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Nutrition and Exercise Interventions for Stem Cell Exhaustion in Aging

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Abstract

Aging is characterized by progressive stem cell exhaustion, leading to impaired tissue regeneration and organ dysfunction. While stem cell transplantation has been extensively explored for aging interventions, preserving endogenous stem cell function through lifestyle strategies might offer a more sustainable approach. This review synthesizes current evidence on how nutritional interventions and physical exercise can mitigate stem cell decline by targeting shared aging pathways. The research method in this study uses narrative review with a systematic approach through literature search in PubMed, Scopus, and Springer Link databases, using combined keywords, Medical Subject Headings terms, and snowballing techniques. Nutritional interventions, including caloric restriction and fasting-mimicking diets, enhance stem cell resilience through metabolic reprogramming involving Adenosine Monophosphate-activated Protein Kinase, mammalian Target of Rapamycin, and autophagy restoration. Plant-derived polyphenols such as fisetin and quercetin emerge as promising adjuncts, targeting senescence clearance and optimizing the stem cell niche. Exercise concurrently activates stem cells via mechanosensitive pathways and systemic factor release while also improving polyphenol bioavailability through enhanced tissue perfusion. Senolytic safety requires careful evaluation due to senescence's tumor-suppressive role, while polyphenol bioavailability limitations may be addressed with nanocarriers and structural modifications. By integrating lifestyle and nutraceutical strategies, this multi-dimensional approach offers a roadmap for maintaining endogenous stem cell pools and extending healthspan.

Keywords

Caloric Restriction, Exercise, Niche Remodeling, Polyphenols, Senolytics, Stem Cell Exhaustion.

1. Introduction

Aging is a complex biological process characterized by the progressive decline of tissue function and regenerative capacity, driven by the accumulation of cellular damage and the dysregulation of homeostatic mechanisms (Jin, 2010; da Costa et al., 2016). Among the twelve hallmarks of aging, stem cell exhaustion has emerged as a central contributor to age-related degeneration, as the depletion and dysfunction of stem cell pools impair tissue repair and accelerate organ dysfunction (López-Otín et al., 2023). While stem cell-based therapies have garnered significant attention for their potential to treat aging, there remains a critical gap in research focusing on preserving endogenous stem cell function as a fundamental anti-aging strategy (El Assaad et al., 2024). This review explores how interventions, particularly plant polyphenols, nutrition and physical activity, can target shared pathways between general aging and stem cell exhaustion.

The decline of stem cells with age is not an isolated phenomenon but rather intertwined with broader aging mechanisms, including genomic instability, epigenetic alterations, mitochondrial dysfunction, and chronic inflammation. Deoxyribonucleic Acid (DNA) damage accumulation in Hematopoietic Stem Cells (HSCs) not only impairs their self-renewal but also contributes to HSC stemness quality (Li et al., 2016). Similarly, oxidative stress and Senescence-Associated Secretory Phenotype (SASP) may disrupt the stem cell niche, disrupting the microenvironment that further accelerates functional decline (Farahzadi et al., 2023; Alqahtani et al., 2025). These overlaps suggest that interventions targeting general aging mechanisms such as oxidative stress or epigenetic dysregulation may concurrently rejuvenate stem cell pools. Phytochemicals, with their pleiotropic bioactivities, are uniquely positioned to address these shared pathways (Luo et al., 2021). These effects are amplified by lifestyle factors such as physical activity and nutrition strategy.

While extensive research has investigated exogenous stem cell transplantation for age-related diseases, far less attention has been paid to strategies that enhance the body's innate stem cell reserves. This disparity is notable because endogenous stem cell maintenance could provide a more sustainable and less invasive alternative to cell-based therapies, which face challenges such as immune rejection, high costs, and ethical concerns (Volarevic et al., 2018; Petrus-Reurer et al., 2021). Lifestyle interventions, including caloric restriction, micronutrient optimization, and structured exercise, have shown promise in modulating key pathways such as Adenosine Monophosphate-activated Protein Kinase (AMPK), mammalian Target of Rapamycin (mTOR), and Nikotinamida Adenin Dinukleotida (NAD+) metabolism that govern both aging and stem cell health (Bodine, 2006; Weir et al., 2017; Tulsian et al., 2018). For example, exercise-induced activation of muscle satellite cells. Neurogenesis highlights the potential of non-pharmacological approaches to alleviate stem cell exhaustion. Recent advances reveal that phytochemicals not only directly enhance stem cell function but also potentiate the benefits of exercise (Wu et al., 2008; Bazgir et al., 2017; Ahmadi et al., 2024).

Despite a growing body of evidence on the molecular mechanisms that drive stem cell exhaustion, there are still limited studies that comprehensively link lifestyle and nutraceutical interventions to efforts to maintain stem cell function across tissue types. Filling this gap is crucial because strategies that focus on maintaining intrinsic repair mechanisms have the potential to provide both preventive and translational benefits in dealing with age-related degenerative diseases. The novelty of this study lies in the effort to integrate findings from aging biology, nutraceuticals, and exercise physiology to show how synergistic lifestyle interventions, especially polyphenols, nutritional strategies, and physical activity can improve stem cell mechanisms. Therefore, this review not only presents a synthesis of mechanistic findings, but also

emphasizes the practical implications of nutrition, polyphenol, and physical activity-based interventions in tackling stem cell exhaustion while promoting healthy aging.

By synthesizing evidence from nutraceutical science, exercise physiology, and stem cell biology, this review aims to bridge the divide between basic research and practical interventions, positioning lifestyle synergy as a cornerstone of anti-aging strategies. This review covers all aging-related stem cell decline, including but not limited to Hematopoietic Stem Cells (HSC), Mesenchymal Stem Cells (MSC), and tissue specific stem cells.

2. Methods

This narrative review was conducted to synthesize and critically evaluate the current evidence regarding interventions to counteract stem cell exhaustion, a central hallmark of the aging process. To ensure a comprehensive and unbiased analysis, a systematic approach to literature identification and selection was employed. The literature search was performed using the electronic databases PubMed, Scopus, and Springer Link for relevant articles. The search strategy was built by combining keywords and Medical Subject Headings (MeSH) terms related to three primary conceptual categories: (1) stem cells (e.g., "stem cell," "progenitor cell," "satellite cell," "hematopoietic stem cell," "mesenchymal stem cell"); (2) aging and exhaustion (e.g., "aging," "ageing," "senescence," "stem cell exhaustion," "regeneration"); and (3) interventions (e.g., "caloric restriction," "fasting," "exercise," "physical activity," "polyphenols," "senolytics." Boolean operators (AND, OR) were used to logically combine these terms. Furthermore, the reference lists of all retrieved articles were manually examined to identify additional pertinent publications through a snowballing technique.

The review considered studies involving both preclinical models, such as in vitro stem cell cultures, and in vivo animal models of ageing and human populations. Interventions of interest included nutritional strategies such as caloric restriction, fasting-mimicking diets, and administration of specific phytochemicals, as well as structured physical exercise protocols. The primary outcomes of interest were measures of stem cell function, including quantitative changes in pool size, functional capacity for self-renewal and differentiation, markers of cellular senescence, and alterations in the stem cell niche. Studies focusing solely on embryonic stem cells, induced pluripotent stem cells (iPSCs), or non-English publications were excluded.

Given the significant heterogeneity in methodologies and outcomes across the included studies, a narrative synthesis approach was chosen. This allowed for the thematic organisation of evidence, which is structured in this review first to elucidate the pathophysiology of stem cell exhaustion and then to evaluate the mechanistic basis and efficacy of nutritional, exercise, and nutraceutical interventions. Throughout this process, emphasis was placed on highlighting robust, reproducible findings from high-quality studies, while also acknowledging exploratory data from emerging fields to provide a balanced, forward-looking perspective.

3. Results

3.1. Nutritional Strategies for Anti-Aging

Aging is characterized by a progressive decline in tissue regeneration capacity, most evident in delayed wound healing among the elderly compared to younger individuals (Gould et al., 2015). This impaired regeneration stems from reduced cellular turnover, leading to the accumulation of senescent cells, gradual organ dysfunction, structural tissue changes, and pathological alterations such as fibrosis (Brack et al., 2007; Cuanalo-Contreras et al., 2023). The decline in regenerative potential is driven by interconnected hallmarks of aging, including chronic inflammation ("inflammaging"), oxidative stress, mitochondrial dysfunction, loss of

proteostasis, impaired autophagy, and disrupted intercellular communication (López-Otín et al., 2023). These systemic processes collectively compromise the body's ability to replace damaged cells and maintain tissue homeostasis.

Adult stem cells serve as tissue-specific reservoirs for cellular replenishment, with distinct populations residing in each organ, such as satellite cells in skeletal muscle and limbal stem cells in the cornea (Bazgir et al., 2017; Gonzalez et al., 2018). These cells exhibit varying differentiation potentials, ranging from multipotent to unipotent (Singh et al., 2016). Stem cells maintain tissue integrity through two division modes: symmetric division, producing two identical stem cells or two differentiated cells, and asymmetric division, yielding one self-renewing stem cell and one differentiated progeny (Evano et al., 2020). The precise balance between these modes is critical for preserving the stem cell pool throughout life (Kawahigashi et al., 2024).

As the primary drivers of regeneration, stem cells are themselves vulnerable to ageing processes. Stem cell exhaustion is the age-related decline in stem cell number, function, and regenerative capacity that arises from both shared and stem cell-specific mechanisms. General ageing pathways that include cellular senescence, replicative arrest, epigenetic drift, mitochondrial dysfunction, and niche deterioration might converge with stem cell-intrinsic dysregulation, such as quiescence exit defects and niche signalling failures (Zhou et al., 2022; Brunet et al., 2023; López-Otín et al., 2023). While the exact aetiology remains unclear, this dual vulnerability positions stem cell exhaustion as a central mediator of age-related regenerative decline.

One of the primary mechanisms driving stem cell exhaustion is cellular senescence, a state of irreversible cell cycle arrest triggered by persistent DNA damage, telomere attrition, or oxidative stress. Replicative senescence is often linked to telomere shortening, which activates the DNA Damage Response (DDR) pathway involving p53/p21 and $p16^{INK4a}$/Rb tumour suppressor networks (Coppé et al., 2010). While these pathways protect against cancer, their chronic activation depletes the stem cell pool (Nelson et al., 2014). The length of telomere has been shown to reduce stem cell self-renewal capacity (Hao et al., 2005). This was shown on patients with aplastic anaemia who did not respond well to treatment, had shorter telomere length (Lee et al., 2001). Similarly, accumulated similar senescence cell SASP factors create an inflammatory microenvironment that further impairs regeneration (de Lima & Hardiany, 2021).

Ageing is accompanied by epigenetic drift, including DNA methylation changes, histone modifications, and chromatin remodelling, which disrupt stem cell identity and function (Wang et al., 2022). Studies in aged neural stem cells show that H3K27me3 depletion derepresses lineage-specific genes, pushing stem cells toward differentiation and depleting the reserve pool (Cao et al., 2021; Signal et al., 2024). Additionally, Sirtuin (SIRT)1 and SIRT6, NAD+-dependent deacetylases that maintain genomic stability against stressors, decline with age, exacerbating epigenetic dysregulation (Owczarz et al., 2020).

Stem cells depend on metabolic flexibility, shifting between glycolysis and Oxidative Phosphorylation (OXPHOS), but aging disrupts this balance through mitochondrial decay marked by Reactive Oxygen Species (ROS), mtDNA mutations, and impaired mitophagy (Zhang et al., 2018; Li et al., 2023). Mitochondrial dysfunction lowers regenerative capacity in HSCs and reduces Adenosine Triphosphate (ATP) production in MSCs, impairing differentiation, while declining SIRT3 further compromises function (Denu, 2017; Hinge et al., 2020; Yu et al., 2023). Ageing also deteriorates stem cell niches, with Extracellular Matrix (ECM) stiffening, chronic inflammation, and altered signalling (Alakhdar et al., 2024). Elevated Transforming Growth Factor-beta (TGF-β) and cytokines in aged HSC niches reduce regeneration, ECM cross-linking limits repair, and dysregulated

Wnt/β-catenin skews satellite cells toward fibrosis (Brack et al., 2007; Rajendran et al., 2021; Matteini et al., 2021; Chinvattanachot et al., 2024). Glycation and vascular ageing further impair niche function (Xiao et al., 2020; Fleischhacker et al., 2024). These overlapping mechanisms show that targeting ageing pathways may also preserve endogenous stem cell pools.

Caloric Restriction (CR) and Fasting-Mimicking Diets (FMDs) have emerged as effective nutritional interventions for ageing. CR, defined as a sustained reduction in calorie intake without malnutrition, has been shown to extend lifespan and health span across multiple species, from yeast to primates (Flanagan et al., 2020). The beneficial effects of CR on stem cell function are mediated through evolutionarily conserved metabolic and stress-response pathways that enhance cellular repair mechanisms while reducing oxidative damage and inflammation (Bosch-Sierra et al., 2024). On the other hand, FMDs are periodic short-term dietary regimens that mimic the effects of fasting while providing essential nutrients. FMD offers a more clinically feasible alternative to chronic CR, with comparable benefits for anti-ageing (Brandhorst et al., 2024).

At the molecular level, CR and FMDs exert their effects primarily through metabolic reprogramming and activation of nutrient-sensing pathways (Dilova et al., 2007). Reduced calorie availability lowers circulating glucose and Insulin-Like Growth Factor 1 (IGF-1) levels, which in turn downregulates the pro-ageing mTOR pathway and upregulates AMP-Activated Protein Kinase (AMPK) (Fontana et al., 2016; Tulsian et al., 2018). AMPK activation promotes mitochondrial efficiency, autophagy, and stress resistance, all of which are critical for preserving stem cell function (Rossin et al., 2025). For example, calorie restriction supports repopulation of HSC, thereby preventing premature differentiation and maintaining the quiescent stem cell pool (Chen et al., 2025). Likewise, Intestinal Stem Cells (ISCs) exhibit enhanced regenerative capacity under CR (Bruens et al., 2020).

Another key mechanism by which CR and FMDs protect stem cells is through the induction of autophagy, a cellular recycling process that removes damaged organelles and protein aggregates (Chung & Chung, 2019; Shabkhizan et al., 2023). Age-related decline in autophagy contributes to stem cell exhaustion by allowing the accumulation of toxic cellular debris (Chen et al., 2018). CR robustly stimulates autophagy via activation of sirtuins and Forkhead Box O (FOXO) transcription factors, which are essential for stem cell self-renewal and stress resistance (Guarente, 2012). In muscle satellite cells, CR preserves stem cell function by activating SIRT1 and FOXO, which clear damaged mitochondria and maintain genomic stability (Cerletti et al., 2012; Jeong & Haigis, 2015). Similarly, FMDs have been shown to enhance neurogenesis by upregulating Brain-Derived Neurotrophic Factor (BDNF) and promoting the clearance of senescent cells through autophagy-mediated pathways (Seidler & Barrow, 2022).

In addition to metabolic and autophagic effects, CR and FMDs modulate systemic factors that influence stem cell niches. Chronic low-grade inflammation, or "inflammaging," is a major contributor to stem cell decline, as pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) disrupt niche signalling and impair stem cell function (Ambrosi et al., 2021). CR reduces inflammation by suppressing the SASP secretion (Justice et al., 2024). Research in aged mice demonstrates that CR decreases circulating levels of inflammatory cytokines, thereby preserving the bone marrow microenvironment and enhancing HSC function (Dogan et al., 2017; Ho & Takizawa, 2022).

Preclinical and clinical studies highlight the translational potential of caloric restriction (CR) and Fasting-Mimicking Diets (FMDs) in maintaining stem cells. In humans, fasting reduces IGF-1 and CRP while improving metabolic health, and clinical trials show fasting protects hematopoietic stem cells during chemotherapy (Fontana et al., 2016; Kemalasari et al., 2022; Xie et al., 2024). However, issues such

as adherence and malnutrition risk necessitate optimized FMDs with adequate micronutrients. Complementing nutritional strategies, physical activity enhances stem cell niches, while phytochemicals, particularly polyphenols, emerge as promising agents targeting aging pathways with multi-target effects and low toxicity (de Araújo et al., 2021; Zhang et al., 2022; Chen et al., 2022; Rodríguez-Vera et al., 2022; Rathod et al., 2023).

3.2. Dietary Phytochemicals

Several polyphenols have emerged as potential anti-ageing medicines with senolytic action. Fisetin, a naturally occurring flavonoid found in strawberries, apples, and persimmons, has emerged as a potent senolytic compound capable of selectively clearing senescent cells, thereby mitigating stem cell exhaustion and promoting tissue regeneration (Yousefzadeh et al., 2018). Senescent cells accumulate with age and contribute to chronic inflammation and stem cell dysfunction through their SASP, which disrupts the stem cell niche (Lorenzo et al., 2023). Fisetin targets these harmful cells by inhibiting pro-survival pathways, particularly the PI3K/AKT/mTOR networks, which senescent cells rely on to evade apoptosis (Sun et al., 2021). Reduced senescence cell population may lead to improved stem cell function and tissue repair capacity through the reduction of senescence cell producing SASP (Ambrosi et al., 2021; Wölfel et al., 2024). In preclinical models, fisetin administration has been shown to rejuvenate aged stem cell culture through its senolytic actions, reducing ROS and the number of senescent cells (Mullen et al., 2023). The senolytic action of fisetin, therefore, may also be applied to protect the stem cell niche from senescent cell accumulation. Fisetin in combination with training was shown to exhibit better neurogenesis in the Alzheimer's disease model compared to fisetin and training alone (Dehkordi et al., 2024).

Dietary senolytics represent a promising anti-ageing intervention that may synergise with nutritional approaches and exercise regimens. Quercetin in combination with dasatinib has been studied as a senolytic drug in patients with diabetic kidney disease, which showed a decrease in p16 and p21 expressing cells on skin epidermis and adipose tissue (Baker et al., 2023). However, the safety of senolytics as wellness supplements in healthy individuals requires rigorous evaluation, particularly given concerns that cellular senescence may serve as a physiological tumour-suppressive mechanism (Campisi, 2001).

The anti-inflammatory and antioxidant properties of various polyphenols provide additional benefits by creating a more favourable microenvironment for stem cell activity and protection against generated ROS during differentiation (Tsao, 2010; Yahfoufi et al., 2018; Zhang et al., 2022). By suppressing pro-inflammatory cytokines through NF-κB inhibition and downregulating NLRP3 inflammasome activity, polyphenols like resveratrol and quercetin mitigate chronic inflammation that otherwise disrupts stem cell niche signalling (Ren et al., 2013; Chang et al., 2015). Simultaneously, their redox-modulating capacity via Nrf2 pathway activation and direct free radical scavenging neutralises ROS generated during stem cell proliferation and differentiation, periods of heightened metabolic stress (Suraweera et al., 2020). Quercetin, as an oral supplement, improves post-exercise antioxidant capacity and reduces inflammation, resulting in better endurance and recovery (Gholami & Ardestani, 2018; Tsao et al., 2022). Flavonoid supplementation also further increases the antioxidant and anti-inflammatory effect of calorie restriction (Navajas-Porras et al., 2025). While antioxidants demonstrate clear benefits for stem cell maintenance, excessive administration may paradoxically induce pro-oxidant effects that counteract their protective mechanisms, potentially impairing stem cell function as a result (Pérez-Torres et al., 2017).

Polyphenols also exhibit different effects on stem cell differentiation. Fisetin inhibits osteogenic differentiation while promoting fibroblast differentiation.

Meanwhile, a number of studies consistently reported that quercetin increases osteogenic differentiation (Lorthongpanich et al., 2021; Bian et al., 2021; Hu et al., 2025). Quercetin's promotion of osteogenic differentiation is mediated by activation of the Wnt pathway, while kaempferol also promotes osteogenic differentiation through a different mechanism (Gan et al., 2022; Hu et al., 2025). This functional specificity highlights how distinct polyphenols can differentially benefit endogenous stem cells in an organ-dependent manner. While exercise may benefit stem cell differentiation in their own respective niche, polyphenol, on the other hand, should be directed to the intended target through multiple strategies.

The transition from dietary polyphenols to clinically viable drugs requires overcoming bioavailability challenges through innovative formulations. Nanotechnology has emerged as a game-changer. Curcumin encapsulated in Poly Lactic-Co-Glycolic Acid (PLGA) nanoparticles achieves 40-fold higher plasma concentrations than free curcumin. While liposome loading of quercetin shows targeted delivery to bone as a potential antiosteoporotic agent (Tsai et al., 2012; Xing et al., 2023). Recent advances in structural modification further enhance efficacy; for example, the glucoside quercetin exhibits improved intestinal absorption (Liu et al., 2025). Interestingly, extracellular vesicle derived from MSCs is also a promising vehicle for quercetin as a spinal cord injury regenerative agent (Yang et al., 2024).

3.3. Exercise Intervention

Physical activity represents one of the most potent, non-pharmacological interventions for mitigating ageing manifestations and improving healthpan (Lu et al., 2025). Regular physical activity has been associated with an increase in life expectancy (Reimers et al., 2012). A growing body of evidence demonstrates that exercise induces profound activation and rejuvenation of stem cells across multiple tissues, including skeletal muscle, brain, bone, and the cardiovascular system (Blackmore et al., 2009; Marędziak et al., 2015; Marino et al., 2021; Fukada & Nakamura, 2021). The mechanisms underlying exercise-mediated stem cell stimulation involve a complex interplay of mechanical, metabolic, and systemic factors that collectively enhance regenerative capacity.

Skeletal muscle demonstrates perhaps the most well-characterised response to exercise-induced stem cell activation. Muscle satellite cells, which reside in a quiescent state beneath the basal lamina of muscle fibres, are rapidly mobilised in response to mechanical loading and muscle damage (Forcina et al., 2019). Exercise, particularly resistance training, improves satellite cell self-renewal capacity through mitochondrial respiratory inhibition and decrease inflammation (Abreu & Kowaltowski, 2020). Aged individuals exhibit impaired satellite cell function due to elevated levels of TGF-β and Wnt signalling, which promote fibrogenic rather than myogenic differentiation (Chinvattanachot et al., 2024). However, chronic exercise has been shown to mitigate this age-related dysfunction by downregulating TGF-β and restoring Notch signalling, a critical pathway for satellite cell self-renewal (Widiastuti et al., 2021; Pinto et al., 2025). Additionally, exercise enhances mitochondrial biogenesis in satellite cells via PGC-1α upregulation, improving their metabolic fitness and regenerative potential (Dinulovic et al., 2016).

Physical forces generated during exercise activate critical mechanotransduction pathways in stem cells and their niches (Vining & Mooney, 2017). In skeletal muscle, satellite cells respond to shear stress and muscle fibre stretch through integrin-mediated activation of Focal Adhesion Kinase (FAK) and Yes-Associated Protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) signaling (Sun et al., 2017). These pathways promote myogenic gene expression while suppressing adipogenic differentiation. Similarly, osteocytes in bone tissue translate mechanical loading into biochemical signals through connexin 43 hemichannels and

prostaglandin E_2, stimulating Wnt/β-catenin signaling in MSC to promote osteogenesis over adipogenesis (Chen et al., 2021; Zhao et al., 2023). The piezoelectric properties of the bone matrix further enhance this response, demonstrating how tissue-specific physical properties affect stem cell behavior (Carter et al., 2021).

Exercise preserves stem cell function across multiple tissues by integrating mechanical, metabolic, and systemic effects. In the CNS, it promotes neurogenesis through BDNF release and TrkB activation, reduces microglial-driven inflammation, and supports NSC survival via lactate metabolism (Morgan et al., 2015; Spielman et al., 2016; Lee & Soya, 2017; Pansri et al., 2021; Zhang et al., 2024; Li et al., 2025). Exercise also mobilises HSCs and EPCs through VEGF release to enhance vascular repair (Baker et al., 1985; Tang et al., 2010; Li et al., 2017; Mitsiou et al., 2022; Zhu et al., 2024). Directs MSCs toward osteogenesis via Wnt/β-catenin and PPARγ suppression, improving bone health (Li et al., 2015; Yuan et al., 2016; Ahn & Kim, 2016; Yu et al., 2024; Xiaoya et al., 2025). Endocrine mediators such as irisin and GDF11 further regulate stem cell activity while anti-inflammatory effects protect niches (Lee et al., 2019; Zhao et al., 2020; Maak et al., 2021; Blanc et al., 2025). At the metabolic level, exercise enhances ATP generation through PGC-1α–mediated mitochondrial biogenesis and OXPHOS efficiency while reducing ROS, with lactate shuttling providing additional fuel for stem cell activation (Wanet et al., 2015; Mohammad et al., 2019; Bisetto et al., 2019; Li et al., 2025). Collectively, these mechanisms position exercise as an accessible, multi-target strategy to counter stem cell exhaustion and promote healthy aging (Liu et al., 2023).

The paradoxical effect of exercise on oxidative stress that generates transient ROS bursts while enhancing long-term antioxidant capacity is particularly important for stem cell maintenance (Powers et al., 2020). Moderate exercise increases nuclear factor erythroid 2-related factor 2 (Nrf2) activity in stem cells, upregulating antioxidant enzymes like superoxide dismutase (SOD2) and catalase (Martinez-Canton et al., 2024). This hormetic response prepares the body, which includes endogenous stem cells, to better handle subsequent oxidative challenges (Ji et al., 2010). HSC from subjects with regular exercise has been shown to exhibit better resistance toward oxidative stress compared to HSC from sedentary subjects (Jenkins et al., 2011). However, the response is biphasic, as excessive exercise can overwhelm these protective mechanisms, highlighting the importance of exercise dosing for optimal benefit (Lichtenstein et al., 2017). Exercise remodels stem cell niches across tissues, enhancing regenerative capacity by improving HSC function through vascular changes, reorganising the muscle ECM to favour satellite cell activation, and modulating neural niches via cerebrospinal fluid flow and growth factor availability (Yin et al., 2013; Morishita et al., 2020; Li et al., 2024). These mechanisms highlight exercise as a practical strategy for stem cell health, though future research must define optimal intensity, duration, and type for personalised benefits.

4. Conclusion

The shared mechanisms between stem cell exhaustion and general aging underscore that successful stem cell maintenance fundamentally depends on whole-body physiological conditions. This interdependence highlights the critical importance of comprehensive anti-aging strategies in preserving endogenous stem cell function and combating age-related regenerative decline. Despite limited studies on the combination of polyphenol consumption and exercise toward stem cell exhaustion, preliminary evidence suggests synergistic benefits between exercise intervention, nutritional strategy, and phytochemicals supplementation in general aging intervention. Ultimately, preserving endogenous stem cell function offers a

more sustainable alternative to cell replacement therapies. By integrating lifestyle medicine with targeted phytochemicals, this approach aligns with global healthy aging initiatives, not merely extending lifespan but ensuring prolonged healthspan. As the population ages, such strategies must be rigorously validated and democratized to benefit diverse socioeconomic groups

This review acknowledges several limitations that should be considered when interpreting the findings. The reliance on narrative synthesis, driven by substantial heterogeneity in study design, model systems, intervention types, and outcome measures, limits the ability to draw direct causal comparisons or establish standardized recommendations. A significant proportion of the evidence is derived from preclinical animal and in vitro studies, which may not fully translate to human physiological complexity, especially regarding long-term safety and dose optimization of caloric restriction, fasting-mimicking diets, polyphenol supplementation, and exercise protocols. Additionally, variability in polyphenol bioavailability and differences in exercise intensity across studies create uncertainty in determining clinically effective regimens. Future research should prioritize large-scale, well-controlled human clinical trials to verify the therapeutic potential of these interventions in diverse populations, establish precise intervention thresholds tailored to age and health status, and explore synergistic effects between lifestyle strategies and novel delivery technologies for enhanced targeting and efficacy.

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