CHAPTER-1
INTRODUCTION

Alzheimer’s disease (AD) is the most prevalent form of dementia in aged population (Ritchie and Lovestone, 2002). About 25-30 million people are suffering from AD worldwide, which is expected to increase 3 folds by 2040 due to increased life expectancy (Ferri et al., 2005). It is characterized by progressive memory impairment and cognitive deficits along with confusion, impaired social judgment, language disturbance and agitation (Harvey et al., 2003). It also represents a major health problem being among the most costly diseases, considered as the physiological economic burden for the society (Mayeux and Stern, 2012).

The major pathological characteristic of AD brain is extracellular senile plaques composed of amyloid-β (Aβ) peptide and intra-neuronal neurofibrillary tangles containing hyper-phosphorylated tau protein (Selkoe, 2001). The Aβ peptide and the tau protein were considered as the key players of AD. There are two primary types of AD as defined by age, early-onset AD (familial form), and late-onset AD (sporadic form) (Duyckaerts et al., 2009). Each has a different set of causative or risk modifying genetic factors. Familial form of AD has been associated with enhanced Aβ accumulation and senile plaques generation caused by accumulation in either amyloid precursor protein (APP), Presenilin1 (PSEN1) or Presenilin2 (PSEN2) (Papassotiropoulos et al., 2006). In contrast with familial AD, Aβ clearance mechanism has been impaired in sporadic form of AD (Singh et al., 2013). However, causing factors and the pathological mechanisms underlying sporadic form are still unknown. Various risk factors, which might be responsible for the development of sporadic AD include age, genetic susceptibility, type 2 diabetes, trauma and mitochondrial dysfunctions (Hoyer, 2004; Brouwers et al., 2008). Furthermore, microtubular dysfunction and changes in cholinergic functioning are also associated with sporadic AD, which are directly involved in cognitive deficits (Iqbal et al., 1986; Szutowicz et al., 2006).

AD has been associated with neuropsychological alterations which are accompanied by structural, electrophysiological and neurochemical abnormalities (Smith et al., 2007). Structural changes include cortical and hippocampal atrophy, degenerative changes, neuronal loss, demyelination, gliosis and enlarged ventricles (Chao et al., 2010; Dickerson et al., 2011). A progressive loss of cholinergic neurons and a consequent acetylcholine deficit has been reported in AD. Various factors such as reduced choline acetyltransferase activity, alteration in
Acetylcholine receptors can influence the cholinergic transmission (Weiland et al., 2000). It has been demonstrated that Aβ binding to alpha-7 nicotinic acetylcholine receptors alters several neurochemical processes including Ca\(^{2+}\) homeostasis and acetylcholine release, and thereby modulates neuronal physiological functions implicated in cognition (Wang et al., 2003). Aβ has also been involved in the impairment of synaptic plasticity by dysregulating the ion fluxes across membranes (Wu et al., 1995; Lambert et al., 1998). It has been reported that locus cerulus (source of noradrenergic neuron) and serotonergic neurons were damaged in AD leading to altered monoamine neurotransmitter levels (Palmer et al., 1987; Hoogendijk et al., 1995; Cohen et al., 2003).

Various factors contributed in accelerating the pathological changes in AD including oxidative stress, lipid dysfunction, inflammation, signaling deficits and neuronal dysfunction (Fernandez et al., 2009; Bobba et al., 2010). Dysregulated Aβ and hyper-phosphorylated tau proteins could lead to mitochondrial dysfunction or abnormal accumulation of transition metals resulting excessive production of reactive oxygen species (ROS) (Xie et al., 2013). Conversely, oxidative stress may augment Aβ aggregation and tau hyper-phosphorylation (Blurton-Jones and Laferla, 2006), which could further enhance ROS production, thus forming a vicious cycle that promotes the initiation and progression of AD (Perez et al., 2005). Oxidative stress mediated mitochondrial dysfunction could induce inflammation and activate microglia, which is another source of ROS (Ferrer, 2009). The activated microglia driven inflammatory response resulted in an elevated release of various pro-inflammatory mediators such as cytokines and prostaglandins (Colangelo et al., 2002; Heneka and O'Banion, 2007). Inflammatory mediators enhance the abnormal processing of APP to amyloid β-42 (Aβ-42) peptide production. (Del Bo et al., 1995; Fassbender et al., 2000; Atwood et al., 2003). On the other hand, Aβ promotes the expression of proinflammatory cytokines which further activates inducible nitric oxide synthase (iNOS), cyclooxygenase enzyme (COX-2); inflammatory enzyme systems resulting in neuronal dysfunction and cell death (Lindberg et al., 2005; Abbas et al., 2002). Therefore, suppression of oxidative stress might delay the onset or slow down the progression of AD through multiple mechanisms including, attenuation of Aβ production and aggregation, reduction in tau phosphorylation and polymerization, and restoration of mitochondria functioning and metal homeostasis (Giordano et al., 2014; Umukoro et al., 2014).
Colchicine-induced cognitive dysfunction is an accepted model of sporadic dementia of Alzheimer’s type (Nakayama and Sawada, 2002). Colchicine, a microtubule disrupting agent, produces cytoskeletal modifications and impairs axonal transport (Muller et al., 2006) leading to neuronal death (Goldschmidt and Steward, 1982). In addition, central administration of colchicine resulted in excessive free radical generation and oxidative damage which was correlated with the extent of cognitive impairment (Kumar and Gupta, 2002). Thus, colchicine model is relevant to AD in humans which is characterized by progressive deterioration of cognitive functions, elevated oxidative stress, microtubule destruction and decrease in choline acetyltransferase activity (Nakagawa et al., 1987; Bensimon and Chermat, 1991).

However, various treatments are available to cure AD, but their outcomes are often unsatisfactory with many side effects (Nakagawa et al., 1987; Rogers et al., 1998). Medicinal properties of various plants have been documented for many centuries which have shown to be effective in memory disorder (Howes and Houghton, 2012). Clinical and experimental studies have shown the beneficial effects of plant products in AD (Anekonda and Reddy, 2005; Dos Santos-Neto et al., 2006). Curcumin has been found to inhibit the Aβ fibril formation both in in vitro as well as in animal models (Ono et al., 2004; Yang et al., 2005). Stackman et al. (2003) have reported that Ginkgo biloba extract prevented Aβ induced neurotoxicity via interference with Aβ fibril formation and also prevented age-dependent decline in spatial cognition.

Bacopa monnieri (BM) commonly known as Brahmi, is a perennial herb found in a marshy area belonging to the family Scrophulariaceae (Shinomol et al., 2012). BM is commonly used in Indian traditional system of medicine as a memory enhancer (Bhattacharya et al., 2000). It has also been reported to possess anti-inflammatory, analgesic, anti-pyretic, sedative and antiepileptic properties (Deepak et al., 2005). Mishra and co-workers have documented free radical scavenging ability of BM (Mishra et al., 2013). Zhou et al. (2009) have shown that bacosides from the plant show nootropic activity against scopolamine-induced memory impairment. Further, BM extract has been reported to reduce amyloid levels and improve memory function in PSAPP mice that are characterized by spontaneous amyloid plaque formation (Holcomb et al., 2006). Limpeanchob et al. (2008) have shown the neuroprotective effect of BM on Aβ induced cell death in primary cortical neurons which was thought to be mediated through antioxidant effect of BM. Uabundit et al. (2010) reported that BM administration mitigated the memory impairment and the degeneration of neurons in
hippocampus in ethylcholine aziridinium induced animal model of AD. Although, several studies demonstrated memory enhancing effects of BM, the precise mechanism of its action is not fully understood.

In order to elucidate the mechanism underlying the cognitive deficits in AD type dementia in colchicine induced experimental model and to evaluate the possible beneficial effects of BM supplementation on AD type complication, the present study was designed with following objectives.

**OBJECTIVES**

1. To establish colchicine-induced model of dementia in rat.
2. To examine the role of oxidative stress and alterations in lipid component and membrane fluidity in colchicine-induced model of dementia.
3. To study the involvement of inflammation in colchicine-induced dementia.
4. To correlate biochemical alterations with the behavior and histological alterations in control and colchicine treated animals.
5. To study the neuroprotective effect of *Bacopa monnieri* in colchicine-induced dementia.