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Diabetes mellitus is characterized by derangements in carbohydrate, protein and fat metabolism caused by the complete or relative insufficiency of insulin secretion and/or insulin action. There are two main forms of diabetes, Type 1 (Insulin dependent diabetes mellitus) and Type 2 (Non-insulin dependent diabetes mellitus). Type 1 diabetes is due to autoimmune-mediated deterioration of pancreatic β-cells, resulting in absolute insulin deficiency. Type 2 diabetes is far more common and characterized by insulin resistance and/or abnormal insulin secretion, either of which may predominate. People with Type 2 diabetes are not dependent on exogenous insulin, but may require it for the control of blood glucose levels, if this is not achieved with diet alone or oral hypoglycaemic agents. Insulin resistance is a state of reduced insulin sensitivity, an inability of insulin to lower plasma glucose levels through suppression of hepatic glucose production in liver and stimulation of glucose uptake in skeletal muscles and adipose tissue. The coexistence of insulin resistance and hyperinsulinemia appears to contribute directly or indirectly to many other disorders, such as dyslipidemia, hypertension, atherosclerosis and a procoagulant state, linking together with insulin resistance, which has now assumed the status of syndrome, namely Syndrome X.

Numerous plants have been reported to possess hypoglycaemic activity and mechanisms for the antidiabetic action of such plants have been described. There are plants, which exhibit properties similar to the well known sulfonylurea drugs like glybenclamide, effecting hypoglycaemia in normal animals by stimulating insulin release from pancreatic β-cells, besides reducing hepatic clearance of insulin hormone while others act like the biguanides specifically, metformin which, although antihyperglycaemic, does not effect hypoglycaemia in normal state. Metformin-like activities of plants, augments insulin action by increasing the number of glucose transporters, inhibit gluconeogenesis, reduces absorption from the intestine but increases glucose metabolism in the liver. Because of many side effects and doubt about the efficacy and safety of the present day oral hypoglycaemic agents which have promoted a search for safer and more effective drugs for the treatment of
diabetes in particular type 2 diabetes mellitus. This has led to explore alternative medicines including natural therapies. A multitude of herbs, spices and other plant materials are being used in the management of diabetes mellitus especially in third world countries and many more are being explored for the antidiabetic activity. Streptozotocin was top priority diabetogenic agent for inducing diabetes mellitus into rats because of its less mortality.

Antihyperglycaemic effect of nearly 18 plants was studied in STZ-induced diabetic rats and 3 marine extracts both in sucrose loaded rat model and STZ-induced diabetic rats. Sucrose loaded rat model was primarily used to identify the lead molecule from plant/marine extracts. Streptozotocin (STZ)-induced diabetic rat model was later used to confirm the antihyperglycaemic activity of plant/marine extracts under diabetic conditions. Significant antihyperglycaemic activity was noted in the ethanolic extracts of the tuberous root of Gloriosa superba, Berberis aristata, Tephrosia purpurea, stem bark of Taxus baccata Wallichiana spp, leaves of Verbascum thapsus, Lycopodium clavatum, Boerhaavia diffusa, Eclipta alba, Acacia nilotica, Strobilanthes perrottitiana, stem wood of Cedrus deodara, fruits of Myristica fragrans, stem bark of Betula utilis, hard wood of Acacia catechu and leaves of Tectona grandis. The average antihyperglycaemic activity profile were 22.0 (p<0.01), 23.0 (p<0.05), 16.0 (p<0.05), 13.6 (p<0.05), 10.0 (p<0.05), 35.8 (p<0.001), 12.0 (p<0.05), 16.9 (p<0.05), 10.3 (p<0.05), 19.6 (p<0.01), 19.5 (p<0.01), 11.0 (p<0.05), 12.4 (p<0.05) and 10.6 (p<0.05) respectively. The marine extracts which were found to have antihyperglycaemic effect in sucrose loaded rat model were of Ceriops tagal, Simularia erecta and Simularia firma. The average antihyperglycaemic activity were noted in this model i.e. 12.4%, 12.7% and 13.0% respectively; whereas, the similar extracts showed 25.8%, 16.1% and 18.8% antihyperglycaemic effect in STZ-induced diabetic rats. This is being the first report for any antihyperglycaemic property in the said plant/marine extracts.

Search for lead based antidiabetic molecules/natural substances was one of the objectives of our studies. Three major in-vitro antidiabetic targets were standardised i.e. α-glucosidase, aldose reductase and protein tyrosine phosphatase-1B.
α-Glucosidase, a major target for antidiabetic drug discovery, is located on the brush border membrane of small intestine. If any agent found to inhibit this enzyme, there is possibility that agent may delay glucose absorption across small intestine and consequently prevent the postprandial hyperglycaemia. The next target which directly deals with secondary diabetic complications like cataract, neuropathy, nephropathy etc. is Aldose reductase. The enhanced expression and activity of this enzyme was found in diabetic situation. It converts more and more glucose to sorbitol, which give rise to multifaceted problems that later on give rise to macro and microvascular complication of diabetes mellitus. Any inhibitor of aldose reductase would be developed as drug for the treatment of diabetic complications for which no drug is available yet in the market. Protein tyrosine phosphatase-1B, an enzyme of high importance, play important role in carrying out insulin signaling cascade together with protein tyrosine kinase. In normal circumstances there is a synchronization in between these two enzymes i.e. protein tyrosine kinase and protein tyrosine phosphatase. In the case of insulin resistance the activity of protein tyrosine phosphatase-1B was found to be increased because of the high expression of PTP gene. Therefore, for the treatment of insulin resistance and non-insulin dependent diabetes mellitus one has to inhibit the activity of protein tyrosine phosphatase-1B. An inhibitor of protein tyrosine phosphatase can be used effectively to reverse insulin resistance and consequently insulin sensitivity for liver and muscles can be increased. Some library compounds i.e. L-000-17-10, L-000-17-11, L-000-17-16 and L-000-17-17 were found to inhibit both α-glucosidase and aldose reductase to the tune of 90 to 100% at 250 μM. Compound L-001-8-26, L-001-8-27, L-001-8-28, L-001-8-36, L-001-8-37, L-001-8-62 and L-001-8-63 were found to inhibit protein tyrosine phosphatase-1B to the tune of 93 to 100% at 100 μM. Their percent inhibitions were also compared with their standard inhibitors like Acarbose which inhibits α-glucosidase upto 68.4% at 250 μM, Quercitrin, a known inhibitor of aldose reductase was found to inhibit this enzyme by 69.6% at 250 μM in the present study and the next known mammalian inhibitor i.e. peroxovanadate could inhibit protein tyrosine phosphatase-1B to the tune of 80.5% at 100 μM concentration.
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The two standardized antidiabetic preparations \textit{i.e.} CDR-134 and CT-1 proved their antihyperglycaemic property in STZ-induced diabetic rats. CDR-134 and CT-1 showed 25.4\% (p<0.01) and 21.4\% (p<0.01) lowering of blood glucose in diabetic rats. Both preparations showed dose dependency in STZ-induced diabetic rats and their ED$_{50}$ values were calculated to be around 243 and 94.6 mg/kg, respectively. It seemed that CDR-134 and CT-1 exert their glucose lowering effect by inhibiting $\alpha$-glucosidase present in the brush border membrane of small intestine, with IC$_{50}$ of 42 and 40 $\mu$g/ml respectively. The nature of inhibition was found to be non-competitive in each case.

Two rat models have been standardised by manipulating the diet and injecting diabetogenic agent Streptozotocin (STZ), respectively for studying the pathophysiology of insulin resistance, hyperinsulinemia and type 2 diabetes mellitus. Fructose-enriched diet fed rat and neonatal-STZ rat model were used as animal models for non-insulin dependent diabetes mellitus (type 2 diabetic condition \textit{i.e.} impaired glucose tolerance and insulin resistance). These animal models of type 2 diabetes were used for the evaluation of antihyperglycaemic and insulin resistant reversal activity of standardized preparations \textit{i.e.} CDR-134 and CT-1. These animal models were used to evaluate the short and long term effects of CDR-134 and CT-1 on primary and secondary biochemical changes during diabetes and insulin resistance. Biomolecules and regulatory enzymes of carbohydrate metabolism were chosen for the study. These include blood glucose, oral glucose tolerance test (OGTT), serum insulin, pyruvate kinase, phosphofructokinase, glycogen phosphorylase, glucose-6-phosphatase, phosphoenolpyruvate carboxykinase, lactate dehydrogenase and protein tyrosine phosphatase. These animals showed slightly elevated fasting blood glucose, impaired glucose tolerance and the state of insulin resistance and hyperinsulinemia. These preparations (CDR-134 and CT-1) have shown promising results in these models as indicated by correction in impaired fasting blood glucose profile, impaired glucose tolerance and normalization of the elevated serum insulin level, as well as activating the rate limiting/regulatory enzymes of carbohydrate metabolism responsible for insulin resistance and type 2 diabetes.
After 10 weeks feeding of Fructose enriched diet to Sprague Dawley, significant amount of deterioration occur in oral glucose tolerance curve. In the case of neonatal rats oral glucose tolerance curve was significantly altered after 8 weeks post STZ injection. On week 13th, 15th, 18th, 20th and 22nd impairedness in oral glucose tolerance became more prominent. Serum insulin level was also found to be significantly higher in fructose fed and neonatal-STZ rats. During five weeks treatment with CDR-134 in neonatal rats and fructose fed rats, oral glucose tolerance found to become normal. CDR-134 helped in normalizing the oral glucose tolerance in these two rat models for non-insulin dependent diabetes mellitus. Three weeks feeding of CT-1 to these models also improved impaired glucose tolerance by correcting impaired glucose tolerance (IGT).

These preparations were found to alter the activities of regulatory enzymes of carbohydrate metabolism in these two animal models for type 2 diabetes and insulin resistance. CDR-134 and CT-1 were found to decrease the activities of glucose-6-phosphatase and Phosphoenolpyruvate carboxykinase and consequently reducing hepatic glucose production by the process of gluconeogenesis in tissues like liver and muscles. These agents also assisted in glucose uptake and its utilization by increasing the activities of pyruvate kinase, phosphofructokinase and lactate dehydrogenase. Pyruvate kinase plays an important role in the utilization of glucose and thereby helping glucose uptake. Its activity was found to be decreased in the liver and muscle of both animal models, however, treating with CDR-134/CT-1 helped in bringing the activity back to normal levels. The activity of other key enzyme of glucose metabolism i.e. phosphofructokinase was found to be diminished in the liver and muscles of fructose fed and STZ- neonatal rats. Both CDR-134 and CT-1 helped in the enhancement of PFK activity. However, both have no effect on kidney PFK. These preparations helped in the restoration of lactate dehydrogenase activity of liver only. The beneficial effect of these antihyperglycaemic and insulin resistant reversal agents might be due to the elevation in insulin sensitivity to glucose as observed by sufficient reduction in the activity of protein tyrosine phosphatase, one of the key enzymes of insulin signaling cascade involved in insulin resistance, reduction in its activity would definitely help in insulin action. These preparations have the potency
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to normalize the impaired glucose tolerance and altered enzyme activities involved in glucose catabolism and anabolism; possibly they are doing so by declining the activities of glucose-6-phosphatase and PEPCK and therefore helping in the decrease of hepatic glucose production, one of main reason of hyperglycaemia. It is evident that these agents improve insulin resistance by decreasing hyperinsulinemia and by declining the activity of PTPase (protein tyrosine phosphatase), glucose intolerance and normalizes many of the altered biochemical parameters of liver, kidney and muscles associated with non-insulin dependent diabetes mellitus and insulin resistance.

Insulin resistance was measured using HOMA index (homeostasis model assessment). It is a mathematical model utilizing ratio of fasting glucose (mM): fasting insulin (μU/ml) that has been used to indicate the degree to which they combine to give hyperglycaemia with low, normal or raised basal plasma insulin concentrations. As mentioned both standardized preparations i.e. CDR-134 and CT-1 were found to correct hyperinsulinemia by decreasing fasting serum insulin in fructose fed and neonatal-STZ rat models, respectively. CDR-134 and CT-1 prevented the rise in serum insulin levels following glucose load during insulin kinetic studies in STZ-induced diabetic rats. Insulin resistance was found to be established as calculated by HOMA index formula using fasting glucose and fasting serum insulin. Fructose fed and neonatal-STZ rats exhibited insulin resistance index 5.0-6.0 which returned back to normal levels after the treatment with either CDR-134 or CT-1. It is again proved that CDR-134 and CT-1 possess the property of reversing insulin resistance and enhancing insulin action by increasing insulin sensitivity towards glucose. This is being the first report about the existence of insulin resistant reversal property in natural products like CDR-134 and CT-1.