PREFACE

This thesis is submitted for the degree of Doctor of Philosophy at Indian Institute of Technology (Banaras Hindu University), Varanasi. The research described herein was conducted under the supervision of Prof. Ranjana Patnaik in the School of Biomedical Engineering, Indian Institute of Technology (Banaras Hindu University), Varanasi between July 2014 and February 2019.

This work is to best of my knowledge original, except where acknowledgements and references are made to previous work. Neither this, nor substantially similar thesis has been or is being submitted for any other degree, diploma or other qualification at any other university.

Cerebral ischemia remains a leading contributor of global mortality and disability rate. Lack of therapeutic strategies for combating this disorder, makes it even more menacing. The present study identifies suitable compounds with pharmacological properties that can serve as potential neuroprotectants against cerebral ischemia pathophysiology. The compounds are screened in-silico using molecular docking techniques based on their drug like properties and ability to inhibit major molecular mediators of ischemic cell death cascade. The molecules deemed suitable from virtual screening are further studied in-vivo to evaluate their neuroprotective ability.

The thesis identifies Withanolide A, a major phytochemical constituent of Withania somnifera (Aswagandha), an Ayurvedic Indian herb and Estetrol, a fetal Estrogen, as highly potent inhibitors of PARP-1 and RIPK1, respectively. PARP-1 and RIPK1 happens to be major molecular mediators of caspase independent ischemic cell death pathway. The compounds are

further evaluated for their neuroprotective ability against global cerebral ischemia induced inmice by bilateral common carotid artery occlusion (BCCAO) method. It is observed that compounds significantly ameliorates marked characteristics of ischemic pathophysiology. The compounds are able to reduce cerebral infarction, restore blood brain barrier damage and combat cerebral edema. The compounds also significantly lowered ischemia induced elevated levels of neurotransmitter and biochemical levels in different brain parts. The compounds were also able to combat ischemia inflicted brain tissue damage and cell death.

The current study also explored the efficacy of the pleiotropic neuropeptide Prolactin in combating in-vivo global cerebral ischemia. It was observed that Prolactin successfully restored physiological, biochemical and brain tissue damage in BCCAO model of adult rat.

The present study for the first time reports efficacy of Withanolide A, Estetrol and Prolactin as neuroprotective agents against global cerebral ischemia pathophysiology in rodent model. The work presented in this study will be significant interest to academicians, researchers and scientists involved in the field of neurodegenerative diseases, neuroprotection and cerebral ischemia.