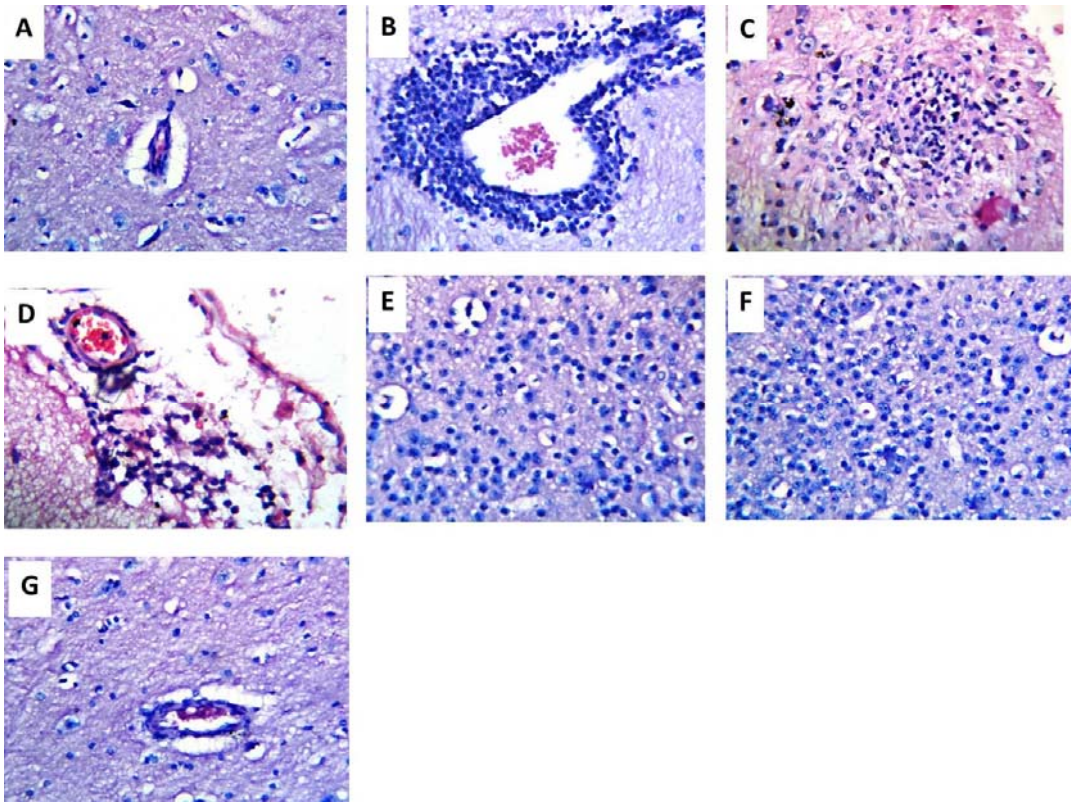

Figure 3: Effects of curcumin on rabbit brain histopathological results. (A) Brain tissue showing normal blood vessel in control group animal; (B) Brain tissue showing perivascular cuffing by lymphocytes in cerebral cortex in high fat diet fed animal; (C) Brain tissue showing edema, gliosis and lymphocytic infiltration in high fat diet fed animal; (D) Lymphocytes in subarachnoid space and around blood vessels in in high fat diet fed animal; (E) Brain tissue showing gliosis characterized by proliferation of astroglial cells in simvastatin treated animal; (F) Brain tissue showing gliosis characterized by proliferation of astroglial cells in curcumin treated animal; (G) Brain tissue showing normal blood vessel in curcumin treated animal.

4. DISCUSSIONS AND CONCLUSION

In this study, we demonstrated that the protective effect of curcumin against the neuroinflammation induced by feeding high fat diet in rabbits as wells as high cholesterol incubation in cell lines. The present *in- vitro* study highlights the inflammatory effect of cholesterol on PC12 cell lines mediated through nitrosative stress and cytokines expression such as IL-β1 and TNF-α. This is a fist kind of report that PC12 cell lines incubated with cholesterol for 48 hrs leads to accumulation of nitrite level as well as cytokine expression *in-vitro*. Report indicated HFD causes increased pro-inflammatory cytokines release in reproductive senescent female rats. However, it has been shown by many investigators that free cholesterol treatment causes impairment of anti-oxidants, mitochondrial dysfunction and NFκB activation and advent cell to apoptosis [27, 28]. For example, 7-ketocholesterol is an oxidation product of cholesterol, has shown apoptosis in PC12 cells by increasing the levels of phospho-IκB-a, NFκB p65 and NFκB p50 with the ROS-dependent NFκB activation [29].

The cholesterol induced neurotoxic effect was attenuated by curcumin as shown by significant reduction in the level of IL-1β and TNF-α in PC12 cells. This finding suggests that the cholesterol as such can trigger cytokine gene expression in PC 12 cell lines and that curcumin, possibly through its cytokine inhibition property. The various pharmacological activities of curcumin including inhibition of cytokines gene expression are at least partially mediated by inhibition of GSK-3 β [30]. Previously we have reported that *per se* curcumin inhibit the GSK-3β, is protein kinase family enzyme in *in-silico* which is involved in gene expression for cytokines [31]. In this investigation we used simvastatin, a HMG-Co-A inhibitor (1µg/ml) used as a standard did not shown any cytokine inhibition property except it does attenuates nitrate and cholesterol level in PC 12 cell lines. This effect was in accordance with the published report on simvastatin against dopaminergic neurotoxin (6-OHDA) mediated nitrosative stress in PC 12 cell lines [32]. This clearly indicates the direct scavenging role of curcumin on cytokines evoked by free cholesterol in PC 12 cell lines.

Ever growing scientific evidence demonstrates that the clear link between hypercholesterolemia and oxidative stress associated neurodegeneration in brain [33, 34]. There are various *in-vivo* rodent high fat diet models mimics the pathology of AD dementia and it was attenuated by lipid lowering drugs [35] as well as neuronal inflammation [36]. It has been shown that cholesterol mediated oxidative stress, increased the expression of inducible nitric oxide synthase (iNOS) produces excessive levels of nitric oxide

in the activated microglia lead to a disruption of neuronal mitochondrial electron transport chain function [37, 38]. Lakshmi et al (2008) [1] has been shown the involvement of cytokines like IL-6, TNF-α and chemokine MCF 1 in mouse brain treated with high fat diet meal. Simvastatin is a HMG-CoA reductase drugs extensively using in the treatment of hyperlipidemia have been implicated in the study of neuroinflammation and neurodegeneration [39, 40]. Farmer et al (2010) [41] have demonstrated that rosuvastatin treatment resulted in significant reduction of neuroinflammation in an animal model of high cholesterol diet induced hypercholesterolemia.

The results from *in-vivo* experiments further confirms the neuroprotective effect of curcumin administered twenty weeks following high fat meal fed rabbits. The significant reduction in plasma and brain cholesterol level was observed in curcumin treatment associated with attenuation of iNOS and TNF-α expression in hippocampus. Further, curcumin treatment restored the brain superoxide dismutase level and decreased the CAT and MDA level in high fat diet treated rabbits. Balusamy et al (2008) [42] have shown that curcumin prevents protein oxidation and protect mitochondrial complex-I by restoring depleted antioxidant glutathione (GSH). They have also suggested that curcumin has vital role for preventing neurodegenerative disorder linked with GSH depletion mediated by oxidative stress. Various doses of curcumin reduce the oxidative stress and amyloid induced neuroinflammation has been implicated in Alzheimer's transgenic mouse model [16]. This study further supports the neuropathological changes observed in high fat fed rabbit brain cortex with focal inflammation associated with lymphocytic infiltration and this effect was reversed by curcumin administration.

It can be concluded that curcumin has shown neuroprotective effect in HFD model of neuronal inflammation and the neuroprotective effect is might be due to the inhibition of brain cytokines, oxidative stress and reduction in cholesterol.

COMPETING INTERESTS

None

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