Cellular and Molecular Neurobiology (2025) 45:43
https://doi.org/10.1007/s10571-025-01559-9

REVIEW PAPER

Let-7 Family as a Mediator of Exercise on Alzheimer's Disease

Shanbin Ke[1] · Zhengqiong Liu[1] · Yuwen Wan[2]

Received: 28 February 2025 / Accepted: 28 April 2025

Abstract
Memory loss, and behavioral impairments. Hallmark pathological features include amyloid-beta (Aβ) plaques, tau neurofibrillary tangles, chronic inflammation, and impaired neuronal signaling. Physical exercise is increasingly recognized as a non-pharmacological intervention to attenuate Alzheimer's disease (AD) risk and progression by enhancing neuroplasticity, improving mitochondrial function, and modulating immune responses. The let-7 family of microRNAs is critically involved in AD pathology. Elevated levels of let-7b and let-7e have been reported in the cerebrospinal fluid of AD patients, with let-7b levels correlating positively with total tau and phosphorylated tau concentrations. Overexpression of let-7a enhances Aβ-induced neurotoxicity, increases neuronal apoptosis by up to 45%, and alters autophagy-related signaling via the PI3K/Akt/mTOR pathway, as shown by 1.8-fold increases in LC3-II/I ratios and 2.2-fold upregulation of Beclin-1 expression. Exercise modulates let-7 expression in a tissue-specific and context-dependent manner. Aerobic training reduces skeletal muscle expression of let-7b-5p by 30–35%, while increasing its suppressor Lin28a by 40%, thereby improving mitochondrial respiration. Overall, modulation of let-7 by exercise influences neuronal survival, autophagy, and inflammation, offering a potential mechanism through which physical activity exerts neuroprotective effects in AD. Quantitative characterization of let-7 expression patterns may support its use as a diagnostic and therapeutic biomarker, though further research is needed to establish optimal modulation strategies.

Keywords Exercise · Alzheimer's disease · Let-7 · MicroRNAs

Introduction

Alzheimer's disease (AD) is responsible for the many cognitive decline and dementia in people over the age of 65 worldwide (Atri 2019). AD is marked by a slow and steady advancement, beginning with alterations in the brain structure of those impacted that take place well in advance of any noticeable indications or manifestations (Jack et al. 2013). The negative impact on the body is caused by several changes, like the accumulation of destructive variants of Aβ, the formation of clusters of hyperphosphorylated tau protein called neurofibrillary tangles, and the decline of nerve cells due to uncontrolled activation of microglia in the brain. This results in the secretion of toxic substances that harm neurons and cause inflammation (Scheltens et al. 2016; Španić et al. 2019; Li et al. 2022). People who have these changes in their body may not show any symptoms, or they could experience a range of clinical signs, from minor memory gaps to intense and incapacitating impairment of memory and cognitive abilities (Jack et al. 2013). As AD continues to develop, individuals may experience more neuropsychiatric symptoms such as disorientation, aggression or agitation, confusion, mood swings, and ultimately delusions or hallucinations in advanced stages. The number AD patients is already substantial, and it is expected to rise as the population grows older (Montgomery et al. 2018; Asada 2017; Alzheimer's Association 2020). Based on various research findings, it can be concluded that approximately 3 to 4 percent of individuals in their later working or retired years' experience the impacts of AD dementia(Takizawa et al. 2015; Niu et al. 2017; Fiest et al. 2016).

✉ Yuwen Wan
1084922924@qq.com

Shanbin Ke
1049033551@qq.com

Zhengqiong Liu
274992385@qq.com

[1] College of Education, Jiangxi Institute of Applied Science and Technology, Nanchang 330100, China

[2] College of Education, Jiangxi Institute of Applied Science and Technology, Nanchang 330100, China

Published online: 19 May 2025

In 2016, adults in high-income countries had a significantly higher rate of low physical activity (36.8%) than those in low-income countries (16.2%). This gap is even more prominent when examining gender discrepancies, as women were found to be less active than men, particularly in the United States and Eastern Mediterranean regions (Spanoudaki et al. 2023). Studies have revealed that participating in physical exercise can significantly decline the risk of AD progression and dementia, regardless of the intensity level (Smith et al. 2010; Hamer and Chida 2009; Erickson et al. 2009; Yaffe et al. 2001). Participating in exercise can decrease the occurrence of AD and dementia, leading experts to suggest it as a lifestyle intervention. Evidence from past research provides support for this idea, with one study finding that up to 54% of risk factors for AD could potentially be prevented through exercise (Barnes and Yaffe 2011). A different research report calculated the potential demographic threat of worldwide AD, taking into account seven modifiable risk factors through the use of relative risks from previous meta-analyses (Norton et al. 2014). In the elderly population, a correlation was found between increased sedentary activities and a greater likelihood of developing all forms of dementia. Further investigation is necessary to establish if there is a direct causation between a sedentary lifestyle and susceptibility to developing dementia (Raichlen et al. 2023).

A newly investigated area of study, specifically looking at the immediate effects of exercise on bodily functions, revolves around miRNAs. These molecules, comprised around 22 nucleotides, occur naturally in the body (Furer et al. 2010). There have been over 2000 miRNAs discovered in the human genome (Alles et al. 2019), and they have significant functions in numerous biological processes, including but not limited to multiplication, cell growth, chemical reactions, specialization, and apoptosis (Xiao and Rajewsky 2009). They hinder the expression of target genes by breaking down mRNA and subsequently inhibiting the translation process that converts mRNA into a usable protein (Churov et al. 2015). Moreover, it is predicted that they make up approximately 1 to 2 percent of the entire genome and have the ability to control 30 percent of genes responsible for producing proteins (Furer et al. 2010). The alterations in miRNA levels caused by physical activity are believed to control long-term modifications in skeletal muscle, aerobic capacity, and cardiovascular well-being (Silva et al. 2017; Zhou et al. 2020). The let-7 family, composed of various miRNAs, could potentially serve as valuable biomarkers for designing optimal exercise plans to promote overall health and enhance physical performance. The functions of these miRNAs are quite diverse in neural growth, adaptability, and protection against damage. Through their regulation by exercise, they impact vital signaling pathways related to brain well-being and the improvement of performance (Shamsuzzama et al. 2016b; Patterson et al. 2014; Lehmann et al. 2012). Disruption of the normal function of let-7 has been linked with impairment in cognitive abilities and neuroinflammation, indicating that engaging in physical activity may help regulate let-7 and potentially reduce these negative outcomes (Shamsuzzama et al. 2016b; Patterson et al. 2014; Lehmann et al. 2012). let-7 inhibits mTOR pathway activity, which is critical for autophagy regulation. Reduced autophagy leads to accumulation of toxic protein aggregates, a hallmark of neurodegenerative diseases like Alzheimer's, Parkinson's (PD), and Huntington's (HD) (Wang et al. 2022; Petri et al. 2017). Elevated let-7 in cerebrospinal fluid (CSF) of PD patients is transported via exosomes. Neuronal uptake of exosomal let-7 activates toll-like receptor 7 (TLR7), triggering neuroinflammation and degeneration (Shaheen et al. 2024). Let-7 family members, especially let-7b, can act as signaling molecules for Toll-like receptor 7 (TLR7), initiating innate immune pathways and apoptosis in the central nervous system. In vitro studies have shown that extracellular let-7b and let-7e can mediate neuronal injury, with let-7b causing significant axonal and dendritic damage as well as neuronal loss (Derkow et al. 2018a, b). Let-7 family members, particularly let-7a, have been shown to exacerbate Aβ1–40-induced neurotoxicity and apoptosis in neuronal cell models (Gu et al. 2017).

Although numerous studies have explored the roles of microRNAs in Alzheimer's disease and the benefits of physical exercise on brain health, the specific interplay between exercise-induced modulation of the let-7 miRNA family and its implications for AD progression remains underexplored. Current literature often examines let-7 in isolated cellular or animal models without integrating its dual role across different physiological contexts or evaluating its clinical potential. Moreover, few reviews address how exercise might differentially regulate let-7 expression depending on variables such as age, sex, or disease stage. This review fills a critical gap by synthesizing evidence on how physical activity influences let-7 expression and how this, in turn, impacts key AD-related pathways including inflammation, autophagy, and neuronal survival. By integrating molecular, mechanistic, and emerging translational findings, this paper provides a comprehensive and forward-looking perspective on the potential of targeting let-7 through personalized lifestyle interventions as part of AD prevention or management strategies.

Exercise and Alzheimer's Disease

Alzheimer's Disease Pathogenesis

AD is a progressive neurological condition that deteriorates with time and currently stands as the leading contributor

to dementia worldwide (Better 2023; Avan and Hachinski 2021). AD is a condition marked by changes in cognitive abilities, loss of memory, and altered behavior. The progress of this disease is intricate and impacted by a multitude of elements such as heredity, environment, and individual behaviors. Vital components in its advancement consist of the accumulation of Aβ plaques, twisted NFTs made up of hyperphosphorylated tau protein, continuous neuroinflammation, and eventual harm to nerve cells (Sun et al. 2024; Kok et al. 2022).

The theory of the amyloid-beta cascade is still a fundamental concept for comprehending the progression of AD. Aβ peptides are produced from the breakdown of the APP by BACE1 and γ-secretase enzymes. This production results in fragments of Aβ, with Aβ42 being highly susceptible to clumping together (O'Brien and Wong 2011; Pfundstein et al. 2022). In AD, a lack of equilibrium between the generation and removal of Aβ results in its buildup within the brain, creating destructive oligomers, plaques, and fibrils (Gandy 2005; Selkoe 2001). The Aβ oligomers have a harmful impact on the nervous system, as they interfere with NMDA receptor activity and trigger excitotoxicity, leading to impaired synaptic communication (Babaei 2021; Snyder et al. 2005). Moreover, they cause a condition of neuroinflammation where stimulated astrocytes and microglia release inflammatory signaling molecules, exacerbating harm to neurons. Additionally, Aβ contributes to oxidative stress by hindering mitochondrial function, resulting in an abundance of ROS and causing more harm to neurons (Ganguly et al. 2021; Thakur et al. 2023). Another critical feature of AD pathology is the formation of NFTs, which consist of hyperphosphorylated tau protein (Hondius et al. 2021; Moloney et al. 2021). Tau is an essential protein that preserves the structural integrity of microtubules in nerve cells (Wu et al. 2016). In AD, tau undergoes an abnormal process of phosphorylation, causing it to lose its capability to efficiently attach to microtubules (Rawat et al. 2022). The destabilization of the cytoskeletal structure has a notable effect on axonal transport and disrupts the functioning of neurons. The accumulation of hyperphosphorylated tau leads to the formation of NFTs, which harm neurons through toxic mechanisms that cause an increase in function, such as interfering with protein degradation pathways and mitochondrial activity. It is important to emphasize that there is a remarkable connection between tau pathology and the degree of cognitive decline in AD, underscoring its pivotal role in the progression of the condition (Desai et al. 2021; Rabin et al. 2022). In the development of AD, neuroinflammation has an important part and is frequently triggered by the accumulation of Aβ (Thakur et al. 2023; Onyango et al. 2021). The microglia, attempt to remove Aβ by engulfing it, but this process can lead to continuous activation. This ongoing activation causes the release of inflammatory substances that damage neurons and exacerbate the accumulation of Aβ and tau abnormalities (Leng and Edison 2021; Thakur et al. 2023). Astrocytes can create an inflammatory environment, which ultimately intensifies the progression of neurodegeneration (Singh 2022; Di Benedetto et al. 2022). As time passes, persistent inflammation causes the breakdown of the protective barrier between the blood and brain, making it easier for immune cells from outside the brain to enter and worsening the process of nerve cell deterioration (Lee and Funk 2023).

Another important factor in AD progression is brain insulin resistance which impairs insulin signaling pathways, leading to decreased glucose utilization and disrupted energy metabolism. Insulin resistance causes downregulation of insulin receptors and insulin-degrading enzyme (IDE), exacerbating amyloid-β accumulation (Wei et al. 2021). Insulin resistance activates microglia, triggering inflammation and increased production of pro-inflammatory cytokines (IL-6, IL-1β, TNF) (Wei et al. 2021). Recent evidence suggests that reduced biliverdin reductase-A (BVR-A) impairs GSK3β phosphorylation, causing mitochondrial dysfunction and exacerbating brain insulin resistance in both T2DM and AD (Chen et al. 2024).

A key characteristic of AD is synaptic dysfunction, which can decline cognitive abilities gradually (Pelucchi et al. 2022). The existence of Aβ oligomers has a damaging effect on synaptic plasticity by disrupting the normal operation of NMDA and AMPA receptors, causing a hindrance in LTP, which is a crucial mechanism for acquiring new knowledge and retaining memories (Ruiz-Pérez et al. 2021; Zhang et al. 2022; John and Reddy 2021). Moreover, in AD, the presence of tau pathology is strongly linked to a remarkable decrease in dendritic spines, which are responsible for transmitting signals between neurons (Tzioras et al. 2023).

The development of Alzheimer's disease (AD) involves a combination of genetic factors and environmental influences. Changes in the genes PSEN2, PSEN1, and APP, pivotal components of γ-secretase, are associated with the emergence of familial AD at an early age (Xiao et al. 2021). These mutations lead to increased production of Aβ42, promoting its aggregation (Rostagno 2022; Course et al. 2023; Xiao et al. 2023). The APOE ε4 allele involves in the progression of late-onset AD, by aiding in the removal of Aβ and promoting its accumulation (Raulin et al. 2022). Environmental elements, including lack of physical activity, cardiovascular illness, and metabolic issues, also can increase the likelihood of developing AD by intensifying neuroinflammation and oxidative stress pathways (Leszek et al. 2021; Ezkurdia et al. 2023; López-Ortiz et al. 2021).

Exercise Impact on Alzheimer's Disease

Participating in consistent physical exercise has been scientifically demonstrated to lower the chances of experiencing AD and can also assist in controlling the disorder. Studies propose that frequently engaging in physical activity can diminish the likelihood of acquiring dementia and prolong the deterioration of cognitive abilities (De la Rosa et al. 2020). Smith et al. conducted a thorough examination of RCT spanning from 1966 to 2009, exploring the link between cognitive function and exercise (Smith et al. 2010). The researchers carefully selected studies with significant impact, which involved closely monitored aerobic exercise interventions and comparison groups. The study found that the exercise group showed processing speed, improvements in attention, memory, and executive function. However, there was some variation in the impact on working memory, possibly due to the intensity and length of the exercise. As previously mentioned, individuals with dementia often experience deterioration of the hippocampus. Erikson and his team conducted research on this topic (Erickson et al. 2009) examined the connection between exercise and the hippocampus, as they proved that it is a successful method for reducing cortical deterioration in older individuals. Through MRI scans of 165 elderly individuals without dementia, it was discovered that those who were physically active had better overall health, larger hippocampal volume, and improved spatial memory. Long-term studies in Germany showed that regular exercise can lower the risk of cognitive decline and dementia, as well as improve performance on neuropsychological tests (Sattler et al. 2011). A different study investigated the theory that accurately measuring daily activities could predict the occurrence of MCI and AD (Buchman et al. 2012). Participants used wrist activity monitors instead of self-reported questionnaires to accurately monitor their physical activity. The findings indicated a link between regular exercise and the progression of overall cognitive decline as well as AD after a 4-year monitoring period. The statistics indicated that people who participated in more intense physical activity had a significantly reduced risk of AD progression. Additionally, an 8-year study on women demonstrated that those who engaged in regular walking experienced less deterioration in cognitive abilities over the entire duration of the investigation (Yaffe et al. 2001). The Cochrane study focused on the impact of aerobic exercise on the cognitive functioning of older adults who did not have any mental health problems. The main objective was to assess the relationship between cardiovascular health and the effect of exercise on cognition (Forbes et al. 2015). Their main goal was to incorporate studies that have proven a positive impact on cardiovascular well-being by conducting a VO2 max assessment. However, their results did not reveal any indication of exercise improving cognitive function, and the studies they examined were deemed to have a significant possibility of prejudice (Forbes et al. 2015). It is important to note that their remarks do not take into account research that does not involve cardiovascular health, such as light aerobic exercise, stretching, or weightlifting. Incorporating tests for VO2 max or other indicators of heart health, our research indicates that caution should be exercised when interpreting these findings for a specific population. Furthermore, multiple reviews and analyses have revealed the positive impact of physical activity on cognitive function (Farina et al. 2014).

A study with randomized and controlled elements was created in order to address these concerns by examining the potential effects of exercise regimens on the decrease of daily functional abilities in individuals with AD (Rolland et al. 2007). Following a 12-month program involving two weekly workouts focused on enhancing strength, balance, and flexibility, individuals demonstrated reduced proficiency in everyday tasks compared to those who did not participate in physical exercise. Nonetheless, there was no observable effect on behavioral problems, mood disorders, or dietary habits. In a distinct investigation, scientists sought to assess the impacts of medication and physical activity on AD and mild cognitive impairment (Ströhle et al. 2015). The research permitted the inclusion of either pharmacological or exercise treatment as the experimental group. In terms of AD, exercise showed a moderate to significant overall effect, while only having a minor impact on MCI. On the other hand, using a cholinesterase inhibitor as a treatment option for AD had a minimal effect on cognition, but did not show any improvement in MCI. It should be noted that there is a high rate of discontinuation with drug therapy, whereas the exercise group has a significantly lower rate. Furthermore, meta-analyses and systematic reviews of information from multiple sources have consistently shown that exercise can lead to favorable results in individuals with dementia, including a decrease in neuropsychiatric symptoms and a minor decrease in their daily living activities (Smith et al. 2010; Hamer and Chida 2009; Forbes et al. 2015). A comprehensive analysis revealed that exercise resulted in fewer adverse reactions and higher adherence rates compared to medications (Ströhle et al. 2015). Physical activity has inherent advantages for both cardiovascular well-being and individual health. However, due to the limited evidence, it is challenging to recommend particular exercises for individuals with AD or for reducing the risk of developing it. The research on exercise and its effects on AD involves a variety of types of physical activity, which are determined by the length of time they are implemented.

An RCT is done to examine how moderate to high-intensity aerobic exercise programs impact individuals with mild AD (Hoffmann et al. 2016). The participants in this study engaged in a 60-min training session three times per week

for a total of 16 weeks. However, there was no observed improvement in cognitive ability, although there was a significant improvement in neuropsychiatric symptoms. The study focused on individuals who followed the training program, but it is worth noting that many studies tend to use intentional treatment models. Longer intervention studies may also face challenges with maintaining compliance over time, which raises questions about the reliability of observation support. In a separate 3-month randomized study, participants were supervised during their exercise program three times per week (Chapman et al. 2013). While training, they noticed enhancements in delayed and immediate memory. Resting, physically active individuals had increased blood flow in the anterior cingulate region. However, results from participants with Alzheimer's cannot be compared directly to those with regular cognitive function. Another study with eight individuals with mild cognitive impairment also completed a 9-month exercise intervention and 2-month training program (Sacco et al. 2016). The Cochrane study looked at the effect of exercise on people with AD and determined that although it improved their cognitive abilities, its overall impact was reduced by training interruptions (Forbes et al. 2015). Following a thorough examination, it was concluded that there is insufficient proof to substantiate the notion that exercise has a favorable effect on cognitive abilities. Nonetheless, the exercises did demonstrate some enhancements in the capacity to carry out routine tasks. It is important to acknowledge that the studies and results gathered by the researchers were varied and lacked quality due to limited evidence. The suggestion is to perform more stringent experimentation in order to assess varying forms and severities of dementia, ultimately improving the dependability of assessments (Forbes et al. 2015). In conclusion, through numerous thorough assessments and their respective results, it has been shown that a limited amount of six RCTs have demonstrated the effectiveness of exercise programs for those with AD (Farina et al. 2014). Farina et al. A study showed a reduction in cognitive decline and a positive impact on overall cognitive ability (Farina et al. 2014).

Let7 Family

Biogenesis and Mechanisms of the Action of miRNAs

The process of generating miRNA involves altering the transcripts of RNA polymerase II/III, which can occur during or after transcription (Ha and Kim 2014). Roughly half of the currently recognized miRNAs originate from within genes, primarily from introns, with a smaller number from protein-coding exons. The remainder lies between genes, undergoes its own transcription, and is controlled by distinct promoters (Kim and Kim 2007; de Rie et al. 2017). Sometimes, miRNAs are formed as clusters where these collections may have similar seed regions and, therefore, are classified as a group (Tanzer and Stadler 2004). There are two main pathways involved in the formation of miRNA, referred to as non-canonical and canonical. The predominant process for miRNA production is the canonical pathway, which entails the creation of pri-miRNAs from designated genes. The microprocessor, made up of Drosha and DGCR8, enzymes that belong to the ribonuclease III family, processes these pri-miRNAs (Denli et al. 2004). DGCR8 identifies certain patterns, such as N6-methyladenylated GGAC sequences, on the pri-miRNA. Drosha then cuts the hairpin structure at its base, creating pre-miRNAs with a 2-nucleotide overhang at the 3'end. XPO5 and the RanGTP complex transport these pre-miRNAs to the cytoplasm, where Dicer removes the terminal loop and forms a mature miRNA duplex (O'Brien et al. 2018; Han et al. 2004; Alarcón et al. 2015; Denli et al. 2004).

The two parts of the double-stranded structure, 5p and 3p, are designated according to where they come from on the pre-miRNA hairpin, either the 5′ or 3′ end. These strands are inserted into AGO proteins, and the guide strand, usually the one with less stability at the 5′ end or a uracil at that position, is chosen to stay. The other strand is separated and broken down, either by AGO2 cutting it or naturally when there are mismatches in the middle (Khvorova et al. 2003; O'Brien et al. 2018).

Apart from the traditional pathway, there are several alternative ways in which miRNA can be produced, utilizing elements of the traditional pathway in distinct combinations. These non-traditional pathways can be divided into two types: those that do not require Drosha and DGCR8, and those that do not involve Dicer (O'Brien et al. 2018).

In pathways that do not involve Drosha and DGCR8, pre-miRNAs are formed directly from spliced introns, referred to as mirtrons, or from transcripts with a 7-methylguanosine (m7G) cap. These pre-miRNAs do not undergo cleavage by Drosha and are instead transported to the cytoplasm through exportin 1. The presence of an m7G cap can lead to a preference for the 3p strand, as it prevents loading of the 5p strand into AGO proteins (Xie et al. 2013; Ruby et al. 2007).

In pathways that do not involve Dicer, Drosha is responsible for converting endogenous shRNAs into pre-miRNAs. However, these pre-miRNAs are too brief to be cleaved by Dicer. Instead, they are inserted into AGO2 and undergo further maturation through the slicing of the 3p strand and trimming of the 5p strand, which is dependent on AGO2 (Cheloufi et al. 2010; Yang et al. 2010).

MiRNAs regulate gene expression by utilizing multiple methods including inhibiting translation, breaking down mRNA, and controlling transcription. Most studies suggest that miRNAs attach to specific sections in the 3′ UTR of target mRNAs, causing a block in translation and leading

to the breakdown of the mRNA (Ipsaro and Joshua-Tor 2015; Huntzinger and Izaurralde 2011). miRNAs can bind to different regions of mRNAs, including the 5′ untranslated region (UTR), coding sequences, and promoter regions. While binding to the 5′ UTR or coding regions typically suppresses gene expression, interaction with promoter regions may lead to gene activation (Zhang et al. 2018; Dharap et al. 2013).

Although the majority of research is centered on miRNAs causing gene silencing, it should be noted that miRNAs can also trigger gene expression in certain circumstances (O'Brien et al. 2018). AGO2 and FXR1 have been observed to interact with AREs located in the 3′ UTR during periods of serum starvation or cell cycle arrest. This interaction results in the activation of translation, specifically with miRNAs like let-7. Unlike in actively dividing cells where GW182 plays a key role, non-dividing cells rely on AGO2 and FXR1 for the promotion of translation via miRNA involvement (Truesdell et al. 2012; Vasudevan and Steitz 2007). Moreover, in situations of low amino acid levels, miRNAs have been proven to boost protein production by binding to the 5′ UTR of specific mRNAs that code for ribosomal proteins (Ørom et al. 2008). miRNAs can operate in the nucleus by utilizing AGO2, which moves back and forth between the nucleus and cytoplasm with the assistance of TNRC6 A, a protein from the GW182 family (Pitchiaya et al. 2017; Nishi et al. 2013). AGO2 and miRISC have been found to interact with active chromatin at gene loci, indicating potential functions in both post-transcriptional and co-transcriptional processes. In the nucleus, miRISC is able to facilitate mRNA degradation or directly control transcription by binding to promoter regions (Xiao et al. 2017; Havens et al. 2014).

Let7 Family Role in Health and Diseases

The initial miRNA, lin-4, was identified in 1993 within *C. elegans* (Lee et al. 1993). The discovery of Let-7, the second miRNA in *C. elegans*, also has an important part in regulating the development of the organism, along with lin-4 (Reinhart et al. 2000). Currently, there are over 2000 miRNAs discovered in humans (MiRBase 2013).

The let-7 family is composed of a total of 13 members which are found on 9 different chromosomes. These include let-7a-1, −7a-2, −7a-3, −7b, −7c, −7d, −7e, −7f-2, −7f-1, −7g, as well as the microRNAs mir-202 and mir-98 (Roush and Slack 2008). Certain ones are found in the genome as groups. For instance, let-7a-1, let-7f-1, and let-7 d are part of a cluster on chromosome 9q22.32, while let-7a-3 and let-7b are part of a cluster on chromosome 22q13.31 (Roush and Slack 2008).

Let-7 is typically upregulated during the final stages of development in many organisms, and any changes in its expression can result in various pathological disorders, including diabetes, neurodegenerative diseases, and cancer (Shamsuzzama et al. 2016a). Overexpressing miR-98 impairs phosphorylation and inhibits the ERK and Akt pathways, both known as contributors to cancer growth (Chen et al. 2014; Ning et al. 2017; Dai et al. 2016). Let-7 was discovered to directly decrease the aggressive characteristics of Ewing's sarcoma by targeting STAT3 (Zhang et al. 2016). The STAT3 pathway has a remarkable effect on cell cycle and survival by regulating a specific group of genes. If this pathway becomes excessively active, it can promote the progression of cancer. This can lead to unfavorable results and increased resistance to traditional cancer treatments such as chemotherapy and radiotherapy (Bosch-Barrera et al. 2017; Chirshev et al. 2019). Studies have revealed that Let-7 activates the WNT signaling pathway through binding to estrogen receptors in breast cancer and TCF-4 in HCC, leading to elevated cancer stem cell levels and aggression (Sun et al. 2016a, b). The WNT pathway is involved in various cellular activities, like cell growth, migration, and differentiation, tumor development, and generation of cancer stem cells (Jin et al. 2016; Sun et al. 2016a, b). According to the data, let-7 inhibits the aggressive phenotype by suppressing carcinogenic signaling pathways (Chirshev et al. 2019).

A recent study showed that a specific oligonucleotide, which targets let-7 in human cells, promotes cancer cell growth. This serves as additional evidence for the function of let-7 as a cancer inhibitor by impeding pathways associated with cellular growth (Johnson et al. 2007). Johnson et al. showed how let-7 plays a significant role in cancer by acting as a suppressor of tumors through inhibition of the let-60/RAS pathway (Johnson et al. 2005). Let-7 blocked the activity of various tumor-promoting genes, including RAS, PBX3, LIN28, E2 F1, E2 F5, ARID3B, Myc, HMGA2, and H19 (Wu et al. 2015; Liu et al. 2012). Experiments involving the use of specific ASOs demonstrated that reducing the expression of these genes resulted in the suppression of tumors, a process that typically relies on let-7 (Chirshev et al. 2019). Lan et al. suggested that let-7 acted as a tumor suppressor (Lan et al. 2011). Overproduction of let-7 g in HepG2 liver cancer cells decreased cell growth by suppressing the c-Myc oncogene. This was demonstrated by decreases in both mRNA and protein levels. This effect was reversed by introducing a let-7 g inhibitor via transfection (Lan et al. 2011). The increase of let-7 g also boosted the levels of p16INK4 A, a protein known for its tumor suppressing abilities. This suggests that the tumor suppressor role of let-7 g is likely attributed to its direct regulation of c-Myc in the regulatory axis involving Bmi-1 and p16 (Nobori et al. 1994; Gupta et al. 2014). The data indicate that let-7 g may function as a tumor suppressor in HCC by directly suppressing the c-Myc oncogene, resulting in elevated levels of p16INK4

A which has tumor inhibiting properties (Lan et al. 2011). Hence, let-7 can inhibit the activity of various factors associated with cancer development.

Despite being known as a tumor suppressor in many cancers, let-7 has also exhibited some cancer-promoting qualities. New research suggests that let-7 may act as an oncogene, contradicting its typical role as a tumor inhibitor. Analysis has revealed greater methylation of the let-7a3 gene in healthy tissue compared to lower levels in cancers like ovarian and lung cancer. Additionally, elevated levels of let-7a are observed in these particular cancer types (Lu et al. 2007; Brueckner et al. 2007; Chirshev et al. 2019). Brueckner and his team discovered that higher levels of let-7a3 caused a more aggressive behavior in detached lung cancer cells, possibly due to changes in the expression of growth factors and cell adhesion genes. This could lead to accelerated tumor growth and spread (Brueckner et al. 2007). Furthermore, increased levels of various members of the let-7 family, such as let-7a3, let-7c, and let-7b, were strongly linked to unfavorable outcomes and reduced survival rates among individuals diagnosed with ovarian and liver cancer (Chirshev et al. 2019). According to Ma et al., the heightened expression of let-7e in ESCC cells resulted in enhanced migration and invasion, potentially due to the suppression of ARID3a, a transcription factor that inhibits pluripotency. This downregulation may contribute to the development of cancer stemness (An et al. 2010; Ma et al. 2017). It is proved that the mir-98 member of the let-7 family can increase cancer cell resistance to chemotherapy by suppressing Dicer1 and thus inhibiting mir-152. In EOC patients, high levels of miR-98 and mir-152 are linked to regulation of RAD51 recombinase, which is associated with unfavorable outcomes (Wang et al. 2018; Chirshev et al. 2019). In conclusion, the research indicates the intricate connection between cancer cell aggression and let-7, emphasizing the impact of various miRNAs. Each cancer cell may have a unique set of genes regulated by let-7. This family of miRNAs efficiently and directly controls the activity of H-RAS, K-RAS, and N-RAS genes through their 3′UTR sequences (Khodayari et al. 2011; Büssing et al. 2008; Yu et al. 2011). A single miRNA can control numerous signaling pathways by binding to a wide range of target genes. For example, let-7 plays a significant role in reducing GBM tumor growth by binding with Stat3, Cyclin D1, Ras, and c-Myc (Degrauwe et al. 2016; Wang et al. 2013; Xu et al. 2016). The LIN28 protein can inhibit the function of mature let-7, leading to decreased survival rates in glioma patients. Additionally, let-7b can be used as an indicator for resistance to chemotherapy (Guo et al. 2013; Evers et al. 2023). The presence of let-7 in irradiated human glioblastoma cells was found to influence their response to radiotherapy through the regulation of its relative expression (Chaudhry et al. 2010). The significant decrease in let-7 leads to increased expression of cancer-promoting targets, such as RAS, in both gain-of-function and loss-of-function studies (Stainthorp et al. 2023).

The initial response of the body's immune system is triggered when any form of pathogen invades, effectively distinguishing between microbial and host cells (Brubaker et al. 2015). TLRs can detect foreign pathogens and trigger inflammatory responses that activate tailored adaptive reactions to various infections. Inflammatory conditions, including cancer, may arise due to disruptions in TLR signaling pathways that lead to increased inflammation (Mukherjee et al. 2019). Many miRNAs have been recognized as key regulators of TLR signaling pathways (He et al. 2014; Olivieri et al. 2013). Let-7 seems to regulate TLR4 signaling. This was evident when let-7i expression decreased and TLR4 signaling increased following infection with *C. parvum* (Chen et al. 2007). Let-7i's role in regulating host immune responses through TLR4 was discovered. Another study connected let-7b to TLR4 activation during Helicobacter pylori infection. TLR4 controls NF-κB activation and the regulation of certain inflammatory genes. By targeting TLR4 mRNA, Let-7 inhibits translation and decreases the inflammation and innate immune response after infection (Kumar et al. 2015).

The role of Let-7 extends to adaptive immune cells, where it plays a crucial role. The expression level of let-7 significantly affects the development of effector CD8 T cells, which are essential for cytokine release and the destruction of infected target cells. Additionally, let-7 plays a role in thymocyte differentiation, influencing whether they become naive or memory-like CD8 + CTLs. In active CTLs, reduced levels of let-7 promote clonal expansion and enhance efficiency by inhibiting its target genes, Myc and Eomes (Wells et al. 2017). The activity of the PLZF transcription factor, which contributes to the development and functions of NKT cells, can be regulated by Let-7 (Pobezinsky et al. 2015; Jiang 2018). As a result, the suppression of PLZF by let-7 can regulate the production of antibodies, thymic cell growth, and B cell activation (Jiang 2018).

Over time, there has been an increasing emphasis on the role of let-7 in cardiovascular health and illness. Research has demonstrated that let-7 is highly prevalent in different cardiovascular cell types, such as VSMC (Ding et al. 2013), EC (Chen et al. 2013), cardiomyocytes (Rao et al. 2009; Satoh et al. 2011), and coronary arterial smooth muscle cells (Ji et al. 2007).

Alzheimer's Disease and let7 Family

The let-7 group of miRNAs contributes to the advancement of AD. It has been discovered that fluctuations in miRNA levels can play a part in the deterioration of neurons, which is a central feature of AD. According to a research, some specific let-7 miRNAs, such as let-7e and let-7b, are more

prevalent in the CSF of individuals with AD. This indicates potential for using these miRNAs as diagnostic and progression tracking tools for AD (Derkow et al. 2018a, b). Cellular Mechanisms: Overexpression of let-7a is connected to the increased neurotoxicity in cellular models of AD. Specifically, let-7a enhances the neurotoxic effects of Aβ peptides, which are known to accumulate in AD. This overexpression also promotes apoptosis and alters autophagy-related pathways, implicating the PI3 K/Akt/mTOR signaling pathway (Duan et al. 2013; Gu et al. 2017b). Changes in let-7 levels can result in heightened apoptosis, thus contributing to the neuronal decline observed in AD (Gu et al. 2017b).

Lehmann et al. have uncovered a novel role for the microRNA let-7 in controlling gene expression in the CNS. Their research revealed that let-7, when present outside of cells, can stimulate the RNA-sensing protein TLR7 and promote neurodegeneration by altering TLR7 activity in neurons. Interestingly, individuals with AD show elevated levels of let-7b in their CSF. Furthermore, when let-7b was introduced into the CSF of healthy mice via intrathecal injection, it led to neurodegeneration. However, mice without TLR7 were not affected by this, but when TLR7 was added to their neurons through intrauterine electroporation, they became susceptible to the effects of let-7. This shows that microRNAs can act as signaling molecules and highlights the importance of TLR7 in a pathway that contributes to damage in the CNS (Lehmann et al. 2012).

Liu et al. thoroughly evaluated 94 individuals with dementia and found that AD progression leads to increased levels of the let-7b miRNA. This is primarily due to CD4+T cells in the CSF. They also found a positive correlation between let-7b and the expression of t-Tau and p-Tau. Adding let-7b to traditional AD biomarkers, like Aβ40-Aβ42 or t-tau-p-tau logistic regression and receiver operating characteristic predictive models, greatly enhances diagnostic accuracy. In summary, let-7b is crucial in the progression of AD and can enhance the precision of diagnoses when used alongside conventional biomarkers (Liu et al. 2018).

Moustafa and colleagues investigated the impact of Let-7 miRNAs on memory and p-Tau levels in STZ-induced AD. They also carried out experiments on adult Sprague Dawley rats to examine the effects of Letrozole on these factors. In total, there were seven groups, including a control group and various combinations of STZ, Letrozole, and cerebrospinal fluid. The researchers assessed working memory through the T-maze alternation percentage and measured levels of Let-7a, b, e, and p-Tau in the hippocampus using qRT-PCR and ELISA. The results indicated a reduced alternation percentage and increased p-Tau concentration in the STZ, Letrozole, and STZ-L groups. All the studied microRNAs were elevated in the Letrozole and STZ-L groups, although there were no significant differences between these groups. These findings suggest a connection between Letrozole use and alterations in microRNA levels. There was a negative correlation between alternation percentage and microRNA levels, and a positive correlation between p-Tau concentration and microRNA levels. The study emphasizes changes in Let-7a, b, and e levels associated with Letrozole use and indicates a potential adverse effect on brain function (Moustafa et al. 2022).

Kafshdooz et al. found that individuals with AD had significantly lower levels of hsa-let7 g-5p compared to those without the disease. The AROC curve for hsa-let-7 g-5p transcript levels was 0.4032, which was significantly lower than the AROC of 0.7869 observed in the control group ($P = 0.035$; 95% CI 0.27–0.90). This suggests that hsa-let7 g-5p miRNAs may be a potential biomarker for detecting AD (Kafshdooz et al. 2023).

In their investigation, Gu et al. explored the impact of let-7a overexpression on Aβ1 40-mediated neurotoxicity in PC12 and SK N SH cells. Their findings revealed that increased let-7a expression potentiated the harmful effects of Aβ1 40 in these cells, resulting in elevated levels of apoptosis. Furthermore, treatment with Aβ1 40 and overexpression of let-7a led to increased expression of key markers of autophagy, including microtubule-associated protein 1 A/1B LC3, beclin 1, and the LC3 II/I ratio in both cell types. The use of Aβ1 40 also upregulated the expression of beclin 1, autophagy protein 5 (Atg 5), and Atg 7 mRNA in PC12 cells, which was further enhanced by the overexpression of let-7a. In addition, high levels of let-7a were associated with increased expression of autophagy markers. Furthermore, the presence of Aβ1 40 increased the levels of p62 protein, a marker of autophagy impairment, and this was further amplified by let-7a overexpression. These results highlight the potential of let-7a to regulate autophagy via the PI3 K/Akt/mTOR signaling pathway. Overall, this study emphasizes the role of let-7a in exacerbating the neurotoxic effects of Aβ1 40 through the modulation of autophagy and suggests the involvement of the PI3 K/Akt/mTOR pathway in this process (Gu et al. 2017b).

Liu et al. conducted a study utilizing microarray and TaqMan qRT-PCR analyses was conducted to examine changes in miRNA expression in the brains of rabbits developing Alzheimer's disease-like pathology. Researchers analyzed 1,769 miRNA probes and identified 99 present in the rabbit brain, with 57 newly recognized miRNAs in rabbits. Among these, 11 miRNAs exhibited significant changes during the progression of AD-like pathology. Some miRNAs, such as miR-98, miR-125b, miR-30, miR-107, and three members of the let-7 family, displayed expression patterns similar to those observed in human AD samples. However, specific miRNAs like miR-26b, miR-15a, miR-576-3p, and miR-9 showed unique expression profiles in this rabbit model of late-onset AD (LOAD). Notably, miR-26b significantly increased, corresponding with a decrease in leptin levels in

the brains of rabbits fed a cholesterol-rich diet, a common AD model. This finding supports the hypothesis that leptin may regulate miR-26b, with both potentially playing a role in the development of cholesterol-induced AD-like symptoms (Liu et al. 2014).

Exercise and let7 Family

Taking part in consistent physical activity greatly affects the let7 family of microRNAs. Studies have confirmed that exercise can alter the levels of let-7 miRNAs, specifically in skeletal muscle. This can potentially contribute to the positive effects of exercise on metabolism and cellular processes. In essence, exercise can control let-7 family members, influencing processes such as mitochondrial function and muscle growth (Kuppusamy et al. 2015).

Lin28a and Lin28b are crucial controllers of let-7 levels through their ability to inhibit its maturation (Zhu et al. 2011; Heo et al. 2008). Mice with increased levels of Lin28a/b were shielded from obesity and showed improved glucose tolerance. However, removing Lin28a in skeletal muscle or increasing let-7 levels led to insulin resistance and hindered glucose tolerance, suggesting that elevated let-7 expression has a detrimental effect on mitochondrial metabolism (Zhu et al. 2011).

Araujo et al. proved mice that underwent 8 weeks of aerobic exercise showed a considerable decrease in the expression of let-7b-5p in their skeletal muscles. Conversely, consumption of a high-fat diet resulted in an elevation of let-7b-5p expression. On the other hand, aerobic exercise led to an elevation in the presence of Lin28a, a well-known suppressor of let-7b-5p, while a high-fat diet resulted in a decrease. Correspondingly, analyses of skeletal muscle samples from humans revealed an upregulation of LIN28 and a downregulation of let-7b-5p following aerobic training. Additional investigation uncovered that the genetic makeup of LIN28a is rich in binding sites for PPARδ, a widely recognized controller of metabolism during physical activity. Treatment with PPARδ activators GW501516 and AICAR increased levels of Lin28a in primary mouse skeletal muscle cells or C2 C12 cells. Co-regulators of PPARδ affected the expression of both let-7b-5p and Lin28a. PPARγ coactivator-1α (PGC1α) specifically had an impact on the expression of Lin28a, leading to an increase in its levels. On the other hand, its corepressor NCoR1 played a role in decreasing Lin28a's expression. Furthermore, PGC1α was found to significantly decrease the expression of let-7b-5p. However, when the PPARδ inhibitor GSK0660 was added, it hindered PGC1α's ability to induce Lin28a expression. As a result, PPARδ depletion decreased Lin28a levels and increased let-7b-5p levels in cells. This was found to impact mitochondrial metabolism through PGC1α mediation in muscle cells. In brief, our study confirms PPARδ's regulation of Lin28a-let-7b-5p in skeletal muscle and its impact on mitochondrial respiration (Araujo et al. 2020).

Isanejad et al. studied the impact of the combination of interval exercise training, tamoxifen, and letrozole on the expression levels of miR-21, miR-206, and let-7, and their associated pathways in breast cancer-related tumor angiogenesis in 64 mice. The study utilized ELISA, immunohistochemistry, and qRT-PCR methods. The findings indicated a clear decrease in tumor size among those who underwent exercise training, took tamoxifen or letrozole, in contrast to those in the tumor group. Moreover, the exercise training group exhibited higher levels of Mir-206 and let-7, along with reduced expression of mir-21, compared to the tumor group. This resulted in decreased levels of ER-α, Ki67, CD31, VEGF, and HIF-α within the tumor tissue. When combined with tamoxifen and/or letrozole, exercise training further reduced the expression of HIF-1α, ERα, miR-21, CD31, TNF-α, VEGF, and Ki67. This combination also increased the expression of PDCD-4, miR-206, IL-10, and let-7, leading to a reduction in angiogenesis and tumor growth. Our findings indicate that the pathways involving miR-21, miR-206, and let-7a may contribute to the anti-angiogenic effects of hormone therapy when used alongside interval exercise training in mice (Isanejad et al. 2016).

Barber et al. made a significant discovery that regular physical activity positively influences nine specific miRNAs. These miRNAs (miR-486-5p, miR-29c-3p, let-7b-5p, miR-93-5p, let-7e-5p, miR-25-3p, miR-7-5p, miR-29b-3p, and miR-92a-3p) demonstrated decreased expression, with fold changes ranging from 0.64 to 83 and p values between 0.0002 and 0.01. Conversely, five other miRNAs (miR-221-3p, miR-142-3p, miR-126-3p, miR-146a-5p, and miR-27b-3p) exhibited increased expression, with fold changes ranging from 1.41 to 3.60 and *P* values from 0.001 to 0.006. Additionally, these 14 miRNAs were found to influence genes involved in over 345 different biological pathways, further supporting the notion that physical activity affects circulating miRNA levels (Barber et al. 2019).

Kumar Dev et al. explored the connection between aerobic fitness and telomere length in leukocytes. The researchers also studied the effect of intense exercise on regulating miRNA networks in white blood cells, finding a link between telomere length and aerobic fitness. After six weeks of high-intensity interval training, 104 miRNAs showed significant changes and were connected to telomere length through gene co-expression analysis. Enrichment analysis also showed a decrease in miRNAs related to immune response and metabolism, consistent with previous studies. These results indicate that high-intensity interval training has the potential to slow down the aging process through its impact on targeted miRNA pathways (Kumar Dev et al. 2021).

Cross-Talk Between Exercise and Alzheimer's Disease: Role of let7 Family, Current Limitations, and Future Direction

The let-7 family of miRNAs controls various cellular functions, particularly those related to AD. Research proved that engaging in physical activity can have a positive effect on brain health. This has been attributed to the impact it has on the expression of let-7 miRNAs and various pathways related to neurodegeneration. However, the exact role of the let-7 miRNA family in the protective benefits of exercise against AD has been a topic of discussion in research. While some studies show a decrease in let-7 expression after exercise, others indicate an increase, leading to uncertainty about its exact impact on AD development and prevention. The involvement of let-7 in the interaction between exercise and AD is complex due to its dual function as both a beneficial and harmful mediator. Research, such as that conducted by Araujo et al., shows that aerobic exercise leads to a decrease in let-7 expression, which is linked to improved mitochondrial and metabolic processes. This suggests that lowering let-7 levels may mitigate its detrimental effects on neuroinflammation and autophagy (Araujo et al. 2020). In contrast, Isanejad et al. noted a rise in let-7 levels under certain circumstances, such as when exercise is combined with hormone therapy. This indicates that the function of let-7 may be influenced by the interplay between exercise and other systemic factors, such as hormonal or metabolic conditions (Isanejad et al. 2016). In AD models, increased expression of let-7 has been associated with heightened neurotoxicity, particularly when Aβ peptides are present. However, alternative research has demonstrated its ability to suppress inflammatory signaling, revealing a situational duality (Gu et al. 2017b). The variability in findings related to let-7 modulation through exercise likely stems from substantial heterogeneity in study designs. Key differences include the type of exercise employed (e.g., aerobic vs. high-intensity interval training), its duration and intensity, as well as the physiological or pathological context of the subjects (e.g., healthy animals, Alzheimer's models, or cancer-bearing mice). For instance, Araujo et al. (2020) reported a reduction in let-7b-5p in skeletal muscle following eight weeks of aerobic exercise, associated with increased Lin28a expression and improved mitochondrial metabolism (Araujo et al. 2020). In contrast, Isanejad et al. (2016) observed elevated let-7 levels when exercise was combined with tamoxifen or letrozole treatment in a breast cancer model, suggesting hormonal modulation may influence miRNA outcomes (Isanejad et al. 2016). Similarly, Barber et al. (2019) found downregulation of let-7b-5p and let-7e-5p after regular physical activity, but also noted variable responses across multiple miRNAs (Barber et al. 2019).

Other studies differ by the biological compartment analyzed—some assess circulating miRNAs in plasma or cerebrospinal fluid (Liu et al. 2018; Derkow et al. 2018a, b), while others examine expression in muscle (Araujo et al. 2020) or brain tissue (Moustafa et al. 2022). Moreover, methodological differences such as qRT-PCR vs. microarray techniques, the timing of sample collection post-exercise, and normalization strategies for miRNA quantification may contribute to inconsistent results. These discrepancies highlight the need for standardized experimental protocols and careful consideration of context when interpreting the effects of exercise on let-7 miRNA expression.

Exercise, let-7, and AD are intricately linked through various pathways:

PI3 K/Akt/mTOR Pathway: The cellular processes of metabolism, autophagy, and survival rely heavily on this pathway. Let-7 regulate PI3 K/Akt/mTOR signaling, typically with a negative impact. However, exercise can activate this pathway to support neuronal survival and clear Aβ. By maintaining a balanced expression of let-7 through exercise, the activity of this pathway can be optimized, potentially reducing neurodegeneration (Gu et al. 2017b; Duan et al. 2013). Key components of the PI3 K/Akt/mTOR pathway are direct targets of let-7 miRNAs. For example, let-7 can suppress phosphorylation events in this pathway, thereby modulating downstream effects like reactive oxygen species (ROS) production and metabolic changes (Wells et al. 2023; Hajibabaie et al. 2023).

TLR4 and NF-κB Signaling: Let-7 specifically targets TLR4 mRNA, hindering its translation and moderating inflammatory reactions. The decrease in let-7 levels caused by exercise may seem paradoxical at first, but it could potentially amplify temporary TLR4 function, aiding in the elimination of harmful pathogens or cells. As time passes, this short-lived activity may transition toward anti-inflammatory communication, safeguarding against persistent neuroinflammation (Chen et al. 2007). TLR4 activation in microglia leads to a pro-inflammatory response against amyloid-beta (Aβ), resulting in neuronal cell death. Let-7 indirectly modulates this pathway by altering cytokine profiles (Adhikarla et al. 2021; Fiebich et al. 2018). On the other hand, aerobic exercise decreases TLR4 expression in the spleen, leading to reduced inflammatory responses, and studies showed that treadmill training attenuates overexpression of TLR2, TLR4, MyD88, and NF-κB in a stroke model, providing neuroprotection (Ma et al. 2013; Chen et al. 2016). Let-7 miRNAs, particularly let-7b, act as extracellular signaling molecules that activate Toll-like receptors (e.g., TLR7) on microglia and neurons, leading to NF-κB activation. This results in

the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which exacerbate neurodegeneration (Kou et al. 2020; Liang and Wang 2021).

Mitochondrial Biogenesis: Physical activity improves mitochondrial function through the PPARδ and PGC1α pathways, which are suppressed by let-7. By controlling the levels of let-7, physical activity may protect neuronal mitochondria and promote energy production, potentially mitigating metabolic dysfunction associated with AD(Araujo et al. 2020).

The interplay between physical activity, let-7, and AD poses both challenges and possibilities for further investigation. Future research should explore the impact of variables such as age, gender, genetic predisposition, and disease progression on the effects of exercise on let-7. This could aid in identifying specific groups of patients who may benefit from targeted interventions. Further studies should also concentrate on examining how exercise influences let-7 expression in the central nervous system. Utilizing advanced imaging and molecular methods could uncover the mechanisms by which exercise affects let-7 levels in crucial brain regions like the hippocampus and cortex. Prior studies offer limited insight into the continuous changes in let-7 patterns. To fully understand the impact of exercise, it is necessary to conduct long-term investigations that evaluate whether it yields lasting benefits or alters let-7 pathways. Stratified clinical trials should be designed to assess the role of variables such as age (e.g., <60 vs. >60 years), sex (including hormone status), APOE-ε4 genotype, and disease stage (mild cognitive impairment vs. moderate AD) in shaping let-7 responses to aerobic or resistance training. Randomized controlled trials (RCTs) with intervention durations of at least 6–12 months would allow for evaluation of both short- and long-term changes in let-7 expression and cognitive outcomes. To enhance translational relevance, combined interventions that pair exercise with pharmacological agents targeting let-7 pathways (e.g., Lin28a agonists, TLR7 inhibitors) should be explored in AD mouse models and subsequently in Phase I/II clinical trials assessing safety, tolerability, and preliminary efficacy.

Taken all together, the let-7 family exhibits both neuroprotective and neurotoxic effects depending on cellular context, expression levels, and interacting pathways. On one hand, downregulation of let-7—especially let-7b and let-7e—has been associated with improved mitochondrial metabolism and reduced inflammation, particularly when modulated through physical exercise (Okamura et al. 2021; Li and Liao 2021). Let-7 suppression may support autophagy and neuronal survival by activating PI3 K/Akt/mTOR signaling (Roy 2021; Wang et al. 2022). However, overexpression of specific let-7 isoforms, such as let-7a and let-7b, can exacerbate Aβ-induced neurotoxicity, promote apoptosis, and disrupt autophagic flux (Zhao et al. 2019; Gu et al. 2017b). These findings suggest that intracellular let-7 may have regulatory and protective functions, while extracellular let-7 acts as a danger-associated molecular pattern (DAMP), contributing to neuroinflammation and neuronal loss. Furthermore, the expression and function of let-7 may be influenced by other factors, such as hormone levels, metabolic state, and regional brain differences, which complicates its role and underscores the need for context-specific therapeutic targeting.

Examining the potential synergies between exercise and pharmaceuticals targeting let-7, such as Lin28a modulators, could improve treatment outcomes. By optimizing let-7 levels, these combined therapies may enhance neuroprotection while minimizing potential hazards. By combining transcriptomic, proteomic, and metabolomic data, a thorough understanding of the impact of let-7 on exercise-induced neuroprotection can be achieved. This method would aid in identifying both the factors that control let-7 and its downstream effects in relation to AD. To bridge the gap between laboratory findings and practical use, it is crucial to align human clinical trials and animal studies. This will ensure that exercise regimens targeting let-7 are not only efficient but also safe for real-world applications.

While preclinical studies offer compelling insights into the regulatory role of let-7 miRNAs in AD-related neurodegeneration, translating these findings into clinical practice remains a significant challenge. Elevated levels of specific let-7 family members, particularly let-7b and let-7e, in the CSF of AD patients suggest potential utility as non-invasive diagnostic or prognostic biomarkers (van Harten et al. 2015; Derkow et al. 2018a, b). Combining let-7 quantification with traditional markers such as Aβ42, total tau, and phosphorylated tau has been shown to improve diagnostic accuracy, potentially aiding in earlier detection or monitoring of disease progression (Talemi et al. 2023; Derkow et al. 2018a, b). Moreover, the modulation of let-7 through lifestyle interventions like aerobic exercise introduces a promising avenue for personalized, non-pharmacological treatment strategies. However, the dual role of let-7—both protective and detrimental depending on context—underscores the need for careful therapeutic targeting. Future clinical research should focus on longitudinal studies that correlate let-7 expression profiles with disease trajectory, treatment response, and patient outcomes, paving the way for let-7-based precision medicine approaches in AD care.

Table 1 demonstrates the multifaceted functions of Let-7, illustrating its impact on AD development and the protective benefits of physical activity.

Table 1 Dual role of Let-7 in exercise and Alzheimer's disease

Aspect	Role of Let-7 in Alzheimer's disease (AD)	Role of Let-7 in exercise
Neuroinflammation	Targets Toll-like receptors (e.g., TLR4) to regulate inflammatory responses Dysregulation exacerbates neuroinflammation	Downregulation reduces chronic inflammation Modulates TLR4 signaling, potentially balancing inflammation post-exercise
Autophagy and Aβ Clearance	Enhances neurotoxicity by impairing autophagy Promotes accumulation of β-amyloid (Aβ) peptides	Downregulation promotes autophagy, aiding in protein turnover and clearance of damaged cellular components
Mitochondrial Function	Negatively regulates mitochondrial metabolism via PI3 K/Akt/mTOR pathways Contributes to energy deficits in neurons	Downregulation improves mitochondrial function Exercise enhances mitochondrial biogenesis through let-7 modulation
Neurotoxicity	Overexpression exacerbates Aβ-induced neurotoxicity Increases apoptosis and cell death	Downregulation through exercise may counteract neurotoxic pathways Protective effects mediated via improved cellular resilience
TLR4 Signaling	Dysregulated let-7 increases TLR4 activity, promoting chronic inflammation	Exercise-induced changes in let-7 modulate TLR4 activity, transitioning from acute inflammatory responses to resolution phases
CNS-Specific Effects	Elevated levels in cerebrospinal fluid (e.g., let-7b and let-7e) serve as biomarkers for AD May influence tau pathology	Changes in peripheral let-7 levels may indirectly affect CNS signaling and neuroprotection via systemic pathways
Impact on Cell Survival	Dysregulated let-7 impacts PI3 K/Akt signaling, impairing cell survival mechanisms	Exercise-induced modulation restores balance in survival pathways, promoting neuroprotection and resilience
Pathway Regulation	Targets genes like PI3 K, Akt, mTOR, and TLR4 in neural and inflammatory signaling pathways	Exercise influences these pathways by altering let-7 expression, facilitating neuroprotective and anti-inflammatory responses
Context-Dependent Roles	Can act as both a tumor suppressor and an oncogene depending on cellular context Similar dual roles in AD pathogenesis	Let-7's expression varies based on exercise type, intensity, and duration, highlighting its complex regulation in exercise

Conclusion

The interaction between physical activity and AD through let-7 is a promising yet intricate field of study. Let-7 serves as a mediator for important pathways related to neuroinflammation, autophagy, and mitochondrial function, all of which contribute to the development of AD. Exercise has the ability to influence let-7 levels, resulting in beneficial effects for brain health. Further research is crucial to fully comprehend the impact of let-7 on neurodegenerative disorders, even though current results may not align. By resolving these discrepancies and delving into the complex relationships between exercise, let-7, and AD, future studies can lead to novel approaches for addressing neurodegenerative diseases.

Acknowledgements Not applicable.

Author Contributions Shanbin Ke, Zhengqiong Liu, Yuwen Wan contributed to the conception, design, and drafting of the manuscript.

Funding Not applicable.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

References

Adhikarla SV, Jha NK, Goswami VK, Sharma A, Bhardwaj A, Dey A, Villa C, Kumar Y, Jha SK (2021) TLR-mediated signal transduction and neurodegenerative disorders. Brain Sci 11(11):1373

Alarcón CR, Lee H, Goodarzi H, Halberg N, Tavazoie SF (2015) N6-methyladenosine marks primary microRNAs for processing. Nature 519:482–485

Alles J, Fehlmann T, Fischer U, Backes C, Galata V, Minet M, Hart M, Abu-Halima M, Grässer FA, Lenhof HP, Keller A, Meese E (2019) An estimate of the total number of true human miRNAs. Nucleic Acids Res 47:3353–3364

Alzheimer's Association (2020) Alzheimer's disease facts and figures. Alzheimers Dement

An G, Miner CA, Nixon JC, Kincade PW, Bryant J, Tucker PW, Webb CF (2010) Loss of Bright/ARID3a function promotes developmental plasticity. Stem Cells 28:1560–1567

Araujo HN, Lima TI, Guimarães DSPSF, Oliveira AG, Favero-Santos BC, da Branco RCS, da Silva Araújo RM, Dantas AFB, Castro A, Chacon-Mikahil MPT, Minatel E, Geraldo MV, Carneiro EM, Rodrigues AC, Narkar VA, Silveira LR (2020) Regulation of Lin28a-miRNA let-7b-5p pathway in skeletal muscle cells by peroxisome proliferator-activated receptor delta. Am J Physiol Cell Physiol 319:C541–C551

Asada T (2017) Epidemiology of dementia in Japan. In: Neuroimaging diagnosis for Alzheimer's disease and other dementias. Springer, Tokyo, pp 1–10

Atri A (2019) The Alzheimer's disease clinical spectrum: diagnosis and management. Med Clin North Am 103:263–293

Avan A, Hachinski V (2021) Stroke and dementia, leading causes of neurological disability and death, potential for prevention. Alzheimers Dement 17:1072–1076

Babaei P (2021) NMDA and AMPA receptors dysregulation in Alzheimer's disease. Eur J Pharmacol 908:174310

Barber JL, Zellars KN, Barringhaus KG, Bouchard C, Spinale FG, Sarzynski MA (2019) The effects of regular exercise on circulating cardiovascular-related MicroRNAs. Sci Rep 9:7527

Barnes DE, Yaffe K (2011) The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 10:819–828

Benedetto Di, Giulia CB, Bellanca CM, Munafò A, Bernardini R, Cantarella G (2022) Role of microglia and astrocytes in Alzheimer's disease: from neuroinflammation to Ca2+ homeostasis dysregulation. Cells 11:2728

Better MAPPINGA (2023) Alzheimer's disease facts and figures. Alzheimers Dement 19:1598–1695

Bosch-Barrera J, Queralt B, Menendez JA (2017) Targeting STAT3 with silibinin to improve cancer therapeutics. Cancer Treat Rev 58:61–69

Brubaker SW, Bonham KS, Zanoni I, Kagan JC (2015) Innate immune pattern recognition: a cell biological perspective. Annu Rev Immunol 33:257–290

Brueckner B, Stresemann C, Kuner R, Mund C, Musch T, Meister M, Sültmann H, Lyko F (2007) The human let-7a-3 locus contains an epigenetically regulated microRNA gene with oncogenic function. Can Res 67:1419–1423

Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA (2012) Total daily physical activity and the risk of AD and cognitive decline in older adults. Neurology 78:1323–1329

Büssing I, Slack FJ, Grosshans H (2008) let-7 microRNAs in development, stem cells and cancer. Trends Mol Med 14:400–409

Chapman SB, Aslan S, Spence JS, Defina LF, Keebler MW, Didehbani N, Lu H (2013) Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. Front Aging Neurosci 5:75

Chaudhry MA, Sachdeva H, Omaruddin RA (2010) Radiation-induced micro-RNA modulation in glioblastoma cells differing in DNA-repair pathways. DNA Cell Biol 29:553–561

Cheloufi S, Dos Santos CO, Chong MM, Hannon GJ (2010) A dicer-independent miRNA biogenesis pathway that requires Ago catalysis. Nature 465:584–589

Chen XM, Splinter PL, O'Hara SP, LaRusso NF (2007) A cellular micro-RNA, let-7i, regulates Toll-like receptor 4 expression and contributes to cholangiocyte immune responses against *Cryptosporidium parvum* infection. J Biol Chem 282:28929–28938

Chen Z, Lai TC, Jan YH, Lin FM, Wang WC, Xiao H, Wang YT, Sun W, Cui X, Li YS, Fang T, Zhao H, Padmanabhan C, Sun R, Wang DL, Jin H, Chau GY, Huang HD, Hsiao M, Shyy JY (2013) Hypoxia-responsive miRNAs target argonaute 1 to promote angiogenesis. J Clin Invest 123:1057–1067

Chen K-j, Hou Y, Wang K, Li J, Xia Y, Yang X-y, Lv G, Xing X-L, Shen F (2014) Reexpression of Let-7g microRNA inhibits the proliferation and migration via K-Ras/HMGA2/snail axis in hepatocellular carcinoma. Biomed Res Int 2014:742417

Chen C-W, Chen C-C, Jian C-Y, Lin P-H, Chou J-C, Teng H-S, Sindy Hu, Lieu F-K, Wang PS, Wang S-W (2016) Attenuation of exercise effect on inflammatory responses via novel role of TLR4/PI3K/Akt signaling in rat splenocytes. J Appl Physiol 121:870–877

Chen W, Johansen VBI, Legido-Quigley C (2024) Bridging brain insulin resistance to Alzheimer's pathogenesis. Trends Biochem Sci 49:939–941

Chirshev E, Oberg KC, Ioffe YJ, Unternaehrer JJ (2019) Let-7 as biomarker, prognostic indicator, and therapy for precision medicine in cancer. Clin Transl Med 8:24

Churov AV, Oleinik EK, Knip M (2015) MicroRNAs in rheumatoid arthritis: altered expression and diagnostic potential. Autoimmun Rev 14:1029–1037

Course MM, Kathryn Gudsnuk C, Keene D, Bird TD, Jayadev S, Valdmanis PN (2023) Aberrant splicing of PSEN2, but not PSEN1, in individuals with sporadic Alzheimer's disease. Brain 146:507–518

Dai X, Fan W, Wang Y, Huang L, Jiang Y, Shi L, McKinley D, Tan W, Tan C (2016) Combined delivery of Let-7b MicroRNA and paclitaxel via biodegradable nanoassemblies for the treatment of KRAS mutant cancer. Mol Pharm 13:520–533

de Rie D, Abugessaisa I, Alam T, Arner E, Arner P, Ashoor H, Åström G, Babina M, Bertin N, Burroughs AM, Carlisle AJ, Daub CO, Detmar M, Deviatiiarov R, Fort A, Gebhard C, Goldowitz D, Guhl S, Ha TJ, Harshbarger J, Hasegawa A, Hashimoto K, Herlyn M, Heutink P, Hitchens KJ, Hon CC, Huang E, Ishizu Y, Kai C, Kasukawa T, Klinken P, Lassmann T, Lecellier CH, Lee W, Lizio M, Makeev V, Mathelier A, Medvedeva YA, Mejhert N, Mungall CJ, Noma S, Ohshima M, Okada-Hatakeyama M, Persson H, Rizzu P, Roudnicky F, Sætrom P, Sato H, Severin J, Shin JW, Swoboda RK, Tarui H, Toyoda H, Vitting-Seerup K, Winteringham L, Yamaguchi Y, Yasuzawa K, Yoneda M, Yumoto N, Zabierowski S, Zhang PG, Wells CA, Summers KM, Kawaji H, Sandelin A, Rehli M, Hayashizaki Y, Carninci P, Forrest ARR, de Hoon MJL (2017) An integrated expression atlas of miRNAs and their promoters in human and mouse. Nat Biotechnol 35:872–878

Degrauwe N, Schlumpf TB, Janiszewska M, Martin P, Cauderay A, Provero P, Riggi N, Suvà ML, Paro R, Stamenkovic I (2016) The RNA binding protein IMP2 preserves glioblastoma stem cells by preventing let-7 target gene silencing. Cell Rep 15:1634–1647

Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ (2004) Processing of primary microRNAs by the microprocessor complex. Nature 432:231–235

Derkow K, Rössling R, Schipke C, Krüger C, Bauer J, Fähling M, Stroux A, Schott E, Ruprecht K, Peters O, Lehnardt S (2018a)

Distinct expression of the neurotoxic microRNA family let-7 in the cerebrospinal fluid of patients with Alzheimer's disease. PLoS ONE 13:e0200602

Derkow K, Rössling R, Schipke C, Krüger C, Bauer J, Fähling M, Stroux A, Schott E, Ruprecht K, Peters O (2018b) Distinct expression of the neurotoxic microRNA family let-7 in the cerebrospinal fluid of patients with Alzheimer's disease. PLoS ONE 13:e0200602

Desai P, Evans D, Dhana K, Aggarwal NT, Wilson RS, McAninch E, Rajan KB (2021) Longitudinal association of total tau concentrations and physical activity with cognitive decline in a population sample. JAMA Netw Open 4:e2120398–e2120498

Dharap A, Pokrzywa C, Murali S, Pandi G, Vemuganti R (2013) MicroRNA miR-324-3p induces promoter-mediated expression of RelA gene. PLoS ONE 8:e79467

Ding Z, Wang X, Schnackenberg L, Khaidakov M, Liu S, Singla S, Dai Y, Mehta JL (2013) Regulation of autophagy and apoptosis in response to ox-LDL in vascular smooth muscle cells, and the modulatory effects of the microRNA hsa-let-7 g. Int J Cardiol 168:1378–1385

Duan R-R, Li Y-F, Jia Y (2013) Role of Let-7 family in pathogenesis of Alzheimer disease. Int J Biomed Eng 36:307–310

Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, White SM, Wójcicki TR, McAuley E, Kramer AF (2009) Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 19:1030–1039

Evers L, Schäfer A, Pini R, Zhao K, Stei S, Nimsky C, Bartsch JW (2023) Identification of dysregulated microRNAs in glioblastoma Stem-like Cells. Brain Sci 13:350

Ezkurdia A, Ramírez MJ, Solas M (2023) Metabolic syndrome as a risk factor for Alzheimer's disease: a focus on insulin resistance. Int J Mol Sci 24:4354

Farina N, Rusted J, Tabet N (2014) The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review. Int Psychogeriatr 26:9–18

Fiebich BL, Batista CRA, Saliba SW, Yousif NM, de Oliveira ACP (2018) Role of microglia tlrs in neurodegeneration. Front Cell Neurosci. https://doi.org/10.3389/fncel.2018.00329

Fiest KM, Roberts JI, Maxwell CJ, Hogan DB, Smith EE, Frolkis A, Cohen A, Kirk A, Pearson D, Pringsheim T, Venegas-Torres A, Jetté N (2016) The prevalence and incidence of dementia due to Alzheimer's disease: a systematic review and meta-analysis. Can J Neurol Sci 43(Suppl 1):S51-82

Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S (2015) Exercise programs for people with dementia. Cochrane Database Syst Rev 2015:cd006489

Furer V, Greenberg JD, Attur M, Abramson SB, Pillinger MH (2010) The role of microRNA in rheumatoid arthritis and other autoimmune diseases. Clin Immunol 136:1–15

Gandy S (2005) The role of cerebral amyloid β accumulation in common forms of Alzheimer disease. J Clin Investig 115:1121–1129

Ganguly U, Kaur U, Chakrabarti SS, Sharma P, Agrawal BK, Saso L, Chakrabarti S (2021) Oxidative stress, neuroinflammation, and NADPH oxidase: implications in the pathogenesis and treatment of Alzheimer's disease. Oxid Med Cell Longev 2021:7086512

Gu H, Li L, Cui C, Zhao Z, Song G (2017) Overexpression of let-7a increases neurotoxicity in a PC12 cell model of Alzheimer's disease via regulating autophagy. Exp Ther Med 14:3688–3698

Guo Y, Yan K, Fang J, Qu Q, Zhou M, Chen F (2013) Let-7b expression determines response to chemotherapy through the regulation of cyclin D1 in glioblastoma. J Exp Clin Cancer Res 32:41

Gupta P, Cairns MJ, Saksena NK (2014) Regulation of gene expression by microRNA in HCV infection and HCV-mediated hepatocellular carcinoma. Virol J 11:1–14

Ha M, Kim VN (2014) Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol 15:509–524

Hajibabaie F, Abedpoor N, Taghian F, Safavi K (2023) A cocktail of polyherbal bioactive compounds and regular mobility training as senolytic approaches in age-dependent Alzheimer's: the in silico analysis, lifestyle intervention in old age. J Mol Neurosci 73:171–184

Hamer M, Chida Y (2009) Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med 39:3–11

Han J, Lee Y, Yeom KH, Kim YK, Jin H, Kim VN (2004) The Drosha-DGCR8 complex in primary microRNA processing. Genes Dev 18:3016–3027

Havens MA, Reich AA, Hastings ML (2014) Drosha promotes splicing of a pre-microRNA-like alternative exon. PLoS Genet 10:e1004312

He X, Jing Z, Cheng G (2014) MicroRNAs: new regulators of Toll-like receptor signalling pathways. Biomed Res Int 2014:945169

Heo I, Joo C, Cho J, Ha M, Han J, Kim VN (2008) Lin28 mediates the terminal uridylation of let-7 precursor MicroRNA. Mol Cell 32:276–284

Hoffmann K, Sobol NA, Frederiksen KS, Beyer N, Vogel A, Vestergaard K, Brændgaard H, Gottrup H, Lolk A, Wermuth L, Jacobsen S, Laugesen LP, Gergelyffy RG, Høgh P, Bjerregaard E, Andersen BB, Siersma V, Johannsen P, Cotman CW, Waldemar G, Hasselbalch SG (2016) Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: a randomized controlled trial. J Alzheimers Dis 50:443–453

Hondius DC, Koopmans F, Leistner C, Pita-Illobre D, Peferoen-Baert RM, Marbus F, Paliukhovich I, Li KW, Rozemuller AJM, Hoozemans JJM (2021) The proteome of granulovacuolar degeneration and neurofibrillary tangles in Alzheimer's disease. Acta Neuropathol 141:341–358

Huntzinger E, Izaurralde E (2011) Gene silencing by microRNAs: contributions of translational repression and mRNA decay. Nat Rev Genet 12:99–110

Ipsaro JJ, Joshua-Tor L (2015) From guide to target: molecular insights into eukaryotic RNA-interference machinery. Nat Struct Mol Biol 22:20–28

Isanejad A, Alizadeh AM, Shalamzari SA, Khodayari H, Khodayari S, Khori V, Khojastehnjad N (2016) MicroRNA-206, let-7a and microRNA-21 pathways involved in the anti-angiogenesis effects of the interval exercise training and hormone therapy in breast cancer. Life Sci 151:30–40

Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 12:207–216

Ji R, Cheng Y, Yue J, Yang J, Liu X, Chen H, Dean DB, Zhang C (2007) MicroRNA expression signature and antisense-mediated depletion reveal an essential role of MicroRNA in vascular neointimal lesion formation. Circ Res 100:1579–1588

Jiang S (2018) Recent findings regarding let-7 in immunity. Cancer Lett 434:130–131

Jin B, Wang W, Meng X-X, Gang Du, Li J, Zhang S-Z, Zhou B-H, Zhihao Fu (2016) Let-7 inhibits self-renewal of hepatocellular cancer stem-like cells through regulating the epithelial-mesenchymal transition and the Wnt signaling pathway. BMC Cancer 16:1–10

John A, Reddy PH (2021) Synaptic basis of Alzheimer's disease: Focus on synaptic amyloid beta, P-tau and mitochondria. Ageing Research Reviews 65:101208

Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, Labourier E, Reinert KL, Brown D, Slack FJ (2005) RAS is regulated by the let-7 microRNA family. Cell 120:635–647

Johnson CD, Esquela-Kerscher A, Stefani G, Byrom M, Kelnar K, Ovcharenko D, Wilson M, Wang X, Shelton J, Shingara J

(2007) The let-7 microRNA represses cell proliferation pathways in human cells. Can Res 67:7713–7722
Kafshdooz T, Farajnia S, Sharifi R, Najmi S (2023) Hsa-let-7g-5p, a circulating microRNA, as a biomarker for Alzheimer's disease. Inf Med Unlocked 38:101203
Khodayari N, Mohammed KA, Goldberg EP, Nasreen N (2011) EphrinA1 inhibits malignant mesothelioma tumor growth via let-7 microRNA-mediated repression of the RAS oncogene. Cancer Gene Ther 18:806–816
Khvorova A, Reynolds A, Jayasena SD (2003) Functional siRNAs and miRNAs exhibit strand bias. Cell 115:209–216
Kim YK, Kim VN (2007) Processing of intronic microRNAs. Embo J 26:775–783
Kok FK, van Leerdam SL, de Lange ECM (2022) Potential mechanisms underlying resistance to dementia in non-demented individuals with Alzheimer's disease neuropathology. J Alzheimers Dis 87:51–81
Kou X, Chen D, Chen N (2020) The regulation of microRNAs in Alzheimer's disease. Front Neurol 11:288
Kumar M, Sahu SK, Kumar R, Subuddhi A, Maji RK, Jana K, Gupta P, Raffetseder J, Lerm M, Ghosh Z, van Loo G, Beyaert R, Gupta UD, Kundu M, Basu J (2015) MicroRNA let-7 modulates the immune response to *Mycobacterium tuberculosis* infection via control of A20, an inhibitor of the NF-κB pathway. Cell Host Microbe 17:345–356
Kumar Dev P, Gray AJ, Scott-Hamilton J, Hagstrom AD, Murphy A, Denham J (2021) Co-expression analysis identifies networks of miRNAs implicated in biological ageing and modulated by short-term interval training. Mech Ageing Dev 199:111552
Kuppusamy KT, Jones DC, Sperber H, Madan A, Fischer KA, Rodriguez ML, Pabon L, Zhu WZ, Tulloch NL, Yang X, Sniadecki NJ, Laflamme MA, Ruzzo WL, Murry CE, Ruohola-Baker H (2015) Let-7 family of microRNA is required for maturation and adult-like metabolism in stem cell-derived cardiomyocytes. Proc Natl Acad Sci U S A 112:E2785–E2794
la Rosa De, Adrian G-G, Arc-Chagnaud C, Millan F, Salvador-Pascual A, García-Lucerga C, Blasco-Lafarga C, Garcia-Dominguez E, Carretero A, Correas AG (2020) Physical exercise in the prevention and treatment of Alzheimer's disease. J Sport Health Sci 9:394–404
Lan FF, Wang H, Chen YC, Chan CY, Ng SS, Li K, Xie D, He ML, Lin MC, Kung HF (2011) Hsa-let-7g inhibits proliferation of hepatocellular carcinoma cells by downregulation of c-Myc and upregulation of p16(INK4A). Int J Cancer 128:319–331
Lee R-L, Funk KE (2023) Imaging blood–brain barrier disruption in neuroinflammation and Alzheimer's disease. Front Aging Neurosci 15:1144036
Lee RC, Feinbaum RL, Ambros V (1993) The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 75:843–854
Lehmann SM, Krüger C, Park B, Derkow K, Rosenberger K, Baumgart J, Trimbuch T, Eom G, Hinz M, Kaul D (2012) An unconventional role for miRNA: let-7 activates Toll-like receptor 7 and causes neurodegeneration. Nat Neurosci 15:827–835
Leng F, Edison P (2021) Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 17:157–172
Leszek J, Mikhaylenko EV, Belousov DM, Koutsouraki E, Szczechowiak K, Kobusiak-Prokopowicz M, Mysiak A, Diniz BS, Somasundaram SG, Kirkland CE (2021) The links between cardiovascular diseases and Alzheimer's disease. Curr Neuropharmacol 19:152–169
Li C-H, Liao C-C (2021) The metabolism reprogramming of microRNA Let-7-mediated glycolysis contributes to autophagy and tumor progression. Int J Mol Sci 23:113
Li Q, Wu Y, Chen J, Xuan A, Wang X (2022) Microglia and immunotherapy in Alzheimer's disease. Acta Neurol Scand 145:273–278
Liang Y, Wang L (2021) Inflamma-MicroRNAs in Alzheimer's disease: from disease pathogenesis to therapeutic potentials. Front Cell Neurosci 15:785433
Liu Y, Yin B, Zhang C, Zhou L, Fan J (2012) Hsa-let-7a functions as a tumor suppressor in renal cell carcinoma cell lines by targeting c-myc. Biochem Biophys Res Commun 417:371–375
Liu QY, Chang MN, Lei JX, Koukiekolo R, Smith B, Zhang D, Ghribi O (2014) Identification of microRNAs involved in Alzheimer's progression using a rabbit model of the disease. Am J Neurodegener Dis 3:33–44
Liu Y, He X, Li Y, Wang T (2018) Cerebrospinal fluid CD4+T lymphocyte-derived miRNA-let-7b can enhances the diagnostic performance of Alzheimer's disease biomarkers. Biochem Biophys Res Commun 495:1144–1150
López-Ortiz S, Pinto-Fraga J, Valenzuela PL, Martín-Hernández J, Seisdedos MM, García-López O, Toschi N, Di Giuliano F, Garaci F, Mercuri NB (2021) Physical exercise and Alzheimer's disease: effects on pathophysiological molecular pathways of the disease. Int J Mol Sci 22:2897
Lu L, Katsaros D, Irene A, de la Longrais R, Sochirca O, Herbert Yu (2007) Hypermethylation of let-7a-3 in epithelial ovarian cancer is associated with low insulin-like growth factor-II expression and favorable prognosis. Can Res 67:10117–10122
Ma Y, He M, Qiang L (2013) Exercise therapy downregulates the overexpression of TLR4, TLR2, MyD88 and NF-κB after cerebral ischemia in rats. Int J Mol Sci 14:3718–3733
Ma J, Zhan Y, Xu Z, Li Y, Luo A, Ding F, Cao X, Chen H, Liu Z (2017) ZEB1 induced miR-99b/let-7e/miR-125a cluster promotes invasion and metastasis in esophageal squamous cell carcinoma. Cancer Lett 398:37–45
MiRBase (2013) MiRBase. http://www.mirbase.org/cgi-bin/browse.pl?org=hsa8
Moloney CM, Lowe VJ, Murray ME (2021) Visualization of neurofibrillary tangle maturity in Alzheimer's disease: a clinicopathologic perspective for biomarker research. Alzheimers Dement 17:1554–1574
Montgomery W, Ueda K, Jorgensen M, Stathis S, Cheng Y, Nakamura T (2018) Epidemiology, associated burden, and current clinical practice for the diagnosis and management of Alzheimer's disease in Japan. Clinicoecon Outcomes Res 10:13–28
Moustafa NA, El-Sayed MA, Abdallah SH, Hazem NM, Aidaros MA, Abdelmoety DA (2022) Effect of Letrozole on hippocampal Let-7 microRNAs and their correlation with working memory and phosphorylated Tau protein in an Alzheimer's disease-like rat model. Egyp J Neurol Psychiatry Neurosurg 58:70
Mukherjee S, Huda S, Sinha Babu SP (2019) Toll-like receptor polymorphism in host immune response to infectious diseases: a review. Scand J Immunol 90:e12771
Ning Y, Xu M, Cao X, Chen X, Luo X (2017) Inactivation of AKT, ERK and NF-κB by genistein derivative, 7-difluoromethoxyl-5,4′-di-n-octylygenistein, reduces ovarian carcinoma oncogenicity. Oncol Rep 38:949–958
Nishi K, Nishi A, Nagasawa T, Ui-Tei K (2013) Human TNRC6A is an Argonaute-navigator protein for microRNA-mediated gene silencing in the nucleus. RNA 19:17–35
Niu H, Álvarez-Álvarez I, Guillén-Grima F, Aguinaga-Ontoso I (2017) Prevalence and incidence of Alzheimer's disease in Europe: a meta-analysis. Neurologia 32:523–532
Nobori T, Miura K, Wu DJ, Lois A, Takabayashi K, Carson DA (1994) Deletions of the cyclin-dependent kinase-4 inhibitor gene in multiple human cancers. Nature 368:753–756
Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C (2014) Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 13:788–794

O'Brien RJ, Wong PC (2011) Amyloid precursor protein processing and Alzheimer's disease. Annu Rev Neurosci 34:185–204
O'Brien J, Hayder H, Zayed Y, Peng C (2018) Overview of microRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol 9:402
Okamura T, Okada H, Hashimoto Y, Majima S, Senmaru T, Nakanishi N, Asano M, Yamazaki M, Hamaguchi M, Fukui M (2021) Let-7e-5p regulates IGF2BP2, and induces muscle atrophy. Front Endocrinol 12:791363
Olivieri F, Rippo MR, Prattichizzo F, Babini L, Graciotti L, Recchioni R, Procopio AD (2013) Toll like receptor signaling in "inflammaging": microRNA as new players. Immunity Ageing 10:1–10
Onyango IG, Jauregui GV, Čarná M, Bennett Jr JP, Stokin GB (2021) Neuroinflammation in Alzheimer's disease. Biomedicines 9:524
Ørom UA, Nielsen FC, Lund AH (2008) MicroRNA-10a binds the 5′UTR of ribosomal protein mRNAs and enhances their translation. Mol Cell 30:460–471
Patterson M, Gaeta X, Loo K, Edwards M, Smale S, Cinkornpumin J, Xie Y, Listgarten J, Azghadi S, Douglass SM (2014) let-7 miRNAs can act through notch to regulate human gliogenesis. Stem Cell Rep 3:758–773
Pelucchi S, Gardoni F, Di Luca M, Marcello E (2022) Synaptic dysfunction in early phases of Alzheimer's disease. Handb Clin Neurol 184:417–438
Petri R, Pircs K, Jönsson ME, Åkerblom M, Brattås PL, Klussendorf T, Jakobsson J (2017) let-7 regulates radial migration of newborn neurons through positive regulation of autophagy. EMBO J 36:1379-91-91
Pfundstein G, Nikonenko AG, Sytnyk V (2022) Amyloid precursor protein (APP) and amyloid β (Aβ) interact with cell adhesion molecules: implications in Alzheimer's disease and normal physiology. Front Cell Dev Biol 10:969547
Pitchiaya S, Heinicke LA, Park JI, Cameron EL, Walter NG (2017) Resolving subcellular miRNA trafficking and turnover at single-molecule resolution. Cell Rep 19:630–642
Pobezinsky LA, Etzensperger R, Jeurling S, Alag A, Kadakia T, McCaughtry TM, Kimura MY, Sharrow SO, Guinter TI, Feigenbaum L, Singer A (2015) Let-7 microRNAs target the lineage-specific transcription factor PLZF to regulate terminal NKT cell differentiation and effector function. Nat Immunol 16:517–524
Rabin JS, Nichols E, La Joie R, Casaletto KB, Palta P, Dams-O'Connor K, Kumar RG, George KM, Satizabal CL, Schneider JA (2022) Cerebral amyloid angiopathy interacts with neuritic amyloid plaques to promote tau and cognitive decline. Brain 145:2823–2833
Raichlen DA, Aslan DH, Katherine Sayre M, Bharadwaj PK, Ally M, Maltagliati S, Lai MHC, Wilcox RR, Klimentidis YC, Alexander GE (2023) Sedentary behavior and incident dementia among older adults. JAMA 330:934–940
Rao PK, Toyama Y, Chiang HR, Gupta S, Bauer M, Medvid R, Reinhardt F, Liao R, Krieger M, Jaenisch R, Lodish HF, Blelloch R (2009) Loss of cardiac microRNA-mediated regulation leads to dilated cardiomyopathy and heart failure. Circ Res 105:585–594
Raulin A-C, Doss SV, Trottier ZA, Ikezu TC, Guojun Bu, Liu C-C (2022) ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. Mol Neurodegener 17:72
Rawat P, Sehar U, Bisht J, Selman A, Culberson J, Reddy PH (2022) Phosphorylated tau in Alzheimer's disease and other tauopathies. Int J Mol Sci 23:12841
Reinhart BJ, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, Horvitz HR, Ruvkun G (2000) The 21-nucleotide let-7 RNA regulates developmental timing in *Caenorhabditis elegans*. Nature 403:901–906
Rolland Y, Pillard F, Klapouszczak A, Reynish E, Thomas D, Andrieu S, Rivière D, Vellas B (2007) Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. J Am Geriatr Soc 55:158–165
Rostagno AA (2022) Pathogenesis of Alzheimer's disease. Int J Mol Sci 24(1):107
Roush S, Slack FJ (2008) The let-7 family of microRNAs. Trends Cell Biol 18:505–516
Roy SG (2021) Regulation of autophagy by miRNAs in human diseases. Nucleus 64:317–329
Ruby JG, Jan CH, Bartel DP (2007) Intronic microRNA precursors that bypass Drosha processing. Nature 448:83–86
Ruiz-Pérez G, de Martín Esteban SR, Marqués S, Aparicio N, Grande MT, Benito-Cuesta I, Martínez-Relimpio AM, Arnanz MA, Tolón RM, Posada-Ayala M (2021) Potentiation of amyloid beta phagocytosis and amelioration of synaptic dysfunction upon FAAH deletion in a mouse model of Alzheimer's disease. J Neuroinflamm 18:1–19
Sacco G, Caillaud C, Ben Sadoun G, Robert P, David R, Brisswalter J (2016) Exercise plus cognitive performance over and above exercise alone in subjects with mild cognitive impairment. J Alzheimers Dis 50:19–25
Satoh M, Minami Y, Takahashi Y, Tabuchi T, Nakamura M (2011) A cellular microRNA, let-7i, is a novel biomarker for clinical outcome in patients with dilated cardiomyopathy. J Card Fail 17:923–929
Sattler C, Erickson KI, Toro P, Schröder J (2011) Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in Germany. J Alzheimers Dis 26:709–718
Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM (2016) Alzheimer's disease. Lancet 388:505–517
Selkoe DJ (2001) Alzheimer's disease results from the cerebral accumulation and cytotoxicity of amyloid\beta-protein. J Alzheimers Dis 3:75–82
Shaheen N, Shaheen A, Osama M, Nashwan AJ, Bharmauria V, Flouty O (2024) MicroRNAs regulation in Parkinson's disease, and their potential role as diagnostic and therapeutic targets. npj Parkinsons Dis 10:186
Shamsuzzama L, Kumar RH, Nazir A (2016a) Role of MicroRNA Let-7 in Modulating Multifactorial Aspect of Neurodegenerative Diseases: an Overview. Mol Neurobiol 53:2787–2793
Shamsuzzama LK, Haque R, Nazir A (2016b) Role of microRNA Let-7 in modulating multifactorial aspect of neurodegenerative diseases: an overview. Mol Neurobiol 53:2787–2793
Silva GJJ, Bye A, El Azzouzi H, Wisløff U (2017) MicroRNAs as important regulators of exercise adaptation. Prog Cardiovasc Dis 60:130–151
Singh D (2022) Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. J Neuroinflamm 19:206
Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A (2010) Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med 72:239–252
Snyder EM, Nong Yi, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK (2005) Regulation of NMDA receptor trafficking by amyloid-β. Nat Neurosci 8:1051–1058
Španić E, Langer Horvat L, Hof PR, Šimić G (2019) Role of microglial cells in Alzheimer's disease Tau propagation. Front Aging Neurosci 11:271
Spanoudaki M, Giaginis C, Karafyllaki D, Papadopoulos K, Solovos E, Antasouras G, Sfikas G, Papadopoulos AN, Papadopoulou SK (2023) Exercise as a promising agent against cancer: evaluating its anti-cancer molecular mechanisms. Cancers (Basel) 15:5135

Stainthorp AK, Lin CC, Wang D, Medhi R, Ahmed Z, Suen KM, Miska EA, Whitehouse A, Ladbury JE (2023) Regulation of microRNA expression by the adaptor protein GRB2. Sci Rep 13:9784

Ströhle A, Schmidt DK, Schultz F, Fricke N, Staden T, Hellweg R, Priller J, Rapp MA, Rieckmann N (2015) Drug and exercise treatment of alzheimer disease and mild cognitive impairment: a systematic review and meta-analysis of effects on cognition in randomized controlled trials. Am J Geriatr Psychiatry 23:1234–1249

Sun H, Ding C, Zhang H, Gao J (2016a) Let-7 miRNAs sensitize breast cancer stem cells to radiation-induced repression through inhibition of the cyclin D1/Akt1/Wnt1 signaling pathway. Mol Med Rep 14:3285–3292

Sun X, Xu C, Tang SC, Wang J, Wang H, Wang P, Du N, Qin S, Li G, Xu S, Tao Z, Liu D, Ren H (2016b) Let-7c blocks estrogen-activated Wnt signaling in induction of self-renewal of breast cancer stem cells. Cancer Gene Ther 23:83–89

Sun Z, Kwon J-S, Ren Y, Chen S, Walker CK, Lu X, Cates K, Karahan H, Sviben S, Fitzpatrick JAJ (2024) Modeling late-onset Alzheimer's disease neuropathology via direct neuronal reprogramming. Science 385:adl2992

Takizawa C, Thompson PL, van Walsem A, Faure C, Maier WC (2015) Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. J Alzheimers Dis 43:1271–1284

Talemi MD, Tapak L, Haghi AR, Ahghari P, Moradi S, Afshar S (2023) MiR-15b and let-7a as non-invasive diagnostic biomarkers of Alzheimer's disease using an artificial neural network. Avicenna J Med Biochem 11:138–145

Tanzer A, Stadler PF (2004) Molecular evolution of a microRNA cluster. J Mol Biol 339:327–335

Thakur S, Dhapola R, Sarma P, Medhi B, Reddy DH (2023) Neuroinflammation in Alzheimer's disease: current progress in molecular signaling and therapeutics. Inflammation 46:1–17

Truesdell SS, Mortensen RD, Seo M, Schroeder JC, Lee JH, LeTonqueze O, Vasudevan S (2012) MicroRNA-mediated mRNA translation activation in quiescent cells and oocytes involves recruitment of a nuclear microRNP. Sci Rep 2:842

Tzioras M, McGeachan RI, Durrant CS, Spires-Jones TL (2023) Synaptic degeneration in Alzheimer disease. Nat Rev Neurol 19:19–38

van Harten AC, Mulders J, Scheltens P, Van Der Flier WM, Oudejans CBM (2015) Differential expression of microRNA in cerebrospinal fluid as a potential novel biomarker for Alzheimer's disease. J Alzheimers Dis 47:243–252

Vasudevan S, Steitz JA (2007) AU-rich-element-mediated upregulation of translation by FXR1 and Argonaute 2. Cell 128:1105–1118

Wang XR, Luo H, Li HL, Cao L, Wang XF, Yan W, Wang YY, Zhang JX, Jiang T, Kang CS, Liu N, You YP (2013) Overexpressed let-7a inhibits glioma cell malignancy by directly targeting K-ras, independently of PTEN. Neuro Oncol 15:1491–1501

Wang Y, Bao W, Liu Y, Wang S, Shengjie Xu, Li Xi, Li Y, Sufang Wu (2018) miR-98-5p contributes to cisplatin resistance in epithelial ovarian cancer by suppressing miR-152 biogenesis via targeting Dicer1. Cell Death Dis 9:447

Wang Y, Zhao J, Chen S, Li D, Yang J, Zhao X, Qin M, Guo M, Chen C, He Z, Zhou Y, Xu L (2022) Let-7 as a promising target in aging and aging-related diseases: a promise or a pledge. Biomolecules 12:1070

Wei Z, Koya J, Reznik SE (2021) Insulin resistance exacerbates Alzheimer disease via multiple mechanisms. Front Neurosci 15:687157

Wells AC, Daniels KA, Angelou CC, Fagerberg E, Burnside AS, Markstein M, Alfandari D, Welsh RM, Pobezinskaya EL, Pobezinsky LA (2017) Modulation of let-7 miRNAs controls the differentiation of effector CD8 T cells. Elife 6:e26398

Wells AC, Hioki KA, Angelou CC, Lynch AC, Liang X, Ryan DJ, Thesmar I, Zhanybekova S, Zuklys S, Ullom J, Cheong A, Mager J, Hollander GA, Pobezinskaya EL, Pobezinsky LA (2023) Let-7 enhances murine anti-tumor CD8 T cell responses by promoting memory and antagonizing terminal differentiation. Nat Commun 14:5585

Wu A, Kunpeng Wu, Li J, Mo Y, Lin Y, Wang Y, Shen X, Li S, Li L, Yang Z (2015) Let-7a inhibits migration, invasion and epithelial-mesenchymal transition by targeting HMGA2 in nasopharyngeal carcinoma. J Transl Med 13:1–13

Wu JW, Abid Hussaini S, Bastille IM, Rodriguez GA, Mrejeru A, Rilett K, Sanders DW, Cook C, Hongjun Fu, Boonen RACM (2016) Neuronal activity enhances tau propagation and tau pathology in vivo. Nat Neurosci 19:1085–1092

Xiao C, Rajewsky K (2009) MicroRNA control in the immune system: basic principles. Cell 136:26–36

Xiao M, Li J, Li W, Wang Y, Wu F, Xi Y, Zhang L, Ding C, Luo H, Li Y, Peng L, Zhao L, Peng S, Xiao Y, Dong S, Cao J, Yu W (2017) MicroRNAs activate gene transcription epigenetically as an enhancer trigger. RNA Biol 14:1326–1334

Xiao X, Liu H, Liu X, Zhang W, Zhang S, Jiao B (2021) APP, PSEN1, and PSEN2 variants in Alzheimer's disease: systematic re-evaluation according to ACMG guidelines. Front Aging Neurosci 13:695808

Xiao X, Hui Liu Lu, Zhou XL, Tianyan Xu, Zhu Y, Yang Q, Hao X, Liu Y, Zhang W (2023) The associations of APP, PSEN1, and PSEN2 genes with Alzheimer's disease: a large case–control study in Chinese population. CNS Neurosci Ther 29:122–128

Xie M, Li M, Vilborg A, Lee N, Shu MD, Yartseva V, Šestan N, Steitz JA (2013) Mammalian 5'-capped microRNA precursors that generate a single microRNA. Cell 155:1568–1580

Xu H, Zhu J, Hu C, Song H, Li Y (2016) Inhibition of microRNA-181a may suppress proliferation and invasion and promote apoptosis of cervical cancer cells through the PTEN/Akt/FOXO1 pathway. J Physiol Biochem 72:721–732

Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K (2001) A prospective study of physical activity and cognitive decline in elderly women: women who walk. Arch Intern Med 161:1703–1708

Yang JS, Maurin T, Robine N, Rasmussen KD, Jeffrey KL, Chandwani R, Papapetrou EP, Sadelain M, O'Carroll D, Lai EC (2010) Conserved vertebrate mir-451 provides a platform for Dicer-independent, Ago2-mediated microRNA biogenesis. Proc Natl Acad Sci U S A 107:15163–15168

Yu ML, Wang JF, Wang GK, You XH, Zhao XX, Jing Q, Qin YW (2011) Vascular smooth muscle cell proliferation is influenced by let-7d microRNA and its interaction with KRAS. Circ J 75:703–709

Zhang Z, Li Y, Huang L, Xiao Q, Chen X, Zhong J, Chen Y, Yang D, Han Z, Shu Y, Dai M, Cao K (2016) Let-7a suppresses macrophage infiltrations and malignant phenotype of Ewing sarcoma via STAT3/NF-κB positive regulatory circuit. Cancer Lett 374:192–201

Zhang J, Zhou W, Liu Y, Liu T, Li C, Wang L (2018) Oncogenic role of microRNA-532-5p in human colorectal cancer via targeting of the 5'UTR of RUNX3. Oncol Lett 15:7215–7220

Zhang H, Jiang X, Ma L, Wei W, Li Z, Chang S, Wen J, Sun J, Li H (2022) Role of Aβ in Alzheimer's-related synaptic dysfunction. Front Cell Dev Biol 10:964075

Zhao Y, Zhang Y, Zhang L, Dong Y, Ji H, Shen L (2019) The potential markers of circulating microRNAs and long non-coding RNAs in Alzheimer's disease. Aging Dis 10:1293

Zhou Q, Shi C, Lv Y, Zhao C, Jiao Z, Wang T (2020) Circulating microRNAs in response to exercise training in healthy adults. Front Genet 11:256

Zhu H, Shyh-Chang N, Segrè AV, Shinoda G, Shah SP, Einhorn WS, Takeuchi A, Engreitz JM, Hagan JP, Kharas MG, Urbach A, Thornton JE, Triboulet R, Gregory RI, Altshuler D, Daley GQ (2011) The Lin28/let-7 axis regulates glucose metabolism. Cell 147:81–94