Discussion
Effect of losartan on IDDM and NIDDM rats

STZ is reported to produce diabetogenic effect in rats ranging from mild to moderate diabetes to severe ketotic stage at higher doses (Hoffeizer, 1973). STZ-treatment produced hyperglycemia in Wistar rats by its selective β - cell toxic effect. It produces fragmentation of pancreatic β - cell DNA due to a general alkylating effect and thereby stimulating poly (ADP – ribose) synthase and NAD depletion. Depletion of NAD has cytotoxic effect on islet β - cell. Pancreatic β - cell death causes insulin deficiency that eventually causes hyperglycemia in STZ-treated rats. In our study also, STZ-diabetic rats produced significant hyperglycemia associated with hypoinsulinemia as compared to Wistar control. This is similar to that of earlier reports (Kawashima, 1978; Rodrigues et al, 1986; Goyal et al, 1987). Different laboratories have used different doses of STZ ranging from 30 to 80 mg/kg. In our laboratory, a dose ≥ 50 mg/kg produced a very high mortality (>80%) and a dose ≤ 35 mg/kg failed to induce diabetes mellitus. The dose of STZ in the present study (45mg/kg) produced not only increase in glucose levels but also significant hypoinsulinemia and glucosuria (>2%). Animals showed significant loss of body weight, polyphagia, polyuria and polydipsia. Animals could survive without insulin injection at this dose. These findings are consistent with those previously reported (Hoffeizer, 1973; Shah et al, 1995; Sevak et al.1996). Loss of body weight may be due to dehydration (Hoffeizer, 1973) and catabolism of fats and proteins during diabetes mellitus (Oakley, 1968).

Treatment with losartan significantly prevented STZ-induced hyperglycemia in diabetic rats without altering insulin levels. This can be explained on the basis of antagonistic nature of the drug to Ang II receptors (Tomlinson et al, 1990). In spite of insulin deficiency, losartan significantly decreased glucose levels in diabetic rats. However, losartan did not alter glucose levels in the nondiabetic rats. These results suggest that, ANG II modulates hyperglycemia and that AT1 receptor blockade by
losartan prevents elevation of blood glucose possibly by causing an increase blood supply to the peripheral tissues or improvement in insulin sensitivity as evident from the result from NIDDM model mentioned below.

Administration of STZ to neonatal rats produces a condition of NIDDM in later life. It was reported that STZ (90 mg/kg Body weight) when given intraperitonially to 5 day old pups produced transient hyperglycemia in the neonates, followed by normoglycemia until 5 weeks of age and hyperglycemia (>120 mg/dl) emerged, which was maintained up to 13 weeks (Weir et al, 1981). It was reported from our laboratory that administration of STZ (70mg/kg body weight) i.p. to 5 day old pups is sufficient to induce NIDDM (Gokhale et al, 1998). The same dose was used in our studies to induce NIDDM.

In neonatal STZ-diabetes model, STZ destroys pancreatic β - cells, but neonatal β - cells are able to regenerate. However, this regeneration is incomplete and cell mass remains reduced. Consequently, hyperinsulinemia and hyperglycemia gradually develops as rat grows (Weir et al, 1981). In our study also NIDDM control rats showed significantly higher levels of fasting and fed glucose levels as compared to non-diabetic control rats. Hyperinsulinemia with low hepatic excretion and hypersecretion of beta cells is also reported in mild glucose intolerant obese subjects (Bonora et al, 1983). We also found increase in insulin levels and AUC_{insulin} after glucose load in neonatal STZ-diabetic rats. The high insulin concentration found in neonatal STZ-diabetic rats need not be of pancreatic origin. It could be due to metabolic alterations at extra pancreatic levels. In these rats, the metabolic clearance rate of insulin might have been altered. Insulin degradation following hormone receptor binding (Gliemann and Sonne, 1978) and reduced binding of insulin to its receptor have been reported in mild glucose intolerance (Olefsky, 1981). Therefore, the hyperinsulinemia in neonatal STZ-diabetic rats could be due to either decreased hepatic excretion of insulin or decreased number of insulin receptors, resulting in decreased insulin binding and lowered insulin degradation. When animals were subjected to OGTT, the AUC_{insulin} of NIDDM control rats was significantly greater as
compared to the non-diabetic rats. Despite high insulin levels the $AUC_{\text{glucose}}$ of the diabetic animals was greater than non-diabetic rats. Treatment with losartan did not alter $AUC_{\text{insulin}}$ in non-diabetic rats. However, $AUC_{\text{insulin}}$ of NIDDM rats treated with losartan was found to be significantly lower as compared to NIDDM control rats. This suggests that in normal animals losartan does not alter the release of insulin, but in conditions like hyperinsulinemia, it increases the insulin sensitivity for effective glucose disposal.

The $K_{\text{ITT}}$ was found to be significantly lower in neonatal STZ–diabetic rats as compared to controls. This indicates that NIDDM rats are insulin resistant. The specific mechanisms underlying in insulin resistant states are heterogeneous and may include a receptor defect (decrease in insulin sensitivity) or post receptor defect (decrease in responsiveness to insulin) or combination of both (Kahn, 1978, Crettaz and Jeanrenand, 1980). Losartan treatment significantly increased $K_{\text{ITT}}$ values.

Insulin tolerance test (ITT) which represents the response to exogenously administered insulin on blood glucose has been used to estimate insulin sensitivity (Alford et al, 1971). ITT is a simple, reasonabley accurate and rapid method for screening the insulin resistance (Grulet et al, 1993). ITT indicates net result of resistance to insulin action at target level including receptor and post receptor defects. In the present investigation the rate of glucose disposal was found to be significantly decreased in NIDDM control rats as compared to Wistar control rats.

Hyperinsulinemia in NIDDM control animals was found to be associated with high blood pressure as reported earlier by many other laboratories and may be due to a direct sodium retaining effect of insulin (DeFronzo and Cooke, 1975; Kichner, 1988) or an increase in sympathetic activity (Rowe et al, 1981) or sensitivity to norepinephrine, angiotensin II etc. (Bunag et al, 1982). Insulin is also reported to cause an increase in vascular smooth muscle cell growth in vitro (King and Goodman, 1985; Banskota and Taub, 1989). Thus chronic hyperinsulinemia may cause vascular hypertrophy leading to narrowing of the lumen, and hence causes
Increase in blood pressure after treatment with alloxan or STZ to adult rats (IDDM diabetic rats) has been reported previously by other investigators (Bunag et al, 1982; Cavaliere et al, 1980). The mechanism of hypertension caused by STZ or alloxan treatment may also be the renal disease (Rasch, 1977). STZ induced diabetic rats develop changes in renal function including altered renal haemodynamics and structural changes. STZ does not possess any significant nephrotoxic potential hence, its direct effect on the kidney need not be considered when using the drug in order to study the effect of diabetes on renal function and structure (Evan and Mong, 1984). Kidney dysfunction is indicated by elevated serum creatinine levels as reported in patients with diabetes mellitus (Thomson et al, 1989). In our study IDDM rats showed significantly higher creatinine levels as compared to Wistar control rats thereby suggesting the development of kidney dysfunction in rats.

Hyperglycemia leads to elevated glucose levels in mesangial cells which activates protein kinase C (Kriesberg et al, 1994) and increases the synthesis of fibronectin, laminin and type (IV) collagen (Kriesberg et al, 1994a). This results in imbalance in matrix proteins leading to development of mesangial hypertrophy and eventually nephropathy. Increase in blood pressure occurs early in diabetic renal disease (Ritz et al, 1989; Mogensen and Christensen, 1985). Hyperfiltration and microproteinuria, resulting from glomerular leakage are hallmarks of diabetic nephropathy (Corry and Tuck, 1996). Decrease in glomerular filtration rate (GFR) and renal plasma flow (RPF) have been reported in type I (IDDM) patients (Mogensen et al, 1979) as well as in variety of experimental models of renal disease in rat including experimentally induced diabetes mellitus (Zatz et al, 1986). The early phase of hypertensive renal disease is also characterized by a decreased in GFR, and decrease in RBF with and elevated filtration fraction. Untreated hypertension is therefore, associated with declining renal function (National High Blood Pressure
The co-existence of hypertension and diabetes will therefore accelerate further the decline in renal function. In experimental animals, ACE inhibitors have been shown to normalize the raised glomerular capillary pressure (Zatz et al, 1986; Nath et al, 1986). ACE inhibitors have shown to decrease albuminuria in hypertensive type I diabetic patient with established nephropathy (Hommel et al, 1986) as well as in normotensive type I diabetic patients with microalbuminuria (Marre et al, 1987). In the present investigation we found severe kidney dysfunction as evident from decrease in creatinine clearance, renal hypertrophy and several histopathological alterations. Rise in serum creatinine, urea and blood urea nitrogen (BUN) levels has been reported in patients with diabetes (Mulec, 1990).

Several studies have shown an increased correlation between creatinine clearance and arterial pressure in diabetic patients (Ritz et al, 1989; Mogensen and Christensen, 1985). Renal dysfunction can also be defined in terms of creatinine clearance. It is an accurate and useful measure of the glomerular filtration rate (GFR) and also the excretory capacity of the kidney (Godkar, 1994). In the present study STZ-diabetic animals showed a significant decrease in creatinine clearance as compared to control animals. The decrease in creatinine clearance may be due to hyperglycemia, that causes osmotic diuresis and depletion of extracellular fluid volume (McCance and Widdowson, 1939). Treatment with losartan was found to increase creatinine clearance and decrease in serum creatinie levels. This may be correlated with decrease in glucose levels by losartan and thereby decrease in osmotic diuresis and depletion of extracellar fluid volume. This is further supported by the reports that in STZ treated rats with low protein diet or ACE inhibitors delay or prevent kidney damage by decreasing the intra glomerular pressure (Dunn and Zatz, 1986).

It is well established that ACE inhibitors are effective drugs in controlling the systemic hypertension accompanying clinical diabetic nephropathy (Hommel et al, 1986; Valvo et al, 1988; Bjorck et al, 1990). In experimental animals ACE inhibitors
have been shown to normalize the raised glomerular capillary pressure. ACE inhibitor enalapril has been shown to prevent development of albuminuria and glomerulosclerosis in STZ-diabetic Munich Wistar rats (Zatz et al, 1986). There are several such reports that clearly indicate renoprotective effects of ACE inhibitors in diabetic animals and patients (Hricik et al, 1983; Hommel et al, 1986; Winocour et al, 1986; Taguma et al, 1985; Lewis et al, 1993). This and the findings of the present investigation that AT1 receptor antagonist losartan prevents STZ-induced hypertension along with renal dysfunctions (as indicated by decrease in creatinine levels, urea and BUN, increase in creatinine clearance and prevention of histopathological alteration in STZ-diabetic rats) suggest involvement of AT1 receptors in STZ-induced hypertension and nephropathy. Such a mechanism has also been suggested by Mochizuki et al. (1995). The release of norepinephrine from sympathetic nerve terminals is facilitated by Ang II through activation of the AT1 receptors (Zimmerman, 1981; Timmermans et al, 1993). It is possible that the decrease in norepinephrine release from vascular sympathetic nerve terminals contributes additionally to the antihypertensive effect of losartan. In the later stage of therapy, the protective effect of losartan against the renal damage induced by Ang II may additionally contribute to its antihypertensive effect. Increase in extracellular fluid volume may be because of retention of sodium and potassium ions in the body. In our study also we found a significant decrease in the urinary sodium and potassium excretion. Further, treatment with losartan was found to cause increase in sodium and potassium excretion. It is possible that, AT1 receptors may be involved at the site of tubular reabsorption and blockade of these receptors enhances the excretion of electrolytes. Similar finding have been reported in healthy subjects (Burnier et al, 1995).

Increase in intraglomerular pressure in STZ-diabetic rats may also be due to vasoconstrictor action of angiotensin II in efferent arterioles (Lafayette, 1992; William et al, 1989). Blockade of angiotensin II receptors by losartan may lead to a reduction in intraglomerular capillary pressure i.e., enhancement of efferent arteriolar tone as well as relaxation of afferent arteriol. Various hemodynamic effects of angiotensin II
on glomeruli may produce glomerulosclerosis in diabetic rats. It has been reported that ACE inhibitors or angiotensin II receptor antagonists attenuate the severity of glomerulosclerosis by producing several beneficial effect on glomerular hemodynamics (Masahiro et al, 1995; Lafayette et al, 1992). From histological point of view typical lesion of diabetes include nodular changes in glomerulus (William, 1961). Histopathological examination of kidney obtained from STZ-diabetic rats did not show any such changes. However partial cortico medullary necrosis, focal mesangial prominence and tubular degeneration and patchy infiltration of mixed cellular inflammatory infiltrate with interstitial fibrosis were observed. Medium caliber arteries showed moderate fibrointemal proliferation and endothelialitis. Treatment with losartan prevented many of these structural alterations but to smaller extent. All these result indicate prominent glomerulosclerosis in diabetic kidney and partial renoprotective action by losartan.

Rasch (1979a) reported that the kidney and the glomeruli become enlarged in rats with high plasma glucose concentrations maintained for 6 months. Furthermore, glomerular basement membrane becomes thicker (Rasch, 1979b) and the masangial regions enlarged with increased amounts of basement membrane like material (Rasch, 1980). If the plasma glucose is kept at levels close to normal, these changes in the kidney do not develop (Rasch, 1980). In experimental diabetes a rapid increase in renal size occurs 48 – 72 h after the injection of streptozotocin (i.e., about 36 h after the onset of glucosuria), that is not due to accumulation of water but it is due to the increase in total protein content in the kidney (Hansen, 1983). In other words, the initial diabetic kidney growth is due to both cellular hypertrophy and hyperplasia. In our study there was a significant increase in kidney weight/body weight ratio of IDDM rats as compared to control group. Increase in total RNA was reported when glucose levels were maintained high for 24 – 36 h (Hansen, 1983). During this period cellular pools of RNA precursors and the incorporation of orotate into uridine triphosphate are increased (Cortes et al, 1980). This finally causes an increase in protein / DNA ratio (cell size) and the cellular hypertrophy. Total DNA however remains unchanged for the first four days (Hansen, 1983). By means of thymidine incorporation techniques it
has been shown that the hyperplastic response is primarily located in the proximal and distal tubules, with almost no hyperplasia in the glomeruli (Rash and Rytter-Norgaard, 1983). We also found that in IDDM rats there was a significant increase in protein/DNA (cell size), RNA/DNA ratio and increase in protein synthesis in diabetic animals as compared to control animals. Similar results were reported by Levin et al (1975) in STZ-diabetic rats. Peterson et al, (1971) reported an increased incorporation of amino acid into protein in kidney ribosomes of diabetic rats occurring after 24 h of the injection of anti-insulin serum or 72 h after the injection of alloxan or streptozotocin.

Use of different ACE inhibitors, as well as angiotensin II receptor antagonists, under normal and hyperglycemic conditions demonstrated the effects of angiotensin II on cell size and growth (Bakris et al, 1994). Some of these effects of angiotensin II are modulated through stimulation of cellular production of endothelin (Reddi et al 1991). Therefore, ACE inhibitors or angiotensin II antagonists modulate the action of cytokines that contribute to the genesis of mesangial matrix expansion associated with diabetic nephropathy.

In the rat glomerulus, mesangial cells have high affinity (Type A) for angiotensin II receptor, which stimulate the intramembrane release of Diacylglycerol (DAG) and the intracellular release of Ionoosine Triphosphate (IP3). IP3 in turn causes cytosolic calcium release, which activates actin-myosin contraction. The diabetic milieu may alter one or more of the signaling steps (Whiteside and Thompson, 1983). Limula et al (1995) showed that ACE inhibitor like enalapril and Ang II antagonist improve insulin sensitivity in fructose fed rats and also in insulin resistant hypertensive patients suggesting that insulin sensitivity - improving effects of the ACE inhibitor or Ang II antagonist, which may be mediated through inhibition of angiotensin II signaling. Hence the increased insulin sensitivity by losartan may be due to inhibition of angiotensin II signaling or by blocking aldosterone secreting effects of angiotensin II. In our study we found that treatment with losartan significantly prevented STZ-induced hypertrophy. This was associated with decrease
in protein content, cell size and RNA/DNA ratio.

Hansen et al (1980) studied the morphological features of the hypertrophying diabetic kidney in both light and electron microscopy and found a non-uniform growth in its early stages, presenting an anatomical glomerulo tubular imbalance. Within four days of streptozotocin diabetes the total glomerular volume increases by 30%, while tubules, which constitute the greater part of the kidney, grow relatively more slow. Cortes et al (1983) reported that initial renal metabolic changes and hypertrophy are due to increased kidney function and exaggerated workload. However, the exact relationship between increased renal mass and hyperfunction is controversial. But, glomerular size is a dynamic entity that can vary rapidly (probably on a minute to minute basis). At mesangium contraction of myofilaments in response to metabolic or hormonal changes can reduce the glomerular filtration area rapidly, thus lowering the filtration rate (Dworkin et al, 1983). This could readily occur without a detectable change in kidney size, because major part of kidney is composed of tubules and glomeruli accounts for only 2 percent of the total renal volume (Elias and Hennig, 1967). A study in rats (Rasch and Rytter-Norgaard, 1983) indicates that although diabetes induces both hypertrophy and hyperplasia of the tubules, hypertrophy of the glomeruli is more important and glycemic control may decrease hypertrophy more readily than hyperplasia.

As reported previously patients with diabetes mellitus have a lower glomerular filtration rate than non-diabetic subjects (Mogensen, 1971) and kidney is larger in size in diabetics (Mogensen and Andersen, 1973). Treatment with insulin preserves kidney function and thereby kidney size returns to normal (Mogensen and Andersen, 1975). Ross and Goldman (1971) also showed that compensatory renal hypertrophy is augmented in diabetic rats after treatment with insulin. Mazzocchi et al, (1997) by insitu perfusion technique of isolated rat adrenal gland demonstrated that Ang II increases DNA synthesis in Zona glomerulosa but not fasciculata – reticularis cells. Both R031 – 8220, an inhibitor of protein kinase C (PKC) and tyrphostin – 23, an inhibitor of tyrosine kinase (TK) evoked a partial reversal of Ang II effect and
phospholipase C inhibitor U-73122 alone was able to induce a complete blockade of Ang II effect on DNA synthesis. These findings suggest that, Ang II stimulates rat zona glomerulosa cell proliferation acting via \( \text{AT}_1 \) receptors coupled with phospholipase C, which activates both PKC and TK signalling systems. Hypertrophy of renal proximal tubular cells occurs as an adaptive response to a variety of stimuli and may be involved with the progression of renal disease. Ang II, either acting alone or in combination with other growth factors has been implicated in this process. In a primary cultures of human proximal tubular cells Chatterjee et al (1997) found that losartan inhibits Ang II induced DNA and protein synthesis and this is dependent upon the inhibition of adenylate cyclase. Based on these reports it is reasonable to assume that, losartan inhibits DNA synthesis in diabetic rats and thereby prevents development of hypertrophy in STZ-diabetic rats.

In conclusion losartan produces a number of beneficial effects in diabetic models of rat. It not only prevents STZ-induced hypertension and hyperlipidemia but also nephropathy. Prevention of long term complications of hypertension associated with diabetes mellitus, by losartan appear to be through the improvement in insulin sensitivity. Thus losartan may be considered as drug of choice when there is co-existence of diabetes mellitus and hypertension with compromised kidney function.

**Effect of *Enicostemma littorale* in diabetic rats and patients**

Insulin resistance (IR) appears to be very important link between diabetes and hypertension in producing several complications like nephropathy, cardiomyopathy and vascular reactivity (Reaven, 1988; Sowers & Zemel 1990; Kotchen et al, 1991). Several antihypertensives and antidiabetics available have been evaluated for their effectiveness on IR. It has emerged out as one of the common etiological factor responsible for about 72 – 80% of total diabetics. In general practice sulfonylurea like glibenclamide, glipizide etc. and biguanides like metformin are commonly used for the
treatment of diabetes mellitus. An antidiabetic agent that can maintain normoglycemia for longer duration (>3-5 years) in diabetics still remains a challenge (The diabetes controlled and complications trial research group, 1995). On long term therapy with sulfonylurea NIDDM patient requires insulin injections for adequate control of glucose levels. Further, inspite of antidiabetic therapy patients have hyperglycemia, hyperinsulinemia and may suffer from dyslipidaemia with an increase in circulating triglycerides leads to development of nephropathy with an increase in creatinine levels (Winocour and Laker, 1990; Durrington, 1993).

Herbal medicines are now looked upon as supplementary therapy or like a food additive to many chronic disorders. Workshop conducted by WHO on selection of traditional remedies in primary health care, unanimously showed the essentiality for the development of herbal formulation for the treatment of diabetes mellitus (Chowdhary, 1992). There is a tremendous interest in world over for the use of herbs as an alternative system of medicine. Results of our study indicate that, aqueous extract of *Enecostemma littorale* can be considered not only a potential antidiabetic agent but also be given as supplementary therapy for treatment of insulin resistance.

In IDDM rats treatment with *Enicostemma littorale* was found to significantly prevent STZ-induced hyperglycemia without effecting STZ-induced change in insulin levels. In NIDDM rats which exhibited hyperglycemia as well as hyperinsulinemia, *Enicostemma littorale* was found to decrease not only fasting as well as fed glucose levels but also the increased insulin levels. It is possible that *Enicostemma littorale* decreases glucose levels by improving insulin sensitivity. Treatment with *Enicostemma littorale* was also found to significantly decrease both AUC$_{\text{glucose}}$ and AUC$_{\text{insulin}}$ in NIDDM rats. This further suggests that *Enicostemma littorale* may not alter the release of insulin, but in conditions like hyperinsulinemia, it increases insulin sensitivity for effective glucose disposal. The finding that treatment with *Enicostemma littorale* also prevented decrease in KTT value, the insulin sensitivity index in NIDDM rats, further supports the contention that *Enicostemma littorale* possesses the potential to improve insulin sensitivity.
As mentioned in previous paragraph insulin resistance or insulin deficiency is associated with hypercholesterolemia and hypertriglyceridemia. STZ-diabetes showed increase plasma levels of cholesterol, triglyceride, free fatty acid and phospholipids (Rodrigues et al, 1986). Insulin deficiency or IR may be responsible for dyslipidemia, because insulin has an inhibitory action on HMG - COA reductase, a key rate-limiting enzyme responsible for the metabolism of cholesterol rich LDL particles. The mechanisms responsible for the development of hypertriglyceridemia in uncontrolled diabetes in humans (possibly in insulin deficient STZ-diabetic rats) are due to number of metabolic abnormalities that occur sequentially. Acute insulin deficiency initially causes an increase in free fatty acid mobilization from adipose tissue, resulting in increased secretion of VLDL – triglyceride from liver (Balasse et al, 1972). With longer insulin deficiency liver converts free fatty acids in to ketone bodies and VLDL – triglyceride secretion diminishes (Basso and Havel, 1970). At the same time, lipoprotein lipase activity falls (Nikkila et al, 1977) resulting in impaired clearance of VLDL and chylomicronmes from plasma (Bagdade et al, 1968). Reaven (1988) proposed that IR in diabetic (or non diabetic) subjects led to compensatory hyperinsulinemia, which is associated with, increased LDL and reduced HDL concentrations. In our study also both IDDM and NIDDM rats showed hypercholesterolimia and hypertriglyceridemaia and the treatment with Enicostemma littorale significantly decreased both cholesterol and triglyceride levels. These findings also support the hypothesis that Enicostemma littorale causes improvement in insulin sensitivity.

A good correlation was found between the results of animal studies with those of clinical studies. Administration of Enicostemma littorale produced a significant decrease in not only glucose but also insulin levels in patients with hyperinsulinemia. Insulin levels were found to be high in most of the patients except those on biguanides or receiving some antihypertensive therapy. It is very well documented that biguanides (Bailey, 1992) and many antihypertensive agents produce improvement in insulin sensitivity (Goyal, 1999). Thus, it is possible that, these
patients did not have hyperinsulinemia because of the effects of the biguanides and antihypertensives. The observation that treatment with *Enicostemma littorale* decreased glucose levels although decrease in insulin levels in diabetic patients suggests that *Enicostemma littorale* may act by improving insulin sensitivity.

Hyperinsulinemia is frequently reported in Asian Indians (Singh, 1997). Obesity, hypertension and hypertriglyceridemia are other common characteristics associated with hyperinsulinemia. The diabetic patients included in our study had higher Body mass index (BMI) and hip/waist ratio. It has long been known that both hypertension and NIDDM are often associated with overweight (Sims and Berchtold, 1982). Obesity appears to cause insulin resistance, compensatory hyperinsulinemia and hypertension through parallel but not necessarily linked mechanisms.

As mentioned earlier hyperglycemic condition leads to the development of renal dysfunction in both IDDM and NIDDM rat models, characterised by elevated levels of creatinine, urea and BUN levels. In diabetic patients included in the current study were also found to have higher creatinine levels as compared to non-diabetic subjects. This suggests that diabetic patients have a tendency to develop renal dysfunction. Treatment with *Enicostemma littorale* in patients and rats prevented the raise in creatinine levels.

In conclusion our data suggest that *Enicostemma littorale* possess potential antidiabetic activity. In addition to decrease in serum glucose and lipids it can also preserves kidney dysfunction in diabetic patients. *Enicostemma littorale* may be considered as supplementary herbal therapy in diabetic patients to prevent long term complications of diabetes mellitus.