**Preface**

Free radicals are beneficial to the cell owing to their involvement in the cellular defence system and signalling pathways. Though, a proper regulation of free radical generation is crucial, as they cause severe harmful cellular damage in higher concentrations. To sustain oxidative homeostasis, the cells possess a complicated antioxidant defence system to neutralize them. The central nervous system is more susceptible to oxidative damages because of its high rate of oxygen consumption and lower capacity of cellular regeneration.

Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s disease. It is clinically characterized by motor symptoms such as muscle tremors at rest, bradykinesia, stiffness of limbs as well as non-motor abnormalities such as sleep disorders and alterations in their circadian rhythms. In most of the PD cases interaction of genetic and environmental factors play a critical role in pathology of the disease. The α-synuclein gene is among the main genetic factors implicated in PD. In view of the fact that most cases of PD are sporadic and individuals develop the disease symptoms at later part of life, hence, lifelong accumulation of oxidative damage can be the main cause of functional senescence of neurons. Involvement of oxidative stress (OS) in the molecular pathways underlying onset of PD symptoms is an important issue, which can provide clues to improve or treat this disease. For that reason, a simple model organism would be useful to address the role of OS in progression of PD symptoms at tissue and molecular levels.
*Drosophila melanogaster* is an ideal model organism to understand mechanisms involved in neurodegenerative disorders and environmental toxin-induced Parkinsonism. *Drosophila* is also used as a convenient model to screen therapeutic agents for their effects on the cellular, biochemical and genetic systems. It has short lifespan, exclusive behavioral responses and many age-related functional senescence similarities with human. More than 65% of human disease-causing genes are present at least in one copy in fruit fly genome. Furthermore, ectopic expression of a variety of characterized human genes resulting in neurodegenerative diseases is feasible in *Drosophila*. Indeed, transgenic manipulations in *Drosophila* are a valuable method for study of behavioural and molecular alterations downstream of a genetic mutation. Nevertheless, lack of intensive study with respect to involvement of OS in onset of PD by use of *Drosophila* model and all other above mentioned features formed the basis to carry out the present study. Experiments were designed to explore the role of OS in induction of behavioural impairments and alterations in antioxidant defense system in wild-type flies and also in onset of PD symptoms in transgenic *Drosophila*. In this study, the neurotoxic effect of PQ and ethanol on the levels of oxidative markers, behavioural impairments and efficiency of cellular antioxidant defense system of wild-type and transgenic flies have been also investigated.

To create *Drosophila* model of PD, two different strategies were used. In one case, the available and characterized stocks carrying A30P and A53T mutant forms of human α-synuclein gene were over expressed in *Drosophila* brain and the subsequent defects in their climbing ability and circadian rhythm of locomotor activity, level of oxidative markers and activity of antioxidant enzymes such as CAT and SOD and neurotransmitter AchE were evaluated. In another approach, human E46K α-synuclein gene was selected. The cDNAs
of E46K α-synuclein gene were cloned in to pUAST vector and micro injected to the embryos of \( w^{1118} \) stock and thereby the first \textit{Drosophila} transgenic constructs carrying E46K α-synuclein gene under the control of UAS were generated. Western blot analysis was undertaken to confirm the expression of concerned gene. Its ability to induce neuronal degeneration was evaluated by scanning electron microscopy of surface morphology of ommatidial structures. Additionally, behavioural and biochemical studies in E46K α-synuclein transgenic flies were carried out.

Paraquat and ethanol were used to induce excess generation of ROS and thereby the role of OS in pathological conditions mediated by over expression of (A30P, A53T and E46K) mutant forms of α-synuclein gene and ethanol or paraquat exposure could be studied. The results revealed that transgenic flies showed severe behavioural impairments and sensitivity to PQ and ethanol.

Due to positive qualities, the herbal medicines have engaged today’s clinical requirements and thus have become the focus of lots of investigations. In this connection, the neuromodulatory action of root extract of \textit{Decalepis hamiltonii} (Wight & Arn.) (family: \textit{Asclepiadaceae}) which is consumed as pickles and general vitalizer in ayurvedic preparations in southren India has been studied. DHA-I, an isolated and characterized novel molecule from aqueous extract of \( Dh \) with strong antioxidant and free radical scavenging potential among other isolated and characterized molecules has been undertaken in this study to examine all the features mentioned for \( Dh \) aqueous extract. Bulk of knowledge on potent antioxidant properties of \textit{Decalepis hamiltonii} (\( Dh \)) and DHA-I was the basis of the present study to evaluate their neuromodulatory action on oxidative stress induced by PQ and ethanol in wild-type and transgenic \textit{Drosophila} model.
of PD. The neuromodulatory action of Dh and DHA-I to prevent or delay the onset of PD symptoms in transgenic flies has been also investigated.

The results of present work have been compiled and organized in to a single chapter which is divided into four sections including introduction and review of literature, materials and methods, results and discussion. In the first section, literature review includes an overview on definition and incidence of PD, neuropathology of PD, genes which are associated with familial forms of PD, etiology and pathogenesis of PD, accumulation of OS by age and antioxidant defenses, involvement of OS in PD, therapeutic potential of herbal-based antioxidants, Dh as a potent herbal medicine for treatment of PD and D. melanogaster as a suitable model for neurodegenerative disease studies. In the second section, materials and methods that have been undertaken for conducting experiments has been provided in detail. The results obtained in the present study have been dealt in the results section and are presented with appropriate figures and tables. In the last section, the results of the present experiments have been discussed with adequate support of literature on oxidative stress-mediated malfunctions in the nervous system. Based on the experimental evidence from the present work some propositions could be made to explain the probable mechanisms by which herbal extract used in this study may play a role in alleviating the neurodegenerative disorders.