Diabetes mellitus, long back considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century. After the introduction of insulin, life expectancy of diabetic patients has increased and instead the problem with chronic complications evolved, cardiovascular disease and renal failure becoming the major causes of death among patients with diabetes. Today, patients with diabetes still have an excess morbidity and mortality when compared with the general population, the major causes still being cardiovascular disease and renal failure.

Unfortunately, chronic complications of diabetes show a rising trend among the patients living longer. Diabetes, formerly thought to be a problem of glucose metabolism, actually produces large number of micro and macro vascular complications. Patients with diabetes are characterized by an increased likelihood for developing congestive heart failure through coronary artery disease (CAD), hypertension, specific cardiomyopathy and endothelial dysfunction. Diabetic nephropathy is the leading cause of end-stage renal disease in developed countries and leads to a heavy burden of dialysis and transplantation. The risk of premature death in patients with diabetic nephropathy is increased by the factor of 40-100, and other complications such as retinopathy and neuropathy cluster in these patients.

Lagerstroemia speciosa L (L. speciosa) (Lythracease), commonly known as Crepe Myrtle, a popular folk medicine, is a widely growing plant in tropical countries including Philippines, India, Malaysia, China and Australia. Tea, prepared from the leaves of L. speciosa has been used for the treatment of diabetes mellitus. The antihyperglycemic effect of L. speciosa has been demonstrated in animals and in in-vitro studies. The leaves of L. speciosa contain large amount of corosolic acid, which has been shown to possess antidiabetic properties and we also estimated corosolic acid concentration in Petroleum ether fraction of MEL (PFML) (0.25%). So far there are no published reports on the effects of L. speciosa on hepatic glucose metabolism affecting enzymes like hexokinase and phosphoenolpyruvate carboxykinase (PEPCK). Further, the effect of L. speciosa in diabetic complications is not yet explored.

In the present study, fed and fasting serum glucose levels were found to be significantly higher in STZ induced type 1 diabetic Sprague-Dawley (SD) rats as compared to control rats. Treatment with 50% methanolic extract of Lagerstroemia speciosa leaves (MEL) (100, 300, 500 mg/kg, p.o.) reduced the fasting serum glucose levels but did not affect the serum insulin levels in STZ-induced type 1 diabetic rats when compared with diabetic control rats. This effect was comparable to the effect of insulin (5 IU/kg, i.p.) on STZ-induced type 1 diabetic group. The possible underlying mechanism could be increased peripheral glucose utilization. Treatment with MEL (100, 300, 500 mg/kg, p.o.) and insulin (5 IU/kg, i.p.) also reduced fed serum glucose level in diabetic rats when compared with diabetic control rats. Delaying or inhibiting glucose absorption at intestinal level or decrease in the endogenous glucose production in the liver could be the underlying mechanism. During oral glucose tolerance test (OGTT), when further glucose load was given STZ-induced type 1 diabetic rat there was further rise in glucose levels observed at 0, 30, 60 and 120 min when compared with non diabetic control rats. Treatment with MEL 500 mg/kg p.o., significantly reduced AUC_{glucose} while, 100 and 300 mg/kg, p.o. dose failed to produce this effect in STZ-induced type 1 diabetic rats when compared with diabetic control rats. No significant change was found in AUC_{insulin} at any dose of MEL. This effect was comparable to the effect of insulin (5 IU/kg, i.p.) on STZ-induced type 1 diabetic group. These results support the hypothesis of delaying or inhibiting glucose absorption at intestinal level by MEL.
The activity of liver hexokinase enzyme was found to be decreased in the STZ-induced type 1 diabetic rats when compared with that of non-diabetic control rats. Treatment with MEL (500 mg/kg, p.o.) increased the activity of liver hexokinase enzyme in the STZ-induced type 1 diabetic rats when compared with diabetic control rats. This effect was comparable to the effect of insulin (5 IU/kg, i.p.) on STZ-induced diabetic group. This indicates that MEL effectively increases the utilization of glucose.

Gluconeogenesis significantly contributes to the endogenous hepatic glucose production. The activity of gluconeogenic enzyme PEPCK was found to be increased in the STZ-induced type 1 diabetic rats when compared with that of non-diabetic control rats. Treatment with MEL (500 mg/kg, p.o.) reduced PEPCK activity when compared with the STZ-induced type 1 diabetic control rats. This effect was comparable to the effect of insulin (5 IU/kg, i.p.) on STZ-induced type 1 diabetic group. This indicates that the gluconeogenesis was suppressed by treatment with MEL.

Results indicate that the induction of diabetes in rats with STZ elevated the circulating lipid levels. Serum cholesterol level and various fractions of lipoproteins such as LDL, VLDL and triglycerides were found to be increased, while HDL were found to be decreased when compared with non-diabetic control rats. Treatment with MEL (500 mg/kg, p.o.) produced significant decrease in cholesterol, triglyceride, LDL and VLDL while increased the HDL levels in STZ-induced type 1 diabetic rats when compared with STZ-induced type 1 diabetic control indicating the rebalancing of lipoprotein fraction in favor of HDL and thereby lowering the cardiovascular complications.

In the present study, a significant elevation in SGOT and SGPT levels were observed with STZ-induced type 1 diabetic rats when compared with non-diabetic control rats. Treatment with MEL (500 mg/kg, p.o.) and insulin (5 IU/kg, i.p.) reduced the elevated SGOT and SGPT levels in STZ-induced type 1 diabetic rats when compared with diabetic control rats thereby suggesting their beneficial effects on altered liver functions in conditions of diabetes.

In the present investigation, we found significant elevation in serum creatinine and urea levels in STZ-induced type 1 diabetic rats when compared with non-diabetic control rats. Treatment with MEL (500 mg/kg, p.o.) and insulin (5 IU/kg, i.p.) prevented rise in serum creatinine and urea levels STZ-induced type 1 diabetic rats when compared with diabetic control rats. Hence, it could be beneficial as it provides some protection against diabetic nephropathy.

In the present investigation, HFD control rats showed significant increase in fed and fasting serum glucose levels when compared with non-diabetic control rats. HFD/STZ-induced type 2 diabetic rats showed significant increase in fed and fasting serum glucose level when compared with HFD control rats. Treatment with MEL (100 mg/kg, p.o.) for 3 weeks, failed to produce any significant change in fasting serum glucose level in HFD/STZ-induced type 2 diabetic rats when compared with HFD/STZ-induced diabetic control rats, while at higher doses, i.e. 300, 500 mg/kg, p.o. decrease in fasting serum glucose level was significant. This glucose lowering effect of MEL was comparable to the effect produced by glipizide (10 mg/kg, p.o.) and pioglitazone (20 mg/kg, p.o.). This treatment was extended till 8 weeks for investigating diabetic complications and MEL (100, 300, 500 mg/kg, p.o.) was found to be effective on fasting serum glucose and additionally fed serum glucose was also found to be reduced at 300, 500 mg/kg, p.o. dose. This effect was comparable to the insulin sensitizing effect of pioglitazone (20 mg/kg, p.o.).

In OGTT, HFD/STZ-induced type 2 diabetic rats showed significant increase in glucose levels when compared with HFD control rats. MEL (100, 300 and 500 mg/kg, p.o.) and pioglitazone (20 mg/kg, p.o.) groups of HFD/STZ-induced diabetic rats produced significant decrease in serum glucose level when compared with HFD/STZ-induced diabetic
control rats. Importantly, no significant change in glucose level in OGTT was observed in glipizide (10 mg/kg, p.o.) group. The $AUC_{glucose}$ was found to be significantly higher in HFD/STZ-induced type 2 diabetic rats as compared to HFD control rats. Treatment with MEL 300, 500 mg/kg p.o., significantly reduced $AUC_{glucose}$ while, 100 mg/kg, p.o. dose failed to produce this effect in HFD/STZ-induced type 2 diabetic rats when compared with HFD/STZ-induced diabetic control rats. Treatment of HFD/STZ-induced type 2 diabetic rats with glipizide (10 mg/kg, p.o.) and pioglitazone (20 mg/kg, p.o.) group did not produce any change in $AUC_{glucose}$ when compared with HFD/STZ-induced diabetic control rats. This indicates that MEL might act through decrease in intestinal glucose absorption while glipizide and pioglitazone are probably acting through this mechanisms and the decrease in fed glucose level further support our this hypothesis.

In the present study, liver hexokinase activity was found to be decreased in HFD/STZ-induced type 2 diabetic control rats when compared with the HFD control rats. Treatment with MEL (500 mg/kg, p.o.) increased the activity of liver hexokinase enzyme in the HFD/STZ-induced type 2 diabetic rats when compared with the HFD/STZ-induced diabetic control rats probably by increasing the utilization of glucose. In the present study, the activity of gluconeogenic enzyme PEPCK was also found to be increased in HFD/STZ-induced type 2 diabetic rats when compared with that of HFD control rats. Further, HFD/STZ-induced type 2 diabetic rats treated with MEL (500 mg/kg, p.o.) showed lower levels of PEPCK activity as compared to HFD/STZ-induced type 2 diabetic control rats. Since, gluconeogenesis significantly contributes to the endogenous hepatic glucose production; suppression of gluconeogenesis can contribute to the antihyperglycemic action of MEL.

Control rats receiving HFD showed significant increase in serum insulin levels when compared with non diabetic control rats. HFD/STZ-induced type 2 diabetic rats showed significant decrease in fed and fasting serum insulin levels when compared with HFD control rats after 3 weeks. Following 3 weeks treatment in MEL (100, 300, 500 mg/kg, p.o.) groups and pioglitazone (20 mg/kg, p.o.) group, HFD/STZ-induced type 2 diabetic rats did not show significant change in fasting serum insulin levels when compared with HFD/STZ-induced type 2 diabetic control group while glipizide (10 mg/kg, p.o.) produced significant increase in serum insulin levels. After 8 weeks, HFD showed significant increase in serum insulin levels when compared with non diabetic control rats. HFD/STZ-induced type 2 diabetic rats showed significantly higher fed and fasting serum insulin levels as compared to HFD control rats. Following 8 weeks treatment with MEL 300, 500 mg/kg p.o., significantly reduced fed and fasting serum insulin levels while, 100 mg/kg, p.o. dose failed to produce this effect in HFD/STZ-induced type 2 diabetic rats when compared with HFD/STZ-induced diabetic control rats. This effect was comparable to the effect of pioglitazone (20 mg/kg, p.o.). Glipizide did not produce any effect on insulin level at this time. Non diabetic control rats treated with MEL (500 mg/kg, p.o.) did not produce any significant change in insulin levels when compared with non diabetic control rats. In OGTT, HFD/STZ-induced type 2 diabetic rats showed significant increase in $AUC_{insulin}$ when compared with HFD control rats. Treatment of HFD/STZ-induced type 2 diabetic rats with MEL (300, 500 mg/kg, p.o.) produced significant decrease in $AUC_{insulin}$ when compared with HFD/STZ-induced diabetic control group. Above results indicate that the glucose lowering effects of MEL was like pioglitazone and not similar to glipizide as MEL did not reduce glucose level by release of insulin from beta cells of pancreas but, reduced insulin resistance. This was further confirmed by KITT. In our study, HFD/STZ-induced type 2 diabetic rats showed significant decrease in insulin sensitivity and increase in $T_{1/2}$ when compared with HFD control rats. Treatment with MEL (500 mg/kg, p.o.) and pioglitazone (20 mg/kg, p.o.) in HFD/STZ-induced type 2 diabetic rats produced significant decrease in serum insulin and $T_{1/2}$ when
compared with HFD/STZ-induced diabetic control group. Glipizide (10mg/kg, p.o.) was not found to be effective on serum insulin and T_{1/2}. This result indicates that MEL might be acting through increasing insulin sensitivity like pioglitazone.

In the present study, HFD/STZ-induced type 2 diabetic rats were found to exhibit increased in cholesterol, triglyceride, LDL, VLDL, atherogenic index, LDH, CK, Blood pressure and collagen level in left ventricle, force of contraction, LV hypertrophy and cardiac hypertrophy of heart while decrease in HDL levels and heart rate when compared with HFD control rats. Our data suggest beneficial effects of MEL (500 mg/kg, p.o.) on cardiovascular complications in diabetic animals. This may be due to reduction in cholesterol, triglyceride, LDL, VLDL, atherogenic index, LDH, CK, Blood pressure, collagen level in left ventricular muscle, LV hypertrophy and cardiac hypertrophy while increase in HDL levels, heart rate and prevention of increase in force of contraction in diabetic hearts by MEL (500 mg/kg, p.o.).

In our study, HFD/STZ-induced type 2 diabetes produced significant increase in serum sodium and potassium levels and significant decrease in urine sodium and potassium when compared with HFD control rats. Treatment with MEL (500 mg/kg, p.o.) in HFD/STZ-induced type 2 diabetic rats produced significant decrease in serum sodium and potassium levels while rise in urine sodium and potassium levels when compared with HFD/STZ-induced diabetic control group. This effect was comparable to the effect of pioglitazone (20 mg/kg, p.o.) on HFD/STZ-induced diabetic group. Glipizide (10 mg/kg, p.o.) was not found to be effective on serum and urine levels of sodium and potassium in HFD/STZ-induced diabetic rats.

In the present study, HFD/STZ-induced type 2 diabetes produced significant increase in serum urea and creatinine, while significant decrease in serum albumin and total protein levels when compared with non diabetic control rats. HFD control rats exhibited significant decrease in urine creatinine and creatinine clearance while increase in urine albumin and total protein levels when compared with non diabetic control rats. HFD/STZ-induced diabetic rats showed significant increase in serum urea and creatinine levels while decrease in serum albumin and total protein levels when compared with HFD control rats. HFD/STZ-induced type 2 diabetic rats produced significant decrease in urine creatinine and creatinine clearance while increase in urine albumin and total protein levels when compared with HFD control rats. Administration of MEL (500 mg/kg, p.o.) to HFD/STZ-induced type 2 diabetic rats produced significant decrease in urea and creatinine levels while increase in serum albumin and total protein levels when compared with HFD/STZ-induced diabetic control group. Administration of MEL (500 mg/kg, p.o.) to HFD/STZ-induced type 2 diabetic rats produced significant increase in urine creatinine and creatinine clearance while decrease in urine albumin and total protein levels when compared with HFD/STZ-induced diabetic control group. This effect was comparable to that of pioglitazone (20 mg/kg, p.o.). Glipizide (10 mg/kg, p.o.) had no effect on serum urea, creatinine, albumin, total protein, urine creatinine, creatinine clearance, albumin and total protein levels in HFD/STZ-induced diabetic rats.

In our study, HFD/STZ-induced diabetes produced significant increase in kidney to body weight ratio when compared with HFD control rats. Treatment of MEL (500 mg/kg, p.o.) to HFD/STZ-induced type 2 diabetic rats produced significant decrease in kidney to body weight ratio when compared with HFD/STZ-induced diabetic control group. This effect was comparable to the effect of pioglitazone (20 mg/kg, p.o.). There was no effect of Glipizide (10 mg/kg, p.o.) on kidney weight to body weight ratio in HFD/STZ-induced type 2 diabetic rats.

In severely hyperglycemic rats without insulin treatment, the glomerular volume is reported to be continuously increased during the first eight months of diabetes. Intriglomerular hypertension is consequent upon hyperfiltration that leads to mesangial
expansion and basement membrane thickening. These features can be the hallmarks of diabetic glomerulosclerosis. Diabetic nephropathy in humans presents several structural changes that are characterized by early hypertrophy of both glomerular and tubuloepithelial elements, thickening of the glomerular basement membrane, progressive accumulation of extracellular matrix components in the glomerular mesangium, and less well recognized lesions such as tubulointerstitial fibrosis and renal arteriosclerosis. The histopathology of kidney of HFD/STZ-induced diabetic rats showed thickening of glomeruli and focal sclerosis. HFD/STZ-induced diabetic rats treated with PFML (300 mg/kg, p.o.) showed normal structure—both outer cortex and inner medulla while Cortex show glomerulus, DCT and PCT with interstitium and associated blood vessels same as in case of non diabetic control. Our data suggest beneficial effects of MEL (500 mg/kg, p.o.) on diabetic renal complications in diabetic animals. Thus, study with MEL in type 1 and type 2 diabetic rats showed beneficial effects in treatment of diabetes and associated complications. Further fractionation of MEL was done to have a more active fraction.

When we compared effectiveness of PFML with MEL and TFML in diabetes and diabetic complications, PFML was found to produce comparable effect in lower dose (300mg/kg, p.o.) when compared with MEL (500 mg/kg, p.o.) and solvent ether insoluble fraction or tannin fraction of MEL (TFML) (500 mg/kg, p.o.).

All these results indicate that PFML, MEL and TFML extracts does not induce any stimulation of pancreatic β cells as their effects were comparable to pioglitazone and not to glipizide. Thus the possibility of their inducing insulin secretion to elicit antihyperglycemic activity can be ruled out. They might be acting through increasing insulin sensitivity. Other possible mechanisms for the antihyperglycemic activity of these extracts might be through delaying or inhibiting glucose absorption at intestinal level. The mechanisms may also involve inhibition of liver PEPCK and/or stimulation of liver hexokinase leading to lowering of blood glucose levels. Petroleum ether fraction of MEL (PFML) was found to be more beneficial not only in diabetes but also in diabetic complications like diabetic cardiomyopathy and diabetic nephropathy and diabetes related liver disorders as compared to 50% methanolic extract of Lagerstroemia speciosa leaves (MEL) and solvent ether insoluble fraction or tannin fraction of MEL (TFML). Corosolic acid found to be present in the PFML may be responsible for this beneficial effect in diabetes mellitus and associated complications.