Chapter 8
Conclusion

8 Conclusion

Nanoscaffolds opens up a world of possibilities for both current and novel formulations paving the path for the future development of innovative therapeutic interventions for AD. Various researches are in progress to develop a suitable candidate for safer and efficacious therapy in AD. Crossing of BBB is a major limitation faced by a large number of neurological drugs and nanocarriers. Nanoscaffolds can help in deep penetration of memantine across BBB, and intrathecal administration of memantine-loaded nanoscaffolds helps to improve its retention and penetration in brain tissue. The use of drug-loaded nanoscaffolds can provide a handy tool for the treatment of neurodegenerative AD due to its biocompatibility, biodegradability, and cost-effectiveness. However, rigorous experimental trials are required before such therapeutic approaches could be translated to clinics. Despite the profound impact of AD, the conventional treatments are unable to achieve satisfactory therapeutic effects or stop the progression of the disease. Restorative therapies of neurological disorders become important tool which require new strategies for repair and stimulation of neurogenesis against mental deterioration and neurodegenerative disorders.

In this study, treating the fundamental cause of AD could lead to memory and cognitive enhancement, as well as a reduction in neurodegenerative damage. Furthermore, the use of stimuli like pH can help in assembly of nanostructures which can create extracellular matrix to facilitate regeneration. Moreover, the biocompatibility and biodegradability of polymers used in the self-assembled nanoscaffolds minimizes the systemic toxicity and could be safe therapy for the patients. The biodegradable nature PLGA nanoscaffolds is an important aspect to deal with this challenge for the treatment of brain disorders, and is effective for all kinds of patient populations with complications. Moreover, the PEG coating imparts hemocompatibility to nanoscaffolds and stealth nature which in turn minimizes surface interaction with opsonin thus preventing macrophage uptake and clearance from the body. However, AChE, BUChE and β secretase enzymatic inhibition study showed maximum inhibition of enzymes in the extract from the hippocampus as compared to cortex region of brain indicating towards retention of acetylcholine, butyrylcholine and APP in brain that helps to preserve cognitive functions in brain. In addition, (PEG-MEM-PLGA) SANs-BMSc treated animals showed higher neophobic activity in the Y-maze study, indicating recovery and retention of memory due to the combined effect of PEG, memantine and stem cells. The observations in the present study also help to understand contribution of proinflammatory cytokines in the pathogenesis of CNS in triggering adaptive innate immune response during the course of chronic neurodegeneration. Although

these markers are not specific to the disease but effects of IL-1β, IL-6, IL-10, and TNF-α were found insightful to act as biomarkers. IL-6 level in serum, hepatic and renal tissue and IL-1β in serum and cerebral tissue, IL-10 in serum, and TNF-α in cerebral tissue or cerebrospinal fluid were enhanced in diseased conditions. The expression of each cytokine is different in different organs, so understanding the presence of specific cytokines in each organ will further help to develop a suitable identifiable marker for the detection of neurodegeneration. Furthermore, incorporation of serum, cerebral and hepatic biomarkers can provide more diagnostic/prognostic information by detecting abnormally low or high level of pro-inflammatory cytokines that can help predict pathological changes associated with AD. Also, additional studies are required to further understand the role of pro-inflammatory cytokines as biomarkers in neuroinflammation, neurodegeneration, and for disease-modifying therapies for AD. We found that after induction of AD in mice the level of cytokines spiked unexpectedly which indicates that neurodegeneration or neuroinflammation also triggers the release of cytokines. The outcomes of the study of estimation of pro-inflammatory cytokines in serum, cerebral, hepatic and renal has revealed that the level of IL-1β, IL-6, IL-10 and TNF-α cytokines were mostly affected by nanocarriers in serum, cerebral tissue of scopolamine induced amnesia model of mice. The nanocarriers exerts its potential contributory effect on reducing the level of pro-inflammatory cytokines (IL-1β, IL-6 (serum), IL-10 and TNF-α) in all organ which was found elevated in case of AD and indicates the reduction in neuroinflammation mediated neurodegeneration. The level of cytokines might be beneficial as a tool or biomarker to detect inflammation trigged neurodegeneration. Moreover, The biodistribution study of (PEG-MEM-PLGA) SANs has shown its maximal accumulation in the brain followed by liver and kidney whereas (MEM-PLGA)SANs was maximally quantified in kidney followed by brain and liver may be due to uptake of memantine via mononuclear phagocyte system which is mainly found in the liver and kidneys. Distribution of memantine in brain upon administration of (PEG-MEM-PLGA) SANs might be due to stealth behaviour of PEG which imparts stability against opsonisation of nanoscaffolds and accumulation in mononuclear phagocyte system and reticuloendothelial uptake. The histological study has showed dark appearance of neurons that are bilaterally arranged within two major midbrain nuclei of brain with an intense accumulation of amyloid β protein and neurodegenerative neurons in diseased animal. PEG coated memantine-loaded PLGA nanoscaffolds showed a decrease in the accumulation of amyloid β plaque and degenerated neurons and improvement in memory and learning skill.

Thus, this nanocarrier systems are believed to be feasible and promising in neurodegenerative therapy like Alzheimer's Disease which allow targeting of the particles to increase their

concentration at the site of interest, while reducing their systemic side effects. A deeper understanding of pharmacokinetic, pharmacodynamic and biodistribution studies helps to provide innovative treatment strategy for several diseases, with improvement in the safety, efficacy, and pharmacokinetics of drugs.