Obesity (defined as a body mass index [BMI] of greater than 30 kg/m²) results when energy intake exceeds energy output with the excess being stored as fat in adipose tissue and ectopically in other tissues (Yao and MacKenzie, 2010). The most frequent pathologic condition associated with excess body fat and particularly with visceral obesity is known as the ‘Metabolic Syndrome’, a group of symptoms, signs and pathophysiologic conditions which includes visceral obesity, insulin resistance, impaired glucose metabolism, type 2 diabetes, dyslipidemia, elevated blood pressure, and other comorbidities including a prothrombotic and proinflammatory state and nonalcoholic fatty liver disease (Capurso and Capurso, 2012). Most of the individuals diagnosed with type 2 diabetes are found to be obese (Ramarao and Kaul, 1999).

Increasing levels of obesity, arising from energy-rich diets and sedentary lifestyles, are driving a global pandemic of type 2 diabetes. Optimal management of type 2 diabetes is focused on maintaining glycemic levels as close as possible to the normal range, and this approach has been shown to be effective in delaying the progression of diabetes related long-term complications (DCCT, 1993; UKPDS, 1998). Effective weight management greatly facilitates the achievement of target goals in glycemic, lipid and blood pressure control to reduce cardiovascular disease risk. While lifestyle intervention in combination with metformin remains the cornerstone therapy for type 2 diabetes, it is a progressive disease where therapy with further treatments such as oral sulphonylureas, thiazolidinediones, incretins and injectable glucagonlike peptide-1(GLP-1) receptor agonists and/or insulin is often required within 10 years of onset (Turner et al., 1999). Unfortunately, some of these therapies are associated with weight gain, and the 10-year follow-up results of the large United Kingdom Prospective Diabetes Study (UKPDS) showed that all pharmacotherapies available at that time except metformin were associated with weight gain, with the largest gain of 6.5 kg observed in insulin-treated patients (Holman et al., 2008).

Many herbal drug extracts derived from traditional medicines showed therapeutic superiority as compared with single constituents thereof. Synergy effects of the mixture of bioactive constituents and their byproducts contained in plant extracts are claimed to be responsible for the improved effectiveness of many extracts. Synergistic effects can be
produced, if the constituents of an extract affect different targets or interact with one another in order to improve the solubility and thereby enhance the bioavailability of one or several substances of an extract (Wagner and Ulrich-Merzenich, 2009). The selected problem for the present study was entitled ‘Evaluation of ethanolic extract of *Embelia ribes* in high fat diet plus low dose streptozotocin induced type-2 diabetes in Wistar rats’. Before evaluating antidiabetic potential of ethanolic extract of *E. ribes* in high fat diet plus low dose streptozotocin induced type-2 diabetes, a preliminary study was planned to investigate the antiobesity potential of ethanolic extract of *E. ribes* in high fat diet-induced obesity model. The study also included isolation of pure embelin from dry fruits of *E.ribes* and to investigate the antiobesity potential in high fat diet-induced obesity model.

In the present study, chemical characterization of the main biologically active constituent of *E.ribes* extract was achieved by HPTLC and HPLC, showing the presence of embelin, a naturally occurring alkyl substituted hydroxy benzoquinone. Further, characterization of isolated embelin from *E.ribes* was done by UV spectroscopy, HPLC, and FT-IR spectroscopy.

**In Plan-I, ‘Antiobesity potential of ethanolic extract of *E.ribes* in HFD-induced obesity in wistar rats’** was investigated. The data obtained from the present study showed that HFD-feeding for the period of 4 weeks in Wistar rats resulted in significant (p< 0.01) increase in body weight gain, BMI, organ’s and visceral fat pad weights (perirenal, mesenteric, epididymal), heart rate and blood pressure, blood glucose, serum insulin, HOMA-IR values, leptin, total cholesterol, triglycerides, LDL-C, VLDL-C, atherogenic and coronary risk indices, apolipoprotein-B, LDH, tissue TBARS levels, while significant (p< 0.01) decrease in serum HDL-C, tissue Na⁺K⁺ ATPase content, antioxidants such as GSH, SOD, CAT, GPx, GR and GST levels as compared to normal control rats. In addition, congestion and fatty degeneration was observed in cardiac and hepatic tissue of HFD-fed rats by histopathological analysis. Based on several aspects described above, in the present study, HFD-fed Wistar rat model considered a practical and accurate one for studying obesity.

Treatment with ethanolic extract of *E.ribes* (100 mg/kg bw, p.o) and orlistat (10 mg/kg bw, p.o) for 21 days in HFD-fed obese rats significantly (p < 0.01) reduced the body weight
gain in HFD-fed rats by 1.31- and 1.42-folds, and BMI by 21.47% and 29.3%, respectively. Further, epididymal, perirenal, and mesenteric fat pad weights were decreased by 1.19-, 1.13-, 1.19-folds, respectively, in ethanolic extract of E.ribes (100 mg/kg, p.o) treated rats then in their HFD-fed counterparts. Orlistat (10 mg/kg bw, p.o) administration decreased epididymal fat pad weight by 1.46-folds, perirenal fat pad weight by 1.25-folds, and mesenteric fat pad weight by 1.3-folds when compared to HFD-fed obese group. Furthermore, heart, liver, and kidney weights were decreased by 1.10-, 1.19-, 1.29-folds, respectively, in ethanolic extract of E.ribes (100 mg/kg bw, p.o) treated rats then in their HFD-fed obese counterparts. Orlistat (10 mg/kg bw, p.o) administration decreased heart weight by 1.18-folds, liver weight by 1.21-folds, and kidney weight by 1.73-folds when compared to HFD-fed obese group. Though there was a significant difference in the body weights between the experimental groups, no significant difference in the daily food intake and water intake between groups was observed.

Treatment with ethanolic extract of E.ribes (100 mg/kg bw, p.o) and orlistat (10 mg/kg bw, p.o) for 21 days produced a statistically significant (p < 0.01) decrease in heart rate, systolic, diastolic and mean arterial blood pressure as compared to HFD-fed obese rats. The reference drug, orlistat treated group exhibited better activity than ethanolic extract of E.ribes treated group in all the above hemodynamic parameters (p < 0.01).

Ethanolic extract of E.ribes (100 mg/kg bw, p.o) treatment for 21 days caused a significant (p < 0.01) decrease in serum total cholesterol, triglycerides, LDL-C and VLDL-C levels by 1.21, 1.32-, 1.37- and 1.32- folds, and Orlistat (10 mg/kg bw, p.o) 1.28-, 1.38-, 1.55- and 1.38-folds, respectively, as compared with those in HFD-fed obese group. There was a significant (p < 0.01) increase in serum HDL-C by 1.31- and 1.36-folds in ethanolic extract of E.ribes (100 mg/kg bw) and orlistat (10 mg/kg bw) treated group, respectively, as compared to HFD-fed obese group.

Treatment with ethanolic extract of E.ribes (100 mg/kg bw, p.o) and orlistat (10 mg/kg bw, p.o) for 21 days showed a significant (p < 0.01) decrease in the levels of serum apo-B by 75.05% and 77.02%; blood glucose levels by 27.92% and 24.98%; serum insulin levels by 36.60% and 42.48%; serum leptin levels by 44.78% and 48.55%; serum LDH levels by 45.09% and 87.78% respectively, as compared to HFD-fed obese group. Further, ethanolic
extract of *E.ribes* (100 mg/kg bw, p.o) treatment caused significant reduction (*p* < 0.01) in HOMA-IR value from 15.29 ± 0.05 to 6.99 ± 0.03; whereas orlistat (10 mg/kg bw, p.o) treatment produced significant reduction in HOMA-IR value from 15.29 ± 0.05 to 6.60 ± 0.02 when compared to HFD-fed group.

Treatment with ethanolic extract of *E.ribes* (100 mg/kg bw, p.o) and orlistat (10 mg/kg bw, p.o) for 21 days produced a significant (*p* < 0.01) increase in the content of hepatic Na\(^+\)/K\(^+\)ATPase by 36.96% and 89.13%, cardiac Na\(^+\)/K\(^+\)ATPase by 44.19% and 74.42%, respectively, as compared to HFD-fed group.

Administration of ethanolic extract of *E.ribes* (100 mg/kg bw, p.o) produced a significant (*p* < 0.01) decrease in hepatic TBARS levels by 41.43% and cardiac TBARS levels by 43.84% as compared to HFD-fed obese control group. Orlistat (10 mg/kg bw, p.o) showed 61.93% reduction in hepatic TBARS levels and 63.01% reduction in cardiac TBARS levels as compared to HFD control group.

Treatment with ethanolic extract of *E.ribes* (100 mg/kg bw, p.o) and orlistat (10 mg/kg bw, p.o) for 21 days produced a significant (*p* < 0.01) increase in the levels of hepatic GSH by 2.5- and 2.8-folds; SOD by 1.19- and 2.7-folds; CAT by 1.64- and 3.07-folds; GPx by 1.51- and 1.46-folds; GST by 1.22- and 1.69-folds; GR by 1.66- and 1.53-folds respectively, as compared to HFD-fed group. Similarly, ethanolic extract of *E.ribes* (100 mg/kg bw, p.o) and orlistat (10 mg/kg bw, p.o) treatment for 21 days produced a significant (*p* < 0.01) increase in the levels of cardiac GSH by 2- and 1.41-folds; SOD by 1.44- and 1.61-folds; CAT by 1.77- and 1.89-folds; GPx, by 1.32- and 1.45- folds; GST by 1.76- and 1.88-folds; GR by 1.6- and 1.79-folds respectively, as compared to HFD-fed obese group.

The impaired architecture with morphology of hepatic cells were improved and normalized by treatment with ethanolic extract of *E.ribes* (100 mg/kg bw, p.o), which showed mild congestion, but no fatty changes. Orlistat (10 mg/kg bw, p.o) also showed no fatty changes and normal architecture of hepatocytes was preserved. Similarly, the impaired architecture with morphology of myocardial cells were improved and normalized by treatment with ethanolic extract of *E.ribes* (100 mg/kg bw, p.o) and Orlistat (10 mg/kg bw, p.o) and showed no fatty changes.
In the present study, no significant difference (p > 0.05) was observed in body weight gain, fat pad weights, body mass index (BMI), mean arterial blood pressure, serum lipid profile, serum leptin, insulin, glucose and oxidative stress markers between *E.ribes* (100 mg/kg bw) *per se* and normal control group, suggesting that ethanolic extract of *E.ribes* has no effect *per se* in HFD-induced obesity in Wistar rats.

After evaluating the anti-obesity potential of ethanolic extract of *E.ribes* (100 mg/kg bw, p.o) in HFD-induced obesity in Wistar rats, **embelin-the active principle of the *E.ribes* fruits was investigated for anti-obesity potential in HFD-induced obesity in Wistar rats (Plan-II).**

Treatment with embelin (50 mg/kg bw, p.o.) and orlistat (10 mg/kg bw, p.o.) for 21 days in HFD-fed rats significantly (p < 0.01) reduced the body weight gain by 35.36% and 38.38%; BMI by 15.33% and 18.91% respectively. Further, perirenal, mesenteric, and epididymal fat pad weights were decreased by 1.29-, 1.17-, and 1.25-folds on treatment with embelin (50 mg/kg, p.o.); 1.58-, 1.28-, and 1.35-folds on treatment with orlistat (10 mg/kg bw, p.o.), respectively, as compared to their respective counterparts in HFD-fed group. Treatment with embelin (50 mg/kg bw, p.o.) also decreased heart, liver, and kidney weights by 1.15-, 1.29-, and 1.37-folds, and orlistat (10 mg/kg bw, p.o.) treatment by 1.2-, 1.37-, and 1.49-folds, respectively than their respective counterparts in HFD-fed group (p < 0.01). However, there was no significant (P > 0.05) difference observed among treatment groups in daily food and water intake during the entire study period.

Treatment with embelin (50 mg/kg bw, p.o.) and the orlistat (10 mg/kg bw, p.o.) for 21 days produced a statistically significant (p < 0.01) decrease in heart rate, systolic, diastolic and mean arterial blood pressure as compared to HFD-fed rats.

Treatment with embelin (50 mg/kg bw, p.o.) for 21 days produced a significant (p < 0.01) decrease in serum total cholesterol, triglycerides, LDL-C and VLDL-C levels by 1.29, 1.41, 1.62- and 1.41- folds, and orlistat (10 mg/kg bw, p.o.) 1.31-, 1.43-, 1.65- and 1.43-folds, respectively, as compared with those in HFD-fed group. There was a significant (p < 0.01) increase in serum HDL-C by 1.53- and 1.49-folds in embelin (50 mg/kg bw) and orlistat (10 mg/kg bw) treated group, respectively, as compared to HFD-fed group. Further, treatment with embelin (50 mg/kg bw, p.o.) caused significant reduction in AI (from 0.78 ±
0.03 to 0.45 ± 0.08) and CRI (from 6.37 ± 0.75 to 3.23 ± 0.36) when compared to HFD-fed group. Orlistat, standard drug (10 mg/kg bw; i.e. group IV) treatment produced significant reduction in AI (from 0.78 ± 0.03 to 0.45 ± 0.04) and CRI (from 6.37 ± 0.75 to 3.26 ± 0.82) when compared to HFD-fed group. Treatment with embelin (50 mg/kg bw, p.o.) and orlistat (10 mg/kg bw, p.o.) for 21 days showed a significant (p < 0.01) decrease in the levels of serum apolipoprotein-B by 75.05% and 77.02%; blood glucose by 24.77% and 18.15%; serum insulin by 35.03% and 38.22%; serum leptin by 43.39% and 48.55% respectively, as compared to HFD-fed group. Further, treatment with embelin (50 mg/kg bw, p.o.) caused significant reduction (p < 0.01) in HOMA-IR value from 15.41 ± 0.03 to 7.53 ± 0.01; whereas orlistat (10 mg/kg bw, p.o.; i.e. group IV) treatment produced significant reduction in HOMA-IR value from 15.41 ± 0.03 to 7.79 ± 0.01 when compared to HFD-fed group.

Treatment with embelin (50 mg/kg bw, p.o.) and orlistat (10 mg/kg bw, p.o.) for 21 days produced a significant (p < 0.01) increase in the content of hepatic Na⁺/K⁺ATPase by 34.78% and 91.3%; cardiac Na⁺/K⁺ATPase by 53.66% and 87.8% respectively, as compared to HFD-fed group. Treatment with embelin (50 mg/kg bw, p.o.) and orlistat (10 mg/kg bw, p.o.) for 21 days produced a significant (p < 0.01) decrease in the levels of hepatic TBARS by 53.52% and 66.20%; cardiac TBARS levels by 62.67% and 61.33% respectively, as compared to the respective levels in HFD-fed group.

Treatment with embelin (50 mg/kg bw, p.o.) and orlistat (10 mg/kg bw, p.o.) for 21 days produced a significant (p < 0.01) increase in the levels of hepatic GSH by 2.52- and 2.85-folds; SOD by 1.39- and 1.49-folds; CAT by 2.13- and 2.15-folds; GPx by 1.7- and 1.52-folds; GST by 1.33- and 1.86-folds; GR by 1.83- and 1.73-folds respectively, as compared to the respective levels in HFD-fed group. Similarly, treatment with embelin (50 mg/kg bw, p.o.) and orlistat (10 mg/kg bw, p.o.) for 21 days produced a significant (p < 0.01) increase in the levels of cardiac GSH by 2.19- and 2.86-folds; SOD by 1.34- and 1.44-folds; CAT by 1.78- and 1.92--folds; GPx by 1.34- and 1.46-folds; GST by 1.31- and 1.94-folds; GR by 1.56- and 1.72-folds respectively, as compared to the respective levels in HFD-fed group.
Treatment with test drug embelin (50 mg/kg bw, p.o.) and standard drug orlistat (10 mg/kg bw, p.o.) improved the impair architecture and morphology of hepatocytes, myocardium, glomeruli and proximal convoluted tubules and no fatty changes were observed by histopathological analysis.

The results of the present study showed comparable effect of ethanolic extract of *E.ribes* and embelin on different parameters of obesity. Possible explanation for therapeutic equivalence between embelin and *E.ribes* extract is synergistic effects produced by constituents present in the *E.ribes* extract. Many herbal drug extracts derived from traditional medicines showed therapeutic superiority as compared with single constituents thereof.

Hence, in Plan-III, ‘Antidiabetic potential of ethanolic extract of *E.ribes* in high fat diet-fed and low dose streptozotocin-induced type 2 diabetes in wistar rats’ was investigated.

The HFD-fed and low dose STZ-treated rats simulate natural disease progression and metabolic characteristics typical of individuals at increased risk of developing type 2 diabetes because of insulin resistance and obesity. Further, it is also cost-effective and suitable for expedient *in vivo* evaluation of anti-diabetic agents. In the present study, HFD-fed and STZ-induced diabetic rats had significant (p < 0.01) increase in body weight, organ’s weight, blood pressure, fasting blood glucose levels, oral glucose tolerance (OGTT), serum lipid levels, atherogenic (AI) and coronary risk index (CRI), HOMA-IR values, serum lipase, LDH, creatinine, ALP, hepatic Glc-6-Pase activity, and tissue lipid peroxidation (TBARS) while significant (p < 0.01) decrease in serum HDL-C, insulin, leptin, adiponectin, total protein, albumin, hepatic glycogen content, and tissue GSH, SOD and CAT levels. Further, histopathological changes in pancreas tissue of diabetic rats showed damaged and shrunken islets Langerhans; cardiac tissues showed fatty changes and lymphocytic infiltration in myocardial cells; hepatic tissues showed congested central hepatic vein and hepatic fatty degeneration; kidney tissues showed tubular degeneration and congestion of capillaries.

Following 21 days (i.e. week 3) of treatment with ethanolic extract of *E.ribes* at 100- and 200 mg/kg bw, and metformin at 180 mg/kg bw, significantly (p < 0.01) reduced the body
weight in diabetic rats by 5.04%, 6.37% and 12.10% respectively. Further, ethanolic extract of \textit{E.ribes} (100- and 200 mg/kg v) and metformin (180 mg/kg bw) in diabetic rats resulted in a significant (p< 0.05) reduction in organ’s weight (i.e. heart, liver and kidney) and their indices.

After 21 days of the ethanolic extract \textit{E.ribes} treatment (100-and 200 mg/kg bw, p.o.) and metformin (180 mg/kg bw), heart rate, systolic, diastolic, and mean arterial blood pressure was significantly (p< 0.01) decrease as compared to diabetic control rats.

Treatment with ethanolic extract of \textit{E.ribes} (100- and 200 mg/kg bw) significantly (p< 0.01) reduced fasting blood glucose levels in diabetic rats by 54.38% and 65.93%, respectively at week 3. Similarly, administration of metformin at a dose of 180 mg/kg in diabetic rats produced 66.47% reduction in fasting blood glucose levels compared with diabetic control group at week 3. Further, compared with the diabetic control, treatment with ethanolic extract of \textit{E.ribes} (100- and 200 mg/kg bw, p.o.) and metformin (180 mg/kg bw, p.o.) showed a significant improvement in oral glucose tolerance. \textit{E.ribes} extract treatment significantly (p< 0.01) reduced blood glucose excursion by 46.37% and 60.08% at tested doses of 100- and 200 mg/kg bw respectively, as shown by AUC\textsubscript{0-120 min}. Metformin (180 mg/kg bw, p.o.) also significantly (p< 0.01) lowered glucose excursion (AUC\textsubscript{0-120 min}) by 61.78%.

Compared to the diabetic control group, treatment with ethanolic extract of \textit{E.ribes} (100- and 200 mg/kg bw, p.o.) and metformin (180 mg/kg bw, p.o.) resulted in a significant increase in the serum insulin levels following oral glucose loading in Wistar rats at all the time points. The AUC\textsubscript{0-120 min} of insulin during the OGTT was significantly lower (p< 0.01) in the diabetic control group as compared to normal control, ethanolic extract of \textit{E.ribes} (100- and 200 mg/kg bw), and metformin (180 mg/kg bw) treated groups.

\textit{E.ribes} extract treatment with 100- and 200 mg/kg bw dose for 21 days in diabetic rats produced significant (p< 0.01) decrease in triglycerides (-30.84% and -44.04%), total cholesterol (-15.60% and -23.97%), LDL-C (-22.24% and -31.92%) and VLDL-C (-30.84% and -44.04%) concentrations, respectively as compared to diabetic control rats. In contrast, treatment with \textit{E.ribes} extract at 100- and 200 mg/kg bw, significantly (p< 0.01) increased HDL-C concentrations in diabetic rats by 71.88% and 84.66%, respectively. Metformin
(180 mg/kg bw, p.o) treatment for 21 days in diabetic rats significantly (p< 0.01) reduced triglycerides by 47.46%, total cholesterol by 25.68%, LDL-C by 30.83%, VLDL-C by 47.47%, while increased HDL-C by 63.65% (p< 0.01). In addition, E.ribes extract and metformin treatment caused significant reductions in the atherogenic and coronary risk indices in diabetic rats (p < 0.01).

Treatment with ethanolic extract of E.ribes at 100- and 200 mg/kg bw dose for 21 days caused significant (p< 0.01) increase in serum leptin levels by 29.58% and 38.03%; insulin levels by 28.57% and 43.70%; adiponectin levels by 0.39% and 0.50%; total protein levels by 28.15% and 33.18%; albumin levels by 19.78% and 29.85% respectively, as compared to diabetic control group. Similarly, metformin (180 mg/kg bw, p.o) in diabetic rats significantly (p< 0.01) increased serum leptin levels by 42.25%, insulin levels by 65.55%, adiponectin levels by 0.56%, total protein levels by 32.27%, albumin levels by 34.33%, respectively, as compared to diabetic control group.

Treatment with ethanolic extract of E.ribes at 100- and 200 mg/kg bw dose for 21 days caused significant (p< 0.01) decrease in serum lipase activity by 1.67-folds and 2.15-folds; LDH levels by 26.63% and 38.86%; creatinine levels by 33.16% and 45.38%; ALP levels by 24.52% and 36.14% respectively as compared to diabetic control group. Similarly, metformin (180 mg/kg, p.o) treatment for 21 days in diabetic rats significantly (p< 0.01) decreased serum lipase activity by 2.31-folds; LDH levels by 44.24%; creatinine levels by 49.74%; ALP levels by 41.05% as compared to diabetic control group. Treatment with ethanolic extract of E.ribes at 100 mg/kg bw dose caused significant reduction (p < 0.01) in HOMA-IR values from 26.62 ± 0.03 to 15.63 ± 0.01; whereas 200 mg/kg bw dose of ethanolic extract of E.ribes caused significant reduction (p < 0.01) in HOMA-IR values from 26.62 ± 0.03 to 13.04 ± 0.01 as compared to diabetic control group. Metformin (180 mg/kg bw, p.o) treatment produced significant (p < 0.01) reduction in HOMA-IR value from 26.62 ± 0.03 to 14.76 ± 0.04 as compared to diabetic control group.

Treatment with ethanolic extract of E.ribes at 100-and 200-mg/kg bw dose and metformin (180 mg/kg, p.o) in diabetic rats decreased hepatic Glc-6-Pase activities by 26.15%, 36.92%, and 37.31%, respectively when compared to the diabetic control group (p< 0.01).
There was a significant (p < 0.01) increase in hepatic glycogen content by 23%, 50.3%, and 33.12% in ethanolic extract of *E. ribes* at 100- and 200 mg/kg bw and metformin (180 mg/kg bw, p.o) treated groups respectively, as compared to diabetic control group after 12 hour fasting period.

Treatment with ethanolic extract of *E. ribes* at 100-and 200-mg/kg bw dose, and metformin (180 mg/kg bw, p.o) in diabetic rats decreased cardiac TBARS levels by 32.43%, 40.24%, and 48.95%; hepatic TBARS levels decreased by 20.45%, 26.02%, and 29%; kidney TBARS levels decreased by 1.55-, 1.97-, and 2.14-folds respectively when compared to the diabetic control group (p< 0.01).

Treatment with ethanolic extract of *E. ribes* at 100-and 200-mg/kg bw bw dose, and metformin (180 mg/kg, p.o) in diabetic rats increased cardiac GSH levels by 3.94-, 4.16- and 4.21-folds; hepatic GSH levels increased by 2.42-, 2.47- and 2.5-folds; kidney GSH levels increased by 1.57-, 1.62- and 1.65-folds respectively, when compared to the diabetic control group (p< 0.01).

Treatment with ethanolic extract of *E. ribes* at 100-and 200-mg/kg bw dose, and metformin (180 mg/kg bw, p.o) in diabetic rats increased cardiac SOD levels by 23.56%, 35.62% and 37.26%; hepatic SOD levels increased by 1.93-, 2.06- and 2.09-folds; kidney SOD levels increased by 1.28-, 1.36- and 1.39-folds respectively when compared to the diabetic control group (p< 0.01). Further, ethanolic extract of *E. ribes* at 100-and 200-mg/kg bw dose, and metformin treated diabetic rats had their cardiac CAT levels increased by 1.94-, 2.3- and 2.46-folds; hepatic CAT levels increased by 1.95-, 2.35- and 2.39-folds; kidney CAT levels increased by 2.66-, 3.22- and 3.39-folds respectively when compared to the diabetic control group (p< 0.01).

Treatment with test drug, ethanolic extract of *E. ribes* (100- and 200 mg/kg bw, p.o.) and standard drug metformin (180 mg/kg bw, p.o.) showed restoration of normal cellular population size of islets of Langerhans and absence of islet damage and presence of hyperplasia in pancreas tissue; cardiac tissue showed no fatty changes with retention of normal morphology architecture of myocardium; hepatic tissue showed improvement in the impaired architecture and morphology of hepatocytes and no fatty changes were observed;
and kidney tissue showed improvement in the impaired architecture and morphology of glomeruli and proximal convoluted tubules and no fatty changes were observed.

Between the two doses *i.e.* 100- and 200 mg/kg bw of ethanolic extract of *E.ribes*, the dose 200 mg/kg bw dose was found to be more effective in reducing fasting blood glucose levels, hepatic glucose-6-phosphatase activity, hepatic fatty degeneration, oxidative changes; restoring the elevated blood pressure and liver glycogen; and reversal of circulating levels of serum lipids, lipase, insulin, leptin and adiponectin towards normal in diabetic rats. The results were comparable to the standard drug metformin (180 mg/kg bw, p.o.).

**In conclusion**, the present research work revealed reduction in body weight gain, BMI, organ’s and visceral fat pad weights, heart rate, blood pressure, serum lipids, apolipoprotein-B, blood glucose, insulin, HOMA-IR, leptin, LDH, hepatic and myocardial tissue lipid peroxidation, and improvement in HDL-C levels, hepatic and myocardial Na’K’ATPase content, fatty degeneration and antioxidant enzyme levels suggesting that ethanolic extract of *E.ribes* (100 mg/kg bw, p.o) possesses significant anti-obesity potential (Plan I).

The present study provides new findings on the preventive effects of embelin on obesity, hyperlipidemia and oxidative stress. Embelin (50 mg/kg bw, p.o) treatment decreased body weight, BMI, visceral fat pad weights, blood pressure, serum lipid levels and tissue lipid accumulation, inhibited formation of a lipid peroxidation product, adjust metabolic disturbance of lipoprotein, insulin and leptin, increased antioxidant enzyme activity and repressed development of hyperlipidemia in HFD-fed obese rats. Embelin could be valuable in the development of new drug therapies to prevent obesity, hyperlipidemia and oxidative stress (Plan II).

The results of this study clearly show that ethanolic extract of *E.ribes* possess strong antidiabetic potential in HFD- and low dose STZ-induced type 2 diabetic rats. The treatment significantly reduced the body weight gain, hyperglycemia, insulin resistance, hyperlipidemia, elevated blood pressure and oxidative stress in adult diabetic Wistar rats. Further, ethanolic extract of *E.ribes* was also found to prevent progression of diabetic
nephrotoxicity in type 2 diabetic rats. Administration of ethanolic extract of *E.ribes* improved renal function and ameliorated renal histopathological changes in HFD fed and low dose STZ-induced type 2 diabetic rat model. The possible mechanisms of antidiabetic activity of *E.ribes* extract involve, at least in part, to its strong antioxidant effect and the reversal of low circulating levels of leptin and adiponectin in diabetic rats which is responsible for development of insulin resistance. Improved pancreatic exocrine activities can be ascribed to insulin secretion from existing residual β-cell of islets. In future, if these data will be validated in clinical trials, *E.ribes* seems to offer potential as a plant extract that is useful for alleviating metabolic syndrome (*Plan III*).

Preclinical studies provide a key resource for justifying clinical development. *E.ribes* is a plant origin medicine without any apparent toxicity and reported LD$_{50}$ of its active constituent embelin is higher than 2000 mg/kg bw in rats and mice indicating its safety. After physicochemical standardization of the test drug *E.ribes* extract its effectiveness was carefully tested in well characterized diet-induced model of obesity and type-2 diabetes in the preclinical setting. In the present study, *E.ribes* extract treatment shows promising results on obesity and type 2 diabetes.

Before being able to translate these preclinical data and observations into possible clinical outcomes, a series of experiments are needed to determine efficacy of the test material. Quantitative translation from preclinical to clinical is model based and requires PK (pharmacokinetic) and PK/PD (pharmacokinetic / pharmacodynamics) models linking drug exposure with effect. Another important limitation our study is that the experimental animals used were genetically identical, a situation quite unlike the human population. Data from animal models of varied genetic backgrounds are required. If aforementioned experiments provide promising results, preclinical to clinical translation of *E.ribes* extract in obesity and type-2 diabetes is possible.