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Palm Tocotrienol-Rich Fraction for Osteosarcopenia in Aging: Mitochondrial Energetics, Myogenic Regeneration, Inflammaging, and Bone–Muscle Crosstalk—A Translational Qualitative Review

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Abstract

Sarcopenia and osteoporosis frequently coexist in older adults as osteosarcopenia, a high-risk phenotype associated with falls, fractures, disability, and mortality. Palm tocotrienol-rich fraction (TRF) has emerged as a potential multi-target geroscience intervention because tocotrienols influence redox homeostasis, inflammatory signaling, cellular senescence, mitochondrial function, and musculoskeletal metabolism. This qualitative literature review critically synthesizes contemporary evidence concerning TRF and related tocotrienol interventions across aging skeletal muscle, bone remodeling, and bone–muscle crosstalk. Cellular studies indicate that TRF can improve the regenerative phenotype of senescent human myoblasts. Aging-animal metabolomics demonstrates modulation of amino-acid, carnitine, and energy-related pathways, while recent γ-tocotrienol studies show suppression of MuRF-1 and Atrogin-1, preservation of mitochondrial function, and improved muscle strength in inflammatory atrophy models. Tocotrienols also exert skeletal effects involving osteoblasts, osteoclasts, osteocytes, Wnt-related signaling, RANKL/OPG, and sclerostin. However, direct human evidence for sarcopenia or osteosarcopenia remains inadequate. The major translational challenge is therefore to determine whether molecular and metabolomic effects translate into improvements in muscle strength, physical performance, appendicular lean mass, bone mineral density, falls, and fracture risk. A precision-geroscience trial framework combining standardized palm TRF with resistance exercise and integrated musculoskeletal and multi-omics endpoints is proposed.

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Introduction

Population aging has increased the clinical importance of disorders that diminish mobility and independence rather than merely shortening life expectancy. Sarcopenia represents one of the most consequential of these conditions because deterioration in skeletal-muscle strength, quantity, quality, and function directly affects locomotion, balance, resilience to illness, and the capacity to live independently. Contemporary definitions increasingly emphasize that sarcopenia cannot be reduced to low lean mass alone. The Sarcopenia Definition and Outcomes Consortium highlighted weakness and slowness as clinically consequential features, whereas the Global Leadership Initiative in Sarcopenia later emphasized muscle mass, muscle strength, and muscle-specific strength as the conceptual core, with impaired physical performance treated as a major clinical outcome (Bhasin et al., 2020; Kirk et al., 2024; Zhang et al., 2024).

Regional diagnostic frameworks continue to evolve. The Asian Working Group for Sarcopenia 2019 consensus provided operational thresholds for handgrip strength, muscle quantity, gait speed, chair-rise performance, and the Short Physical Performance Battery, whereas the 2025 update reframed sarcopenia through a life-course muscle-health perspective and emphasized the metabolic and endocrine roles of skeletal muscle (Chen et al., 2020; Chen et al., 2025). This broader perspective is relevant because skeletal muscle interacts continuously with bone, adipose tissue, the immune system, and endocrine organs rather than functioning as an isolated contractile compartment.

The epidemiological burden is substantial but varies according to population and diagnostic approach. Large syntheses estimate that sarcopenia affects a meaningful proportion of community-dwelling older adults and is even more common in many disease-specific populations, with prevalence estimates strongly influenced by the diagnostic definition applied (Petermann-Rocha et al., 2022; Yuan and Larsson, 2023). Sarcopenia is associated with falls, fractures, hospitalization, functional decline, disability, mortality, and reduced health-related quality of life (Su et al., 2022; Mayhew et al., 2023; Beaudart et al., 2023). These outcomes make preservation of muscle function a major objective of healthy-longevity strategies rather than a narrowly cosmetic goal.

Aging muscle does not deteriorate in isolation. Bone mineral loss and microarchitectural deterioration frequently occur in the same individuals, producing osteosarcopenia, conventionally defined as coexisting sarcopenia and osteopenia or osteoporosis. The combined phenotype magnifies vulnerability because reduced muscle force and impaired balance increase fall probability at the same time that fragile bone increases the likelihood that a fall will produce fracture. Clinical and longitudinal evidence associates osteosarcopenia with greater risks of falls, fractures, disability, and mortality than musculoskeletal health or isolated disorders (Kirk et al., 2020; Salech et al., 2021; Teng et al., 2021; Polito et al., 2022; Chen et al., 2024; Veronese et al., 2024).

Recent geroscience scholarship provides a mechanistic explanation for this overlap. Osteosarcopenia can be mapped onto several hallmarks of aging, including mitochondrial dysfunction, cellular senescence, chronic inflammation, impaired proteostasis, altered nutrient sensing, genomic instability, and disturbed intercellular communication (Franulic et al., 2024). Muscle and bone also communicate through mechanical loading, myokines, osteokines, and shared signaling pathways, supporting the view that osteosarcopenia is a coupled bone–muscle disorder rather than the accidental coexistence of two independent diagnoses (Aryana et al., 2022; Sheng et al., 2023; Dong et al., 2025; Malvandi et al., 2025).

Palm tocotrienol-rich fraction is attractive within this framework because tocotrienols are unsaturated members of the vitamin E family with biological activities that extend beyond conventional radical scavenging. Palm-derived TRF typically contains mixtures of alpha-, gamma-, and delta-tocotrienol together with smaller quantities of tocopherols. Contemporary reviews describe antioxidant, anti-inflammatory, metabolic, neuroprotective, and skeletal effects, while musculoskeletal reviews identify plausible roles in osteoporosis, muscle aging, sarcopenia, and joint disease (Saud Gany et al., 2023; Chin, 2024; Looi et al., 2025).

The intervention identity nevertheless requires careful handling. Palm TRF is not biologically identical to purified γ-tocotrienol or to predominantly delta-tocotrienol preparations obtained from annatto. These preparations differ in isoform composition, formulation, absorption, plasma exposure, and potentially tissue distribution. Evidence from purified γ-tocotrienol or annatto-derived tocotrienols can strengthen class-level mechanistic plausibility, but it should not be represented as direct efficacy evidence for palm TRF (Shen et al., 2021; Chong et al., 2025; Looi et al., 2025).

This review therefore asks whether palm TRF has a coherent translational pathway to osteosarcopenia through simultaneous effects on mitochondrial energetics, inflammaging, cellular senescence, myogenic regeneration, muscle catabolism, bone remodeling, and bone–muscle communication. The central proposition is deliberately cautious: palm TRF is a multi-target geroscience candidate, but it is not yet an established treatment for sarcopenia, osteoporosis, or osteosarcopenia. The decisive test is whether molecular and metabolomic effects can be converted into meaningful improvements in muscle strength, physical performance, muscle quantity or quality, skeletal integrity, and ultimately falls and fractures.

Literature Review

Skeletal muscle is an energetically demanding tissue, and mitochondrial function is central to contraction, substrate oxidation, calcium handling, redox regulation, and adaptation to physical activity. Aging is associated with deterioration in mitochondrial respiratory capacity, biogenesis, fusion and fission dynamics, mitophagy, and metabolic flexibility. These changes interact with physical inactivity, endocrine alterations, inflammatory signaling, and neuromuscular decline rather than functioning as a single isolated defect. Contemporary sarcopenia research therefore positions mitochondrial dysfunction as a key convergence node linking energetic insufficiency, oxidative damage, inflammation, and impaired adaptive capacity (Bellanti et al., 2021; Xu and Wen, 2023; Zhu et al., 2023; Marzetti et al., 2024; Huang et al., 2025; Zhang et al., 2025).

Mitochondrial impairment can amplify muscle aging through several routes. Reduced oxidative phosphorylation may limit ATP availability, while dysfunctional mitochondria can become important sources of reactive oxygen species. Excessive ROS can damage membrane lipids, proteins, mitochondrial DNA, and nuclear DNA and can activate inflammatory and catabolic signaling. Defective mitophagy permits damaged organelles to accumulate, whereas inadequate biogenesis compromises replacement with functionally competent mitochondria. This feedback between energetic failure, redox imbalance, and inflammation is especially relevant to tocotrienols because experimental evidence suggests effects at several points within the network (Saud Gany et al., 2022; Chong et al., 2025; Saud Gany et al., 2026).

Sarcopenia also has a measurable metabolic phenotype. Recent metabolomic and lipidomic investigations have identified alterations in amino-acid pathways, acylcarnitines, sphingolipids, phospholipids, and other circulating metabolites associated with low muscle mass or function. Sphingolipid profiles have shown potential diagnostic value in men, while broader metabolomic studies reinforce the concept that muscle aging is accompanied by systemic metabolic remodeling (Seo et al., 2024; Hsu et al., 2024). A clinical systematic review of circulating biomarkers concluded that sarcopenia involves heterogeneous inflammatory, hormonal, metabolic, and molecular signatures and that standardization remains a major challenge (Veronesi et al., 2024).

Inflammaging adds another layer to the aging-muscle phenotype. Persistent low-grade inflammatory activity can impair anabolic signaling, increase proteolysis, alter mitochondrial function, and promote insulin resistance; it is increasingly recognized as a modifiable biological process linking aging with multimorbidity and functional decline (Dugan et al., 2023). TNF-α and IL-6 are among the most frequently discussed mediators, whereas NF-κB links inflammatory stimuli to transcriptional programs involved in cytokine production and catabolism. Oxidative stress can amplify these responses, while mitochondrial dysfunction can further increase ROS and inflammatory signaling, creating self-reinforcing loops (Xu and Wen, 2023; Franulic et al., 2024; Huang et al., 2025).

Cellular senescence is also relevant because aged muscle exhibits diminished regenerative reserve. Senescent cells can develop a senescence-associated secretory phenotype and release cytokines, chemokines, proteases, and growth-modulating factors that alter the local tissue environment. Satellite-cell and myoblast dysfunction reduce repair capacity after injury and repeated mechanical stress. Human studies show age-related changes in muscle-fiber characteristics and myosin-heavy-chain distributions that affect muscle quality, indicating that the phenotype is not explained by mass alone (Lee et al., 2024).

One of the most directly relevant palm-TRF findings concerns senescent human myoblasts. Tan et al. (2021) reported that TRF modulated the proliferation marker Ki67 and myogenic regulatory factors including MyoD and myogenin, with improvements in features of the myogenic program. These results imply that TRF may influence regenerative biology rather than merely lower oxidative markers. The findings are mechanistically important, but a cell-culture model lacks neural input, endocrine regulation, capillary supply, extracellular-matrix complexity, and mechanical loading; therefore, improved differentiation in vitro cannot be equated with improved strength in older people.

The transition toward metabolomics has strengthened the direct TRF evidence base. In aging rats, Saud Gany et al. (2022) found age-related differences in skeletal-muscle metabolites associated with amino-acid, lipid, and energy pathways, with TRF supplementation modifying several metabolic patterns. The subsequent 2026 study linked oxidative stress, inflammation, DNA damage, and altered metabolomics in aged muscle and found that TRF improved antioxidant enzyme activities, reduced lipid-peroxidation products, attenuated inflammatory markers, preserved DNA integrity, and improved histological features (Saud Gany et al., 2026). Importantly, those molecular improvements did not clearly restore muscle mass or overall body composition, establishing a critical boundary between biochemical efficacy and structural recovery.

Purified γ-tocotrienol provides additional mechanistic specificity. Chong et al. (2025) demonstrated preservation of myotube size, suppression of MuRF-1 and Atrogin-1, proteomic changes involving extracellular-matrix and mitochondrial pathways, reduced inflammatory signaling, and restored mitochondrial biogenesis in an inflammation-induced atrophy model. Because MuRF-1 and Atrogin-1 are central components of ubiquitin-proteasome-related muscle catabolism, these findings provide a biologically coherent anti-atrophy mechanism. They nevertheless constitute isoform-level supportive evidence rather than direct proof of palm-TRF efficacy in age-related human sarcopenia.

Tocotrienol research in bone provides a complementary reason to examine osteosarcopenia. Experimental evidence suggests effects on osteoblast survival and differentiation, osteoclastogenesis, oxidative stress, inflammation, Wnt-related pathways, the mevalonate pathway, and the RANKL/OPG axis. Reviews of glucocorticoid-induced osteoporosis and broader skeletal protection identify consistent preclinical signals but emphasize that human evidence remains limited (Ekeuku et al., 2022; Chin, 2024).

Osteocytes create an especially interesting bridge because these cells coordinate skeletal mechanosensing and influence remodeling through sclerostin, RANKL, DKK1, DMP1, and FGF23. Recent tocotrienol scholarship has proposed osteocytes as potential mediators of tocotrienol skeletal effects, while broader bone–muscle literature recognizes sclerostin and other osteokines as contributors to cross-tissue communication (Aryana et al., 2022; Zahanordin et al., 2026; Shahid et al., 2025). The direct causal chain from TRF to osteocyte signaling to muscle outcomes remains untested.

Bone–muscle crosstalk is now understood as both mechanical and endocrine. Muscle contraction loads bone, whereas skeletal architecture determines mechanical leverage and movement. Myokines and exerkines such as irisin, myostatin, IL-6, IL-15, and FGF21 can affect bone cells, while osteocalcin, sclerostin, RANKL, and FGF23 can influence muscle metabolism or regeneration. Shared Wnt/β-catenin, NF-κB, mitochondrial, redox, and RANKL–RANK pathways integrate these signals, and recent reviews increasingly treat bone and muscle as a functional endocrine unit rather than two independent tissues (Sheng et al., 2023; Jang and Choi, 2024; Falsetti et al., 2024; Hu et al., 2024; Kaji, 2025; Dong et al.,

2025; Malvandi et al., 2025; Shahid et al., 2025). This shared signaling architecture is the theoretical basis for evaluating TRF against osteosarcopenia rather than against muscle and bone separately.

Method

This study was designed as a critical qualitative literature review rather than a systematic literature review or meta-analysis. Its purpose was interpretive and translational: to integrate evidence from palm-TRF chemistry, aging-muscle biology, tocotrienol isoform research, bone remodeling, osteosarcopenia epidemiology, bone–muscle crosstalk, multi-omics, and contemporary intervention science. A qualitative design was selected because the evidence spans markedly different biological levels and intervention types that cannot be meaningfully combined into a single pooled treatment estimate.

The review emphasized peer-reviewed journal literature published from January 2020 through September 2026. Literature identification was conceptually organized around PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and major journal-publisher databases. Search concepts included combinations of "palm tocotrienol-rich fraction," "tocotrienol sarcopenia," "tocotrienol skeletal muscle," "myoblast senescence," "gamma tocotrienol muscle atrophy," "tocotrienol osteoporosis," "osteocyte tocotrienol," "osteosarcopenia," "bone muscle crosstalk," "mitochondrial dysfunction sarcopenia," "inflammaging muscle," "muscle metabolomics," "resistance exercise," "protein supplementation," "vitamin D," and "creatine."

The search was purposive rather than exhaustive. Priority was given to direct palm-TRF studies, contemporary consensus and epidemiological literature, mechanistic research using relevant aging or atrophy models, recent human intervention studies, and evidence needed to position TRF against established sarcopenia care. The review therefore does not claim PRISMA compliance, exhaustive retrieval, formal risk-of-bias scoring across every included study, or quantitative pooling.

To reduce overinterpretation, evidence was organized into four tiers. Tier 1 comprised direct human palm-TRF evidence; Tier 2 included direct palm-TRF cellular and animal evidence; Tier 3 comprised supportive tocotrienol-class or individual-isoform evidence from other formulations; and Tier 4 included contextual geroscience, osteosarcopenia, bone–muscle crosstalk, and intervention literature. This hierarchy prevents positive findings with purified γ-tocotrienol or annatto tocotrienols from being incorrectly attributed to a mixed palm-TRF product.

Thematic coding focused on mitochondrial energetics and metabolomics, oxidative stress and inflammaging, cellular senescence and myogenic regeneration, muscle-protein catabolism, bone remodeling and osteocyte biology, bone–muscle endocrine crosstalk, and clinical translation. The synthesis explicitly distinguished mechanistic biomarkers from clinically meaningful outcomes. Changes in antioxidant enzymes, inflammatory mediators, metabolites, or signaling proteins were treated as intermediate evidence, whereas grip strength, chair-rise performance, gait speed, SPPB, appendicular lean mass, muscle quality, bone mineral density, falls, and fractures were treated as more clinically proximal endpoints.

Results: Thematic Findings

The first thematic finding is that osteosarcopenia is best interpreted as a shared geroscience phenotype. Contemporary epidemiological and mechanistic literature shows that sarcopenia and osteoporosis frequently share upstream drivers and that their coexistence magnifies adverse outcomes (Kirk et al., 2020; Papadopoulou et al., 2021; Polito et al., 2022; Chen et al., 2024; Franulic et al., 2024). This shared-pathway model is relevant to TRF because the biological effects attributed to tocotrienols span several of the same nodes rather than a single muscle- or bone-specific target.

Figure 1 integrates the shared hallmarks of musculoskeletal aging with the principal mechanistic domains through which palm TRF may theoretically influence osteosarcopenia. It also distinguishes upstream biological modulation from the downstream functional and skeletal outcomes required to support a clinically meaningful claim.

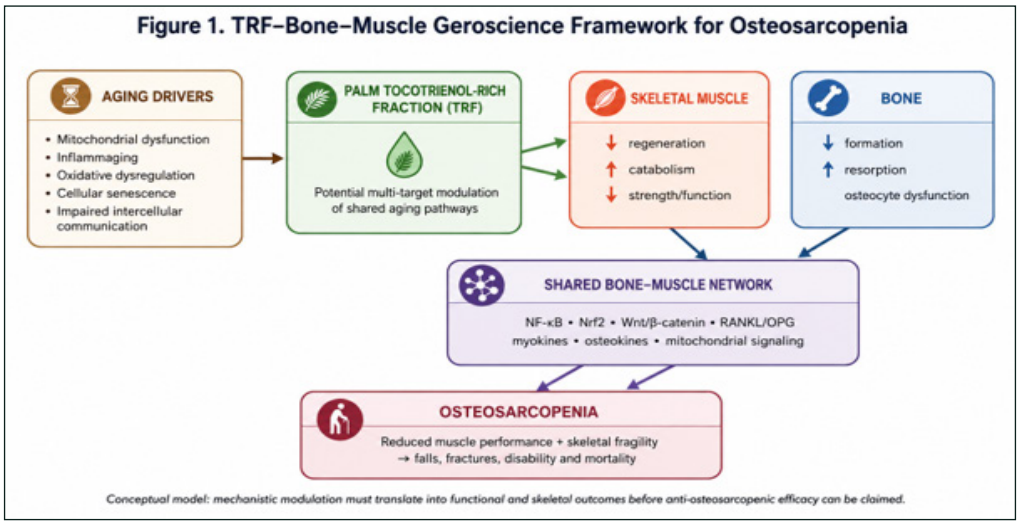

Figure 1: TRF–Bone–Muscle Geoscience Framework for Osteosarcopenia.

The framework places mitochondrial dysfunction, inflammaging, oxidative dysregulation, cellular senescence, and impaired intercellular communication upstream of parallel deterioration in muscle and bone. TRF is positioned against these shared nodes rather than portrayed as independently treating sarcopenia and osteoporosis. The key translational requirement is explicit: upstream biological modification must eventually produce measurable improvement in muscle function and skeletal integrity before anti-osteosarcopenic efficacy can be claimed.

The second finding is that direct TRF research currently demonstrates metabolic, redox, and inflammatory modulation more consistently than restoration of muscle mass. Aging-rat metabolomics indicates that TRF can modify energy-, amino-acid-, carnitine-, and lipid-related patterns, while more recent aging research reports favorable effects on antioxidant enzymes, lipid peroxidation, inflammatory biomarkers, DNA integrity, and histological features (Saud Gany et al., 2022; Saud Gany et al., 2026). The absence of clear recovery in muscle mass in the latter work is particularly informative because it indicates that biochemical improvement is not automatically anabolic.

The third finding concerns regenerative biology. Senescent human myoblasts treated with TRF show modulation of Ki67 and myogenic regulators, providing direct evidence that the intervention can influence proliferation and differentiation pathways in aging muscle cells (Tan et al., 2021). This is a more specific biological claim than generic antioxidant activity, but it remains several translational steps away from demonstrating improved satellite-cell function or muscle strength in vivo.

The fourth theme is that tocotrienol isoform research has begun to identify specific anti-catabolic pathways. γ-Tocotrienol suppresses MuRF-1 and Atrogin-1 and supports mitochondrial biogenesis and muscle strength in inflammation-induced atrophy models (Chong et al., 2025). These findings are highly relevant to sarcopenia mechanisms, but they should be interpreted as supportive evidence until comparable pathway engagement is demonstrated with standardized palm TRF in aging humans.

Figure 2 summarizes the proposed mechanisms through which TRF and tocotrienol isoforms may affect aging skeletal muscle while maintaining a clear distinction between mechanistic targets and human clinical outcomes. The diagram therefore treats muscle quality, strength, physical performance, and muscle mass as translational endpoints rather than established consequences of supplementation.

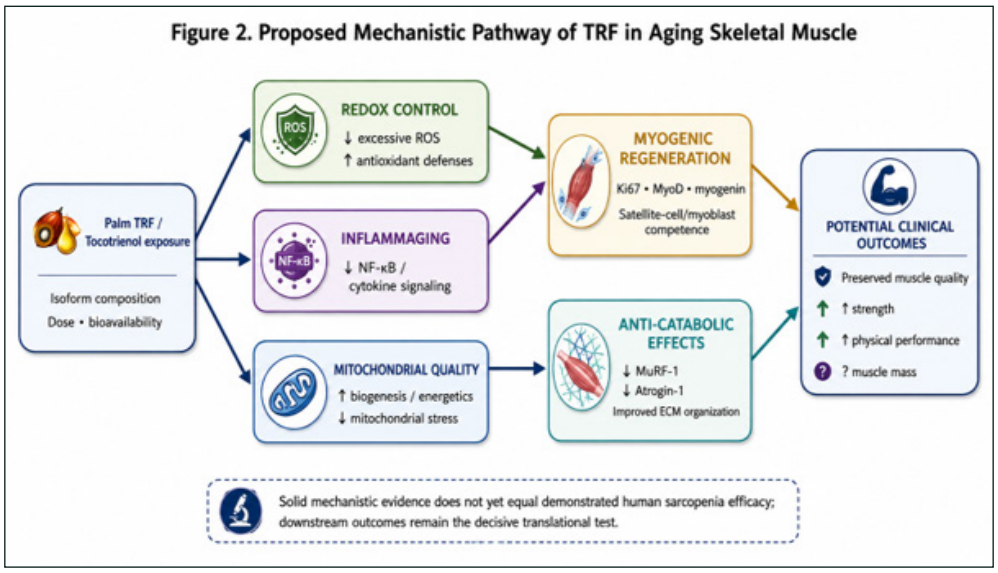

Figure 2: Proposed Mechanistic Pathway of TRF in Aging Skeletal Muscle.

The pathway begins with tocotrienol exposure and potential modulation of redox, inflammatory, and mitochondrial processes. These effects may improve myogenic differentiation and reduce ubiquitin-proteasome-related catabolism, but downstream changes in muscle mass, quality, strength, and performance remain hypotheses that require direct human confirmation. The figure therefore separates evidence-supported mechanisms from the clinically decisive endpoints that are still missing.

The fifth thematic finding is that tocotrienol skeletal effects are promising but predominantly preclinical. Experimental studies and contemporary reviews describe favorable changes in osteoblast, osteoclast, Wnt-related, mevalonate, and RANKL/OPG pathways (Ekeuku et al., 2022; Chin, 2024). Human metabolomic work in postmenopausal osteopenic women demonstrates that non-palm tocotrienol formulations can modify circulating lysophospholipids and acylcarnitines, but this cannot be treated as proof of palm-TRF bone efficacy (Shen et al., 2021).

The sixth finding is that osteocytes may provide an integrative bridge. Tocotrienol-related changes in sclerostin, DKK1, DMP1, FGF23, and RANKL are biologically compatible with altered mechanosensing and remodeling, while sclerostin, osteocalcin, RANKL, and other osteokines participate in the endocrine bone–muscle unit (Aryana et al., 2022; Zahanordin et al., 2026; Dong et al., 2025; Shahid et al., 2025). Direct demonstration that palm TRF modifies this crosstalk in humans does not yet exist.

Figure 3 illustrates the bidirectional mechanical and biochemical communication between muscle and bone and the shared signaling nodes that could plausibly intersect with tocotrienol biology. The proposed network is deliberately hypothesis-generating and highlights where direct human pathway-validation studies remain necessary.

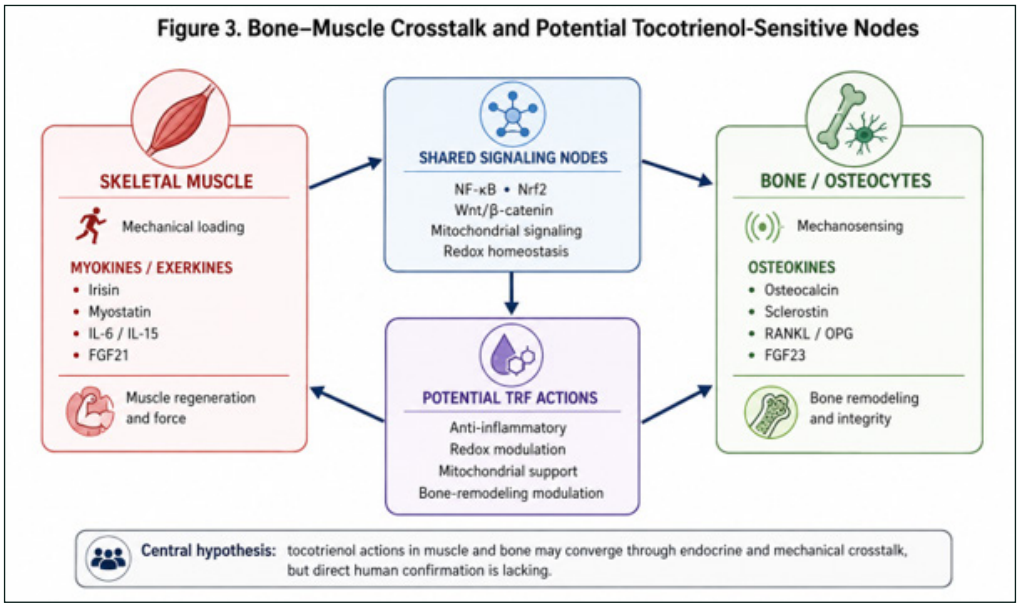

Figure 3: Bone–Muscle Crosstalk and Potential Tocotrienol-Sensitive Nodes.

In the proposed network, skeletal muscle communicates with bone through mechanical loading and myokines such as irisin and myostatin, whereas bone communicates with muscle through osteocalcin, sclerostin, RANKL-related signaling, and other osteokines. Shared inflammatory, redox, Wnt, and mitochondrial pathways provide potential convergence points. The figure is intentionally hypothesis-generating and does not imply that TRF has been shown to regulate every pathway simultaneously in humans.

The seventh theme is that human evidence remains the weakest link. Palm-TRF randomized trials across health domains demonstrate that human exposure is feasible and provide information on safety and biological response, but a systematic review of randomized trials identified substantial heterogeneity in dose, formulation, duration, population, and outcomes and did not establish anti-osteosarcopenic efficacy (Looi et al., 2025). A current older-adult TRF trial protocol includes body composition and bone-mineral-density outcomes, but a protocol cannot substitute for unblinded efficacy results (Amir Razak et al., 2025).

Other human work illustrates biological activity without answering the musculoskeletal question. A tocotrienol-enriched beverage trial reported changes in psychological well-being, antioxidant defense, and genomic-stability markers in older adults, whereas human tocotrienol trials in other domains have explored metabolic, inflammatory, neurological, and immune endpoints (Sharif et al., 2025; Looi et al., 2025). These studies contribute to a broader translational safety context, but none demonstrates clinically meaningful improvement in diagnosed osteosarcopenia.

Discussion and Analysis

The integrated evidence supports a qualified conclusion that TRF targets biology relevant to osteosarcopenia. Redox homeostasis, inflammatory signaling, mitochondrial function, myoblast differentiation, protein degradation, osteoblast/osteoclast regulation, and osteocyte signaling are all implicated in the condition and are also affected by TRF or related tocotrienols. The conceptual coherence is substantial. The translational problem is that osteosarcopenia develops over years through interacting neural, endocrine, mechanical, nutritional, inflammatory, and metabolic influences, and changing several biomarkers for weeks or months may not create a sufficient anabolic or skeletal effect to reverse that accumulated phenotype.

The 2026 aging-muscle study provides an especially useful caution. TRF improved redox, inflammatory, genomic,

and histological indices without clearly restoring muscle mass or body composition (Saud Gany et al., 2026). This result suggests that the intervention may be better conceptualized as modifying the biological environment in which adaptation occurs than as independently rebuilding muscle. Such a role could still be clinically valuable if TRF increases resilience or enhances responsiveness to resistance exercise.

Mitochondrial preservation is a strong candidate for a central mechanistic role because it links ATP production, ROS generation, metabolic flexibility, inflammation, and exercise adaptation. Direct TRF metabolomics and γ-tocotrienol anti-atrophy research converge on mitochondrial pathways (Saud Gany et al., 2022; Chong et al., 2025; Saud Gany et al., 2026). Yet mitochondrial dysfunction should not become an overly simple master explanation because neural remodeling, neuromuscular-junction deterioration, capillary rarefaction, extracellular-matrix change, endocrine shifts, and anabolic resistance also contribute to sarcopenia.

Future human mechanistic studies should therefore measure mitochondrial function more directly where feasible. Possible approaches include targeted plasma and muscle metabolomics, acylcarnitine profiling, mitochondrial biogenesis and mitophagy proteins, phosphocreatine recovery using phosphorus magnetic resonance spectroscopy, and ex vivo respirometry in mechanistic subcohorts. The purpose would be to determine whether circulating tocotrienol exposure engages mitochondrial pathways strongly enough to explain functional adaptation rather than merely changing systemic antioxidant indices.

A second conceptual advance is to interpret TRF through cellular senescence rather than only antioxidant chemistry. The senescent-myoblast data demonstrate changes in proliferation and myogenic differentiation, and the aging-animal data demonstrate reduced oxidative and inflammatory damage (Tan et al., 2021; Saud Gany et al., 2026). These findings are compatible with a senomorphic-like interpretation, but direct evidence involving p16INK4a, p21, senescence-associated secretory phenotype markers, epigenetic aging measures, or senescent-cell burden is insufficient. Future trials should include a focused senescence panel if geroscience claims are to be made.

Bone and muscle should also be measured simultaneously. An intervention that increases bone mineral density without improving strength may have limited impact on falls, while improved strength without adequate skeletal integrity may fail to reduce fracture risk. Osteosarcopenia trials should therefore combine functional, structural, and clinical outcomes from both tissues. DXA can quantify appendicular lean mass and BMD in one assessment, while grip strength, chair rise, gait speed, SPPB, and muscle-quality imaging provide complementary information. High-resolution peripheral quantitative computed tomography can characterize cortical and trabecular microarchitecture in mechanistic substudies (Polito et al., 2022; Chen et al., 2024).

The bone–muscle endocrine system deserves particular attention. Irisin, myostatin, osteocalcin, sclerostin, RANKL/OPG, FGF21, and FGF23 participate in cross-tissue signaling and overlap with Wnt, NF-κB, mitochondrial, and RANKL–RANK pathways relevant to tocotrienol biology (Falsetti et al., 2024; Hu et al., 2024; Jang and Choi, 2024; Kaji, 2025; Dong et al., 2025; Malvandi et al., 2025; Shahid et al., 2025). Measuring a selected panel of these biomarkers could test whether a TRF intervention modifies muscle and bone in parallel or whether the two tissue responses remain independent.

Metabolomics offers an especially promising bridge between molecular effect and precision geroscience. Aging-muscle and human sarcopenia studies demonstrate that amino-acid, sphingolipid, phospholipid, and acylcarnitine profiles differ according to muscle phenotype, while TRF changes several of these metabolic classes in experimental aging (Saud Gany et al., 2022; Seo et al., 2024; Hsu et al., 2024). A future trial could therefore combine plasma tocotrienol pharmacokinetics with targeted and untargeted metabolomics to identify biological responders and to test whether specific metabolic shifts mediate changes in muscle or bone outcomes.

The most important comparator for TRF is resistance exercise, which has a much stronger evidence base for sarcopenia. Systematic reviews and network meta-analyses consistently indicate that resistance-based interventions improve strength and physical performance and may improve muscle quantity, particularly when training intensity and adherence

are sufficient (Shen et al., 2023; Chen et al., 2023). Importantly, a 2025 randomized trial conducted specifically in community-dwelling postmenopausal women with osteosarcopenia showed that six months of supervised resistance training can improve clinically relevant musculoskeletal outcomes, providing a direct disease-specific benchmark against which adjunctive TRF should be evaluated (Lee et al., 2025). Any trial of TRF in sarcopenic older adults that ignores structured exercise would therefore have limited clinical relevance.

The more appropriate question is whether TRF adds benefit to standardized progressive resistance exercise. This design has both methodological and ethical advantages. It avoids withholding evidence-based care, reduces confounding caused by uncontrolled differences in activity, and tests whether TRF improves adaptation beyond a strong anabolic stimulus. The biological hypothesis would be that TRF reduces inflammatory, oxidative, or mitochondrial constraints on training adaptation rather than replacing the mechanical signal required for muscle and bone remodeling.

Protein intake should similarly be standardized. Meta-analyses indicate that protein supplementation can increase appendicular muscle mass in sarcopenic older adults, although effects on strength and performance vary and depend on protein source, total intake, resistance training, and baseline nutritional status (Kwon et al., 2023; Cuyul-Vásquez et al., 2023; Song et al., 2023; Liao et al., 2024; Whaikid & Piaseu, 2024). A first definitive TRF trial should ensure adequate protein intake in both arms rather than combine several experimental supplements at once, which would complicate attribution.

Vitamin D and creatine illustrate why biological plausibility alone is insufficient. Vitamin D is biologically important for bone and muscle, yet meta-analytic evidence does not show consistent improvement across all sarcopenia endpoints when supplementation is applied broadly (Widajanti et al., 2024). Creatine has stronger evidence when paired with resistance training and has been proposed specifically for osteosarcopenia, but direct trials in clinically diagnosed osteosarcopenia remain limited (Davies et al., 2024; Candow et al., 2025; Liu et al., 2025). TRF should be developed with the same discipline: combination with proven care, defined populations, and clinically meaningful endpoints.

Formulation and pharmacokinetics are another major gap. Palm TRF preparations contain mixtures of tocotrienol isoforms, and the administered mass does not reveal actual plasma or tissue exposure. Future trials should report quantitative α-, β-, γ-, and δ-tocotrienol composition, tocopherol content, excipients, dosing relative to meals, adherence, and serial plasma concentrations. This is necessary to compare mixed TRF with isoform-specific evidence and to determine whether specific exposure patterns predict musculoskeletal responses (Looi et al., 2025).

Sex and menopause may modify response. Postmenopausal women are an obvious target population because estrogen loss accelerates bone loss and can influence muscle and fat distribution. Existing tocotrienol work in osteopenic women provides a translational precedent for metabolomic assessment (Shen et al., 2021). However, men should not be neglected because sex differences in muscle mass, strength decline, fracture epidemiology, and metabolic response may produce different treatment effects. Future trials should be adequately powered for prespecified sex-stratified analyses or should deliberately target a defined phenotype such as postmenopausal osteosarcopenia.

The most informative next study would be a multicenter, randomized, double-blind, placebo-controlled trial enrolling adults approximately 65–85 years old with probable or confirmed sarcopenia and osteopenia or osteoporosis. Contemporary consensus criteria should be specified in advance, and all participants should receive standardized progressive resistance exercise with adequate protein intake; the recent ERTO-K trial provides a useful disease-specific precedent for supervised resistance training in postmenopausal osteosarcopenia (Bhasin et al., 2020; Chen et al., 2020; Kirk et al., 2024; Lee et al., 2025). Participants would then be randomized to placebo or a chemically standardized palm-TRF preparation for at least six to twelve months so that the incremental contribution of TRF can be distinguished from the background exercise effect.

Primary muscle outcomes should include handgrip strength and a lower-extremity functional measure such

as five-times chair stand or SPPB, with appendicular lean mass and muscle quality as structural outcomes. Gait speed and patient-reported mobility should complement these measures. Primary skeletal outcomes should include hip, femoral-neck, and lumbar-spine BMD, with bone-turnover markers and potentially high-resolution imaging in mechanistic substudies. Falls should be captured prospectively, whereas fractures would require substantially larger samples and longer follow-up.

Mechanistic measures should include circulating tocotrienol isoforms, targeted metabolomics, TNF-α, IL-6, CRP, lipid-peroxidation indices, antioxidant enzymes, osteocalcin, sclerostin, RANKL/OPG, irisin, and myostatin. Pre-specified mediation analyses could then test whether changes in inflammation, metabolites, or bone–muscle signaling explain improvements in function. This approach would move the field from descriptive supplementation toward precision geroscience.

Safety, Formulation, and Long-Term Feasibility

A clinically relevant osteosarcopenia intervention would probably require supplementation for many months or years rather than the short periods typical of exploratory nutraceutical studies. This raises a safety question that cannot be resolved by mechanistic experiments alone. The current palm-TRF randomized-trial literature provides a useful general tolerability context, but the populations, doses, formulations, and durations are heterogeneous, and older adults with multimorbidity and polypharmacy are underrepresented (Looi et al., 2025; Amir Razak et al., 2025). Future trials should therefore treat safety as a co-primary developmental domain rather than as a passive list of adverse events.

Longer-term studies should monitor hepatic and renal chemistry, hematological parameters, gastrointestinal symptoms, falls potentially related to dizziness, and clinically relevant interactions with antiplatelet, anticoagulant, lipid-lowering, antihypertensive, glucose-lowering, osteoporosis, and anti-inflammatory therapies. Product quality is equally important. A standardized TRF intervention should specify isoform composition, tocopherol content, excipients, oxidative stability, storage conditions, and batch-to-batch analytical variability. Without these data, apparently inconsistent efficacy could reflect inconsistent exposure rather than genuine biological heterogeneity (Looi et al., 2025).

The feasibility of long-term adherence also deserves attention. Resistance exercise requires sustained behavioral engagement, and adding a supplement may improve acceptability only if dosing is convenient and adverse effects are minimal. Clinical development should therefore record adherence to both the supplement and the exercise program, dietary protein intake, vitamin D status, and changes in concurrent medications. These variables are not ancillary because they can materially alter muscle and bone outcomes and may obscure or exaggerate the apparent effect of TRF (Papadopoulou et al., 2021; Kwon et al., 2023; Widajanti et al., 2024).

Research Priorities and Evidence Thresholds

A useful evidence threshold for future work is concordance across biological levels. A credible anti-osteosarcopenic signal would ideally consist of verified tocotrienol exposure, change in a prespecified mechanistic pathway, and improvement in at least one clinically meaningful muscle endpoint together with a skeletal endpoint. Biomarker changes without functional benefit should be interpreted as mechanistic engagement, whereas isolated changes in lean mass without improved strength or performance should be considered structurally interesting but clinically incomplete. This hierarchy is consistent with contemporary sarcopenia frameworks that emphasize function and strength rather than tissue quantity alone (Bhasin et al., 2020; Mayhew et al., 2023; Kirk et al., 2024).

Replication by independent research groups should also be a priority. Tocotrienol research remains concentrated within a relatively small scientific community, and independent confirmation would strengthen confidence that favorable effects are not dependent on a specific laboratory model, product formulation, analytical platform, or population. Multicenter trials using harmonized outcome definitions would also improve generalizability across ethnicity, sex, baseline nutritional status, and healthcare settings (Chen et al., 2020; Petermann-Rocha et al., 2022; Chen et al., 2024).

Finally, future research should avoid framing osteosarcopenia as a condition that can be corrected

by a single nutraceutical. The strongest translational model is multimodal: progressive resistance exercise supplies mechanical and anabolic stimulation; adequate protein provides substrate; osteoporosis treatment is used when clinically indicated; and TRF is tested for an incremental geroprotective effect on inflammatory, redox, mitochondrial, or regenerative constraints. Demonstrating such an additive effect would be scientifically more persuasive and clinically more useful than showing another isolated antioxidant biomarker response (Shen et al., 2023; Cuyul-Vásquez et al., 2023; Davies et al., 2024; Candow et al., 2025; Liu et al., 2025).

Figure 4 summarizes the translational evidence staircase and the recommended clinical-development sequence for palm TRF. It emphasizes that progression from mechanistic studies to confirmatory osteosarcopenia trials should be accompanied by standardized composition, pharmacokinetic characterization, metabolomics, and prespecified responder phenotyping.

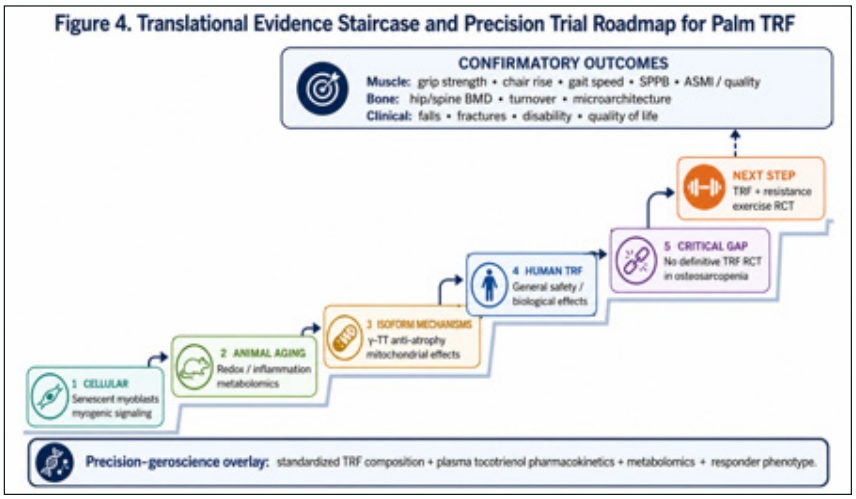

Figure 4: Translational Evidence Staircase and Precision Trial Roadmap for Palm TRF.

The evidence base is presently asymmetrical: mechanistic rationale is broad, cellular and animal evidence is encouraging, isoform-level anti-atrophy evidence is increasingly specific, bone evidence is predominantly preclinical, and direct human osteosarcopenia efficacy evidence is absent. The next critical step is therefore not another generic antioxidant study but a rigorously phenotyped trial testing standardized palm TRF as an adjunct to resistance exercise. Progression to long-term falls and fracture outcomes should occur only if such trials demonstrate concordant functional and skeletal benefits.

Conclusion

Palm tocotrienol-rich fraction occupies an unusual position in musculoskeletal geroscience because its biological actions intersect with several mechanisms implicated simultaneously in age-related deterioration of muscle and bone. Contemporary studies support effects on redox regulation, inflammatory signaling, mitochondrial metabolism, myogenic differentiation, protein-catabolic pathways, and aspects of bone remodeling and osteocyte biology. These convergent mechanisms provide a stronger rationale than the traditional description of tocotrienols as general antioxidants.

The evidence remains weighted strongly toward mechanisms rather than clinically established efficacy. Senescent human myoblast studies support regenerative effects, aging-animal metabolomics demonstrates modulation of redox and metabolic networks, and purified γ-tocotrienol produces specific anti-atrophy and mitochondrial effects. Bone studies similarly identify osteoblast, osteoclast, osteocyte, Wnt-related, RANKL/OPG, and sclerostin pathways. However, molecular improvement does not necessarily restore muscle mass, and direct trials showing simultaneous improvement in muscle function and skeletal integrity in osteosarcopenic older adults are not yet available.

The most important future question is therefore whether standardized palm TRF produces incremental clinical benefit when added to evidence-based musculoskeletal care. Resistance exercise should form the background standard, protein intake should be adequate and controlled, and future trials should simultaneously measure strength, physical performance, appendicular lean mass or muscle quality, bone mineral density, bone turnover, and mechanistically relevant biomarkers.

A precision-geroscience strategy integrating tocotrienol pharmacokinetics, metabolomics, inflammatory phenotype, sex or menopausal status, and responder analysis could substantially strengthen the field. If rigorous independent trials demonstrate concordant improvements in muscle and bone, palm TRF could evolve from a mechanistically plausible nutraceutical into a credible adjunctive intervention for osteosarcopenia. Until that evidence is available, its role should remain characterized as promising, biologically coherent, and translationally unproven.

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