Effects of sodium-orthovanadate and *Trigonella foenum-graecum* seeds on hepatic and renal lipogenic enzymes and lipid profile during alloxan diabetes

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Sodium-orthovanadate (SOV) and seed powder of *Trigonella foenum-graecum* Linn. (common name: fenugreek, family: Fabaceae) (TSP) besides being potential hypoglycemic agents have also been shown to ameliorate altered lipid metabolism during diabetes. This study evaluates the short-term effect of oral administration of SOV and TSP separately and in concert (for 21 days) on total lipid profile and lipogenic enzymes in tissues of alloxan diabetic rats. Diabetic rats showed 4-fold increase in blood glucose. The level of total lipids, triglycerides and total cholesterol in blood serum increased significantly during diabetes. During diabetes the level of total lipids increased significantly ($P < 0.001$) in liver and in kidney by 48% and 55%, respectively, compared to control. Triglycerides level increased by 32% ($P < 0.01$) in liver and by 51% ($P < 0.005$) in kidney, respectively, compared to control. Total cholesterol level also increased significantly in both liver and kidney ($P < 0.01$ and $P < 0.001$, respectively). The activities of NADP-linked enzymes; namely glucose-6-phosphate dehydrogenase (G6PDH), malic enzyme (ME), isocitrate dehydrogenase (ICDH), and the activities of lipogenic enzymes namely ATP-citrate lyase (ATP-CL) and fatty acid synthase (FAS) were decreased significantly in liver and increased in kidney during diabetes as compared to control. SOV and TSP administration to diabetic animals prevented the development of hyperglycemia and alteration in lipid profile in plasma and tissues and maintained it near normal. Maximum prevention was observed in the combined treatment with lower dose of SOV (0.2%) after 21 days. We are presenting for the first time effectiveness of combined treatment of SOV and TSP in amelioration of altered lipid metabolism during experimental type-I diabetes.

1. **Introduction**

Insulin-dependent diabetes mellitus (IDDM) or type-I diabetes is an autoimmune disorder caused by autoaggressive T-lymphocytes that infiltrate the pancreas and destroy insulin producing $\beta$-cells. This leads to hypoinsulinemia and thus a hyperglycemic condition (Bach 1995), which over a period of time develops diabetic complications such as nephropathy, retinopathy, neuropathy, and cardiac problem (Arky 1982). Most of the metabolic complications associated with type-I diabetes are due to insulin deficiency and related glucose under-utilization of the insulin-dependent tissue, such as liver, and glucose over-utilization in insulin-independent tissue, such as kidney (Sochor et al 1985). The insulin deficiency causes excessive break down of lipid in adipose depots, resulting in

**Keywords.** Alloxan diabetes; lipogenic enzymes; sodium-orthovanadate; total lipid; *Trigonella* seed powder

Abbreviations used: FAA, Free fatty acids; FAS, fatty acid synthase; G6PDH, glucose-6-phosphate dehydrogenase; ICDH, isocitrate dehydrogenase; SOV, sodium-orthovanadate; TSP, *Trigonella* seed powder.

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increased level of free fatty acids (FAA) (Gupta et al 1999). Liver plays a central role in the glucose and lipid metabolism and gets severely affected due to insulin deficiency. The liver tissue is involved in the lipid metabolism through uptake, oxidation and metabolic conversion of FAA, synthesis of cholesterol and phospholipids and secretion of plasma lipoproteins. A profound alteration in the concentration and composition of lipid profile in the body occurs during diabetes. The liver cells show a marked increase in the lipid concentration during diabetes (Arky 1982; Sochor et al 1987). Further, the accumulation of triglycerides and long chain fatty acyl Co-A in liver leads to reduction in insulin-mediated metabolic activity and can cause type-II diabetes resulting into metabolic syndrome (Moller 2001). There is decrease in the lipogenic enzyme activity in liver and overall rates of hepatic lipogenesis. The decrease in liver weight during diabetes may be attributed to these alterations (lipogenesis and lipolysis) in lipid metabolism (Gupta et al 1999).

Diabetes mellitus affects the kidney and is the leading cause of diabetic nephropathy. In addition to prominent roles played by factors such as oxidative stress, advanced glycation end-products and others, abnormal lipid metabolism and renal accumulation of lipids have also been proposed to play a role in the pathogenesis of diabetic nephropathy (Kimmelsteil and Wilson 1936). Several workers have shown the presence of lipid deposits in the kidney of diabetic human and experimental animals and they have proposed that these deposits may play an important role in the pathogenesis of diabetic kidney disease (Gujiarro et al 1995; Lee et al 1991). Earlier these lipid deposits in kidney were attributed to increased levels of serum lipids. However, Sun et al (2002) showed an increased renal lipid synthesis to be responsible for this. They showed the marked increase in SREBP-1 and fatty acid synthase expression in STZ-diabetic rats, resulting in increased renal lipid accumulation and glomerulosclerosis. Other workers have also shown increase in the activities of lipogenic enzymes in kidney during diabetes (Raju et al 2001).

The isolation of insulin by Banting and Best was considered as the beginning of a new era for the treatment of diabetes by insulin (Bloom and Ireland 1992), however, existence of NIDDM (type-II diabetes), where long-term insulin therapy becomes ineffective due to insulin resistance, and severe hypoglycemia particularly affecting the brain (Cryer 1992; Reichard et al 1993) from insulin therapy in case of type-I diabetes, led the march for the search of an alternative to insulin therapy (Ramasarma 1996). It is well established that complications associated with diabetes can be markedly reduced through good glucose control. Certain metal elements such as vanadium, selenium, molybdenum, tungstate, zinc and manganese (Heyligar et al 1985; Baquer et al 1998; Ezaki 1990; Goto et al 1992; Shisheva et al 1992; Baquer et al 2003) with potential hypoglycemic activities have been studied earlier. However, vanadium and its various complexes have been particularly favoured for their insulinomimetic effects (Ramasarma 1996). Similarly, extracts from various plant materials have been tested in animal model system and their hypoglycemic effects have been elucidated (Murthy 1995). The absence of toxic effects of plant extracts makes the use of such natural products for their antidiabetic properties favourable. Plant extracts which have been studied so far including Alium sativum (garlic bulbs) (Sheela and Augusti 1992), Momordica charantia (bitter gourd) fruit extract (Shibib et al 1993; Ahmed et al 1998), Trigonella foenum-graecum (bitter gourd) seed powder (Moorthy et al 1989; Raju et al 2001) among others, have been confirmed to possess antidiabetic properties.

The biological potential of sodium-orthovanadate (SOV) as an insulin mimetic and antidiabetic agent is, however, hampered by its toxicity (Dafnis and Sabatini 1994; Domingo et al 1995). Several workers have observed short-term toxic responses in animals treated with diabetic compounds such as severe diarrhoea, decrease in weight gain, deaths due to dehydration etc (Ramasarma 1996). In addition, long-term complications such as hemato logical and biochemical alterations, nephrotoxicity, immunotoxicity, reproductive and developmental toxicity have also been observed (Domingo 2002). To exploit the potential of vanadium compounds and to enhance their bioavailability by reducing their toxicity, attempts are being made to use the complex-forming capability of vanadium compounds with organic compounds (Nandhini et al 1993; Srivastava 2000). In the present work, attempts have been made to reduce the toxicity without compromising on their biological effects by reducing the dose of vanadate and combining the treatment with plant product such as Trigonella seed powder (TSP). Alteration in lipid metabolism during diabetes, leading to cardio-vascular problems have been studied extensively. However, very few studies have emphasized the role of renal lipid metabolism in this context. Therefore, present work was undertaken to determine alterations in lipid profile and lipogenic enzymes in liver and kidney in diabetic rats, and to compare the effects of these antidiabetic compounds given separately and in combination.

The activities of key lipogenic enzymes such as glucose-6-phosphate dehydrogenase (G6PDH) (EC 1.1.1.49), malic enzyme (EC 1.1.1.40), NADP-linked isocitrate dehydrogenase (ICDH) (EC 1.1.1.42), ATP-citrate lyase (EC 4.1.3.8) and fatty acid synthase (FAS) (EC 2.3.1.85) were assayed in cytosolic fraction of rat liver and kidney in control, diabetic, and treated conditions. Our results demonstrate normalization of blood glucose and marked prevention in alteration of plasma lipid profile and tissue