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Review

Newer Therapeutic Approaches in Treating Alzheimer's Disease: A Comprehensive Review

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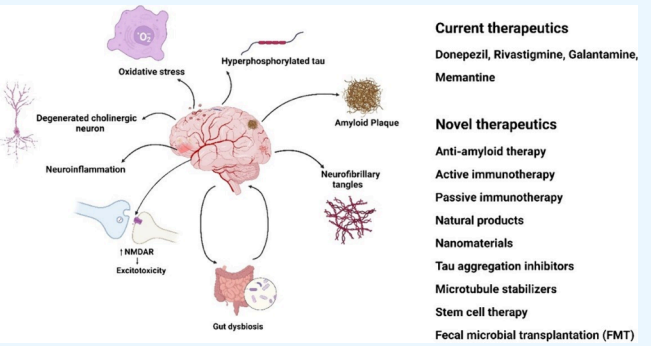
ABSTRACT: Alzheimer's disease (AD) is an aging-related irreversible neurodegenerative disease affecting mostly the elderly population. The main pathological features of AD are the extracellular Aβ plaques generated by APP cleavage through the amyloidogenic pathway, the intracellular neurofibrillary tangles (NFT) resulting from the hyperphosphorylated tau proteins, and cholinergic neurodegeneration. However, the actual causes of AD are unknown, but several studies suggest hereditary mutations in *PSEN1* and *-2*, *APOE4*, *APP*, and the *TAU* genes are the major perpetrators. In order to understand the etiology and pathogenesis of AD, various hypotheses are proposed. These include the following hypotheses: amyloid accumulation, tauopathy, inflammation, oxidative stress, mitochondrial dysfunction, glutamate/excitotoxicity, cholinergic deficiency, and gut dysbiosis. Currently approved therapeutic interventions are donepezil, galantamine, and rivastigmine, which are cholinesterase inhibitors (ChEIs), and memantine, which is an *N*-methyl-D-aspartate (NMDA) antagonist. These treatment strategies focus on only symptomatic management of AD by attenuating symptoms but not regeneration of neurons or clearance of Aβ plaques and hyperphosphorylated Tau. This review focuses on the pathophysiology, novel therapeutic targets, and disease-altering treatments such as α-secretase modulators, active immunotherapy, passive immunotherapy, natural antioxidant products, nanomaterials, antiamyloid therapy, tau aggregation inhibitors, transplantation of fecal microbiota or stem cells, and microtubule stabilizers that are in clinical trials or still under investigation.



1. INTRODUCTION

Alzheimer's disease (AD) ranks as the top disease with the most prevalent irreversible neurodegenerative conditions worldwide, primarily impacting individuals aged 65 and older, with its prevalence increasing exponentially over time, doubling approximately every 5 years.[1,2] In 1906, Alois Alzheimer introduced his initial hallmark case and outlined the disease's pathological characteristics during the 37th meeting of the Southwestern German Psychiatrists gathering. AD was named after him by his co-worker Emil Kraepelin in 1910. Electron microscopy analysis was then performed by Robert Terry and Michael Kidd, who showed the presence of neurofibrillary tangles (NFTs) in brain biopsies of two advanced AD patients. This discovery further led to subsequent research on the pathological features and mechanism of AD.[3−5] In this review, we elaborate on the pathophysiological mechanisms of the disease and discuss various hypotheses that have been put forward to explain etiology progression and pathological features of the disease. It is the primary contributor to adult-onset dementia, making up approximately 60% of all dementia cases worldwide.[6] Currently, it is negatively impacting nearly 50 million individuals, with the number of cases being projected to reach around 150 million by the year 2050.[2] AD is rapidly evolving into one of the most economically burdensome and life-threatening conditions in the 21st century since AD affects not only the daily activities of individual patients but also their family members and caretakers.[7] Patients in advanced stages of AD dementia face significant expenses to their families and societies with respect to their formal medical and nonmedical care (direct costs). Additionally, patients and caregivers encounter emotional distress and financial hardships due to reduced productivity of both groups.[8,9]

The likelihood of developing AD dementia rises as individuals move from normal cognition without amyloid-

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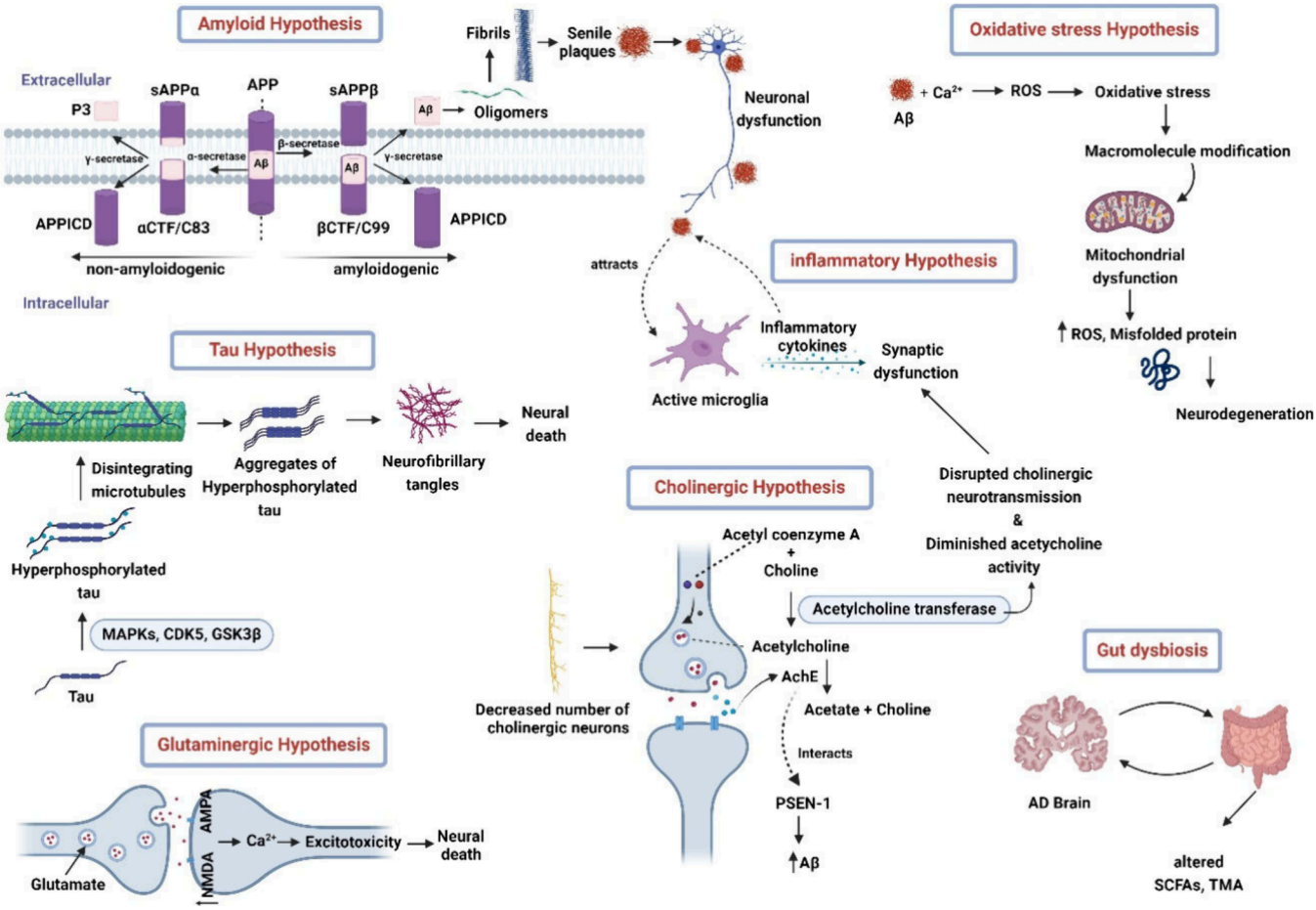

Figure 1. Diagram depicting the different pathophysiology hypotheses of Alzheimer's disease.

beta (Aβ) accumulation to early neurodegeneration and then to mild cognitive impairment (MCI).[10] MCI is an intermediate stage between normal cognitive function and the onset of AD.[11] MCI includes subtypes like amnestic MCI (aMCI), single-domain nonamnestic MCI, and multiple-domain MCI. Individuals diagnosed with aMCI and multiple-domain MCI are at increased risk of progressing to AD. The transition from MCI to AD is estimated to occur at a conservative rate of 5−10% per year.[11] MCI has incidence in same age group as AD.[12]

Dementia is the fifth most frequently occurring cause of death worldwide, while AD holds the position of being the fourth most significant cause of disability-adjusted life years (DALYs) lost among individuals aged 65 and older.[12,13] AD is identified by progressive declines in cognition, daily functioning, and behavioral patterns, usually initiated by memory loss, particularly related to recent events. Genetics has a notable impact on the risk of developing AD, accounting for around 70% of the overall hereditary transmission risks. However, the risk of developing AD can be further amplified by acquired factors such as cerebrovascular diseases, stroke, diabetes (insulin resistance), hypertension, obesity, dyslipidemia, poor nutritional intake, insufficient sleep, depression, mental stress, excessive alcohol drinking, traumatic brain injury, and exposure to heavy metals.[14,15] Diabetes, hypertension, obesity, and depression attribute to AD at 2%, 5%, 2%, and >10% respectively.[16] The majority of AD cases, known as sporadic AD (sAD), lack a clearly identified cause. However, approximately 1% of AD cases can be attributed to specific genetic mutations related to amyloid metabolism such as those in *APP, PSEN1*, and *PSEN2* genes. These mutations lead to the hereditary form of AD known as familial AD (fAD). Unlike sporadic AD, which typically manifests after the age of 65, fAD onset tends to be much earlier in life.[17]

At present, there are no existing treatments that can cure AD but only aim at managing its symptoms. This can be due to the pathological features of AD, which consist of extensive extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs, hyperphosphorylated microtubule-associated tau) that develop over several years (usually 10−20 years) before the onset of memory loss, resulting from significant neuronal and synaptic damage with elevated neuroinflammation. By the time of clinical diagnosis, the neuronal damage is extensive and virtually irreversible in most cases.[2,18−20] The Aβ plaques initially originate in particular brain regions such as the basal, temporal, and orbitofrontal neocortex. In the later stages, these plaques spread to other brain areas, such as the hippocampus, amygdala, diencephalon, and basal ganglia. In cases of pronounced severity, AD is detected in the mesencephalon, lower brain stem, and cerebellar cortex, leading to tau-tangle formation.[21]

2. PATHOPHYSIOLOGY

AD is defined by three major neuropathological hallmarks as follows:

- extracellular plaques of β-amyloid protein (amyloid plaques),

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- intracellular neurofibrillary tangles (NFTs),
- neurodegeneration.

All of these markers can be seen during normal aging, but they are manifested in specific regions of the AD brains and at much higher concentration depending on the AD stages. Numerous hypotheses have been proposed to elucidate this complex disorder. These are depicted in Figure 1 and listed in Table 1.

2.1. Aβ (Amyloid beta) Hypothesis. The Aβ hypothesis is associated with mutation in the amyloid beta precursor protein (APP) gene on chromosome 21. APP (695 amino acid residues) undergoes cleavage via two different pathways: the nonamyloidogenic pathway and amyloidogenic pathway. In the nonamyloidogenic pathway, APP is subjected to α-secretase hydrolysis, yielding a soluble ectodomain of APP (sAPPα) and a carboxy terminal fragment (αCTF/C83). This is followed by γ-secretase cleavage, leading to the formation of the APP intracellular cytoplasmic domain (APPICD/AICD) and a soluble peptide P3. In this scenario, α-secretase plays a protective role by cleaving the APP at a location that hinders the formation of Aβ. In the amyloidogenic pathway, a portion of APP is hydrolyzed by β-secretase (BACE1) to produce sAPPβ and βCTF/C99 followed by a cleavage in the presence of γ-secretase, resulting in the formation of insoluble Aβ fragments such as Aβ38, Aβ40, Aβ42, and APPICD/AICD, which is then transported to extracellular space via exocytosis. Aβ peptides spontaneously cluster into soluble oligomers, which then combine to create fibrils with insoluble beta-sheet structure and are eventually deposited in diffuse senile plaques.[22] Among the Aβ produced, Aβ42 has the tendency to aggregate and form plaques eventually.[22−24] Although Aβ40 is the most abundant Aβ species preceding Aβ42, Aβ42 is the predominant component/main Aβ species of amyloid plaques in AD brains, while Aβ40 is found only in a subset of plaques.[25] An increase in the level of Aβ42 or a higher Aβ42 to Aβ40 ratio promotes the formation of Aβ amyloid fibrils, which subsequently accumulate and evolve into senile plaques.[24] Under normal physiological conditions, the non-amyloidogenic pathway acts predominantly, and hence, Aβ production is limited. A small portion of Aβ produced is removed by the immune system. In case of hereditary mutations near the BACE1 cleavage site and PSEN1 and -2 (component of γ-secretase), APP is more prone to hydrolysis from the second system.[23]

2.2. Tau Hypothesis. Tau protein belongs to the family of microtubule-associated proteins and plays an important role in maintaining the stability of tubulin assemblies. Stabilization of microtubules is absolutely necessary as they are actively involved in connectivity and differentiation of neuronal cells.[26,27] The human *TAU* gene is present on chromosome.[17] In the case of AD and hereditary mutations in the coding region of the *TAU* gene,[24,28] tau proteins undergo hyperphosphorylation by many different protein kinases, including mitogen-activated protein kinases (MAPKs),[29−31] cell-cycle-dependent protein kinase 5 (CDK5), and glycogen synthetase kinase 3β (GSK3β),[32−35] leading to the destabilization of their connections to microtubules. This, in turn, leads to the collapse of microtubule structures and the impairment of the neuron's transport and communication systems.[5] The accumulation of modified tau proteins occurs inside cells as the hyperphosphorylated tau transforms into paired helical filaments, giving rise to NFTs, which ultimately lead to the

Table 1. Comparison of AD Hypotheses

hypothesis	mechanism	% contributing	ref
Aβ	amyloidogenic pathway hydrolysis of APP by BACE1 and γ-secretase to produce Aβ	99%	82
tau	aggregation of hyperphosphorylated tau protein to NFTs	43%	83
cholinergic	degeneration of cholinergic neurons; amplification of PSEN-1 by AChE expression, resulting in elevated Aβ levels	40−50%	84
inflammatory	inflammatory reactions of microglia and astrocytes	40−80%	85
glutamatergic/excitotoxicity	excitotoxicity caused by increased NMDAR activity	20−50%	86
oxidative stress-related mitochondrial dysfunction, impaired proteostasis, decreased autophagy/mitophagy with accumulation of aggregated proteins, and cell death−therapies−antioxidants	increased ROS and oxidative and nitrative stress by elevated Ca^{2+} surges and accumulated Aβ42 oligomers; oxidatively modified proteins result in mitochondrial dysfunction, leading to greater ROS production, accumulation of misfolded proteins, and decreased neural network, ultimately leading to neuroinflammation, cell death of neuronal cells and neurodegeneration in AD	30−40%	87
gut dysbiosis, endotoxemia, and neuronal cell damage via the gut−brain axis	altered gut microbiota, irregular bowel movements, intestinal barrier dysfunction, and inflammation; changed levels of the bacteria-produced metabolites, such as SCFAs, TMA, and endogenous ethanol, due to increased harmful bacteria and decreased beneficial bacteria, leading to intestinal hyperpermeability, releasing endotoxins to cause systemic inflammation, including the brain, through the bidirectional gut−brain axis	30%	88

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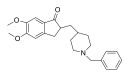
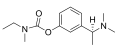
Table 2. Commonly Prescribed FDA-Approved Drugs That Treat AD Symptoms[89,92−96,97]

Drug name (generic/brand)	Chemical structure	AD symptom	Drug class	AD stage indication	Common side effects	References
Donepezil (Aricept)		Cognitive symptoms (memory and thinking)	Cholinesterase inhibitors	approved to treat AD all stages	Nausea, vomiting, loss of appetite, muscle cramps and increased frequency of bowel movements	92,93
Rivastigmine (Razadyne)				approved for mild-to-moderate dementia- AD and Parkinson's disease	Nausea, vomiting, loss of appetite and increased frequency of bowel movements	92,94
Galantamine (Exelon)				approved for mild-to-moderate AD stages	Nausea, vomiting, loss of appetite and increased frequency of bowel movements	92,95
Memantine (Namenda)			Glutamate regulators	approved for moderate-to-severe AD	Headache, constipation, confusion and dizziness	92
Donepezil and Memantine extended-release (Namzaric)			Combination therapeutics Cholinesterase inhibitor + Glutamate regulator	approved for moderate-to severe AD	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, headache, constipation, confusion and dizziness	89,92
Aducanumab		Cognitive symptoms, and Aβ levels	Monoclonal antibody	approval for early stage AD	amyloid related imaging abnormalities – edema (ARIA-E), ARIA-hemosiderin deposition (ARIA-H) microhemorrhage, Headache, confusion, delirium, altered mental status, disorientation, dizziness, vision abnormality, nausea	96
Lecanemab				Early stage of AD	Infusion reactions, headache, falls, ARIA in the brain	97

neurodegeneration and deterioration of cognitive function in AD.[36,23]

2.3. Cholinergic Hypothesis. A shortage of the neurotransmitter acetylcholine (ACh) in neurons is a prominent characteristic of AD. ACh is excitatory in nature, and it plays a significant role in learning, memory, and other advanced behaviors.[37] Degeneration of deep and early basal forebrain cholinergic neurons (BFCN) is observed in patients with AD. Acetylcholine transferase activity experiences a significant decline.[38] Acetylcholine esterase (AChE) is directly associated with PSEN-1. This interaction amplifies the expression of PSEN-1, resulting in elevated Aβ levels, which, in turn, triggers the initiation and accelerates the progression of cognitive dysfunction.[39] Abnormal cholinergic variations centrally can also lead to abnormal phosphorylation of tau protein, inflammation of nerve cells, and metabolism of APP, resulting in neurotoxicity, neuroinflammation, and death of neurons.[40]

2.4. Inflammatory Hypothesis. The inflammatory reactions of microglia and astrocytes within the central nervous system (CNS) contribute significantly to the progression of

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AD.[41] Aβ42 senile plaques supposedly attract microglia and infiltration of circulating monocytes/leukocytes into the CNS.[22] Ordinarily, stimulation of microglia results in the generation and secretion of pro-inflammatory cytokines such as IL-1β, TNF-α, and IFN-γ as well as chemokines. In response, these cytokines trigger neighboring astrocyte−neuron interactions, leading to increased production of Aβ42 oligomers, which, in turn, amplifies Aβ42 generation and its expansion throughout the CNS.[22]

2.5. Glutamatergic/Excitotoxicity Hypothesis. The neurotransmitter glutamate is involved in advanced brain functions like learning and memory through its receptors, particularly the *N*-methyl-D-aspartate (NMDA) type, and also by establishing connections with various regions of the brain, including the cholinergic neurons.[42] Glutamate neurotransmission is very essential for the synaptic plasticity and viability of neurons. However, overabundance of NMDAR activity can lead to excitotoxicity and contribute to cell death, consequently serving as a possible mechanism underlying the neurodegeneration observed in AD.[43] The disruption of NMDA receptors by Aβ and the resulting disturbances in calcium (Ca^{2+}) balance are believed to be connected to the initial cognitive impairments seen in AD.[43]

2.6. Oxidative Stress-Related Mitochondrial Dysfunction, Impaired Proteostasis, Decreased Autophagy/Mitophagy with Accumulation of Aggregated Proteins, and Cell Death−Therapies−Antioxidants. Elevated Ca^{2+} surges and accumulated Aβ42 oligomers in AD individuals are known to increase ROS and oxidative and nitrative stress.[44−46] Increased oxidative stress can cause covalent modifications of cellular macromolecules, nucleic acids, lipids, and proteins, leading to cell loss in many tissues.[47−53] For instance, various protein modifications, such as oxidation, carbonylation, nitration, phosphorylation, acetylation, succinylation, and adduct formation, usually result in their functional impairments, mitochondrial dysfunction, energy depletion, abnormal proteostasis, and impaired autophagy/mitophagy, ultimately leading to cell and organ damage in many tissues, as reviewed.[54−57] In fact, comparative redox proteomics analyses with autopsied brain specimens from AD individuals and control people revealed different or often elevated levels of oxidatively modified proteins.[55,58−65] These oxidatively modified proteins suggested their inactivation, resulting in mitochondrial dysfunction, impairments of proteasomal degradation pathways, as well as disturbed axonal growth and guidance, leading to greater ROS production, insufficient energy supply, accumulation of misfolded proteins, and decreased neural network, ultimately resulting in neuroinflammation,[66,67] cell death of neuronal cells, and neurodegeneration in AD.

Similarly, elevated accumulation of oxidative stress and subsequent oxidatively modified and misfolded proteins were also observed in murine models of AD,[68,69] suggesting conserved mechanisms between humans and experimental rodent models. The conserved mechanisms of AD disease pathology and outcomes allow prevention and treatment approaches by many naturally occurring compounds, including pomegranates, figs, and dates.[70−73] Other naturally occurring antioxidants and anti-inflammatory agents are summarized later (Table 4).

2.7. Gut Dysbiosis, Endotoxemia, and Neuronal Cell Damage via the Gut−Brain Axis. Numerous reports revealed that people with neurodegenerative diseases, such as AD, Parkinson's disease, ischemic stroke, and depression, suffer from the problems in the gastrointestinal tract (GIT), including altered gut microbiota, irregular bowel movements, intestinal barrier dysfunction, and inflammation before the actual appearance and/or diagnosis of the symptoms of various neurodegenerative diseases, including AD, as recently reviewed.[74−78] Metagenomic sequencing analyses revealed that increased abundance of harmful bacteria and decreased beneficial bacteria were frequently observed in several neurodegenerative diseases. These alterations of intestinal microbiota composition usually change the levels of the bacteria-produced metabolites, such as short-chain fatty acids (SCFAs), trimethylamine (TMA),[79] LPS, phenylacetylglutamine,[80] and endogenous ethanol, leading to local inflammation and intestinal hyperpermeability, releasing endotoxins to cause systemic inflammation and tissue damage, including the brain, through the bidirectional gut−brain axis.[76,77] In addition, some pathogenic bacteria, such as Streptococcus, Staphylococcus, Salmonella, and Klebsiella, are known to promote protein misfolding, subsequently contributing to accumulation of Aβ and tau aggregates in AD. Also, the endogenous lipopolysaccharide (LPS) released from Gram-negative bacteria due to leaky gut causes systemic and central inflammation, leading to Aβ-mediated microglial reactions, astroglia hyperactivation, TLR-MD2 complex activation, and tau hyperphosphorylation, leading to initiation and progression of AD.[81]

3. CURRENT PHARMACOTHERAPY

The current approach to AD medication treatment and management is centered on diminishing the advancement of symptoms and minimizing disability. It is anticipated that pharmacological treatments will moderately delay the expected worsening of the clinical conditions that remain significant burdens to the patients and caregivers.[89] Medications approved by the FDA for AD are listed in Table 2. They include the following:

- cholinesterase inhibitors (ChEIs)—donepezil (Aricept), rivastigmine (Razadyne), and galantamine (Exelon),[90]
- *N*-methyl-D-aspartate (NMDA) antagonist—memantine (Namenda),
- monoclonal antibodies—aducanumab and lecanemab.

These drugs have been reported to have the potential to slow down the progression of clinical symptoms and decrease cognitive and memory disabilities.[89,91,92]

The pharmacological basis for AD treatments, whether using cholinesterase inhibitors or memantine alone or ultimately combining them as an add-on dual-combination therapy, has consistently shown advantages in both the short and long terms. These treatments have been proven to slow down cognitive and functional decline, mitigate the disease onset and impact neuropsychiatric symptoms, and postpone the need for nursing home care, but all were ineffective in extending the time of life until death.[89]

ChEIs work by enhancing the central cholinergic activity. They inhibit the enzyme acetylcholinesterase (AChE), which is responsible for breaking down the critical neurotransmitter ACh in the synaptic cleft. As a result, ChEIs prevent the degradation of ACh, henceforth, leading to increased cholinergic neurotransmission.[89,91]

Donepezil and rivastigmine are FDA-approved drugs for the treatment of all AD stages, including mild, moderate, and

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severe dementia, while galantamine has received FDA approval specifically for mild and moderate AD.[92]

Memantine was the most recent FDA-approved therapy for moderate to severe AD, where approval was granted in 2003, and it continues to be the only medication in its category. It impacts glutamatergic transmission and operates as a blocker with low to moderate affinity to NMDA receptors, accordingly inhibiting the increased calcium influx and oxidative stress.[92] It is given as a stand-alone treatment or in conjunction with a ChEI, often as an addition to the existing ChEI therapy.[89]

In 2021, the FDA granted approval to aducanumab for early-stage AD despite inadequate clinical evidence demonstrating the drug's cognitive benefits. In June 2022, the Phase IV confirmatory trial required by the FDA was started. Results are expected by 2026.[98]

BAN2401 (lecanemab) under the brand name of Leqembi is a humanized IgG1 monoclonal Aβ-directed antibody.[99] It is the recent MAB to progress into Phase III clinical trials. BAN2401 exhibited safety and good tolerability during Phase I, and the initial findings from Phase II trial (NCT01767311) indicated a noteworthy deceleration of cognitive decline and a reduction in brain Aβ levels.[100,101] Phase III trial of BAN2401 began in March 2019, enrolling patients with prodromal to mild AD. The study is projected to conclude in July 2024.[102] On July 6, 2023, the FDA granted lecanemab a traditional, full approval for patients in the early stages of AD.[103]

4. SHORTCOMINGS OF THE CURRENT THERAPIES

The existing medications are associated with significant adverse effects, including issues like muscle complications during anesthesia, bradycardia (slow heartbeat), fainting, elevated gastric acid levels, and even seizures and thus are contra-indicated in those conditions.[89,104] Other common side effects include headache, nausea, vomiting, loss of appetite, confusion, and dizziness. In a meta-analysis, the efficacy and possible side effects of combination of memantine and donepezil (n = 269) was tested against donepezil and placebo (n = 251) treatment groups in moderate to severe AD patients. Over a period of 24 weeks, it was observed that the incidence of adverse events in combination of memantine and donepezil included dizziness (7.4%), agitation(6.3%), confusional state (5.6%), diarrhea (5.2%), nasopharyngitis (5.2%), and falls (4.1%). These adverse events have to be managed to decrease the treatment-associated disadvantages to the patients.[105] ChEIs particularly have certain drawbacks since they tend to be unstable in the bloodstream. They exhibit unpredictable absorption and availability in the body and could potentially cause gastrointestinal issues,[106] such as diarrhea, nausea, and vomiting. Rapid eye movement sleep behavior has also been noted in a few individuals. All of these symptoms can be reduced by taking the medication in the morning after a meal.[89] Medications currently available are able to simply help temporarily reduce symptoms but cannot reverse degeneration of lost neurons.[104] Hence, there is a requirement to explore options that offer more advantages than disadvantages in the course of treatment. Moreover, the present pharmacotherapy aims only at AD management, but other novel therapies such as stem-cell therapies are required for improvement in the lifestyle of the patients and to decrease their daily burdens and dependency on other caregivers.

5. NOVEL THERAPEUTICS

Comprehending the etiology and pathogenesis of AD has unveiled novel pathways and potential targets for biomolecular modulation, thus paving the way for the development of innovative therapeutic strategies to treat the detrimental conditions with potential reversal. In light of the limited effectiveness of existing treatments in altering the trajectory of AD, extensive endeavors have been undertaken to identify novel compounds and approaches with the capacity to influence the disease's progression, known as disease-modifying therapies. As of the year 2020, there were a cumulative 226 trials that had been completed or were currently underway.[102]

5.1. Antiamyloid Therapy. Antiamyloid therapy targets the accumulation of amyloid proteins in the brain, which is a characteristic feature of AD. Amyloid proteins, specifically Aβ, can aggregate and then accumulate, potentially leading to the formation of plaques in the brain. Subsequently, they are believed to contribute to the cognitive decline and other neurological symptoms in AD.[5] The strategy of this therapy is to bring down enlargement of amyloid plaques or promote the removal of pre-existing brain plaques.[107] There are currently three primary methods being utilized to address AD by targeting Aβ for both treatment and prevention. These approaches include inhibiting the production of Aβ, preventing its assembly (or encouraging its breakdown), and enhancing its removal.[108]

As individuals age, there is a reported decline in the appearance of LRP (low-density lipoprotein receptor-related protein), which plays a crucial role in removing Aβ oligomers from the brain. The decreased LRP leads to the prolonged presence of Aβ plaques in the brain. Antibodies targeting LRP have been shown to reduce the efflux of Aβ oligomers from the brain. Therefore, targeting LRP could be a possible therapy strategy for AD.[109]

Furthermore, it has been previously observed that Aβ oligomers have a high affinity for the receptor for RAGE (receptor for advanced glycation end products), which is a multifunctional receptor located at the blood−brain barrier (BBB). This interaction facilitates the ingress of Aβ oligomers within the CNS, thus contributing to increased Aβ accumulation within the brain, inflammation, and neuronal cell death.[110] There are several other approaches to antiamyloid therapy, as described below.

5.1.1. Probes and Theragnostic Molecules. Theragnostic agents are the molecules that provide both diagnostic information and therapeutic activity simultaneously.[111] Aβ is a suitable target for a theragnostic approach as it is both a therapeutic target as well as a pathological hallmark of AD.[112] In vivo imaging of Aβ is a suitable option for diagnosing early stages of AD as Aβ deposition several years prior to the onset of clinical symptoms. This approach addresses the failure of Alzheimer drugs, which are usually administered at a late stage, where the disease pathology is too advanced.[113]

Probes for diagnosis of AD are derived from amyloid dye structures like thioflavin T or Congo red; both have the ability to bind Aβ. Along with their ability to bind and mark Aβ, a few of them such as Congo red and its analogue chrysamine G have additional therapeutic potentials to inhibit Aβ aggregation.[113] Thioflavin T exhibits fluorescence emission in the visible range with a noticeable increase in the fluorescent intensity upon amyloid binding.[114] However, Thioflavin T is

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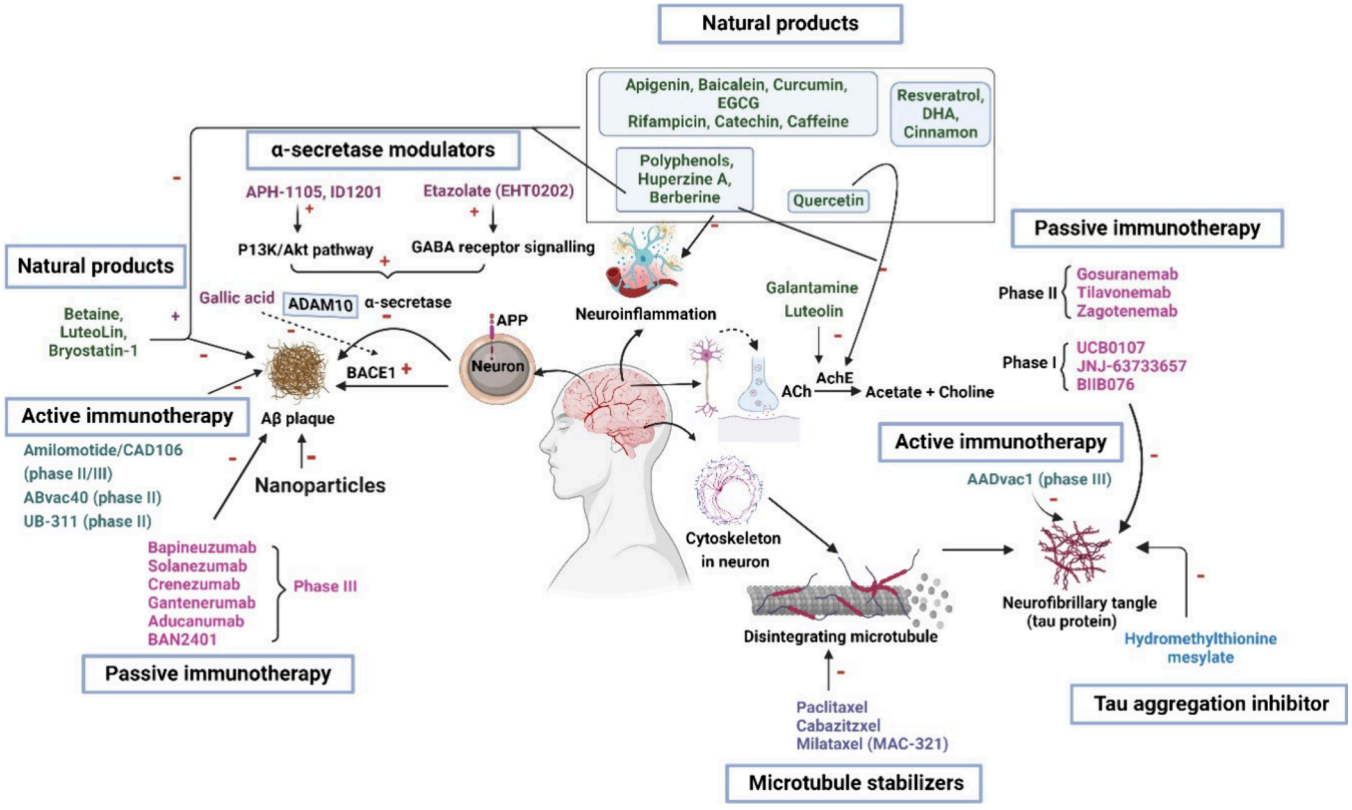

Figure 2. Schematic representation of novel therapeutic approaches to Alzheimer's disease.

positively charged, which makes have it poor permeability across the BBB.[115] Several thioflavin T compounds with increased lipophilicity were developed and tested for their binding to Aβ and NFT. One of such derivatives is ^{11}C-BTA-1. The administration of ^{11}C-BTA-1, a radioactive derivative lacking the methyl residue in position 6 of benzothiazole, resulted in high brain uptake, and imaging of amyloid deposits was verified by multiphoton microscopy for its nonlabeled analogue BTA-1.[113]

Chrysamine G, X-34, and BSB are Congo red derivatives that bind to Aβ. Methoxy-X04, another Congo red derivative, is a fluorescent probe that binds and marks Aβ while exhibiting a relatively high lipophilic character and ability to cross membranes. NIAD-4, the initial probe for amyloid staining, was the first to exhibit fluorescence in the near-infrared range. These diagnostic agents represent a significant advancement in optical imaging and pave the way for future developments in this field, utilizing both thioflavin and Congo red. These compounds exhibited a high degree of specificity and affinity for binding Aβ, effectively labeling the aggregates with exceptional spatial resolution. NIAD-4 has the capability to traverse the BBB and binds correctly to amyloid aggregates, displaying an efficient brain uptake. NIAD-11 and NIAD-16 present better spectral properties with an emission maximum over 690 nm than NIAD-4.[113]

Methylene blue, a phenothiazine typically employed in the treatment of hemoglobin-related issues and as a staining agent for cells and tissues during endoscopic procedures,[116,117] has exhibited antiamyloid properties. More specifically, it has been proven to hinder the oligomerization of amyloidogenic proteins through distinct mechanisms. For example, concerning the prion protein (PrP), methylene blue prevents oligomer formation by influencing fibril development.[118,119] It has shown improvements in cognitive function, reductions in the buildup of Aβ plaques, enhancements in memory and cognitive function among animal subjects, and possession of antioxidant properties capable of alleviating oxidative stress and inflammation in the brain.[120]

5.1.2. Anthracyclines and Tetracyclines. Because of their anti-inflammatory properties through microglial/macrophages inhibition, tetracyclines are considered as potential candidates for treating neurodegenerative diseases.[121] Doxycycline and minocycline are being investigated because of their safety profile and BBB crossing ability. Preclinical studies showed tetracyclines to have antiamyloidogenic property.[122] In recent studies carried out on minocycline and doxycycline, it was found that minocycline reduced the hyperphosphorylation of tau protein and Aβ synthesis in the hippocampal region, whereas minocycline therapeutic intervention improved cognition and learning in APP/PS1 mice by inhibiting the stimulation of the Cdk5/p25 signaling pathway.[123] Doxycycline was shown to improve spatial memory in APP/PS1 mice.[124] Since these drugs have already been approved by the FDA, clinical trial studies in evaluating their efficacies in treating AD individuals are expected.

5.1.3. α-Secretase Modulator. α-Secretase is the enzyme involved in hydrolysis of APP by the nonamyloidogenic pathway; thus, it prevents the formation and accumulation of Aβ plaques, which is a primary cause for AD. Thus, enhancement or modulation of α-secretase activity can be a potential therapeutic target to treat AD.[125]

It is presumed that α-secretase stimulation is promoted through the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and through the GABA receptor signaling mechanism.[126] Thus, modulators or stimulators of the PI3K/Akt pathway or

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GABA receptor can be considered as potential therapeutics to treat AD.[126,127]

Etazolate (EHT0202) is classified as an α-secretase modulator with selective effects on GABA-A receptors (Figure 2). It activates the nonamyloidogenic pathway by increasing α-secretase activity, sAPP alpha secretion, and PDE-4 inhibition. A Phase IIa clinical trial, involving 159 randomized AD patients with mild to moderate symptoms, indicated that etazolate is safe and well tolerated.[128] However, the advancement of etazolate for further evaluation in Phase III trials has been halted. Currently, it is undergoing assessment in animal studies to explore its potential in addressing post-traumatic stress disorder.[129]

APH-1105 and 1D1201 that act as α-secretase modulators through PI3/Akt pathway (Figure 2) were studied in a Phase II clinical trial as described by Cummings et al.[130] APH-1105 was assessed in individuals with mild to moderate AD and was administered intranasally. It is noteworthy to mention that 1D1201, which was evaluated in mild AD, is derived from the fruit extract of *Melia toosendan*.[126]

In an in vivo study using AD transgenic mice carried out by Mori et al.,[131−133] gallic acid, which showed dual activity of elevating the nonamyloidogenic pathway and decreasing the amyloidogenic pathway (Figure 2), was adopted as a test item. The reason behind this action may be linked to its capability to enhance α-secretase ADAM10 activity (α-disintegrin and metalloproteinase domain-containing protein 10) (Figure 2) and to inhibit β-secretase BACE-1 (β-site APP cleaving enzyme 1).

5.1.4. β-Secretase Inhibitors. The initial stage in the formation of Aβ includes the cleavage of APP by the BACE1 enzyme. Inhibiting BACE1 represents an early intervention in the amyloid cascade, irrespective of the specific form or aggregation state of Aβ responsible for its harmful effects.

Research conducted on mice lacking BACE1 and BACE2 has shown that these enzymes have a broad impact on various natural substrates and functions, both within and outside of the nervous system.[116,117] Extended administration of BACE1 inhibitors has been observed to have adverse effects on various aspects of neural function in wild-type mice, including spine formation and density, hippocampal long-term potentiation (LTP), as well as cognitive abilities.[134] However, several BACE inhibitors that were under development did not progress to Phase III clinical trials due to their toxicity in humans.[135] Verubecestat and lanabecestat, that have been thoroughly studied BACE-1 inhibitors in animal models, have demonstrated their effectiveness in reducing soluble Aβ levels in CSF in mild to moderate AD patients.[136] Despite the reduction in Aβ levels in CSF, these inhibitors do not lead to improvements in cognitive function or brain functionality, suggesting that Aβ accumulation may not be as important as Tau protein aggregates in AD pathologies. Besides, there have been reports of cognitive decline worsening with their use.[136,137]

5.1.5. Aβ Aggregation Inhibitors. Metal protein attenuating compounds (MPACs) have garnered considerable interest as promising agents to combat Aβ aggregates.[138] Their effectiveness lies in their ability to strongly bind excessive copper and zinc ions, effectively preventing these ions from interacting with the Aβ peptides. This binding mechanism actively hampers the formation of Aβ oligomers. Clioquinol, alternatively referred to as PBT1, belongs to the hydroxyquinoline ionophore class of compounds. It has exhibited remarkable efficacy in inhibiting the buildup of Aβ deposits in mouse AD models.[139] Moreover, it has demonstrated the capacity to mitigate the harmful effects of Aβ in neuronal cell culture models. Clinical investigations have provided evidence that the use of clioquinol resulted in a substantial decrease in the levels of Aβ42 in the bloodstream. This reduction was particularly beneficial for patients with MCI (as indicated by an Alzheimer's Disease Assessment Scale-Cognitive Score or ADAS-cog Score greater than 25) when compared to the administration of a placebo drug.[140] However, it is worth noting that the long-term use of clioquinol raised safety concerns, including the development of neuropathy in some patients.[141] To address these safety issues, a second-generation version of clioquinol known as PBT2 was developed. PBT2 exhibits improved penetration into the brain and better pharmacokinetics. Importantly, it has been shown to maintain synaptic health in transgenic mice with APP abnormalities.[142]

5.1.6. γ-Secretase Modulators. According to this approach, the amyloidogenic pathway involves the consecutive clefts of the APP by two enzymes: β-secretase (BACE1) and γ-secretase. Inhibiting these enzymes has been considered a possible therapeutic approach to bring down Aβ formation and mitigate AD symptoms. However, there are some challenges and concerns, particularly regarding γ-secretase inhibitors.[143] A notable one is the lack of specificity, suggesting that they not only handle APP cleavage but also cleave a wide range of transmembrane proteins such as the Notch receptor, which is a crucial signaling pathway for regular cell differentiation and communication in various tissues and organs. Inhibiting these signals can lead to adverse effects at various cellular processes.[144]

Several clinical trials with γ-secretase inhibitors, such as semagacestat,[145] avagacestat, and tarenflurbil, have shown limited efficacy and significant safety concerns. Semagacestat was terminated in Phase III as it was associated with cognitive worsening, increased rates of infections, risk of skin cancer, immunosuppression, and GI bleeding due to NOTCH inhibition.[146] Avagacestat was linked to cognitive decline and skin cancer as dose-limiting effects and thus was terminated in Phase II. Avagacestat like semagacestat has lack of selectivity and caused adverse effects by interfering NOTCH signaling.[147] Tarenflurbil, a γ-secretase modulator which has no NOTCH inhibition activity, was developed.[148] However, it has limited brain penetration, leading to failed clinical outcomes in Phase III trials in spite of attenuating cognitive decline in mild AD patients in Phase II studies.[146] All of these adverse effects were observed in clinical trials and raised serious safety concerns about the use of γ-secretase inhibitors as a therapeutic approach for AD.

These modulators have faced many setbacks due to their lack of specificity, adverse side effects, and limited effectiveness in clinical trials. These challenges have raised questions about their appropriateness as potential therapies for AD. Consequently, it is essential to continue investigating γ-secretase and explore alternative approaches to develop safe and efficacious treatments for AD.

5.1.7. Serum miRNAs and Proteins for Accurate Diagnosis and Therapies of AD Pathology. As mentioned in the earlier sections, production and accumulation of Aβ and tau proteins are regulated by different cleavage enzymes and various PTMs catalyzed by protein kinases, phosphatases, ubiquitin-conjugating enzymes, etc. In addition to these protein modifications, it is also known that expression of these genes was regulated by genetic and epigenetic mechanisms. Recent reports showed

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that many different miRNAs of small, single-stranded noncoding RNA species, such as miR921-39, miR-320a, and miR132-3p, can bind the target mRNA to regulate the expression of the target protein (in this case Tau), while other miRNAs can regulate tau-modulating enzymes GSK-3β and CDK5.[33,149] Ryo Kimura et al. performed an experiment to understand the correlation between beta-amyloid production and tau phosphorylation in AD. They observed that in neuroblastoma cells, Aβ increased DYRK1A transcription, leading to tau phosphorylation. So, the upregulation of DYRK1A could be a due to Aβ loading. Similar observations were made in the hippocampal region of AD patients where DYRK1A mRNA levels were significantly higher ($P < 0.01$) in AD patients compared to healthy controls.[150] Further, a panel of 7 miRNAs miR-let-7d-5p, miR-let-7g-5p, miR-15b-5p, miR-142-3p, miR-191-5p, miR-301a-3p, and miR-545-3p was detected in plasma samples of AD patients and used as diagnostic markers for AD.[151] In addition, many other miRNAs are known to regulate the accumulation of Aβ and its structural derivatives by modulating the expression of the genes/proteins involved in different steps of amyloidogenic APP transcripts, BACE1 transcripts, and their regulating enzymes, as recently reviewed.[33] It is also known that many dietary supplement agents listed in Table 4 can alter the activities of many enzymes such as GSK-3β and CDK5 involved in Aβ and tau modifications but also affect the levels of miRNA transcripts for these genes.[152] Additionally, because of the changes in the levels of various miRNAs associated with AD development, some of them can be used as a potential diagnosis tool as well as therapeutics for AD. Since many different miRNAs can be contained in circulating extracellular vesicles (EVs) or exosomes, use of EVs and exosomes for diagnostic and therapeutic (theragnostic) purposes for AD patients or animal models need to be further characterized. Consequently, clinical validation for efficacy studies in these miRNA areas alone or contained in circulating EVs needs additional studies in the future.

5.2. Active Immunotherapy (Vaccination). Active immunotherapy activates the immunity of the patient to generate antibodies against Aβ/tau protein by injecting Aβ or tau or any of its fragments.[102] The reasoning for utilizing immunization to target pathological tau or Aβ variants is to disrupt the uptake and spread of abnormal tau or Aβ. Employing high-affinity antibodies against phosphorylated tau or abnormal Aβ is an approach intended to avoid interfering with the normal function of tau or Aβ while actively immunizing against its phosphorylated or abnormal form.[104] This area of research is nicely reviewed and summarized by Song et al.[98]

5.2.1. Anti-Aβ Vaccine. AN-1792, Table 3, the first anti-Aβ vaccine (Figure 2), is comprised of a synthetic preaggregated Aβ42 along with an immunogenic adjuvant (QS-21).[98] A Phase II clinical trial with mild to moderate AD patients was halted in 2002 because 6% of the participants experienced aseptic meningoencephalitis. This adverse reaction is assumed to result from cytotoxic T-cell response (presence of T-cell activation domain epitope in it). Hence, further active immunotherapy agents are being formulated using Aβ peptides that lack epitopes known to trigger T-cell activation.[153]

Amilomotide, also referred to as CAD106 (Figure 2), is a virus-like particle-based vaccine. The intent with this vaccination is to elicit a strong antibody response while circumventing inflammatory T-cell activation. Despite the reasonable balance between antibody response and tolerability, the clinical trial was halted due to unpredicted changes in cognitive function, brain volume, and body weight to patients.[98]

Table 3. Status of Vaccines and Immunotherapies

SI no.	vaccine/immunotherapy	status	ref
1	AN-1792	halted in 2002	98
2	amilomotide	approved for clinical trials	174
3	ABvac40	completed Phase II in March 2023	175
4	UB-311	May 2022, the US FDA granted UB-311 fast-track designation to expedite development and review; to date, the clinical trial has not been registered or initiated	176
5	AADvac1	Phase II	177
6	bapineuzumab	aborted	178
7	donanemab	approved by the FDA on July 2, 2024	
8	ponezumab	ceased in Phase II	179
9	gosuranemab, tilavonemab, and zagotenemab	discontinued	
10	bepranemab	under enrolment and expected to be completed in November 2025	180
11	semorinemab	failed in Phase II	

ABvac40, an immunotherapy focused on the C-terminal segment of the Aβ40 peptide, represents one of the initial therapeutic interventions aimed at Aβ40 (Figure 2). The outcomes from the Phase I trial involving individuals with mild to moderate AD indicated that the vaccine was both safe and well tolerated, and it also prompted a favorable antibody response. As a result, a Phase II trial was then performed.[102,154] The trial was completed in March 2023 by the biotech company. In November 2023, clinical trials on an AD (CTAD) conference presentation suggested that the vaccine has met its primary safety and efficacy end points. No other details were available as of the end of December 2023.

UB-311 is another immunotherapy that underwent clinical investigation. UB-311 vaccine consists of two synthetic Aβ1−14 sequences conjugated to Th cells. Phase I and II findings showed a favorable safety profile and positive immunogenicity.[102,155] The clinical trial findings concluded that "*A 97% antibody response rate was observed and maintained at 93% by the end of the study across both UB-311 arms*".[155] However, in December 2019, the extension of this trial was terminated based on "a treatment assignment error". No further information is available. In May 2022, the US FDA granted UB-311 fast-track designation to expedite development and review. To date, the clinical trial has not been registered or initiated.[98]

5.2.2. Antitau Vaccine. AADvac1 is constructed to elicit an immune response against the modified forms of tau protein. It consists of a synthetic peptide derived from amino acids 294−305 coupled to KHL with aluminum hydroxide as an adjuvant. This pioneering antitau vaccine (Figure 2) underwent successful clinical testing as the first-in-man of its kind vaccine. Following promising safety results from two Phase I trials, a Phase II trial was conducted focusing on individuals with mild AD.[156,157] In September 2019, the Phase II study revealed that AADvac1 exhibited favorable immunogenicity with 98.2% of the patients producing specific antitau antibodies while maintaining a strong safety and tolerability profile.[157] Furthermore, AADvac1 resulted in statistically noteworthy changes in blood and cerebrospinal fluid biomarkers,

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Table 4. Potential Neuroprotective Nutraceuticals for Dementia Treatment[73,91,181,183,185−210]

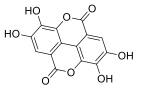
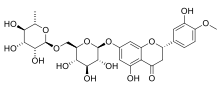
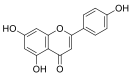
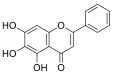
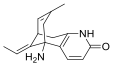
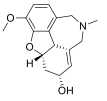
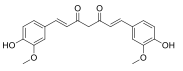
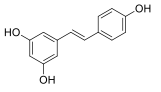
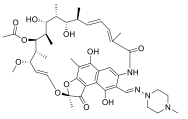
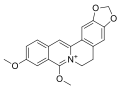
Active constituent	Source	Structure	Property	References
Ellagic acid, Urolitic acid Polyphenols	*Punica granatum* Linn (Pomegranate), chestnut, blackberries, raspberries, strawberries		• Reduces oxidative stress • Anti-inflammatory • Inhibition of AChE • Diminish the concentrations of Aβ 1-40 and Aβ 1-42 in the blood stream • Enhance behaviours associated with anxiety and spatial learning capabilities	73,185
Naringenin (Hesperidin)	Orange, tangerine, lime, lemon, grapefruit		• Antioxidant • Anti-inflammatory • Anti-Aβ aggregation	186,187
Apigenin	Tea, parsley, celery		• Antioxidant • Anti-inflammatory • Anti-Aβ aggregation	188,189
Baicalein	*Scutellaria* genus		• Decrease oxidative stress & inflammation • Anti-amyloid	190
Huperzine A	*Huperzia* species		• Antioxidant, anti-inflammatory • Diminish Aβ plaque accumulation, • AChE activity inhibition	181,191
Galantamine	*Galanthus woronowii*		• Inhibition of AChE activity • Antioxidant	192,193
Curcumin	*Curcuma longa* (Turmeric)		• Reduce Aβ oligomers, and fibril formation • Anti-inflammatory • Prevent oxidative stress	194−196
Resveratrol	Red grapes, mulberries, peanuts		• Antioxidant • Anti-inflammatory	197
Rifampicin	Semisynthetic antibiotic		• Anti-inflammatory • Anti–Tau • Anti-amyloid activity	198
Berberine	Berberis		• Anti-inflammatory, Antioxidant • Improves memory function • Inhibits AchE activity • Anti-amyloid activity	199

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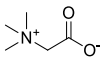
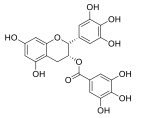
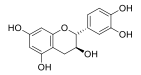
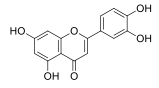
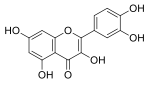
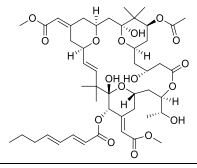
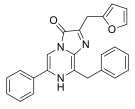
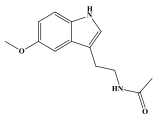
Table 4. continued

Active constituent	Source	Structure	Property	References
Betaine	Beet, spinach, whole grains		• Reduces Aβ production by downregulating BACE1 and upregulating α-secretase regulation	200
Epigallocatechin-3-gallate (EGCG)	Green tea		• Antioxidant • Anti-inflammatory	201
Catechin	Tea		• Antioxidant • Anti-inflammatory • Inhibition of Aβ accumulation	202,203
Caffeine	Coffee		• Antioxidant • Anti-apoptotic • Anti-inflammatory • Anti-amyloidogenic	204
Docosahexaenoic acid (DHA)	Marine foods		• Anti-inflammatory • Protects against age-related cognitive decline in the elderly	205
Cinnamon	Cinnamomum	Cinnamic acid  Cinnamaldehyde  Eugenol  Cinnamyl acetate 	• Antioxidant • Anti-inflammatory • Reduces AD symptoms	206
Luteolin	Broccoli, peppers, thyme, celery		• Prevents Aβ accumulation • AChE inhibitor • Antioxidant	207
Quercetin (rutin)	Apple, onion		• Reduces extracellular Aβ, tauopathy. • Antioxidant • Inhibits AChE • Anti-inflammatory	187,205,208
Bryostatin-1	*Bugula neritina*		• Improves learning and memory • Anti-amyloid	91
Lunasin	*Glycine max* (Soyabean)		• Antioxidant • Anti-inflammatory • Block neurodegeneration	183
Melatonin	Pineal Gland, intestine		• Decreases Aβ accumulation • Prevents memory deficit in metabolic AD and toxin-induced AD model	209,210

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suggesting its potential to decelerate the progression of tau-related issues. These encouraging outcomes should pave the way for the transition to Phase III.[158] Additionally, later a post hoc analysis of Phase II clinical trial subgroups indicated "*higher antibody titers correlated with clinical response and slowing of brain atrophy*".[159] As a result, the biotech company announced that it is planning a larger Phase 2b study of this vaccine.

5.3. Passive Immunotherapy. Passive immunotherapy involves administering monoclonal antibodies (MABs) that target abnormal versions of the Aβ or tau protein through injection.[102] MABs are designed to target and bind β-amyloid proteins or abnormal tau proteins, which can help to clear them from the brain. In contrast to active vaccination, passive immunization might represent a more favorable approach for the treatment of AD.[104]

5.3.1. MAB Injection Directed against Aβ. Seven antibodies have advanced to Phase III clinical trials including bapineuzumab, solanezumab, crenezumab, gantenerumab, and donanemab (LY3002813) (Figure 2). Three Phase III clinical trials with bapineuzumab have been aborted since studies did not show clinical benefit. Up to this point, the trials of the other MABs have yielded unsatisfactory clinical efficacy, despite demonstrating partial effectiveness in lowering cerebrospinal fluid (CSF) biomarker levels and reducing Aβ plaques.[160−162]

Donanemab (LY3002813) was approved by the FDA in July 2024.[163] Furthermore, additional clinical trials have examined the effectiveness of different anti-Aβ antibodies, namely, GSK933776 and ponezumab. GSK933776 is no longer in the pipeline for further development for AD. During a Phase II trial, the development of ponezumab was ceased as the results did not indicate clinical benefits or modifications in CSF biomarkers as the primary end point, although it was found to be safe and well tolerated.[102,164] Subsequently, further development of ponezumab has been discontinued.

Bapineuzumab and gantenerumab are associated with high incidence of ARIA-E, whereas solanezumab and crenezumab have low incidence of ARIA-E.[165] ARIA can arise from two main causes: the pathological buildup of amyloid in the walls of cerebral blood vessels, also known as cerebral amyloid angiopathy (CAA), or the administration of monoclonal antibodies designed to remove Aβ plaque. This accumulation of amyloid and impaired clearance often trigger an immune response within the vessel walls, leading to inflammation. Consequently, this inflammation transiently weakens the vessels, causing leakage of proteinaceous fluid or blood, resulting in either ARIA-E or ARIA-H, respectively. There is some evidence to suggest that with repeated immunization, the risk of extravasation decreases, thereby lowering the risk of ARIA.[166]

5.3.2. MAB Injection Directed against Tau Protein. This method has gained much attention for its perceived safety compared to tau vaccines, leading to extensive exploration. Antitau antibodies, namely, gosuranemab, tilavonemab, and zagotenemab (Figure 2), are discontinued,[167−169] while a clinical trial of bepranemab (UCB0107) is under enrollment and expected to be completed in November 2025. Previously, semorinemab (RO705705) has failed in Phase II clinical trials.[98] Several tau antibodies are currently in early drug development: these include BIIB076, JNJ-63733657, E2814, Lu AF87908, PNT001, and RG7345[102,170] (Figure 2).

Gosuranemab, also known as BIIB092, exhibited a favorable safety and tolerability record in two Phase I trials. It underwent evaluation in a Phase II trial involving individuals with prodromal to mild AD symptoms. This study was anticipated to continue until the year 2024.[171] However, both Phase II clinical trials have been terminated in June 2021.[98]

Tilavonemab, also termed ABBV-8E12, entered a Phase II trial. This trial aims to evaluate the effectiveness and safety of tilavonemab in individuals with prodromal to mild AD.[172] However, in 2021 it did not demonstrate benefit over the placebo, and consequently, the company stopped its development and delisted it from its pipeline. Zagotenemab (LY3303560) has progressed to a Phase II trial as well for prodromal to mild AD subjects.[102] Again, the clinical trial missed its primary benefit end point, and the company ended its development.[98] In addition, a MAB to acetylated tau (Ac-Lys280-Tau) has been developed, and this MAB Y01 prevented progression of tauopathy with elevated neuronal viability in cultured neuronal cells and Tau-transgenic mice.[173] Consequently, experimental and preclinical studies evaluating the efficacies of many other MABs against a structurally altered tau are expected, which is known to be modified by many different PTMs.[32]

5.4. Natural Products. Nutraceuticals are substances extracted from natural herbs, and they often exhibit lower levels of toxicity and fewer side effects compared to synthetic medications. Additionally, they tend to be more cost effective. In recent times, natural products have gained significant popularity as supplements or alternative medicines, primarily because of their effectiveness and the reduced occurrence of side effects.[181,182] Certain pharmacologically bioactive-derived herbal compounds and phytochemicals like lunasin, polyphenols, flavonoids, alkaloids, and tannins possess medicinal properties that hold promise for treating neurological conditions, including AD, Table 4. Their properties include acting as anticholinesterase agents, reducing inflammation, providing antioxidant effects, and offering neuroprotective capabilities.[183] Several natural compounds, including vitamin C and E, ellagic acid, luteolin, melatonin, naringenin (hesperidin), curcumin, quercetin (rutin), resveratrol, huperzine A (Figure 2), rosmarinic acid, and EGCG have been administered to individuals with AD, yielding positive and beneficial results.[91,184] These naturally occurring agents, usually contained in the Mediterranean diet,[152] exhibit anti-inflammatory effects by general antioxidant activities directly working on decreasing many risk factors, including oxidized DNAs, lipid peroxides, and proteins, in AD and other neurodegenerative diseases. Although we list several well-established antioxidants in Table 4, it is possible that many other naturally occurring compounds can also exhibit similar antioxidant and anti-inflammatory activities, leading to attenuation or improvement of the severity of AD conditions in experimental models and affected individuals.

Elevated oxidative stress and inflammation represent two major risk factors and pivotal features of AD and other neurodegenerative diseases. From the above-mentioned natural products, it can be concluded that the majority of them are bioactive and possess both antioxidant and anti-inflammatory properties, which can be associated with the inflammatory hypothesis in AD development. Certain phytochemicals, including polyphenols, huperzine A, berberine, quercetin (rutin), galantamine, and luteolin, have demonstrated AchE inhibitory activity with the potential to serve as a novel

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Table 5. Nanomedicines Employed in Neurodegenerative Disorders[a]

nanoparticle form	potential drug candidate	target	ref
liposomal	curcumin derivative	Aβ	227
		cholinergic dysfunction	
gold (Au) NPs	anthocyanin	amyloid cascade	228
		Tau hyperphosphorylation	
mesoporous silica NPs (MSN)	rivastigmine hydrogen tartarate	cholinergic system	229
polymeric NPs	iminodiacetic acid	amyloid cascades	230
	cerium(III) acetate	oxidative stress	231
carbon dots	tunable zero dimension	amyloid cascades	232
		AchE enzyme	
dendrimers	*O*-phenylenediamine	amyloid cascades	233
metallic NPs	iron oxide	amyloid cascade	234
extracellular vesicles	stem-cell derived	amyloid cascade	188−191,209
		microglia	

[a]Employing nanoparticles as carriers improves the efficacy of drug delivery toward the specific target(s). Targets can be Aβ plaques, hyperphosphorylated Tau, AchE, and so on.

therapeutic agent given that elevated AchE activity levels are a well-established characteristic of AD. Additionally, specific phytochemicals demonstrate antiamyloid and antitau activities that can be linked to the amyloid and tau hypotheses in AD development.

5.5. Nanotechnology-Based Therapies. Nanoparticles refer to highly compact structures in which therapeutic agents are either enclosed within the colloid matrix or attached to the particle's surface through adsorption or conjugation.[211] For diagnosis of AD, nanosensors such as carbon nanomaterials, nanoparticles, and nanopolymers are being investigated.[211] Inorganic nanoparticles like gold nanoparticles, iron nanoparticles, cerium oxide nanoparticles, carbon nanotubes, carbon dots, and organic/polymeric nanoparticles, such as nanoliposomes and nanomicelles, have been analyzed for their efficacies in treatment of AD.[211,212] Nanoparticles have significant potential as carriers for drug delivery to enhance AD therapy and other diseases.[212] Nevertheless, nanoparticles can disrupt amyloid protein structures (Figure 2) through nonspecific interactions, irrespective of their size, structure, shape, and chemical composition.[213] In addition, small-size EVs or exosomes have been developed as a direct therapeutic agent or a BBB-penetrating carrier for certain drugs to treat various neurological diseases.[214−217] In addition, recent reports showed that administration of EVs from various stem cells can be used to alleviate neurodegeneration and improve AD pathologies in rodent models.[217−220] Mesenchymal stem-cell-derived EVs were effective as neuroprotective agents in AD animal models, Table 5.[218,221−226]

5.6. Tau Aggregation. Elevated levels of cytosolic tau result from various PTMs, including phosphorylation, glycosylation, glycation, nitration, polyamination, ubiquitination, truncation, etc.,[210,211] and the subsequent loss of its ability to bind to microtubules[238] and mitochondrial dysfunction, eventually contributing to neuronal cell damage and neurodegeneration in murine models.[239] This increase in cytosolic tau enhances the potential chance for self-interaction between tau proteins and promotes their polymerization and aggregation as NFTs.[235−237] Importantly, in humans, the aggregation of tau and the presence of NFTs (tauopathies) show a closer correlation with the severity of symptoms and the loss of neurons than do Aβ lesions. In the context of AD, there is a fully established connection between the distribution of NFTs and the clinical symptoms observed in affected individuals. These findings suggest that therapies focused on targeting NFTs and tau protein or its regulating enzymes, including MAPK and GSK3β, could hold promise as potential drug targets for addressing neurodegeneration.[240]

Currently, therapies aimed at tau protein seek to achieve various objectives, including decreasing, stabilizing, and inhibiting the aggregation, or various PTMs, including hyperphosphorylation of tau protein.[241] Some specific therapeutic approaches have been proposed with the potential to modify the course of the disease.[242] These approaches include the following.

(1) Inhibition of tau phosphorylation, which can be achieved by either suppressing tau kinases or triggering tau phosphatases.
(2) Enhancement of microtubule stability, which is critical for normal cellular function.
(3) Increasing the elimination/clearance of tau protein from the brain.
(4) Preventing the aggregation of tau protein.

It is important to note that some of these approaches have advanced to clinical trials, indicating that they are being actively investigated for their potential to treat AD and related tauopathies.[243] Hydromethylthionine mesylate (HMTM/TRx0237) is a medication developed to impede the formation of tau protein aggregates in the brain (Figure 2). Two Phase III clinical trials have been conducted to assess its effectiveness in individuals with slight to intermediate AD. The results of these trials indicate that the drug's ability to slow cognitive decline and reduce brain atrophy is dependent on the level of exposure, with higher exposure levels yielding more significant pharmacological effects.[244] However, TauRx Therapeutics Ltd. announced in the 2022 CTAD conference that the clinical trial failed in its primary end points.

Methylene blue's potential as a pharmaceutical candidate stems from its capacity to thwart the polymerization of tau protein in laboratory settings. It accomplishes this by locking tau monomers into a configuration that hinders their aggregation. This characteristic has displayed potential in early research, notably in transgenic mouse models of tauopathy, where methylene blue successfully lessened tau-related issues and enhanced cognitive results.[245] Furthermore, methylene blue is advantageous as a drug candidate because it can penetrate the BBB, allowing it to target brain-related

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conditions effectively.[120] Additionally, it has a well-established track record of being safely used in humans over an extended period, making it an attractive option for potential therapeutic applications. These factors collectively make it a promising candidate for further investigation and progression as a treatment for conditions associated with tauopathy.[243] A study discussed methylene blue's ability to only inhibit tau fibrils formation rather than tau granule formation, which can be a reason for its failure in clinical trials.[246]

5.7. Microtubule Stabilizers. Microtubules, which are hollow, dynamic filaments within cells, are constructed from $\alpha-\beta$-tubulin heterodimers.[247] These heterodimers are created in the course of protein synthesis, aided by molecular chaperones.[248] In mammals, there are six distinct α-tubulin isoforms and eight β-tubulin isoforms, and their expression varies according to the type of tissue being studied. These $\alpha-\beta$-tubulin heterodimers come together to form microtubules. A fully developed microtubule typically comprises of 13 protofilaments and possesses a diameter of around 25 nm.[249,250] Microtubules are essential constituents of the cytoskeleton, fulfilling vital functions in cellular metabolism, moving substances within cells, maintaining cell structure to facilitate intracellular transport, and ensuring the success of crucial cellular processes like mitosis and cell division.[251] Their dynamic nature and inherent polarity make them versatile elements in the intricate world of cellular biology.[249] Thus, structural alterations of microtubules and their tubulin components, potentially by various PTMs, can lead to many disease states including AD.

Paclitaxel (Taxol), an approved cancer drug, is used as a first-line drug for treatment of breast and ovarian cancer. It attaches to the interior (lumen) of microtubules (MTs) (Figure 2) by binding to a specific site located within the β-tubulin subunit. The region inside the lumen, where binding occurs, is commonly known as the "taxane binding site".[252] It is important to mention that the microtubule-binding segments of tau also interact with this taxane binding site, which is a protein involved in stabilizing microtubules. Importantly, when paclitaxel binds to this site, it can displace tau from microtubules.[252] In an animal model of neurodegenerative tauopathies, namely, the T44 tau transgenic mouse, paclitaxel became the inaugural microtubule-stabilizing agent to undergo testing.[253] However, paclitaxel's inability to effectively penetrate the brain limited further investigations in mouse models that closely resemble human tauopathies, where tau-related issues primarily manifest in the brain.[254] The difficulty in achieving brain penetration of paclitaxel and docetaxel is mainly associated with the presence of the P-glycoprotein (Pgp) efflux pump, which is prominently expressed in the BBB.[255] To address this issue, researchers have explored taxane analogues that can overcome Pgp-mediated transport, resulting in improved brain penetration. Several such compounds have been identified.

(a) Some are weak Pgp substrates, like cabazitaxel, an FDA-approved semisynthetic taxane that can saturate the active transporter.[256]

(b) Some are taxoids that also act as Pgp inhibitors, such as SB-T-1213, SB-T-1214, and IDN-5109.[257,258]

(c) Others are taxoids that do not interact with Pgp, like TX-67.[259]

In this group of taxanes that are not affected by Pgp, cabazitaxel (Figure 2) was identified as having a superior ability to enter the brain compared to paclitaxel. Furthermore, pharmacokinetic investigations involving SB-T-1213 indicated that delivering the drug through fast infusions could substantially enhance its presence in the brain. This approach led to plasma drug concentrations exceeding the necessary threshold for saturating Pgp.[260] Other examples of taxanes capable of bypassing Pgp-mediated efflux include orally active BMS-275183 and milataxel (Figure 2), also known as MAC-321.[261]

Epothilone D, initially recognized as an antifungal compound, was subsequently discovered to have microtubule-stabilizing properties.[262,263] In preclinical trials on tau transgenic mice both young and very old, it enhanced the quantity of microtubules and lessened the number of axons displaying irregular shapes.[264] A Phase I clinical study was launched to evaluate its safety, effectiveness, and pharmacodynamic effects in patients with AD, but the trial was discontinued likely due to adverse effects.[265]

Davunetide, also known as NAP, constitutes an eight-amino acid segment of the activity-dependent neuroprotective peptide (ADNP).[266] In AD transgenic models, NAP decreased the presence of tau- and amyloid-related issues, improved cognitive performance, and enhanced axonal transportation.[252] During a Phase II trial involving individuals with mild cognitive impairment (MCI), NAP was well tolerated, although no substantial distinctions were observed compared to a placebo group.[265] Nevertheless, there was a trend toward enhancements in working memory and attention. In the most recent Phase II/III study with individuals diagnosed with progressive supranuclear palsy (PSP), no notable variations were found between patients administered with a placebo and those treated with NAP.[267]

5.8. Administration of Stem Cells. It is well established that AD is associated with death of neurons and other supporting cells with activated microglia and astrocytes in the brain through vicious cycles of elevated oxidative stress, mitochondrial dysfunction, energy depletion, neuroinflammation, and altered cell signaling pathways.[268,269] Thus, applications of various stem cells from neuronal origin and peripheral tissues have been widely attempted to replace the dead or dysfunctional neurons to improve cognitive function and behavior in the experimental models of AD. One example would be usage of neural stem cells or progenitor cells (NSPCs) derived from other tissues, including adipose tissues.[270] A recent meta-analysis of 22 mice and 8 rat studies showed that both xenogenic and allogeneic transplantation of NSPC significantly improved cognitive function and attenuated progression of AD-associated pathologies in the recipient rodents, as recently summarized.[271] Based on the positive outcomes from experimental models, clinical trials using NSPC in treating AD patients have been actively studied. As of March 1, 2024, there have been 50 clinical trials (Clinicaltrials.gov) of using the keywords "Alzheimer's disease" and "stem cells". Because of the great need for treating AD pathologies, we expect to see additional clinical studies. However, due to practical inconvenience in NSPC transplantation and strict FDA regulations, many scientists have considered alternative usages of NSPC by using their secreted materials, including small-size EVs and exosomes, as recently demonstrated in experimental models.[217−220] As mentioned earlier, these EVs and exosomes derived from stem cells could contain various nucleic acids, including miRNAs, proteins, and lipids, which can be used as diagnostic tools as well as therapeutic purposes

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against many different targets earlier (section 2).[218,221−226,272] However, the clinical benefits and potential toxicities of quality-controlled EVs and exosomes need to be rigorously evaluated in randomized clinical trials.

5.9. FMT as a New Treatment Candidate. As described earlier in the section on risk factors of AD, gut dysbiosis with an elevated abundance of pathogenic bacteria, decreased beneficial microorganisms, and altered metabolites is often found in prodromal stages of AD-affected individuals. These initial changes in the GIT are followed by intestinal barrier dysfunction (gut leakiness) and systemic endotoxemia, leading to acceleration of organ damage, including the brain. These phenomena were observed in AD patients[74−76] as well as animal models of AD.[273,274] Furthermore, transplantation of intestinal microbiota from AD mice or patients into microbiota-depleted rodents decreased their cognitive function and hippocampal neurogenesis.[275−277] These results indicate the importance of gut dysbiosis as a risk factor in regulating brain cognitive function and behavior through the gut (microbiota)−brain axis. Based on these findings of crosstalk between gut dysbiosis and neuronal impairment in AD patients and rodent models, fecal microbial transplantation (FMT) from healthy animals has been developed to improve the gut microbiota composition. To support this notion, recent studies showed that FMT from healthy mice improved the cognitive function and behaviors of AD mice.[278] The gut bacteria used in FMT may theoretically modulate the composition and abundance of gut microbiota in host rodents and may also change the gut-derived metabolites of polyunsaturated fatty acids, SCFAs, various neurotransmitters, and TMA, leading to alterations of the intestinal barrier function and neuroinflammation status that contribute to regulation of the brain function and behavior. Based on the results of rodent studies, FMT from healthy donors may improve cognitive function and behavior in AD individuals. However, the number of human clinical trials of FMT against neurodegenerative diseases has been very small. As of March 1, 2024, there was only one registered clinical trial for a feasibility study with oral FMT for AD pathology (Clinicaltrials.gov), but this study was terminated by some unknown reason. Thus, this area of FMT for treating or preventing AD pathology needs further investigations.

5.10. ATP-Binding Cassette (ABC) Transporters. High cholesterol levels in neurons contribute to the amyloidogenic pathway and hyperphosphorylated Tau accumulation.[279] High plasma membrane cholesterol levels accelerate the hydrolysis of APP with β- and γ-secretase, stimulating the amyloidogenic pathway and thus Aβ production. Conversely, lowering cholesterol levels favors the nonamyloidogenic pathway, which inhibits Aβ production. Use of cholesterol-lowering agents such as statins is associated with decreased risk of AD.[280]

ABC transporters are transmembrane proteins that use energy from ATP to move a wide variety of substances into and out of cells. This movement involves binding to ATP, breaking it down, and releasing ADP, all precisely coupled to the transport process. They handle a vast array of molecules, ranging from vitamins, steroids, lipids, and ions to peptides, proteins, polysaccharides, and xenobiotics.[281] ABC transporters are classified into seven distinct groups (ABCA to ABCG) based on their genetic makeup: the ABCA group contains 12 active transporters (ABCA1−ABCA13).[280] Several members of the ABC transporter family, including ABCA1, ABCA5−ABCA10, ABCG1, and ABCG4, play a crucial role in cholesterol efflux from cells, thus affecting the cholesterol balance (homeostasis). Among these, ABCA1 and ABCA7 have been extensively studied for their roles in AD.[282]

6. CONCLUSION

One of the best ways of managing healthy aging without AD (and other neurodegenerative conditions) is to avoid or prevent many environmental risk factors by maintaining good habits with positive emotions, a proper diet, sleep, and physical exercise. In the case of AD, a variety of therapeutic targets are currently under investigation in numerous clinical trials. Aβ plaque, abnormal tau, α-secretase, β-secretase, γ-secretase, microtubules, vaccine approaches, miRNAs, and gut dysbiosis are the potential targets that have been investigated in the last few decades. The mechanistic understanding of AD pathologies has led to advancing novel therapeutic approaches such as active and passive immunization targeting hyperphosphorylated tau or Aβ accumulation and nanoparticles for enhanced drug delivery. However, many of the novel drugs have not shown promising results in clinical trials, mainly due to adverse effects and their inability to reduce cognitive decline in AD patients. In conclusion, although there is ongoing research on promising drugs, including the newly emerging MABs and circulating EVs/exosomes from stem cells, further investigation is necessary to gain a clear understanding of Alzheimer's disease pathogenesis. This knowledge will help identify new biomarkers and clinical targets essential for the development of genuinely disease-modifying treatments.

■ ASSOCIATED CONTENT

Data Availability Statement

The data that support the findings of this study are available in standard research databases such as PubMed, Science Direct, or Google Scholar, and/or on public domains that can be searched with either keywords or DOI numbers.

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■ ABBREVIATIONS

AD: Alzheimer's disease
NFT: neurofibrillary tangles
Aβ: amyloid beta
MCI: mild cognitive impairment
aMCI: amnestic mild cognitive impairment
sAD: sporadic Alzheimer's disease
PSEN-1: presenilin 1
APP: amyloid precursor protein
sAPP: soluble ectodomain of APP
APPICD/AICD: APP intracellular cytoplasmic domain
BACE 1: β-secretase
MAPK: mitogen-activated protein kinase
CDK: cell-cycle-dependent protein kinase
GSK: glycogen synthetase kinase
ACh: acetylcholine
BFCN: basal forebrain cholinergic neurons
AChE: acetylcholinesterase
OLG: oligodendroglia
ROS: reactive oxygen species
NMDA: *N*-methyl-D-aspartate
NMDAR: *N*-methyl-D-aspartate receptor
SCFA: short-chain fatty acid
TMA: trimethylamine
ARIA-E: amyloid-related imaging abnormalities−edema
ChEI: cholinesterase inhibitor
LRP: low-density lipoprotein
BBB: blood−brain barrier
EVs: extracellular vesicles
MAB: monoclonal antibody
PTMs: post translational modifications
Pgp: P-glycoprotein
NSPC: neural stem or progenitor cells
FMT: fecal microbial transplantation

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