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Neurodegeneration is a progressive damage of both structure and function of neurons involving numerous cellular pathways leading to a condition designated as neurodegenerative disorders (NDD). These affect the normal functioning of motor activity as well as cognition. Although various pathways and cascades are demonstrated to be involved in initiation and progression of NDD, oxidative stress mechanism/s emerges as a chief runner in executing the severity of NDD. Both, oxidative stress and mitochondrial dysfunction are known to play key roles in the pathophysiology of various NDD.

Owing to the incurable status of major CNS disorders which has a huge socio-economic impact, researchers are constantly attempting to develop newer and efficient therapeutic approaches, which act on multiple biochemical targets, without detrimental side reactions. Both epidemiological and experimental evidence suggest that the propensity of phytomedicines and polyphenols to attenuate the redox status in vivo can be successfully exploited to achieve neuroprotection. Accordingly, various plant extracts in Ayurvedic medicine products are being explored as therapeutic adjuvants. Since mitochondria play a significant role in oxidative stress and associated neurodegeneration, various chemical compounds that induce mitochondrial dysfunctions are used for mimicking neurodegeneration in rodent and other laboratory models. In recent times, Drosophila melanogaster is employed as an experimental model in elucidating not only the pathophysiology and molecular mechanism/s of NDD, but also as a primary screening platform to develop novel therapeutic approaches.

The primary objective of this thesis was to comprehensively assess the neuromodulatory propensity of Withania somnifera (Ashwagandha, Indian ginseng) and its flavonoids in Drosophila, and mice models of neurotoxicity. For this purpose, a standardized extract of Withania somnifera was chosen. Evidence obtained in the chemical systems in vitro clearly demonstrated the potential antioxidant activity of WSE. Initially, the hypothesis was tested in a Drosophila model (adult flies) of neurotoxicity employing the neurotoxin, Rotenone, a mitochondrial (complex I) inhibitor. Interestingly WSE markedly diminished the endogenous levels of oxidative markers in adult flies. Further,
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extracts robustly offset ROT–induced lethality, locomotor phenotype, and significantly ameliorated oxidative stress in *Drosophila* with concomitant restoration of antioxidant enzyme activity. Ferulic acid a well-known polyphenol offered significant protection in the Rotenone model of neurotoxicity. Further, significant synergistic protections was evidenced in flies exposed to ferulic acid (FA) enriched with WSE neurotoxicity and suggested the utility value of the model.

As a proof of principle, the neuroprotective efficacy of WSE was validated in animal models of ROT (Parkinson’s model). WSE prophylaxis significantly modulated the endogenous levels of brain oxidative markers in the mice model. Further, in the Rotenone model of neurotoxicity WSE, markedly alleviated the locomotor phenotype, motor dysfunctions, and alleviated oxidative stress, restored antioxidant defenses and mitochondrial function in cerebellum and striatum. Interestingly, both cholinergic and dopaminergic functions were restored to varying degree in this model clearly suggesting the neurorestorative efficacy of WSE under neurotoxicant exposure. The neuroameliorative effect of WSE was also evaluated in a Streptozotocin diabetic mice model. Involvement of oxidative stress, mitochondrial dysfunctions are known to be involved in the development of diabetic complications such as encephalopathy and neuropathy. In the mice model, the neuroprotective effects of WSE were evidenced in terms of restoration of behavioral phenotype, attenuation of brain oxidative stress, and mitochondrial dysfunctions and neurotransmission.

Collectively, these experimental data clearly demonstrate the neuromodulatory potential of WSE in experimental models of neurotoxicity in alleviating NDD–related symptomatic manifestations and striatal oxidative stress.