CONCLUSIONS
1. Based on the in vitro evidence obtained in chemical and biological systems, it can be reasonably concluded that the standadarized *Withania somnifera* extract (WSE) possess multiple free radical scavenging potential which is attributable to the presence of withanolides, polyphenols and other minor bioactives in the extract.

2. Prior to the asessement of the neuroprotective efficacy of WSE in *Drosophila* system, a rotenone model of neurotoxicity was standardized in wild type *Drosophila melanogaster* (Oregon K strain). Adult flies exposed to rotenone (ROT) in the medium developed typical locomotor phenotype and showed concentration –dependent lethality response.

3. Exposure of adult male flies to ROT (500μM, 7d) resulted in biochemical phenotype (oxidative stress) which was characterized by diminution of redox homeostasis, mitochondrial dysfunction and neurotoxicity in whole body homogenates.

4. Flies fed with WSE enriched diet showed marked diminution in the endogenous levels of oxidative markers with concomitant enhancement in antioxidant defense suggesting their ability to cope with the neurotoxin exposure.

5. In a co-exposure paradigm, WSE enrichment not only attenuated the ROT-induced mortality response, but also significantly improved the locomotor phenotype of the survivors.

6. Biochemcially, the protective effects of WSE were attributabale to the abrogation of ROT –induced global oxidative stress as reflected by the reduction of levels of ROS, PC and HP in whole body homogenates.

7. The protective nature of WSE was also evident in the mitochondrial milieu as evident by the attenuation of mitochondrial HP and PC. Further, WSE caused significant improvement in the mitochondrial function.

8. The neuromodulatory potential of WSE in this model was reflected by restoration of cholinergic deficits and dopamine levels among flies exposed to Rotenone.
9. In a prophylactic paradigm, WSE enriched diet significantly enhanced the ability of flies to withstand neurotoxicants (Paraquat and Acrylamide) induced lethality, locomotor phenotype and oxidative stress.

10. In the Drosophila model, Ferulic acid (FA) enrichment caused marked diminution in the endogenous levels of oxidative markers and improved the antioxidant defense suggesting its antioxidant potential.

11. In a co-exposure paradigm, FA enriched diet offered significant protection against ROT-induced mortality, alleviated the locomotor deficits, and biochemical measurements revealed its potential to offset ROT-induced global oxidative stress in both cytosol and mitochondrial fractions.

12. FA enrichment effectively offset ROT-induced perturbations in the neuronal function markers viz., activity levels of AChE and DA levels.

13. Interestingly a combination of FA and WSE provided a higher degree of protection against ROT-induced mortality, locomotor phenotype, oxidative damage clearly suggesting that specific polyphenols such as FA along with WSE are likely to provide enhanced neuroprotection.

14. In the in vivo mice model, oral supplements of WSE significantly diminished the endogenous levels of oxidative markers (MDA, HP, and ROS) and protein carbonyls brain regions (cerebellum and striatum).

15. A rotenone model of neurotoxicity was employed to validate the neuro-protective efficacy of WSE in vivo; Rotenone administration caused significant locomotor deficits and WSE treatment significantly offset these deficits.

16. In the co-exposure paradigm, mice provided with oral supplements of WSE 400mg/kg b.w) and administered ROT exhibited markedly improved motor function clearly suggesting the protective action of extracts.

17. WSE enhanced the GSH levels in striatal region and the effect was dosage dependent; Markers of Oxidative stress in both cytosol and mitochondria of striatum /cerebellum among ROT administered mice were attenuated with oral supplementation of WSE. Concomitantly, antioxidant enzyme activities in striatal tissues were also ameliorated.
18. Interestingly, WSE supplements significantly alleviated ROT–induced diminution in the activity levels of mitochondrial marker enzymes in striatum.
19. ROT–induced AChE activity was normalized with WSE supplements while the DA levels were only partially restored.

19. Endogenous levels of oxidative markers were significantly reduced among mice provided with FA supplements and was accompanied by enhanced GSH levels and increased activity of enzymic antioxidant machinery.

20. Prophylactic treatment of mice with FA supplements effectively ameliorated rotenone-induced oxidative impairments, in cytosol and mitochondrial milieu of brain regions (albeit differentially) suggesting specific effect in cerebellum and striatum.

21. FA prophylaxis resulted in elevated redox status and antioxidant defenses in brain regions among rotenone administered mice; further a significant reduction in protein oxidation and NO levels were also evident with FA prophylaxis.

22. In the Rotenone model, FA prophylaxis restored mitochondrial dysfunction, cholinergic and dopaminergic deficits.

23. Taken together these findings in the mice model clearly demonstrate the protective efficacy of WSE supplements against rotenone induced oxidative stress, mitochondrial dysfunctions and neurotoxicity and also suggest that FA enrichment provides additional neuroprotection against exposure to toxicants. This strategy suggests that polyphenols at low doses can be effectively employed along with standard extract of WSE in order to achieve higher neuroprotective efficacy.

24. With an objective of assessing the therapeutic potential of WSE under diabetic conditions, the neuromodulatory potential of WSE supplements was studied in a mice model of diabetes employing low multiple doses of STZ protocol.
25. Mice administered STZ exhibited marked hyperglycemia (nearly 3-fold higher than controls), showed polyphagy and gained relatively less weight, while WSE supplements significantly attenuated these parameters.

26. WSE supplements exerted significant hypoglycemic effect, ameliorated sensory functions (hyperalgesia and allodynia) among diabetic mice and improved the stride length and LFSD measurements.

27. Among diabetic mice provided with WSE supplements, brain regions showed diminished lipid peroxidation characterised by levels of ROS, MDA and hydroperoxide levels both in the cytosol and mitochondria.

28. Further WSE supplements restored the enzymic antioxidant defences in brain regions with concomitant elevation in GSH levels among diabetic mice.

29. WSE markedly enhanced the activity of GST among diabetic mice suggesting its vital role in detoxification process under diabetic condition.

30. In the mitochondrial milieu, WSE supplements significantly attenuated diabetes associated diminution in the activity levels of ETC enzymes (SDH, Complex I-II, and Complex II-III).

31. WSE supplements among diabetic mice resulted in restoration of cholinergic deficits and dopaminergic function.

32. Significant up regulation of VEGF (a trophic factor) evident in the hippocampus of Diabetic mice provided with WSE supplements suggested its neuroprotective role in alleviating diabetes-associated hippocampal dysfunctions.

33. Collectively these findings suggest that oral supplements of a standardized extract of WS roots can effectively attenuate hyperglycemia, locomotor deficits, brain oxidative stress and brain function in an experimental diabetic model.