Chapter 10

Summary & Scope for Further Work

10.1. Summary

The current study for the first time validated 6-OHDA-induced model of PD to evaluate GCase-targeting compounds for PD management. The primary findings which are reported for the first time in the current study also include: GCase-activating property of rebamipide; alleviation of 6-OHDA-induced toxicity by sub-acute administration of ambroxol and rebamipide; neurorestorative potential of ambroxol and rebamipide in sub-chronic doses against 6-OHDA-induced model of PD; and Nrf2 activity as important mechanism for rebamipide-mediated attenuation of 6-OHDA toxicity in rats. Additionally, the transdermal patches of rebamipide were prepared and observed to be advantageous over oral route for management of PD in terms of low dose and high potency. The overall outcomes of the thesis work have been summarized in **Figure 10.1.**

10.2. Scope for Further Work

Further studies can be performed for the evaluation of compounds for GCase activity and their potential use as disease-modifying agents in PD. Detailed mechanistic interlink between GCase pathway and other factors involved in PD pathogenesis can be elucidated. The physico-chemical compatibility of these GCase modulators has to be attentively observed to design novel medicated formulation in order to confirm the use of low dose and high patient compliance. These observations would prove helpful in the drug discovery process for the management of PD cases.

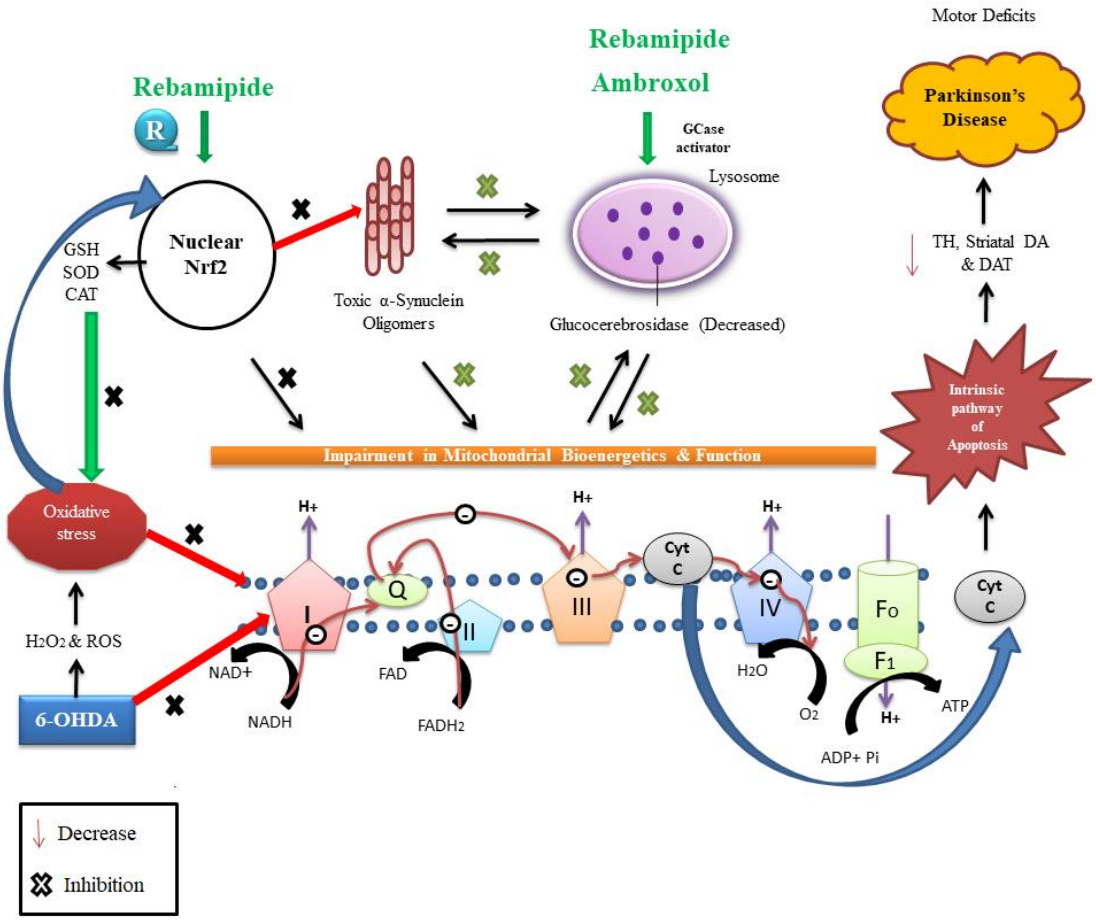

Figure 10.1 The overall outcomes of the thesis work. 6-OHDA could induce dopaminergic cell death either by direct inhibition of mitochondrial respiratory chain or undergo oxidation process to generate ROS and H_2O_2 leading to oxidative stress. This leads to impairment in mitochondrial complex enzyme activities and respiration. Oxidative stress also causes nuclear translocation of Nrf2 which regulate antioxidant system including GSH, SOD and CAT. Nrf2 takes part in α-synuclein degradation and regulation of mitochondrial biogenesis. However, mitochondrial dysfunction leads to GCase deficiency which further increases the concentration of oligomeric aggregates of α-synuclein. Toxic α- synuclein aggregates not only take part in GCase deficiency, but also impair mitochondria function. Additionally, reduction in GCase is one of the reasons behind mitochondrial impairment. Mitochondrial dysfunction is responsible for the release of cytochrome C, followed by apoptosis and deficiency of TH, DAT and DA in nigrostriatal pathway. These pathophysiological changes are responsible for behavioral deficits in PD. The outcome of thesis work can be summarized as follows:

✓ Rebamipide proved to be GCase activator.

- ✓ 6-OHDA inhibits GCase enzymatic activity due to mitochondrial dysfunction and α-synuclein aggregation. Ambroxol in sub-acute doses stimulates GCase activity, which is followed by attenuation of mitochondrial dysfunction, α-synuclein pathology, loss of nigral cells, mitochondrial-linked apoptosis and motor impairment along with the upregulation of striatal DA content against 6-OHDA mediated toxicity.
- ✓ Sub-acute administration of rebamipide mitigates impairment in mitochondrial bioenergetics, followed by GCase deficiency. It decreases oxidative stress with α-synuclein pathology and thereby attenuates 6-OHDA-induced DA striatal degeneration, intrinsic pathway of apoptosis and motor deficits in hemiparkinson's model in rats.
- ✓ Co-administration of Nrf2i inhibits rebamipide-mediated attenuation of 6-OHDA toxicity in rats, indicating the involvement of Nrf2 activity in rebamipide action.
- ✓ Ambroxol and rebamipide in sub-chronic doses restore dopaminergic system even after drug-administration is initiated after the full development of 6-OHDA induced motor deficits, indicating neurorestorative potential of both the drugs.
- ✓ Newly developed rebamipide-loaded transdermal patches also inhibit 6-OHDA toxicity and recovered motor behavior. The effects are found to be similar with oral rebamipide along with the same plasma and CSF drug concentration in both the groups, indicating the equal efficacy of patches and oral rebamipide. However, drug-containing patches show high potency.