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Beta-Secretase 1 and gamma-Secretase Activating Protein-Related MicroRNAs in Alzheimer's Disease: A Narrative Review

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ABSTRACT

Alzheimer's Disease (AD) represents an advancing neurodegenerative condition, and early diagnostic biomarkers are crucial to detect it in the pre-dementia stage. The formation of Amyloid beta relies on the proteolytic processing of precursor proteins, a critical biological stage controlled by the enzymes Beta-Secretase 1 (BACE1) and gamma-Secretase activating protein (GSAP). Multiple factors regulate the expression of BACE1 and GSAP, with microRNAs (miRs) playing a particularly significant role. Notably, fluctuations in the expression of certain miRs can precede any detectable changes in AD-associated genes. This is probably related to the unique and dynamically regulated expression pattern of specific miRs, such as members of the miR-29 family, miR-124, and miR-455-3p, which have shown significant regulatory roles in the pathophysiological context of AD. Thus, miRs may serve as non-invasive, cost-effective biomarkers for AD screening and diagnosis. For this purpose, a thorough literature search was conducted across the PubMed, Scopus, and Web of Science databases to find original English-language articles published between 2008 and 2025. The search focused on studies examining miRs that target BACE1 or GSAP in the context of Alzheimer's amyloidogenic pathways. Study selection was performed according to narrative review principles. Therefore, this review aims to pinpoint the specific microRNAs that modulate BACE1 and GSAP and to assess their clinical utility as new biomarkers for early-stage AD detection.

Keywords: miRs, Beta-Secretase 1 (BACE1), Gamma-Secretase Activating Protein (GSAP), Alzheimer's Disease

1. Introduction

Alzheimer's Disease (AD) represents a highly common and debilitating neurodegenerative condition marked by an advancing loss of cognitive capabilities. The disease predominantly affects the agingpopulation. Approximately 39% of AD diagnoses occur in individuals aged 75–84, and 26% in those aged 65–74 (1). The disease exhibits gender differences, affecting 12% of women and 9% of men aged 65 and older, with the highest prevalence (33.2%) in individuals aged 85 and above (2).

The creation and aggregation of amyloid-beta (Aβ) plaques represent a primary pathological characteristic of AD (3, 4). Beta-secretase 1 (BACE1) and gamma-secretase are essential enzymes in Aβ production. The amyloidogenic cascade begins with the proteolytic processing of the amyloid precursor protein (APP) at its β-site by the BACE1 enzyme, yielding the C99 fragment. Subsequently, gamma-secretase acts on this fragment to generate Aβ (5). Gamma-secretase activating protein (GSAP) regulates this process by interacting with both the gamma-secretase complex and C99, facilitating Aβ generation and amyloid plaque formation, a hallmark of AD pathology (6). Timely and accurate diagnosis of AD is essential to prevent irreversible dementia, but it remains challenging due to the disease's complexity and

heterogeneity. Current diagnostic methods mainly rely on cognitive tests that do not fully evaluate all affected domains, limiting their efficiency (7). Consequently, many cases remain undiagnosed, leaving an increasing demand for biomarker-based confirmation and pressure on memory clinics (8).

A combination of neuroimaging modalities and biochemical assays is utilized for the clinical diagnosis of AD. Magnetic Resonance Imaging (MRI) and Functional Magnetic Resonance Imaging (fMRI) are primary neuroimaging tools. MRI is useful for predicting AD (9); however, studies have indicated that its sensitivity and accuracy may not fully meet diagnostic needs (10). Positron Emission Tomography (PET) serves as an alternative imaging method, capable of revealing Aβ deposition and patterns of brain hypometabolism in patients with AD (11). While PET has demonstrated some effectiveness in the diagnosis of AD, it is often limited to specialized medical centers. Additionally, factors such as cost and the perception of invasiveness may hinder its widespread use in clinical practice (12).

Modulation of BACE1 in AD models directly impacts Aβ production, highlighting BACE1's critical role in the amyloidogenic pathway (13). Furthermore, decreased Aβ42 levels in cerebrospinal fluid (CSF) serve as an early biochemical marker for AD (9). However, obtaining CSF is an invasive procedure that carries risks of adverse effects, including severe back pain, nausea, and general weakness, which are particularly concerning for elderly individuals (10). These challenges have highlighted the need for minimally invasive or non-invasive markers. Biomarkers, which encompass molecules, genes, or natural characteristics, serve as indicators of specific pathological or physiological processes. Ideal AD biomarkers should improve diagnostic accuracy and detect the disease pre-symptomatically.

MicroRNAs (miRs), discovered in 1993, have gained special attention due to their unique regulatory roles (14). Changes in miR levels, which regulate over 60% of genes through post-transcriptional silencing, often occur before gene expression alterations, making them promising early AD biomarkers (15). In biological fluids like serum, plasma, and urine, miRs exhibit a high degree of stability due to their presence within extracellular vesicles or their association with protective proteins, shielding them from enzymatic degradation. This stability ensures miRs remaining intact during handling, making them promising minimally invasive biomarkers for early detection of diseases such as AD, as they can be repeatedly measured non-invasively in blood using sensitive techniques (16).

Investigating miRs as early AD biomarkers enables timely intervention, improves outcomes, and aids the development of treatments that may modify disease progression (17). The distinct expression patterns of serum miRs position them as specific biomarkers for AD diagnosis that can be accessed through noninvasive methods, emphasizing the need for innovative approaches to further facilitate early detection. Compared to conventional methods, miR-based assays are non-invasive, cost-effective, and offer high sensitivity for the early detection of AD. In addition to enabling personalized diagnostics, they facilitate repeated monitoring by using easily accessible samples such as blood. Nonetheless, technical and biological variabilities—including differences in sample processing and factors like hemolysis—demand standardized protocols and rigorous validation to ensure reliable and accurate clinical application (18). Selecting relevant miRs involves using validated databases (e.g., miRTarBase, miRGate) and analytical methods such as sequence analysis and experimental validation to warrant the identification of biologically significant early biomarkers (19).

BACE1 initiates APP processing, while GSAP regulates gamma-secretase activity, and both are crucial for Aβ production in AD pathology. Dysregulation of specific miRs is a promising AD biomarker, emphasizing the importance of key genes such as BACE1 and GSAP. GSAP, a less explored regulator in the secondary pathway, plays a pivotal role in β-amyloid processing a specific single-nucleotide polymorphism (SNP) within the GSAP gene that has been associated with changes in brain expression and a higher risk of developing AD (20). Since the dysregulation of microRNAs is a fundamental aspect of AD pathology (21), the 3′-untranslated regions (3′-UTR) of BACE1 and GSAP transcripts represent key targets for these molecules. These miRs play essential roles in AD and exhibit altered expression patterns during disease progression.

This review primarily aims to identify miRs regulating BACE1 and GSAP as potential early diagnostic markers for AD. Early detection is critical for timely intervention and slowing disease progression. Furthermore, a greater insight into the regulatory pathways controlling these miRs could help create new therapies that target the amyloidogenic pathway, offering new treatment strategies for AD. Moreover, unlike previous broader reviews, this study places special emphasis on miRs regulating GSAP, a less explored secondary pathway in amyloidogenesis.

2. Materials and Methods

This review synthesizes information gathered from a targeted literature survey of the PubMed, Scopus, and Web of Science databases, along with the authors' domain expertise. Our search strategy utilized keywords such as “Alzheimer's disease”, “microRNAs”, “BACE1”, “GSAP”, and “amyloidogenic pathway.” The inclusion criteria specified original English-language research articles published between 2008 and 2025 that examined miRs with a regulatory role on BACE1 or GSAP within the AD amyloidogenic pathway. Titles and abstracts were screened to ensure relevance. Reviews, meta-analyses, non-English publications, and studies unrelated to this pathway were excluded. Study selection was guided by scientific merit and the relevance of findings, in line with the authors’ expertise and the objectives of a narrative review.

miRs -modulating BACE1 Expression

2.1 Downregulated miRs

A substantial body of research indicates that disequilibrium between the synthesis and removal of extracellular Aβ42 is a central mechanism in AD pathogenesis (22). Reinforcing this view, Koyama's team has established that plasma Aβ levels are a statistically and clinically powerful predictor for both dementia and cognitive deterioration (23). Specifically, Aβ is generated through the sequential cleavage of APP by two enzymes: BACE1 and gamma-Secretase. Studies have demonstrated increased concentrations of BACE1 in the cerebral tissue of patients with sporadic AD (24). Notably, complete genetic deletion of BACE1 in mutant APP mice has been shown to prevent Aβ formation and the associated cognitive deficits (25). In individuals with a mutated APP gene, a diminished ability of BACE1 to cleave APP has been reported, highlighting its potential protective effect in AD patients (26). These findings lend support to the amyloid hypothesis and underscore the importance of targeting BACE1 as a viable strategy in sporadic AD research.

Additionally, increased serum levels of BACE1 have been observed in cases of late-onset AD (27). Research conducted by Vakillian et al. revealed significant differences in both plasma levels and peripheral blood gene expression of BACE1 when comparing AD patients to healthy controls. These findings further emphasize BACE1's potential role as a diagnostic marker and target for treatment in AD (28).

A notable decline in the concentration of the miR-29a/b-1 family in AD patients was first shown by Hébert et al (29). They noted that this reduction correlated with an unusual rise in the BACE1 expression, suggesting a potential link between miR levels and BACE1 regulation (Table 1).

Table 1. miRNAs and protein targets.

Sample Examined	Target	miRNAs	Expression Pattern	Reference
Human	BACE1 protein	miR- 29- a/b-1 family	Downregulated	Hébert et al (29)
Cell lines	BACE1 protein	miR-298 and miR-328	Downregulated	Boissonneault et al (30)
Mouse	BACE1 protein	miR-485-5p	Downregulated	Faghihi et al (31)
Cell lines	BACE1 protein	miR-135a-5p	Downregulated	Ding et al (32)
Human	BACE1 protein	miR-124	Downregulated	Fang et al (33)
Cell lines	BACE1 protein	miR-200 b and 135a	Downregulated	Liu et al (34)
Mice	BACE1 protein	miR-186	Downregulated	Kim et al (35)
Mouse	BACE1 protein	miR-29a	Upregulated	Müller et al (36)
Transgenic mice	BACE1 protein	miR-124	Downregulated	An et al (37)
Mouse	BACE1 protein	miR-455-3p	Upregulated	Kumar et al (38)
Human	BACE1 protein	miR-9	Upregulated	Xie et al (39)
Human	BACE1 protein	miR-15b	Downregulated	Gong et al (40)
AD cell lines, transgenic mice, and brain tissue of AD patients	BACE1 protein	miR-431	Downregulated	Ross et al (41)
Rat	BACE1 protein	miR-133b	Downregulated	Yang et al (42)
Brain tissues	BACE1 protein	miR-146a and miR-181a	Upregulated	Ansari et al (43)
Cell lines	BACE1 protein	miR-361-3p	Upregulated	Ji et al (44)
Cell culture and animal model	BACE1 protein	miR-298	Downregulated	Chopra et al (45)
Serum of AD patients	BACE1 protein	miR-15b	Downregulated	Li and Wang (46)
SH-SY5Y cells	BACE1 and GSAP protein	miR-4422	Downregulated	Hajjari et al (47)
Human	BACE1 protein	miR-29b	Downregulated	Jash et al (48)

Sample Examined	Target	miRNAs	Expression Pattern	Reference
Cell lines	BACE1 protein	miR-29c-3p	Downregulated	Cao et al (49)
Cell line	BACE1 protein	miR-149	Downregulated	Du et al (50)
Mice	BACE1 protein	miR-29c-3p	Downregulated	Wang et al (51)
SH-SY5Y cells	BACE1 protein	miR-15a-5p and miR-19b-3p	Downregulated	Rasadi et al (52)

Notably, the overexpression of miR-29a/b-1 in cell cultures was shown to reduce BACE1 activity and decrease Aβ generation, indicating a possible causal relationship. The study highlighted that miR-29a and miR-29b-1 could effectively regulate BACE1 expression in vitro, influencing luciferase activity and suppressing endogenous BACE1 levels (29). These findings propose that targeting miR-29a/b-1 may offer therapeutic strategies to lower BACE1 levels and Aβ production in AD, though it was acknowledged that other mechanisms may also contribute to changes in BACE1 expression. Further research is needed to elucidate the specific cell types affected by alterations in miR-29a/b-1 levels (29). Subsequently, a 2009 study from Boissonneault's group reported reduced levels of miR-298 and miR-328 in a murine AD model, while BACE1 transcript levels were not altered. Accordingly, these miRs act by binding to specific sites within the 3'-UTR of the BACE1 transcript, thus controlling its protein expression within neuronal cell cultures. Experiments confirmed that miR-298 and miR-328 bind BACE1 mRNA, reducing its expression (30). Moreover, neuronal cells under the influence of miR-298 and miR-328 showed reduced BACE1 protein levels. These collective findings suggest that the deregulation of miRNA-mediated control over BACE1 may significantly contribute to the pathology of AD, presenting potential targets for therapeutic intervention (30). Additional research by Faghihi et al (31) verified that inducing the elevated expression of miR-485-5p resulted in reduced BACE1 levels. A putative binding location for miR-485-5p on the BACE1 transcript, initially predicted via bioinformatics, was later confirmed experimentally using luciferase assays. Inhibition of miR-485-5p abolished its suppressive effect on BACE1 expression, confirming the specificity of its binding site. Conversely, the overexpression of miR-485-5p in HEK293T cells significantly reduced BACE1 protein levels. Furthermore, the study revealed that miR-485-5p is downregulated in AD, which may contribute to elevated BACE1 levels and Aβ formation (31). Ding et al (32) focused on miRs expression in the brain tissue of transgenic mice, reporting a marked reduction in the expression of miR-135a-5p compared to normal controls.

The study suggested that miR-135a-5p directly interacts with the 3'-UTR of BACE1 mRNA, where it's reduced expression likely results in the elevated levels of both BACE1 and Aβ. Thus, miR-135a-5p likely plays a role in the pathogenesis of AD (53).

The research group of Marong Fang established that fluctuations in miR-124 concentration directly impact the degree of neuronal death caused by Aβ neurotoxicity. Their findings indicate that the overexpression of miR-124 leads to a reduction in BACE1 levels and a corresponding decrease in cell death, whereas inhibition of miR-124 results in increased BACE1 expression and cell mortality. This suggests that miR-124 functions as a regulatory factor that modulates BACE1 expression, potentially mitigating cell death associated with the progression of AD. The study utilized cultured PC12 cell lines and primary hippocampal neurons to investigate the role of miR-124 in AD, proposing that it could emerge as a novel therapeutic target for patients with AD (33). Moreover, miR-135a has been identified as significantly downregulated in the hippocampi of both APP/PS1 transgenic mice and AD patients. This miR interacts directly with the 3'-UTR of BACE1, thereby repressing its expression and activity. Similarly, miR-200b has also been found to be significantly downregulated in the hippocampi of APP/PS1 transgenic mice. miR-200b targets the 3'-UTR of APP, resulting in a reduction in APP expression. Notably, Aβ42 can downregulate miR-200b, suggesting a potential feedback loop that increases Aβ42 accumulation. These observations indicate that both miR-135a and miR-200b play critical roles in regulating proteins associated with AD and could serve as potential biomarkers. miR-200b, in particular, has been highlighted for its capability to facilitate early detection of AD, including mild cognitive impairment (MCI) and dementia of Alzheimer's type (DAT) (34). Furthermore, a gradual reduction in miR-186 levels has been observed in the cerebral cortices of aging mice, a factor that could potentially elevate the risk of AD development. The expression of BACE1 in neuronal cells is repressed by miR-186 through a direct interaction with the 3'-UTR of its mRNA. The overexpression of miR-186 has been linked to a significant decrease in Aβ levels through the inhibition of BACE1 expression in cells with human pathogenic mutant APP. Conversely, the inhibition of endogenous miR-186 leads to an increase in BACE1 levels in neuronal cells, underscoring its role as a negative regulator in the context of AD.

Research by Kim and colleagues suggests that miR-186 is a significant factor in the aging brain, potentially increasing the vulnerability to developing AD (35). In the brain tissues of AD patients, miR-124 levels were significantly reduced compared to normal controls. miR-124 specifically targets the 3'-UTR of BACE1 mRNA,

inhibiting its expression. A reduction in miR-124 concentration leads to elevated BACE1 production, a critical step for the generation of Aβ (37). The overexpression of miR-124 has been shown to suppress BACE1 levels, thereby enhancing neuronal cell viability and reducing apoptosis. In contrast, the inhibition of miR-124 results in higher BACE1 expression, reduced cell viability, and elevated apoptosis. This positions miR-124 as a strong suppressor of BACE1, which highlights its promise as a point of therapeutic intervention for alleviating AD symptoms by modulating BACE1 activity (37). In a recent investigation conducted by the author, a significant downregulation of miR-4422 expression was observed in the serum of AD patients compared to healthy controls (47). The findings revealed that miR-4422 binds directly to the 3'-UTR of both BACE1 and GSAP, resulting in a corresponding reduction of reporter activity within HEK293T cells. This evidence substantiates miR-4422's function as a negative regulator for both BACE1 and GSAP in the context of AD (47).

In another aspect of the study, miR-29b expression was reduced in SH-SY5Y cells cultured under hyperglycemic conditions and in the presence of advanced glycation end products. Increasing miR-29b levels in these cells led to a decrease in BACE1 activity. The administration of human miR-29b resulted in improved short-term and spatial memory, reduced oxidative stress, and diminished BACE1 activity in the brain in diabetic mouse models. These findings position miR-29b as a promising candidate for addressing Alzheimer 's-like cognitive impairment associated with diabetes (48).

An exploration into the miR-29c-3p in Aβ-driven cellular processes revealed that inhibiting this microRNA decreased Aβ-induced apoptosis, whereas its overexpression enhanced cell proliferation. Importantly, it was indicated that miR-29c-3p has specific binding sites in the 3'-UTR of BACE1, allowing it to negatively regulate BACE1 levels and influence the progression of AD (49). Du et al (50) initially proposed a putative binding site for miR-149 within the BACE1 3'-UTR by employing bioinformatics tools. Subsequent validation with luciferase assays confirmed that miR-149 directly targets BACE1. They reported that miR-149 can reduce Aβ accumulation and enhance neuronal survival in a cellular model of AD through the inhibition of BACE1. Furthermore, decreased serum levels of miR-149 may serve as a potential diagnostic biomarker for disease severity in AD patients (50). miR-149 displayed high diagnostic accuracy for distinguishing AD patients from healthy controls, with a sensitivity of 91.1% and specificity of 86.7%. The levels of miR-149 also correlated with the severity of AD, effectively differentiating between severe, mild, and moderate cases. Collectively, these findings establish miR-149 as a reliable biomarker for the diagnosis and assessment of AD severity (50). In conclusion, miRs including miR-29a/b-1, miR-485-5p, miR-149, miR-124, and miR-4422 in humans; miR-298, miR-328, miR-135a-5p, miR-135a, miR-200b, and miR-186 in animal models; and miR-29c-3p and miR-29b in cell lines consistently exhibit downregulation in AD and regulate BACE1 expression. Among these, the miR-29 family stands out due to its robust regulatory effect on BACE1 and its potential as a leading diagnostic marker and target for treatment in AD.

2.2 Upregulated miRs

Moreover, miR-29a levels were observed to be substantially elevated in the CSF of AD patients compared to healthy subjects, yielding a sensitivity of 89% and a specificity of 70%. This increase in miR-29a levels in the CSF corroborates earlier findings and aligns with its elevated expression in the medial frontal gyrus of individuals with AD (54, 55). In contrast, miR-125b levels were only slightly higher in AD patients, showing a sensitivity of 78% and specificity of 60%. Consequently, due to its connection with BACE1 regulation and its higher level in AD, miR-29a is regarded as a strong candidate biomarker for disease diagnosis (36). miR-455-3p was observed to be upregulated in the serum and postmortem brain tissues of AD patients, as well as in APP transgenic mice and AD cell lines treated with Aβ peptide. Analysis demonstrated significant diagnostic accuracy for miR-455-3p in differentiating AD patients from healthy controls. This evidence indicates that miR-455-3p may function as a viable and specific peripheral biomarker for the initial detection and subsequent monitoring of AD (38).

Research conducted by Xie et al (39) established a key regulatory function for miR-9 in modulating BACE1 expression, a process mediated through the inhibition of cAMP response element-binding protein (CREB), a critical factor in dementia pathology. This highlights the potential of miR-9 as a specific biomarker for AD. The study found that miR-9 was overexpressed in the hippocampus and cortex of rats with chronic brain hypoperfusion, indicating its involvement in dementia. Moreover, suppressing miR-9 in these rats improved dementia symptoms, indicating its potential as a therapeutic target (39). A study by Ansari et al. identified elevated circulating levels of miR-146a and miR-181a in the MCI patient population. It was noted that higher levels of these microRNAs were negatively correlated with Aβ levels in the CSF. Furthermore, both miR-146a and miR-181a were found to be substantially elevated in individuals with MCI who subsequently progressed to AD. Among these, miR-181a demonstrated slightly superior predictive performance in logistic regression models compared to miR-146a. Although both miRs have potential as predictive biomarkers for AD conversion, their effectiveness is limited compared to existing biomarkers (43). In conclusion, a consistent pattern of upregulation is observed for miR-29a, miR-455-3p, miR-146a, and miR-181a in individuals with AD, while miR-9 is validated in animal models, all involved in BACE1 regulation and amyloid pathology. These miRs, particularly miR-29a and miR-455-3p, are promising biomarkers for AD diagnosis and monitoring due to their detectable increases in CSF, serum, and brain tissues.

2.3 Multifunctional miRs

Ji and colleagues have reported that elevated expression of miR-361-3p is associated with improved memory performance and enhanced spatial learning abilities.Overexpressing miR-361-3p in SH-SY5Y cells led to reduced levels of BACE1 and Aβ, while the inhibition of miR-361-3p resulted in elevated levels of both proteins. Behavioral assessments using the Morris water maze showed that miR-361-3p overexpression alleviated cognitive impairment. Additionally, miR-361-3p was found to decrease apoptosis in neuronal cells, potentially offering protection against neurodegeneration associated with AD. As a result, miR-361-3p is proposed as a promising therapeutic target for AD (44). Ccording to Chopra et al., miR-298 suppresses APP and BACE1 in human cell cultures, lowering Aβ40 and Aβ42 levels. Although the overexpression of miR-298 in mice tended to lower APP, BACE1, and tau levels, these changes were not statistically significant. Particularly, miR-298 is downregulated in AD models, highlighting its potential as a therapeutic target due to its regulation of multiple AD-related proteins (45). Lastly, it has been corraborated that miR-15b directly binds to the 3'-UTR of BACE1 and NF-κB1 and this interaction results in reduced expression of these target proteins that consequently diminishes Aβ production and inflammatory signaling. Experiments have confirmed that increasing miR-15b levels in cells led to a significant reduction in Aβ and BACE1. Notably, miR-15b is typically downregulated in AD models and contributes to increased BACE1 expression and neuroinflammation. Therefore, miR-15b is a promising molecular target for AD therapies due to its dual role in mitigating Aβ accumulation and inflammation (46).

The function of miR-15b in downregulating BACE1 expression within AD was additionally substantiated by the research of Gong et al, who found a negative correlation between miR-15b levels and BACE1 expression in AD-affected brain tissues. miR-15b directly targets the 3'-UTR of BACE1 mRNA, resulting in a reduction of BACE1 expression at both the mRNA and protein levels (40). Additionally, it was observed that suppressing miR-15b in SH-SY5Y cells counteracted Aβ-induced toxicity by enhancing cell viability and concurrently diminishing apoptosis. These results suggest that miR-15b is crucial for the cellular response to Aβ toxicity, indicating that targeting miR-15b could be a viable therapeutic approach for counteracting Aβ-induced neurotoxicity and apoptosis in AD (40). In further investigations of microRNA functions, miR-431 was identified as a protective factor against Aβ-induced synapse loss within a neuronal cell culture model of AD. The findings specify that miR-431 is essential for maintaining synaptic plasticity and preventing neurodegeneration associated with AD, positioning it as a potential therapeutic target (41). Additionally, a marked reduction in the serum concentration of miR-133b was observed in AD patients relative to the healthy group, with a sensitivity of 90.8% and specificity of 74.3% for diagnosing AD, positioning miR-133b as a valuable biomarker for AD. Furthermore, the overexpression of miR-133b in SH-SY5Y cells treated with Aβ 25-35 resulted in increased cell viability and reduced apoptosis, indicating its protective effect against neurotoxicity related to AD (42). miR-29c-3p is typically downregulated in AD models, which contributes to increased BACE1 expression and amyloid pathology. It directly binds to the 3′-UTR of BACE1 mRNA, suppressing its expression and thereby reducing Aβ-induced neurotoxicity. Additionally, miR-29c-3p mitigates apoptosis, oxidative stress, and inflammation, exerting neuroprotective effects. The overexpression of miR-29c-3p in animal models improves cognitive function, decreases amyloid plaque accumulation, and reduces neuronal death. These characteristics nominate miR-29c-3p as a viable point for therapeutic intervention and potential biomarker for the diagnosis and monitoring of AD (51).

A notable increase in BACE1 mRNA was seen in the peripheral blood mononuclear cells (PBMCs) from patients with late-onset AD. This change occurred concurrently with a marked reduction in the abundance of both miR-15a-5p and miR-19b-3p. These miRs directly target the 3′-UTR of BACE1, regulating its expression post-transcriptionally. Besides controlling BACE1, miR-15a-5p and miR-19b-3p influence inflammatory and apoptotic pathways. Their reduced expression is associated with increased neuroinflammation, oxidative stress, and cognitive decline. These findings confirm the link between molecular changes and cognitive impairment in AD. Moreover, miR-15a-5p and miR-19b-3p are elected as minimally invasive markers for early diagnosis, calling for further clinical validation research (52).

Collectively, this functionally diverse set of miRs, which includes the human-validated miR-133b (in serum) and miR-15a-5p, and miR-19b-3p (in PBMCs), as well as animal-model and cell-line confirmed miR-298, miR-15b, miR-361-3p, and miR-431, modulates numerous pathways associated with AD. These include BACE1 regulation (miR-298, miR-15b), cognitive function (miR-361-3p, miR-15a-5p, and miR-19b-3p), neuroprotection (miR-133b), neuroinflammation and oxidative stress (miR-15a-5p and miR-19b-3p), and synaptic maintenance (miR-431). The complementary evidence from human studies and experimental models positions these miRNAs as particularly valuable candidates for both biomarker development and multi-target therapeutic strategies in AD.

2.4 miRs -modulating Gamma Secretase Activity Protein

Gamma-secretase is an essential membrane-bound aspartyl protease composed of four key components: presenilin 1 (PS1), nicastrin (NCSTN), anterior pharynx defective 1 homolog A (APH1A), and presenilin 2 (PS2) (56). These components are crucial for forming the active gamma secretase complex, serving a critical function in the production of Aβ, thereby positioning gamma-secretase as a molecule with diagnostic potential in AD. However, the activity of gamma-secretase is also

influenced by other associated proteins, notably GSAP, first being characterized by He et al (57) GSAP has gained recognition for its significant contribution to the pathogenesis of AD. Evidence from biochemical and genetic studies establishes that there is an interaction between GSAP and the APP complex in turn affecting the trafficking and processing of APP within the brain. This interaction is critical as it regulates lipid homeostasis through the amyloidogenic processing of APP, which is implicated in the formation of amyloid plaques characteristic of AD (8). The knockdown of GSAP leads to selective reduction of Aβ levels, and silencing GSAP in an AD animal model decreased the accumulation of Aβ plaques (57). These findings suggest that GSAP may enhance Aβ production by facilitating the proteolytic processing of C99 by gamma-secretase, thereby presenting GSAP as a potential therapeutic target (58). He et al (57) reported that GSAP functions as a selective modulator of Aβ synthesis, asserting that inhibiting GSAP expression through artificial RNA could diminish Aβ levels (57). In 2012 Satoh et al (58) verified that silencing the GSAP gene reduced Aβ production and the deposition of plaques in the cerebral tissue of transgenic mice. Their immunohistochemical analysis of GSAP expression in the frontal cortex and hippocampus of AD models compared to controls nominated GSAP as a key determinant of APP cleavage and Aβ accumulation, marking it as an ideal target for the design of gamma secretase modulators with minimal side effects (58). Further studies indicated that reduced gamma secretase activity following GSAP gene knockout directly links GSAP to the regulation of gamma secretase activity (59). Newer studies have emphasized GSAP's significance in the amyloidogenic process, particularly its interaction with the APP C-99 fragment, making GSAP a highly attractive target for both diagnostic and therapeutic strategies in AD (6). Investigations of the frontal cortex and hippocampus in patients with AD confirmed that GSAP modulates gamma-secretase and enhancing Aβ production and accumulation (58). Conversely, reduced expression of GSAP in neuronal cells is associated with decreased Aβ formation and accumulation (60).

Research by Perez et al (61) identified a significant presence of the 98 kDa neocortical transcript of GSAP in Alzheimer's patients, correlating it with cognitive impairment. This was further supported by Satoh et al (58) who revealed that increased GSAP levels in the post-mortem brains of AD patients (58), suggesting that pharmacological inhibition of GSAP could be an effective therapeutic strategy to lower Aβ levels (62).

Although numerous miRs are known to modulate BACE1 expression, miR-4422 is currently the sole microRNA documented to exert a regulatory influence on GSAP. The levels of miR-4422 in the serum of the Alzheimer's group showed a marked reduction relative to the healthy control group. In vitro studies demonstrated that the miR-4422 mimic caused a notable reduction in the levels of GSAP protein within the A549 cell line (63). Furthermore, luciferase assays indicated that miR-4422 effectively reduced the luciferase activity of GSAP in HEK293T cells. This set of findings offers strong evidence for the direct targeting of the GSAP 3'-UTR by miR-4422, a mechanism that results in the negative regulation of its protein expression. Thus, miR-4422 is identified as a key regulator of both BACE1 and GSAP, highlighting its potential significnce in AD research (47). GSAP is a key component of the amyloidogenesis pathway and is involved in amyloid plaque formation and AD pathogenesis (60). It has been shown that reduced GSAP expression leads to decreased Aβ levels and amyloid plaque accumulation in animal models, underscoring its viability as a treatment approach (58). Despite its significant role, only one miR—miR-4422—has been reported to regulate GSAP to date, highlighting a notable research niche and emphasizes the need for further studies to identify additional miR regulators of GSAP. A comprehensive literature review confirms that miR-4422 is currently the only identified miR regulating GSAP, reflecting the current state of knowledge. In recent years, miR-based biomarkers have emerged as promising tools for AD diagnosis, offering several advantages over conventional methods (64). Unlike standard cognitive evaluation tools, including the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), which can be subjective and influenced by factors including patient cooperation and educational background, miR biomarkers provide objective molecular insights into disease pathology. Moreover, compared to neuroimaging modalities such as MRI and PET, miR detection is less invasive, more cost-effective, and more accessible, as it relies on biofluids such as blood or CSF (65). Nevertheless, challenges remain regarding the standardization of miR detection protocols, variability in sample handling, and the need for extensive validation in large clinical cohorts. Therefore, while miR-based biomarkers hold considerable promise for enhancing the feasibility and accessibility of AD diagnosis, they currently complement rather than replace existing diagnostic approaches (66).

3. Discussions

This study acknowledges several limitations in both its findings and methodology. Notably, the regulation of BACE1 is multifactorial and cannot be fully explained by alterations in miR expression alone, underscoring the necessity for more comprehensive investigations into the specific cell types affected by these miRs. Moreover, the mechanisms by which natural antisense transcripts (NATs) modulate gene expression remain insufficiently understood, thereby warranting further examination of the interactions between miRNAs and NATs.

The reliance on cellular and animal models poses another challenge, as the applicability of these findings to human AD pathology may be limited. This concern is exacerbated by small sample sizes and a lack of diversity within the study populations. Moving forward, future research should prioritize in vivo studies and incorporate larger, more diverse cohorts to validate findings across different demographic groups, thereby enhancing the

relevance of results to broader populations affected by AD. Longitudinal studies will be crucial for understanding the dynamics of miR expression throughout disease progression. Additionally, larger and more diverse cohorts will bolster the generalizability of the findings. Future research should also focus on the therapeutic potential of targeting specific miRs in both animal models and clinical trials to assess their efficacy and safety as potential treatments for AD.

Moreover, it will be essential to investigate how miRs influence the behavior and lifespan of AD models to achieve a more comprehensive understanding of their roles in the disease. Addressing these limitations will not only deepen our knowledge of miRs in the context of AD but also facilitate the development of more effective diagnostic and therapeutic strategies.

4. Conclusion

Recent studies have conclusively demonstrated that a range of miRs directly regulate the expression and function of key enzymes such as BACE1 and GSAP, both of which play pivotal roles in the amyloidogenic pathway of AD. Through the modulation of these proteins, miRs substantially affect the accumulation of Aβ and thereby impact disease progression. The elucidation of the regulatory networks involving these miRs not only paves the way for highly accurate and early diagnosis of AD—establishing miRs as reliable biomarkers—but also builds a strong foundation for innovative targeted therapies aiming to disrupt the amyloidogenic process. Compelling evidence confirms that precise adjustment of miR levels can attenuate clinical symptoms and potentially modify the natural course of AD, marking a significant progress in the clinical management of this disorder. Nevertheless, the widespread application of miR-based strategies may be constrained by factors such as specialized laboratory requirements and increased associated costs. Overall, substantial scientific evidence supports the potential clinical application of microRNAs (miRs) as both diagnostic biomarkers and therapeutic targets, suggesting considerable promise for improving the management and treatment of AD.

5. Declarations

5.1 Acknowledgments

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5.2 Ethical Considerations

This review article was conducted in accordance with the ethical standards of Tabriz University of Medical Sciences. The study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences (Ethical Code: IR.TBZMED.VCR.REC.1404.245).

5.3 Authors' Contributions

Seyedeh Nazanin Hajjari conceived the original idea, collected the data, and wrote the manuscript. Narges Daneshafrooz commented on the manuscript and revised the manuscript for important intellectual content. All authors participated in reviewing the manuscript and its revision, and they were involved in research, interpretation, and finalizing the manuscript.

5.4 Conflict of Interest

The authors have no conflict of interest.

5.5 Fund or Financial Support

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5.6 Using Artificial Intelligence Tools (AI Tools)

The authors declare that no AI tools were used.

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