Review

Biochemical modulators of synaptic plasticity: New horizons in Alzheimer's disease treatment

Journal of Alzheimer's Disease
2026, Vol. 113(2) 501–518

DOI: 10.1177/13872877261469864
journals.sagepub.com/home/alz

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Abstract

Synaptic dysfunction is the earliest and most critical pathological feature of Alzheimer's disease (AD), directly contributing to cognitive decline. This review provides an integrative overview of the molecular and biochemical modulators governing synaptic plasticity and their disruption in AD. We discuss how the collective impairment of Aβ aggregation, tau pathology, calcium imbalance, oxidative stress, and neuroinflammation affects dendritic spine morphology and synaptic connectivity. Particular attention is given to neurotrophins such as brain-derived neurotrophic factor and TrkB signaling, hormonal influences, likewise glucocorticoids, estrogens, testosterone, endocannabinoid pathways, lipid and cholesterol regulators like ApoE and lipid rafts, and epigenetic mechanisms that modulate synaptic resilience. We further evaluate the therapeutic potential of pharmacological agents, including cholinesterase inhibitors, NMDA receptor modulators, and multi-target directed ligands alongside nutraceuticals such as resveratrol, curcumin, omega-3 fatty acids, *Withania somnifera*, and *Bacopa monnieri*. Emerging technologies, including iPSC-derived neuronal models, optogenetics, and advanced neuroimaging biomarkers like SV2A PET, cerebrospinal fluid/plasma neurogranin, are also highlighted for their role in elucidating and monitoring synaptic integrity. Ultimately, targeting the biochemical modulators of synaptic plasticity offers a promising avenue for AD therapy, especially through combinatorial and precision-medicine strategies aimed at restoring synaptic function and cognitive performance.

Keywords

Alzheimer's disease, metabotropic, modulators, neurotrophins, synaptic plasticity

Received: 30 March 2026; accepted: 10 June 2026

Introduction

Synaptic plasticity, the activity-dependent change in neuronal connection strength, has been recognized as a crucial component of learning and memory.[1] Activity-dependent synaptic plasticity is a prevalent property of the nervous system that permits neurons to connect and alter their connections as a function of past experiences. The nervous system may reorganize itself by changing synaptic strengths, producing long-lasting memories that are the biological foundation for mental functions.[2] The strength of a synapse is increased or decreased with time hence, synaptic plasticity is considered to be a crucial cellular basis for learning and memory. The process has been reported in several learning associated brain regions, such as the hippocampus, cerebral cortex, cerebellum, amygdala and striatum.[3]

Alzheimer's disease (AD) is an irreversible brain disorder characterized by slow, progressive damage to the brain functions mostly affecting in older people. The pathological processes underlying AD begin years before clinical symptoms emerge, reducing the efficacy of late-stage

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therapeutic interventions.[4] AD is characterized by two pathognomonic indications (1) extracellular clusters of amyloid-β (Aβ) fibrils as neuritic plaques; and (2) the intracellular assemblage of abnormally phosphorylated tau protein that enhances the development of neurofibrillary tangles in the cerebral cortex and subcortical gray matter. Here, endogenous "damage signals" like Aβ oligomers have been hypothesized to initiate microglial cell activation with the subsequent release of proinflammatory cytokines, which would initiate signaling cascades in neurons leading to hyperphosphorylation and aggregation of tau protein.[5]

AD is linked to cognitive decline and progressive memory loss. Indications such as synaptic impairment, reduced synaptic density and cognitive decline become notable as AD progresses. The formation of senile plaques, neurofibrillary tangles, hyperphosphorylation of tau protein and disruption of redox homeostasis may leads to AD.[6,7] Factors that advance to interfere with the performance of everyday activities, such as apathy, depression, impaired communication, disorientation, poor judgment, difficulty in swallowing and walking and behavioral changes, characterize this ailment depending on the stage of the disease.[8]

At present, there are approximately 50 million AD patients globally and this number is expected to double every 5 years. Estimated global expenses of US$1 trillion annually are attributed to AD burden that affects individuals, their families and the economy.

Synaptic dysfunction is closely related to AD which is also considered as synaptic ailment. Aβ which interrupts synaptic plasticity and mediates the synaptic toxicity through different mechanisms, is one of the main pathogenic factors in AD. Aβ disrupts glutamate receptors, such as NMDA and AMPA receptors, which facilitates calcium dyshomeostasis and impairs synapse plasticity characterized by long-term potentiation (LTP) suppression and long-term depression (LTD) enrichment.[9]

This review specifically focuses on biochemical modulators that regulate synaptic plasticity in AD, emphasizing how these pathways influence LTP, dendritic spine integrity, neurotransmission, and synaptic resilience. Particular attention is given to distinguishing established synaptic mechanisms from emerging experimental targets and translational therapeutic strategies.

Synaptic plasticity: mechanisms and types

The concept of plasticity of the synapses that allow or modify the strength of the synapses is the basis of learning, adaptation, and storing of information within the brain. It entails different processes that strengthen or weaken the synapses thereby defining neural circuits and mental processes. The most researched processes among them include LTP and LTD which are underpins by the neurotransmitter signaling and the calcium dynamic and the receptor activity.[10]

LTP and LTD

LTP and LTD are among the best-known types of plasticity and are considered as complementary mechanisms to tune neuronal networks. LTP reinforces synapses, not only by enhancing the effectiveness of neurotransmission and reinforcing those links which are frequently used, but also in the process aids in memory trace consolidation.[11] LTD, on the other hand, attenuates the synaptic connection via activity-dependent decrease in the efficiency of the synaptic connection, which removes redundant or irrelevant inputs. The combination of these two-way processes is what the structural and functional foundations of the existing processes of neural circuit remodeling are necessary to provide to make sure that maintenance of information storage is dynamic and flexible.[12]

Typically, the stimulation of the LTP is observed to cause influx of calcium, and, consequently, stimulation of the signaling cascade, resulting in the alteration of receptor composition, synapses reorganization, and enhancement of neurotransmitter releases. The relative changes that come with this are the enlargement of the dendritic spines, the increase of the density of the postsynaptic receptors that facilitate the synaptic contact.[12] Although endocannabinoid system (ECS) modulation demonstrates promising synaptoprotective properties in preclinical models, its translational potential remains limited due to insufficient clinical validation and the complexity of cannabinoid receptor signaling.

Role of neurotransmitters (glutamate, GABA)

The two crucial neurotransmitters that coordinate the synaptic plasticity in the brain are the glutamate as well as gamma-aminobutyric acid (GABA) which are the main transmitters of the excitatory and the inhibitory synapses in the brain Interacting with the ionotropic receptor, i.e., NMDA and AMPA, the glutamate is as well able to excite excitatory postsynaptic potentials, which cause LTP by entering calcium and phosphorylating receptors and remote modification GABA on the other hand controls the post synaptic potentials which are inhibitory and stability of the network of neurons. This type of excitation and inhibition is necessary because exorbitant glutamatergic effect will cause excitotoxicity, and inhibitory responses will dominate and inhibit plastic events (Table 1).[13]

The joint action of glutamate and GABA establish whether to excite or to inhibit the synaptic input therefore the direction of LTP or the direction of LTD. Neuronal activity modulation patterns and external stimulation protocols including repetitive trans cranial magnetic stimulation (rTMS) and theta-burst stimulation (TBS) also influence such neurotransmitter systems.[14] On the other hand,

Table 1. Summary of the important mechanisms and functional consequences of synaptic plasticity processes in the context of Alzheimer's disease.

Mechanism / type	Key process	Molecular players	Functional role	Implications	Ref.
LTP	Persistent strengthening of synaptic transmission	NMDA, AMPA receptor insertion, CaMKII, PKA	Enhances synaptic strength, supports memory storage	Central to learning and long-term memory consolidation	10
LTD	Activity-dependent weakening of synapses	NMDA receptors, mGluRs, AMPA receptor internalization, PP1	Removes less relevant synapses, refines circuits	Prevents overexcitation and maintains plasticity balance	10
Glutamate signaling	Fast excitatory neurotransmission	AMPA, NMDA, mGluRs	Drives depolarization and intracellular cascades	Excess activity may cause excitotoxicity	13
GABA signaling	Major inhibitory neurotransmission	GABA-A, GABA-B receptors	Maintains excitatory–inhibitory balance	Deficits are linked to hyperexcitability and memory loss	13
Calcium influx	Second messenger entry via NMDA channels and VGCCs	CaMKII, PKC, calcineurin	Triggers kinase and phosphatase cascades	Amplitude and duration determine LTP vs LTD	16
Intracellular cascades	Downstream signaling of calcium and neurotransmitters	MAPK, CREB, PI3K, PKC	Regulates gene expression and synaptic remodeling	Supports long-term structural changes	19
NMDA receptors	Ligand- and voltage-gated ion channels	GluN1, GluN2 subunits	Coincidence detectors, allow Ca^{2+} influx	Overactivation is linked to excitotoxic damage	16,17
AMPA receptors	Ionotropic glutamate receptors	GluA1–GluA4, TARPs, PSD-95	Mediate fast excitatory currents, receptor trafficking	Their insertion/removal defines synaptic strength	17
Overall integration	Balance of potentiation and depression	Cross-link among all receptors and cascades	Enables learning, memory, and adaptability	Imbalance leads to cognitive decline, as in AD	17,19

however, is the observation that low frequency or sparse stimulation is biased to LTD that is easily caused by relatively weak NMDA stimulation and maintenance of GABAergic inhibitory tone that causes low synaptic activity. These processes give credence to the fact that neurotransmitter regulations require activity whereby frequency, intensity and duration of inputs dictate whether the neural circuits will strengthen or prune.[14]

Calcium signaling and intracellular cascade

Calcium signaling which links neuronal activity to energy metabolism and structural remodeling is a key linkage of plasticity of synapses. Using NMDA receptors and voltage-gated calcium channels, calcium activates the postsynaptic cascades and triggers the processes of production of ATP and smooths the intracellular calcium level. It is this local energy supply and control in calcium microdomains that guaranteed the needs of the synapses were met in the appropriate time, during LTP and LTD. Mitochondrial docking maintains synapses that are active and in a highly energized state as well and is also calcium sensitive proteins mediated. Such a manner of mediation is what links the electrophysiological inputs and the metabolic outputs to form a dynamic relationship between the activity and the adaptability. The interaction of such pathways results in the fact that the calcium becomes necessary to the long-term changes in the synaptic efficiency.[15] In such a way, the calcium mediates the electrophysiological inputs and the metabolic outputs to establish a dynamic connection between the activity and the adaptability. The coordination of these pathways leads to the fact that calcium is indispensable to long-term modifications to the synaptic efficiency (Table 1).[16]

NMDA, AMPA, and metabotropic glutamate receptors

The recent studies on interaction of NMDA, AMPA, and metabotropic glutamate receptors demonstrate the inseparable nature of excitatory transmission to the learning and memory process. The NMDA receptors are coincidence detectors, which encode the activation of the synapses to the calcium-dependent signaling and the AMPA receptors are the fast response that elevates the postsynaptic depolarization. Their trafficking and phosphorylation status are dynamic, so, the brain can disturb synaptic connections at a very rapid rate depending on the demands. Meanwhile,

the more specific receptors in an intracellular cascade regulate the timing and persistence of changes in the synaptic changes, the metabotropic glutamate receptors.[16, 17] It is through these receptors that flexibility and stability can co-exist in synaptic communication that is achieved through the coordination of fast ionotropic signaling of slower modulatory effects.[18]

Collectively, these signaling mechanisms are essential for maintaining synaptic plasticity, neuronal communication, and memory formation. Disruption of these pathways by AD-associated pathological processes contributes to impaired LTP, synaptic weakening, and progressive cognitive decline.

Synaptic dysfunction in AD

One of the primary characteristics of the AD is synaptic dysfunction, which occurs long before the occurrence of overt neuronal loss and cognitive impairment.[9]

Amyloid-β and tau pathology disrupting synaptic plasticity

Accumulation of Aβ peptides is the initial pathological feature of AD that gradually becomes insoluble and forms extracellular plaques. These peptides, in particular, longer ABB isoform, are generated due to the abnormal cleavage of amyloid-β protein precursor (AβPP) through 2 and 7 – secretases.[20] Their accretion distorts clearance processes and increases oxidative stress, deregulated calcium influx, activation of caspase and is generally detrimental to the synaptic connection. Soluble A2-aggregates at low concentrations impair cell communication and excitatory transmission and trigger neurotoxic cascades that inhibit synaptic strength long before cells are killed.[21] At the same time, Aβ plaques can be considered as inflammatory stimuli, which stimulates the microglia and cytokines released, which further disrupt the homeostasis of the synapses. As Aβ pathology advances, tau protein is hyperphosphorylated leading to destabilization of microtubules and the breakdown of neuronal cytoskeleton. At low concentrations, soluble Aβ aggregates disrupt cell communication.[20] Aβ oligomers inhibit the glutamatergic signaling leading to excitotoxicity, calcium overload and deficit of LTP due to excessive stimulation of the NMDA receptors.[9] Soluble Aβ oligomers and pathological tau collectively impair synaptic plasticity through NMDA receptor dysregulation, calcium dyshomeostasis, mitochondrial dysfunction, dendritic spine destabilization, and suppression of hippocampal LTP. These synaptic alterations are considered among the earliest pathological correlates of cognitive decline in AD. Collectively, Aβ oligomers and tau pathology impair synaptic plasticity by disrupting NMDA receptor signaling, altering calcium homeostasis, destabilizing dendritic spines, and suppressing LTP, ultimately contributing to memory impairment in AD.

Loss of dendritic spines and synapse number

Synaptic plasticity of the healthy brain through LIMK1-cofilin-actin pathway occurs in the dendritic spines. Calcium influx triggered by the NMDA receptors provokes the activation of the Rho-GTPases and their downstream kinases, leading to the activation of LIMK1. Activated LIMK1 phosphorylates cofilin at serine 3 blocking its actin-severing activities and promoting actin filament stabilization, spine growth and glutamatergic receptor uptake. It is this controlled actin remodeling that allows growing spines to grow bigger and stronger in addition to bridging structural plasticity to LTP and memory consolidation. In the case of AD, this well-controlled system is not in order.[22, 23] Amyloid-2 and tau pathology alters LIMK1-cofilin signaling to lead to either hyperphosphorylation of cofilin and actin filament lockage or dephosphorylation and uncontrolled actin filament.[24] The two disorders impair remodeling of the spine, dysfunctional synapse transmission and favor synapse loss. To exacerbate the condition, cofilin actin rods along with Hirano bodies accumulate in the neuron, impeding the trafficking, and cytoskeleton, integrity. This pathological inclusions together with the dysfunctional actin dynamics augment the gradual degradation of dendritic spines and synapses, and ends up in cognitive impairment in AD.[25]

Mitochondrial dysfunction and oxidative stress

The brain is extremely susceptible to oxidative stress due to the high rate of oxygen usage, lipid-containing membranes, and reliance on the metabolism of energy in mitochondria. The excess of reactive oxygen species (ROS) and reactive nitrogen species formation in AD leads to destruction of lipids, proteins, and DNA resulting in a cascade of cellular dysfunction.[26] Lipid peroxidation changes the integrity of membranes and neuronal signaling, oxidation of proteins inactivates necessary enzymes like glutamine synthetase and creatine kinase resulting in excitotoxicity and decreased energy metabolism.[27] Therefore, oxidative stress is not only a trigger, but also an enhancer of the pathology of AD by strengthening amyloid and tau-mediated neurodegeneration (Table 2).[28]

Neuroinflammation and microglial activation

One of the key pathological features of AD is neuroinflammation, which arises from an abnormal response of glial cells to Aβ fibrils and neurofibrillary tangles. In this process, microglia and astrocytes become activated and release pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, which not only accelerate amyloid deposition but also contribute to synaptic dysfunction and neuronal

Table 2. Key pathological process of synaptic dysfunction in Alzheimer's disease.

Pathological process	Key pathological event	Mechanistic pathway	Outcome on synaptic function	Ref.
Aβ and tau pathology	Aβ plaques and tau tangles accumulate	Interfere with neurotransmitter signaling, impair LTP, destabilize microtubules	Synaptic weakening and cognitive impairment	20,29
Loss of dendritic spines and synapse number	Dysregulation of actin dynamics in spines	LIMK1–cofilin–actin axis altered → cofilin hyper/inactivation → abnormal actin remodeling	Reduced spine density, impaired excitatory transmission	23,25
	Aβ oligomers disrupt cofilin activity	Promote spine shrinkage, loss of synaptic proteins (PSD95)	Deficits in LTP, memory decline	26
Mitochondrial dysfunction and oxidative stress	Mitochondria generate excess ROS	ROS damage proteins, lipids, DNA → energy deficits	Synaptic fatigue, neuronal apoptosis	27,28
	Impaired Ca^{2+} buffering	Dysregulated signaling cascades, excitotoxicity	Disrupted plasticity and neuronal death	30
Neuroinflammation and microglial activation	Microglia/astrocyte chronic activation	Release of IL-1β, TNF-α, IL-6 + ROS → NF-κB, JNK, JAK/STAT pathways activated	Synaptic loss, BBB disruption, progressive neurodegeneration	31
	BBB breakdown due to endothelial injury	Infiltration of peripheral immune cells → sustained inflammation	Self-perpetuating cycle of neurotoxicity and cognitive decline	32,33

injury.[33] Persistent inflammatory signaling establishes a self-sustaining cycle in which cytokines and ROS amplify each other, leading to excitotoxicity, oxidative stress, and neuronal apoptosis (Table 2).[32] In addition, microglial activation adversely affects vascular integrity by damaging endothelial cells and disrupting the blood–brain barrier (BBB), thereby allowing peripheral immune cells and inflammatory mediators to infiltrate the central nervous system.[31] The compromised BBB further facilitates the entry of fibrinogen into the brain, which perpetuates microglial activation and oxidative stress. Although microglia initially play a protective role by clearing Aβ, chronic activation shifts them toward a sustained pro-inflammatory phenotype that exacerbates neuronal damage.

Overall, the interplay among microglial activation, Aβ accumulation, tau pathology, and vascular dysfunction forms a vicious cycle that drives synaptic impairment and cognitive decline. Targeting regulatory pathways that maintain microglial homeostasis, such as TREM2 signaling or anti-inflammatory cytokine pathways, may represent a promising therapeutic strategy to restore balance and slow the progression of AD.[33]

Given that synaptic dysfunction arises through multiple interconnected pathological mechanisms in AD, attention has increasingly shifted toward biochemical modulators capable of restoring synaptic plasticity and neuronal communication.

Biochemical modulators

Neurotrophins

The nervous system secretes neurotrophins, which are thought to regulate the survival, growth, plasticity, and development of brain cells.[34] These molecules include glial cell derived neurotrophic factor (GDNF), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF), the most significant neuroplastic-inducing trophic factor.[35] LTP consolidation in the *dentate gyrus* requires BDNF and its receptor, TrkB. When given exogenously, BDNF promotes AMPA receptor trafficking within the membrane and is linked to increase in the synaptic density as shown in Figure 1.[36] In the hippocampal area CA3, exogenous BDNF injection has also been linked to a distinct type of synaptic plasticity.[37]

The aberrant hyperphosphorylation and buildup of tau in important areas known to be associated with AD neurofibrillary pathology were significantly reduced.[34] In the hippocampus, P021 caused a notable drop in the soluble Aβ levels and a little propensity to lower the Aβ plaque load, indicating a decrease in Aβ production. P021 also improved plasticity, but only when given early in development (from birth to postnatal day 120).[38]

Among the various biochemical modulators, BDNF–TrkB signaling represents one of the most extensively validated mechanisms regulating synaptic plasticity in AD. Impairment of this pathway contributes to reduced dendritic spine density, weakened synaptic transmission, and defective memory-associated signaling pathways.

Hormones

Patients with AD are known to exhibit markedly elevated levels of glucocorticoids in both the brain and the periphery. These alterations might be important contributors to the pathophysiology of AD rather than only being the result

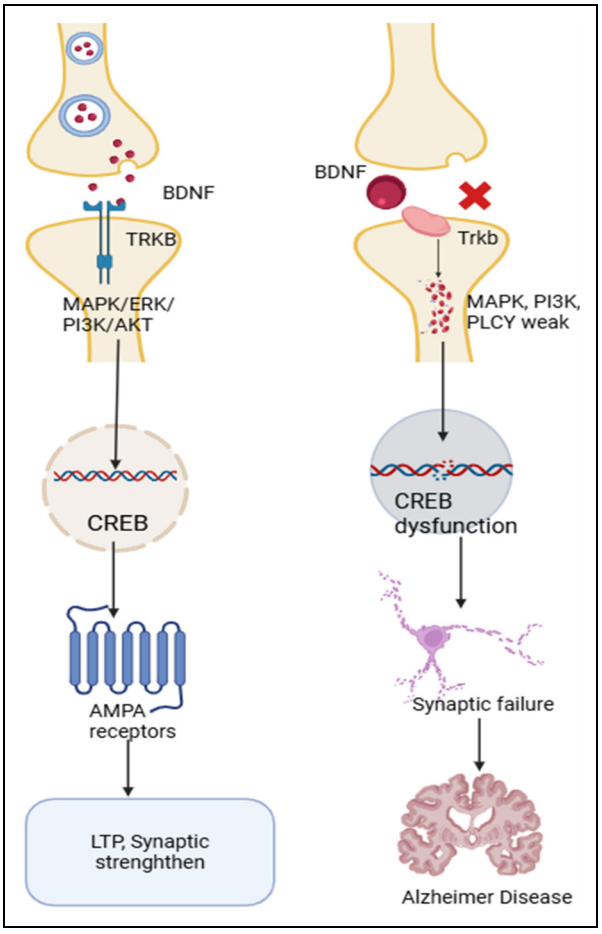

Figure 1. BDNF–TrkB signaling pathway regulating synaptic plasticity in Alzheimer's disease. Binding of BDNF to TrkB activates PI3K/Akt, MAPK/ERK, and CREB signaling pathways, promoting AMPA receptor trafficking, dendritic spine stabilization, and LTP. In AD, Aβ-mediated disruption of BDNF signaling contributes to synaptic weakening and cognitive decline.

of the disease's progression.[39] In mouse models, elevated Aβ aggregation has been associated with hypersecretion of glucocorticoids. This could be because the β-secretase gene's promoter region contains a glucocorticoid responsive element (GRE), to which glucocorticoids bind to increase β-secretase expression and the ensuing amyloidogenic processing.[40] By upregulating GSK3β activity, elevated glucocorticoid levels have been shown a contributing factor to excessive tau hyperphosphorylation.[41] Reduced hippocampus LTP and impaired memory retrieval have been linked to synaptotoxicity and enhanced microglial-mediated inflammation, caused by the excessive glucocorticoid receptor activation linked to early life. Chronic stress exposure during the postnatal 2–9 days was enough to dramatically raise cortisol level and Aβ buildup.[42]

Alterations in estrogen signaling may contribute to the increased susceptibility of females to AD. The women are more likely than men to present with AD; approximately two-thirds cases of females.[43] Based on the hormone treatment and established roles of the sex hormones in cognition, this might be due to differences in the sex hormones & their function in brain, even though it may also be caused by sex variations apart from the circulation of distinct sex hormones.[44] Female hormone dysregulation in AD has received more than older men who have reduced testosterone levels are also at a much higher risk of developing AD and cognitive problems.[45] Testosterone stimulates non-amyloidogenic AβPP processing over amyloidogenic processing by activating androgen receptors, which results in decreased production of β-secretase and increased expression of α-secretase (Table 3).[46] These hormonal alterations directly influence synaptic plasticity by modulating neuroinflammatory signaling, dendritic spine stability, BDNF expression, and glutamatergic neurotransmission within hippocampal circuits.

Pathophysiology of the endocannabinoid system

The molecular process that operated inside the ECS throughout the pathophysiology of neurodegenerative diseases has been better understood. Normal brain activities are hampered by cellular dysregulation.[50] Another drawback of interventions aimed at effectively preventing or demonstrated neuroprotective effects in preclinical models and repair processes is the molecular level analysis of each component.[51] The ECS and associated receptor-mediated networks are complex due to remarkable possible pathways. The participation of the microglial and the astrocyte CB2R and CB1R receptors respectively, as well as molecular pathways across synapses as shown in Figure 2.[52] Through regulation of excitatory inhibitory balance, neuroinflammation, and synaptic signaling cascades, ECS modulation may contribute to preservation of synaptic plasticity in AD models. Emerging preclinical evidence suggests that ECS modulation may preserve synaptic plasticity through regulation of excitatory–inhibitory balance, neuroinflammatory signaling, and mitochondrial homeostasis. However, the long-term therapeutic efficacy and safety of cannabinoid-based interventions in AD remain insufficiently validated in clinical settings.

Functioning of endocannabinoid receptors (CBRs). eCBs bind to CBRs to fulfil cellular demands. The activation with eCBs, the receptors play a critical part in the ECS signaling pathways.[53] These CB1R and CB2R and G protein-coupled receptors (GPCRs) interact with cellular processes and interact with the other receptors, including TRPV1, a mouse astrocyte-isolated transient receptor potential channel subfamily V.[54] A few of palmitoylethanolamide's (PEA) analgesic and anti-inflammatory properties are mediated by G protein-coupled receptor 119 (GPR119), a transient receptor potential channel that is present in vascular endothelial cells and mediates the local vasodilation

Table 3. Summary of hormone-related therapeutic intervention in Alzheimer's disease.

Name of treatment	Stage tested	Impact on AD pathology	References
Mifepristone	Rodent models	Glucocorticoid receptor antagonist, improves learning and memory, reduces β-secretase expression and Aβ production. Reduces tau pathology, may attenuate synaptic deficits.	47
CORT108297 and CORT113176	Rodent models	Selective glucocorticoid receptor antagonists. Hippocampal atrophy, neuroinflammation, Reverse Aβ production. Re-establish levels of synaptotagmin and PSD95	39
Estrogen (hormone replacement therapy)	Rodent models and human AD patients	Improves behavioral performance, Starting early or prior to menopause lowers the load of Aβ plaque, reduces brain atrophy, enhances LT, improves neurotransmission.	45
STX	cultured cells and Rodent models	Reduces Aβ levels, estrogen receptor modulator, improves spatial memory and associated mitochondrial toxicity.	46
FSH-Ab	Rodent models	Increases dendritic spine & synapse number. blocks δ-secretase-mediated amyloidogenic AβPP processing, Reduces FSH levels and tau neurofibrillary tangle production.	48
Leuprolide acetate	Rodent models	Inhibits GSK3β signaling, reduces LH levels, increases BDNF transcription, rescues spatial memory	40
Testosterone	Rodent models & cultured cells	Improves memory retention, presynaptic protein levels, Increases dendritic spine number, PSD95, Aβ clearance. preserves mitochondrial function, reduces tau hyperphosphorylation via GSK3β inhibition,	49

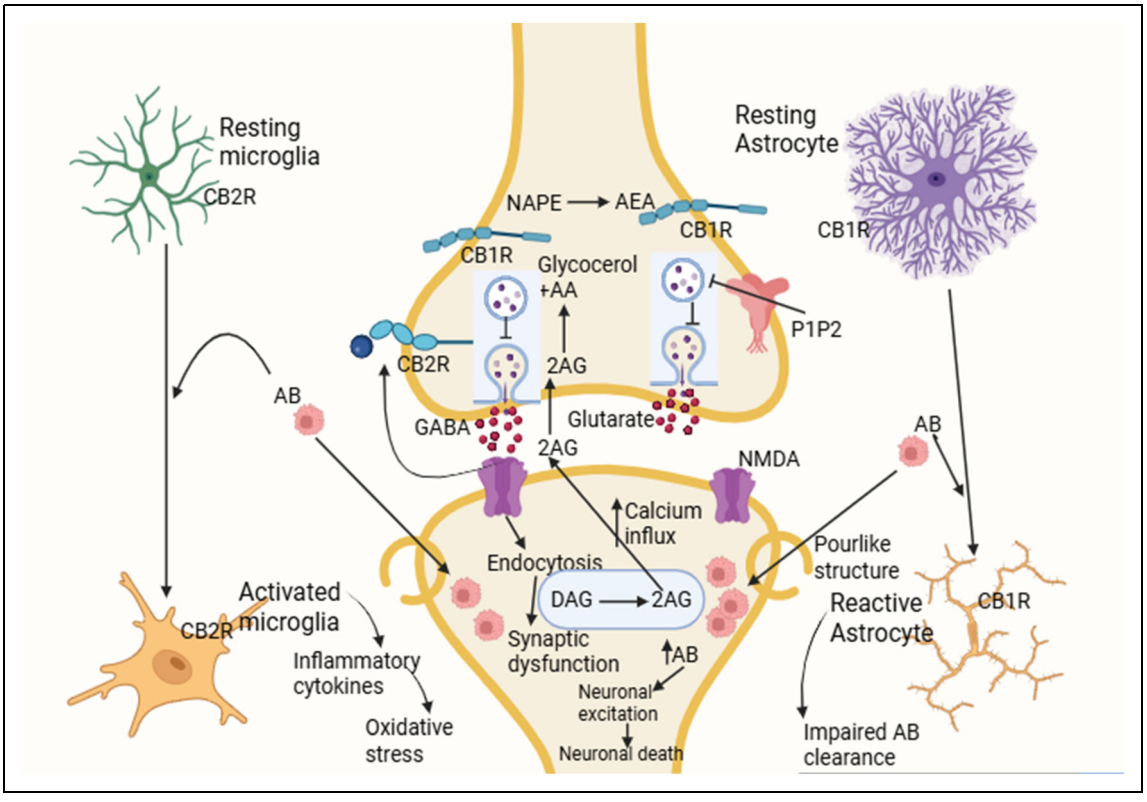

Figure 2. Diagrammatic illustration of the potential pathophysiology of AD by taking ECS, highlighting numerous facets of microglia and astrocytes and how they become activated when encountering Aβ plaques.

effect of AEA. Other transient receptors that may be involved include the vanilloid TRPV1 receptor and Peroxisome proliferator-activated receptor alpha (PPARα).[55] Seven hydrophobic transmembrane domains make up the distinctive structure of the CBRs, which are integral proteins. These GPCRs have higher protein

expression levels in the brain than other GPC receptor, γ-aminobutyric acid type A (GABA-A) receptor, or N-methyl D-aspartate receptor (NMDA).[56]

Neuroprotective roles of CB1R and CB2R

Emerging preclinical evidence suggests that ECS modulation may influence synaptic resilience through anti-inflammatory and neuroprotective signaling pathways. CB1R levels remain constant in AD, indicating that they also play a significant role in maintaining cognitive abilities. Postmortem brain tissues from AD patients showed Aβ plaques along with CB1R and CB2R. Thus, CB1R is a possible target for AD treatment.[57] The expressions of CB1R observed in the distinct neuronal locations, such as glutamatergic neurons exhibiting downregulation and GABAergic neurons exhibiting overexpression, due to the dorsal portion of the hippocampus being implicated in memory-related processes. CB1R gene demonstrated the dysregulation of the CNR1-cannabinoid receptor 1 gene, which codes for CB1R.[58] The intricate control of the CNR1 gene, however, may lead to the development of novel treatment approaches in which CB1R may prove to be a viable cellular target.

The main locations of CB2R was on peripheral organs and endocrine immune cells. They are regarded as peripheral CBRs. Subsequently, their overexpression was observed up to 100 times in the inflammatory processes, following brain damage, peripheral tissue injuries, and tissue injuries as well as through disturbed homeostasis.[59] Under stress, CB2R detected on astrocytes, brainstem and microglia. Through proinflammatory cytokines, CB2R produced anti-inflammatory cytokines in activated microglia.[60] Similar reactions from brain-infiltrated immune cells and microglia during neuroprotection lower oxidative stress, neuroinflammation, cellular death, and harmful neuronal excitability in AD.[61] Chronic oxidative stress and neuroinflammatory signaling further exacerbate synaptic dysfunction by impairing neurotransmitter homeostasis, reducing synaptic protein expression, and promoting microglial-mediated synaptic elimination within vulnerable hippocampal and cortical circuits.

Given that synaptic dysfunction in AD arises through multiple interconnected pathological pathways, increasing attention has focused on biochemical modulators capable of restoring synaptic signaling, neuronal resilience, and synaptic plasticity. These modulators target diverse molecular mechanisms involved in neurotransmission, neuroinflammation, calcium regulation, and dendritic spine maintenance.

Lipid metabolism changes in AD

Lipid metabolism changes significantly, and these changes are especially important in the setting of AD. For example, as people aged, their brain's cholesterol levels rise, which might worsen the development of plaque and Aβ buildup, two of AD's main symptoms.[62] As people aged, their lipid transport pathways' effectiveness declines, which can result in lipid imbalances and neurodegeneration.[63] Lipid metabolism and AD risk are significantly influenced by sex variations. Compared to men, women often have higher levels of HDL cholesterol and a different makeup of fatty acids.[64] These variations may have an impact on AD progression and vulnerability. Postmenopausal women see a considerable decrease in estrogen, which has neuroprotective qualities and regulates lipid metabolism, which may raise their chance of developing AD.[65]

Cholesterol metabolism

There are obvious fluctuations in cholesterol levels. In cell cultures, a lack of cholesterol can change the characteristics of cell membranes, impact the production of neurosteroid hormones, and raise the risk of excitotoxicity-related damage.[66] Through the stimulation of neuronal C/EBP/AEP signaling, rodent studies have demonstrated a correlation between HFD and the beginning of AD pathology and cognitive impairments. The severity of AD is correlated with greater blood and brain cholesterol levels in AD patients than in healthy people.[67]

Cholesterol and ApoE

The amyloidogenic pathway is regulated by cholesterol levels. In a mouse model of AD, amyloid and tau pathology are significantly reduced when astrocytes' cholesterol production is suppressed. Lipid-related processes of AD showed that the transfer of cholesterol from astrocytes to neurons is disturbed.[68] ApoE is the main conduit for cholesterol and is involved in the binding and elimination of Aβ peptides. The ApoE4 allele, a genetic variant of ApoE, is connected to alterations in sphingolipids and cholesterol and is linked to AD risk, underscoring its crucial role in lipid homeostasis and AD pathogenesis.[63] Altered lipid metabolism and ApoE dysfunction contribute to synaptic impairment by disrupting membrane integrity, receptor trafficking, amyloid processing, and neuronal signaling pathways associated with synaptic plasticity.

Cholesterol and lipid rafts

Signal transduction, cell adhesion, and the sorting of lipids and proteins depend on lipid rafts, which are dynamic structures found in cell membranes. Sphingolipids, cholesterol, and saturated FAs make up the majority of these structures; PUFAs are less common.[69] These structures play a key role in the amyloidogenic processing of AβPP, where the anchoring of AD-related proteins like secretase and beta site APP cleaving enzyme 1 (BACE1) is facilitated by the concentration of cholesterol and sphingolipids. The cholesterol in lipid rafts helps AβPP and BACE1 become closer,

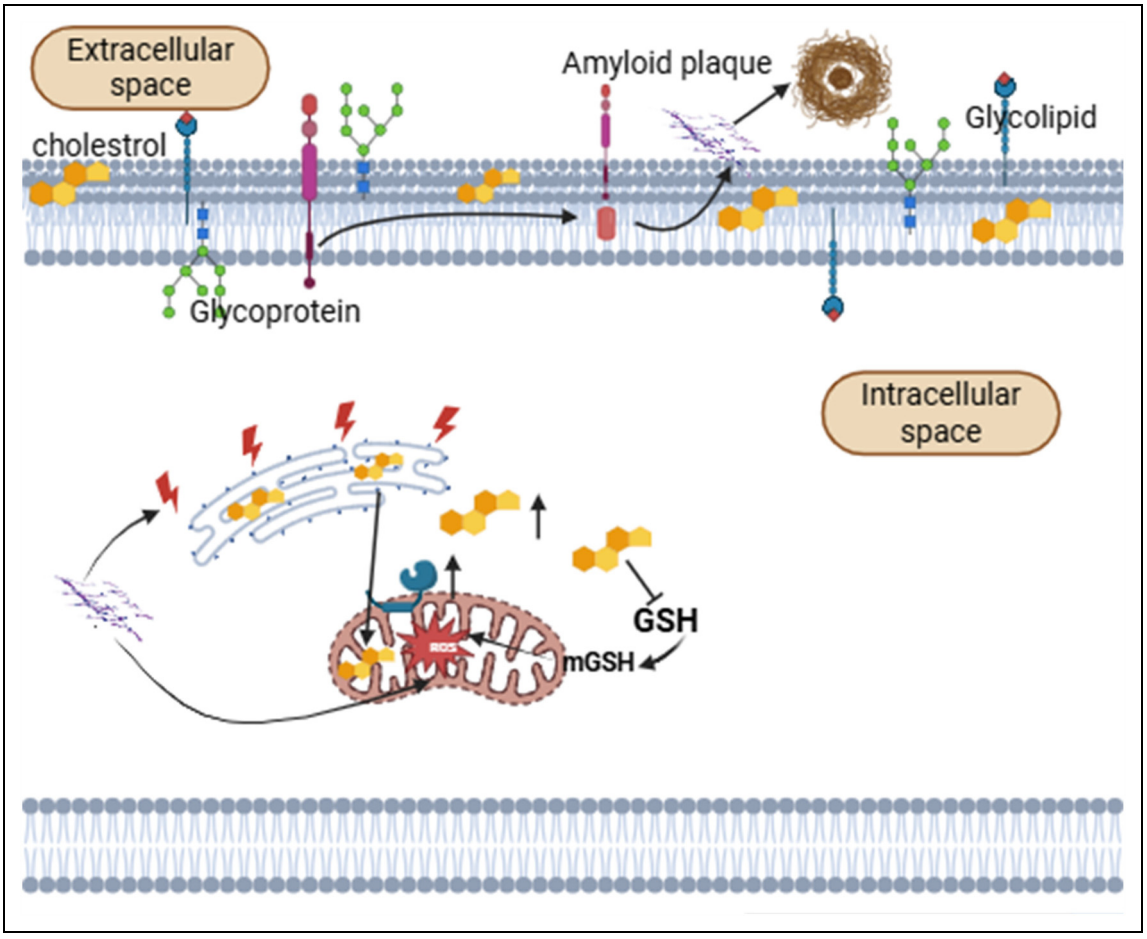

Figure 3. Role of lipid rafts and MAMs (mitochondria-associated ER membranes) in amyloidogenic AβPP processing. Lipid rafts rich in cholesterol and sphingolipids help β- and γ-secretases cleave AβPP, producing Aβ peptides that build up into plaques.

which speeds up endocytosis as shown in Figure 3.[64] BACE1 and secretase activities are impacted by cholesterol levels, suggesting that cholesterol metabolism has a major effect on AD.[70] The disruption of lipid rafts, which are crucial platforms for signaling cascades, can result in aberrant protein distribution and aggregation, which can exacerbate neurodegeneration.[71]

Although several biochemical modulators demonstrate synaptoprotective potential in experimental systems, translating these findings into clinically effective therapies requires improved pharmacological strategies and biomarker-guided validation.

Epigenetic regulation of synaptic dysregulation in Alzheimer's disease

DNA methylation

DNA methylation is a crucial technique, works by methylating cytosine in cytidine phosphate dinucleoside at CpG site. DNA methyltransferase does this by converting cytosine to 5-methylcytosine (5mC) when methyl donor S-adenosylmethionine (SAM) is present.[72] DNA methylation can alter the stability, conformation, chromatin structure, and interactions between DNA and proteins, all of which can affect how genes are expressed. A genome-wide DNA methylation analysis was performed on hippocampal tissues from ten patients and ten healthy controls.[73] The methylation levels of the entire genome dropped, and the levels of 5-mC and 5-hydroxymethylcytosine were lower in AD patients than in healthy controls (Table 4).[74] Epigenetic regulation represents a promising but still evolving therapeutic strategy for modulating synaptic plasticity in AD. Additional mechanistic studies and clinical investigations are required to establish the long-term safety and translational feasibility of epigenetic-targeted interventions. Table 4 highlights genome-wide hypo-methylation, gene-specific changes, and the therapeutic potential.

Pharmacological and nutraceutical interventions

Pharmacological treatment involves mainly neurotransmitter anomalies that are related to the AD. Cholinesterase

Table 4. Summary of key studies on DNA methylation alterations in Alzheimer's disease, highlighting genome-wide hypo-methylation, gene-specific changes, and the therapeutic potential of nutritional and epigenetic interventions.

Model / sample	Key findings	Implications in AD	References
Hippocampal tissues (10 AD patients vs. 10 controls)	Significant decrease in 5mC and 5hmC levels; global hypomethylation	Suggests genome-wide epigenetic dysregulation in AD	[73]
Multiple brain regions at different AD stages	Early AD → genome-wide decrease in 5mC and 5hmC	DNA methylation loss linked to early AD pathology	[74]
Epigenomic association study	Identified 948 CpG sites in 918 genes; promoter TMEM59 hypomethylated → ↑ expression, APP misregulation	Synaptic disorder via impaired APP trafficking	[75]
AD patients vs. healthy elderly (brain & blood samples)	No significant difference in DNA methylation across regions	Methodological limitations; highlights variability in detection	[76]
AD transgenic mice, HT-22 cells	Folic acid ↑ methylation of PSEN1 & APP promoters; SAM supplementation ↓ PSEN1 expression & Aβ production	Nutritional supplementation may restore methylation and reduce Aβ pathology	[77]
Blood samples & SH-SY5Y cells (folate-deficient)	Folate deficiency → hypomethylation, ↑ DR4 expression, ↑ DNMTs, apoptosis	Folate deficiency worsens epigenetic imbalance & neuronal death	[78]

inhibitors, which increase cholinergic neurotransmission and enhance memory and cognition, are the most commonly used medications. Examples of these include donepezil, rivastigmine, and galantamine.[79] Although acetylcholinesterase inhibitor (AChEI) and N-methyl-D-aspartate (NMDA) receptor antagonists (Memantine), have been used as traditional symptomatic interventions in the treatment of AD. Since synaptic dysfunction is the main pathological correlate of cognitive decline, the treatment approach has changed dramatically toward disease-modifying agents.[80] The present approach with pharmacological agents approved by the FDA in clinical use mainly focuses on synaptic symptoms through two fundamental mechanisms: cholinergic enhancement and glutamatergic modulation (Table 5).[81]

Pharmacological intervention is aimed at regulating the overall variety of neuromodulators such as neuropeptides, hormones, and neurotrophins which mediate synaptic transmission above classical neurotransmitter systems.[39] Compounds such as LM11A-31 that target the p75 neurotrophin receptor (p75NTR), is one of the therapeutic approaches directed at increasing the survival and resilience of the neurons and synapses. These modulators attempt to suppress the ensuing neuronal disconnection by blocking the harmful chemical signals triggered by Aβ toxicity. The recent clinical trials have proved that this category of drug is safe and tolerable and showed potential neuroprotective and synaptoprotective effects in preclinical models of AD (Figure 4).[82, 83]

Dietary constituents (flavonoids and other polyphenolic substances common in the Mediterranean diet, such as those in berries, green tea, and cocoa) regulate synaptic plasticity involving the up-regulation of key proteins, including BDNF.[89] Resveratrol, a phytoalexin predominantly found in grapevine species (Vitis sp.) and various fruits, stimulates Sirtuin 1 (SIRT1), resulting in neuroprotection in AD cases. SIRT1 controls the action of many substrates, such as p53 and peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α) (Figure 5). These substrates reduce the accumulation of Aβ and enhance mitochondrial function and neural resilience.[90] The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are also highly critical constituents of neuronal membranes.[91] Herbal and vitamin supplements also show some notable neuroprotective actions. Ashwagandha (*Withania somnifera*) has been found to promote neurite growth and alleviate the burden of Aβ protein through the regulation of molecular chaperone proteins involved in cellular stress processes.[92] *Bacopa Monnieri* (Brahmi) is well-researched as an enhancer of cognitive function. It has been found to alter the cholinergic system (e.g., reducing acetylcholinesterase activity and increasing acetylcholine concentration) and increase the growth of neurons in structure[93] (Table 6).

Emerging technologies and experimental models

The complexity of the development of AD requires the use of new research methods, further standard animal models and drug screenings. New technologies and experimental models have offered new paths in the mechanisms of diseases and treatments in recent years. These approaches attempt to more closely model human pathology and identify biomarkers or targets for intervention.

Stem cell-based models

Stem cells offer tremendous potential for regenerative medicine and play an important role in personalized medicine by finding a cure for various diseases. ESCs are

Table 5. FDA-approved pharmacological drugs.

Drugs	Class	Mechanism	Pathway	References
Donepezil	Cholinesterase inhibitor (AChE)	Inhibits acetylcholinesterase	Cholinergic neurotransmission enhancement	84
Rivastigmine	AChE & Butyrylcholinesterase (BuChE)	Reversible inhibition of AChE and BuChE	Cholinergic neurotransmission enhancement	85
Galantamine	AChE & Allosteric Nicotinic receptor Modulator	Reversible inhibition of AChE & positive allosteric modulation of neuronal nicotinic acetylcholine receptors (nAChR)	Enhancement of cholinergic neurotransmission and synaptic plasticity	86, 87
Memantine	N-Methyl-D-Aspartate (NMDA) receptor antagonist	Non-competitive antagonist at NMDA receptors	Glutamatergic pathway (reduce excitotoxicity and neuronal damage)	88

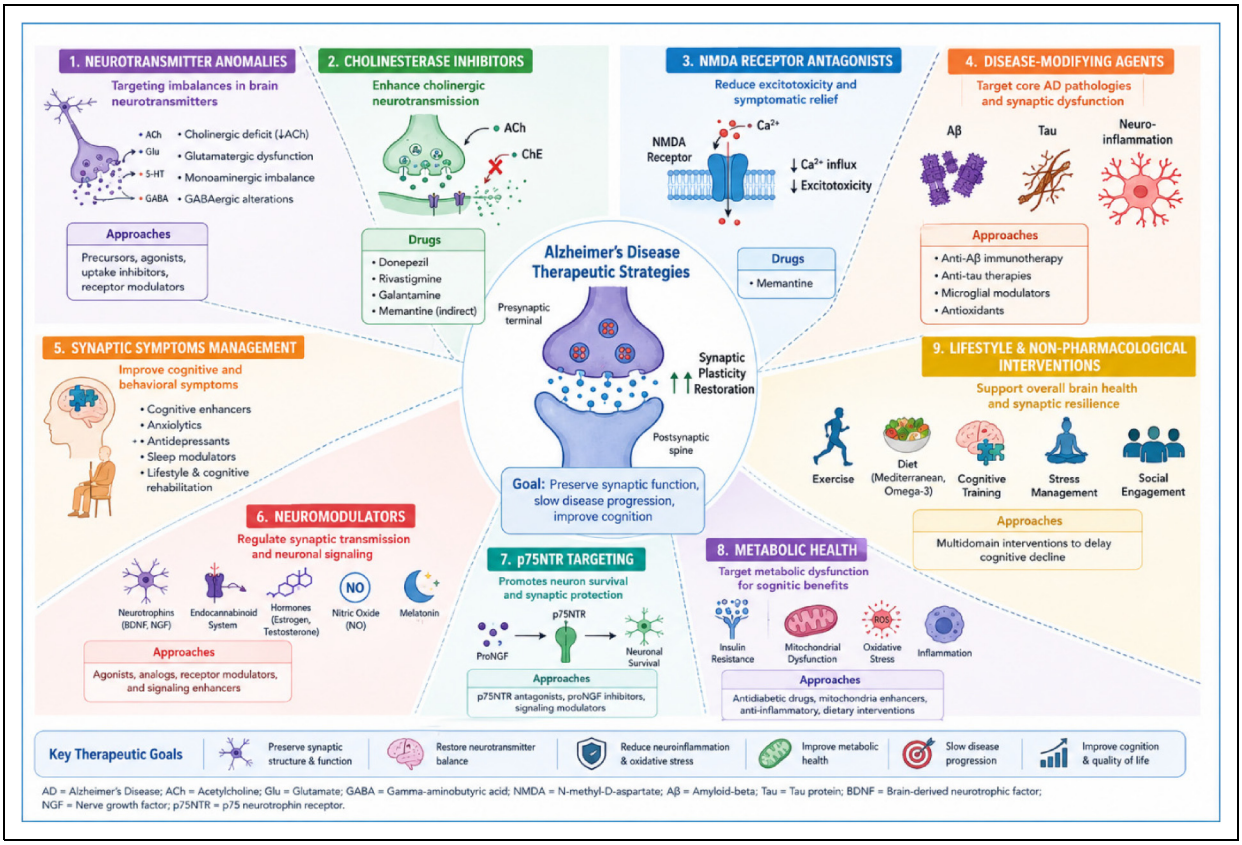

Figure 4. Comprehensive Alzheimer's disease treatment overview.

pluripotent cells with the potential and potency to differentiate into all three germ layers: ectoderm, mesoderm, and endoderm, as has been proven, and many studies have been conducted in this field. It can be used to repair damaged tissue or a specific cell lineage.[94]

Complex genetic variation and environmental factors in human diseases such as the different ApoE isoforms, epigenetic alterations, and other environmental factors make necessary models that faithfully recapitulate the pathological conditions specific to each patient. Human induced pluripotent stem cells (hiPSCs) can overcome this challenge by enabling the creation of patient-derived neurons, glia, and organoids that preserve donor-specific genomic and molecular features (Figure 6). This will allow the development of

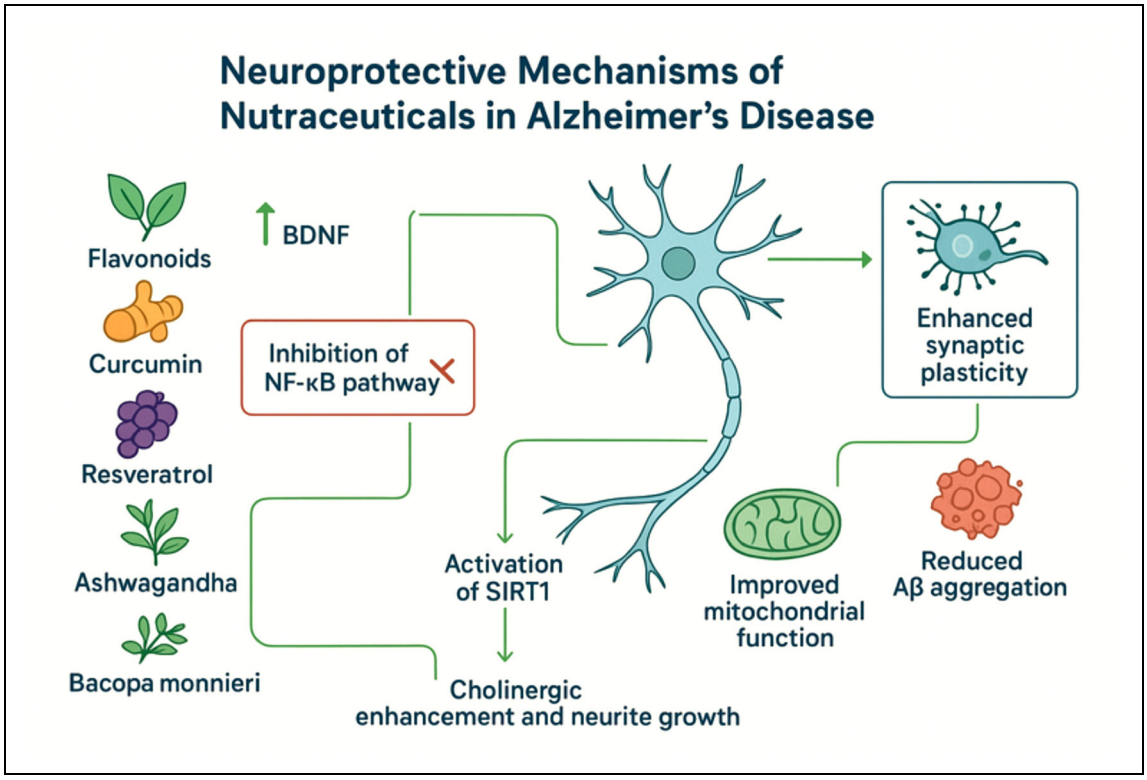

Figure 5. Unveiling the neuroprotective power of nutraceuticals.

Table 6. Neutraceuticals targeting Alzheimer's disease: mechanism and molecular pathway.

Nutraceuticals	Target	Pathway	References
Curcumin (Polyphenol)	Neuroinflammation / Aβ Aggregation	Inhibition of NF−κB signaling and oxidative stress scavenging	[90]
Resveratrol (Stilbenoid)	Mitochondrial Dynamics / Neuronal Stress	Activation of SIRT1 (sirtuin 1) and modulation of apoptotic factors	[90]
Flavonoids (e.g., Quercetin)	Neurotrophin Synthesis	Upregulation of Brain-Derived Neurotrophic Factor (BDNF)	[89]
Omega-3 Fatty Acids (DHA/EPA)	Synaptic Membrane Structure/ Function	Modulate lipid raft composition and reduce pro-inflammatory eicosanoid metabolites	[91]
Ashwagandha (*W. somnifera*)	Chaperone Modulation / Aβ clearance	Enhances neurite outgrowth and reduces Aβ plaque load through stress response	[92]
Bacopa monnieri (Brahmi)	Cholinergic System / Dendrite Growth	Modulates cholinergic system and promotes dendritic arborization	[93]

individualized disease models that faithfully recapitulate the heterogeneity of individual patients and allow researchers to explore the molecular heterogeneity in AD and to develop individualized therapeutic approaches.[95] Two major forms of experiments have developed: iPSC-derived two-dimensional (2D) co-cultures and three-dimensional (3D) cerebral organoids. Two-dimensional iPSC co-cultures are normally composed of neurons and one or more glial cell types, differentiated and grown as adherent monolayers. These systems are easy to handle and can be used for single-cell experiments, live-imaging, electrophysiology, and high-throughput screening.[96] In addition, the use of genome-editing tools like CRISPR -Cas9 also allows the production of isogenic cell lines. This allows for the correction of specific risk factors, such as removing the PSEN1 mutation, in patient-derived neurons. It provides a strong experimental control to clearly assess the therapeutic effect of a biochemical agent against the backdrop of a known genetic defect. This moves the field closer to personalized therapeutic testing.[97]

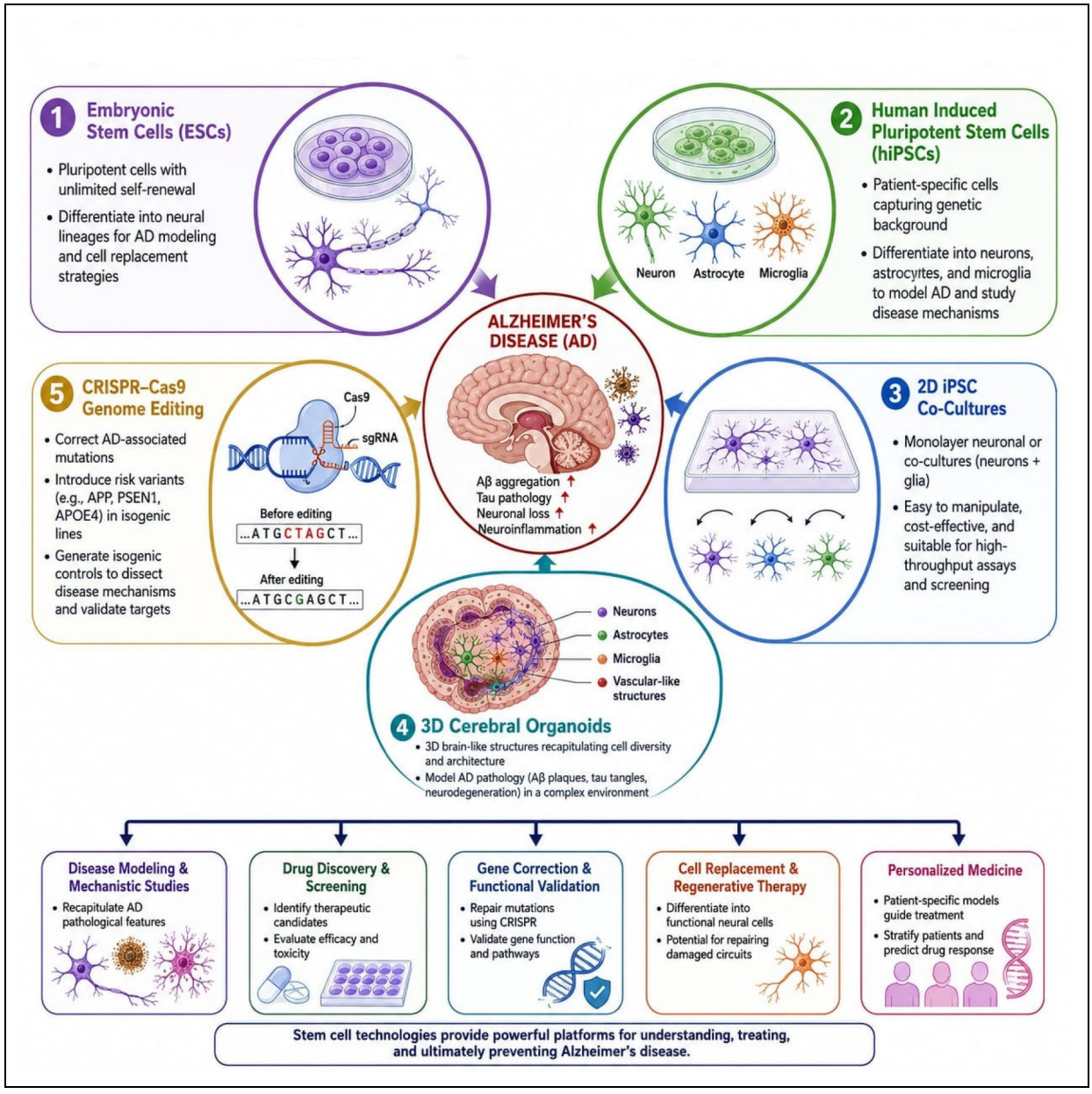

Figure 6. Applications of stem-cell technologies in Alzheimer's disease (AD). Human induced pluripotent stem cells (hiPSCs), embryonic stem cells (ESCs), 2D neuronal cultures, and 3D cerebral organoids are widely used for AD disease modeling, drug screening, and mechanistic studies. CRISPR-Cas9 genome editing enables the correction or introduction of AD-associated mutations, facilitating the generation of isogenic cell lines. These stem-cell-based platforms provide valuable tools for personalized medicine and the development of regenerative therapies.

Optogenetics and electrophysiology in synaptic plasticity studies

Electrophysiological methods remain the gold standard for testing synaptic integrity in different experimental systems. These include hippocampal slice culture, transgenic mouse models, and neuronal systems created from iPSCs. LTP in models of AD is typically disrupted by exposure to A2 peptides and hence evoke LTD, leading to defective synaptic transmission and cognitive decline. It is, therefore, the reestablishment of regular LTP in the region of the hippocampus, CA1, in the conditions of A2 neurotoxicity, which can be defined as an imperative functional biomarker to any prospective candidate compound that expresses neuroprotective or synaptoprotective activity.[98]

In the area of AD research, it is now possible to integrate optogenetic activation or silencing with biochemical modulators and hence effect of a therapeutic modulator on the

synaptic and cognitive output of a specific neural circuit. Genetic, optical and pharmacological probes therefore offer a mechanistic way of tracking interventions to rescue synaptic integrity and network function in AD.[99]

Biomarkers for synaptic health

For biochemical modulators to be translated successfully, their efficacy must be measurable in the living human patient, ideally long before cognitive symptoms are severe. This need is driving the rapid development of synaptic biomarkers, which fall primarily into two categories: fluid-based and imaging-based. Fluid biomarkers offer accessible and reliable measures of synaptic damage. Neurogranin (Ng) is a small, postsynaptic protein found primarily in dendritic spines and is released into the cerebrospinal fluid and, more recently, detected in plasma upon synaptic degradation. Elevated (Ng) levels are strongly correlated with the rate of cognitive decline and neurodegeneration, making it a powerful prognostic indicator for the stage of synaptopathy.[100] Imaging biomarkers allow spatial visualization of synaptic health *in vivo*, to link molecular disease with functional brain imaging. The traditional focus of PET imaging in AD has been on Aβ and tau deposition, but the development of synaptic vesicle glycoprotein 2A (SV2A) tracers, now allows direct measurement of presynaptic terminal density.[101] Despite promising preclinical findings, several biochemical modulators face substantial translational limitations. Many compounds demonstrate poor oral bioavailability, insufficient blood–brain barrier penetration, rapid metabolic degradation, and inconsistent reproducibility across experimental models. In addition, most nutraceutical and endocannabinoid-based interventions lack robust large-scale clinical validation. Variability in animal models and differences between experimental systems and human pathology further complicate translation into effective therapies.

Challenges and future directions

The development of useful biochemical modulators for AD is still plagued by deep challenges. To begin with, the BBB remains a significant hurdle to brain-targeted treatment, because many of therapeutic molecules are not able to enter synaptic clefts in effective concentrations without toxicity.[102] Second, the multifactorial pathophysiology of AD involving Aβ aggregation, tau pathology, neuroinflammation, vascular dysfunction, and metabolic dysregulation implies that single-target strategies (e.g., anti-amyloid antibodies) have yielded only modest clinical benefit, highlighting the requirement for therapeutic strategies with wider mechanistic reach.[103] The multi-target directed ligands are becoming increasingly popular; these are drugs specifically designed to interact with several disease-relevant pathways (e.g., cholinesterase inhibition combined with metal chelation or MAO-B inhibition) in a single molecule.[104] Within the near future, various specific agents for each patient could be utilized in a 'precision medicine' context. In this model aberrant biomarkers in conjunction with a specific pattern of neuropsychology and neuroimaging results may identify a specific treatment regimen within a personalized therapeutic schema.[105] Although multi-target-directed ligands represent a promising therapeutic concept capable of simultaneously targeting multiple pathological pathways, their pharmacokinetic optimization, long-term safety, and clinical efficacy remain insufficiently established. Despite substantial advances in understanding biochemical modulators of synaptic plasticity, multiple translational challenges remain unresolved. Many candidate compounds exhibit poor pharmacokinetic properties, inadequate blood–brain barrier penetration, rapid metabolic degradation, and limited target specificity. Furthermore, variability among experimental models and differences between animal systems and human AD pathology complicate interpretation of therapeutic efficacy. Most emerging interventions, including nutraceuticals, cannabinoid-based therapies, and epigenetic modulators, lack robust large-scale clinical validation. Future therapeutic development will require biomarker-guided precision approaches, improved drug delivery systems, and carefully designed longitudinal clinical studies. Together, efficient future treatments will likely need enhanced delivery methods (such as receptor-mediated transcytosis, targeted ultrasound, or exosome therapeutics) that not only traverse the BBB but also are able to target modulators to injured synapses to reestablish network activity, instead of attempting to address one disease marker.

Conclusion

In summary, biochemical modulators of synaptic plasticity represent promising therapeutic targets for mitigating synaptic dysfunction and cognitive decline in AD. However, most strategies remain in preclinical or early translational stages, and substantial challenges related to clinical validation, pharmacokinetics, and disease heterogeneity must still be addressed. A more integrated understanding of synaptic signaling pathways may facilitate development of targeted interventions capable of improving neuronal resilience and slowing AD progression. Although substantial progress has been made in understanding synaptic modulators in AD, most therapeutic strategies remain in preclinical or early translational stages. Further mechanistic validation, biomarker-guided clinical studies, and improved delivery approaches are required before these interventions can be translated into routine clinical practice.

Acknowledgements

Figures in this manuscript were prepared using a combination of BioRender and AI-assisted image generation tools. The authors

conceived the figure content, verified all scientific information, and performed the final editing and quality control. AI tools were used solely to assist with graphical visualization and did not contribute to the scientific interpretation, analysis, or conclusions of the study. The final versions of all figures were reviewed and approved by the authors.

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Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
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