent, meaning that some connections proposed in this article remain hypotheses generated from converging rather than direct evidence. Finally, focusing on recent literature can underrepresent historically important foundational studies, although recent reviews were used to maintain conceptual continuity.

Conclusion and Future Research Recommendations

Palm-oil-derived tocotrienols occupy a potentially valuable but still developing position at the interface of nutritional bioactives, musculoskeletal biology, regenerative medicine, and rehabilitation. The contemporary evidence indicates biologically coherent antioxidant, anti-inflammatory, osteogenic, chondroprotective, and muscle-protective actions. Collectively, these effects support a multi-tissue model involving cartilage, subchondral bone, and skeletal muscle rather than a narrow interpretation focused solely on joint cartilage. The evidence, however, is not equally strong across the proposed translational continuum. Molecular and preclinical support is substantially more developed than evidence for human structural regeneration, objective physical-function improvement, or enhanced rehabilitation responsiveness. Palm-derived tocotrienols therefore should not presently be described as proven cartilage-regenerating agents or established rehabilitation treatments.

A more defensible interpretation is that tocotrienols may contribute to a biologically favourable environment for musculoskeletal preservation and adaptation. Their potential value in regenerative rehabilitation lies in the hypothesis that reduced oxidative-inflammatory stress, improved osteogenic signalling, carti-

lage preservation, and skeletal-muscle protection could increase an individual's capacity to respond to therapeutic loading and exercise. Future research should consequently move beyond isolated biomarker studies toward adequately powered randomised trials integrating standardised palm-TRF formulations with structured rehabilitation. Such trials should concurrently assess molecular, structural, functional, and patient-centred outcomes and should distinguish palm TRF from individual tocotrienol isoforms. Dose, bioavailability, formulation, participant phenotype, disease stage, sex, age, obesity, metabolic health, and baseline nutritional status should be examined as potential response modifiers. The most important next scientific step is therefore not to establish another mechanism through which tocotrienols might protect musculoskeletal tissues, but to determine whether those mechanisms can be translated into clinically meaningful improvements in strength, mobility, rehabilitation capacity, participation, and sustained functional recovery. Demonstrating that translational link would provide the evidence needed to judge whether tocotrienols have a clinically meaningful role in regenerative rehabilitation.

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