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Review

Genetic and epigenetic targets of natural dietary compounds as anti-Alzheimer's agents

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From the Contents

Abstract

Alzheimer's disease is a progressive neurodegenerative disorder and the most common cause of dementia that principally affects older adults. Pathogenic factors, such as oxidative stress, an increase in acetylcholinesterase activity, mitochondrial dysfunction, genotoxicity, and neuroinflammation are present in this syndrome, which leads to neurodegeneration. Neurodegenerative pathologies such as Alzheimer's disease are considered late-onset diseases caused by the complex combination of genetic, epigenetic, and environmental factors. There are two main types of Alzheimer's disease, known as familial Alzheimer's disease (onset < 65 years) and late-onset or sporadic Alzheimer's disease (onset ≥ 65 years). Patients with familial Alzheimer's disease inherit the disease due to rare mutations on the amyloid precursor protein (*APP*), presenilin 1 and 2 (*PSEN1* and *PSEN2*) genes in an autosomal-dominantly fashion with closely 100% penetrance. In contrast, a different picture seems to emerge for sporadic Alzheimer's disease, which exhibits numerous non-Mendelian anomalies suggesting an epigenetic component in its etiology. Importantly, the fundamental pathophysiological mechanisms driving Alzheimer's disease are interfaced with epigenetic dysregulation. However, the dynamic nature of epigenetics seems to open up new avenues and hope in regenerative neurogenesis to improve brain repair in Alzheimer's disease or following injury or stroke in humans. In recent years, there has been an increase in interest in using natural products for the treatment of neurodegenerative illnesses such as Alzheimer's disease. Through epigenetic mechanisms, such as DNA methylation, non-coding RNAs, histone modification, and chromatin conformation regulation, natural compounds appear to exert neuroprotective effects. While we do not purport to cover every in this work, we do attempt to illustrate how various phytochemical compounds regulate the epigenetic effects of a few Alzheimer's disease-related genes.

Key Words: Alzheimer's disease; epigenetics; genes; methylation; natural products

Introduction

Alzheimer's disease (AD) is a fatal neurological condition that affects about 50 million people worldwide. It is also the most common cause of dementia among the elderly population (Prince, 2015). Some of the pathological and clinical characteristics of AD are amyloid beta (Aβ) peptide deposits, neurofibrillary tangles (NFTs), dystrophic neurites, inflammation, oxidative stress, genotoxicity, cholinergic disorder, and massive neuronal death (Lue et al., 1999; Castillo et al., 2016; Castillo and Aristizabal-Pachon, 2017). Clinically, AD patients have a steady decline in their memory and ability to carry out daily tasks. Additionally, as the disease progresses, patients manifest limitations such as language impairment, thinking skills, depression, hostile behavior, hallucination, and psychosis, and in the ultimate stage of AD, require total care from caretakers (Anand et al., 2014).

Although a substantial amount of research has been conducted to comprehend the pathogenic mechanisms that cause AD, a consensus has not yet been reached and new theories on its causes are constantly being developed. AD is a chronic neurodegenerative disorder characterized by a number of genetic alterations and the subsequent dysregulation of gene activity and function. However, Alzheimer like other neurodegenerative diseases is not an entirely genetic disorder, and a variety of different biological processes, including immunological function, the microenvironment of the tissue, and epigenetic mechanisms, all play a role in how the disease evolves (Adwan and Zawia, 2013).

The study of epigenetics as a whole has grown rapidly over the past few years thanks to the identification of new regulatory mechanisms and substances, as well as the emergence of new paradigms. In its broadest meaning, epigenetics is an additional layer of information and processes that sits atop the genome and contributes to the regulation of genetic material (Locke et al., 2019). The term "epigenetics" includes the Greek prefix "epi", which implies these are processes that are "on top of" or "in addition to" the genetic effect (Nightingale, 2015). As such, genetic impacts refer to modification in the DNA sequence (i.e., when genes are mutated or rearranged) that result in changes in gene function and phenotype. In contrast, a heritable change in gene expression without any alterations in the nucleotide sequences of the DNA is referred to as an epigenetic modification.

The interest in this area is due to three: (i) epigenetic mechanisms are frequently supported by innovative, intriguing mechanisms and involved in various key domains of biology. (ii) Since epigenetic control affects gene expression significantly, it contributes to the development of disease processes and is occasionally to blame. (iii) Numerous novel proteins and enzymes are involved in epigenetic processes, making attractive targets for small-molecule (Carey, 2015).

DNA methylation, covalent histone modifications, small non-coding RNAs (ncRNAs), and chromatin conformation are the primary mechanisms of epigenetic control (Babenko et al., 2012; Gangisetty and Murugan, 2016). Overall, all these pathways act as mediators between the environment and the genome. Neurodegenerative pathologies such as AD are considered late-onset diseases caused by the complex interplay of genetic and epigenetic environmental factors. The likelihood of developing a neurodegenerative disease later in life can be altered by early environmental influences that occur even during development (Iraola-Guzmán et al., 2011).

Since most cases of AD are sporadic and develop over time, there is a significant contribution of environmental factors to the onset of this neurodegenerative pathology. Late-onset or sporadic AD (SAD, onset ≥ 65 years) exhibits numerous non-Mendelian anomalies that suggest an epigenetic component in disease etiology (Wang et al., 2008; Adwan and Zawia, 2013; Chen et al., 2019). In contrast, a different picture to seem emerge for familial AD (FAD, onset < 65 years) whose disease is inherited in

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an autosomal-dominantly fashion with close 100% penetrance, and is known to be associated with rare mutations on the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and *PSEN2* genes. The dynamic nature of epigenetic marks and their participation in adaptive processes such as maturation and neural plasticity, aging, reprogramming of gene expression, and response to external stimuli, makes them important candidates to be involved in the etiology of complex diseases, such as AD (Karpova et al., 2017).

Regarding therapeutic strategies, although AD has been studied for over a century, there is not a treatment that gets to change the course of the disease. To date, cholinergic inhibitors are the drugs approved by the US Food and Drugs Administration (FDA) for their treatment; however, they only provide symptomatic treatment but do not alter the course of the disease. The three acetylcholinesterase inhibitors (AChEi) approved by FDA (donepezil, rivastigmine, and galanthamine) are widely used in clinical therapy. The dysfunction of the cholinergic system in memory processing and storage is the base of the commonly accepted cholinergic hypothesis (Hampel et al., 2019). The identification of natural compounds is an emerging approach in medical chemistry. In this context, identifying plants or their metabolites as epigenetic regulators to treat neurodegenerative diseases has been of great interest in recent years. Several dietary components such as polyphenols, flavonoids, and alkaloids have been shown to selectively modulate gene expression through DNA methylation, acetylation homeostasis, and miRNA (Reuter et al., 2011; Gangisetty and Murugan, 2016). As a result of the evolutionary process, compounds of natural origin are often complex and may affect multiple targets. Diet consists of a complex mixture of biologically active molecules that can be either micronutrients (in the nano-to-micromolar concentration range), such as vitamins, or macronutrients, such as carbohydrates, proteins, and fats. In this context, this work describes the main genetic and epigenetic targets of some natural compounds in the prevention and treatment of AD. These compounds may act by modulating gene expression or by altering the activity of enzymes involved in epigenetic regulation.

Search Strategy

We conducted a comprehensive literature search using the PubMed, Scopus, and Web of Science databases. The search was based on the following keywords: "Alzheimer's disease," "epigenetics," "natural products," "phytochemicals," "DNA methylation," "histone modification," "non-coding RNAs," and "chromatin conformation." We limited the search to articles published in English within the last ten years up to March 2023. We included studies that investigated the effects of natural products on epigenetic modifications in Alzheimer's disease-related genes.

Alzheimer´s Disease Genetic Mutations Targeted by Natural Dietary Products

A better understanding of the genetic and environmental risk factors that contribute to the development of AD is essential for finding new therapeutic strategies (**Figure 1**). Although most cases of AD are sporadic, familial mutations in either presenilin 1 or 2 (*PSEN1*, *PSEN2*) or the amyloid precursor protein (*APP*) account for 1% of cases. These mutations correspond to FAD, which is more common in patients under 65 years of age (Bekris et al., 2010). In contrast, the main risk factor for SAD, besides age, is carrying the E4 allele of the apolipoprotein (*APOE*) gene (Roses and Saunders, 1994; Coon et al., 2007; Bagaria et al., 2022). Numerous lifestyle factors have been associated with a lower risk of developing AD. For instance, AD is less likely to develop in those who have more years of formal education, have mentally challenging jobs, or maintain social engagement (Almeida et al., 2015; Sommerlad et al., 2019; Amelianchik et al., 2022); however, it is not entirely clear how these variables influence the reduction of the risk of developing cognitive impairment or dementia, which are the main symptoms of AD.

Somatic mutations are mutations that occur only in a subset of cells, creating a mosaic pattern of heterogeneous genomes in an organism. These mutations can arise from different causes and at different times, affecting either a single cell (private) or many cells (clonal) (Miller et al., 2021). Previous studies have shown that somatic mutations accumulate in neurons during normal aging at a similar rate as in dividing cells, suggesting that genetic factors, environmental exposure, or disease conditions may influence this process (Alexandrov et al., 2015; Miller et al., 2022). Because somatic mutations in neurons accumulate throughout normal aging at a rate similar to dividing cells, it is possible that genetic variables, environmental exposure, or disease states may have an impact on this accumulation (Lodato et al., 2018; Starling, 2018).

The bulk of mutations are the consequence of accumulated changes brought on by endogenous and environmental variables over the course of a person´s lifetime, with some mutations being inheritable. Diet is one of the most important lifestyles variables, as it has shown have a significant impact on the occurrence and onset of neurodegenerative disorders. It has been suggested that plant-derived chemicals have a variety of neuroprotective effects on the brain, including the ability to protect neurons from damage brought on by neurotoxins and to enhance memory, learning, and cognitive function (Vauzour et al., 2008). Because of their capacity to interact with the molecular and cellular architecture involved in memory consolidation, storage, and maintenance, bioactive phytochemical have been shown to have an impact on neurocognitive performance. Accordingly, epidemiological evidence suggests that consuming a variety of fruits and vegetables may provide a number of bioactive phytochemical compounds that may combine to reduce the risk for neurodegenerative disorders such as AD (Kumar and Khanum, 2012; **Figure 2**).

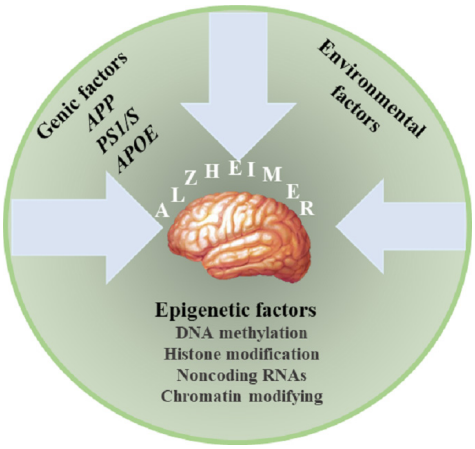

Figure 1 | **Alzheimer's disease is the result of the interaction between genetic, epigenetic, and environmental factors.**
Adapted with permission from Castillo-Ordoñez (2022).

Figure 2 | **Consumption of fruits and vegetables against neuroprotection.**
The intake of fruits and vegetables provides bioactive phytochemical compounds that work synergically to decrease the risk for neurodegenerative disorders (e.g., Alzheimer's disease). Created using Microsoft PowerPoint. AChE: Acetylcholinesterase.

The following subsection covers four common genetic mutations (*APP*, beta-site APP cleaving enzyme 1 [*BACE1*], *PSEN1/2*, and *APOE*) targeted by dietary compounds; however, there are few studies aimed at evaluating the effect exerted by natural compounds on these genes:

APP

The APP gene located in chromosome 21, codes a member of the APP family of proteins. Even though its physiological function has not been clearly elucidated, it is known to be an important factor for the brain's neural tissue development during processes including neurogenesis, proliferation, and cell fate specification of neural stem cells. Mechanistically, the enzymatic cleavage of APP produces amyloid-β (Aβ) protein, one of the major constituents of the extracellular senile plaques that characterize the brain of AD patients (Weggen and Beher, 2012). Therefore, it has been assumed that both peptides play a central role in its pathogenesis. Diverse enzymatic proteolysis mechanisms that result in the formation of various Aβ peptide variants are involved in the differential processing of APP by β- and γ-secretases. Each variant has a unique biological role in the physiological and pathological intracellular processes that occur during AD.

The observed modified processing of APP by these secretases is due in part to pathogenic mutations on APP which cause either, an increase of the overall Aβ production or a change in the ratio of different Aβ peptides (Goldgaber et al., 1987). Thus, it is considered an important aspect in designing the therapeutic intervention, which has been mainly focused on reducing the levels of Aβ in AD.

More than 270 highly penetrant gene mutations related to AD have been reported including 53 *APP* constitutive mutations and duplications that cause its differential enzymatic processing (www.alzforum.org/mutations). Some of them have been linked to the neuropathology of early-onset familial types of AD. The Swedish mutation, which increases the processing of APP at the β site by 10- to 50-fold, has the highest risk effect for the early onset of AD (Zhou et al., 2022). A new mutation at exon 17, named the Uppsala deletion, increases APP cleavage by BACE1 generating the rapid aggregation of Aβ peptides which lack amino acids 19–24 due to the elimination of non-amyloidogenic processing of APP (Li et al., 2015). This mutation causes autosomal dominant inheritance of the disease which adds in favor of the amyloid cascade hypothesis (Pagnon de la Vega et al., 2021).

Various mutations near to the BACE1 cleavage site modify Aβ production and have been associated with the risk of developing AD. Mutation A673T confers resistance to cleavage by the APP protease BACE1 which causes a reduction

of Aβ production and their oligomers present reduced aggregation capacity (Kero et al., 2013). Due to its variable frequency, this mutation seems to be a genetic protection factor that has shown a reduction of around 28% in AD risk development in some populations but low to imperceptible risk modulation in others (Wang et al., 2015). On the contrary, three mutations: A to V mutation at the same site, K to N on residue 670, and M to L on residue 671, all increase BACE1 cleavage activity and Aβ production and are related to an increased risk of AD (Mullan et al., 1992).

Alterations of epigenetic marks have been shown to affect *APP* gene. Since 1995, several authors have shown an association between age and progressive hypomethylation of the *APP* promoter element in postmortem brains of AD patients (Salameh et al., 2020). However, conflicting results have been reported by more recent studies. In addition, the relationship between *APP* epigenetic alterations and proposed mechanisms about the role of stem-like cell subpopulations in the development of AD is being explored with the purpose of gaining a clearer understanding of the causes that underlie such epigenetic variations (De Strooper and Karran, 2016). The results suggest that epigenetic factors may play a role in the emergence of pathogenic cell subpopulations when embryonic stem or progenitor cells encounter chronic inflammation or oxidative stress (Chouliaras et al., 2013).

Therefore, there is a lot of potential for translational goals in understanding the molecular pathways involved in the programming and maintenance of epigenetic aberrations in associated genes in both early and late-onset forms of AD. This knowledge has already been applied in the discovery of epigenetic biomarkers and in the use of pharmacological targeting to undo AD-specific epigenetic changes.

BACE1

BACE1, also named memapsin, is a type I transmembrane secretase of the pepsin family of proteases largely expressed in neuronal cells of the brain, although the majority of body tissues display β-secretase activity at variable low levels except for the pancreas (Haass et al., 1992; Yan et al., 1999).

High activity and concentration of BACE1 have been detected at the synaptic terminals and also next to Aβ plaques in AD brains (Yang et al., 2003). BACE1 produces the amyloidogenic APP proteolysis forming soluble amyloid precursor protein β and β-C-terminal fragment called C99, which is further cleaved by γ-secretase to produce monomeric soluble $Aβ_{40}$ and insoluble $Aβ_{42}$ peptides that aggregate in senile plaques in AD, causing synaptic disruption and inflammation respectively (Vassar et al., 1999; Yan et al., 1999). Alteration of normal posttranslational modifications of *BACE1* during the progression of AD has been reported which affect its trafficking, activity, and degradation. Despite the documented importance of BACE1 gene in the etiology of AD, so far, gene mutations modulating the risk of the disease have not been reported. However, regulation of BACE1 by epigenetic mechanisms has been largely documented, including posttranscriptional degradation of mRNA by a variety of microRNAs including miR-107, miR-29c, miR-339-5p, miR-186, miR-195, miR-135b, miR-135a, miR-124, and miR298/328. These ncRNAs evidence cell type specificity and mRNA site of binding length variations, such as miR298 that was recently reported to reduce both APP and BACE1 protein levels *in vitro* in an astrocytic but not in a neuron-like cell line with the truncated binding site on the target 3'-UTR mRNA (Wang and Lahiri, 2022).

As the enzyme responsible for initiating Aβ generation, BACE has been identified as a key druggable molecule for early therapeutic inhibition of Aβ production in AD. Therefore, it is an ongoing interest in the search for molecules that safely inhibit β- or γ-secretase proteolytic action. Despite a few FDA-approved BACE1 inhibitors are available in the market, their usage is limited as they have shown adverse secondary effects. In addition, clinical trials with several molecules have not yet succeeded due to safety limitations or because have not shown acceptable therapeutic effects (Moussa-Pacha et al., 2020). These observations, could be due to the fact that other BACE1substrates, in addition to APP, have been discovered with central roles in the physiology of synapsis (Kuhn et al., 2012). Recent studies have shown the involvement of BACE1 in insulin and leptin signaling explaining the association between type two diabetes and the risk of AD (Zhao and Townsend, 2009; Taylor et al., 2022). Therefore, the exact substrate interactions of BACE1 need to be completely identified as well as their involvement in the unintended adverse responses exerted by BACE1 inhibitors. To address this issue, a recent *in silico* docking analysis combined with molecular dynamics simulation protocols were able to identify among 26,467 natural food compounds, the Musella lasiocarpa's bioactive component 4-(3,4-dihydroxyphenyl)-2-hydroxy-1H-phenalen-1-one, as a safe potential inhibitor of BACE1 (Mukerjee et al., 2022). Further *in vitro* and *in vivo* analyses need to be conducted to confirm its potential as an effective AD treatment.

PSEN1 and PSEN2

The majority of early-onset, autosomal dominant AD has been linked to the *PSEN1* and *PSEN2* genes as pathogenic loci (Hutton and Hardy, 1997; Miller et al., 2021). In these two genes have been identified a series of (predominantly) missense mutations, which lead to pathology. Although the pathogenic mechanisms of these mutations are not clear, the effects of presenilin mutations are similar to those of the pathogenic mutations in the APP gene, which cause an increase in the production amyloid-β42, both patients and *in vitro* models (Hernández-Sapiéns et al., 2022). Therefore, the published studies on PSENs provide independent confirmation of the amyloid cascade hypothesis regarding Alzheimer's etiology (Hutton and Hardy, 1997). Most of the autosomal dominantly transmitted mutations associated with AD are accounted for by *PSEN1*. It has been noted that this complex has more than 300 mutations. In contrast, less than 80 mutations in *PSEN2* have so far been found, making them uncommon (Tanzi, 2012; Cai et al., 2015; Hernández-Sapiéns et al., 2022) (www.alzforum.org/mutations). PSEN2 mutation-carrying AD patients, in contrast to *PSEN1* patients, show a wide range of age of onset, from 40 to 80 years (Youn et al., 2014). Mutations in *PSEN2* seem to be associated with other diseases such as frontotemporal dementia, dementia with Lewy bodies, breast cancer, and dilated cardiomyopathy (Cai et al., 2015).

Several natural agents show their neuroprotective properties through *PSEN1/2*-dependent regulation. Among flavonoids, luteolin has shown positive effects on the nervous system. The neuroprotection mechanisms have been associated with the selective inactivation of the GSK-3α isoform, which is responsible for the phosphorylation of *PSEN1*, the catalytic core of the γ-secretase complex thereby decreasing *PSEN1*-APP interaction and Aβ generation (Fu et al., 2014; Wang et al., 2016). Natural compounds such as Curcumin present in turmeric have been used widely as an herbal medicine for its neuroprotective activity against cognitive impairment, and one of its action mechanisms has been associated with the capacity to modulate the expression of *PSEN1/2*. Studies conducted by Sayevand et al. (2022) showed that mRNA expression of proteolytic components of γ-secretase (*PSEN1/2*) was attenuated by curcumin and improved mRNA expression of catabolic enzymes involved in Aβ degradation and clearance. Another study shows that the administration of Curcumin to APPswe/ PSEN1dE9 double transgenic mice decreased the γ-secretase component and stimulated the degradation of aggregated Aβ (Yang et al., 2005). In addition, Curcumin such as natural polyphenol exerts a potent anti-amyloidogenic effect. Curcumin also decreased levels of oxidized proteins and plaque burden in APP-transgenic mice (Salminen et al., 2013). However, clinical trials on the properties of Curcumin in AD have provided inconsistent results that are difficult to interpret.

The dried root of ginseng (Panax ginseng C. A. Meyer), a perennial herb belonging to the Araliaceae family, has long been utilized in Asian medicine. The primary components and main biologically active compounds of ginseng are known as ginsenoside, which are a subclass of triterpenoid saponins and steroid glycosides (Zheng et al., 2018). Ginsenosides have received a lot of interest recently for their neurotrophic and neuroprotective properties against neurodegenerative diseases such as AD, Parkinson's disease, and vascular dementia (Huang et al., 2019; Li et al., 2022). In a transgenic AD model constructed through the overexpression of APP and PSEN1, treatment with ginsenoside Rg1 improved memory and reduced the accumulation of β-amyloid and p-Tau. Additionally, proteins associated with synaptic plasticity were upregulated following ginsenoside Rg1 application in the APPswe/ PSEN1dE9 transgenic mouse model (Li et al., 2016).

APOE

The primary carrier of lipids and cholesterol in the central nervous system is APOE. Humans possess three main polymorphisms: *APOE2*, *APOE3*, and *APOE4*. The genetic expression of *APOE4* is one of the most significant risk factors for the emergence of late-onset Alzheimer's disease. This categorization is founded on an arbitrary age cut-off range that corresponds to the age at which clinical symptoms first appear (Fernández-Calle et al., 2022). APOE4 is less effective at removing Aβ from the blood-brain barrier (BBB) than other APOE isoforms (APOE2 and APOE3) because it has a lesser affinity for Aβ. Additionally causing improper brain cholesterol metabolism, APOE4 also increases Aβ production and promotes AD risk (Huang et al., 2022).

Growing epidemiological evidence indicates that a variety of environmental factors and lifestyle factors may interact with *APOE* alleles to influence the likelihood of developing AD. Among them, dietary practices such as consuming fat and following a ketogenic diet, physical activity, higher education, traumatic brain injury, cigarette smoking, coffee drinking, alcohol consumption, and exposure to pesticides and sunlight have drawn more and more attention. Although there is conflicting evidence at this time, it appears that younger *APOE4* carriers in the preclinical stages may benefit mostly from preventive lifestyle interventions, whereas older *APOE4* noncarriers with dementia may experience the most pronounced impact. The significant discrepancies in the epidemiological studies may be attributable to disparities in sample sizes, methodological designs, and participant demographics, including age and sex, as well as potential confounding factors such as associated exposures and comorbidities (Angelopoulou et al., 2021).

Currently, it is still unclear whether the effect of lifestyle on cognition varies by genetic dementia risk represented by different *APOE* genotypes. Prior studies have reported inconsistent results on the interactions between *APOE* genotype and lifestyle factors on cognitive outcomes. Some studies showed significant interactions between *APOE* genotype and single lifestyle factors, such as physical activity, alcohol consumption, and diet, or the combined effect of lifestyle factors, with stronger effects among *APOEε4* carriers than noncarriers (Anttila et al., 2004; Rovio et al., 2005; Laitinen et al., 2006). Nevertheless, other studies failed to detect such an interaction (Lourida et al., 2019).

Based on *APOE*, dietary quality may affect individual genetic information; in this context, the utilization of genotype-based health information needs to be better understood in order to achieve long-term changes in the prevention of lifestyle-related disorders (Hietaranta-Luoma et al., 2014). Several studies have shown a negative correlation between the consumption of fruit

and vegetable and the development of AD regardless of education level, tea intake, tobacco use, amount of physical activity, and *APOE* genotype. However, antioxidant vitamins cannot solely explain the inverse association between fruit and vegetable consumption and AD. To ascertain whether substances other than antioxidants vitamins, such as polyphenols may have protective benefits, additional research is required.

Mechanisms of Epigenetic Modifications

The term "epigenetic" describe molecular processes that initiate and sustain heritable modifications in gene expression without modifying the DNA itself. Epigenetic pathways are crucial to embryonic development and normal physiology. In evolutionary terms, the epigenetics interface between the genome and the environmental milieu is undoubtedly one of the most ingenious designs introduced by nature. Epigenetic systems provide potential as therapeutic targets since dysregulation of epigenetic events is linked to a number of disorders, including AD (Cacabelos, 2017).

DNA methylation, chromatin remodeling, histone modification, and long ncRNAs, are effective regulators of activity-dependent changes in gene expression. A significant number of these epigenetic alterations in the brain have been strongly associated with synaptic plasticity and memory formation. However, it has only recently been investigated how these pathways are dysregulated throughout life and how they affect memory loss with aging and AD (Maity et al., 2021).

Particularly epigenetic modifications have the power to alter transcriptional activity coherently across thousands of genes and dozens of cellular pathways, but they behave differentially in monozygotic twins, the same organism at different periods of development, or adjacent cells in the same organ, all of which share the same genetic makeup. Therefore, the epigenetic landscape offers a way by which environmental factors including diet, risky exposures, and lifestyles can affect gene expression. Epigenetic pathways may therefore offer a point of convergence for many risk factors and pathophysiologic processes linked to AD (Mastroeni et al., 2011; Alcalà-Vida et al., 2021). Thus, epigenetic modifications can be desirable and viable targets for the prevention and treatment of AD.

DNA Methylation

In the human body, the distinct gene expression repertoire of each cell determines its individuality. It must be retained and passed on to daughter cells via epigenetic mechanisms, being DNA methylation one of the most studied (Maity et al., 2021). One epigenetic mechanism known as DNA methylation causes direct changes to DNA molecules through the addition of a methyl group at the fifth position of cytosine (5mC) in a CpG dinucleotide (**Figure 3**). CpG dinucleotides are not equivalently distributed across the genome, but these are commonly abundant in the promoters and regions of large repetitive sequences such as ALU and LINE retrotransposons elements. CpG islands are discrete regions found in the promotors of 50% to 70% of human genes (Shen et al., 2007). The transcriptional silence of repetitive DNA and genes that are not needed in a particular cell type is frequently linked to DNA methylation.

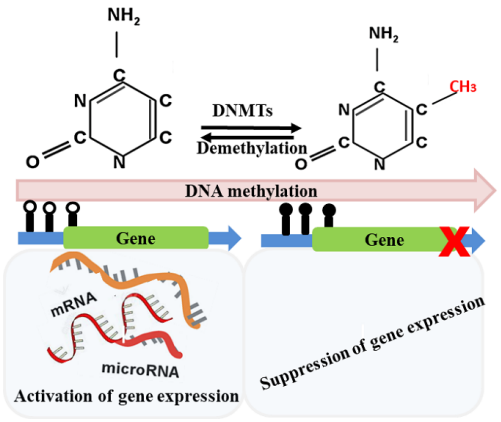

Figure 3 | **Epigenetics regulation by DNA methylation.**
Proximal promoter DNA methylation at cytosine-phosphate-guanine dinucleotide islands result in gene silencing by transcriptional repression, while DNA demethylation results in the activation of gene expression. Created using Microsoft PowerPoint. DNMTs: DNA methyltransferases.

DNA methylation is linked to transcriptional control due to the covalent addition of a methyl group to cytosine at carbon 5 by the enzyme DNA methyltransferases (DNMTs), which transfer a methyl group from S-adenosylmethionine (SAM) onto 5′-cytocine positions adjacent to guanine nucleobase to stablish the 5-methylcytosine mark (5mC). DNMTs are divided into various subgroups, each with its special function. So far, there are three main DNMTs identified such as DNMT1, DNMT3a, and DNMT3b. DNMT1 maintains previously marked methylation on DNA by methylating the opposing DNA strand (Nakao, 2001; Bandyopadhyay and Medrano, 2003; Cacabelos, 2017), while DNMTs (3a and 3b) have identical affinity for both unmethylated and hemimethylated DNA and are required for global de novo methylation (Okano et al., 1999).

The somatic cell´s DNA methylation pattern is an example of an epigenetic program that keeps the genome under general repression and imprinted genes in a particular environment. This mechanism is essential to preserve the DNA methylome during replication. However, during some developmental phases, such as the preimplantation phase and the formation of primordial germ cells, DNA methylation takes place. This biological pathway creates pluripotent states in early embryos and removes parental-origin-specific imprints in developing primordial germ cells (da Rocha and Gendrel, 2019). In the context of neuroepigenetics, its regulation is critical for the normal development and functioning of our brain. In principle, neuroepigenetics is based on the same mechanisms as all other of our tissues and cell types. This way, genome-wide DNA methylation patterns significantly change in the course of brain development and maturation; these mechanisms are the basis for neuronal plasticity (Carlberg and Molnár, 2019). The regulation of gene activity in the adult brain has been linked to DNA methylation (Mehler, 2008; Ratnu et al., 2017). It has to do with how synaptic activity affects whether genes are activated or suppressed. Such systems control the expression of particular sets of neuronal genes, which are necessary for the survival, morphogenesis, and neural activity of neurons.

In the context of neurodegenerative disorders, the plastic nature of the dynamic part of the neural epigenome through demethylation has significant implications for possible epigenetic reprogramming. Target genes that are primarily involved in the pathogenesis of AD, such as *APP*, *PSEN1*, *APOE*, and *BACE1*, have shown altered methylation patterns. In the post-mortem brains of AD patients, it has been found that the APP gene's promoter CpGs are hypomethylated. These changes in DNA methylation patterns affect how the *APP* gene is expressed, which may contribute to the gradual deposition and accumulation of Aβ (West et al., 1995). The few human investigations of *PSEN1* methylation AD patients, however, have been contradictory. According to certain studies, the post-mortem brain of AD patients had hypomethylated *PSEN1* (Wang et al., 2008), additional research has been unable to support these findings, both in the peripheral tissue and post-mortem brain (Barrachina and Ferrer, 2009; Carboni et al., 2015; Tannorella et al., 2015). However, these results need to be interpreted carefully, since small changes in methylation profiles, might not be easily detected; nevertheless, by relating to chronic degenerative diseases, subtle changes in vulnerable neurons may be sufficient to change methylation patterns and modulate disease progression.

Among widely studied epigenetic regulatory drugs, include DNA methylation inhibitors and histone deacetylases (HDAC) inhibitors (HDACIs). DNA methylation inhibitors such as zebularine and 5-AZA deoxycytidine are more frequently utilized to treat cancer. These drugs integrate into target DNA and attach to DNMT1 during DNA replication to impede its activity and therefore require DNA replication to be active (Wu and Santi, 1985; Gangisetty and Murugan, 2016). However, in neurodegernative disorders, such as AD, the use of these drugs has limitations since most of the neurons are postmitotic.

Together, neuroepigenetic associated with DNA methylation provide alternative and/or additional mechanistic explanations for the onset of neurodegenerative disorders. In this way, neuroepigenetic has the potential to direct the development of novel treatment approaches for reducing the negative effects of cognitive impairment and neurodegeneration.

Histone Modification

The epigenome's physical representation is chromatin. Histones are the main protein components of chromatin and form octamers cores, around which DNA molecule is wrapped. Histones are enormously basic proteins that bind with chromatin´s DNA molecule via a substantial portion of their N-terminal tail. Structural approaches show that the N-terminal tail of histone proteins protrudes from the chromatin core and take place the post-translational modifications, which play a crucial role in controlling DNA structure and gene transcription (Luger et al., 1997). The majority of histone modifications, including methylation, acetylation, and sumoylation occur at the N-terminal. These mechanisms impact chromatin organization and all DNA-template processes, including replication, repair, and transcription. Depending on the type and position of the modification and the implicated residues, histone modification can either activate or inhibit gene expression (Mühlbacher et al., 2006; Gangisetty and Murugan, 2016).

Histone modifications are dynamically governed by groups of enzymes and are potentially reversible. The best-characterized modification within histone tails is methylation/demethylation, acetylation/deacetylation, events that are regulated by two groups of enzymes, histone acetyltransferases (HATs) which relaxes chromatin by adding acetyl groups, and HDACs, which removes acetyl groups (Adwan and Zawia, 2013).

The positive charge of the amino acid lysine is neutralized when a HAT attaches an acetyl group to the amino group in the side chain. In the other direction, an HDAC can take the acetyl group off H3K4ac and reinstate the positive charge on the lysine residue. The balance between HATs and HDACs defined as acetylation homeostasis, and the context of neuroepigenetics is a key event in the control of neuronal growth and differentiation (Saha and Pahan, 2006; Beaver et al., 2020).

HDACs have been classified into four classes: class I (HDAC1, 2, and HDAC 8), class II (HDAC4-7 and HDAC9-10). Class III (SIRT1-7), and HDAC11 (Class IV) (Seto and Yoshida, 2014; Linciano et al., 2021). In particular, HDAC2, HDAC3, and HDAC7expression are associated with brain regions implicated in memory and learning, such as the hippocampus and cortical areas (Guan et al., 2009; Maiarù et al., 2016). In contrast, the loss function of HDAC7 leads to the increased expression of c-jun and c-fos, an essential feature of neural death (Ma and D'Mello, 2011; Jagirdar et al., 2016).

Another special mechanism of post-translational modification is the histone methylation. Histone methyltransferases, which can transfer up to three methyl groups from S-adenosine methionine to the lysine residues of the histone tail, catalyze the addition of methyl groups to a histone protein (Maity et al., 2021). Histone methylation is a more durable change in the protein than acetylation, and it also indicates a more persistent epigenetic state because of its lower turnover rate (**Figure 4**). Histone methylation, in contrast to histone acetylation, can result in either transcriptional activation or repression depending on the pattern of methylation. In particular, the number of methyl groups added and the specific histone location being modified both affect the direction of transcriptional control. For instance, methylation of histone H3 lysine 4 (H3K4me), H3K36me, and H3K79me is linked to transcriptional activation, while the addition of a methyl group at H3K9me, H3K27me, and H4K20me result in transcriptional repression (Hyun et al., 2017; Kumari et al., 2022).

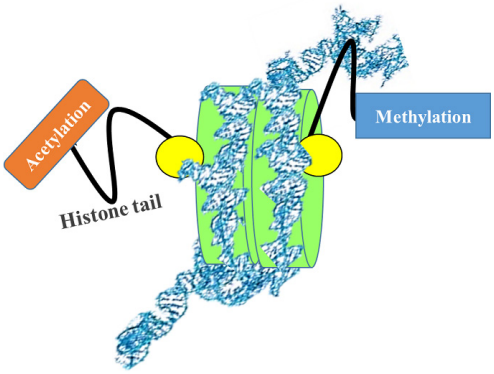

Figure 4 | **Histone modification.**
Histone methylation, in contrast to histone acetylation, can result in either transcriptional activation or repression depending on the pattern of methylation. Created using Microsoft PowerPoint.

It is thought that epigenetic mechanisms such as methylation and histone modification are also crucial elements to the pathophysiology of AD as a complex and interacting link between genes and the environment. A new avenue for the study of AD has been made possible through epigenetic alteration. One of the most important research hotspots is the relationship between DNA methylation and histone modification. Because of this, attention and interest in HDACIs as a potential therapy option for neurodegenerative illnesses have grown. HDACIs were first used in the treatment of cancer (Yang et al., 2017). However, Hahnen et al. discovered in 2008 that HDACIs could be used as a therapeutic approach for neurodegenerative diseases. Histone acetylation has been found to be decreased in a variety of neurodegenerative disorders, including AD (Hahnen et al., 2008; Lockett et al., 2010). *In vitro* studies showed that trichostatin A, an HDAC inhibitor, caused a significant up-regulation of Aβ-degrading enzyme neprilysin (NEP) expression in the SH-SY5Y cell line (Kerridge et al., 2014). On the other hand, the treatment of APP/PS1 models with HDACI MS-275 showed ameliorated microglial activation, decreased Aβ deposition, and reduced inflammatory activation (Zhang and Schluesener, 2013).

In several recent investigations, HDACIs have been identified to be novel, promising therapeutic agents, particularly for AD and other neurodegenerative diseases. HDACIs can improve cognitive impairment; these encouraging outcomes in AD animal models and cell lines, however, are rarely replicated in clinical trials. To lessen adverse side effects, it is imperative to address the development of HDACIs with enhanced isoform selectivity or seek other approaches (Yang et al., 2017).

HDACIs show good promise for cognitive improvement and are being considered for drug development in neurological diseases. Hence, HDACIs could be used as promising therapeutic agents for diseases associated with dementia and cognitive impairments. So far, class I HDACIs such as sodium valproate and sodium butyrate improve memory in AD mouse models (Kilgore et al. 2010).

Non-coding RNAs

ncRNAs are a group of diverse RNA molecules that are not translated into proteins but act through two main functions: housekeeping or regulatory RNAs. The regulatory role of ncRNA is played during pre and post-transcriptional phases and is considered fundamental epigenetic controller of gene expression through different mechanisms. Based on their size, ncRNAs are generally classified as small ncRNAs with a length smaller than 200 nucleotides and include microRNAs, small interfering RNAs (siRNA), piwi-interacting RNAs (piRNAs); ncRNAs longer than 200 nucleotides are named long ncRNAs and include intergenic lincRNAs, intronic ncRNAs, and sense and antisense lncRNAs (Zhang et al., 2019). The development of modern technologies of transcriptome analysis and big data analysis during the last decades has allowed a deep understanding of the key genetic processes that control expression such as the ones that are exerted by ncRNAs and how their dysregulation underlie the molecular bases of diverse human diseases. This knowledge offers novel strategies for preclinical diagnosis and specific treatments.

Among the ncRNAs implicated in AD pathogenesis, microRNAs are of great importance. They are the most abundant types of small ncRNA in the cell and mediate gene silencing at the post-transcriptional level by suppressing the stability and translation of target mRNAs when binding to its 3′ untranslated region (3′-UTR) or the promoter region. MicroRNAs are regulated by chromatin remodeling modifications and DNA methylation, which are associated with AD by obstructing mRNA expression (Jackson and Standart, 2007). A wide variety of microRNAs have been shown to be involved in neuronal physiology including proliferation, cell death, and cellular communication. MicroRNA346 is a microRNA with a well-characterized function in AD, which directly upregulates APP and Aβ production. Interestingly, MicroRNA346 binds the APP mRNA 5′-UTR where an active site for an iron-responsive element for the iron-dependent translational repressor is located (Rogers et al., 2002; Long et al., 2019). The overlapping with the iron-responsive element explains the role of iron on the APP upregulation activity of MicroRNA346, whose disruption has been reported during the late stages of AD (Long et al., 2019).

In other mechanisms of action, microRNAs have been found to interact with lncRNA, which have elements that bind specific microRNAs causing a suppression of its functions in degrading target mRNA. It has also been discovered that miRNA can be made out of precursor lncRNAs, which undergo splicing to generate specific miRNAs post-transcriptionally regulating their activity. That is the case of BACE1-antisense transcript (BACE1-AS) that can act on miR-761 causing suppression of its degradation activity and upregulating BACE1 expression. Deregulation of BACE1-AS is likely to initiate a cascade of events that lead to Alzheimer's and other neurodegenerative diseases (Costa et al., 2012).

Brain-derived neurotrophic factor (BDNF) has been studied as an important protein in promoting neurogenesis and their protection against apoptosis allowing neuronal plasticity. BDNF is a target of miR-206 and drops its expression. In healthy individuals, a regulatory negative feedback loop between ubiquitous BDNF and miRNAs is maintained in constant equilibrium which BDNF induces miRNA expression. However, in neurons of AD, characterized by reduced levels of BDNF, the balance is lost and the miRNAs change towards inhibition of BDNF (Keifer et al., 2015). Other microRNAs have been documented to regulate BDNF to control cellular signaling pathways such as miR-10a and miR-134-5p (Zhang et al., 2018; Khani-Habibabadi et al., 2019). On the other hand miR-9-5p inhibitors were able to reverse the effect of siBDNF-AS on amyloid deposition (Ding et al., 2022). These observations and a mounting of others, give evidence on the usefulness of ncRNAs for elucidating mechanisms that inspire new approaches for a more effective treatment of AD.

Chromatin Conformation

Mounting evidence has clearly recognized the importance of the mechanisms that control the three-dimensional (3D) organization of chromatin inside the nucleus as a fundamental epigenetic aspect that explains nearly 70% of the genome expression and maintenance of cell identity in tissues including the brain (Gosselin et al., 2017). Recent studies (Dileep and Tsai, 2021; Harabula and Pombo, 2021; Schaeffer and Nollmann, 2023) have revealed the processes that allow unique 3D chromatin conformation in the diverse cell types of the brain and their role in its development and function, as well as their impact in different pathologies including AD.

Topologically associating domains, which are self-interacting chromatin loops, are the basic hierarchically level of chromatin organization that give rise to transcriptionally active and repressive compartments of the chromatin by allowing the formation of circuits of interactions between specific regulatory sequences (enhancer-promoter) and their target genes. At its highest organization, transcriptionally active chromatin remains compartmentalized to the nuclear interior whereas the repressive chromatin is localized towards the nuclear periphery attached to the nuclear membrane (Schoenfelder and Fraser, 2019). Therefore, disruptions at topologically associating domains affect the entire 3D genome organization and these pre-transcriptional events have been implicated in several diseases.

Chromatin remodeling affects its nuclear organization, and whole genome sequencing studies have revealed that mutations in genes coding for chromatin remodeler factors are overrepresented in patients with several neurodegenerative disorders, including AD (Won et al., 2016). This evidence highlights the importance of this epigenetic mechanism and how it contributes to the early pathogenic continuum of events during disease development.

Bendl et al. (2021) conducted a case-control study consisting of a detailed comparison of genome-wide chromatin accessibility maps of neurons and non-neurons from 403 brain tissue samples dissected from the entorhinal cortex and superior temporal gyrus, two brain regions affected in AD. Their results show significant alterations in 3D chromatin conformation in samples from AD patients that affect accessibility and transcriptional regulatory processes. This significant study provides the multilevel type of information that contributes to elucidating the biological link between the extensive genetic, epigenetic, and transcriptional mechanisms that alter the 3D conformation of chromatin and act in concert during the pathogenesis of AD and are responsible for the massive neuronal loss that characterizes this pathology (Bendl et al., 2021).

Epigenetic Targets Modified by Natural Dietary Products against Alzheimer's Disease

In the last decade, a new wealth of information has emerged to explain how nutrition and diet could influence epigenetic status, as most human diseases are significantly influenced by diet to varying degrees. Among plants, phytochemicals compounds are considered nonessential complex chemicals found particularly in fruits and vegetables. Despite not being classified as necessary nutrients for humans, phytochemicals have a significant positive impact on health and well-being. Several natural compounds have shown potential epigenetic effects in diseases such as cancer. However, very few researchers have focused on the pleiotropic function of natural products in modifying epigenetic pathways in brain disorders. Bioactive substances obtained from food can influence both epigenetic processes and their targets. For instance, genistein, a soy-derived compound is an isoflavone that affects tumorigenesis/carcinogenesis through epigenetic regulations. According to studies, genistein can control gene expression by deleting DNA methylation at the promoter level and could be implicated in suppressing the DNMTs. On the other hand, genistein inhibits DNMT3b expression in the neuroblastoma model, which suggests that genistein could be used as an adjuvant therapeutic drug for the treatment of neuroblastoma (Gangisetty and Murugan, 2016). In terms of histone modification, it has been demonstrated that genistein increases the acetylation of histones H3 and H4 at the transcriptional site of p21 and p16 in prostate cancer cells (Zhang and Chen, 2011).

Green tea contains a large amount of epigallocatechin gallate (EGCG), a catechin that also occurs naturally in the ester form of epigallocatechin and gallic acid. According to studies, EGCG inhibits a number of enzymes involved in the epigenetic process, including DNA methyltransferase and histone acetyltransferase (Choi et al., 2009). With various health advantages, ECGC has the capacity to inhibit both DNMT and HDAC. According to studies, EGCG decreased the expression of UHR1 and DNMT1 in Jurkat cells, which led to an increase in the expression of the tumor suppressor genes p73 and p16 INK4A In addition, EGCG inhibited not only the DNMTs and HDACs, and histone methyltransferase EzH2, which adds a methyl group to the position H3K27 and results in gene silencing (Achour et al., 2013).

Lycopene is a carotenoid (tetraterpene) that exhibits strong antioxidant activity. This compound is mostly found in fruits and vegetables, including watermelon, pink guava, grapefruit, tomatoes, and papaya. Studies show that lycopene modifies DNA methylation and upregulates the *GSTP1* gene in the breast cancer cell line (King-Batoon et al., 2008).

Curcuma longa

Curcumin is the principal curcuminoid with antioxidant, antitumor, and anti-inflammatory properties. It is known to have an anti-disease effect in various animal models and humans. Curcumin inhibits Aβ aggregation and Aβ-induced inflammation; in addition, it has been shown that Curcuma exerts the AChEi effect (Hamaguchi et al., 2010; Pulido-Moran et al., 2016). In addition, it has been shown to inhibit certain epigenetic enzymes (such as HATs, HDAC1, HDAC3, and HDAC8) *in vitro* (Reuter et al., 2011; Vahid et al., 2015). Given that it was able to silence AD-related genes including presenilin 1 (PS1) and BACE1 in murine neuroblastoma cells by inhibiting H3 acetylation, curcumin has a promising future as an AD treatment (Lu et al., 2014). In Asiatic countries, Curcuma has a long history of use as a food and medicinal, and its intake is associated with better cognitive performance in old age, which could be a reason why senior citizens in India, where curcuma is a staple food, have a lower rate of AD and better cognitive performance (Ng et al., 2006).

Resveratrol

Resveratrol is a polyphenol present in plant foods including grape skin, red wine, and almonds. Due to its potential medical use in modifying aging-related epigenetic pathways, it is currently attracting more and more interest. Resveratrol is frequently referred to as the "French Paradox" for its ability to prevent a variety of illnesses, including neurological such as AD, PD, and stroke (Gangisetty and Murugan, 2016). Numerous studies have demonstrated that the positive benefits of resveratrol extend beyond its anti-inflammatory and antioxidant properties. These benefits also result from the activation of Sirtuin 1 (SIRT1), a class III HDAC. Sirtuins are a family of signaling proteins that exert a role in the control of metabolism and are involved in aging. These are nicotinamide adenine dinucleotide (NAD (+))-dependent HDACs. Because resveratrol activates SIRT1, it slows the proliferation of cancer cells and delays aging processes (Baur, 2010). *In vitro* studies using cell lines have shown that resveratrol acts as a weak inhibitor of DNMT activity (Paluszczak et al., 2010). Through the activation of SIRT, resveratrol's antioxidant action also contributes to the neural differentiation. The activation of SIRT1, which is expressed mostly in neurons in the adult mammalian brain, is one of the major neuroprotective mechanisms exerted by resveratrol (Guida et al., 2015). Resveratrol induces SIRT1 activation, which decreases Aβ-induced microglial death and enhances cognitive performance (Chen et al., 2005). Although the fundamental mechanisms of resveratrol are linked to SIRT1 overexpression, the subsequent neuroprotective impact that follows is still unknown. However, SIRT1 overexpression is crucial for neuronal preservation because it controls the generation of proinflammatory cytokines, reactive oxygen species, nitric oxide (NO), and A in the brains of AD patients (Salminen et al., 2013; Li et al., 2017).

Amaryllidacea family

With around 85 genera and 1100 species, the Amaryllidaceae family is a large family of bulbous plants. The tropical and warm regions of the world including the Mediterranean, Southern Africa, and Andean South America are habitats for several species of this family. The galantamine alkaloid is naturally found in several Amaryllidaceae species. Galantamine inhibits the AChE enzyme while also allosterically modulating nicotinic acetylcholine receptors, resulting in a dual-action mechanism. Additionally, it regulates the non-amyloidogenic processing of APP by inhibiting beta-site APP cleaving enzyme expression and thus the aggregation and toxicity of Aβ (Li et al., 2010). Moreover, this alkaloid also exerts antioxidant and antigenotoxic effects (Castillo et al., 2016; Castillo and Aristizabal-Pachon, 2017). Regarding the Amaryllidaceae family, we have previously shown the neuroprotective and antigenotoxic effects and AChEi activity exerted by crude extracts from *Caliphruria subedentata* (Varita de San José), a plant belonging to the Amaryllidaceae family, which among its alkaloids has galantamine (Castillo et al., 2018). However, *in silico* approaches have shown that other alkaloids found in this plant exhibited major or equal AChEi activity compared to galantamine (Castillo-Ordóñez et al., 2017). To better understand the role of *Caliphruria subedentata* alkaloids in neuroprotection, our laboratory has combined a set of concepts and models to explore these mechanisms (**Figure 5**). Plants such as Caliphruria subedentata seem to exhibit neuroprotective effects through various biological pathways, which offer a potential opportunity to target different unregulated mechanisms in multifactorial diseases such as Alzheimer's and other neurodegenerative disorders.

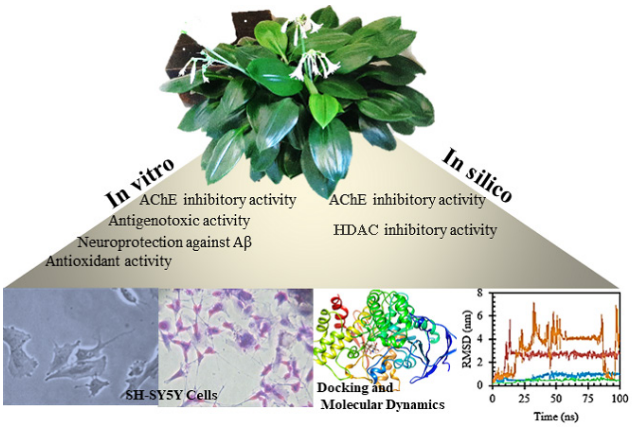

Figure 5 | **Neuroprotective effects of *Caliphruria subedentata*.**
In vitro and *in silico* studies show that Caliphruria subedentata extract and its alkaloids modulate the neurotoxicity and neuronal death induced by the amyloid-beta (Aβ) peptide, through acetylcholinesterase (AChE) inhibition, antigenotoxicity, and mitochondrial and histone deacetylases (HDAC) regulating. SH-SY5Y cell line is a common experimental model to study molecular events leading to Alzheimer's disease. Created using Microsoft PowerPoint. RMSD: Root-mean-square deviation.

Limitations and Challenges in the Development of Anti-Alzheimer's Drugs

The genomic era began in 2001 with the decoding of the first human genome. This was the biggest collaborative biology research initiative in the world. It allowed scientists to see the full DNA sequence, which changed how they approached biological questions related to humans. Genomic science faced significant challenges in the medical field at the beginning of the twenty-first century, due to the limitations of existing DNA sequencing techniques, computational methods, and information technologies. To overcome these limitations, innovations were needed that would increase the speed and accuracy of sequencing, analysis, and storage of genomic data, while reducing the cost and complexity. Some of these innovations included next-generation sequencing platforms, cloud computing, and artificial intelligence, which enabled breakthroughs in precision medicine, gene therapy, and synthetic biology.

Thanks to the new genomic approaches, this decade has witnessed some groundbreaking conceptual shifts in the research of AD. These shifts recognize the risk factors and the complex spectrum of the underlying pathophysiology.

However, despite decades of exploration in the therapeutic field, no curative treatment has been found yet, and prevention remains the priority (Arafah et al., 2023). The limitations that hinder the development of an anti-Alzheimer drug are varied. Among them are: drug delivery to the central nervous system remains a complex process and represents a challenge for developing therapeutic and preventive strategies (Passeri et al., 2022) The BBB is the most important factor that limits the development of new drugs for the central nervous system. Most central nervous system drug candidates cannot penetrate the brain because of the BBB. This includes 100% of large-molecule pharmaceutics, such as peptides, recombinant proteins, monoclonal antibodies, RNA interference-based drugs, and gene therapies. A common misconception is that small molecules can easily cross the BBB. However, this is not true. More than 98% of all small molecules are also blocked by the BBB (Pardridge, 2007). Some drugs such as (Tysabri®) is FDA approved for the treatment of multiple sclerosis but this monoclonal antibody does not cross the BBB and works by blocking the trafficking of lymphocytes across the brain endothelial wall (Engelhardt and Coisne, 2011).

The passage of a substance across the BBB is mainly determined by passive diffusion; however, optimal physicochemical properties may not be enough to overcome the efflux transporters such as P-glycoprotein (P-GP), a protein from BBB, which limit the entry of molecules into the brain. Molecules that can bypass this barrier and become suitable candidates for developing neuroprotective agents should possess certain physicochemical and biological characteristics. For instance, the alkaloids of the Amaryllidaceae family are within the narrow range of P-GP substrates (270–320 Da). They are positively loaded with physiological pH (pka: 7.1–9.1) and have negative logD7.4 values indicating relative hydrophilicity, which can contribute to their low or absent interaction with P-GP (Eriksson et al., 2012). Among Amaryllidaceae alkaloids, galantamine has a low affinity for P-GP, while licorine does not interact with it (Heinrich and Lee Teoh, 2004; Namanja et al., 2009). The absence of interaction between natural compounds and the efflux protein in the BBB makes alkaloids become promising metabolites that can reach different brain targets. As for the compounds that do not cross the blood-brain barrier, but still have bioactive properties such as antioxidant, antigenotoxic, and anti-inflammatory activity, they could modulate peripheral pathways that are affected by the disease.

Another important challenge is the multifactorial nature of the disease, which hinders the development of effective therapeutic strategies to tackle this pathology. Elderly patients frequently have multiple illnesses, a condition known as multimorbidity, which is a common feature among Alzheimer's patients (Hijioka et al., 2023). On the other hand, AD progresses through three stages: the pre-symptomatic stage, the prodromal stage of mild cognitive impairment (MCI), and the clinical form of AD. However, the available biomarkers have limitations in detecting and categorizing these pathophysiological stages (Klyucherev et al., 2022). A biomarker is an indicator that evaluates a biological process, which can be normal or pathogenic. It also measures the pharmacological response to therapeutic intervention, playing a crucial role in drug development. Furthermore, AD biomarkers have some limitations. For example, some biomarkers may not be specific to AD and can also be present in other neurodegenerative diseases. Additionally, there may be variability in biomarker measurements due to factors such as age, sex, and comorbidities. Finally, the use of biomarkers alone may not be sufficient to demonstrate clinical benefit, and additional clinical endpoints may be necessary (Cummings, 2019).

According to experts, developing an effective treatment for AD has several challenges. One of the principal challenges is the complexity of disease-related processes and pathways. Another challenge is the difficulty in diagnosing the disease early, when treatments may be more effective. Additionally, clinical trials for AD drugs have historically had a high failure rate, which can be costly and time-consuming for drug developers. Finally, the COVID-19 pandemic has also slowed down clinical trials temporally, which has further complicated the drug development process (Cummings et al., 2022).

In addition, currently, it is clear that epigenetics plays a crucial role in medicine. In light of that fact, future advances in diagnostic, prognostic, and therapeutic methods will very probably depend more and more on individualized epigenetics for the best management of many, if not most, diseases (Rasool et al., 2015; Kronfol et al., 2017). Personalized genetic biomarkers have had a significant impact on cancer treatment by allowing for tailored therapies based on the individual patient's genetic makeup and disease characteristics. This approach, known as precision medicine, has led to improved outcomes and reduced side effects compared to traditional treatments. Similarly, precision medicine strategies could be applied to AD by identifying specific predisposing risk alleles in young individuals, and intervening before symptoms appear. Recent advancements in AD genetics and genotyping technologies include the identification of several predisposing risk alleles involved in different pathogenic pathways. These risk alleles can be identified accurately and on a large scale using high-throughput genotyping technologies such as genome-wide association studies and whole-genome sequencing. These advances have created an optimal environment to move the AD field toward precision medicine (Di Meco and Vassar, 2021).

Current research on the role of epigenetics in the mechanism of AD focuses on four aspects: DNA methylation, chromatin remodeling, histone modifications, and ncRNA regulation. However, more details about these mechanisms and their biological significance in the brain are needed to understand the course of the disease, the epigenetic variability among the population, and vulnerable cells such as neurons. Additionally, epigenetic changes in AD could potentially be used as biomarkers for early diagnosis and evaluation of therapeutic strategies. Epigenetic mechanisms are reversible: this feature will enable precise evaluation of the direct effects of therapeutic interventions and the measurement of modifications through biomarkers; thus, epigenetic mechanisms offer a promising avenue for drug discovery and development (Liu et al., 2018).

Conclusions

Epigenetic pathways are diverse and new modifications are constantly being discovered. In the last 20 years, there has been compelling evidence that these epigenetic pathways play a role in the formation of memories in the brain. However, despite the wide range of epigenetic changes that have been explored and linked to the formation and consolidation of memory, the exact pathways by which these modifications influence these processes remain poorly understood. Moreover, the dynamic nature of epigenetics could facilitate illness prevention, as well as advance clinical treatment.

Some authors argue that modern medicine and pharmacology are reductionist, as they rely on a single compound for a specific disease. However, due to the multifactorial nature of AD, where a series of proteins and biochemical events are involved, natural products emerge as a strategy capable of acting simultaneously on multiple molecular targets. The development of epigenetic regulators with increased selectivity to reduce unwanted side effects is a key issue to be addressed. One promising approach is to use small molecules that target specific epigenetic enzymes or pathways to modulate gene expression and restore normal cellular function, and plants are a source of substances or metabolites with properties that make them promising candidates for the development of pharmaceuticals addressed to reach the brain.

In conclusion, developing effective treatments for AD is a challenging task that requires overcoming various obstacles, such as the complexity of the disease, the difficulty in early diagnosis, and the high failure rate of clinical trials. However, despite these challenges, researchers and drug developers continue to work hard to find new and better ways to treat this devastating disease. With continued research and innovation, it may be possible to develop epigenetic therapies that can slow or even reverse the progression of AD and improve the quality of life for millions of people around the world.

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References

Achour M, Mousli M, Alhosin M, Ibrahim A, Peluso J, Muller CD, Schini-Kerth VB, Hamiche A, Dhe-Paganon S, Bronner C (2013) Epigallocatechin-3-gallate up-regulates tumor suppressor gene expression via a reactive oxygen species-dependent down-regulation of UHRF1. Biochem Biophys Res Commun 430:208-212.
Adwan L, Zawia NH (2013) Epigenetics: a novel therapeutic approach for the treatment of Alzheimer's disease. Pharmacol Ther 139:41-50.
Alcalà-Vida R, Awada A, Boutillier AL, Merienne K (2021) Epigenetic mechanisms underlying enhancer modulation of neuronal identity, neuronal activity and neurodegeneration. Neurobiol Dis 147:105155.
Alexandrov LB, Jones PH, Wedge DC, Sale JE, Campbell PJ, Nik-Zainal S, Stratton MR (2015) Clock-like mutational processes in human somatic cells. Nat Genet 47:1402-1407.
Almeida RP, Schultz SA, Austin BP, Boots EA, Dowling NM, Gleason CE, Bendlin BB, Sager MA, Hermann BP, Zetterberg H (2015) Effect of cognitive reserve on age-related changes in cerebrospinal fluid biomarkers of Alzheimer disease. JAMA Neurol 72:699-706.
Amelianchik A, Sweetland-Martin L, Norris EH (2022) The effect of dietary fat consumption on Alzheimer's disease pathogenesis in mouse models. Transl Psychiatry 12:1-13.
Anand R, Gill KD, Mahdi AA (2014) Therapeutics of Alzheimer's disease: past, present and future. Neuropharmacology 76:27-50.
Angelopoulou E, Paudel YN, Papageorgiou SG, Piperi C (2021) APOE genotype and Alzheimer's disease: The influence of lifestyle and environmental factors. ACS Chem Neurosci 12:2749-2764.
Anttila T, Helkala E-L, Viitanen M, Kåreholt I, Fratiglioni L, Winblad B, Soininen H, Tuomilehto J, Nissinen A, Kivipelto M (2004) Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. BMJ 329:539.
Arafah A, Khatoon S, Rasool I, Khan A, Rather MA, Abujabal KA, Faqih YAH, Rashid H, Rashid SM, Bilal Ahmad S, Alexiou A, Rehman MU (2023) The future of precision medicine in the cure of Alzheimer's disease. Biomedicines 11:335.
Babenko O, Kovalchuk I, Metz GA (2012) Epigenetic programming of neurodegenerative diseases by an adverse environment. Brain Res 1444:96-111.
Bagaria J, Moon Y, Bagyinszky E, Shim KH, An SSA, Kim S, Han SH (2022) Whole exome sequencing reveals a novel APOE mutation in a patient with sporadic early-onset Alzheimer's disease. Front Neurol 13:899644.
Bandyopadhyay D, Medrano EE (2003) The emerging role of epigenetics in cellular and organismal aging. Exp Gerontol 38:1299-1307.
Barrachina M, Ferrer I (2009) DNA methylation of Alzheimer disease and tauopathy-related genes in postmortem brain. J Neuropathol Exp Neurol 68:880-891.

Baur JA (2010) Resveratrol, sirtuins, and the promise of a DR mimetic. Mech Ageing Dev 131:261-269.
Beaver M, Bhatnagar A, Panikker P, Zhang H, Snook R, Parmar V, Vijayakumar G, Betini N, Akhter S, Elefant F (2020) Disruption of Tip60 HAT mediated neural histone acetylation homeostasis is an early common event in neurodegenerative diseases. Sci Rep 10:18265.
Bekris LM, Yu CE, Bird TD, Tsuang DW (2010) Genetics of Alzheimer disease. J Geriatr Psychiatry Neurol 23:213-227.
Bendl J, Hauberg ME, Girdhar K, Im E, Vicari JM, Rahman S, Dong P, Misir R, Kleopoulos SP, Reach SM (2021) The three-dimensional landscape of chromatin accessibility in Alzheimer's disease. BioRxiv [Preprint] DOI: 10.1101/2021.01.11.426303.
Cacabelos R (2017) Some news on old concepts and the epigenetics of Alzheimer's disease. J Clin Epigenet 3:45.
Cai Y, An SS, Kim S (2015) Mutations in presenilin 2 and its implications in Alzheimer's disease and other dementia-associated disorders. Clin Interv Aging 10:1163-1172.
Carboni L, Lattanzio F, Candeletti S, Porcellini E, Raschi E, Licastro F, Romualdi P (2015) Peripheral leukocyte expression of the potential biomarker proteins Bdnf, Sirt1, and Psen1 is not regulated by promoter methylation in Alzheimer's disease patients. Neurosci Lett 605:44-48.
Carey N (2015) Epigenetics for drug discovery. ChemMedChem DOI:10.1002/cmdc.201600097
Carlberg C, Molnár F (2019) Human epigenetics: How science works. Cham, Switzerland: Springer
Castillo WO, Aristizabal-Pachon AF, de Lima Montaldi AP, Sakamoto-Hojo ET, Takahashi CS (2016) Galanthamine decreases genotoxicity and cell death induced by β-amyloid peptide in SH-SY5Y cell line. Neurotoxicology 57:291-297.
Castillo WO, Aristizabal-Pachon AF (2017) Galantamine protects against beta amyloid peptide-induced DNA damage in a model for Alzheimer's disease. Neural Regen Res 12:916-917.
Castillo WO, Aristizabal-Pachon AF, Sakamoto-Hojo E, Gasca CA, Cabezas-Fajardo FA, Takahashi C (2018) Caliphruria subedentata (Amaryllidaceae) decreases genotoxicity and cell death induced by β-amyloid peptide in SH-SY5Y cell line. Mutat Res Genet Toxicol Environ Mutagen 836:54-61.
Castillo-Ordóñez WO, Tamarozzi ER, da Silva GM, Aristizabal-Pachón AF, Sakamoto-Hojo ET, Takahashi CS, Giuliatti S (2017) Exploration of the acetylcholinesterase inhibitory activity of some alkaloids from amaryllidaceae family by molecular docking in silico. Neurochem Res 42:2826-2830.
Castillo-Ordoñez WO (2022) Biología del Alzhéimer Evolución y demencia. Editorial Universidad del Cauca, Popayán Colombia.
Chen J, Zhou Y, Mueller-Steiner S, Chen LF, Kwon H, Yi S, Mucke L, Gan L (2005) SIRT1 protects against microglia-dependent amyloid-beta toxicity through inhibiting NF-kappaB signaling. J Biol Chem 280:40364-40374.
Chen L, Guo X, Li Z, He Y (2019) Relationship between long non-coding RNAs and Alzheimer's disease: a systematic review. Pathol Res Pract 215:12-20.
Chouliaras L, Mastroeni D, Delvaux E, Grover A, Kenis G, Hof PR, Steinbusch HW, Coleman PD, Rutten BP, van den Hove DL (2013) Consistent decrease in global DNA methylation and hydroxymethylation in the hippocampus of Alzheimer's disease patients. Neurobiol Aging 34:2091-2099.
Coon KD, Myers AJ, Craig DW, Webster JA, Pearson JV, Lince DH, Zismann VL, Beach TG, Leung D, Bryden L, Halperin RF, Marlowe L, Kaleem M, Walker DG, Ravid R, Heward CB, Rogers J, Papassotiropoulos A, Reiman EM, Hardy J, Stephan DA (2007) A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease. J Clin Psychiatry 68:613-618.
Costa V, Esposito R, Aprile M, Ciccodicola A (2012) Non-coding RNA and pseudogenes in neurodegenerative diseases: "The (un)Usual Suspects". Front Genet 3:231.
Cummings J (2019) The role of biomarkers in Alzheimer's disease drug development. Adv Exp Med Biol 1118:29-61.
Cummings J, Lee G, Nahed P, Kambar MEZN, Zhong K, Fonseca J, Taghva K (2022) Alzheimer's disease drug development pipeline: 2022. Alzheimers Dement (N Y) 8:e12295.
da Rocha ST, Gendrel AV (2019) The influence of DNA methylation on monoallelic expression. Essays Biochem 63:663-676.
De Strooper B, Karran E (2016) The cellular phase of Alzheimer's disease. Cell 164:603-615.
Di Meco A, Vassar R (2021) Early detection and personalized medicine: Future strategies against Alzheimer's disease. Prog Mol Biol Transl Sci 177:157-173.
Dileep V, Tsai LH (2021) Three-dimensional chromatin organization in brain function and dysfunction. Curr Opin Neurobiol 69:214-221.
Ding Y, Luan W, Shen X, Wang Z, Cao Y (2022) LncRNA BDNF-AS as ceRNA regulates the miR-9-5p/BACE1 pathway affecting neurotoxicity in Alzheimer's disease. Arch Gerontol Geriatr 99:104614.
Engelhardt B, Coisne C (2011) Fluids and barriers of the CNS establish immune privilege by confining immune surveillance to a two-walled castle moat surrounding the CNS castle. Fluids Barriers CNS 8:4.
Eriksson AH, Rønsted N, Güler S, Jäger AK, Sendra JR, Brodin B (2012) In-vitro evaluation of the P-glycoprotein interactions of a series of potentially CNS-active Amaryllidaceae alkaloids. J Pharm Pharmacol 64:1667-1677.
Fernández-Calle R, Konings SC, Frontiñán-Rubio J, García-Revilla J, Camprubí-Ferrer L, Svensson M, Martinson I, Boza-Serrano A, Venero JL, Nielsen HM, Gouras GK, Deierborg T (2022) APOE in the bullseye of neurodegenerative diseases: impact of the APOE genotype in Alzheimer's disease pathology and brain diseases. Mol Neurodegener 17:62.
Fu X, Zhang J, Guo L, Xu Y, Sun L, Wang S, Feng Y, Gou L, Zhang L, Liu Y (2014) Protective role of luteolin against cognitive dysfunction induced by chronic cerebral hypoperfusion in rats. Pharmacol Biochem Behav 126:122-130.
Gangisetty O, Murugan S (2016) Epigenetic modifications in neurological diseases: natural products as epigenetic modulators a treatment strategy. Adv Neurobiol 12:1-25.
Goldgaber D, Lerman MI, McBride OW, Saffiotti U, Gajdusek DC (1987) Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease. Science 235:877-880.
Gosselin D, Skola D, Coufal NG, Holtman IR, Schlachetzki JCM, Sajti E, Jaeger BN, O'Connor C, Fitzpatrick C, Pasillas MP, Pena M, Adair A, Gonda DD, Levy ML, Ransohoff RM, Gage FH, Glass CK (2017) An environment-dependent transcriptional network specifies human microglia identity. Science 356:eaal3222.
Guan JS, Haggarty SJ, Giacometti E, Dannenberg JH, Joseph N, Gao J, Nieland TJ, Zhou Y, Wang X, Mazitschek R, Bradner JE, DePinho RA, Jaenisch R, Tsai LH (2009) HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 459:55-60.
Guida N, Laudati G, Anzilotti S, Secondo A, Montuori P, Di Renzo G, Canzoniero LM, Formisano L (2015) Resveratrol via sirtuin-1 downregulates RE1-silencing transcription factor (REST) expression preventing PCB-95-induced neuronal cell death. Toxicol Appl Pharmacol 288:387-398.
Haass C, Schlossmacher MG, Hung AY, Vigo-Pelfrey C, Mellon A, Ostaszewski BL, Lieberburg I, Koo EH, Schenk D, Teplow DB, Selkoe DJ (1992) Amyloid β-peptide is produced by cultured cells during normal metabolism. Nature 359:322-325.
Hahnen E, Hauke J, Tränkle C, Eyüpoglu IY, Wirth B, Blümcke I (2008) Histone deacetylase inhibitors: possible implications for neurodegenerative disorders. Expert Opin Investig Drugs 17:169-184.
Hamaguchi T, Ono K, Yamada M (2010) Curcumin and Alzheimer's disease. CNS Neurosci Ther 16:285-297.
Hampel H, Mesulam MM, Cuello AC, Khachaturian AS, Vergallo A, Farlow MR, Snyder PJ, Giacobini E, Khachaturian ZS (2019) Revisiting the cholinergic hypothesis in alzheimer's disease: emerging evidence from translational and clinical research. J Prev Alzheimers Dis 6:2-15.
Harabula I, Pombo A (2021) The dynamics of chromatin architecture in brain development and function. Curr Opin Genet Dev 67:84-93.
Heinrich M, Lee Teoh H (2004) Galanthamine from snowdrop--the development of a modern drug against Alzheimer's disease from local Caucasian knowledge. J Ethnopharmacol 92:147-162.
Hernandez-Sapiens MA, Reza-Zaldívar EE, Márquez-Aguirre AL, Gómez-Pinedo U, Matias-Guiu J, Cevallos RR, Mateos-Díaz JC, Sánchez-González VJ, Canales-Aguirre AA (2022) Presenilin mutations and their impact on neuronal differentiation in Alzheimer's disease. Neural Regen Res 17:31-37.
Hietaranta-Luoma H-L, Tahvonen R, Iso-Touru T, Puolijoki H, Hopia A (2014) An intervention study of individual, apoE genotype-based dietary and physical-activity advice: impact on health behavior. J Nutrigenet Nutrigenomics 7:161-174.
Hijioka M, Manabe T, Saito T (2023) Multifactorial glial responses and their contributions to Alzheimer's disease continuum. Clin Exp Neuroimmunol:1–10.
Huang X, Li N, Pu Y, Zhang T, Wang B (2019) Neuroprotective effects of ginseng phytochemicals: recent perspectives. Molecules 24:2939.
Huang Y, Wei Y, Xu J, Wei X (2022) A comprehensive review on the prevention and regulation of Alzheimer's disease by tea and its active ingredients. Crit Rev Food Sci Nutr:1-25.
Hutton M, Hardy J (1997) The presenilins and Alzheimer's disease. Hum Mol Genet 6:1639-1646.
Hyun K, Jeon J, Park K, Kim J (2017) Writing, erasing and reading histone lysine methylations. Exp Mol Med 49:e324.
Iraola-Guzmán S, Estivill X, Rabionet R (2011) DNA methylation in neurodegenerative disorders: a missing link between genome and environment? Clin Genet 80:1-14.
Jackson RJ, Standart N (2007) How do microRNAs regulate gene expression? Sci STKE 2007:re1.
Jagirdar R, Drexel M, Bukovac A, Tasan RO, Sperk G (2016) Expression of class II histone deacetylases in two mouse models of temporal lobe epilepsy. J Neurochem 136:717-730.
Karpova NN, Sales AJ, Joca SR (2017) Epigenetic basis of neuronal and synaptic plasticity. Curr Top Med Chem 17:771-793.
Keifer J, Zheng Z, Ambigapathy G (2015) A MicroRNA-BDNF Negative Feedback Signaling Loop in Brain: Implications for Alzheimer's Disease. Microrna 4:101-108.
Kero M, Paetau A, Polvikoski T, Tanskanen M, Sulkava R, Jansson L, Myllykangas L, Tienari PJ (2013) Amyloid precursor protein (APP) A673T mutation in the elderly Finnish population. Neurobiol Aging 34:1518.e1-3.
Kerridge C, Belyaev ND, Nalivaeva NN, Turner AJ (2014) The Aβ-clearance protein transthyretin, like neprilysin, is epigenetically regulated by the amyloid precursor protein intracellular domain. J Neurochem 130:419-431.
Khani-Habibabadi F, Askari S, Zahiri J, Javan M, Behmanesh M (2019) Novel BDNF-regulatory microRNAs in neurodegenerative disorders pathogenesis: An in silico study. Comput Biol Chem 83:107153.
Klyucherev TO, Olszewski P, Shalimova AA, Chubarev VN, Tarasov VV, Attwood MM, Syvänen S, Schiöth HB (2022) Advances in the development of new biomarkers for Alzheimer's disease. Transl Neurodegener 11:25.
Kronfol MM, Dozmorov MG, Huang R, Slattum PW, McClay JL (2017) The role of epigenomics in personalized medicine. Expert Rev Precis Med Drug Dev 2:33-45.
Kuhn PH, Koroniak K, Hogl S, Colombo A, Zeitschel U, Willem M, Volbracht C, Schepers U, Imhof A, Hoffmeister A, Haass C, Roßner S, Bräse S, Lichtenthaler SF (2012) Secretome protein enrichment identifies physiological BACE1 protease substrates in neurons. EMBO J 31:3157-3168.
Kumar GP, Khanum F (2012) Neuroprotective potential of phytochemicals. Pharmacogn Rev 6:81-90.
Kumari A, Bhawal S, Kapila S, Yadav H, Kapila R (2022) Health-promoting role of dietary bioactive compounds through epigenetic modulations: a novel prophylactic and therapeutic approach. Crit Rev Food Sci Nutr 62:619-639.
Laitinen MH, Ngandu T, Rovio S, Helkala EL, Uusitalo U, Viitanen M, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M (2006) Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study. Dement Geriatr Cogn Disord 22:99-107.
Li D, Liu N, Zhao L, Tong L, Kawano H, Yan HJ, Li HP (2017) Protective effect of resveratrol against nigrostriatal pathway injury in striatum via JNK pathway. Brain Res 1654:1-8.
Li F, Wu X, Li J, Niu Q (2016) Ginsenoside Rg1 ameliorates hippocampal long-term potentiation and memory in an Alzheimer's disease model. Mol Med Rep 13:4904-4910.
Li Q, Wu D, Zhang L, Zhang Y (2010) Effects of galantamine on β-amyloid release and beta-site cleaving enzyme 1 expression in differentiated human neuroblastoma SH-SY5Y cells. Exp Gerontol 45:842-847.
Li Q, Rubin L, Silva M, Li S, Yang C, Lazarovici P, Zheng W (2022) Current progress on neuroprotection induced by artemisia, ginseng, astragalus, and ginkgo traditional Chinese medicines for the therapy of Alzheimer's disease. Oxid Med Cell Longev 2022:3777021.
Li S, Hou H, Mori T, Sawmiller D, Smith A, Tian J, Wang Y, Giunta B, Sanberg PR, Zhang S, Tan J (2015) Swedish mutant APP-based BACE1 binding site peptide reduces APP β-cleavage and cerebral Aβ levels in Alzheimer's mice. Sci Rep 5:11322.
Linciano P, Benedetti R, Pinzi L, Russo F, Chianese U, Sorbi C, Altucci L, Rastelli G, Brasili L, Franchini S (2021) Investigation of the effect of different linker chemotypes on the inhibition of histone deacetylases (HDACs). Bioorg Chem 106:104462.
Liu X, Jiao B, Shen L (2018) The epigenetics of Alzheimer's disease: factors and therapeutic implications. Front Genet 9:579.
Locke WJ, Guanzon D, Ma C, Liew YJ, Duesing KR, Fung KYC, Ross JP (2019) DNA methylation cancer biomarkers: translation to the clinic. Front Genet 10:1150.
Lockett GA, Wilkes F, Maleszka R (2010) Brain plasticity, memory and neurological disorders: an epigenetic perspective. Neuroreport 21:909-913.
Lodato MA, Rodin RE, Bohrson CL, Coulter ME, Barton AR, Kwon M, Sherman MA, Vitzthum CM, Luquette LJ, Yandava CN, Yang P, Chittenden TW, Hatem NE, Ryu SC, Woodworth MB, Park PJ, Walsh CA (2018) Aging and neurodegeneration are associated with increased mutations in single human neurons. Science 359:555-559.

Long JM, Maloney B, Rogers JT, Lahiri DK (2019) Novel upregulation of amyloid-β precursor protein (APP) by microRNA-346 via targeting of APP mRNA 5′-untranslated region: Implications in Alzheimer's disease. Mol Psychiatry 24:345-363.
Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, Llewellyn DJ (2019) Association of lifestyle and genetic risk with incidence of dementia. JAMA 322:430-437.
Lu X, Deng Y, Yu D, Cao H, Wang L, Liu L, Yu C, Zhang Y, Guo X, Yu G (2014) Histone acetyltransferase p300 mediates histone acetylation of PS1 and BACE1 in a cellular model of Alzheimer's disease. PLoS One 9:e103067.
Lue LF, Kuo YM, Roher AE, Brachova L, Shen Y, Sue L, Beach T, Kurth JH, Rydel RE, Rogers J (1999) Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. Am J Pathol 155:853-862.
Luger K, Mäder AW, Richmond RK, Sargent DF, Richmond TJ (1997) Crystal structure of the nucleosome core particle at 2.8 Å resolution. Nature 389:251-260.
Ma C, D'Mello SR (2011) Neuroprotection by histone deacetylase-7 (HDAC7) occurs by inhibition of c-jun expression through a deacetylase-independent mechanism. J Biol Chem 286:4819-4828.
Maiarù M, Morgan OB, Tochiki KK, Hobbiger EJ, Rajani K, Overington DW, Géranton SM (2016) Complex regulation of the regulator of synaptic plasticity histone deacetylase 2 in the rodent dorsal horn after peripheral injury. J Neurochem 138:222-232.
Maity S, Farrell K, Navabpour S, Narayanan SN, Jarome TJ (2021) Epigenetic mechanisms in memory and cognitive decline associated with aging and Alzheimer's disease. Int J Mol Sci 22:12280.
Mastroeni D, Grover A, Delvaux E, Whiteside C, Coleman PD, Rogers J (2011) Epigenetic mechanisms in Alzheimer's disease. Neurobiol Aging 32:1161-1180.
Mehler MF (2008) Epigenetics and the nervous system. Ann Neurol 64:602-617.
Miller MB, Reed HC, Walsh CA (2021) Brain somatic mutation in aging and Alzheimer's disease. Annu Rev Genomics Hum Genet 22:239-256.
Miller MB, Huang AY, Kim J, Zhou Z, Kirkham SL, Maury EA, Ziegenfuss JS, Reed HC, Neil JE, Rento L (2022) Somatic genomic changes in single Alzheimer's disease neurons. Nature 604:714-722.
Moussa-Pacha NM, Abdin SM, Omar HA, Alniss H, Al-Tel TH (2020) BACE1 inhibitors: Current status and future directions in treating Alzheimer's disease. Med Res Rev 40:339-384.
Mühlbacher F, Schiessel H, Holm C (2006) Tail-induced attraction between nucleosome core particles. Phys Rev E Stat Nonlin Soft Matter Phys 74:031919.
Mukerjee N, Das A, Jawarkar RD, Maitra S, Das P, Castrosanto MA, Paul S, Samad A, Zaki MEA, Al-Hussain SA, Masand VH, Hasan MM, Bukhari SNA, Perveen A, Alghamdi BS, Alexiou A, Kamal MA, Dey A, Malik S, Bakal RL, et al. (2022) Repurposing food molecules as a potential BACE1 inhibitor for Alzheimer's disease. Front Aging Neurosci 14:878276.
Mullan M, Crawford F, Axelman K, Houlden H, Lilius L, Winblad B, Lannfelt L (1992) A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid. Nat Genet 1:345-347.
Nakao M (2001) Epigenetics: interaction of DNA methylation and chromatin. Gene 278:25-31.
Namanja HA, Emmert D, Pires MM, Hrycyna CA, Chmielewski J (2009) Inhibition of human P-glycoprotein transport and substrate binding using a galantamine dimer. Biochem Biophys Res Commun 388:672-676.
Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH (2006) Curry consumption and cognitive function in the elderly. Am J Epidemiol 164:898-906.
Nightingale KP (2015) Chapter 1: Epigenetics–What it is and Why it Matters. In: Epigenetics for Drug Discovery (Carey N, ed). Royal Society of Chemistry Books.
Okano M, Bell DW, Haber DA, Li E (1999) DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. Cell 99:247-257.
Pagnon de la Vega M, Giedraitis V, Michno W, Kilander L, Güner G, Zielinski M, Löwenmark M, Brundin R, Danfors T, Söderberg L, Alafuzoff I, Nilsson LNG, Erlandsson A, Willbold D, Müller SA, Schröder GF, Hanrieder J, Lichtenthaler SF, Lannfelt L, et al. (2021) The Uppsala APP deletion causes early onset autosomal dominant Alzheimer's disease by altering APP processing and increasing amyloid β fibril formation. Sci Transl Med 13:eabc6184.
Paluszczak J, Krajka-Kuźniak V, Baer-Dubowska W (2010) The effect of dietary polyphenols on the epigenetic regulation of gene expression in MCF7 breast cancer cells. Toxicol Lett 192:119-125.
Pardridge WM (2007) Blood–brain barrier delivery. Drug Discov Today 12:54-61.
Passeri E, Elkhoury K, Morsink M, Broersen K, Linder M, Tamayol A, Malaplate C, Yen FT, Arab-Tehrany E (2022) Alzheimer's disease: treatment strategies and their limitations. Int J Mol Sci 23:13954.
Prince MJ (2015) World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends: Alzheimer's Disease International.
Pulido-Moran M, Moreno-Fernandez J, Ramirez-Tortosa C, Ramirez-Tortosa M (2016) Curcumin and health. Molecules 21:264.
Rasool M, Malik A, Naseer MI, Manan A, Ansari S, Begum I, Qazi MH, Pushparaj P, Abuzenadah AM, Al-Qahtani MH, Kamal MA, Gan S (2015) The role of epigenetics in personalized medicine: challenges and opportunities. BMC Med Genomics 8 Suppl 1:S5.
Ratnu VS, Emami MR, Bredy TW (2017) Genetic and epigenetic factors underlying sex differences in the regulation of gene expression in the brain. J Neurosci Res 95:301-310.
Reuter S, Gupta SC, Park B, Goel A, Aggarwal BB (2011) Epigenetic changes induced by curcumin and other natural compounds. Genes Nutr 6:93-108.
Rogers JT, Randall JD, Cahill CM, Eder PS, Huang X, Gunshin H, Leiter L, McPhee J, Sarang SS, Utsuki T (2002) An iron-responsive element type II in the 5′-untranslated region of the Alzheimer's amyloid precursor protein transcript. Journal of Biological Chemistry 277:45518-45528.
Rogers JT, Randall JD, Cahill CM, Eder PS, Huang X, Gunshin H, Leiter L, McPhee J, Sarang SS, Utsuki T, Greig NH, Lahiri DK, Tanzi RE, Bush AI, Giordano T, Gullans SR (2002) An iron-responsive element type II in the 5′-untranslated region of the Alzheimer's amyloid precursor protein transcript. J Biol Chem 277:45518-45528.
Roses AD, Saunders AM (1994) APOE is a major susceptibility gene for Alzheimer's disease. Curr Opin Biotechnol 5:663-667.
Rovio S, Kåreholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, Soininen H, Nissinen A, Kivipelto M (2005) Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 4:705-711.
Saha R, Pahan K (2006) HATs and HDACs in neurodegeneration: a tale of disconcerted acetylation homeostasis. Cell Death Differ 13:539-550.
Salameh Y, Bejaoui Y, El Hajj N (2020) DNA methylation biomarkers in aging and age-related diseases. Front Genet 11:171.
Salminen A, Kaarniranta K, Kauppinen A (2013) Crosstalk between oxidative stress and SIRT1: Impact on the aging process. Int J Mol Sci 14:3834-3859.
Sayevand Z, Nazem F, Nazari A, Sheykhlouvand M, Forbes SC (2022) Cardioprotective effects of exercise and curcumin supplementation against myocardial ischemia-reperfusion injury. Sport Sci Health:1-9.
Schaeffer M, Nollmann M (2023) Contributions of 3D chromatin structure to cell-type-specific gene regulation. Curr Opin Genet Dev 79:102032.
Schoenfelder S, Fraser P (2019) Long-range enhancer–promoter contacts in gene expression control. Nat Rev Genet. 20:437-455.
Seto E, Yoshida M (2014) Erasers of histone acetylation: the histone deacetylase enzymes. Cold Spring Harb Perspect Biol 6:a018713.
Shen L, Kondo Y, Guo Y, Zhang J, Zhang L, Ahmed S, Shu J, Chen X, Waterland RA, Issa JP (2007) Genome-wide profiling of DNA methylation reveals a class of normally methylated CpG island promoters. PLoS Genet 3:2023-2036.
Sommerlad A, Sabia S, Singh-Manoux A, Lewis G, Livingston G (2019) Association of social contact with dementia and cognition: 28-year follow-up of the Whitehall II cohort study. PLoS Med 16:e1002862.
Starling S (2018) Somatic mutations accumulate in ageing and diseased neurons. Nat Rev Neurol 14:64.
Tannorella P, Stoccoro A, Tognoni G, Petrozzi L, Salluzzo MG, Ragalmuto A, Siciliano G, Haslberger A, Bosco P, Bonuccelli U, Migliore L, Coppedè F (2015) Methylation analysis of multiple genes in blood DNA of Alzheimer's disease and healthy individuals. Neurosci Lett 600:143-147.
Tanzi RE (2012) The genetics of Alzheimer disease. Cold Spring Harb Perspect Med 2:a006296.
Taylor HA, Przemylska L, Clavane EM, Meakin PJ (2022) BACE1: More than just a β-secretase. Obes Rev 23:e13430.
Vahid F, Zand H, Nosrat–Mirshekarlou E, Najafi R, Hekmatdoost A (2015) The role dietary of bioactive compounds on the regulation of histone acetylases and deacetylases: a review. Gene 562:8-15.
Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, Luo Y, Fisher S, Fuller J, Edenson S, Lile J, Jarosinski MA, Biere AL, Curran E, Burgess T, Louis JC, et al. (1999) Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science 286:735-741.
Vauzour D, Vafeiadou K, Rodriguez-Mateos A, Rendeiro C, Spencer JP (2008) The neuroprotective potential of flavonoids: a multiplicity of effects. Genes Nutr 3:115-126.
Wang H, Wang H, Cheng H, Che Z (2016) Ameliorating effect of luteolin on memory impairment in an Alzheimer's disease model. Mol Med Rep 13:4215-4220.
Wang LS, Naj AC, Graham RR, Crane PK, Kunkle BW, Cruchaga C, Murcia JD, Cannon-Albright L, Baldwin CT, Zetterberg H, Blennow K, Kukull WA, Faber KM, Schupf N, Norton MC, Tschanz JT, Munger RG, Corcoran CD, Rogaeva E; Alzheimer's Disease Genetics Consortium, et al. (2015) Rarity of the Alzheimer disease-protective APP A673T variant in the United States. JAMA Neurol 72:209-216.
Wang R, Lahiri DK (2022) Effects of microRNA-298 on APP and BACE1 translation differ according to cell type and 3′-UTR variation. Sci Rep 12:3074.
Wang SC, Oelze B, Schumacher A (2008) Age-specific epigenetic drift in late-onset Alzheimer's disease. PLoS One 3:e2698.
Weggen S, Beher D (2012) Molecular consequences of amyloid precursor protein and presenilin mutations causing autosomal-dominant Alzheimer's disease. Alzheimers Res Ther 4:9.
West RL, Lee JM, Maroun LE (1995) Hypomethylation of the amyloid precursor protein gene in the brain of an Alzheimer's disease patient. J Mol Neurosci 6:141-146.
Won H, de la Torre-Ubieta L, Stein JL, Parikshak NN, Huang J, Opland CK, Gandal MJ, Sutton GJ, Hormozdiari F, Lu D, Lee C, Eskin E, Voineagu I, Ernst J, Geschwind DH (2016) Chromosome conformation elucidates regulatory relationships in developing human brain. Nature 538:523-527.
Wu JC, Santi DV (1985) On the mechanism and inhibition of DNA cytosine methyltransferases. Prog Clin Biol Res 198:119-129.
Yan R, Bienkowski MJ, Shuck ME, Miao H, Tory MC, Pauley AM, Brashier JR, Stratman NC, Mathews WR, Buhl AE, Carter DB, Tomasselli AG, Parodi LA, Heinrikson RL, Gurney ME (1999) Membrane-anchored aspartyl protease with Alzheimer's disease beta-secretase activity. Nature 402:533-537.
Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM (2005) Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 280:5892-5901.
Yang LB, Lindholm K, Yan R, Citron M, Xia W, Yang XL, Beach T, Sue L, Wong P, Price D, Li R, Shen Y (2003) Elevated beta-secretase expression and enzymatic activity detected in sporadic Alzheimer disease. Nat Med 9:3-4.
Yang SS, Zhang R, Wang G, Zhang YF (2017) The development prospection of HDAC inhibitors as a potential therapeutic direction in Alzheimer's disease. Transl Neurodegener 6:19.
Youn YC, Bagyinszky E, Kim H, Choi BO, An SS, Kim S (2014) Probable novel PSEN2 Val214Leu mutation in Alzheimer's disease supported by structural prediction. BMC Neurol 14:105.
Zhang P, Wu W, Chen Q, Chen M (2019) Non-Coding RNAs and their Integrated Networks. J Integr Bioinform 16:20190027.
Zhang XY, Tang XY, Li N, Zhao LM, Guo YL, Li XS, Tian CJ, Cheng DJ, Chen ZC, Zhang LX (2018) GAS5 promotes airway smooth muscle cell proliferation in asthma via controlling miR-10a/BDNF signaling pathway. Life Sci 212:93-101.
Zhang Y, Chen H (2011) Genistein, an epigenome modifier during cancer prevention. Epigenetics 6:888-891.
Zhang ZY, Schluesener HJ (2013) Oral administration of histone deacetylase inhibitor MS-275 ameliorates neuroinflammation and cerebral amyloidosis and improves behavior in a mouse model. J Neuropathol Exp Neurol 72:178-185.
Zhao WQ, Townsend M (2009) Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. Biochim Biophys Acta 1792:482-496.
Zheng M, Xin Y, Li Y, Xu F, Xi X, Guo H, Cui X, Cao H, Zhang X, Han C (2018) Ginsenosides: A Potential Neuroprotective Agent. Biomed Res Int 2018:8174345.
Zhou B, Lu JG, Siddu A, Wernig M, Südhof TC (2022) Synaptogenic effect of APP-Swedish mutation in familial Alzheimer's disease. Sci Transl Med 14:eabn9380.

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