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New Insights for Alzheimer Disease and other Neurodegenerative Diseases

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ABSTRACT

Neurodegeneration is the progressive shrinkage and loss of function of neurons that occurs in neurodegenerative disorders including Alzheimer's disease (AD) and Parkinson's disease. Neurodegenerative illnesses are growing more common as the population ages, yet the processes that cause synapse instability and neuronal death remain unknown. All neurodegenerative illnesses are characterized by neuronal malfunction and death. However, they differ in terms of genetics, diseases, phenotypes, and treatments. Most neurodegenerative diseases are considered to be complex, with interactions between external environmental and internal genetic risk factors acting cumulatively over a lifetime to establish an individual's 'allostatic burden'. Allostatic load regulates the rate of brain aging and causes the differential breakdown of neuro-anatomical pathways based on their relative usage or disuse during life. The result is the production of one or more pathogenic proteins, some of which may exhibit 'prion-like' behavior and propagate across the brain from their initial sites of formation along neuro-anatomical pathways to harm related brain regions. Pathological protein variations and anatomical dissemination lead to diverse disease manifestations. The negative psychological and physiological repercussions of neurodegenerative illnesses impose a significant societal and health cost. Alzheimer's disease (AD) is regarded as a significant neurodegenerative ailment and a major cause of dementia in the elderly. AD is classified as a neurodegenerative disorder that gradually compromises cognitive function and memory (3). Current epidemiological data show that approximately 50 million people globally suffer from Alzheimer's disease.

The major signs of Alzheimer's disease are practically imperceptible, and they typically include forgetting about recent occurrences. AD is caused by oxidative stress (OS) from mitochondrial dysfunction, intracellular accumulation of hyperphosphorylated tau (τ) proteins in the form of neurofibrillary tangles, excessive accumulation of extracellular beta-amyloid (Aβ) plaques, genetic and environmental factors. alleviate symptoms and temporarily slow cognitive development linked with Alzheimer's disease. This implies that most treatments are focused solely on symptom control, especially in the early stages of the disease. Previously, natural ingredients were the preferred therapeutic option. In this view, varied natural products (NPs) have the potential to reduce symptoms and slow the progression of a variety of disorders, including Alzheimer's disease, attracting the interest of the scientific community and the pharmaceutical business. Numerous nanoparticles, including flavonoids, gingerols, tannins, anthocyanins, triterpenes, and alkaloids, have been demonstrated to have anti-inflammatory, antioxidant, anti-amyloidogenic, and anti-cholinesterase activity.

Abbreviations: AD: Alzheimer's Disease; OS: Oxidative Stress; NPs: Natural Products; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; NSAIDs: Nonsteroidal Anti-Inflammatory Medicines; iNOS: Inducible Nitric Oxide Synthase; CB2: Cannabinoid Receptor 2; MAO: Monoamineoxidase; NGF: Nerve Growth Factor; VEGF: Vascular Endothelial Growth Factor

Cholinesterase Inhibitors

Herbs are currently one of the most effective medications for treating and slowing the progression of a variety of ailments, including diabetes, cancer, and neurological disorders such as Alzheimer's disease [2]. Natural products have recently gained popularity as supplements or alternative medicine due to their efficacy and low risk of negative effects [3]. It has been demonstrated that therapeutic interventions can delay or prevent the progression of age-related neurocognitive deterioration. Grape is one of the most widely farmed traditional fruits in the world, and grape-derived extracts have been shown to have a variety of biological actions that prevent the neurological damage caused by AD. Grape-derived extracts are natural sources of polyphenols that may promote healthy brain aging by exerting anti-oxidative, anti-inflammatory, anti-acetylcholinesterase, and anti-amyloidogenic properties [3]. According to Araya-Quintanilla [4], there is no consistent evidence that omega-3 supplementation improves cognitive function in AD patients in the short to medium term. It is widely recognized that coenzyme Q10 (CoQ10) has significant antioxidant capabilities.

Because one of the main mechanisms involved in the pathogenesis of Alzheimer's disease (AD) and other neurodegenerative diseases is oxidative stress, analysis of the concentrations of CoQ10 in different tissues of AD patients and with other dementia syndromes, as well as the potential therapeutic role of CoQ10 in AD, have been addressed in several studies. We conducted a comprehensive review and meta-analysis of these studies evaluating tissue CoQ10 levels in patients with dementia and controls, and found that AD patients had similar serum/plasma CoQ10 levels as controls. We also reviewed the potential therapeutic effects of CoQ10 in AD and other dementia models (which revealed significant neuroprotective effects of coenzyme Q10) and in patients with AD, other dementias, and moderate cognitive impairment (with ambiguous results). The possible involvement of CoQ10 treatment in AD and improving memory in elderly rodents demonstrated in laboratory models warrants further investigation in individuals with AD, other forms of dementia, and mild cognitive impairment [5].

Acetylcholinesterase Inhibitor for the Treatment of Alzheimer's Disease

The cholinergic hypothesis is an essential hypothesis for understanding the pathophysiology of Alzheimer's disease. This concept describes how AD is caused by a reduction in the neurotransmitter acetylcholine. Many medications used to treat Alzheimer's disease are based on the cholinergic theory [6]. Cell death causes neurotransmitter deficits in the brain, including acetylcholine (Ach), serotonin, and norepinephrine. Many studies have found that a low level of neurotransmitters in the cholinergic system causes cognitive decline and memory loss in Alzheimer's patients [6-8]. Acetylcholinesterase (AChE) is a key enzyme that breaks down the ACh neurotransmitter. Several treatment techniques raise ACh neurotransmitter levels before increasing cholinergic transmission by inhibiting ACh hydrolysis with AChE inhibitors, activating nicotinic and muscarinic receptors, or administering cholinomimetic drugs [8]. Drugs including galantamine, tacrine, donepezil, metrifonate, and rivastigmine block AChE, increase Ach levels, and improve cholinergic transmission. These medications have been used to treat the symptoms of Alzheimer's disease, which are caused by cholinergic neuron degeneration and impaired transmission. However, inhibiting AChE has not proven to be highly beneficial in Alzheimer's treatment [8]. Side effects of AChE inhibitors include nausea, vomiting, diarrhea, stomach pain, dyspepsia, and skin rash [9]. Tacrine has also been linked to hepatotoxicity in clinical trials [10]. Physostigmine was removed from the drug market due to numerous downsides. As a result, it is critical to discover new AChE inhibitors, such as those found in medicinal plant resources, that have less side effects.

Antioxidants for the Treatment of Alzheimer's Disease

Many research have found that oxidative stress affects brain tissues in Alzheimer's disease patients. Oxidative stress causes protein, lipid, and DNA oxidation, as well as glycoxidation [11]. Oxidative stress is defined as an imbalance between the formation of reactive oxygen species (ROS) and the antioxidative defense mechanism, which is responsible for ROS elimination. It causes age-related neurodegeneration and cognitive deterioration [12]. ROS, including superoxide anion radical ($O2^{\cdot}-$), hydrogen peroxide (H2O2), hydroxyl radical ($^{\cdot}OH$), singlet oxygen (1O2), alkoxyl radicals ($RO^{\cdot}$), peroxyl radicals ($ROO^{\cdot}$), and reactive nitrogen species (RNS), such peroxynitrites (ONOO−), contribute to many human degenerative illnesses [13]. Oxidative stress arises when ROS and RNS levels exceed the antioxidant system's clearance capacity, causing cell metabolic malfunction and other pathological diseases or aging [14]. The major signs of Alzheimer's disease include increased protein oxidation, lipid oxidation, DNA oxidation, and glycoxidation [15]. In Alzheimer's patients, oxidative stress is frequently induced by an imbalance between ROS levels and the antioxidative defense system. As a result, antioxidant treatment is a promising way to prevent disease development.

A recent study found a relationship between antioxidant intake and decreased dementia symptoms [16]. Antioxidants, such as vitamin E, vitamin C, selegiline, estrogen, and Ginkgo biloba, may slow the progression of Alzheimer's disease [17]. Furthermore, several medicinal herbs that contain antioxidants have the ability to treat Alzheimer's disease. Jung et al. found that three primary alkaloids in Coptidis rhizoma, groenlandicine, berberine, and palmatine, may have anti-AD effects by decreasing AChE activity and Aβ buildup, as well as antioxidant capacity to lower ROS and RNS levels [13]. Silibinin, a flavonoid isolated from Silybum marianum, possesses antioxidant properties. Silibinin can reduce memory impairment and oxidative damage caused by Aβ in mice, making it a possible therapeutic for

Alzheimer's disease [18]. As a result, more research into medicinal plants with antioxidant qualities for Alzheimer's disease treatment is needed.

Amyloid Hypothesis and Alzheimer Drugs Targeting B-Amyloid

The amyloid theory was developed in 1991. Extracellular β-amyloid deposits are believed to be the primary etiology of Alzheimer's disease [19]. β-amyloid, a small fragment of the amyloid precursor protein (APP), results from a processing mistake in the brain. Amyloid plaques refer to aggregated clumps of β-amyloid proteins. Amyloid plaques in the brain cause neuronal cell death, which leads to Alzheimer's disease. APP is a lengthy protein that has up to 771 amino acids. Two enzymes cleave APP, producing β-amyloid [20]. The APP is initially cut by β-secretase, followed by another cut by gamma-secretase to produce β-amyloid, which can be 38, 40, or 42 amino acids long. β-amyloid's length of 42 amino acids makes it more chemically sticky than other lengths, causing clumps and plaque development. β-Amyloid plaques can cause tau protein tangles. These tangles also harm brain cells, resulting in dementia [21]. The creation of β-amyloid plaques causes oxidative stress in neurons, accelerating the progression of Alzheimer's disease [22].

Amyloid plaques primarily include the 42 amino acid type of Aβ, one of multiple isoforms present. Other isoforms reported include Aβ1−40 and Aβ25−35. Several studies have employed Aβ1−42 and Aβ25−35 to induce oxidative stress and investigate the neuroprotective effects of natural products on various cell lines [23]. Aβ exposure causes increased ROS generation, mitochondria malfunction, apoptosis, and downregulation of antioxidant genes, resulting in neuronal cell dysfunction and worsening AD symptoms [24]. The APOE4 isoform of apolipoprotein is an important familial risk factor for Alzheimer's disease. This APOE4 may lead to β-amyloid accumulation in the brain [19]. Alzheimer's disease patients have more amyloid plaques. Researchers suggest that medications that suppress β-amyloid accumulation could potentially treat Alzheimer's disease. PBT2, a therapeutic candidate, is the second generation of eight-hydroxyquinoline analogs for Alzheimer's disease. In animal models, PBT2 effectively detoxifies Aβ and increases β-amyloid clearance [25]. A clinical investigation found that a 250 mg dosage of PBT2 lowered Aβ1−42 levels in the brain [26]. Drugs that decrease β-amyloid buildup could be a potential treatment for Alzheimer's disease. β-amyloid plaques in the brain cause inflammation and damage to neurons. Neuroinflammation is another hallmark of Alzheimer's disease. Cytokines, including interleukin-1, interleukin-6 (IL-6), and tumor necrosis factor alpha, have been linked to neuroinflammation. β-amyloid peptide increases the expression of several cytokines.

These cytokines measure the buildup of β-amyloid peptide [27]. Some studies hypothesized that these cytokines play a significant role in the course of Alzheimer's disease [28]. Long-term usage of nonsteroidal anti-inflammatory medicines (NSAIDs) has been shown to slow the progression of Alzheimer's disease [29]. NSAIDs may help reduce Alzheimer's symptoms by inhibiting COX enzymes and activating PPARγ [29]. NSAIDs have been demonstrated to reduce COX expression, which enhances prostaglandin synthesis while decreasing cytokine production [30]. Transgenic mice with Alzheimer's disease and cell cultures of peripheral, glial, and neuronal NSAIDs, including ibuprofen, indomethacin, and sulindac, have been shown to reduce Aβ levels [29]. However, the favorable effects of NSAIDs in Alzheimer's disease treatment are still being debated due to the little evidence offered [31].

Herbal Medicine for the Treatment of Alzheimer's Disease

Medicinal plants have been demonstrated to slow the progression and symptoms of a number of disorders, including Alzheimer's [32]. Many studies have been undertaken to look into the effects of total medicinal plant extracts on Alzheimer's disease, as well as to isolate and identify the active ingredients [33]. Many substances, including lignans, flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids, have been demonstrated to have diverse positive pharmacological effects, such as anti-inflammatory, anti-amyloidogenic, anticholinesterase, and antioxidant properties [32]. Some substances, such as aged garlic extract, curcumin, melatonin, resveratrol, Ginkgo biloba extract, green tea, and vitamins C and E, have been utilized in Alzheimer's patients and have shown promising benefits [34]. Below is a summary of several medicinal plants and isolated chemicals used to treat Alzheimer's disease.

Natural Product-Based Therapeutics for Alzheimer's Disease

Natural products can prevent the aggregation of Aβ and tau peptides and improve cholinergic transmission. Natural compounds that target many pathogenic pathways may be able to slow or even prevent the onset and progression of Alzheimer's disease [35]. Because there are no effective pharmacological therapies for Alzheimer's disease, alternative activities have concentrated on preventing the illness through diet changes, the use of dietary supplements, the intake of functional food ingredients, and organic products [36]. Novel medications are critical for enhancing patient care and alleviating symptoms. There are several pharmacological therapies for diagnosis and control Alzheimer's disease are presented in recent times, but none have yielded optimistic results in clinical studies. Recent research has shown that certain dietary variables reduce the risk of Alzheimer's disease, prompting scientists to study the benefits of phytoconstituents and extracted bioactive compounds [37]. Natural remedies have drug-like properties that allow them to penetrate across cellular membranes and interfere with protein-protein interactions [37,38]. Chemicals produced from various plant parts, such as roots, bulbs, tubers, rhizomes, foliage, pods, seeds, and buds, suppress the formation of damaging amyloid plaques while increasing cholinergic signaling [39].

Antioxidant-rich diets have been demonstrated to reduce oxidative stress in the CNS. As a result, natural chemicals have a wide range of pharmacological properties, piqueing the interest of scientists seeking to use them in the development of therapeutic molecules to treat a number of disorders [40,41]. The use of food and other natural sources as supplements to treat a variety of illnesses is a common practice in Ayurveda, Siddha, Unani, Chinese Herbal Medicines, and other traditional therapies. The strategy of harnessing these bioactive phytocompounds has evolved throughout the decades. Previously, research was mostly focused on showing the pharmacological effects of distinct plant components or the entire extract itself [42,43]. With the advent of nutraceuticals, the uses of bioactive phytocompounds have expanded beyond the consumption of natural products as dietary supplements to include the investigation of their unique medicinal qualities in order to produce prospective medications.

Medicinal Plants Used for the Treatment of Alzheimer's Disease

Curcuma Longa

Curcuma longa is a rhizomatous perennial plant of the ginger family, Zingiberaceae. The active molecules are water-insoluble curcuminoids such as curcumin, demethoxycurcumin, and bis-demethoxycurcumin. Curcumin is the primary curcuminoid that gives turmeric its yellow color [44]. Curcumin exhibits anti-inflammatory, antioxidant, anticancer, and antibacterial properties, among others [45]. A earlier analysis found that curcumin could be a potential chemical for the treatment of Alzheimer's disease [46]. Another study found that feeding curcumin to aged animals with β-amyloid plaque accumulation reduced plaque deposition [47]. Curcumin can reduce oxidative damage in the brain [48]. Curcumin can cure β-amyloid pathology in an Alzheimer's transgenic mice model [49]. Curcumin's antioxidant and anti-inflammatory qualities also helped to lessen some Alzheimer's symptoms [49]. *In vitro*, curcumin may reduce lipid peroxidation and neutralize ROS levels, making it more powerful than vitamin E [50]. Curcumin (5-10 μM) rescued PC12 cells from Aβ-induced neurotoxicity by reducing oxidative damage and tau hyperphosphorylation [47]. Curcumin has been shown in a clinical trial to benefit healthy middle-aged individuals by reducing plasma β-amyloid protein levels. More tests are required to determine the precise mechanism of *C. longa*.

Bacopa Monnieri

Bacopa monnieri is widely used in traditional medicine as a nerve tonic, diuretic, and cardiotonic agent, as well as to treat asthma and rheumatism. It also applies to epilepsy and insomnia [51]. *B. monnieri* is mostly composed of saponins and triterpenoids. These chemicals, including bacopasides III, IV, and V, as well as bacosides A, B, bacosaponins A, B, and C, were isolated from *B. monnieri*. *B. monnieri* has been found to contain several saponin glycosides, including jujubogenin bisdesmosides, bacopasaponins D, E, and F. *B. monnieri* also contains additional antioxidant-active chemicals such as alkaloids, sterols, betulic acid, polyphenols, and sulfhydryl [52]. Traditional medicine has employed *B. monnieri* to improve memory and cognitive function [53]. Many research on the neuropharmacological effects and nootropic activity of *B. monnieri* extracts have been undertaken extensively [54]. *B. monnieri* increases protein kinase activity in the hippocampus, providing nootropic effects [55]. In an experimental Alzheimer model, rats administered *B. monnieri* extract demonstrated reduced cholinergic degradation and improved cognition [56]. Another investigation found that *B. monnieri* reduced AChE activity and elevated ACh levels [56]. Furthermore, *B. monnieri* extracts rescued neurons from β-amyloid damage. Furthermore, neuronal cells treated with *B. monnieri* extract had lower levels of ROS, implying that it reduced intracellular oxidative stress [56]. A clinical investigation of AD patients found that a polyherbal formulation comprising *B. monnieri* extract successfully enhanced cognitive functioning while decreasing inflammation and oxidative stress [56]. Nonetheless, more research is needed to determine the possible neuroprotective activity of *B. monnieri* against AD.

Convolvulus Pluricaulis

The phytochemicals of *Convolvulus pluricaulis* suggest that it may include active components such as triterpenoids, flavonol glycosides, anthocyanins, and steroids. They provide nootropic and memory-enhancing action to *C. pluricaulis* [56]. Another study found that *C. pluricaulis* can soothe nerves by controlling stress hormone, adrenaline, and cortisol levels in the body [56]. *C. pluricaulis* has traditionally been used to treat nervous system disorders such as stress, anxiety, mental tiredness, and sleeplessness [57]. Rats' learning and memory were greatly improved after being fed an ethanolic extract of *C. pluricaulis*, as well as its ethyl acetate and water fractions [58]. Oral treatment of *C. pluricaulis* reduced scopolamine's neurotoxic effects by lowering tau and AβPP protein and mRNA levels [59]. Unfortunately, there is no clinical data on the effects of *C. pluricaulis* on Alzheimer's patients. Further research is needed to study the potential beneficial effects of *C. pluricaulis* on AD treatment.

Centella Asiatica

Traditional treatments have employed *Centella asiatica* to rejuvenate neural cells. It has also been shown to improve IQ, lifespan, and memory [56]. Asiatic acid and asiaticoside found in *C. asiatica* have been proven to lower H2O2-induced cell cytotoxicity, free radical levels, and prevent β-amyloid cell damage *in vitro*. *C. asiatica* extracts reduced β-amyloid pathology and oxidative stress in a mouse model of Alzheimer's disease [60]. *C. asiatica* ethanol extracts have been shown to protect neurons from Aβ1-40-induced neurodegeneration. *C. asiatica* can also reduce ROS production and alter the antioxidative defense system in cells by increasing the activity of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione and glutathione disulfide. These activities show that *C. asiatica* plays a significant role in the prevention and treatment of Alzheimer's disease [56].

Ginkgo Biloba

Ginkgo biloba leaves have been used in traditional medicine to improve cognition and prevent age-related deteriorations. Ginkgo biloba leaf extracts contain flavonoids, organic acids, and terpenoids, which have neuroprotective properties. Ginkgo biloba leaf extracts may inhibit neuronal death by scavenging free radicals, reducing mitochondrial dysfunction, activating JNK and ERK pathways, and inducing cytotoxicity against β-amyloid. Bilobalide, a key terpenoid found in Ginkgo biloba leaves, exhibits significant neuroprotective properties [61]. Bilobalide has been demonstrated to lower the expression of p53, Bax, and caspase-3 proteins in PC12 cells while also inhibiting ROS-induced apoptosis [62]. Bilobalide also promoted neurogenesis and synaptogenesis in neural cells by raising the amounts of phosphorylated transcription factor CREB and neurotrophin BDNF [56]. Furthermore, a clinical trial of selling a dietary supplement containing Ginkgo biloba extract showed that it was effective in treating cognitive impairment associated with aging and the early stages of Alzheimer's disease [56].

Zingiber Officinaleis

Zingiber officinaleis is commonly used in dietary supplements as extracts or as ginger tea ingredients. Gingerols, shagols, bisabolene, zingiberene, and monoterpenes have all been identified from *Z. officinaleis* [57]. *In vitro* studies have demonstrated that *Z. officinaleis* inhibits AChE. Inhibiting the AChE enzyme increases ACh levels in synapses, boosts cholinergic pathway activity, and improves cognitive performance in Alzheimer's disease patients. Furthermore, *Z. officinaleis* has the ability to reduce lipid peroxidation, providing a protective effect against AD. In rats fed with *Z. officinaleis* extract, lipid peroxidation levels were lowered, according to an in vivo study. The potential of *Z. officinaleis* extract to minimize overstimulation of N-methyl-D-aspartate (NMDA) receptors and prevent free radicals formation [63].

Allium Sativum

Allium sativum has been utilized as a dietary and medical supplement. Bui and Nguyen found that aged garlic extract had a neuroprotective impact in a Tg2576 mouse model, with mice fed old garlic extracts showing improved memory in the hippocampus region [56]. The process has scavenged free radicals, boosted enzyme antioxidants such superoxide dismutase, catalase, glutathione peroxidase, and glutathione, inhibited lipid peroxidation, and lowered inflammatory prostaglandins [64]. Furthermore, aged garlic extracts inhibited 3-hydroxy-3-methylglutaryl-CoA reductase, resulting in lower cholesterol production. Aged garlic extracts can protect neurons from β-amyloid neurotoxicity and apoptosis, reducing cognitive decline, ischemia or reperfusion-related neuronal death, and improving learning and memory retention [56]. A recent study found that aged garlic extracts were useful in improving short-term memory and reduce neuroinflammation in Aβ-induced rats [65] and microglial cells [56].

Others

Some natural product compounds have also been isolated from medicinal plants for the treatment of AD.

Quercetin

Quercetin is a flavonoid component present in a wide range of therapeutic plants, including apples, onions, berries, green tea and red wine. Quercetin is a potent antioxidant that scavenges ROS [66]. Additionally, it has anticancer, antiviral, antiinflammatory, and antiamyloidogenic effects [67]. Quercetin at a concentration of 10 μM inhibits the accumulation of β-amyloids, showed antiamyloidogenic action. Quercetin inhibited Aβ-induced apoptosis in neuronal cells. However, at higher doses (40 μM), quercetin may cause cytotoxicity [56]. A recent study found that nanoencapsulated quercetin in zein nanoparticles effectively corrected cognitive and memory impairments in senescence-accelerated P8 mouse models. The mechanism could be connected to decreased expression of the hippocampus astrocyte marker.

Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate is a flavonoid catechin found in Camellia sinensis. Epigallocatechin-3-gallate has strong antioxidant properties, and numerous research have looked at its effects on a variety of disorders, including cancer, cardiovascular disease, and neurological disease [68]. Epigallocatechin-3-gallate has been demonstrated to improve glutathione peroxidase activity, limit AChE activity, and reduce NO metabolite production and ROS generation in mice with streptozotocin-induced dementia [69]. In mutant PS2 Alzheimer mice, epigallocatechin-3-gallate decreased γ-secretase enzyme activity while increasing memory formation [70]. Epigallocatechin-3-gallate reduced LPS-induced memory loss and death by decreasing amyloid precursor protein expression, suppressing beta-site APP cleaving enzyme 1 activity, and lowering β-amyloid levels. Furthermore, it has been shown to reduce the expression of inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin 1β, IL-6, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), soluble intracellular adhesion, and molecule-1 macrophage colony-stimulating factor, and to prevent astrocyte activation in neuronal cells [56]. Epigallocatechin-3-gallate has been demonstrated to diminish Aβ buildup and increase neprilysin enzyme expression, which is the rate-limiting enzyme for Aβ breakdown in senescence-accelerated P8 mice [56].

Berberine

Berberine is a quaternary ammonium salt and isoquinoline alkaloids derived from Coptis chinensis [56]. Berberine has numerous biological effects, including antioxidant activity, inhibition of AChE and butyrylcholinesterase, monoamine oxidase, and cholesterol-lowering activity (58). Tg mice administered 100 mg/kg of berberine orally exhibited significant increases in learning and spatial memory [71]. Berberine treatment of BV2 microglia cells significantly reduced

β-amyloid-induced expressions of IL-6, COX-2, and iNOS [72]. Berberine inhibits the PI3K/protein kinase B and MAPK pathways, reducing NF-κB expression significantly [56]. A study found that berberine can improve memory, lower Aβ and APP levels, inhibit Aβ plaque deposition in the hippocampus [56], and prevent the rise.

Resveratrol

Resveratrol is a stilbene-type polyphenolic molecule. Resveratrol is present in red wine, almonds, grape and fruit skins [73]. Many studies have demonstrated that it possesses anti-cancer, anti-inflammatory, antioxidant, and cardiovascular protective qualities, as well as the ability to reduce blood glucose levels and provide neuroprotection [74]. Resveratrol has strong antioxidant properties, scavenging ROS, boosting glutathione levels, and enhancing endogenous antioxidants. Resveratrol can lower β-amyloid levels by promoting non-amyloidogenic cleavage of APP and improving β-amyloid clearance [56]. Resveratrol (15, 45, and 135 mg/kg) also reduced AChE activity in neural cells [56]. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer's disease found that it is safe, well-tolerated, and can reduce CSF and plasma Aβ40 levels [56]. He et al. [75] has demonstrated that resveratrol protects against hyperphosphorylation and/or facilitates tau protein dephosphorylation. Furthermore, they discovered that resveratrol mitigated the negative effects of Alzheimer's disease in a rat model by inhibiting cholinergic pathways, lowering oxidative stress and increasing spatial memory. Resveratrol may control neuroinflammation and generate adaptive immunity by activating SIRT1 [56].

Huperzine A

Huperzine A is a sesquiterpene alkaloid discovered in Huperzia serrata. Traditional medicine has utilized Huperzine A to alleviate fever and edema. H. serrate extract can also be taken as a dietary supplement to improve memory [76]. Huperzine A has a significant anti-AChE activity. Its mechanism is similar to that of rivastigmine, donepezil, and galantamine, which are used to treat Alzheimer's disease. Huprines, a novel combination of tacrine and Huperzine A, are effective AChE inhibitors that can dramatically attenuate Aβ-induced memory damage [56]. Clinical research have indicated that huperzine A has very few side effects, including gastroenteric symptoms, dizziness, headaches, nausea, and a slower heart rate. This is an advantage of huperzine A over other AChE inhibitors for Alzheimer's disease treatment [76]. Huperzine A may inhibit various apoptotic factors, including caspase-3, Bax, and p53. Huperzine A also controlled the expression and secretion of nerve growth factor. Huperzine A improved Tg mice's learning capacity and memory in a Morris water maze test. The method involves inhibiting PKC/MAPK, γ-secretases, and BACE, while also increasing phospho GSK-3 [77].

Huperzine A reduces β-amyloid plaques and oligomeric A levels in the cortex and hippocampus [78]. Moreover, huperzine A can inhibit the NMDA receptor and potassium chanel in the brain [56]. A phase II trial of huperzine A in mild to moderate AD found that huperzine A 200 μg did not exhibit cognitive improvements; however, huperzine A 400 μg improved the Alzheimer's Disease Assessment Scale-cognitive [56]. However, more research is needed to properly understand the efficacy of huperzine A against AD.

Rosmarinic Acid

Rosmarinic acid is a polyphenolic carboxylic acid found in numerous Lamiaceae species [56]. Rosmarinic acid contains numerous pharmacological activity, including antioxidant, antibacterial, anti-inflammatory, anticancer, antiviral, and neuroprotective properties [79]. Rosmarinic acid can effectively prevent β-amyloid-induced memory loss by inhibiting NF-κB and TNF-α expressions [80]. Rosmarinic acid has also been found to protect neuronal PC12 cells from beta-amyloid-induced cytotoxicity. Furthermore, it may reduce the hyperphosphorylation of tau proteins. Rosmarinic acid's ability to prevent ROS production, caspase-3 activation, and DNA fragmentation may explain why it inhibits apoptotic pathways [81]. Rosmarinic acid may also prevent locomotor activity, short-term spatial memory, and biochemical changes in brain tissue in a rat model of Alzheimer's disease by lowering lipid peroxidation and inflammation [56]. More clinical trials are needed to demonstrate rosmarinic acid's efficacy against Alzheimer's disease.

Luteolin

Luteolin is a flavonoid found in numerous medicinal plants, including *Magnoliophyta, Pteridophyta, Bryophyta*, and *Pinophyta*. Luteolin has been demonstrated to exhibit a variety of biological activities, including anti-inflammatory, antioxidant, anticancer, antibacterial, and neuroprotective properties [56]. Luteolin can also inhibit zinc-induced tau protein hyperphosphorylation, which could be explained by its antioxidant properties and capacity to modulate the tau phosphatase/kinase system. Luteolin can diminish amyloid precursor protein expression and β-amyloid production [82]. Luteolin can also reduce apoptosis by lowering intracellular ROS levels, boosting the antioxidant endogenous system by increasing SOD, CAT, and GPx activity, and activating the NRF2 pathway [56]. Luteolin has also been demonstrated to alleviate cognitive dysfunction, considerably boost the antioxidant system, reduce lipid peroxide formation, and regulate inflammatory responses in rats' brain tissue caused by chronic cerebral hypoperfusion [83]. Another study found that luteolin improved cognitive function and memory in a streptozotocin-induced AD rat model [56]. Despite these findings, more clinical trials are needed to validate luteolin's protective properties against Alzheimer's disease.

Alkaloids

Alkaloids can relieve the pathogenesis of Alzheimer's disease by acting as muscarinic receptor agonists, anti-oxidants, anti-amyloid inhibitors, AChE and BuChE inhibitors, α-synuclein agglomeration inhibitors, and dopaminergic and nicotine agonists [84]. In biomedicine, alkaloids have a wide range of therapeutic efficacy, including

analgesics (e.g., morphine), anti-diabetic (e.g., piperine), anti-tumor (e.g., berberine), and anti-microbial properties (e.g., ciprofloxacin). Certain alkaloids, such as cocaine, caffeine, and nicotine, have both stimulating and neuropsychiatric effects on the central nervous system (for example, psilocin). Although alkaloids have a long history and a wide spectrum of qualities, few are offered as useful and effective medicines. They have a wide range of protective effects in situations such as seizures, psychological difficulties, cerebral ischemia, Alzheimer's disease, memory lapses, anxiety, stress, and many more. Alkaloids inhibit the development of neurodegenerative illnesses by a variety of mechanisms, including inhibiting AChE, increasing GABA levels, and functioning as NMDA antagonists [84,85].

Terpenoids

Multiple studies and clinical trials have confirmed that essential oils have favorable effects on Alzheimer's disease patients. Plant essential oils and particular terpenes have been shown to exhibit antioxidant and AChEI activity [86]. Terpenoids like ginsenosides and ginkgolides, as well as cannabinoids, are effective anti-AD substances. Ginsenoside Rg3 reduced Aβ generation by 84% in CHO-2B7 cells and 31% in Tg2576 transgenic mice [87]. Ginsenoside Rg3 reduces Aβ levels via increasing Aβ breakdown and the synthesis of neprilysin, a key enzyme in Aβ degradation. Ginsenoside Re protects PC12 cells from neurotoxicity caused by Aβ. Ginsenoside Rb1 lowers neuroinflammatory indicators in hippocampus cells and reverses Aβ-induced cognitive impairment in mice. Ginsenoside Rb1 improves spatial working memory by increasing brain synaptic plasticity [88]. Ginkgolides, a labdane-form of cyclic diterpenes, are commonly isolated from Ginkgo biloba. Ginkgolide A and B therapy protects nerve cells from synaptic damage as determined by synaptophysin loss, a presynaptic synaptic biomarker, and improves nerve cell survival despite A-induced toxicity. Ginkgolide B protects nerve cells in the hippocampus from Aβ-induced cell death by increasing brain-derived neurotrophic factors are synthesized, and nerve cell death is reduced in hemorrhaging rat brain cells [89].

Phenols

Resveratrol has been shown to reduce the expression of pro-inflammatory molecules like NF-kB and TNF-α in glial cells while raising the quantity of anti-inflammatory cytokine IL-10, which is connected to Alzheimer's disease. Resveratrol enhances spatial cognitive ability in Alzheimer's disease rats by improving antioxidant activity. Resveratrol promotes SIRT1 expression, protecting neuronal cells from ROS, free radicals, and Aβ-induced inflammation [90]. Oxyresveratrol, a substance produced from the Morus alba tree, decreases iNOS molecule synthesis in LPS-mediated macrophages, reducing NO generation. Oxyresveratrol possesses neuroprotective benefits against Aβ protein-mediated neurotoxicity in cortical nerve cells, as well as anti-inflammatory and anti-apoptotic capabilities by lowering TNF-α, IL-1β, and IL-6 production and suppressing caspase-1 and NF-kB expression [91]. Quercetin has been proven to have neuroprotective characteristics due to its antioxidant activity and ROS (OH, superoxide anions) scavenging activities across the BBB. Quercetin's neuroprotective qualities are mostly evidenced by dysregulation of cytokines via MAPK signaling pathways and p13K/Akt networks. Quercetin has also been shown to block the LOX and COX proteases, which are involved in the production of eicosanoids and the activation of NF-kB [92].

New Promising Synthetic Compounds

Theories such as excitatory neurotransmitter neurotoxicity, altered insulin signaling, oxidative stress, and inflammation can all help to explain the causes of dementia and provide a new theoretical foundation and therapeutic target for the development of new AD medicines.5 Acetylcholine esterase (AChE) is the most important enzyme that regulates acetylcholine levels. Numerous studies have revealed a link between learning and memory functions and AChE activity in experimental animals.6 Thus, the use of acetylcholinesterase (AChE) inhibitors like as rivastigmine or dopenzil, which increase the availability of acetylcholine at cholinergic synapses, constitutes a significant therapeutic strategy for the condition.7 A literature review revealed that the coumarin in nucleus, also known as 2H-1-benzopyran-2-one, is the primary structural component of several natural products and synthetic compounds with a wide range of biological activities . Coumarins are fascinating molecules for drug discovery in the field of AChEIs due to the possibility of chemical substitutions at multiple locations within this core structure. Recent *in vitro* studies have shown that the coumarin moiety can inhibit cholinesterase enzymes.

In addition to AChE suppression, the coumarin nucleus has a number of biological effects on Alzheimer's disease, including inhibition of the enzyme secretase-1 (BACE-1), cyclooxygenase (COX)/lipoxygenase (LOX) antagonists, cannabinoid receptor 2 (CB2) antagonists, gamma amino butyric acid (GABA) receptor agonists, NMDA receptor antagonists, and monoamineoxidase (MAO) inhibitors. Many coumarin natural compounds, including esculetin I, decursinol II, scopoletin III, and mesuagenin IV, exhibit anti-Alzheimer properties. [13,93]. N′ - (2,3-Dihydro-1H-inden-1-ylidene)2-((4-methyl-2- oxo-2H-chromen-7-yl)oxy)acetohydrazide N′- (2,3-Dihydro-1H-inden-1-ylidene)2-((4-methyl-2-oxo-2H-chromen-7-yl)oxy)acetohydrazide design and synthetic route for the manufacture of novel 2-oxo-coumarin-7-oxymethylene acetohydrazide derivatives 4a–d. The chemical structures of the novel analogues were investigated using IR, 1H-NMR, 13C-NMR, and mass spectra. The newly synthesized compounds were tested as acetylcholinesterase (AChE) inhibitors and antioxidants in comparison to donepezil and ascorbic acid, which served as reference medications. Compound 4c was the most effective AChE inhibitor, with an IC50 of 0.802 mM and DPPH scavenging activity of 57.14 ± 2.77.

Furthermore, the T-maze test revealed that AD groups treated with 4c had a significant reduction in the time it took rats to approach food when compared to donepezil, with percentages of improvement

reaching 148.37% versus the usual treatment (181.70%). Furthermore, compound 4c enhanced the expression of the Bcl-2 gene while decreasing the expression of the Bax and Tau genes in the brain samples of AD-induced rats treated with compound 4c in a way similar to that found with the reference drug donepezil. In silico investigations revealed that compound 4c has a promising binding mechanism within the active site of acetylcholine esterase and is regarded as the most stable binding mode among compounds 4a, 4b, and 4d. Also, compound 4c had the lowest binding energy score. Furthermore, the pharmacokinetic profile revealed that compound 4c followed Lipinski's rule, with good oral bioavailability, high human intestine absorption, and inactivation by the CYP3A4 enzyme. Compound 4c is not mutagenic or tumorigenic and not an annoyance. Fortunately, it indicated a safe toxicity profile.

As a result, the coumarin analogue 4c may be considered a basic nucleus in the yield of drug development for new multi-targeted directed ligands against Alzheimer [93]. Abd El-Karim, et al. [94], Based on molecular docking studies, the anticholinesterase activity of novel benzofuran compounds was investigated, and the compounds demonstrated varying inhibitory effects with IC 50 values that were very near to donepezil levels.

Stem Cells

The standard mediations tested provided no therapeutic advantages for AD. As a result, there is a significant unmet demand among Alzheimer's disease patients. Stem cells have recently acquired popularity as a viable alternative to conventional treatments and surgery. Several attempts have been made to comprehend the clinical applications of stem cells in terms of sophisticated cellular and molecular mechanisms of neuroregeneration and neurodegeneration [95]. Stem cell-based therapy has the potential to be a promising technique for treating a variety of neurologic conditions that now lack effective treatments, such as stroke, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. This article examines the current literature by stem cell type and considers the future of stem cell-based therapy in Alzheimer's disease.

Expected Mode of Action

Stem cells can integrate with existing brain networks [95]. They also produce a number of neurotrophic factors to regulate neuroplasticity and neurogenesis [95], which appear to boost brain acetylcholine levels, resulting in better memory and cognitive performance in an animal model. Stem cell-based therapy has two basic modes of action: endogenous and exogenous, depending on the mechanisms of action [95]. Traditionally, cell-based therapies have attempted to repair injured tissue through tissue repopulation, either via transdifferentiation or direct participation of infused stem cells. However, current evidence suggests that engrafted stem cells are not the primary source of freshly produced neurons. Furthermore, unlike Parkinson's disease, AD is distinguished by the death of multiple unique nerve cell types. Because of this diversity, transplanting certain mature cell types is not feasible [95]. Rather than employing the cell replacement paradigm, there is a rising interest in stimulating endogenous repair through paracrine mechanisms.

Transplanted stem cells offer trophic support to the microenvironment, which enhances the survival of affected/remaining nerve cells [96]. Using this method, the primary goal is to increase hippocampus neoneurogenesis (to compensate for neurodegeneration) by increasing the number of resident neural stem cell niches. Hippocampal neoneurogenesis is thought to play an important function in memory and learning. Neurotrophic factor (BDNF), nerve growth factor (NGF), insulin growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) have been proposed as paracrine mediators from transplanted stem cells [97]. Unfortunately, in humans, the potential for neurogenesis declines significantly with age, which is primarily when AD occurs [98]. Furthermore, regulation of inflammation has been hypothesized as additional mode of action [99].

Nanoparticles

BBB: A Limiting Factor in Drug Delivery to Brain

The blood-brain barrier serves an important function in transporting biomolecules into and out of the brain neuronal system. Therefore, knowing the structural and functional properties of the BBB is critical for optimizing medication transport to the brain. This protective unit factor, which is made up of vascular endothelial cell layers tied back by tight junctions and other supportive structures, helps to prevent chemicals from being shuttled between the blood and the brain [100]. The endothelial cells are bordered by a basement membrane covered with astrocyte end-feet and are constantly watched by microglial cells [100]. Cohesive domains, which are coupled to endothelial cells, allow for the selective transit of tiny molecules across the BBB [100]. Transcytosis is a regulated intracellular transport mechanism that meets the protein and peptide requirements for brain homeostasis. Depending on the type of the molecules (hydrophilic or hydrophobic), endothelial cells may aid transport via a variety of unique transporting proteins. Preclinical research have shown that various nanocarriers can be used to treat brain diseases such as Alzheimer's. These carriers encapsulate anti-AD medications as cargo and transport them across the blood-brain barrier. Recent reviews on transcytosis and nanocarrier transport over the BBB are recommended for a more in-depth understanding [101].

Nanomedicines: A Promising Approach for Drug Delivery Through BBB

Several small-sized nanocarriers have been used to treat brain disorders such as brain cancer and Alzheimer's disease in order to distribute FDA-approved [102], commercially available medications in a safe and effective manner. These nanocarriers carrying specific pharmaceuticals are classified as nanomedicines. While there is no treatment for Alzheimer's disease, it demonstrates how currently

FDA-approved medications address its symptoms. Current anti-AD medications can only treat clinical symptoms, not reverse or prevent disease progression. To deliver these indicated medications to the afflicted area of the AD brain, NP-functionalized nanomedicine is regarded as the most practical technique. Nanomedicines have special features that allow them to deliver anti-AD pharmaceuticals to specific regions in the brain. Nanomedicines have the advantages of smaller size and enhanced biocompatibility, making it easier to deliver therapeutic chemicals into the brain [103].

Nanomedicines are small (about 100-10,000 times smaller than a human cell) and can easily interact with proteins and chemicals both on the cell surface and inside the cell [100]. NP-functionalized nanomedicines contain central core structures that ensure drug encapsulation or conjugation while also providing protection and sustained blood circulation [104]. Nanomedicines can transport drugs directly to specific cells or intracellular compartments, such as Aβ, at predetermined dosages [105]. Nanomedicines can reduce dose and frequency, hence improving patient compliance [106]. Regardless of some clinical issues, nanomedicines may have advantages over other conventional methods of drug delivery to the brain in terms of brain favorability, greater stability, biocompatibility and biodegradability, protection from enzymatic degradation, increased half-life, improved bioavailability, and controlled release to cure Alzheimer's disease. NPs were used to traverse the BBB, utilizing various transport pathways to achieve anti-AD effects from the delivered payloads.

Nanomedicines to Manage AD

Nanomaterials are being extensively studied for their potential to treat Alzheimer's disease pathology. The following sections discuss how nanostructure-based delivery systems are being used to diagnose and treat Alzheimer's disease [100].

Lipid-Based NPs for AD Therapy

Many studies have shown the amazing importance of lipid-based nanocarriers for use in drug delivery systems to treat CNS illnesses such as Alzheimer's. Lipid nanoparticles have great promise for delivering anti-AD medicines via nasal methods to treat AD [107].

NP-Chelation-Based AD Therapy

Neuronal degeneration is a significant pathology in Alzheimer's disease, and oxidative stress has been identified as one of the primary risk factors for initiating and promoting neurodegeneration. Compared to the normal brain, the AD brain has dysregulated metal levels such as iron, aluminum, zinc, and copper, which may enhance oxidative stress, toxic radical production, and disruption in DNA activity, as well as mediate the onset of AD symptoms [108]. Nanotechnology successfully contributes to chelation therapy in the inhibition of oxidative stress in dealing with metal accumulation and the resulting oxidative stress in the brain. To lower the levels of corresponding metals in the AD brain, Fe and Cu metal nanoparticles in the form of chelators were used. These chelators are intended for safe administration with minimal damage to healthy brain tissues [109].

Chelation treatment effectively dissolves Aβ plaques in Alzheimer's disease brains. Copper is the most important trace element in metal chelation, with 54 copper-binding proteins discovered in human proteomes [110]. Copper ions modulate the production of amyloid precursor proteins, and chelators can lower Aβ buildup by up to 50% in AD transgenic mice. Cu-conjugated NP formulation in the form of chelator clioquinol (CQ) has the ability to reverse metal precipitation of amyloid protein in Alzheimer's patients [100]. NP-chelator conjugates suppress Aβ aggregation and protect neurons from neurotoxicity, without altering proliferation [100]. To improve intake and concentration, NP-iron chelator conjugates are coated with polysorbate 80, which mimics low-density lipid (LDL) receptors on brain cells and facilitates passage across the BBB [111].

In vitro investigations have revealed that 8-hydroxyquinoline derivatives, particularly compound-5b chelation, significantly prevent self-induced Aβ aggregation in AD. Furthermore, they have minimal toxic effects and good penetrative ability across the BBB [112]. Similarly, xanthone derivatives in the chelation form block acetylcholinesterase, a neuronal enzyme. These compounds have the potential to cure Alzheimer's disease due to their cholinergic inhibitory and antioxidant activities [113]. Another study develops deferasirox and tacrine chelators and investigates their supportive roles in the therapy of Alzheimer's disease. The compounds exhibit good multifunctional activity in inhibiting acetylcholinesterase [114]. Nano-N2PY, an NP-chelator conjugate, helps protect cortical neurons from Aβ-related damage [100]. Similarly, other metal chelators, such as ethylene diamine tetraacetic acid (EDTA), iodochlorhydroxyquin (clioquinol), and deferoxamine, are being utilized to treat AD pathologies and show encouraging outcomes [100].

Nanomedicine–Theranostics Formulations

Gold (Au) NPs

The process for treating Aβ fibrils with gold-containing NPs (AuNPs) is similar to treating cancer cells with metallic NPs [115]. Molecular docking, system biology, and time course simulation studies confirm AuNPs' synergistic function in preventing Aβ production in the brain [115]. AuNPs show promise in identifying Alzheimer's disease both in their naked form and when conjugated with other chemicals. AuNP exposure can reduce brain damage in the AD model due to its antioxidant and anti-inflammatory properties [116]. AuNPs combined with decreased graphene or coated with anti-tau antibodies can function as neuroprobes, detecting Tau-441 target proteins in both blood and cerebrospinal fluid [117]. AuNPs coupled with Co^{2+} can be employed to study Aβ peptide aggregation kinetics and self-assembly in MRI images [102]. AuNPs use biosensory techniques to diagnose Alzheimer's disease pathology. AuNPs, for example, are employed to create an electrochemical immunosensor capable of detect-

ing tau proteins [118]. Chiral identification of stable AuNPs improves their ability to prevent Aβ aggregation [119].

Protein-Coated NPs

The use of protein-coated NPs in multifunctional therapeutic techniques is very important in the treatment of Alzheimer's disease [120]. SA-NP formulation improves the efficacy of R-flurbiprofen, an anti-AD medication, in lowering Aβ peptide toxicity in the brain [121]. SA-NPs, including R-flurbiprofen, are employed to transport tacrine and can sustain bioavailability while causing minimal hepatotoxicity [100]. In addition, NPs combined with BSA and sialic acid have been employed to identify early Aβ production in the start of AD [122]. Furthermore, administered protein-based NPs act as contrast agents in the brain, allowing for improved imaging to examine Aβ plaques [122]. Antibody (Ab)-Decorated NPs. To cure Alzheimer's disease, using immunotherapy dosages against amyloid aggregates causes major adverse effects such as meningoencephalitis [123]. To reduce the negative effects of immunotherapy, the use of NPs coated with antibodies for specific target proteins may be the most effective way to identify and dissolve protein aggregations in brain cells. Secondary ion mass spectrometry is used to image AD-associated proteins in the brain using antibodies coated with metal oxide nanoparticles [124].

Chitosan-based nano-vehicles coated with modified Ab fragments are employed to target Aβ amyloids in AD cells. NP-Ab formulation is used with contrast agents such as FITC and Alexa Fluor [100] to improve absorption across the BBB and diagnostic accuracy. NP-Ab formulations are used with contrast agents as FITC and Alexa Fluor [100]. W20/XD4-SPIONs, a combination of super paramagnetic iron oxide NPs and Aβ oligomer-specific scFv-AbW20 and class A scavenger receptor activator XD4, show promise for treating Alzheimer's disease [125]. Another study found that superparamagnetic iron oxide NPs coupled with Aβ oligomer-specific scFv-antibody and class A scavenger receptor activator have promising early diagnostic potential for Alzheimer's disease [125]. PEG-NPs coated with particular Abs can breakdown Aβ-42 [126]. Decorating the surface of PLGA NPs with 83-14 monoclonal Ab could substantially attenuate the neurotoxicity generated by Aβ fibrils in AD brain [127-130].

Conclusion

AD is a progressive neurological disease that currently lacks an effective treatment. Current approved pharmacological treatments are exclusively focused on symptom control and slowing disease progression. Obstacles to understanding the etiology of the disease, the development of medications that target a specific therapeutic target, and the following design of clinical trials are all reasons for the failure of available therapies.

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