5. DISCUSSION
5.0 DISCUSSION

The results of the present investigations indicate the molecular interaction between the dopaminergic pathway and mevalonate pathway in depression. The potentiation and inhibition of antidepressant action of simvastatin was observed when combined with bromocriptine and haloperidol respectively, in terms of either immobility time in FST and TST or sucrose intake in CMS, has indirectly suggested the preliminary hint for such molecular interaction. However, such results do not answer the question of whether the behavioural sampling data of any animal models of depression could reliably be compared with clinical outcome of depression since the screening for the antidepressant agents through the animal models of depression always demand the accurate validation of models with its greater construct validity, predictive validity and face validity. Forced swim test and tail suspension test were reported as the first line acute animal models of depression due to its higher predictive validity which screens the antidepressants accurately, can be used more apparently in human (Willner, 1984) whereas chronic mild stress model was reported as one of the chronic models of depression with higher construct validity which can establish empirical relationship between the feature being modelled and depression in humans (Willner, 1984). However, despite the higher predictive validity of FST and TST or the higher construct validity of CMS model which might enable us to correlate the clinical symptoms, more evidences are required to be furnished to confirm above mentioned molecular interaction.

Although, we were unable to measure dopaminergic agents induced alteration in the phosphorylation state of either cAMP response element binding protein (CREB) or HMGR, the results of lipid data which have indicated the potentiation of hypolipidemic action of simvastatin in presence of bromocriptine have enabled us to indirectly suggest the effect of the dopaminergic agents on simvastatin induced phosphorylation state of
the HMGR. Lipid parameters as mentioned in the results were found to be increased significantly by the haloperidol alone but it was not affected by the combination of simvastatin with haloperidol which indicates the surmountable effect of simvastatin in the presence of haloperidol which further strengthened the hypothesis for the molecular interaction between above mentioned pathways.

The mechanism that underlies the effect of dopaminergic agents as mentioned above on the hypolipidemic function of simvastatin remains to be elucidated. However, several recent pathways such as inflammatory pathways, cell-mediated immune pathways etc may hint the newer targets for the exploration of the effect of dopaminergic agents on the function of simvastatin. The synthesis as well as reuptake of dopamine (Moreno et al., 2013) and up regulation of dopamine transporter (Krishnadas and Cavanagh, 2012) was reported to be altered by proinflammatory cytokines. Hence, we suggest to examine if the statins would inhibit or reverse a cascade of immune-mediated dopamine depletion due to its anti-inflammatory and immunomodulatory properties (Cucchiara and Kasner, 2001; Rajanikant et al., 2007).

Due to relatively high concentration of cholesterol in the brain, the detection of specific changes in membrane cholesterol is difficult. Although, we were unable to measure changes in membrane cholesterol levels but further research work is suggested to examine if the alteration of brain cholesterol would be influenced by dopamine D₂ receptor modulators alone or in combination with simvastatin in depression. The study is also required to be done to examine if the effect of above mentioned combination would affect the transfer rate of circulating plasma cholesterol to the brain.

In accordance with the above mentioned results collectively and the results for the effect of the dopaminergic agents on simvastatin induced expression of exon II transcripts of BDNF gene have enabled us to directly suggest the possible molecular interaction between above mentioned pathways.
However, the results for the expression of exon II transcripts of BDNF gene have also revealed that stimulation of the appropriate adaptive changes has occurred in neuronal systems in terms of differential expression of exon II transcripts of BDNF gene. It is possible that there occur adaptive changes in the mice brain in response to either direct effect of CMS treatment or CMS induced total cholesterol level, as evidenced by the increase in the expression of exon IIB transcripts of central BDNF gene and its negative correlation with total cholesterol level in stressed mice. It is also possible that alteration in the expression of specific exon IIC transcripts of BDNF gene occurs in response to either stress or stress induced lipid levels that are related to specific dopamine D2 receptors, since significantly decrease in simvastatin induced expression of exon IIC transcripts of BDNF gene was found in the presence of haloperidol to stressed mice.

The ability of simvastatin to increase the expression of exon IIC transcript of BDNF in stressed mice, which was not affected by the stress treatment. It is possible that there is a link between HMGR and that the expression of exon IIC transcript of BDNF.

The mechanism that underlies the significant effect of haloperidol or insignificant but partial effect of bromocriptine on the function of simvastatin in mediating the expression of specific exon IIC transcript of BDNF gene, remains to be elucidated but results of correlation analysis in the present study may show the possible influence of alteration in the lipid levels in the expression of exon IIC transcripts. However, recent advances for the role for specific intracellular cascades, target genes and structural neuronal plasticity in the action of antidepressants may also hint for the possible interaction between dopaminergic agents and simvastatin in mediating the expression of exon IIC transcript of BDNF gene in depression.
Considering diversity and heterogeneity of GPCRs with differential pharmacological and signalling properties (Moreno et al., 2013), we have hypothesized that the expression of exon IIA and exon IIB transcripts of BDNF gene may be affected by the other type of dopamine receptors such as dopamine D$_1$ like receptors which were not reported be affected significantly in the present study by the combination of simvastatin either with bromocriptine or haloperidol or levodopa.

Our behavioural sampling data, in vivo lipid data, expression data for the exon II transcripts of BDNF gene and correlation analysis data suggest the molecular interaction between dopaminergic pathway and mevalonate pathway in depression, but additional work (e.g., in vivo microdialysis, Real Time PCR, Flow Cytometry and western blot method etc.) is required for further exploration of the present investigations. Regardless, these are the first reports for the possible involvement of dopamine or dopamine D$_2$ receptor in simvastatin induced beneficial treatment in chronic mild stress in mice and possible interaction between dopaminergic pathway and mevalonate pathway in depression, having its potential implication in the pathogenesis and treatment of depression.
6. CONCLUSIONS
6. CONCLUSIONS

The results of the present investigations indicate the possible involvement of dopamine or dopamine D$_2$ receptor in simvastatin induced beneficial effect in mice treated with acute or chronic mild stress, having its potential implication in the treatment and pathogenesis of depression. Thus, it raised the possibility for the possible interaction between the dopaminergic pathway and mevalonate pathway in depression. The present study also suggests the preferential effects of dopaminergic agents on the function of statins which demonstrated that the signal transduction mechanism in the receptor effector linkage of dopamine D$_2$ receptor may be mediated through HMGR pathway, which in turn may regulate the expression of exon II transcripts of BDNF gene especially of BDNF exon IIC transcript, having its potential utilization in the future treatment of depression.