Exploring Alzheimer's disease: Biomarkers, Herbal Treatments, Therapies, and Non-Aβ Modulators of Neuroinflammation

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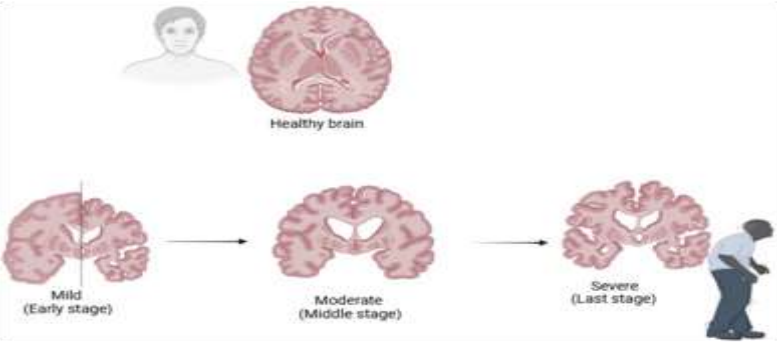
ABSTRACT The most frequent cause of dementia in older persons is Alzheimer's disease (AD), a progressive neurological illness. It has a major influence on people's everyday lives and quality of life and is typified by behavioral changes, memory impairment, and cognitive decline. Alzheimer's disease is pathologically linked to the buildup of tau protein tangles and amyloid-beta plaques in the brain, which causes neuronal death and dysfunction. Although the precise cause is yet unknown, lifestyle, environmental, and genetic variables all play a part. Age, family history, and the existence of the APOE-ε4 allele are risk factors. Alzheimer's disease currently has no known cure, despite scientific advancements; the main goals of available treatments are to control symptoms and delay the illness's progression. By focusing on fundamental systems including the tau and amyloid pathways, ongoing research attempts to create disease-modifying treatments. A healthy lifestyle, cardiovascular health, and cognitive engagement are examples of preventive methods that have the potential to lower risk.

KEYWORDS: Alzheimer disease (AD), Neurodegenerative, Hyperphosphorylated, Tau-protein tangles, Dementia, Neuroinflammation, Cholinergic dysfunction, Biomarkrs.

INTRODUCTION

Clinically, Alzheimer disease (AD) is a neurodegenerative condition marked by a progressive loss of cognitive abilities. Neuronal and synaptic loss, extracellular deposition of amyloid-β (Aβ) peptides in the form of amyloid plaques, neuritic dystrophy, intraneuronal accumulation of hyperphosphorylated tau (p-tau) in the form of neurofibrillary tangles (NFTs), vascular changes, and inflammatory responses, which are mediated by microglia and astrocytes, are pathological features of AD [1]. Given the rising life expectancy rates, it is anticipated that by 2050, 139 million people worldwide would have dementia, up from the current estimated 50 million who suffer from dementia in some capacity [2]. Chronic and acquired memory impairment, cognitive deficiencies in language, spatiotemporal orientation, and executive function, and behavioral changes are all hallmarks of AD, which ultimately results in a gradual loss of personal autonomy [3]. [4] AD has been classified into two types: sporadic and familial. Autosomal dominant familial AD presents as early onset (EOAD) in people under 65 (representing 1 to 5% of cases), and is typified by changes in certain genes, including the presenilin 1 gene (PSEN1, 14q24.2), which is found in up to 70% of cases of familial AD; the presenilin 2 gene (PSEN2, 1q42.13); and the Amyloid precursor protein gene (APP, 21q21.3). The late-onset (LOAD) sporadic presentation affects those over 65. It is believed that age is the primary risk factor [5]. Numerous theories, such as the amyloidogenic cascade, tauopathy, vascular theory, oxidative stress, neuroinflammation, and bacterial infection theory, have been proposed to explain the onset of AD [6].

STAGES OF ALZHEIMER DISEASE



SPECIFIC ATTENTION TO ALZHEIMER'S DISEASE BIOMARKERS

Alzheimer's disease (AD) biomarkers are particular biological markers that aid in the illness's diagnosis, prognosis, and progression monitoring[7] They can be employed to identify the illness, distinguish it from other types of dementia,[8] and track how well treatment plans are working[9]. Usually, these biomarkers are found in physiological fluids (such as blood and cerebrospinal fluid, or CSF) or by using neuroimaging methods [10]

Category	Examples of biomarkers	Special consideration	Clinical relevance
Amyloid pathology[11]	Amyloid PET and Amyloid-beta (Aβ42, Aβ40)[12]	Cut-off levels vary by assay type and demographic. Imaging diagnostics such as PET scans are expensive.[13]	Alzheimer's disease early diagnosis and detection. **[14]**
Tau pathology[15]	Tau PET, phosphorylated tau (p-tau), and total tau (t-tau)[16]	Correlation with the stages of neurodegeneration. Variability in the techniques used to collect cerebrospinal fluid (CSF)[17].	Tracking progress and distinguishing this dementia from others. **[18]**
Neurodegeneration[19]	Neurofilament light chain (NfL), brain atrophy based on MRI[20]	Not exclusive to Alzheimer's disease; it is also high in other neurodegenerative conditions. Longitudinal measures are necessary[21].	Monitoring the course of the illness and the effects of treatment[22].
Blood based biomarkers[23]	Plasma NfL, Plasma Aβ, and Plasma p-tau[24].	- Newer and easier to use, but less sensitive than imaging or CSF. Assay standardization is still necessary[25].	Diagnostic instruments that are less intrusive and easier to use are being developed[26].
Synaptic function[27]	Neurogranin and synaptosomal-associated protein 25 (SNAP-25)[28].	Neurogranin: Limited assay standardization. Predictive value varies in this emerging field[29].	Early on in the course of the disease, reflect synaptic damage[30].
Inflammation [31]	YKL-40, GFAP, Cytokines (IL-6, TNF-α)[32]	It is challenging to differentiate systemic inflammation in general from Alzheimer's-specific inflammation[33].	Potential contribution to our knowledge of illness mechanisms[34].

THERAPIES USED IN ALZHEIMER DISEASE(AD)[35]

Therapy type

1. **Cholinesterase inhibitor**
   Example: Donepezil
   Rivastigmine
   Galantamine[36]

Mechanism of action: In order to support cognitive function, increase acetylcholine by preventing its breakdown[37].

Clinical use/stage: For mild to moderate AD, approved[38].

Challenges and consideration: Restricted to gastrointestinal adverse effects and symptomatic alleviation[39].

2. **NMDA Receptor antagonist**
   Example : Memantine[40]

Mechanism of action: Reduces excitotoxicity by adjusting the brain's glutamate activity[41].

Clinical use/stage: For moderate to severe AD, approved[42]

Challenges and consideration: Ideal when used with inhibitors of cholinesterase[43]

3. **Anti tau therapies:**
   Example: Semorinemab
   Gosuranemab[44]

Mechanism of action: Prevent the creation of neurofibrillary tangles by targeting and inhibiting tau aggregation[45].

Clinical use/stage: Experimental[46]

Challenges and consideration: Currently being studied in clinical studies[47].

4. **Neuroinflammatory mediators[48]**

Example: NSAIDs, microglial inhibitors, and

Mechanism of action: Diminish the neuroinflammatory mechanisms linked to the pathophysiology of AD[49].

Clinical use/stage: Experimental [50]

Challenges and consideration: limited trial success and possible systemic impacts[51].

5. **Neuroprotective therapies[52]**

Example: PPAR agonists (e.g., pioglitazone), NGF or Nerve growth factor

Mechanism of action: less oxidative stress and increase neuronal survival[53]

Clinical use/stage: Experimental[54]

Challenges and consideration: Limited information, continuing efficacy trials[55].

6. **Hormonal modulators[56]**

   Example : Estrogen, Insulin (intranasal),

Mechanism of action: Address any hormonal or metabolic abnormalities that are causing AD pathology[57].

Clinical use/stage: Experimental[58]

Challenges and consideration: Results are mixed, although insulin may help with memory[59]

7. **Plasma therapy[60]**

Example : Albumin therapy, Plasma exchange

Mechanism of action: Eliminates inflammatory or amyloid-beta mediators by means of blood or plasma treatments[61].

Clinical use/stage : Experimental[62]

Challenges and consideration: Invasive, with inconsistent results in trials[63].

8. **Combination therapy[64]**

Example: Memantine + Donepezil

Mechanism of action: For improved management, target several paths at once[65].

Clinical use/stage : Approved for AD that is moderate to severe[66].

Challenges and consideration : Needs careful observation for adverse consequences[67].

HERBAL TREATMENT USED IN ALZHEIMER DISEASE (AD)[68]

The goal of herbal remedies for Alzheimer's disease (AD) is to control symptoms, enhance cognitive function, and delay the progression of the illness by utilizing natural plant-based chemicals69]. These remedies are not a cure and should only be used under a doctor's supervision to prevent drug interactions, even though they might supplement traditional medicines[70]. The following plant extracts and herbs have been investigated for possible advantages in Alzheimer's disease:

1. **Ginkgo Biloba**[71]

Benefits: Increases memory and cognitive function, lowers oxidative stress, and improves blood flow to the brain[72].

Mechanism: Reduces neuroinflammation and protects neurons by containing antioxidants[73].

Studies: Although the findings have been conflicting, it might be helpful in the early stages of dementia[74].

2. **Brahmi, or Bacopa Monnieri**[75]

Benefits: Well-known for improving memory and having neuroprotective qualities[76].

Mechanism: Contains bacosides that improve brain function and lessen the buildup of amyloid-betaplaque[77].
Evidence: Research indicates that it enhances older people's cognitive processing, memory, and attention[78].

3. **Withania somnifera, or ashwagandha**[79]

Benefits include increased brain plasticity, less anxiety, and improved memory[80].

Mechanism: Prevents neurodegeneration and increases neurogenesis[81].

Studies: Initial findings suggest that Alzheimer's disease-related damage may be reversible[82].

4. **Centella Asiatica, or gotu kola**[83]

Benefits: Improves cognitive and memory performance[84]

Mechanism: Enhances neuronal regeneration and repair by raising brain-derived neurotrophic factor (BDNF)[85].

Evidence: Research on animals points to enhanced learning and neuroprotective benefits[86].

Benefits : Include a reduction in inflammation and the development of amyloid plaque[88]

Mechanism: Curcumin, the active ingredient, possesses potent anti-inflammatory and antioxidant qualities[89].

Research: Curcumin may slow the progression of Alzheimer's disease pathology because it passes the blood-brain barrier[90].

5. **Sage (Salvia Officinalis and Salvia Lavandulaefolia)**[91]

Benefits : Helps individuals with mild to moderate Alzheimer's disease pay better attention and remember things better[92].

Mechanism: Increases acetylcholine levels in the brain by inhibiting acetylcholinesterase[93].

Clinical Evidence: Research indicates that after 16–24 weeks of use, cognitive function improves[94].

6. **Chinese Club Moss's (Huperzine A)** [95]

Benefits include memory enhancement and nerve cell protection[96].

Mechanism: like various Alzheimers drugs, it functions as a natural acetylchlinesteras inhibitor[97].

Studies: In several therapeutic trials, there is evidence of cognitive improvement[98].

7. **Benefits of Ginseng (Panax ginseng)** [99].

Benefits include improved cognitive function and decreased neuroinflammation[100].

Mechanism: Ginsenosides have anti-inflammatory and neuroprotective properties[101].

Research: Could enhance memory and mental clarity[102].

8. **Green tea (Camellia sinensis)**[103]

Benefits : Include protection against cognitive decline, a lower risk of neurodegenerative illnesses[104]

Mechanism : Epigallocatechin gallate (EGCG) lowers oxidative stress and amyloid-beta plaques[105].

Consideration [107]

Efficacy: Although certain herbs appear promising, the majority of trials are small or exploratory, and the data varies[108].

Safety: Drug interactions are possible with anticoagulants and anticholinesterase inhibitors[109].

Consultation: Always get medical advice before using herbal remedies, particularly if they are used with traditional medications[110]

NON-Aβ MODULATORS OF NEUROINFLAMMATION

Non-amyloid beta (Aβ) modulators of neuroinflammation refer to compounds or therapeutic approaches that target pathways involved in neuroinflammation without directly modifying amyloid beta (Aβ) plaques[111]. Aβ accumulation and aggregation are hallmark features of Alzheimer's disease, but recent research has focused on neuroinflammation as a critical factor in neurodegenerative diseases[112]. While Aβ-modulating treatments focus on reducing amyloid plaques, non-Aβ modulators aim to control the inflammatory response in the brain, which can contribute to neuronal damage and disease progression.

1. Inhibition and Activation of Microglia

Compounds or therapy strategies that target neuroinflammation pathways without directly altering amyloid beta (Aβ) plaques are referred to as non-amyloid beta (Aβ) modulators of neuroinflammation[113]. Alzheimer's disease is characterized by Aβ buildup and aggregation, but neuroinflammation has been the subject of current studies as a crucial component of neurodegenerative illnesses[114]. Non-Aβ modulators try to regulate the brain's inflammatory response, which can lead to neuronal damage and the advancement of disease, whereas Aβ-modulating therapies concentrate on lowering amyloid plaques.

2. Modulation of Cytokine and Chemokine

Chronic inflammation is caused by inflammatory cytokines such TNF-α, IL-1β, and IL-6, which are increased in neurodegenerative disorders[115].

Inhibitors of TNF-α: The possibility of medications that target tumor necrosis factor alpha, like etanercept or infliximab, to alter neuroinflammation in diseases like Parkinson's and Alzheimer's is being investigated[116].

IL-1β inhibition: By focusing on the IL-1β signaling pathway, medications such as canakinumab (an IL-1β monoclonal antibody) can reduce inflammation[117].

3. Glial Cell Alteration

The secretion of pro-inflammatory cytokines is one way that astrocytes contribute to neuroinflammation[118]. By altering astrocytic function, neuroinflammation can be decreased[119].

Epigenetic modification: HDAC inhibitors, like valproic acid, are epigenetic regulators that have demonstrated promise in lowering neuroinflammation by altering the expression of genes that promote inflammation[120].

4. Pathway Modulators of NF-κB

One important transcription factor that controls inflammatory genes is NF-κB. Neuroinflammation and neurodegeneration are associated with long-term NF-κB activation. NF-κB signaling inhibitors like parthenolide and BAY 11-7082 may have neuroprotective and neuroinflammatory effects[[121].

5. Activators of Sirtuin

Sirtuins are proteins that play a role in inflammation, aging, and cellular stress reactions. It has been demonstrated that sirtuin activators, especially SIRT1, lower neuroinflammation and may have neuroprotective effects[122].

Resveratrol: In models of Parkinson's and Alzheimer's illnesses, this polyphenolic substance enhances neuronal survival, lowers neuroinflammation, and activates SIRT1[123].

CONCLUSION: Alzheimer's disease (AD) is the most prevalent type of dementia, mostly affecting older persons, and is a chronic, progressive neurological illness. Memory, thinking, and reasoning skills gradually deteriorate, which eventually makes it harder to carry out daily tasks. Amyloid-beta plaque buildup and tau protein tangles, which impair neuronal transmission and cause cell death, are two of

the brain's defining pathological characteristics. Alzheimer's is caused by a confluence of environmental and lifestyle factors, aging, and genetic predisposition, while the precise causes are yet unknown. The existence of specific genetic markers, like the APOE-ε4 allele, a family history of the disease, and advanced age are risk factors. Alzheimer's disease currently has no known treatment. In order to slow cognitive decline and enhance quality of life, treatment focuses on managing symptoms with pharmaceutical and non-pharmacological approaches. The condition may be prevented by adopting lifestyle modifications such consistent exercise, a balanced diet, mental stimulation, and cardiovascular health maintenance.

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