Summary & Conclusion
Chapter I: It deals with review of literature and provides an insight into the neurodegenerative disorder, cognitive impairment (Alzheimer's disease). The initial part of review gives us the picture of the basics of Alzheimer's disease, history, signs and symptoms, risk factors, brain parts affected, drugs in use, and various measures to evaluate the degree of brain damage by diverse methods. The mid section of the review gives the picture of the drugs that have been used in the study, which are synthetic and herbal based. Main stress is given on the drugs, their nutritional and antioxidant properties. Last section provides the picture of the various pathophysiological mechanism of Alzheimer's disease. It gives an insight in the evolution of cell death after the damage has incurred.

Chapter II: *Nardostachy Jatamansi* and Crocetin in conjunction with Selenium has Potent Neuroprotection in Cognitive impairments (Alzheimer's Disease).

Generally, it has been evaluated the conjunctions of two or more drugs are more potent for neuroprotection. The study was designed to check the potency of combination of the minimum doses of *Nardostachy jatamansi* (N), Crocetin (C), Selenium (Se) as sodium selenite in neuroprotection in cognitive impairment of animal model. A combine drug with minimum doses (N, 200 mg/kg + C 25 µg/kg + Se 0.05 mg/kg) was given orally for 15 days to the cognitive impaired animal model. The elevated level of thiobarbituric acid reactive substances and depleted level of glutathione were protected significantly. The significantly decreased activity of glutathione peroxidase, glutathione-S-transferase, and catalase in lesioned group was protected significantly with combined drug. Thus, our study reflects that the combined drugs at their minimum concentration have shown more potent neuroprotection and synergistic effect on cognitive impairment in rats. Moreover, behavioral activities have shown wonderful support to the study.

Chapter III: Combination therapy of antioxidants prevents cognitive deficits caused by intracerebroventricular administration of streptozotocin in rats. Oxidative stress plays a crucial role in age-related neurodegenerative disorders. Here we examined the protective role of combined drugs, Vitamin C, F and selenium (CESc) on the cognitive impairment in male Wistar rats. Intracerebroventricular single injection of streptozotocin (3.0 mg /kg b wt) leads to severe deficits in learning and memory. We observed that CESc pretreated rats when lesioned with single streptozotocin injection has significantly restored the biomarker enzymes (glutathione peroxidase, glutathione reductase, glutathione-S-transferase, superoxide dismutase and catalase) and cholinergic markers such as acetylcholine esterase and choline acetyltransferase as well as non-enzymatic biomarkers (lipid peroxidation, hydrogen peroxide, reduced glutathione, calcium overload and protein carbonyl) in comparison to vehicle treated intracerebroventricular-streptozotocin (ICV-STZ) injected rats in hippocampus. Histopathological morphology of the hippocampus shows the effect of ICV-STZ on neuronal cell body neurodegeneration and protection by CESc. The administration of CESc improved the cognition of rats in Morris water maze test. These effects probably occurred directly within the brain, as the CESc crosses directly or indirectly the blood-brain barrier and acts on the neurons. Another possibility, that CESc treatment may overcome the effects of streptozotocin neurotoxicity in the brain and maintain the integrity of the neuronal circuit. These results support the hypothesis that oxidative stress can lead to cognitive dysfunction and provide evidence for a therapeutic role for antioxidant. Thus, our study reflects that CESc play an important role for neuroprotection as antioxidant.

Chapter IV: Restoration of cognitive impairment by *Bacopa monniera*. In this study selected dose of Brahmi (*Bacopa monniera*) (30 mg/kg b wt) used orally for 15 days has protected significantly the learning and memory test analyzed by Morris water maze when compared with the group treated with 3 mg/Kg streptozotocin. The antioxidant markers, TBARS, reduced
glutathione, glutathione peroxidase, glutathione-S-transferase, superoxide dismutase, catalase, Na+-K+ ATPase and caspases-3 were altered significantly with ICV-STZ administration and was protected significantly with Bacopa monniera. ICV-STZ induced alterations in the expression of p53 and bcl2 proteins in the hippocampus. The immunohistochemistry of Cu/Zn-SOD which was depleted significantly, and protected by the extract of Bacopa monniera. These data suggest that ICV-STZ might cause its neurotoxic effects via the production of free radicals and secondary perturbations in the expression of genes known to be involved in apoptosis and cell death machinery. The Bacopa monniera extract has restored their levels, activity and expression in hippocampus. Thus, our study suggests that herbal extract of Bacopa monniera has potential role against oxidative stress and more potent neuroprotection on antioxidant.

Chapter V: Regulation of stem cells in the cognitive impairments by fibroblast growth factor-2 and Nardostachys jatamansi. This chapter presents the lesions in the brain of male mouse induced with streptozotocin (STZ) and studied the effect of Nardostachys jatamansi (NJ) in the lesioned recovery. The study has been further followed by the administration of FGF-2 to monitor proliferation of stem cells and its migration from subventricular zone to hippocampal regions. Efforts are made to quantitate and identify the neuronal population affected by this study. The behavioral (Morris water maze), biochemical parameters (lipid peroxidation, reduced glutathione, glutathione peroxidase, glutathione-S-transferase, superoxide dismutase and catalase) and immunohistochemical changes were studied. The animals were divided in to six groups each having twelve animals for the initiation of each experiment. The first group serves as sham and saline was given, second was STZ group, third was post treated STZ with FGF2 i.e. STZ+FGF2, fourth was post treated STZ with NJ i.e. STZ+NJ, fifth was post treated FGF2 and sixth was post treated NJ alone. The spatial navigation task (path length and escape latency) was studied in all the groups and compared. The control (sham) group showed reduced escape latency during the acquisition period from day 1 to day 7 as compared to other groups. However, STZ treated group showed maximum escape latency as compared to other groups. The path length was increased gradually in STZ treated group where as all the groups showed reduced path length gradually from day 1 to day 7. After the behavioral test animals were sacrificed and hippocampus was dissected out for biochemical assays. The content of LPO (TBARS) was significantly increased in STZ group and was decreased significantly in STZ group post treated with FGF2 and NJ as compared with STZ group. The antioxidant enzymes (glutathione peroxidase, glutathione reductase, glutathione-S-transferase, superoxide dismutase and catalase) activity and reduced glutathione level were depleted significantly in STZ group as compared sham group, which were attenuated significantly in STZ group post treated with NJ and FGF2. In sham group insignificant immunoreactivity to GFAP (red) was observed. But, streptozotocin treatment resulted in a significant neuroinflammatory response and loss of neuronal cells in the hippocampus. Conversely, there was a significant increase in GFAP (red) positive cells in the same regions following diabetogenic stress indicative of astroglial cell proliferation. Streptozotocin treatment resulted in loss of significant number of cells in the hippocampus as seen by the DAPI staining (blue), which diminished with stress. Conversely, there was a significant increase in GFAP (red) positive cells in the same regions following diabetogenic stress indicative of astroglial cell proliferation. In normal mice there was an abundance of NeuN (green) positive cells indicating an environment rich in neuronal progenitor cells. Following streptozotocin treatment there was loss of significant number of cells in the hippocampus as seen by the DAPI staining (blue), which diminished with stress. Conversely, there was a significant increase in GFAP (red) positive cells indicating an environment rich in neuronal progenitor cells. Following streptozotocin treatment there was loss of significant number of cells in the hippocampus. Treatment with NJ as well as FGF-2 sustains the cell proliferation/differentiation. Newly formed cells are migrating, forming neuronal network in areas where there was a significant number of cell loss. Enrichment in NeuN positive (green) neuronal progenitor cells. Following
Summary & Conclusion

Streptozotocin treatment there was loss of significant number of cells in the hippocampus. Treatment with NJ as well as FGF-2 sustains the cell proliferation/differentiation as seen herewith. NeuN (green) positive cells. This promising effect may be because of the administration of FGF-2 and NJ who may offer combating the oxidative stress generating by streptozotocin.

Conclusion

Cognitive impairment (Alzheimer’s disease) is a multifactorial disease and millions people worldwide are suffering from this devastating neurological disorders. Lack of early diagnosis and poor neuropharmacological intervention might be a central lacuna of this disease. To overcome the rate of mortality and neurological dysfunctions are the main objectives from various therapeutic approach. Synergistic or combined effects of the synthetic drugs are widely accepted than single. Herbal drugs on the other hand, have been used since long time worldwide and facilitate the satisfactory improvement. However, their uses in patients are confined. It has been believe that chemical compound, active constituents present in these herbal drugs play a central agency for ameliorating the neurological disorders. The research work carried out in this study, both synthetic (as a combination) and herbal either in combination with synthetic or alone was used for their efficacy as a neuroprotectant.

Nordostochium (herbal drug) was used with the combination of crocetin (active constituent of saffron) and selenium (as a sodium selenite). The other combination of vitamin C, vitamin E and selenium was tested for its possible role in neuroprotection. Bacopa monniera, a memory enhancer herbal drug was used alone and its wonderful effect was seen in the rat model of the cognitive impairment. Bacopa monniera, an herbal drug was tested alone in mice model of cognitive impairment and its efficacy was studied for the recovery of lesions induced with streptozotocin (STZ) of the brain of male mouse. FGF-2 (a synthetic drug) was tested and it plays a significant role in neurogenesis followed by lesions induced with STZ. Cognitive impairment in rat and mice model was used in this study. STZ causes generation of free radical, oxidative stress, neurobehavioral abnormality, learning and memory loss and cell death by apoptosis pathway. It was shown in the research studies, herbal and synthetic drugs significantly afforded neuroprotection against cognitive impairment (Alzheimer’s disease) by maintaining the oxidative damage, neuronal integrity, behavioral outcomes and cell death by apoptosis in drug administered group. These drugs may be added in the armamentarium of neuroprotective drugs in human kind.

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