REVIEW OF LITERATURE

The generation and cell death of newly generated cells have critical roles in brain development and maintenance in the embryonic and adult brain, and alterations in these processes are seen in neurodegenerative diseases. It is a hereditary and a sporadic condition which are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of affected central or peripheral structures of the nervous system. They include diseases such as Alzheimer’s disease (AD), Epilepsy, Parkinson’s disease, Multiple sclerosis, Amyotrophic Lateral Sclerosis, Huntington’s disease and Prion disease.

Historical perspective of Parkinson’s disease (PD)

Parkinson’s disease (PD) is a late onset, progressive neurodegenerative disorder characterized by selective degeneration of nigrostriatal dopaminergic neurons in A9 substantia nigra pars compacta (SNpc) region. Parkinsonian syndrome has four cardinal clinical features consisting of tremor, rigidity, bradykinesia and characteristic disturbance of gait and posture. The disease syndrome was first described in detail in a monograph “An essay on the Shaking Palsy” by a London physician, Dr James Parkinson in 1817 (Langston, 2002; Parkinson, 2002). Dr. Parkinson described it as “involuntary tremulous motion with lessened muscular power, in parts not in action and even supported with propensity to bend the trunk forward and to pass from walking to a running pace; the senses and intellect being unimpaired”. In 1892, a French neurologist Dr. Charcot suggested that “paralysis agitans or shaking palsy” is not the appropriate term to define this disorder in which “muscular strength was well maintained until the late stage and shaking was not considered wholly appropriate, as disease may manifest in severe form without tremor”.

The neuronal circuitry involved in coordinated movement is complex; the disabling symptoms of Parkinson’s disease are predominantly due to the demise of dopaminergic neurons in the substantia nigra pars compacta (SNpc) (Forno et al., 1993).

The cause of Parkinson’s disease was the loss of pigment from SN, which is normally colored due to the presence of neuromelanin. Later the pathology of idiopathic Parkinson’s disease was found to be due to progressive loss of neurons from SNpc region, which contains the neurotransmitter, dopamine (3, 4-dihydroxyphenylethylamine or 3,13 hydroxytyramine, DA). Since these neurons project their axons to the striatum and utilize dopamine as their neurotransmitter (Dahlstroem and Fuxe, 1964), a profound reduction in striatal dopamine represents the primary neurochemical alteration in PD. In addition to dopamine, there is a loss of dopamine metabolites homovanillic acid and 3, 4-dihydroxyphenylacetate and an increase in dopamine receptor sites (Hornykiewicz, 1966; Bernheimer et al., 1973; Lee et al., 1978). The symptoms usually begin when 80% of dopamine in the brain has been lost. The level of dopamine will continue to fall over time worsening the symptoms. Since these neurons project their axons to the striatum and utilize dopamine as their neurotransmitter (Dahlstroem and Fuxe, 1964), a profound reduction in striatal dopamine represents the primary neurochemical alteration in PD.

**Etiology of PD**

Despite extensive research on brain of PD patients or experimental animal models, etiology of PD and mechanism for selective neuronal loss have not yet been fully understood.
PATHOGENESIS OF PD

PD is the second most common progressive neurological disorder with a prevalence of 0.1 to 0.2 percent (Shastry et al., 2001). However, after the age of 50, incidence raises up to 1-2 per cent. It is a multi-factorial disease and contributed by a combination of age, genetic and environmental factors (Veldman et al., 1998). Herbicide/pesticide exposure (Petrovitch et al., 2002, Wesseling et al., 2001). The other contributing factors include higher intake of dietary fats, genetic predisposition, free radicals, accelerated aging, male gender (Behari et al., 2001). Conservative pre-Parkinson's personality and family history. Different hypotheses have been postulated to explain the pathophysiology of Parkinson’s disease.

Environmental factors

The late onset and slow-progressing nature of PD has prompted that environmental exposure to pesticides as a risk factor. Epidemiological, case control studies have implicated pesticide exposure as a potential risk factor for PD (Gorell et al., 1998). Also several neurotoxicants induce PD, such as N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), paraquat (PQ), dieldrin, manganese (Mn), and salsolinol (Chun et al., 2001). Environmental toxins lead to the impairment in mitochondrial function in the nerve cells. They affect structure of several genes and increase susceptibility of disease (Allan et al., 1987). Excessive degeneration of dopaminergic system might be the outcome of extended insults by environmental or endogenous neurotoxins in individuals, genetically susceptible to PD. Toxic effects, resulting from excess oxygen damage, combined with exposure to pesticides such as rotenone could act synergistically to cause PD (Sherer et al., 2002).
**Oxidative stress**

Genome and proteome-based studies also revealed that oxidative stress played a role in onset and progression of sporadic or chemically-induced PD. The vulnerability of dopaminergic neurons in substantia nigra (SN) of PD patients was correlated with the presence of neuromelanin (NM) that act as an endogenous iron-binding molecule in dopaminergic neurons of the SN in human brain (Adams et al., 2001). Interaction between NM and iron leads to an increase in indices of oxidative stress in PD (Double et al., 2003). Increased iron level was implicated in induction of cytotoxicity through excessive accumulation of hydroxyl radical in PD (Double et al., 2000). Significant inverse correlation was found between amount of superoxide radicals and specific activities of mitochondrial enzymes in PD, mitochondrial function was significantly affected in both males and females (Zhang et al., 2003). Oxidants remarkably induce sequential molecular events such as augmentation in ROS level, activation of JNK MAP kinases, PITSLRE kinase, p110 etc., by both caspase-1 and 3-like activities and apoptotic cell death. Pharmacological intervention using combination of antioxidant trolox and a pan-caspase inhibitor Boc (Asp)-fmk (BAF) exerted significant neuroprotection against ROS-induced dopaminergic cell death (Chun et al., 2001).

**Mitochondrial dysfunction**

The imbalance in the mitochondrial homeostasis will affect the cell physiological processes. It has been reported that mitochondrial complex-I (NADH:ubiquinone oxidoreductase) is inhibited in SNpc of Parkinson’s disease patients (Mizuno et al., 1989; Schapira, 1993). Other studies have reported a reduced complex-I activity in the platelets (Bindoff et al., 1989; Parker et al., 1989) and in skeletal muscle (Blin et al., 1994) in PD patients. There are reports suggesting that in Parkinson’s disease patients there has been selective loss of GSH in SN. GSH
depletion potentiates oxidant-induced loss of mitochondrial functions, oxidative stress and there is oxidative damage to DNA, lipids, and protein (Dexter et al., 1989).

**Heavy metals**

Heavy metals help in catalyzing free radical reactions that destroy DA-producing cells and, therefore, implicated as causative agent in onset and progression of PD (Yantiri et al., 1999). Persons who were exposed to high environmental levels of Mn, such as miners, welders and those living near ferro-alloy processing plants display a syndrome known as manganism, best characterized by debilitating symptoms, resembling PD (Roth et al., 2003). Mn decreases monoamine oxidase (MAO) activity and inhibits the respiratory chain that accumulates in mitochondria and inhibits efflux of calcium (Zhang et al., 2003). Iron is implicated in neuronal damage associated with PD due to DA and motor disturbances (Kaur et al., 2002). Population exposed to aluminium contamination in the drinking water also has a high risk of developing PD (Gorell et al., 1999).

**Apoptosis**

Apoptosis refers to the death of a cell resulting from a normal series of genetically programmed events, when a cell is no longer needed. It is characterised by a number of distinct morphological alterations, such as chromatin condensation and marginalisation, cell shrinkage and plasma membrane blebbing, which are accompanied by biochemical features such as DNA fragmentation, membrane alterations (that is, exposure of phosphatidylserine on the outside of the plasma membrane), and degradation of specific cellular proteins, as a result of the massive activation of a large number of intracellular proteases and endonucleases. In the latest stages, the dying cell is fragmented into membrane bound vesicles containing relatively intact organelles and chromatin residues named “apoptotic bodies”
(Wyllie et al., 1980). In neuronal cell apoptosis, the family of Bax/Bcl-2, interleukin 1β converting enzyme (ICE) and caspases have attained more attention. Increased expression of Bax or caspases promotes apoptosis, whereas increased expression of Bcl-2 or Bcl-xL, promotes survival. It has been shown that c-jun is expressed only in the early stages of neuronal apoptosis. Antisense oligonucleotides that block the translation of c-jun mRNA and over expression of a negative c-jun mutant reduced apoptosis, and facilitated neuronal survival (Schlingensiepen et al., 1994). In contrast, over expression of c-jun increases apoptosis (Ham et al., 1995). There are reports that suggest p53 gene knock-out transgenic mice are resistant to MPTP neurotoxicity (Trimmer et al., 1996) and Bcl-2 over expression protected catecholaminergic cells against MPTP neurotoxicity (Yang et al., 1998).

**Genetic basis**

Parkinson’s diseases can be caused by rare familial genetic mutations, but in most cases it is likely to result from an interaction between multiple genetic and environmental risk factor (Schulte et al.). There are four genes associated to Parkinson’s disease, and many other genes or genetic linkages have been identified to the cause of PD. The first “Parkinson’s disease gene”, PARK1, was identified as mutant forms of the gene encoding the presynaptic protein α-synuclein. The second Parkinson’s disease gene, PARK2, is characterized by mutations in the gene for parkin. Deletion and point mutations in the parkin gene have been described in a number of Japanese families with an early onset, Lewy body–negative parkinsonism and autosomal recessive inheritance, and it leads to autosomal recessive juvenile parkinsonism (AR-JP) (Kitada et al., 1998). The third Parkinson’s disease gene, PARK7, results from mutations in DJ-1 (Bonifati et al., 2003). Mutations in α-synuclein, parkin, and DJ-1 definitely cause Parkinson’s disease. The fourth PD gene
is park5, a mutation (PARK5) in the gene encoding ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) in two family members of a small German kindred with autosomal dominant PD has been described (Polymeropoulos et al., 1997). Among the selected genes, the downexpression of TUBA6 and TUBA3 genes in PD was also detected by its protein level using Immunohistochemistry, although a decrease in each protein was specifically not detected. These results indicate that the downregulation of TUBA6 and TUBA3 genes couples transcription to translation. In addition, genes related to cell death were identified from some of the selected target genes. In particular, MBP, PBP, GNAS and PAQR6, which are upregulated in PD, were shown to have activity with accelerating cell death. Among them, it was reported that PBP, also known as RKIP, may represent a novel effector of signal transduction pathway leading to apoptosis (Chatterjee et al., 2004).

**Excitotoxicity**

a. One mechanism of excitotoxicity involves in the increased glutamate formation. SNpc dopaminergic neurons are rich in glutamate receptors that receive extensive glutamate from the cortex and the STN, and demonstrate a pattern of burst firing in response to exogenously administered glutamate (Johnson et al., 1992). Glutamatergic cortical input also exists in NCP. Glutamatergic pathways project from basal ganglia to thalamus and back to cortex. There are three types of glutamatergic receptors - (i) NMDA, (ii) α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and (iii) kainate. The excitatory amino acids become more cytotoxic if released in excess, or if the mechanism of inactivation is impaired.

b. The other excitotoxic mechanism is due to a reduction in energy metabolism due to a defect in mitochondrial function, resulting in loss of the ATP-dependent Mg-blockade of NMDA receptors, causing physiological concentrations of
glutamate to mediate a calcium influx into the cell. Excitotoxic damage is also mediated at least in part, via \( \cdot \)NO. A glutamate-mediated rise in cytosolic calcium results in activation of nitric oxide synthase (NOS) with increased \( \cdot \)NO production. \( \cdot \)NO reacts with superoxide radical to form peroxynitrite and hydroxyl radical, both powerful oxidizing agents (Dawson et al., 1991).

**EXPERIMENTAL ANIMAL MODELS OF PARKINSON’S DISEASE**

Animal models of PD are used to examine the early phases of neurodegeneration and proteomic approaches have been able to shed important light on the pathways involved. The model should reproduce the progressive, selective nigrostriatal dopaminergic neurodegeneration and recapitulate most of the features of Parkinson’s disease with preferential loss of dopaminergic neurons within the SNpc, leading to motor dysfunction. In addition to the loss of nigrostriatal dopamine neurons, a key determinant that differentiates this disorder from other neurodegenerative diseases is the Lewy bodies inclusion formation. Genetic models utilizing known mutations found in familial PD cases have also been utilized to establish how such mutant proteins affect mitochondrial and ultimately cell function. Mutation in three different gene, including \( \alpha \) – synuclein, have been associated with familial Parkinson’s disease (Polymeropoulos et al., 1997). This model system focused on the use of transgenic mice or drosophila, which express the wild type or mutate \( \alpha \) – synuclein. Transgenic mice over expressing human \( \alpha \) – synuclein demonstrated a number of features of Parkinson’s disease, including loss of nigrostriatal dopaminergic nerve terminal in striatum, development of \( \alpha \) – synuclein and ubiquilitin-positive cytoplasmic inclusion, and motor impairment (Masliah et al., 2000).
6-Hydroxydopamine (6-OHDA) model

6-Hydroxydopamine is a neurotoxin commonly used to lesion dopaminergic pathways and generate experimental models for Parkinson disease, however, the cellular mechanism of 6-hydroxydopamine-induced neurodegeneration is not well defined it is traditionally thought that 6-OHDA enters neurons via dopamine transporters (DAT) (Ljungdahl et al.,).

6-Hydroxydopamine was the first chemical agent discovered that has specific neurotoxic effect on catecholaminergic pathways (Ungerstedt, 1971; Sachs and Jonsson, 1975). It is a hydroxylated analogue of dopamine and thus uses the same catecholamine transport system. This produces specific degeneration of catecholaminergic neurons. Systemically administrated 6-OHDA is unable to cross the blood–brain barrier. Stereotaxically, 6-OHDA injected into SNpc or the ascending medial fore brain (MFB) or the striatum for the specific target to nigrostriatal dopaminergic pathway. Injection of 6-OHDA directly to the striatum causes a retrograde degeneration of the nigrostriatal system over a period of weeks and has been used to mimic the slow progressive nature of PD (Przedborski et al., 1995). Drawback of the 6-OHDA model is that it differs from progressive degeneration of the dopaminergic nigral neurons in PD. The 6-OHDA model lesion has been used to ascertain the efficacy of antiparkinsonian compounds (Schwarting and Huston, 1996).

Reserpine model

Reserpine is an indole alkaloid antipsychotic and antihypertensive drug that has been used to control high blood pressure and relief from psychotic symptoms, because of its numerous side-effects, it is rarely used today. When systemic administration of reserpine causes depletion of brain catecholamines, leading to an
akinetic state, in rabbits (Carlsson et al., 1957). The movement deficiency is due to loss of dopamine storage capacity in the intracellular vesicles (Bernheimer et al., 1973). The main drawback of this model are that reserpine induced changes are less intense and do not show any morphological changes in the dopaminergic neurons.

**Methamphetamine model**

They are psychostimulatory drugs primarily associated with dopamine-releasing mechanism. At very high doses, it has neurotoxic effects on rodents and non-human primates (Seiden et al., 1976). Like reserpine, methamphetamine induces dopamine depletion at the level of dopaminergic nerve terminals (striatum) with minimal effect in the nigral cell bodies (Fibiger and Mogeer, 1971). Methamphetamine animal model has been used extensively for biochemical and physiological studies of the dopamine depleted striatum. The limitation of this animal model is the lack of histological changes.

**MPTP model**

After injection of MPTP remarkable clinical symptoms similar to sporadic Parkinson’s disease in humans were noted (Langston et al., 1984). After administration, MPTP crosses the blood brain barrier and is metabolized in astrocytes to its active metabolite 1-methyl-4-phenylpyridinium ion (MPP⁺), by monoamine oxidase-B (MAO-B). MPP⁺ is selectively taken up by dopaminergic neurons due to its affinity for the dopamine transporter and these results in selective toxicity to dopaminergic neurons (Javitch et al., 1985). Exposure to MPTP results in nigrostriatal dopaminergic pathway with 50% to 93% cell loss in the substantia nigra pars compacta and more than 99% loss of dopamine in the striatum (Hantraye et al., 1993).
Rats are resistant to MPTP toxicity and mouse strains vary widely for sensitivity to the toxin.

**Fig 1** - 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine

**Fig 2. MPTP inhibition on Mitochondrial ETC**

**Neurochemical changes following MPTP injection are**

1. Decreased level of dopamine and its metabolites in the striatum.
2. Increased oxidative damage as evidenced by increased lipid peroxidation.
3. Increased 3-nitrotyrosine levels.
4. Diminished concentration of antioxidants, such as glutathione (GSH) and superoxide dismutase (SOD).

Limitations of MPTP model are its failure to mimic progressive nature of Parkinson’s disease. Additionally, the MPTP model does not produce Lewy bodies in rodents.
MPP$^+$ model

Administration of MPP$^+$ into the median forebrain bundle in rats caused significant loss of dopaminergic neurons in the SNpc with ensuring behavioral, neurochemical and 30 biochemical changes characteristic of the lesion (Heikkila et al., 1985). Unilateral intranigral administration of MPP$^+$ produced dose-dependent depletion of dopamine in the ipsilateral striatum of rats following two weeks of infusion (Sun et al., 1988).

Rotenone model

The rotenone model appears to be an accurate model, since chronic exposure to rotenone resulted in uniform and selective dopaminergic neuronal damage, selective striatal oxidative damage, and formation of ubiquitin and α-synuclein-positive inclusions in nigral cells. Rotenone, a pesticide and complex I inhibitor, causes nigrostriatal degeneration similar to Parkinson disease pathology in a chronic, systematic, in vivo model (Alam et al., 2002). Result of complex I inhibition is increased formation of ROS, increased oxidative damage to lipids (Dexter et al., 1989). Rotenone is a lipophilic compound that easily crosses the blood brain barrier. The major problem associated with this animal model is its nature of variability, with only some animals showing lesions.

Genetic model

Genetic defects cases Parkinson’s disease in a small percentage of populations. Mutation in three different gene, including α-synuclein, have been associated with familial Parkinson’s disease (Polymeropoulos et al., 1997). Since α-synuclein is a major component of lewy bodies, and mutations in α-synuclein may result in nigrostriatal dopaminergic degeneration in familial Parkinson’s disease,
animal model have been developed to investigate the role of α-synuclein in the etiology of Parkinson’s disease.

**Treatment**

The experimental therapies for Parkinson’s disease that are under investigation at present assure improvement on the limitations of existing treatments. The prospect of progress in understanding the pathogenesis of the disorder will improve the development of novel molecules and treatments that will retard, or revert, the currently inexorable progressive course of Parkinson’s disease. Existing drugs are symptomatic and temporarily ameliorate the symptoms of Parkinson’s disease.

**Pharmacotherapy for PD**

**Levodopa (L-dopa)**

The most effective drug for relieving the symptoms of Parkinson’s disease is L-DOPA. A combination of L-DOPA and carbidopa is widely used. The carbidopa reduces L-DOPA’s peripheral conversions to dopamine by inhibiting DOPA decarboxylase. This in turn reduces side effects and increases the amount of L-DOPA available for uptake into the central nervous system (CNS). Long – term L-DOPA therapy is associated with motor complications like abnormal involuntary movements, dyskinesia, dystonia, drowsiness and confusion.

**DA agonist**

DA agonist is the class of drugs includes bromocriptine mesylate, pergolide mesylate, cabergoline, pramipexole, lisuride and ropinirole hydrochloride. These drugs stimulate dopamine receptors and some of them have been used for many years in the treatment of Parkinson’s disease.
**MOB-B inhibitors**

Selegiline (deprenyl) is a type of MOB-B inhibitor. Selegiline hydrochloride does not stop the progression of PD but has been, delaying the need for L-DOPA therapy. It has few side effects, but like other MAO-B inhibitors, it cannot be used in a patient taking selective serotonin reuptake inhibitors. Also it has a disadvantage of causing sleep disturbance.

**Anticholinergics**

Anticholinergics like benztropine mesylate and trihexyphenidyl were prescribed for specifically controlling tremor and rigidity. The favorable side effects like dry mouth, decline of cognitive functions, dizziness and urinary retention.

**COMT inhibitors** (Catechol-O-methyltransferase)

COMT inhibitors are the newest class of drugs, which includes entacapone and tolcapone. These drugs can be used to supplement levodopa late in the disease and to extend the interval between doses of levodopa. Side effect includes Nausea, involuntary movements, confusion, diarrhea, back pain, and discoloration of the urine.

**Beta-blocker**

Propranolol is a type of beta-blocker used as a therapy for PD which reduces the severity of tremors. Side effect includes spasm of the airways (bronchospasm), an abnormally slow heart rate (bradycardia), heart failure, impaired peripheral circulation, insomnia, fatigue, shortness of breath and depression.

Other novel therapeutic candidate molecules under clinical trials identified by Committee to Identify Neuroprotective Agents for Parkinson’s (CINAPS) include remacimide, acamprostate and topiramate (glutamate antagonist), riluzole [N-methyl-D-aspartate (NMDA) antagonist], caffeine and theophylline (adenosine antagonists),
antioxidants such as coenzyme Q10, ropinirole and trophic factors such as GM1 ganglioside, GPI 1485 which are currently under investigation (Ravina et al., 2003).

**Surgical treatment for PD patients.**

The surgical treatment was first introduced by Cooper, who found that ligation of anterior choroidal artery abolished parkinsonian tremor and rigidity. This led to further intensive research in the area and established clinical criteria for acceptance of surgery to alleviate tremor or rigidity (Cooper, 1965). The target of such procedures is the disrupted activities of the motor thalamus, Gpi or STN. The introduction of Magnetic Resonance Imaging (MRI) (Zhu et al., 2002) Positron Emission Tomography scan (PET) with \[^{18}\text{F}]\)-fluorodeoxyglucose (Carbon and Eidelberg, 2002), and the use of microelectrode recording techniques have improved the safety and accuracy of functional neurosurgical procedures.

**Treatment of neurodegeneration by natural antioxidant.**

A number of naturally occurring antioxidants have been shown to have protective effects against the degeneration induced by elevated ROS levels in cases of mitochondrial dysfunction. There is great depth to the number of potentially beneficial compounds which can be derived naturally; for example, there has been over 4000 species of flavanoids, a group of established plant-derived antioxidants identified (Nijveldt et al., 2001). Green tea polyphenols have proven to be protective in SH-SY5Y cells against 6-OHDA toxicity (Guo et al., 2005).

**Centella Asiatica**

*Centella Asiatica* (Gotu kola) is a member of the parsley family that thrives in and around water. It is a perennial plant native to India, Japan, China, Indonesia, South Africa, Sri Lanka and the South Pacific. The leaves and stems of the gotu kola plant are used for medicinal purposes. Historically, gotu kola has also been used to
treat syphilis, hepatitis, stomach ulcers, mental fatigue, epilepsy, diarrhea, fever, and asthma.

The National Medicinal Plants Board was set up under the ministry of Health and Family Welfare, Govt. of India during 2000 and the board has initially identified 31 species of importance. In a report to the Scientific Advisory Committee to the Cabinet (SAC-C) Govt. of India, Technology Information, Forecasting and Assessment Council (TIFAC) has mentioned 45 medicinal plant species and specifically recommended 7 plants for immediate attention during 2001-2005. They are as follows,


**Four main bioactive compounds in C. Asiatica are asiatic acid, asiaticoside, madecassic acid and madecassoside.** Among them asiaticoside is the principal bioactive ingredient in C. asiatica since asiaticoside retains the most profound effect on antibacterial and fungicidal activity against pathogens and fungi.
(Hausen et al., 1993). Asiatic acid also exhibits bioactive efficacy (Park et al., 2007). For example, asiatic acid is known to control cell division in human hepatoma, colon cancer, breast cancer, melanoma cells and cytotoxic activity on fibroblast cell (Coldren et al., 2003). Centella asiatica was effective in preventing the cognitive deficits, as well as the oxidative stress caused by intracerebroventricular administration of streptozotocin, indicating that CA can act as a free radical scavenger (Veerandra Kumar et al., 2003).

**Asiatic Acid**

Asiatic acid is one of the constituent triterpenes found in the plant Centella asiatica. Asiatic acid has been found to prevent UV – mediated photoaging, to inhibit amyloid – induced neurotoxicity, and to possess antiulcer and antihepatofibric activities (jew et al., 2000; Lee et al., 2000; Soo Lee et al., 2003; Ko yang et al., 2004).

![](image)

**Molecular Formula; C\textsubscript{30}H\textsubscript{48}O\textsubscript{5}, Molecular Weight; 488.70**

**Asiaticoside**

Asiaticoside (AS), a triterpenoid product isolated from centella asiatica. It has the potential of protecting from inflammatory injury via its ability to up-regulate of PPAR\(\gamma\) (Peroxisome Proliferator-activated receptor –gamma) expression which in turns inhibits the MAPKs and NFkB signal transduction pathways (Zhang et al., 2010).
Molecular Formula; $\text{C}_{48}\text{H}_{78}\text{O}_{19}$, Molecular Weight; 959.12

The leaf extract contained the highest amount of Asiaticoside in both of the accessions tested (zainol \textit{et al.}, 2008). A similar result was reported by zainal \textit{et al.}, 2003 noticed that the leaves of Centella asiatica exhibits higher antioxidant activity compared to other plant part tested. The key compound for antioxidant activity is Asiaticoside.