Conclusion

The onset of spontaneous seizures triggers a cascade of molecular and cellular events that eventually leads to neuronal injury and cognitive decline. The present study investigated the effect of *Withania somnifera* (WS) root extract and Withanolide A (WA) in restoring behavioural deficit by inhibiting oxidative stress induced alteration in glutamergic neurotransmission. The subdued performance in behavioural tests shows impaired motor coordination and memory. Histopathological investigations revealed significant neuronal loss in hippocampus of epileptic rats indicating glutamate mediated excitotoxicity. The treatment with WS and WA restored behavioural deficit and ameliorated neuronal loss. An altered redox homeostasis leading to oxidative stress is a hallmark of TLE. The antioxidant potential was afflicted in epileptic rats, evident from altered activity of SOD and CAT, down regulation of SOD and GPX expression and enhanced lipid peroxidation. The antioxidant property of WS and WA restored altered antioxidant capacity. Alteration in GDH activity and down regulation of GLAST expression resulted in enhanced glutamate content in the brain regions. The metabolism of glutamate was altered in the form of down regulated GAD expression. The alteration in synthesis, transport and metabolism resulted in further increase of the glutamate concentration at the synapse leading to glutamate mediated excitotoxicity. The decreased NMDA and AMPA receptor binding and down regulated NMDA R1, NMDA 2B and AMPA (GluR2) mRNA expression indicated altered glutamergic receptor function. The treatment with WS and WA reversed altered glutamergic receptor function, synthesis, transport and metabolism. The enhanced levels of second messenger IP3 responsible for Ca$^{2+}$ mediated toxicity was reversed after treatment with WS and WA. Neurotoxic concentration of glutamate resulted in up regulation of pro apoptotic factors Bax and Caspase 8 and down regulation of anti apoptotic factor Akt resulting in neuronal death. The treatment with WS and WA resulted in activation of Akt and down regulation of Bax and caspase 8 leading to blocking of apoptotic pathway. The treatment with WS and WA resulted in reduced seizure frequency and amelioration of associated alterations suggesting the therapeutic role of *Withania somnifera* in temporal lobe epilepsy.