Summary & Conclusion
Diabetes mellitus is a chronic disorder of metabolism characterized by hyperglycemia and long-term complications causing metabolic and physiological changes in various organs including brain (Genet et al., 2002). In diabetes mellitus, long-term complications have multiple effects on central nervous system i.e., autonomic and peripheral neuropathy, and is associated with gradually-developing end organ damage in the central nervous system (Brands et al., 2004) and referred as diabetic encephalopathy. It is characterized by impairment of cognitive functions and electrophysiological changes (Allen et al., 2004). These functional changes are accompanied by neurochemical and structural abnormalities, as well as by degenerative changes in the brain (Weigner and Jacobsen, 1998; McCall, 2004). Both micro and macrovascular cerebral diseases occurring in diabetic patients and the direct neuronal damage caused by chronically elevated intracellular glucose concentrations are implicated in encephalopathy. The direct glucose toxicity in the neurons is especially due to increased intracellular glucose oxidation (Nishikawa et al., 2000) which leads to an increase in free radical production (Evans et al., 2002). The oxidative stress associated with diabetes mellitus may play an important role in the initiation and progression of diabetic complications (Vucic et al., 1997). In man and also experimental diabetic animals, hyperglycemia induced oxidative stress seems to play a central role in brain damage (Aragano et al., 2000). Control of oxidative stress may play an important role in the prevention of diabetic complications. Hence, compounds with both antihyperglycemic and antioxidative properties would be useful as antidiabetic agents.

Inspite of the availability of known antidiabetic medicine in the pharmaceutical market, remedies from medicinal plants are used with success to treat this disease (Bhattaram et al., 2002). Ayurveda, the oldest medicinal system in the world, provides lots of lead to find active and therapeutically useful compounds from plants. Plant drugs (Bailey and Day, 1989) and herbal formulations (Mitra et al., 1996; Bhattacharya et al., 1997; Annapurna et al., 2001) are frequently considered to be less toxic and more free from side effects than synthetic ones. There are many cases where in natural products themselves exert multiple pharmacological actions.
These pharmacological multi-actions become practical prerequisites for identifying highly efficacious drugs for treating multifactorial symptoms of diabetes.

*Commiphora mukul* belonging to the family Burseraceae, a plant that is native to India, and its extracts include compounds known for their hypolipidemic properties—the Z- and E- isomers of guggulsterone and its related guggulsterols, the presumed bioactive compounds of guggul, may antagonize two nuclear hormone receptors involved in cholesterol metabolism, which is a possible explanation for hypolipidemic effects of these extracts. As an anti-diabetic remedy, it was believed to promote insulin production or to increase the body's utilization of sugars from food.

Even though antidiabetic and hypoglycemic activities are included in the traditional uses of *C. mukul* gum resin, no scientific evidence is available in literature regarding its antidiabetic and antihyperglycemic activity. Further no information is available on the efficacy of this plant on biochemical alterations observed in the brain of STZ-induced diabetic rats. However the studies conducted in our laboratory, revealed the antihyperglycemic and hypolipidemic activity of *C. mukul* in STZ diabetic rats and fructose fed insulin resistant rat models (Ramesh et al., 2008). Guggulipid, the gum resin exudates from *C. mukul* is an established hypolipidemic agent in clinical studies. The plethora of pharmacological effects of guggulu particularly anti-dyslipidemic effect is suggestive of its potential as cognitive enhancer. Patients receiving lipid-lowering drugs like statins have a reduced risk of dementia (Jick et al., 2000). Further studies of Saxena et al., (2007) demonstrated that guggulipid has significant protective effect against streptozotocin-induced memory deficits model of dementia that can be attributed to anti-oxidant and anti-AchE activity of guggulipid.

No toxic effect of *C. mukul* (200 mg/kg body weight) treatment was observed in NT rats. STZ induced diabetic rats showed hyperglycemia, decreased body weight, polyuria, polydipsia and polyphagia. Whereas, the clinical symptoms of diabetes were rectified within 2-3 weeks of *C. mukul* administration in DT rats.
Brain is rich in lipid composition which plays an important role in structural and functional activity. Lipids, especially phospholipids and glycolipids are essential components of myelin sheath of nerves including cholesterol. STZ induced diabetic rat brain tissue showed altered lipid content and composition (increase of TG levels and decrease of PL, GL, and cholesterol levels). In diabetic rats the total lipid content decreased and it may be due to oxidative stress mediated demyelination and nerve degeneration. *C. mukul* treated diabetic rats showed a significant recovery to normal levels indicating its protective effect on CNS against diabetes induced oxidative stress. Increased breakdown of proteins for providing substrate for gluconeogenesis and the absence of anabolic effect of insulin are responsible for muscle wasting and loss of weight under diabetic conditions. Decreased protein content with enhanced activities of transaminases D in rat brain indicates altered protein metabolism under diabetic conditions. Significantly increased protein content and decreased transaminases activities of DT rats compared to D rats indicates the beneficial effect of *C. mukul* administration in rectifying the alteration of protein content and transaminases activities in diabetic rats to normal values. Enhanced oxidative stress under diabetic conditions cause damage to macromolecules like lipids, proteins, and DNA. Nucleic acid oxidation causes the production of free nucleotide pool and leads to enhanced purine catabolism. Significantly enhanced activity of XO of D rat brain indicates enhanced purine catabolism under diabetic conditions contributing to the production of H$_2$O$_2$. *C. mukul* treatment resulted in significantly decreased activity of XO in the brain of both NT and DT rats compared to N and D groups respectively indicating the protective effect of *C. mukul* by preventing H$_2$O$_2$ generation. In hyperglycemia conditions an increased flux of glucose to tissue leads to enhanced non-enzymatic protein glycation and polyol pathway operation. Increased operation of polyol pathway results in accumulation of sorbitol in tissues. Significantly enhanced protein glycation was observed in the brain of D rats compared to N rats which was brought to near normal values in DT group. Similarly increased SD activity of D rat brain was also brought to near normal values by *C. mukul* treatment in DT group.
Thus *C. mukul* treatment prevented the excessive operation of polyol pathway and controlling the protein glycation process observed under diabetic conditions.

In diabetic condition there is an alteration of acetylcholine and its degrading enzyme acetylcholine esterase due to degeneration of neural membranes. In the present study AchE activity decreased leading to increased Ach levels in diabetic brain. Treatment with *C. mukul* normalizes the levels of Ach by enhancing the activity of AchE in DT group to near normal values.

The enhanced tissue LPO and decreased GSH content in brain of diabetic rats indicates the existence of oxidative stress in D rats whereas *C. mukul* treated diabetic rats showed a significant reduction in LPO with enhanced GSH levels in DT rats which indicates the protective effect of *C. mukul* against diabetes induced oxidative stress. The enhanced tissue GSH content of NT group compared to N group represents increased reserves of free radicals scavengers by *C. mukul* treatment. This indicate that *C. mukul* administration probably stimulated the GSH synthesis and reduction in LPO may be responsible for the reduced oxidative stress observed in DT group compared to D group.

The significantly decreased GR, GPx, SOD, and increased GST, CAT antioxidant enzyme activities of D rats were restored to near normal levels by *C. mukul* treatment in DT rats. Thus the present study reveals that *C. mukul* treatment provided protection against enhanced oxidative stress in brain under diabetic conditions.

Thus our results strongly support the notion that supplementation with *C. mukul* to diabetic subjects would help in achieving good glycemic and metabolic control due to its antidiabetic effect. Due to antioxidant potential it could be beneficial for protection and alleviation of the diabetic complications especially diabetic neuropathy.