3. SCOPE AND OBJECTIVE

Parkinson’s disease (PD) is a second mostly occurring neurodegenerative disease characterizes the loss of dopaminergic neurons in the substantia nigra pars compacta and also degenerate nondopaminergic systems like noradrenergic, serotonergic and cholinergic systems (67). The important symptoms of PD like bradykinesia, rigidity and resting tremors could be relieved by dopamine improving therapies such as levodopa (L-dopa), dopamine receptor agonists and monoamine oxidase B (MAO-B) inhibitors, amongst this, L-dopa is gold standard drug. But, L-dopa gives only symptomatic relief and fails to cease the progression of PD. Eventhough L-dopa shows undesirable side effects, like motor fluctuations and dyskinesias also after about two years of treatment its therapeutic effect get weakens. Moreover, the use of L-dopa for long term may actually damage neurons, and accelerating apoptosis of dopaminergic neurons. One of the key factors of neurodegeneration is programmed cell death in progression of PD. The early stage of PD shows the non-motor symptoms like sleep abnormalities, depression, autonomic failure, and dementia are probably the consequence of degeneration of both dopaminergic and nondopaminergic systems, which still don’t have effective treatments at present (23).

Currently there are three main drug development strategies to treat PD:

1. Improvements in dopaminergic therapies and prevention of the motor complications;
2. The identification of non-dopaminergic drugs for symptomatic improvement; and
3. The discovery of disease modifying or neuroprotective compounds.

Also in past so many chemicals developed as neurotoxins to induce the parkinsonism amongst them 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydro- pyridine (MPTP) and rotenone, are the most successful and common neurotoxic agents used regularly so far to mimic Parkinsonism in vitro and in vivo (68).

For the new era it is the need that we can change our mindset to treat the Parkinson disease by targeting the molecular pathway by which neurons can survive for longer period of time. This indicates that neuroprotective agents may improve the prognosis of PD. It is very important to identify new target apart from dopaminergic pathway to treat Parkinsonism from their root. In this context, the present study tries to identify non-dopaminergic pathway by which we can treat Parkinson disease by altering causative molecular pathway with less or no side effects.
In modern drug therapy lots of allopathic drug treatments are available to treat Parkinson disease, but they either control symptoms or relieve the discomfort but can never eliminate the origin of ailment and also they have lots of limitation. Hence emphasis is given on third strategy of drug development by assessing the improvements in motor function after damaging the dopaminergic neurons by neurotoxins like 6-OHDA and MPTP, then check the effectiveness of H3-receptor antagonists and c-Jun-N-terminal kinase (JNK) inhibitors in the treatment of Parkinson disease. Besides, studies are also extended to find a possible molecular mechanism of action of both H3-receptor antagonists and c-Jun-N-terminal kinase (JNK) inhibitors against neurotoxicity of toxic chemicals, oxidative stress, apoptotic pathway in neuronal cell So with these findings the study would give a clear picture on molecular mechanism of H3-receptor antagonists and c-Jun-N-terminal kinase (JNK) inhibitors in treating Parkinsonism and assist for the development of suitable and effective neuroprotective agent.

Objective
Research on histamine H3-receptor antagonists/inverse agonists and c-Jun-N-terminal kinase (JNK) inhibitor has thought to be potentiate turnover of dopamine neurotransmitter and can diminish the chances of Parkinson’s disease. In this respect our objects of study are

- To find out the targeted mechanism on specific etiology of Parkinson disease and try to explore the treatment based on etiology.
- To find out Structure activity relationship (SAR) of selected molecules of H3-Antagonist and c-Jun-N-terminal kinase (JNK) inhibitor.
- To evaluate possible molecular mechanisms of H3-Antagonist and c-Jun-N-terminal kinase (JNK) inhibitors agents by which they can increase the turnover of dopamine level in striatum.
- To develop lipid nanoparticles containing drug molecules to target brain through oral delivery system for limiting the activity of drug molecule in peripheral tissue.
- Physicochemical characterization of developed formulations.
- Pharmacokinetic and pharmacodynamic studies of developed formulation.