Literature Review:

1. Allard S, et al., (2012) investigated that Impact of NGF Maturation and Degradation Pathway on the Cortical Cholinergic System Phenotype which plays a significant role in the cognitive loss seen with aging and in Alzheimer's disease (AD) basal forebrain cholinergic neurons in the mature and fully differentiated CNS together, the data point to a mechanism explaining cholinergic loss in neurodegenerative conditions such as AD and provide a potential therapeutic target for the protection or restoration of this CNS transmitter system in aging and AD.

2. Cuello AC, et al., (2007) discussed on NGF-cholinergic dependency in brain aging, MCI and Alzheimer's disease. Forebrain cholinergic neurons are highly dependent on nerve growth factor (NGF) for phenotype maintenance, the application of either NGF or TrkA NGF-mimetic agonists successfully rescues the age-dependent loss of cortical cholinergic boutons in aged-impaired rats degradation of mature NGF explains the preferential vulnerability of the cholinergic system in the AD pathology.

3. Imanishi T, et al., (2012) investigated the effect of a CNS-Sensitive Anticholinesterase Methane Sulfonyl Fluoride on Hippocampal Acetylcholine Release in Freely Moving Rats. The comparative effects of two antiChEs, methanesulfonyl fluoride (MSF) and donepezil, results suggest that MSF is a suitable candidate for the treatment of Alzheimer's disease.

4. Hartz S, et al., (2012) evaluated the cost effectiveness of donepezil in the treatment of Alzheimer's disease in Germany using discrete event simulation. Donepezil leads to savings in 95% of replications versus memantine and is highly cost-effective in patients with AD in Germany, leading to improvements in health outcomes and substantial savings compared to no treatment. This holds across a variety of sensitivity analyses.

5. Lara Pizzorno et al. (2012) reviewed on current research on AD etiology, progression and available pharmaceutical options, which remain ineffective in AD.
prevention or treatment, and will then discuss the peer-reviewed research on promising nutraceutical agents including Turmeric Extract, Ferulic Acid, Ashwagandha Extract, Rosemary Extract, Ginkgo Biloba Extract, Red Ginseng, Myricetin, Vinpocetine, and Huperzine-A, which have demonstrated the ability to: reduce and eliminate soluble Abeta and Abeta plaque in the brain, deliver potent antioxidant protection to neurons prevent A beta-related neurotoxicity, help regenerate brain neural networks, restore Abeta-related cognitive deficits, improve mental function in patients with AD improve memory and cognitive function in healthy subjects.\(^5\)

6. Counts SE, et al.\(^12\), (2005) investigated the role of nerve growth factor receptors in cholinergic basal forebrain degeneration in prodromal Alzheimer disease. The number of choline acetyltransferase-containing neurons remains stable despite a significant reduction in NGF receptor-positive cells in people with mild cognitive impairment (MCI), suggesting a phenotypic NGF receptor down regulation but not a frank loss of NB neurons during prodromal AD.\(^6\)

7. Schliebs R, et al.\(^13\), (2011) investigated The cholinergic system in aging and neuronal degeneration. The major cholinergic projections to the cerebral cortex and hippocampus. The cholinergic neurons of this complex have been assumed to undergo moderate degenerative changes during aging, resulting progressing memory deficits with aging. An early onset of an anti β-amyloid strategy may additionally be potential in preventing aging-associated cholinergic deficits and cognitive impairments.\(^7\)

8. Bengt Winblad et al.\(^14\), (2012) studied Effectiveness of Donepezil Therapy in Advanced Alzheimer’s Disease. Alzheimer’s disease (AD) is a progressive, degenerative disease. In the advanced stages, cognitive and functional abilities become compromised to the extent that most patients require total, full-time care, usually in specialised nursing homes. Loss of cognition affects functional autonomy, which is gradually lost, and psychiatric and behavioural symptoms often become problematic for both patients and their carers/families. The cholinesterase inhibitor donepezil is licensed for the treatment of mild to moderate AD in many regions
worldwide, with the indication expanded to encompass severe AD in eight countries: the US, Canada, Japan, Australia, India, New Zealand, Thailand and the Philippines. Overall, these studies show that donepezil treatment is associated with functional and cognitive benefits in patients with severe AD, although behavioural benefits were not consistently observed. Donepezil was well tolerated; side effects were transient, mild to moderately severe and generally cholinergic in nature.

9. Ho L, et al.\textsuperscript{15}, (2012) investigated on Dietary supplementation with decaffeinated green coffee improves diet-induced insulin resistance and brain energy metabolism in mice, significantly attenuated the development of high-fat diet-induced deficits in glucose-tolerance response. Improves brain mitochondrial energy metabolism as determined by oxygen consumption rate. Preparation beneficially influences the brain, in particular promoting brain energy metabolic processes.\textsuperscript{9}

10. Fedotova J, et al.\textsuperscript{16}, (2012) investigated on Ropren\textsuperscript{®} a polyprenol preparation from coniferous plants that ameliorates cognitive deficiency in a rat model of beta-amyloid peptide-(25-35)-induced amnesia.. After four weeks, Ropren\textsuperscript{®} treatment significantly improved non-spatial and spatial learning in rats with $\beta$-amyloid peptide-(25-35)-induced amnesia. The results of the present study suggest that Ropren\textsuperscript{®} in an animal model can treat Alzheimer's disease.\textsuperscript{10}

11. Maria Vittoria Spampinato, et al.\textsuperscript{17}, (2012) examined Apolipoprotein E and gray matter volume loss in patients with mild cognitive impairment and Alzheimer disease. examine the influence of apolipoprotein E $\varepsilon$4 allele (APOE4) carrier status on disease progression by evaluating the rate of regional gray matter (GM) volume loss and disease severity in patients with newly diagnosed Alzheimer disease (AD) and stable amnestic mild cognitive impairment (MCI). APOE4 carriers with cognitive decline undergo faster GM atrophy than do non carriers. The involvement of APOE4 in the progression of hippocampal atrophy, neocortical atrophy, or both has potential important implications for diagnosis and therapeutic approaches in patients with AD and should be considered in clinical trials. Prior studies indicate that rate of
hippocampal and neocortical atrophy is greater in association with APOE4 in nondemented elderly subjects, subjects with MCI, and those with AD

12. Gupta YK., et al., (2010) reviewed therapeutic potential of herbal drugs in cerebral ischemia. Cerebral ischemia causes disturbances in a variety of cellular and molecular mechanisms, including oxidative phosphorylation, membrane function, neurotransmitter release, and free radical generation. It has been years since tissue-type plasminogen activator (t-PA) became the first medication approved by the FDA for the management of stroke, with limited success. Thrombolytic therapy is the most effective therapeutic strategy for the prevention of brain injury and reduction of mortality in patients with cerebral infarction. However, a combination of established thrombolytic therapy and effective neuronal protection therapy may have more beneficial effects for patients with cerebral infarction. Because clinical trials of pharmacological neuroprotective strategies in stroke have been disappointing, attention has turned towards approaches which include herbal drugs that can be used in limiting the neurological damage associated with stroke. This review focuses on putative mechanisms underlying the beneficial effects of herbal drugs in patients with stroke and on the possibility of herbal drugs to increase the therapeutic time window in patients with cerebral ischemia

13. Nicolette S.L. Perry et al., (2003) reviewed pharmacological activity and pilot tolerability clinical trial. S. lavandulaefolia Vahl. (Spanish sage) extracts and constituents have demonstrated anticholinesterase, antioxidant, anti-inflammatory, oestrogenic and CNS depressant (sedative) effects all of which are currently relevant to the treatment of Alzheimer’s disease (AD). The essential oil inhibits the enzyme acetylcholinesterase (AChE) from human brain tissue and bovine erythrocyte and individual monoterpenoid constituents inhibit AChE with varying degrees of potency. In vivo AChE inhibition of select brain (striatal and hippocampal over cortical) AChE was obtained following oral administration of the essential oil to rats. In a study in healthy volunteers essential oil administration produced significant effects on cognition. In a pilot open-label study involving oral administration of the essential oil to patients with AD, a significant increase in diastolic and systolic blood pressure was
observed in two patients, however this may have been due primarily to preexisting hypertension and there were no abnormalities in other vital signs or blood samples during the trial period.\textsuperscript{13}

14. Ilkay Orhan, et al.,\textsuperscript{20} (2010) reviewed plant-originated treatment for Alzheimer’s disease. The treatment of AD, the standardized extracts of Ginkgo biloba L. (Ginkgoceae) has been the most prescribed herbal medicine. In addition to that, galanthamine, an alkaloid from Galanthus nivalis L. (Amaryllidaceae), has been the most recent drug available in the market. On the other hand, huperzin A isolated from Huperzia serrata Thunb. (Lycopodiaceae) is also a quite promising alkaloid which will become available in the market in a very near future.\textsuperscript{14}

15. Amy H. Moore et al.,\textsuperscript{21} (2010) reviewed Non-Steroidal Anti-Inflammatory Drugs in Alzheimer's Disease and Parkinson's Disease: Reconsidering the Role of Neuroinflammation. Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative diseases with age as the greatest risk factor. As the general population experiences extended life span, preparation for the prevention and treatment of these and other age-associated neurological diseases are warranted. Since epidemiological studies suggested that non-steroidal anti-inflammatory drug (NSAID) use decreased risk for AD and PD, increasing attention has been devoted to understanding the costs and benefits of the innate neuroinflammatory response to functional recovery following pathology onset. This review will provide a general overview on the role of neuroinflammation in these neurodegenerative diseases and an update on NSAID treatment in recent experimental animal models, epidemiological analyses, and clinical trials.\textsuperscript{15}

16. Chun Shi, et al.,\textsuperscript{22} (2010). reviewed on Ginkgo biloba Extract in Alzheimer’s Disease: From Action Mechanisms to Medical Practice. Standardized extract from the leaves of the Ginkgo biloba tree, labeled EGb761, is one of the most popular herbal supplements. Numerous preclinical studies have shown the neuroprotective effects of EGb761 and support the notion that it may be effective in the treatment and prevention of neurodegenerative disorders such as Alzheimer’s disease (AD). Moreover, various parameters e.g., the dosage and the permeability of the blood brain barrier (BBB), impacting the outcome of the clinical effectiveness of the extract are also discussed. Overall, the findings summarized in this review suggest that, a better understanding of the neuroprotective mechanisms of EGb761 may contribute to better
understanding of the effectiveness and complexity of this herb and may also be helpful for design of therapeutic strategies in future clinical practice. Therefore, in future clinical studies, different factors that could interfere with the effect of EGb761 should be considered.

17. Kirti S. Kulkarni *et al.* (2011) investigated the effect of Prunus amygdalus (PA) nuts on cognitive functions total cholesterol levels and cholinesterase activity in scopolamine induced amnesia in rats the paste of PA nuts was administered orally all doses (150, 300 and 600 mg/kg) for 7 and 14 consecutive days to the respective group of rats piracetam (200 mg/kg) was used as a standard nootropic agent, passive avoidance and motor activity paradigms brain ChE activity and serum biochemical parameters like total cholesterol, total triglycerides and glucose were evaluated.

18. Keyvan dastmalchi, *et al.* (2012) reviewed herbs used in the management of alzheimer’s disease. Plants have been used since antiquity in the treatment therefore ethenopharmacological screening of plants belonging to 21 families used in traditional system medicine eg Chinese, Indian and European for treatment of cognitive dysfunction phytochemical substances with pharmacological activities relevant to alzheimer’s disease treatment have been highlighted.

19. Fang Wang *et al.* (2012) A Peptide That Binds Specifically to the b-Amyloid of Alzheimer’s Disease: Selection and Assessment of Anti-b-Amyloid Neurotoxic Effects. In order to develop new Ab-specific peptides for AD, a randomized 12-mer peptide library with Ab1-10 as the target was used to identify peptides in the present study. After three rounds of selection, specific phages were screened, and their binding affinities to Ab1-10 were found to be highly specific. Finally, a special peptide was synthesized according to the sequences of the selected phages. In addition, the effects of the special peptide on Ab aggregation and Ab-mediated neurotoxicity in vitro and in vivo were assessed. In conclusion, we selected a peptide that specifically binds Ab1-10 and can modulate Ab aggregation and Ab-induced neuronal damage. This opens up possibilities for the development of a novel therapeutic approach for the treatment of AD.
20. M. Ramanathan et al. (2010) investigated neuroprotection effect of chloroform methanolic (80:20) extract of casicatica (CA: 100 & 200 mg/kg) was evaluated on the course of free radicals generation and excitotoxicity in monosodium glutamiate treated female Sprague dawley rats. The extract showed significant improvement in catalase superoxide glutathione level was not not altered with CA treatment similar observation was made with dextromethorphan. The general behaviour locomotor activity aCA a region of the hippocampus was significantly protected by CA.

21. Joshi. H et al., (2010) investigated potential role of Ocimum tenuiflorum linn as a nootropic and anticholinesterase agent in mice. Ethanol extract of dried whole plant ameliorated the amnesic effect of scopolamine (0.4 mg/kg) and aging induced memory deficits in mice passive avoidance paradigm served as the exteroceptive behavioural model. The extract also increased step-down latency and cetyl cholinesterase inhibition significantly hence it can be employed in the treatment of cognitive disorders such as dementia and alzheimer’s disease.

22. F.J. Wippold et al. (2010) pathology review on Neuropathology for the Neuroradiologist Plaques and Tangles Histologically identified intracellular and extracellular inclusions and structures often provide a tissue diagnosis of a specific disease process. Histologically identified cellular deposits often provide a tissue diagnosis as well as clues about the pathogenesis of the disease that they represent. Moreover, neuroradiologists are likely to play important roles in the future regarding the detection and differential diagnosis of AD, given the increasing prevalence of DAT in the aging population and promising research aided by such tools as positron-emission tomography (PET), quantitative structural imaging, molecular imaging, diffusion tensor imaging, and functional MR imaging. The purpose of this report is to review the significance of plaques and tangles in AD.

23. Anil Kumar., et al., (2007) investigated that Colchicines-induced neurotoxicity as an animal model of sporadic dementia of Alzheimer’s type cognitive dysfunction as evidenced by poor retention of memory in both Morris water maze and elevated plus-maze task paradigms that is associated with excessive free radical generation, results
indicated that colchicines-induced cognitive impairment and oxidative stress can be used as an animal model for drug screening for Alzheimer's disease\textsuperscript{23}.

Hanumanthachar Joshi, et al.\textsuperscript{30}, (2006) investigated on Nootropic Activity of Calyces of \textit{Hibiscus sabdariffa} Linn. To delineate the possible mechanism through which \textit{H. sabdariffa} elicits the anti-amnesic effects, \textit{H. sabdariffa} significantly decreased acetyl cholinesterase activity in mice. The aqueous extract of calyces of \textit{H. sabdariffa} might prove to be a useful memory restorative agent in the treatment of dementia seen in elderly. mechanism of action can be attributed to its anti acetylcholinesterase property\textsuperscript{24}.

R. Douglas Shytle et al.,\textsuperscript{31} (2009) investigated that Optimized Turmeric Extracts have Potent Anti-Amyloidogenic effects. Other extracts and the individual curcuminoinds on AD aggregation. Only simple additive effects were observed for the AD aggregation inhibition, supporting the notion that the known curcuminoinds are not strong inhibitors of this activity. novel bioactive molecules in this extract that might be important leads for future AD drug discovery efforts\textsuperscript{25}.

Milind Parle et al.,\textsuperscript{32} (2009) investigated on memory enhancing activity of \textit{Abana} An Indian polyherbal formulation shown increasingly brain cholinesterase activity will be reduced by Abana administrated orally for 15 days it may prove to be a useful remedy for the management for AD\textsuperscript{26}.

Toshiaki Irie, et al.\textsuperscript{33}, (1995) investigated on Brain Acetylcholinesterase Activity: Validation of a PET Tracer in a Rat Model of Alzheimer's Disease(AD) the method suggest lipophilic analog diffuses into the brain where it is metabolized by AchE to produce a metabolite, which is trapped at the site of its production. MP4Pesters had sufficient sensitivity to enable AchE activity changes in the rat cortex of less than 50% to be detected, indicating that method is applicable to PET diagnosis of AD\textsuperscript{27}.

Gupta Shikha et al.\textsuperscript{34}, (2012) formulated and evaluated herbal anti-demential tablets Here, Piracetam a nootropic agent will be employed as a standard drug. Sodium
Nitrite will be used to induce amnesia in young experimental model, and which is comparable with that of the age related amnesia in old rats. Administration of tablets produces significant dose dependant improvement of memory and were almost similar with that of standard drug Piracetam\textsuperscript{28}.

29. Alikunju Shanavas \textit{et al.}\textsuperscript{35}, (1995) investigated those t kinases in the rat heat shock model: Possible implications for Alzheimer disease. Increased activation and inhibition of kinases after heat shock were statistically significant in comparison with controls. Because t is hyperphosphorylated in Alzheimer disease these findings suggest that JNK, GSK-3b, and Cdk5 may play a role in its pathogenesis\textsuperscript{29}.

30. Manish Kumar Saraf \textit{et al.}\textsuperscript{36}, (2011) investigated that \textit{Bacopa monniera} Attenuates Scopolamine-Induced Impairment of Spatial Memory in Mice employed Morris water maze scale to test the amnesic effect of scopolamine and its reversal by \textit{B. monniera}. Rotarod test will be conducted to screen muscle coordination activity of mice. \textit{B. monniera}’s effects on cholinergic system may be helpful for developing alternative therapeutic approaches for the treatment of Alzheimer’s disease\textsuperscript{30}.

31. Julio Rubio \textit{et al.}\textsuperscript{37}, (2011) investigated that Aqueous Extract of BlackMaca (\textit{Lepidium meyenii}) on Memory Impairment Induced by Ovariectomy in Mice two different doses of aqueous extract of black maca on learning and memory in ovariectomized (OVX) mice and their relation with malonalehyde (MDA), acetylcholinesterase (Ache) and monoamine oxidase (MAO) brain levels. improved experimental memory impairment induced by ovariectomy, due in part, by its antioxidant and Ache inhibitory activities\textsuperscript{31}.

32. Joab Chapman, \textit{et al.}\textsuperscript{38}, (1989) investigated on Immunization of Rats with Cholinergic Neurons Induces Behavioral Deficits experiments revealed that the cholinergic PK immunized rats displayed a significant deficit in short term memory. The association of antibodies to cholinergic neurons with cognitive deficits in this rat model suggests that such antibodies may be involved in the pathogenesis of AD\textsuperscript{32}. 
33. Mohammad Hossein Dashti-R et al.,\textsuperscript{39} (2009) investigated the effects of \textit{Syzygium aromaticum} (clove) on learning and memory in mice. An experimental study will be conducted in normal male mice. In this study we used a Shuttle Box device to evaluate the active avoidance learning and memory in mice. Acute administrations of ethanolic extracts of clove enhance the learning and memory recall ability in mice in an inverse dose-dependent manner\textsuperscript{33}.

34. Govind Pandey, \textit{et al.},\textsuperscript{40} (1989) evaluated pharmacological activities of \textit{Ocimum sanctum} (tulsi): a review. The AIE of dried whole plant of OS ameliorated the amnesic effect of scopolamine (0.4 mg/kg) and aging-induced memory deficits in mice. Passive avoidance paradigm served as the exteroceptive behavioural model. OS extract increased step-down latency (SDL) and acetylcholinesterase inhibition\textsuperscript{34}.

35. Julie Vining Smith \textit{et al.},\textsuperscript{41} (2003) elevated that oxidative free radicals in Alzheimer’s disease models can be attenuated by \textit{Ginkgo biloba} extract EGb 761. Furthermore, an age-dependent increase in H2O2-related ROS will be observed in wild type C. elegans, which is accelerated in the AD-associated C. elegans mutant. The results support the hypothesis of the involvement of A\textsubscript{\beta} and ROS in association with AD\textsuperscript{35}.

36. Yuen-Shan Hoa et al.,\textsuperscript{42} (2007) investigated on Characterizing the neuroprotective effects of alkaline extract of \textit{Lycium barbarum} on \textit{β}-amyloid peptide neurotoxicity. Lycium barbarum is an oriental medicinal herb that has long been used for its anti-aging and cell-protective properties. Results suggested that the glycoconjugate isolated from novel alkaline extraction method can open up a new avenue for drug discovery in neurodegenerative diseases\textsuperscript{36}.

37. Mani Vasudevan \textit{et al.},\textsuperscript{43} (2007) investigated on Memory-Enhancing Activity of \textit{Thespesia populnea} in Rats. Cholesterol-lowering, anticholinesterase, anti-inflammatory, and antioxidant properties of \textit{Thespesia populnea} may favorably contribute to its memory-enhancement effect. Therefore, \textit{Thespesia populnea} bark appears to be a promising candidate for improving memory, and it would be
worthwhile to explore the potential of this plant in the management of Alzheimer patients\textsuperscript{37}.

38. Bhattacharya, S.K., et al.,\textsuperscript{44} (2007) investigated that effect of Mentat, a Herbal Formulation, on Experimental Models of Alzheimer’s Disease and Central Cholinergic Markers in Rats. The present study will be undertaken to study the cognition-facilitating effect of Mentat in experimentally validated models of Alzheimer’s disease (AD) in rats, and to investigate the role of the central cholinergic system in the nootropic effect\textsuperscript{38}.

39. John M. Ringman, et al.,\textsuperscript{45}, (2010) investigated on Potential Role of the Curry Spice Curcumin in Alzheimer’s Disease. Curcumin has antioxidant, anti-inflammatory, and anti-amyloid activity. In addition, studies in animal models of Alzheimer's disease (AD) indicate a direct effect of curcumin in decreasing the amyloid pathology of AD. As the widespread use of curcumin as a food additive and relatively small short-term studies in humans suggest safety, curcumin is a promising agent in the treatment and/or prevention of AD\textsuperscript{39}.

40. Hanumanthachar Joshi et al.,\textsuperscript{46} (2010) investigated that \textit{Zingiber officinale}: evaluation of its nootropic effect in mice. \textit{Z. officinale} might prove to be a useful memory restorative agent in the treatment of dementia seen in the elderly. The underlying mechanism of its action may be attributed to its antioxidant and acetyl cholinesterase inhibition property\textsuperscript{40}. 