1.0 Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease that usually starts slowly and gets worse over time for elderly population and doubles every 5 years between 65 – 85 years (Prince et al., 2016; Qiu et al., 2009) and is recognized as the most common form of dementia (Maffei et al., 2017). Dementia is not defined as a specific disease but rather as a complex clinical condition characterized by several cognitive impairments that interfere with patient independence in executing everyday tasks (Delgado-Morales et al., 2017). Various neurodegenerative disorders have dementia in common among their clinical manifestations. Such as Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies and frontotemporal dementia, share molecular alterations at the neuropathological level (Gates and Sachdev, 2014). AD is chronic or progressive in nature with deterioration in cognitive thinking or the ability to process the thoughts beyond the normal ageing (Maffei et al., 2017; Saez et al., 2014).

1.1. History of AD

Alzheimer’s disease was discovered in 1906 by Alois Alzheimer, a German neurologist and psychiatrist (Alzheimer's Association, 2010; Hippius and Neundörfer, 2003). The disease was initially observed in a 51-year-old woman named Auguste D, reported with changes in personality, behavioral deficits, memory, difficulty in speaking and impaired comprehension. Dr. Alzheimer noted many abnormal symptoms, including difficulty with speech, agitation, and confusion (Alzheimer's Association, 2010; Hippius and Neundörfer, 2003). Following her death, Dr. Alzheimer performed an autopsy, during which he found dramatic shrinkage of the cerebral cortex, fatty deposits in blood vessels, and atrophied brain cells. He discovered neurofibrillary tangles and senile plaques, which have become indicative of AD. The condition was first discussed in medical literature in

1.2. Disease Presentation

AD progresses gradually and can last for decades. AD is regarded as an age-related but not an age-dependent disease (Maffei et al., 2017). AD symptoms include confusion, mood swings, irritability, aggression, impairment of cognitive and memory function, trouble with language and communication, personality changes, erratic behavior, deterioration in emotional control, social behavior or motivation (Maffei et al., 2017; Querfurth and LaFerla, 2010). In later stages, mild coordination problems, visual spatial problems followed by bedridden condition, aspiration, prone to pneumonia, weight loss and bedsores will be observed. Gradually, loses the ability to talk resulting in loss of bodily function and ultimately leads to death (Graham et al., 2017). With an aging society comes the increase in age related frailties, which may lead to cognitive impairments and to dementia, mostly in the form of Alzheimer’s disease (AD) (Maffei et al., 2017).

1.3. Changes in the Brain

Brains affected by Alzheimer's disease often display the abnormal deposits of proteins as paired fiber tangles within nerve cells (neurofibrillary tangles) and clusters of degenerating nerve endings (amyloid or neuritic plaques) throughout the brain and once-healthy neurons stop functioning, lose connections with other neurons and die. The damage initially appears to take place in the hippocampus, the part of the brain essential in forming memories. As more neurons die, additional parts of the brain are affected, and they begin to shrink. By the final stage of Alzheimer’s, damage is widespread, and brain volume has shrunk significantly (Figure. 1) (Alzheimer’s Association, 2016).
Another characteristic feature of Alzheimer's disease is the reduced production of neuro-transmitters necessary for communication between nerve cells, especially acetylcholine, as well as nor epinephrine, serotonin and somatostatin.

Advances in basic and clinical research have provided detailed knowledge of the molecular mechanisms underlying the pathogenesis of AD over the past decades. Accumulation of aberrant or misfolded proteins, protofibril formation, oxidative and nitrosative stress resulting in mitochondrial injury, synaptic failure ensuring the failure of axonal and dendritic transport represent unifying events in progressive neurodegenerative AD (Jellinger, 2010). AD is a complex progressive condition involves sequentially interacting pathological cascades, including interaction of β-amylloid (Aβ) aggregation of plaque development, deposition (proteopathy) and the hyper phosphorylation and aggregation of tau protein with formation of neuro fibrillary tangles (NFT or taupathies) (Shah et al., 2017) surrounded by dystrophic neuritis.

![Figure 1: Brain in normal versus Alzheimer’s disease state (Shah et al., 2017; Jellinger, 2010)](image)

Associated processes, such as inflammation and oxidative stress, nitrosative stress, mitochondrial injury, synaptic failure, altered metal homoeostasis and failure of axonal and dendritic transport contribute to loss of synaptic integrity and progressive neurodegeneration pathological cascades (Shah et al., 2017; Jellinger, 2010).
1.3. Prevalence of Alzheimer’s disease

As per world Alzheimer report 2016, it was estimated that 47 million people were affected with AD worldwide. It is estimated that by the year 2020, approximately 70% of the world’s population will be ≥ aged 60 in developing countries. The prevalence of AD, is said to be about 14.2% in India (Mathuranath et al., 2012). According to world health organization (WHO) the worldwide prevalence rate of Alzheimer disease would quadruple by 2050 than the AD patients in 2010 (Alzheimer’s Association, 2016). The estimated lifetime risk of Alzheimer’s specifically at age 65 was one in six (17%) for women and one in 11 (9%) for men. Estimated risk of AD at age 75 was 19% for women and 10% for men. At age 85 estimated risk of AD was 20% for women and 12% for men (Figure. 2).

![Figure. 2: Estimated lifetime risk for Alzheimer’s disease, by Age and Sex (Alzheimer’s Association, 2016)](image)

1.4. Causes and risk factors of AD

Suspected causes of AD often include age, family history, certain genes, abnormal protein deposits in the brain, immune system problems, comorbid conditions and other risk and environmental factors. Basic and clinical research advances over the past decades
gradually disclosing the molecular basis underlying the pathogenesis of neurodegenerative disease, AD.

1.5. Amyloid Cascade Hypothesis

Amyloid cascade hypothesis elucidates the neurodegenerative process observed in AD brains as a series of events triggered by the abnormal processing of the amyloid precursor protein (APP) (Figure. 3) (Shah et al., 2017; Sugiki et al., 2013). APP is cleaved sequentially by β-secretase and γ-secretase to release an extracellular amyloid-β 40/42, neurotoxic fragments frequently aggregates and oligomerizes to form Aβ plaques which, results in blocked ion channels, disruption of calcium homeostasis, mitochondrial oxidative stress, impaired energy metabolism and ultimately neuronal cell death. Hyper phosphorylation of Tau results in the dissociation of Tau from tubulin and oligomerizes to form neuro fibrillary tangles (NFT) ensuring the neuronal apoptosis. (Shah et al., 2017; Nizzari et al., 2012). Antioxidant activity involved in defensive mechanism against oxidative stress (OS) have been implicated in the etiology of Alzheimer’s disease (Birben et al., 2012). Increased free radicals and absurdity in potentiality to detoxify reactive intermediates associated with diluted activity of anti-oxidant enzymes (GpX-1 and GpX-2) results in mitochondrial membrane damage ensuring the neuronal energy loss leading to neuronal cell death (Oka et al., 2016). Plaque deposition, NFT aggregation, oxidative stress elevation altogether activates the executioner caspases (Casp-8) and other apoptotic regulator proteins (BAX, BAD) resulting in neuronal apoptosis.
As formation and aggregation of plaques and tangles increases to lose the effective functioning of healthy neurons, gradually lose their ability to communicate subsequently neuronal cells die, resulting in an overall shrinkage of brain tissue. Neuron death, particularly in the hippocampus, restricts the patient’s ability to form new memories.

1.7. Existing treatments for Alzheimer’s disease

Currently five approved drugs are used to treat the cognitive problems of AD. They are acetyl cholinesterase inhibitors (tacrine, rivastigmine, galantamine and donepezil); N-methyl-D-aspartate (NMDA) receptor antagonist (memantine). On average, these drugs are effective for about six to 12 months for about half of the individuals (Wollen et al., 2010). Available treatments offer relatively small symptomatic benefit but remain palliative in nature.

AD can appear as young as age 30, but is typically diagnosed at the age of 60 and disease proliferates with age (Holtzman et al., 2011). Once diagnosed and living with AD
for nearly another 15-20 years is not all that usual. Alzheimer's caregivers frequently report experiencing high levels of stress, anger or frustration at person with AD and social with drawl (https://www.caregiver.org/alzheimers–disease–caregiving). Overwhelming take care of AD patients for prolonged period of time increases stress to the caregivers which leads to other diseases that can be harmful to both the AD patient and caregivers. As the available drugs are palliative in nature, an effective therapeutic agent for AD is remained to be elucidated.

Pathogenesis of AD involves Aβ plaque aggregation and NFT formation which induces oxidative stress mediated mitochondrial injury and neuronal apoptosis. Elevated levels of BACE1, γ-secretase, PKCγ, ApoE4, SOD1 are resulting in formation of Aβ plaque aggregation. Tau, GSK-3β, Akt1, CDK5, p35, p25, ERK2, BIN1 are involved in NFT formation, thus these targets were selected to reduce the Aβ toxicity by designing inhibitors. Reduced activity of PKA-α, BDNF, GpX1 and GpX2 induces oxidative stress in neurons resulting in mitochondrial dysfunction. Thus, these targets were selected to increase the anti-oxidant activity by designing activators. Hence, the proteins involved in senile plaque formation, NFT formation and oxidative stress were selected as targets to propose novel leads with the following aim and objectives.
**Aim:** Multiple docking strategies and pharmacophore design for amyloid pathway proteins.

**Objectives**

- To analyze selected proteins of amyloid pathway
- To predict three dimensional (3D) structure of target proteins using molecular modeling/threading if structure is not available.
- To identify potential lead molecules through structure based/ligand based pharmacophore modeling, rigid receptor docking and binding free energy ($\Delta G$) calculations using Prime/MM-GBSA against in-house library having more than 21 million small molecules.
- To perform polarized charge calculations through quantum polarized ligand docking (QPLD) for top ranked leads and $\Delta G$ calculations using Prime/MM-GBSA.
- To perform induced fit docking and binding free energy calculations for the best lead and $\Delta G$ calculations using Prime/MM-GBSA.
- To perform molecular dynamics simulations for the best lead-receptor complex to check stability of their interactions.
- To develop Alzheimer’s disease therapeutic target database (ADTTD).