CHAPTER 1

INTRODUCTION

Age is the biggest risk factor for many chronic diseases such as neurodegenerative disorders, cancer, cardiovascular disease, diabetes and metabolic syndrome. Senile dementia of Alzheimer's Type is one of the major kinds of age related neurodegenerative disorders affecting the elderly population. Improvements in the global health technology have increased the life span of individual's thus increasing the percentage of geriatrics worldwide especially in the developed and developing countries. Statistics of the World Health Organization in the year 2013 stated that about 2 billion people will be aged 60 and above by the year 2050 and this increase in the proportion of elderly will double from 11 to 22% of which 4-6% will be from high income/developed nations. Epidemiological studies state that about 25-30% of people above the age 80 have cognitive decline or senile dementia and it is projected that by 2050, 400 million people in the world population will be above 80 years (WHO 2015).

Dementia of Alzheimer's Type (DAT) is a progressive fatal neurodegenerative disorder which is characterized by deterioration in cognition and memory, gradual impairment in daily living activities and increase in neuropsychological and behavioral symptoms [1]. DAT is the most common form of dementia among the elderly. It accounts for about two third cases of dementia and 60-70% of progressive cognitive dysfunction among the elderly [2-3]. The cognitive, behavioral and functional decline in senile dementia of alzheimer's type patients places a drastic burden on the health care system and caretakers [4]. Senile Dementia of Alzheimer's Type (SDAT) is therefore a growing medical, social and economic burden as the incidence increases with the increase in the elderly population.
In general it is hard to differentiate normal ageing form SDAT as the difficulty arises in the diagnosis at its early stage. The changes that occur in SDAT and ageing are very similar,

differing only in degree and not in kind. They share common biological changes within the neurotransmitter system, antioxidant defense mechanism, inflammatory response and other physiological process, thus vindicating ageing as most prominent risk factor for SDAT. Though the diagnosis and etiology of dementia is not known clearly, researches have hypothized various factors associated with its pathogenesis like oxidative stress, abnormal phosphorylation of tau protein, altered homeostasis of calcium, age, inflammatory markers, β- amyloid peptide accumulation etc. [5-10].

Ageing is accompanied with a remarkable decline in cognitive function and mood disturbance which creates a health burden to the society. The biological and biochemical parameters associated with cognitive decline are reduced neurotransmitter function especially acetylcholine, dopamine, serotonin and nor epinephrine. This reduction in neurotransmitter function is in turn correlated to degeneration of neurons of the brain such as cholinergic and dopamergic neurons and cognitive dsyfunction in ageing as well as SDAT [11].

Oxidative stress and decreased energetic metabolism in association with inflammation were reported to play an integral role in the progressive age related neurochemical and neurobehavioral deficits and SDAT [12]. Therefore, there is need to search for multimodal therapeutic interventions which may exhibit multi-targeted action by modulating various mechanistic pathways and help in delaying the age associated neurodegeneration. Several studies have evidenced that progressive oxidative damage is a conserved, central mechanism of age related functional decline [13]**.** Gene expression studies showed an age dependant up regulation of oxidative stress response genes in ageing human's pre frontal cortex suggesting a positive relationship between oxidative damage and biological ageing [14].

Age related oxidative stress was first revealed at the molecular levels and includes the accumulation of macromolecular damage and changes in signal transduction pathways. These alterations subsequently have an impact on the cellular responses, such as organelle dysfunction, inflammation, cell proliferation, survival and death. Eventually,

dysfunction caused by oxidative stress was manifested at systemic levels which would likely include decline in organ function, reduced stress tolerance and increased incidence of neurodegenerative diseases and death. Therefore, the development of future therapeutic interventions may target the molecular and cellular pathways of oxidative stress which are useful in protecting the neuronal damage in ageing and SDAT.

Ageing is also accompanied by an increased inflammatory signaling as well as immune system dysfunctioning. Numerous evidences pointed out the dysregulated neuroimmune response along with an increased production of pro inflammatory cytokines with ageing [15]. Over expression of IL-1β along with other cytokines and changes on glio transmission contribute significantly to the age related cognitive disabilities [16, 17]. Microglia seems to be a major drive for brain ageing, since they were found to be activated in the elderly as well as in SDAT patients [18]. Microglial cells obtained by cell sorting from ageing rat showed the presence of lipofuscin granules, decreased process complexity, altered granularity and increased mRNA levels of pro-inflammatory cytokines. However, interestingly pro–inflammatory genes were up-regulated during ageing whereas this effect was accentuated in SDAT [19]. Therefore, therapeutic interventions which may modulate the aberrant inflammatory signaling associated with ageing may also act as a potent candidate for the early prevention of neurodegenerative pathologies like SDAT.

Apart from the above stated pathways, there are several other mechanisms such as protein aggregations & degradation, calcium homeostasis and glutamate excite toxicity which has been linked to neurodegeneration. Thus, from the above evidences it is clear that ageing results in characteristic molecular and cellular changes which interface with SDAT and age associated cognitive impairment.

Current class of drugs in the market for SDAT and AD are cholinesterase inhibitors and glutamate inhibitors which include Donepezil, Tacrine, Memantine, Galantamine and Rivastigmine. These drugs are used in the various stages of disease and they have their own level of side effects such as nausea, vomiting, diarrhea, fatigue, weight loss, insomnia, confusion, dizziness and headache. Therefore, there arises the need for a safe and effective drug which can be employed for the long term intervention.

An inadequate level of attention has been focused in preventing and delaying the risk of SDAT and promotion of healthy brain ageing. Since ageing is a natural process it is impossible to stop it but it is always feasible to mitigate its complication by converting normal ageing to successful and healthy brain ageing which exhibits a) less disease acquiring b) increased mental and physical function and c) active social life. Therefore, there is an immense need to search for drugs/therapeutics to achieve this.

In context to the above, the first thought that arises on developing a safe and efficient drug strike with the application of plants or herbal based therapy, which has low or least side effect. The Indian system of medicine like ayurveda, siddha is one such helpful remedy which is recently gaining much attention worldwide. A unique concept of rejuvenation measures for biological sustenance to bodily tissue exists in Ayurveda. 'Rasayan' are a class of drug used to strengthen the whole biological system as well as part divine property to it. 'Medhyarasayana' are drugs that act on brain and cognition and *Bacopa monnieri* or brahmi is one of such plants widely used by many practitioners to cure disease of the nervous system.

Polyherbal formulation

Several polyherbal formulations has been used in Ayurveda for treating cognitive decline and AD, in recent times studies were conducted by various researchers on polyherbal formulation such as Memory plus, SR-105, Mentat and Transia and vitamin formula, for its nootrophic, cognitive enhancing and effects on the central cholinergic neurons using experimental models. But there are very few studies which have focused on the neuroprotective and disease modifying effect of the investigational drugs.

Rationale for plant selection

The polyherbal formulation consists of three plants *Bacopa monnieri*, *Hippophae rhamnoides* and *Dioscorea bulbifera*. The rationale for selection of these plants is as follows.

B. monnieri- belongs to scrophulariaceae family, it is a nootrophic drug; the active constituent Bacosides present in the plant promotes protein synthesis in the neuron and acts effectively on the cholinergic system.

H. rhamnoides- belongs to Elaeagnaceae family, it is house of natural antioxidant such as flavonoids, phenols, vitamins etc, it is known for its immunomodulatory, hypolipidemic, homocysteine lowering activity.

D. bulbifera- it belongs to the family Dioscoreaceae and is known for its antioxidant property and the marker compound diosogenin is a phytoestrogen and act as an effective neuroprotectant.

In the extension of the above previous reports the present series of studies was carried out to evaluate the neuroprotective mechanism of action of the herbal formulation on the neurotransmitter system, anti-oxidative stress markers, inflammation and cognition in cell line, animal model and humans. Thus the present study will add on to the scientific evidence regarding the mode of action of the polyherbal formulation for its neuroprotective activity in aged as well as its potential to prevent progression of SDAT.