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**Figure 57:** Effect of UD on diabetes induced alterations in TNF-α expression using immunofluorescence study. CTRL = control; STZ = streptozotocin; UD50 = Urtica dioica extract 50 mg/kg; ROSI = rosiglitazone.

**Figure 58:** Effect of UD on diabetes mediated neuronal damage using histopathology study. CTRL = control; STZ = streptozotocin; UD50 = Urtica dioica extract 50 mg/kg; ROSI = rosiglitazone.

**Figure 59:** An overview on mechanism of action of UD extract: Shh signaling in normal control mice (A), stressed mice (B), stressed mice treated with UD or HYP extract (C) and normal control mice treated with UD or HYP extract (D).
Abstract
Clinically, depression and diabetes are co-morbid. Diabetes makes the symptoms of depression worse. Depression reduces overall physical and mental health, not only by increasing the risk for diabetes but making diabetic symptoms worse. Both depression and diabetes are the risk factor for cognitive impairment. Cholinergic system, autophagy (ATG), insulin signaling pathway and sonic hedgehog (Shh) pathway are involved in many regulatory processes, including learning and memory. Stinging nettle (*Urtica dioica*, UD) extract has been claimed for its beneficial effects against depression, diabetes and cognition. The present study was performed to evaluate whether chronic unpredictable mild stress (CUMS) or diabetes mediated cognitive deficit is associated with dysfunction in cholinergic system, ATG, insulin signaling and Shh pathway. In addition, standardized UD extract was used to evaluate its effect on CUMS or diabetes mediated neuronal dysfunction. Rosiglitazone, fluoxetine and St. John’s wort were used as standard drugs for comparison. CUMS (3 weeks) and multiple dose of streptozotocin (STZ) (50 mg/kg, i.p. for 5 consecutive days) resulted in depressive like behaviour, cognitive impairments and hypolocomotion in mice. CUMS induced insulin resistance and hypercorticosteronemia in mice. CUMS and diabetes impaired insulin signaling pathway, ATG and muscarinic cholinergic system in the hippocampus. In addition, CUMS impaired Smoothened (Smo)-Glioma associated oncogene-1 (Gli1) pathway in the hippocampus. CUMS and diabetes downregulated muscarinic cholinergic receptor-4 (mAChR4) expression in striatum but not in hippocampus. Both CUMS and diabetes were associated with oxidative stress, inflammation and apoptosis. Chronic UD treatment (50 mg/kg, p.o.) significantly reverted CUMS and diabetes mediated cognitive impairment, depressive like behaviour and insulin resistance. UD reduced hypercorticosteronemia in stressed mice. Chronic UD administration modulated insulin signaling pathway, ATG and muscarinic cholinergic system in the hippocampus of chronically stressed and diabetic mice. Chronic UD administration effectively modulated hippocampal Smo-Gli1 pathway in stressed mice. UD treatment significantly reduced hyperglycemia, body weight loss and polydypsia in diabetic mice. UD administration significantly ameliorated hippocampal glucose transporter-4 (GLUT4) membrane translocation in diabetic but not in stressed mice. UD administration did not modulate mAChR4 expression in striatum and hypolocomotion. Chronic UD administration attenuated oxidative stress, inflammation and apoptosis in stressed and diabetic mice. These results suggest that chronic administration of UD extract might prove to be effective for depression and diabetes related neurological disorders.