Chapter-1

Introduction
Alzheimer’s disease is a neurodegenerative disorder with unknown etiology leading to severe incapability and ultimately death. It is named after Dr. Alois Alzheimer, a German doctor, 1906, who noticed changes in the brain tissue of a woman, died of an unusual mental illness. He found abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary tangles) (Maurer et al., 1997) in the brain of the lady (Frau Auguste D). Today, these plaques and tangles in the brain are considered the main pathological hallmarks of AD (Martin, 1999). Connections between nerve cells are disrupted in areas of the brain that are vital to memory and other mental abilities. There are lower levels of some neurotransmitters in the brain that carry messages back and forth between nerve cells. AD may impair thinking and memory by disrupting these messages.

As more people live to old age, AD has become the fifth-leading cause of death for those aged 65 and older (Minino et al., 2010). An estimated 35 million people worldwide are suffering from AD making it a major medical and social problem.

Alzheimer’s disease can affect different people in different ways, but the most common symptom pattern begins with gradual worsening difficulty in remembering new information. This is because disruption of brain cells function usually begins in the regions involved in forming new memories. As damage spreads, individuals experience other difficulties.

Individuals progress from mild Alzheimer’s disease to moderate and severe disease at different rates. As the disease progress, the individual’s cognitive and functional abilities decline. In advanced Alzheimer’s, people need help with basic activities of daily living, such as bathing, dressing, using the bathroom and eating. Those in the final stages of the disease lose their ability to communicate, fail to recognize loved ones and become bed-bound and
reliant on a round-the-clock care. The inability in late-stage Alzheimer’s disease to move around can make a person more vulnerable to infections, including pneumonia (infection of the lungs). Alzheimer’s disease is ultimately fatal, and Alzheimer-related pneumonia is often the cause.

There is not a single cause but several factors working together in the pathogenesis of AD. Like several other adult late onset neurodegenerative diseases, AD also has both genetic (Lovestone, 1999; Roses, 1997; Selkoe, 1997) and non-genetic factors. Research studies in the past have revealed four genes associated with this disease. These genes are amyloid precursor protein (APP), presenilin 1 (PS1), presenilin 2 (PS2) and apolipoprotein E (ApoE). The APP gene encodes the APP, which is normally cleaved to form amyloid β. Mutations in APP result in incorrect cleavage of the protein, producing a version of amyloid β that is more likely to form plaques. The PS (presenilin) genes encode proteins that function in the cleavage of APP. Mutations in both PS1 and PS2 result in incorrect cleavage of APP, and are associated with development of familial early-onset AD. Sporadic late-onset AD accounts for the majority of all AD cases, and this form can likely be caused by a number of gene mutations. The most well established genetic risk factor for development of sporadic late-onset AD is the inheritance of the ε4 allele of the apolipoprotein E (APOE) gene. Age is the most important risk factor of AD. Family history is another risk factor for AD. Other risk factors like heart disease and stroke, such as high blood pressure, high cholesterol, and low levels of the vitamin folate, head trauma and traumatic brain injury may also increase the risk of AD.

A diagnosis of Alzheimer’s disease is most commonly made by an individual’s primary care physician. The physician obtains a medical and family history, including psychiatric history and history of cognitive and behavioral changes. Ideally, a family member or other individual close to the patient is available to provide inputs. The physician also conducts cognitive tests and physical and neurological examinations. In addition, the patient may undergo magnetic resonance imaging (MRI) scans to identify brain changes that have occurred so the physician can rule out other possible causes of cognitive decline.
The initiating events leading to AD are unknown. The pathophysiology of AD is complex and may involve many overlapping pathways of neuronal loss. One of the pathways of neuronal loss is mediated by free radical injury (Chong et al., 2003; Wang et al., 2003). Other pathway linked to AD is neuroinflammation (Tuppo and Arias, 2005; Akiyama et al., 2000a).

Free radicals are produced in the body as a result of normal metabolism. Excess production of these reactive oxygen species (ROS) can lead to oxidative stress. Oxidative stress is caused by an imbalance between the production of reactive oxygen and a biological system’s ability to readily detoxify the reactive intermediates or easily repair the resulting damage. The brain is very susceptible to the damage caused by oxidative stress, due to its rapid oxidative metabolic activity, high polyunsaturated fatty acid content, relatively low antioxidant capacity, and inadequate neuronal cell repair activity (Collino et al., 2006; Halliwell, 2001; Neumar, 2000). Oxidative stress plays a critical role in the pathogenesis of AD (Gary and Hsueh-Meei 2005; Butterfield, 2004). Oxygen radicals can attack on proteins, nucleic acids and lipid membranes, thereby disrupting cellular functions and integrity.

The other mechanism is gliosis which include the activation of astrocytes and microglia. Once astrocytes and microglia are activated, they produce proinflammatory signal molecules, including cytokines, growth factors, complement molecules, chemokines, and cell adhesion molecules (Rubio-Perez and Morillas-Ruiz, 2012; Tuppo and Arias, 2005; Akiyama et al., 2000a) which finally lead to the induction of inflammatory enzyme systems such as the inducible nitric oxide synthase (NOS-2) and the cyclooxygenase enzyme (COX-2). Cytokines activation induces the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway that is again required for cytokine production (Combs et al., 2001).

Several lines of evidence suggest that all of these factors can contribute to neuronal dysfunction and cell death or apoptosis, either alone or in concert (Brown and Bal-Price, 2003; Abbas et al., 2002; Bezzi et al., 2001).

No treatment is available to slow or stop the deterioration of brain cells in AD. The U.S. Food and Drug Administration (FDA) have approved
five drugs that temporarily slow worsening of symptoms for about 6 to 12 months. They are effective for only about half of the individuals who take them. Researchers believe that treatments to slow or stop the progression of AD and preserve brain function will be most effective when administered early in the course of the disease. Much research in recent years has focused on identifying biomarkers that will aid in early detection and tell physicians which patients should receive treatment during these very beginning stages of Alzheimer’s. Despite the current lack of disease-modifying therapies, studies have consistently shown that the active medical management of Alzheimer’s and other dementias can significantly improve quality of life through all stages of the disease for individuals with Alzheimer’s and their caregivers. Active management includes:

- Appropriate use of available treatment options
- Effective integration of coexisting conditions into the treatment plan
- Coordination of care among physicians, other healthcare professionals and lay caregivers and

- Use of activity and support groups, adult day care programs and supportive services such as counseling.

Apart from the above measures, studies have also suggested that oxidative stress may be one of the pathways accounting to the pathogenesis of AD. Many studies have indicated that antioxidants play a protective role in the prevention of the pathogenesis of AD (Javed et al., 2012; Khan et al., 2012; Ishrat et al., 2009a). More work has to be done in this field as great results are obtained by the antioxidant therapy. As mentioned above there is no therapy which can cure or delay AD. Therefore, it is imperative to have an alternative line of therapy, which should not only promote symptomatic relief but should also have a neuroprotective activity. Till date no such wonder drugs are available, so it is imperative to intensify the search in this field. Since antiquity chemicals/ herbs/ herbal drugs are providing a treasure of treatments for all diseases from slight headache to dreaded cancer. The search of active principles from the herbs for the prevention or protection of neuronal death will give a major breakthrough in the field of neuroscience.
Aims and objectives:

- To study the viability of cells after treatment with β-amyloid protein.

- The \textit{in vivo} study of the neurobehavioral and neurochemical biomarkers of AD.

- To screen some active principles from herbs/chemicals or nanoformulation for the prevention of AD, \textit{in vitro} and \textit{in vivo} using various biochemical parameters.