https://doi.org/ 10.33472/AFJBS.6.10.2024.4845-4857

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

REVIEWING THERAPEUTIC APPROACHES FOR ALZHEIMER'S DISEASE: ADDRESSING SYNAPTIC DEGENERATION BY TARGETING AMYLOID – B AND TAU INTERACTIONS

Binita Ghosh[1], Bhavya Jindal[1], Rajesh Kumar Sharma[1], Mekha Monsi[2], Diptendra Deb[2], Rewak Tyagi[2], Sanket Kumar[2], Darpan Joshi[3], Chandan Kumar[3], Akhilesh Patel[3*]

[1,2,3*] Department of Pharmacy Practice, Nims Institute of Pharmacy, Nims University Rajasthan, Jaipur, 303121

Corresponding Author: Akhilesh.patel0912@gmail.com

Article History

Volume 6,Issue 10, 2024

Received:29 Apr 2024

Accepted : 27 May 2024

doi: 10.33472/AFJBS.6.10.2024.4845-4857

Abstract

Alzheimer's disease (AD) is primarily indicated by the abnormal accumulation of amyloid-β (Aβ) and neurofibrillary tangles (NFTs) composed of phosphorylated tau proteins. Synaptic degradation and loss, which precede the emergence of amyloid plaques and NFTs, are closely related to cognitive impairments in patients. Soluble oligomeric Aβ initiates AD development, while tau protein facilitates later synaptic dysfunction during early AD stages. The review explores the mechanisms through which Aβ and tau contribute to synaptic disorientation and dysfunction. Aβ oligomers accumulate in synapses and induce synaptic degeneration through various mechanisms, including modulation of receptor tyrosine kinases, disruption of calcium balance, and activation of caspases and calcineurin. Hyperphosphorylated tau is highly present in the synapses. Synaptic impairments induced by Aβ are contingent upon the presence of tau, and soluble, hyperphosphorylated tau is strongly associated with cognitive deterioration in AD patients. Given the failure of Aβ-targeted therapeutics in treating AD, there has been increased attention on treatments targeting tau. Moreover, therapeutic approaches focusing on synaptic tau during the initial phases of AD may improve the disease's pathogenesis. Hyperphosphorylated tau, which can dissolve in water, interacts with receptors on cell surfaces, scaffold proteins, or molecules involved in intracellular signalling, thereby impairing synaptic function. This study looks forward to providing a current understanding of the involvement of oligomeric Aβ and soluble hyperphosphorylated tau in the initial development of AD and proposes a treatment approach to control AD.

Keywords: Alzheimer's Disease, Amyloid-β-peptides, Neurofibrillary Tangles, Synaptic impairments, Hyperphosphorylated tau

1. INTRODUCTION

Alzheimer's disease (AD) is a degenerative neurological condition that gradually impairs cognitive function and memory, impacting a large number of individuals globally. The defining neuropathological characteristics of AD consist of the buildup of atypical protein aggregates within the brain. The buildup mostly comprises amyloid-beta (Aβ) plaques located outside neurons and tau protein tangles found inside neurons.[1] The pathogenic changes result in the dysfunction and degeneration of neurons, leading to a deterioration in cognitive abilities. As AD advances, patients may possess symptoms like memory loss, cognitive impairment, disorientation, impaired problem-solving abilities, and alterations in behaviour and personality. As time passes individuals may need help with regular activity in their everyday lives due to the deterioration of their cognitive and physical functions.[2] Aβ and tau peptides are important factors in the progression of AD, a condition marked by gradual cognitive decline and memory loss. The importance of each is explained as:

1.1 Amyloid beta (Aβ) peptides: [3]

Aβ peptides lead to plaque formation, which are fragments of the amyloid precursor protein (APP). These plaques are insoluble and serve as a characteristic pathological feature of AD.

Neurotoxicity: Aβ peptides cause harm to the nervous system by disrupting the function of synapses and causing the death of neurons. This contributes to the cognitive decline observed in AD.

Propagation of Pathology: Aβ pathology can spread across the brain, resulting in the gradual progression of AD.

1.2 Tau peptides: [4]

Neurofibrillary Tangles (NFTs) are formed through the aggregation of Tau, a protein that binds to and supports the stability of microtubules in neurons. Irregular phosphorylation of tau causes it to separate from microtubules and form clumps inside cells known as NFTs, which are another characteristic feature of AD.

Neuronal Function Disruption: Tau pathology disrupts axonal transport and synaptic function. Moreover, it correlates with the degree of functional decline in AD.

Propagation of Pathology: Just like Aβ, the presence of tau pathology can extend across the brain, which contributes to the progress of the disease.

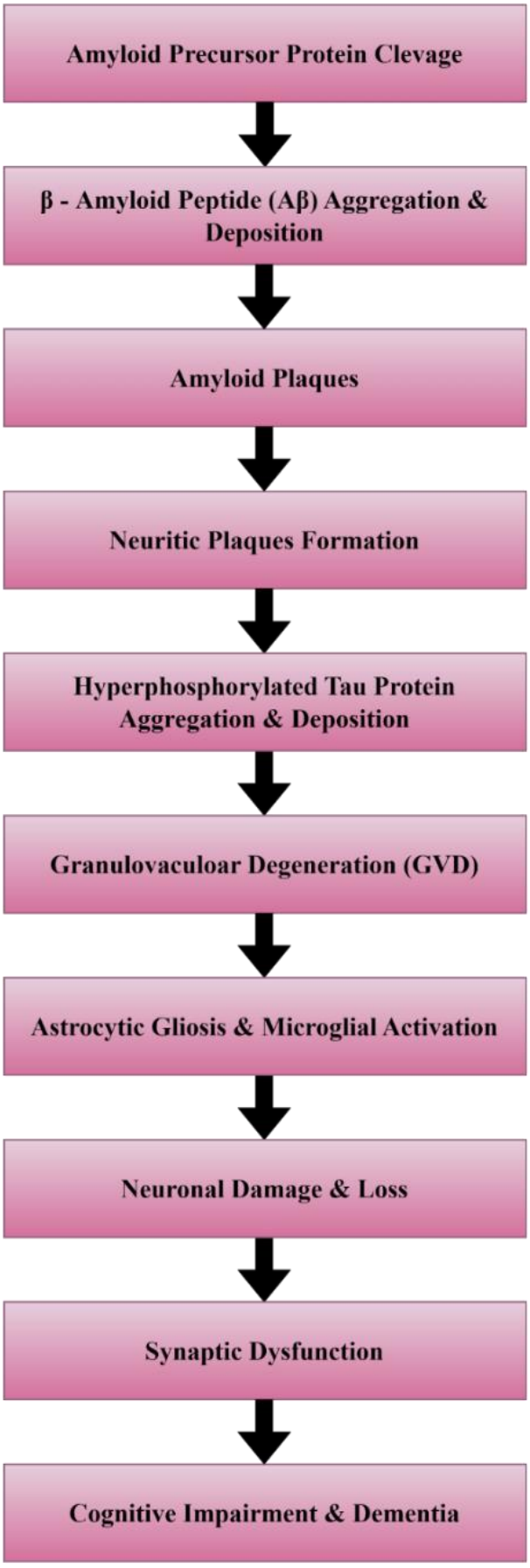

Figure No.1: Histopathological brain lesions in Alzheimer's disease

2. AMYLOID BETA (Aβ) PEPTIDES

2.1 Formation and Accumulation of Aβ Peptides in the Brain

The clustering and aggregation of Aβ peptides in the brain is a pivotal factor in AD progression. Aβ peptides are produced through the enzymatic breakdown of APP, a protein embedded in the cell membranes of neurons and other cell types. The process of APP cleavage involves the consecutive activity of enzymes referred to as β-secretase and γ-secretase, resulting in the liberation of Aβ peptides into the extracellular space.

2.1.1 Production of APP: [5] APP is a sizable transmembrane protein synthesised in neurons and several cell types across the body. The exact role of APP remains partially understood, it is hypothesised that it is involved in neuronal function, synaptic function and the restoration of neuronal damage.

2.1.2 Proteolytic cleavage of the APP: [6] APP can undergo processing via two pathways: in the non-amyloidogenic pathway, α-secretase breaks APP within the Aβ, resulting in the generation of soluble APP-alpha (sAPPα) and C-terminal segment (CTFα). In the amyloidogenic pathway, the first stage entails the cleavage of APP by β-secretase at the N-terminal region of the Aβ, leading to the production of a soluble extracellular fragment called soluble sAPPβ and membrane-bound C-terminal segment CTFβ

2.1.3 γ-Secretase cleavage: [7] The fragments produced by the cleavage of β-secretase at the C-terminal are subsequently cleaved by γ-secretase, leading to the discharge of Aβ peptides into the extracellular space. γ-Secretase cleavage is an intricate process that produces a heterogeneous population of Aβ peptides with different lengths, where Aβ40 and Aβ42 are the most prevalent variants. In general, Aβ42 is considered more neurotoxic than Aβ40. It exhibits a greater tendency to create oligomers and fibrils, which might ultimately result in the development of amyloid plaques.

2.1.4 Agglomeration of Aβ peptides: [8] After being released into the extracellular space, Aβ peptides can undergo several structural modifications and form soluble oligomers, protofibrils, and ultimately insoluble fibrils. The process of aggregation is affected by elements such as the concentration of Aβ, pH levels, metal ions, and interactions with other molecules. Soluble Aβ oligomers are thought to have a particularly harmful effect on neurons, as they interfere with synaptic function, trigger oxidative stress, and contribute to neuronal depletion. Over some time, Aβ aggregates gradually build up, resulting in the formation of insoluble amyloid plaques. These plaques are a distinctive pathological characteristic of AD.

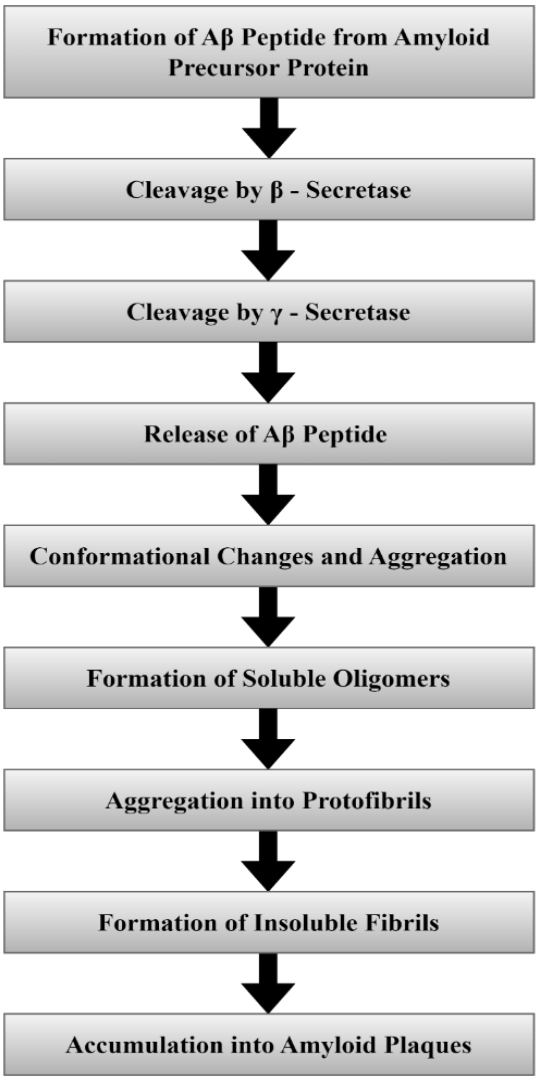

Figure No.2: Formation and Aggregation of Aβ in Amyloid Plaque Development

3. Various hypotheses regarding the neurotoxic effects of Aβ accumulation

The aggregation of Aβ is a distinctive characteristic of AD, and it is largely accepted to have a key function in the development of the disease. However, the precise processes responsible for the neurotoxic consequences of Aβ accumulation are now being investigated. Various hypotheses have been put forward to explain these effects:

3.1 The Amyloid Cascade Hypothesis: Proposed by Hardy and Higgins in 1992, is widely recognised as one of the most prominent hypotheses. As per this hypothesis, the aggregation of Aβ peptides starts a series of processes that result in impaired functioning and eventual demise of neurons. The events encompass the creation of neurofibrillary tangles comprising of excessively phosphorylated tau protein, inflammation, oxidative stress, and finally the demise of neurons. [3]

3.2 Tau Hypothesis: The Tau theory posits the abnormal aggregation of tau protein plays an important part in the pathophysiology of AD, in contrast to the amyloid cascade theory focuses on the accumulation of Aβ as the main event. From this perspective, the main cause of neurodegeneration is tau pathology, which involves the development of neurofibrillary tangles.

The accumulation of Aβ, on the other hand, is seen as the initial factor that sets off tau pathology. [9]

3.3 Synaptic Dysfunction Hypothesis: It suggests that the accumulation of Aβ disrupts the release of neurotransmitters, modifies the ability of synapses to change and adapt (synaptic plasticity), and leads to the loss of synapses. The synaptic dysfunction theory posits that the mental decline observed in AD is primarily caused by abnormalities in the transmission and connection of synapses, which are a result of the toxic effects of Aβ. [10]

3.4 Calcium Dysregulation: Aβ peptides have been demonstrated to disturb the balance of calcium levels in neurons. An excessive amount of calcium ions entering neurons can result in excitotoxicity, impaired mitochondrial activity, and ultimately cell demise. The calcium dysregulation theory suggests that the disruption of calcium signalling by Aβ leads to the neurotoxicity observed in AD. [11]

3.5 Oxidative Stress: Oxidative stress (OS) occurs when there is a buildup of Aβ, which triggers the production of reactive oxygen species (ROS). Neuronal function and viability can be compromised by oxidative damage. The OS theory suggests that the damage caused by Aβ leads to OS, which is a major contributor to the generation of AD. [12]

3.6 Inflammatory Response: Aβ peptides can stimulate microglia and astrocytes, resulting in the discharge of inflammatory cytokines and neurotoxic chemicals. AD is thought to involve chronic neuroinflammation, which is caused by the continuous buildup of Aβ. This neuroinflammation is thought to contribute to impairment and demise of neurons. The concept of the inflammatory response proposes that neuroinflammation caused by Aβ is a fundamental mechanism that causes neurotoxicity in AD. [13]

3.7 Mitochondrial dysfunction: It occurs when Aβ peptides accumulate in mitochondria and disrupt their normal functioning. Impaired functioning of mitochondria can cause a decrease in energy levels, an increase in the generation of ROS, and the initiation of programmed cell death pathways, ultimately leading to the demise of neurons. The mitochondrial dysfunction hypothesis posits that the disruption of mitochondrial activity caused by Aβ contributes to the neurotoxicity observed in AD. [14]

4. Tau Peptides

The identification of tau protein originated in the 1970s. At first, it was recognised as a protein that can withstand high temperatures and is found in large quantities in the CNS, specifically in the axons of neurons. The term "tau" was coined based on the Greek letter τ (tau), which represents its existence in the axonal microtubules. The pioneering investigation into tau protein commenced with the research of Marc Kirschner and his associates throughout the latter part of the 1970s. The researchers extracted and identified tau protein from bovine brain tissue, acknowledging its connection with microtubules. Their research established the fundamental basis for comprehending the function of tau in managing the balance of microtubules and its significance in the structure and operation of neurons. [15]

Tau proteins are important for microtubules, which are essential components of the neuronal cytoskeleton. These proteins are mostly found in the CNS. Tau's association with tubulin dimers, the basic element of microtubules, is responsible for coordinating this stabilisation process. Tau enhances the formation of microtubules and prevents their breakdown by attaching to tubulin subunits. This process helps to maintain the structural strength and stability of microtubule networks in neurons. Tau proteins regulate the polymerization and

depolymerization processes of microtubules, hence influencing their dynamic behaviour. This regulatory function affects the dynamics of the cytoskeleton, which is crucial for various neuronal processes like the growth of axons, the branching of dendrites, and synaptic plasticity. Tau preserves the structure of neurons and facilitates their optimal functioning by engaging with microtubules. Moreover, tau proteins not only stabilise microtubules but help in intracellular transport by interacting with molecular motors, specifically kinesin and dynein. These interactions enable the transportation of cellular cargos along microtubule tracks, coordinating the passage of organelles, vesicles, and proteins to precise locations within neurons. The stabilisation of microtubules by Tau protein helps to preserve the structural integrity of these tracks, which is essential for the accurate and targeted transportation that is vital for neuronal homeostasis. Tau maintains the integrity of microtubules in dendrites and axons, which in turn promotes connection and communication across synapses. This is vital for cognitive functions including learning and memory. [16,17]

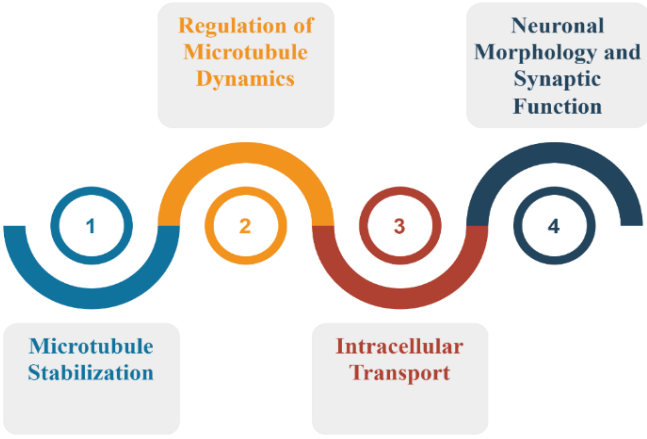

Figure No.3: Functions of Tau Protein

The excessive phosphorylated tau protein in the brain is associated with the cognitive deterioration observed in patients with AD and other disorders characterised by tau pathology. Injecting tau aggregates obtained from brains affected by tauopathy into mice's brains generates comparable pathology in the recipient mice, so indicating the disease-causing function of tau that is improperly phosphorylated. Compounds that regulate the clustering of hyperphosphorylated tau are likely to be modulators for the illness. Tau becomes more susceptible to aggregates and causes damage to cell viability as a result of hyperphosphorylation. [18] Neurofibrillary tangles (NFTs) form when tau protein in neurons abnormally clumps together, primarily in AD. Tau typically serves to stabilize microtubules, which are crucial for maintaining the structure of neurons. Tau undergoes misfolding in AD, resulting in the loss of its usual functionality. Tau proteins that are misfolded congregate as oligomers, which then assemble into larger formations known as NFTs. These tangles disrupt the functioning of neurons, causing a disruption in communication and ultimately resulting in the death of cells. NFTs propagate within the brain, potentially through the release of tau protein and its absorption by adjacent neurons, or through the involvement of other cells such as astrocytes and microglia. Despite continuous study efforts, the precise mechanisms behind the development and spread of NFTs are still not fully comprehended. Even so, the buildup of these substances is a distinctive characteristic of numerous neurodegenerative disorders, emphasizing their crucial involvement in the development of

these diseases. Gaining a comprehensive understanding of the formation of NFTs is crucial for devising efficacious therapeutic approaches that specifically address tau pathology in AD and related disorders. [19,20]

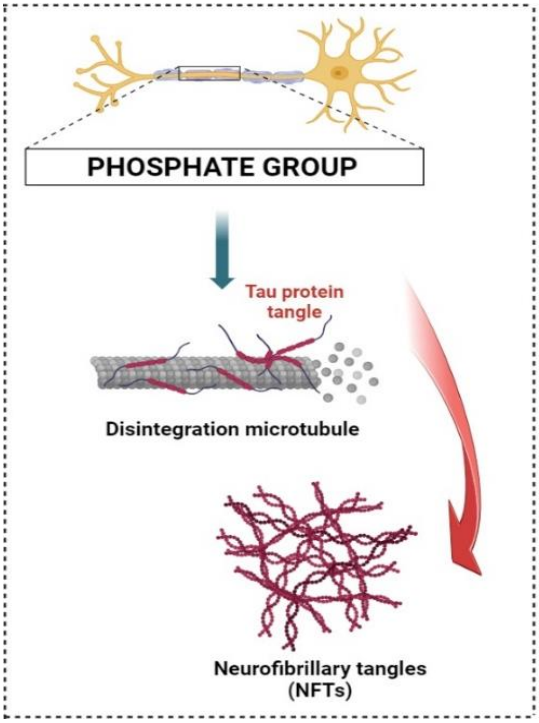

Figure No.4: Formation of Neurofibrillary tangles (NFTs)

5. Relationship between Aβ and tau

AD is defined by two primary characteristics: the buildup of Aβ plaques and the presence of NFTs made up of hyperphosphorylated tau protein. Gaining a comprehensive understanding of their intricate interconnection is crucial to devising efficacious interventions. [21] Aβ and tau are pivotal proteins implicated in the neuropathology of AD. However, current research indicates a link that is complex and delicate:

5.1 Aβ May Initiate Tau Pathology: The accumulation of Aβ may stimulate the excessive phosphorylation and aggregation of tau, leading to the development of neurofibrillary tangles. This is associated with the amyloid cascade hypothesis. [22]

5.2 Tau May Contribute to the Development of Aβ Pathology: Certain studies propose that tau pathology can, in turn, exert an influence on the production or deposition of Aβ. [23]

5.3 Individual Contributions: Both Aβ and tau pathologies may autonomously contribute to neuronal degeneration, and their interaction may additionally intensify the harm. [24]

5.4 Additional Factors: The association may be altered by other variables such as genetic predisposition, inflammation, and vascular health.

6. Current Therapeutic Approaches Targeting Aβ and Tau Pathology

Research efforts are being focused on finding viable therapeutics that specifically target the Aβ and tau pathologies associated with AD. Multiple promising techniques are now being developed at different levels. [25]

6.1 Anti-Amyloid Therapies: [26]

6.1.1 Monoclonal antibodies: These include such as aducanumab, gantenerumab, and crenezumab, specifically targeting Aβ aggregates, facilitating their removal and potentially slowing down the advancement of the disease.

6.1.2 Beta-secretase inhibitors: Such as verubecestat and lanabecestat, act by inhibiting the enzyme beta-secretase (BACE), which plays a role in the synthesis of Aβ. As a result, these drugs effectively lower the levels of Aβ.

6.1.3 Gamma-Secretase Modulators: Compounds such as semagacestat modify gamma-secretase activity, hence changing the synthesis of Aβ peptides.

6.2 Tau-Targeted Therapies: [27]

6.2.1 Tau Vaccines: Vaccines such as AADvac1 and ACI-35 are designed to specifically target the abnormal tau aggregates, with the potential to decrease the tau pathology and the resulting neurodegeneration.

6.2.2 Tau aggregation inhibitors: Such as methylene blue and leuco-methylthioninium inhibit the process of tau aggregation, therefore limiting the formation of neurofibrillary tangles.

6.2.3 Tau Kinase Inhibitory: Pharmacological agents that specifically act on kinases involved in the process of tau phosphorylation, such as inhibitors of GSK-3β, are designed to decrease the excessive phosphorylation of tau protein and prevent its aggregation.

7 Combination Therapies: [28]

7.1 Dual Aβ and Tau Targeting: Certain therapeutic approaches aim to simultaneously target both Aβ and tau pathology to address some aspects of Alzheimer's disease aetiology.

7.2 Multimodal approaches: They involve the use of medication combinations that target Aβ, tau, neuroinflammation, and synaptic dysfunction. These combinations have the potential to provide synergistic effects, leading to a slowdown in the progression of the disease.

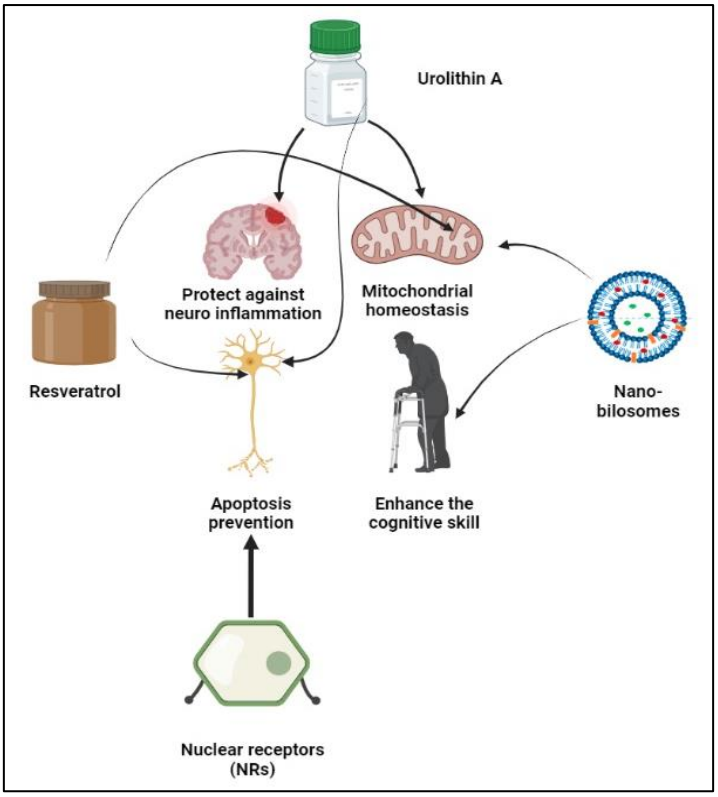

Figure No.5: The Therapeutics of Alzheimer's Disease

Discussion

AD is defined by the cognitive deterioration and deposition of Aβ plaques and NFTs in the brain, which are enriched for the hyperphosphorylated form of tau protein. These are the pathologic correlates of this disease and explain the gradual cognitive deterioration in patients with AD. However, recent studies indicate that the proteins are interdependent, and can induce the accumulation and toxicity of each other. It has been postulated that the consequences of Aβ aggregation led to several neurotoxic phenomena (amyloid cascade hypothesis, tau hypothesis, synaptic dysfunction hypothesis, calcium dysregulation, oxidative stress, inflammatory response, and mitochondrial dysfunction). Together, these findings illustrate the complex, multifactorial nature of the pathogenesis of AD and suggest that AD likely arises through the convergence of multiple biological pathways. Focusing efforts to develop therapies aimed solely at Aβ and/or tau pathologies in current research efforts. These include anti-amyloids, enzyme inhibitors, tau vaccinations and kinase inhibitors. A quadruple therapy distributed at the same time to Aβ, tau, neuroinflammation, and synaptic dysfunction, seems to be the most promising way to halt the progression of AD. This relationship is highly relevant for the efficient creation of therapeutic interventions for AD that aim to halt, or at the very least slow, disease progression, and thus a detailed understanding of this complex interplay is important. Consequently, it is hoped that revolutionary therapeutic strategies are likely to emerge and come out of the shadows of the intricacies of AD pathology to efficiently overcome the burden of this dreadful neurodegenerative disorder.

Conflict of Interest

No conflict of interest

Funding Source

Nil

Acknowledgement

This review would not have been possible without the substantial help and guidance received from our mentors and peers during the preparation of this review — we acknowledge our heartfelt gratitude to all for their support and consideration.

Abbreviations

AD – Alzheimer's Disease
A β- peptide - Amyloid-β-peptide
NFTs - Neurofibrillary Tangles
SAPPα - Soluble APP-alpha
CTFα C- Terminal Fragment
APP - Amyloid Precursor Protein
ROS - Reactive Oxygen Species
OS – Oxidative Stress

References:

1. DeTure, M.A., Dickson, D.W. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegeneration* **14**, 32 (2019). https://doi.org/10.1186/s13024-019-0333-5

2. Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules (Basel, Switzerland)*, *25*(24), 5789. https://doi.org/10.3390/molecules25245789
3. Mandal S, Vishvakarma P. Nanoemulgel: A Smarter Topical Lipidic Emulsion-based Nanocarrier. Indian J of Pharmaceutical Education and Research. 2023;57(3s):s481-s498.
4. Mandal S, Jaiswal DV, Shiva K. A review on marketed Carica papaya leaf extract (CPLE) supplements for the treatment of dengue fever with thrombocytopenia and its drawback. International Journal of Pharmaceutical Research. 2020 Jul;12(3).
5. Bhandari S, Chauhan B, Gupta N, et al. Translational Implications of Neuronal Dopamine D3 Receptors for Preclinical Research and Cns Disorders. African J Biol Sci (South Africa). 2024;6(8):128-140. doi:10.33472/AFJBS.6.8.2024.128-140
6. Tripathi A, Gupta N, Chauhan B, et al. Investigation of the structural and functional properties of starch-g-poly (acrylic acid) hydrogels reinforced with cellulose nanofibers for cu2+ ion adsorption. African J Biol Sci (South Africa). 2024;6(8): 144-153, doi:10.33472/AFJBS.6.8.2024.141-153
7. Sharma R, Kar NR, Ahmad M, et al. Exploring the molecular dynamics of ethyl alcohol: Development of a comprehensive model for understanding its behavior in various environments. Community Pract. 2024;21(05):1812-1826. doi:10.5281/zenodo.11399708
8. Mandal S, Kar NR, Jain AV, Yadav P. Natural Products As Sources of Drug Discovery: Exploration, Optimisation, and Translation Into Clinical Practice. African J Biol Sci (South Africa). 2024;6(9):2486-2504. doi:10.33472/AFJBS.6.9.2024.2486-2504
9. Kumar S, Mandal S, Priya N, et al. Modeling the synthesis and kinetics of Ferrous Sulfate production: Towards Sustainable Manufacturing Processes. African J Biol Sci (South Africa). 2024;6(9):2444-2458. doi:10.33472/AFJBS.6.9.2024.
10. Revadigar RV, Keshamma E, Ahmad M, et al. Antioxidant Potential of Pyrazolines Synthesized Via Green Chemistry Methods. African J Biol Sci (South Africa). 2024;6(10):112-125. doi:10.33472/AFJBS.6.10.2024.112-125
11. Sahoo S, Gupta S, Chakraborty S, et al. Designing, Synthesizing, and Assessing the Biological Activity of Innovative Thiazolidinedione Derivatives With Dual Functionality. African J Biol Sci (South Africa). 2024;6(10):97-111. doi:10.33472/AFJBS.6.10.2024.97-111
12. Mandal S, Bhumika K, Kumar M, Hak J, Vishvakarma P, Sharma UK. A Novel Approach on Micro Sponges Drug Delivery System: Method of Preparations, Application, and its Future Prospective. Indian J of Pharmaceutical Education and Research. 2024;58(1):45-63.
13. Mishra, N., Alagusundaram, M., Sinha, A., Jain, A. V., Kenia, H., Mandal, S., & Sharma, M. (2024). Analytical Method, Development and Validation for Evaluating Repaglinide Efficacy in Type Ii Diabetes Mellitus Management: a Pharmaceutical Perspective. Community Practitioner, 21(2), 29–37. https://doi.org/10.5281/zenodo.10642768
14. Singh, M., Aparna, T. N., Vasanthi, S., Mandal, S., Nemade, L. S., Bali, S., & Kar, N. R. (2024). Enhancement and Evaluation of Soursop (Annona Muricata L.) Leaf Extract in Nanoemulgel: a Comprehensive Study Investigating Its Optimized Formulation and Anti-Acne Potential Against Propionibacterium Acnes, Staphylococcus Aureus, and Staphylococcus Epidermidis Bacteria. Community Practitioner, 21(1), 102–115. https://doi.org/10.5281/zenodo.10570746

15. Khalilullah, H., Balan, P., Jain, A. V., & Mandal, S. (n.d.). Eupatorium Rebaudianum Bertoni (Stevia): Investigating Its Anti-Inflammatory Potential Via Cyclooxygenase and Lipooxygenase Enzyme Inhibition - A Comprehensive Molecular Docking And ADMET. Community Practitioner, 21(03), 118–128. https://doi.org/10.5281/zenodo.10811642
16. Mandal, S. Vishvakarma, P. Pande M.S., Gentamicin Sulphate Based Ophthalmic Nanoemulgel: Formulation and Evaluation, Unravelling A Paradigm Shift in Novel Pharmaceutical Delivery Systems. Community Practitioner, 21(03), 173-211. https://doi.org/10.5281/zenodo.10811540
17. Mandal, S., Tyagi, P., Jain, A. V., & Yadav, P. (n.d.). Advanced Formulation and Comprehensive Pharmacological Evaluation of a Novel Topical Drug Delivery System for the Management and Therapeutic Intervention of Tinea Cruris (Jock Itch). Journal of Nursing, 71(03). https://doi.org/10.5281/zenodo.10811676
18. Mishra, N., Alagusundaram, M., Sinha, A., Jain, A. V., Kenia, H., Mandal, S., & Sharma, M. (2024). Analytical Method, Development and Validation for Evaluating Repaglinide Efficacy in Type Ii Diabetes Mellitus Management: A Pharmaceutical Perspective. Community Practitioner, 21(2), 29–37. https://doi.org/10.5281/zenodo.10642768
19. Singh, M., Aparna, T. N., Vasanthi, S., Mandal, S., Nemade, L. S., Bali, S., & Kar, N. R. (2024). Enhancement and Evaluation of Soursop (Annona Muricata L.) Leaf Extract in Nanoemulgel: a Comprehensive Study Investigating Its Optimized Formulation and Anti-Acne Potential Against Propionibacterium Acnes, Staphylococcus Aureus, and Staphylococcus Epidermidis Bacteria. Community Practitioner, 21(1), 102–115. https://doi.org/10.5281/zenodo.10570746
20. Gupta, N., Negi, P., Joshi, N., Gadipelli, P., Bhumika, K., Aijaz, M., Singhal, P. K., Shami, M., Gupta, A., & Mandal, S. (2024). Assessment of Immunomodulatory Activity in Swiss Albino Rats Utilizing a Poly-Herbal Formulation: A Comprehensive Study on Immunological Response Modulation. Community Practitioner, 21(3), 553–571. https://doi.org/10.5281/zenodo.10963801
21. Mandal S, Vishvakarma P, Bhumika K. Developments in Emerging Topical Drug Delivery Systems for Ocular Disorders. Curr Drug Res Rev. 2023 Dec 29. doi: 10.2174/0125899775266634231213044704. Epub ahead of print. PMID: 38158868.
22. Abdul Rasheed. A. R, K. Sowmiya, S. N., & Suraj Mandal, Surya Pratap Singh, Habibullah Khallullah, N. P. and D. K. E. (2024). In Silico Docking Analysis of Phytochemical Constituents from Traditional Medicinal Plants: Unveiling Potential Anxiolytic Activity Against Gaba, Community Practitioner, 21(04), 1322–1337. https://doi.org/10.5281/zenodo.11076471
23. Arnsten, A. F. T., Datta, D., Del Tredici, K., & Braak, H. (2021). Hypothesis: Tau pathology is an initiating factor in sporadic Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*, *17*(1), 115–124. https://doi.org/10.1002/alz.12192
24. Salvadores, N., Gerónimo-Olvera, C., & Court, F. A. (2020). Axonal Degeneration in AD: The Contribution of Aβ and Tau. *Frontiers in aging neuroscience*, *12*, 581767. https://doi.org/10.3389/fnagi.2020.581767
25. Congdon, E. E., & Sigurdsson, E. M. (2018). Tau-targeting therapies for Alzheimer disease. *Nature reviews. Neurology*, *14*(7), 399–415. https://doi.org/10.1038/s41582-018-0013-z

26. Cummings J. (2023). Anti-Amyloid Monoclonal Antibodies are Transformative Treatments that Redefine Alzheimer's Disease Therapeutics. *Drugs*, *83*(7), 569–576. https://doi.org/10.1007/s40265-023-01858-9
27. VandeVrede, L., Boxer, A. L., & Polydoro, M. (2020). Targeting tau: Clinical trials and novel therapeutic approaches. *Neuroscience letters*, *731*, 134919. https://doi.org/10.1016/j.neulet.2020.134919
28. Salloway, S. P., Sevingy, J., Budur, K., Pederson, J. T., DeMattos, R. B., Von Rosenstiel, P., Paez, A., Evans, R., Weber, C. J., Hendrix, J. A., Worley, S., Bain, L. J., & Carrillo, M. C. (2020). Advancing combination therapy for Alzheimer's disease. *Alzheimer's & dementia (New York, N. Y.)*, *6*(1), e12073. https://doi.org/10.1002/trc2.12073
29. Grossberg G. T. (2003). Cholinesterase inhibitors for the treatment of Alzheimer's disease: getting on and staying on. *Current therapeutic research, clinical and experimental*, *64*(4), 216–235. https://doi.org/10.1016/S0011-393X(03)00059-6