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Review

Re-envisioning Alzheimer's Disease Through Nutrigenomics: Toward a Precision Medicine Paradigm. Narrative review

Stroia Carmina [1], Anca Dicu [2*], Lorena Filip [3], Maria Vrânceanu [4]

[1] PhD Candidate, Doctoral School of Biomedical Sciences, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania. E-mail: stroia.carminamariana@student.uoradea.ro
[2] Habilitated Assistant Professor, Department of Technical and Natural Sciences, Faculty of Food Engineering, Tourism and Environmental Protection, Aurel Vlaicu University of Arad, Arad, Romania. E-mail: anca.dicu@uav.ro
[3] Habilitated Professor, Department of Bromatology, Hygiene, Nutrition, «Iuliu Haţieganu» University of Medicine and Pharmacy, Cluj-Napoca, Romania. E-mail: lfilip@umfcluj.ro
[4] Associate Professor, Department Nutrition and Dietetics, Faculty of Food Engineering, Tourism and Environmental Protection, Aurel Vlaicu University of Arad, Arad, Romania. E-mail: marievranceanu@gmail.com

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Abstract

Alzheimer's disease is a complex neurodegenerative disorder shaped by interactions between genetic, metabolic, inflammatory, and environmental factors. Although scientific understanding has advanced, therapeutic progress remains limited because the condition arises from multiple interconnected mechanisms, including amyloid-beta accumulation, tau hyperphosphorylation, mitochondrial dysfunction, oxidative stress, vascular impairment, and chronic neuroinflammation. Familial early-onset Alzheimer's disease is associated with mutations in APP, PSEN1, and PSEN2, whereas most cases represent sporadic late-onset Alzheimer's disease influenced by polygenic variation and lifestyle exposures. Among genetic factors, the APOE ε4 allele is the strongest risk determinant, affecting lipid metabolism, inflammatory activity, oxidative injury, and amyloid-beta clearance. Variants such as MTHFR C677T further influence susceptibility by altering homocysteine metabolism, methylation capacity, and redox balance. Nutrigenomics and nutrigenetics offer a framework for understanding how dietary components interact with genetic architecture to modulate pathways relevant to Alzheimer's disease. Nutritional deficiencies that accompany cognitive decline can intensify metabolic dysfunction and accelerate neurodegeneration, whereas targeted nutritional interventions may improve cognitive and functional outcomes. Key nutraceuticals—including omega-3 fatty acids, B vitamins, quercetin, resveratrol, and benfotiamine—modulate pathways linked to oxidative stress, inflammation, mitochondrial activity, and synaptic resilience via Nrf2 activation, NF-κB suppression, and brain-derived neurotrophic factor signaling. Gene–diet interactions also indicate that individuals carrying genotypes such as APOE ε4 or BDNF Val66Met may respond differently to nutritional strategies. Integrating genomic, metabolic, and nutritional perspectives supports the development of precision-nutrition approaches for Alzheimer's disease prevention and management. Personalized interventions aligned with genetic background may reduce oxidative and inflammatory burden, enhance neuroprotective pathways, and delay disease progression.

Keywords: Alzheimer's disease, nutraceuticals, APOE, BDNF, genetic risk, cognitive decline.

1. Introduction

Alzheimer's disease (AD) is among the most prevalent neurodegenerative conditions, presenting significant challenges not only in clinical care but also in societal and economic domains on a global scale. Currently, dementia affects an estimated 25 million people worldwide, and projections suggest that with rising life expectancy, this number will reach at least 115.4 million by 2050. Among all dementia types, Alzheimer's disease (AD) accounts for 60–80% of cases, making it the most prevalent form globally. The impact of this disease is compounded by the absence of effective treatments that can modify its course, thereby contributing to increased rates of morbidity and mortality. Consequently, Alzheimer's and related disorders are recognized as major global health concerns, particularly as increasing life expectancy is expected to amplify the associated socioeconomic burden [1]. The disease is characterized by a range of interrelated cellular and molecular abnormalities, including disrupted protein homeostasis, mitochondrial dysfunction, oxidative damage, genomic instability, and impaired neurotrophic signaling. Inflammatory dysregulation within the central nervous system further contributes to disease progression [2]. Emerging research has highlighted a strong association between systemic inflammation and AD. Elevated levels of circulating pro-inflammatory markers in affected individuals suggest a bidirectional relationship between neuroinflammation and peripheral immune dysregulation [3,4].

However, the precise mechanisms underlying the disease remain insufficiently understood. Evidence indicates that certain interventions can slow their progression, with nutritional strategies emerging as an increasingly important component. Nutrigenomics—the study of how nutrients influence gene expression—offers a promising approach for reducing AD risk and slowing its progression. Because AD arises from interactions between genetic susceptibility, oxidative stress, inflammation, and metabolic dysfunction, diet-driven gene regulation can meaningfully influence disease pathways. Nutrigenomic compounds such as polyphenols, omega-3 fatty acids, vitamins, and antioxidants can activate protective genetic pathways (e.g., Nrf2) and suppress pro-inflammatory signaling (e.g., NF-κB). These processes reduce oxidative damage, modulate microglial activation, and support mitochondrial stability—key mechanisms underlying AD progression. Epigenetically, nutrients like folate, vitamin B12, and polyphenols influence DNA methylation and histone modifications, helping maintain neuroprotective gene expression. Gene–diet interactions further shape individual responses: APOE ε4 affects lipid metabolism and omega-3 utilization, MTHFR variants alter homocysteine regulation, and the BDNF Val66Met polymorphism impacts neuroplasticity, highlighting the need for personalized nutritional strategies. Through these mechanisms, nutrigenomics supports cognitive resilience by enhancing antioxidant defenses, regulating inflammation, improving mitochondrial function, and promoting neurotrophic factors such as BDNF. Together, these effects position nutrigenomics as a key component of precision medicine approaches aimed at preventing or mitigating Alzheimer's disease.

2. Methodology

We conducted a narrative literature review, using the academic databases Pubmed and ScienceDirect for the search and collection of literature. Major keywords, such as "Alzheimer", "genetic", "gene expression", "diet", "neuroinflammation", "oxidative stress", "nutraceuticals", "quercetin", "resveratrol", "omega 3 fatty acids", "vitamins", and "in vitro", "in vivo", and "clinical studies", were used individually or in combination during the literature survey (Figure 1). We considered original research articles written in English and based our search on their importance and relevance to the field. Due to the large number of published articles on nutraceuticals included in the study, as well as the limited number of references allowed, it was necessary to focus on the most impactful and relevant aspects, and we included published review articles where appropriate. In general, we focused on recently published articles but did not impose limits on the date of publication.

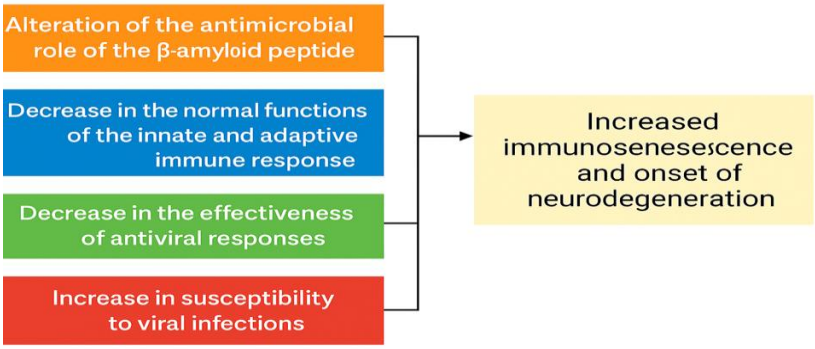

Figure 1 - Immune alterations leading to increased immunosenescence and onset of neurodegeneration

3. Neuropathological and Genetic Factors in AD

On a cellular scale, AD is marked by extensive synaptic dysfunction and vascular abnormalities, which together compromise cognitive function [5,6]. The core pathological signatures of the disease include the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein [7,8]. Insights into the pathophysiology of AD have largely been informed by studies on familial early-onset Alzheimer's disease (FAD), which typically develops before the age of 65. FAD is linked to genetic mutations in *Amyloid Beta Precursor Protein (APP), Presenilin 1 (PSEN1)*, and *Presenilin 2 (PSEN2)*, all of which regulate Aβ production. These findings underscore the central role of Aβ dysregulation in disease onset [9]. However, over 95% of cases are classified as sporadic or late-onset AD (LOAD), arising from complex interactions between genetic predisposition and environmental factors [10]. The genetic variability in *LOAD* complicates the identification of direct causative genes. Nonetheless, the Apolipoprotein E (APOE) gene—particularly the ε4 allele—has been consistently identified as the strongest genetic risk factor for late-onset AD [11]. Therapeutically targeting *APOE* pathways is an emerging area of interest, with potential applications across diverse patients [12].

APOE Gene and Alzheimer's Disease. Humans carry three primary alleles of the APOE gene—ε2 (APOE2), ε3 (APOE3), and ε4 (APOE4)—each of which confers varying degrees of susceptibility to Alzheimer's disease. Among them, the APOE ε4 allele is the most strongly associated with increased AD risk. Individuals who inherit one copy of APOE ε4 have a higher likelihood of developing the disease, while those with two copies may face a risk increase of up to 15-fold [13]. In contrast, the APOE ε2 variant is considered protective, reducing the risk of AD by approximately 50% and contributing to greater longevity in some individuals [14]. Research suggests that APOE ε4 influences disease progression through both gain-of-toxic-function and loss-of-normal-function mechanisms, disrupting neuronal maintenance, repair, and lipid metabolism [15]. Furthermore, APOE ε4 is not exclusive to Alzheimer's pathology; it has also been linked to Lewy body dementia, even in the absence of co-existing AD features [16]. These findings imply a broader role for APOE ε4 in neurodegenerative processes.

MTHFR Gene, Homocysteine, and Alzheimer's Disease. Another gene implicated in AD risk is Methylenetetrahydrofolate reductase (MTHFR), which plays a critical role in regulating folate metabolism and homocysteine levels. A well-studied variant of this gene, known as C677T (rs1801133), involves a substitution that leads to an amino acid change (alanine to valine) at codon 222. This mutation reduces MTHFR enzyme activity, thereby contributing to elevated plasma homocysteine concentrations [17,18]. Elevated homocysteine, or hyperhomocysteinemia, is an established independent risk factor for cognitive decline and AD. High levels of homocysteine can influence numerous molecular processes including DNA methylation [19], DNA repair capacity [20], oxidative stress responses [21], amyloid-beta aggregation [22], tau hyperphosphorylation [23], endothelial dysfunction, and inflammation [24]. Importantly, gene–environment interactions involving MTHFR may modulate individual risk by influencing epigenetic patterns that

regulate gene expression, which may further contribute to disease susceptibility.

Epigenetic Regulation in AD. Epigenetic mechanisms—such as DNA methylation, histone modifications, and non-coding RNA activity—have emerged as important contributors to the development of Alzheimer's disease. These processes are highly responsive to environmental stimuli, including diet, toxins, stress, and infections, which can alter the expression of genes without changing their underlying sequence. For instance, changes in the methylation status of genes involved in inflammation, metabolism, and synaptic function have been documented in AD patients. Additionally, epigenetic interactions between MTHFR variants and other genes may influence key biological pathways involved in cognitive function and neurodegeneration.

Insights from Genome-Wide Association Studies (GWAS). Large-scale genome-wide association studies (GWAS) have been instrumental in identifying genetic variants associated with late-onset Alzheimer's disease. These studies analyze hundreds of thousands of single nucleotide polymorphisms (SNPs) across large populations to detect subtle genetic associations with disease risk [25,26]. While the APOE ε4 allele remains the most significant genetic contributor to AD risk, GWAS have uncovered numerous additional loci with modest effect sizes. These include genes involved in lipid metabolism, inflammation, endocytosis, and innate immunity. Notably, while these variants do not individually cause Alzheimer's, they contribute to the broader genetic landscape of susceptibility. The cumulative evidence suggests that disruptions in cholesterol regulation and immune system function may play central roles in the initiation and progression of AD [27]. Interestingly, amyloid-β peptides—long implicated in the formation of extracellular plaques in AD—have recently been shown to possess antimicrobial properties. Research suggests that Aβ may act as an innate immune effector molecule, responding to the presence of bacteria, fungi, and viruses by forming aggregates that neutralize microbial threats [28]. This raises the possibility that amyloid deposition could be, at least in part, a protective response to chronic microbial exposure, though excessive accumulation ultimately contributes to neurotoxicity. Figure 1 summarizes our interpretation of Alzheimer's disease pathogenesis according to which mild immunodeficiency—both peripheral and central—associated with aging represents one of the major risk factors. Both central (neural) and peripheral immune systems undergo changes with age, including reduced responsiveness and dysregulated inflammation. This mild immunodeficiency may make the aging brain more susceptible to accumulating damage and initiating neurodegenerative processes.

Given the multifactorial nature of Alzheimer's disease, it is likely that a combination of genetic predispositions, environmental exposures, such as stress, toxins, and infections, immune dysregulation, and lifestyle habits interact to influence disease onset and progression. A complex disorder such as Alzheimer's disease arises from multiple etiological contributors and numerous pathogenic mechanisms that influence both its onset and its clinical progression (Figure 2).

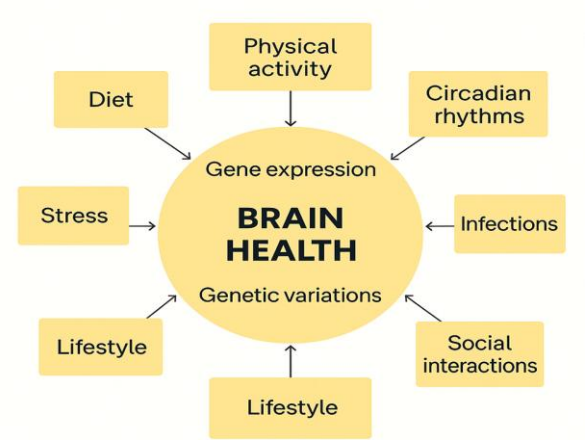

Figure 2 - Integrated framework of determinants influencing brain health.
The figure illustrates how genetic factors (gene expression and genetic variations) interact with modifiable lifestyle determinants – including diet, physical activity, circadian rhythms, stress, social interactions, infections, and overall lifestyle behaviors—to shape cognitive function and long-term brain resilience

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4. Nutritional support in AD

Proper functioning of the central nervous system (CNS) depends on a complex interplay of nutritional and lifestyle factors. Macronutrients, micronutrients, plant-derived bioactive compounds, and sufficient energy intake are all critical in maintaining neuronal health and protecting against neurodegeneration [29]. Beyond their physiological roles, dietary nutrients also serve as key modulators of gene activity, exerting influence over fundamental molecular processes such as gene transcription, translation, and post-transcriptional modifications [30]. These nutrient-gene interactions can affect cellular signaling pathways, synaptic plasticity, and neuroinflammation, ultimately shaping cognitive function and brain resilience throughout the lifespan.

Nutritional deficiencies and unintended weight loss are frequently observed in individuals with cognitive decline and have been shown to exacerbate neurological deterioration, increase mortality risk, and impair cognitive performance. Recent evidence by Wu et al. [31] suggests that providing adequate nutritional interventions can lead to substantial improvements in quality of life, cognitive performance, and both psychological and nutritional well-being in elderly patients with AD. Additionally, the study reported that enhanced nutritional support was linked to improved sleep quality, as evaluated using the Pittsburgh Sleep Quality Index (PSQI).

In conditions like Alzheimer's disease and mild cognitive impairment (MCI), inadequate caloric intake can lead to a metabolic crisis in the brain—often described as "cerebral starvation" or Type III diabetes [32]. Individuals with MCI and low BMI face a markedly increased risk of converting to AD, particularly among elderly, hypertensive, and female populations [33,34]. Interestingly, while undernutrition worsens outcomes, metabolic disorders like obesity and type 2 diabetes are also associated with elevated AD risk [35]. This apparent paradox is attributed to the dual role of insulin—either deficient due to undernutrition or dysfunctional in the context of insulin resistance—reinforcing insulin's critical importance in cognitive health.

Nutrigenomics, nutrigenetics and Alzheimer's Prevention. Nutrigenetics and nutrigenomics are interdisciplinary fields that explore the interaction between nutrition and genetics in determining health outcomes. Nutrigenetics focuses on how individual genetic variations affect the body's response to nutrients, while nutrigenomics investigates how dietary components influence gene expression, protein synthesis, and metabolic pathways [36]. Dietary inputs can modulate the genome through mechanisms such as chromatin remodeling, transcriptional control, and post-translational modifications [37]. Over time, these molecular adaptations can affect the metabolism of carbohydrates, fats, proteins, and micronutrients, thereby influencing the risk of chronic conditions such as diabetes, cardiovascular disease, and obesity.

Several nutrigenomic pathways are especially relevant in neurodegenerative contexts. Activation of the Nuclear factor erythroid 2–related factor 2 (Nrf2) pathway by compounds like sulforaphane leads to increased transcription of detoxifying and antioxidant genes, countering oxidative damage implicated in AD. In contrast, chronic activation of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, often triggered by Western-style diets, promotes pro-inflammatory gene expression in microglia and astrocytes, accelerating neurodegeneration. Dietary modulation of these pathways may tilt the balance between resilience and decline in vulnerable neural circuits.

The Brain-Derived Neurotrophic Factor (BDNF) rs6265 genotype (A/G) represents a heterozygous Val66Met variant, which has been associated with intermediate levels of activity-dependent BDNF secretion. This polymorphism may confer a modest reduction in neurotrophic signaling efficiency, potentially increasing susceptibility to oxidative and inflammatory stressors. Individuals with this genotype may benefit from targeted nutritional and lifestyle interventions—such as elevated intake of omega-3 fatty acids, polyphenol-rich foods, and consistent physical activity—known to enhance BDNF expression and synaptic resilience [38].

In Alzheimer's disease, disruptions in cholesterol transport and lipid homeostasis have been linked to cerebrovascular dysfunction and progressive neuronal damage. Moreover, DNA damage accumulation, a hallmark of aging and neurodegeneration, is strongly influenced by nutritional status. Micronutrients that support genomic stability—such as folate, vitamin B12, and zinc—are essential for DNA repair and replication. The optimal intake of these nutrients may vary depending on genetic polymorphisms, especially in genes involved in nutrient absorption and metabolism [39].

In sum, nutrigenomics offers a mechanistic framework to understand how environmental and lifestyle signals—particularly dietary patterns – interact with the genome to shape brain aging.

By integrating gene regulation, metabolism, and diet, this field opens new avenues for personalized

interventions in Alzheimer's disease prevention and management.

Oxidative Stress modulation in AD. Oxidative stress plays a pivotal role in AD and is intimately linked with both nutrition and genetics. Neurons are highly susceptible to damage from ROS such as superoxide and hydrogen peroxide, which can oxidize membrane lipids, proteins, and DNA. AD brains exhibit extensive oxidative damage, thought to be triggered by aggregated amyloid-β (Aβ) and impaired mitochondrial function early in the disease course [40]. *APOE* genotype influences oxidative stress burden: *APOE ε4* is associated with less efficient repair of oxidative damage and a relative deficiency in antioxidant capacity. Indeed, *APOE ε4* can impair mitochondrial dynamics, leading to excess free radical generation and oxidative injury. In the absence of APOE's normal antioxidant properties (as with *APOE ε4*), there is a higher risk of Aβ aggregation and oxidative stress, creating a vicious cycle of neuronal damage. Nutritional factors are critical modulators of oxidative stress. Diets abundant in antioxidants (e.g. vitamins C and E, flavonoids, carotenoids) and polyphenol-rich foods help neutralize free radicals and have been associated with lower oxidative damage in the aging brain [41]. For example, evidence suggests that polyphenol-rich diets (fruits, vegetables, spices) can delay AD onset by scavenging free radicals and bolstering endogenous antioxidant defenses. By contrast, nutrient deficiencies or pro-oxidant diets can exacerbate oxidative stress [42]. Elevated iron or copper intake, for instance, may catalyze ROS formation if not properly balanced by antioxidants. Nutrigenomic interventions can induce the expression of antioxidant enzymes via pathways like *Nrf2*; many phytochemicals (such as curcumin or sulforaphane) activate these cytoprotective genes.

Furthermore, lifestyle interventions that reduce systemic oxidative stress (regular exercise, caloric moderation) also reduce neuronal oxidative injury [43]. Oxidative damage and AD pathology reinforce each other – ROS can promote Aβ production (e.g. via upregulating amyloid precursor protein) and Aβ in turn induces more ROS [44]. Breaking this cycle is a therapeutic goal. In summary, controlling oxidative stress through diet and antioxidant strategies is considered a key avenue to protect neurons, especially in genetically susceptible individuals. Multiple clinical studies are examining whether antioxidant nutraceuticals or diets can slow cognitive decline, although results have been mixed, indicating that timing and genetic context (such as *APOE* status) may determine efficacy. Modulating oxidative stress through personalized dietary and lifestyle strategies may offer neuroprotection, particularly in genetically susceptible individuals such as *APOE ε4* carriers. Although clinical trials on antioxidant interventions have yielded mixed outcomes, emerging evidence suggests that timing, dosage, and genetic background critically influence their efficacy.

Modulation of silent inflammation in AD. Chronic inflammation in the brain (neuroinflammation) is a hallmark of AD and closely interacts with both genetics and diet. In AD, microglia and astrocytes – the resident immune cells of the CNS – become persistently [45]. These cells produce pro-inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α) that can lead to synaptic dysfunction, exacerbate amyloid and tau pathology, and ultimately contribute to neuronal death [46].Genetic evidence strongly supports the role of innate immunity in AD: for example, rare variants in microglial genes, such as Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) and Cluster of Differentiation 33 (CD33) substantially increase AD risk by altering inflammatory responses [47–49].

While APOE ε4 is classically associated with lipid metabolism, it also appears to promote a pro-inflammatory state in the brain; APOE4 carriers show elevated baseline inflammation and may experience greater microglial reactivity to insults (though APOE's immunomodulatory role is complex). BDNF, on the other hand, is generally anti-inflammatory in its effects (enhancing neuronal resilience can dampen inflammatory damage), and low BDNF levels have been linked to higher inflammation and metabolic dysfunction in aging brains [50]. Diet has emerged as a powerful modulator of inflammation. It is well known that certain dietary patterns, such as the Western diet high in saturated fats and refined carbohydrates, can induce systemic inflammation and, indirectly, neuroinflammation. In animal models, long-term consumption of a high-fat/high-sugar diet provokes robust glial activation and neuroinflammatory changes reminiscent of those seen in AD. Conversely, diets rich in anti-inflammatory components are associated with neuroprotection.

For instance, the Mediterranean, DASH, and MIND diets emphasize fruits, vegetables, whole grains, nuts, fish, and unsaturated fats – these diets are correlated with lower circulating inflammatory markers and a reduced risk of cognitive decline [51]. Mechanistically, many nutrients influence inflammation: omega-3 fatty acids (from fish oil) can shift microglia toward an anti-inflammatory phenotype and suppress cytokine production; polyphenols (like curcumin, resveratrol, and flavonoids from berries) inhibit inflammatory signaling pathways in the brain;

and antioxidant vitamins (C, E, and carotenoids) reduce oxidative triggers for inflammation [52,53]. Indeed, several bioactive dietary components have been shown to simultaneously attenuate oxidative stress and neuroinflammation [54,55]. In contrast, diets high in saturated and trans fats or excess calories can activate inflammatory pathways – saturated fatty acids can directly engage toll-like receptors on microglia, promoting release of Interleukin-1 beta (IL-1β) and Tumor Necrosis Factor alpha (TNF-α) [56–58]. Gut microbiota may be an intermediary: pro-inflammatory diets alter gut microbes and increase circulating endotoxins, which can exacerbate neuroinflammation, whereas high-fiber diets produce anti-inflammatory metabolites (short-chain fatty acids) that benefit microglial regulation.

From a nutrigenetic perspective, individuals with pro-inflammatory genetic profiles might benefit most from anti-inflammatory diets. Overall, controlling inflammation through nutrition and lifestyle is a promising strategy to modify AD risk. Epidemiological studies link higher adherence to anti-inflammatory dietary patterns with slower cognitive decline and lower incidence of dementia [59–62], though causality is still under investigation via clinical trials.

5. Nutraceuticals in AD

The term nutraceutical is derived from the combination of "nutrition" and "pharmaceutical," and refers to bioactive compounds present in foods that exert health-promoting or disease-preventive effects. These substances typically originate from plants, microbial, or food sources. The concept was introduced in 1989 by Dr. Stephen L. De Felice, who coined the term to describe food-derived components that possess pharmacological benefits, positioning them at the intersection between conventional foods and medicinal products [63].

Importantly, a distinction exists between nutraceutical and functional foods: while nutraceuticals are isolated or purified substances with specific therapeutic actions, functional foods are whole or fortified food products that convey health benefits when consumed as part of a regular diet. Nutraceuticals are recognized for their preventative, restorative, and protective biological properties and are commonly used as dietary supplements.

Recent research has highlighted the therapeutic potential of nutraceuticals in a range of chronic diseases, including cancer, metabolic disorders such as diabetes, cardiovascular diseases, and neurodegenerative conditions [64]. Many of these disorders are linked to oxidative stress, inflammation and a significant number of nutraceutical compounds exhibit antioxidant properties that help restore redox balance and anti-inflammatory potential. These compounds are often standardized plant extracts that contain specific active ingredients, and current studies suggest that many of these agents may influence gene expression, further supporting their role in modulation and prevention [65].

Omega-3 Fatty Acids. Omega-3 fatty acids are essential polyunsaturated fats known for their neuroprotective and anti-inflammatory properties. This group includes alpha-linolenic acid (ALA), stearidonic acid (SDA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) [66]. ALA, predominantly derived from plant-based sources like seeds and vegetable oils, serves as the precursor for the synthesis of EPA and DHA through enzymatic reactions involving elongases and desaturases.

Omega-3s exert numerous biological effects: they reduce inflammation by downregulating cyclooxygenase-2(COX2), nitric oxide synthase-2(iNOS), and NF-κB signaling, leading to lower cytokine production. Additionally, they exhibit antioxidant, anti-apoptotic, and neurotrophic activities, including the stimulation of nerve growth factor (NGF) synthesis [67]. DHA, in particular, supports neuronal membrane integrity and synaptic function. Its metabolic derivatives have been shown to influence glial cell behavior and cognitive performance, especially in early stages of Alzheimer's disease [68]. Epidemiological studies indicate that individuals with higher dietary intake or circulating levels of omega-3s—particularly DHA—are at reduced risk of developing AD and other forms of dementia [69,70].

However, the relationship between omega-3s and cognitive decline may be influenced by genetic factors—especially the APOE ε4 allele. Some studies report that APOE ε4 carriers may experience limited cognitive benefits from omega-3 supplementation due to impaired lipid transport to the brain [71].

Conversely, other studies suggest that APOE ε4 carriers may derive greater benefit from higher omega-3 intake, with slower rates of decline [72], though findings remain inconsistent [73].

Folate and vitamin B12 supplementation in AD. Numerous studies have linked elevated levels of homocysteine, along with deficiencies in folate and vitamin B12, to an increased risk of dementia [74], but findings across the literature are not fully consistent. A meta-analysis evaluating 31 randomized, placebo-controlled clinical trials did not find strong evidence that reducing homocysteine levels results in cognitive benefits [75]. Maintaining adequate folate and vitamin B12 levels is essential not only for controlling homocysteine but also for supporting methylation processes critical to brain function. Deficiency in these vitamins leads to hyperhomocysteinemia, which exerts neurotoxic effects by overstimulating N-methyl-D-aspartate (NMDA) receptors and triggering excitotoxic cell death [76]. It has also been hypothesized that ischemic damage to brain regions like the hippocampus may promote amyloid-β deposition and neurofibrillary tangle formation, ultimately contributing to Alzheimer's pathology.

A meta-analysis of 11 studies reported a higher frequency of the MTHFR C677T polymorphism in individuals with vascular dementia, especially among Asian populations [77]. The same genetic variant has also been associated with cardiovascular and metabolic conditions, including coronary heart disease, ischemic stroke, hypertension, and diabetic nephropathy—that are considered risk factors for vascular cognitive impairment. A number of randomized controlled trials and meta-analyses have demonstrated that combined supplementation with folic acid, vitamin B12, and vitamin B6 (pyridoxine) can lower the relative risk of stroke by approximately 23% [78]. Despite these encouraging results, variability in outcomes across studies is likely influenced by differences in supplementation regimens, including dose, type of vitamin used, and duration of treatment. However, caution is warranted in individuals with compromised kidney function, as the use of cyanocobalamin (a common form of vitamin B12) has been associated with worsening functional outcomes in this subgroup [79]. In general, daily supplementation with 0.5 to 5 mg of folic acid and around 0.5 mg of methylcobalamin is estimated to reduce total homocysteine (tHcy) concentrations by roughly one-third in populations consuming Western diets [80].

Beyond reducing homocysteine, folic acid supplementation may enhance specific aspects of cognitive performance, such as information processing speed, sensorimotor coordination, and complex reaction times. The underlying molecular mechanism involves the action of DNA methyltransferases, which mediate the process of DNA methylation. This epigenetic regulation is supported by adequate levels of folate and vitamin B12, both of which promote methylation reactions essential for neuronal function. In response to this, several countries have mandated the fortification of certain foods with folic acid to improve public health outcomes. Given the neurological implications, some experts have suggested that vitamin B12 fortification may also be beneficial in reducing the prevalence of cognitive disorders such as dementia.

6. Polyphenols in AD, Quercetin and Resveratrol

Quercetin is a widely distributed flavonoid found in various fruits, vegetables, and plants, including onions, apples, berries, garlic, grapes, tomatoes, capers, asparagus, and red leaf lettuce [81]. While its antioxidant activity is one of its most recognized pharmacological attributes, quercetin has also demonstrated potential in modulating neurological processes, particularly in the context of neurodegenerative diseases.

Despite its promising bioactivity, quercetin's clinical application is limited due to poor aqueous solubility, rapid metabolism in the gastrointestinal tract, and generally low oral bioavailability Nevertheless, certain studies have indicated that quercetin is capable of crossing the blood–brain barrier (BBB) to a limited extent and can accumulate in brain tissue [82].

Neuroprotective effects of quercetin have been extensively reported in preclinical models of Alzheimer's disease (AD). In one study, Shimmyo et al. demonstrated that quercetin inhibits β-site amyloid precursor protein cleaving enzyme-1 (BACE1) in a concentration-dependent manner. Exposure to 20 μM quercetin in primary neuronal cultures led to a marked reduction in both Aβ1–40 and Aβ1–42 peptide levels [83]. Quercetin's chemical structure includes hydrophobic regions that facilitate interaction with the β-sheet domains of amyloid fibrils, potentially preventing their formation [84]. However, further experimental validation is necessary to confirm this mechanism.

Quercetin could inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in cell-free in vitro systems, thereby helping to preserve acetylcholine levels—a key neurotransmitter involved in cognition [85]. In vivo, administration of 25 mg/kg of quercetin intraperitoneally every 48 hours for 3 months in the 3xTg-AD mouse model resulted in a significant increase in hippocampal cell density. This treatment also reduced β-amyloid plaque accumulation, tau tangles, astrocyte and microglial activation in both the hippocampus and amygdala, ultimately leading to improved memory and learning performance [86].

In another study using APPswe/PSEN1dE9 transgenic mice, daily oral administration of 20–40 mg/kg quercetin for 16 weeks alleviated cognitive deficits. This effect was attributed to the restoration of mitochondrial function through enhanced AMPK activation, improved mitochondrial membrane potential, increased ATP production, and decreased reactive oxygen species (ROS). Additionally, quercetin treatment reduced Aβ burden, likely through modulating amyloid precursor protein (APP) processing and enhancing Aβ clearance [87].

Furthermore, a one-month oral quercetin regimen (40 mg/kg/day) in rats injected with Aβ1–42 promoted neural progenitor cell proliferation in the dentate gyrus. This was associated with increased expression of neurotrophic and plasticity-related genes such as BDNF, nerve growth factor (NGF), cAMP response element-binding protein (CREB), and early growth response protein 1 (EGR-1), resulting in improved spatial learning and memory [88].

Although pre-clinical research has consistently shown the neuroprotective potential of quercetin, its clinical efficacy is currently limited by poor penetration across the BBB. Therefore, future efforts should focus on improving its pharmacokinetic properties and delivery systems to enhance bioavailability and therapeutic impact in neurodegenerative disorders like AD.

Quercetin, also, has been found to enhance apolipoprotein E levels by inhibiting its degradation in immortalized astrocyte cultures, without directly affecting APOE gene transcription or lipidation. In a transgenic mouse model of amyloidosis, quercetin administration led to elevated APOE levels in brain tissue and a corresponding reduction in cortical amyloid-β (Aβ) accumulation. These outcomes highlight the therapeutic potential of quercetin as a candidate for APOE-targeted strategies in the treatment of Alzheimer's disease [89].

7. Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring stilbenoid polyphenol, classified as a phytoalexin—compounds synthesized by plants in response to biotic stress such as pathogenic attacks. This molecule is present in various plant-based foods, including grapes, blueberries, raspberries, mulberries, and peanuts. Resveratrol exists in two geometric isomers: cis (Z) and trans (E), with the trans configuration being the more biologically stable form under natural conditions. However, upon exposure to ultraviolet (UV) light, trans-resveratrol can isomerize into the cis form, which is associated with various biological activities.

Emerging studies indicate that resveratrol (RV) may offer therapeutic benefits in the context of AD [90]. Its proposed efficacy is attributed to several mechanisms, including mitigation of oxidative stress, inhibition of amyloid-β aggregation, activation of silent information regulator-1 (SIRT1) [91], neuroprotective activity, enhancement of neurogenesis.

Resveratrol demonstrates potent antioxidant and anti-inflammatory effects, often surpassing traditional antioxidants such as vitamins C and E. Unlike many flavonoids that act downstream in oxidative pathways, resveratrol can interfere at earlier stages—specifically, by chelating transition metals like copper, which act as pro-oxidant catalysts in free radical-generating reactions [92].

Beyond its direct antioxidant action, resveratrol influences the expression of genes involved in oxidative stress regulation. It upregulates key antioxidant enzymes such as superoxide dismutase 1 (SOD1) and glutathione peroxidase 1 (GPX1) in a dose-dependent manner. Concurrently, it downregulates prooxidant enzymes like NADPH oxidase, thereby reducing reactive oxygen species (ROS) generation [93].

A significant portion of these gene regulatory effects are mediated through the activation of the transcription factor Nrf2, which orchestrates the cellular antioxidant response. Additionally, resveratrol enhances the activity of tetrahydrobiopterin-GTP-cyclohydrolase, further promoting the expression of protective antioxidant enzymes [94].

Long-term dietary administration of resveratrol (RV) at a dose of 150 mg/kg per day has been shown to significantly improve cognitive performance and reduce AD-related biomarkers in SAMP8 mice. These improvements were associated with decreased levels of

amyloid-β42 and phosphorylated tau, increased inhibitory phosphorylation of glycogen synthase kinase-3β (GSK-3β) at Ser9, and reduced expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β [95].

Resveratrol has been reported to influence the processing of amyloid precursor protein (APP) by promoting the non-amyloidogenic pathway, thereby decreasing the generation of amyloid-β peptides, including Aβ40 and Aβ42 [96].

Beyond its other neuroprotective functions, RV has been shown to enhance the expression of SIRT1 in both healthy individuals and those with AD [97]. SIRT1, a member of the sirtuin family primarily localized in neuronal nuclei, plays a critical role in regulating cellular mechanisms involved in aging, metabolism, and neuroprotection. Notably, individuals diagnosed with AD or mild cognitive impairment tend to have significantly lower SIRT1 levels compared to cognitively healthy controls, suggesting that serum SIRT1 may serve as a potential early diagnostic biomarker for AD [98].

In AD animal models, amyloid-β (Aβ) accumulation has been found to suppress SIRT1 expression, whereas RV treatment—known to activate SIRT1—leads to a marked reduction in cerebral Aβ deposits [99]. In a rat model of AD induced by ibotenic acid, intraperitoneal administration of resveratrol at a dose of 20 mg/kg effectively counteracted the neurotoxic effects of the toxin. This therapeutic effect is believed to be mediated through the upregulation of SIRT1, which in turn modulates the expression of NMDA receptor subunits NR2A and NR2B. This modulation contributes to the normalization of acetylcholine receptor gene expression and acetylcholinesterase activity. Additionally, resveratrol treatment was associated with alleviation of histopathological alterations in the hippocampus, ultimately leading to improved spatial memory performance [100].

8. Benfotiamine

Benfotiamine is a synthetic lipid-soluble derivative of thiamine (vitamin B1), designed to improve the bioavailability and cellular uptake of thiamine. Unlike conventional thiamine, benfotiamine is more efficiently absorbed and transported across cellular membranes, including the blood-brain barrier, allowing for greater central nervous system penetration [101].

Benfotiamine acts as a cofactor for several enzymes involved in glucose metabolism, most notably transketolase, which is a key enzyme in the pentose phosphate pathway. Activation of this pathway helps reduce the accumulation of advanced glycation end-products (AGEs), reactive oxygen species (ROS), and other metabolic byproducts that are strongly implicated in the pathophysiology of Alzheimer's disease and other neurodegenerative conditions [102].

Several preclinical and clinical studies have indicated that benfotiamine may exert neuroprotective effects in models of AD.

In transgenic mouse models of tauopathy, benfotiamine administration has been shown to reduce neurofibrillary tangle formation, activate the Nrf2/ARE antioxidant signaling pathway, provide neuroprotection, and alleviate behavioral impairments [103]. In models exhibiting amyloid plaque accumulation, benfotiamine treatment resulted in a reduction in amyloid plaque burden and phosphorylated tau levels. It also enhanced the phosphorylation of glycogen synthase kinase-3α and -3β (GSK-3α/β), which was associated with improved cognitive performance [104]. Additional studies have demonstrated that benfotiamine can modulate GSK-3β activity, promote neurogenesis restoration, influence AMPA receptor expression [105, 106], and reduce oxidative stress. Collectively, these findings support the therapeutic potential of benfotiamine in the context of Alzheimer's disease. A study by Tapias et al. [107] showed that benfotiamine significantly reduced hippocampal neuroinflammation—evidenced by decreased iNOS, COX 2, NF κB activation, and pro inflammatory cytokines—and lowered oxidative stress markers such as lipid peroxidation and ROS. These biochemical improvements were accompanied by enhanced cognitive performance and reduced amyloid pathology in APP/PS1 mice.

In another study, clinical measures such as the Clinical Dementia Rating (CDR), FDG-PET imaging, and advanced glycation end-product (AGE) biomarkers indicated that individuals with AD who do not carry the APOE ε4 allele showed a more favorable response to benfotiamine treatment. The reduced efficacy observed in APOE ε4 carriers does not appear to stem from differences in drug bioavailability, as increases in blood thiamine levels (+46%) and its esters were noted in this group post-treatment, although the changes were not statistically significant [108]. The presence of the APOE ε4 allele has been associated with a more aggressive manifestation of AD, including an earlier onset and increased amyloid plaque deposition compared to non-carriers. Additionally, individuals carrying this allele

exhibit elevated concentrations of reactive glycation compounds such as glyoxal and fluorescent AGEs, as well as higher levels of soluble receptor for AGE (sRAGE), with statistically significant differences reported when compared to those without the allele ($p = 0.018$) [109].

Benfotiamine plays a critical role in numerous cellular and neurological functions. Emerging research suggests its potential neuroprotective and therapeutic effects in neurodegenerative disorders, including dementia and Alzheimer's disease. Preliminary findings also indicate its possible benefits in modulating neuroinflammation, which is a contributing factor in cognitive decline. While current studies report a favorable safety profile, comprehensive clinical trials are necessary to confirm its long-term efficacy and safety.

9. Discussion

This integrative review highlights that nutrigenetics, nutrigenomics, oxidative stress, and inflammation are deeply interconnected in the context of Alzheimer's disease. Mechanistically, these processes converge on key pathways of neurodegeneration. A pro-inflammatory and pro-oxidative environment can accelerate Aβ accumulation, tau hyperphosphorylation, and neuronal death, whereas an anti-inflammatory and antioxidative milieu – achievable through targeted diet and lifestyle – may bolster brain resilience. Nutrigenetic factors (like APOE and BDNF genotypes) mediate individual susceptibility by altering how one's brain responds to metabolic and inflammatory challenges. Meanwhile, nutrigenomic effects of diet can directly regulate the expression of genes involved in AD pathology (for example, diets can induce enzymes that degrade Aβ or increase expression of synaptic proteins). Notably, oxidative stress and inflammation often act in concert as a feed-forward loop in AD; interventions aimed at one frequently influence the other. This underscores the value of multi-targeted interventions. For instance, adopting a Mediterranean-style diet in an APOE4 carrier might simultaneously reduce oxidative damage (through high antioxidant intake), lower inflammation (via abundant omega-3 fatty acids and polyphenols), and favorably modulate gene expression (enhancing neurotrophic and metabolic genes [110, 111]. In contrast, a Western diet in a genetically susceptible person could trigger a cascade of metabolic stress, inflammation, and epigenetic changes that expedite neurodegeneration.

From a translational perspective, these insights suggest future directions for research and prevention. One important avenue is precision nutrition for AD: developing genotype-tailored dietary guidelines or interventions. Large longitudinal studies and clinical trials are needed to determine, for example, if APOE ε4 carriers derive particular benefit from certain diets (such as low-saturated-fat, antioxidant-rich diets) in terms of cognitive outcomes. Similarly, does the BDNF Val66Met polymorphism modify response to exercise or nutritional supplements targeting BDNF up-regulation? Unraveling such gene–diet interactions could enable personalized nutritional counseling for those at risk of AD [112]. Another future direction is leveraging biomarkers to monitor nutrigenomic effects – for instance, epigenetic marks (DNA methylation signatures or histone acetylation patterns of AD-related genes) could serve as indicators of dietary impact on the brain. Interventions might then be adjusted to "tune" the epigenome toward a neuroprotective state. Additionally, combining dietary interventions with other lifestyle modifications (cognitive training, physical activity) may have synergistic effects. Multi-domain intervention trials (such as FINGER [113] and similar studies) have already hinted that diet plus exercise and vascular risk management can improve cognitive function in at-risk older adults; incorporating genetic stratification into such trials is a logical next step. On the molecular front, research into nutraceuticals that activate endogenous antioxidant and anti-inflammatory pathways (for example, compounds that activate Nrf2 or inhibit NF-κB) is ongoing, and future studies should evaluate their efficacy in AD models and patients.

Finally, as omics technologies advance, integrated analyses of genomics, transcriptomics, metabolomics, and epigenomics in dietary intervention studies will deepen our understanding of how exactly nutrition alters brain aging trajectories.

In summary, tackling AD will likely require a multipronged strategy. Nutrigenetics and nutrigenomics provide the blueprint for one prong – personalized dietary and metabolic interventions – which can complement pharmacological and other lifestyle approaches. Given that AD pathology develops over decades, early-life and mid-life preventive nutrition (especially in genetically predisposed individuals) could significantly postpone disease onset. Continued interdisciplinary research is needed to translate these mechanistic insights into effective guidelines. The convergence of diet, genes, oxidative stress, and inflammation in AD offers both a challenge, in terms of

complexity, and an opportunity: by intervening on several fronts simultaneously, we may finally bend the curve of AD incidence. As one recent paradigm posits, "food is medicine" for the aging brain – but optimizing that medicine will require accounting for the patient's unique genetic makeup and molecular profile.

10. Conclusions

Alzheimer's disease (AD) arises from the convergence of genetic vulnerability, metabolic imbalance, oxidative injury, and chronic inflammation. This review highlights that nutrigenetics and nutrigenomics provide a mechanistic framework for understanding how these factors interact to influence disease onset and progression. Key genetic polymorphisms—including APOE ε4, MTHFR/ C677T, and BDNF Val66Met—shape individual susceptibility by altering lipid metabolism, methylation capacity, oxidative stress responses, neurotrophic signaling, and microglial activity. At the same time, nutritional components can modulate these pathways through direct effects on gene expression, antioxidant defenses, and inflammatory signaling.

Evidence shows that diets rich in polyphenols, omega-3 fatty acids, B vitamins, and antioxidant phytochemicals can attenuate several mechanisms central to AD pathology, including Aβ accumulation, tau hyperphosphorylation, mitochondrial dysfunction, and neuroinflammation. Nutraceuticals such as quercetin, resveratrol, and benfotiamine exhibit multi-targeted neuroprotective actions—enhancing Nrf2-mediated antioxidant responses, downregulating NF-κB-driven inflammation, supporting neuronal bioenergetics, and influencing neurotrophic pathways such as BDNF and CREB.

Importantly, the effectiveness of such interventions is not uniform across individuals. Genetic background modulates the brain's response to dietary inputs, suggesting that precision nutrition—the alignment of dietary strategies with genetic and metabolic profiles—may offer a more effective approach than generalized dietary recommendations. Early, sustained nutritional optimization may reduce oxidative and inflammatory burden, support synaptic resilience, and ultimately delay or mitigate cognitive decline, particularly in genetically at-risk populations.

Overall, integrating genomic information with targeted nutritional and lifestyle interventions represents a promising, multi-dimensional strategy for AD prevention and management. Future clinical trials should incorporate genetic stratification, epigenetic biomarkers, and multi-omics approaches to fully realize the potential of nutrigenomics in Alzheimer's disease. As understanding deepens, personalized nutrition may become a central pillar of comprehensive AD risk reduction and therapeutic care.

Conflict of interests. Authors must declare the presence / absence of a conflict of interest

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References

1. Ghavami, S., Shojaei, S., Yeganeh, B., Ande, S. R., Jangamreddy, J. R., Mehrpour, M., Christoffersson, J., Chaabane, W., Moghadam, A. R., Kashani, H. H., Hashemi, M., Owji, A. A., & Łos, M. J. (2014). Autophagy and apoptosis dysfunction in neurodegenerative disorders. Progress in Neurobiology, 112, 24–49. https://doi.org/10.1016/j.pneurobio.2013.10.004

2. Cetin, S., Knez, D., Gobec, S., Kos, J., & Pišlar, A. (2022). Cell models for Alzheimer's and Parkinson's disease: At the interface of biology and drug discovery. Biomedicine & Pharmacotherapy, 149, 112924. https://doi.org/10.1016/j.biopha.2022.112924

3. Shen, X. N., Niu, L. D., Wang, Y. J., Cao, X. P., Liu, Q., Tan, L., … & Larbi, A. (2019). Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies. Journal of Neurology, Neurosurgery & Psychiatry, 90(5), 590–598. https://doi.org/10.1136/jnnp-2018-319148

4. King, E., O'Brien, J., Donaghy, P., Williams-Gray, C. H., Lawson, R. A., Morris, C. M., Barnett, N., Olsen, K., Martin-Ruiz, C., Burn, D., Yarnall, A. J., Taylor, J.-P., Duncan, G., Khoo, T. K., & Thomas, A. J. (2019). Inflammation in mild cognitive impairment due to Parkinson's disease, Lewy body disease, and Alzheimer's disease. International Journal of Geriatric Psychiatry, 34(8), 1244–1250. https://doi.org/10.1002/gps.5124

5. Bu, G. (2009). Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. Nature Reviews Neuroscience, 10, 333–344. https://doi.org/10.1038/nrn2620

6. Guo, T., Zhang, D., Zeng, Y., Huang, T. Y., Xu, H., & Zhao, Y. (2020). Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Molecular Neurodegeneration, 15(1), 40. https://doi.org/10.1186/s13024-020-00391-7

7. Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. Cold Spring Harbor Perspectives in Medicine, 1(1), a006189. https://doi.org/10.1101/cshperspect.a006189

8. Deture, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. Molecular Neurodegeneration, 1491), 32. https://doi.org/10.1186/s13024-019-0333-5

9. Cacace, R., Sleegers, K., & Van Broeckhoven, C. (2016). Molecular genetics of early-onset Alzheimer's disease revisited. Alzheimer's & Dementia, 12, 733–748. https://doi.org/10.1016/j.jalz.2016.01.012

10. Kennedy, A. M., Brown, J., & Rossor, M. (2012). The Genetics of Alzheimer's Disease. Scientifica (Cairo), 2012, 246210. Srinivasan, E., Chandrasekhar, G., Chandrasekar, P., Anbarasu, K., Vickram, A. S., Karunakaran, R., ... & Srikumar, P. S. (2021). Alpha-synuclein aggregation in Parkinson's disease. Frontiers in medicine, 8, 736978. https://doi.org/10.3389/fmed.2021.736978

11. Wightman, D. P., Jansen, I. E., Savage, J. E., Shadrin, A. A., Bahrami, S., Holland, D., … Posthuma, D. (2021). A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. Nature Genetics, 53(9), 1276–1282. https://doi.org/10.1038/s41588-021-00921-z

12. McDade, E., Llibre-Guerra, J. J., Holtzman, D. M., Morris, J. C., & Bateman, R. J. (2021). The informed road map to prevention of Alzheimer Disease: A call to arms. Molecular Neurodegeneration, 16, 49. https://doi.org/10.1186/s13024-021-00467-y

13. Strittmatter, W. J., Saunders, A. M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G. S., & Roses, A. D. (1993). Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proceedings of the National Academy of Sciences of the United States of America, 90(5), 1977–1981. https://doi.org/10.1073/pnas.90.5.1977

14. Corder, E. H., Saunders, A. M., Risch, N. J., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Rimmler, J. B., Locke, P. A., Conneally, P. M., & Schmader, K. E. (1994). Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nature Genetics, 7(2), 180–184. https://doi.org/10.1038/ng0694-180

15. Liu, C.-C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. Nature Reviews Neurology, 9(2), 106–118. https://doi.org/10.1038/nrneurol.2012.263

16. Dickson, D. W., Heckman, M. G., Murray, M. E., Soto, A. I., Walton, R. L., Diehl, N. N., van Gerpen, J. A., Uitti, R. J., Wszolek, Z. K., Ertekin-Taner, N., Knopman, D. S., Petersen, R. C., Graff-Radford, N. R., Boeve, B. F., … Ross, O. A. (2018). APOE ε4 is associated with severity of Lewy body pathology independent of Alzheimer pathology. Neurology, 91(12), e1182–e1195. https://doi.org/10.1212/WNL.0000000000006212

17. Frosst, P., Blom, H. J., Milos, R., Goyette, P., Sheppard, C. A., Matthews, R. G., Boers, G. J. H., den Heijer, M., Kluijtmans, L. A. J., van den Heuvel, L. P., & Rozen, R. (1995). A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nature Genetics, 10(1), 111–113. https://doi.org/10.1038/ng0595-111

18. Huang, X., Qin, X., Yang, W., Liu, L., Jiang, C., Zhang, X., Jiang, S., Bao, H., Su, H., Li, P., He, M., Song, Y., Zhao, M., Yin, D., Wang, Y., Zhang, Y., Li, J., Yang, R., Wu, Y., Hong, K., Wu, Q., Chen, Y., Sun, N., Li, X., Tang, G., Wang, B., Cai, Y., Hou, F. F., Huo, Y., Wang, H., Wang, X., & Cheng, X. (2018). MTHFR gene and serum folate interaction on serum homocysteine lowering: Prospect for precision folic acid treatment. Arteriosclerosis, Thrombosis, and Vascular Biology, 38(3), 679–685. https://doi.org/10.1161/ATVBAHA.117.310211

19. Coppedè, F. (2010). One-Carbon Metabolism and Alzheimer's Disease: Focus on Epigenetics. Current Genomics, 11(4), 246–260. https://doi.org/10.2174/138920210791233090

20. Bednarska-Makaruk, M., Graban, A., Sobczyńska-Malefora, A., Harrington, D. J., Mitchell, M., Voong, K., Dai, L., Łojkowska, W., Bochyńska, A., Ryglewicz, D., Wiśniewska, A., & Wehr, H. (2016). Homocysteine metabolism and the associations of global DNA methylation with selected gene polymorphisms and nutritional factors in patients with dementia. Experimental Gerontology, 81, 83–91. https://doi.org/10.1016/j.exger.2016.05.002

21. Deep, S. N., Mitra, S., Rajagopal, S., Paul, S., & Poddar, R. (2019). GluN2A-NMDA receptor–mediated sustained Ca^{2+} influx leads to homocysteine-induced neuronal cell death. Journal of Biological Chemistry, 294(29), 11154–11165. https://doi.org/10.1074/jbc.RA119.008820

22. Esse, R., Barroso, M., Tavares de Almeida, I., & Castro, R. (2019). The contribution of homocysteine metabolism disruption to endothelial dysfunction: state-of-the-art. International Journal of Molecular Sciences, 20(4), 867. https://doi.org/10.3390/ijms20040867

23. Sontag, J.-M., Wasek, B., Taleski, G., Smith, J., Arning, E., Sontag, E., & Bottiglieri, T. (2014). Altered protein phosphatase 2A methylation and Tau phosphorylation in the young and aged brain of methylenetetrahydrofolate reductase (MTHFR) deficient mice. Frontiers in Aging Neuroscience, 6, 214. https://doi.org/10.3389/fnagi.2014.00214

24. Di Meco, A., Li, J.-G., Barrero, C., Merali, S., & Praticò, D. (2018). Elevated levels of brain homocysteine directly modulate the pathological phenotype of a mouse model of tauopathy. Molecular Psychiatry, 24(10), 1696–1706. https://doi.org/10.1038/s41380-018-0062-0

25. Lambert, J.-C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., Combarros, O., Zelenika, D., Bullido, M. J., Tavernier, B., Letenneur, L., … & Amouyel, P., European Alzheimer's Disease Initiative. (2009). Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nature Genetics, 41(10), 1094–1099. https://doi.org/10.1038/ng.439

26. Hollingworth, P., Harold, D., Sims, R., et al. (2011). Common variants in ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nature Genetics, 43, 429–435. https://doi.org/10.1038/ng.803

27. Feringa, F. M., van der Kant, R. (2021). Cholesterol and Alzheimer's disease: From risk genes to pathological effects. Frontiers in Aging Neuroscience, 13, 690372. https://doi.org/10.3389/fnagi.2021.690372

28. Zhang, W., Xiao, D., Mao, Q., & Xia, H. (2023). Role of neuroinflammation in neurodegeneration development. Signal Transduction and Targeted Therapy, 8, 267. https://doi.org/10.1038/s41392-023-01486-5

29. Das, S., Banerjee, P., Jana, S., & Mondal, H. (2025). Unveiling the mechanistic nexus: how micronutrient enrichment shapes brain function, and cognitive health. Frontiers in Molecular Biosciences, 12, 1623547. https://doi.org/10.3389/fmolb.2025.1623547

30. Mierziak, J., Kostyn, K., Boba, A., Czemplik, M., Kulma, A., & Wojtasik, W. (2021). Influence of the bioactive diet components on gene expression regulation. Nutrients, 13(11), 3673. https://doi.org/10.3390/nu13113673

31. Wu, H., Wen, Y., & Guo, S. (2022). Role of nutritional support under clinical nursing path on the efficacy, quality of life, and nutritional status of elderly patients with Alzheimer's disease. Evidence-Based Complementary and Alternative Medicine, 2022, Article ID 9712330. https://doi.org/10.1155/2022/9712330

32. Gibas, K. J. (2017). The starving brain: Overfed meets undernourished in the pathology of mild cognitive impairment (MCI) and Alzheimer's disease (AD). Neurochemistry International, 110, 57–68. https://doi.org/10.1016/j.neuint.2017.09.001

33. Cova, I., Clerici, F., Maggiore, L., Pomati, S., Cucumo, V., Ghiretti, R., Galimberti, D., Scarpini, E., Mariani, C., & Caracciolo, B. (2016). Body mass index predicts progression of mild cognitive impairment to dementia. Dementia and Geriatric Cognitive Disorders, 41(3–4), 172–180. https://doi.org/10.1159/000444216

34. Stroia, C. M., Pallag, A., Vrânceanu, M., de Lorenzo, D., Grimaldi, K. A., Pallag, C. R., Vindis, K., Bei, D., Burlou-Nagy, C. (Fati), & Ghitea, T. C. (2025). The Association of VDR, CYP2R1, and GC Gene Polymorphisms, Dietary Intake, and BMI in Regulating Vitamin D Status. Diseases, 13(7), 219. https://doi.org/10.3390/diseases13070219

35. Amin, A. M., Mostafa, H., & Khojah, H. M. J. (2023). Insulin resistance in Alzheimer's disease: The genetics and metabolomics links. Clinica Chimica Acta, 539, 215–236. https://doi.org/10.1016/j.cca.2022.12.016

36. Fenech, M., El-Sohemy, A., Cahill, L., Ferguson, L. R., French, T. A., Tai, E. S., Milner, J., Koh, W. P., Xie, L., Zucker, M., Buckley, M., Cosgrove, L., Lockett, T., Fung, K. Y. C., Head, R. (2011). Nutrigenetics and nutrigenomics: Viewpoints on the current status and applications in nutrition research and practice. Journal of Nutrigenetics & Nutrigenomics, 4(2), 69–89. https://doi.org/10.1159/000327772

37. de Souza, A. P., Marinho, V., & Marques, M. R. (2025). The fundamental role of nutrients for metabolic balance and epigenome integrity maintenance. Epigenomes, 9(3), 23. https://doi.org/10.3390/epigenomes9030023

38. Xue, B., Waseem, S. M. A., Zhu, Z., Alshahrani, M. A., Nazam, N., Anjum, F., Habib, A. H., Rafeeq, M. M., Nazam, F., & Sharma, M. (2022). Brain-derived neurotrophic factor: A connecting link between nutrition, lifestyle, and Alzheimer's disease. Frontiers in Neuroscience, 16, 925991. https://doi.org/10.3389/fnins.2022.925991

39. Fenech, M. (2002). Micronutrients and genomic stability: A new paradigm for recommended dietary allowances (RDAs). Food and Chemical Toxicology, 40(8), 1113–1117. https://doi.org/10.1016/S0278-6915(02)00028-5

40. Botchway, B. O. A., Okoye, F. C., Chen, Y., Arthur, W. E., & Fang, M. (2022). Alzheimer disease: Recent updates on apolipoprotein E and gut microbiome mediation of oxidative stress, and prospective interventional agents. Aging and Disease, 13(1), 87–102. https://doi.org/10.14336/AD.2021.0616

41. Ramesh, B. N., Sathyanarayana Rao, T. S., Prakasam, A., Sambamurti, K., & Jagannatha Rao, K. S. (2010). Neuronutrition and Alzheimer's disease. Journal of Alzheimer's Disease, 19(4), 1123–1139. https://doi.org/10.3233/JAD-2010-1312

42. Gülçin, İ. (2025). Antioxidants: a comprehensive review. Archives of Toxicology, 99, 1893–1997. https://doi.org/10.1007/s00204-025-03997-2

43. Lei, X. G., Zhu, J.-H., Cheng, W.-H., Bao, Y., Ho, Y.-S., Reddi, A. R., Holmgren, A., & Arnér, E. S. J. (2015). Paradoxical roles of antioxidant enzymes: Basic mechanisms and health implications. Physiological Reviews, 96(1), 307–364. https://doi.org/10.1152/physrev.00010.2014

44. Fakhri, K. U., Sharma, D., Fatma, H., Yasin, D., Alam, M., Sami, N., Ahmad, F. J., Shamsi, A., & Rizvi, M. A. (2025). The dual role of dietary phytochemicals in oxidative stress: Implications for oncogenesis, cancer chemoprevention, and ncRNA regulation. Antioxidants, 14(6), 620. https://doi.org/10.3390/antiox14060620

45. AbuAlrob, M. (2024). Neuroinflammation in Alzheimer's disease: Mechanistic insights, pathological implications, and emerging therapeutic strategies. Authorea Preprints. https://doi.org/10.22541/AU.172838938.84403346/V1

46. McGrattan, A. M., McGuinness, B., McKinley, M. C., Kee, F., Passmore, P., Woodside, J. V., & McEvoy, C. T. (2019). Diet and inflammation in cognitive ageing and Alzheimer's disease. Current Nutrition Reports, 8(2), 53–65. https://doi.org/10.1007/s13668-019-0271-4

47. Griciuc, A., & Tanzi, R. E. (2021). The role of innate immune genes in Alzheimer's disease. Current Opinion in Neurology, 34(2), 228–236. https://doi.org/10.1097/WCO.0000000000000911

48. Li, Y., Xu, H., Wang, H., Yang, K., Luan, J., & Wang, S. (2023). TREM2: Potential therapeutic targeting of microglia for Alzheimer's disease. Biomedicine & Pharmacotherapy, 165, 115218. https://doi.org/10.1016/j.biopha.2023.115218

49. Gratuze, M., Leyns, C. E. G., & Holtzman, D. M. (2018). New insights into the role of TREM2 in Alzheimer's disease. Molecular Neurodegeneration, 13, 66. https://doi.org/10.1186/s13024-018-0298-9

50. Xue, B., Waseem, S. M. A., Zhu, Z., Alshahrani, M. A., Nazam, N., Anjum, F., Habib, A. H., Rafeeq, M. M., Nazam, F., & Sharma, M. (2022). Brain-derived neurotrophic factor: A connecting link between nutrition, lifestyle, and Alzheimer's disease. Frontiers in Neuroscience, 16, 925991. https://doi.org/10.3389/fnins.2022.92599

51. Seo, D.-O., & Holtzman, D. M. (2024). Current understanding of the Alzheimer's disease-associated microbiome and therapeutic strategies. Experimental & Molecular Medicine, 56(1), 86–94. https://doi.org/10.1038/s12276-023-01146-2

52. Devassy, J. G., Leng, S., Gabbs, M., Monirujjaman, M., & Aukema, H. M. (2016). Omega-3 polyunsaturated fatty acids and oxylipins in neuroinflammation and management of Alzheimer disease. Advances in Nutrition, 7(5), 905–916. https://doi.org/10.3945/an.116.012187

53. Miquel, S., Champ, C., Day, J., Aarts, E., Bahr, B. A., Bakker, M., Bánáti, D., Calabrese, V., Cederholm, T., Cryan, J. F., Dye, L., Farrimond, J. A., Korosi, A., Layé, S., Maudsley, S., Milenkovic, D., Mohajeri, M. H., Sijben, J., Solomon, A., Spencer, J. P. E., Thuret, S., Vanden Berghe, W., Vauzour, D., Vellas, B., Wesnes, K., Willatts, P., Wittenberg, R., & Geurts, L. (2018). Poor cognitive ageing: vulnerabilities, mechanisms and the impact of nutritional interventions. Ageing Research Reviews, 42, 40–55. https://doi.org/10.1016/j.arr.2017.12.004

54. Pistollato, F., Calderón Iglesias, R., Ruiz, R., Aparicio, S., Crespo, J., López, L. D., Manna, P. P., Giampieri, F., & Battino, M. (2018). Nutritional patterns associated with the maintenance of neurocognitive functions and the risk of dementia and Alzheimer's disease: A focus on human studies. Pharmacological Research, 131, 32–43. https://doi.org/10.1016/j.phrs.2018.03.012

55. Minihane, A. M., Vinoy, S., Russell, W. R., Baka, A., Roche, H. M., Tuohy, K. M., Teeling, J. L., Blaak, E. E., Fenech, M., Vauzour, D., McArdle, H. J., Kremer, B. H. A., Sterkman, L., Vafeiadou, K., Benedetti, M. M., Williams, C. M., & Calder, P. C. (2015). Low-grade inflammation, diet composition and health: Current research evidence and its translation. British Journal of Nutrition, 114(7), 999–1012. https://doi.org/10.1017/S0007114515002093

56. Pistollato, F., Calderón Iglesias, R., Ruiz, R., Aparicio, S., Crespo, J., López, L. D., Manna, P. P., Giampieri, F., & Battino, M. (2018). Nutritional patterns associated with the maintenance of neurocognitive functions and the

risk of dementia and Alzheimer's disease: A focus on human studies. Pharmacological Research, 131, 32–43. https://doi.org/10.1016/j.phrs.2018.03.012

57. Huang, S., Rutkowsky, J. M., Snodgrass, R. G., Ono-Moore, K. D., Schneider, D. A., Newman, J. W., Adams, S. H., & Hwang, D. H. (2012). Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. Journal of Lipid Research, 53(9), 2002–2013. https://doi.org/10.1194/jlr.D029546

58. Peres, A. M., Dantas, R. M., Ferreira, A. C., Silveira, A. C. S., Raphaelli, G., Felipe, L., Souza, L., Costa, M., Machado, A., Machado, D., Herrmann, R., de Oliveira, J., Netto, C. A., Wyse, A., Dalmaz, C., & Bast, R. K. S. (2025). Extra virgin olive oil supplementation attenuates hippocampal inflammation in high-fat diet-induced obesity animals with a depressive phenotype. Brain Behavior and Immunity Integrative, 12, 100137. https://doi.org/10.1016/j.bbii.2025.100137

59. Freitas, H. R., Ferreira, G. D. C., Trevenzoli, I. H., Oliveira, K. D. J., & De Melo Reis, R. A. (2017). Fatty acids, antioxidants and physical activity in brain aging. Nutrients, 9(11), 1263. https://doi.org/10.3390/nu9111263

60. van de Rest, O., Berendsen, A. A. M., Haveman-Nies, A., & de Groot, L. C. P. G. M. (2015). Dietary patterns, cognitive decline, and dementia: A systematic review. Advances in Nutrition, 6(2), 154–168. https://doi.org/10.3945/an.114.007617

61. Jin, Y., Lai, G., Li, S., Lee, J., Chan, V., Lu, Z., Leung, J., Lai, K., Lam, K., Auyeung, T. W., Kwok, T., Chui, K. T., Woo, J., & Lo, K. K.-h. (2025). Adhering to healthy dietary patterns prevents cognitive decline of older adults with sarcopenia: The Mr. OS and Ms. OS Study. Nutrients, 17(19), 3070. https://doi.org/10.3390/nu17193070

62. Stroia, C. M., Ghitea, T. C., Vrânceanu, M., Mureșan, M., Bimbo-Szuhai, E., Pallag, C. R., & Pallag, A. (2024). Relationship between Vitamin D_3 deficiency, metabolic syndrome and VDR, GC, and CYP2R1 gene polymorphisms. Nutrients, 16(9), 1272. https://doi.org/10.3390/nu16091272

63. Vrânceanu, M., Galimberti, D., Banc, R., Dragoș, O., Cozma-Petruț, A., Hegheș, S-C., Voştinaru, O., Cuciureanu, M., Stroia, C. M., Miere, D., & Filip, L. (2022). The anticancer potential of plant-derived nutraceuticals via the modulation of gene expression. Plants, 11(19), 2524. https://doi.org/10.3390/plants11192524

64. Bergamin, A., Mantzioris, E., Cross, G., Deo, P., Garg, S., & Hill, A. M. (2019). Nutraceuticals: Reviewing their role in chronic disease prevention and management. Pharmaceutical Medicine, 33(4), 291–309. https://doi.org/10.1007/s40290-019-00289-w

65. Taylor, J. B., & Triggle, D. J. (Eds.). (2007). Comprehensive Medicinal Chemistry II (2nd ed.). Elsevier. ISBN 978-0-08-044513-7

66. Chávez-Castillo, M., Gotera, M. P., Duran, P., Díaz, M. P., Nava, M., Cano, C., Díaz-Camargo, E., Cano, G., Cano, R., Rivera-Porras, D., & Bermúdez, V. (2025). Neuroprotective role of omega-3 fatty acids: Fighting Alzheimer's disease. Molecules, 30(15), 3057. https://doi.org/10.3390/molecules30153057

67. Ajith, T. A. (2018). A recent update on the effects of omega-3 fatty acids in Alzheimer's disease. Current Clinical Pharmacology, 13(4), 252–260. https://doi.org/10.2174/1574884713666180807145648

68. Heras-Sandoval, D., & Pedraza-Chaverri, J., & Pérez-Rojas, J. M. (2016). Role of docosahexaenoic acid in the modulation of glial cells in Alzheimer's disease. Journal of Neuroinflammation, 13, 61. https://doi.org/10.1186/s12974-016-0525-7

69. Sala-Vila, A., Satizabal, C. L., Tintle, N., Melo van Lent, D., Vasan, R. S., Beiser, A. S., Seshadri, S., & Harris, W. S. (2022). Red blood cell DHA is inversely associated with risk of incident Alzheimer's disease and all-cause dementia: Framingham Offspring Study. Nutrients, 14(12), 2408. https://doi.org/10.3390/nu14122408

70. Otsuka, R., Tange, C., Nishita, Y., Kato, Y., Imai, T., Ando, F., & Shimokata, H. (2014). Serum docosahexaenoic and eicosapentaenoic acid and risk of cognitive decline over 10 years among elderly Japanese. European Journal of Clinical Nutrition, 68(4), 503–509. https://doi.org/10.1038/ejcn.2013.264

71. Ebright, B., Duro, M. V., Chen, K., Louie, S., & Yassine, H. N. (2024). Effects of APOE4 on omega-3 brain metabolism across the lifespan. Trends in Endocrinology & Metabolism, 35(8), 745–757. https://doi.org/10.1016/j.tem.2024.03.003

72. van de Rest, O., Wang, Y., Barnes, L. L., Tangney, C., Bennett, D. A., & Morris, M. C. (2016). APOE ε4 and the associations of seafood and long-chain omega-3 fatty acids with cognitive decline. Neurology, 86(22), 2063–2070. https://doi.org/10.1212/WNL.0000000000002719

73. Whalley, L. J., Deary, I. J., Starr, J. M., Wahle, K. W., Rance, K. A., Bourne, V. J., & Fox, H. C. (2008). n-3 fatty acid erythrocyte membrane content, APOE ε4, and cognitive variation: An observational follow-up study in late adulthood. American Journal of Clinical Nutrition, 87(2), 449–454. https://doi.org/10.1093/ajcn/87.2.449

74. Liu, H., Yang, M., Li, G. M., Qiu, Y., Zheng, J., Du, X., Wang, J.-L., & Liu, R.-W. (2010). The MTHFR C677T polymorphism contributes to an increased risk for vascular dementia: A meta-analysis. Journal of Neurological Sciences, 294(1–2), 74–80. https://doi.org/10.1016/j.jns.2010.04.00

75. Clarke, R., Bennett, D., Parish, S., Lewington, S., Skeaff, M., Eussen, S. J.P.M., Lewerin, C., Stott, D. J., Armitage, J., Hankey, G. J., Lonn, E., Spence, J. D., Galan, P., de Groot, L. C. P. G. M., Halsey, J., Dangour, A. D., Collins, R., & Grodstein, F. (2014). Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. American Journal of Clinical Nutrition, 100(2), 657–666. https://doi.org/10.3945/ajcn.113.076349

76. Boldyrev, A., Bryushkova, E., Mashkina, A., & Vladychenskaya, E. (2013). Why is homocysteine toxic for the nervous and immune systems? Current Aging Science, 6(1), 29–36. https://doi.org/10.2174/18746098112059990007

77. Liu, H., Yang, M., Li, G. M., Qiu, Y., Zheng, J., Du, X., Wang, J.-L., & Liu, R.-W. (2010). The MTHFR C677T polymorphism contributes to an increased risk for vascular dementia: A meta-analysis. Journal of Neurological Sciences, 294(1–2), 74–80. https://doi.org/10.1016/j.jns.2010.04.001

78. Román, G. C., Mancera-Páez, O., & Bernal, C. (2019). Epigenetic factors in late-onset Alzheimer's disease: MTHFR and CTH gene polymorphisms, metabolic transsulfuration and methylation pathways, and B vitamins. International Journal of Molecular Sciences, 20(2), 319. https://doi.org/10.3390/ijms20020319

79. Spence, J. D., Yi, Q., & Hankey, G. J. (2017). B vitamins in stroke prevention: time to reconsider. The Lancet Neurology, 16(9), 750–760. https://doi.org/10.1016/S1474-4422(17)30238-0

80. Ułamek-Kozioł, M., Pluta, R., Bogucka-Kocka, A., Januszewski, S., Kocki, J., & Czuczwar, S. J. (2016). Brain ischemia with Alzheimer phenotype dysregulates Alzheimer's disease-related proteins. Pharmacological Reports, 68(3), 582–591. https://doi.org/10.1016/j.pharep.2016.01.006

81. Carrillo-Martinez, E. J., Flores-Hernández, F. Y., Salazar-Montes, A. M., Nario-Chaidez, H. F., & Hernández-Ortega, L. D. (2024). Quercetin, a flavonoid with great pharmacological capacity. Molecules, 29(5), 1000. https://doi.org/10.3390/molecules29051000

82. Aghababaei, F., & Hadidi, M. (2023). Recent advances in potential health benefits of quercetin. Pharmaceuticals, 16(7), 1020. https://doi.org/10.3390/ph16071020

83. Shimmyo, Y., Kihara, T., Akaike, A., Niidome, T., & Sugimoto, H. (2008). Flavonols and flavones as BACE-1 inhibitors: Structure–activity relationship in cell-free, cell-based and in silico studies reveal novel pharmacophore features. Biochimica et Biophysica Acta (BBA) – General Subjects, 1780(5), 819–825. https://doi.org/10.1016/j.bbagen.2008.01.017

84. Yu, Z., Wei, X., Dai, L., Ma, W., Li, W., Li, X., & Han, X.-L. (2025). Dual binding modes of Quercetin to BSA: Insights from spectroscopy and molecular simulations in amyloid suppression. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 348(Pt 2), 127093. https://doi.org/10.1016/j.saa.2025.127093

85. Kaur, K., Kulkarni, Y. A., & Wairkar, S. (2024). Exploring the potential of quercetin in Alzheimer's disease: Pharmacodynamics, pharmacokinetics, and nanodelivery systems. Brain Research, 1834, 148905. https://doi.org/10.1016/j.brainres.2024.148905

86. Sabogal-Guáqueta, A. M., Muñoz-Manco, J. I., Ramírez-Pineda, J. R., Lamprea-Rodríguez, M., Osorio, E., & Cardona-Gómez, G. P. (2015). The flavonoid quercetin ameliorates Alzheimer's disease pathology and protects cognitive and emotional function in aged triple transgenic Alzheimer's disease model mice. Neuropharmacology, 93, 134–145. https://doi.org/10.1016/j.neuropharm.2015.01.027

87. Wang, D.-M., Li, S.-Q., Wu, W.-L., Zhu, X.-Y., Wang, Y., & Yuan, H.-Y. (2014). Effects of long-term treatment with quercetin on cognition and mitochondrial function in a mouse model of Alzheimer's disease. Neurochemical Research, 39(8), 1533–1543. https://doi.org/10.1007/s11064-014-1343-x

88. Karimipour, M., Rahbarghazi, R., Tayefi, H., Shimia, M., Ghanadian, M., & Mahmoudi, J. (2019). Quercetin promotes learning and memory performance concomitantly with neural stem/progenitor cell proliferation and neurogenesis in the adult rat dentate gyrus. International Journal of Developmental Neuroscience, 74, 18–26. https://doi.org/10.1016/j.ijdevneu.2019.02.005

89. Zhang, X., Hu, J., Zhong, L., Wang, N., Yang, L., Liu, C.-C., Li, H., Wang, X., Zhou, Y., Zhang, Y., Xu, H., Bu, G., & Zhuang, J. (2016). Quercetin stabilizes apolipoprotein E and reduces brain Aβ levels in amyloid model mice. Neuropharmacology, 108, 179–192. https://doi.org/10.1016/j.neuropharm.2016.04.032

90. Bukhari, S. N. A. (2022). Dietary polyphenols as therapeutic intervention for Alzheimer's disease: A mechanistic insight. Antioxidants, 11, 554. https://doi.org/10.3390/antiox11030554

91. Quadros Gomes, B. A., Bastos Silva, J. P., Rodrigues Romeiro, C. F., Monteiro dos Santos, S., Azulay Rodrigues, C., Rodrigues Gonçalves, P., Sakai, J. T., Santos Mendes, P. F., Pompeu Varela, E. L., & Monteiro, M. C. (2018). Neuroprotective mechanisms of resveratrol in Alzheimer's disease: Role of SIRT1. Oxidative Medicine and Cellular Longevity, 2018, 8152373. https://doi.org/10.1155/2018/8152373

92. Alarcón de la Lastra, C., & Villegas, I. (2007). Resveratrol as an antioxidant and pro-oxidant agent: Mechanisms and clinical implications. Biochemical Society Transactions, 35(5), 1156–1160. https://doi.org/10.1042/BST0351156

93. Ugusman, A., Zakaria, Z., Hui, C. K., & Nor Anita Megat Mohd Nordin, N. A. M. M. (2011). Piper sarmentosum inhibits ICAM-1 and Nox4 gene expression in oxidative stress-induced human umbilical vein endothelial cells. BMC Complementary and Alternative Medicine, 11, 31. https://doi.org/10.1186/1472-6882-11-31

94. Ungvari, Z., Bagi, Z., Feher, A., Recchia, F. A., Sonntag, W. E., Pearson, K., de Cabo, R., & Csiszar, A. (2010). Resveratrol confers endothelial protection via activation of the antioxidant transcription factor Nrf2. American Journal of Physiology – Heart and Circulatory Physiology, 299(1), H18–H24. https://doi.org/10.1152/ajpheart.00260.2010

95. Chen, Z.-J., Yang, Y.-F., Zhang, Y.-T., & Yang, D.-H. (2018). Dietary total prenylflavonoids from the fruits of Psoralea corylifolia L. prevents age-related cognitive deficits and down-regulates Alzheimer's markers in SAMP8 mice. Molecules, 23(1), 196. https://doi.org/10.3390/molecules23010196

96. Sathya, M., Moorthi, P., Premkumar, P., Kandasamy, M., Jayachandran, K. S., & Anusuyadevi, M. (2017). Resveratrol intervenes cholesterol- and isoprenoid-mediated amyloidogenic processing of AβPP in familial Alzheimer's disease. Journal of Alzheimer's Disease, 60(suppl. 1), S3–S23. https://doi.org/10.3233/JAD-161034

97. Zhang, M., & Tang, Z. (2023). Therapeutic potential of natural molecules against Alzheimer's disease via SIRT1 modulation. Biomedicine & Pharmacotherapy, 161, 114474. https://doi.org/10.1016/j.biopha.2023.114474

98. Yan, L., Guo, M.-S., Zhang, Y., Yu, L., Wu, J.-M., Tang, Y., Ai, W., Zhu, F.-D., Law, B. Y.-K., Chen, Q., Yu, C.-L., Wong, V. K.-W., Li, H., Li, M., Zhou, X.-G., Qin, D.-L., & Wu, A.-G. (2022). Dietary plant polyphenols as the potential drugs in neurodegenerative diseases: current evidence, advances, and opportunities. Oxidative Medicine and Cellular Longevity, 2022, 5288698. https://doi.org/10.1155/2022/5288698

99. Zhu, L., Lu, F., Zhang, X., Liu, S., & Mu, P. (2022). SIRT1 is involved in the neuroprotection of pterostilbene against amyloid β(25–35)-induced cognitive deficits in mice. Frontiers in Pharmacology, 13, 877098. https://doi.org/10.3389/fphar.2022.877098

100. Karthick, C., Periyasamy, S., Jayachandran, K. S., & Anusuyadevi, M. (2016). Intrahippocampal administration of ibotenic acid induced cholinergic dysfunction via NR2A/NR2B expression: Implications of resveratrol against Alzheimer disease pathophysiology. Frontiers in Molecular Neuroscience, 9, 28. https://doi.org/10.3389/fnmol.2016.00028

101. Pomero, F., Molinar Min, A., La Selʙa, M., Allione, A., Molinatti, G. M., & Porta, M. (2001). Benfotiamine is similar to thiamine in correcting endothelial cell defects induced by high glucose. Acta Diabetologica, 38(3), 135–138. https://doi.org/10.1007/s005920100171

102. Bozic, I., & Lavrnja, I. (2023). Thiamine and benfotiamine: Focus on their therapeutic potential. Heliyon, 9, e21839. https://doi.org/10.1016/j.heliyon.2023.e21839

103. Tapias, V., Jainuddin, S., Ahuja, M., Stack, C., Elipenahli, C., Vignisse, J., Gerges, M., Starkova, N., Xu, H., Starkov, A. A., … & Przedborski, S. (2018). Benfotiamine treatment activates the Nrf2/ARE pathway and is neuroprotective in a transgenic mouse model of tauopathy. Human Molecular Genetics, 27(16), 2874–2892. https://doi.org/10.1093/hmg/ddy201

104. Pan, X., Gong, N., Zhao, J., Yu, Z., Gu, F., & Chen, J. (2010). Powerful beneficial effects of benfotiamine on cognitive impairment and β-amyloid deposition in amyloid precursor protein/presenilin-1 transgenic mice. Brain, 133(5), 1342–1351. https://doi.org/10.1093/brain/awq069

105.Sambon, M., Napp, A., Demelenne, A., Vignisse, J., Wins, P., Fillet, M., & Bettendorff, L. (2019). Thiamine and benfotiamine protect neuroblastoma cells against paraquat and β-amyloid toxicity by a coenzyme-independent mechanism. Heliyon, 5, e01710. https://doi.org/10.1016/j.heliyon.2019.e01710

106.Vignisse, J., Sambon, M., Gorlova, A., Pavlov, D., Caron, N., Malgrange, B., Shevtsova, E., Svistunov, A., Anthony, D. C., Markova, N., Bazhenova, N., Coumans, B., Lakaye, B., Wins, P., Strekalova, T., & Bettendorff, L. (2017). Thiamine and benfotiamine prevent stress-induced suppression of hippocampal neurogenesis in mice exposed to predation without affecting brain thiamine diphosphate levels. Molecular and Cellular Neuroscience, 82, 126–136. https://doi.org/10.1016/j.mcn.2017.05.005

107.Tapias, V., Jainuddin, S., Ahuja, M., Stack, C., Elipenahli, C., Vignisse, J., Gerges, M., Starkova, N., Xu, H., Starkov, A. A., Bettendorff, L., Hushpulian, D. M., Smirnova, N. A., Gazaryan, I. G., Kaidery, N. A., Wakade, C., Calingasan, N. Y., Thomas, B., Gibson, G. E., Dumont, M., & Beal, M. F. (2018). Benfotiamine treatment activates the Nrf2/ARE pathway and is neuroprotective in a transgenic mouse model of tauopathy. Human Molecular Genetics, 27(16), 2874–2892. https://doi.org/10.1093/hmg/ddy201

108.Schmechel, D. E., Saunders, A. M., Strittmatter, W. J., Crain, B. J., Hulette, C. M., Joo, S. H., Pericak-Vance, M. A., Goldgaber, D., & Roses, A. D. (1993). Increased amyloid β-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. Proceedings of the National Academy of Sciences of the United States of America, 90(20), 9649–9653. https://doi.org/10.1073/pnas.90.20.9649

109.Deo, P., Dhillon, V. S., Chua, A., Thomas, P., & Fenech, M. (2020). APOE ε4 carriers have a greater propensity to glycation and sRAGE which is further influenced by RAGE G82S polymorphism. The Journals of Gerontology: Series A, 75(10), 1899–1905. https://doi.org/10.1093/gerona/glz259

110.Park, H., Ni, M., & Le, Y. (2025). Neuroinflammation and nutrition in Alzheimer's disease. Frontiers in Neurology, 16, 1622571. https://doi.org/10.3389/fneur.2025.1622571

111.Xue, B., Waseem, S. M. A., Zhu, Z., Alshahrani, M. A., Nazam, N., Anjum, F., Habib, A. H., Rafeeq, M. M., Nazam, F., & Sharma, M. (2022). Brain-derived neurotrophic factor: A connecting link between nutrition, lifestyle, and Alzheimer's disease. Frontiers in Neuroscience, 16, 925991. https://doi.org/10.3389/fnins.2022.925991

112.Yassine, H. N., & Finch, C. E. (2020). APOE alleles and diet in brain aging and Alzheimer's disease. Frontiers in Aging Neuroscience, 12, 150. https://doi.org/10.3389/fnagi.2020.00150

113.Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., Laatikainen, T., Lindström, J., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T. E., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2015). A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. The Lancet, 385(9984), 2255–2263. https://doi.org/10.1016/S0140-6736(15)60461-5

Нутригеномика арқылы Альцгеймер ауруына жаңа көзқарас: Дәлдік медицина парадигмасына жол. Нарративтік шолу

Stroia Carmina [1], Anca Dicu [2*], Lorena Filip [3], Maria Vrânceanu [4]

[1] PhD докторант, Биомедициналық ғылымдар докторантура мектебі, Медицина және фармация факультеті, Орадэа университеті, Орадэа, Румыния. E-mail: stroia.carminamariana@student.uoradea.ro

[2] Хабилитацияланған қауымдастырылған профессор, Тағам инженериясы, туризм және қоршаған ортаны қорғау факультеті, «Aurel Vlaicu» Арад университеті, Арад, Румыния. E-mail: anca.dicu@uav.ro

[3] Хабилитацияланған профессор, Броматология, гигиена, тағамтану кафедрасы, «Iuliu Hatieganu» медицина және фармация университеті, Клуж-Напока, Румыния. E-mail: lfilip@umfcluj.ro

[4] Қауымдастырылған профессор, Тағам инженериясы, туризм және қоршаған ортаны қорғау факультеті, «Aurel Vlaicu» Арад университеті, Арад, Румыния. E-mail: marievranceanu@gmail.com

Түйіндеме

Альцгеймер ауруы генетикалық, зат алмасу, қабыну және қоршаған орта факторларының өзара әрекеттесуінен қалыптасатын күрделі нейродегенеративті бұзылыс болып табылады. Ғылыми түсінік тереңдегеніне қарамастан, тиімді терапиялық жетістіктер шектеулі болып отыр. Себебі ауру патогенезі

көптеген бір-бірімен байланысты механизмдерге негізделеді: амилоид-бета жиналуы, тау-протеиннің гиперфосфорлануы, митохондриялық дисфункция, оксидативті стресс, қантамырлық бұзылыстар және созылмалы нейроқабыну. Ерте басталатын отбасылық Альцгеймер ауруы APP, PSEN1, PSEN2 гендеріндегі мутациялармен байланысты, ал жағдайлардың басым бөлігі өмір салты мен полигендік вариациялар әсерінен дамитын спорадикалық кеш басталатын форма болып табылады. Генетикалық факторлардың ішінде APOE ε4 аллелі ең маңызды қауіп белгісі болып саналады. Себебі аталмыш фактора липидтік алмасуды, қабынуды, оксидативті зақымдануды және амилоид-бета клиренсін өзгертеді. MTHFR C677T вариациясы гомоцистеин алмасуын, метилдену қабілетін және редокс-тепе-теңдігін өзгерту арқылы осалдықты күшейтеді.

Нутригеномика мен нутригенетика диеталық компоненттердің генетикалық архитектурамен өзара әрекеттесуін және Альцгеймер ауруымен байланысты молекулалық жолдарды қалай модуляциялайтынын түсінуге мүмкіндік береді. Когнитивтік қасиеттің құлдырауымен қатар жүретін қоректік тапшылықтар заталмасу бұзылыстарын күшейтіп, нейродегенерацияны жеделдетуі мүмкін. Ал мақсатты нутрицевтикалық араласулар когнитивтік және функционалдық көрсеткіштерді жақсарта алады. Омега-3 май қышқылдары, В витаминдері, кверцетин, резвератрол және бенфотиамин сияқты негізгі нутрицевтиктер оксидативті стресс, қабыну, митохондриялық функция және синапстық тұрақтылыққа қатысты жолдарды Nrf2 активациясы, NF-κB тежелуі және BDNF сигнализациясы арқылы модуляциялайды. «Ген–диета» өзара әрекеттесулері APOE ε4 немесе BDNF Val66Met генотипін тасымалдаушылардың нутритивтік стратегияларға әртүрлі жауап беруі мүмкін екенін көрсетеді. Геномдық, метаболикалық және нутритивтік деректерді біріктіру Альцгеймер ауруының алдын алу мен басқаруда салауатты тамақтану тәсілдерінің дамуына негіз болады. Генетикалық профильге бейімделген жеке араласулар оксидативті және қабынулық жүктемені азайтып, нейропротекторлық жолдарды күшейтуі және аурудың үдеуін баяулатуы мүмкін.

Түйін сөздер: Альцгеймер ауруы, нутрицевтиктер, APOE, BDNF, генетикалық қауіп, когнитивтік төмендеу, салауатты тамақтану, нутригеномика, нутригенетика.

Новый взгляд на болезнь Альцгеймера через нутригеномику: Путь к парадигме прецизионной медицины. Нарративный обзор

Stroia Carmina [1], Anca Dicu [2*], Lorena Filip [3], Maria Vrânceanu [4]

[1] PhD докторант, Школа биомедицинских наук, факультет медицины и фармации, Университет Орадя, Орадя, Румыния. E-mail: stroia.carminamariana@student.uoradea.ro

[2] Хабилитированный ассоциированный профессор, кафедра питания и диетологии, факультет пищевой инженерии, туризма и охраны окружающей среды, Университет Aurel Vlaicu, Арад, Румыния. E-mail: anca.dicu@uav.ro

[3] Хабилитированный профессор, кафедра броматологии, гигиены и питания, Медицинско-фармацевтический университет «Iuliu Hatieganu», Клуж-Напока, Румыния. E-mail: lfilip@umfcluj.ro

[4] Ассоциированный профессор, кафедра питания и диетологии, факультет пищевой инженерии, туризма и охраны окружающей среды, Университет Aurel Vlaicu, Арад, Румыния. E-mail: marievranceanu@gmail.com

Резюме

Болезнь Альцгеймера представляет собой сложное нейродегенеративное заболевание, формирующееся под влиянием генетических, метаболических, воспалительных и экологических факторов. Несмотря на значительный прогресс в изучении патогенеза, терапевтические достижения остаются ограниченными, поскольку заболевание возникает в результате взаимодействия многочисленных взаимосвязанных механизмов, включая накопление амилоид-β, гиперфосфорилирование тау-белка, митохондриальную дисфункцию, окислительный стресс, сосудистые нарушения и хроническое нейровоспаление. Ранняя семейная форма болезни Альцгеймера связана с мутациями в генах APP, PSEN1 и PSEN2, тогда как большинство случаев относится к спорадической поздней форме и определяется полигенными вариациями и факторами образа жизни. Среди генетических факторов наибольший риск связан с аллелем APOE ε4, влияющим на липидный обмен, воспалительные процессы, окислительное повреждение и клиренс амилоида. Варианты, такие как MTHFR C677T, дополнительно изменяют восприимчивость к заболеванию за счет влияния на метаболизм гомоцистеина, метилирование и антиоксидантный баланс. Нутригеномика и нутригенетика предлагают концептуальную основу для изучения взаимодействия между питательными компонентами и генетической архитектурой, определяющего модуляцию ключевых патогенетических путей болезни Альцгеймера. Дефициты питательных веществ, часто сопровождающие когнитивное снижение,

усугубляют метаболические нарушения и ускоряют нейродегенерацию, тогда как таргетированные нутрицевтические вмешательства могут улучшать когнитивные и функциональные показатели. Ключевые нутрицевтики, включая омега-3 жирные кислоты, витамины группы B, кверцетин, ресвератрол и бенфотиамин, проявляют нейропротекторные свойства за счет снижения окислительного стресса, подавления воспаления, улучшения митохондриальной функции и активации путей Nrf2, подавления NF-κB и модуляции сигнального пути BDNF. Взаимодействия «ген–диета» указывают на то, что носители генотипов, таких как APOE ε4 или BDNF Val66Met, могут по-разному реагировать на нутритивные стратегии. Интеграция геномных, метаболических и нутриционных данных поддерживает развитие персонализированных нутритивных подходов к профилактике и лечению болезни Альцгеймера. Индивидуализированные вмешательства, соответствующие генетическому профилю, способны уменьшать окислительную и воспалительную нагрузку, усиливать нейропротекторные механизмы и замедлять прогрессирование заболевания.

Ключевые слова: болезнь Альцгеймера, нутрицевтики, APOE, BDNF, генетический риск, когнитивное снижение, нутригеномика, нутригенетика.