SUMMARY AND CONCLUSION

Chronic stress is a major risk factor for the development of several neurological diseases, ranging from cardiovascular disorders to mental illness. Stress exposure induces several changes in the multiple neural systems of the body, among which the most important is generation of oxidative stress, inflammatory mediators and the activation of hypothalamo-pituitary-adrenal (HPA) axis. It is not surprising that chronic stress exposure also significantly caused potential tissue damage in peripheral and central nervous systems. There exist a complex relationship between stressful situations, mind and body's reaction to stress, and related neurological disturbances. Chronic stress-induced depression is one of the common psychiatric disorders and a global burden. Depression is identified as a major neuropsychiatric problem which comprises a wide group of disabilities that further results into a multifactorial condition. Cognitive dysfunction, another consequence of chronic stress, is known to be at risk following head trauma due to the selective vulnerability of hippocampus, which plays a crucial role in the processing of spatial learning and memory. From last four decades extensive research has been done to elucidate stress mechanism, its neurobiology and to develop suitable therapeutic agents for the management of stress and related problems. Besides, chronic stress or persistent stressful situations are main triggering factors in the genesis of chronic pathologies such as depression and cognitive dysfunction. However, the exact relation of stress and its mechanism in chronic pathologies or neurological problems are not still fully understood.

With this background, the present study was designed to evaluate the neuroprotective mechanism of curcumin, ginseng and quercetin on chronic stress-induced neurological disorders such as depression and cognitive deficits using different animal models. Moreover, the involvement of oxidative-
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Nitrosative stress, inflammatory mediators and apoptotic cascade in the development of these complications was elucidated.

CHAPTER 1: NEUROPROTECTIVE EFFECTS OF CURCUMIN AND GINSENG AGAINST EXPERIMENTAL MODEL OF CHRONIC UNPREDICTABLE STRESS INDUCED COGNITIVE DEFICITS

Chronic unpredictable stress (CUS) experimental model has been validated /standardized to study the development and progress of stress pathology and related cognitive disorders. In the present study, chronic unpredictable stress (CUS) for a period of 28 days significantly caused deficits in cognitive behaviour (Morris water maze and elevated plus maze), decreased sucrose consumption, increased oxidative-nitrosative stress (increased lipid peroxidation, nitrite concentration, depletion of reduced glutathione, superoxide dismutase and catalase activity), impaired mitochondrial enzyme complex (I to IV) activities and increased corticosterone levels. However, treatment with curcumin (200 and 400 mg/kg, p.o.) and ginseng (100 and 200 mg/kg, p.o.) for 28 days, significantly improved these behavioral, biochemical, mitochondrial and molecular alterations. Further, co-administration of curcumin (100 and 200 mg/kg, p.o.) with piperine (20 mg/kg, p.o.) for 28 days significantly potentiated their protective effects as compared to their effects alone. The results clearly suggest that piperine enhanced the bioavailability of curcumin and potentiated its protective effects against CUS induced cognitive impairment and associated oxidative-mitochondrial damage in mice. On the other hand, pretreatment of L-NAME (10 mg/kg; i.p.); a non-specific NO synthase inhibitor with subeffective dose of ginseng (100 mg/kg; p.o) for 28 days potentiated the beneficial effects of ginseng as compared to their effects alone. However, pretreatment with L-arginine (100 mg/kg; i.p.); a nitric oxide donor with subeffective dose of ginseng (100 mg/kg; p.o) reversed the effects of ginseng (100 mg/kg; p.o). These results suggest the involvement of nitric oxide mechanism in the protective effects of ginseng against chronic unpredictable stress-induced cognitive deficits.
CHAPTER 2: NEUROPROTECTIVE FUNCTIONS OF CURCUMIN AND QUERCETIN AGAINST EXPERIMENTAL MODEL OF OLFACTORY BULBECTOMY INDUCED DEPRESSION

Olfactory bulbectomy (OBX) is known to cause complex alterations in behavioral, biochemical and cellular cascades, many of which are comparable to those seen in patients with major depression. In the present study, ablation of olfactory bulbs caused depression-like symptoms as evidenced by an increased immobility time in forced swim test, hyperactivity in open field arena, and anhedonic like response in sucrose preference test, along with increased serum corticosterone levels and oxidative-nitrosative damage. These deficits were integrated with increased inflammatory cytokines (TNF-α) and depleted levels of brain derived neurotrophic factor (BDNF) in cerebral cortex and hippocampal regions of OBX rats. Treatment with curcumin (200, 400 mg/kg, p.o.) and quercetin (40, 80 mg/kg; p.o.) for 14 days significantly attenuated these behavioral, biochemical and molecular alterations associated with OBX induced depression. Further, co-administration of piperine (20 mg/kg; p.o.) with curcumin (100 and 200 mg/kg, p.o.), for 14 days, significantly potentiated their neuroprotective effects as compared to their effects alone. On the other hand, interaction of quercetin (20, 40 mg/kg; p.o.) with minocycline (25 mg/kg; p.o.), a microglial inhibitor, for 14 days, significantly potentiated their protective effects as compared to their effects alone. The findings suggest that microglial inhibitory pathway might be involved in the neuroprotective effects of quercetin against OBX-induced neuroinflammation and depression behavior.

CHAPTER 3: THERAPEUTIC ROLE OF GINSENG AND QUERCETIN AGAINST EXPERIMENTAL MODEL OF MILD TRAUMATIC BRAIN INJURY INDUCED COGNITIVE LOSS

Mild traumatic brain injury (mTBI) produces several neuropathological alterations; some of them are analogous to patients suffering from memory
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disorders. In the present study, traumatic brain injury caused significant memory impairment in Morris water maze task as evident from increased escape latency time and total distance travelled to reach the hidden platform. This was followed by decrease in frequency of appearance and time spent in target quadrant. Further, there was enhanced acetylcholinesterase (AChE) activity along with increased oxidative-nitrosative stress, inflammatory cytokines (TNF-α) and apoptotic factor (caspase-3) levels in brain hippocampus region of traumatized rats, which was further supported by reports from histopathological studies. Treatment with ginseng (100 and 200 mg/kg; p.o) and quercetin (20, 40 mg/kg) for 14 days significantly attenuated the cognitive deficits and other biochemical, molecular and histopathological alterations associated with mTBI. Furthermore, pretreatment of L-NAME (10 mg/kg, i.p.) with subeffective dose of ginseng (100 mg/kg), for 14 days, potentiated their protective effects; however, pretreatment of L-arginine (100 mg/kg; i.p.) reversed the protective effects of ginseng. The study suggests that nitric oxide modulatory mechanism might be involved in the neuroprotective effects of ginseng against mTBI-induced cognitive deficits, neuroinflammation, and apoptotic signaling cascade. On the other hand, co-administration of sub-effective doses of quercetin (20, 40 mg/kg) with minocycline (25 mg/kg), for 14 days, potentiated their protective effect which was significant as compared to their effects alone. The results suggest that the therapeutic effects of quercetin might involve inhibition of microglial pathway against head trauma-induced cognitive impairment and neuroinflammation.