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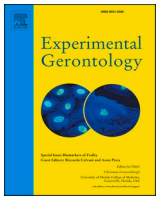

Review article

Exercise and exerkines: Mechanisms and roles in anti-aging and disease prevention

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ABSTRACT

Aging is a complex biological process characterized by increased inflammation and susceptibility to various age-related diseases, including cognitive decline, osteoporosis, and type 2 diabetes. Exercise has been shown to modulate mitochondrial function, immune responses, and inflammatory pathways, thereby attenuating aging through the regulation of exerkines secreted by diverse tissues and organs. These bioactive molecules, which include hepatokines, myokines, adipokines, osteokines, and neurokines, act both locally and systemically to exert protective effects against the detrimental aspects of aging. This review provides a comprehensive summary of different forms of exercise for older adults and the multifaceted role of exercise in anti-aging, focusing on the biological functions and sources of these exerkines. We further explore how exerkines combat aging-related diseases, such as type 2 diabetes and osteoporosis. By stimulating the secretion of these exerkines, exercise supports healthy longevity by promoting tissue homeostasis and metabolic balance. Additionally, the integration of exercise-induced exerkines into therapeutic strategies represents a promising approach to mitigating age-related pathologies at the molecular level. As our understanding deepens, it may pave the way for personalized interventions leveraging physical activity to enhance healthspan and improve quality of life.

1. Introduction

Aging is a complex physiological process characterized by a decline in basal metabolic rate, increased blood pressure, and reduced maximal heart rate, cardiac output, and muscle mass (Allen and Morelli, 2011). In addition to these physiological changes, aging is closely associated with a variety of chronic diseases, such as systemic inflammation, type 2 diabetes, osteoporosis, and cancer (Bruunsgaard et al., 2001; Muñoz-Espín and Serrano, 2014). In the brain, aging typically manifests as cognitive decline, memory impairment, and an increased risk of neurodegenerative disorders (Viviani and Boraso, 2011). A key factor contributing to these changes is chronic, low-grade inflammation, often referred to as "inflammaging," which underlies the pathogenesis of many age-related diseases, created by Franceschi et al. (Franceschi et al., 2017; Rea et al., 2018). Although inflammation is a necessary part of the body's defense mechanism, particularly in response to infections or injuries, the inflammation associated with aging is persistent and harmful, disrupting normal physiological processes.

Exercise has long been recognized for its role in promoting health and longevity. Regular physical activity not only helps prevent and delay the onset of chronic diseases but also reduces functional decline and the risk of premature death (Mora and Valencia, 2018). The anti-inflammatory effects of exercise are well-documented, as it helps lower the levels of pro-inflammatory cytokines and fosters an anti-

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inflammatory state across the body (Lavin et al., 2020). As the originator of 'Exerkines', Mark Tarnopolsky first proposed the concept of exerkines as a motion-induced humoral factor consisting of peptides, metabolites, DNA, mRNA, microRNA (miRNA), and other RNA species (Safdar et al., 2016). These exerkines play a vital role in combating aging by modulating the body's inflammatory response, shifting it from a pro-inflammatory to an anti-inflammatory state (Nash et al., 2023; Pedersen, 2017). Furthermore, exerkines have been shown to improve cognitive function, memory, and insulin sensitivity in elderly individuals, and protect against other aging-related diseases, such as osteoporosis and type 2 diabetes (Chow et al., 2022).

While aging induces systemic chronic inflammation and increases susceptibility to various diseases, regular exercise can counteract these processes. Through the secretion of exerkines, exercise offers a powerful tool to resist the negative effects of aging, enhancing both physical and cognitive health. This review will explore the function and mechanisms by which exercise-induced exerkines contribute to anti-aging, focusing on their impact on metabolic health, inflammation, and tissue homeostasis.

2. Effects of common exercise training on anti-aging

The International Conference on Frailty and Sarcopenia Research Working Group (ICFSR) has developed guidelines that recommend a variety of exercise for seniors in good health as well as for those with chronic conditions or syndromes, including resistance exercise, aerobic training, and balance training that can help older adults to prevent or mitigate geriatric syndromes including sarcopenia, falls, and cognitive impairment (Izquierdo et al., 2021).

Resistance exercise, also commonly referred to as weight training, strength training or resistance training, is a type of exercise that requires muscles to be held or worked by an applied force or weight (Hurst et al., 2022). Resistance exercise improves muscle strength and mass and is one of the most important forms of exercise that benefit seniors (Grgic et al., 2020; Straight et al., 2016). For appropriate exercise, it is often recommended that older adults target the 8 to 10 major muscle groups involved in function and mobility in the upper and lower body with resistance training 2 to 3 times per week, gradually increasing from 1 to 2 sets to 2 to 3 sets of 8 to 12 repetitions at the beginning. In terms of exercise intensity, start with 30 % ~ 40 % of 1 repetition of maximal strength and gradually increase to 70 % ~ 80 %, resting 1–3 min between each set. Recommended training movements include bench presses and squats, knee extensions and flexions, and unilateral and bilateral exercises by changing body posture, grip strength, and hand and foot positions (Izquierdo et al., 2021). With proper resistance exercise, the muscle mass of different muscle groups of the elderly is improved and muscle size is increased, which has improved and prevented osteoporosis and rheumatoid arthritis (Lange et al., 2019).

Aerobic exercise training is associated with improved aerobic capacity, cardiovascular function and metabolic regulation, and is an effective indicator of cardiorespiratory fitness in older adults (Schootemeijer et al., 2020). Usually, the elderly carry out aerobic training 3 to 7 times a week for 20 to 60 min each time is more appropriate for the human body. Different forms of exercise such as walking, stair climbing and ball games can improve the aerobic and metabolic capacity of the elderly. Depending on their tolerance, older adults can limit the intensity of exercise to 55 %–70 % of their maximum heart rate (Izquierdo et al., 2021). Veronica Guadagni et al. revealed that aerobic exercise improves cognitive and memory performance in older adults (Guadagni et al., 2020; Morris et al., 2017; Yu et al., 2021). Among them, BDNF plays an important role as exerkines, delaying and improving the atrophy of the hippocampus for the benefit of Alzheimer's patients (Erickson et al., 2011a).

Balance ability is one of the important indicators to evaluate the physical function of middle-aged and elderly people, and the reduction of balance ability is believed to be related to the all-cause mortality of middle-aged and elderly people (Xie et al., 2023).Therefore, balance training can be effective in reducing the fear of falling and improving dynamic balance and isometric strength in the elderly (Gusi et al., 2012). Typically, it is appropriate for seniors to perform balance exercises containing 4–10 different static and dynamic postures 1–7 times per week in 1–2 sets. Exercises include standing on one leg without hand support, crossing obstacles or slowly walking up and down steps, playing tai chi, and rotational movements (Izquierdo et al., 2021). According to available research, tai chi is the best form of balance training for all-round improvement of posture and core muscle strength, thus regulating balance (Eckstrom et al., 2020; Xie et al., 2024). (Table 1).

3. Biological pathways of exercise in anti-aging

Exercise exerts profound effects on aging by influencing various physiological processes at both the cellular and molecular levels (Safdar and Tarnopolsky, 2018). Aging is typically characterized by some major hallmarks, including genomic instability, telomere shortening, epigenetic alterations, loss of protein homeostasis, nutrient-sensing dysregulation, mitochondrial dysfunction, cellular senescence, stem cell depletion, and impaired intercellular communication (N, Blasco and Partridge López-Otín et al., 2013; Lopez-Otin et al., 2023). Among these, mitochondrial dysfunction is a central feature, leading to telomere shortening, oxidative stress, inflammation, and genomic instability. In the exercise state, mitochondria lose and regain the activities lost due to aging including the modulation of Ca2+ and reactive oxygen species (ROS) and the production of adenosine tricarboxylate (ATP), thus blocking the vicious cycle of cell death, aging, and inflammation (Nilsson and Tarnopolsky, 2019).

Table 1
Recommended forms of exercise workouts for older adults.

Exercise Recommendation	Resistance training	Aerobic exercise training	Balance training
Training purpose	Improves muscle strength and mass	Improves aerobic capacity, cardiovascular function and metabolic regulation	Improve dynamic balance and isometric muscle strength
Frequency (days per week)	2–3	1–7	3–7
Intensity	1–2 sets gradually increase to 2–3 sets, repeat 8–12 times Start at 30 % ~ 40 % of max strength for 1 repetition and gradually increase to 70 % ~ 80 % (rest 1–3 min between each set)	1–2 sets of 4–10 different static and dynamic postures of balancing exercises at a time	20–60 min each time 55 % to 70 % of maximum heart rate
Recommended Exercise Forms	Bench Press and Squat knee extensions and flexions Unilateral and bilateral movements to change body position, grip, hand and foot position Seated rises Step-ups	Taijiquan Standing on one leg without hand support Stepping over obstacles Going up and down steps slowly Standing Yoga Ballet movements Tandem walking Rotational movements Balancing on a moving vehicle	Walking Climbing slopes, hills, or stairs Pushing a wheelchair or cart Bicycling Water activities Tennis Golf Dancing

3.1. Improving mitochondrial dysfunction

Mitochondria are the powerhouses of the cell, responsible for the final oxidative exergy of sugars, fats, amino acids and other substances, controlling the tricarboxylic acid cycle and oxidative phosphorylation, and are essential for maintaining cellular energy metabolism and overall health. As we age, mitochondrial function gradually declines, leading to a decrease in energy metabolism efficiency and an imbalance between ROS generation and antioxidant defense, ultimately leading to oxidative stress (N, Blasco and Partridge López-Otín et al., 2013; Pingitore et al., 2015). In this process, there is a negative interaction between mitochondria and lysosomes, and reactive oxygen species produced by mitochondria affect long-lived post-mitotic cells. Since these cells cannot be replaced in vivo, it is difficult for them to remove damaged structures, leading to the accumulation of cell membrane protein aggregates, and also lipofuscin produced by the lysosomes in vivo is difficult to digest, further affecting mitochondrial function and generating negative feedback (Terman et al., 2010). Regular exercise can improve mitochondrial metabolic disorders, induce adaptive responses, stop the sustained attack of harmful substances, and ultimately improve energy metabolism, enhance stress tolerance, and achieve the purpose of prolonging life (Distefano and Goodpaster, 2018; Mendham et al., 2021; Ristow and Zarse, 2010; Zamora et al., 1995).

On one hand, exercise promotes the expression of several antioxidant enzymes and complexes, boosting the body's antioxidant defenses. Key enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and heme oxidase-1 (HO-1) are increased during exercise, which can scavenge free radicals from the body and protect cells from oxidative damage (Ji et al., 1998; Mestre-Alfaro et al., 2011). In addition, exercise increases the expression of NADPH oxidase 4 (NOX4) in skeletal muscle, leading to the production of H2O2, which activates the expression of nuclear factor erythroid 2-related factor 2 (NFE2L2). NFE2L2 translocates into the nucleus and drives the expression of up to 200 endogenous antioxidant and xenobiotic detoxification enzymes in the body, thus functioning to promote antioxidant defense and mitochondrial biogenesis (Xirouchaki et al., 2021). During aging, mitochondrial function is greatly diminished due to damage and mutation of mitochondrial DNA (mtDNA) and dysfunction of the respiratory chain (Larsson, 2010). Under the influence of exercise, deficiencies in the neurotransmitters such as acetylcholine, glutamate, and aspartate are ameliorated, allowing efficient transmission of messages between neurons and effector cells (Clark-Matott et al., 2015). At the same time, exercise promotes the expression of respiratory chain components including mitochondrial complex IV, which improves mitochondrial oxidative capacity and respiratory chain assembly, restores mitochondrial morphology, and attenuates apoptosis at pathological levels in multiple tissues of senescent individuals (Safdar et al., 2011).

On the other hand, exercise activates various signaling pathways, triggering cascades that protect cells from oxidative damage and slow down the aging process. Key pathways include AMP-activated protein kinase (AMPK), calcium/calmodulin-dependent protein kinases (CaMKs) signaling and sirtuins, which are involved in promoting mitochondrial biogenesis, energy metabolism, and autophagy-mediated cellular repair (Dehghani et al., 2018; Garatachea et al., 2015). In particular, both AMPK and sirtuins pathways promote the up-regulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which is associated with mitochondrial health, and the production of PGC-1α has an important role in skeletal muscle adaptations, which further enhances the anti-aging effects of exercise (Sutherland et al., 2009). However, it is important to note that strenuous or prolonged exercise may cause oxidative damage to muscle cells, highlighting the importance of moderation (Spanidis et al., 2018).

3.2. Combating inflammation and supporting immune function

A fundamental feature of the cellular senescence process is the secretion of an inflammatory transcriptome, also known as senescence-associated phenotype (SASP) (Lopes-Paciencia et al., 2019). SASP, encompasses a range of chemokines, growth factors, proteins and non-protein factors, most of which are pro-inflammatory factors secreted by senescent cells. SASP-induced senescent cells and chronic inflammation are involved in the pathogenesis of many age-related diseases, such as atherosclerosis neurodegenerative diseases, frailty and osteoarthritis (OA) (Sun et al., 2022b, b; Wang et al., 2024). Exercise provides powerful anti-inflammatory benefits by inhibiting the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α and promoting the release of anti-inflammatory cytokines such as IL-4, IL-10, and TNF-β. This dual action regulates the immune system and reduces systemic inflammation, contributing to healthy aging and resistance to the effects of tumors (Alikhani and Sheikholeslami Vatani, 2019; Liu et al., 2023; Nilsson et al., 2019). For example, resistance exercise enhances the expression of IL-10 and interleukin-1 receptor antagonist (IL-1ra), increasing the body's anti-inflammatory levels and immune capacity (de Sá Souza et al., 2022).

Human immune cell populations, particularly monocytes and lymphocyte subsets, shift between pro-inflammatory and anti-inflammatory states during aging and under various metabolic diseases. Exercise helps balance these populations, including classical and non-classical CD16+ monocytes, and T-helper lymphocytes (Th1/Th2 and Th17) alongside regulatory T cells (Tregs) (Figueiredo et al., 2022). Through this balancing act, exercise restores immune function and reduces inflammation. Remarkably, a recent study by David Walzik et al. demonstrates that single bouts of exercise alter nicotinamide adenine dinucleotide (NAD+) coenzymes metabolism in peripheral blood mononuclear cells, resulting in resistance to aging and a variety of immune disorders (Walzik et al., 2025). NAD+ coenzymes, as the central electron carriers of bioenergy metabolism, are produced primarily through the NAD+ rescue pathway, of which nicotinamide phosphoribosyltransferase (NAMPT)is the rate-limiting enzyme, and NMNAT expression is negatively correlated with age. Previous findings have revealed that aerobic and resistance exercise increase nicotinamide mononucleotide adenylyltransferase (NAMPT) expression in skeletal muscle of older adults (de Guia et al., 2019). Thus, exercise-stimulated expression of NAD+ in immune cells may exert the same effect on the organism as NAD+ produced by other pathways. For example, NAD+ inhibits autophagy and IFN-β release in patients with systemic lupus erythematosus; and restricts the expression of oncogenes to regulate the metabolic and functional status of CD8+ T cells, which in turn exerts anti-tumor functions (Wan et al., 2023; Wu et al., 2022). However, long-term vigorous exercise can strain the immune system and exacerbate inflammation, highlighting the need for moderate, regular activity to counteract aging-induced inflammation (Pedersen and Toft, 2000).

3.3. Protecting neuroplasticity and brain health

Cognitive decline is one of the most prominent and concerning aspects of aging, often manifesting as impairments in memory, attention, and executive function (Sikora et al., 2021). Exercise plays a crucial role in supporting brain health and neuroplasticity by stimulating the formation of new neurons and enhancing synaptic connections (Voss et al., 2010). These benefits are partly due to increased cerebral blood flow and the upregulation of neurotrophic factors, including insulin-like growth factor I (IGF—I) and vascular endothelial growth factor (VEGF), which promote neurogenesis, particularly in the hippocampus, a region vital for learning and memory. Exercise has also been shown to elevate levels of glycosylated phosphatidylinositol-specific phospholipase D1 (GPLD1) in the blood, which is linked to improvements in cognitive dysfunction in aged animals (De Miguel et al., 2021). Furthermore, exercise reduces neuroinflammation and oxidative stress, protecting neurons from damage and helping to prevent cognitive decline. By enhancing brain plasticity and resilience, exercise helps preserve cognitive function and supports healthy aging (Hillman et al.,

2008).

4. Sources and classification of exerkines

Exerkines are bioactive molecules released by various tissues in response to exercise and are essential mediators in the anti-aging effects of physical activity. Initially, it was believed that exerkines were primarily produced by skeletal muscle, but recent studies have shown that multiple organs, including the liver, adipose tissue, bone, and the nervous system, also secrete these molecules (Bostrom et al., 2012; Egan and Zierath, 2013; Pedersen, 2013). These exerkines not only act locally but also exert systemic effects across the body, regulating metabolic processes, reducing inflammation, supporting tissue repair, and maintaining cognitive function (Gleeson et al., 2011; Handschin and Spiegelman, 2008). The release of exerkines is a highly coordinated process that involves multiple tissues and organs. These exerkines function in a synergistic manner to combat the cellular and molecular changes associated with aging, such as oxidative stress, inflammation, mitochondrial dysfunction, and tissue degeneration (Fiuza-Luces et al., 2013). By enhancing the production of these molecules, regular exercise creates an environment that promotes tissue maintenance, metabolic balance, cardiovascular health, and cognitive resilience. This highlights the central role of exerkines in the anti-aging benefits of exercise, as they help to preserve functional capacity and overall health as we age (Fig. 1).

4.1. Skeletal muscle-derived myokines act on systemic metabolism

Skeletal muscle is a major source of motor factors, collectively referred to as "myokines" by Pedersen et al. These include molecules such as interleukin-6 (IL-6), irisin, and brain-derived neurotrophic factor (BDNF) (Anon., 2021; Pedersen and Febbraio, 2012). These myokines play a critical role in regulating muscle metabolism, promoting glucose uptake, enhancing neuroplasticity, and modulating inflammatory responses (Zunner et al., 2022). For example, IL-6, which typically functions as a pro-inflammatory cytokine, exhibits anti-inflammatory properties during exercise, improving insulin sensitivity and lipid metabolism (Steensberg et al., 2000a; Wedell-Neergaard et al., 2019). Irisin, out-membrane part of fibronectin type III domain-containing 5 protein (FNDC5), was activated by Peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α during physical exercise in skeletal muscle tissues (Liu et al., 2022a). Irisin increases both osteocytic survival and production of sclerostin, a local modulator of bone remodeling (Kim et al., 2018).

4.2. Hepatokines: a powerful weapon against age-related metabolic diseases

Exercise can produce hepatokines through the liver, such as fibroblast growth factor 21 (FGF21) and angiopoietin-like protein 4 (ANGPTL4), which are involved in regulating lipid metabolism, glucose homeostasis, and energy expenditure (Ingerslev et al., 2017; Weigert et al., 2019). These hepatokines are crucial for protecting against age-related metabolic diseases, such as type 2 diabetes and cardiovascular disorders, and help maintain overall energy balance (Seo et al., 2021). FGF21 can act on the central nervous system, thereby inducing sympathetic activity and energy expenditure (Owen et al., 2014). In addition, the increased expression of thermogenic genes, increased total and uncoupled respiration, and enhanced glucose oxidation was also observed in FGF21-treated brown adipocytes (Hondares et al., 2010). Meanwhile, FGF21 also promotes islet beta cell survival and increases insulin sensitivity in peripheral tissues to maintain glucose and lipid homeostasis (Yang et al., 2023; Yang et al., 2020). As for ANGPTL4, it regulates lipid metabolism by inhibiting lipoprotein lipase activity and stimulating lipolysis in adipose tissue (Gorecka et al., 2020).

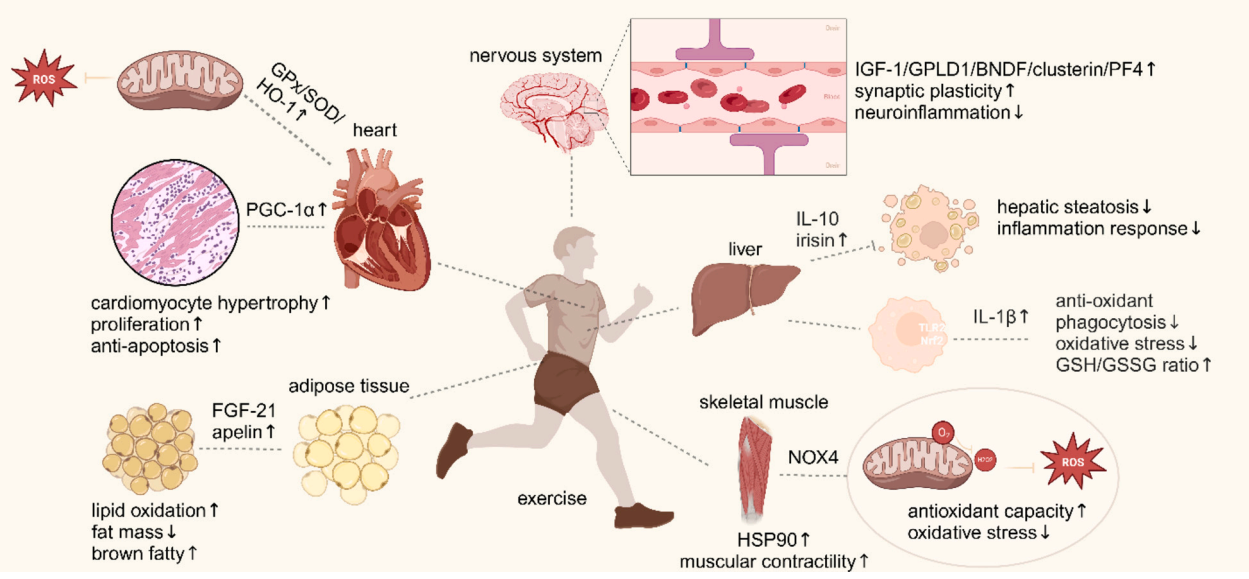

Fig. 1. The systemic impact of exercise-induced exerkines on aging and health.
Exercise promotes the release of exerkines such as IGF-1, GPLD1, BDNF, clusterin, and PF4, leading to enhanced synaptic plasticity, improved neuroprotection, and reduced neuroinflammation. The upregulation of PGC-1α in response to exercise contributes to cardiomyocyte hypertrophy, increased proliferation, and anti-apoptotic effects, which support overall cardiac health and longevity. Exercise decreases hepatic steatosis and modulates the inflammatory response via the increased secretion of IL-10 and irisin, reducing liver inflammation and improving metabolic homeostasis. Exerkines like FGF-21 and apelin stimulate lipid oxidation, decrease fat mass, and promote the browning of adipose tissue, contributing to improved metabolic function and fat utilization. NOX4 and HSP90 are upregulated during exercise, improving muscular contractility, and enhancing the antioxidant capacity of mitochondria, thereby reducing oxidative stress. IGF-1, insulin like growth factor 1; GPLD1, glycosylphosphatidylinositol-specific phospholipase D; BDNF, rain-derived neurotrophic factor; PF4, platelet factor 4; IL-10, interleukin-10; IL-1β, interleukin-1β; NOX4, NADPH oxidase 4; HSP90, heat shock protein90; ROS, reactive oxygen species; FGF21, fibroblast growth factor 21; PGC-1α, peroxisome proliferators-activated receptor γ coactivator lalpha; GPx, glutathione peroxidase; SOD = superoxide dismutase; HO-1 = heme oxygenase-1.

4.3. Adipokines regulate energy homeostasis in the aging state

Adipose tissue secretes adipokines, including adiponectin and leptin, which regulate fat metabolism, energy balance, and inflammatory responses (Fève et al., 2016; Xie and Chen, 2019). Exercise induces changes in adipokine secretion that promote an anti-inflammatory environment, which is essential for countering the low-grade chronic inflammation commonly associated with aging and metabolic dysfunction (Garcia-Hermoso et al., 2017; Sargolzaei et al., 2018). Adiponectin stimulates fatty acid oxidation in skeletal muscle and inhibits glucose production in the liver, resulting in an improvement in whole-body energy homeostasis. Adiponectin is also a classic anti-inflammatory agent, reducing inflammation in various cell types through AdipoR1 and R2 signaling mechanisms (Fang and Judd, 2018). Adiponectin's anti-inflammatory and anti-apoptotic properties results in protection of the vasculature, heart, lung, and colon (Shklyaev et al., 2022).

4.4. Osteokinin maintains bone and peripheral vascular health

Bone releases osteokinin, such as osteocalcin, which are involved in bone remodeling and metabolic regulation (Jurimae et al., 2016; Le Doan and Marcil, 2017). Exercise, particularly weight-bearing and resistance training, has been shown to stimulate the secretion of osteocalcin, enhancing its role in maintaining bone strength and density. Osteocalcin, in particular, is linked to glucose metabolism and bone strength, helping to maintain bone density and reduce the risk of osteoporosis, a condition commonly associated with aging (Komori, 2020; Mizokami et al., 2017). In addition, osteocalcins are involved in the regulation of atherosclerotic vascular disease. Osteocalcin can reverse autophagy and endoplasmic reticulum stress, while restoring the deficiency of insulin sensitivity of vascular endothelial cells and vascular smooth muscle cells (VSMC) (Liu et al., 2024).

4.5. Neurokines reduce risk of neurodegenerative diseases

The nervous system produces neurokines, including BDNF and nerve growth factor (NGF), which are vital for cognitive function, promoting neuronal survival and synaptic plasticity (Chaldakov et al., 2009). These neurokines play a key role in maintaining brain health, protecting against age-related cognitive decline, and reducing the risk of neurodegenerative diseases (Ruan, Zhang and Ruan et al., 2018; Hegazy et al., 2022). BDNF is considered an instructive mediator of functional and structural plasticity in the central nervous system (CNS), influencing dendritic spines and, at least in the hippocampus, the adult neurogenesis (Cheeran et al., 2008). In addition, exercise promotes beneficial adaptations of the brain by improving learning, memory, and cognitive processes in people with depression, as well as antidepressant effects. BDNF is thought to be a major factor in the mechanism behind this result, as BDNF levels are higher after various exercise states (Murawska-Cialowicz et al., 2021).

5. The role of exerkines in combating aging-related diseases

As humans age, they encounter various physiological changes that increase susceptibility to chronic diseases, including cardiovascular disease, type 2 diabetes mellitus (T2DM), neurodegenerative disorders, and cancer (Liguori et al., 2018). Exerkines, which regulate molecular pathways in age-related diseases, play a critical role in maintaining metabolic homeostasis, controlling inflammation, and promoting tissue repair. By modulating cellular responses to stress and injury, exerkines represent promising therapeutic targets for age-related diseases (Félix-Soriano and Stanford, 2023).

5.1. Inhibition of aging-induced inflammatory responses by exerkines

Inflammaging is a key driver of age-related diseases, including cardiovascular disease, neurodegenerative disorders, and metabolic dysfunction (Baechle et al., 2023). Dysregulation of pro-inflammatory cytokines is a hallmark of inflammaging. However, regular exercise has been shown to modulate this inflammatory state, primarily through the production of exerkines such as interleukin-6 (IL-6) and interleukin-10 (IL-10) (Fischer, 2006). IL-6 is traditionally known as a pro-inflammatory cytokine due to its role in acute immune responses. However, during exercise, IL-6 functions as a myokine secreted by skeletal muscles, where it acts in an anti-inflammatory manner (Eaton et al., 2018; Steensberg et al., 2000b). IL-6 released into the bloodstream signals to various tissues, including adipose tissue and the liver, promoting the release of anti-inflammatory cytokines such as IL-10 and suppressing the production of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) (Brandt et al., 2012). This shifts the systemic inflammatory profile towards an anti-inflammatory state. In addition, insulin sensitivity is usually impaired during aging, and IL-6, a biomarker of insulin sensitivity, may reflect the pathological stage of insulin resistance (Park et al., 2015). IL-10, a potent anti-inflammatory cytokine, is crucial for reducing inflammation in various tissues (Saraiva and O'Garra, 2010). It suppresses the production of pro-inflammatory cytokines like TNF-α and interleukin-1 beta (IL-1β) and inhibits immune cell activation (Elenkov et al., 2000). Regular exercise has been shown to increase circulating levels of IL-10, contributing to reduced systemic inflammation and promoting tissue repair after exercise-induced stress. By stimulating the production of IL-6 and IL-10, regular physical activity helps counteract the chronic inflammatory cascade associated with aging, reducing the risk of age-related chronic diseases. Incorporating both aerobic and resistance training into daily routines can mitigate the effects of inflammaging and promote healthy aging.

5.2. Exerkines improve insulin resistance in T2DM

Exercise is widely recognized as a crucial intervention for preventing and managing T2DM, particularly in elderly populations (Poblete-Aro et al., 2018; Sampath Kumar et al., 2019). Several exerkines, including irisin, heat shock protein 72 (HSP72), and fibroblast growth factor 21, play pivotal roles in improving insulin sensitivity, regulating glucose homeostasis, and enhancing overall metabolic function (Turkel et al., 2022).

Irisin, a myokine secreted primarily by skeletal muscle in response to physical activity, has garnered attention for its role in metabolic regulation (Alves et al., 2022). In human studies, exercise induces the transcription of FNDC5, which is subsequently processed into irisin (Bilek et al., 2022). Irisin stimulates the browning of white adipose tissue, promoting thermogenesis and increasing energy expenditure by converting white adipocytes into beige adipocytes. This process enhances mitochondrial biogenesis and improves oxidative metabolism, thereby enhancing insulin sensitivity and glucose tolerance (Perakakis et al., 2017). Additionally, statistical analyses indicate that irisin can inhibit hepatic gluconeogenesis, and its circulating level is inversely correlated with the risk of T2DM (Liu et al., 2015; Rana et al., 2017). This indicates that irisin may become a therapeutic target to control diabetes.

HSP72, a member of the heat shock protein family, can be induced by resistance exercise, stimulates an anti-inflammatory heat shock response, and has an ameliorative effect on T2DM disease in the elderly (de Lemos Muller et al., 2018; Smuder et al., 2019). It helps protect cells from metabolic stress by facilitating the proper folding of proteins and promoting cell survival (Hecker and McGarvey, 2011). During the course of T2DM, HSP72 ensures the integrity of pancreatic beta cells by preventing protein misfolding and aggregation, thus promoting effective insulin secretion (Kondo et al., 2011). In skeletal muscle and adipose tissue, HSP72 improves glucose uptake by enhancing insulin signaling pathways, contributing to better glucose homeostasis (Archer et al., 2018).

FGF21, primarily synthesized in the liver but also expressed in adipose tissue and skeletal muscle, is a critical regulator of glucose and lipid

metabolism (Planavila et al., 2013). In vivo experiments have shown that exercise increases circulating levels of FGF21, which improves T2DM insulin sensitivity by promoting glucose uptake and utilization by peripheral tissues via glucose transporter protein 4 (GLUT4) (Duan and Lu, 2024; Gao et al., 2020). FGF21 also plays a role in lipid metabolism by facilitating adipose tissue lipolysis and suppressing hepatic lipogenesis. For example, FGF21 plays a role in energy expenditure and promotes the browning of white adipose tissue, contributing to improved body composition and metabolic flexibility (Geng et al., 2019). Thus, these findings confirm that exercise sensitizes the action of FGF21 in adipose tissue, which in turn sends humoral signals to coordinate multiorgan crosstalk to maintain metabolic homeostasis (Kharitonenkov and Shanafelt, 2008).

In conclusion, exerkines such as irisin, HSP72, and FGF21 are critical mediators of improved insulin sensitivity and glucose metabolism, offering potential therapeutic targets for the prevention and management of T2DM. By leveraging the molecular pathways activated by these exerkines, regular exercise can enhance metabolic health in elderly patients.

5.3. Exerkines improve cognitive and memory impairments caused by aging

Aging is associated with cognitive decline and an increased risk of neurodegenerative diseases. Exercise-induced exerkines such as clusterin, brain-derived neurotrophic factor, CXCL4 (PF4), and glycosylphosphatidylinositol-specific phospholipase D1 have been shown to possess significant neuroprotective effects, enhancing cognitive function and mitigating age-related memory impairments (Tsai et al., 2018).

Clusterin is a multifunctional glycoprotein that plays a crucial role in neuroprotection (Wilson et al., 2022). It has anti-apoptotic properties, protecting neurons from cell death, and exhibits anti-inflammatory effects, reducing neuroinflammation, which is a key factor in neurodegenerative diseases like Alzheimer's (Wilson and Zoubeidi, 2017). A study by Miguel et al. demonstrated that exercise increases complement cascade inhibitors of clusterin in plasma in mice. And in a mouse model of acute brain inflammation and a mouse model of Alzheimer's disease, intravenously injected clusterin binds to brain endothelial cells and reduces the expression of neuroinflammatory genes, thereby decreasing inflammation in the hippocampus (De Miguel et al., 2021).

BDNF is a neurotrophic factor that supports neuronal survival and promotes synaptic plasticity (Colucci-D'Amato et al., 2020). It is now well-documented that regular exercise is a powerful stimulus for BDNF production, increasing hippocampal volume and improving cognitive function, enhancing memory, and preventing neurodegeneration (Erickson et al., 2011b; Palasz et al., 2020). Increases in BDNF during exercise have been associated with a range of events that strengthen synaptic connections and promote brain health, which strongly suggests the cognitive relevance of BNDF as an exercise factor for brain health, which could provide neuroprotection for patients with aging-related diseases such as Alzheimer's disease (Erickson et al., 2012; Gaitán et al., 2021; Walsh and Tschakovsky, 2018).

CXCL4 (also known as blood platelet factor 4) is one of the platelet chemokines which is most abundantly secreted to plasma (in micromolar concentrations) after the activation of blood platelets (Makarewicz-Wujec et al., 2020). In past studies, circulating levels of CXCL4 were significantly elevated in patients with systemic sclerosis, whereas CXCL4 levels were decreased in all patients receiving immunosuppressive therapy (Meldi et al., 2015; Volkmann et al., 2016). A recent study now confirms that exercise activates CXCL4 production and induces proliferation of hippocampal precursor cells in aged mice, thereby ameliorating age-related regenerative and cognitive deficits in a hippocampal neurogenesis-dependent manner (Leiter et al., 2023). This underscores the role of platelet-derived exerkines in mediating the regenerative effects of exercise on the aging brain.

GPLD1, an enzyme upregulated by exercise, improves synaptic plasticity and neurotransmitter dynamics, influencing the release of neurotransmitters like dopamine and serotonin, which are crucial for mood regulation and cognitive processes (Cao et al., 2023; Horowitz et al., 2020). Exercise-induced upregulation of GPLD1 enhances synaptic communication, thereby strengthening memory and cognitive resilience (Li et al., 2022b).

Collectively, these exerkines—clusterin, BDNF, CXCL4, and GPLD1—contribute to neuroprotection, enhance cognitive function, and mitigate the adverse effects of aging on the brain.

5.4. Exerkines prevent osteoporosis and maintain muscle mass

Osteoporosis, characterized by decreased bone density and increased fracture risk, and sarcopenia, the age-related loss of muscle mass and strength, are significant health concerns for aging populations (Brown, 2021; Srivastava and Deal, 2002). Exercise-induced exerkines, such as insulin-like growth factor 1, transforming growth factor-beta 1 (TGF-β1), and apelin, play pivotal roles in maintaining bone density and muscle mass, offering significant protection against these conditions (Jia et al., 2023).

IGF-1 is a key regulator of bone metabolism, stimulating osteoblast proliferation and differentiation, which increases bone mineral density (BMD) and enhances bone strength (Yakar et al., 2002). IGF-1 also promotes the synthesis of type I collagen, the main component of the bone matrix, enhancing bone quality. Beyond its effects on bone, IGF-1 exerts anabolic effects on skeletal muscle, helping preserve muscle mass and function during aging (Chen, Chung and Chen et al., 2017; Angulo et al., 2020). Arazi et al. showed that strength and endurance training significantly elevated serum levels of IGF-1 in older men (Arazi et al., 2021). These findings, together with IGF-1's known biological functions, underscore its vital role as an exerkine in mitigating age-related bone and muscle loss.

TGF-β1 is another important factor in bone metabolism. It regulates bone remodeling by promoting osteoblast differentiation while inhibiting osteoclast activity, maintaining a balance between bone formation and resorption. This balance between bone formation and resorption is essential for preserving bone mass and structural integrity (Sun, Wang and Wu et al., 2022). Furthermore, Xinzheng Sun et al. showed that exercise induces analgesia by promoting TGF-β1 activation and inhibiting astrocyte proliferation in a mouse study. Nerve-injured mice produce mechanical and cold pain in the hind paw, elevated expression of latency-related peptide TGF-β1, and activation of astrocytes in the spinal cord, whereas exercise attenuates neuropathic pain (Li et al., 2022a). It is evident that TGF-β1 may not only play a role in bone metabolism, but may also have potential functions in areas such as nerve injury.

Apelin, a peptide hormone, plays a dual role in bone-muscle crosstalk (Xie et al., 2006). Exercise-induced apelin promotes osteoblast differentiation and mineralization, thereby enhancing bone formation (Kon et al., 2021). At the same time, apelin exerts anabolic effects on skeletal muscle, promoting muscle hypertrophy and improving contractile function (Vinel et al., 2018). Apelin works synergistically with other exerkines, such as IGF-1 and TGF-β1, to coordinate the maintenance of bone and muscle maintenance. Apelin enhances the activity of IGF-1, amplifying its anabolic effects on both bone and muscle tissues. This coordination between apelin and IGF-1 contributes to increased bone density and muscle mass, which are critical in preventing conditions such as osteoporosis and sarcopenia, both of which are prevalent in aging populations (Son, Kim and Son et al., 2017). Additionally, apelin potentiates TGF-β1 activity, which further aids in maintaining the balance between bone formation and resorption, supporting overall bone integrity and functional mobility. Through its dual effects on bone and muscle, apelin plays a crucial role in promoting skeletal and muscular health, emphasizing the importance of exercise in combating age-related declines in these tissues (Bae et al., 2019).

5.5. Exerkines' anti-tumor properties

In recent years, research has revealed that certain exerkines possess anti-tumor properties, positioning them as potential candidates for cancer prevention and treatment. Among them, myostatin, irisin, and other exercise-induced factors have shown significant promise in modulating tumor growth, enhancing immune responses, and affecting the tumor microenvironment (Liu et al., 2022b; Liu et al., 2019).

Myostatin, also known as growth differentiation factor 8 (GDF-8), is a member of the transforming growth factor-beta superfamily, primarily expressed in skeletal muscle (Esposito et al., 2022; Knapp et al., 2023). While traditionally recognized as a negative regulator of muscle growth, recent research by Brown et al. suggests that the beneficial effects of exercise on cancer outcomes may be mediated, at least in part, by changes in the concentration of exercise-induced factors, including myostatin (Brown et al., 2024). Myostatin inhibits tumor cells proliferation and promotes apoptosis (programmed cell death) in cancerous tissues (Smith et al., 2015). For example, myostatin has been shown to suppress the growth of prostate cancer cells by inhibiting the Akt signaling pathway, which is involved in promoting cell survival and proliferation (Kim et al., 2021; Schiaffino et al., 2013). Additionally, in vitro studies suggest that irisin may provide therapeutic benefits in the prevention and treatment of breast cancer by inducing an anti-inflammatory response, promoting apoptotic cell death, and enhancing tumor sensitivity to common antitumor drugs, such as doxorubicin (Hulmi et al., 2013).

Irisin, another exercise-induced myokine, has also demonstrated potential anti-tumor effects. Research suggests that irisin can reduce the viability of cancer cells, particularly in breast and colorectal cancers, by promoting apoptosis and inhibiting cancer cell proliferation (Abd and Aqeel, 2021; Brown et al., 2024). A study by Provatopoulou et al. showed that serum levels of Irisin were significantly lower in breast cancer patients and that each 1-unit increase in Irisin levels was associated with a nearly 90 % reduction in the likelihood of developing breast cancer (Provatopoulou et al., 2015). In another in vitro study, irisin may provide therapeutic benefit in the prevention and treatment of breast cancer through an anti-inflammatory response, induction of apoptotic cell death, or enhancement of tumor sensitivity to common antitumor drugs such as Dox (Gannon et al., 2015).

Additionally, other exerkines have been implicated in anti-tumor activity through their ability to modulate the tumor microenvironment, improve immune surveillance, and reduce systemic inflammation, all of which are critical in cancer prevention and progression. In summary, exerkines such as myostatin and irisin exhibit considerable potential as therapeutic agents in the fight against cancer. By suppressing tumor growth, inhibiting angiogenesis, and enhancing immune cell activity, these molecules provide promising avenues for future cancer therapies. Exercise, as a natural stimulator of these exerkines, holds great potential as an adjunct therapy in cancer prevention and management, underscoring the multifaceted role of physical activity in health and disease (Table 2).

Table 2
The role of exerkines in combating aging-related diseases.

Exerkines	Organ source	Benefits
IL-6	Skeletal muscle	↑Hepatic glucose ↓Differentiation of white adipocytes ↑Lipolysis and fat oxidation
IL-10	Skeletal muscle	↓Lipogenesis
Irisin	Skeletal muscle	↑Anti-inflammatory ↑Energy Expenditure ↓Insulin resistance ↓Differentiation of white adipocytes ↑Osteoblast differentiation ↓Neurodegenerative diseases ↓Tumor proliferation
HSP72	Liver, skeletal muscle	↓Insulin resistance ↑Lipid metabolism
FGF21	Liver	Regulate glucose homeostasis ↓Body weight, blood glucose, triglyceride and fasting insulin levels ↑Differentiation of brown adipocytes
Clusterin	Brain, liver, cardiomyocyte	↓Hippocampal inflammation ↑Anti-inflammatory
BDNF	Brain, skeletal muscle, adipose tissue	↑Neuronal excitability and synaptic plasticity Regulate nerve cell differentiation and stock
GpId1	Liver	Improve regenerative capacity and cognitive impairment
Cxcl4 (PF4)	Platelet	↑Hippocampal neurogenesis and cognitive function
IGF-1	Skeletal muscle, liver	Promote cell cycle progression ↑Cell proliferation, differentiation and survival Repair and maintenance of muscle
TGF-β	Skeletal muscle	↓Differentiation of white adipocytes
Myostatin	skeletal muscle	↓Tumor proliferation
Apelin	Adipose tissue	↓Differentiation of white adipocytes

Note: ↑denotes increase; ↓denotes decrease.
IL-6, interleukin-6; IL-10, interleukin-10; HSP72, heat shock protein 72; FGF21, fibroblast growth factor 21; BDNF, rain-derived neurotrophic factor; GpId1, glycosylphosphatidylinositol-specific phospholipase d1; Cxcl4 (PF4), platelet factor 4; IGF-1, insulin like growth factor 1; TGF-β, transforming growth factor-β.

6. Conclusion and future perspectives

In conclusion, exercise is not merely a tool for physical fitness; it is a powerful biological modulator with the potential to reshape the trajectory of aging and disease. By understanding and harnessing the therapeutic potential of exerkines, we are not only extending life expectancy but also enhancing the quality of life during those extended years. These bioactive molecules, induced by physical activity, serve as natural mediators of tissue repair, cognitive enhancement, muscle maintenance, and bone health. As research advances, the therapeutic application of exerkines could lead to innovative treatments for age-related diseases, offering solutions for those who may be unable to engage in regular physical activity due to health limitations.

Moreover, the future of anti-aging therapies will likely be shaped by the development of exercise mimetics—molecular treatments designed to replicate the beneficial effects of exercise. These mimetics could revolutionize healthcare by providing targeted therapies that promote healthy aging at a cellular level. As we continue to explore the intersection between exercise science and molecular biology, we move closer to a future where longevity is not only about living longer but also about living stronger and healthier. This interplay between physical activity and cutting-edge therapeutic strategies promises to redefine our approach to aging, offering new hope in the fight against chronic diseases and the quest for extended health span.

Abbreviations

AMPK AMP-activated protein kinase
ANGPTL4 angiopoietin-like protein 4
BDNF brain-derived neurotrophic factor
BMD bone mineral density
CNS central nervous system
FGF21 fibroblast growth factor 21
FNDC5 fibronectin type III domain-containing 5 protein
GDF-8 growth differentiation factor 8
GPLD1 glycosylated phosphatidylinositol-specific phospholipase D1
GPx glutathione peroxidase
HO-1 heme oxygenase-1
HSP72 heat shock protein 72
IGF-I insulin-like growth factor I
IL-10 interleukin-10

IL-1β	interleukin-1 beta
IL-6	interleukin-6
Nrf2	nuclear factor erythroid 2-related factor 2
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-α
PPARγ	peroxisome proliferator-activated receptor γ
ROS	reactive oxygen species
SOD	superoxide dismutase
T2DM	type 2 diabetes mellitus
TGF-β1	insulin- transforming growth factor-beta 1
TNF-α	tumor necrosis factor-alpha
Tregs	regulatory T cells
VEGF	vascular endothelial growth factor
VSMC	vascular smooth muscle cells

CRediT authorship contribution statement

Xuan Lu: Writing – review & editing, Writing – original draft. **Ying Chen:** Writing – review & editing, Writing – original draft. **Yue Shi:** Writing – review & editing, Writing – original draft, Conceptualization. **Yi Shi:** Visualization, Conceptualization. **Xianbin Su:** Writing – review & editing, Writing – original draft, Conceptualization. **Peijie Chen:** Writing – review & editing, Writing – original draft, Funding acquisition. **Die Wu:** Writing – review & editing, Writing – original draft, Funding acquisition. **Hui Shi:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of competing interest

No conflicts of interest, financial or otherwise, are declared by the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2025.112685.

Data availability

No data was used for the research described in the article.

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