INTRODUCTION

Parkinson's disease (PD) is one of the major neurodegenerative disorders, characterized by the progressive loss of dopaminergic neurons in the nigro-striatal region of the basal ganglia (Ehringer and Hornykiewicz, 1960). Deficiency of dopamine causes a decreased dopaminergic control over cholinergic receptors in striatum, results in an imbalance of dopaminergic-acetylcholine system and hence, the motor disturbances (Albin et al., 1989; Richardson et al., 1977).

Approximately, 1-2% of the population older than 65 years of age suffers from PD (Bornebroek et al., 2007; de Lau and Breteler, 2006). However, PD can also manifest earlier in life, before 40 to 50 years, referred as early onset PD (Thomas and Beal, 2007). Currently, levodopa is the mainstay of the current treatment, but its long term use has been associated with motor complications and its advancement disease is associated with non-dopaminergic features such as dementia, depression etc, which are not controlled by the current therapies (Poewe et al., 2010). Thus, the current disease trend demands the urgent need to move beyond the symptomatic drug therapy for a suitable neuroprotective strategies so as to prevent or impede the natural course of PD.

Present research on the development and pathogenesis of PD using various animal models indicate the involvement of continuous complex pathological processes in PD and can be determinantial in the pathophysiology of the disease. Recent evidences suggest the substantial role of neuroinflammation which contributes to a cascade of numerous complex events that can result in the progressive neurodegeneration in PD (Farooqui and Farooqui, 2011; Tufekci et al., 2011). During neuroinflammation, the hallmark factor is the activation of glial cells, such as microglia (McGeer and McGeer, 2008; Wu et al., 2003; Kim and Joh, 2006). Activation of glial cells produces reactive oxygen species (ROS) and nitric oxide (NO) via induction of NADPH oxidase and inducible nitric oxide synthase (iNOS). This results in the release of NO, hydrogen peroxide (H$_2$O$_2$) and other free radicals like superoxide (O$_2^-$) all of which perpetuate dopaminergic neuronal injury. Further,
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It is hypothesized that a cascade of neuroinflammatory events activate microglia and up-regulate cyclooxygenase (COX) and lipoxygenase (LOX) isoenzymes which are involved in the synthesis of prostaglandins (PGs) and leukotrienes (LTs), respectively in the body. Animal models of PD have also shown the presence of activated striatal microglial and astroglial cells (Bartels and Leenders, 2007; Kim and Joh, 2006; Smith, 2008). Mounting evidence suggests that during neuronal damage, NO and COX acts as major players in the oxidative damage by the production of free radicals as well as release of certain proinflammatory cytokines, which further hastens the survival of the striatal neurons (Okuno et al., 2005; Ferger et al., 1998; Sanchez-Pernaute et al., 2004; Vijitruth et al., 2006).

Similarly, Chen and colleagues (2003) in their prospective study found that the incidence of PD among the chronic users of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) was 45% lowered in comparison to that of age-matched non-users. Animal studies have also shown that anti-inflammatory drugs such as pioglitazone (a peroxisome proliferator-activated receptor, PPAR agonist) and minocycline (a tetracycline derivative) demonstrated beneficial effects in neurotoxin-induced PD (Hirsch et al., 2003). Although the course of the disease is unknown, the leading hypothesis for the death of specific groups of neurons establishes the alterations in protein aggregation, proteasomal system impairment, mitochondrial dysfunction and oxidative stress that could be the major events that act synergistically causing this devastating disease (Bartels and Leenders, 2007; Block and Hong, 2007). Since postmortem examination of substantia nigra (SN) reveals astrogliosis, presence of activated microglia and elevated levels of inflammatory cytokines, an emerging area of interest involves developing strategies to inhibit the glial activation/reaction or targeting inflammatory pathway, which promotes apoptosis of dopaminergic neurons and sustains the levels of oxidative stress induced by microglial activation (Hirsch et al., 2003; Nagatsu et al., 2000).

In the past few years, research has been focused to unveil the probable role of COX and LOX in neurodegenerative disorders such as PD. Interestingly, the postmortem studies of PD patients have revealed the presence of activated
microglia that express iNOS and COX-2 in substantia nigra paras compacta (SNpc) region of the brain (McGeer and McGeer, 1998; Knott et al., 2000). Various epidemiological studies have also indicated that NSAIDs treatment may prevent or delay the progression of PD (Bornebroek et al., 2007; Esposito et al., 2007). COX-2 is induced by many cellular mediators such as growth factors, proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), environmental toxins, immunological insults (lipopolysaccharide, bacteria and viruses) and elevated intracellular calcium concentration (Consilvio et al., 2004). Similarly, phenidone, a dual COX/LOX-inhibitor has been demonstrated a significant neuroprotective effect on nigral dopaminergic neurons against LPS-induced neurotoxicity (Li et al., 2008).

With this background, the present study has been undertaken to elucidate the interaction of neuroinflammatory cascades in the pathophysiology of PD in experimental paradigm. The present research work has been divided primarily into four parts. The first part focuses on the neuromodulatory role of COX-inhibitors in perphenazine-induced catatonia and MPTP model of PD. In the initial section, role of selective and non-selective COX-inhibitors in attenuating perphenazine-induced catatonia model of PD was studied. The next section deals with the neuroprotective role of selective COX-2 inhibitors against systemic administration of MPTP in mice. The second part of the present thesis deals with modulatory effect of LOX-inhibitors against MPTP-induced neurotoxicity in mice. In this section, the effect of 5-LOX inhibitor and LT receptor antagonists in modulating neurodegeneration induced by MPTP was investigated. The third part of the thesis focuses was to investigate the effect of PPAR and PPAR ligands in experimental paradigm of PD where their role in attenuating the neuroinflammatory cascades was studied. The fourth part of the present thesis deals with the neuroprotective role of nutritional supplements and antioxidants in the management of PD in experimental paradigm.