Introduction
Aging is defined as the gradual alterations in structure and function that occur over time, eventually leading to an increased probability of death not associated with disease or trauma (Poon et al., 2004). “Aging” is also specifically defined as the process of system’s deterioration with time, thus allowing for existence of non-aging systems and anti-aging interventions.

The detrimental effects of aging are best observed in postmitotic tissues, where cells that are irreversibly damaged or lost cannot be replaced by mitosis of intact ones. Among such tissues, the brain is most important, owing to its main role in homeostasis of the organism. Therefore, in recent years, research on the neurobiological aspects of aging is gaining interest. During normal aging, the brain suffers both morphological and functional modifications affecting dendritic trees and synapses, neurotransmitters, brain circulation and metabolism, motor and sensory systems, sleep, memory and learning, and lipofuscin accumulation (Timiras, 2003).

Oxidative stress, an unavoidable consequence in the metabolism of oxygen in aerobic cells, is a major factor in the aging process and in the course of many chronic diseases associated with aging as well as a risk factor for some neurodegenerative diseases in aging (Mattson, 2002). Increased production of oxidants in vivo can cause damage to intracellular macromolecules, which can translate into oxidative injury, impaired function and cell death in vulnerable brain tissues (Radak et al., 2001).

The rationale that brain suffers oxidative stress in aging is based on the following premise: brain has a high content of easily peroxidizable
unsaturated fatty acids (especially high in 20:4 and 22:6 fatty acids); brain requires very high amounts of oxygen per unit weight (about 20% of the total amount used in humans); brain has a high content of iron (crucial in causing membrane lipid peroxidation); brain is not highly enriched in antioxidant protective defenses and this then adds to its otherwise readily poised potential for oxidative damage; since the neurons are postmitotic; the scarcity of antioxidant defense systems (Floyd, 1999).

Basic concepts of oxidative stress

Reactive oxygen species (ROS) collectively refer to molecules that contain oxygen with higher reactivity than the ground state O₂ and oxygen radicals and non-radicals that are readily converted to radicals (Contestabile, 2001; Cuzzocrea et al., 2001; Evans and Halliwell, 2001). It includes, among others, superoxide (O₂⁻), hydroxyl radical (OH⁻), hydrogen peroxide (H₂O₂), and hypochlorous acid (HOCl). ROS are the by-products of normal aerobic metabolism (Beckman and Ames, 1998; Droge, 2002). It is estimated that approximately 2–5% of the oxygen consumed by a cell is subsequently converted to free radicals (Floyd and Hensley, 2002; Wickens, 2001).

The generation of various free radicals is closely linked with the participation of redox-active metals (Valko et al., 2005). The redox state of the cell is largely linked to an iron redox couple and is maintained within strict physiological limits. It has been suggested that iron regulation ensures that there is no free intracellular iron; however, in vivo, under stress conditions, an excess of superoxide releases "free iron" from iron-containing molecules (Liochev and Fridovich, 1994). The released Fe (II) can participate
in the reaction, generating highly reactive hydroxyl radical (Floyd and Carney, 1993).

Numerous cellular defense mechanisms exist to prevent the buildup of ROS, and collectively help to protect living organisms against oxidative damage. These systems include: (i) superoxide dismutase (SOD) and catalase (which collectively remove superoxide and hydrogen peroxide from the cytoplasm), (ii) glutathione peroxidase (GSH-Px) and glutathione (GSH) (reduce $\text{H}_2\text{O}_2$ to $\text{H}_2\text{O}$) and (iii) vitamins E and C (Mates et al., 1999; McCall and Frei, 1999). Vitamin C is able to scavenge a broad spectrum of ROS and is therefore one of the most important exogenous antioxidants in the body. Termination of propagation of the radical by vitamin E, a chain-breaking antioxidant has been widely reported and is mostly considered as the secondary defense in inactivation of the propagating radical of the chain (Esterbauer et al., 1991). Oxidative stress arises when concentrations of ROS exceed the cellular ability to remove ROS and repair cellular damage, and ultimately results in the widespread oxidation of biomolecules, including lipids (Cai et al., 1996), proteins (Dean et al., 1997) and DNA (Hamilton et al., 2001).

Lipid peroxidation (LPO) is an autocatalytic, free radical mediated, destructive process, whereby polyunsaturated fatty acids in cell membranes undergo degradation to form lipid hydroperoxides (Sevani\n\n and Hochstein, 1985; Slater, 1984). These latter compounds then decompose to form a wide variety of products, including low molecular mass hydrocarbons, hydroxy aldehydes, fatty acids, ketones, alkenals and alkanals, in particular malondialdehyde (MDA) (Zeyuan et al., 1998). The peroxidation of
membrane phospholipids might change membrane fluidity; fluidity is an important physical property of cell membranes closely related to permeability because it has a crucial role in the maintenance of normal cellular function (Schreier et al., 1978) and may affect membrane embedded enzymes adenosine triphosphatases (ATPases) activities (Moryama et al., 1989). The peroxidation process eventually leads to loss of membrane integrity and finally, to cell death.

The biological consequences of radical attack on proteins include site-specific amino acid modification, protein cross linking, fragmentation and increased susceptibility to proteolysis (Davies, 1987; Schacter et al., 1994; Stadtman, 1990). Damage to proteins can occur by direct attack of ROS upon them (Huggins et al., 1993), or by 'secondary damage', involving attack by end products of lipid peroxidation, such as malondialdehyde and 4-hydroxy-2-nonenal (4-HNE). Numerous oxidant-induced protein modifications are used as markers. The most commonly analyzed marker is protein carbonyls (PCO). Carbonyl groups are composed of the stable C=O organic radicals (e.g. ketones, aldehydes, carboxylic acids, and esters) on lysine. arginine, proline, histidine, cysteine, and threonine residues (Stadtman et al., 1988). Aldehydes, such as 4-HNE and MDA can be incorporated into proteins by reaction with either the ε-amino moiety of lysine or the sulfhydryl group of cysteine residues to form carbonyl derivatives (Uchida and Stadtman, 1993). Carbonyl groups can also be introduced into proteins by glycation and glycooxidation reactions (Baynes, 1991).

The damage to DNA is more variable, and attack by free radicals can produce structural damage (i.e., strand breaks) and/or modification of the
bases (8-hydroxy 2'-deoxyguanosine) (Dizdaroglu, 1991). The hydroxyl radical can induce strand breaks as well as chemical changes in the deoxyribose and in the purine and pyrimidine bases (Cochrane, 1991). Cells with damaged DNA display increased migration of DNA fragments from the nucleus, generating a “comet” shape (Ross et al., 1994). 8-hydroxy 2'-deoxyguanosine (8-OHdG) is one of the most common adducts formed from the reaction of oxyradical with DNA (Dizdaroglu, 1991). The 8-OHdG modification is associated with transcriptional base mismatching errors, reduced levels of transcription and changes in DNA methylation state, profoundly altering gene transcription (Cerda and Weitzman, 1997; Kaneko et al., 2001; Liu et al., 2001). DNA protein complexes represent bulky molecular lesions, which are hardly repaired, thereby interfering with the transcriptional functions and causing cell death whenever these lesions fall in an essential region (Oleinick et al., 1987).

**Lipofuscin - An age pigment**

A common feature of aging is the progressive accumulation of lipofuscin in neurons and other post-mitotic cells (Harman, 1989; Porta, 1991; Porta, 2002; Terman and Brunk, 1998), and growing research evidence suggests it imparts a deleterious effect upon various cellular processes (Gray and Woulfe, 2005). Lipofuscin is a class of lipopigments, characterized by autofluorescent properties when excited with light at 450 nm wavelength (Ellemer, 1981). Lipofuscin granules are the final products of the autoxidation of the molecular components of cells, particularly, unsaturated lipids (Katz and Robison, 1986). It is composed primarily of protein (30–70%) and lipid
(20–50%), the vast majority of which has been oxidized (Szweda et al., 2003) with trace amounts of carbohydrates and trace metals.

**Neurotrophic factors and Neurotransmitters**

The numbers of neurotrophic factors and neurotransmitters, and the signal transduction pathways they activate, are diverse and, in many cases, are restricted to particular populations of neurons within the brain. Attention has been particularly focused on the neurotrophin family, considered as genuine molecular mediators of synaptic plasticity (McAllister et al., 1999; Poo, 2001). This family, including the nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 and neurotrophin-4/5 in mammals, is essentially involved in survival, outgrowth and differentiation of neurons.

The word “tropic” is derived from the Greek word trophikos, which means “nourishment”. The word “neurotrophic” can therefore be translated as “neuron nourishing”. In modern usage, the term neurotrophic is applied to substances (generally proteins), which promote the survival of neurons. The first neurotrophic factor to be discovered was NGF.

It was discovered that NGF is released from target tissue during development, bound to specific receptors, and retrogradely transported back to cell body where it exerts its effects on gene expression (Hendry et al., 1974). Of the neurotrophins, BDNF appears to be the most potent in promoting the survival of motor neurons. It may both exert local effects and act as a target-derived trophic factor in multiple systems. There are two types of receptors for the neurotrophins, the low-affinity neurotrophin receptor, to
which all neurotrophins are able to bind, and factor-specific high-affinity receptors belonging to the tyrosine kinase (Trk) family (Saragovi and Gehring, 2000). These transmembrane tyrosine kinase receptors have a molecular weight of around 140-kDa and after neurotrophin binding presumably initiate a cascade of events leading to phosphorylation of one or more protein substrates. NGF binds to TrkA, BDNF to TrkB, NT-3 to TrkC, and NT-4 to TrkB (Saragovi and Gehring, 2000). Most neuronal effects of BDNF are mediated through specific high affinity TrkB, namely TrkB receptors. BDNF binding to TrkB induces receptor dimerization, phosphorylation, and activation of the intracellular tyrosine kinase domain (Kaplan and Miller, 2000; Patapoutian and Reichardt, 2001). It is known that, in rodents, alternative splicing of mRNA encoding for TrkB (trkB mRNA) generates at least three different TrkB receptors with different signaling capabilities (Klein et al., 1989; Klein et al., 1990; Soppet et al., 1991): the full-length catalytic receptor (TrkB.FL) and two truncated forms (TrkB.T1 and TrkB.T2). The truncated forms lack intracellular tyrosine kinase activity (Klein et al., 1990; Middlemas et al., 1991) but do possess biological activity (Yacoubian and Lo, 2000) since they trigger transduction signals (Baxter et al., 1997; Rose et al., 2003).

Neurotrophic factors and neurotransmitters are two major classes of intercellular signals that mediate neuroplasticity throughout life. Neuronal communication mediated by the myriads of synapses is mainly mediated by neurotransmitters, although there are also electrical synapses. Neurotransmitters can be defined as chemicals released from neurons that can act on specific receptors. The transmitters affect formation of synaptic contacts, maturation of synapses, and structural refinement of connectivity by
regulating electrical activity, excitability, and release of neurotrophins (Zhang and Poo, 2001). The major neurotransmitters in the brain are acetylcholine (Ach), dopamine (DA), norepinephrine (NE) and serotonin (5-HT). The amount of each neurotransmitter varies in different regions of the brain and particular subsets of neurons within those regions. Alterations in the levels of individual neurotransmitters or in their synthesis or release can affect synaptic transmission.

Glutamate, aspartate are the excitatory neurotransmitters in the mammalian brain, whereas gamma amino butyric acid (GABA) and glycine mediate the main inhibitory input on neurons. The appropriate balance between the effects of these neurotransmitter systems appears essential for normal neuronal function, and deviations from this balance may lead to seizures and neuronal cell death (Choi, 1988; Rothman and Olney, 1987).

**Calcium theory of aging**

Changes in calcium homeostasis determine gross alterations in neuronal physiology, possibly contributing to the age-associated deterioration of synaptic transmission and neuronal plasticity. The "calcium theory of aging" hypothesizes that the cellular mechanisms that regulate calcium homeostasis play a crucial role in brain aging, because numerous nervous processes depend on calcium. Calcium has assumed an important role as a universal messenger of extracellular signals in a great variety of cells (Cheung, 1980; Carvalho, 1982; McGraw et al., 1982; Rasmussen, 1986a,b). Intracellular calcium seems to be essentially involved in the mechanism of apoptosis (McConkey and Orrenius, 1996). These functions are modified in
brain aging (Landfield et al., 1989); calcium is also involved in various neuronal functions, such as neurotransmitter synthesis and release (Zucker and Lando, 1986) and the control of neuronal membrane excitability. Recent studies underlined the involvement of this ion in long-term processes, like memory (Morris et al., 1988), and changes in protein synthesis through the induction of specific genes (Morgan and Curran, 1989).

**Apoptotic cascade**

The apoptotic process is designed to rapidly remove cells from tissues, tagging them for phagocytosis and recycling their constituent molecules (Savill and Fadok, 2000).

Apoptosis, which plays a critical role in the normal development and maintenance of tissue homeostasis, plays an important role in neurodegenerative diseases and aging (Sastry and Rao, 2000). The biochemical basis of two major apoptotic pathways is well established (Honig and Rosenberg, 2000; Joaquin and Gollapudi, 2001; Troy and Salvesen, 2002; Yakovlev et al., 2001). Apoptosis can either be initiated by activation of death receptors on the plasma membrane (extrinsic pathway) or by mitochondria (intrinsic pathway). Both pathways converge on the activation of downstream executioner caspases, such as caspase-3, -6 and -7. Proteolytic activation of caspase-3 is a key event in the execution of apoptosis in the central nervous system (Yamashima, 2000) marking the point at which the cell is committed to die. Many stimuli that trigger apoptosis without binding to death receptors cause mitochondria to release the electron transport protein cytochrome c into the cytosol (Green and Reed, 1998; Joaquin and Gollapudi, 2001).
Release of cytochrome c from the mitochondria has been shown to involve two distinct pathways, one implicates the opening of the mitochondria permeability transition pore (MTP), and the second, triggered by the proapoptotic Bax, is independent of the MTP opening (Eskes et al., 1998). While Bax has been shown to trigger cell death (Gross et al., 1998; Wolter et al., 1997), the antiapoptotic Bcl-2 can block cytochrome c release and caspase activation (Adams and Cory, 1998; Reed, 1998). Aged cells have been associated with increased mitochondrial oxidant production (Pollack and Leeuwenburge, 2000) and elevated intracellular Ca$^{2+}$ levels (Squier and Bigelow, 2000; Nitahara et al., 1998). These events lead to a favourable intracellular environment of MTP formation and the release of apoptogenic factors. Once this translocation occurs, cytochrome c in its holoform (i.e., with its haem group attached) binds to another cytoplasmic factor, Apaf-1 (apoptotic protease-activating factor 1), caspase-9, and adenosine triphosphate (ATP) to form a complex called an apoptosome (Zou et al., 1999). When the apoptosome is formed, it can proteolytically activate initiator caspase-9, that in turn, activates the effector caspases, of which caspase-3 (also known as Yama, apopain and CPP32) (cysteine-containing aspartate specific proteases), is a prominent member (Li et al., 1997; Srinivasula et al., 1998). In order to be effective, the inactive form of caspase 3, a 32 kDa protein, must be cleaved into a short (12 kDa) and a long (17–20 kDa) subunit (Cain et al., 1999; Clark et al., 2000; Springer et al., 1999). This cleavage permits the formation of active caspase 3; a tetramer composed of two small and two large subunits (Nicholson et al., 1995; Wilson et al., 1994).

Active caspases initiate a process by which chromosomal DNA is cleaved into fragments that are segregated and eliminated from a dying cell
(Janicke et al., 1998; Wyllie, 1997; Yakovlev et al., 1997). Thus, caspases are activated in a specific sequence and subsequently cleave a set of regulatory and structural proteins (Kothakota et al., 1997), resulting in the distinctive apoptotic morphology of chromatin condensation, nuclear fragmentation and membrane blebbing (Kerr, et al., 1972) followed by cell death (Kuida, 2000; Thornberry and Lazebnik, 1998; Troy and Salvesen, 2002). Phospholipid asymmetry is maintained by amino phospholipid translocase in viable cells; phosphatidyl serine exposure that results when asymmetry is lost is thought to trigger phagocytosis (Tang et al., 1996; Fadeel et al., 1999). Phosphatidyl serine externalization is usually considered to be a downstream event of caspase activation (van Engeland et al., 1998).

Oxidative stress and neurodegenerative diseases

Enhanced oxidative stress seems to have an important contribution to brain aging in general and neurodegenerative diseases in specific (Emerit et al., 2004). The last couple of decades have seen enormous advances in our understanding of molecular pathogenic mechanisms mediating disorders with predominantly genetic causes, such as Huntington’s disease (HD) and other trinucleotide repeat expansion disorders, as well as those occurring in both familial and nonfamilial forms, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD).

Alzheimer’s disease

AD constitutes the most prominent cause of dementia in the elderly and is clinically characterized by memory dysfunction, loss of lexical access, spatial and temporal disorientation and impairment of judgment.
Histopathologically, AD is characterized by synaptic loss, nerve cell loss (mostly in the cerebral cortex, in the hippocampus and in the amygdala), extracellular deposition of beta-amyloid protein (forming senile plaques) and intracellular precipitation of hyperphosphorylated tau protein (forming neurofibrillary tangles). The exact biochemical mechanism of the pathogenesis of AD is still unknown, but much attention is given to the role of the massive loss of the neurotransmitter acetylcholine (necessary for cognition and memory) and to the possible implication of oxidative stress in its development. Excitotoxicity and oxidative stress-induced triggering of degenerative signaling, including activation of stress kinases such as JNK, also appears to play an important role (Longo and Massa, 2004). Age is a strong risk factor for AD, and several studies show logarithmic age-dependent increases in oxidized proteins, lipids and DNA in AD patients (Floyd and Hensley, 2002).

*Mild cognitive impairment (MCI)*

MCI is a condition in which memory or other cognitive abilities are slightly abnormal but coexist with normal function in the activities of daily living, normal general cognitive function, and absence of dementia (Petersen *et al.*, 2001). This condition is at significant increased risk of future conversion to dementia, especially to AD (Goldman and Morris, 2001). An increased DNA oxidative damage in peripheral leukocytes of MCI subjects, as evaluated by comet assay, has been recently reported (Migliore *et al.*, 2005). Increased levels of the isoprostanate 8,12-iso-PF2α-VI-a specific marker of *in vivo* lipid peroxidation (Pratico, 1999) were found to be significantly elevated in cerebro spinal fluid, plasma and urine of MCI subjects compared
with controls (Pratico et al., 2002), suggesting that lipid peroxidation may be an early event in the pathogenesis of the disease. MCI and AD subjects showed lower means of peripheral levels and activities of a broad spectrum of non-enzymatic and enzymatic antioxidants suggesting that they may have an antioxidant enzymatic activity inadequate to counteract the hyperproduction of free radicals during the condition of oxidative stress. An accumulation of oxidatively damaged aconitase in mitochondria might constitute a continuous source of free radical damage (Vasquez-Vivar et al., 2000) able to modulate the progression of MCI to AD.

*Parkinson’s disease*

Apparently, there is a specific chemical fingerprint indicative of the damaging oxidative events: higher levels of cholesterol hydroperoxide, malondialdehyde, and protein adducts of 4-hydroxy-2-nonenal and of 8-hydroxy 2’-deoxyguanosine, which point to the presence of ROS-induced DNA nicks (Jenner and Olnaw, 1996; Yoritaka et al., 1996). The evidence of an involvement of free radicals in PD comes from the observation that oxidation of dopamine yields potentially toxic semiquinones, and that the accelerated metabolism of dopamine by monoamine-oxidase-B may induce an excessive formation of hydrogen peroxide, superoxide anions, and hydroxyl radicals (Olanow, 1990). Further evidence for the role of oxidative stress in PD patients comes from studies regarding the reduced levels of ferritin (Dexter et al., 1990).
**Amyotrophic lateral sclerosis (ALS)**

ALS is characterized by a selective and progressive degeneration of the lower motor neurons in the spinal cord and the upper motor neurons in the cerebral cortex, usually beginning in midlife. It can be sporadic or familial. Rosen and co-workers demonstrated 11 missense mutations in the gene encoding copper-zinc-superoxide dismutase in families with an autosomal dominant form of Amyotrophic lateral sclerosis. There is an evidence of oxidative damage to DNA in ALS: increased levels of 8-OHdG were found in plasma, urine, and cerebro spinal fluid (CSF) of ALS patients and the rate of increase with time was significantly correlated with disease severity (Bogdanov et al., 2000); a large increase in protein carbonyls was found both in ALS frontal and motor cortex (Ferrante et al., 1997).

**Huntington’s disease**

Huntington’s disease is an autosomal neuronal disorder characterized as a movement disorder and caused by repetition of a CAG trinucleotide sequences encoding for a polyglutamine tract at the N terminus of the gene encoding a protein named huntingtin. There is a progressive, massive loss of neurons, particularly in the striatum (Bartzokis et al., 1999). Most hypotheses for the pathogenesis of Huntington’s disease include a role for oxidative damage (Beal, 1996). Several studies have shown DNA strand breaks in HD post-mortem tissue as detected by *in situ* end labeling of DNA. Increased 8-OHdG levels have been found in mtDNA from HD parietal cortex (Polidori et al., 1999). The contribution of oxidative stress to the pathogenesis of HD has also been studied by measuring the levels of F2-isoprostanes in the CSF.
of 20 patients in the early phase of the disease (Montine et al., 1999). F2-isoprostane concentration was moderately but significantly higher in HD patients than in the control group (35% of increase). Several studies have also demonstrated that the disease is associated with increased levels of MDA, 3-nitrotyrosine and heme-oxygenase in areas of degeneration (Browne et al., 1999).

**Therapeutic implications**

Basic research into the mechanistic basis of oxidative stress in aging brain has provided many new leads and approaches for the possible treatment of neurodegenerative diseases. Antioxidant nutrients vitamin E, C, A and beta-carotene, may play a beneficial role in the prevention of aging and age related neurodegenerative diseases (Diplock, 1998). In the case of aging, explicit agents such as Acetyl-L-Carnitine, Alpha Lipoic Acid, Carnosine, Deprenyl, Phosphatidyl Serine and Sulphur have been used (Kumaran et al., 2004; Arivazhagan et al., 2002; Hipkiss et al., 2001; de Lima et al., 2005; Gatti et al., 1985). Flavonoids, tannins, anthocyanin and other phenolic constituents present in food of plant origin are potential antioxidants (Salah et al., 1995; Saskia et al., 1996). There has been a growing interest in natural antioxidant, namely phenols, present in medicinal and dietary plants that might help prevent oxidative damage and thus help slow the rate of both cognitive and functional declines associated with aging with view towards maintaining a positive quality of life. Popularity of *Centella asiatica* as one of the local medicinal plants, is mostly due to its reputation as a wound healing agent and brain stimulant (Bonte et al., 1994) Antioxidative property of *Centella asiatica* is mainly due to the low molecular weight phenolic compounds (Zainol et al., 2003); particularly the flavonoids are known to be potent antioxidant. *Centella asiatica* has been reported to contain numerous
caffeic acid derivatives and flavonols and in particular, quercetin and kaempferol (Castellani et al., 1981), catechin, rutin and naringin (Zainol et al., 2003), several pentacyclic triterpene derivatives (Farnsworth and Bunyapraphatsara, 1992), some of which have been shown to be powerful antioxidants. The whole plant of *Centella asiatica* has been shown to beneficial in improving memory and neurodegenerative diseases.

*Centella asiatica*

**Name:** Gotu Kola; **Biological Name:** *Centella asiatica, Hydrocotyle asiatica*; **Family:** Apiaceae (Umbelliferae); **Other Names:** Brahmi, Chi-hsueh Ts'ao, man t'ien hsing, Indian Pennywort, Brahma-manduki; **Parts Used:** The entire plant is used medicinally. **Active Compounds:** The primary active constituent is polyphenols (Zainol et al., 2003) and triterpenoid compounds (Farnsworth and Bunyapraphatsara, 1992).

**Description of the plant**

*Centella asiatica* is a perennial plant native to India and other tropical countries. It is a small creeping herb with shovel shaped leaves emerging alternately in clusters at the stem nodes. The runners lie along the ground and the inch long leaves with their scalloped edges rise above on long reddish petioles. The insignificant greenish to pinkish-white flowers are borne in dense umbels (clusters in which all the flower stalks arise from the same point) on separate stems in the summer. The seeds are pumpkin-shaped nutlets 0.1-0.2 in
(3-5 mm) long. Its appearance changes, depending on growing conditions. In shallow water, the plant puts forth floating roots and the leaves rest on top of the water. In dry locations, it puts out numerous small roots and the leaves are small and thin. Typically, the constantly growing roots gives rise to reddish stolons.

**History**

*Cenella asiatica* (Linn) is an ethnomedical plant used in different continents by diverse ancient cultures and tribal groups. In India, it is usually described under the name of Mandukaparni in the Ayurvedic system of medicine (Nadkarni, 1986). It has been used as a medicine in the Ayurvedic tradition of India for thousands of years. It is listed in the historic *Susruta Samhita*, an ancient Indian medical text (Sanjay, 2000). The herb is also used by the people of Java and other Indonesian islands. In China, *Centella asiatica* is one of the reported "miracle elixirs of life". This was attributed to a healer named LiChing Yun who, legends say, lived 256 years by taking a tea brewed from *Centella asiatica* and other herbs. In the nineteenth century, *Centella asiatica* and its extracts were incorporated into the pharmacopoeia (Jayaweera, 1982).

**Location**

Asiatic coinwort appears to have originated in the wetlands of Asia. China, India, and Malaya were probably within its original range. It apparently spread through the South Pacific and to Mauritius, Madagascar, East and South Africa and Turkey (or perhaps millennia) ago. Since *Centella asiatica* probably invaded these regions naturally (may be by seeds carried on
the feet of wading birds), and has long been integrated into their ecosystems, it should be regarded as a pan tropical species and managed as a native wherever evidence for recent human introduction is lacking. Recent genetic studies have shown that *Centella asiatica* in the southeastern United States is in fact a distinct species, to be called *Centella erecta* (American coinwort), but it is very closely related to *Centella asiatica*, and practically indistinguishable to all but the geneticists.

**Medicinal use**

*Centella asiatica* is considered the most powerful of the rejuvenating herbs in Indian Ayurvedic medicine. It is recommended for nervous disorders, including epilepsy, senility, and premature aging. As a brain tonic, it is said to aid intelligence and memory. *Centella asiatica* is considered "food for the brain". It is said to combat stress and depression, energize flagging mental powers, ward off a nervous breakdown, and improve reflexes.

In the Ayurvedic tradition, it is recommended for treatment of mental disorders, immune system deficiencies, circulatory problems, skin conditions, liver ailments, epilepsy, asthma and bronchitis, hair loss, tetanus, inflammation, rheumatism, and intestinal complaints. In India, *Centella asiatica* is considered "the herb of enlightenment" and is sometimes burned in incense prior to meditation. In Western medicine, *Centella asiatica* is acknowledged to have value in strengthening the blood vessels and thereby improving circulation, in combating stress/depression/fatigue, in decreasing inflammation, and burns, and in treating rheumatism and intestinal and
urinary disorders. It is regarded as particularly valuable in promoting circulation, healing, and positive attitude in the bedridden (Zainol et al., 2003).

Fresh extracts of this plant have been used by the people of Java and the Malay Peninsula for many years, as both topical and internal agents, for healing of wounds (Kartnig, 1988). In Malaysia, although this herb is commonly eaten fresh as a vegetable (salad), especially among the Malay communities, it is also said to have beneficial effects in improving memory and in treating mental fatigue, anxiety (Goh et al., 1995).

*Centella asiatica* or ‘pegaga’ is one of the local herbs that is claimed to possess various physiological effects. Reports from different places have revealed that *Centella asiatica* has been used for memory improvement, treating mental fatigue (Goh et al., 1995), bronchitis, asthma, dysentery, leucorrhoea, kidney trouble, urethritis (Jaganath and Ng, 1999), antiallergic and anticancer purposes, curing leukorrhea and toxic fever (Kan, 1986). It is also commonly used as porridge for feeding pre-school children in Sri Lanka in combating nutritional deficiencies (Cox et al., 1993).

*Centella asiatica*, which grows wild in both tropical and sub-tropical countries, is closely related to the species Hydrocotyle and produces characteristic essential oil (Yoshinori et al., 1982) and various types of flavonoid (Nakoki and Morita, 1960).

In the course of pharmacological studies, the plant showed CNS depressant activity (Sakina and Dandiya, 1990), antitumor activity (Babu et al., 1995; Shi et al., 1992), and an inhibitory effect on the
biosynthetic activity of fibroblast cells (Veechio et al., 1984). The whole plant of CA has been shown to be beneficial in improving memory (Mukerji, 1953; Vaidyaratnam, 1994) and is also reported to improve the general mental ability of mentally retarded children (Apparao et al., 1973; Kakkar, 1990). Nalini et al. (1992) have shown that fresh leaf juice improves passive avoidance task in rats. Katare and Ganachari (2001) have reported that the *Centella asiatica* has an anticonvulsant effect with an associated decrease in the oxidative stress in the lithium pilocarpine model of status epilepticus.

Asiatic acid, a pentacyclic triterpene found in *Centella asiatica*, has been shown to protect β-amyloid induced neurotoxicity (Jew et al., 2000). Sharma and Sharma (2005) suggested that *Centella asiatica* could be useful in preventing radiation induced tissue damage in clinical radiotherapy. Amala et al. (2005) results indicate that oral administration of ethanolic extract of *Centella asiatica* for accelerating nerve regeneration in the peripheral nervous system *in-vivo*.

The use of asiaticoside in the treatment of leprosy and wound healing has shown encouraging results (Bailey, 1945; Boiteau et al., 1949; Viala et al., 1977). Brahmic acid, an active triterpenoid present in the plant, has therapeutic value in the treatment of ulcerations, extensive wounds and eczema (Yoshinori et al., 1982; Shukla et al., 1999; Suguna et al., 1996; Chatterjee et al., 1992), as well as an inhibitory effect on the biosynthetic activity of fibroblast cells (Veechio et al., 1984). Apart from these chemical constituents, *Centella asiatica* also contains asiatic acid and madecassic acid, which are known to possess neuroprotective properties (Grimaldi et al., 1990;
Lee et al., 2000). Recently, Veerendra Kumar and Gupta, (2002) have demonstrated that an aqueous extract of *Centella asiatica* has cognitive enhancing properties in different paradigms, such as the shuttle box, step through, step down and elevated plus-maze, with associated decreases in brain oxidative stress parameters, in normal rats.

This plant has been reported to have many biological activities, including wound healing activity (Brinkhaus et al., 2000), anti-ulcer activity (Cheng and Koo, 2000), anti-herpes simplex virus activity (Yoosook et al., 2000). *Centella asiatica* extract and triterpene saponins have also been reported to inhibit abnormal proliferation of keratinocytes (Sampson et al., 2001). *Centella asiatica* components are closely related to some of the triterpenes in Polanisia dodecandra that have anti-tumor activity (Shi et al., 1992). *Centella asiatica* has been shown to inhibit the proliferation of transformed cell lines and to retard the development of solid and ascites tumors (Babu et al., 1995). Considerable attention has been given to the total triterpenic fraction of *Centella asiatica* used for treatment of venous hypertensive microangiopathy (Cesarone et al., 2001a,b,c,d; De Sanctis et al., 2001; Incandela et al., 2001a,b,c).