Fig. 1.1. Differentiation between ischemic and hemorrhagic brain damage and 2 respective occurrence percentages globally Fig. 1.2. Broad categorization of cerebral ischemic damage 2 Fig. 2.1. Cerebral ischemia pathophysiological cascade 17 Fig. 2.2. Chemical Structure of Withanolide A 25 Fig. 2.3. Structure of Estrogen Hormones 26 Fig. 2.4.: Chemical Structures of (a) Progesterone and (b) Allopregnanolone 27 Fig. 2.5.: Structure of Prolactin 28 Fig. 2.6. : Types of experimental models in cerebral ischemia 29 Fig. 2.7. : Representation of Circle of Willis 30 Fig. 2.8. : Induction of global cerebral ischemia by bilateral common carotid artery 31 occlusion Fig. 3.1.: PARP-1 plays a pivotal role in caspase-independent cell death by recruiting 47 AIF and depleting cell energy reservoir Fig. 3.2: Structures for known PARP-1 inhibitors 48 Fig. 3.3. : Comparison of binding energies of inhibitors and W. somnifera 52 phytochemicals Fig. 3.4.a-c: Interaction pattern of inhibitors FR257517, PJ34 and Talazoparib with 56 amino acid residues of catalytic domain of PARP-1 Fig. 3.5.a-e: Interaction pattern of W. somnifera phytochemicals having binding 57 energy lower than -11.00 kcal/mol with PARP-1 catalytic domain Fig. 3.6.: Stigmasterol binding at (a) the catalytic site; (b) off-target domain 59 Fig. 3.7.: Withaferin A binding at (a) the catalytic site; (b, c) off-target domains. 59 Fig. 3.8.: Withacnistin binding at (a) the catalytic site; (b) off-target domain 59 Fig. 3.9. : Comparison of hydrogen binding and hydrophobic interaction pattern of 64 Talazoparib and Withanolide A with PARP-1 catalytic domain. Fig. 4.1.: Schematic for study of neuroprotection by WA in mice model of global 76

LIST OF FIGURES

xvi

cerebral ischemia.

Fig. 4.2. (a) Brain Penetration of WA following intra-nasal administration; (b) UV- HPLC chromatogram of WA obtained from brain homogenate after 30 minutes of intra nasal administration.	81
Fig. 4.3.: Effect of WA on cerebral infarction.	82
Fig. 4.4.: Effect of WA on BBB disruption	83
Fig. 4.5.: Effect of WA on cerebral edema	84
Fig. 4.6.: Restoration of neurotransmitter levels by WA post-treatment	85
Fig. 4.7.: Effect of WA on cerebral calcium and nitrate levels	86
Fig. 4.8.: Effect of WA post-treatment on brain histopathology	87
Fig. 4.9. Evaluation of effect of WA on brain cell death	88
Fig. 5.1: Role of Rip-1 Kinase in necroptosis pathway	00
Fig. 5.2.: Chemical structures of (a) Necrostatin-1; (b) Necrostatin-4	100
Fig. 5.3. Interation pattern of RIPK1 and Estrogen hormones.	100
Fig. 5.4. (a) Interaction pattern of Necrostatin-1; Interaction pattern of Necrostatin-4 (ball and stick) with RIPK1 (ribbon)	107 108
bonded inhibitors Fig. 61: Schemetic	110
Fig. 6.2.: Effect of different doses of E4 or	121
Fig. 6.3.: Effect of E4 post-treatment on ED	125
Fig. 6.4.: Effect of E4 post-treatment on L and the stravasation in mice brain	126
Fig. 6.5.: Effect of E4 post-treatment on glutomet	127
Fig. 6.6.: Effect of different doses of E4 on GABA to the	128
Fig. 6.7.: Effect of different doses of E4 on cerebral and	129
b.8.: Effect of E4 post-treatment on brain nitrate	130
Fig. 6.9.: Effect of E4 post-treatment on CBF	131
	132

Fig. 6.10.: Hematoxylin and Eosin staining of brain cortical region of different experimental groups	133
Fig. 7.1.: Experimental workflow for cerebral ischemia induction and PRL administration	144
Fig. 7.2.: Changes in physiological parameters due to PRL post-treatment	148
Fig. 7.3.: Effect of different doses of PRL on changes in neurotransmitter levels	149
Fig. 7.4.: Restoration of calcium levels in different brain parts upon PRL treatment	150
Fig. 7.5.: Effect of different doses of PRL on nitrate levels in various brain regions	151
Fig. 7.6.: Dose dependent reduction of cerebral infarction as an effect of PRL treatment	152
Fig. 7.7.: Reduction of cerebral edema with treatment of different doses of PRL	153
Fig. 7.8.: Effect of different doses of PRL on brain cell death	154