# Alzheimer's Disease Related Target and Therapies

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**Abstract.** Alzheimer's disorder (AD) affects about seven percent of people above the age of sixty-five and about forty percent of persons above eighty years, and the burden of the disease is likely to be threefold by 2040. The disease process is marked by a buildup of misfolded proteins, inflammatory changes, and oxidative destruction. Nowadays, four approved drugs: memantine, donepezil, rivastigmine, and galantamine have been used as first-line treatment approaches for AD because of their safety profiles and promising tolerability. However, their effectiveness and benefits are relatively limited and modest. The failure of these cholinesterase inhibitors to alter the disease process calls for more innovations for future therapies. The promising future therapies discussed include anti-amyloid, anti-tau therapy, microtubule stabilization, restore lysosomal acidification, ApoE Lipidation, and microglia targeted therapies. These potential disease-modifying interventions target the pathological features of the disorder, including the tau protein and the amyloid plaques. Further investigations are required to evaluate the efficaciousness and benefits of future therapies to lower the burden of the disease locally and internationally.

**Keywords:** Alzheimer's Disease, Therapies, Tau protein, Amyloid.

## 1. Introduction

Alzheimer's disorder (AD) is a common disorder affecting about seven percent of people over sixty-five and about forty percent of those above eighty years old. About twenty-five to thirty million people are diagnosed with the disease internationally, and experts forecast a threefold rise by 2040 [1]. The estimated chance of developing the disorder is approximately ten and twenty percent for men and women above sixty-five years, respectively. Alois Alzheimer first described the disease as a continuous degenerative brain disorder about one hundred years ago. AD's process is marked by a buildup of misfolded proteins, inflammatory changes, and oxidative destruction, leading to region-particular synaptic contacts loss and neuronal cell damage. Patients are observed with loss of functional abilities, behavioral changes, cognitive impairment, and memory loss [2].

The disorder can have both familial and sporadic etiology. The familial form relates to alterations in the genes encoding "presenilin-2" (PSEN2), "presenilin-1" (PSEN1), and "amyloid precursor protein" (APP), a transmembrane protein that takes a vital part in cell-cell adhesion. About ninety-five percent of AD cases result from sporadic etiology, which has a late onset at about 65 years. In the sporadic forms, "apolipoprotein E" (ApoE) can change the gamma-secretase action, even though the ultimate pathway is not established. Individuals' risk of developing AD can be altered by somatic elements connected to environmental exposures, such as diabetes and obesity, psychosocial factors such as chronic stress, and environmental factors, including pesticide and metal exposure, infections, smoking, and exposure to the Mediterranean diet [1]. Epigenetic processes can also play a part in the AD process, and research in peripheral leucocytes and brain samples has pinpointed various links between epigenetic deregulations, AD, and aging, including histone and methylation changes.

Currently, inhibitors of acetylcholinesterase enzyme (AchE) have been approved for treatment of AD, however, these drugs can only improve symptoms while fail to prevent progressive deterioration of cognition. With more people being diagnosed with this disorder and the absence of curative therapies, identifying strategies to avert the progression of the disease would be imperative. This review elucidates the current and future targeted therapies that can help reduce the burden of the disease in the population, aiming to offer an insight into novel therapeutic approaches for the next few years.

# 2. Current Therapies

## 2.1. The structure of BP neural network

There are no productive treatment approaches for most patients of AD [3]. The current pharmacotherapeutic methods are categorized into symptomatic modalities that work on AD's cognitive signs, safeguarding clients from further cognitive loss [1], disorder-modifying modalities termination or illness progression reversal [4], and treatments that hinder the disease onset by isolating the principal progenitors [5]. The current management approach for AD is symptomatic and has relatively moderate gains. The "Food and Drug Administration" (FDA) approved medications for AD management include memantine, donepezil, rivastigmine, and galantamine [2]. Rivastigmine, galantamine, and donepezil are "acetylcholinesterase enzyme" (AChE) inhibitors, while memantine is a receptor antagonist for "N-methyl-D-aspartate" (NMDA) [6]. Among these, AChE is a crucial treatment target for AD symptomatic improvement because its inhibition is examined as attainable as a therapeutic target [3].

The mechanism and pathogenesis of AD progression are not fully clear, and the two primary neuropathological hallmarks are "intracellular neurofibrillary tangles" (NFT) and extracellular deposition of $\beta$-amyloid in substrate form [2]. Patients with AD have lower levels of acetylcholine chemical that helps conveyance of information between particular nerve cells. An overtime aggravation of AD manifestations leads to the loss of some of the nerve cells that utilize acetylcholine. Numerous studies have elucidated the various pathogenic processes underlying the reasons why AD compromises cholinergic neuronal degeneration, mitochondrial dysfunction, abnormal cholesterol homeostasis, imperfect insulin signaling, lowered glucose utilization, iron metabolism dysregulation, calcium theory, oxidative stress, neuroinflammation, $\tau$ protein phosphorylation, and the amyloid cascade hypothesis [3]. The cholinergic supposition presumes that the development of AD manifestations is generally connected to the death of acetylcholine-generating neurons, loss of particular acetylcholine receptors subtypes, structural alterations in cholinergic synapses, and thus, the cholinergic neurotransmission deterioration.

The prevailing pharmacotherapeutic strategies based on ChE inhibitors provide a practical treatment focus for the moderation of care burden in AD clients, ameliorated well-being and partial cognitive function stabilization. This is the destruction of cholinergic neuron represents a continuous and key result in the states of the illness. The most essential kinds of cholinesterases are indicated by butyrylcholinesterase (BuChE) and AChE, differing in kinetic, structure, and genetics. Most AChE inhibitors presented for AD treatment target both BuChE and AChE [5]. Notably, rivastigmine inhibits both AChE and BuChE while donepezil inhibits AChE selectively. Galantamine is a competitive, quickly reversible potent AChE inhibitor that is well absorbed with an eighty-five to one hundred percent bioavailability in oral delivery. The metabolism of galantamine happens through CYP isoenzymes 3A4 and 2D6. Rivastigmine is a non-competitive, spurious-irreversible of both BuChE and AChE with equal capacity. Rivastigmine is quickly and primarily broken down by cholinesterase; its elimination half-life is about two hours and has a forty percent bioavailability. Donepezil is also non-competitive, quickly reversible AChE inhibitor that is readily absorbed after oral intake [3]. The formulation has a bioavailability of one hundred percent and is also mainly broken down by CYP 450 isoenzymes 3A4 and 2D6. The three AChE inhibitors have shown efficacy in people presenting with moderate and mild forms of the disease. Nevertheless, the effects of these formulations are short-lived, usually one to three years, and they cannot affect the illness's evolution. Additionally, the formulations do not avert brain atrophy, neuronal loss, and hence, the continuous worsening of cognition [2].

Glutamate is the principal brain neurotransmitter with excitation characteristics that acts at metabotropic and ionotropic glutamate receptors. NMDA receptor plays a critical part in the synaptic plasticity and transmission thought to underlie memory and learning. Most NMDA receptors are distinct in that they need the coincidence of both strong postsynaptic membrane and presynaptic

glutamate release to relieve magnesium ion block of the channel. The identifying characteristics of AD entail conspicuous alterations in both brain behavior and histology.

Memantine is an NMDA that doesn't compete, and its route of action is hypothesized to lessen the effects of glutamate excitatory neurotoxicity. Memantine has demonstrated a safety and efficacy profile in managing moderate to grievous AD when utilized as monotherapy [2]. The impaired NMDA receptor function processes with age include subunit composition and expression, translation modifications, oxidative stress, and microglia interaction [7]. The combined modality with AChE inhibitors also suggests gains when compared to monotherapy. Combined therapy has notable effects on clinical global impression and cognition [8].

Current medications, including memantine and the three ChE inhibitors, for AD management, try to counterbalance the neurotransmitter disturbance. To avert AD progression, the formulations are required to alter the pathogenic steps accountable for clinical manifestations, including intracellular neurofibrillary tangle formation and extracellular amyloid beta-plaque's deposition. Current investigations also remain centered on the establishment of treatment approaches to stop or slow the development of AD, considering every new aspect in its diagnostic markers, the disease's biology, the accurate diagnosis state, and clinical trial design. Their modest benefits in the symptomatic management of AD call for manufacturing formulations that can change the disease progression. Besides, while current drugs can stabilize or lessen manifestations for some time, they cannot halt the damage AD causes to the brain cells.

## 3. Future Therapies

Although AchE inhibitors and memantine have been widely utilized, these medications only provide relatively limited benefits in managing the disorder. Because of the lack of effectiveness of the present interventions to improve the disorder's development, great strides have been made to uncover new compounds that can change the course of AD. This has made the establishment of illness-modifying modalities to alter AD progression an international priority. Nevertheless, the FDA has not approved any new formulation since the approval of memantine in 2003. Potential future therapeutics opportunities include anti-amyloid, anti-tau therapy, microtubule stabilization, restoring lysosomal acidification, ApoE Lipidation, and microglia.

### 3.1. Anti-Amyloid

Since its formulation in 1992, the "*amyloid cascade hypothesis*" has been the center of various investigations [2]. The Aβ peptide is produced by "*amyloid precursor protein (APP)"* cleavage facilitated by γ-and α-secretase enzymes leading to the biosynthesis of neurotoxic peptide Aβ. The buildup of this peptide extrinsic the cell results in its aggregation in its fibrils, protofibrils, and oligomers and subsequent gradual toppling in the nature of insoluble plaques. With this consideration, investigators have suggested that AD progression can slow down if the deposition of amyloid plaques and Aβ levels decreases [3]. The strategies investigated in anti-amyloid therapy include promoting Aβ clearance, preventing Aβ aggregation, and reducing Aβ production.

Notably, γ-secretase and (BACE1, sometimes referred to as 1 -site enzyme for cleaving amyloid precursor proteins) enzyme secretase activities seem to be crucial to the Aβ generation [3]. BACE1 inhibitors can hinder the rate-restricting phase of Aβ generation, and a number of these compounds have been manufactured in the last few years, but only five passed to stage three experimental evaluation. These compounds include elenbecestat, umibecestat, atabecestat, lanabecestat, and verubecestat. All five compounds effectively reduced Aβ levels in the cerebrospinal fluid (CSF) of AD clients. Nevertheless, the lack of functional or cognitive benefits led to their discontinuation.

γ-secretase modulators or inhibitors provide another target for Aβ production reduction [3]. γ-secretase tarenflurbil and avagacestat and agacestat γ-secretase inhibitors showed clinically promising results, but they failed to show clinical benefits and had higher grievous drug effects.

Tarenflurbil regulates the action of γ-secretase, resulting in discriminatory production of shorter, less toxic Aβ fragments and reduction of Aβ42 generation, with the least effect on other enzyme substrates.

According to experts' hypotheses, people with AD have synaptic dysfunction and neuronal death as a result of A aggregating into fibrils, oligomers, and amyloid plaques [9]. Despite being the primary pathogenic species, amyloid plaques have a poor correlation with the progression of AD. According to recent investigations, the most neurotoxic A form is thought to be soluble oligomers. Consequently, anti-aggregation formulations constitute a sound approach for AD-changing treatment [3]. They attach to soluble Aβ molecules, limit their aggregation into oligomers, and avert successive neurotoxicity. Researchers have studied two Aβ aggregation inhibitors, including tramiprosate and scyllo-inositol.

Another logical strategy considered for future therapy is the promotion of Aβ clearance. Considering the buildup and aggregation as the significant causes of the neurodegradation process of the disease, stimulating its clearance via particular anti- Aβ antibodies is logical. The most guaranteeing approaches to slow the development of the disease include immunotherapy targeting Aβ. The approach can be categorized into passive and active immunization and immune system induction to establish antibodies. Active immunotherapy triggers the production of antibodies against Aβ through the injection of its fragments or Aβ. Passive immunotherapy involves introducing monoclonal antibodies directed against Aβ [3].

### 3.2. Anti-Tau Therapy

In recent years, investigators have given more attention to tau pathology [2]. Medications that target tau protein have shown positive outcomes in pre-investigation works and are now in the first phases of the experiments. Tau protein's role is not fully comprehended, but investigations show that it possesses an essential role in the stabilization and assembly of cytoskeletal microtubules. Additionally, it has been shown that unusual hyperphosphorylation of tau lowers its affinity to attach microtubules. The interruption of the tau-microtubule connections results in microtubule impairment and raises the cytosolic levels of hyperphosphorylation tau, and other aggregated kinds are linked to neuronal loss and synapse dysfunction.

The amyloid cascade supposition presumes that Aβ accumulation triggers tau pathology. Experts propose that tau pathology can have a principal function in AD development. AD's cognitive impairment severity is best linked to the occurrence or buildup of tau than Aβ. As a result, the establishment of AD modifying treatments targeting tau is gaining more recognition [3]. Microtubule stability, tau clearance stimulation, and prevention of tau aggregation and hyperphosphorylation are some of the anti-tau treatments.

A crucial step of tau pathology is the abnormal tau molecule hyperphosphorylation because of kinases activity and phosphophatases activity, such as the “glycogen synthase kinase 3-beta” (GSK-3β) [3]. GSK-3β seems to carry the vital function in this operation because its deregulation is linked to the production of phosphorylated tau and successive neurodegradation in this disease. Therefore, experts have considered GSK-3β inhibition a logical approach to AD treatment [10]. For instance, lithium is used to manage bipolar disease, and its function in Alzheimer’s has also been investigated because of its ability to hamper GSK-3β.

Tau aggregation prevention is also examined because of the link between tau aggregates buildup and spread, clinical impairment, and neuronal loss in AD [11]. As a result, tau aggregation inhibition comprises a logical strategy in an illness modifying treatment in AD. Methylthioninium chloride has demonstrated tau aggregation inhibition capacity in vitro [3]. Experts have also examined active immunotherapy, where anti-tau vaccines trigger the development of antibodies against illness-casuing forms of tau molecule. The first anti-tau vaccine evaluated in experiments was AADvac1, which demonstrated a suitable safety profile, immunogenicity, and tolerability in phase one and two trials. Pre-experiment tests of ACI-35 also revealed an acceptable safety profile and a decrease in tau pathology indices.

Experts have also examined passive immunotherapy, where a monoclonal antibody focused to counter the atypical forms of tau molecule is injected [3]. Anti-tau antibodies that have gone to phase two trials include Zagotenemab, Semorinemab, Tilavonemab, and Gosuranemab.

### 3.3. ApoE Lipidation

Cholesterol homeostasis imbalances are linked to a higher risk of neurodegenerative disorders like AD [4]. ApoE is the primary cholesterol carrier in the encephalon, impacting different usual cellular activities, including neuroinflammation, degradation, and clearance of amyloid beta, synaptogenesis, membranes remodeling and repair, and neuronal growth [12]. ApoE goes through an intense structural modification upon lipid attachment to stabilize and accommodate the lipids via its amphiphilic helix [4]. After lipid attachment, ApoE adopts a biologically active shapes needed for attachment and recognition to the low-density lipoprotein receptor group and internalization.

In the brain, astrocytes primarily synthesize ApoE in situ, but it is also generated by oligodendrocytes, microglia, and sometimes by injured neurons [4]. The choroid plexus is another ApoE source, where it is quickly conveyed into the brain and CSF through glymphatic fluid transport. Investigations of ApoE in the CSF and periphery have given essential knowledge on the impacts of its genotype on the secretion and generation of ApoE in the AD [13]. ApoE2 carriers have increased ApoE levels in the plasma and cerebrospinal fluid, while ApoE4 carriers have decreased ApoE levels compared to ApoE3 [4]. This corresponds with the ApoE genotype impacts on parenchyma ApoE levels.

ApoE hold an essential part in preserving lipid homeostasis. The demand for cholesterol in mature neurons is high. ApoE triggers the production of “high-density lipoprotein-like” (HDL-like) molecules by taking phospholipids and cholesterol via the action of the “adenosine-triphosphate-binding cassette (ABC)” family of transporters ABCG1 and ABCA1 [4]. ABCA1 plays an essential part in AD, and both differ in their role in the pathogenic processes of AD. The ABCA1 transporter regulates ApoE lipidation in the encephalon and transports cholesterol from cells to apolipoproteins that lack lipids.

Lipids and cholesterol are allotted to neurons and other encephalon structures to preserve good cellular activity, including synaptogenesis, organelle biogenesis, membrane remodeling and repair, and neuronal growth [4]. ApoE must be properly lapidated and secreted to perform activities like Aβ degradation and clearance, immune modulation, synapse regeneration, and cholesterol or lipid transport. The ApoE lipidation status influences the ApoE function and receptor attaching ability because crucial residues involved in receptor binding ability depends on the ApoE lipidation status [4].

ApoE4 lipidation insufficiency presumes that increasing ApoE lipidation, in general, can be a potent treatment opening for Alzheimer’s and other neuronal impairments. Biophysical investigations utilizing high-density lipoprotein-like discoidal ApoE and lipid-free ApoE molecules inclined to combine *in vitro* in an “isoform-dependent” way [4]. Ameliorating the ApoE lapidated state improves cognitive shortfalls in the absence or presence of amyloid pathogenesis, notwithstanding the ApoE genotype. Therefore, ApoE lipidation can avert or correct outcomes related to neuron degradation, and ApoE-targeted interventions may be efficacious in averting AD instead of managing existing neurodegradation. Present genotyping platforms and innovations stimulate access to information about a person's predisposition to AD at early ages, enabling primary interventions for high-risk groups.

### 3.4. Microglia Targeted Therapy

The brain comprises heterogeneous groups of macrophages that play a notable part in preserving physiologic balance and reacting to pathogenic impetus in various regions [2]. Microglia form the primary macrophage kind found in the brain parenchyma [14], where they intermix with oligodendrocytes, astrocytes, and neurons. They hold a critical part in encephalon functions and homeostasis. In the stable form, microglia scavenge and monitor destroyed cells and inundate

synaptic component to form the synapse network via a pruning technique, intensifying the neuronal transmission efficiency [2]. Synaptic pruning dysfunction or defects can result in cognitive impairment, and microglia-derived proinflammatory cells can cause neurotoxicity and neuroinflammation, affecting dendritic spine formation.

Researchers implicate impaired microglia function in AD and other neuron degradation disorders [15]. Genetic proof shows microglia impairment may donate to the occurrence and development of neuron degradation. Consequently, comprehending microglial involvement in the neurodegenerative process can show potential treatment strategies for AD.

Numerous studies have demonstrated that extrinsic administration of chemical or pharmaceutical agents can convert microglia from an inflammatory to a phagocytic phenotype, which can relieve cognitive deficiency and increase aggregate clearance and destruction. A possible strategy for ameliorating the useful impacts of microglia in neurodegradation is replacing its proinflammatory form of one possessing genetic defects with allogeneic or genetically improved autologous.

### 3.5. Lysosomal Acidification

$H^+$ is essential for a wide range of physiological cell activities. Crucial activities rely on the "luminal pH" inside an organelle, including macromolecule degeneration, ligand targeting in the endosome pathway, and posttranslational changes in the secretory pathway. Organelles preserve a featured internal pH vital for enabling action, and diseases that impair organellar acidification can cause life-threatening or severe illnesses.

The final phase of autophagy-lysosomal degeneration is disrupted in most illnesses linked to autophagy anomalies. Ineffective lysosomal acidification in AD donates to proteolytic failure [16]. The inability to preserve lysosomal acidic pH is linked to neurodegenerative disorders and aging. Recent improvements in comprehending lysosomal dysfunction and function in disorders have brought up promising new opportunities for treatment by targeting lysosomes [17]. Cellular-based investigations have shown that lysosomal cathepsins play a part in the production and degradation of Aβ peptides. Therefore, lysosomal regulators working on cathepsin action can have useful impacts in managing neurodegenerative disorders. Possible therapeutic opportunities include chaperone modulators, farnesyl transferase inhibitors, phosphatidylinositol kinase modulators, v-ATPase inhibitors, cathepsin modulators, and small molecule chaperones and substrate reduction therapies.

### 3.6. Microtubule Stabilization

The function and structural integrity of axonal microtubules rely on tau. Microtubules play critical roles in various cellular processes, including cargo transport, cell division, migration, and polarization [18]. Atypical chemical variations in AD make tau to disintegrate from microtubules and stick to other tau compounds, developing links that finally attach to make twists inside neurons [19]. Stimulating microtubule stabilization improves mental deficiencies and improves disease phenotype in the amyloidogenic AD framework. Microtubule stabilizers can be examined as treatment compounds for slowing Aβ and tau pathology progression [20].

## 4. Conclusions

Currently drugs for AD are mostly based on AchE inhibitors and NMDA receptors. These drugs restore cholinergic function by blocking the enzymes that destroy acetylcholine, increasing acetylcholine availability at brain synapses. Though approved for AD management, these therapeutic approaches do not alter the disease process, calling for more innovations for therapeutic improvements.

Future therapies include anti-amyloid, anti-tau therapy, microtubule stabilization, restore lysosomal acidification, ApoE Lipidation, and microglia targeted therapies. These approaches can offer promising outcomes for AD management. For instance, anti-amyloid therapy can promote Aβ clearance, avert Aβ aggregation, and reduce Aβ production. Anti-tau formulations can effectively

reduce tau levels, with GSK-3β kinase effectively decreasing phosphorylated tau. ApoE lipidation therapies can avert or correct outcomes related to neuron degradation. Therefore, ApoE-targeted interventions can help avert AD instead of managing existing neuron degradation. Modifying microglia to a phagocytic phenotype through external provision of chemical or pharmacological compounds can ameliorate cognitive insufficiency by ameliorating A$\beta$ aggregates degradation and clearance. Replacing the proinflammatory microglia of one possessing genetic defects with allogeneic or autologous can ameliorate the useful impacts of microglia in neuron degradation. In addition, lysosomal regulators that act on cathepsin activity can offer useful outcomes in AD management. Microtubule stabilizers can slow Aβ and tau pathology progression. While potential medications are being studied right now, further research is urgently required to understand AD etiology and associated targets that will support the creation of really disease-modifying therapies.

## References

[1] Ghavami S, Shojaei S, Yeganeh B, et al. Autophagy and apoptosis dysfunction in neurodegenerative disorders [J]. Progress in neurobiology. 2014,112: 24-49.

[2] Wang S, Colonna M. Microglia in Alzheimer's disease: a target for immunotherapy [J]. Journal of leukocyte biology. 2019,106(1): 219-227.

[3] Vaz, M., Silvestre, S. Alzheimer's disease: recent treatment strategies [J]. European Journal of Pharmacology. 2020,887: 173554.

[4] Lanfranco, M. F., Ng, C. A., et al. ApoE lipidation as a therapeutic target in Alzheimer's disease [J]. International journal of molecular sciences. 2020,21(17): 6336.

[5] Stanciu, G. D., Luca, A., Rusu, et al. Alzheimer's disease pharmacotherapy in relation to cholinergic system involvement [J]. Biomolecules. 2019,10(1): 40.

[6] Yian Yiannopoulou, K. G., Papageorgiou, S. G. Current and future treatments in Alzheimer disease: an update [J]. Journal of central nervous system disease. 2020, 12: 1179573520907397.

[7] Kumar, A. NMDA receptor function during senescence: implication on cognitive performance [J]. Frontiers in neuroscience. 2015, 9: 473.

[8] Glinz, D., Gloy, V. L., Monsch, A. U., et al. Acetylcholinesterase inhibitors combined with memantine for moderate to severe Alzheimer's disease: a meta-analysis [J]. Swiss medical weekly. 2019,149: w20093.

[9] Zhang, X., Fu, Z., Meng, L., et al. The early events that initiate β-amyloid aggregation in Alzheimer's disease [J]. Frontiers in aging neuroscience. 2018, 10: 359.

[10] Ando K., Houben S., Homa M., et al. Alzheimer's Disease: Tau Pathology and Dysfunction of Endocytosis [J]. Frontiers in Molecular Neuroscience. 2021, 13: 583755.

[11] Congdon, E. E., Sigurdsson, E. M. Tau-targeting therapies for Alzheimer disease [J]. Nature Reviews Neurology. 2018,14(7): 399-415.

[12] Lanfranco, M. F., Ng, C. A., Rebeck, G. W. ApoE lipidation as a therapeutic target in Alzheimer's disease [J]. International journal of molecular sciences. 2020, 21(17): 6336.

[13] Williams, T., Borchelt, D. R., Chakrabarty, P. Therapeutic approaches targeting Apolipoprotein E function in Alzheimer's disease [J]. Molecular neurodegeneration. 2020, 15(1): 1-19.

[14] Zhao, N., Francis, N. L., et al. Microglia-targeting nanotherapeutics for neurodegenerative diseases [J]. APL Bioengineering. 2020, 4(3): 030902.

[15] Xu, Y., Jin, M. Z., Yang, Z. Y., et al. Microglia in neurodegenerative diseases [J]. Neural Regeneration Research. 2021,16(2), 270.

[16] Wolfe, D. M., Lee, J. H., Kumar, A., et al. Autophagy failure in Alzheimer's disease and the role of defective lysosomal acidification [J]. European journal of neuroscience. 2013,37(12): 1949-1961.

[17] Bonam, S. R., Wang, F., Muller, S. Lysosomes as a therapeutic target [J]. Nature Reviews Drug Discovery. 2019, 18(12): 923-948.

[18] Varidaki, A., Hong, Y., Coffey, E. T. Repositioning microtubule-stabilizing drugs for brain disorders [J]. Frontiers in cellular neuroscience. 2018,12: 226.

[19] Pradhan, B., Jit, B. P., Maharana, S., et al. Bio-nano Interface and Its Potential Application in Alzheimer's Disease. In Bio-Nano Interface (pp. 209-224) [J]. Springer, Singapore. 2022.

[20] Fernandez-Valenzuela, J. J., Sanchez-Varo, R., Muñoz-Castro, C., et al. Enhancing microtubule stabilization rescues cognitive deficits and ameliorates pathological phenotype in an amyloidogenic Alzheimer's disease model [J]. Scientific reports. 2020,10(1): 1-17.