Summary
SUMMARY

Diabetes is a disorder of glucose intolerance in general. But it is a multifacet condition characterized by hyperglycemia also. The most serious threat is the complications from diabetes mellitus, such as cardiac diseases, pulmonary vascular disease, neuropathy, amputations, renal failure and blindness (Amos 1997). India is facing a diabetic explosion having world largest diabetic population i.e about 25 millions, which may rise up to 35 million by 2010 and to a level of 57 million by 2025. The factors assigned are to be genetic or sedentary life style (Sicree et al. 2006).

There are two major types of clinical syndromes due to increased hyperglycemia. The first one called Insulin dependent Diabetes Mellitus (IDDM) or type I normally occurs at early age, with symptoms of weight loss and ketonuria (Passing of ketone in urine). The second is Non-Insulin Dependent Diabetes Mellitus (NIDDM), or type II which shows insensitivity to insulin and partial insulin deficiency. NIDDM is spiraling upward in developed as well as developing countries. Poorly controlled diabetes aggravates the metabolic disorders and enhances the risk of various other diseases including cardiovascular diseases (Mayes, 1993).

The diabetic condition increases the generation of free radicals and leading to oxidative damage of biomolecules and metabolism. The experimental evidences suggest the involvement of free radicals in pathogenesis also in diabetes (Matteucci and Giampietro 2000) which further complicate the diabetic (Oberlay 1988, Baynes and Thorpe 1997, Lipinski 2001). However, antioxidants neutralizing free radicals effectively are implicated in controlling diabetes in animal models (Kubish et al.1997, Naziroglu and Cay 2001) and reducing the severity of diabetic complications as well (Lipinski 2001).

A network of antioxidants and antiyoxygenic enzymes, superoxide dismutase, catalase, glutathione and glutathione-dependent enzymes are employed by
the organism for defense. Under diabetes metabolic disorders cause slow or little/late healing of wounds and organism compromising with compromise cellular immunity thereby increased susceptibility to microbial infection mostly periodontal diseases and urinary tract infection. Like *Candida albicans* have a glucose inducible protein which is identical to a complement receptor on human phagocytes. This protein promotes adhesion and prevents phagocytosis by the host cell (Danielle et al. 1996).

The effect of *Capparis aphylla* extract on blood glucose levels of normal rats was considerable (fig.12). Interestingly, a similar effect was found with active compound under test required little dose as compared with that of crude extract or other organic solvent extracts. Further, hypoglycemic effect of glibenclamide a standard drug was much lower than that of our plant products. The active compound hypoglycemic potential was found 16.5 % higher than that standard drug glibenclamide normally applied (600µg/kg bw).

For treatment of diabetes with insulin secretagouge drugs, sulphonylurea and nonsulphonylurea are used normally in form of glimepride and repaglinide respectively to reduce glucose level (Marbury et al. 1999). But prolonged severe hypoglycemia lead to renal or hepatic impairment (Inzucchi 2002) and initiate gain in body weight (Lebovitz 2001, Nattrass and Lauritzen 2000). In addition the β-cells are at greater risk of oxidative damage than the other tissues, because of lower levels of antioxidant and low tissue sensitivity towards it (Robertson et al 2003). During pathogenesis of diabetes mellitus, oxidative stresses are implicated in fast destruction of insulin-producing beta cells. The inability to suppress hepatic glucose production is also a major contributor to the fasting hyperglycemia under diabetic condition (Wang et al. 2006).

On the other hand, it was reported that treatment of type 2 diabetes patients with sulfonylureas and biguanides is always associated with side effects (Gandhipuram et al., 2006). Hence, search for a drug with low cost, high potential with no adverse side effect has been in focus and is being pursued in several laboratories around the world. Our efforts appear to be at the same path with logical ends.
The present study showed that the insulin-producing \( \beta \)-cells were degenerated or necrosed in the streptozotocin induced diabetic rat might lead to decrease in insulin secretion and an increase in the blood glucose level. However, oral administration of prepared compound from \textit{C. aphylla} stem through specific steps under different precise conditions in varied organic solvent agents/medium showed a significant antihyperglycemic activity in STZ-induced diabetic rats (fig.12).

The active compound led to increase in catalase activity by 17.8, 76.2 and 39.3\% higher than standard drug glibenclamide (600\( \mu \)g/kg bw) after 7 days of treatment in liver, heart and kidney tissue of diabetic rat respectively (fig. 20), indicating precise hypoglycemic effect of natural compound. These finding supported the previous reports about \textit{Capparis aphylla}, where numerous possible bioactive compounds utility for the management of various ailments including diabetes mellitus based on folkloric medicine are enumerated (Mishra et al. 2007). However, the management of diabetes mellitus depends on continuous hypoglycemic therapy for long period in life, which may not be consistently being adhered by the patient leads to many problems and become costly affair.

Here, remarkable hypoglycemic effect of repeated oral administration of solvent extract to diabetic rats was observed (fig.13) might be able to cut short longer treatment. The FBG decreases from 310.3 to 110.3 mg/dl after 7 days of treatment with solvent extract and from 410 to 102.3 under active compound administration compared with that of 427.3 to 234.5 by glibenclamide and 401.6 to 288.5 with the conventional extract. The total reduction of blood glucose level by 28.16\%, 64.4\%, 45.1\% on 8\textsuperscript{th} day by conventional, solvent extract, glibenclamide respectively, while 75\% with active compound.

These finding demonstrated hypoglycemic activity of \textit{Capparis aphylla} suggests the presence of some potent biomolecules may be alkaloid, phenols and terpenoids which are further potentiated under various isolation steps performed here (patent applied). The present study showed significant increase in GSH content in liver, heart and kidney tissues of diabetic rat after repeated oral administration of solvent extract and active compound (fig.15). However, active compound
administration increased GSH level by 45, 9 and 11% higher than that standard drug glibenclamide (600µg/kg bw) after 7 days of treatment in those tissues.

Applying active compound also increased SOD activity by 39.5, 4 and 12.2% higher than standard drug glibenclamide after 7 days of treatment of diabetic rats (fig.20). This indicated that antioxidative potential of plant under study. Oral administration of solvent extracts of stem enhanced the GPx activity in liver, heart and kidney tissues by 51.5%, 16.9% and 55.5% respectively as compared to diabetic control (fig.21). Whereas, there was considerable increase in GPx activity after 7 days of treatment of active compound over standard drug glibenclamide, further support the hypothesis of potent antidiabetic nature of our compound. Reduced activity of CAT in liver, heart and kidney in diabetic rats was reverted to near normal with solvent extract and our compound under test (fig.20).

Fig.21 illustrates that diabetic rats with a significant decrease in GSTs activity in liver, heart and kidney tissues after administration of solvent extract and that was more prominent over standard drug glibenclamide. The quantitative estimation of total phenol and flavonoids in all preparations of stem extract suggest that active compound is having less amount compared with other preparation here (fig.26), which are considered to be possessing antioxidative property (Georgetti et al.2003). It further indicates that our compound may be of some specific nature.

The compound obtained from the stem of C. aphylla significantly decreased serum cholesterol, serum creatinine and urea levels in STZ-diabetic rats (fig.24, 25). The administration of the extract at specific dose for 7 days bring down triglycerides by 33.8%, VLDL by 44.5%, LDL 70.9%, total cholesterol 36.8% and simultaneously elevated serum HDL by 116.2% tending toward normal level (fig.24). Further, Capparis aphylla stem extract under evaluation showed precise antibiological potential like an antifungal and antibacterial.

In vivo growth inhibition with solvent extracts after 7 days of oral treatment for growth of E.coli, P. aeruginosa, S.aureus, and C. albicans in diabetic rats was found significant (fig.22). The maximum inhibitory effect of active compound was 62.8%,
78.2% and 69.2%, for *E. coli*, *P. aeruginosa*, *S. aureus*, and *C. albicans* respectively (fig.23). However, active compound antimicrobial potential in terms of percent growth inhibition was found to be higher for *E. coli*, *P. aeruginosa*, *S. aureus* and *C. albicans* respectively than standard drugs. The possible mechanism of action of compound under reference could be attributed to its antioxidative properties also. However, mass spectroscopy confirmed 803.5 mass of isolated compound. The complete structural elucidation on the basis of spectral analysis of isolated compound (active compound) is under process.

The results obtained here prompted to suggest that *Capparis aphylla* stem having potential to decrease the infectivity of pathogens under study in diabetic rat (fig.22, 23) along with hypoglycemic & hypolipidemic could be a one future compound for composite treatment of diabetic patients. The compound evaluated here could be able to control effectively the diabetic metabolic disorder and microbial infections, which may be of great economic value as well.