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Epigenetic Remodeling in Alzheimer's Disease: Mechanistic Insights and Therapeutic Opportunities

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ABSTRACT

Background: Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder and a leading cause of dementia, involving the gradual loss of cognitive function, memory, and neurons. While the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs), caused by hyperphosphorylation of the protein tau, continue to be recognized as hallmarks of AD pathology, emerging evidence suggests that epigenetic dysregulation plays a crucial role in disease initiation and progression.

Purpose: The current review highlights the role of epigenetic remodeling in AD pathogenesis, emerging biomarkers associated with epigenetics, therapeutic strategies, and translational challenges.

Methods: This narrative review was conducted through a structured literature search of PubMed, Scopus, and Web of Science databases following the PRISMA framework. Relevant studies on epigenetic mechanisms, biomarkers, and therapeutic strategies in AD were screened and critically reviewed.

Results: Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA-mediated regulation, affect gene expression without changing the underlying DNA sequence and serve as a critical interface between genetic susceptibility, aging, and environment. Aberrant DNA methylation, changes in histone acetylation, methylation, phosphorylation, and ubiquitination, along with the dysregulation of microRNAs and long noncoding RNA, all play a role in amyloidosis, tauopathy, inflammation, oxidative damage, synaptic dysfunction, and neuronal loss. Additionally, several biomarkers related to epigenetics such as ANK1 methylation, miR-29a/b, miR-107, miR-132, miR-146a, and BACE1-AS have been discovered as potential disease biomarkers. Epigenetic therapeutics involving histone deacetylase inhibitors, DNA methyltransferase regulators, sirtuin-targeting agents, and RNA-based therapeutics have demonstrated neuroprotective effects in preclinical models of AD. Nevertheless, there are certain obstacles that limit their utility, such as insufficient blood-brain barrier (BBB) permeability, off-target effects, and poor clinical translation.

Conclusion: Advancing our understanding of the epigenetic landscape of AD may facilitate the development of precision diagnostics and disease-modifying therapies.

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1. Introduction

AD is a neurodegenerative condition that is accompanied by cognitive impairment, memory loss, impaired language skills, and executive dysfunction, which ultimately results in loss of independence and death. AD is identified through the presence of Aβ plaques, NFTs caused by hyperphosphorylated tau protein, hippocampal atrophy, oxidative stress, and neuroinflammation mediated by microglia activation. AD is categorised into two broad categories: early-onset familial AD (EOFAD) due to mutations in the APP, PSEN1, and PSEN2 genes; and late-onset sporadic AD (LOAD) due to multiple causes, including strong genetic risk factors like the APOE ε4 allele, ageing, and environmental exposures. Despite the well-known pathological hallmarks, the exact molecular basis behind AD development and its progression is not fully elucidated yet (Qin *et al.*, 2020).

The deposition of the insoluble Aβ protein in the brain is widely considered the hallmark of AD pathology. Other possible mechanisms for AD include the formation of hyperphosphorylated tau protein (tauopathy), persistent inflammation of the brain (neuroinflammation), and oxidative stress due to defects in mitochondria arising from mutations in mitochondrial DNA (mtDNA) (Garbuz *et al.*, 2021). Tau is a microtubule-binding protein that is essential for microtubule formation and stabilisation as well as protein interaction with membranes and DNA. Its function is tightly regulated by post-translational mechanisms like hyperphosphorylation, glycosylation, ubiquitination, glycation, polyamination, nitration, and truncation (Alonso *et al.*, 2008). Significantly, there has been increasing evidence that such pathological processes are associated with epigenetics, implying an additional level of regulation beyond mutation of genes. Alterations in epigenetic markers have been associated with the development of different diseases, including AD (Hesson *et al.*, 2019). Research in this area has mainly focused on DNA methylation and hydroxymethylation, histone post-translational modifications, and non-coding RNA regulation. In addition, mitochondrial gene expression is regulated by epigenetic mechanisms like DNA methylation and non-coding RNAs, making mitoepigenetics an emerging field of study for AD (Nikolac Perkovic *et al.*, 2025).

Epigenetics is defined as the structural alteration of the chromatin structure, leading to a change in the phenotype without any change in the genotype. Several epigenetic changes, including DNA methylation, histone modification, and noncoding RNA expression, have been identified in AD and play an important role in the development of the disease. The vast majority of AD patients are characterised by late-onset and sporadic AD, representing 90–95% of the cases, while the remaining 5–10% of patients are affected by early-onset mutations of APP and PSEN1. This underscores the significance of epigenetics as a bridge between genetic susceptibility and environment in AD (Li *et al.*, 2018).

1.1. Search Methodology

A structured literature search was conducted in PubMed, Scopus, and Web of Science to identify relevant studies published between January 2000 and March 2026. Keywords included "Alzheimer's Disease", "Biomarkers", "DNA methylation", "Epigenetics", "Histone modifications", "Non-coding RNAs", and "Therapeutics". The selection of studies was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework, as shown in Figure 1.

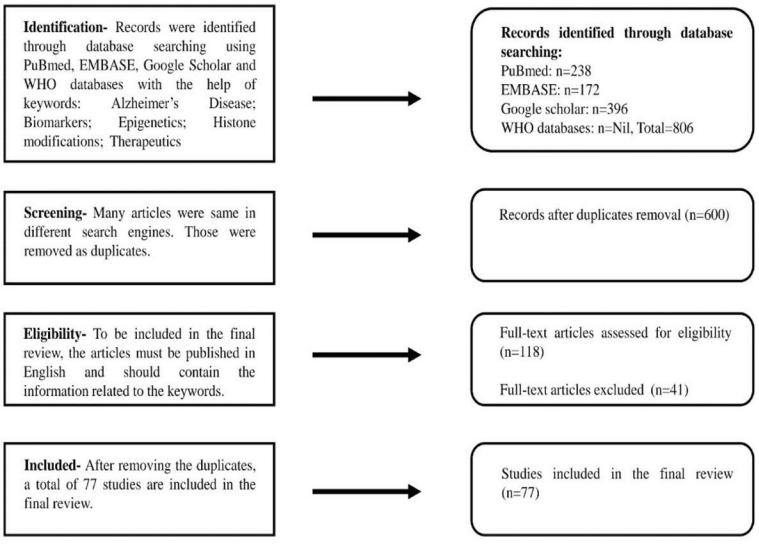

Figure 1: PRISMA Flow Diagram Illustrating the Literature Search and Study Selection Process for Epigenetic Remodeling in AD

2. Epigenetic Alterations in AD

2.1. DNA Methylation

DNA methylation plays a crucial role in the epigenetic mechanism involved in controlling gene expression in vertebrates (Mastroeni *et al.*, 2010). This process is extremely well-conserved and involves enzymes known as DNA methyltransferases (DNMTs), which catalyze the addition of a methyl group from S-adenosylmethionine to the cytosine residue through CpG dinucleotides (Bird, 2002). The four main DNMTs in mammals include DNMT1, DNMT2, DNMT3A, and DNMT3B. In particular, DNMT1 is the

most common and is responsible for DNA methylation maintenance in somatic cells. The lack of DNMT1 causes nuclear disorganization, increased histone acetylation, and apoptosis (Tajima *et al.*, 2022). Aberrant patterns of DNA methylation have been increasingly associated with gene expression profiles in AD, thus suggesting an association between epigenetic regulation and disease progression.

2.2. Histone Modifications

Histone modifications take place in the DNA-bound proteins that make up the histone octamer and play a key role in chromatin structure (Fenoglio *et al.*, 2018). These posttranslational modifications control gene expression through two major mechanisms: by changing chromatin accessibility and by recruiting regulatory proteins (Pal *et al.*, 2016). Histone modifications have been shown to be highly linked to learning, memory, synaptic plasticity, and cognition, all of which are impaired in AD (Nativio *et al.*, 2018). Histone proteins make up the nucleosome, which is a building block of chromatin, where DNA strands with 147 base pairs are wrapped around a core made of an octamer of histones, which includes histones H2A, H2B, H3, and H4 (Pal *et al.*, 2016; Levenson *et al.*, 2005). Linker histone H1 assists in the formation of high-order structures of chromatin (Höllmüller *et al.*, 2021). N-terminal tails of histones undergo various post-translational modifications such as acetylation, methylation, phosphorylation, ubiquitylation, and SUMOylation (Hwang *et al.*, 2017; Levenson *et al.*, 2005).

Histone acetylation is the most extensively studied histone modification and is commonly linked with transcription activation. The process of histone acetylation is facilitated by histone acetyltransferases (HATs), and histone deacetylases (HDACs) cause the removal of acetyl groups from histone proteins, causing transcriptional repression (Hwang *et al.*, 2017; Bosch-Presegué *et al.*, 2015; Bannister *et al.*, 2011; Kumar *et al.*, 2021). Histone acetylation decreases their positive charges, thereby reducing their interaction with DNA molecules and facilitating transcription initiation (Hwang *et al.*, 2017; Bannister *et al.*, 2011). The histone acetylation process is crucial for memory formation, memory consolidation, and synaptic plasticity (Peixoto *et al.*, 2013). The process is necessary for long-term potentiation (LTP) induction and synaptic transmission within the hippocampus (Geng *et al.*, 2021). The acetylation of H3 was reported to increase at the brain-derived neurotrophic factor (BDNF) promoter in animal models during learning processes (Lubin *et al.*, 2008). Transcription factors, including NF-κB, were found to be involved in the acetylation process (Federman *et al.*, 2013; De la Fuente *et al.*, 2015). Mutations associated with the CREB-binding protein (CBP) affect memory formation, and the use of HDAC inhibitors has been shown to reverse such changes. HDAC inhibitors (HDACi) have been proposed as promising drugs for cognitive improvement due to their role in promoting histone acetylation and increasing gene expression (Shukla *et al.*, 2020; Fischer *et al.*, 2007; Vecsey *et al.*, 2007; Kosik *et al.*, 2012; Gräff *et al.*, 2013).

Histone methylation may either facilitate or suppress the transcription of genes, depending on the specific modification of the histone. For instance, histone methylation at position H3K9 has been reported to be related to transcriptional activation in case of mono-methylation and transcriptional repression in case of di- and tri-methylation (Hwang *et al.*, 2017). The processes are facilitated by histone methyltransferases and histone demethylases (Kaniskan *et al.*, 2018; Morera *et al.*, 2016). Histone methylation also interacts with DNA methylation to regulate chromatin structure and gene expression (Gupta *et al.*, 2010; Hyun *et al.*, 2017; Tsankova *et al.*, 2006).

Histone phosphorylation is linked to chromatin remodeling, DNA repair, apoptosis, and activation of transcription (Bannister *et al.*, 2011; Rossetto *et al.*, 2012). Histone phosphorylation is linked with memory formation and the activation of immediate-early genes in the neurons (Kim *et al.*, 2018; Gonzales *et al.*, 2019). Ubiquitination and SUMOylation, which are less studied, are believed to regulate transcription and provide neuroprotection by eliminating aggregated proteins such as Aβ (Tau *et al.*, 2017; Gupta *et al.*, 2021).

2.3. Non-coding RNAs

Non-coding RNAs (ncRNAs), which are not translated into proteins, are categorized into two categories: housekeeping ncRNAs and regulatory ncRNAs. Regulatory ncRNAs consist of small interfering RNAs (siRNAs), microRNAs (miRNAs), piwi-interacting RNAs (piRNAs), and long ncRNAs (lncRNAs). They function in modulating transcription and post-transcription of genes and are important for cell differentiation (Wei *et al.*, 2017). There is increasing evidence that ncRNAs function as essential intermediates mediating the interaction between epigenetics and several pathophysiological characteristics of AD, such as synaptic pathology and neuronal degeneration (Figure 2).

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs, regulate gene expression without altering the underlying DNA sequence. These processes influence chromatin structure, determining transcriptionally active (euchromatin) or repressed (heterochromatin) states and thereby controlling cellular function and identity.

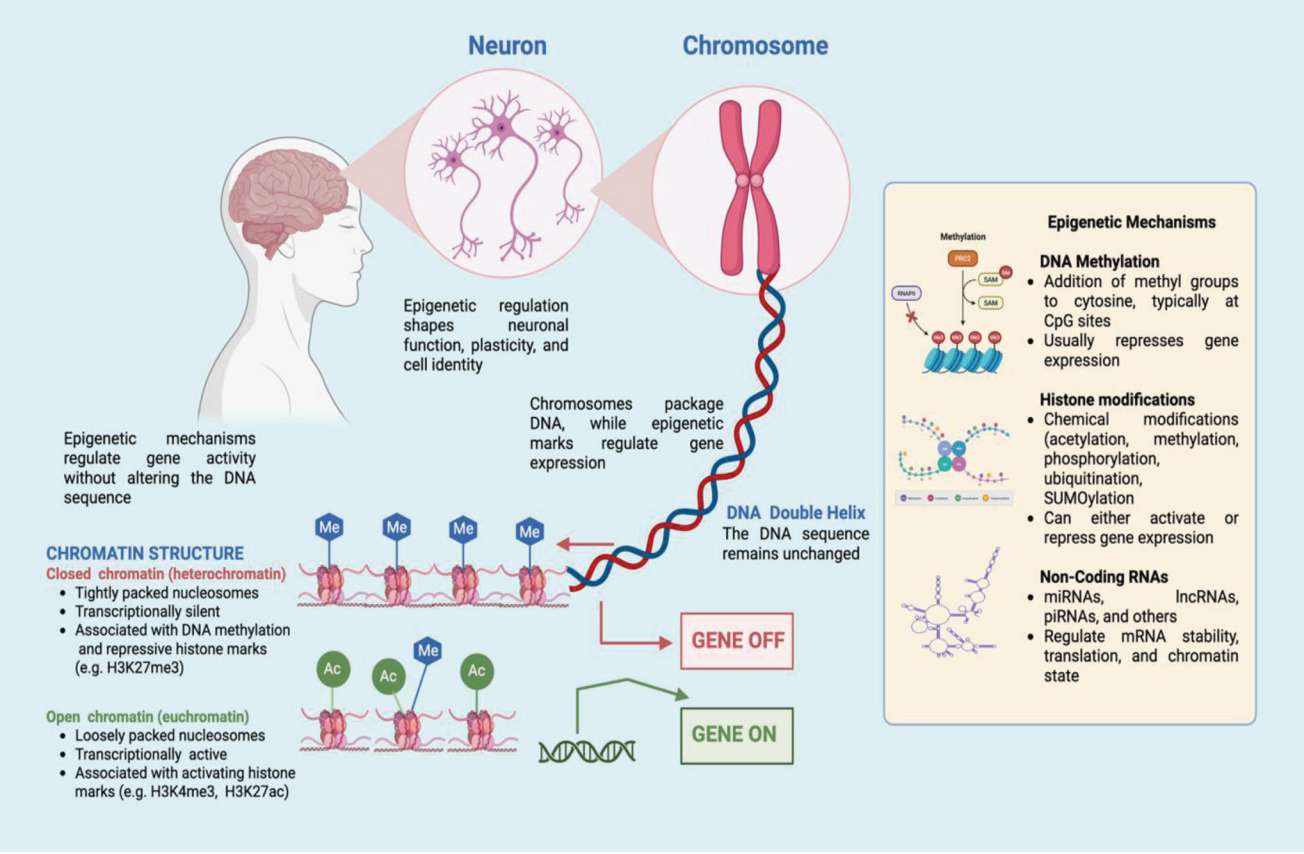

Figure 2: Overview of Epigenetic Mechanisms Regulating Gene Expression

3. Epigenetic Alterations driving AD pathology

3.1. Histone Acetylation in AD

In AD, dysregulation of histone acetylation results in changes in synaptic plasticity and memory functions (Schueller *et al.*, 2020; De Plano *et al.*, 2024). In AD patients, hyperacetylation in the cerebellum and slight hypoacetylation in the hippocampus have been reported, which is mediated by Rho GTPase pathway activation and cytoskeleton abnormalities (Santana *et al.*, 2022). Also, it has been noticed that there is a 50% decrease in H4 acetylation during learning in the hippocampus of APP/PS1 mice.

The beneficial effects of HDAC inhibitors on AD pathology have been demonstrated in several transgenic mouse models, where they improved cognitive function and attenuated Ab and tau pathology (Green *et al.*, 2008; Govindarajan *et al.*, 2011; Kilgore *et al.*, 2010; Ricobaraza *et al.*, 2009); however, their use clinically has been restricted owing to issues related to selectivity and side effects (He *et al.*, 2022). Among HAT enzymes, CREB-binding protein (CBP), P300, and PCAF are involved in the process of long-term memory. Modulation in their function has produced positive outcomes in AD models; for example, enhanced PCAF levels resulted in the improvement of memory loss in 3xTg-AD mice (Creighton *et al.*, 2022). In addition, the disruption of CREB activation under conditions of increased activity in young 3xTg-AD mice was reversed by upregulating CBP levels (De Plano *et al.*, 2024).

3.2. Histone Methylation in AD

There is considerable evidence concerning histone methylation alterations in AD. Several laboratories have also found that histone methylation alterations occur in AD patients. It has been reported that there is a significant decrease in histone methylation on residue K108 of H2B by 25% and on residue R55 of H2B by 35% in AD brains' frontal cortex (Anderson and Turko, 2015). Despite the relatively small number of AD brain samples, the findings were highly significant. Additionally, it has also been verified that AD patients had significantly lower levels of H3K4me3 and increased H3K27me3. Several hypotheses have been put forward about the connection between histone methylation and AD. Direct methylation of the MAPT gene has been

correlated with the accumulation of tau proteins and neurodegeneration (Balmik *et al.*, 2021). Moreover, a change in histone methylation could lower autophagy activity (Li *et al.*, 2019), which could be responsible for AD pathology. Several studies have suggested that autophagy controls the degradation of both Aβ and tau protein aggregates in AD brains (De Plano *et al.*, 2024). Overall, more investigation is required to understand the causes and consequences of methylation changes in histone modification in AD.

3.3. Histone Phosphorylation in AD

In AD, it has been reported that the phosphorylation of H4 (H4S47p) is positively associated with disease progression. Consistently, phosphorylation of H3 was found to increase in the frontal cortex of AD patients. After the occurrence of DNA double-strand breaks, the cells express a histone variant known as H2AX, which undergoes phosphorylation on S139. Elevated levels of H2AX Ser139 phosphorylation have been found in cortical and hippocampal astrocytes from AD patients compared to controls, highlighting a potential link between astrocytes and AD, although further studies are required (De Plano *et al.*, 2024). Several hypotheses have been proposed, but the exact mechanism for neuronal death in AD is still unknown (Balusu *et al.*, 2023; Goel *et al.*, 2022; Caccamo *et al.*, 2017). One of the widely accepted hypotheses proposes that the neurons attempt to reenter the cell cycle, resulting in cell death (Caccamo *et al.*, 2017). The reason behind this is that the level of histone H3 phosphorylated at Ser10 increases in the cytoplasm of AD hippocampal neurons, indicating cell cycle reactivation. As discussed above, concordance among various studies concerning selective epigenetic modifications is not always present, but this issue does not arise as much in connection with histone phosphorylation (De Plano *et al.*, 2024). Additional research would be required to determine the molecular mechanisms that relate histone phosphorylation to AD.

3.4. Histone Ubiquitylation in AD

Histone lysine ubiquitination is a posttranslational process in which ubiquitin becomes linked to specific lysine residues. This modification affects chromatin in various ways based on the specific lysine targeted and how many ubiquitin molecules have been added. It may promote or repress gene transcription. The modification also changes chromatin structure through its effect on interactions between histones and DNA, as well as interactions among nearby nucleosomes. The other significant impact of this modification is epigenetic inheritance because it acts as a marker determining the transmission of chromatin states through divisions and possibly even generations. Histone ubiquitination dysregulation has been associated with a variety of diseases affecting humans, such as neurodegenerative diseases. It has been noted that there is a significant 91% elevation in ubiquitination of H2B at K120 in the frontal cortex in AD patients (Anderson and Turko, 2015). Similarly, it has been documented that there is a ~50% increase in ubiquitination of H2A at K119 and a ~2-fold elevation in monoubiquitinated and pentaubiquitinated H2A in the cortex of AD patients (Guo *et al.*, 2022). Although these observations are remarkable, both studies utilized only a few samples from AD patients (6 and 7, respectively), suggesting the requirement for additional research before concluding that there is a connection between histone ubiquitination and AD.

Collectively, epigenetic changes converge on several molecular pathways that contribute to the progression of AD. The genes related to amyloid precursor protein (APP) processing, tau phosphorylation, synaptic plasticity, oxidative stress responses, and neuroinflammatory signaling are aberrantly methylated, modified by histone modifications, and dysregulated by non-coding RNA (De Plano *et al.*, 2024; Nativio *et al.*, 2018). DNA methylation and histone acetylation changes affect the transcription of APP-processing enzymes, such as BACE1, which leads to the accumulation of A. Likewise, epigenetic modifications of the MAPT gene and tau-associated kinases affect tau phosphorylation and contribute to the formation of neurofibrillary tangles (De Plano *et al.*, 2024; Balmik and Chinnathambi, 2021). In addition, epigenetic dysregulation promotes microglial activation and NF-κB-mediated inflammatory signaling, leading to increased expression of pro-inflammatory cytokines that further exacerbate neuronal injury (Seddon *et al.*, 2024). In addition, epigenetic dysregulation leads to a decrease in antioxidant defense mechanisms, which increases oxidative stress, synaptic dysfunction, and progressive neuronal degeneration (De Plano *et al.*, 2024). These interrelated mechanisms place epigenetic remodeling as a key player in the regulation of the major pathological hallmarks of AD.

4. Epigenetic Therapeutic Strategies in Experimental Models of AD

Preclinical studies have increasingly shown that pharmacological modulation of epigenetic remodeling has great potential as a therapeutic approach for Alzheimer's disease. Epigenetic modulators, especially histone deacetylase (HDAC) inhibitors and related compounds, have been shown to have beneficial effects in experimental models of AD, such as enhancing cognitive function, restoring synaptic plasticity, and reducing important pathological features such as amyloid-β accumulation and tau hyperphosphorylation. A summary of representative preclinical studies of these epigenetic modulators is provided in Table 1.

Table 1: Therapeutic Potential of Epigenetic Modulators in Experimental AD Models

S. No.	Drug/ Compound	Target	Experimental Model	Findings	Reference
1.	Vorinostat	Class I/II HDAC inhibitor	APPswe/PS1dE9 mice	Reversed contextual memory deficits	(Kilgore *et al.*, 2010)
2.	4-Phenylbutyrate	HDAC inhibitor	Tg2576 mice	Prevented spatial memory deficits and reduced tau pathology	(Ricobaraza *et al.*, 2009)
3.	Valproic acid	Class I HDAC inhibitor	APP23 transgenic mice	Reduced Aβ production and neuritic plaques	(Qing *et al.*, 2008)
4.	Sodium butyrate	Pan-HDAC inhibitor	APPPS1-21 mice	Improved associative memory and increased hippocampal histone acetylation	(Govindarajan *et al.*, 2011)
5.	Nicotinamide	Sirtuins/ class III NAD(+)-dependent HDACs inhibitor	3xTg-AD mice	Reduced phosphorylated tau and improved cognition	(Green *et al.*, 2008)
6.	RGFP966	Selective HDAC3 inhibitor	N2a mouse neuroblastoma cells and organotypic brain cultures (OBCSs) from 5XFAD mice	Increased APP expression without altering Aβ42 levels, reduced microglial and astrocyte activation, and promoted neuroregenerative pathways related to neurogenesis, axonogenesis, dendritic spine formation, and neuronal differentiation	(Davis *et al.*, 2024)
7.	CM-414	Dual HDAC/ PDE5 inhibitor	Tg2576 mice	Reduced Aβ and phosphorylated tau, restored dendritic spine density, improved LTP and cognitive function	(Cuadrado-Tejedor *et al.*, 2017)
8.	W2	Class II HDAC inhibitor	Aged hAPP 3xTg-AD mice	Reduced Aβ40/ Aβ42 levels, decreased tau phosphorylation, and improved learning and memory	(Sung *et al.*, 2013)

Collectively, these preclinical studies highlight the therapeutic potential of epigenetic modulators in attenuating multiple pathological features of Alzheimer's disease. Despite these encouraging results, however, their clinical translation is hindered by several factors, including low BBB permeability, off-target effects, and a lack of long-term safety data, which necessitates the need for well-designed clinical studies to demonstrate their long-term efficacy and safety in AD patients.

5. Clinical Evaluation of Epigenetic Biomarkers and Multi-Omics Approaches in AD

Table 2: Clinical Translation of Epigenetic Biomarkers and Integrated Multi-Omics Approaches in AD

S.No.	Study Title	Outcome Measure	Study Status
1.	Epigenetic Biomarkers for Alzheimer's Disease	Assessment of DNA methylation patterns, RNA sequencing (RNA-seq)-based-microbiome profiling, and cognitive performance using Alzheimer's disease Assessment Scale-cognitive subscale (Adas-Cog)	Completed
2.	Identification of Epigenetic Markers Common to Obesity and Alzheimer's Disease in Women (Oba)	Evaluation of CpG island methylation in genomic DNA and methylation status of AD-related genes including APP, SorLA/LR11, BACE1, and LRP in obese and AD subjects	Unknown

3.	Precision Medicine and Neurodegenerative Diseases: Advanced Systems for the Diagnosis and Treatment of Parkinson's Disease and Alzheimer's Disease. (NEUROTECHNO)	Cognitive evaluation using MMSE, MOCA test, and clock tests; neuroimaging assessments including MRI, CT, and PET; peripheral blood collection for DNA, plasma, and serum analysis; whole-exome sequencing; transcriptomic profiling using RNA-seq and microRNA omics; and global DNA methylation analysis using illumina infinium Methylation EPIC BeadChips arrays	Recruiting

6. Translational Challenges Associated with Epigenetic Therapy in AD

Table 3: Key Translational Challenges Limiting the Clinical Development of Epigenetic Therapies in AD

S.No.	Translational Challenge	Impact in AD	Reference
1.	Blood-Brain Barrier Penetration	Limited CNS delivery reduces efficacy of epigenetic therapeutics	(Pereira *et al.*, 2024)
2.	Lack of Target Specificity	Non-selective HDAC/DNMT inhibitors may cause off-target gene regulation	(Cacabelos & Teijido, 2018)
3.	Limited clinical translation of epigenetic therapeutics	Many promising preclinical findings fail in human trials	(Xiao *et al.*, 2020)

7. Biomarkers

Table 4: Major Epigenetic Biomarkers in AD and their biological significance

S.No.	Biomarker	Epigenetic Class	Sample	Alterations in AD	Significance	Reference
1.	ANK1	DNA methylation	Human cortex	Hypermethylation	Associated with neuroinflammation and AD pathology	(De Jager *et al.*, 2014; Lunnon *et al.*, 2014)
2.	BIN1	DNA methylation	Human cortex	Differential methylation	Influences tau pathology and endocytosis	(De Jager *et al.*, 2014)
3.	ABCA7	DNA methylation	Human cortex	Differential methylation	Regulates Aβ clearance	(De Jager *et al.*, 2014)
4.	HDAC2	Histone deacetylase	Hippocampus, cortex	Increased expression	Represses synaptic plasticity genes	(Gräff *et al.*, 2012)
5.	SIRT1	Class III histone deacetylase	Brain tissue	Reduced expression	Neuroprotection, tau regulation, amyloid metabolism	(Julien *et al.*, 2009)

6.	miR-29a/b-1	microRNA	Human brain	Downregulated	Increases BACE1 expression and Aβ generation	(Hébert *et al.*, 2008)
7.	miR-107	microRNA	Temporal cortex	Downregulated	Regulates BACE1 expression	(Wang *et al.*, 2008)
8.	miR-132	microRNA	Brain tissue, CSF	Downregulated	Controls synaptic plasticity and tau metabolism	(Smith *et al.*, 2015)
9.	miR-146a	microRNA	Brain tissue, serum	Upregulated	Mediates neuroinflammatory signaling	(Lukiw *et al.*, 2008)
10.	BACE1-AS	Long non-coding RNA	Brain tissue, plasma	Upregulated	Stabilizes BACE1 mRNA and enhances amyloidogenesis	(Faghihi *et al.*, 2008)

Although several epigenetic biomarkers have demonstrated strong associations with AD pathology, their clinical translation remains challenging (De Plano *et al.*, 2024; Villa and Combi, 2024). Variability in disease stage, patient heterogeneity, tissue source, and analytical methodologies can influence biomarker reproducibility (Villa and Combi, 2024). Moreover, many epigenetic alterations are not exclusive to AD and may overlap with other neurodegenerative disorders, thereby limiting their diagnostic specificity (Villa and Combi, 2024). Therefore, further large-scale longitudinal studies are required to validate these biomarkers before their routine clinical use (Villa and Combi, 2024).

8. Limitations of Current Epigenetic Research in AD

Despite significant advances in understanding the role of epigenetic mechanisms in AD, several limitations continue to hinder their clinical translation (De Plano *et al.*, 2024; Villa and Combi, 2024). Most preclinical evidence is derived from experimental animal models and in vitro studies, which may not fully recapitulate the complexity and heterogeneity of human AD (De Plano *et al.*, 2024). In addition, epigenetic alterations are highly dynamic, cell-type specific, and influenced by aging, environmental factors, and disease stage, making it challenging to distinguish causal epigenetic changes from secondary disease-associated alterations (Nativio *et al.*, 2018; Villa and Combi, 2024). Variability in experimental design, analytical methodologies, and sample sources further limits the reproducibility and comparability of findings across studies (Villa and Combi, 2024). Moreover, the lack of standardized epigenetic biomarkers and selective epigenetic modulators with adequate blood-brain barrier penetration remains a major obstacle to clinical application (De Plano *et al.*, 2024; Villa and Combi, 2024). Addressing these limitations through standardized experimental protocols, longitudinal human studies, and integration of multi-omics and single-cell approaches will be essential for translating epigenetic discoveries into effective diagnostic and therapeutic strategies for AD (De Plano *et al.*, 2024; Villa and Combi, 2024).

9. Conclusion and Future Perspectives

AD continues to pose a serious health problem across the world, as the available interventions only provide limited symptomatic relief. There is accumulating evidence suggesting the involvement of epigenetics in AD pathology by connecting genetic risk factors, age, environmental exposures, and lifestyle habits to the development of disease. Alterations in DNA methylation, histone modifications, and non-coding RNAs collectively contribute to disease progression by disrupting multiple epigenetic pathways involved in neuronal function and homeostasis. The identification of epigenetic biomarkers such as ANK1 methylation, miR-29a/b-1, miR-107, miR-132, miR-146a, and BACE1-AS further highlights the potential of epigenetic signatures for improving disease diagnosis, prognosis, and patient stratification. Although there have been encouraging developments, a number of challenges that hinder the clinical translation of epigenetic findings still persist. The intricate process of epigenetics, cellular heterogeneity of the brain, poor blood-brain barrier permeability of drugs, and the potential off-target effects are some of the major obstacles. In addition, most epigenetic therapies have demonstrated efficacy primarily in preclinical models, underscoring the need for rigorous clinical validation.

The future research directions could be towards the integration of epigenomic, transcriptomic, proteomic, metabolomic, and neuroimaging data sets in order to gain a comprehensive understanding of AD pathobiology. This can be achieved through the use of single-cell and spatial multi-omics techniques that will help identify cell-type-specific epigenetic changes and their temporal evolution during disease progression. The development of RNA-based therapies, selective epigenetic modifiers, and epigenome editing using CRISPR technology will have high potential for the development of targeted and personalized therapies. Further large-scale longitudinal studies will be essential to confirm the role of epigenetic biomarkers and demonstrate their clinical relevance in diagnostic and treatment settings. In conclusion, epigenetic remodeling plays an essential role in regulating AD and provides novel avenues for discovering biomarkers and developing therapeutics. Further understanding of these epigenetic mechanisms may help develop precision-based therapeutic approaches for AD.

Abbreviations

Aβ: amyloid-β; **AD**: Alzheimer's disease; **APP**: amyloid precursor protein; **BBB**: blood–brain barrier; **BDNF**: brain-derived neurotrophic factor; **CBP**: CREB-binding protein; **DNMTs**: DNA methyltransferases; **EOFAD**: early-onset familial Alzheimer's disease; **HATs**: histone acetyltransferases; **HDACi**: histone deacetylase inhibitors; **HDACs**: histone deacetylases; **lncRNAs**: long non-coding RNAs; **LOAD**: late-onset sporadic Alzheimer's disease; **LTP**: long-term potentiation; **miRNAs**: microRNAs; **mtDNA**: mitochondrial DNA; **ncRNAs**: non-coding RNAs; **NFTs**: neurofibrillary tangles; **OBCSs**: organotypic brain cultures; **piRNAs**: Piwi-interacting RNAs; **siRNAs**: small interfering RNAs.

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Authorship Contribution

Geeta Aggarwal contributed to the conceptualization of the review, preparation of the original draft, and manuscript revision. Amanpreet Kaur served as the corresponding author and contributed to conceptualization, investigation, critical review, and supervision of the manuscript. Vetriselvan Subramaniyam and Amanpreet Kaur contributed to reviewing and editing the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflicts of interest or competing interests related to this work.

Declaration

The authors affirm that this manuscript is original, has not been published previously, and has not been plagiarized. All authors have read and approved the final manuscript and take full responsibility for the accuracy, integrity, and originality of its contents.

Ethical Approval

The authors declare that no ethical approval was required for this study.

Human and Animal Rights

No human participants or animals were involved in this study. Therefore, ethical approval and informed consent were not required.

Data Availability Statement

Data sharing is not applicable to this article because no new data were generated or analyzed during this study. All information discussed in this review was obtained from previously published literature cited within the manuscript.

Figure Permission

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AI Disclosure Statement

The authors confirm that any use of artificial intelligence-assisted tools was limited to language editing and manuscript preparation support. The authors take full responsibility for the accuracy, integrity, and originality of the manuscript.

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