

CHAPTER I

INTRODUCTION



Alzheimer's disease (AD) is a progressive neurodegenerative disorder. The initial clinical presentation typically involves memory impairment and poor judgment. Clearly, this disease is a major social and health-care problem for which there is no cure or effective treatment. The major neuropathological changes in the brains of AD patients are neuronal death, particularly in regions related to memory and cognition, and the presence of abnormal intra- and extracellular proteinaceous filaments. Intracellularly, bundles of paired helical filaments, composed largely of phosphorylated tau protein and referred to as neurofibrillary tangles, accumulate in large numbers in dying neurons. Extracellularly insoluble aggregates of proteinaceous debris, termed "amyloid", appear in the form of senile or neuritic plaques and cerebrovascular amyloid deposits. The frequency and distribution of neurofibrillary tangles and neuritic plaques appear to correlate well with the extent of cognitive impairment, synaptic loss and neurotransmitter depletion, which are also characteristic of AD. β -amyloid peptide ($A\beta$) itself can be neurotoxic and can induce oxidative stress (OS) in cultured neurons (Behl, 1997; Harris et al., 1995). The OS from $A\beta$ results in a reactive oxygen species-mediated process which damages neuronal membrane lipids, proteins and nucleic acids (Butterfield et al., 1997; Huang et al., 1999a, b; Smith et al., 1996, 1998; Stadtman, 1990). Consequently, antioxidant approaches for the prevention and therapy of AD are of central interest. One therapeutic strategy is to delay onset of AD sufficiently long as to slow the neuronal damage associated with $A\beta$ -induced OS.

Centella asiatica (*C. asiatica* (Linn.)) Urban is a small perennial herbaceous plant, belonging to the Apiaceae/Umbelliferae family. Native areas are Sri Lanka and South Africa. Both leaves and the entire plant can be used therapeutically. It was first used in India where it is a part of Ayurvedic medicine and is popular as a nerve tonic to promote relaxation and enhance memory. Indian healers use this herb to treat skin inflammations and as a mild diuretic. Oriental healers rely on *C. asiatica* to treat emotional disorders such as depression. *C. asiatica* has also been employed as an

energy tonic, an aphrodisiac, and as a treatment for high blood pressure and mental disorders. *C. asiatica* is a vital herb in Ayurveda, the traditional science of health in India, where it is used to "strengthen both the white and gray matter of the brain", stimulate learning, memory and alertness, and calm or sedate anxiety. Traditional Chinese medicine believed that *C. asiatica* provided longevity, and thus called it the "fountain of youth" herb in China. In the United States, *C. asiatica* is found in countless energy formulas and tonics.

C. asiatica has even been used as "food for the brain" after a nervous breakdown to rebuild energy reserve, or to prevent a nervous breakdown. It has an energizing effect on the cells of the brain, relieves high blood pressure, mental fatigue, senility and helps the body defend itself against various toxins. *C. asiatica* promotes blood circulation in the lower limbs and reduces the pain and swelling due to phlebitis, as well as leg cramps, swelling of legs and heaviness or tingling in the legs. It is particularly useful for bedridden people. Recent studies showed that *C. asiatica* has positive effects on circulatory system (Arpaia et al., 1990; Belcaro, Ruol and Grimaldi, 1990; Cesarone et al., 1994). It seems to improve blood flow throughout the body by strengthening the veins and capillaries. Several researchers also found antihypertensive effect of *C. asiatica* (Hansen et al., 1995; Kukongviriyapan et al., 1998; Ratthanoo et al., 2000; Tsutsumi et al., 2000). The extract of plant significantly inhibits gastric ulceration induced by cold restraint stress (Chatterjee et al., 1992) and by ethanol (Cheng and Koo, 2000) in rats. *C. asiatica* affects various stages of tissue development, including keratinization (the process of replacing skin after sores or ulcers). It has been found to have significant results in healing of skin, other connective tissues, lymph tissues, blood vessels (decreasing capillary fragility), and mucus membranes (Chen et al., 1999; Maquart et al., 1999; Suguna, Sivakumar and Chandrakasan, 1996; Unikumar, Parameshwaraiah and Shivakumar, 1998).

C. asiatica contains a group of triterpenes that possess strong antioxidant properties. The triterpene constituents are eliminated primarily in the feces in a period of 24 to 76 hours, with a small percentage eliminated via the kidneys. An extract containing asiatic acid, madecassic acid, madasiatic acid and asiaticoside reached

peak plasma concentrations in 2 to 4 h, irrespective of whether it is administered in tablet, oily injection, or ointment formulation (Bossé et al., 1979).

Antioxidants have been reported to play a significant role in the wound healing process. In this regard, asiaticoside enhanced healing activity which may be attributable to increased collagen formation and angiogenesis (Bonte et al., 1994; Shukla et al., 1999b). It was found that asiaticoside increased enzymatic and non-enzymatic antioxidants, i.e., superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), vitamin E and ascorbic acid in newly formed tissues and also resulted in a several fold decrease in lipid peroxide levels (Shukla, Rasik and Dhawan, 1999a). Furthermore, asiaticoside also protected neuronal cell death that involved in free radical injury and apoptosis from amyloid peptide (Mook-Jung et al., 1999). In clinical studies, asiaticoside increased the mean concentrations of blood sugar, serum, cholesterol, total protein, lowered blood urea and serum acid phosphatase concentrations. It had anxiolytic effect, reduced acoustic startle response (ASR) amplitude in the patients (Bradwejn et al., 2000). It also improved the general ability and behavioral pattern of mentally retarded children, when given over a period of 12 weeks.

In recent years, brain-accessible antioxidants are considered as the means of therapeutic approach to delay the onset of neurodegenerative disorders including AD. As evidenced by previous studies that asiaticoside possesses antioxidant property; therefore, it is considerable that asiaticoside might be useful in AD prevention and therapy. The present study was designed to investigate the potential ability of asiaticoside to prevent or attenuate the outcome of brain damages in an animal model of neurodegeneration.