1. INTRODUCTION

Ageing is defined as the progressive deterioration in the homeostasis and repair capacity of an organism over time with increased likelihood to develop age associated pathologies like Senile Dementia of Alzheimer’s Type (SDAT). With advances in health care facilities, even in the developing countries, the ageing population is increasing in number. In the year 2005, the world population stood at 6514.7 million, with India accounting for 1134.4 million and it has reached to 1147 million in the year 2008 (WHO report 2002). Of this, nearly 7.9% (90 million) were aged above 60 years and 0.65% was above the age of 80 years. As per WHO projections among 1.2 billion people aged 60 years about 81.1 million cases of dementia will occur by 2025 (WHO report 2002; Ferri et al. 2005). In addition, it has been estimated that among all the dementia cases 60% fulfilled the criteria of SDAT (McKhann et al. 1984). These epidemiological studies thus clearly indicate that the advances in medical technology have decreased the mortality rate and prolonged the life span, however the health – span largely remains unaltered.

The transition or prodromal stage between normal ageing and dementia or SDAT is a heterogenous entity and it is far from straight forward to separate the non pathological from pathological cognitive decline. This was due to the lack of identification of those changes which were unique to SDAT, since the changes observed were confounded with age related changes, the changes differing in degree but not in kind. Moreover, the diagnosis of dementia, in the mild or early stage, would be particularly difficult among the individuals who have reached the advancing old age. The exact mechanism through which ageing converges to neurodegenerative pathologies like SDAT is poorly understood, however pre clinical and clinical studies unequivocally suggest that ageing and SDAT share the common changes within the neurotransmitter systems, antioxidant defense mechanism, energy transduction system and inflammatory responses, thus substantiating ageing as the most prominent risk factor for SDAT.

Ageing was accompanied with significant cognitive decline and mood disturbances which pose health care burden as well as social problem for the society. The biochemical or morphological basis of cognitive decline and depression could be attributed to the reduced neurotransmitter function especially acetylcholine, serotonin (5 - HT), nor epinephrine (NE) and dopamine (DA), which in turn was due to the
degeneration of brain stem NE neurons, cholinergic neurons and substantia nigra situated dopaminergic neurons in ageing as well as SDAT (Zarrow et al. 2003). Moreover, the mood, cognition and movement dysfunctions were also the result of convergent pathways, as evident by the involvement of different neurotransmitter systems in cognitive behavior. For eg, D1 and D2 receptors agonists were found to be involved in memory performance possibly through the regulation of acetylcholine release (Umegaki et al. 2001) whereas alpha-2 adrenergic antagonists may improve memory in neuropsychological disorders (Mohammad Zarrindast R 2006). Similarly, cholinergic – serotonergic interactions have been suggested to play important role in learning and memory (Cassel & Jeltsch 1995).

Recent studies have proposed the involvement of several pathways in the age associated functional decline and thus increased vulnerability to develop SDAT. Among them, oxidative stress and decreased energetic metabolism due to mitochondrial impairment in association with inflammation were reported to play intricate interplay in the progressive age related neurochemical and neurobehavioral deficits and SDAT (Forster et al. 1996; Navarro et al. 2002). Therefore, search for the multimodal therapeutic interventions which may exhibit pleiotropic action by modulating various mechanistic pathways may have an immediate impact in preventing and/or delaying the age associated neurodegeneration.

Multiple lines of evidence suggest that progressive oxidative damage is a conserved, central mechanism of age related functional decline (Muller et al. 2007). Gene expression studies showed an age dependant up regulation of oxidative stress response genes in ageing humans pre frontal cortex suggesting a positive relationship between oxidative damage and biological ageing (Frasee et al. 2005). Recently, it has been indicated that a selective population of neurons like hippocampal CA1 neurons in the brain were more vulnerable for oxidative stress in ageing and these neurons were usually the first to exhibit functional decline and cell death during normal ageing and SDAT (Muellor et al. 2007; O’Banion 1994). Thus, the selective vulnerability of hippocampal neurons to oxidative stress might underlie the poor cognitive functions in the aged and SDAT patients. Age related oxidative stress was revealed first at molecular levels and include the accumulation of macromolecular damage and changes in signal transduction pathways. These alterations subsequently impact on cellular responses, such as organelle dysfunction, inflammation, cell proliferation, survival and death. Eventually, dysfunction 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 which may target the molecular and cellular pathways of oxidative stress will be useful in protecting the neuronal damage in ageing and SDAT and thus improved functioning of the brain.

Mitochondrial function also reported to be compromised with ageing and SDAT in the human brain (Shigenaga et al. 1994; Cassarino & Bennett 1999). In normal ageing, mitochondrial respiratory chain activity declined (Ojaimi et al. 1999), mitochondrial metabolism associated enzymes decreased (Yan et al. 1997) and the rate of somatic mitochondrial DNA mutations increased (Michikawa et al. 1999). In SDAT, similar types of losses in respiratory chain activity (Hirai et al. 2001; Bosetti et al. 2002) and increase in mitochondrial DNA mutations (Coskun et al. 2004) were observed, when compared to age matched controls. In addition, gene expression studies suggested that reduced expression of mitochondrial genes is a strongly conserved feature of brain ageing (Lu et al. 2004; Loerch et al. 2008). The accumulation of higher percentage of defective mitochondria in the aged brain disrupts metabolism, energy production, calcium signalling, with exacerbated ROS and RNS production, and apoptosis, which in turn cumulatively influence age dependant neurochemical and neurobehavioral deficits. This was supported by the studies, where administration of mitochondrial nutrients such as acetyl-L-carnitine (ALCAR) and lipoic acid (LA) significantly improved the behavioral decrements and reduced the oxidative damage in the brain of aged rodents (Haripriya et al. 2004; Crouch et al. 2007). In the human brain declining mitochondrial function may selectively affect neuronal population with large bioenergetic demands, such as the large pyramidal neurons that degenerate in ageing and SDAT. Mitochondrial function seems to be an important influencing factor for lifespan and reduction of mitochondria function would be expected to impair health and shorten lifespan. Recently, in the senescence accelerated mouse (SAMP8), which exhibited a shortened life span and learning impairments, significant mitochondrial dysfunction was observed (Mori et al. 1998; Nakahara et al. 1998). Considering the facts that declining mitochondrial function contributes significantly in brain ageing and render neurons vulnerable to SDAT, it is hypothesized that therapeutic interventions which improve mitochondrial function may promote the cognitive functioning in ageing and SDAT.
Ageing is also accompanied by an increased inflammatory signalling as well as immune system dysfunctioning. Numerous evidences pointed out the dysregulated neuroimmune response along with an increased production of pro inflammatory cytokines and cytotoxicity with ageing (Yung & Julian 2008). Over expression of IL – 1β along with other cytokines and changes on gliotransmission contribute significantly to the age related cognitive disabilities (Holmes et al. 2003; Tarkowski et al. 2003). 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 (Mcgeer et al. 1987). Microglial cells obtained by cell sorting from ageing rat showed the presence of lipofuscin granules, decreased processes 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 (Colangelo et al. 2002; Lukiw 2004). Therefore, therapeutic interventions which may modulate the aberrant inflammatory signalling associated with ageing may act as a potent candidate for the prevention of neurodegenerative pathologies like SDAT.

Apart from the above discussed pathways, several other mechanisms like alterations in protein aggregation and degradation, calcium homeostasis, glutamate excitotoxicity etc. also links ageing to neurodegeneration. Thus, from the various evidences it is clear that ageing results in characteristic molecular and cellular changes which interface with SDAT and age associated cognitive impairment and SDAT involved vulnerability of similar neuronal circuits.

Since, the treatment of SDAT still remains a challenge and is less than adequate, considerable attention has been focussed to prevent or delay the risk of developing SDAT by promoting the healthy brain ageing. Ageing itself cannot be prevented, but its complications can be mitigated by transforming “usual” ageing into “successful” ageing. Usual ageing, is defined where extrinsic factors heighten the deleterious effect of ageing whereas successful ageing have three main components viz., a) the low probability of disease and disease related ability, b) a high capacity for cognitive and physical functioning and c) an active engagement with life. Therefore, search for the therapeutic interventions that can effectively transform usual ageing to successful ageing and thus prevent and/or delay the progression of SDAT is highly demanded. In this context, the health promotive, disease preventive and rejuvenation approach available in Indian System of Medicine like “Ayurveda” is gaining greater
attention and popularity worldwide. The “Rasayana chikitsa” in Ayurveda mainly involve the use of crude plant extracts alone or in combination and deals with the preservation and promotion of health by revitalizing the metabolism and enhancing immunity. There has been a plenty of research on the plants used as Rasayana drugs in order to reason them in modern context. Puri (1970a, b, 1971, 1972, 2003) gave an account of herbs used in various “Rasayana” preparations while Udupa (1973) studied the effects of “Rasayana” drugs on psychosomatic stress. In the present series of study two medicinal plants viz., *Bacopa monnieri* (L) and *Curcuma longa* (L) of Indian System of Medicine were investigated for their neuroprotective effect in age associated neurodegeneration and its relevance in SDAT progression.

*Bacopa monnieri* (L.), popularly named as Brahmi, is a revered Ayurvedic medicinal plant effective against cognitive impairment, mental illness and epilepsy (Badmaev V 1998). The active principles of *Bacopa* are steroidal saponins, collectively named as bacosides and are attributed with the capability to enhance nerve impulse transmission and thereby strengthen memory and general cognition. In addition, the anti – inflammatory, antioxidant, cardiotonic and other pharmacological effects of *Bacopa monnieri* were also reported. The commercial preparations of *Bacopa monnieri* has shown cognitive enhancing effects in young as well as aged human subjects (Dave et al. 1993; Roodenrys et al. 2002). It has been suggested that *Bacopa monnieri* exhibited neuroprotective and cognitive enhancing effects, in part due to its capacity to modulate the cholinergic system (Bhattacharya et al. 1999) and to contrast oxidative stress (Bhattacharyya et al. 2000; Russo et al. 2003a, b). In extension to the previous reports the present series of studies have investigated the neuroprotective mechanism of action of bacosides on lipofuscin, oxidative stress markers, energy transduction system, inflammation, neurochemical and neurobehavioral deficits in the aged rat brain. Our study is the first to report the protective effect of bacosides, the bioactive saponins of *Bacopa monnieri* over mitochondrial complexes and ultrastructural changes in mitochondria in the aged brain. Thus, the present study will add the scientific evidences regarding the mode of action of bacosides for their neuroprotective activity in the aged brain as well as its potential to prevent and/or delay the age associated pathologies like SDAT.

*Curcuma longa* (L.) rhizomes have been widely used in traditional Indian system of medicine to treat dyspepsia, flatulence, liver disease, urinary tract disease and as a blood purifier. Various components of *Curcuma longa* are currently
undergoing scientific evaluation at clinical levels for their utility as anti-inflammatory agents (Vlietinck et al. 1998), prevention and treatment in cancer (Aggarwal et al. 2003), treatment of HIV infection (Vlietinck et al. 1998) and most recently for cystic fibrosis (Egan et al. 2004). The major biological activities of *Curcuma longa* was attributed to its nonflavanoidic polyphenols, curcuminoids, which comprises of curcumin, bis demethoxycurcumin and demethoxycurcumin. Polyphenols can act as important neuroprotective agents due to their ability to cross blood brain barrier (BBB) as well as their potent antioxidant and anti-inflammatory activity. Epidemiological studies have raised the possibility that this molecule used by Asian Indian population is involved for the significantly lower prevalence of SDAT in India compared to US (4.4 fold) (Ganguli et al. 2000). Recently, the anti-amyloidogenic effects of curcumin were also reported in in-vitro and in-vivo studies (Ono et al. 2004). Curcumin was reported to inhibit Abeta aggregation (Yang et al. 2005) and therefore curcumin supplementation has been recently considered as an alternative, nutritional approach to reduce oxidative, inflammatory damage and amyloid pathology in elderly as well as SDAT (Wu et al. 2006). In addition to curcumin, curcuminoids containing three components were reported to possess the ability to inhibit lipid peroxidation in rat brain homogenate better than α-tocopherol (Sreejayan & Rao 1994), enhance Aβ clearance by promoting uptake through macrophages (Zhang et al. 2006) and protect cells from Aβ (1 - 42) insults as well as inhibiting Aβ fibril formation in – vitro (Kim et al. 2001, 2005). In another study, curcuminoids were reported to pose better therapeautic profile than its three individual components over enzyme *acetylcholinesterase* inhibition activity and thus cognitive enhancing property in scopolamine induced amnesia (Ahmed et al. 2009). These data indicate that curcuminoids as a whole may serve as a better treatment option for SDAT in comparison to curcumin. Therefore, in the present series of study, curcuminoids has been investigated for their neuroprotective effect in age associated neurodegeneration and its implications in prevention of SDAT progression. The effect of the chronic treatment of curcuminoids was observed on lipofuscin, oxidative stress markers, mitochondrial impairment and inflammatory cytokines in aged rat brain cortex. To our knowledge this is the first report providing evidence for the activity of curcuminoids over mitochondrial dysfunction, anti-lipofuscinogenic activity and neurochemical alterations in aged brain and its influence in promotion of healthy brain ageing and prevention and/or delaying of SDAT progression.