Mechanistic advances in exercise-mediated regulation of autophagy dysfunction in Alzheimer's disease (Review)

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disorder marked by progressive cognitive decline and whose pathology is closely linked to cellular autophagy dysfunction. Autophagy is a key process involved in cell clearance. Impaired autophagy can drive neuronal damage and death related to AD pathology. Therefore, targeting autophagy dysfunction has emerged as a promising therapeutic strategy. Exercise, as a non-pharmaceutical and low-cost intervention method, can enhance autophagy activity and alleviate AD symptoms. However, the mechanism by which it regulates autophagy in AD remains unclear. The present review summarizes evidence that exercise acts as an effective early intervention. Exercise activates key cellular signaling pathways (mammalian target of rapamycin, sirtuin 1 and adiponectin receptor 1) and regulates microRNAs (small non-coding RNAs) and irisin (a muscle hormone) to restore normal autophagy. The present review also explores the use of exercise combined with natural products for potential synergistic therapeutic effects. This review provides insights into developing new AD prevention and management strategies by detailing how exercise corrects AD-related autophagy dysfunction.

Contents

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Abbreviations: Aβ, amyloid β-protein; ATG, autophagy-associated protein; APP, amyloid precursor protein; APN, adiponectin; AdipoR1, APN receptor 1; AdipoR2, APN receptor 2; BACE-1, β-secretase 1; CMA, chaperone-mediated autophagy; FNDC5, fibronectin type III structural domain-containing 5 protein; GSK-3β, glycogen synthase kinase-3β; HIIT, high intensity interval training; LC3, microtubule-associated protein 1 light chain 3; LAMP2A, lysosomal-associated membrane protein 2A; LAP, LC3-associated phagocytosis; LANDO, LC3-associated endocytosis; MICT, moderate intensity continuous training; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; NSE/htau23, neuron-specific enolase/human tau23; NFT, neurofibrillary tangle; OPTN, optineurin; PS1, presenilin 1; P301S, proline-301-serine; p-tau, hyperphosphorylated tau; PGC-1α, PPARγ coactivator-1α; ROS, reactive oxygen species; SQSTM1/p62, sequestosome 1; SIRT1, sirtuin 1; 3xTg, triple-transgenic (PS1m146v/APPswe/TauP301L); TFEB, transcription factor EB; TSC2, tuberous sclerosis complex 2; TSC1, tuberous sclerosis complex 1; ULK, UNC 51-like kinase; VPS34, vesicular protein sorting 34

Key words: Alzheimer's disease, autophagy dysfunction, exercise, mechanism

1. Introduction

Alzheimer's disease (AD), the leading cause of dementia, is characterized by irreversible cognitive decline. AD currently affects ~55 million people globally, a number projected to nearly triple by 2050 (1). Despite its prevalence, no effective treatments or preventive measures exist, and a comprehensive understanding of its pathogenesis remains elusive (1-3). The hallmarks of AD include extracellular amyloid β-protein (Aβ) plaques and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau (p-tau) (4). Aβ plaques disrupt inter-neuronal communication (5) and trigger neuroinflammation, while NFTs impair neuronal function by affecting axoplasmic transport and disrupting the cytoskeleton (6). Therapeutic strategies targeting the amyloid cascade or p-tau have yielded unsatisfactory clinical outcomes, indicating the limitations of single-target therapies (7). AD pathology also involves other critical alterations, including neuronal loss, synaptic dysfunction, oxidative stress and aberrant energy metabolism (8-10), which interact synergistically to drive disease progression. While the exact pathogenesis of AD is not fully understood, emerging evidence implicates impaired autophagic clearance as a key cellular mechanism in AD pathogenesis (11) and as a significant influence on its progression (12,13).

Autophagy, an essential intracellular degradation pathway, plays a critical role in clearing damaged organelles and protein aggregates (14-16). This process is significantly impaired in AD (17), manifesting as defects in autophagosome formation and maturation, dysregulated lysosomal function and inefficient autophagosome-lysosome fusion (18). These disruptions compromise the clearance of Aβ and tau proteins, leading to the accumulation of toxic species both inside and outside neurons, which in turn amplifies neuronal injury and cell death (19,20). Autophagy dysfunction also contributes to mitochondrial deficits, oxidative stress and chronic neuroinflammation; it ultimately blocks energy production, disrupts energy utilization and perturbs metabolic homeostasis, thereby disturbing neuronal energy metabolism, impairing synaptic function and promoting apoptosis (21). Thus, strategies aimed at restoring autophagic activity have become a major focus of AD therapeutic research (22).

Over the past few decades, mounting epidemiological and clinical evidence has unequivocally established that regular physical activity confers substantial benefits for the prevention and management of various chronic diseases, particularly cardiovascular diseases, type 2 diabetes mellitus and certain malignancies (for example, breast, colon and liver cancer) (23-25). This evidence provides a framework for developing non-pharmacological interventions in chronic disease management. Beyond non-modifiable factors such as genetic susceptibility (1), physical inactivity is recognized as a significant modifiable risk factor for AD, accounting for ~13% of cases worldwide (26,27). Clinical and preclinical evidence shows that regular exercise not only reduces the risk of AD incidence (28) but also improves cognitive outcomes in patients with AD (29-32). Mechanistically, dysregulated autophagy serves as a key pathogenic driver in AD, and exercise modulates neurodegeneration by regulating autophagic pathways. Reports have confirmed that physical activity significantly promotes autophagic activation, alleviates cerebral neuroinflammation and mitigates AD-related pathological damage in human and animal models, such as transgenic mouse models of AD (33,34). Thus, clarifying the molecular signaling pathways underlying exercise-regulated autophagy in AD is critical for elucidating the core mechanisms of exercise-based interventions and developing targeted therapeutic strategies. Although existing reviews have independently addressed the role of autophagy in AD or the neuroprotective effects of exercise in AD, a systematic overview of the mechanisms by which exercise modulates autophagic signaling pathways to affect AD is lacking. Clarification of this network pathway is required to translate exercise-based interventions from basic research to clinical practice in AD. The current review systematically explores the recent research progress on how exercise influences the autophagy signaling pathway in AD, emphasizing its core molecular mechanisms. The review also assesses the potential synergy between exercise and natural products in AD intervention, offering a theoretical foundation and research direction for the future development and clinical application of exercise-based AD-targeted interventions.

2. Autophagy dysfunction in AD

Neuronal autophagy is an essential intracellular degradation system that mediates the delivery and breakdown of cytoplasmic components within lysosomes (35,36). Autophagy is classified into three forms based on the mechanisms of cargo delivery to lysosomes: Macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) (19) (Fig. 1A). The initial step in macroautophagy (commonly termed autophagy) is the formation of a double-membrane vesicle known as the autophagosome (37). This process is regulated by a set of highly conserved autophagy-associated proteins (ATGs) (36). The initial step involves the activation of the UNC 51-like kinase (ULK) complex, consisting of ULK1/2, ATG13, FAK family kinase-interacting protein of 200 kDa and ATG101 (38,39). Subsequent phagophore nucleation requires the class III PI3K complex, which includes vesicular protein sorting 34 (VPS34), VPS15, beclin-1 and ATG14L (38). Phagophore expansion and autophagosome maturation depend on two ubiquitin-like conjugation systems: One results in the ATG5-ATG12-ATG16L complex that facilitates membrane elongation, and the other conjugates phosphatidylethanolamine to microtubule-associated protein 1 light chain 3 (LC3), generating the lipidated form LC3-II that associates with autophagosomal membranes (40). These steps are critical for autophagosome biogenesis, cargo recognition and eventual fusion with lysosomes to form autolysosomes (38).

By contrast, microautophagy involves the direct engulfment of cytoplasmic material through lysosomal membrane invagination (41). CMA, a selective process, recognizes substrate proteins via the chaperone heat shock cognate 70-kDa protein bearing a Kex2-Fer1-Endo U1-Qc-2 motif and translocates them into lysosomes through lysosomal-associated membrane protein 2A (LAMP2A) (19,37,38). CMA deficiency has been linked to exacerbated AD pathology (42). Nutrient deprivation typically induces non-selective autophagy, whereas selective autophagy targets damaged organelles such as mitochondria and peroxisomes, as well as protein aggregates (37,43)

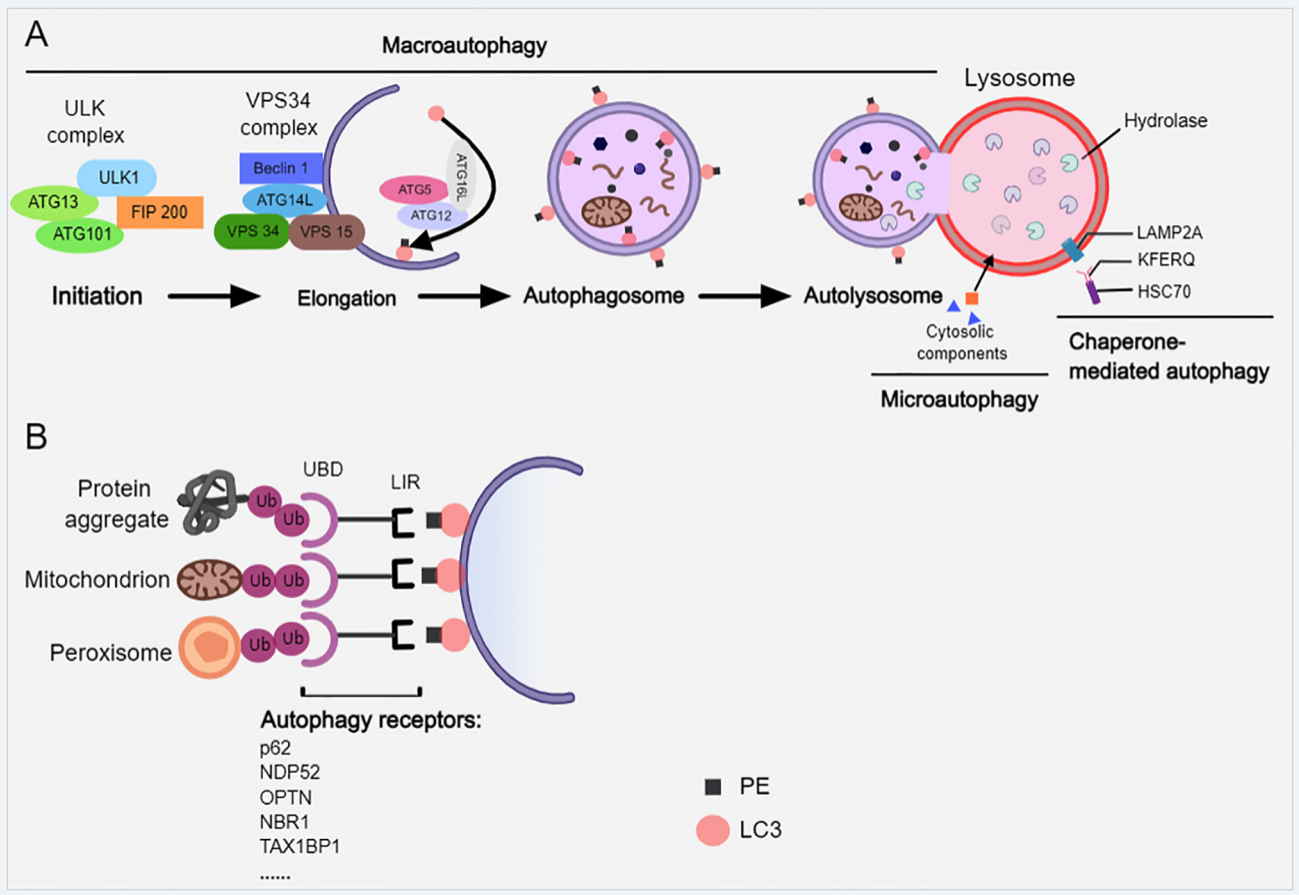

Figure 1. Overview of autophagy pathways. (A) The three types of autophagy. Macroautophagy is initiated by the ULK complex (comprising ULK1, ATG13, ATG101, and FIP200), with phagophore nucleation and elongation driven by the VPS34 complex (beclin-1, ATG14L, VPS34 and VPS15) and the ATG5-ATG12-ATG16L complex. During this process, LC3 is covalently conjugated with PE to form membrane-associated LC3-II, a hallmark of maturing autophagosomes, which subsequently fuse with lysosomes to generate autolysosomes where luminal hydrolases degrade sequestered cytoplasmic cargo. Microautophagy entails the direct invagination of lysosomal membranes to engulf cytosolic components without the formation of an autophagosome intermediate, facilitating direct degradation. Chaperone-mediated autophagy, a selective degradative pathway, relies on cytosolic HSC70 to recognize target proteins bearing the KFERQ motif, which are then translocated into the lysosomal lumen via the lysosomal membrane protein LAMP2A for targeted proteolysis. (B) Three forms of selective autophagy and cargo receptors. Selective autophagy specifically targets distinct cytoplasmic cargoes, including protein aggregates, mitochondria and peroxisomes, through a repertoire of autophagy receptors (for example, p62, NDP52, OPTN, NBR1 and TAX1BP1) that harbor a UBD for binding Ub cargo and a LIR to anchor the receptor-cargo complex to LC3 on the autophagosomal membrane, thereby enabling the selective sequestration and degradation of damaged organelles or toxic protein aggregates by the autophagic machinery. ATG5, autophagy-associated protein 5; ATG12, autophagy-associated protein 12; ATG13, autophagy-associated protein 13; ATG14L, autophagy-associated protein 14L; ATG16L, autophagy-associated protein 16L; FIP 200, FAK family-interacting protein of 200 kDa; HSC70, heat shock cognate 70-kDa protein; LC3, microtubule-associated protein 1 light chain 3; LC3-II, microtubule-associated protein 1 light chain 3-II; LAMP2A, lysosomal-associated membrane protein 2A; KFERQ, Kex2-Fer1-Endo U1-Qc-2 motif; NBR1, next to BRCA1 gene 1; NDP52, nuclear dot protein 52; OPTN, optineurin; p62, sequestosome 1; PE, phosphatidylethanolamine; TAX1BP1, tax1 (human T-cell leukemia virus type I) binding protein 1; UBD, ubiquitin-binding domain; Ub, ubiquitinated; LIR, LC3 interaction region; ULK, UNC 51-like kinase; ULK1, UNC 51-like kinase 1; VPS15, vesicular protein sorting 15; VPS34, vesicular protein sorting 34.

(Fig. 1B). Selective autophagy is mediated by receptors such as p62, nuclear dot protein 52, optineurin (OPTN), next to BRCA1 gene 1 and tax1 (human T-cell leukemia virus type I) binding protein 1, which contain a ubiquitin-binding domain and LC3 interaction region that connect ubiquitinated cargo to the autophagic machinery (37,44,45).

3. Mechanism of autophagy dysfunction in AD

Autophagic flux and the expression of lysosome-associated proteins are significantly reduced in both patients with AD and AD animal models (46). This dysregulation is hypothesized to contribute to AD pathogenesis by impairing multiple steps in the autophagy-lysosome pathway, from autophagosome formation to lysosomal degradation (47). In brains affected by AD, neuronal autophagy is disrupted at the initiation phase, partly due to mammalian target of rapamycin (mTOR) hyperactivation, which suppresses the ULK1 complex and impedes autophagosome biogenesis (48,49). Moreover, mutations and the downregulation of autophagy-related genes have been linked to AD. For example, beclin-1 expression is markedly decreased in AD-affected brains (50,51), and beclin-1-deficient microglia in AD models have been reported to exhibit impaired phagocytosis and reduced Aβ clearance (52). LC3, a key autophagosomal membrane protein, shows altered processing in AD, with reduced conversion of LC3-I to LC3-II, thereby inhibiting autophagy initiation (53). Emerging evidence also implicates non-canonical autophagic processes [e.g., LC3-associated phagocytosis (LAP) and LC3-associated endocytosis (LANDO)] in AD pathology, and

this pathway has been discovered in microglia of the brain and the central nervous system. LANDO deficiency exacerbates neurodegeneration and cognitive deficits in AD mice (54,55). The mechanisms of LAP and LANDO are distinct from those of autophagy (54). However, no current evidence exists on how exercise affects these pathways. Therefore, the present review will not elaborate further on these processes.

Lysosomal dysfunction further aggravates autophagic impairment in AD. Decreased autolysosomal acidification occurs prior to extracellular Aβ deposition (17), leading to defective proteolysis, increased lysosomal membrane permeability (56,57) and impaired cathepsins, which are lysosomal proteases essential in Aβ and tau clearance (58,59). Notably, Aβ accumulation both results from and exacerbates lysosomal dysfunction, creating a vicious cycle that promotes neurodegeneration (60). Restoring lysosomal function enhances the clearance of Aβ and p-tau (57). The autophagy receptor sequestosome 1 (SQSTM1/p62), which facilitates cargo delivery to LC3, exerts protective effects in AD models by improving memory and modulating autophagic activity (61,62).

Transcription factor EB (TFEB), a master regulator of autophagy-lysosomal biogenesis, plays a critical role in AD (63-65). The activity of TFEB is inhibited by mTOR complex 1 (mTORC1); however, TFEB-mediated endocytosis is essential for mTORC1 activation and autophagy function (57,66). Oxidative stress also contributes to AD progression by promoting the amyloidogenic processing of amyloid precursor protein (APP) and tau hyperphosphorylation (67). Reactive oxygen species (ROS) accumulation damages mitochondria, leading to dysfunction that triggers mitophagy, a selective autophagic process essential for maintaining mitochondrial quality (45,68). Collectively, these disruptions in the autophagy-lysosome pathway significantly exacerbate AD pathology (63,69,70).

Considering the pivotal role that autophagy dysfunction plays in the development of AD, restoring compromised autophagic flux has become a promising approach for therapy. Among the different interventions available, exercise is as a non-pharmacological treatment that is safe, cost-effective and easy to implement. Recent studies have reported the significant potential of exercise to regulate autophagy and ameliorate AD pathology (71,72). The subsequent sections focus on the ways in which exercise serves as a potential modulator to restore autophagic homeostasis in AD.

4. Exercise as a modulator of autophagy in AD

Exercise provides a multi-targeted physiological intervention strategy to address the complex autophagy dysfunction aforementioned. Preclinical studies have shown that exercise can improve memory, promote neurogenesis, and enhance hippocampal structure and synaptic plasticity in AD transgenic mouse models [e.g., APP/presenilin 1 (PS1) and proline-301-serine (P301S)] (73,74). Both human and animal studies have shown that a wide range of physical activities, ranging from low-intensity walking to high-intensity training, support cognitive health (75,76). For example, adolescents performing treadmill exercises demonstrated significant cognitive improvements, particularly at moderate to high intensity exercise (28).

In one study, 16 weeks of voluntary running significantly improved autophagy dysfunction in mice with five familial Alzheimer's disease mutations (5xFAD transgenic mice) and exerted neuroprotective effects (77). Notably, more recent studies demonstrated that moderate-intensity exercise was more effective in modulating brain autophagy in AD models than low or high-intensity exercise, whereas low-intensity exercise was associated with higher AD risk, and very high intensity increased oxidative stress (78-82). Aerobic exercise modalities, such as treadmill running, voluntary wheel exercise and swimming, were shown to specifically facilitate the autophagy-mediated clearance of pathogenic proteins (82,83).

Exercise enhances autophagic activity through multiple pathways. In APP/PS1 mice, 12 weeks of aerobic treadmill exercise restored autophagy-lysosomal flux, increased autophagosome numbers in the hippocampus and cortex, promoted Aβ clearance, and improved cognitive performance (71,84,85). Similarly, extended treadmill exercise reduced tau pathology in P301S mice, and autophagy was shown to play a crucial role in tau degradation through a ubiquitin-mediated mechanism (84,86). Exercise also upregulates the expression of core autophagy-related proteins such as LC3-II and beclin-1, as observed following both high intensity interval training (HIIT) and moderate intensity continuous training (MICT) (78). However, a separate animal study reported no significant changes in LC3, p62 or beclin-1 in whole hippocampal lysates after HIIT, suggesting that HIIT has specific effects on brain regions or motor programs (81).

In summary, preclinical studies consistently confirmed that moderate-intensity exercise enhances autophagic flux, particularly in the hippocampus of AD model mice, in a manner associated with spatial memory improvement. These preclinical findings underscore a bidirectional, functionally significant relationship between exercise and autophagy in AD.

5. Mechanisms of exercise in regulating autophagy dysfunction in AD

Exercise exerts neuroprotective effects against AD primarily by restoring impaired autophagy flux, which serves as a pivotal link between exercise-induced signaling activation and the amelioration of AD-specific pathological phenotypes. A well-orchestrated causal chain underpins this process. Exercise triggers the activation of key signaling pathways [(mTOR, sirtuin 1 (SIRT1) and adiponectin (APN) receptor 1 (AdipoR1)] and the modulation of microRNAs (miRNAs/miRs)/irisin, which in turn corrects defects in autophagosome biogenesis, lysosomal function and autophagosome-lysosome fusion. This restoration of physiological autophagic flux directly enhances the clearance of neurotoxic Aβ aggregates and p-tau, mitigates chronic neuroinflammation, preserves mitochondrial integrity by improving mitophagy and rescues synaptic dysfunction (87). In summary, these effects alleviate neuronal damage and apoptosis, and ultimately improve cognitive function in AD models and patients. Notably, the regulatory effect of exercise on autophagy is not mediated by a single mechanism but is achieved through complex crosstalk between signaling pathways and a cooperative regulatory network. These interactions have not been fully

elucidated and analyzing them can be helpful in understanding the overall neuroprotective effect of exercise.

mTOR signaling. mTOR, a serine/threonine kinase within the PI3K-related kinase family, plays a central role in regulating multiple cellular processes. mTOR functions through two distinct complexes: mTORC1 and mTORC2 (88), of which mTORC1 acts as a key negative regulator of autophagy (89,90). Under nutrient-sufficient conditions, active mTORC1 phosphorylates and inhibits the ULK1 complex, thereby suppressing the initiation of autophagy. mTORC1 activity is suppressed during nutrient deprivation or cellular stress, leading to the ULK1-mediated induction of autophagy (89).

In AD studies, analyses of animal and post-mortem human brain tissue have shown that mTORC1 is often hyperactivated (48,91). Preclinical research has demonstrated that regulating mTOR expression can salvage autophagy deficiency and enhance cognitive function in AD models [e.g., triple-transgenic (PS1m146v/APPswe/TauP301L) (3xTg)-AD mice] (92). The post-exercise activation of mTORC1 in the brains of experimental animals has also been associated with improved learning and memory (93). Moreover, treadmill exercise in neuron-specific enolase/human tau23 (NSE/htau23) transgenic mice reduced glycogen synthase kinase-3β (GSK-3β) activity and tau hyperphosphorylation by enhancing PI3K/AKT signaling, an effect potentially mediated by AMPK activation and downstream mTORC1 inhibition (94) (Fig. 2A). Notably, this inhibition of mTORC1 by exercise directly reversed the pathological suppression of the ULK1 complex, restoring autophagosome formation and the subsequent clearance of p-tau aggregates. Additionally, both HIIT and MICT were reported to inhibit overactive PI3K/AKT/mTOR signaling in the hippocampus, with HIIT displaying a more prominent inhibitory effect. This signaling suppression, in turn, facilitated autophagy flux and mitigated Aβ deposition, which were mediated by augmented lysosomal acidification and enhanced cathepsin activity (78).

Exercise increases neuronal energy demand by increasing the AMP/ATP ratio and activating AMPK. This energy-sensitive kinase promotes autophagy by phosphorylating both tuberous sclerosis complex (TSC)2 and TSC1, thereby enhancing the inhibition of ras homolog enriched in brain, mTORC1 and raptor (a core component of mTORC1), further inhibiting their activity (95). Elevated AMPK phosphorylation during exercise has been observed in the brains of AD model animals (96). Moreover, exercise-induced mTOR increased VMA21 expression in APP/SP1 mice, contributed to the recovery of autolysosomal function, reduced Aβ accumulation and improved cognitive impairment (71) (Fig. 2A). Restoring autolysosomal activity breaks the vicious cycle of Aβ accumulation and lysosomal dysfunction in AD, ultimately reducing neuronal toxicity and improving synaptic transmission.

SIRT1 signaling. SIRTs, a conserved family of nicotinamide adenine dinucleotide-dependent deacetylases known as 'longevity proteins', comprise seven isoforms (SIRT1-SIRT7) (97). SIRT1, one of the most extensively studied members, is highly expressed in the hippocampus and prefrontal cortex, and its levels are significantly reduced in AD (98). Previous studies have shown that serum SIRT1 levels are reduced in patients with mild cognitive impairment and AD, highlighting its potential as a therapeutic target (98-101). Aerobic exercise has been shown to mitigate cognitive decline, improve synaptic function, promote neuronal survival and reduce Aβ accumulation in AD models by activating the SIRT1 pathway (65,102). Similarly, resistance training was reported to increase hippocampal and prefrontal SIRT1 activity and alleviate tau pathology in AD mice (82). Recent studies demonstrated that high-intensity training over 6 weeks increased PPARγ coactivator-1α (PGC-1α) and SIRT1 activity in human skeletal muscle (101). Further animal experiments indicated that 12 weeks of moderate-intensity treadmill training inhibited the production of Aβ in NSE/APPsw transgenic mice by upregulating SIRT1, enhancing PGC-1α expression, increasing a disintegrin and metalloprotease 10 levels, and reducing β-secretase 1 (BACE1) (a rate-limiting enzyme in APP processing and Aβ production) activity (103) (Fig. 2B). This evidence supports the critical role of SIRT1 in AD progression.

Exercise also counteracts impaired mitophagy in AD. The PTEN-induced kinase 1-Parkin pathway, essential for mitochondrial quality control, is potentiated by treadmill training via the SIRT1-FOXO1/3 axis, enhancing mitophagy and mitochondrial integrity (102,104-106). This SIRT1-mediated mitophagy not only reduces oxidative stress by eliminating dysfunctional mitochondria but also decreases Aβ aggregation by reducing ROS-induced APP amyloidogenic processing, while preserving synaptic function by maintaining mitochondrial energy supply. In a study using SIRT1-inhibited model mice, researchers found that acute wheel running for 1 h increased TFEB levels in the nuclei of the cerebral cortex within 2-4 h. This increase was driven by an upregulation of the AMPK-SIRT1 signaling pathway. Moreover, after 8 weeks of wheel running, TFEB levels were significantly increased in the cortex, hippocampus and striatum. Exercise effectively activated the autophagy-lysosomal pathway, enhancing lysosomal function and biogenesis in the mouse brain (107). Further research indicated that inhibiting SIRT1 did not prevent TFEB nuclear translocation, suggesting that other mechanisms might contribute to exercise-induced TFEB increases (Fig. 2B). Similar to SIRT1, SIRT3 has also been implicated in mitophagy regulation (108). Single-nucleus RNA sequencing in a clinical study showed the decreased expression of neuronal SIRT5 in patients with AD, suggesting its role in autophagy flux (46). However, the effects of exercise intensity on SIRT activation and the specific roles of SIRT3 and SIRT5 in exercise-induced neuroprotection require further investigation.

AdipoR1 signaling. APN, a protein hormone secreted by adipose tissue, acts through receptors, including AdipoR1, AdipoR2 and T-cadherin. AdipoR1 is highly expressed in the brain, where it regulates energy homeostasis, hippocampal neurogenesis and synaptic plasticity (109-111). Maintaining the APN metabolic balance is increasingly recognized to be important in AD, with reduced APN levels in patients with AD correlating with elevated $A\beta_{42}$ and p-tau in the cerebrospinal fluid and impaired hippocampal function (111).

APN promotes hippocampal progenitor cell and Neuro2A cell proliferation via AdipoR1 signaling, which suppresses

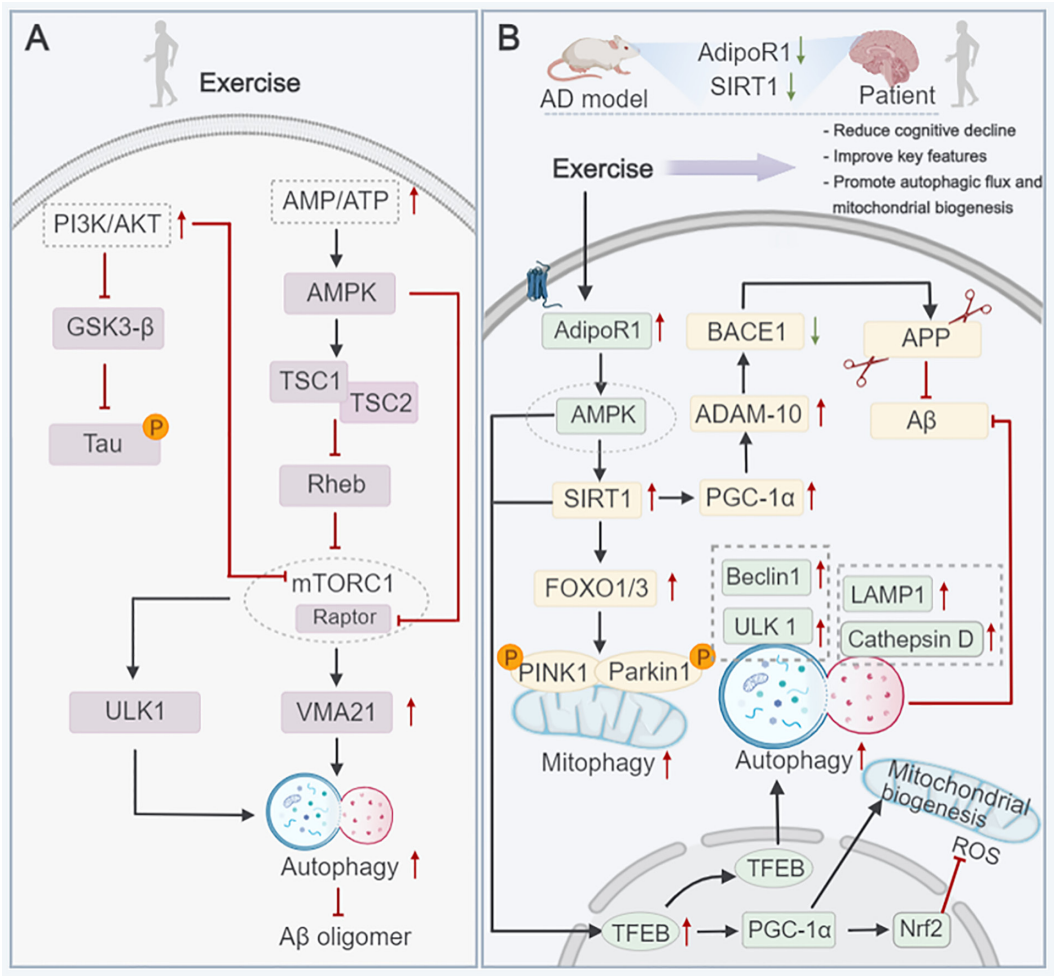

Figure 2. Signaling pathways behind the exercise regulation of autophagy dysfunction in AD. (A) Exercise activates the PI3K/AKT signaling cascade, which subsequently activates GSK-3β to modulate Tau protein phosphorylation. Simultaneously, exercise elevates the cellular AMP/ATP ratio, triggering AMPK activation. Activated AMPK then inhibits mTORC1 through the TSC1/2-Rheb signaling cascade, upregulates VMA21 expression and activates ULK1. Collectively, these events augment autophagic flux and reduce Aβ oligomer accumulation. (B) Exercise activates the AdipoR1-AMPK-SIRT1 signaling axis, which upregulates PGC-1α to suppress BACE1 and ADAM-10, thus reducing APP processing and Aβ production. Concomitantly, SIRT1 modulates FOXO1/3 to activate PINK1/Parkin-mediated mitophagy, while upregulating Beclin-1, ULK1, LAMP1 and cathepsin D to enhance autophagic degradation. Furthermore, exercise upregulates TFEB and PGC-1α, which coordinately promote autophagy and mitochondrial biogenesis, and activates Nrf2 to mitigate ROS accumulation, ultimately ameliorating cognitive decline and core pathological hallmarks of AD by restoring autophagic and mitochondrial homeostasis. Red arrows represent upregulation, while green arrows represent downregulation. Black arrows indicate promotion and red lines with a line across represent inhibition. AD, Alzheimer's disease; Aβ, amyloid β-protein; APP, amyloid precursor protein; AdipoR1, adiponectin receptor 1; ADAM-10, a disintegrin and metalloprotease 10; AKT, protein kinase B; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; BACE-1, β-secretase 1; FOXO1/3, forkhead box O1/3; GSK-3β, glycogen synthase kinase-3β; LAMP1, lysosomal-associated membrane protein 1; mTORC1, mammalian target of rapamycin complex 1; Nrf2, nuclear factor erythroid 2-related factor 2; Tau, microtubule-associated protein tau; PI3K, phosphatidylinositol 3-kinase; PINK1, PTEN-induced kinase 1; Parkin, parkin E3 ubiquitin ligase; PGC-1α, PPARγ coactivator-1α; Raptor, a core component of mTORC1; Rheb, ras homolog enriched in brain; ROS, reactive oxygen species; SIRT1, sirtuin 1; TFEB, transcription factor EB; TSC2, tuberous sclerosis complex 2; TSC1, tuberous sclerosis complex 1; ULK1, UNC 51-like kinase 1; VMA21, vacuolar ATPase assembly factor VMA21.

GSK-3β through p38-mitogen-activated protein kinase activation and phosphorylation at Ser-389, thereby supporting neurogenesis (109). Impaired AdipoR1 expression has been reported in both patients with AD and AD animal models (111,112). The activation of autophagy through the AdipoR1/AMPK pathway exerts neuroprotective effects in AD progression (113). Recent studies have found that APN enhances autophagy through the AdipoR1/AMPK/SIRT1 pathway, thereby promoting the clearance of Aβ in APP/SP1 mice (114). Notably, Aβ deposition and associated pathology were significantly reduced in APP/PS1 mice after 12 weeks of moderate-intensity aerobic intervention. These changes were related to improvements in lysosomal function and the recovery of autophagy flux through the AdipoR1/AMPK/TFEB signaling pathway (115). Specifically, AdipoR1 activation by exercise-induced APN upregulation phosphorylates AMPK, which in turn activates TFEB. TFEB nuclear translocation upregulates genes involved in autophagosome formation (e.g., ULK1 and beclin-1) and lysosomal function (e.g., LAMP1 and cathepsin D), thereby enhancing the clearance of Aβ and p-tau, reducing neuroinflammation by activating microglial autophagy and preserving synaptic plasticity by maintaining neuronal energy metabolism (115). Thus, the translocation of the TFEB nucleus is not only regulated by SIRT1, but also by AMPK. Additionally, Aβ aggregation increases ROS levels, triggers oxidative stress and disrupts mitochondrial autophagy. Exercise was reported to promote the nuclear translocation of TFEB, increase the expression of PGC-1α

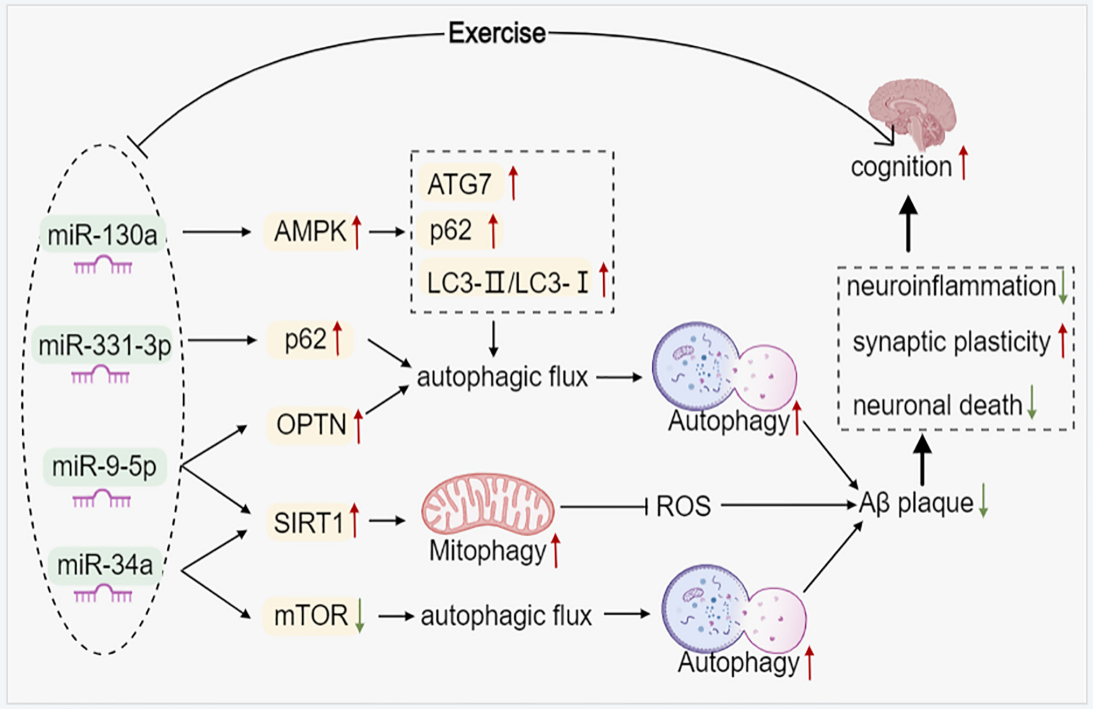

Figure 3. Exercise regulates autophagy through miRNA-mediated mechanisms. Exercise modulates several crucial miRNAs, such as miR-130a, miR-331-3p, miR-9-5p and miR-34a. Specifically, miR-130a activates AMPK, which subsequently upregulates ATG7, p62 and the LC3-II/LC3-I ratio, thereby enhancing autophagic flux. miR-331-3p increases the expression of p62 and OPTN, thereby promoting autophagic flux. Meanwhile, miR-9-5p and miR-34a work together to upregulate SIRT1 and downregulate mTOR. SIRT1 enhances mitophagy, which suppresses ROS generation, while mTOR inhibition further boosts autophagic flux. Enhancing both autophagy and mitophagy significantly reduces Aβ plaque deposition, mitigates neuroinflammation, improves synaptic plasticity and inhibits neuronal death. This combined effect ultimately leads to a marked improvement in cognitive function within AD-related pathological contexts. Red arrows represent upregulation, while green arrows represent downregulation. Black arrows indicate promotion and red lines with a line across represent inhibition. Aβ, amyloid β-protein; AMPK, adenosine monophosphate-activated protein kinase; ATG7, autophagy-associated protein 7; LC3-II, microtubule-associated protein 1 light chain 3-II; LC3-I, microtubule-associated protein 1 light chain 3-I; mTOR, mammalian target of rapamycin; miR/miRNA, microRNA; OPTN, optineurin; p62, sequestosome 1; ROS, reactive oxygen species; SIRT1, sirtuin 1.

and nuclear factor e2-related factor 2, improve mitochondrial autophagy, and thereby reduce mitochondrial damage and neuronal death (65). However, the mechanism by which exercise regulates AdipoR1 and the complex signaling pathways of AdipoR1 require further preclinical research.

miRNAs in exercise-mediated autophagy dysfunction in AD. miRNAs are small endogenous non-coding RNAs that post-transcriptionally regulate gene expression (116). The majority are highly expressed in the nervous system and play important roles in neuronal development, synaptic plasticity and the pathogenesis of neurodegenerative diseases (117). In a previous study, clinical data showed that miR-4763-3p was upregulated in the early stage of AD compared with that in the healthy control group (118). A preclinical study has shown that inhibiting miR-4763-3p can improve learning and memory disorders in 3xTg-AD mice, accompanied by reduced neuroinflammation, neuronal death and synaptic alterations (118). miRNAs modulate transcript stability and translation by binding to the 3'-UTR of target mRNAs; their dysregulation can disrupt protein homeostasis, leading to imbalances in Aβ production and clearance (119). Growing evidence indicates that miRNA dysfunction contributes to impaired autophagy in AD, with miRNAs indirectly influencing disease progression by regulating autophagy (73,120).

Studies have begun to reveal the role of miRNAs in exercise-induced autophagy in AD. For instance, miR-34a and miR-130 have been implicated in mediating the effects of exercise on autophagic processes (121) (Fig. 3). Swimming training was reported to improve cognitive function and delay aging in rats by counteracting miR-34a-mediated autophagic impairment and abnormal mitochondrial dynamics (122). Another study has shown that miR-34a-mediated autophagy may be related to the activation of the SIRT1 signaling pathway and the inhibition of mTOR signaling (123). Furthermore, cell experiments using SH-SY5Y cells have identified miR-331-3p and miR-9-5p as regulators of autophagy receptors, targeting SQSTM1/p62 and OPTN, respectively. Overexpressing these miRNAs in SH-SY5Y cells impaired autophagy flux and promoted Aβ plaque formation (124) (Fig. 3). Ginsenoside Rg1 treatment of APP/PS1 mice activated miR-9-5p/SIRT1-mediated mitophagy, alleviated mitochondrial dysfunction and effectively improved cognitive function in AD mice (125). However, all these studies lack a connection with exercise. A preclinical study showed that the expression of miR-130a in aging rats (21 months) was significantly downregulated compared with that in young rats (3 months). However, voluntary wheel running (8 weeks) significantly increased the expression of miR-130a, whereas the expression of autophagy-related protein p62 decreased. The increase in the LC3II/LC3I ratio and the expression of ATG7 reduced apoptosis in senescent rats. The expression of p-AMPK increased, while SIRT1 remained unchanged, suggesting that voluntary wheel running activates the AMPK

signaling pathway but not the SIRT1 pathway in aging rats (96). Additionally, D-gal-induced SH-SY5Y cells showed results consistent with the animal experiments (96). miRNA can activate multiple signaling pathways, which may be related to the targeted activation of upstream signaling molecules in various signaling pathways. Therefore, more research on using miRNA as a potential target for AD treatment, in which its comprehensive regulatory network in exercise-regulated AD autophagy is analyzed, is required.

Irisin in exercise-mediated autophagy dysfunction in AD. Irisin is a PGC-1α-dependent myokine that was originally identified in skeletal muscle. Irisin is produced by the proteolytic cleavage of the membrane protein fibronectin type III structural domain-containing 5 protein (FNDC5) (126,127), is widely expressed in multiple tissues and exhibits neuroprotective properties (128-130). Studies have reported decreased levels of FNDC5/irisin in the hippocampus and cerebrospinal fluid of patients with AD. Exercise-induced increases in irisin have been shown to exert beneficial effects in AD models (127,131,132). A recent study demonstrated that irisin suppressed Aβ aggregation by promoting the release of enkephalin from astrocytes by inhibiting the ERK-STAT3 signaling pathway (133). Research have reported that exercise-induced irisin could regulate the AMPK pathway by activating it and inhibiting mTOR, thereby increasing autophagy and clearing amyloid proteins and toxic aggregates in the brain (134-136) (Fig. 4). However, no experimental evidence has verified that exercise regulates autophagy dysregulation in AD by upregulating irisin. In addition, the miRNA regulation of irisin may play an important role in the clinical prevention and treatment of AD (128); however, relevant research data are lacking. Therefore, this gap in the research field of exercise-induced irisin autophagy in AD remains to be explored.

6. Natural products combined with exercise regulate autophagy

Given the complexity of AD pathology, single-target therapies often fail in clinical trials. AD drug development projects are targeting multiple mechanisms (1). Natural products derived from herbal or dietary sources (e.g., curcumin, catechins and quercetin) have shown favorable safety profiles and multi-target efficacy in clinical studies focused on AD (137). For instance, quercetin and curcumin have entered phase II clinical trials and have significantly demonstrated improvements in cases of mild cognitive impairment (1). These studies highlight the essential role of natural products in treating AD. Additionally, a number of studies have shown the effects of natural products in regulating autophagy in AD (138-140). For instance, Esculentoside A is a kind of triterpene saponin isolated from *Phytolacca esculenta* that activates the autophagy pathway in an AMPK-dependent manner, thereby promoting the clearance of p-tau and alleviating cognitive decline in 3xTg-AD mice (138). Ginsenoside Rg2, a steroidal glycoside derived from *Panax ginseng*, activates autophagy via AMPK-dependent but mTOR-independent signaling pathways. This activation facilitates the clearance of Aβ aggregates and enhances cognitive function in 5xFAD transgenic mice (139). Notably, only a few studies have focused on the synergistic effect of exercise and natural products in the autophagy regulation of AD. Consequently, the following review section will focus on representative natural products in AD research. Their synergistic effects and underlying mechanisms in regulating autophagy and alleviating AD pathology upon combination with exercise will be systematically summarized.

Resveratrol. Resveratrol, a natural polyphenolic compound extracted from various plants (e.g., grapes and peanuts) (141), demonstrates antioxidant and neuroprotective effects *in vitro* (142). Studies in AD models have shown that resveratrol decreases Aβ aggregation and hippocampal toxicity, promotes neurogenesis and mitigates hippocampal degeneration (143-145). Clinical trials showed that resveratrol sustainably decreased $A\beta_{40}$ levels in the cerebrospinal fluid and plasma of patients with AD, and that on oral administration of high-dose resveratrol (500-1,000 mg/day) was safe and well-tolerated (117,146). The therapeutic potential of resveratrol in AD involves modulating AMPK-SIRT1-mediated autophagy and miRNA-dependent pathways, as well as the direct activation of autophagy via the mTOR signaling pathway, through which it regulates tau hyperphosphorylation, neuroinflammation, BACE1 activity and Aβ accumulation (117). After 5 months of moderate to vigorous exercise combined with resveratrol treatment (557 mg/kg/day, diet), the expression of autophagy-related markers (LC3-I), lysosomal proteins (cathepsin B/D and LAMP2) and ubiquitination markers (Ub1) was significantly reduced in 3xTg-AD mice. The expression levels of p62 and SIRT1 proteins were significantly increased, while the expression of AMPK was elevated but not significantly different. These findings suggest that the combination of exercise and resveratrol may synergistically enhance autophagy via the AMPK-SIRT1 pathway, reduce Aβ oligomer levels, decrease apoptosis and ultimately improve cognitive function (147). However, differences in the degree of AMPK-SIRT1 activation or that of other pathways, cognitive improvements from different doses of resveratrol combined with different exercise intensities, the impact of resveratrol supplementation timing (such as before, after or simultaneously with exercise) on bioavailability and synergistic effects, as well as clinical trials, should all be explored in the future.

Luteolin. Luteolin, a natural flavonoid in a variety of fruits, vegetables and herbs [e.g., honeysuckle (*Lonicera japonica*) and Perilla (*Perilla frutescens*)] (148), confers significant neuroprotection against glutamate-induced hippocampal neuronal death (149). A clinical trial of patients with AD showed that no dose-limiting toxicity occurred when luteolin was administered at a dose of 100 mg/day (150). Preclinical studies have shown that luteolin can improve cognitive function and protect AD neurons by alleviating Aβ-induced oxidative stress, reducing mitochondrial damage and alleviating neuroinflammation (148,151). In $A\beta_{1-42}$ oligomer-induced AD mice, a combination of luteolin (100 mg/kg/day, gavage) and 4 weeks of voluntary wheel exercise was more effective than either treatment alone. This dual approach significantly improved cognitive function, reduced Aβ accumulation and inhibited microglial activation, thereby alleviating neuroinflammation. The approach also enhanced autophagy activity in the hippocampus and cortical regions, as indicated by a notable

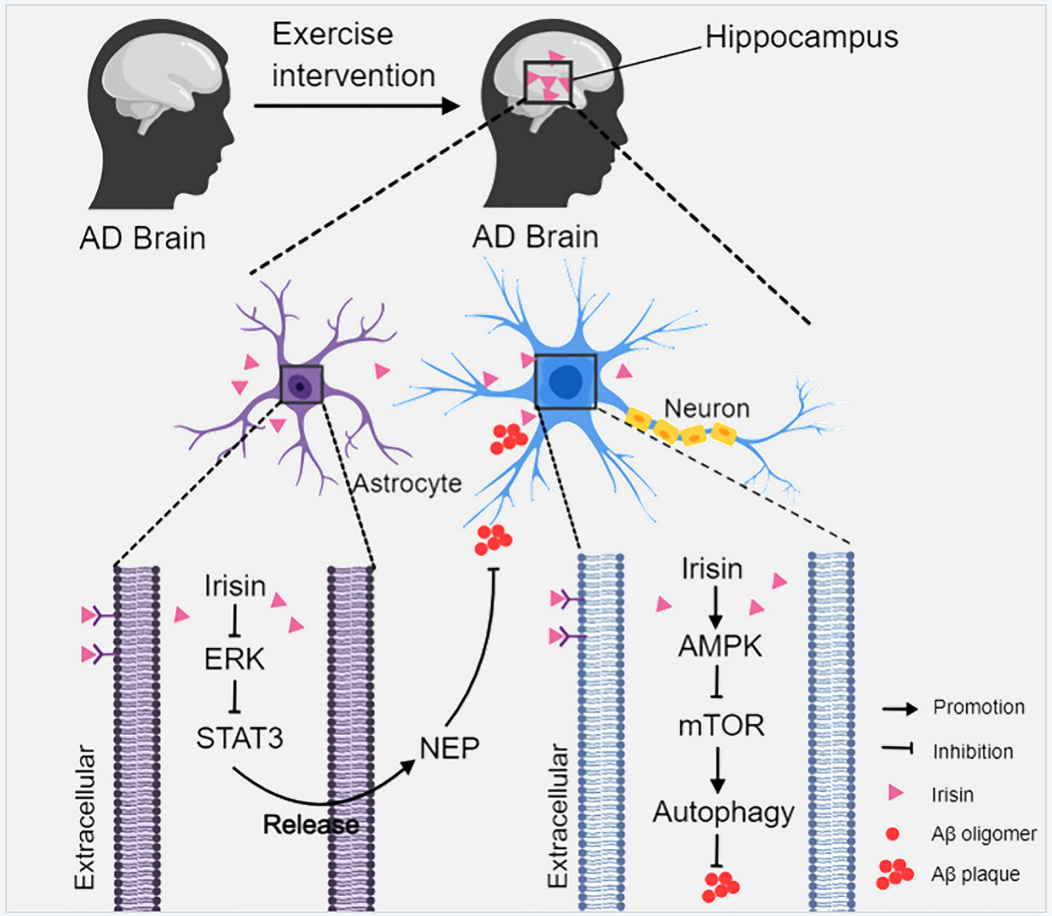

Figure 4. Irisin is involved in the regulation of autophagy. Physical exercise stimulates the release of irisin, which specifically targets astrocytes and neurons in the hippocampus of brains affected by AD. In astrocytes, irisin activates the ERK-STAT3 signaling pathway, promoting the secretion of NEP, an essential enzyme for degrading Aβ. In neurons, irisin binds to cell-surface receptors and activates AMPK, which inhibits the mTOR pathway. This inhibition enhances autophagic flux, facilitating the degradation of Aβ oligomers and thereby reducing Aβ plaque burden. Irisin-driven mechanisms in astrocytes and neurons collaboratively alleviate Aβ-related pathology in the AD hippocampus. This positions irisin as a key molecular connection among physical exercise, autophagy regulation and the mitigation of AD pathological features. Aβ, amyloid β-protein; AMPK, adenosine monophosphate-activated protein kinase; ERK, extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; NEP, enkephalin; STAT3, signal transducer and activator of transcription 3.

decrease in p-ULK1 protein expression and an increase in LC3II/LC3I expression in the cerebral cortex. Notably, luteolin, exercise and their combination each reduced p62 protein expression to varying degrees, although no significant differences were observed among them (152). A recent study further confirmed that luteolin combined with exercise could alleviate AD-related cognitive impairment. Untargeted metabolomics was also used to reveal the key role of autophagy in this combined mechanism (153). In conclusion, further research is warranted to elucidate how varying doses of luteolin modulate its bioavailability and exert synergistic effects when combined with distinct exercise intensities and supplementation timing (before, after or during exercise). Additionally, more robust clinical trials are necessary to investigate these topics.

The combination of natural products and exercise demonstrates synergistic potential in treating AD. Both resveratrol and luteolin, two distinct types of natural products, have been confirmed to possess neuroprotective effects and can modulate autophagy pathways relevant to AD. Treatment of AD model mice with either of the two natural products and exercise exerted effects superior to individual interventions. This combined strategy more significantly improves cognitive function, alleviates neuroinflammation and reduces abnormal Aβ deposition.

In summary, the combined application of exercise and natural products coordinated the regulation of autophagy processes and pathological protein metabolism through multiple targets and multiple pathways, and provides a promising intervention strategy for preventing and treating AD. This combined protocol enhances the autophagy-mediated neuroprotective cascade response, simultaneously targeting multiple nodes of AD pathology, from the activation of upstream signaling pathways to the clearance of downstream pathological substrates, thereby avoiding the inherent limitations of single-target interventions and achieving greater systemic intervention efficacy.

7. Conclusions and outlook

AD is a devastating neurodegenerative disorder with no curative treatments. Autophagy dysfunction is a key pathogenic driver underlying the accumulation of neurotoxic Aβ aggregates, p-tau, neuronal loss and synaptic impairment. The present review systematically highlights current evidence

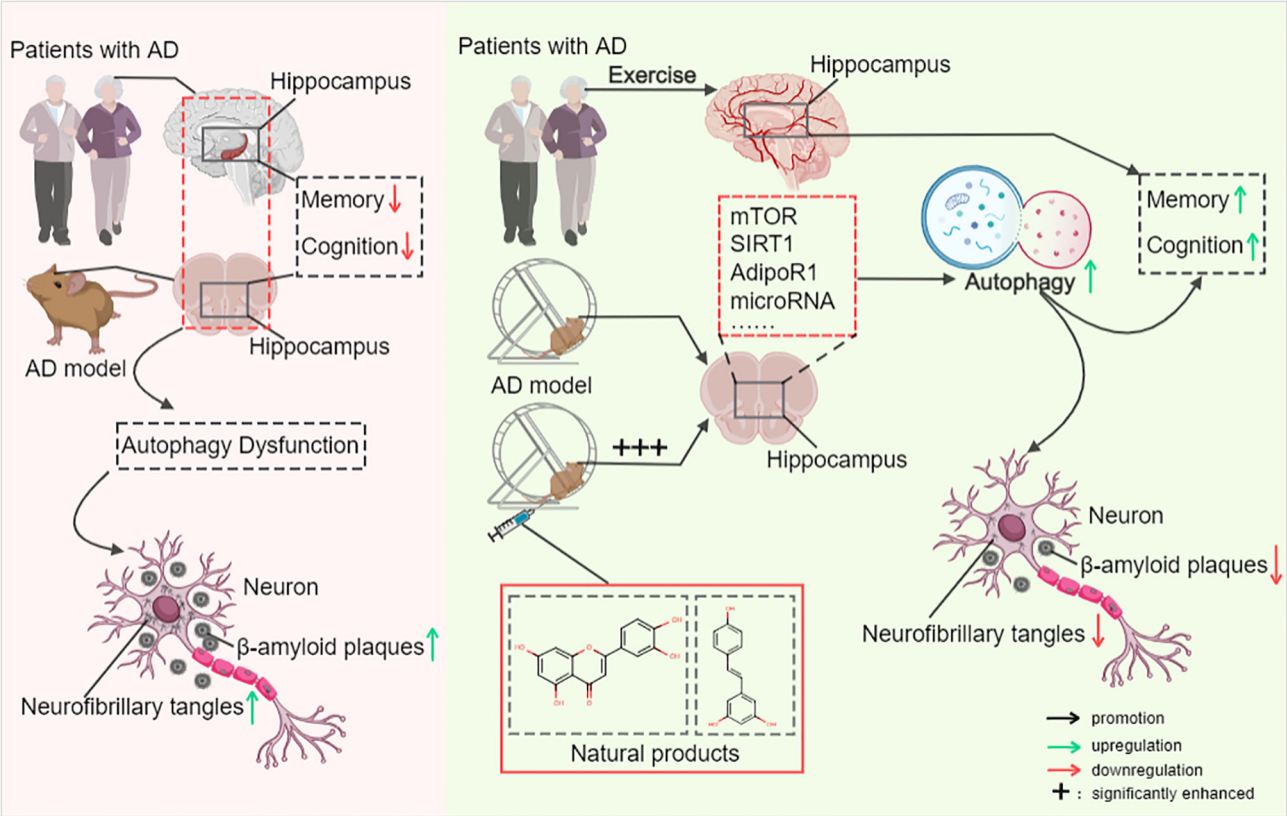

Figure 5. A visual summary of the core content of the present review. In patients with AD and preclinical models of AD, autophagy dysfunction in hippocampal neurons leads to the accumulation of Aβ plaques and neurofibrillary tangles, resulting in severe memory and cognitive impairments. Exercise intervention modulates key molecular regulators, such as mTOR, SIRT1, AdipoR1 and microRNAs, to enhance autophagic flux in the hippocampus. This process alleviates the pathological burden of Aβ plaques and neurofibrillary tangles, consequently restoring impaired memory and cognitive function. Additionally, the combination of exercise and natural products significantly potentiates the favorable regulatory effects on autophagic flux, enhancing autophagy-mediated neuroprotective outcomes in AD. AD, Alzheimer's disease; mTOR, mammalian target of rapamycin; SIRT1, sirtuin 1; AdipoR1, adiponectin receptor 1.

demonstrating that mild-to-moderate intensity physical exercise represents a safe, cost-effective and multi-targeted non-pharmacological intervention for AD (Table I; Fig. 5). Specifically, exercise restores impaired autophagic flux in AD by modulating core signaling pathways (mTOR, SIRT1 and AdipoR1), regulating miRNAs such as miR-34a and miR-130a, and upregulating irisin. These regulatory effects collectively enhance autophagosome biogenesis, improve lysosomal function and promote autophagosome-lysosome fusion, thereby facilitating the clearance of Aβ and p-tau, alleviating neuroinflammation and mitochondrial dysfunction, and ultimately ameliorating cognitive deficits in both preclinical AD models and clinical settings. Additionally, combining exercise with natural products (e.g., resveratrol and luteolin) exerts synergistic neuroprotective effects by enhancing autophagy-mediated clearance of pathological proteins, highlighting a promising multi-modal intervention strategy for AD.

Despite this valuable insight, this review has several specific limitations that warrant acknowledgment. First, while the roles of key signaling pathways (mTOR, SIRT1 and AdipoR1) in exercise-mediated autophagy regulation are summarized, molecular crosstalk among these pathways (e.g., the AMPK-mTOR-SIRT1 regulatory axis) remains incompletely elucidated, and how exercise coordinates these interconnected networks to fine-tune autophagic flux demands the further integration of multi-omics data. Second, this review did not address the potential regulation of non-canonical autophagic pathways (e.g., LAP and LANDO) through exercise due to limited existing experimental evidence. These pathways have been implicated in AD pathology but remain a critical knowledge gap in the field. Third, the miRNA regulatory network underlying exercise-induced autophagy restoration remains incompletely understood, with only a handful of miRNAs (e.g., miR-34a and miR-130a) characterized, and interactions between miRNAs and irisin/FNDC5 in AD remain largely unvalidated. Fourth, preclinical studies on combinations of exercise and natural products are scope-limited, and data on the optimization of key parameters are lacking, including natural product dosage, exercise intensity and intervention timing (e.g., pre- or post-exercise supplementation), which hinders the translation of these synergistic effects into clinical practice. Finally, the current evidence is predominantly derived from rodent models, and the generalizability of these mechanisms to human AD populations, particularly across different disease stages and genetic backgrounds, remains to be fully established.

Future research should focus on novel, practical and translationally relevant directions to address these gaps and advance the field. Leveraging single-cell RNA sequencing and spatial metabolomics to dissect cell-type-specific mechanisms of exercise-regulated autophagy (e.g., in neurons, microglia and astrocytes) will yield unprecedented insight into cell-cell communication networks underlying neuroprotection. High-throughput

Table I. Summary of the model characteristics and experimental findings in AD studies associated with exercise.

Authors, year	Age	Protocol	Duration	Model	Effects	Mechanism	(Refs.)
Kang and Cho, 2015	18 weeks	Treadmill, 50 min/day, 5 days/week	12 weeks	NSE/htau23	GSK-3β↓, p-tau↓	mTOR signaling	(94)
Li *et al*, 2021	4 weeks	Treadmill, 5 days/week	8 weeks	T2DM	p62↓, beclin-1↑, LC3-II/LC3-I↑	mTOR signaling	(78)
Wu *et al*, 2024	8 months	Treadmill, 40 min/day, 5 days/week	12 weeks	APP/PS1	Aβ↓, VMA21↑	mTOR signaling	(71)
Zhao *et al*, 2023	3 months	Treadmill, 45 min/day, 5 days/week	12 weeks	APP/PS1	PINK1↓, Parkin↑, LC3-II/LC3-I↑, p62↓	SIRT1-FOXO1/3 signaling	(106)
Jian *et al*, 2022	8 weeks	Treadmill, 45 min/day, 5 days/week	12 weeks	APP/PS1	Aβ↓, Bcl-2/Bax↓, adipoR1↑, beclin-1↑, p62↓	AdipoR1 signaling	(115)
Shen *et al*, 2021	21 months	Voluntary wheel running, 24 h	8 weeks	SD (aging)	miR-130a↑, miR-125b↑, LC3-II/LC3-I↑, ATG7↑, p62↓	miR-130a-mediated	(96)
Kou *et al*, 2017	8 weeks	Swimming, 90 min/day	6 weeks	SD (D-gal)	PGC-1α↑, LC3↑, BECN1↑, ATG7↑, p62↓, miR-34a↑	miR-34a-mediated	(122)

↑, upregulation; ↓, downregulation. Aβ, amyloid β-protein; APP, amyloid precursor protein; AdipoR1, adiponectin receptor 1; ATG7, autophagy-associated protein 7; BECN1, beclin-1; Bcl-2, b-cell lymphoma 2; Bax, bcl-2-associated x protein; D-gal, D-galactose; FOXO1/3, forkhead box O1/3; GSK-3β, glycogen synthase kinase-3β; LC3, microtubule-associated protein 1 light chain 3; LC3-II, microtubule-associated protein 1 light chain 3-II; LC3-I, microtubule-associated protein 1 light chain 3-I; mTOR, mammalian target of rapamycin; miR, microRNA; NSE/htau23, neuron-specific enolase/human tau23; PS1, presenilin 1; p-tau, hyperphosphorylated tau; PINK1, PTEN-induced kinase 1; Parkin, parkin E3 ubiquitin ligase; PGC-1α, PPARγ coactivator-1α; p62, sequestosome 1; SIRT1, sirtuin 1; SD, standard deviation; T2DM, type 2 diabetes mellitus; ULK, UNC 51-like kinase; VMA21, vacuolar ATPase assembly factor VMA21.

CRISPR screening can identify uncharacterized miRNAs or long non-coding RNAs that link exercise and autophagy regulation, facilitating the development of targeted nucleic acid-based therapeutics (e.g., miRNA mimics or inhibitors) for combination with exercise interventions. Large-scale stratified clinical trials are urgently needed to establish personalized exercise prescriptions, using peripheral biomarkers (e.g., serum irisin and TFEB) to tailor exercise intensity, duration and modality for individual patients with AD or high-risk populations. Integrating network pharmacology and *in vitro* high-throughput assays to identify shared molecular targets of natural products and exercise (e.g., the AMPK-SIRT1-TFEB axis) will expedite the development of combination preclinical strategies with optimized synergistic efficacy. In addition, genetically engineered AD mouse models will clarify the role of non-canonical autophagy (e.g., LAP and LANDO) in exercise-mediated neuroprotection, filling a critical knowledge gap in the current literature. Finally, exploring the long-term sustainability of exercise-induced autophagy restoration and its impact on AD progression (e.g., delaying conversion from mild cognitive impairment to clinical AD) will provide critical evidence to support the integration of exercise into routine clinical care.

In summary, exercise is a potent intervention to counteract autophagy dysfunction in AD, supported by preclinical and clinical evidence of its neuroprotective effects. Addressing the aforementioned limitations and pursuing innovative, translationally focused research directions will further unravel the mechanistic complexity of exercise-autophagy crosstalk and enable the development of more effective, personalized strategies for AD prevention and management. Given the current challenges in AD drug development, integrating exercise alone or its combination with natural products into clinical practice holds considerable theoretical significance and potential for improving patient outcomes.

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Authors' contributions

WL and WW conducted the literature search, drafted the manuscript and prepared the figures. YS, XL and YL drafted, edited and revised the manuscript. XW and TT contributed to figure design and edited the manuscript. XH and LZ commented on and edited the manuscript, and provided substantial improvements. All authors have read and approved the final manuscript. Data authentication is not applicable.

Availability of data and materials

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Ethics approval and consent to participate

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Patient consent for publication

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Competing interest

The authors declare that they have no competing interests.

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