CHAPTER 1
INTRODUCTION

Parkinson’s disease (PD) is a progressive neurodegenerative disorder with devasting symptoms affecting approximately 1% of the population worldwide. The term Parkinson was named after a physician, James Parkinson in 1817. PD is mainly characterized by bradykinesia, resting tremor, rigidity and postural instability along with non-motor symptoms like autonomic, cognitive and psychiatric problems (Schapira 1991). Epidemiological studies revealed that 10% of PD has strict familial etiology whilst majority of cases are sporadic (Thomas and Beal 2007).

1.1. Etiological Factors
Age, gender, drugs, environmental toxins and genetic factors are most common etiological factors that may induce PD.

1.1.1. **Age:** Young adults are less prone to PD when compared to the middle and old age populace. The incidence rapidly increased over the age of 60 years, with only 4% of the cases being under the age of 50 years (Rajput and Rajput 2007).

1.1.2. **Gender:** Male is more prone to PD than women. Meta-analysis suggests that the risk of PD in men is 1.5% more when compared to women. Although women have less susceptibility to PD, but the mortality rate remains same for both men and women. Increased exposure to environmental toxins, high incidence / probability of head trauma, mitochondrial dysfunction, or X linkage of genetic risk factors may be the possible reasons for the increased risk in men (Rajput and Rajput 2007).
1.1.3. **Drug-induced:** Central dopaminergic antagonists, antidepressants, calcium channel blockers, peripheral dopaminergic antagonists, H1 antihistamines, valproic acid, lithium, amiodarone, anticholinesterase, meprobamate, timetazidine, rifampicin increased the risk of PD (Bondon-Guitton et al. 2011). Antipsychotic drugs used in the treatment of psychosis and schizophrenia reported to elicit the symptoms of PD due to dopamine lowering effect. Reduced estrogen levels in post menopausal women with little or no hormone therapy may be at risk of PD (Rajput and Rajput 2007).

1.1.4. **Environmental toxins:** Suspicion on environmental risk factors triggered only after the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced Parkinsonism (Behari et al. 2001). This finding came across in 1982 during accidental exposure of MPTP, a contaminant in a synthetic opioid drug - 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP) to drug abusers. Within 3 days of ingestion, PD symptoms were observed in those patients and destruction of dopaminergic neurons were discovered upon autopsy, which lead to the development of MPTP induced PD model and awareness on environmental exposure as well. Exposure to toxins like lipophilic pesticides, rotenone etc., causes selective dopaminergic neurodegeneration which is associated with hypokinesis and rigidity. Direct contact with pesticides and herbicides, drinking well / ground water and farming occupation increases the susceptibility to dopaminergic degeneration and PD. This is due to the use of agricultural pesticides / herbicides, whose chemical structure is similar to that of MPTP (Priyadarshi et al. 2001). Behari et al. (2001) reported that well water consumption for more than 10 years increases the risk for PD since the ingestion of contaminated drinking water is the potential vehicle for pesticide exposure in human.

1.1.5. **Genetic factors:** Genetic factor plays an important role in early onset of PD. α-synuclein (α-syn) knockout mice are resistance to MPTP toxicity, suggesting a new link between genes and PD (Schluter et al. 2003). PARK2 is the parkin gene that forms the basis for autosomal recessive juvenile - PD without lewy bodies (LBs) formation due to mutation in parkin protein (Fahn and Sulzer 2004). Studies showed that the heterozygous mutations in glucocerebrosidase (GBA) and mutations in novel genetic loci – Ubiquitin carboxyl-terminal hydrolase isozyme
L1 (UCHL1), Parkinson disease protein 7 (PARK7/DJ1), Omi/HtrA2, GRB10 interacting GYF protein 2 (GIGYF2), fibroblast growth factor 20 (FGF20), pyridoxal (pyridoxine, vitamin B6) kinase (PDXK), eukaryotic translation initiation factor 4 gamma, 1 (EIF4G1) and Parkinson disease protein 16 (PARK16) increased the risk of PD (Wider et al. 2010). In addition, genetic variation in leucine-rich repeat and Ig containing 1 gene (LINGO1) increased the risk of PD and essential tremor, which confirms the link between the genetic alterations in PD and tremor (Wider et al. 2010).

1.1.6. Other factors: Depression is one of the most common psychiatric disturbances in PD. In global PD survey, 58% of the patients have variations in quality of life and attributed to depression when compared to only 17% with physical symptoms. The pathophysiology of depression in PD is not clear, although it is suggested that the loss of norepinephrine and serotonin transmissions may influence PD onset (Chung et al. 2003). Evidences suggest that head trauma also increase the risk of PD, presumably the trauma damages dopaminergic neurons (Jafari et al. 2013).

1.2. Pathophysiology of PD
The most common pathological clinical features in PD are the death of neuromelanin containing dopaminergic neurons in the SNpc and depletion of dopamine levels in caudate-putamen complex (CPu) of ST. In addition, other groups of neuronal degeneration were also noted in PD brains, which includes alteration in cholinergic, serotonergic, noradrenergic systems (Winner et al. 2009). Evidence of LBs, a distinctive neuronal inclusion develops spindle- or thread-like Lewy neuritis (LNs) in cellular processes and in the form of globular LBs in neuronal perikarya were diagnosed in PD post-mortem brains (Lucking and Brice 2000).
Various biochemical alterations were identified in the affected brain regions that shed light to understand how genetic and environmental factors provoke dopaminergic cell death. There are three major types of cellular dysfunctions in PD viz., abnormal proteins aggregation, mitochondrial dysfunction and oxidative stress (Figure 1.1). Pathologically, there is an overlap with other neurodegenerative disorders including Alzheimer's disease, and this has been used to support the view that these diseases may share some common pathogenetic mechanisms.
1.2.1. Mutations leading to PD

Inherited PD occurs mainly due to the mutation in genes such as Parkin, α-syn, DJ-1, Leucine-rich repeat kinase 2 (LRRK2), Phosphatase and tensin (PTEN) - induced putative kinase 1 (PINK1), ubiquitin carboxyl terminal hydrolase L1 (UCH-L1), adenosine triphosphate 13A2 (ATP13A2) which adversely affects mitochondrial functions in brain. Reports also suggest that the phosphorylation of ser129 in C-terminal region of α-synuclein catalyzed by the G-protein coupled receptor kinase-5 is one of the main causes for the α-synuclein aggregation in PD. The mutation in α-synuclein gene triggers protein aggregation, hydroxyl radical generation and finally leads to oxidative stress induced cell death. This mutation also causes golgi vesicuolar trafficking which results in endoplasmic reticulum stress. Further, it increases catecholamine concentration leading to the selective degradation of dopaminergic neurons in PD (Yang et al. 2008).

Mutations in PINK1 gene increases reactive oxygen species (ROS) formation and accumulation of which leads to apoptotic cell death. Reports have shown mitochondrial DNA deletions and decreased cytochrome oxidase activity in brain of PD patients (Bender
et al. 2006). DJ-1, LRRK2 and Parkin were essential for antioxidant and neuroprotective functions, defect in these genes leads to the mitochondrial dysfunction and oxidative stress leading to dopaminergic neurodegeneration (Huang et al. 2004).

1.2.2. Protein misfolding and PD
Misfolding, aggregation and accumulation of proteins in synaptic vesicles lead to apoptosis and finally brain damage. α-synuclein is a homologue of 14-3-3 protein, a protein chaperon that normally exist as dimer; rapidly aggregates on exposure to metals like copper, iron etc., which leads to the activation of Fenton’s reaction, resulting in the oxidative stress. Overexpression of α-synuclein gene is one of the causes for protein aggregation which may be due to ubiquitin proteosome system (UPS) and oxidative stress (Stefanis 2012). UPS functions in degrading the normal and abnormal proteins by mutation, misfolding or unassembling of proteins. This protein aggregates forms Lewy’s bodies and accumulates in cytoplasm of the dopaminergic neurons in PD patients. Overexpression of α-synuclein may also induce iron dependent protein aggregation. Another mechanism of α-synuclein aggregation involves the action of free radicals by oligomers as a toxic intermediates. Several studies suggested that α-synuclein misfolding or its aggregation occurs due to the lipidic environment (Ruiperez et al. 2010; Breydo et al. 2012).

1.2.3. Mitochondrial dysfunction and PD
During mitochondrial respiration, electrons from nicotinamide adenine dinucleotide (NADH) are transferred to complex I (NADH: ubiquinone oxidoreductase) and forms a final product, H₂O via complex III and IV activity. During the transfer of electrons, ATP is formed to restore or to regain the energy. Inhibition of complex I results in the impaired electron flow and ATP production. This leads to the increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) which triggers apoptotic cascade. Recent studies showed oxidative damage in the catalytic subunits of complex I in frontal cortex region of PD patients, which correlates with the complex I misassembly and dysfunction (Keeney et al. 2006). Under the condition of high proton motive force, the electron supplied from complex II to ubiquinone is reversibly transferred to complex I and reduces NAD⁺ to NADH resulting in alkaline pH or high membrane potential favouring ROS production. ROS promotes the transfer of single electron through the complexes and forms superoxide anion leading to over production of free radicals (Winklhofer and Haass
Increased ROS production in mitochondria or decreased ROS removal by mitochondrial defence system leads to the damage in mitochondrial DNA, proteins and lipids. This damage compromises the respiratory chain establishing a new link between the oxidative stress and bioenergetic failure (Winklhofer and Haass 2010).

1.2.4. Dopamine and PD

Over expression of α-syn, especially its mutant forms, enhances the metabolism of dopamine, which in turn produces ROS and highly reactive chemical species such as dopamine-quinones and peroxynitrites. This ultimately leads to lipid peroxidation, DNA damage, inhibition of complex I and finally cell death (Stefanis 2012). Studies have shown that abnormal expression of α-syn inhibits TH synthesis and induced apoptosis in dopaminergic neurons (Yu et al. 2004). Reduced dopamine decarboxylase gene expression and cofactor which catalyses TH activity were observed in α-syn mutation leading to the decreased production of dopamine (Xu et al. 2002). Hence, loss of α-syn activity or its aggregation interrupt dopamine homeostasis and affects the dopaminergic neurons leading to cell death.

1.2.5. Neuroinflammation and PD

Neuroinflammation plays an important role in the pathogenesis of PD either by infectious agents or neurotoxins with proinflammatory characteristics. Earlier reports demonstrated that dopamine induced oxidative stress contribute to inflammatory reactions in PD patients. Consistent production of ROS potentiates chronic inflammatory reactions by altering various biomolecules leading to the destruction of neurons. Exposure to infectious agents or neurotoxins alters glial cell functions including the astrocytes and microglia which releases neurotoxic factors like phagocyte oxidase induced H2O2 and cytokines (TNFα, IL-1β etc.,). These cytokines activate receptor mediated proapoptotic pathways within the dopaminergic neurons and upregulates inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2) by stimulating microglia. Thus increased generation of NO and ROS leads to DNA damage, protein disruption and lipid peroxidation. Knockout mice studies of autosomal recessive factors such as parkin (PARK2), PINK1 (PARK6), and DJ-1 (PARK7) reveals the crucial role of these factors in the negative regulation of neuroinflammation (Barnum and Tansey 2010; Sekiyama et al. 2012).
1.2.6. Oxidative stress and PD

Oxidative stress and cell damage occurs mainly due to decline in antioxidant defence mechanism and increased mitochondrial dysfunction, which leads to overproduction of superoxide radicals (O$_2^{-}$) and triggers iron sulphur containing enzyme - superoxide dismutase (SOD) resulting in hydrogen peroxide (H$_2$O$_2$) radical formation. These H$_2$O$_2$ in turn produces hydroxyl radicals (‘OH), the most harmful free radical of all ROS, by fenton’s reaction. O$_2^{-}$ and H$_2$O$_2$ also reacts rapidly with nitric oxide (NO) and forms peroxynitrite anions (ONOO⁻) which then forms nitrotyrosine with CO$_2$. These results in oxidation of lipids, proteins and ultimately DNA damage, which leads to cell death.

Furthermore, increased DNA damage leads to the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a major DNA lesion product, alters the base pairing properties of guanine causing increased incidence of cancer. In addition to base modification, oxidative stress causes strand break, deletion mutation, discontinuous loss of heterozygosity etc. This leads to loss of genome stability malignant transformation, cell cycle reentry. Forced cell cycle of the terminally differentiated neurons does not proliferate but they die (Klien and Ackerman 2003).

Considerable evidences demonstrated that ROS contributes to the loss of dopaminergic neurons, resulting in dopamine metabolism, reduced glutathione and high levels of iron and calcium levels in SNpc region of PD brain (Jenner and Olanow 2006). Further overproduction of ROS oxidises polyunsaturated fatty acids, usually present in high concentration in brain, leads to lipid peroxidation in PD brain (Liu et al. 2008). These findings suggest that oxidative stress plays an important role in damaging the neurons of SNpc.

1.3. Astrocytes in PD

Besides neuronal damage, astrocytes plays a major role in various neurodegenerative disorders. Astrocytes enter a state called reactive astrogliosis in PD, which is characterized by increase glial fibillary acidic protein (GFAP) expression (Eddleston and Mucke 1993).

Though astrocytes are beneficial to neurons by maintaining extracellular glutamate levels and homeostasis in ST after dopaminergic neuronal loss, it’s over activation leads to the detrimental effects on the surrounding neurons. Changes in astrocyte glutamate content and its associated synaptic functions are major causative factors in the progression of PD.
Numerous animal and post mortem studies showed that reactive astrocytes were observed in PD brain but the mechanism of its activation and role on the progression of neuronal damage is still not well defined. Mutated α-syn in astrocytes induces inflammatory signalling, which in turn contributes to the reactive oxygen species (ROS) generations and finally neuronal loss (Mallajosyula et al. 2008). A major problem with therapies targeting neuroprotection is as long as the neuronal death are not prevented, there will be no enough neurons left to manipulate. On the other hand, astrocytes increase in numbers when neuronal loss increases. Therefore, astrocytes can be manipulated to slow down or stop the disease progression and possibly even stimulates the repair mechanism in chronic stages. It is clear that restoration of dopamine alone may not be sufficient in the management of PD. Regulation of astrocytes as well become a promising therapeutic target in PD.

1.4. Current treatment strategies in PD
The clinical symptoms of PD become apparent only when 70-80% of dopaminergic neuronal loss occurs in SNpc and 80% dopamine loss in ST regions (Deumens et al. 2002). These complicate the treatment in PD. The following are the few current therapeutic strategies employed in the management of PD.

1.4.1. Medical therapy
Although many drugs were used in the treatment of PD, their side effects on long-term exposure eliminate their usage or it requires another drug to counteract the side effects.

1.4.1.1. Prodrugs
**Levodopa:** Levodopa (L-dopa, L-3,4-dihydroxyphenylalanine) is one of the standard drugs used for the treatment of PD particularly for tremor and movement problems. Levodopa is a precursor of dopamine that easily crosses blood brain barrier and increase dopamine levels. Activation of dopamine receptors improve the symptoms of PD, whereas activation of peripheral dopaminergic receptors causes nausea and vomiting. Hence, this drug is normally prescribed only with the combination of other drugs like carbidopa which cannot cross the blood brain barrier. However, it also prevents peripheral conversion of levodopa to dopamine and thereby reduces the peripheral side effects of levodopa. Reports have shown that majority of the patients experience motor fluctuation, dyskinesia and some other complications after 5 years of treatment. Since these side effects were primarily
related to the dose and duration of levodopa, the addition of Catechol O-methyltransferase (COMT) inhibitors, monoamine oxidase (MAO) inhibitors or dopamine agonists is used in the management of levodopa-induced dyskinesia. When levodopa is administered orally, decarboxylation occurs rapidly and only small portion of the drug enters the brain unchanged. Thus, high dose of levodopa is required for the desired effects. Moreover, the administration of levodopa showed delayed or poor response when administered in the morning. Continuous dopaminergic stimulation to prevent or control levodopa-related motor fluctuation is presumably associated with levodopa dosing, although this concept is being challenging (Simola et al. 2010).

1.4.1.2. Dopamine agonists: Dopamine agonists exert their pharmacological effects directly by activating the dopamine receptors bypassing the presynaptic synthesis of dopamine (Simola et al. 2010). Experimental evidences shown that dopamine receptor 2 (D2) activation by dopamine agonist is important in mediating the beneficial effects of Parkinsonism. But concurrent D1 and D2 activation is required for optimal physiological and behavioral effects. In contrast to the dopamine agonists (Levodopa, bromocriptine and pergolide), pramipexole and ropinirole are nonergolines and therefore are expected to have a lower risk of complications such as peptic ulcer disease, vasoconstrictive effects, erythromelalgia, pulmonary and retroperitoneal fibrosis and valvular heart disease (Zanettini et al. 2007). Pramipexole causes idiosyncratic peripheral edema most commonly, because of its potential for valvular heart disease, the ergot dopamine agonists were discontinued from medical practice.

1.4.1.3. COMT inhibitors: COMT inhibitors are administered in combination with levodopa. Entacapone, Tolcapone are some of the COMT inhibitors commonly used for the treatment of PD. Entacapone requires frequent administration (200 mg, 8 times per day) because of its shorter life span. Most patients use this inhibitor along with each dose of levodopa. Some studies shown that tolcapone causes acute liver failure leading to black box warning and intensive monitoring requirements. Simola et al. (2010) reported that tolcapone, when administered along with levodopa, induces hepatotoxicity and other symptoms like vomiting, nausea and hypotension.
1.4.1.4. **MAO-B inhibitors:** MAO-B inhibitors usually administered in combination with levodopa. It prevents the *in vivo* metabolism of dopamine and enhances its anti-parkinsonism effects. Reports have shown that MAO-B inhibitors protect neuronal cells from the consequences of oxidative stress (Simola et al. 2010) and induce the release of neuronal growth factors. The most commonly used MAO-B inhibitor for the management of PD is rasagiline. However, it shows only mild therapeutic benefits on the management of PD.

1.4.1.5. **Anti-glutamatergic drugs:** Interactions between dopamine and glutamate in striatal neurons found to play an important role in PD. Experimental evidences support that anti-glutamatergic drugs or glutamate antagonist have potential role in PD treatment (Simola et al. 2010).

1.4.1.6. **Anti-cholinergic drugs:** Anti-cholinergics provides satisfactory symptomatic relief in early phases of anti-parkinson therapy (Rezak 2007). Anticholinergic drugs such as trihexyphenidyl or benztropine are primarily useful in younger patients with tremor. Although quite effective, these drugs cause cognitive impairment, dry mouth and urinary symptoms.

1.4.1.7. **Nicotine:** Recent studies shown that nicotine, a principal alkaloid in tobacco plays a significant role in preventing dopaminergic degeneration (Quik 2004). Nicotine administration promotes marked decrease in cortical nicotinic binding and also evokes the release of dopamine from striatum thereby reducing dementia and nigrostriatal degeneration in PD. Although nicotine was widely used for the management of PD, administration of this drug causes severe side effects such as primarily nausea, gastrointestinal disturbances, nasal congestion and rhinorrhea (Lemay et al. 2004).

1.4.2. **Physical Therapy (PT)**

PT mainly focuses on training in daily activities, relaxation therapy, breathing exercise, gait training, functional training like walking, grasping, social activities etc. Regular physical exercise including yoga, dance etc., will improve mobility, flexibility, balance and range of motion. Educating the patients about this therapy is one of the important aspects in the treatment of PD. Studies evidenced that PT in PD patients showed approximately
5% substantial improvement in walking speed (0.08 m/s) and stride length (6 cm) (Tsai et al. 2002; Chen et al. 2005; Kwakkel et al. 2007).

### 1.4.3. Speech Therapy

Lee Silverman voice treatment (LSVT) is the most widely used treatment for speech disorder associated with PD. LSVT focuses on increasing vocal loudness (Whitehill et al. 2011).

### 1.5. Why new treatment strategies?

The most important principle in the management of PD is to individualize the therapy and to target the most disabling symptoms. Researchers developed various drugs to improve the quality of life until cure, but none reached the goal. The main impediment in the development of neuroprotectants is the unclear information on target molecular events that trigger neurodegeneration in PD. Another major problem is that the patients are already in the advanced stages of PD when diagnosed for the first time. Thus aiming on the molecular components that kicks off neurodegeneration and early diagnosis of PD may halt the disease progression and heals PD pathology. Although many drugs were available in the treatment of PD, their effective role is selective and limited. Hence, more attention are being paid in the development of new therapeutic strategies.

### 1.6. Renin angiotensin system (RAS) and PD

Since the discovery of RAS in brain, various studies have linked RAS to many neurological disorders like ischemia, Alzheimer’s disease and depression. Evidences have shown that the central RAS might also play a role in Parkinson’s disease (Kurosaki et al. 2005; Munoz et al. 2006; Rey et al. 2007). Although the exact cause of this progressive neurodegenerative disorder remains unidentified, it has been suggested that inflammation and oxidative stress play key role in the progression of the disease. Angiotensin II, a pro-inflammatoty compound induces the production of reactive oxygen species due to activation of the NADPH dependent oxidase complex. Increased attentions being paid on the development of RAS modulators in the treatment / management of PD (Garrido-Gil et al. 2012; Labandeira-Garcia et al. 2013).

Many studies have linked the crucial role of angiotensin II type 1 receptor (AT1R) in PD (Brown et al. 1996; Rey et al. 2007; Grammatopoulos et al. 2007). AT1Rs are richly
present in the SNpc and ST brain regions of different mammals, including rats and humans (Daubert et al. 1999). Further, modulation of the striatal dopamine release via these AT1Rs also points towards an interaction between the RAS and the central dopaminergic system (Brown et al. 1996; Ge and Barnes 1996; Jenkins et al. 1997). Stimulation of AT1R has been associated with the activation of the NADPH oxidase complex. Interestingly, inhibition of AT1R using angiotensin II receptor blockers may not only result in a reduced activation of NADPH oxidase, but also in an increased synthesis of angiotensin II, which in turn could lead to a preferential activation of the unopposed angiotensin II type 2 receptors (AT2R). Several data suggest the neuroprotective role for this receptor subtype, which under normal conditions is masked, by the opposing role of the AT1R (Steckelings et al. 2005; Grammatopoulos et al. 2005).

Telmisartan (TEL), a highly lipid soluble AT1R blocker is reported to exert neuroprotective effects via modulating AT1 and AT2 receptors signalling in retinal inflammation (Kurihara et al. 2006). The effect of TEL on ROS generation was studied by Pang et al (2012) in SK-N-SH neuroblastoma cells, which showed that TEL directly ameliorates IL-1β-induced neuronal inflammatory response by inhibiting oxidative stress through JNK/c-Jun pathway. Further, it suppresses the expression of pro-inflammatory adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and P-selectin in ischemic brains (Kasahara et al. 2010). Recently, Garrido-Gil et al. (2012) demonstrated that TEL produces anti-inflammatory and neuroprotective effects through peroxisome proliferator-activated receptor gamma (PPARγ) activation. On the other hand, TEL maintains mitochondrial membrane potential through anti-apoptotic signalling. Pang et al (2014) demonstrated that BCL-2, an anti-apoptotic protein, maintains the mitochondrial membrane potential and prevents the release of cytochrome C from mitochondria. Telmisartan increased Bcl-2 protein level, which in turn maintains the membrane potential to prevent neuronal death.

It is hypothesized that the restoration of dopaminergic systems functions or dopamine level alone will not be sufficient in the treatment of PD. It seems that simultaneous alleviation of other causative factors majorly the astrocytic functions is necessary. AT1Rs are rich in both neurons and astrocytes, hence blockade of its action will not only restore dopaminergic function but also the astrocytic functions. Furthermore, exploitation of AT1 receptors will give information on the disease - modifying therapeutic potential of central RAS modulator in PD.
Hence, the present study was aimed to investigate the neuroprotective effects of TEL in acute and chronic MPTP model of Parkinsonism, with respect to the glial-neuronal functions in PD and also to assess the disease-modifying therapeutic potential of central RAS modulator in PD.

The present study fulfills the following objectives

- To investigate the effects of TEL on motor functions and neurotrophic factors such as brain derived neurotrophic factor (BDNF) and glial derived neurotrophic factor (GDNF) protein expression in SNpc and ST brain regions in the acute MPTP intoxicated state
- To study the effects of TEL on oxidative stress and cytokines protein in the acute MPTP intoxicated mice
- To study the role of TEL on nitric oxide and glutathione levels and dopamine transporter (DAT) and tyrosine hydroxylase (TH) expressions on chronic exposure to MPTP in mice brain
- To establish the role of TEL on astrocyte-neuronal associated functions via correlating the dopaminergic recovery with respect to astrocytes functions