The role of neuroinflammation in Alzheimers disease progression

Simham Sudhakar[*1], Dr.M.Madhu[2], U.Narasimhulu[2], Dr.K.Adinarayana[3]
[*1]*Associate Professor, Department of Pharmacology, Annamacharya College of Pharmacy, Andhra Pradesh, India*
[2]*Associate Professor, Department of Pharmaceutical analysis, Annamacharya College of Pharmacy, Andhra Pradesh, India*
[3]*Professor, Department of Pharmaceutical biotechnology, Annamacharya College of Pharmacy, Andhra Pradesh, India*

***Abstract*— Alzheimer's disease (AD) is a progressive neurological disorder characterized by deficits in memory, cognition, behavior, and personality. Neuroinflammation significantly affects AD progression, with immune cells such as microglia and astrocytes playing crucial roles. Activated microglia release inflammatory molecules that can potentially initiate chronic inflammation. Astrocyte activation varies by brain region and disease stage and sometimes precedes microglial activation. Inflammatory proteins, including interleukins and tumor necrosis factor-alpha, promote inflammatory pathways and, with other molecules, induce neuronal death. The activation of the complement system in AD can contribute to and mitigate disease progression. The key features of AD include amyloid-beta accumulation, plaque formation, excessive tau protein phosphorylation, neurofibrillary tangle development, and synaptic impairment and loss, all of which are influenced by neuroinflammation. Initial neuroinflammation may be protective; however, prolonged inflammation exacerbates the disease. Potential therapies include anti-inflammatory drugs, immune system modulation, and treatments targeting microglia and astrocytes. Studying neuroinflammation in AD is challenging because of the complex immune response of the brain, limitations of animal models, and difficulties in translating the findings to humans. Emerging research on novel biomarkers, personalized medicine, and combination therapies targeting multiple aspects of neuroinflammation may lead to more effective prevention and treatment strategies for AD.**

***Keywords*—Alzheimer's disease, Neuroinflammation, Microglia, Astrocytes, Neurodegeneration, Cytokines, Amyloid-beta**

I. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by deterioration of memory, cognitive function, and alterations in behavior and personality [1]. It is the primary etiology of dementia in older adults. AD prevalence varies across geographical regions and demographic groups. In Europe, the overall prevalence rate is estimated to be 5.05%, with a higher incidence in females (7.13%) than in males (3.31%) [2]. The risk of developing AD increases significantly with age, and it is projected that the number of individuals aged ≥ 85 years affected by the disease will quadruple to 8.0 million by 2050 [3]. Moreover, approximately 31% of AD patients exhibit psychotic manifestations such as hallucinations and delusions, which can emerge even in the early stages of the illness [4]. Neuroinflammation significantly affects the progression of Alzheimer's disease (AD). Innate immune cells, particularly microglia and astrocytes, mediate neuroinflammation in AD, thus contributing to its pathogenesis [5]. A key feature of AD is microglial activation, which results in the release of proinflammatory cytokines. This process can potentially create a self-perpetuating cycle between neurons and microglia, leading to persistent low-level inflammation [6]. Chronic elevation of proinflammatory cytokines has been hypothesized to promote neurodegeneration. Certain inflammatory mediators, such as neuronal pentraxins, have demonstrated both neuroprotective and potentially detrimental effects in AD [7]. The JAK/STAT signaling pathway plays a crucial role in promoting neuroinflammation by triggering innate immunity, coordinating adaptive immune responses, and regulating neuroinflammatory processes [8]. Furthermore, extracellular vesicles (EVs) are important mediators of the immune system and are capable of activating molecular pathways that exacerbate neuroinflammatory processes in AD [9]. The objective of this review in Alzheimer's disease

progression is to provide a comprehensive overview of the existing research on monitoring changes over time using cognitive test batteries. It aims to analyze longitudinal investigations that track patients likely to have Alzheimer's, as diagnosed by established criteria, and employ validated assessment methods to evaluate disease progression.

II. ALZHEIMER'S DISEASE

2.1. Overview of Alzheimer's disease Pathology

Alzheimer's disease (AD) is a complex pathology involving interactions between various protein aggregates and vascular changes. It is characterized by progressive neuropathological alterations, mainly the accumulation of β-amyloid (senile plaques) and tau aggregates (neurofibrillary tangles) in the brain. These indicators are crucial for AD diagnosis and are accompanied by synaptic deterioration and vascular amyloid deposits [10]. AD progression is closely associated with the neuropathological changes that lead to brain dysfunction [11]. Rather than being a single disorder, AD comprises of a spectrum of conditions with diverse pathobiological subtypes. These subtypes exhibit distinct tau pathological patterns, clinical manifestations, age and sex distributions, biomarker levels, and network disruptions that cause cognitive decline. Additionally, AD often coexists with age-related co-pathologies such as cerebrovascular lesions, Lewy bodies, and TDP-43 pathology, influencing clinical presentation and accelerating disease progression.

2.2. Key players in neuroinflammation

Neuroinflammation is crucial for the progression of Alzheimer's disease (AD) and involves numerous essential components. Microglias, which are the immune cells of the brain, are pivotal in AD-related neuroinflammation [12]. They are activated in response to amyloid-β (Aβ) accumulation and other AD pathologies, releasing proinflammatory cytokines and potentially creating a self-perpetuating cycle in neurons, leading to chronic low-grade inflammation. The gut microbiome significantly modulates AD-related neuroinflammation. Dysbiosis, or alterations in gut microbiota, disrupts key AD mechanisms, including blood-brain barrier integrity and neurotransmitter regulation [13]. This gut-brain connection provides new insights into AD pathogenesis and therapeutic strategies. Interactions between microglia, the gut microbiota, and inflammatory mediators such as interleukins, tumor necrosis factor-alpha, and inflammasomes contribute to AD's complex neuroinflammatory process in AD [14]. Recent studies have highlighted the role of eicosanoids and polyunsaturated fatty acid metabolites in AD progression through their effects on brain and immune responses [15]. Understanding these factors and their interactions is vital for the development of targeted therapies and innovative approaches to mitigate AD progression.

2.3. The link between neuroinflammation and Alzheimer's

Recent research has highlighted the critical role of neuroinflammation in the disease (AD) etiology and progression of AD. Traditionally viewed as a proteopathy with amyloid-β plaques and neurofibrillary tangles [16], recent studies have emphasized the impact of persistent neuroinflammation on AD onset and progression. The association between neuroinflammation and AD has gained attention, demonstrating its effects on key brain functions, including adult neurogenesis [17]. This has led to the development of therapeutic strategies targeting the activation of the chronic immune system. The relationship between neuroinflammation and AD is bidirectional, as AD pathology induces inflammatory responses and neuroinflammation exacerbates AD progression [18]. Recent investigations have revealed complex interactions between neuroinflammation, the immune system, and AD pathology, focusing on microglia and the brain's primary immune cells. Additionally, studies have explored the systemic inflammation, gut microbiome dysbiosis, and blood-brain barrier dysfunction that contribute to AD-related neuroinflammation [19]. These insights provide a comprehensive view of AD as involving both central and peripheral inflammatory processes, paving the way for new therapies and emphasizing early intervention's importance [20].

III. MECHANISMS OF NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

3.1. Microglial activation and its effects

Microglial activation in Alzheimer's disease (AD) is a complex process. Initially, microglia may be protected by clearing amyloid-beta (Aβ) plaques, with Ccr2-dependent microglial accumulation enhancing Aβ clearance and slowing disease progression in mice [21]. However, prolonged activation produces excessive proinflammatory

cytokines such as interleukin-1 and tumor necrosis factor-α, leading to neuroinflammation and neurodegeneration [22]. Although some studies have shown that microglial activation worsens AD pathology, others have highlighted the importance of microglial activation in brain health. TREM2, a microglial gene, is crucial for Aβ-plaque pathology [23]. The shift from an anti-inflammatory M2 phenotype to a proinflammatory M1 phenotype is key to AD progression [24]. Future therapies may focus on modulating microglial activation, targeting pathways such as TREM2, or using flavonoids to promote the M2 phenotype [24].

3.2. Astrocyte reactivity

Astrocyte reactivity is pivotal in Alzheimer's disease (AD) development. As AD advances, astrocytes become structurally and functionally reactive to stimuli such as amyloid-beta (Aβ) accumulation [25]. This reaction can be both beneficial and harmful depending on the disease stage [26]. Reactivity patterns differ across brain regions and disease phases. Single-nucleus RNA sequencing has shown that astrocyte genes associated with tripartite synapses are dysregulated during the progression of tangle pathology [27]. In presenilin 1/2 conditional knockout mice, astrocyte activation preceded microglial activation in the somatosensory cortex, indicating the involvement of early astrocytes in neurodegeneration [28]. Astrocyte reactivity in AD involves complex molecular pathways and epigenetic mechanisms [29]. Understanding the roles and diversity of reactive astrocytes may reveal new therapeutic targets in AD.

3.3. Proinflammatory cytokines and their roles

Proinflammatory cytokines are crucial in the development of Alzheimer's disease (AD) and contribute to neuroinflammation and neurodegeneration. Specific interleukins (ILs) such as IL-1, IL-6, and IL-8, activate inflammatory pathways, while tumor necrosis factor-alpha (TNFα) can induce neurodegeneration alongside other proinflammatory cytokines [30]. Excessive production of these molecules exacerbates neurotoxicity and AD pathology [31]. Certain cytokines have mixed effects; for example, interferons (IFNs) show neuroprotective properties in some studies but promote neurotoxicity in others by inducing proinflammatory cytokines. Neuronal pentraxins display both protective and harmful effects in AD. The secretion of proinflammatory cytokines promotes neuroinflammation and neuronal damage, highlighting the need for a balanced understanding of neuroinflammation in AD [32].

3.4. Complement system activation

The complement system plays a multifaceted role in the progression of Alzheimer's disease (AD), with both protective and harmful effects. Complement proteins are linked to amyloid plaques and neurofibrillary tangles in AD brains, indicating their involvement in disease pathology [33]. Activation of the complement system can trigger neuroinflammation, microglial activation, and proinflammatory cytokine release, potentially worsening neurodegeneration [34]. While contributing to neuroinflammation and synaptic loss, the complement system may also help eliminate aggregated and toxic proteins, thus offering a protective effect [35]. The balance between these functions is crucial for disease progression. Moreover, the complement system interacts with other risk factors such as TREM2 and ApoE4, influencing neurodegeneration in both amyloid and tau models of AD [36]. Understanding this balance is vital for developing targeted therapies. Inhibiting specific components, such as the C5a receptor, has shown efficacy in reducing pathological markers and enhancing cognitive function in rodent models of AD [37]. Additionally, natural compounds and complement-targeted therapies are emerging as potential strategies for modulating their effects on the central nervous system in AD.

IV. THE RELATIONSHIP BETWEEN NEUROINFLAMMATION AND ALZHEIMER'S HALLMARKS

4.1. Amyloid-beta accumulation and plaques

Amyloid-beta (Aβ) accumulation and plaque formation are central to Alzheimer's disease (AD) progression. The amyloid hypothesis suggests that amyloid precursor protein (APP) cleavage to produce Aβ peptides is crucial for AD pathogenesis [38]. Aβ buildup begins years before cognitive symptoms begin, moving from intracellular to extracellular plaques, causing synaptic loss, energy metabolism impairment, and disruptions in protein and metal homeostasis [39]. However, studies on APP expression in AD are contradictory; some indicate that increased APP expression contributes to the disease, while others report reduced APP expression in AD-affected brains. Research shows that neuronal

APP expression increases with age in non-demented individuals, but decreases in AD patients as Aβ plaques mature [40]. This decline in APP levels may decrease neuronal resilience to stress and exacerbate the disease progression. Aβ accumulation and plaque formation significantly influence AD pathology and therapeutic strategies.

4.2. Tau hyperphosphorylation and neurofibrillary tangles

Excessive tau phosphorylation and neurofibrillary tangles (NFTs) are critical for Alzheimer's disease progression. Tau proteins, which are essential for neuronal microtubule structure, can undergo hyperphosphorylation, leading to NFT development, which is a hallmark of AD. This hyperphosphorylation reduces the microtubule-binding ability of tau, destabilizes the cytoskeleton, and potentially forms paired helical filaments that constitute NFTs [41]. However, tau hyperphosphorylation and NFT formation do not always correlate. Some intracellular tangles contain intact tau proteins that do not react with phosphorylation-specific antibodies, indicating that hyperphosphorylation may not be necessary for the development of NFT in AD. Additionally, research has linked tau hyperphosphorylation with glucose metabolism irregularities, suggesting a connection through hypothermia [42]. The interplay between tau pathology, oxidative stress, and impaired autophagy drives AD progression [43]. Understanding these processes is crucial for developing effective AD treatment and early detection methods.

4.3. Synaptic dysfunction and loss

Early Alzheimer's disease (AD) involves synaptic dysfunction and loss preceding significant neuronal death and is closely linked to cognitive decline. These synaptic changes are the primary cause of cognitive impairment in AD, with synaptic loss being the most reliable predictor of cognitive deterioration [44]. Amyloid-beta (Aβ) peptides and hyperphosphorylated tau proteins substantially contribute to these alterations, leading to memory impairment, cognitive decline, and disorientation [45]. Dysfunction in the locus coeruleus-noradrenaline system also plays a crucial role in AD progression, as reduced noradrenaline levels increase neuroinflammation, amyloid, and tau accumulation, and impair cognition and synaptic plasticity [46]. Additionally, extracellular vesicles from brain cells may mediate early synaptic changes in AD [47]. The anaphase-promoting complex/cyclosome-Cdh1 complex is implicated in synaptic plasticity and neuronal survival, and its inactivation causes dendrite disruption, synapse loss, and neurodegeneration [48]. Understanding the complex factors that contribute to synaptic dysfunction, such as oxidative stress, neuroinflammation, and impaired energy metabolism, could provide insights into the development of effective disease-modifying treatments for AD.

V. NEUROINFLAMMATION IN ALZHEIMER'S PROGRESSION

5.1. Early stages and potential protective roles

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, first evident as amnestic mild cognitive impairment (MCI) [49]. Early detection and intervention of AD are vital for mitigating its progression and potentially delaying its onset. In AD's early stages of AD, including MCI, various neuroimaging and cognitive markers are detectable, with alterations in the brain structure and function observed in both cognitively normal older adults and those with MCI, suggesting potential early detection biomarkers. Declines in working memory and executive function during MCI may signal a transition to AD [50]. Thalamic volume reduction is an early MCI indicator, whereas hippocampal and temporal region atrophy becomes more pronounced later [51]. Protective measures and interventions can slow AD progression, with exercise and physical activity programs targeting modifiable risk factors showing potential in maintaining brain health and preventing dementia [52]. Cognitive therapy during MCI, when neuroplasticity is present, may reduce the likelihood of AD progression. Additionally, certain herbs with neuroprotective, antioxidant, and anticholinesterase properties have shown promise for in the treatment of AD [53].

5.2. Chronic inflammation and disease exacerbation

Progression of Alzheimer's disease (AD) and cognitive decline are significantly affected by persistent inflammation. Systemic inflammatory signals can reach the brain and alter central nervous system (CNS) functioning, often resulting in sickness behavior syndrome. These changes are driven by cytokine and prostaglandin production in both the systemic circulation and CNS, potentially leading to delirium in patients with dementia, exacerbating

cognitive dysfunction and resulting in poor outcomes [54]. Both acute and chronic systemic inflammation are linked to elevated levels of proinflammatory cytokines, particularly tumor necrosis factor α (TNF-α), which is crucial for immune-brain communication. Research has shown that acute systemic inflammation can double the rate of cognitive decline over six months in patients with AD, while high initial TNF-α level can quadruple this rate [55]. This finding highlights the significant effect of inflammation on disease progression. Future studies should aim to develop targeted strategies to manage chronic infections and inflammation, possibly using antibacterial or anti-inflammatory agents to slow disease progression [56].

5.3. Late-stage neuroinflammation and cognitive decline

Neuroinflammation significantly influences Alzheimer's disease (AD) progression, particularly in later stages. Some studies have proposed neuroinflammation as an initial neurodegeneration trigger [57], whereas others have found that elevated inflammatory markers at baseline do not predict faster cognitive decline in mild cognitive impairment or AD dementia [58]. These findings suggest a complex relationship between neuroinflammation and cognitive decline. PET imaging studies have shown that neuroinflammatory biomarkers, along with amyloid and tau markers, predict longitudinal cognitive decline in patients with AD and MCI [59]. Conversely, a post-mortem study linked systemic infections in late-stage AD to reduced inflammatory marker expression and increased anti-inflammatory gene expression, indicating a potential immunosuppressive environment [60].

VI. POTENTIAL THERAPEUTIC TARGETS AND STRATEGIES

6.1. Anti-inflammatory drugs

Research has indicated that anti-inflammatory medications may slow the progression of Alzheimer's disease (AD). Current AD treatments only alleviate symptoms without slowing down the disease, emphasizing the need for new therapies [61]. The connection between the various theories of AD pathogenesis and neuroinflammation makes it a promising therapeutic target. Studies have suggested that anti-inflammatory drugs can delay AD onset and progression. Observational studies have linked NSAIDs to a reduced AD risk, but clinical trials have shown mixed results, with some indicating no benefits or adverse effects from long-term NSAID use [62]. The effectiveness of anti-inflammatory drugs in AD may depend on their target immune cells. Recruiting systemic immune cells, such as CD4+ T cells and monocytes, into the CNS may be necessary to manage harmful local inflammation [63]. This implies that systemic anti-inflammatory therapies might fail to halt neurodegeneration due to the suppression of recruitment.

6.2. Immunomodulation approaches

Innovative immune modulation approaches have shown efficacy in slowing the progression of Alzheimer's disease (AD) by targeting amyloid-β (Aβ) accumulation, tau pathology, and neuroinflammation. Immunotherapy, especially targeting Aβ, has the potential to alter the course of AD by using synthetic peptides or antibodies to reduce brain Aβ and slow disease progression [64]. Passive immunotherapy reduces large aggregates and improves cognitive function [65]. However, translating these successes into human treatments has been challenging, possibly because of the imprecise targeting. Previous studies have suggested that a combination of immunotherapies may be more effective. A vaccine targeting both Aβ and phosphorylated tau (pTau) epitopes showed promising results in 3xTg transgenic mice, eliciting strong antibody responses and significantly reducing Aβ plaques and tau tangles, improving cognitive function, and suppressing neuroinflammation more effectively than single-target vaccines [66]. Additionally, addressing neuroinflammation through LC3-associated endocytosis (LANDO) has the potential to reduce AD pathology and tau phosphorylation [67].

6.3. Microglial and astrocyte-targeted therapies

Recent studies have emphasized therapies that target microglia and astrocytes to slow their progression. Glial cells are crucial for neuroinflammation, which is a key factor in AD pathology. Research suggests that Ccr2-dependent microglial accumulation may protect against early AD stages by enhancing amyloid-beta (Aβ) clearance [68]. Additionally, NLY01, an engineered exedin-4 GLP-1R agonist, targets the glucagon-like peptide-1 receptor (GLP-1R) on microglia and effectively inhibits Aβ-induced microglial activation and reactive astrocyte formation [69]. However, microglia-targeted therapies can have various effects.

Modulation of inflammatory pathways often leads to different effects on tau and amyloid pathology, depending on the astrocyte phenotype and functions in various contexts [70]. This complexity highlights the need for a refined approach to the development of glial cell-targeted therapies.

VII. CHALLENGES AND LIMITATIONS

7.1. Complexity of the immune response in the brain

Alzheimer's disease (AD) involves a complex brain, immune response that engages both innate and adaptive systems. Neuroinflammation, marked by activated microglia and astrocytes, is crucial to AD pathogenesis and can be triggered by brain-specific insults or external factors, such as gut microbiome dysbiosis [71]. The immune response in AD varies according to pathological manifestations. Distinct immune activation patterns occur in the brains with "pure" beta-amyloid and tau pathology compared to those with Lewy body pathology, highlighting the disease-specific nature of neuroimmune interactions [72]. The evolving and region-specific immune landscape in AD complicates the development of targeted therapies [73].

7.2. Limitations of current animal models

The immune response in Alzheimer's disease (AD) progression involves both the innate and adaptive systems. Neuroinflammation, driven by microglial and astrocyte activation, plays a key role in AD pathogenesis and which is marked by the release of proinflammatory cytokines and neurotoxic factors that contribute to neurodegeneration [74]. The AD immune response also involves gut-brain crosstalk; gut microbiota dysbiosis can trigger brain inflammation, worsening AD by recruiting immune cells to the brain. Various molecular pathways and signaling molecules further complicate the immune response in AD. Type-I interferons regulate the innate immune response and contribute to AD progression [75]. MicroRNA-155 is crucial in neuroinflammation, influencing proinflammatory cytokine expression and blood-brain barrier integrity [76]. The interaction between tau pathology and immune responses adds further complexity to AD neuroinflammation [77].

7.3. Difficulties in translating findings to human patients

Despite significant research advancements, translating animal study findings to human Alzheimer's disease (AD) patients remains challenging. The failure to convert rodent data into effective treatments has raised doubts about the validity of the current models [78]. This challenge arises from AD's complexity of AD and the limitations of animal models in replicating the full course of the disease in humans. Animal models cannot accurately represent the entire spectrum of AD pathology and progression, often leading to promising results that do not translate into clinical trials. Researchers are exploring innovative approaches to identifying new biological targets during disease progression [79]. The focus was on developing models that better mimicked human AD pathology. Incorporating new elements such as innovative biomarkers, novel neuropsychological outcomes, and recruiting earlier populations in clinical trials may help bridge the gap between animal research and human applications [80].

VIII. EMERGING RESEARCH AND FUTURE DIRECTIONS

8.1. Novel biomarkers for neuroinflammation

Neuroinflammation is a key factor in the progression of Alzheimer's disease (AD), and has led to the development of novel biomarkers for early diagnosis and monitoring. Inflammatory mediators and glial proteins from microglial cells and astrocytes are promising biomarkers for AD-related neuroinflammation [81]. Advances in imaging and fluid biomarker technologies have identified surrogate markers of neuroinflammation in living individuals, thereby improving understanding of AD pathogenesis. Brain-periphery communication allows blood to reflect AD-related pathological changes, making it a valuable biomarker source [82]. Emerging techniques have identified biomarkers for various aspects of AD, including Aβ oligomers, tau proteins in the plasma and cerebrospinal fluid (CSF), and markers of synaptic dysfunction, neuronal damage, neuroinflammation, blood-brain barrier dysfunction, oxidative stress, and metabolic changes. Minimally invasive fluids such as saliva, urine, and ocular fluid are also being studied for early AD diagnosis and monitoring [83]. These advancements in biomarker research may improve AD diagnosis, prognosis, and therapeutic monitoring, potentially leading to more effective treatment.

8.2. Personalized medicine approaches

Personalized medicine in Alzheimer's disease (AD)

addresses the complexity of the disease by tailoring treatments to individual genetic, environmental, and lifestyle factors, enhancing efficacy, and minimizing adverse effects [84]. Integrating fluid biomarkers, genetic markers, and neuroimaging is essential for early diagnosis, monitoring disease progression, and evaluating treatment responses [85]. Although personalized medicine has advanced significantly in cancer treatment, its application to AD is still under development. However, progress in pharmacogenomics, targeted neurological approaches, and single nucleotide polymorphism detection has improved the diagnosis and treatment of AD [86]. Additionally, sex-related differences in AD suggest that sex may be significant in patient stratification and personalized treatment strategies [87].

8.3. Combination therapies targeting multiple aspects of neuroinflammation

Combination therapies targeting multiple aspects of neuroinflammation in Alzheimer's disease (AD) progression have shown promise. Recent studies have highlighted the efficacy of multi-target directed ligands (MTDLs) and combinational vaccines in addressing AD pathology [88]. A dual AD vaccine combining Aβ and pTau epitopes significantly reduces AD pathology in transgenic mouse models. This approach elicited strong antibody responses against pathological Aβ and pTau, effectively eradicating Aβ plaques and tau tangles, thus improving cognitive abilities more than individual vaccines. Additionally, the combined vaccine suppressed neuroinflammatory factors such as glass and proinflammatory cytokines, targeting multiple aspects of AD pathology. The development of MTDLs with pharmacophores that inhibit cathepsin B (CatB), dual specificity phosphatase 2 (DUSP2), and monoglycerol lipase (MAGL) is a promising strategy for reducing AD-associated neuroinflammation [89]. These targets have shown promising preclinical anti-inflammatory effects in vivo and in vitro, indicating their potential in addressing neuroinflammation in neurodegenerative diseases.

IX. CONCLUSION

In conclusion, elucidating the mechanisms of neuroinflammation in Alzheimer's disease (AD) is crucial for the development of novel preventive and therapeutic strategies. Targeting specific components of the inflammatory cascade, such as the NLRP3 inflammasome, shows promise in decelerating Aβ plaque formation and improving neurological function. Moreover, investigating alternative non-pharmacological interventions, such as microcurrent therapy, which has demonstrated potential in mitigating memory loss and reducing neuronal damage in animal models, may present new avenues for treatment. The impact of neuroinflammatory research on AD management and prevention is significant, potentially facilitating the development of more efficacious interventions that address underlying inflammatory processes and improve patient outcomes.

X. ACKNOWLEDGEMENTS

The authors express their sincere appreciation to all individuals who contributed to this study. This review was conducted with the support of the Department of Pharmacology at Annamacharya College of Pharmacy.

Conflict of Interest

The authors declare no conflict of interest related to this study.

REFERENCES

[1] A. M. Teplyshova and V. K. Datieva, “Alzheimer disease and epilepsy,” *Zhurnal nevrologii I psikhiatrii imeni S.S. Korsakova*, vol. 121, no. 10. Vyp. 2, p. 23, Jan. 2021, doi: 10.17116/jnevro202112110223.

[2] H. No, I. Álvarez-Álvarez, F. Guillén-Grima, and I. Aguinaga-Ontoso, “Prevalence and incidence of Alzheimer’s disease in Europe: A meta-analysis,” *Neurología (English Edition)*, vol. 32, no. 8, pp. 523–532, Aug. 2017, doi: 10.1016/j. Knurling. 2016.02.009.

[3] M. El Haj, P. Allain, C. Boutoleau Bretonnière, G. Chapelet, P. Antoine, and K. Gallouj, “Empathy of individuals with Alzheimer’s disease (AD) toward other AD patients,” *Journal of Clinical and Experimental Neuropsychology*, vol. ahead-of-print, no. ahead-of-print, pp. 293–301, Apr. 2022, doi: 10.1080/13803395.2022.2110573.

[4] D. Briley *et al.*, “Preserved neurogenesis in non-demented individuals with AD neuropathology.,” *Scientific Reports*, vol. 6, no. 1, Jun. 2016, doi: 10.1038/srep27812.

[5] L. J. Van Eldik *et al.*, "The roles of inflammation and immune mechanisms in Alzheimer's disease," *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, vol. 2, no. 2, pp. 99–109, May 2016, doi: 10.1016/j. Tracy. 2016.05.001.

[6] A. Webers, M. T. Heneka, and P. A. Gleeson, "The role of innate immune responses and neuroinflammation in amyloid accumulation and progression of Alzheimer's disease.," *Immunology & Cell Biology*, vol. 98, no. 1, pp. 28–41, Nov. 2019, doi: 10.1111/imcb. 12301.

[7] A. Swanson, T. Wolf, A. Sitzmann, and A. A. Willette, "Neuroinflammation in Alzheimer's disease: Pleiotropic roles of cytokines and neuronal pentraxins," *Behavioural Brain Research*, vol. 347, pp. 49–56, Feb. 2018, doi: 10.1016/j. Bro. 2018.02.015.

[8] M. Rusek, K. El-Khatib, S. J. Czuczwar, R. Pluta, K. Aikins, and J. Smith, "The Role of the JAK/STAT Signaling Pathway in the Pathogenesis of Alzheimer's Disease: New Potential Treatment Target," *International Journal of Molecular Sciences*, vol. 24, no. 1, p. 864, Jan. 2023, doi: 10.3390/ijms24010864.

[9] A. Cabrera-Pastor, "Extracellular vesicles as mediators of neuroinflammation in intercellular and inter-organ crosstalk.," *International journal of molecular sciences*, vol. 25, no. 13, p. 7041, Jun. 2024, doi: 10.3390/ijms25137041.

[10] K. A. Jellinger, "Neuropathological assessment of the Alzheimer spectrum.," *Journal of Neural Transmission*, vol. 127, no. 9, pp. 1229–1256, Aug. 2020, doi: 10.1007/s00702-020-02232-9.

[11] G. Plascencia-Villa and G. Perry, "Neuropathologic Changes Provide Insights into Key Mechanisms of Alzheimer Disease and Related Dementia," *The American Journal of Pathology*, vol. 192, no. 10, pp. 1340–1346, Aug. 2022, doi: 10.1016/j. Apart. 2022.07.002.

[12] Y. Shen, F. Liu, and M. Zhang, "Therapeutic potential of plant-derived natural compounds in Alzheimer's disease: Targeting microglia-mediated neuroinflammation," *Biomedicine & Pharmacotherapy*, vol. 178, p. 117235, Aug. 2024, doi: 10.1016/j. Papa. 2024.117235.

[13] J. Yang *et al.*, "The Gut Microbiota Modulates Neuroinflammation in Alzheimer's disease: Elucidating Crucial Factors and Mechanistic Underpinnings.," *CNS neuroscience & therapeutics*, vol. 30, no. 10, Oct. 2024, doi: 10.1111/cns. 70091.

[14] H. Wang, Y. Ye, L. Zhao, H. Chuang, C. Chiu, and Y. Shen, "Neuroinflammation in Alzheimer's Disease: Microglia, Molecular Participants and Therapeutic Choices.," *Current Alzheimer Research*, vol. 16, no. 7, pp. 659–674, Sep. 2019, doi: 10.2174/1567205016666190503151648.

[15] K. Lohitaksha *et al.*, "Eicosanoid signaling in neuroinflammation associated with Alzheimer's disease," *European Journal of Pharmacology*, vol. 976, p. 176694, May 2024, doi: 10.1016/j. Ejphar. 2024.176694.

[16] Y. Shi and D. M. Holtzman, "Interplay between innate immunity and Alzheimer disease: APOE and TREM2 in the spotlight.," *Nature Reviews Immunology*, vol. 18, no. 12, pp. 759–772, Aug. 2018, doi: 10.1038/s41577-018-0051-1.

[17] Z. Vasileios, D. P. Athanasios, D. D. Andreadis, and Z. Stefanos, "Neuroinflammation: The link between periodontal disease and Alzheimer's disease," *International Journal of Applied Dental Sciences*, vol. 8, no. 1, pp. 393–399, Jan. 2022, doi: 10.22271/oral. 2022. v8. i1f. 1455.

[18] K.-M. Han *et al.*, "Regorafenib regulates ad pathology, neuroinflammation, and dendritic spinogenesis in cells and a mouse model of ad.," *Cells*, vol. 9, no. 7, p. 1655, Jul. 2020, doi: 10.3390/cells9071655.

[19] T.-L. Lin *et al.*, "Gut microbiota dysbiosis-related susceptibility to nontuberculous mycobacterial lung disease," *Gut Microbes*, vol. 16, no. 1, Jun. 2024, doi: 10.1080/19490976.2024.2361490.

[20] G. Gireesh and M. Cs, "Cost minimization analysis of chronic kidney disease management: Evaluating economic strategies for early intervention and treatment optimization," *World Journal of Biological Pharmacy and Health Sciences*, vol. 20, no. 1, pp. 056–062, Oct. 2024, doi: 10.30574/wjbphs. 2024.20.1.0707.

[21] L. Anwar *et al.*, "Signalling pathways involved in microglial activation in alzheimer's disease and potential neuroprotective role of phytoconstituents.," *CNS & neurological disorders drug targets*, vol. 23, no. 7, pp. 819–840, Jul. 2024, doi: 10.2174/1871527322666221223091529.

[22] F. R. Rizzo *et al.*, "Tumor Necrosis Factor and Interleukin-1β Modulate Synaptic Plasticity during Neuroinflammation." *Neural Plasticity*,

vol. 2018, no. 3, pp. 1–12, Jan. 2018, doi: 10.1155/2018/8430123.

[23] T. K. Ulland and M. Colonna, "TREM2 - a key player in microglial biology and Alzheimer disease.," *Nature Reviews Neurology*, vol. 14, no. 11, pp. 667–675, Sep. 2018, doi: 10.1038/s41582-018-0072-1.

[24] E. Medrano-Jiménez, K. F. Meza-Sosa, L. Pérez-Martínez, J. A. Urbán-Aragón, G. Pedraza-Alva, and I. Secundino, "Microglial activation in Alzheimer's disease: The role of flavonoids and microRNAs," *Journal of Leukocyte Biology*, vol. 112, no. 1, pp. 47–77, Mar. 2022, doi: 10.1002/jlb. 3mr1021-531r.

[25] E. Staurenghi *et al.*, "Oxysterols Present in alzheimer 's disease Braininduce Synaptoxicity by Activating Astrocytes: A Major Role for Lipocalin-2." Aug. 14, 2020. Do: 10.21203/rs. 3. R's-52307/v1.

[26] D. Kaur, V. Sharma, and R. Deshmukh, "Activation of microglia and astrocytes: a roadway to neuroinflammation and Alzheimer's disease." *Inflammopharmacology*, vol. 27, no. 4, pp. 663–677, Mar. 2019, doi: 10.1007/s10787-019-00580-x.

[27] A. Serrano-Pozo *et al.*, "Astrocyte transcriptomic changes along the spatiotemporal progression of Alzheimer's disease." Research square platform llc, Dec. 21, 2022. Do: 10.21203/rs. 3. R's-2261934/v1.

[28] W. Peng, C. Li, H. Wang, Y. Xie, Y. Bai, and C. Liao, "Spatiotemporal patterns of gliosis and neuroinflammation in presenilin 1/2 conditional double knockout mice.," *Frontiers in Aging Neuroscience*, vol. 14, no. 137, Sep. 2022, doi: 10.3389/fnagi. 2022.966153.

[29] M. Neal and J. R. Richardson, "Epigenetic regulation of astrocyte function in neuroinflammation and neurodegeneration," *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1864, no. 2, pp. 432–443, Nov. 2017, doi: 10.1016/j. Baddies. 2017.11.004.

[30] E. Bagyinszky, Y. C. Young, S. Kim, and S. S. A. A, "Characterization of inflammatory biomarkers and candidates for diagnosis of Alzheimer's disease," *BioChip Journal*, vol. 8, no. 3, pp. 155–162, Sep. 2014, doi: 10.1007/s13206-014-8301-1.

[31] T. Luo, "Systematic Overview: AD Pathology and Recent Pharmacological Advances," *Transactions on Materials, Biotechnology and Life Sciences*, vol. 3, pp. 630–636, Mar. 2024, doi: 10.62051/sp72fq46.

[32] Z. Chen *et al.*, "Roles of Cytokines in Alzheimer's Disease.," *International journal of molecular sciences*, vol. 25, no. 11, p. 5803, May 2024, doi: 10.3390/ijms25115803.

[33] S. Kashif, S. Feroze, and A. A. Sethi, "Targeting beta-amyloid plaques and neurofibrillary tangles: a proteomics approach towards Alzheimer's disease therapy," *International Journal of Biology and Chemistry*, vol. 17, no. 1, pp. 124–133, Jun. 2024, doi: 10.26577/ijbch2024v17i1-a15.

[34] P. Edison, "Neuroinflammation, microglial activation, and glucose metabolism in neurodegenerative diseases," *International review of neurobiology*, vol. 154, pp. 325–344, Jan. 2020, doi: 10.1016/bs. Iran. 2020.03.017.

[35] D. Hayek *et al.*, "Effect of Neuroinflammation on white matter structure and memory performance in the spectrum from aging to AD," *Alzheimer's & Dementia*, vol. 18, no. S4, Dec. 2022, doi: 10.1002/alz. 060702.

[36] A. F. Batista, M.-T. Papavergi, K. A. Khan, and C. A. Lemere, "The Importance of Complement-Mediated Immune Signaling in Alzheimer's Disease Pathogenesis.," *International journal of molecular sciences*, vol. 25, no. 2, p. 817, Jan. 2024, doi: 10.3390/ijms25020817.

[37] S. James *et al.*, "A population-based study of head injury, cognitive function and pathological markers.," *Annals of Clinical and Translational Neurology*, vol. 8, no. 4, pp. 842–856, Mar. 2021, doi: 10.1002/acn3.51331.

[38] K. S. Orobets and A. L. Karamyshev, "Amyloid Precursor Protein and Alzheimer's Disease.," *International Journal of Molecular Sciences*, vol. 24, no. 19, p. 14794, Sep. 2023, doi: 10.3390/ijms241914794.

[39] E. N. Wilson *et al.*, "Intraneuronal Amyloid Beta Accumulation Disrupts Hippocampal CRTC1-Dependent Gene Expression and Cognitive Function in a Rat Model of Alzheimer Disease.," *Cerebral cortex (New York, N.Y.: 1991)*, vol. 27, no. 2, Jan. 2016, doi: 10.1093/cercor/bhv332.

[40] J. Guptarak *et al.*, "Cognitive integrity in Non-Demented Individuals with Alzheimer's Neuropathology is associated with preservation and remodeling of dendritic spines.," *Alzheimer's & dementia : the journal of the*

Alzheimer's Association, vol. 20, no. 7, pp. 4677–4691, Jun. 2024, doi: 10.1002/alz.13900.

[41] M. I. Cosacak *et al.*, "Human TAUP301L overexpression results in TAU hyperphosphorylation without neurofibrillary tangles in adult zebrafish brain," *Scientific reports*, vol. 7, no. 1, Oct. 2017, doi: 10.1038/s41598-017-13311-5.

[42] D. Metin *et al.*, "The effect of tau hyperphosphorylation on Pin1 expression in primary cortical neurons: in okadaic acid induced AD model," pp. 137–138, Dec. 2016, doi: 10.1002/9783527808465.emc2016.8313.

[43] Z. Liu *et al.*, "The Ambiguous Relationship of Oxidative Stress, Tau Hyperphosphorylation, and Autophagy Dysfunction in Alzheimer's Disease.," *Oxidative Medicine and Cellular Longevity*, vol. 2015, no. 6, pp. 1–12, Jan. 2015, doi: 10.1155/2015/352723.

[44] T. J. Petrisko, A. Gomez-Arboledas, S. Chu, and A. J. Tenner, "Microglial deletion of C1q rescues AD cognitive decline and synaptic loss," *Alzheimer's & Dementia*, vol. 19, no. S13, Dec. 2023, doi: 10.1002/alz. 078448.

[45] Phuong. H. Nguyen, F. Sterpone, and P. Derreumaux, "Self-Assembly of Amyloid-Beta (Aβ) Peptides from Solution to Near In Vivo Conditions.," *The journal of physical chemistry. B*, vol. 126, no. 49, pp. 10317–10326, Dec. 2022, doi: 10.1021/acs. Jpcb. 2c06375.

[46] D. Mercan and M. T. Heneka, "The contribution of the locus coeruleus-noradrenaline system degeneration during the progression of alzheimer's disease.," *Biology*, vol. 11, no. 12, p. 1822, Dec. 2022, doi: 10.3390/biology11121822.

[47] M. Gabrielli, F. Tozzi, N. Origlia, and C. Verderio, "Emerging Roles of Extracellular Vesicles in Alzheimer's Disease: Focus on Synaptic Dysfunction and Vesicle-Neuron Interaction.," *Cells*, vol. 12, no. 1, p. 63, Dec. 2022, doi: 10.3390/cells12010063.

[48] R. Lapresa, J. Agulla, A. Almeida, and J. P. Bolaños, "APC/C-Cdh1-targeted substrates as potential therapies for Alzheimer's disease.," *Frontiers in pharmacology*, vol. 13, Dec. 2022, doi: 10.3389/fphar. 2022.1086540.

[49] D. A. Butterfield, "Oxidative stress in brain in amnestic mild cognitive impairment.," *Antioxidants*, vol. 12, no. 2, p. 462, Feb. 2023, doi: 10.3390/antiox12020462.

[50] A.-M. Kirova, R. B. Bays, and S. Lagalwar, "Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease.," *BioMed Research International*, vol. 2015, no. 1–2, pp. 1–9, Jan. 2015, doi: 10.1155/2015/748212.

[51] L. A. Van De Mortel, G. A. Van Wingen, and R. M. Thomas, "Grey Matter Loss at Different Stages of Cognitive Decline: A Role for the Thalamus in Developing Alzheimer's Disease.," *Journal of Alzheimer's Disease*, vol. 83, no. 2, pp. 705–720, Sep. 2021, doi: 10.3233/jad-210173.

[52] E. Mcgough, T. Liu-Ambrose, and N. Kirk-Sanchez, "Integrating Health Promotion Into Physical Therapy Practice to Improve Brain Health and Prevent Alzheimer Disease," *Journal of Neurologic Physical Therapy*, vol. 41, pp. S55–S62, Jul. 2017, doi: 10.1097/npt. 0000000000000181.

[53] M. Velraj and N. Lavaniya, "Alzheimer disease and a potential role of herbs-A review," *Research Journal of Pharmacy and Technology*, vol. 11, no. 6, p. 2695, Jan. 2018, doi: 10.5958/0974-360x. 2018.00498.5.

[54] M. Amin, K. Uchino, and R. A. Hajj-Ali, "Central Nervous System Vasculitis: Primary Angiitis of the Central Nervous System and Central Nervous System Manifestations of Systemic Vasculitis," *Rheumatic Disease Clinics of North America*, vol. 49, no. 3, pp. 603–616, May 2023, doi: 10.1016/j. Reds. 2023.03.011.

[55] A. R. Kamer, "Systemic inflammation and disease progression in alzheimer disease," *Neurology*, vol. 74, no. 14, pp. 1157–1158, Apr. 2010, doi: 10.1212/wnl. 0b013e3181d5df7f.

[56] F. Bibi *et al.*, "Link between chronic bacterial inflammation and Alzheimer disease.," *CNS & Neurological Disorders - Drug Targets*, vol. 13, no. 7, pp. 1140–1147, Oct. 2014, doi: 10.2174/1871527313666140917115741.

[57] V. Espinosa-Fernández, A. Mañas-Ojeda, M. Pacheco-Herrero, E. Castro-Salazar, F. Ros-Bernal, and A. M. Sánchez-Pérez, "Early intervention with ABA prevents neuroinflammation and memory impairment in a triple transgenic mouse model of Alzheimer´s disease," *Behavioural Brain Research*, vol. 374, p. 112106, Jul. 2019, doi: 10.1016/j. Bro. 2019.112106.

[58] J. Hazen *et al.*, "The association between circulating inflammatory markers and the

progression of alzheimer disease in norwegian memory clinic patients with mild cognitive impairment or dementia.," *Alzheimer Disease & Associated Disorders*, vol. 34, no. 1, pp. 47–53, Aug. 2019, doi: 10.1097/wad. 0000000000000342.

[59] F. Leng, R. Hinz, S. Gentleman, M. Dani, D. J. Brooks, and P. Edison, "Combined Neuroinflammation and Amyloid PET Markers in Predicting Disease Progression in Cognitively Impaired Subjects.," *Journal of Alzheimer's disease: JAD*, vol. 100, no. 3, pp. 973–986, Jul. 2024, doi: 10.3233/jad-230442.

[60] S. Rakic *et al.*, "Systemic infection modifies the neuroinflammatory response in late stage Alzheimer\u2019s disease," *Acta Neuropathologica Communications*, vol. 6, no. 1, Sep. 2018, doi: 10.1186/s40478-018-0592-3.

[61] J. Chu *et al.*, "Biomaterials-based anti-inflammatory treatment strategies for Alzheimer's disease.," *Neural Regeneration Research*, vol. 19, no. 1, pp. 100–115, Jan. 2024, doi: 10.4103/1673-5374.374137.

[62] S. Karceski, "Can naproxen slow the progression of Alzheimer disease?," *Neurology*, vol. 92, no. 18, pp. e2181–e2184, Apr. 2019, doi: 10.1212/wnl. 0000000000007418.

[63] C. L. V. Westhorpe *et al.*, "Effector CD4+ T cells recognize intravascular antigen presented by patrolling monocytes," *Nature Communications*, vol. 9, no. 1, Feb. 2018, doi: 10.1038/s41467-018-03181-4.

[64] A. Barrera-Ocampo and F. Lopera, "Amyloid-beta immunotherapy: the hope for Alzheimer disease?," *Colombia Medica*, vol. 47, no. 4, pp. 203–212, Dec. 2016, doi: 10.25100/cm. v47i4. 2640.

[65] A. Bittar, U. Sengupta, and R. Kayed, "Prospects for strain-specific immunotherapy in Alzheimer\u2019s disease and tauopathies," *npj Vaccines*, vol. 3, no. 1, Feb. 2018, doi: 10.1038/s41541-018-0046-8.

[66] H. Wu *et al.*, "A multi-targeting immunotherapy ameliorates multiple facets of Alzheimer's disease in 3xTg mice." Research square platform llc, Feb. 09, 2024. Do: 10.21203/rs. 3. R's-3927092/v1.

[67] B. Heckmann, "Therapeutic modulation of neuroinflammation in Alzheimer's disease," *Journal of the Neurological Sciences*, vol. 429, p. 118979, Oct. 2021, doi: 10.1016/j. Jeans. 2021.118979.

[68] J. El Khoury *et al.*, "Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease," *Nature Medicine*, vol. 13, no. 4, pp. 432–438, Mar. 2007, doi: 10.1038/nm1555.

[69] J. Park *et al.*, "Blocking microglial activation of reactive astrocytes is neuroprotective in the models of Alzheimer\u2019s disease," *Acta Neuropathologica Communications*, vol. 9, no. 1, Apr. 2021, doi: 10.1186/s40478-021-01180-z.

[70] E. C. Phillips *et al.*, "Astrocytes and neuroinflammation in Alzheimer's disease." *Biochemical Society Transactions*, vol. 42, no. 5, pp. 1321–1325, Sep. 2014, doi: 10.1042/bst20140155.

[71] S.-C. Wu, K.-M. Chang, Z.-S. Cao, and J.-L. Juang, "Intestinal microbial dysbiosis aggravates the progression of Alzheimer\u2019s disease in Drosophila," *Nature Communications*, vol. 8, no. 1, Jun. 2017, doi: 10.1038/s41467-017-00040-6.

[72] T. Bathe *et al.*, "Disease and brain region specific immune response profiles in neurodegenerative diseases with pure and mixed protein pathologies," *Acta Neuropathologica Communications*, vol. 12, no. 1, Apr. 2024, doi: 10.1186/s40478-024-01770-7.

[73] M. K. Kuhn *et al.*, "Dynamic neuroinflammatory profiles predict Alzheimer's disease pathology in microglia-containing cerebral organoids.," *bioRxiv: the preprint server for biology*. Cold spring harbor laboratory, Apr. 03, 2024. Do: 10.1101/2023.11.16.567220.

[74] C. Burgaletto *et al.*, "The immune system on the TRAIL of Alzheimer\u2019s disease," *Journal of Neuroinflammation*, vol. 17, no. 1, Oct. 2020, doi: 10.1186/s12974-020-01968-1.

[75] J. M. Taylor, M. R. Minter, Z. Moore, and P. J. Crack, "Type-I interferon pathway in neuroinflammation and neurodegeneration: focus on Alzheimer's disease.," *Journal of Neural Transmission*, vol. 125, no. 5, pp. 797–807, Jul. 2017, doi: 10.1007/s00702-017-1745-4.

[76] S. H. Rastegar-Moghaddam, A. Mohammadipour, S. Shahba, A. M. Malvandi, and A. Ebrahimzadeh-Bideskan, "Roles of the miR-155 in Neuroinflammation and Neurological Disorders: A Potent Biological

and Therapeutic Target.," *Cellular and Molecular Neurobiology*, vol. 43, no. 2, pp. 455–467, Feb. 2022, doi: 10.1007/s10571-022-01200-z.

[77] C. Laurent, L. Buée, and D. Blum, "Tau and neuroinflammation: What impact for Alzheimer's Disease and Tauopathies?," *Biomedical Journal*, vol. 41, no. 1, pp. 21–33, Feb. 2018, doi: 10.1016/j. Beg. 2018.01.003.

[78] J. Götz, L.-G. Bodea, and M. Goedert, "Rodent models for Alzheimer disease." *Nature Reviews Neuroscience*, vol. 19, no. 10, pp. 583–598, Sep. 2018, doi: 10.1038/s41583-018-0054-8.

[79] M. A. Nowrangi, "Neuropsychiatric Aspects of Alzheimer Dementia: From Mechanism to Treatment," *Psychiatric Clinics of North America*, vol. 43, no. 2, pp. 383–397, Apr. 2020, doi: 10.1016/j. Ps. 2020.02.012.

[80] K. G. Yiannopoulou and S. G. Papageorgiou, "Current and Future Treatments in Alzheimer Disease: An Update.," *Journal of Central Nervous System Disease*, vol. 12, no. 6, p. 117957352090739, Jan. 2020, doi: 10.1177/1179573520907397.

[81] A. Bieger *et al.*, "Neuroinflammation Biomarkers in the AT(N) Framework Across the Alzheimer's Disease Continuum.," *The journal of prevention of Alzheimer's disease*, vol. 10, no. 3, Jan. 2023, doi: 10.14283/jpad. 2023.54.

[82] F. Angiulli *et al.*, "Blood-Based Biomarkers of Neuroinflammation in Alzheimer's Disease: A Central Role for Periphery?," *Diagnostics*, vol. 11, no. 9, p. 1525, Aug. 2021, doi: 10.3390/diagnostics11091525.

[83] A. B. Pomilio, A. J. Lazarowski, and A. A. Vitale, "Uncommon Noninvasive Biomarkers for the Evaluation and Monitoring of the Etiopathogenesis of Alzheimer's Disease.," *Current pharmaceutical design*, vol. 28, no. 14, pp. 1152–1169, Apr. 2022, doi: 10.2174/1381612828666220413101929.

[84] S. Mk, "Understanding Precision Medicine and its applications," *Advances in Pharmacology & Clinical Trials*, vol. 9, no. 3, pp. 1–5, Jul. 2024, doi: 10.23880/apct-16000246.

[85] A. Zarkali, G. E. C. Thomas, H. Zetterberg, and R. S. Weil, "Neuroimaging and fluid biomarkers in Parkinson's disease in an era of targeted interventions," *Nature Communications*, vol. 15, no. 1, Jul. 2024, doi: 10.1038/s41467-024-49949-9.

[86] P. Hays, "Personalized medicine beyond cancer: Impact on other diseases," *Open Access Government*, vol. 44, no. 1, pp. 118–119, Oct. 2024, doi: 10.56367/oag-044-11718.

[87] M. T. Ferretti *et al.*, "Sex differences in Alzheimer disease - the gateway to precision medicine.," *Nature Reviews Neurology*, vol. 14, no. 8, pp. 457–469, Jul. 2018, doi: 10.1038/s41582-018-0032-9.

[88] E. Uliassi *et al.*, "Quinolinetrione-tacrine hybrids as multi-target-directed ligands against Alzheimer's disease," *Bioorganic & Medicinal Chemistry*, vol. 91, p. 117419, Jul. 2023, doi: 10.1016/j. Bums. 2023.117419.

[89] T. J. Wenzel and A. Klegeris, "Novel multi-target directed ligand-based strategies for reducing neuroinflammation in Alzheimer's disease," *Life Sciences*, vol. 207, pp. 314–322, Jun. 2018, doi: 10.1016/j. Leafs. 2018.06.025.