Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i2.4584

EXPLORING EMERGING THERAPEUTIC APPROACHES FOR ALZHEIMER'S DISEASE: A FOCUS ON TARGETING NEUROINFLAMMATION AND MOLECULAR PATHWAYS

Qurat-Ul-Ain Bhutto[1*], Qamreen[2], Dr. Adut Matik[3], Stephen Matthew Chui[4], Mr. V. Sampath[5], Hameed Ullah[6]

[1] * Department of Health, Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro, Pakistan, Email: qurat552@gmail.com
[2]Department of Pediatrics, Research Associate at Aga Khan Medical College, Affiliated with Aga Khan University Medical College, Pakistan, Email: qamreenqamr3@gmail.com
[3]Teaching Assistant, Department of Internal Medicine, University of Juba College of Medicine, South Sudan, Email: adutngor85@gmail.com
[4]University of Nicosia, Cyprus, Email: chuistephenmatthew23@gmail.com
[5]Assistant Professor, Department of Biochemistry, Sri Sankara Arts and Science College (Autonomous) Enathur, Kanchipuram, Tamil Nadu, India-631 561, Email: sampathbio999@gmail.com
[6]Student, Department of Zoology, University of Buner, Pakistan, Email: hameedullah9988749@gmail.com

***Corresponding author:** Qurat-Ul-Ain Bhutto
* Department of Health, Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro, Pakistan, Email: qurat552@gmail.com

Abstract:

Introduction: Alzheimer's disease (AD) is an irreversible neurodegenerative condition marked by cerebral cortical atrophy resulting from the accumulation of beta-amyloid (βA) plaques and neurofibrillary tangles (NFTs). With an alarming global prevalence, estimated at 55 million in 2019 and projected to reach 139 million by 2050, the disease's impact is escalating. This review provides a comprehensive overview of AD, delving into its historical background, clinical manifestations, and the burgeoning significance of neuroinflammation.

Methodology: A literature review was conducted utilizing articles from PubMed, SciELO, and Science databases to compile a comprehensive understanding of AD, emphasizing the role of neuroinflammation.

Molecular Bases: The cholinergic hypothesis, glutamatergic dysfunction, amyloid-beta cascade, oligomeric hypothesis, metallic hypothesis, and tau hypothesis collectively shape our molecular understanding of AD. Despite advancements in pharmacological interventions, questions persist about the natural history and treatment efficacy, particularly in addressing cognitive decline.

Neuroinflammation: The neuroinflammatory process in AD, initiated by microglia and astrocytes responding to βA plaque and tau protein accumulation, is a pivotal aspect of disease progression. Microglial cells, initially beneficial, transform into a neurotoxic force as the disease advances.

Astrocytes also display dual roles, offering neuroprotection in early stages but turning pro-inflammatory in advanced stages.
Anatomophysiological Correlation: The anatomical impact of AD unfolds in a temporal-parietal-frontal course, affecting the medial temporal lobe, including the entorhinal cortex and hippocampus. This progression, intertwined with the limbic system, results in atrophy, episodic memory deficits, and cognitive dysfunction. Imaging modalities such as MRI reveal key anatomical changes associated with disease progression.
Anatomical-Imaginological Correlation: MRI findings, including atrophy of temporal lobes and hippocampus, ventricular enlargement, and cortical sulci widening, offer crucial diagnostic insights. The correlation between anatomical changes and neuroinflammation becomes evident, emphasizing the interplay between structural alterations and disease severity.
Discussion: Neuroimaging tests play a pivotal role in diagnosing AD, relying on volumetric changes in key brain regions. Neuropathological findings underscore neuronal loss, glial cell activation, and the intricate relationship between inflammation and central nervous system degeneration.
Conclusion: In conclusion, neuroinflammation, triggered by βA plaque formation and tau protein accumulation, emerges as a central feature in AD. The interconnection between anatomical changes and neuroinflammation holds significant diagnostic and prognostic value, contributing to a comprehensive understanding of disease evolution and facilitating clinical applications. Further research is essential to unravel the complexities of AD and develop targeted therapeutic interventions.

Keywords: Alzheimer's Disease, Neuroinflammation, Molecular Pathways, Therapeutic Approaches, Cholinergic Hypothesis, Glutamatergic Dysfunction, Amyloid-Beta Cascade.

INTRODUCTION:

Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disease that develops cerebral cortical atrophy secondary to the accumulation of beta-amyloid (βA) plaques and neurofibrillary tangles (NFTs). In 2019, estimates indicate that approximately 55 million people worldwide are affected by this disease, which could reach 139 million in 2050 (WHO) (Quattrini et al., 2024).

In 1907, the psychiatrist and neuropathologist Aloysius “Alöis” Alzheimer carried out the neuropsychological characterization of AD by describing the symptoms of a 51-year-old patient. After the patient's death, Alzheimer examined his brain under the microscope, observing NFT, amyloid angiopathy, and neuritic plaques, features that would later constitute the diagnostic arsenal of AD (De Marchi, Vignaroli, Mazzini, Comi, & Tondo, 2024).
AD manifests clinically with initial amnesia due to dysfunction of the medial temporal lobe (MTL) episodic memory system. The underlying biological processes may be present for decades before the manifestation of symptoms due to NFTs and tau protein staging in the brains of healthy older adults. As the disease progresses, brain tissue shrinks. Additionally, the cerebral ventricles are visibly enlarged. These changes can be evaluated using various imaging methods, including MRI (Nadig & Krishna, 2024).

The neuroinflammatory process is due to the complications of AD, which begin before severe cognitive impairment, through immunological responses of the central nervous system (CNS) via microglial and astrocytic cells associated with the accumulation of tau protein in the brain. As for these CNS cells, their action is beneficial in the initial phase of the disease, providing neuroprotective effects. However, with the progression of AD, the neuroinflammatory process is aggravated by the action of these cells, characterizing it as a neurotoxic effect through the deposition of βA plaques. The present work aims to carry out a review of the literature on neuroinflammation in AD (Wang et al., 2024).

METHODOLOGY:

The present study is a literature review based on selecting articles extracted from the PubMed, SciELO and Science databases .

DEVELOPMENT:

Molecular Bases:

The cholinergic hypothesis of AD development emerged after a series of discoveries in the 1970s, such as the depletion of the neurotransmitter acetylcholine in brain samples from AD patients, in which Raymond T. Bartus published The Cholinergic Hypothesis of Geriatric Memory Dysfunction in 1982, in which he associated this functional loss of cholinergic neurons with cognitive decline and memory loss. This has led researchers in the field, for many years, to search for theories regarding the origin of neuronal degeneration, as well as therapies, which has led to the use of acetylcholinesterase (AChE) inhibitors as a method of treating AD (Shajahan, Kumar, & Ramli, 2024).

These inhibitors decrease the hydrolysis of the neurotransmitter acetylcholine (ACh) released from presynaptic neurons into the synaptic cleft by inhibiting AChE, which stimulates cholinergic receptors. Currently, therapies that inhibit AChE continue to be the primary drugs approved for the treatment of AD, such as the use of donepezil, rivastigmine and galantamine, widely used during the symptomatic phase of the disease. However, there is evidence of the effectiveness of this pharmacological principle in several studies. Its effects are still considered modest, and critical questions about the natural history of AD still need to be answered (Z. Zhang et al., 2024).

In the mid-1980s, the glutamatergic dysfunction hypothesis emerged after studies identified excitotoxicity. The excess excitatory stimulus of NMDA causes deregulation of calcium ions, which causes oxidative stress and, therefore, death of neuronal cells (Viorel, Pastorello, Bajwa, & Slevin, 2024). In this way, attempts have been made to develop drugs with NMDA receptor antagonist action, and even after clinical trials, the expected therapeutic efficacy in providing a definitive drug for AD has not been achieved (Xing et al., 2024).

The amyloid-beta cascade hypothesis was described approximately 30 years ago and has been the basis for pharmaceutical research in recent decades. This hypothesis is based on the cleavage products of APP (amyloid precursor protein), in particular, the 1-42-beta-amyloid peptide, which is more hydrophobic than other products, thus having a more significant potential for aggregation and formation of senile plaques, extracellular insoluble. These plaques give rise to a cascade, including microglial activation and cytokine release, leading to an inflammatory response, culminating in the death of neurons around these plaques (Zhou et al., 2024).

The oligomeric hypothesis is based on the formation of beta-amyloid oligomers, as opposed to the fibrils that give rise to plaques. A 1998 study demonstrates that these oligomers, although more soluble than fibrils, damage synapses, leading to cell death of neurons (Carnevale et al., 2024).
The metallic hypothesis has received a lot of attention in recent years. In it, ions common to human physiology, mainly metal ones, if deregulated, lead to neurotoxicity and are associated with Alzheimer's disease. In the case of zinc, studies demonstrate its connection with the accumulation of amyloid-beta peptides in the extracellular space. This mechanism also occurs with copper and iron. Furthermore, these metals are also associated with the oxidation of nervous tissue cells due to their redox activity (Tijms et al., 2024).

The Tau hypothesis began when researchers isolated a protein in the neurofibrillary tangles found in the brains of individuals with Alzheimer's. To this one, the protein was called tau. Subsequent discoveries identified it as part of microtubules, primarily in neurons, promoting the stabilization of these polymers. According to the hypothesis, there is a link between hyperphosphorylation of the tau

protein and Alzheimer's disease. This is because its hyperphosphorylated form loses affinity with microtubules, resulting in the formation of neurofibrillary tangles. These tangles then lodge in the intracellular space of neurons, which leads to synaptic dysfunction, changes in neuronal morphology, and axonal transport (Ang, Zhang, Azizi, de Matos, & Brorson, 2024; Zarifkar, Zarifkar, & Safaei, 2024).

Neuroinflammation:

The complications resulting from AD consist of the triggering of an immunological response by the CNS, the translation of which is summarized in the neuroinflammatory process. AD patients have chronic brain inflammation (Sadiqa & Khan, 2024).

Neuroinflammation begins decades before severe cognitive impairment, and according to the most recent literature, its pathophysiology centres on the response of microglia and astrocytes to βA plaque deposition and tau protein accumulation in the human brain (Santillán-Morales et al., 2024).
Microglial cells present protective and destructive factors, depending on the evolution of the disease. Activation of microglia for a short period is beneficial, as it removes small aggregates of βA peptides through phagocytosis and secretion of proteolytic enzymes, such as IDE (insulin-degrading enzyme), neprilysin, and MMP9 (matrix metalloproteinase 9). However, as AD progresses, the neuroinflammatory condition is aggravated by the action of these cells (Ivanova et al., 2024).

It is known that the constant deposition of βA1−42 oligomers induces a more significant release of pro-inflammatory cytokines (IL-1β and TNF-α) by microglia, inducing greater recruitment of these and reducing, instead, the secretion of anti-cytokines inflammatory, in particular, TGF-β1. Furthermore, TNF-α inhibits the phagocytic capacity of microglia while at the same time stimulating the secretion of γ-secretase, thus favouring the more excellent formation of amyloid beta plaques and, consequently, the development of the inflammatory cascade in the brain of patients with AD. Together with microglia, astrocytes also have neuroprotective or neurotoxic effects, depending on the stage of the disease. In early AD, they help to degrade Ba (Guglietti, Mustafa, Corrigan, & Collins-Praino, 2024).

However, in more advanced stages, type A1 (pro-inflammatory) astrocytes increase in expression due to the cytokines IL-1α, TNF, and the q subcomponent of complement component 1 (C1q) produced by activated microglia. Furthermore, the A1 profile increases the load of inflammatory cytokines in the brain, contributing to bone secretion. It is also known that, in a pro-inflammatory environment, astrocytes accumulate tau protein in their cytoplasm, impairing many of their cellular functions, i.e., calcium signaling, glutamate clearance, energy metabolism, among others (Nuthikattu, Milenkovic, Norman, & Villablanca, 2024).

Anatomophysiological Correlation:

The brain, corresponding to the prosencephalon, is divided into diencephalon and telencephalon, which present specificities despite being closely related. It refers to the most developed portion of the brain, which occupies 80% of the cranial cavity. The brain divisions are determined only from a functional point of view since they have no physical boundaries. The diencephalon is the midbrain region and provides bilateral symmetry, where the third ventricle, thalamus, hypothalamus, epithalamus, and subthalamus are present. The telencephalon, therefore, occupies the peripheral region and includes the two cerebral hemispheres, composed of cavities (lateral ventricles) and segmented into lobes: frontal, occipital, parietal and temporal (Wu et al.).

On the medial aspect of each hemisphere, there is a continuous cortical ring consisting of the cingulate gyrus, the parahippocampal gyrus and the hippocampus. The entorhinal cortex (EC) represents a nodal

point associated with the cerebral cortex via nerve fibres and is located near the hippocampus and amygdala, as can be seen in Figure 1 (Liu et al., 2024; Massaro & Teive, 2023).

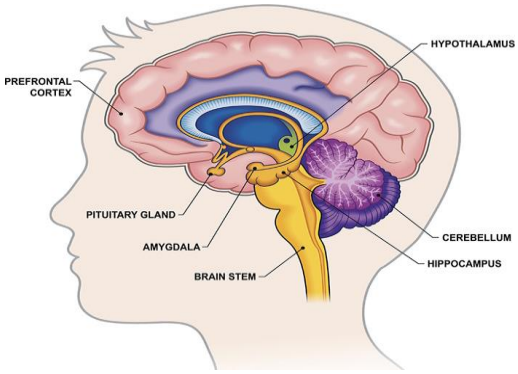

Figure 1. Brain image showing the orientation and connection between the hippocampus, amygdala, and entorhinal cortex.

The central part of the brain related to emotional, olfactory and cognitive behaviors is called the limbic system. It comprises a cortical ring involving the following structures: hippocampus, hypothalamus, amygdala, and cingulate gyrus, as shown in Figures 2 and 3 (Iskusnykh, Zakharova, Kryl'skii, & Popova, 2024).

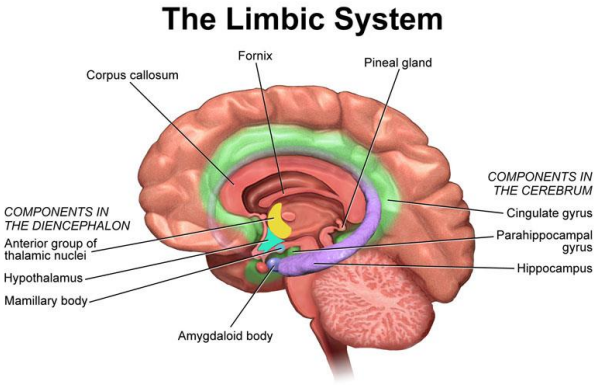

Figure 2. The image above depicts the limbic system in green and blue. The image below represents the hippocampus.

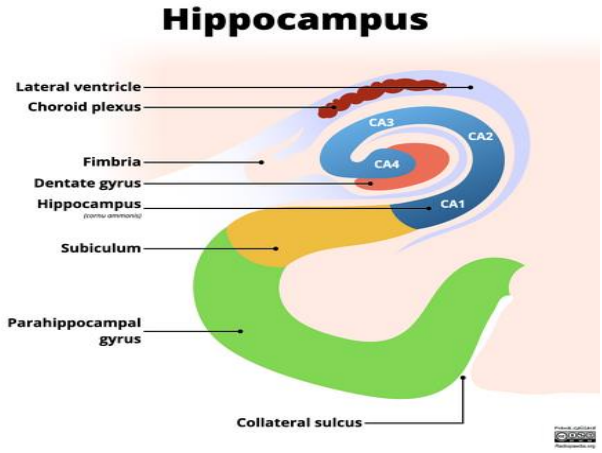

Figure 3. Image of the hippocampus and its anatomical portions.

AD, a proteinopathy that affects the brain slowly and progressively, is morphologically characterized by the accumulation of βA plaques and neurofibrillary tangles. The resulting atrophy of the medial temporal lobe, including the EC and hippocampus, expands to the rest of the isocortex in a temporal-parietal-frontal course. The amygdala, hippocampus, and EC are the first brain regions affected by NFT formation in AD (J. Zhang et al., 2024).

With the affected hippocampus, the involvement of the amygdala and other components of the limbic system also begins, reaching the temporal cortex until it involves the entire cerebral cortex. Amygdala atrophy is prominent and associated with substantial neuronal loss. Impairment of this "medial temporal memory system" is responsible for episodic memory deficits, one of the first clinical signs of AD (Guo et al., 2024; Sefati et al., 2024).

The progression of this disease to an intermediate category is associated with the generalization of large areas in the lateral temporal, parietal and frontal cortex, together with the appearance of language and visuospatial deficits. In a more advanced stage, cognitive functions are even more weakened, making the atrophy of the structures more evident and the observation of increasingly dilated ventricles, as shown in Figure 4 (Xu et al., 2024).

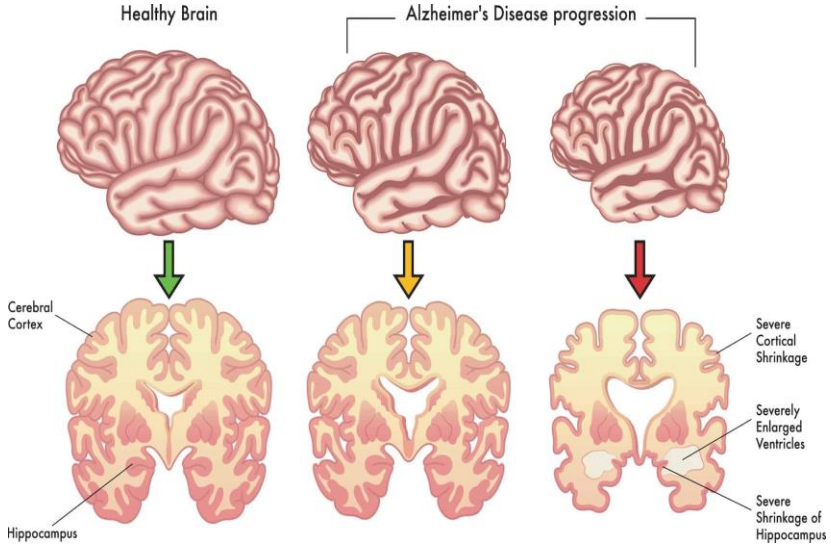

Figure 4. Schematic representation of brain damage in a coronal section during AD progression.

The initial stages of AD are mainly characterized by loss of recent memory and difficulty acquiring new skills and progress to cognitive dysfunctions, such as judgment, calculation, abstract reasoning, and visual and spatial abilities. In the intermediate stages of the disease, there is the possibility of developing aphasia, such as difficulty naming objects or defining a word to express an idea, in addition to apraxia. In the terminal stages, psychotic symptoms stand out, as do changes in the sleep-wake cycle and behaviour, with particular attention to irritability and aggression. Bed restrictions may occur due to the inability to walk and limitations in performing personal care (Raheem, Albazi, Altaee, Al-Thuwaini, & Jhoni).

The central nervous system participates in a few immune reactions, isolated by a selective membrane of macromolecules, the blood-brain barrier (BBB). The defective BBB in people with AD causes inflammation, as the passage of glucose to the brain is prevented, which attenuates the elimination of βA and tau proteins (Fatima et al., 2024).

Considering physiological aspects, βA deposition may initiate the pathological cascade of AD due to its influence on tau protein phosphorylation. The generalization of these proteins occurs because it is an intimately connected system through the cingulate bundle. This causes the accumulation of tau in the posterior cingulate cortex; although tau deposition can occur before βA deposition, this can

increase tau levels in cognitively healthy people; therefore, not understanding the exact relationship between these two proteins influences its possible consequences (Abugaliyeva & Rasool, 2024; Chang et al., 2024).

Anatomical-Imaginological Correlation:

Imaging tests are often used to analyze and diagnose AD, while magnetic resonance imaging (MRI) is the most used test for monitoring and diagnosing patients. Key MRI findings include atrophy of the temporal lobes and hippocampus, enlargement of the lateral ventricles and cerebral sulci, and prominent hippocampal fissures, as seen in Figures 5 and 6. (Li et al., 2024)

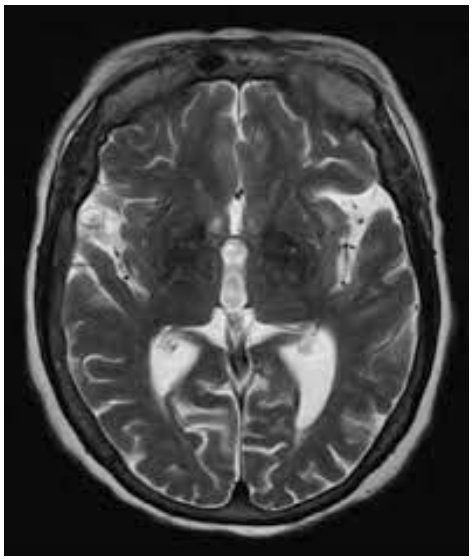

Figure 5. A brain MRI shows the prominence of the hippocampal fissures.

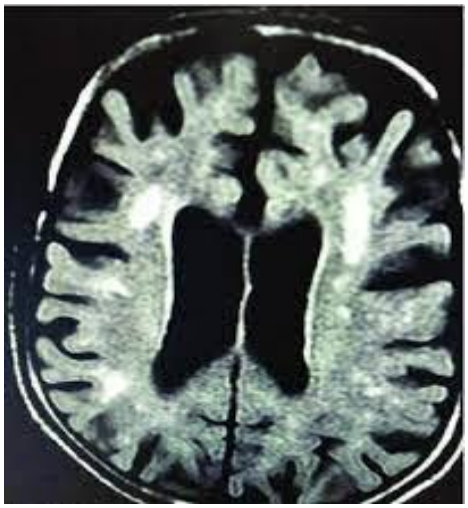

Figure 6. Brain MRI showing prominence of the lateral ventricles and cerebral sulci.

DISCUSSION:

Through neuroimaging tests, such as magnetic resonance imaging and computed tomography (CT), the pathological diagnosis of AD is based on volumetric changes in the MTL, corresponding to the entorhinal cortex and hippocampus (areas of remarkable plasticity) and in the association regions, such as the parietal and frontal lobes. Furthermore, the dilation of the lateral ventricles and the widening of the cortical sulci, especially in the temporal regions, have significant influence importance in aiding the diagnosis and treatment of AD, mainly used by an initial investigation to exclude other causes of dementia (Arnaut, Pastorello, & Slevin, 2024).

Other neuropathological findings show neuronal loss in the pyramidal layers of the cerebral cortex and degeneration of limbic system structures. Indeed, recent studies reveal that these areas present large deposits of βA, consequently stimulating the activity of glial cells, which translates into a neuroinflammatory cascade responsible for progressive neurodegeneration in the brain affected by AD (Altunkaya et al., 2024; Troci et al., 2024).

This correlation between inflammation and CNS degeneration, especially in the more advanced stages of the disease, is supported by the positive feedback mechanism between βA plaques, active microglia and reactive astrocytes. Therefore, in addition to the secretion of high levels of pro-inflammatory cytokines (IL-1β and TNF-α) with cytotoxic action in the central nervous system, the loss of function of these glial cells is noted. These factors lead, for example, to impaired calcium signaling, glutamate clearance, and energy metabolism. Therefore, synaptic and neuronal loss are the main factors responsible for the atrophy of the cerebral cortex, especially the MLT, limbic system and hippocampus (Han et al., 2024).

However, for some researchers, the real cause of the cognitive decline in AD is not linked to the deposition of amyloid plaques since this is already intrinsic to brain ageing itself, but rather to the reduction in the density of presynaptic buttons of pyramidal neurons, mainly in the middle frontal neocortex (Marković, Milošević, Wang, & Cao, 2024).

CONCLUSION:

Therefore, it is possible to conclude that neuroinflammation, generated by the formation of βA plaques and the accumulation of tau protein in the human brain, is one of the main features related to AD, being related to various anatomy-physiological changes, such as medial temporal atrophy of the lobes and amygdala, episodic memory deficits and other cognitive disorders. Furthermore, anatomical changes and those related to the neuroinflammatory process are of great importance for the diagnosis and analysis of the evolution of the disease, presenting significant value for clinical applications.

REFERENCES:

1. Abugaliyeva, A., & Rasool, S. (2024). Computational analysis of Alzheimer's disease-associated missense SNPs to understand underlying molecular mechanisms and identify diagnostic biomarkers. *Brain Disorders, 13*, 100110.
2. Altunkaya, A., Deichsel, C., Kreuzer, M., Nguyen, D.-M., Wintergerst, A.-M., Rammes, G., . . . Fenzl, T. (2024). Altered sleep behavior strengthens face validity in the ArcAβ mouse model for Alzheimer's disease. *Scientific Reports, 14*(1), 951.
3. Ang, P. S., Zhang, D. M., Azizi, S.-A., de Matos, S. A. N., & Brorson, J. R. (2024). The glymphatic system and cerebral small vessel disease. *Journal of Stroke and Cerebrovascular Diseases, 33*(3), 107557.
4. Arnaut, N., Pastorello, Y., & Slevin, M. (2024). Monomeric C-reactive protein: a link between chronic inflammation and neurodegeneration? *Neural Regeneration Research, 19*(8), 1643-1644.
5. Carnevale, L., Perrotta, M., Mastroiacovo, F., Perrotta, S., Migliaccio, A., Fardella, V., . . . Carnevale, R. (2024). Advanced Magnetic Resonance Imaging (MRI) to Define the Microvascular Injury Driven by Neuroinflammation in the Brain of a Mouse Model of Hypertension. *Hypertension*.
6. Chang, J., Li, Y., Shan, X., Chen, X., Yan, X., Liu, J., & Zhao, L. (2024). Neural stem cells promote neuroplasticity: a promising therapeutic strategy for the treatment of Alzheimer's disease. *Neural Regeneration Research, 19*(3), 619-628.
7. De Marchi, F., Vignaroli, F., Mazzini, L., Comi, C., & Tondo, G. (2024). New Insights into the Relationship between Nutrition and Neuroinflammation in Alzheimer's Disease: Preventive and Therapeutic Perspectives. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*.
8. Fatima, K., Ashfaq, U. A., ul Qamar, M. T., Asif, M., Haque, A., Qasim, M., . . . Sadaqat, M. (2024). Advanced network pharmacology and molecular docking-based mechanism study to

explore the multi-target pharmacological mechanism of Cymbopogon citratus against Alzheimer's disease. *South African Journal of Botany, 165*, 466-477.
9. Guglietti, B., Mustafa, S., Corrigan, F., & Collins-Praino, L. E. (2024). Anatomical distribution of Fyn kinase in the human brain in Parkinson's disease. *Parkinsonism & Related Disorders, 118*, 105957.
10. Guo, H., Wang, G., Zhai, Z., Huang, J., Huang, Z., Zhou, Y., . . . Zhao, Z. (2024). Rivastigmine Nasal Spray for the Treatment of Alzheimer's Disease: Olfactory Deposition and Brain Delivery. *International Journal of Pharmaceutics*, 123809.
11. Han, S.-W., Pyun, J.-M., Bice, P. J., Bennett, D. A., Saykin, A. J., Kim, S. Y., . . . Nho, K. (2024). miR-129-5p as a biomarker for pathology and cognitive decline in Alzheimer's disease. *Alzheimer's Research & Therapy, 16*(1), 1-17.
12. Iskusnykh, I. Y., Zakharova, A. A., Kryl'skii, E. D., & Popova, T. N. (2024). Aging, Neurodegenerative Disorders, and Cerebellum. *International Journal of Molecular Sciences, 25*(2), 1018.
13. Ivanova, M., Belaya, I., Kucháriková, N., de Sousa Maciel, I., Saveleva, L., Alatalo, A., . . . Lampinen, R. (2024). Upregulation of Integrin beta-3 in astrocytes upon Alzheimer's disease progression in the 5xFAD mouse model. *Neurobiology of Disease*, 106410.
14. Li, J., Li, X., Chen, F., Li, W., Chen, J., & Zhang, B. (2024). Studying the Alzheimer's disease continuum using EEG and fMRI in single-modality and multi-modality settings. *Reviews in the Neurosciences*(0).
15. Liu, R., Guo, Z., Li, M., Liu, S., Zhi, Y., Jiang, Z., . . . Zhu, J. (2024). Lower fractional dimension in Alzheimer's disease correlates with reduced locus coeruleus signal intensity. *Magnetic Resonance Imaging, 106*, 24-30.
16. Marković, M., Milošević, J., Wang, W., & Cao, Y. (2024). Passive Immunotherapies Targeting Amyloid-β in Alzheimer's Disease: A Quantitative Systems Pharmacology Perspective. *Molecular Pharmacology, 105*(1), 1-13.
17. Massaro, A., & Teive, H. (2023). A journey through 80 years of Brazilian neurology. *Arquivos de Neuro-psiquiatria, 81*(12), 1027-1029.
18. Nadig, A. P., & Krishna, K. (2024). A novel Zebrafish model of Alzheimer's disease by Aluminium chloride; involving nitro-oxidative stress, neuroinflammation and cholinergic pathway. *European Journal of Pharmacology*, 176332.
19. Nuthikattu, S., Milenkovic, D., Norman, J. E., & Villablanca, A. C. (2024). Single nuclei transcriptomics in diabetic mice reveals altered brain hippocampal endothelial cell function, permeability, and behavior. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1870*(2), 166970.
20. Quattrini, G., Pini, L., Boscolo Galazzo, I., Jelescu, I. O., Jovicich, J., Manenti, R., . . . Pievani, M. (2024). Microstructural alterations in the locus coeruleus-entorhinal cortex pathway in Alzheimer's disease and frontotemporal dementia. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 16*(1), e12513.
21. Raheem, H., Albazi, W., Altaee, R., Al-Thuwaini, T., & Jhoni, G. Effect of hypercholestermic diet on the β-amyloid deposition and microglial cells with some biomarkers alterations in male rats.
22. Sadiqa, A., & Khan, M. K. (2024). Mediators of Periodontitis complementing the development of Neural Disorders. *Pakistan Journal of Medical Sciences, 40*(1Part-I), 214.
23. Santillán-Morales, V., Rodriguez-Espinosa, N., Muñoz-Estrada, J., Alarcón-Elizalde, S., Acebes, Á., & Benítez-King, G. (2024). Biomarkers in Alzheimer's Disease: Are Olfactory Neuronal Precursors Useful for Antemortem Biomarker Research? *Brain Sciences, 14*(1), 46.
24. Sefati, N., Esmaeilpour, T., Salari, V., Zarifkar, A., Dehghani, F., Ghaffari, M. K., . . . Rodrigues, S. (2024). Monitoring Alzheimer's disease via ultraweak photon emission. *iScience, 27*(1).
25. Shajahan, S. R., Kumar, S., & Ramli, M. D. C. (2024). Unravelling the connection between COVID-19 and Alzheimer's disease: a comprehensive review. *Frontiers in Aging Neuroscience*.

26. Tijms, B. M., Vromen, E. M., Mjaavatten, O., Holstege, H., Reus, L. M., van der Lee, S., . . . Venkatraghavan, V. (2024). Cerebrospinal fluid proteomics in patients with Alzheimer's disease reveals five molecular subtypes with distinct genetic risk profiles. *Nature Aging*, 1-15.
27. Troci, A., Philippen, S., Rausch, P., Rave, J., Weyland, G., Niemann, K., . . . Franke, A. (2024). Disease-and stage-specific alterations of the oral and fecal microbiota in Alzheimer's disease. *PNAS nexus, 3*(1), pgad427.
28. Viorel, V. I., Pastorello, Y., Bajwa, N., & Slevin, M. (2024). p38-MAPK and CDK5, signaling pathways in neuroinflammation: a potential therapeutic intervention in Alzheimer's disease? *Neural Regeneration Research, 19*(8), 1649-1650.
29. Wang, J., He, Y., Chen, X., Huang, L., Li, J., You, Z., . . . Schibli, R. (2024). Metabotropic glutamate receptor 5 (mGluR5) is associated with neurodegeneration and amyloid deposition in Alzheimer's disease: A [18F] PSS232 PET/MRI study. *Alzheimer's Research & Therapy, 16*(1), 1-13.
30. Wu, L.-Y., Chong, J. R., Chong, J. P., Hilal, S., Venketasubramanian, N., Tan, B. Y., . . . Lai, M. K. Serum Placental Growth Factor as a Marker of Cerebrovascular Disease Burden in Alzheimer's Disease. *Journal of Alzheimer's Disease*(Preprint), 1-10.
31. Xing, L., Lv, X., Guo, Y., Jiang, C., Li, M., Yang, M., . . . Shi, H. (2024). Identification of Alzheimer's Disease by Molecular Imaging: Progress and Prospects.
32. Xu, D., Zhang, C., Bi, X., Xu, J., Guo, S., Li, P., . . . Tian, G. (2024). Mapping enhancer and chromatin accessibility landscapes charts the regulatory network of Alzheimer's disease. *Computers in Biology and Medicine, 168*, 107802.
33. Zarifkar, A. H., Zarifkar, A., & Safaei, S. (2024). Different paradigms of transcranial electrical stimulation induce structural changes in the CA1 region of the hippocampus in a rat model of Alzheimer's disease. *Neuroscience Letters, 818*, 137570.
34. Zhang, J., Liu, S., Wu, Y., Tang, Z., Wu, Y., Qi, Y., . . . Wang, Y. (2024). Enlarged Perivascular Space and Index for Diffusivity Along the Perivascular Space as Emerging Neuroimaging Biomarkers of Neurological Diseases. *Cellular and Molecular Neurobiology, 44*(1), 14.
35. Zhang, Z., Kwapong, W. R., Cao, L., Feng, Z., Liu, P., Wang, R., . . . Zhang, S. (2024). Correlation between serum biomarkers, brain volume, and retinal neuronal loss in early-onset Alzheimer's disease. *Neurological Sciences*, 1-9.
36. Zhou, S., Tu, L., Chen, W., Yan, G., Guo, H., Wang, X., . . . Li, F. (2024). Alzheimer's disease, a metabolic disorder: Clinical advances and basic model studies. *Experimental and Therapeutic Medicine, 27*(2), 1-10.