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Review

Synthetic and Natural Bioactive Molecules in Balancing the Crosstalk among Common Signaling Pathways in Alzheimer's Disease: Understanding the Neurotoxic Mechanisms for Therapeutic Intervention

Abdul Jalil Shah, Prince Ahad Mir, Mohd Adnan, Mitesh Patel, Mudasir Maqbool, Reyaz Hassan Mir,* and Mubashir Hussain Masoodi*

Cite This: *ACS Omega* 2023, 8, 39964−39983

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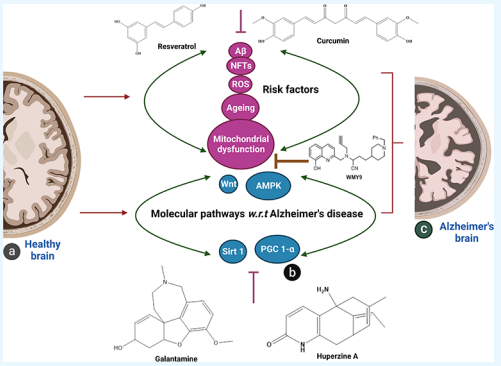
ABSTRACT: The structure and function of the brain greatly rely on different signaling pathways. The wide variety of biological processes, including neurogenesis, axonal remodeling, the development and maintenance of pre- and postsynaptic terminals, and excitatory synaptic transmission, depends on combined actions of these molecular pathways. From that point of view, it is important to investigate signaling pathways and their crosstalk in order to better understand the formation of toxic proteins during neurodegeneration. With recent discoveries, it is established that the modulation of several pathological events in Alzheimer's disease (AD) due to the mammalian target of rapamycin (mTOR), Wnt signaling, 5′-adenosine monophosphate activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), and sirtuin 1 (Sirt1, silent mating-type information regulator 2 homologue 1) are central to the key findings. These include decreased amyloid formation and inflammation, mitochondrial dynamics control, and enhanced neural stability. This review intends to emphasize the importance of these signaling pathways, which collectively determine the fate of neurons in AD in several ways. This review will also focus on the role of novel synthetic and natural bioactive molecules in balancing the intricate crosstalk among different pathways in order to prolong the longevity of AD patients.



1. INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative condition marked by the death of cholinergic neurons over time, resulting in significant behavioral, motor, and cognitive deficits, which are mainly attributed to the deposits of Aβ plaques and hyperphosphorylated tau.[1−3] AD pathology is rather complex in nature; involvement of different signaling molecules, aberrant proteins, and a number of cellular organelles may contribute toward its development. For example, neuronal transmission and calcium fluctuations at synapses depend on the mitochondria;[4,5] thus any imbalance in energy metabolism is critical to the mitochondria and is regarded as a sensitive indicator of cognition in AD.[6] Reduced synaptic activity and subsequent brain injury results from mitochondrial dysfunction and increased Aβ buildup in synapses. Many neurodegenerative diseases, including AD, have been linked to Aβ buildup, synaptic changes, and mitochondrial dysfunction.[7] To sustain the electrochemical gradient, the mitochondria's proper physiological activity relies on their intact structure. Several signaling pathways have been discovered using genetic methods as important mediators of the complex functionality of these neurons, deciding the execution of a process by their intraneuronal communications.[8] Wnt signaling pathways, AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and activation of the silent mating-type information regulator 2 homologue 1 (sirtuin 1) axis are among these signaling pathways (Figure 1). Figure 1 also depicts how the Wnt signaling pathway interacts with AMPK, Sirt1, PGC-1α, mTOR, and peroxisome proliferator-activated receptor gamma (PPAR-γ) that leads to a collective decision, either cell rescue or cell death. When a Wnt ligand binds to the frizzled receptor, it activates both canonical and noncanonical Wnt signaling. The canonical pathway (Figure 1, left) inhibits GSK3β, whereas the noncanonical pathway activates AMPK (Figure 1, right). Sirt1 is also activated by AMPK. Sirt1 deacetylates PGC-1α, which

Received: August 2, 2023
Revised: September 28, 2023
Accepted: October 2, 2023
Published: October 20, 2023

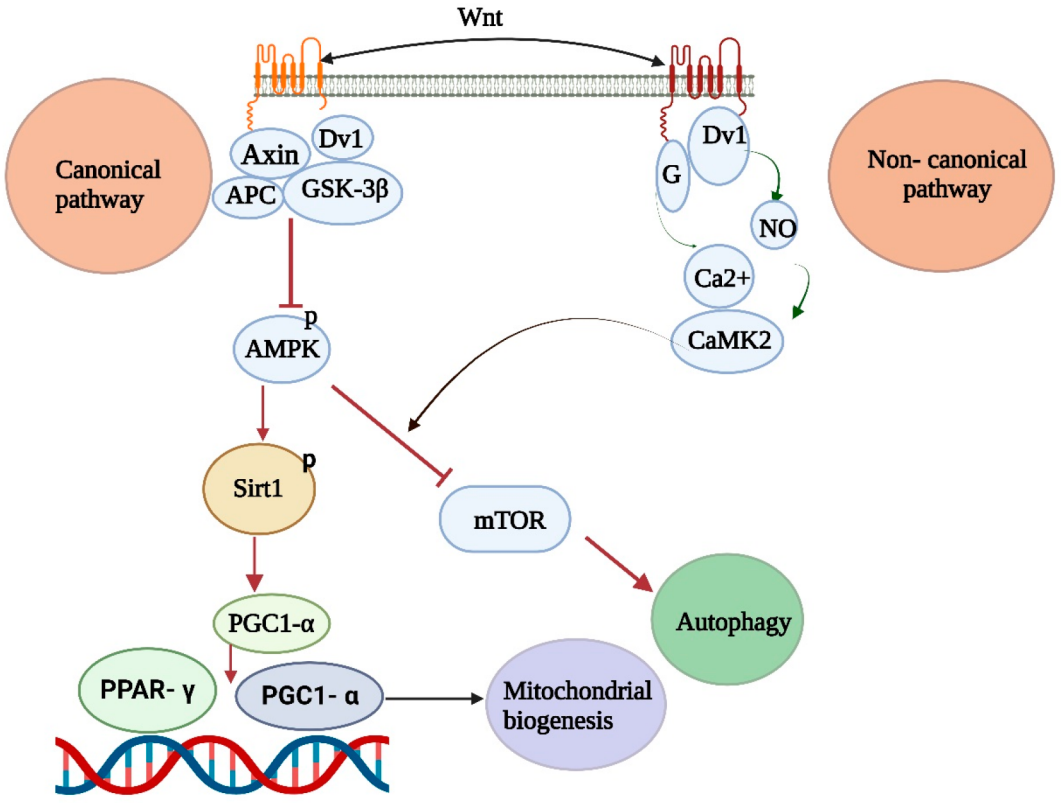


Figure 1. Molecular crosstalk among various important pathways specific to Alzheimer's disease.

translocates to the nucleus and interacts with PPAR-γ to increase the expression of genes promoting mitochondrial biogenesis. AMPK also suppresses the mTOR complex, which stimulates autophagy.

Many natural and synthetic molecules have shown promise to modulate the complex interplay of these pathways. Therefore, it is highly interesting to dictate the present medications swirling around one drug, one target paradigm, despite the reality that AD is multifactorial in nature.[9] As a result, we require tailored therapy based on the one-drug multiple-target approach, keeping in mind not to invite unnecessary adverse effects. Recent findings have revealed that natural bioactive molecules hold a future promise in this category. Such molecules possess powerful antioxidant, anti-inflammatory, and neuroprotective properties; hence they receive special attention for their potential anti-Alzheimer activity.[10−13] However, these natural medicines have various pharmaceutical constraints, such as insufficient lipophilicity and target site selectivity, limiting their potential use against AD.[14] To circumvent these limitations, current research aims to alter these natural medicines by adding or removing distinct functional groups in the pharmacophore. Aside from natural and semisynthetic drugs, combinational therapy, in which a natural medicine is combined with a synthetic agent for optimal therapeutic effect, is also gaining popularity.

In this review, our focus is to propose a potential link between numerous molecular pathways previously known to play strong roles in neurodegenerative disorders and how these processes may also contribute to AD. We believe that better knowledge of the molecular foundation of these pathways, as well as how they interact inside the cell, may help us to reduce or prevent metabolic and neurological impairments seen in AD.

1.1. Crosstalk of AMPK and mTOR in AD. The involvement of these molecular pathways in AD is not clinically proven. However, ample numbers of recent findings have shown that AMPK and mTOR are important targets for dysregulation in AD.[15,16] Various cellular models of AD have revealed that activating AMPK reduces hyperphosphorylation of tau in rat cortical neurons,[17] while others have found that AMPK may phosphorylate tau at many locations (Thr231 and Ser396/404) and disrupt tau attachment to microtubules.[18,19] AMPK activation, on the other hand, has been demonstrated to suppress amyloidogenesis in neurons in multiple investigations.[20,21] AMPK activation also inhibits mTOR signaling while increasing autophagy and the lysosomal breakdown of Aβ.[22,23] Nonetheless, a recent study found that, at therapeutic doses, metformin, a biguanide-class oral antidiabetic drug, can activate AMPK and upregulate transcription of β-secretase (BACE1), the rate-limiting enzyme for Aβ generation, significantly increasing the generation of both intracellular and extracellular Aβ species.[24] These findings suggest narrowing down the use of metformin in diabetic patients having dementia.

The "anti-AD" benefits of nature derived phytochemicals have been found to activate AMPK in several animal studies. For example, protective and beneficial effects of phytic acid against amyloid β pathology in Tg2576 mice were found to be significant. Phytic acid found in dietary grains not only reduces ROS and Aβ oligomers but also increases the expression of autophagic proteins like Beclin-1 and Sirt1 and also upregulates the AMPK pathway.[25] Another phyto compound arctigenin isolated from *Arctium lappa* has been shown to reduce Aβ plaques with an increase in Aβ clearance in APP/PS1 AD mice.[26] This plant belongs to the Asteraceae family and is widely used in Chinese traditional medicine for diabetes, inflammation, improving skin texture, suppressing growth of tumors, and many

https://doi.org/10.1021/acsomega.3c05662
ACS Omega 2023, 8, 39964−39983

viral infections. The mechanism of AMPK activation and inhibition of protein kinase B/mTOR signaling is thought to responsible for the neuroprotective action of arctigenin. Other researchers found that levetiracetam and topiramate,[21] two commonly used epilepsy medications, improved behavioral impairments and reduced plaque formation in APP/PS1 mice. GSK-3 inhibition and AMPK activation were shown to be the mechanisms behind these observed benefits via autophagic degradation of Aβ and its enhanced clearance.[27] Latrepirdine, an antihistaminic medication, also exhibited substantial anti-AD effects in a phase II research. In TgCRND8 animals, latrepirdine promoted mTOR and ATG5-dependent autophagy, resulting in lower levels of Aβ, including APP metabolites, and alleviation of behavioral deficits and autophagic dysfunction.[28] Another drug candidate, rapamycin, improves neuronal survival; otherwise used as an immunosuppressant, it is a highly appealing and interesting molecule in AD.[29] However, due to its severe immunosuppressive impact, it has never been explored as a viable treatment for AD. The mechanism behind rapamycin's anti-AD effects is currently being debated. However, it has been proposed that increasing autophagy by inhibiting mTOR with rapamycin improves cognitive impairments and reduces Aβ pathology and NFTs.[30−32]

1.2. Role of Wnt Signaling in AD. Wnt proteins are a group of secreted cysteine-rich glycosylated proteins named after the *Drosophila* "wingless" protein and the mouse "Int-1" protein.[33] Humans have found 19 of the 24 Wnt genes that express Wnt protein, whereas genetic research in human, mouse, *Drosophila*, zebrafish, and *Xenopus* populations have revealed 80 Wnt target genes.[33,34] Wnt interacts with cell surface Frizzled (Fz) transmembrane receptors, inducing at least three different downstream signaling cascades.[34] The canonical Wnt pathway controls gene transcription via β-catenin, often known as Wnt/β-catenin. The second is the noncanonical route, which is regulated by intracellular Ca^{2+} release, and is also known as Wnt/Ca^{2+}.[35−37] Numerous studies have shown that Wnt signaling components are altered in AD. β-Catenin levels are reduced in AD patients carrying presenilin-1 (PS1) inherited mutations.[38] Alvarez et al. investigated the role of Aβ on cultured hippocampal neurons, Their research team found that Aβ treatment inhibits the canonical Wnt signaling pathway.[39] Similar effects were induced by Dickkopf-1 (Dkk1), a Wnt antagonist;[40] other studies on postmortem brain samples of AD patients further confirmed this study.[41−43]

The risk factor for AD, apolipoprotein E (apoE4), inhibits canonical Wnt signaling;[44] disease progression is caused by a common genetic mutation in the low-density lipoprotein receptor-related protein 6 (LRP6).[45] Clusterin, a multifunctional glycoprotein, has been shown to regulate Aβ toxicity via the noncanonical Wnt/PCP-JNK pathway, a role player in hyperphosphorylation of tau and cognitive deficits.[46] In the APPswe/PS-1 transgenic model of AD, activating both canonical and noncanonical Wnt signaling by using Wnt ligands ameliorates cognitive deficits.[47] These findings indicate that alterations in the Wnt signaling pathway play a role in synaptic development and AD progression.[48] Other pathways such as inflammatory pathways, (PPAR) α and γ, and nicotinic and muscarinic ACh receptors interact with the Wnt pathway and support its neuroprotective potential against AD.[49−51]

As the number of cholinergic neurons decreases, the activity of (AChE) and choline acetyltransferase declines.[52] In hippocampal neurons, it is well-known that Aβ interacts with macromolecules present at synapses, leading to the formation of a complex which disrupts the normal synaptic activity.[53,54] It has also been found that Aβ−AChE complexes carry out more deleterious neurotoxic effects as compared to Aβ,[54] implying its critical role as an anti-AD molecule. Hyperforin, a phytochemical compound, affects the release of acetylcholine in the CNS[55] and has shown its potential to attenuate both neurotoxicity and memory deficits due to Aβ plaques. Using the same molecules, a semisynthetic derivative, tetrahydrohyperforin, was developed. This molecule was tested in the AβPP/PS1 transgenic mouse model of AD and was found effective in restoring activity of brain AChE; reduction in levels of amyloid plaques and protection toward cholinergic neurons were also observed.[55,56] The Wnt signaling pathway may be involved in translocating a subset of acetylcholine receptors (AChRs) to synapses,[57] and mutations in the Wnt ligand may also promote significant behavior deficits.[57] These findings imply that Wnt signaling is involved in synaptic plasticity. The buildup of amyloid is thought to have a crucial role in the cognitive abnormalities seen in Alzheimer's patients. Some evidence suggests that AD is linked to free radicals.[58]

In vitro investigations suggest that oxidative stress is one of the neurotoxic mechanisms of Aβ peptides. Furthermore, depletion of vitamin E has been demonstrated to increase the quantity of Aβ by inhibiting its clearance from the brain, resulting in an increased level of Aβ.[59] Peroxisomal proliferation, in combination with an increase in catalase, has previously been shown to protect cultured rat hippocampal neurons from the neurotoxicity of Aβ, improve spatial memory, protect postsynaptic proteins, and reduce hyperphosphorylation of tau.[60] Wnt signaling may also protect neurons from oxidative damage in AD. In primary hippocampal murine neurons, overexpression of Wnt1 exerts neuroprotection against DNA damage due to oxidative stress mediated by Aβ.[61] Reduced Wnt activity may also make neural cells more vulnerable to oxidative stress; in addition to that, Aβ induces overexpression of glycogen synthase kinase 3 (GSK-3), which causes phosphorylation of β-catenin and depletes it.[62] Also, increased PKC activity, which is controlled by the Wnt pathway, might result in decreased Aβ synthesis.[63] Upregulation of both DSH-1 and DSH-2 reduces NFT formation and increases neuroprotection by inhibiting GSK-3-mediated phosphorylation of tau protein.[62]

1.3. Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1α (PGC-1α) in AD. It has been proposed that mitochondrial biogenesis and sirtuins serve as an essential tool in maintaining energy homeostasis.[64] Recent discovery of Sirt1 inducing PGC-1α acetylation and controlling mitochondrial activity seems fascinating in the case of age related disorders.[65] Nonetheless, despite its popularity, the idea that Sirt1 acts in response to nutrient-sensitive variations in baseline NAD^+ levels has received little experimental support until recently.[66] Natural molecules like resveratrol, found in a number of fruits, is a Sirt1 activator. This compound stimulates mitochondrial biogenesis, although it is unclear if Sirt1 is responsible for such positive outcomes.[67] Experiments on SIRT1 knockout mice using resveratrol as a test substance demonstrated Sirt1 encourages activation of AMPK in a dose-dependent manner. These findings suggest that Sirt1 is required for AMPK stimulation and may prove beneficial for mitochondrial biogenesis.[67] The Sirt1−PGC-1α complex is thought to be linked with the development of AD. In eNOS-deficient mouse brains exposed to a high fat diet, one research found that up- or downregulation of PGC-1α modulates BACE-1 transcription *in vitro* and *in vivo*.[68] Fasting over a short period of time lowered

https://doi.org/10.1021/acsomega.3c05662
ACS Omega 2023, 8, 39964−39983

BACE-1 transcription in the brains of these mice while increasing PGC-1α expression and activity. PGC-1α inhibitory action was dependent on ligand-independent activation of PPAR through Sirt1-mediated deacetylation.[68] Sirt1−PPAR−PGC-1α direct interference with BACE-1 provides a novel noncanonical Sirt1−PGC-1α pathway in transcriptional repression in neurons in response to metabolic limitation.[68]

1.4. Mitochondrial Dysfunction in AD. The "amyloid cascade theory" has dominated our knowledge of the etiology and development of AD for over two decades. This concept proposed that the buildup of Aβ, as a result of APP cleavage, causes significant biochemical alterations in the brain of AD patients, leading to abnormalities like cognitive and memory deficits.[69] PS1 and PS2 were two more genes that were later shown to have mutations in autosomal dominant AD.[70,71] In order to perform the APP processing by the γ-secretase complex, these proteins form essential components of this complex. However, in the case of sporadic AD patients, it is surprising that no mutations in the APP or PS genes has been found.[72] The "mitochondrial cascade theory" was presented in 2004 to explain the continuous association between growing age and the risk of AD, as well as to offer a more correct explanation for the biochemical abnormalities seen in AD patients.[73] The maintenance of mitochondrial activity in AD has received a lot of attention in fundamental research. Strategies aiming at boosting mitochondrial health, preventing mitochondrial Ca^{2+} excess, minimizing membrane destabilization, and improving overall redox status are among the several techniques. Thus, there is a search for novel treatments having good effects on these targets that may prevent dysfunction of mitochondria.[74] In the APP/PS1 animal brain, dietary zeolite (micronized zeolite) supplementation demonstrated reducd mitochondrial ROS, enhanced superoxide dismutase (SOD) levels, and minimized Aβ accumulation.[75] Similarly, *Salvia sahendica* extracts reduced Aβ-induced reductions in NRF1 and mitochondrial transcription factor A (TFAM) levels.[76]

In the mouse model APP/PS1, treatment with melatonin and caffeine greatly improved mitochondrial function and the ATP level.[77] Plant derived apigenin, a flavonoidal compound, reduced the Aβ induced toxicity; however, it was ineffective in reducing APP expression and Aβ load.[78] Other beneficial effects like increased intracellular glutathione and peroxidase activities were significantly improved. Treatment of 3xTgAD animals with nicotinamide enhanced cognitive function and dynamin-like protein 1.[79] Tetrahydrohyperforin, a semisynthetic derivate of St. John's wort, has previously been shown to reduce the production of 4-hydroxynonenal adducts and caspase-3 activation in the brains of APP/PS1 mice.[56] Another research found that upregulation of PGC-1α and Sirt1 mRNA in response to physical activity leads to increased mitochondrial DNA.[80] Exercise also regulates the brain mitochondrial redox balance, and persistent exercise restores apoptotic signaling in the AD brain.[81] Further, polyphenols have been found to reduce membrane disruption produced by the Aβ42 peptide and tau-441 proteins, indicating that aberrant protein aggregates may be interfering with the mitochondrial membrane.[82] Through the activation of oxidative phosphorylation, the regulation of intracellular NAD^+ levels in human brain cells may also be critical for the preservation of cellular viability during situations of chronic oxidative stress and mitochondrial malfunction.[83] NAD^+ is also strongly linked to the PARP, a DNA-binding family of enzymes.[84−86] PARP activation contributes to DNA repair and proper cellular function under physiological settings.[87] Under pathological conditions, however, PARP activation causes an increase in NAD^+ turnover, a decrease in ATP synthesis, and the stoppage of all energy-dependent processes, as well as cell death.[88,89] Cellular damage may be exacerbated by maintaining intracellular NAD^+ pools. PARP-induced astrocyte death has been found to be reduced by NAD^+ therapy.[86] NAD^+ may potentially protect neurons from damage by increasing energy metabolism and/or promoting sirtuin activity.[90]

2. PLANT MATERIALS AND DERIVED PHYTOCHEMICALS FOR TREATMENT OF AD

2.1. Resveratrol. There have been several studies investigating the potential role of resveratrol in AD. This natural compound is found in grapes, berries, and red wine. Due to its multipotent health benefits, studies are being carried out to look for its neuroprotective potential.[91] Like curcumin, it possesses antiamyloidogenic characteristics and reduces the amount of intracellular Aβ peptides without affecting Aβ-producing enzymes or β-secretase.[92] Protein kinase C activation by resveratrol protects SH-SY5Y neuroblastoma cells and hippocampal neurons against Aβ-mediated damage.[93] Resveratrol protects neurons and microglial cells by scavenging free radicals.[94] Inhibiting COX-2 and nitric oxide synthase expression, resveratrol reduces NF-κB activity.[95,96] Numerous animal studies have indicated that *trans*-resveratrol prevents cognitive decline and spatial memory loss.[97−100] Intracerebroventricular (icv) colchicine-induced cognitive impairment and oxidative stress in rats were reversed after chronic resveratrol therapy.[101] In 119 patients, resveratrol was used to treat AD. For a period of 52 weeks, each subject received 1 mg of resveratrol every day. The therapy reduced MMP-9 levels and increased MDC, IL-4, and FGF-2 levels in the CSF compared to the placebo group.[102] Patients' ADAS-Cog, MMSE, and activities of daily living scale (ADLS) scores all improved significantly after 12 months of treatment with a combination of resveratrol, dextrose, and malate. In addition, resveratrol was shown to be safe, efficacious, and tolerable.[103,104]

2.2. Curcumin. Turmeric, known as "golden spice", commonly used in Indian and Middle Eastern cooking style, contains a natural compound called curcumin. Similar to resveratrol, it has been investigated for possible advantages in treating a range of ailments, including AD.[105,106] Curcumin has anti-inflammatory, antitumor, wound healing, and antibacterial properties.[107,108] Amyloid plaques and inflammatory cytokines are both inhibited by curcumin, similar to the JNK-mediated pathway.[109] Curcumin (400 mg) was evaluated by Chin et al.[109] in 60 persons aged 60−65 years for its acute and chronic effects on mood and cognition. Acute therapy with a single dose significantly enhanced a participant's working memory. Curcumin (90 mg twice day for 18 months) was studied by Small et al.[110] in 40 persons for its impact on memory and the production of amyloid plaques and tau tangles. Apart from improving memory and concentration, curcumin also reduced the amyloid and tau buildup in the hypothalamus region.[110]

2.3. Catechins in Green Tea, or Polyphenols. Catechins are polyphenolic phytochemicals found in the leaves of *Camellia sinensis*.[111] Several studies have shown that green tea extract can safeguard neurons from Aβ-induced damage in cellular models of neurodegeneration.[112] A reduction in Aβ production in APP-695 AD mice and also alleviation of the Aβ load in Tg2576 have been demonstrated.[113] Catechins in green tea seem to be more potent antioxidants than vitamin C, vitamin E, or α-

https://doi.org/10.1021/acsomega.3c05662
ACS Omega 2023, 8, 39964−39983

tocopherol.[114,115] Catechins scavenge ROS and lipid peroxidation, and they also reduce cytokine-induced inflammation and COX-2 expression in response to IL-1 and Aβ.[116−118] There was less memory loss in the group receiving catechin-containing water than in the group receiving plain drinking water after (icv) injection of Aβ.[119] A 7 year follow-up study of 7139 Chinese participants was conducted in 2012 to see if there was a relationship between tea drinking and cognitive performance. As a measure of cognitive functioning, a verbal fluency standardized test was employed. Regular tea consumption has been linked to improved cognition.[120] As part of another study, researchers investigated the link connecting tea drinking and the evolution of cognitive deficits. The scoring of the Mini Mental State Examination (MMSE) was being used to assess the results of 1438 community-living Chinese adults in this study. Tea intake in higher amounts has been shown to be linked to a reduced incidence of cognitive deficits and impairment.[121] Similarly, in 2017, Gu et al. examined the link between intake of tea and cognitive decline in adults. There was a positive correlation between cognitive functioning and tea intake in this society-based investigation.[122]

2.4. Ellagic Acid. Ellagic acid, a polyphenolic natural product obtained from various fruits and nuts, is a promising neuroprotective agent that exhibits anti-inflammatory and antioxidant properties.[123−125] Recent research has shown that ellagic acid can affect a wide range of cell signaling pathways. As a result, neurodegenerative disease may be delayed or slowed down. Because of its multiple neuroprotective properties, such as its iron chelating and free radical scavenging abilities and its potential to activate cellular signaling cascades and to lessen mitochondrial dysfunction, ellagic acid can also be employed in pharmaceutical preparations to manage neuronal disorders including AD.[126]

2.5. Epigallocatechin-3-gallate. Epigallocatechin-3-gallate (EGCG) is the main catechin constituent in green tea, and it is employed in the management of carcinoma, cardiovascular (CVS), and CNS disorders due to its antioxidative potential.[127,128] At 10 mg/kg oral dose, EGCG has been reported to block AChE, as well as increase the activity of glutathione peroxidase. The nonamyloidogenic α-secretase proteolytic pathway was promoted by EGCG in Tg2576 mouse neurons transfected with the human "Swedish" mutant APP.[129] This reduced the production of Aβ in these cells and in primary neurons. With fish oil, the bioavailability of EGCG was enhanced and the synergistic effect of EGCG inhibited the accumulation of Aβ in Tg2576 mice.[130] Numerous studies have found that EGCG has multiple neuroprotective properties, such as inhibiting α-secretase and enhancing memory formation,[131] protecting neurons from inflammation and activating astrocytes,[132] and so on. Although more clinical evidence is needed to prove EGCG's therapeutic uses, it may exhibit a key role in the treatment of AD.

2.6. Nicotine. Current research suggests that nicotine possesses protective effects against neurodegenerative disorders.[133] The potential of nicotine in blocking Aβ-mediated caspase activity and programmed cell death, lowering the generation of free radicals as well as enhancing intracellular calcium through nicotinic receptors,[134] and averting mitochondrial abnormalities has been already acknowledged.[135] To reduce β-amyloidosis in transgenic rodents, it can effectively reduce the Aβ deposit, copper, and zinc concentrations.[136,137] The activity and level of iNOS decreased in mice treated with nicotine, which might be linked to reduced NF-κB stimulation and MAP kinase expression. Moreover, nicotine treatment in an AD rat model showed that Aβ-induced declines in learning and short-term cognition could be prevented by nicotine.[138] It is not possible to use nicotine as an agent to treat AD; however, these data imply that nicotine receptors might be a possible therapeutic target for AD.

2.7. Rosmarinic Acid. Rosmarinic acid (Lamiaceae genera) has numerous pharmacological properties, involving anti-inflammatory, antioxidant, neuroprotective, and anticancer actions.[139,140] In rats, rosmarinic acid (intraperitoneally at dose 0.25−4 mg/kg) substantially decreased impairments caused by Aβ, primarily by impeding NF-κB and TNF-α.[141−143] Additionally, this acid was found to constrain tau protein, as well as to shield neurons against Aβ-induced cytotoxicity.[144] As an anti-inflammatory and antilipid peroxidant, rosmarinic acid has already demonstrated enhancing short-term spatial cognition in rat models. Rosmarinic acid cannot be used to treat AD until more clinical trials are performed.[145,146]

2.8. Docosahexaenoic Acid (DHA). Polyunsaturated fatty acids (PUFA), namely docosahexaenoic acid, are included in a popular health supplement (DHA), which has been shown to have multiple effects on neurodevelopment and neurofunction.[147] AD incidence is negatively associated with plasma DHA concentrations in epidemiological studies,[148,149] which show that older adults who consume more DHA have a lower risk of developing the disease. Additional studies have shown that the neuroprotective activities of DHA and polyunsaturated fatty acids, involving antiapoptotic activity, antioxidants, and anti-inflammation, and including neurogenesis, can help prevent the progression of AD symptoms.[150,151] There is scientific evidence that backs the lack of polyunsaturated fatty acids is associated with an upsurge in oxidative stress in the brain of transgenic mice.[152] Polyunsaturated fatty acids are said to increase glutathione concentrations and also reduce NO production and iNOS expression.[153,154] Taking DHA supplements can assist in lessening oxidative anxiety and improve AD's symptoms, making it a useful food supplement to combat the disease.

2.9. Prosapogenin III. Prosapogenin III is a steroidal saponin compound found in the roots of various plants including *Liriope platyphylla*. It possesses a variety of actions such as antiasthmatic, neurogenic, and antiallergic effects as well as prevention of diabetes.[155] The neuroprotective efficacy of *L. platyphylla* extract on SH-SY5Y cells using hydrogen peroxide (H_2O_2) mediated damage was investigated.[156] The results showed neuroprotective effects of an extract via preventing the phosphorylation of the p38 protein triggered by H_2O_2.[156] Prosapogenin III also has anti-inflammatory and antioxidant capabilities, which may enhance its neuroprotective benefits. To fully comprehend its underlying mechanisms of action and potential use for treating AD, further study may prove rewarding.

2.10. Physostigmine. Physostigmine is a naturally occurring alkaloid compound found in the seeds of the *Physostigma venenosum* plant, also known as the Calabar bean. Physostigmine has been found to enhance cognitive function in people with AD, because it readily penetrates the blood−brain barrier (BBB).[157] Physostigmine improved learning in rats to prevent damage to the brain from oxygen deprivation.[158] Many synthetic physostigmine derivatives have been developed as a result of these hopeful discoveries, and some have reached clinical trials for the treatment of AD. In phase IIIb clinical studies,

https://doi.org/10.1021/acsomega.3c05662
ACS Omega 2023, 8, 39964−39983

rivastigmine is the most therapeutically active derivative. This drug blocks AChE G1 in the hippocampus and cortex, which is important for cognition in AD.[159] The clinical pharmacokinetics of physostigmine were evaluated in a randomized, double-blind, placebo-controlled study including nine Alzheimer's patients. Physostigmine inhibited butyrylcholinesterase in a dose-dependent manner. Five people who received butyrylcholinesterase inhibitors saw an improvement in their memory and cognition.[160] Researchers in another study delivered the antidementia drug physigmin to 12 individuals with AD over the course of 3−5 days, at dosages of 0, 0.5, 1, 2, and 2.0 mg every 2 h. There was a significant influence on cognitive behavior in 7 of the 10 subjects.[161]

2.11. Galantamine. *Galanthus woronowii* bulbs, which belong to the Amaryllidaceae family, are used to make galantamine. It was first discovered in 1952 as a tertiary alkaloid. Memory loss and cognitive impairment in Alzheimer's patients may be treated with AChE inhibitors.[162] Galantamine was the subject of seven large-scale, placebo-controlled investigations in people with AD. Galantamine was shown to be both safe and effective in these investigations.[163] Alzheimer's patients have found galantamine to be both beneficial and safe. A randomized, double-blind, placebo-controlled experiment examined galantamine's efficacy and safety in treating AD. The study comprised 653 AD individuals who had symptoms ranging from moderate to severe. Compared to the placebo group, the galantamine group showed superior cognitive abilities after 6 months of treatment. There was a significant difference between the test and placebo groups when it came to the severity of the dementia symptoms they experienced. Galantamine's effects on mild to moderate Alzheimer's patients were studied in a 5 month, placebo-controlled, double-blind study. Galantamine-treated individuals showed higher ADAS-Cog scores after 5 months of therapy. Galantamine has been shown in studies to enhance cognitive and behavioral performances at doses of 16 and 24 mg/day.[164]

2.12. Berberine. There is a lot of berberine, an alkaloid of the benzylisoquinoline group, in the roots, rhizomes, stem, and barks of plants in the family of flowering plants known as Ranunculaceae. Neuroprotective and cardiac protective properties, as well as antitumor and anti-inflammatory and antibacterial properties, are all found in this compound.[165] Berberine works as a neuroprotective agent by suppressing the voltage-gated potassium current.[166] In Alzheimer's patients, the cholinergic system is stimulated, which improves cognitive function. *o*-Chlorothiophenyl berberine, which inhibits AChE and BuChE, is one of several berberine hybrids and analogues developed. Antioxidant properties may also be seen in these substances.[167] Plants like *Berberis aquifolium* (Oregon grape), *Berberis aristata* (tree turmeric), *Berberis vulgaris* (barberry), *Coptis chinensis* (Chinese goldthread), *Hydrastis canadena* (goldenseal), *Phellodendron amurense* (Amur cork tree), and *Tinospora cordifolia* contain the isoquinoline alkaloid berberine (BBR).[168] There is evidence that berberine possesses antioxidant, AChE and butyrylcholinesterase inhibition, cholesterol-lowering, and monoamine oxidase inhibitory effects.[169] Researchers found that BBR inhibited Aβ-induced increase in IL-6, COX-2, and iNOS expression[170] as well as tau hyperphosphorylation and the production of Aβ in vitro.[171−173] BBR reduced NF-κB in microglia by blocking the PI3K/PKB and MAPK pathways.[13,174] It has been observed that the use of BBR (100 mg/kg), which promotes learning and long-term spatial memory retention in Tg mice and decreases the amount of C-terminal APP fragment in N2a murine neuroblastoma, reduces APP and tau protein hyperphosphorylation through AKT/GSK3 signaling.[175]

2.13. Huperzine. Discovered from the club moss *Huperzia serrate*, huperzine is an alkaloid sesquiterpene. In Chinese folk medicine, it is used to treat cognitive deficits, inflammation in the circulatory system, and fever. Huperzine has been shown to be safe for both humans and animals in several studies.[176] Studies in animals and cells have shown that it can be used to treat AD.[177,178] According to a study on rats, huperzine increased the rats' cognitive memory and reduced free radical toxicity and Aβ fragment aggregation in a rat model of AD are prevented by the antioxidant huperzine A.[179] For example, huperzine is less toxic than synthetic AChE inhibitors like donepezil and tacrine, and is more selective for AChE than for BuChE, according to a multicenter, double-blind clinical research.[180] For 12 weeks, a clinical study with 200 patients randomly assigned 100 patients to either 400 g of huperzine A or a placebo. One hundred individuals received 400 g of huperzine A daily for 12 weeks, while the other 100 received a placebo in a randomized, double-blind study.[181] Huperzine's safety and efficacy were evaluated in a multicenter, prospective, double-blind, placebo-controlled, randomized research. Huperzine was given to 50 mild Alzheimer's patients for 8 weeks, whereas a placebo was given to 53. This included the Wechsler memory, Hasegawa dementia, and Mini Mental State Examination assessment scales. According to the study, huperzine improved the mental health of 58% of the participants.[182] One of *H. serrate*'s sesquiterpene alkaloid compounds, huperzine A (HSA), was discovered in this firmoss.[183] Inflammation and fever were treated with *H. serrate* preparations in traditional Chinese medicine, and memory was improved with *H. serrate*. For example, huperzine A, like rivastigmine and donepezil, blocks AChE. It also inhibits the action of apoptotic factors and NGF in the brain. Huperzine A (0.1 mg/kg) has been shown to improve the Morris water maze test results in Tg mice. The activation of β-secretases, the PKC/MAPK pathway, and phosphorylated GSK-3 are thought to be responsible for these effects.[184,185] Another possible mechanism by which huperzine A exerts its neuroprotective effects is by inhibition of the NMDA receptor and the potassium current.[186] Subcellular Aβ accumulation may be reduced by huperzine A, according to a study published in 2013.[187] Using tacrine−huperzine A hybrids developed by Camps and associates, they were able to block AChE and reduce Aβ-induced oxidative damage.[188,189] Tacrine−huperzine A hybrids were shown to have fewer side effects in clinical testing than commercial AChE inhibitors,[190] making them an asset in the search for new treatments for AD.

2.14. Ginger. In order to make ginger, you need the rhizomes of *Zingiber officinale*, which is a member of the Zingiberaceae family. For example, zingiberene is one of the primary active ingredients in gingerols.[191] With the use of colorimetric analysis, its ability to inhibit AChE has been demonstrated *in vitro*.[192] Inhibition of AChE by *Z. officinale* causes a buildup of ACh in the synapses. Stimulation of the cholinergic pathway improves cognitive functioning in the patients of AD. The lipid peroxidation that occurs as a result aids in AD prevention.[193] Antioxidant effects are due to the inhibition of the acetylcholinesterase enzyme, which prevents excess NMDA receptor activation and thus reduces lipid peroxidation.[194] Traditional medicine has long employed ginger extracts, ginger tea, and ginger inclusions in Alzheimer's therapy. Antioxidant as well as AChE-inhibiting actions of ginger's active components have recently been discovered. ACh levels are

https://doi.org/10.1021/acsomega.3c05662
ACS Omega 2023, 8, 39964−39983

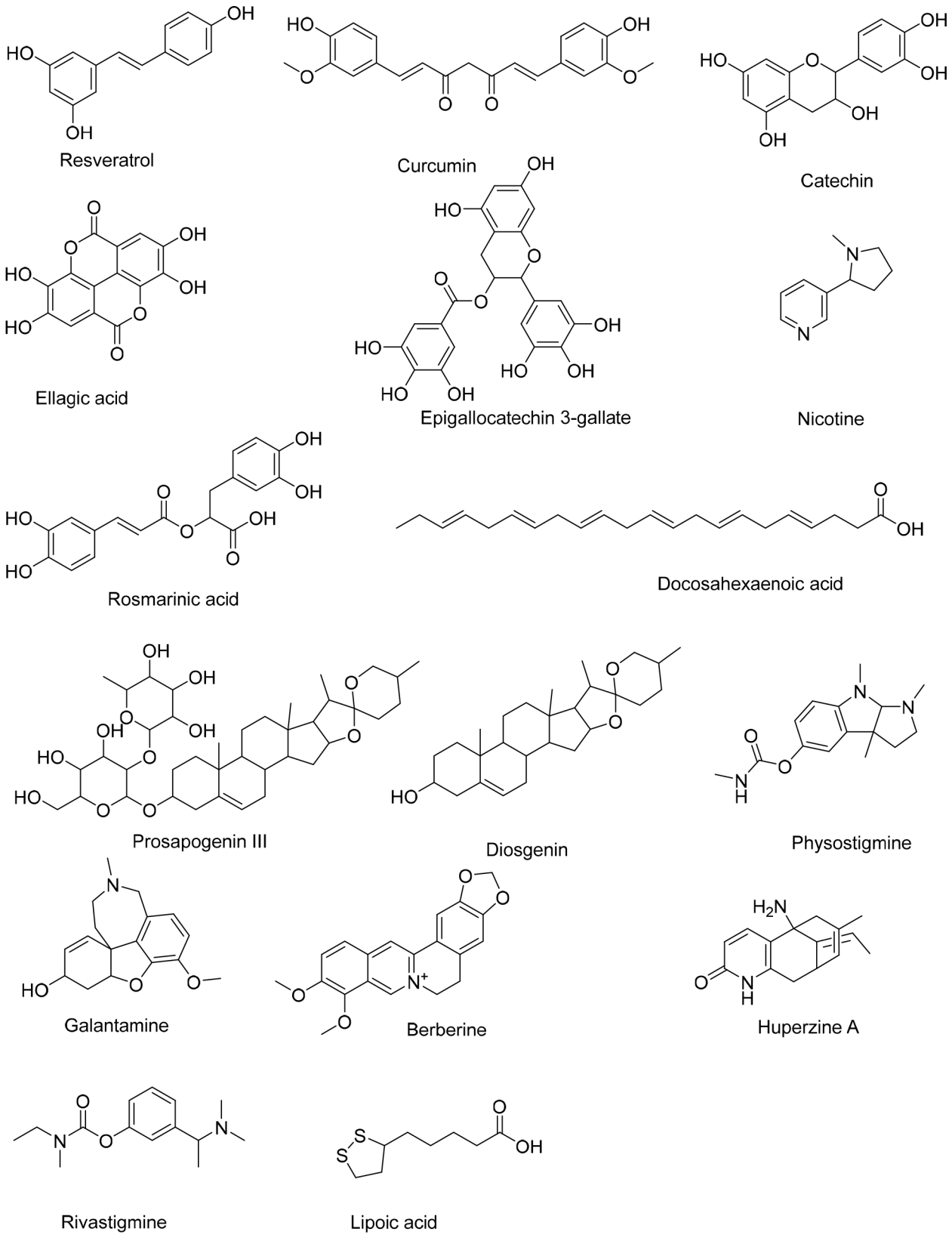


Figure 2. Chemical structures of plant derived phytochemicals for the treatment of Alzheimer's disease.

restored in the brain by ginger extracts, which prevent the quinolinic acid and sodium nitroprusside modulated membranous lipid peroxidation associated with AD.[192] In a secretase test and rodent animal experiments, the reduction amination compound of ginger oil extracts with nitrogen demonstrated a significant antagonistic effect.[195] *Z. officinale* is a popular ingredient in food supplements because of its use in ginger tea. When it comes to *Z. officinale*, the most important constituents are bisabolene (found in large amounts), gingerol, zingiberene, and monoterpenes. *Z. officinale* extracts have been reported to

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ACS Omega 2023, 8, 39964−39983

Table 1. List of Phytochemicals, Plant Materials, Their Source and Mechanism of Action for the Treatment of Alzheimer's Disease

no.	compound	molecular weight	plant source	mechanism	ref
1	resveratrol	228	grapes, berries, and red wine	inhibits COX-2 and nitric acid synthase expression	96, 220
2	curcumin	368	*Curcuma longa*	increases HSP production and reduces amyloid and tau buildup in the brain's amygdala and hypothalamus	108, 221
3	catechins	–	dried leaves of *Camellia sinesis*	protects neurons against Aβ-induced impairment *in vitro*	222
4	ellagic acid	302	derives from ellagitannins found in some nuts, fruits, etc.	activates cellular signaling cascades and minimizes mitochondrial dysfunction	223
5	epigallocatechin-3-gallate	458	extracted from green tea	inhibits AChE and α-secretase, enhances memory formation	224
6	nicotine	162	alkaloid found in the nightshade family of tobacco plant belonging to Solanaceae	blocking Aβ-mediated caspase activity and programmed cell death, lowering generation of free radicals as well as enhancing intracellular calcium through nicotinic receptors	225
7	rosmarinic acid	360	*Rosmarinus officinalis*	substantially decreases impairments caused by Aβ, primarily by impeding NF-κB and TNF-α	226
8	docosahexaenoic acid (DHA)	328	cold-water fish	acts by increasing glutathione concentrations and also reduces NO production and iNOS expression	227
9	prosapogenin III	722	*Liriope platyphylla*	activation of macrophages by restricting MAPK/NF-κB	228
10	physostigmine	275	Calabar beans	blocks AChE G1 in the hippocampus and cortex	229
11	galantamine	287	*Galanthus woronowii*	AChE inhibitor	230
12	berberine	336	*Berberis aquifolium*	inhibits AChE, butyrylcholinesterase, and MAO; also suppresses voltage gated potassium current	105
13	huperzine A	242	*Huperzia serrate*	inhibits NMDA receptor and potassium current	231
14	ginger	568	rhizomes of *Zingiber officinale*	inhibits the acetylcholinesterase enzyme, which prevents excess NMDA receptor activation and thus reduces lipid peroxidation	232
15	anthocyanins	207	blueberries	increases NF-κB and age-related proteins	233
16	rivastigmine	250	Calabar beans	inhibits butyrylcholinesterase	234
17	withanoside	470	*Withania somnifera*	reduces neuronal degeneration	235
18	lipoic acid	206		increases ACh production and hinders free radical hydroxyl chelation	236

have multiple activities in the central nervous system (CNS),[192,196] including inhibition of AChE, lipid peroxidation, NMDA receptors, and reactive oxygen species. There is still a need to conduct clinical trials with *Z. officinale*.

2.15. *Ginkgo biloba*. To make *Ginkgo biloba* extract, the dried green leaves of the plant are pounded into a powder and infused with alcohol. The plant belongs to the Ginkgoaceae family. Writings from 2800 B.C. describe its use as a memory enhancer[197] and antioxidant powerhouse.[198] Flavonoids and terpenoids in the leaf extract provide neuroprotection.[199] Maintaining a redox environment lowers ROS levels. Additionally, *Ginkgo biloba* enhances the enzymes GSH and GCS, which are responsible for reducing glutathione (GSH), and γ-glutamyl cysteinyl (GCS) *Ginkgo biloba* extract was investigated for 24 weeks in a randomized, controlled trial to see whether it had any impact on memory. A total of 404 people (aged 51) with moderate to severe AD or vascular dementia were included in the study. *Ginkgo biloba* extract significantly improved cognitive performance, neuropsychiatric symptoms, and functional abilities in patients with both AD and other forms of dementia.[200] In a recent study, Rapp et al. examined the therapeutic effect of EGb in the treatment of 189 patients with 240 mg/kg EGb per day and positive control groups of 5−10 mg/kg donepezil for 12 months. Neurobehavioral and pathological results were shown to be somewhat improved when compared to donepezil.[201] More research has shown that EGb has beneficial therapeutic effects on a variety of clinical indicators and biomarkers associated with AD.[202,203]

2.16. Blueberries. One of the most popular fruits in the world is *Vaccinium angustifolium*, and it contains methyl butanoate as well as the aromatic compound linalool.[204] The blueberry's capacity to improve memory and focus has been shown in several studies. Blueberry supplementation has been shown to increase cognition and motor coordination in animals.[205] For a period of 16 weeks, consuming wild berry juice improved memory, cognition, and recall of word lists.[206] The striatum, where reversal learning takes place, is targeted by blueberry polyphenols. Antioxidant-rich anthocyanin, present in the hippocampus and the neocortex of aged rats, was observed to accumulate.[207] This region is in charge of the brain's ability to think. Stress signaling was activated in COS-7 cells by transfecting oxidative stress sensitive muscarinic receptors (MAChRs) into the cells, which were subsequently mixed with C-2 ceramide cells. Lowered oxidative stress in cells was reduced by pretreatment with blueberry extract.[208] The expression of NF-κB, an age-related protein that increases with age and oxidative stress, has been demonstrated to be reduced by blueberry-rich diets.[209] Antioxidant properties of anthocyanins in blueberries have been shown in studies on rodent brains and neurons. Wild blueberry juice was administered to nine elderly people with early memory loss over a period of 12 weeks. Memory and cognition in the blueberry juice group were superior to those of the placebo group, with greater learning and word list recall.[210] The antioxidant, anti-inflammatory, and antiapoptotic activities of polyphenols, especially anthocyanins, were shown to be particularly potent in the research. As a whole, these characteristics help to enhance neuronal signaling as well as learning and memory capacity. A well-designed clinical study based on this clinical evaluation may prove its therapeutic effectiveness.

2.17. *Withania somnifera*. Ashwagandha or Indian ginseng is the common name for the Solanaceae plant *Withania somnifera*. The root of this plant is the most often used part of the plant.[211] Sitoindosides, withaferin, glycowithanolides, and withanoside are found in it. It is withanoside[212] that is linked to *Withania*'s neuroprotective properties. It reduces memory loss

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ACS Omega 2023, 8, 39964−39983

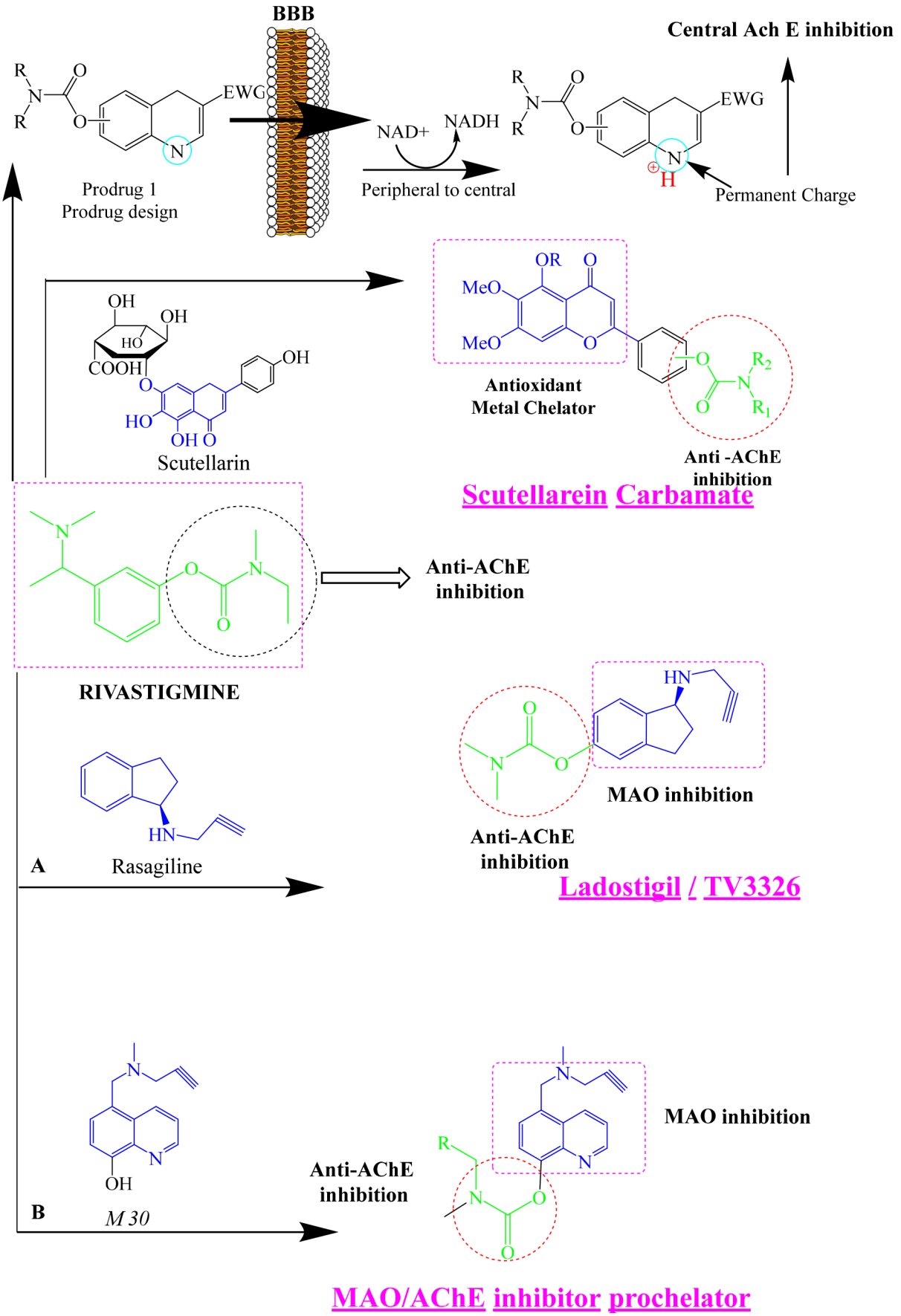

Figure 3. Rivastigmine MTDLs, in which rivastigmine was combined with rasagiline, synthetic M30, and scutellarin (natural) sources to demonstrate a multivariate mode of action, as well as a bio-oxidizing methodology for efficient drug diffusion into the CNS across the BBB.

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ACS Omega 2023, 8, 39964−39983

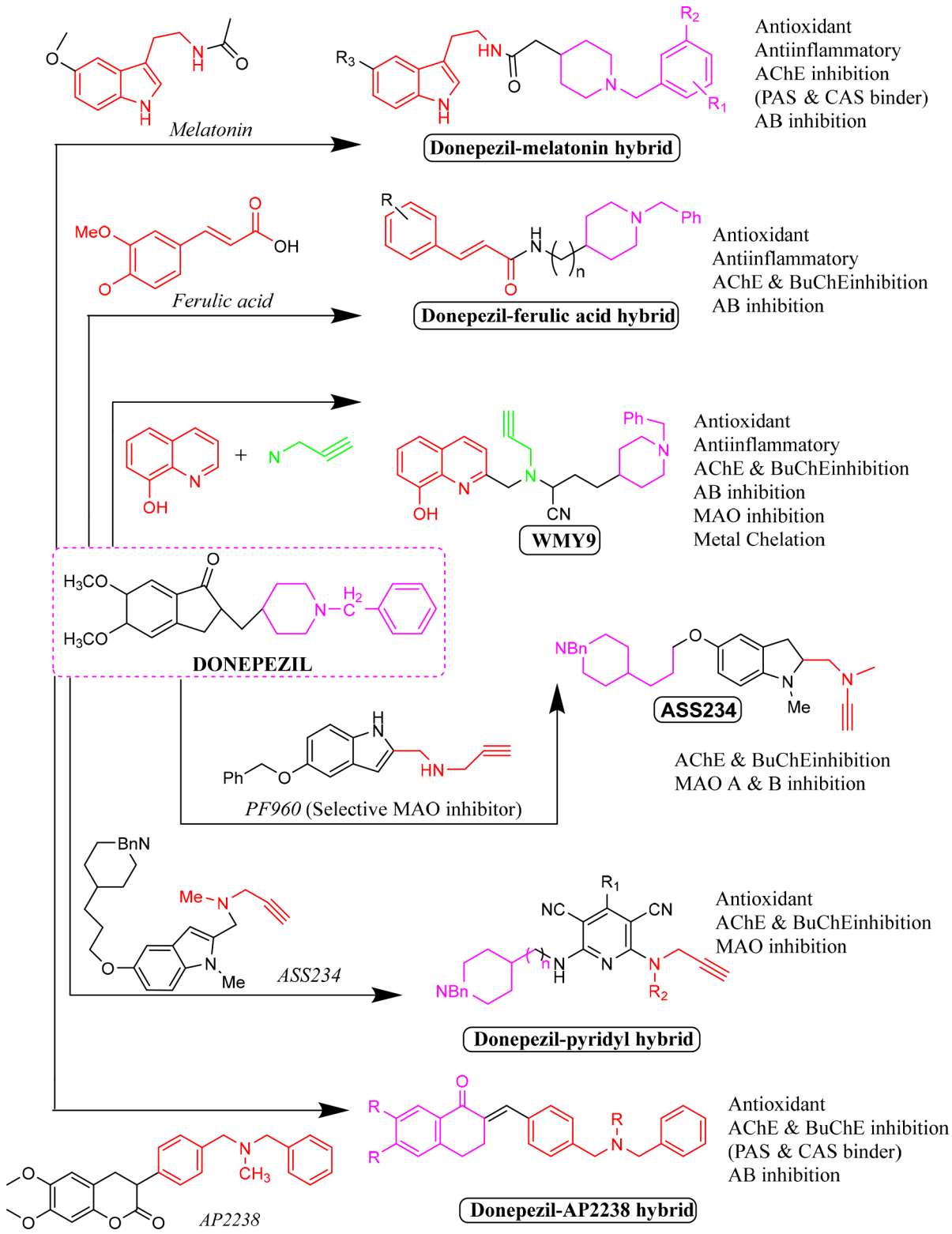

Figure 4. Specifics of multiple donepezil MTDLs in which donepezil was mixed with synthetically derived (propargyl, metal chelator, PF960, ASS234, and AP2238) and naturally derived (melatonin and ferulic acid) drugs to demonstrate a multivariate mode of activity.

as well as axonal degeneration in rats that have been exposed to Aβ.[213] Neuron and synaptic healing are assisted by the metabolization of withanoside into sominone after therapy.[214] Axon and dendrite development were boosted in rats' cortical neurons after they were cultured in Aβ for 4 days and then treated with sominone and anoside. An extract containing sitoindosides and withaferin reversed this effect.[215] Interleukin 1, which has been linked to plaque formation and neurodegeneration, may be reduced by using *W. somnifera* root extract.[216] People with mild to severe cognitive impairment were randomly assigned to receive either *W. somnifera* root extract (300 mg twice day) or a placebo. Ashwagandha root extract

https://doi.org/10.1021/acsomega.3c05662
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treatment for 8 weeks increased cognitive performance compared to a placebo, according to the study.[217]

2.18. Lipoic Acid. α-Lipoic acid, or lipoic acid, is a naturally occurring cofactor for the enzymes pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, which are both mitochondrial enzymes. Animal caprylic acid was used to create this supplement.[218] By activating ChAT and enhancing glucose absorption, lipoic acid may increase the production of acetylcholine. The additional physiological properties of lipoic acid make it effective in treating different central nervous system disorders. TNF-α and INOS are two inflammatory proteins that may be reduced by lipoic acid.[219]

Figure 2 includes the chemical structures of some of the plant derived phytochemicals in this review used for the treatment of AD. Phytochemicals, plant materials, their sources, and mechanisms of action for the treatment of AD are summarized in Table 1.

3. SEMISYNTHETIC MULTITARGETED INHIBITORS FROM NATURAL SOURCES AS POTENTIAL ANTI-ALZHEIMER DRUG CANDIDATES

3.1. Derivatives of Rivastigmine. Carbamylation of AChE's serine-OH is accomplished by rivastigmine (RVS), which binds to the catalytic anion site by the aid of tertiary amines.[237] Figure 3 shows the effective delivery of RVS into the BBB using a bio-oxidizing method. Administration of uncharged medications has both peripheral and central side effects, and their therapeutic application has been severely restricted since charged pharmaceuticals are known to be impermeable to the BBB. Since 1,4-dihydroquinoline has a structural resemblance to RVS, it was chosen for this project.[238] This analogue has an enamine nitrogen that is nonprotonable and so readily penetrates the BBB, oxidized to form charged ammonium metabolites, and permits its attachment to the catalytic anion site.[238] The conversion of NAD^+ to NADH is the mechanism for oxidation.[239] At the C-3 position, the electron-withdrawing group (EWG) was linked in order to avoid this oxidation, which is highly prevalent in the periphery area.[240] As a result, if a medicine can be successfully delivered via this method, it reduces adverse effects and boosts the drug's effectiveness. The combination of scutellarin and rivastigmine has been described by Sang et al.[241] In addition to being a powerful flavone, scutellarin is also known to have properties notably anti-inflammatory, antioxidant, and ion-chelating and also to block the development of Aβ. The downsides of these medicines include limited solubility and bioavailability, as well as BBB impermeability.[242] When these medications are combined with rivastigmine, they show better pharmacokinetic and pharmacodynamic aptitude in terms of Alzheimer's antiaction.[241] Moreover, rasagiline (TV3326), an established MAO-B blocker, and its derivative, M30, which acts as an antioxidant, as well as an iron chelator in combination with RVS have been studied by Weinreb et al.[243] In a study combining RVS with this medicine, the anti-Alzheimer antidepressant effects were improved, while RVS had no significant adverse effects when delivered alone.[243]

3.2. Derivatives of Donepezil. A popular anti-Alzheimer medication with great selectivity for AChE's binding sites, CAS as well as PAS, is donepezil (DNP).[244] While the benzyl group links well with the amino acid Trp-78 at the CAS binding site, the indomethoxy group interacts with PAS amino acids Tyr-70 and Trp-279.[245] H-bonding and AChE inhibition were discovered to be caused by the indanone pharmacophore's inclusion of carbonyl functional groups (Figure 4).[245] As a consequence, it was revealed that AChE PAS is significant in the formation of Aβ. The therapy and management of AD might be improved by using a medication like DNP, which binds to both CAS and PAS. As previously stated, AD is complex in origin, with ROS and inflammation playing a significant part in its development. Computer-aided drug designing has been used to mix DNP with other polyvalent naturally or synthetically derived medications in order to produce MTDLs, so it might have an effect that is multifactorial in nature and therefore be effective. For example, curcumin, trolox, and ferulic acid have been shown to have neuroprotective properties but lack the necessary pharmacokinetics and pharmacodynamics for therapeutic use. Figure 4 shows that these medicines were coupled with DNP, which resulted in significant polyvalent action.[244−248] In the same way that a natural medication was manufactured and coupled with DNP, synthetic medicines were also created. DNP and its propargylamine pharmacophore, ASS234, displayed inhibition of both MAO-A and MAO-B and also inhibition on AChE and BuChE enzymes.[249] DNP-pyridyl hybrid, on the other hand, was synthesized by combining ASS234 with DNP, and it demonstrated an enhanced antioxidant activity above ASS234 alone. A strong synthetic chemical with a similar mode of action to DNP is AP2238. Dual-mode AChE inhibition and A inhibition properties were observed in the hybrid created from DNP-AP2238, which had been fused with the *N*-methylbenzyl amino moiety of AP2238.[250]

3.3. Derivatives of Tacrine. An AChE antagonist known as tacrine was licensed for use in the treatment of AD. Pharmacophores are essential for the drug to work. However, hepatotoxicity forced its removal.[251] Efforts were undertaken to improve its effectiveness and minimize its side effects. Nimodipine, nilvadipine, and huperin A are included in the 2018 formulation of tacrine. Antioxidant and anti-inflammatory nimodipine is often used in subarachnoid hemorrhage (SAH).[252] Tacripyrine was synthesized by combining tacrine with 1,4-DHP nimodipine. It reduces Ca^{2+} levels and inhibits AChE activity.[253] A CCB (antihypertensive) medication, nilvadipine, has been shown to be safe and effective in the treatment of AD.[254] SCR1693, a GSK-3 and A inhibitor created by combining tacrine and nilvadipine, improves memory deficits by raising BDNF and ACh levels.[253] A clinical trial (NCT02017340) is now examining nilvadipine's ability to combat AD in 500 persons. Huperin A (hupertacrine) was developed in the United States and China as a supplement as well. Hupertacrine's antiaction against AD was enhanced.[253] Antioxidant and neuroprotective activities of cinnamic acid, its derivatives, and tacrine were shown to boost the inhibitory effectiveness of AChE by Quintanova et al.[255] Moreover, the compounds were also potent antioxidants, anti-inflammatory, and Aβ inhibitors.[255] Keri et al.[255] and Mantoani et al.[256] also combined tacrine with sulfanilamide and donepezil to generate a triazole−quinoline hybrid, respectively. The MTDLs and tacrine conjugates have not yet been studied in clinical trials.[256] Curcumin permeability and efficacy were improved by tacrine-curcumin hybrids and other semisynthetic medications while tacrine side effects were reduced.[257] The cholinergic system may be utilized to treat and regulate AD, according to current research. Tacrine analogues and hybrids with new classes of multifunctional bioactive properties, such as melatonin, hydroxyquinoline, or thioflavin, have also been discussed.[258]

https://doi.org/10.1021/acsomega.3c05662
ACS Omega 2023, 8, 39964−39983

4. CONCLUSION

AD is one of the most well-known neurodegenerative conditions, and it has a significant impact on patients' overall quality of life. Its care and treatment impose a significant socio-economic cost. New data suggests that various confounding factors, in addition to amyloid-β and tau protein, are involved in the etiology of AD. As a result, AD is thought to have multiple causes. However, available pharmacotherapeutics have thus far been predicated on the one-drug, one-target concept, that they have been unable to exhibit meaningful therapeutic effects. As a result, the focus has shifted to an MTDL approach, in which the pharmacophore of an approved drug is fused or conjugated with other natural or synthetic moieties to create hybrid molecules that moderate multiple targets and signaling pathways at the same time, resulting in a significant therapeutic effect in AD. As a result, this review article discusses the multiple signaling pathways involved in the pathogenesis of AD, as well as the therapeutic effects of various natural products, their pharmacological aspects, and the details of various MTDLs derived from synthetic and natural sources.

AUTHOR INFORMATION

Corresponding Authors

Reyaz Hassan Mir − *Pharmaceutical Chemistry Division, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar 190006 Jammu and Kashmir, India*; orcid.org/0000-0002-6825-1338; Email: mirreyaz.phscct@uok.edu.in

Mubashir Hussain Masoodi − *Pharmaceutical Chemistry Division, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar 190006 Jammu and Kashmir, India*; Email: mubashir@kashmiruniversity.ac.in

Authors

Abdul Jalil Shah − *Pharmaceutical Chemistry Division, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar 190006 Jammu and Kashmir, India*

Prince Ahad Mir − *Khalsa College of Pharmacy, Amritsar 143002 Punjab, India*

Mohd Adnan − *Department of Biology, College of Science, University of Ha'il, Ha'il 81451, Saudi Arabia*

Mitesh Patel − *Research and Development Cell, Department of Biotechnology, Parul Institute of Applied Sciences, Parul University, Vadodara 391760, India*

Mudasir Maqbool − *Pharmacy Practice Division, Department of Pharmaceutical Sciences, University of Kashmir, Srinagar 190006 Jammu and Kashmir, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c05662

Author Contributions

Abdul Jalil Shah, Reyaz Hassan Mir, and Mubashir Hussain Masoodi contributed to the study concept and design, collected/analyzed data, project administration, and drafted the original manuscript. Mohd Adnan, Mitesh Patel, Mudasir Maqbool, and Prince Ahad Mir contributed to the methodology, data curation, investigation, visualization, analysis, review, and editing. Mohd Adnan, Reyaz Hassan Mir, and Mubashir Hussain Masoodi contributed to critical revision of the manuscript, methodology, validation, formal analysis, and study supervision. All authors read and approved the final manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Abdul Jalil Shah acknowledges ICMR New Delhi for providing the financial assistance in the form of a senior research fellowship (ICMR-SRF:8706-2022/TRM/BMS). The authors extend sincere gratitude toward the University of Kashmir for providing necessary facilities to accomplish this work.

ABBREVIATIONS

AChE, acetylcholinesterase; ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognitive Subscale; ADLs, activities of daily living; AMPK, 5′-adenosine monophosphate activated protein kinase; APC, adenomatous polyposis coli protein; Ca^{2+}, calcium ion; CaMK2, Ca^{2+}/CaM-dependent protein kinase 2; COX-2, cyclooxygenase-2; DVL1, segment polarity protein disheveled homologue; EGCG, epigallocatechin gallate; eNOS, endothelial nitric oxide synthase; FGF-2, fibroblast growth factor 2; G, guanine nucleotide-binding proteins; GSK-3β, glycogen synthase kinase 3β; GPCR, G-protein-coupled receptor; IL1, interleukin 1; IL4, interleukin 4; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MDC, major diagnostic categories; MMP-9, matrix metallopeptidase 9; MMSE, Mini Mental State Examination; MTDL, multitarget directed ligand; mTOR, mammalian target of rapamycin; NAD, nicotinamide adenine dinucleotide; NF-κB, nuclear factor κB; NO, nitric oxide; NRF1, nuclear respiratory factor 1; P, phosphorylation; PARP, poly ADP ribose polymerase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α; Sirt1, silent mating-type information regulator 2 homologue 1

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