SUMMARY

Alzheimer’s disease is a progressive neuro degenerative disorder and is the most common cause of dementia. It is caused due to the atrophy of the cortical and sub-cortical areas of the brain which is associated with the deposition of beta amyloid protein, in the form of senile plaques and neurofibrillary tangles. There is also a marked cholinergic deficiency in these parts of the brain. Thus, Alzheimer’s disease is a complex neurodegenerative disease with cognitive, behavioral and neurological manifestation.

Cognitive abnormalities include progressive disturbance in declarative memory, semantic comprehension and naming, visual skills and executive abilities. Neuropsychiatric and behavioral manifestations include psychosis, mood abnormalities, euphoria, depression, agitation, changes in sleep pattern and disturbance of appetite.

Allois Alzheimer, a German psychiatrist, in 1906, described the disease and divided it into early onset Alzheimer’s disease and late onset Alzheimer’s disease. The early onset Alzheimer’s disease is caused by the autosomal dominant mutation in the APP gene on chromosome 21, the three presenilin genes on chromosome -1. The late onset Alzheimer’s disease is associated with the presence of apolipoprotein (APOE) of the E-4 allele. Alzheimer’s disease has been shown to be associated with a history of traumatic head injury, cardiovascular disease,
hypertension in mid life, hypotension, smoking, stroke, diabetes and hypercholesterolemia.

In the year 2000, India had 2.5 million Alzheimer’s disease patients against 4.5 million in U.S. Prevalence of Alzheimer’s disease in urban population is 15.5 per thousand and 17 per thousand in the rural population. The higher prevalence of dementia in the rural community than in the urban community has been reported. The prevalence of Alzheimer’s disease is higher in women than in men and increases with age. It has been recently estimated that, 18 million people live with dementia, world wide. Every year 4.6 million new cases are added. Most people with dementia belong to the low and middle class. It is expected that, this figure will double by 2025 to 34 million. So the study of Alzheimer’s disease is given more priority than other epizootics especially to develop novel drugs to tackle this disease. The currently used medicines are associated with side effects and they are able to tackle Alzheimer’s disease efficiently.

In the present study, new efforts are taken to develop novel, low cost, holistic effective drugs for Alzheimer’s disease. This study also screened the efficacy of available drugs and their synergetic action, with different combinations.

The whole study is divided into 4 chapters. The survey of the Alzheimer’s patients in 4 major cities of Tamilnadu in 2006 – 2007 are given in chapter I, chapter II deals with the selection of novel herbal drug for the treatment of Alzheimer’s disease and comparison of their efficacy with the commercially available front line Alzheimer’s drugs. The \textit{in-vivo} and \textit{in-vitro} evaluation of
herbal drug efficacy are presented in chapter III, chapter IV covers the isolation of the active principles from the selected herb.

In the first chapter, the prevalence of Alzheimer’s disease in the Govt. hospitals of the major cities of Tamilnadu like Chennai, Madurai, Salem and Kanyakumari were studied. As per the results 2.6% of the neuro-pateients suffer from Alzheimer’s disease in Chennai. Among that 36% of the patients were diabetic, 36% patients had high cholesterol and 27% patients were obese. But in Madurai, the percentage has been decreased to 2.3% among those 50% were diabetic, 31% had high cholesterol and 50% were obese. The data available from the Salem government hospital indicates that 2.5% of the total neuro-patients suffer from Alzheimer’s disease, with 44% of diabetics, 44% of high cholesterol and 33% of obesity. Interestingly, Kanyakumari had the least population of Alzheimer patients, less than 2%, among whom 40% were diabetic, 40% had high cholesterol and 40% with obesity. The report also clearly indicated that Alzheimer’s disease is closely linked to diabetes, high cholesterol and obesity. In contrast to other 3 cities, Kanyakumari also had more male Alzheimer patients.

In the second chapter, the number of commercial frontline drugs and herbal extracts were screened for memory enhancing properties and their activities were compared. The major drugs such as Donepezil, Vitamin E, Celecoxib, Simvastin, and the natural drugs such as *Sida cordifolia, Thespesia populnea, Santalum album* extracts were selected and administered orally, for the study. Preliminary toxicity studies were also conducted for dose standardization.
Animals were separated into different groups and amnesia was induced by injecting a medium dose of diazepam and scopolamine, intra peritoneally. The memory enhancing property of the said drugs and extracts, were studied using the two compartment passive avoidance apparatus. The results clearly indicated that the extract of *S. album* and Donepezil possess significant memory enhancing property when compared with the other drugs and extracts. Hence the extract of *S. album* was selected for further studies.

Chapter III deals with the various *in-vivo* and *in-vitro* experiments carried out to evaluate the memory enhancing property of *S. album*. The animal ethical committee approval was obtained from CPCSEA (approval no.-1143/365) for the usage of animals for the study. White albino mice were procured from the King institute Chennai. 4-6 weeks old mice were selected for the study and they were separated into 7 groups. All animals except the animals from the sixth group were injected with beta amyloid (a neurotoxin) through ICV route. Then the animals were treated for 2 months with the respective drugs and/or the combinations. The performance of the animals in the two compartment passive avoidance apparatus, Hebbs William Maze, Elevated plus Maze were recorded. The animal group treated with the *S. album* extract showed a significant improvement in their memory when compared to other groups. In order gain further insight in to the mechanism of action these drugs including that of *S. album* extract the treated animals were sacrificed, their brains removed and the enzyme activities such as acetyl choline esterase and antioxidant property were carried out. The results indicated that there is a significant increase in acetylcholine esterase activity (OD
value 3485) in Donepezil and *S. album* combined drug treatment followed by *S. album* administered groups (OD value 3220). These values are highly significant compared to the control group (OD value 525). This is further supported by the histology of brain. It is of interest to note that the combined dose also shown symptoms of neuro regeneration with formation of neurofibrillary tangles were also seen.

Acute toxicity studies were conducted at different dose levels and the LD$_{50}$ values were determined. The sub-lethal doses were taken for the further study. The results of the above experiments clearly indicated that the extract of *S. album* had a potentiating effect over the activity of Donepezil. Even at a lower dose of Donepezil, there was significant potentiation of activity with *S. album*. This was supported by histopathology reports.

Chapter IV is mainly intended to screen and identify the active principles which are associated with anti Alzheimer’s activity of *S. album*. The TLC and HPTLC studies were carried out to explore the fractions of *S. album* with appropriate techniques. The results of TLC shown 3 bands, but the HPTLC analysis resulted in 11 peaks. The qualitative biochemical analysis of *S. album* also indicated that the presence of terpenoids, sugar, phenol and tannin.

In conclusion this study have evaluated the memory enhancing properties of extracts from three plants namely *Sida cordifolia*, *Thespesia populnea*, *S. album* and identified *S.album* to posses significant memory enhancing property. Significantly this study has also identified a synergetic effect between *S.album* and
the commercially available drug Donepezil. Notably this synergetic effect is also seen at lower doses of the drug Donepezil. An attempt to identify the active principles associated with the anti Alzheimer’s activity of *S. album* have identified phytochemical components like triterpenoids, sugar, phenol and tannins as positive components against Alzheimer’s disease.