1 *Centella asiatica*, an Ayurvedic Medicinal Plant, Prevents the Major Neurodegenerative and Neurotoxic Mechanisms Associated with Cognitive Impairment

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Abstract

Ayurveda is one of the ancient traditional healthcare systems that originated in India. A number of herbal-based medicinal preparations have been used for the treatment of health disorders associated with the nervous system. According to Alzheimer's disease Facts and Figures, millions of people around the world are suffering with cognitive impairment. Cognitive ailments and diseases are a group of disorders associated with mental health. The cognitive disorders mainly comprise of acute and chronic or reversible or irreversible conditions such as amnesia, delirium, and various types of dementia. These disorders primarily cause deficits in cognitive tasks associated with awareness, insight, knowledge, memory, and problem-solving skills. Alzheimer's disease is the most common type of dementia. It is a chronic neurodegenerative disorder that occurs due to excessive protein deposition inside and outside the neuron, oxidative stress, apoptosis, mitochondrial dysfunction, inflammation, and excitotoxicity. These neurotoxic mechanisms cause synaptic disturbance, alteration of neurotransmission leading

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to neurodegeneration. *Centella asiatica* is a well-known medicinal herb used in Ayurveda to improve cognitive functions since ancient times. In this article, we review the therapeutic potential of *Centella asiatica* in relation to its neuroprotective properties.

Keywords

Alzheimer's disease • Ayurveda • Botanicals • *Centella asiatica* • Cognitive disorders • Dementia • Herbal medicine • Neurotoxic mechanisms

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Abbreviations

15-LOX	15- Lipoxygenase
3-NPA	3-Nitropropionic acid
5-HT	Serotonin
Ach	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADDLs	Aβ-derived diffusible ligands
AICD	APP intracellular domain
AMPARs	2-Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propionic acid receptors
APH-1	Anterior pharynx-defective 1
APP	Amyloid β precursor protein
ATP	Adenosine triphosphate
Aβ	Amyloid beta
BACE	Beta-site APP-cleaving enzyme
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
C83	Carboxyl-terminal 83-aa fragment
Ca^{2+}	Calcium
cAMP	Cyclic adenosine monophosphate

CNS	Central nervous system
COX-2	Cyclooxygenase 2
CREB	Cyclic adenosine monophosphate response element-binding protein
CTLs	T-cell lymphocytes
FAD	Familial Alzheimer's disease
GABA	Gamma-aminobutyric acid
GAD	Glutamate decarboxylase enzyme
GLT	Glutamate transporter
IFN	Interferon
IL	Interleukin
$iPLA_2$	Ca^{2+}-independent phospholipase A_2
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase
mGluRs	Metabotropic glutamate receptors
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NADPH	Nicotinamide adenine dinucleotide phosphate oxidase
NE	Norepinephrine
NFTs	The neurofibrillary tangles
NMDARs	N-Methyl-D-aspartate receptors
NO	Nitric oxide
NSAIDs	Nonsteroidal anti-inflammatory drugs
O^{2-}	Superoxide radical
PEN-1	Presenilin 1
PEN-2	Presenilin 2
PKA	Protein kinase A
PLA_2	Phospholipase A_2
PS	Presenilin
SAD	Sporadic Alzheimer's disease
SPs	Senile plaques
TNF	Tumor necrosis factors
β-CTF	Carboxyl-terminal 99-aa fragment

1.1 Introduction

For centuries, substantial extent of the world population (80%) has mainly relied on traditional medicinal practices involving herbal medicine for their routine healthcare needs. Herbal medicines are also referred as botanicals or phytomedicines. These medicines refer to herbs, herbal materials, herbal preparations, botanical formulations, and finished herbal products. The active ingredients of the herbal medicines are made of different plant parts, such as seeds, berries, roots, leaves, bark, or flowers (Sharma and Chaudhary 2015). Herbal medicines are exponentially gaining attention for its use in preventing and treating broad spectrum of health-related disorders (Kumar et al. 2012). Majority of the medical prescriptions used today for the treatment of innumerable chronic disorders are plant-based formulations or

botanical-derived synthetic analogues. In the eastern part of the world, medicinal herbs have been used prophylactically and therapeutically for eras. The herbal medicines are presently practiced as a primary source of medicine for prevention and treatment of various health disorders. However, the herbal medicine practices are actively pursued in the rural areas mostly as compared to the urban places. Eastern countries have the unique distinction of having various medicinal practices associated with herbal medicine. With regard to the Indian herbal medicines, Ayurveda, Siddha, and Unani are well-known ancient medicinal practices in the healthcare system (Pandey et al. 2013).

Ayurveda is considered as a unique and distinct medicinal practice, which takes into consideration the physical, psychological, philosophical, ethical, and spiritual well-being of mankind. Ayurveda literally means "science of life" and has been used since folklore times for both preventive and curative measures. Around 25,000 effective plant-based formulations are used in ethnopharmacological approach and folklore Ayurvedic medicine in India (Alvari et al. 2012). This medicinal system has a holistic approach and thus has different approach in its therapeutic treatment as compared to the modern drug therapy. Instead of adopting the organ-oriented anatomy and physiology theory of the conventional medical science, Ayurveda has its own science which is known as the *Panchamahabhuta.* This is based on the five rudimentary elements: *akasha* (sky), *vayu* (air), *agni* (fire), *prithvi* (earth), and *jala* (water). Ayurveda, through reverse pharmacology, has made a pivotal contribution to the drug discovery processes along with new ways of identifying active compounds, reduction of drug-induced adverse reactions, and development costs. Plant components can act alone or along with other constituents from the same plant that may boost the activity of compounds or counter the toxic effects of compounds. Interestingly, an herbal medicine might have an additive, potentiating, synergistic, or antagonistic effect. This is the main path of action of Ayurvedic medicine where a combination of herbs is often prescribed. A significant number of traditional Ayurvedic medicine has been used to enhance cognitive functions and to ease symptoms that are correlated with cognitive disorders (Howes et al. 2003). The major Ayurvedic botanicals that have been evaluated for their potential to treat cognitive disorders are as follows: *Withania somnifera* (ashwagandha), *Bacopa monnieri* (brahmi), *Curcuma longa* (Indian ginseng), *Convolvulus pluricaulis* (shankapushpi), *Clitoria ternatea* (butterfly pea), *Centella asiatica* (Gotu kola), *Celastrus paniculatus* (jyotishmati), *Terminalia chebula* (yellow myrobalan or chebulic myrobalan), and *Nardostachys jatamansi* (jatamansi) (Ven Murthy et al. 2010; Solanki et al. 2015). The seeds and the seed oil of *Celastrus paniculatus* (Celastraceae) have been used for "stimulating intellectual ability and sharpening the memory" (Warrier et al. 1995; Howes and Houghton 2003). The roots of *Clitoria ternatea* (Leguminosae) have been shown to promote intelligence and enhance memory retention by affecting the cholinergic activity (Warrier et al. 1995; Misra 1998). *Terminalia chebula*'s (Combretaceae) ripe fruit is regarded as a brain power booster and memory promoter (Misra 1998; Manyam 1999; Naik et al. 2002). In the current article, we describe the cognitive neurodegenerative disorders and the therapeutic potential of *Centella asiatica* in relation to its neuroprotective properties.

1.2 Cognitive Disorders

Cognitive disorders are a group of mental disorders that can affect mood, functional activities, and behavior of an individual by impairing perception, memory, communication, reasoning, and judgment. Among cognitive impairments, dementia has attracted global attention for the past few decades. A slow and progressive neuronal dysfunction in the central nervous system (CNS) is the root cause of dementia, which ultimately leads to sensory dysfunction (Solanki et al. 2015). According to the definition given by the physician in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV),* dementia has symptoms such as decline of memory along with at least loss of one of the cognitive abilities such as coherent speech/language, perception, judgment, execution of motor functions, and/or reasoning. A definitive diagnosis of the loss of the cognitive abilities must be present for at least 6 months. There are various types of dementia such as mild cognitive impairment, vascular dementia, mixed dementia, Lewy body dementia, Alzheimer's disease, Parkinson's disease, frontotemporal dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, Huntington's disease, and Wernicke-Korsakoff syndrome (Mori et al. 2012). Dementia is an age-related disorder and affects 10–15% of adults aged above 65 years, and its occurrence increases by 35–50% in adults of ages more than 85 years (Mori et al. 2012). It was estimated that in 2010, about 36 million people were suffering from some form of dementia worldwide. If left unchecked, it is expected to rise to 66 million by 2030 and 115 million by 2050 (Label 2009). Various types of dementias are as given in Table 1.1.

Alzheimer's disease is a chronic progressive neurodegenerative cognitive disorder and is the most common type of age-related dementia (Hage et al. 2010). Alzheimer's disease mainly affects the elderly people. Since the life expectancy in the United States (from 55 years to over 75 years of age) and around the world has increased, a strong correlation with a widespread of age-related cognitive disorders has been established (Gray et al. 2016). In the United States, Alzheimer's disease is one of the most predominant irreversible neurodegenerative disorders, which gradually leads to the overall attenuation of higher cognitive abilities (Alzheimer's Disease International 2009). Amnesic cognitive impairment (mild memory loss) is the early sign of Alzheimer's disease (Howes et al. 2003). Mild memory loss usually leads to the decline in other cognitive abilities such as word finding, vision/spatial issues, and impaired reasoning. Based on time of the onset of disease, Alzheimer's disease can be classified into two categories: familial Alzheimer's disease (FAD) and sporadic Alzheimer's disease (SAD). FAD occurs due to the uncontrolled genetic cause such as genetic mutations in the amyloid β precursor protein (APP) and presenilin (PS) genes which accounts for almost 3% of the cases and usually affects patients at an early age of less than 60 years (Mori et al. 2012). However, SAD is caused by the unknown pathological factors and represents 97% of the cases. SAD affects people of age 65 years or above and accounts for 50–60% of dementia cases (Howes et al. 2003; Label 2009). Irrespective of the types, both FAD and SAD have severe loss of memory, language, visuospatial skills, and emotion followed by inability to walk and swallow. Alzheimer's disease patients with early

Table 1.1 Characteristic features of different forms of dementia

Types of dementia	Characteristic features
Mild cognitive impairment	Memory loss, language impairment, other mental malfunction
Vascular dementia	Elevated cholesterol levels, high blood pressure, hardening of the blood vessels (arterial walls), hyperglycemia, disrupted blood flow to the brain
Mixed dementia	Vascular dementia and Alzheimer's disease occur simultaneously
Lewy body dementia	Alpha-synuclein composed of Lewy body deposition, progressive cognitive decline, memory impairment deterioration in visuospatial ability, visual hallucinations, rapid eye movement, sleep behavior disorder, severe neuroleptic sensitivity
Parkinson's disease	Bradykinesia, rigidity, postural instability, tremor or shaking of limbs, speech impairment, muscle stiffness, loss of autonomic movements. Lewy body deposition, drooling, seborrhea, constipation, sexual dysfunction, olfactory problem
Frontotemporal dementia	Tremor, rigidity, memory impairment, loss of speech
Creutzfeldt-Jakob disease	Progresses rapidly, depression, deposition of prion protein, memory deficit, movement disorders, mood swings
Normal pressure hydrocephalus	Accumulation of cerebrospinal fluid in the ventricles of the brain and spinal cord, seizures, memory deficit, impaired vision
Huntington's disease	Degeneration of striatal neurons, movement, cognitive and psychiatric dysfunction, inherited changes in a single gene
Wernicke-Korsakoff syndrome	Thiamine deficiency, ataxia, memory loss, alcoholism
Other cognitive impairments	
Down syndrome	Due to genetic impairment chromosome 21
Prenatal alcohol/nicotine exposure	Excessive alcohol intake or nicotine exposure
Homocysteinemia	Increased levels of homocysteine

onset tend to have more brain irregularities as compared to the late-onset disease. As this neurodegenerative disease progresses, it is further distinguished and classified depending on the severity of symptoms, such as mild Alzheimer's disease, moderate Alzheimer's disease, and severe Alzheimer's disease. The stages of Alzheimer's disease and their symptoms have been summarized in Table 1.2. However, it is not just the genetic and symptomatic features that are vital, but the prevention, therapy, drug interaction, patient care, and economic aspects also play a critical role in Alzheimer's disease "care." Hence, in the next section, we shall look into the prevalence and economic impacts of Alzheimer's disease.

1.2.1 Prevalence of Alzheimer's Disease

Universally, nearly 44 million people have been diagnosed with Alzheimer's disease or a related dementia. Alzheimer's disease is most common in Western Europe (North America is close behind) and is least prevalent in sub-Saharan Africa (Alzheimer's Disease International). Alzheimer's disease is the sixth leading cause

Table 1.2 Different stages and symptoms of Alzheimer's disease

Stages of Alzheimer's disease	Symptoms
Mild	Mild coordination issues
	Mood swings
	Recurrent recent memory loss
	Repeating questions
Moderate	Confusions, misapprehensions, aggression, and paranoia
	Difficultly in recognizing family and friends
	Disturbances in sleep
	Feeling withdrawn and forgetfulness
	Perpetual memory loss
	Tremors and rigidity
Severe	Completely dependent on support giver for day-to-day activity
	Confusion between past and present
	Immobility
	Problems with swallowing and incontinence
	Severe impairment of speech

of mortality in the United States. Based on Alzheimer's Association statistics in 2015, an estimated 5.3 million Americans of all ages had Alzheimer's disease and other dementia (Alzheimer's Association 2015). These numbers are projected to rise to 15 million by the year 2050 (Jadidi-Niaragh et al. 2012). About 35.6 million people were diagnosed with dementia in 2010 worldwide (World Alzheimer's report 2009). It has been predicted that the number will double every 20 years and rise to 65.7 million in 2030 and 115.4 million in 2050. Men have fewer incidences of Alzheimer's disease and other dementia than women. It is postulated that almost two-thirds of Alzheimer's diagnosed American population are women. It is estimated that in the United States, one in eight people of 65 years and older and nearly half of people of 85 years and older are Alzheimer's patients. About 7.7 million new cases of dementia have been reported each year, thereby implying the prevalence of new case every 4 s in the world.

1.2.2 Etiology and Pathophysiology of Alzheimer's Disease

Even though Alzheimer's disease is an old disease, the specific etiological causes of this disease are still to be precisely elucidated and thus lead to the subject of continuous research. From the various studies carried on so far, it can be concluded that majority of the pathological features observed in the CNS are senile plaques (SPs), neurofibrillary tangles, oxidative stress, apoptosis, inflammation, excitotoxicity, and neurotransmitter disturbances (Howes et al. 2003). Based on the morphology and histology, the Alzheimer's disease occurrence was hypothesized as cerebrovascular accumulation of amyloid beta (Aβ), predominant formation of neurofibrillary tangles in the cortex and hippocampus, followed by neuronal and synaptic loss, brain

atrophy, and enlargement of cerebral ventricles (Khachaturian 1985; Cummings et al. 1998; Imbimbo et al. 2005). Diminutive neuronal loss or reactive gliosis is related with diffused Aβ plaques, whereas the Congo red and thioflavin S-positive plaques made up of fibrillary Aβ are related with neuronal loss, dystrophic neurites, and reactive astrocytes (Rozemuller et al. 1989; Itagaki et al. 1989). The neurofibrillary tangles (NFTs) are intracellular lesions consisting of twisted filaments of a cytoskeleton protein called tau protein (Castellani et al. 2010). The neuritic plaques, also known as senile plaques, are extracellular lesions composed of the 40–42 amino acid-long peptide Aβ fragments derived from amyloid precursor protein (APP) (Gomez-Isla et al. 1996; Selkoe 1998). Biochemically, the SPs are amyloid protein deposits mainly composed of beta-convoluted sheet of amyloid peptide of length 1–40 and 1–42 ($A\beta_{1-40}$ and $A\beta_{1-42}$) that gets cleaved from APP found in the neuronal cell membranes. NFTs are hyperphosphorylated tau proteins in the neuronal cells. Postmortem brain autopsy of Alzheimer's disease expresses SP, NFTs, and atrophy of the cortical and temporal lobes of the brain. Such pathogenic hallmarks also co-localize with activated microglia, astrocytes, inflammatory cytokines, and proteins surrounding the dystrophic neuritis (Akiyama et al. 2000). Most of the cases of genetically inherited Alzheimer's disease (FAD) are due to the mutations in one of the gene that encodes for the APP or in genes encoding APP (presenilin1-PSEN1 and presenilin 2-PSEN2) processing compound cellular machinery (Imbimbo et al. 2005; Piaceri et al. 2013). Conversely, SAD has been associated with several genetic and environmental factors. Despite numerous researches being carried out for almost a century, the etiology of SAD still remains vague (Piaceri et al. 2013). Out of several existing theories that have been put forth for understanding the pathogenesis of Alzheimer's disease, Aβ and tau hypothesis are the widely accepted scientific theories currently. Nevertheless, the certainty of these theories still needs to be further elucidated.

1.2.2.1 Amyloid Beta (Aβ)-Induced Neurotoxicity in Alzheimer's Disease

The main basis of amyloid cascade hypothesis is the characteristic extracellular senile plaques, one of the histological hallmarks of Alzheimer's disease (Imbimbo et al. 2005). According to the Aβ toxicity or amyloid hypothesis, the primary causative agent for Alzheimer's disease is Aβ ($A\beta_{40}$ and $A\beta_{42}$) peptides deposition (Cummings et al. 1998; Farlow 1998; Imbimbo et al. 2005; Karantzoulis and Galvin 2011; Piaceri et al. 2013). The Aβ peptides are derived by proteolysis of a type I transmembrane glycoprotein produced in many cells called the APP. In short, APP is a type I transmembrane protein processed by two competing catabolic pathways, non-amyloidogenic and amyloidogenic pathway (Hage et al. 2010). In non-amyloidogenic pathway, the initial proteolysis with α-secretase enzyme results in the generation of sAPPα and carboxyl-terminal 83-aa fragment (C83 or carboxyl-terminal fragments, CTFα), anchored at the membrane, followed by further proteolysis of C83 fragment with γ-secretase subsequently results in formation of N-terminal peptides, p3, and APP intracellular domain (AICD). Conversely, in the amyloidogenic pathway, the initial proteolysis of APP is performed by APP-cleaving

enzyme, β-secretase that results in the formation of sAPPβ and carboxyl-terminal 99-aa fragment (C99 or β-CTF). The γ-secretase further processes C99 fragment to secrete Aβ peptides and APP intracellular domain (Hage et al. 2010). According to amyloid Alzheimer's disease theory, these Aβ peptides of varying lengths oligomerize to form soluble oligomers and accumulate in the brain (Suh and Checler 2002). This is the significant initiating event in the development of Alzheimer's disease. However, the specific species of Aβ that results in neurotoxicity is one of the many uncertainties that remain to be determined.

Beta-site APP-cleaving enzyme (BACE) is a single protein that is associated with β-secretase. β-site amyloid precursor protein-cleaving enzyme 1 (BACE-1) is a type 1 transmembrane aspartic protease related to the pepsin and retroviral aspartic protease families. It is mainly present in the acidic intracellular compartments (e.g., endosomes, trans-Golgi) with its active site in the lumen of the vesicles. The maximum activity and amount of BACE are found in the CNS (neurons), which is similar to β-secretase. BACE transfection (cDNA) and its antisense oligonucleotide exposure increased or decreased Aβ levels and β-secretase-cleaved APP fragments in APP-overexpressing cells. BACE2 is expressed in neurons (low levels), and it does not have the same cleavage activity on APP as β-secretase. Reformation of γ-secretase activity in yeast has discovered the presence of four components: presenilin, nicastrin, anterior pharynx-defective 1, and presenilin 2 (Gotz et al. 2004). FAD patients with mutations at APP, PSEN-1, and BACE protein confirmed the genetic framework to this theory, in turn confirming the pathological hallmarks of Aβ deposition in the brain of such patients less than 65 years (Citron et al. 1992; Piaceri et al. 2013). Increased BACE activity and linkage to the apolipoprotein E polymorphism found in sporadic Alzheimer's disease patients have further confirmed that these are the key risk factors for developing late-onset Alzheimer's disease (Bales et al. 1997; Farlow 1998). Various other biochemical studies also strengthen the Aβ theory associated with neuronal insult in cholinergic neurodegeneration. Aβ deposition prior to the formation of NFTs, tau fibril formation in the presence of Aβ, neuronal loss, and clinical symptoms of Alzheimer's disease are the notable biochemical processes seen in the early stages of Alzheimer's disease (Lewis et al. 2001; Mayeux et al. 2003; Hurtado et al. 2010; Chiu et al. 2012).

Neuronal toxicity is induced by Aβ via various mechanisms such as oxidative stress (Butterfield et al. 2001), disruption of mitochondrial activity (Schapira and Reichmann 1995), energy imbalance (Carvalho et al. 2012), stimulation of neuroinflammation (Verri et al. 2012), disturbance in calcium (Ca^{2+}) homeostasis (Resende et al. 2007), perturbation of axonal transport (Decker et al. 2010), and activation of apoptotic signaling (Imaizumi et al. 1999; Kudo et al. 2012). These mechanisms eventually lead to the disturbance in neuronal cell integrity and CNS function, thereby resulting in accelerated neuronal cell death and Alzheimer's disease pathogenesis. Excitotoxicity also plays a crucial role in neuronal cell death. This is distinctly evident in several chronic progressive neurodegenerative disorders (Thellung et al. 2013). Glutamate can act on various types of receptors (AMPA, NMDA, and kainate). Glutamate-like acetylcholine is also involved in cognitive functions such as learning and memory in the brain. The form of synaptic plasticity known as

long-term potentiation takes place at glutamatergic synapses in the hippocampus, neocortex, and other parts of the brain. Excitotoxicity is mainly caused by the imbalance of Ca^{2+} homeostasis mediated by slow N-methyl-D-aspartate receptors ion channels resulting in the stimulation of various oxidative stress pathways. One of the theories is that the Aβ peptides induce synaptic discrepancies such as inhibition of long-term potentiation (LTP) in the hippocampal perforant pathway (Rowan et al. 2004; Parameshwaran et al. 2008; Ferreira et al. 2012). Aβ peptides also decrease surface expression and function of 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propionic acid receptors (AMPARs) and NMDARs, thereby impairing glutamatergic transmission (Parameshwaran et al. 2008). This Aβ deposition through induction of these harmful effects may lead to neurotoxicity, thereby resulting in the progression of Alzheimer's disease.

1.2.2.2 Oxidative Stress: A Pathogenic Factor

Oxidative stress is a vital pathogenic factor underlying various neurodegenerative disorders (Karpińska and Gromadzka 2013). Oxidative stress is one of the well-studied neurotoxic mechanisms for the study of Alzheimer's disease and has been investigated both as secondary and primary incident in Alzheimer's disease pathogenesis (Markesbery 1997; Butterfield et al. 2001; Moreira et al. 2008). It is also contemplated that free radical generation and depletion of antioxidants may play a pivotal role in the pathogenesis of Alzheimer's disease, similar to the oxidative stress theory of aging (Choi et al. 2012). In support of this theory, there are direct evidences which suggests that there is an increase in the level of metals (Al^{3+} and Mn^{2+}) in the brains that are capable of stimulating free radical generation (Leskovjan et al. 2011). Remarkable amount and variety of reactive oxygen species (ROS) are generated in the early stages which decline with the disease progression (Nunomura et al. 2001). Studies have also found a significant increase in the lipid peroxidation and its product 4-hydroxynonenal in the ventricular fluids of Alzheimer's disease patients and also in transgenic animals (Siegel et al. 2007). Lipid peroxidation is a product of the direct effect of free radicals on lipids. Lipids are highly vulnerable to oxidative stress. As stated by the amyloid theory, deposition of Aβ is the key initiating factor resulting in the ROS generation via several mechanisms such as interaction with metals. This results in the release of hydrogen peroxide that further induces the lipid peroxidation and consequent production of extremely reactive neurotoxic oxygen species, aldehyde, 4-hydroxynonenal (Abdul et al. 2008). Increased ROS leads to an altered activity of key enzyme complexes involved in energy metabolism and electron transport chain, thereby resulting in superoxide radical (O^{2-}) formation. Such reactive species oxidize other molecules like nitric oxide (NO), leading to the formation of highly reactive peroxynitrite radical, a cytotoxic agent that induces peroxidation of lipid membranes, and other hydroxyl radical/free radicals causing neurotoxicity (Subathra et al. 2005; Chen et al. 2013). Furthermore, the oxidative stress causes an increase in the levels of damaged proteins and DNA in the brains of Alzheimer's disease patients (Markesbery 1997; Moreira et al. 2008). Additionally, mitochondrial dysfunction associated with disrupted energy metabolism, notable Aβ release, and its deposition leads to programmed cell death (Siegel

et al. 2007; Abdul et al. 2008; Chami and Checler 2012; Verri et al. 2012). Free radicals also attack DNA, resulting in DNA cleavage and damage, thereby leading to apoptotic changes in neurons (Kumar and Gupta 2002; Boland and Campbell 2004; Tabner et al. 2005) and, consequently, cell death (Sultana et al. 2006; Moreira et al. 2008; Abdul et al. 2008; Verri et al. 2012). It is known that an elevated ROS production in mitochondria can inhibit adenosine triphosphate (ATP) synthesis, release cytochrome c, and induce mitochondrial permeability transition (Ichas and Mazat 1998; Rizzuto et al. 2000; Tewari et al. 2016). Dysfunction in the powerhouse of the cell, mitochondria, can result in the release of pro-inflammatory and proapoptotic factors which initiate, intensify, and implement various signals resulting in apoptotic cell death (Kroemer and Reed 2000). Moreover, mitochondrial dysfunction and associated bioenergetic breakdown leads to aberrant cellular ion homeostasis, which can result in cellular disruption and swelling of the cells, ultimately causing necrotic cell death (Nieminen 2003). In conclusion, oxidative stress is known to be the earliest, most detrimental event and could be one of the targets for therapeutic interventions for Alzheimer's disease.

1.2.2.3 Neurochemical Alterations

Noticeable change in the levels of several neurotransmitters has been observed in Alzheimer's disease patients, which closely correlates with its different cognitive and noncognitive symptoms (Reinikainen et al. 1990). Various studies have associated the neuropathology resulting in memory loss due to the substantial deficits in cholinergic neurotransmission, one of the severities seen in Alzheimer's disease (Bowen et al. 1976; Bierer et al. 1995; Francis et al. 1999; Gottwald and Rozanski 1999; Howes et al. 2003). Initially, various histological and pathological studies have discovered substantial degeneration of cholinergic nucleus basalis of Meynert in neocortical and hippocampal regions of the brains of Alzheimer's disease patients. Drugs that stimulate cholinergic receptors prolong the availability of acetylcholine (Ach) by inhibiting the hydrolysis of Ach by acetylcholinesterase (AChE), and increased Ach release into the synaptic cleft can increase cholinergic neurotransmission. Cholinesterase inhibitors significantly improved cognitive functions, thereby supporting the pathogenic role of cholinergic deficiency (Gottwald and Rozanski 1999; Howes et al. 2003; Atri 2011; Hong-Qi et al. 2012). However, such treatments did not show permanent improvement in Alzheimer's disease patients, because of neurodegenerative nature. The cortical regions of the brain of patients suffering from Alzheimer's disease also showed variations in norepinephrine (NE) and serotonin (5-HT) levels, thereby resulting in secondary symptoms, such as language deficit, depression, and behavioral problems like agitation, disturbance in mood, aggression, and psychosis (Engelborghs and De Deyn 1997). Likewise, levels of the most abundant excitatory and inhibitory neurotransmitters of the brain, glutamate and gamma-aminobutyric acid (GABA), respectively, were also altered in patients suffering from Alzheimer's disease. However, the glutamatergic system was significantly affected more than the GABAergic system (Hyman et al. 1987; Reinikainen et al. 1990; Engelborghs and De Deyn 1997; Butterfield and Pocernich 2003; Schwab et al. 2013). As mentioned earlier, the surface expression and

function of NMDA and AMPA receptors play a major role in glutamatergic mode of neurotransmission. In neurodegeneration, observation of the synaptic levels of glutamate is imperative for neuronal physiology and survival. Varied levels of glutamate have been seen in different regions of the brains of Alzheimer's disease patients. Glutamatergic transmission in neocortical and hippocampal regions is known to be severely affected in Alzheimer's disease (Hyman et al. 1987; Butterfield and Pocernich 2003). Significantly high level of glutamate is also observed in the occipital lobe, and remarkable decreased content is seen in frontal and temporal lobes (Ernst et al. 1997; Fayed et al. 2011). Additionally, various APP transgenic mice model studies have confirmed the noticeable increase in the level of extracellular glutamate levels (Schallier et al. 2011). It has been hypothesized that the glutamate cytotoxicity is mainly mediated by NMDA subtypes of glutamate receptors. As mentioned earlier, NMDA receptors also mediate glutamate-induced processing of APP, which in turn results in enhanced Aβ secretion. Further increase in the level of Aβ in the brain results in oxidative stress leading to the oxidation of various lipids, sugars, and protein molecules in the neuronal cells. Glutamine synthetase is an enzyme involved in the conversion of glutamate to glutamine. In Alzheimer's disease patients, reduced brain activity was noticed because of oxidized glutamine synthetase (Bowen et al. 1976). Similarly, both clinical and experimental cases of Alzheimer's disease have observed reduction in activity and protein expression of glial glutamate transporter (GLT-1) (Sheldon and Robinson 2007). Due to the significant reduction in the glutamine synthetase activity and decreased GLT-1 levels in Alzheimer's disease patients, there is a remarkable decrease in synaptic clearance of glutamate, which in turn causes NMDA-mediated neuronal injury. Additionally, NO production in response to the excitatory NMDA receptors activation causes extensive damage to cerebral neurocytes (Wang et al. 2010). Glutamate decarboxylase enzyme (GAD) converts glutamate to GABA. Recent studies show that 50% increase in the mRNA of GAD in the brains of Alzheimer's disease patients indicates an increase in the GABAergic stimulation in the dorsal striatum (Reinikainen et al. 1990; Schwab et al. 2013). Increase in the level of GABA via presynaptic $GABA_A$ receptors results in prolonged inhibition of CNS neurons, which eventually leads to neuronal dystrophy, deafferentation, and increased neuronal degeneration (Schwab et al. 2013). All the above studies suggest that alteration in glutamate and GABA levels may play critical role in the pathogenesis of Alzheimer's disease. Nevertheless, due to their narrow pathogenic potential and analgesic therapeutic effects, these neurotransmitter alterations are considered to be the indicators of collateral damage occurring as a result of severe neuronal degeneration in Alzheimer's disease (Robichaud 2006). Changes in the cholinergic and glutamatergic system are considered to be the key element in the current treatment of Alzheimer's disease.

1.2.2.4 Synaptic Deficits and Cognitive Dysfunction

Based on the electron microscopy and immunohistochemical staining in the cortical and hippocampal areas of the brains of Alzheimer's disease patients, a significant decrease in synaptic density and loss of presynaptic and postsynaptic markers were observed (Masliah et al. 2001; Reddy et al. 2005). The loss of synapses is an early

and consistent characteristic feature of Alzheimer's disease that strongly associates with the severity of cognitive impairment (Masliah et al. 2001; Scheff et al. 2007). Various studies have proposed that synaptic dysfunction and neuronal loss are caused by Aβ peptides and hyperphosphorylated tau, respectively (Frautschy and Cole 2010). Soluble non-fibrillar Aβ assemblies [also known as Aβ-derived diffusible ligands (ADDLs)], oligomers, paranuclei, and protofibrils emerge long before the Aβ deposits and are thought to be the main culprit. Aβ-induced synaptic deficits are caused by three basic mechanisms: (1) toxic gain of function (due to novel interactions by new conformations of Aβ), (2) loss of usual physiological function, and (3) precipitation of physiological dysfunction by excessive Aβ. Under normal conditions, Aβ peptides play a vital role in homoeostatic plasticity by altering the excitatory transmission through AMPA and NMDA subtypes of glutamatergic receptors. Moreover, Aβ can also hinder LTP in the hippocampal perforant pathway (Chen et al. 2000; Wang et al. 2002; Rowan et al. 2004). It also decreases AMPAR and NMDAR surface expression and function. Dysfunctions caused by Aβ are internalization of NMDA receptors through calcineurin-dependent pathway (Dewachter et al. 2009) and weakening of synaptic transmission and plasticity via activation of group I metabotropic glutamate receptors (mGluRs) with p38 mitogen-activated protein kinase (MAPK) and calcineurin as downstream effectors (Hsieh et al. 2006; Li et al. 2009). Excitotoxicity and the resultant cell death caused by Aβ are primarily because of its interaction with NMDA receptors and disruption of the Ca^{2+} balance inside the cell. In several in vivo and in vitro studies, it has been observed that ADDLs readily bind to the dendritic arbors of a specific type of cultured neurons (Lacor et al. 2004; Laurén et al. 2009). In such studies, it has also been observed that ADDLs facilitate dendritic spine loss (Lacor et al. 2007), increase ROS generation, and disrupt excitatory and inhibitory neurotransmission balance, which in turn leads to epileptic behavior in transgenic mice. In various transgenic animal studies, synaptic deficits are the common disorders that are introduced for observing various pathophysiological aspects of Alzheimer's disease. Therefore, damage to the synaptic connections and impairment of synaptic plasticity are elementary in pathogenesis of memory impairment in Alzheimer's disease. Thus, further research in elucidating the underlying mechanisms of synaptic toxicity may help in the development of novel therapeutic medications.

1.2.2.5 Inflammation and Neuronal Cell Death

Inflammation also plays a pivotal role in various neurodegenerative and neurological disorders such as multiple sclerosis, Parkinson's disease, Huntington's disease, Alzheimer's disease, and traumatic brain injury (Blasko et al. 2004). According to the inflammatory hypothesis of Alzheimer's disease, chronic inflammation developing independently (due to several unknown factors) or as a result of Aβ pathology, plays a pivotal role in neurodegeneration. Along with oxidative stress, Aβ plaques, and NFTs, brain inflammation is an early pathological indication of Alzheimer's disease (McGeer et al. 1989; Eikelenboom et al. 2010). Neuroinflammation is a chronic and self-sustaining pathogenic process which is specific to Alzheimer's disease and is extremely capable of neuronal injury and neurodegeneration. Various direct and

indirect evidences confirm the pathophysiological significance of neuroinflammation in Alzheimer's disease (Akiyama et al. 2000). One of the confirmations is the co-localization of activated microglia, astroglia, and monocytes around the Aβ plaques and dystrophic neurites, specifically in the frontal neocortex and limbic cortex; however, no signs of inflammation are observed in the cerebellum (Rogers et al. 1988; Dickson et al. 1988). Furthermore, prudent but remarkable inflammation is observed in patients with low Braak scores for Alzheimer's disease pathology (i.e., patients without any history of dementia but ample amount of Aβ and neurofibrillary tangles at autopsy). There is an upregulation of the pro-inflammatory genes (gene encoding for complement factors; major histocompatibility complex proteins II, cell adhesion molecules) and pro-inflammatory enzymes resulting in the enhanced synthesis of prostaglandin and various other pro-inflammatory cytokines (Lue et al. 1996; Blalock et al. 2004; Parachikova et al. 2007). Likewise, in numerous in vitro and in vivo studies, Aβ has demonstrated to activate complement cascade and stimulate secretion of pro-inflammatory cytokines, chemokines, and other inflammatory markers from the activated monocytes (O'Barr and Cooper 2000), microglia (Del Bo et al. 1995; Chong 1997), astrocytes (Hu et al. 1998), endothelial cells (Suo et al. 1998), and neurons (Del Bo et al. 1995; Du Yan et al. 1997). Nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) and myeloperoxidase pathway are induced by Aβ, resulting in the ROS and cytokines generation via stimulated monocytes, microglia, and neurons (Bianca et al. 1999).

Recent studies have demonstrated that the pro-inflammatory mediators such as interleukins 1 (IL-1) and 6 IL-6 and interferon-γ (IFN-γ) induce APP secretion and processing and also annihilate the production of soluble APP (sAPP; a well-known neuroprotectant) leading to Aβ deposition and neurotoxicity (Blasko et al. 1999). Patients suffering from Alzheimer's disease have shown increased levels of gliosis, pro-inflammatory markers like IL-1, and conspicuous complement activation in postmortem brain (Rozemuller et al. 2005). Due to pathogenic role, anti-inflammatory therapies are known to be effective in delaying the onset of inflammation in Alzheimer's disease or slowing the progression of Alzheimer's disease (Jaturapatporn et al. 2012). Clinical trials have shown that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the risk of developing Alzheimer's disease. This hypothesis is supported further when rheumatoid arthritis patients, who frequently use NSAIDs, have a lower incidence of Alzheimer's disease (Breitner and Welsh 1995; Breitner 1996; McGeer et al. 1996; Howes et al. 2003). In addition to this, it is found that passive immunization therapy with Aβ antibodies have been proven beneficial to the Alzheimer's disease suffering individuals (Aisen and Vellas 2013). All the above indications establish the pathogenic significance of chronic neuro-inflammatory processes in pathophysiology and progression of Alzheimer's disease.

Even though T-helper cells' role in Alzheimer's disease is controversial, recent studies have shown that the T-cell-regulated inflammatory response plays a role in either pathophysiology, progression, or both in the most common dementia-related neurodegenerative disorder (Togo et al. 2002; Panossian et al. 2003; Magnus et al. 2005). It has also been observed that the blood-brain barrier (BBB) is permeable to

activated T cells, which is intensely increased during systemic infection or other neurodegenerative diseases (Ransohoff et al. 2003). However, the number of T cells affecting the brains of Alzheimer's disease patients is far less as compared to other neurodegenerative disorders like multiple sclerosis. A study by Itagaki et al. (1988) showed that the CD4 (T-helper-inducer) and CD8 (T-cytotoxic-suppressor) T-cell trafficking was altered in significantly large amounts in the hippocampus and temporal cortex of the brains of Alzheimer's disease patients when compared to the normal brain tissues. Recent investigations are indicative of the involvement of dendritic and microglia cells in orchestrating the T-cell response in the brains of Alzheimer's disease patients (Rogers et al. 1988; Magnus et al. 2005; Fisher et al. 2011). Microglia protects and supports the neurons as well as act as an immunoprotectant in the CNS. It is able to express major histocompatibility complex II, release cytokines, complement proteins, and in an activated states also possess scavenger and phagocytic properties (Moore and O'Banion 2002). Activated microglia expresses co-stimulatory molecules like CD80, CD86, and CD40 during CNS inflammation in neurodegenerative disorders. These molecules interact with T cells and modulate T-cell-mediated response, thereby promoting either their proliferation, T-effector functions (cytokine secretion), or both (Aloisi 2001; Magnus et al. 2005; Wirenfeldt et al. 2011). Microglia activation and T-cell-induced cytotoxic inflammatory response is mediated by the release of pro-inflammatory cytokines. Cytokines, IL-1, IL-2, IL-17a, and other secreted cellular products also play a vital role in the neuronal immune response by regulating the neuronal cell viability or BBB permeability (Huppert et al. 2010). These cytokines also play a role in the development and differentiation of T cell in a given disease state. In case of multiple sclerosis, an autoimmune disorder, the integrity of BBB is impaired by the IL-17 producing T-helper cells, which leads to the increase in its permeability to other lymphocytes. Increase in the tumor necrosis factors (TNF)-α protein expression is directly related with inflammatory response in Alzheimer's disease (Fillit et al. 1991; Blasko et al. 1999; Perry et al. 2001). Tumor necrosis factor-alpha (TNF-alpha) is a potent central regulator of inflammation. The expression of TNF-α and IFN-γ helps Aβ peptides production, which leads to the deposition of Aβ. This leads to the disruption of homeostatic balance and plaque formation (Blasko et al. 1999). Additionally, production and release of prostaglandins are also stimulated by these cytokines, which may result in neurotoxic effects associated with Alzheimer's disease pathology (Prasad et al. 1998).

1.3 Therapeutic Efficacy of *Centella asiatica*

Centella asiatica is a slender creeping perennial herb belonging to Umbelliferae (also known as Apiaceae) family. This plant has delicately scalloped hairy leaves with barely visible flowers. It is commonly found in tropical swampy areas. *Centella* species are widespread throughout tropical and subtropical countries worldwide (Awang 1998; Wattanathorn et al. 2008; Vasavi et al. 2014). *Centella asiatica* has numerous common names depending on the geographical location of origin. It is

known as *Gotu kola* in Sinhala, *mandukaparni* in Sanskrit, *kodakan* in Malayalam, *pegaga* in Malayasia, Indian pennywort and Indian water navelwort in India, *tsubokusa* in Japan, and *tungchian* or *luei gong gen* in China. Botanically it is known as *Hydrocotyle asiatica* Linn and *Trisanthus cochinchinensis* Lour (Kalshetty et al. 2012). As described earlier, *Centella asiatica* is an ancient medical herbal drug and has been traditionally used for its plethora of therapeutic purposes in Indian Ayurvedic medicinal practices for eras. According to the *Charaka Chikitsa I*, an ancient Indian literature, the juice of *Centella asiatica* promotes longevity and cures a variety of diseases. *Centella asiatica* is an active component of "Medhya Rasayana" (Bhavna and Jyoti 2011) and considered as crucial herb for the treatment of various health-related disorders (Thomas et al. 2010; Ermertcan et al. 2008; Somboonwong et al. 2012; Subathra et al. 2005; Bian et al. 2013; Di Tomo et al. 2015; Abas et al. 2015; Jayathirtha and Mishra 2004; Belcaro et al. 2011; Shukla et al. 1999; Cesarone et al. 2001a, b; De Sanctis et al. 2001; Incandela et al. 2001; Paocharoen 2010).

Therapeutically, the whole aerial part of *Centella asiatica* is useful as it is very rich in numerous bioactive compounds (Kumar and Gupta 2002). Various in vitro and in vivo (animals and human clinical) studies have been undertaken to evaluate its bioactive components and the medicinal value of *Centella asiatica.* The basic molecular mechanisms related to the therapeutic efficacy are being investigated. *Centella asiatica* has been used extensively for the dermatological pathologies. It has been widely used in the treatment of wounds, burns, and ulcerous skin ailments and for the prevention of keloid and hypertrophic scars (Belcaro et al. 2011; Brinkhaus et al. 2000; Gohil et al. 2010; Paocharoen 2010). This botanical is also used to treat second- and third-degree burns and topically to accelerate healing, mainly in cases of chronic postsurgical and post-trauma wounds (Belcaro et al. 2011). Details of medicinal applications of *Centella asiatica* are summarized in Table 1.3.

1.3.1 Active Components of *Centella asiatica*

The major active chemical components of *Centella asiatica* are identified as triterpenes, flavonoids, polyphenols, and other compounds (Bhattachryya and Lythgoe 1949; Singh and Rastogi 1969; Zainol et al. 2003; Mangas et al. 2006; Zheng and Qin 2007; Shinomol and Muralidhara 2008a; Zhang et al. 2008; James and Dubery 2009; Thomas et al. 2010; Gohil et al. 2010; Kalshetty et al. 2012; Long et al. 2012; Tiwari et al. 2013). The triterpenoids exist in the forms of saponins and glycosides, such as asiaticoside and madecassoside with its respective ursane-type sapogenins (Fig. 1.1). Other compounds reported in *Centella asiatica* with therapeutic efficacy are amino acids (alanine, serine, aminobutyrate, aspartate, glutamate, histidine, lysine, and threonine), fatty acids (linoleic acids, linolenic acid, lignocene, oleic acid, palmitic acid, and stearic acid), phytosterols (campesterol, sitosterol, and stigmasterol), resin, tannin, and various other terpenoids (beta-caryophyllene, trans-beta-farnesene and germacrene D, alpha-pinene, and beta-pinene) (George

Table 1.3 Medicinal use of *Centella asiatica* in cognitive disorders

Plant part used	Medicinal use	References
Whole plant	Enhances learning and memory	Rao et al. (2005)
Whole plant	Effective against MPTP-induced Parkinsonism	Ittiyavirah and Hameed (2014)
Whole plant	Enhances cognitive functions	Gray et al. (2016)
Whole plant	Significantly prevents the cognitive impairments	Gupta et al. (2003)
Whole plant	Memory enhancer in Alzheimer's disease	Hage et al. (2010)
Whole plant	Prevents Alzheimer's disease development	Chen et al. (2015)
Whole plant	Enhances cognitive function	Kumar and Gupta (2002)
	Improves learning and memory	
Whole plant	Neuroprotective and beneficial in Alzheimer's disease	Soumyanath et al. (2012)
Whole plant	Prevents memory deficits	Kumar et al. (2011)
	Improves the memory impairment	
Whole plant	Significant neuroprotective effects	Subathra et al. (2005)
	Protects brain against age-related diseases	
Whole plant	Enhances the cognitive function	Omar et al. (2011)
	Neuroprotective actions	
Whole plant	Anti-Parkinson's effect	Khotimah et al. (2015)
	Improves learning and memory	
	Protects the brain from age-related oxidative damage	
Whole plant	Neuroprotective properties	Shinomol et al. (2011)
	Improves memory	
	Prevents cognitive impairment	
Whole plant	Restores memory	Howes and Houghton (2012)
	Prevents dementia	
	Improves cognitive function	
Whole plant	Cognitive enhancement	Iqbal et al. (2011)
Whole plant	Increase memory	Krishna (2013)
Whole plant	Enhances learning	Mohd Salim et al. (2013)
Whole plant	Neuroprotective effect against Parkinson's disease and Alzheimer's disease	Orhan (2012)
Whole plant	Memory-enhancing effects	Singh et al. (2008)
Whole plant	Improves memory retention	Kumar and Gupta (2003)
	Prevents cognitive impairment	
Whole plant	Enhances cognitive performances	Xu et al. (2008)
Whole plant	Possesses neuroprotective properties against Alzheimer's disease	Dhanasekaran et al. (2009)
Whole plant	Improves cognitive function Neuroprotective effects	Gray et al. (2015)

(continued)

Table 1.3 (continued)

Plant part used	Medicinal use	References
Whole plant	Improves both speed and accuracy of working memory	Wattanathorn et al. (2008)
	Increases accuracy of word recognition	
Whole plant	Improves symptoms of Parkinson's disease	Barbosa et al. (2008)
	Enhances memory	
Leaves	Improves memory and cognitive function	Howes and Houghton (2003)
	Prevent dementia	
Leaves	Alternatives for the treatment of Alzheimer's disease	Akagi et al. (2015)
Leaves	Increases memory power in children	Sarkar et al. (2015)
Leaves	Memory-enhancing properties	Seevaratnam (2012)
	Protection against age-related changes in brain	
Leaves	Augments memory power	Tiwari et al. 2016)
Leaves	Potent in reducing the Parkinsonian symptoms	Siddique et al. (2014)
Leaves	Enhances memory	Mohandas Rao et al. (2012)
Leaves	Neuroprotective properties	Kasture et al. (2014)
Leaves	Protects against age-related changes in brain	Sugunabai and Karpagam (2015)
Leaves	Memory improvement and improves symptoms of Alzheimer's disease	Patel et al. (2014)
Leaves	Neuroprotective effect	Bhavna and Jyoti (2011)
Leaves	Improves memory against dementia and aging	Stafford et al. (2008)
Leaves	Prophylactic neuroprotective action	Shinomol and Muralidhara (2008a, b)
	Brain stimulant	
Leaves	Neuroprotective effects against neurodegenerative disorders including Alzheimer's disease and Parkinson's disease	Zhang et al. (2012)
Leaves	Improves memory	Ashalatha and Shenoy (2015)
	Brain tonic	
Leaves	Brain booster for improving memory	Wanakhachornkrai et al. (2013)
Leaves	Enhances memory retention	Rasoanaivo (2011)
Leaves and stem	Improves symptoms of Alzheimer's disease	Khatun et al. (2011)
	Neuroprotective effect in Parkinsonism	
Pure compound (asiatic acid)	Neuroprotective effects	Xu et al. (2012)
	Improves cognitive function against glutamate-induced dementia	

(continued)

Table 1.3 (continued)

Plant part used	Medicinal use	References
Pure compound (asiatic acid)	Enhances working memory	Sirichoat et al. (2015)
Pure compound (asiaticoside)	Improves memory	Chen et al. (2014)
	Delays the onset and progression of neurological disorders	
Pure compound (madecassoside)	Improves cognitive function in Alzheimer's disease	Du et al. (2014)

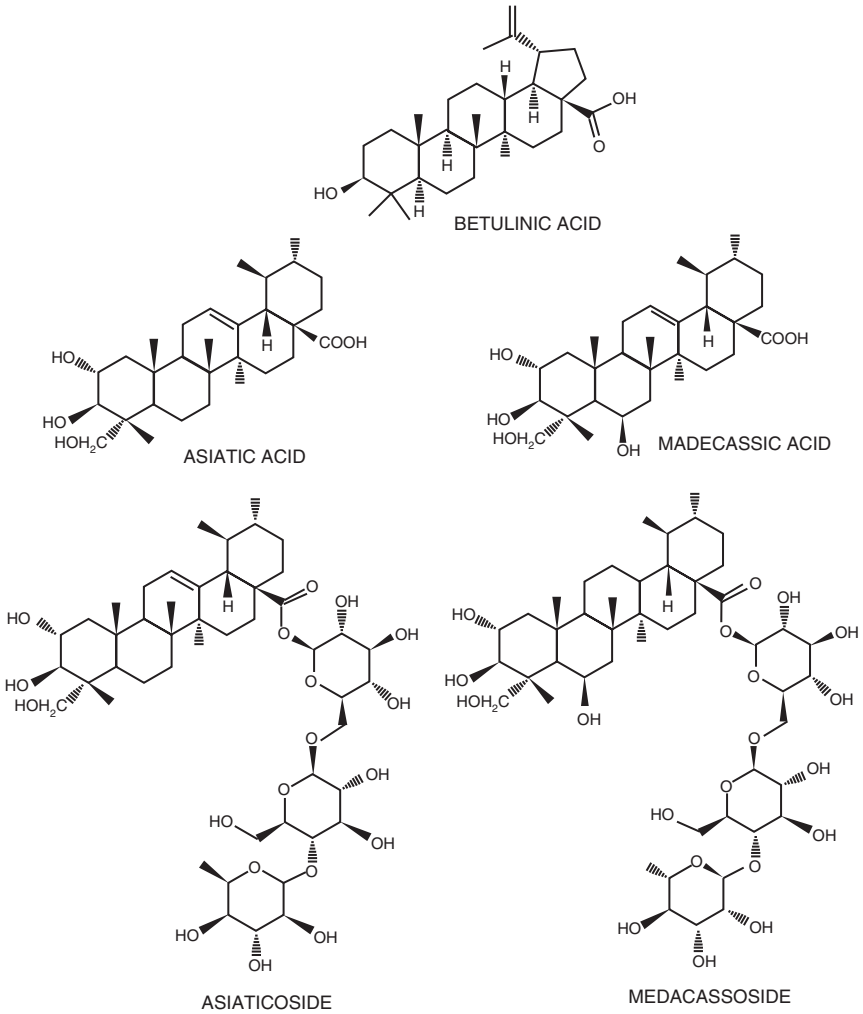

Fig. 1.1 Bioactive triterpenoids isolated from *Centella asiatica*

and Gnanarethinam 1975). Madecassoside, a pentacyclic triterpenoid derivative saponin, is reported to possess anti-inflammatory (Li et al. 2009; Liu et al. 2008; Wu et al. 2012), antioxidant (Luo et al. 2014), and cardioprotective (anti-myocardial infraction) activities (Bian et al. 2008). Main compounds responsible for the antioxidant activity of *Centella asiatica* are reported to be flavonoids and phenolic compounds (Hussin et al. 2005).

1.3.2 Learning and Memory-Enhancing Capability in Alzheimer's Disease

Centella asiatica extract was well enumerated and may have pro-cognitive effects in humans and rodents (Dhanasekaran et al. 2009; Kumar and Gupta 2002; Wattanathorn et al. 2008; Gohil et al. 2010; Shinomol et al. 2011; Xu et al. 2012b). Pharmacological studies have established the cognitive enhancing capability of *Centella asiatica* extract in a series of behavioral tests and memory retention tasks such as active and passive avoidance, object recognition, and water maze in rodents (Nalini et al. 1992; Kumar and Gupta 2002; Gupta and Pansari 2003). In a clinical study, *Centella asiatica* extract positively modulated cognition and mood-enhancing quality of life in healthy elderly volunteer (Wattanathorn et al. 2008; Mato et al. 2011; Nasir et al. 2011). Additionally, a few human clinical studies have reported that *Centella asiatica* extract substantially improved cognitive ability of mentally retarded children (Appa Rao et al. 1973).

The activation of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) leads to the increase in BDNF which in turn modulates the NMDA receptor activity and its expression on the pre- and post- synaptic sites (Madara and Levine 2008). It is also observed that the synaptic localization of pre- and postsynaptic proteins such as synaptobrevin is enhanced by BDNF through activation of TrkB receptor. Synaptobrevin plays an important role in maintaining synaptic plasticity (Minichiello et al. 2002; Huang and Reichardt 2003). Several pathways such as protein kinase A (PKA), NO signaling and CaMKII activation lead to the phosphorylation of CREB. As mentioned in previous sections, Aβ initiates numerous cytotoxic pathways in the CNS which leads to neurodegeneration and progression of Alzheimer's disease. Besides neuronal plaques formation, Aβ also stimulates the immune system of the CNS, which leads to the inflammatory-mediated response (Lue et al. 1996; Gupta and Pansari 2003). Additionally, it has been proven that the inflammatory mediators increase the APP processing in the neuronal cells, thereby accelerating and augmenting the secretion and deposition of Aβ (Blasko et al. 1999). It can thus be concluded that chronic inflammation may indirectly act as the main pathogenic agent in the formation of Aβ plaques in the brains of Alzheimer's disease patients. Therefore, studies were conducted with *Centella asiatica* to evaluate its neuroprotective properties against Aβ toxicity in association with BDNF and inflammation (Xu et al. 2008).

Centella asiatica plays a key role in neuronal regeneration by stimulating the dendrites of rat brains, neurite elongations in human SH-SY5Y cells, and increasing

axonal regeneration in rats. Synaptic strengthening and cognitive enhancement activities of *Centella* are by increasing CREB phosphorylation and thereby aiding the neuronal dendritic arborization and axonal regeneration in rats (Rao et al. 2005; Soumyanath et al. 2005). One of the physiological processes of memory formation is generally induced by CREB (a transcription factor) during LTP. The important early genes like c-fos and proteins such as brain-derived neurotrophic factor (BDNF) responsible for neuronal survival and protein synthesis are regulated by CREB (Malinow et al. 2000). Phosphorylation of CREB leads to the activation of factors such as several protein kinases, MAPK, calcium-/calmodulin-dependent protein kinase II (CaMKII), protein kinase C, and signaling factors like Wnt, which play an important role in neuronal survival and arborization (Wayman et al. 2006). Numerous studies have demonstrated BDNF to robustly stimulate the dendrite outgrowth by triggering TrKB receptors, resulting in the stimulation of various proteins including the activation of CAMKII (Minichiello et al. 2002; Huang and Reichardt 2003). Overall, these studies have concluded that one of the mechanisms mediating cognitive enhancement activity of *Centella asiatica* can be via increasing CREB signaling (Xu et al. 2008, Fig. 1.2).

1.3.3 Neuroprotective Activity in Alzheimer's Disease

Numerous experiments have established that *Centella asiatica* has neuroprotective mechanisms of action significant to the therapeutic treatment of Alzheimer's disease. As pointed out earlier, excessive levels of the neurotransmitter, glutamate, is found in the brains of Alzheimer's disease patients. It has been demonstrated that *Centella asiatica* may have a neuroprotective effect when cultured neurons are exposed to glutamate (Lee et al. 2000; Ramanathan et al. 2007). Some studies have proven that *Centella asiatica* extract influences neurotransmitter systems such as dopamine and serotonin (5-HT) that regulate the production of Aβ peptide (Sakina and Dandiya 1990; Nalini et al. 1992; Nitsch et al. 1996), which consequently may serve to limit the production of Aβ peptide.

Centella asiatica alters fabrication of extracellular matrix molecules (Maquart et al. 1999). Deposition of fibrillar Aβ is known to promote extracellular matrix molecule, perlecan, in rodent brain (Snow et al. 1994; Holcomb et al. 2000). Whereas, laminin, an extracellular matrix molecule, has recently been demonstrated to hinder Aβ fibril formation (Castillo et al. 2000). *Centella asiatica* may function as an anti-fibrillogenic agent, limiting the formation of amyloid deposits through alterations in the production of key extracellular matrix proteins. *Centella asiatica* has shown to exhibit preventive effects on cognitive deficits in streptozotocin-treated animal model of memory deficit (Kumar and Gupta 2003). Furthermore, reduction in the protein carbonyl production was seen in the brains of aged rats when treated with *Centella asiatica* (Subathra et al. 2005). Overall, these studies have demonstrated that *Centella asiatica* may reduce neuropathologies of Alzheimer's disease.

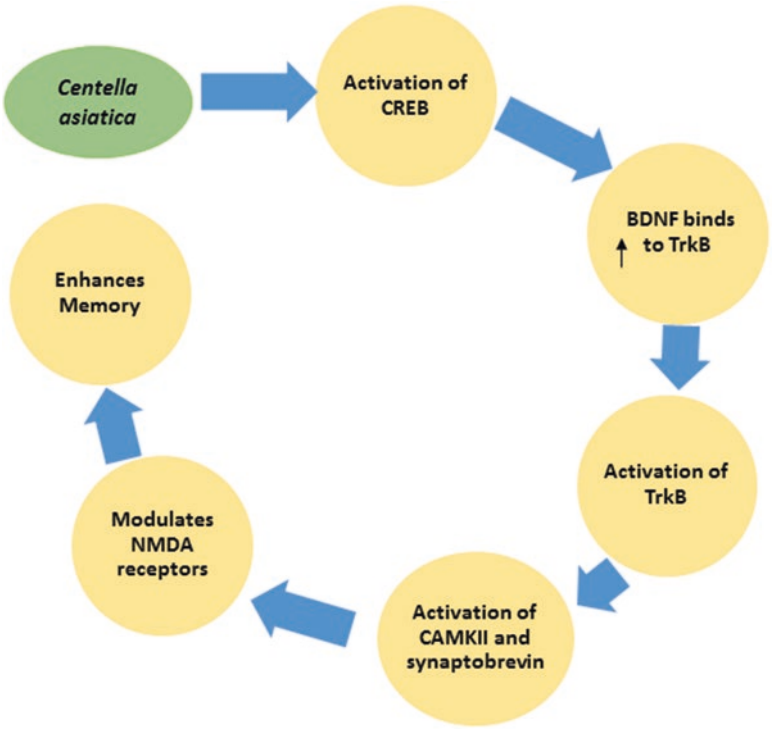

Fig. 1.2 Mechanisms of action

Researchers have found that prior to the increase of Aβ 1–40 and 1–42 levels or noticeable Aβ deposition in the Alzheimer's disease mouse model, augmented lipid peroxidation takes place (Praticò et al. 2001). Studies conducted in our research laboratory (Dhanasekaran et al. 2009) have found that *Centella asiatica* could block lipid peroxidation, thereby suggesting that the primary action could be hindering the hydroxyl radical-generated membrane damage. This study further documented that *Centella asiatica* may also help in reducing Aβ deposition and elicited protection to proteins, sugars, and nucleic acids from oxidative and Aβ damage.

Asiatic acid and asiaticoside present in *Centella asiatica* provoke the acceleration of learning and memory performance (Kumar and Gupta 2003; Gupta et al. 2003; Rao et al. 2005). Asiatic acid from *Centella* also exhibits neuroprotective properties and has shown to protect cortical neurons from glutamate-induced excitotoxicity in vitro (Mook-Jung et al. 1999; Lee et al. 2000; Xiong et al. 2009; Krishnamurthy et al. 2009).

Ceramides derived from sphingosine are known to cause mitochondrial dysfunction which results in neuronal cell death (Arboleda et al. 2009; Zhang et al. 2012b). Several researchers have found that ceramides may play a role in various neurological disorders such as Alzheimer's disease (Cutler et al. 2004; Jana et al. 2009), Parkinson's disease (France-Lanord et al. 1997; Bras et al. 2008), and cerebral

ischemia (Novgorodov and Gudz 2009). Specifically, C2-ceramide (short chain active analog of ceramide) causes mitochondrial disruptions and apoptosis. Zhang et al. (2012) demonstrated that *Centella asiatica* exhibited protective activity against C2-ceramide-induced mitochondria-dependent apoptosis may be by regulating the ERK1/2 signaling pathway (Movsesyan et al. 2002; Stoica et al. 2005).

Apoptosis is seen in peripheral chronic disorders and in various neurological disorders mainly in Alzheimer's disease and Parkinson's disease. Neurodegeneration is mainly caused by apoptosis that can be triggered by various pathways (LeBlanc 2005). In a recent study, it has been hypothesized that early induction of caspase-6 leads to the activation of downstream apoptotic mediators such as the caspase-3. Induction of caspase-6 results in the disruption of the cytoskeleton of neurites and also leads to the damage of proper trafficking of proteins and organelles, thereby resulting in neurodegeneration and synaptic loss in Alzheimer's disease (LeBlanc 2005). Prakash and Kumar (2012) showed that *Centella asiatica* exhibited anti-apoptotic activity by effectively inhibiting the caspase activity induced by D-galactose neurotoxicity in rats.

In the double transgenic mice model of Alzheimer's disease, Aβ plaque accumulation occurs in the frontal cortex and has DNA fragmentation (Feng et al. 2004; Wang et al. 2005; Migliore et al. 2005). A single-strand break in DNA may lead to the double-strand breaks, which may result in apoptosis, or may inactivate vital genes, or may also cause chromosomal aberrations (Barzilai and Yamamoto 2004). Disturbance of the supercoiled form of the plasmid DNA caused by exposure to hydrogen peroxide and UV light was inhibited by *Centella asiatica*, thereby preventing the single-strand or double-strand breaks formation of DNA.

In addition to improving cognition, *Centella asiatica* may also be used to treat the motor agitation and mood changes of people suffering from Alzheimer's disease. It is postulated that *Centella* also helps in promoting a deep state of relaxation and mental calmness during meditation practices (Brown 1995). Formulations of *Centella asiatica* in combination with other herbs are used to alleviate depression and anxiety (Bradwejn et al. 2000). The antidepressant and anxiolytic activities of *Centella asiatica* are thought to be mediated through the hypothalamic-pituitary-adrenocortical axis, which relieves stress and alters the components of the monoaminergic neurotransmitters (Chen et al. 2005; Bobade et al. 2015 Fig. 1.3). In addition, *Centella asiatica* has been shown to possess antioxidant activity in the hippocampus and corpus striatum (Ittiyavirah and Hameed 2014).

1.3.4 Antioxidant and Anti-inflammatory Activities in Alzheimer's Disease

Phenolic compounds exhibit potent antioxidant activity and also act as mitochondrial energizers. Free radicals are responsible to initiate cell injury (Spiteller 1993; Maxwell 1995; Howes et al. 2003). Thus, the use of antioxidants has been considered to slow the neuronal degeneration and progression of Alzheimer's disease (Howes et al. 2003). *Centella asiatica* is known to have an effective antioxidant and

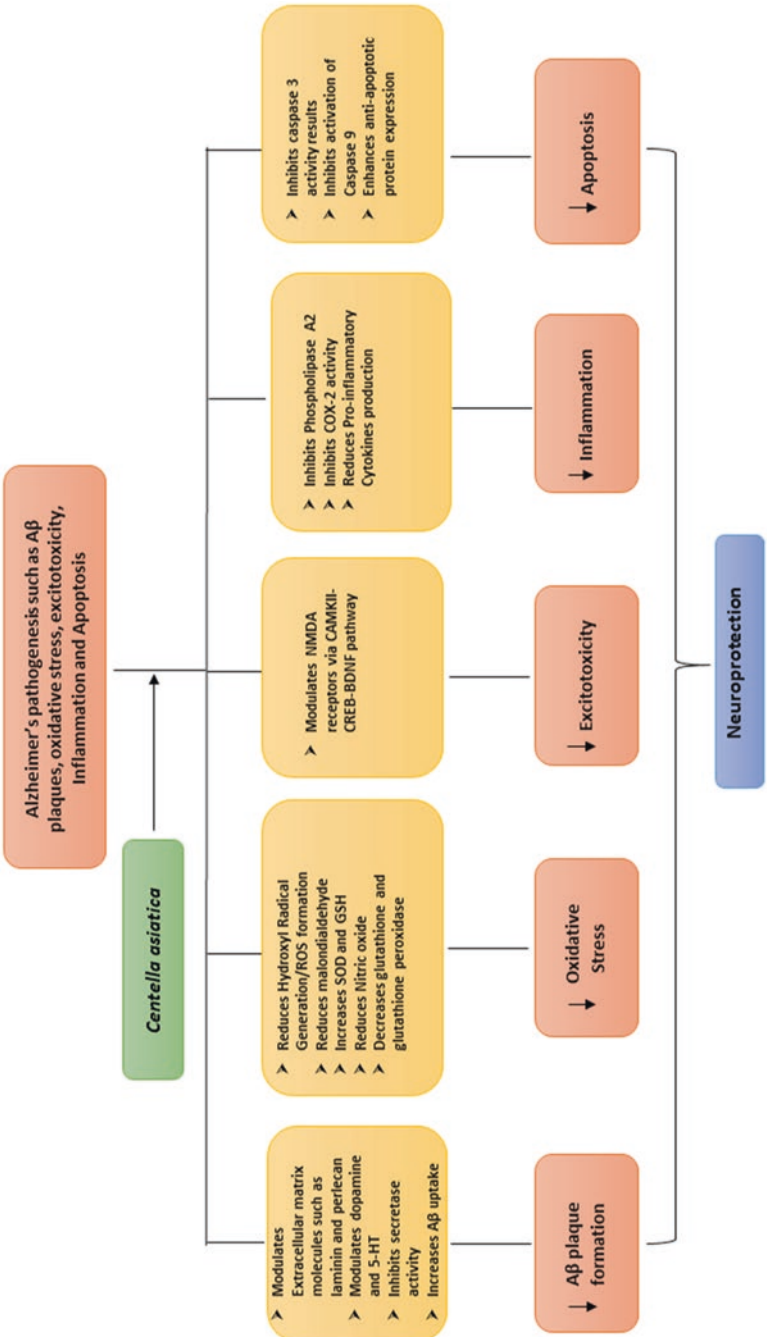

Fig. 1.3 Mode of action of *Centella asiatica* in the pathogenesis of Alzheimer's disease

anti-inflammatory capabilities since it has shown to attenuate cyclooxygenase, lipoxygenase, and phospholipase expression. A study by Shinomol and Muralishara demonstrated that *Centella asiatica* reduces endogenous oxidative markers, enhances antioxidant defenses in cytosol and other brain regions of prepubertal mice (Shinomol and Muralidhara 2008a), and has neuroprotective properties (Shinomol and Muralidhara 2008b). *Centella* inhibits phospholipase 2, thereby highlighting its significant role in anti-inflammatory activities (Defillipo et al. 2012). The two major components of arachidonic pathway are COX-2 and 15-lipoxygenase (15-LOX) enzymes. The arachidonic pathway leads to the formation of pro-inflammatory prostaglandins, leukotrienes, and other mediators, which are associated with numerous chronic neurological disorders (Hoozemans et al. 2004). *Centella asiatica* significantly inhibits the activity of Ca^{2+}-independent phospholipase A_2 ($iPLA_2$) and cytosolic phospholipase A_2 (PLA_2) in the rat brain. Drugs affecting either of the phospholipase will hinder the profound inflammatory reaction and reduce neurodegeneration (Kolko et al. 2002, Burnett et al. 2011, Fig. 1.3).

1.3.5 Study in Double Transgenic Alzheimer's Disease Mice Model

Based on the extensive scientific literature, it is clear that *Centella asiatica* has been used for memory enhancement in Ayurvedic medicine for years. In our laboratory, we had undertaken a chronic study to evaluate the neuroprotective effects of *C. asiatica* extract on amyloid pathology in the PSAPP mouse model of Alzheimer's disease (Dhanasekaran et al. 2009). PSAPP mice expressing the "Swedish" amyloid precursor protein and the M146L presenilin 1 mutations are a well-characterized model for spontaneous Aβ plaque formation. PSAPP doubly transgenic mice were obtained by crossbreeding Tg2576 mouse line with "Swedish" APP mutation (APPK670NM671L) with mutant presenilin 1 mouse line (PS- 1M146L6.2). The resultant breed was due to these two mutations that caused and elevated the production of Aβ peptide with a measureable deposition of plaques as early as 3–4 months of age (Holcomb et al. 1998, 1999; McGowan et al. 1999; Emilien et al. 2000). In a chronic therapeutic approach (8 month treatment), we had demonstrated that *C. asiatica* extracts decline the Aβ 1–40 and 1–42 levels in the hippocampus and cortex. Extracts of *C. asiatica* decreased the amyloid load due to fibrillar Aβ. Dense-core plaque formation has recently been shown to occur predominantly and is associated with the vasculature in PSAPP mice, suggesting a malfunction of the clearance of Aβ through the neurovascular system that may impact amyloid deposition (Kumar-Singh et al. 2005). It has been reported that *C. asiatica* effects in regulating the Aβ clearance or deposition as noticeable plaques are due to the alteration of extracellular matrix composition, perlecan or fibril formation subdued by other extracellular matrix molecule, laminin (Holcomb et al. 2000; Castillo et al. 2000). Asiaticoside upregulates biglycan, another heparin sulfate proteoglycan in other amyloidosis, which is also known to bind Aβ (Snow et al. 1994). *Centella asiatica* extract-based treatment thus may cause the regional alterations of extracellular

matrix molecules and influence the fibrillar amyloid load detected in PSAPP mouse brain. In Tg2576 mouse, one of the PSAPP parental lines, previous researches have concluded that there is a significant elevation in lipid peroxidation before the increase of Aβ 1–40 and 1–42 levels or noticeable amyloid deposition (Praticò et al. 2001). *Centella asiatica* blocked lipid peroxidation, which in turn infers that the basic mechanism is by inhibiting the membrane damage caused by the hydroxyl free radical, thereby reducing the oxidative stress. It can thereby be concluded that the continuous and chronic treatment with *C. asiatica* may alter the Aβ pathology in the PSAPP Alzheimer's disease mouse model. Based on our research data, it is clear that the antioxidant and anti-inflammatory properties of *C. asiatica* may prevent neurodegeneration (Table 1.4).

1.3.6 Other Neurological Disorders

3-Nitropropionic acid (3-NPA) is an irreversible complex II inhibitor of the electron transport chain and Krebs cycle in the mouse brain (Shinomol and Muralidhara 2008b). 3-NPA is a fungal neurotoxin known to induce selective striatal pathology that is encountered in Huntington's disease. It was observed that upon administration of 3-NPA, there was a significant increase in the level of ROS and malondialdehyde (MDA) indicating the oxidative stress in cytoplasmic and mitochondrial fractions of striatum and other brain regions of prepubertal mice (Binienda et al. 1998; Hussin et al. 2005). Upon treatment, it has been demonstrated that the prophylactic activity of *C. asiatica* resulted in the protection against the glutathione depletion, protein oxidation damage, and diminishing of Na^+, K^+ ATPase activity caused by 3-NPA (Shinomol and Muralidhara 2008b). The study thereby concluded that *Centella asiatica* helps in the protection of oxidative stress and mitochondrial dysfunction which is usually observed in the neurodegenerative disorders (Shinomol and Muralidhara 2008b).

Cerebral ischemia which can result in cerebral infarction or stroke is the leading cause of disability and mortality in the world (Lo et al. 2003) and can only be cured by the restoration of adequate blood flow in brain. However, the reperfusion can cause tissue damage that is well past the ischemia, via is excitotoxicity, oxidative stress, inflammation, and apoptosis (Luo et al. 2014). Madecassic acid from *Centella asiatica* is reported to reduce oxidative stress by diminishing 3,4-methylenedioxyamphetamine level, increasing glutathione and superoxide dismutase activity, and reducing COX-2 expression and production of prostaglandin E2. It also reduces the plasma levels of TNF-α and IL-6 (Won et al. 2010). Generally, oxidative stress regulates anti-inflammatory activity by triggering toll-like receptors and NF-κB. Activation of NF-κB is known to mediate inflammation and apoptosis and augment the expression of various inflammation markers (TNF-α, IL-1β, COX-2), inducible nitric oxide synthase, and additional mediators such as adhesion molecules (Tak and Firestein 2001). Madacasic acid reduces activation of NF-κB, thereby suppressing the IL-1β, IL-6, and TNF-α levels, which in turn suppresses neuronal apoptosis. Madacasic acid found in *Centella asiatica* is protected against

Table 1.4 Various studies on *Centella asiatica* to validate its efficacy

Model used	Toxin/task	Mechanism of action (MOA)	References
B103 cells	H_2O_2	Inhibition of Aβ and free radical-induced cell death	Mook-Jung et al. (1999)
	Staurosporine		
Mice	Passive avoidance task	Modulate dopamine, 5-HT and noradrenaline systems	Sakina and Dandiya (1990) and Nalini et al. (1992)
Albino rats			
Male Wistar rats	H_2O_2	Antioxidant, reduce the oxidative stress by decreasing the lipid peroxidation	Kumar and Gupta (2002)
Rat cortical neurons cells	Glutamate	Increase the levels of glutathione and glutathione peroxidase and reduced the overproduction of NO	Lee et al. (2000)
Mice	Nootropic, radial arm maze	Increase release of acetylcholine in the hippocampus	Rao et al. (2005)
		Increase dendritic arborization of hippocampal CA3 neurons	
Neonatal mice in vivo	Glutamate	Restores lipid peroxidation and glutathione content	Xu et al. (2012b)
Human neuroblastoma SH-SY5Y cells in vitro		Reinstates superoxide dismutase activity in the hippocampus and cortex	
		Regulates NMDA receptors	
		Reduced reactive oxygen species	
		Stabilizes the mitochondrial membrane potential	
		Promotes the expression of PGC-1α and Sirt1	

(continued)

Table 1.4 (continued)

Model used	Toxin/task	Mechanism of action (MOA)	References
Male Sprague-Dawley rats Human SH-SY5Y cells	Aβ	Increasephosphorylation of cyclic AMP response element-binding protein and thereby aiding the neuronal dendritic arborization and axonal regeneration	Soumyanath et al. (2005)
Neonatal Wistar rat pups	Aβ	Increase phosphorylation of cyclic AMP response element-binding protein and thereby aiding the neuronal dendritic arborization and axonal regeneration	Mohandas Rao et al. (2006)
N2a neuroblastoma cells expressing Aβ1–42 Rat embryonic cortical cells	Aβ H_2O_2	Increase phosphorylation of cyclic AMP response element-binding protein that leads to the increase in BDNF Modulates the NMDA receptor	Xu et al. (2008)
Wistar rats	$FeCl_2$	Antioxidant action Reduces lipid peroxidation and protein carbonyl production	Subathra et al. (2005)
PSAPP mice	Aβ H_2O_2	Decreases amyloid beta deposition Antioxidant effect Scavenged free radicals, reduced lipid peroxidation, and protected against DNA damage	Dhanasekaran et al. (2009)
Rat embryonic cortical cells	C2-ceramide	Inhibits caspase 3 and the dephosphorylation of ERK1/2	Zhang et al. (2012a)
Rat embryonic cortical cells	Arachidonic acid	Inhibits cytosolic phospholipase A2 and secretory phospholipases A2	Defillipo et al. (2012)

Swiss albino mice	D-galactose	Anti-apoptotic activity by effectively controlling the caspase-3 activity	Prakash and Kumar (2012)
Prepubertal male CFT-Swiss mice	3-Nitropropionic acid (3-NPA)	Antioxidant activity	Shinomol and Muralidhara (2008a)
		Enhances GSH and thiols levels	
RAW 264.7 murine macrophage cells	Lipopolysaccharide	Inhibits inducible nitric oxide, COX-2, tumor necrosis factor-alpha, interleukin-1 beta, and IL-6 via the downregulation of nuclear factor-kappaB activation which in turn suppresses neuronal apoptosis	Won et al. (2010)
Male Wistar rats	Pentylenetetrazol	Inhibits oxidative stress	Gupta et al. (2003)
		Reduce malondialdehyde levels and increase in the glutathione levels	
Adult male Wistar rats	Arachidonic acid	Inhibits the activity of Ca^{2+}-independent phospholipase A2 and cytosolic phospholipase A2	Barbosa et al. (2008)
Female Sprague-Dawley rats	Glutamate	Antioxidant effects	Ramanathan et al. (2007)
		Reduces catalase, superoxide dismutase, and lipid peroxides	
C57Bl/6 mice	Glutamate	Modulates antioxidant and mitochondrial pathways	Gray et al. (2016)
		Increased the expression of synaptic genes	
MC65	Tetracycline	Modulates antioxidant and mitochondrial pathway	Gray et al. (2015)
SH-SY5Y neuroblastoma cells			

(continued)

Table 1.4 (continued)

Model used	Toxin/task	Mechanism of action (MOA)	References
Human neuroblastoma SH-SY5Y cells	Buthionine sulfoximine (BSO)	Inhibits the activation of caspase-9 pathway	Omar et al. (2011)
Male Sprague-Dawley rats	Ischemia reperfusion injury	Reduce the levels of malondialdehyde, nitric oxide, pro-inflammatory cytokines and nuclear factor kappa-light-chain-enhancer of activated B cells	Luo et al. (2014)
Mouse NG108-15 neural cell line	Aβ25–35	Blocks the conversion of light chain3-I to light chain3-II (protects microtubule-associated proteins)	Du et al. (2014)
Human neuroblastoma cell SH-SY5Y		Reduce Beclin-1	
		Increase anti-apoptotic protein Bcl-2 level	
Adult zebra fish	Rotenone	Decreases reactive oxygen species probability of radical attack to a-synuclein protein	Khotimah et al. (2015)
		Increase dopamine level	
Rat PC12 pheochromocytoma cells	Aβ1–40	Modulates the activities of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase and alters the levels of glutathione and glutathione disulfide	Chen et al. (2015)
Human IMR32 neuroblastoma cells			
Male Wistar rats	Colchicine	Reduces AChE activity	Kumar et al. (2009)
IMR-32 human neuroblastoma cells	Aβ	Upregulates the level of activated ERK1/2 and protein kinase B (Akt)	Wanakhachornkrai et al. (2013)
Tg2576 mouse	Glutamate	Modulates the toxic effects of Aβ by inhibiting Aβ-induced nitric oxide (NO)	Soumyanath et al. (2012)
SH-SY5Y cells and MC65 human neuroblastoma cells	Aβ		

PD model *Drosophila* flies	Transgenic *Drosophila* fly lines that expresses wild-type human synuclein	Reduces lipid peroxidation, protein carbonyl, GST, and MDA content	Siddique et al. (2014)
		Increase GSH content	
Male Laca mice	D-Galactose	Upregulates NADH dehydrogenase, succinate dehydrogenase activity,	Kumar et al. (2011)
		Increased neuronal viability	
		Reduces acetylcholine esterase	
Adult Wistar rats	Silver nitrate	BDNF-like action	Mohandas Rao et al. (2012)
		Activate the expression of the early genes such as activity-regulated cytoskeleton-associated protein (arc) leading to enhancement of the dendritic arborization	
In vitro	Markers of oxidative stress	Antioxidants prevent chain initiation, binding of transition metal ion, decomposition of peroxides in addition to free radical scavenging	Sugunabai and Karpagam (2015)
Male Wistar rats	Streptozotocin	Decreases MDA and increase in glutathione and catalase levels	Kumar and Gupta (2003)
		Improves acetylcholine synthesis	
Male Sprague-Dawley rats	Behavioral cognitive	Increase doublecortin (DCX) and Notch1 protein levels in the hippocampus	Sirichoat et al. (2015)
Male ICR mice	Transient cerebral ischemia-reperfusion	Reduced the microglial overactivation and the phosphorylation of p38 mitogen-activated protein kinases	Chen et al. (2014)
Adult male Wistar rats	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	Antioxidant maintain the metabolic balance of dopamine and increasing ratio of apoptosis regulator Bcl-2/apoptosis regulator Bax	Xu et al. (2012a)

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neurotoxicity.

It is postulated that Aβ peptide increases vasoactivity in a single transgenic mouse model of Alzheimer's disease (Paris et al. 2000). *C. asiatica* is also known to exert a positive effect in the treatment of venous insufficiency (Cataldi et al. 2001), wound healing by stimulating type 1 collagen synthesis in fibroblast cells, and has been shown to help normalize the vasculature (Widgerow et al. 2000; Brinkhaus et al. 2000; Lee et al. 2006).

1.4 Conclusions

An old Sinhalese proverb righteously depicts about the therapeutic effect of *Centella asiatica,* "Two leaves (of *Centella asiatica*) a day keeps old age away." True to the above, *Centella asiatica* has shown to possess significant neuroprotective phytochemicals and nutrients. These neuroprotectants exhibit multiple pharmacological effects which can prevent cell injury, attenuate toxic insults, and protect against endogenous and exogenous lethality. *Centella asiatica* has significantly shown to protect against dermal and CNS disorders. Without any uncertainties, it is definite to conclude that *Centella asiatica* possesses significant memory-enhancing effects with very minimal adverse effects. Hence, *Centella asiatica* and its active components can be a potent botanical with memory-enhancing properties, prevent neurodegeneration, and additionally have therapeutic value in preventing cognitive impairment.

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