CHAPTER II
LITERATURE REVIEW

1. Alzheimer's Disease

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorders and the most common causes of dementia among the elderly (LaFerla and Oddo, 2005). It is a chronic neurodegenerative disease that usually starts slowly and gets worse over time (Waldemar *et al.*, 2007). It has been reported that as the age advances, the risk of this disease is also increases especially at age over 65. Neurodegeneration in Alzheimer's disease is estimated to start 20–30 years before clinical onset (Prohovnik I. *et al*, 2006).

The clinical symptoms of AD include (Alzheimer's association, 2011)

1. Memory loss that disrupts daily life
2. Challenges in planning or solving problems
3. Difficulty completing familiar tasks at home, at work, or at leisure
4. Confusion with time or place
5. Trouble understanding visual images and spatial relationships
6. New problems with words in speaking or writing
7. Misplacing things and losing the ability to relationships
8. Decreased or poor judgment
9. Withdrawal from work or social activities
10. Changes in mood and personality

Since no definite biological marker of AD is available, the clinical diagnosis of this disorder depends on inclusion and exclusion criteria that rely on clinical and laboratory information. Several biomarkers have been linked to AD, such as the cerebrospinal fluid tau, β-amyloid, urine F2-isoprostane, and brain atrophy detected by PET/MRI scan (Polikar *et al.*, 2008). It was reported that molecular hallmarks of the disease are characterized by extracellular deposition of the amyloid β peptide (Aβ) in senile plaques, the appearance of intracellular neurofibrillary tangles (NFT), cholinergic deficit, extensive neuronal loss and synaptic changes in the cerebral cortex and hippocampus and other areas of brain essential for cognitive and memory functions.

1.1 Pathogenesis of Alzheimer's disease

Numerous hypotheses have been proposed to explain the pathogenesis of Alzheimer's disease, including abnormalities in proteins regulating the cell cycle, inflammatory mechanisms, oxidative stress and mitochondrial dysfunction with disruption in neuronal energy metabolism (Aisen, 2002; Gibson and Huang, 2005; Reddy and Beal, 2005; Webber *et al.*, 2005).

Senile plaque and Alzheimer's disease

Senile plaques are composed of a central amyloid core surrounded by dystrophic neurites and glial elements (Brion *et al.*, 1991). The classic senile plaque consistsof amyloid β (Aβ) protein (Terry *et al.*, 1994). Normally, 2 forms of Aβ comprising of Aβ 40 and 42 residues are produced. It has been reported that Aβ40 is the main type of Aβ (Younkin, 1998).

A substantial evidence has demonstrated that prior to the deposition of Aβ, the mutations of the amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) genes occur giving rise to the increased production of Aβ42 residue which is less soluble leading to Aβ aggregation. The Aβ aggregation is proposed to be an important factor of neurodegeneration and brain dysfunction especially dementia.

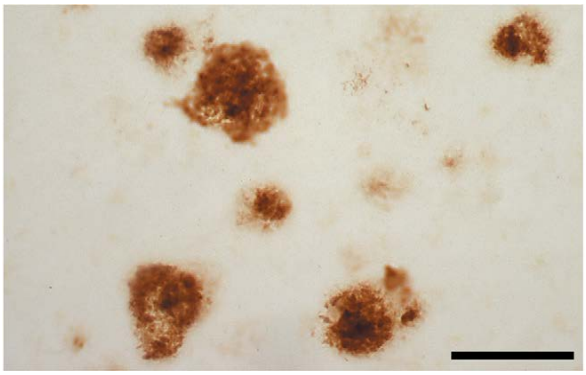


Figure 2-1 A representative microphotograph of amyloid plaques in the AD brain (LaFerla and Oddo, 2005)

Tau and Alzheimer's disease

Accumulative lines of evidence have revealed that data obtained from brain autopsy of Alzheimer's brains show the accumulation of neurofibrillary tangles. Neurofibrillary tangles, the important hallmarks of Alzheimer's disease, are the aggregation of hyperphosphorylated Tau protein, a microtubule-associated protein (Goedert *et al.*, 1988; Grundke-Iqbal *et al.*, 1986). It has been reported that this condition markedly disturbs a vital cell transport system which in turn disturbs the supplies of nutrients and other essential supplies leading to the neurodegeneration. Since, protein kinases plat the important role pn the phosphorylation of protein, the role of protein kinase on the hyperphosphorylation of tau protein has been proposed (Iqbal and del C, 2005).

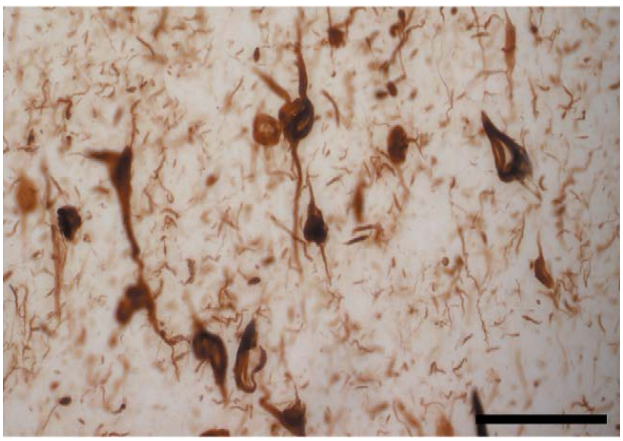


Figure 2-2 A representative microphotograph of neurofibrillary tangles (LaFerla and Oddo, 2005)

Oxidative stress and Alzheimer's disease

Excess oxidative stress which occurs as the result of the buffering capacity of antioxidant system and the formation of reactive oxygen species (ROS) (Chauhan and Chauhan, 2006) and can attack various molecules including proteins, lipids, DNA and RNA (Aksenov et al., 2001; Ding et al., 2005; Markesbery *et al*., 2005; Wang *et al*., 2006; Wang *et al*., 2005) leading to the malfunctions of cell organelles and finally results in the cell degeneration. A pile of evidence has shown

that the oxidation of the molecules such as protein and lipid, DNA and RNA play a critical role on the pathology of AD. It has been reported that the brains of Alzheimer's patients show the abnormal protein oxidation (Korolainen *et al*., 2005) and the increased lipid peroxidation products such as 4-hydroxynonenal (HNE) or 2-propenal (acrolein)(Arlt et al., 2002). In addition, ROS-mediated oxidative damage of proteins also involves in Aβ fibrillization and NFT formation in AD.

Neurotrophic factor and Alzheimer's disease

A considerable attention has been focused on the role of neurotrophins, a family of highly basic proteins including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (Barbacid, 1995) due to their crucial roles both growth, differentiation and on survival of various types of neurons including peripheral sympathetic neurons (Micera et al., 2007), sensory neurons and cholinergic forebrain neurons in the central nervous system (CNS) (Nicol and Vasko, 2007). Post-mortem studies have indicated that levels of the NGF in hippocampus and cortex of AD patients are decreased (Hock et al., 2000). Since NGF plays a pivotal role on the survival of cholinergic neuron and the proliferation of axon, the deficiency of NGF transport to cholinergic neurons might contributeto the loss of this cell population (Davis *et al*., 1992).

Cholinergic system and Alzheimer's disease

Numerous studies have demonstrated that a loss of cholinergic function in the central nervous system contributes a significant role on the pathophysiology of age-related memory impairment and AD (Bartus, 2000; Terry and Buccafusco, 2003). It has been found that the memory impairment in AD is associated with the decreased cholinergic neurotransmission, the decreased ChAT and ACh (Bartus et al., 1982; Blokland, 1995). In addition, the alteration in high-affinity choline uptake, impaired acetylcholine release, decreased nicotinic and muscarinic receptors, neurotrophin dysfunction and the impairment of axonal transport are also observed in early phase of AD as shown in figure 2-3 (Terry and Buccafusco, 2003). Based on the crucial role of cholinergic system on the memory impairment in AD, abundant of pharmacological regimen for AD therapy have focused the cholinergic system as target (Babic, 1999).

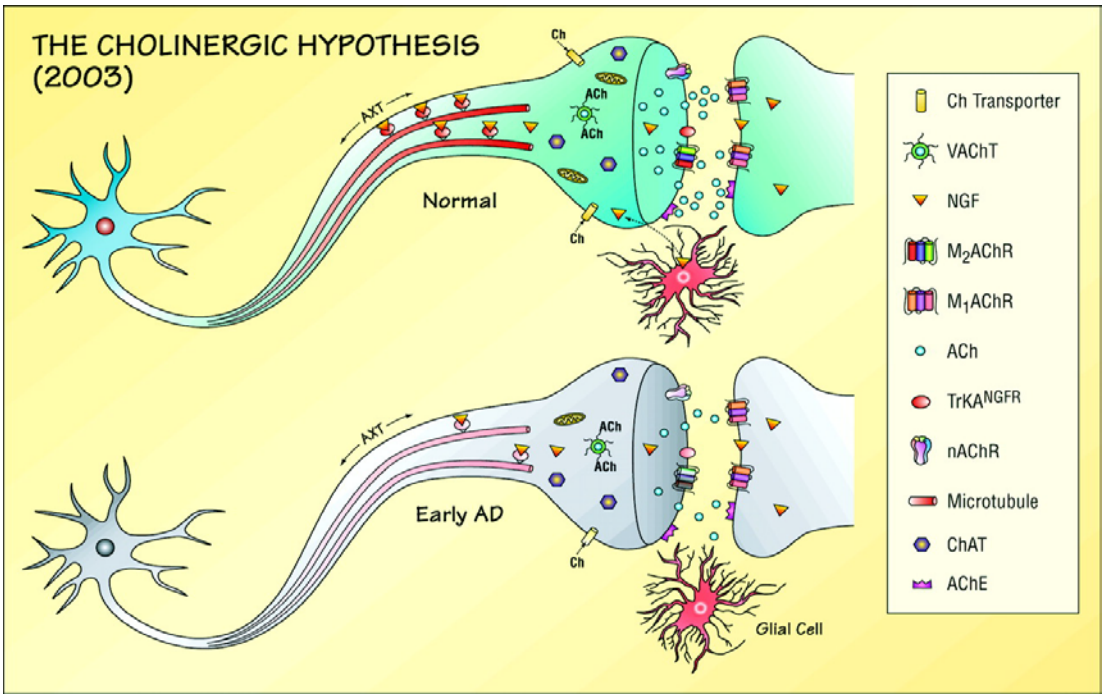


Figure 2-3 Schematic diagram illustrating the changes of cholinergic neurons in normal condition and early phase of AD (Terry and Buccafusco, 2003)

Mitochondria dysfunction and Alzheimer's disease

During the last decade, a substantial evidence has demonstrated that mitochondrial dysfunction plays an important role in the pathogenesis of many common age-related neurodegenerative diseases including Alzheimer's disease (AD) (Hauptmann *et al.*, 2006). It has been reported that the elevation of oxidative stress induced by mitochondrial dysfunction also plays a major role on neurodegeneration in AD. In AD, the mitochondria decreased the capacity to generate adenosine triphosphate (ATP) but increased reactive oxygen species (ROS). Mitochondria also lose calcium (Ca^{2+}) buffering capacity, which in turn can initiate in a cascade of deleterious within the cell. The impaired mitochondria also release several pro-apoptotic factors leading to apoptosis. These factors can directly triggers apoptosis via the formation of apoptosome. Some mitochondrial, pro-apoptotic proteins also translocate into the nucleus to induce deoxyribonucleic acid (DNA) fragmentationand neurodegeneration (Moreira *et al.*, 2010).

Calcium dysregulation and Alzheimer's disease

Calcium is involved in many facets of neuronal physiology including growth and differentiation, synaptic plasticity and learning and memory (Bezprozvanny, 2009). Disturbances in Ca^{2+} signaling have been observed in both sporadic and familial cases of AD (LaFerla, 2002). The precise understanding how the dysregulation of calcium homeostasis occur in aging is still not clearly understood. However, it has been shown that the age-related calcium homeostasis dysregulation is directly correlated with the enhanced activity of calpain, a calcium-dependent cysteine protease contributing a role on the regulation of intracellular signaling pathways and calpain-dependent apoptotic neuronal cell death (Hajieva *et al*., 2009). It has been reported that the elevation of calpain activity can modulate the function and metabolism of amyloid precursor protein (APP) and tau leading to neurodegeneration especially in hippocampus and cerebral cortex of Alzheimer patients (Lebart and Benyamin, 2006). In addition, calcium-dependent signaling pathways play essential role in hippocampal synaptic function and plasticity. The changes in neuronal calcium dynamics lead to the augmented susceptibility to an induction of long-term depression (LTD) and an increase in the threshold frequency for induction of LTP in aged neurons (Foster, 2007).

1.2 Chemical animal model in Alzheimer's disease

There is no single animal model can mimic all changes including the cognitive impairment, behavioral, biochemical, and histopathological abnormalities observed in patients with AD. However, the inductions of some changes in AD such as the neuropathological changes and cognitive deficit have been achieved with pharmacological and genetic approaches (Yamada and Nabeshima, 2000).

1) Amyloid β-peptide-related animal models

Accumulation of aggregated β-amyloid protein (Aβ) in the brain has been proposed to be one of the causal events inducing AD (Hardy and Selkoe, 2002). Therefore, the induction of amyloidogenic cascade phenomenon and related amyloid peptide pathological pathways have been developed as one model of AD. According to this model, amyloid peptide was injected in to the brain of the animal (Lecanu and Papadopoulos, 2013). Aβ1-40 (Malin *et al*., 2001; Stephan *et al*., 2001) and Aβ1-42 (Lecanu *et al*., 2005; Nakamura *et al*., 2001) are the most commonly

used either by intracerebroventricular infusion or by intrahippocampal injection. However, the weak point of this model is that the development of neurotoxic effects of Aβ is still controversial (Yamada and Nabeshima, 2000).

2) Cholinergic dysfunction-related animal models

Since degeneration of the basal forebrain cholinergic neurons occurs early in the course of AD and is correlated with cognitive deficits (Coyle *et al*., 1983; Winkler *et al*., 1998), cholinergic lesion paradigms have been used to study the role of the cholinergic system in cognitive function.

AF64A (ethylcholine aziridinium)

The neurotoxin AF64A (ethylcholine aziridinium), an irreversible inhibitor of sodium-dependent high affinity choline transport (HAChT) causes a pronounced reduction in hippocampal cholinergic markers similar to those reported in senile dementia of the Alzheimer type (SDAT). These changes include reductions in ACh content, synthesis, and release. It also decreases HAChT, ChAT and AChE activities following AF64A treatment (Fisher *et al.*, 1982; Leventer *et al.*, 1985; Mantione *et al.*, 1981). AF64A is structurally similar to choline as shown in figure 4. However, it also contains a cytotoxic aziridinium moiety which produces an irreversible inhibition of HAChT, the rate-limiting step in ACh synthesis (Freeman and Jenden, 1976).

Behavioral studies have shown that AF64A treatment impaired the performance in learning and memory tasks such as passive avoidance and radial maze trials with a corresponding reduction in ACh content in the hippocampus (Mouton *et al.*, 1988). These deficits can be alleviated by the treatment with cholinergic drugs such as arecoline and physostigmine (Yamazaki *et al.*, 1991).

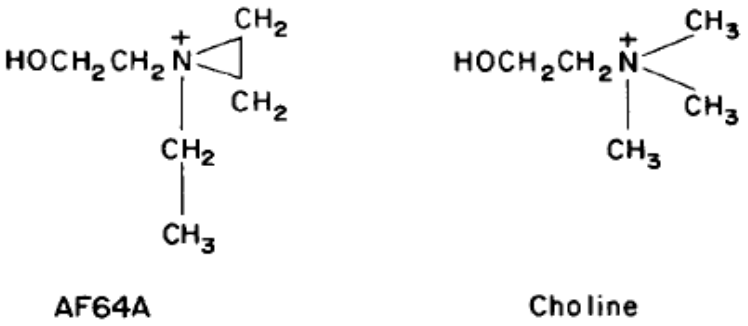


Figure 2-4 Chemical structures of AF64A (ethylcholine mustard aziridinium ion) and choline (Walsh *et al.*, 1984)

Scopolamine

Scopolamine, a competitive inhibitor of muscarinic acetylcholine, is often used both for prophylaxis and for treatment of motion sickness (Rozzini *et al.*, 1988). This compound has been shown to produce a reversible and well-described impairment in the attention and processing of information and in the ability to recall new knowledge in both rodents (Bejar *et al.*, 1999; Zhang and O'Donnell, 2000) and human (Jones *et al.*, 1991). Reversal of the scopolamine effect may be used to examine the cognition-enhancing potential of a compound. It was reported to block the muscarinic cholinergic receptors, which are involved in learning and memory. The inhibition of cholinergic function via muscarinic receptor induced by scopolamine can produce amnesic condition which is similar to memory impairment observed in Alzheimer's disease. Therefore, it has been used as one of the tools to develop animal model of Alzheimer's disease (Ebert and Kirch, 1998).

2. Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and primarily considered as a movement disorder defined by the presence of motor symptoms, such as bradykinesia, tremor, rigidity and postural instability (Alves *et al.*, 2008). Besides motor features, patients attacked by Parkinson's disease also show other neurological symptoms which cause a considerable burden to the patient such as dementia, depression and anxiety.

2.1 Pathogenesis

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder associated with a selective loss of the dopaminergic neurons in the substantia nigra pars compacta and the degeneration of projecting nerve fibers in the striatum. Numerous hypotheses have been proposed to explain the pathogenesis of Parkinson's disease including oxidative stress, mitochondrial dysfunction, protein aggregation, Ubiquitin–proteasome system (UPS) dysfunction, and abnormal gene regulation.

Oxidative stress and Parkinson's disease

Oxidative stress which occurs as a result of the imbalance between reactive oxygen species (ROS) formation and buffering capacity of antioxidant system has been reported to play a major role in the pathogenesis of Parkinson's disease (PD). Recently, postmortem study demonstrated that ROS and reactive nitrogen species (RNS) are involved in the degeneration of dopaminergic neurons (Danielson and Andersen, 2008). Dopamine, a neurotransmitter of dopaminergic pathway, is metabolized to hydrogen peroxide (H_2O_2) which in turn converted to hydroxyl radicals (OH) (Graham *et al*., 1978; Maker *et al*., 1981). Then, these molecules can attack and induce damage to various biomolecules. In addition, glutathione levels especially in substantia nigra and midbrain of Parkinson patient are decreased whereas the level of lipid peroxidation and protein oxidation are increased (Perry, 1982; *Sian et al*., 1994). The changes of oxidative damage markers in the substantia nigra mentioned earlier are observed at the very early stage of preclinical PD (Dalf *et al*., 2005).

Mitochondria dysfunction and Parkinson's disease

The elevation of oxidative stress induced by mitochondrial dysfunction has been proposed to play the critical role on the pathogenesis of PD. The elevation of oxidative stress until beyond the cellular buffering capacity can give rise to the attack of various organelles which in turn leads to the neurodegeneration. In addition, the oxidative stress also induces the peroxidation of the mitochondria-specific lipid cardiolipin results in release of cytochrome c to the cytosoland triggers apoptosis. In addition to the increased oxidative stress formation, the mitochondrial Complex I dysfunction in the electron transport chain can also increase the leakage of electrons leading to the increased ROS generation (Hwang, 2013). Since dopaminergic neurons

are intrinsically high capability in ROS-generating, they are vulnerable to the degeneration induced by oxidative stress.

Protein aggregation

Based on the findings of α-synuclein in Lewy bodies of PD's brain, the possible role of protein aggregation as key factor playing an important role on the pathophysiology of PD had been suggested. Although the precise role of α-synuclein is unclearly known, it has been proposed that the aggregation of this substance may possibly exert its toxic action by creating pores in lipid membranes leading to the leakage of dopamine from vesicles into cytoplasm (Sherer *et al.*, 2003; Volles and Lansbury, 2002). However, it is also reported that the aggregation of α-synuclein fail to show positive correlation with neuronal loss (Bianco *et al.*, 2002). Thus the precise mechanism underlying the neurodegeneration induced by α-synuclein aggregation is still required further investigation.

Ubiquitin–proteasome system (UPS) dysfunction

The UPS is a major pathway mediating the degradation of abnormal cellular proteins (McNaught *et al.*, 2001). Several studies have proposed that its dysfunction may serve as a key factor in the pathogenesis of PD and LB formation (Olanow and McNaught, 2006) due to an impairment of the capacity of the UPS to handle an overwhelming quantity of altered proteins.Under normal condition proteins destined for proteasomal degradation are tagged with a chain of ubiquitin (Ub) proteins via multiple rounds of a linear reaction catalyzed by ubiquitin activating (E1), conjugating (E2) and ligating enzymes (E3). These reactions are driven by ATP. In addition, α-synuclein also promotes disruption of the UPS and conceivably results in the accumulation of protein aggregates or abnormal protein intermediates that can directly produce a detrimental effect to neuronal survival. An attempt by the cell to sequester these abnormal proteins gave rise to the formation of Lewy bodies (Hegde, 2004; Ross and Pickart, 2004).

Abnormal gene regulation

Gene expression and quantitative proteomics have allowed the identification of genes and proteins differentially expressed in the brain of PD and related animal models (Xun *et al.*, 2008; Yacoubian *et al.*, 2008). Focusing on the substantia nigra and striatum, several genes are up-regulated and others down-

regulated in PD (Miller *et al.*, 2006). In addition, genetic studies led to the discovery of a small percentage of familial PD cases linked directly to genetic mutations, as well as gene duplications and triplications (Klein and Schlossmacher, 2007). In PD, susceptibility genes are involved with protein phosphorylation and degradation, mitochondrial function and oxidative stress such as parkin, ubiquitin carboxy-terminalhydrolase-L1, PINK1, DJ-1 and LRRK2 (dardarin) (Benbunan *et al.*, 2004). It has been reported that Parkin has been shown to play a role in protein degradation as a ubiquitinprotein ligase (Shimura *et al.*, 2000). These finding suggests that abnormal accumulation of proteins or abnormal regulation of the half-life of normal cellular proteins may play a role in cell death.

2.2 Dementia in Parkinson's disease

Dementia is a very common non-motor feature in PD. There is a high variation in reported prevalence rates of Parkinson's disease with dementia (PD-D) ranging from 20–80%. It has been estimated that approximate 30% of PD patients develop dementia (Aarsland *et al.*, 2005). In addition, it is also reported that PD is associated with a six - fold higher risk of developing dementia when compared to healthy elderly controls (Emre, 2003). The cognitive deficit in PD patients are including decrements in planning, sequencing, concept formation and working memory.

2.3 Animal model in Parkinson's disease

The most frequently used toxins in rodent models of PD is either the neurotoxin 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), or 6-hydroxydopamine (6-OHDA) (Cannon and Greenamyre, 2011; Dauer and Przedborski, 2003). Both neurotoxins selectively and rapidly destroy dopaminergic neuronswhereas the progression of PD in human is very slow(Schober, 2004). Although MPTP is a valuable model of PDin mice and non-human primates, it is limited for several reasons: MPTP injection causes a bilateral Parkinson syndrome, thereby ruling out all behavioral tests based on a side bias. Cell loss is strain-dependent, age-dependent and gender-dependent in mice (Sundstrom *et al.*, 1990). Moreover, a spontaneous recovery of Parkinsonian symptoms has been described in both, monkeys (Taylor *et al.*, 1997) and mice (Sedelis *et al.*, 2001) after MPTP administration.

Therefore, it is not convenient to use this model for an assessment of long-term intervention. Due to the limitation of MPTP model, this study used 6-hydroxy-dopamine (6-OHDA) model as experimental PD model.

6-OHDA

6-Hydroxydopamine (6-OHDA) is a hydroxylated analogue of the natural neurotransmitter dopamine (Blum *et al.*, 2001). Rats with substantia nigra, compact part (SNc) lesion induced by intracerebral administration of 6-hydroxydopamine (6-OHDA) have been successfully used to study the physiology of nigrostriatal pathway disruption (Schwarting and Huston, 1996). It has been reported that 6-OHDA induced neuron degeneration via the generation of hydrogen peroxidase and hydroxyl radicals in the presence of iron (Sachs and Jonsson, 1975). 6-OHDA is easily oxidized and can also take part in free radical forming reactions, like the metabolic monoamine oxidation. Finally, 6-OHDA is not only a respiratory toxin, it also acts as clastogen and mutagen (Gee *et al.*, 1992; Glinka *et al.*, 1997). The advantage of 6-OHDA animal model is easy to assess the motor impairments by utilizing tests that examine for a side bias, e.g. drug-induced rotation tests (Ungerstedt and Arbuthnott, 1970) and spontaneous motor tests. Furthermore, intracerebral injection of 6-OHDA into the rat nigrostriatal pathway has been shown to produce the permanent degeneration of all dopaminergic neurons in the SN pars compacta (Jeon *et al.*, 1995) ending to stable motor deficits over time.

3. Acupuncture and Meridian System

According to Traditional Chinese Medicine (TCM), it is believed that there is a distribution network for the fundamental substance of Qi throughout the body. This distribution network called the meridian system (Povolny, 2008). It has been reported that the stimulation of acupoint along various meridians can improve the imbalance in the flow of Qi. There are 14 main meridians and eight extra meridians(World Health Organization, 1991). Accumulative lines of evidence have shown that the acupoints along the meridians have low skin surface electrical resistance or high conductance. It is believed that high skin conductance may be associated with the high density of gap junctions (Ahn *et al.*, 2008; Bergsmann and Woolley-Hart, 1973; Jingyu *et al.*, 1990).

Previously, the stimulation of acupoint had been performed by piercing the needle in to the skin. To date, the stimulation of acupoint can be performed by various means including the high pressure such as in acupressure and by either tiny amount of herb or by laser beam.

4. Laser Acupuncture

Laser acupuncture is the application of photobiostimulation, instead of needle stimulation, at an acupoint. It has been demonstrated that laser acupuncture is a non-infectious and easy to use technique. It can avoid the pain and psychological fear associated with needle acupuncture.

Several biological parameters such as wavelength, output power, power density, continuous or pulsed laser, energy density and wavelength should be considered for the application of laser acupoint. It has been shown that laser beams at various wavelengths show the different penetration capability as shown in figure 2-5. Among various visible wave length, the red laser light shows the deepest penetration (Litscher and Schikora, 2005).

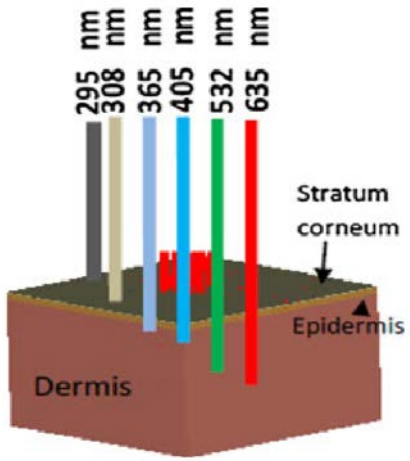


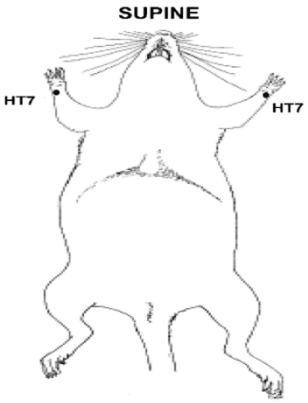
Figure 2-5 The schematic diagram illustrating the penetration capability through the skin of the laser beams at various wavelengths (Mustafa and Jaafar, 2013)

Although the violet laser shows less ability to penetrate through skin, it has been demonstrated to successfully produce an increased brain circulation (Anderson and Parrish, 1981; Esnouf *et al.*, 2006; Litscher *et al.*, 2010; Litscher *et al.*, 2013). In addition, violet laser (405 nm, 110 mW, 500 μm) also elicit the feeling of De Qi or a feeling as an electrical current running along the treated meridians (Litscher *et al.*, 2010). Violet laser beam is associated with the photochemical rather than thermal effects because low irradiation levels are used and no appreciable temperature rise takes place. It has been believed that photochemical energy can interacts with chromophores (organic molecules) which in turn modulate cellular activities (Beckerman *et al.*, 1992; Kitchen and Partridge, 1991).

5. HT7 Acupuncture point

Numerous acupoints have been stimulated to improve various neurological disorders. Among various acupoints, HT7 or shenmen is scientifically shown to improve the cognitive function (Lee *et al.*, 2011). It has been reported that HT7, an acupoint located at the ulnar end of the transverse crease of the writs, in the depression on the radial side of the tendon muscle flexor carpi ulnaris, has been long-term used for treating many neuropsychological impairments such as amnesia, insomnia, mania, epilepsy, stupor. In addition, it also regulates the physical response to emotional stimuli such as anxiety, fear and panic (Hecker and Steveling, 2011; MacPherson, 2007). Schematic localization of HT7 acupuncture point was shown in table 2-1.

Table 2-1 Schematic localization of HT7 acupuncture point

Anatomical position	Points	Location
	HT7	Ulnar end of the transverse crease of the writs, in the depression on the radial side of the tendon muscle flexor carpiulnaris

6. Herbal medicines

At present, herbal medicines (HMs) has gained much attention in global healthcare based on their great medicinal and economic importance. According to the World Health Organization, about 80% of world's population relies on HMs for some aspect of their primary healthcare (Tilburt and Kaptchuk, 2008). It has been reported that traditional medicine is used widely throughout Thailand. Numerous Thai medicinal plants have provided the foundation for modern pharmaceuticals and drug leads (Farnsworth and Bunyapraphatsara, 1992). Herbs can be used either by single herb or polyherbal recipes. However, the polyherbal recipes have been very much widely used than the single plant based on the concept that the synergistic effect of the plants can provide more beneficial effects (Jayakumar, 2010). *Anethum graveolens* Linn, *Anacardium occidentale* Linn, *Moringa oleifera* Lam, *Zingiber officinale* Roscoe and *Cyperus rotundus* Linn are widely used as food and as medicine in the Northeast Thailand. These plants possess numerous benefits and the prices are not expensive so it is of interesting to investigate the potential health benefits to protect against neurodegenerative disease.

6.1 *Anethum graveolens* Linn.

Figure 2-6 *Anethum graveolens* Linn.

Anethum graveolens Linn. or Dill is a plant in a family of Apiaceae (Umbelliferae). It has been reported that aerial part of *A. graveolens* exhibits a remarkable antioxidant activity (Delaquis *et al.*, 2002; Elzaawely *et al.*, 2007; Mohammad, 2004). It contains flavonoids, phenolic compounds, courmarins, xanthones and triterpenes (Kaur and Arora, 2009). *A. graveolens* possesses many pharmacological effects such as antimicrobial, antihyperlipidemic, anticancer and antioxidant activities (Kaur and Arora, 2009; Singh *et al.*, 2005). In addition, *A. graveolens* also exhibits anti-stress, antioxidant and memory enhancing activities in scopolamine induced amnesic rats (Koppula and Choi, 2011).

6.2 *Anacardium occidentale* Linn.

Figure 2-7 *Anacardium occidentale* Linn.

Anacardium occidentale Linn. or cashew tree is a plant in a family of Anacardiaceae. It has been reported that the leaves of *A. occidentale* contain various flavonoids, mainly quercetin glycosides. Traditionally, *A. occidentale* leaves have been used to treat rheumatic disorders, mouth ulcers, washing wounds and in dyspepsia and hypertension (Andarwulan *et al.*, 2012; Konan and Bacchi, 2007). The leaves are also used in Brazil for eczema, psoriasis, scrofula, dyspepsia, genital problems, and venereal diseases, as well as for impotence, bronchitis, cough, intestinal colic, leishmaniasis, and syphilis-related skin disorders (Doss and Thangavel, 2011). Recently, two studies have reported the antioxidant activities of the leaves of *A. occidentale* (Abas *et al.*, 2006; Roach *et al.*, 2003).

6.3 *Moringa oleifera* Lam.

Figure 2-8 *Moringa oleifera* Lam.

Moringa oleifera Lam. or horseradish or drumstick tree, a plant in a family of Moringaceae has been claimed as wonder tree in Thailand (Chumark *et al.*, 2008). *Moringa oleifera* leaves contain nutrients especially essential amino acids, vitamins, minerals and β-carotene (Sabale *et al.*, 2008; Sharma *et al.*, 2012). Moreover, it also possesses antiulcer, antimicrobial, anti-inflammatory, antitumor and antioxidant activities (Mishra *et al.*, 2011; Siddhuraju and Becker, 2003). In addition, it has been found that *ethanolic extract of M.oleifera leaves* can attenuate memory impairment, decreases oxidative stress and inhibits the alteration of monoamine oxidase (Ganguly and Guha, 2008; Prabsattroo *et al.*, 2015). Recent study also shows that *M.oleifera* leaves attenuate learning and memory and oxidative damage in focal cerebral ischemia (Kirisattayakul *et al.*, 2012).

6.4 *Cyperus rotundus* Linn.

Figure 2-9 *Cyperus rotundus* Linn.

Cyperus rotundus Linn. or nut grass is a plant in the family of Cyperaceae. It contains oils, alkaloids, glycosides, saponins, flavonoids, tannins, starch and carbohydrates (Raut and Gaikwad, 2006). *C. rotundus* is used for the treatment of spasms, stomach disorder and anti-inflammatory diseases (Gupta *et al.*, 1971; Seo *et al.*, 2001). Recent study has suggested that aerial part of *C. rotundus* showed the presence of antioxidant, antimicrobial and antigenotoxic activities (Kilani-Jaziri *et al.*, 2011). In addition, it appears that aerial part of *C. rotundus* exhibit a potential use as a natural antioxidant and an apoptosis activities (Soumaya *et al.*, 2014).

6.5 *Zingiber officinale* Roscoe.

Figure 2-10 *Zingiber officinale* Roscoe

Zingiber officinale Roscoe or ginger, a plant in a family of Zingiberaceae, is commonly used as a spice, dietary supplement and medicine. The root extracts contain compounds (6-gingerol and its derivatives), which have a high antioxidant activity (Yeh *et al.*, 2014). It also possesses anti-inflammatory activity (Chrubasik *et al.*, 2005), blood circulation (Murata *et al.*, 2002), antioxidant (Al Amin *et al.*, 2006; Krishnakantha and Lokesh, 1993) and anti-motion sickness (Chrubasik *et al.*, 2005). In the animal models, *Z. officinale* extract can improve memory deficit in an animal model of ischemic stroke and can inhibit acetylcholinesteres activity (Oboh *et al.*, 2012; Wattanathorn *et al.*, 2010).