Conclusions
1. Evidence obtained in the *Drosophila* model for the first time demonstrated the utility value of the system in understanding the neurotoxicity of ACR. Development of locomotor phenotype and induction of oxidative stress in adult flies was consistent with earlier reports in experimental animals subjected to ACR intoxication. Mitochondrial oxidative stress coupled with altered cholinergic activity and depleted DA levels among ACR exposed flies significantly corroborate with biochemical perturbations demonstrated in the brain/ peripheral nerves of rodents.

2. Spice active enriched diet markedly abrogated ACR- induced lethality, locomotor dysfunction, oxidative stress (head/ body) with concomitant increase in GSH levels. EU enhanced the depleted DA levels in head region, while IE/ EU restored the AChE activity in both head/ body regions.

3. Flies maintained on medium enriched with GE/ CU exhibited robust decrease in the levels of ROS and HP suggesting their propensity to attenuate oxidative damage which may be related to enhanced levels of GSH and activities of antioxidant enzymes (SOD, CAT, and TRR). Further, a similar protective effect was also discernible in the mitochondrial milieu (as evidenced by activities of SDH and CS) and neurochemical markers (restoration of AChE activity and DA levels).

4. ACR (24 h exposure) induced oxidative stress in the III instar larvae model was accompanied with significant perturbations in the activities of antioxidant enzymes, enhanced cytosolic calcium levels, elevated AChE activity and diminished DA levels.

5. Elevated expression levels of HSP70 caused by ACR in the transgenic strain were further enhanced by the spice actives.

6. In the pretreatment paradigm, spice actives effectively ameliorated oxidative stress which was probably mediated by enhanced levels of GSH and the activities of GST and SOD among III instar larvae. Further, in the co-exposure paradigm, the protective effect of spice actives was discernible in terms of attenuation of locomotor function.

7. In the *in vivo* study, ACR administration to growing rats (3 times/ week, 5 weeks) induced characteristic symptoms of neuropathy as assessed by a
battery of behavioral tests and consistent biochemical alterations in SN and brain regions.

8. Interestingly in the ACR model, co-treatment with spice actives viz., IE/ EU effectively improved the locomotor functions, lowered the oxidative stress and enhanced GSH levels in SN and brain regions.

9. Among ACR rats, spice actives significantly restored the cholinergic functions and more importantly the dopaminergic function.

10. In the ACR model, similar protective effect was also evident with GE and CU treatment. ACR rats, provided with either GE or CU treatment exhibited improved performance in various behavioral assays which was accompanied by diminished oxidative impairments, higher levels of enzymatic/ non-enzymatic antioxidants, reduced calcium levels, improved cholinergic activity and DA levels.

11. Further, both the bioactives significantly attenuated ACR-induced mitochondrial oxidative damage and reduction in the ETC enzyme activities.

12. EU exhibited significant neuroprotective efficacy in a curative model, as evidenced by higher rate of recovery of rats in the behavioral assessments for sensory (hyperalgesia and allodynia) and motor function clearly suggesting its specific effects.

13. EU treatment in the curative model was discernible both in cytosol and mitochondria suggesting its possible usage as an adjuvant under various other neuropathic conditions.

14. EU effectively restored the cholinergic function (AChE activity only in brain regions) and the DA levels (in SN and brain regions) suggesting their efficacy in normalization of motor function among ACR rats.

15. Collectively data obtained in the ACR model of neuropathy clearly suggests that spice actives/ phytoconstituents can be effectively employed to attenuate the neuropathic signs and some of the underlying biochemical perturbations in SN and brain regions.

16. In the SHSY5Y cell model, spice actives (EU, CU and GE) offset the hyperglycemia associated oxidative stress, depletion of GSH levels, protein
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oxidation, altered HSP70 expression levels clearly suggesting their potential to intervene specific targets under diabetic conditions.

17. Typical signs of neuropathy were demonstrable in a STZ rat model wherein development of sensory deficits preceded (2 weeks) the motor dysfunction (at 6 weeks). Interestingly oxidative stress response in brain regions was discernible earlier than in SN.

18. GE treatment of diabetic rats appeared to markedly abrogate the various diabetes-associated complications. Salient improvements were: increased resistance to hot and cold stimuli (tail immersion tests); diminished levels of motor deficits, decreased oxidative stress response in SN and brain regions with concomitant elevation in GSH levels.

19. Further GE treatment also attenuated the mitochondrial oxidative stress, enhanced the activities of ETC enzymes, restored DA levels in SN/St and caused diminution in the activity of AChE (SN, Cb, St) suggesting improved cholinergic function.

20. In the intervention model, EU treatment was effective in reducing the blood glucose levels and prevented the rate of progression of hyperalgesia and allodynia among diabetic rats.

21. EU treatment significantly abrogated diabetes induced elevation in the levels of oxidative markers and cytosolic calcium with improvement in the compromised antioxidant status and cholinergic function.

22. EU treatment markedly elevated the activities of mitochondrial enzymes viz., SDH, CS, complex I–III and MTT reduction among diabetic rats.

23. In the interactive model, STZ diabetic rats showed higher vulnerability to a low dose of ACR as evidenced by advancement in the development of sensory and motor deficits, degree of oxidative dysfunctions, enhanced cholinergic activity and higher depletion in the DA levels.
Collectively, from the studies conducted in different models, it clearly emerges that the spice actives EU, IE, CU and GE possess the potential to interfere with the antioxidant system and the inflammatory reactions in the nervous system. These actives may be acting via HSP70 activation and improving the antioxidant defence status of the cells. They possibly have the ability to target mitochondria as evidenced by improved redox balance and enzymatic activities. These actives play an important role in the turn-over of acetylcholine by acting on the AChE enzyme emphasizing on their possible effect on cholinergic function. Restoration or maintenance of the levels of the DA by these actives clearly suggests their role in dopaminergic neurotransmission. Further, data from the cell model suggest that these actives prevent or reduce the accumulation of neurofilaments facilitating the normalized neuronal activity in terms of vesicle movement and turn-over of the neurotransmitters. Thus these actives exhibit neuro-modulatory properties both in in vitro and in vivo systems of experimental neuropathy. Collectively from these data, it is hypothesized that these actives are promising agents as potential adjuvant therapeutics in the management of neuropathy.