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Review Article

Anatomy Section

Neurotoxicity of Amyloid Beta and its Association with other Biomarkers in Pathogenesis of Alzheimer's Disease: A Narrative Review

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ABSTRACT

Amyloid beta (Aβ) deposition in the brain is regarded as an early toxic effect in the aetiopathogenesis of Alzheimer's Disease (AD). Currently, Aβ is considered a key marker for AD and a promising target for drug development for the future management of debilitating diseases such as AD. However, the pathomechanism of Aβ has not yet been precisely understood in terms of AD patients, specifically regarding the pathological forms of Aβ and how it associates with other biochemical markers to cause dementia. Identifying Aβ as a key hallmark, especially at the earliest stages of the disease, is essential for understanding the progression of AD and its applicability for the development of novel therapeutics aimed at managing cognitive impairment and AD. This review aims to explain the neurotoxicity of Aβ and its correlation with various other biological markers that contribute to the induction of AD and memory deterioration.

Keywords: Biomarkers, Dementia, Memory, Neurodegeneration

INTRODUCTION

Alzheimer's Disease (AD) is a chronic progressive neurodegenerative disorder characterised by declining memory, personality changes, brain atrophy, and synaptic dysfunctions [1]. Epidemiological evidence shows that approximately 57.4 million people are currently affected by dementia, and this number is predicted to surpass 152.8 million by 2050, making it one of the major health burdens globally [2]. The aggregation of β-amyloid (Aβ) plaques and Neurofibrillary Tangles (NFT) are well known key pathological hallmarks of AD [3]. The accumulation of β-amyloid in the brain is implicated as the primary trigger of the pathomechanism of AD. However, the pathogenesis of Aβ formation in the cerebral cortex (temporal lobe) is not yet fully understood. In this context, present review aimed to determine the pathomechanism of the protein (Aβ) in the formation of amyloid plaques and its interaction with other biological markers that could aggravate the disease condition.

Risk Factors

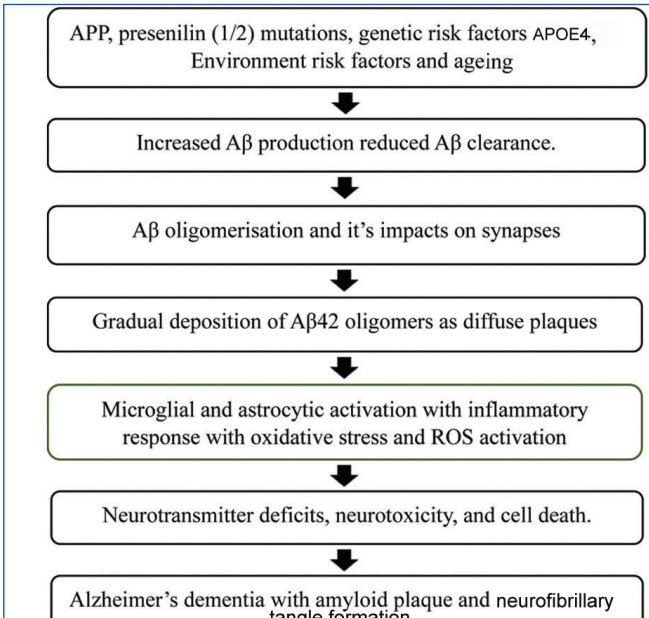
AD is a multifactorial disease that develops from a plethora of known contributing factors, such as ageing, genetic predisposition, and family history. Among these, ageing is one of the most common risk factors. The total number of people with AD dementia is projected to reach 13.8 million by 2050, with 7.0 million individuals aged 85 years or older [4]. Additionally, the APOE4 genotype has a significant impact on increasing Aβ deposition, leading to Late-Onset Alzheimer's Disease (LOAD). Individuals with a family history of Alzheimer's-specifically those who have or had a parent or sibling (first-degree relative) with the disease-are more likely to develop the condition than those without a first-degree relative affected by AD [5].

Genetic factors: The majority of AD cases are sporadic and induced by several pathological markers, while Early-onset AD (EOAD) may result from autosomal dominant mutations in certain genes, including the Amyloid Precursor Protein (APP), Presenilin-1 (PS-1), and Presenilin-2 (PS-2). One of the allelic variants of the apolipoprotein E gene, APOE4, is considered the strongest genetic factor for the initiation of both EOAD and LOAD [6].

Vascular risk factors: Recent literature highlights modifiable risk factors such as hypertension, diabetes, obesity, increased alcohol intake, smoking, and Cerebrovascular Accidents (CVA) that increase the likelihood of developing the pathophysiology of AD or other forms of Alzheimer's-Related Dementia (ARD) [6,7].

Psychosocial factors: Psychosocial factors are also known to contribute to the development of cognitive impairment and dementia. Several studies have identified loneliness, depression, sleep disturbances, anxiety, hallucinations, and low Socio-economic Status (SES) as important contributing factors in the pathogenesis of AD [8].

Amyloid cascade hypothesis: In 1992, Hardy JA and Higgins GA proposed the amyloid cascade hypothesis for the pathophysiology of AD [Table/Fig-1] [9]. This hypothesis illustrates that the aggregation of fibrillary Aβ is the principal contributing factor in the development of AD. Furthermore, the prominent occurrence of Aβ plaques and mutations within the Amyloid Precursor Protein (APP) pathway affect



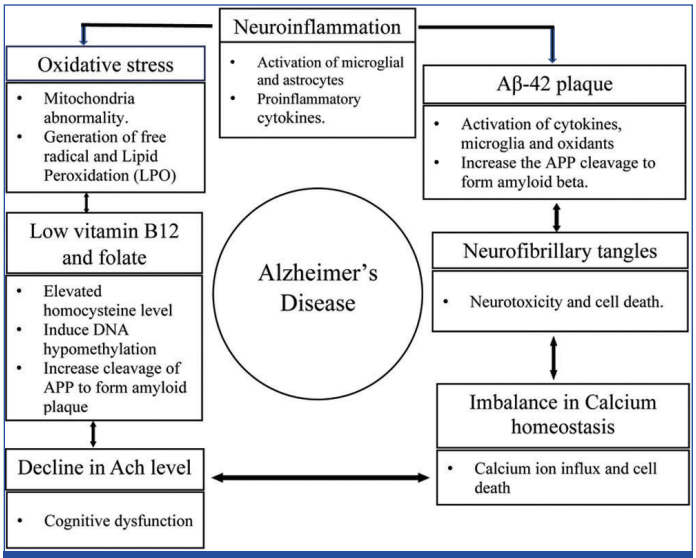
[Table/Fig-1]: Amyloid cascade hypothesis explains the pathogenesis of Alzheimer's Disease (AD) [9].
APP: Amyloid precursor protein; APOE: Apolipoprotein E gene; Aβ: Amyloid beta; ROS: Reactive oxygen species

the generation of Aβ plaques, which leads to Familial Alzheimer's Disease (FAD). Amyloid plaques are insoluble protein clumps formed by the cleavage of APP by the γ-secretase complex, as well as by the production of 42-amino acid peptides known as Aβ-42 or Aβ [10]. These amyloid plaques exacerbate the pathogenesis of AD dementia and cognitive impairment, a phenomenon collectively termed the "amyloid cascade hypothesis." Additionally, the aggregation of beta-amyloid is considered a intrinsic component in the formation of NFT, vascular damage, and cellular death. The cleavage of APP by Beta-site APP-cleaving Enzyme (BACE) and gamma-secretase involves a 695-amino acid membrane protein. The cleavage sites of APP by these enzymes differ at the N-terminal domain of the Aβ sequence, and gamma-secretase initiates the action of presenilins (1 and 2), which cleave APP through endopeptidase and carboxylase activities. Consequently, mutations in APP and presenilins (1 and 2) contribute equally to FAD [11]. However, other mechanisms, including ageing, oxidative stress, and genetic mutations, can disrupt Aβ homeostasis, potentially leading to the accumulation of plaques and the production of Aβ oligomers. These Aβ oligomers are significantly neurotoxic and result in neuronal death, cognitive impairment, and dementia [12].

Formation of Aβ oligomers and fibrils: The transformation of Aβ from a monomeric to a fibrillar form during its molecular life cycle passes through an oligomeric form (Aβos). The unfolded monomers, upon joining with partially folded monomers, form transient small Aβ oligomers. Once structured Aβ oligomers are formed, protofibrils (β-sheets) are added to create fibrils, which aggregate to form amyloid plaques [13]. Cellular degradation and clearance pathways assist in removing misfolded proteins and preventing the aggregation of fibrils. Thus, any disturbances in these pathways result in the deposition of amyloid proteins [14]. During protein aggregation, secondary nucleation on Aβ amyloid fibrils produces Aβ-42 oligomers, which are associated with the process of amyloid genesis [15]. The interaction of monomeric Aβ with the α1β1 complex of Na-K ATPase disrupts neuronal transmembrane potential, while the association between adrenergic receptor α2A and Aβ oligomers activates Glycogen Synthase Kinase 3β (GSK-3β) and induces hyperphosphorylation of tau protein. Additionally, the toxicity of Aβ oligomers substantially causes overactivation of N-methyl-D-aspartate Receptors (NMDAR), resulting in direct neuronal injury and promoting cell death [16].

Aβ biogenesis: Aβ is derived from the breakdown of APP by BACE1 and γ-secretase, while APP is encoded by the APP gene on chromosome 21 [17]. However, α-secretase processes APP through a non toxic mechanism to generate Aβ. The intracellular Aβ is distributed in the neuronal cytosol and the Endoplasmic Reticulum (ER), which are normal sites for its regulation. BACE1 cleaves APP at the Asp1 or Glu11 positions of the Aβ sequence, while γ-secretase cleaves presenilin at the ε-, ζ-, and γ-cleavage sites, releasing the Aβ Intracellular Domain (AICD). Additionally, abnormal mutations in presenilin due to environmental factors can disrupt γ-secretase activity, potentially leading to smaller cuts in the APP molecule and ultimately resulting in a longer Aβ peptide chain [18]. The monomeric form of Aβ clusters to form toxic oligomers, which aggregate into protofibrils and eventually into fibrils containing β-sheets. Thus, increased production of Aβ is a well known contributing factor to the development of AD dementia [19].

Toxicity of Aβ: The formation of Aβ plaques is a key factor that induces neurotoxicity and cell death. Furthermore, Aβ interacts with specific cell surface receptors and proteins, triggering the production of Reactive Oxygen Species (ROS), which causes cytotoxic effects and alterations in the nervous system, as well as mitochondrial dysfunction. Additionally, ROS react with proteins and lipids to form oxidised proteins and oxidised lipids, known as lipid peroxides, which can disrupt biological structures, including membrane integrity, and potentially affect crucial enzymes such as Glutamine Synthetase (GS) and Creatine Kinase (CK), both of which are vital for neuronal function [20,21]. Moreover, Lipid Peroxidation (LPO) generates toxic products like 4-Hydroxy-2-Nonenal (HNE) and 2-propenal (acrolein), which exert hazardous effects on neuronal structures, cellular function, Ca2+ metabolism, and mitochondrial dysfunction, contributing to neurotoxicity. Furthermore, Aβ plaques mediate the release of inflammatory chemicals, including eicosanoids, chemokines, and proinflammatory cytokines, which hinder the microglial clearance of Aβ. As a result, this leads to microglial-mediated apoptosis, loss of synaptic plasticity, inflammation, and excitotoxicity, all of which are associated with neurotransmitter receptors and ultimately contribute to AD. Association of Aβ with other biochemical markers in the pathogenesis of Alzheimer's disease [Table/Fig-2].



[Table/Fig-2]: Association of Amyloid Beta (Aβ) with other principal biomarkers.

Elevated homocysteine levels: Raised homocysteine levels, along with decreased vitamin B12 and folate, are suggestive factors in the development of neurodegenerative disorders, including AD. Homocysteine is a key component of methionine metabolism, which includes its remethylation by Methionine Synthase (MS), influenced by vitamin B12 and folate as intrinsic cofactors, while 5-methyl Tetrahydrofolate (THF) serves as the methyl donor. Furthermore, methionine interacts with Adenosine Triphosphate (ATP) to form S-Adenosyl Methionine (SAM), catalysed by the enzyme S-adenosylmethionine synthase, which utilises the active form of vitamin B6, pyridoxal-5'-phosphate (PLP), as a coenzyme. Later in the metabolic cycle, depletion of SAM results in the formation of S-adenosylhomocysteine (SAH), which is subsequently hydrolysed into homocysteine. Moreover, inborn errors in vitamin B12 and folic acid metabolism affect the regulation of the SAM/SAH ratio, leading to elevated homocysteine levels (hyperhomocysteinemia). Hyperhomocysteinemia exacerbates DNA hypomethylation, which may induce mutations in the presenilin-1 gene (PS1) and promote the cleavage of Amyloid Precursor Protein (APP) by β-secretase, resulting in the formation of amyloid plaques [22,23]. A study using transgenic mouse models confirms that hyperhomocysteinemia induces the phosphorylation of GSK-3β, significantly decreasing its activity while increasing kinase activity, thereby generating elevated Aβ levels via the γ-secretase pathway. Furthermore, dysregulation of the activities of Cyclin-dependent Kinase 5 (CDK5), GSK-3β, and Protein Phosphatase-2A (PP2A) contribute significantly to the development of tau pathology [22].

Oxidative stress: Oxidative stress serves as a potential factor in the progression from normal ageing to AD by disrupting membrane permeability, altering the cytoskeleton, causing mitochondrial damage, and leading to cell death [24,25]. Increased protein oxidation, LPO, free carbonyls, alcohol, aldehydes, and oxidative modifications in nuclear and mitochondrial DNA are well known key elements of oxidative stress [26], which induce cytotoxicity

by generating free radicals and destabilising biological molecules. Additionally, oxidising agents and LPO products, such as 4-HNE, increase the activity and expression of APP, β-site amyloid precursor protein cleaving enzyme 1 (BACE1), and γ-secretase, followed by upregulation of PS-1, ultimately leading to Aβ overproduction [27].

Endoplasmic stress (ER stress): ER stress plays a critical role in various biological functions, including protein biosynthesis, maturation, proper folding, post-translational modification, and the assembly of newly synthesised proteins. The aggregation of amyloid plaques introduces deleterious effects on the ER, which can compromise its integrity and function, leading to the accumulation of unfolded proteins in its lumen. This accumulation further results in irreversible ER stress and activates the Unfolded Protein Response (UPR^{ER}) [28,29]. Additionally, the aggregation of misfolded proteins disrupts intracellular Ca^{2+} balance, initiating a decline in protein synthesis. During ER stress, three stress-responsive transmembrane proteins-Pancreatic ER Kinase (PERK), Activating Transcription Factor-6 (ATF-6), and Inositol-Requiring Enzyme-1 (IRE-1)-are activated to initiate the UPRER. Glucose-Regulated Protein (GRP78) also serves as a key sensor in this response. PERK facilitates the breakdown of ATF-6 (P50) and phosphorylates eukaryotic Initiation Factor 2 (eIF2α), which induces the expression of ER chaperones such as GRP78. Since ER stress is a sensitive factor that can be modulated by the overexpression of chaperone molecules, a decreased expression of these chaperones may alternatively promote the formation of Aβ-42. Moreover, overexpression of BACE-1 and increased levels of APP are significantly linked with ER stress, which in turn leads to the formation of Aβ in the temporal lobes of the cerebrum. Aβ-induced GRP78 dysregulates Ca^{2+} homeostasis via ER stress. This Ca^{2+} imbalance may promote mutations in presenilin-1/2 and activate Reactive Oxygen Species (ROS), leading to oxidative stress and mitochondrial dysfunction, ultimately inducing cytotoxic effects [30,31].

The cholinergic hypothesis: The cholinergic hypothesis states that the neurotoxic effects of Aβ directly correlate with reduced acetylcholine (ACh) levels at the neuronal level or a defect in the biosynthesis of ACh at the synapse [32,33]. However, the concentration of ACh can be affected by a deficiency of choline acetyltransferase (ChAT), which is regarded as the key enzyme for ACh synthesis, catalysing the action of acetylcholinesterase. Acetylcholinesterase is another essential enzyme for cholinergic transmission at the synapse, as it is involved in accelerating the hydrolysis of ACh. Severe deficiencies or defects in cholinergic transmission from the basal frontal lobe can lead to presynaptic cholinergic impairment, which correlates with the severity of dementia and deterioration of memory in AD. Additionally, the interaction of presenilin-1 (PS-1) and acetylcholinesterase enhances APP expression and promotes the formation of Aβ [33].

Metal ions hypothesis: Dyshomeostasis or increased concentrations of metal ions (Copper, Zinc, Iron, Calcium) promote the formation of Aβ in AD. Furthermore, the interaction of Aβ with these metal ions introduces oxidative stress, leading to an increased production of ROS as well as disturbances in hydrogen peroxide (H2O2) levels [34]. Additionally, higher concentrations of metal ions can directly or indirectly disrupt organelles, ER stress, mitochondrial damage, autophagic dysfunction, and impairing Blood-Brain Barrier (BBB) function, including synaptic functions. Consequently, this promotes the generation of amyloid plaque formation and tau hyperphosphorylation by activating protein kinases such as secretases, GSK-3β, CDK5, and Mitogen-Activated Protein Kinases (MAPKs), while inhibiting PP2A [34].

Cholesterol transport: The regulation of lipids, including cholesterol, is a driving factor for normal brain function, synaptogenesis, and neuronal differentiation. Disruptions in phospholipids, cholesterol, or fluctuations in cholesterol concentration negatively impact the formation of amyloid peptides, BBB integrity, mitochondrial function, oxidative stress, inflammation, and neurodegeneration [35]. Moreover, ApoE4 plays a significant role in transporting cholesterol from astrocytes to neurons via lipoproteins, thereby influencing AD pathology [36]. Additionally, APOE4 affects lipid transportation between cells and Aβ clearance, which eventually promotes Aβ aggregation into toxic conformations [37]. Similarly, the oxidised form of cholesterol (oxysterol) also leads to neuroinflammation and cytotoxic effects in the brain [38]. Furthermore, free radicals generated from 7-oxocholesterols increase the production of ROS, leading to mitochondrial dysfunction, including changes in oxidative phosphorylation [39].

Association of AD and synaptic failure: Synaptic failure, a characteristic manifestation of AD, is strongly linked with Aβ deposition and tau hyperphosphorylation [40]. Moreover, extracellular glutamate accumulation and a disturbed glutamate cycle due to the toxicity of Aβ result in synaptic disturbances. Conversely, the formation of Aβ plaques also leads to glutamate spillover through α7 nicotinic ACh receptors (α7nAChR), which stimulates extrasynaptic NMDARs, ultimately contributing to neurotoxicity [40]. Additionally, previous studies have reported that Aβ oligomers activate astrocytes and increase the release of glutamate through nAChR, further stimulating extrasynaptic NMDARs [41]. Similarly, Aβ promotes the induction of extracellular glutamate, considered a detrimental factor, leading to the enhancement of extrasynaptic NMDARs, Long-Term Potentiation (LTP), Long-Term Depression (LTD), and synapse loss. Furthermore, the neurotoxicity of Aβ is also associated with the endocytosis of NMDARs in cortical neurons and a depression of NMDA-evoked currents, which, in turn, activates nAChRs and causes NMDAR agonist-induced delayed cognitive dysfunction. Additionally, the disruption between NMDAR activation and Aβ production leads to the upregulation of NMDAR overactivation and Aβ deposition, ultimately resulting in impaired synaptic plasticity and cognitive function in AD [42].

Neuroinflammation: Neuroinflammation is recognised as a significant event that induces the formation of amyloid plaques and NFTs in AD. Microglia and astrocytes play key roles in processing inflammation in the central nervous system and contribute to the pathogenesis of dementia and cognitive impairment. Furthermore, accumulated neurotoxic proteins like Aβ and tau proteins result in the release of a myriad of proinflammatory cytokines, including Tumour Necrosis Factor alpha (TNF-α) and Interleukin (IL-6). Other important protein kinases that upregulate amyloid plaques include GSK-3β, MAPK, and Cell Division Cycle 2 Kinase (CDC2K), all of which are influenced by inflammatory markers in the progression of AD and cognitive impairment [43]. Moreover, the neurotoxic effects of Aβ contribute to the release of Nitric Oxide (NO), ROS, proinflammatory cytokines, and chemokines, and vice versa. Additionally, Aβ toxicity influences astrocytes and microglia, leading to a process called reactive gliosis, which promotes the expression of an astrocyte-specific intermediate filament protein (GFAP) and Allograft Inflammatory Factor-1 (AIF-1), a microglial-specific protein that is significantly increased in AD. Furthermore, microglial cells produce an abundance of proinflammatory cytokines, including IL-1, IL-6, and other toxic products such as ROS, NO, and cytokines, which likely enhance APP production and Aβ formation. In addition, the deposition of Aβ may interact with various microglial receptors like CD14, CD36, and CD47, while inflammatory activity occurs through the binding of Aβ to CD36 [44].

DISCUSSION

The Aβ peptide can interact with potential receptors and activate downstream pathways, leading to the generation of oxidative stress and ROS. This, in turn, induces the hyperphosphorylation of Tau protein, activates microglial and astrocyte cells, and triggers inflammatory responses, which may result in neuronal death and contribute to AD. The neurotoxic effects of Aβ and its possible interlinking with other biological markers have been compared in [Table/Fig-3] [45-52].

Author(s), publication year	Study place	Sample size	Outcome of study
Torres LL et al., [45], 2011	Romania	45	A study evaluated the enzymatic markers of oxidative stress like Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPX), as well as Lipid Peroxidation (LPO) markers like Malondialdehyde (MDA) in serum level were decreased for Mild Cognitive Impairment (MCI) and AD patients, compared with age-matched healthy controls. Further, they concluded enzymatic markers of oxidative damage could be key components to develop the AD pathology.
Padurariu M et al., [46], 2010	Brazil	29	A study found that increased peripheral oxidative stress markers and reduced antioxidant enzymatic activities were positively linked with memory impairment and Aβ in AD. Additionally, an increase in plasma MDA levels and a decreased glutathione reductase/GPX ratio were also noticed in MCI and AD patients.
Zhang H et al., [47], 2012	USA	30	A study in transgenic mice model advocated formation of protein mixed disulphide (Pr-SSG) might be an indicator for the formation of amyloid plaque. Increased mixed-disulfides in the hippocampus might be the possible inducing element to cause increasing oxidative damage under oxidising conditions [48].
Vishnu VY et al., [48], 2017	India	68	Previous study witnessed that proinflammatory markers (IL-6 and CRP) were not significantly associated with Aβ formation in AD, but the plasma fibrinogen was remarkably linked with vascular dementia.
Rani P et al., [49], 2017	India	45	The study revealed formation of Aβ in AD is directly correlated with LPO. Further, Aβ also evolves into a peroxidant which induces increased oxidative stress and LPO. Additionally, Aβ also strongly linked with the Hydroxy-Non-Enal (HNE) MDA and other pathological markers in AD.
Atluri VSR et al., [50], 2019	USA	84	Recent study revealed deposition of Aβ in the brain is one of the key hallmarks of AD pathology which might be further influenced by neuroinflammatory processes such as Nucleotide-binding oligomerisation domain, leucine-rich repeat and pyrin domain containing 3 (NLRP3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFm-κB) considered as the principle neuroinflammatory pathways to accelerate the AD pathogenesis.
Wilczynska K et al., [51], 2021	Ploand	60	A study found significant association between inflammatory biomarker (YKL-40) and t-tau Aβ1-42/Aβ1-40) and with the severity of cognitive decline.
Foley KE et al., [52], 2024	USA	837	A recent finding found significant association between the plasma biomarkers (Aβ40, Aβ42, Aβ42/40, ptau181, total tau, and NFL) and the peripheral inflammatory biomarkers such as (TNFα, IL6, IL8, IL10, and GFAP) in the Late Onset of Alzheimer's Disease (LOAD).

[Table/Fig-3]: Illustrates the comparative view of neurotoxic effects of Amyloid Beta (Aβ) and it's possible interlinking with other biological markers [45-52].

CONCLUSION(S)

The Aβ peptide is considered a key biological marker for understanding the pathomechanism of AD. Since AD is a complex phenomenon caused by multiple factors, several biochemical markers, such as the hyperphosphorylation of tau protein and oxidative damage, have been established to varying extents to accelerate the pathogenesis of AD. Determining key biological markers, such as Aβ, is essential for understanding the pathomechanism of AD and is crucial for developing novel therapeutics and future management strategies for the disease. Aβ, as an ideal biomarker, must be identified in disease candidates at the earliest stages of the disease through minimally invasive or non invasive approaches, which could be beneficial in slowing down the progression of AD.

Author's contribution: Conceptualisation: RPS, CSV, Data curation: CSV, PP, Investigation: RPS, PP, Methodology: RPS, AKY, PS, supervision: CSV, SJ, PP, Writing original draft: RPS, CSV, Writing-review and editing: AKY, PS, SJ.

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