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## EFFECT OF TETRAHYDROCURCUMIN ON LIPID PROFILES IN STREPTOZOTOCIN-NICOTINAMIDE INDUCED TYPE 2 DIABETES MELLITUS

Pidaran Murugan

Department of Biochemistry, Faculty of Science, Bharathidasan University Model College, Vedharanyam-614810-Tamil Nadu, India

\*E mail: [manomuruganphd@gmail.com](mailto:manomuruganphd@gmail.com)

[pmpranithmurugan18@gmail.com](mailto:pmpranithmurugan18@gmail.com)

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### ABSTRACT

Hyperlipidemia is one of the major risk factors of cardiovascular complication in diabetes. A study was undertaken to evaluate the antihyperlipidemic activity of tetrahydrocurcumin (THC). Oral administration of THC (80mg/kg bodyweight) to streptozotocin-nicotinamide induced diabetic rats for 45 days, significantly reduced the elevated serum very low density lipoprotein (VLDL) and low density lipoprotein (LDL) – cholesterol levels and significantly increased the serum high-density lipoprotein (HDL)-cholesterol. THC showed a better effect when compared with curcumin. Results of the present study indicate that THC showed antihyperlipidemic effect in addition to its antidiabetic effect in type 2 diabetic rats.

**Keywords:** Tetrahydrocurcumin, curcumin, lipoproteins, lipids, diabetes

### INTRODUCTION

Dyslipidemia, plays a significant role in the manifestation and development of premature atherosclerosis leading to cardiovascular (CV) disease, and together, they are the major cause of CV morbidity and mortality in diabetes. Diabetes mellitus is a major risk factor for the development of cardiovascular complications and cardiovascular disease now accounts for 80% of all diabetic mortality (WHO 2004). Lipid-lowering therapy in diabetes was effective in reducing the risk of vascular complications (Deedwania, 2004).

Diabetes is a major health problem affecting major populations worldwide. It is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action associated with chronic hyperglycemia and disturbances of carbohydrate, lipid and protein metabolism. As a consequence of the metabolic derangements in diabetes, various complications develop including both macro and micro-vascular dysfunctions. Pancreatic-cell dysfunction and insulin resistance are the two hallmarks of type 2 diabetes mellitus. Treatment of diabetes without any side effects is still a challenge to the medical system. There is an increasing demand by patients to use the natural products with antidiabetic activity, because insulin and oral hypoglycemic drugs are having so many side effects. Streptozotocin (STZ)-nicotinamide type 2 model shares a number of features with human type 2 diabetes and is characterized by moderate stable hyperglycemia, glucose intolerance, altered but significant glucose-stimulated insulin secretion, *in vivo* and *in vitro* (Novelli *et al.*, 2001). Hence, STZ-nicotinamide induced diabetes model was used in the present study.

Turmeric(*Curcuma longa*) is a gold-colored spice commonly

used in the Indian subcontinent, not only for health care but also for the preservation of food and as a yellow dye for textiles. Considering the recent scientific bandwagon that multi targeted therapy is better than monotargeted therapy for most diseases, curcumin can be considered an ideal “Spice for Life”. *Curcuma longa* (Zingiberaceae) is commonly used in the treatment of diabetes by ayurvedic physicians. Curcumin is a biologically active component isolated from the rhizome of *Curcuma longa* that possess antidiabetic and has been proven scientifically to possess high antioxidant activity and anticancer properties. Tetrahydrocurcumin (THC) is one of the major colourless metabolites of curcumin. THC has been reported to exhibit the same physiological and pharmacological properties of curcumin (Majeed *et al.*, 1995 and Sugiyama *et al.*, 1996). THC is the rapidly metabolized product of curcumin during absorption from the intestine (Ravindranath and Chandrasekara 1980). THC has the strongest antioxidant activity among all curcuminoids (Osawa *et al.*, 1995). Several studies in experimental animals indicate that THC also prevent cancer (Lin and Lin-Shiau 2001), as well as a protective agent against inflammation (Nakamura 1998 and Hong *et al.*, 2004), atherosclerotic lesions (Naito *et al.*, 2002) and hepatotoxicity (Pari and Murugan 2004). In our previous study, we have demonstrated the antidiabetic effect of THC in streptozotocin induced diabetic rats (Pari and Murugan, 2005; Murugan and Pari, 2006; Murugan and Pari, 2007; Murugan and Pari, 2008). Since THC might also contribute to the pharmacological activities of curcumin, in this study we explored the role of THC in prevention of streptozotocin induced hyperglycemia and related lipid complications.

## MATERIALS AND METHODS

### Animals

Studies were performed on adult male albino rats of Wistar strain weighing 180-220g. According to the experimental protocol approved by the Committee for Research and Animal Ethics of Annamalai University, animals were housed in cages and maintained in  $24 \pm 2$ ; °C normal temperature and a 12 hour light/dark cycle. The animals were fed on pellet diet (Lipton India Ltd., Mumbai) and water *ad libitum*.

### Drugs and chemicals

THC was a gift provided by Sabinsa Corporation, USA. Curcumin was purchased from Sigma chemicals company, St Louis, USA. All other chemicals and biochemicals were of analytical grade.

### Induction of diabetes

Non-Insulin dependent diabetes mellitus was induced (Masiello *et al.*, 1998) in overnight fasted rats by a single intraperitoneal injection of 65 mg/kg streptozotocin, 15 min after the i.p administration of 110 mg/kg of nicotinamide. Streptozotocin was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal saline. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined at 72 h and then on day 7 after injection. The animals with blood glucose concentration more than 200 mg/dl were used for the study.

### Experimental design

In the experiment, a total of 24 rats (18 diabetic surviving rats, 6 normal rats) were used. The rats were divided into four groups of six each, after the induction of streptozotocin diabetes. The experimental period was 45 days. Group I: Normal rats. Group II: Diabetic control rats. Group III: Diabetic rats given THC (80 mg/kg) in aqueous suspension daily using an intragastric tube for 45 days. Group IV: Diabetic rats given curcumin (80 mg/kg) in aqueous suspension daily using an intragastric tube for 45 days (Arun and Nalini 2002).

At the end of 45 days, the animals were deprived of food overnight and sacrificed by decapitation. Blood was collected in tubes containing potassium oxalate and sodium fluoride mixture for the estimation of blood glucose. Plasma was separated for the estimation of insulin and other biochemical parameters.

### Analytical Methods

The level of plasma glucose was estimated by using reagent kit from Qualigens diagnostics kit (Mumbai, India) according to the method of Trinder (1969). The high density lipoprotein cholesterol (HDL-C) content in plasma was estimated by using a reagent kit (Qualigens diagnostics, Mumbai, India). Very low density lipoprotein cholesterol (VLDL-C) and low density lipoprotein cholesterol (LDL-C) fractions were calculated as  $VLDL-C = TG/5$  and  $LDL-C = \text{total cholesterol} - (\text{HDL-C} + \text{VLDL-C})$ , respectively. The activity of hydroxy 3-methylglutaryl-

coenzyme A (HMG CoA) reductase in the liver & kidney was assayed by the method of Philipp and Shapiro (1970). The ratio between HMG CoA and mevalonate in the liver was taken as an index of the activity of HMG CoA reductase. The decrease in HMG CoA/Mevalonate ratio indicates the increased activity of the enzyme.

### Statistical analysis

The data for various biochemical parameters were analyzed using analysis of variance (ANOVA), and the group means were compared by Duncan's multiple range test (DMRT). Values were considered statistically significant if  $p < 0.05$  (Duncan 1957).

## RESULTS AND DISCUSSION

The levels of plasma glucose are shown in normal and experimental rats (table 1). There was a significant elevation in the level of glucose was observed in diabetic rats compared to normal rats. Administration of THC and curcumin significantly decreased the levels of glucose in diabetic rats when compared to diabetic rats.

Fig.1 shows the level of blood glucose and plasma insulin of different experimental groups. The diabetic control rats showed a significant increase in the level of blood glucose with significant decrease in the level of plasma insulin. Oral administration of THC to diabetic rats significantly reversed the above biochemical changes. In our previous study (Pari and Murugan, 2005) we have reported that THC at 80 mg/kg body weight showed better effect than 20 and 40 mg/kg body weight, therefore the 80 mg/kg body weight was used in this study. The administration of THC and curcumin to normal rats showed a significant effect on blood glucose and plasma insulin levels. The THC administration showed more effective than curcumin.

Table 2 demonstrates the level of serum and tissue total cholesterol (TC), lipoproteins and the activity of HMG-CoA reductase in normal and experimental rats. The levels of TC, low-density lipoprotein-cholesterol (LDL-C), very low-density lipoprotein-cholesterol (VLDL-C) and hepatic HMG-CoA reductase activity were significantly increased whereas the level of high density lipoprotein – cholesterol (HDL-C) was significantly decreased in diabetic control rats. Administration of THC and curcumin to diabetic rats the decreased levels of TC, LDL-C, VLDL-C levels and the activity of HMG-CoA reductase along with significant increase in the level of HDL-C.

Type 2 diabetes is characterized by progressive deterioration of normal pancreatic -cell function. Generally, hepatic and muscle tissues lose sensitivity to the action of insulin (Porte and Kahn, 2001). In the early stages of the disease, the -cells of the pancreatic islets compensate for decreased insulin sensitivity by increasing insulin secretion. As the disease progresses, diabetes ensues when cell is no longer able to compensate for insulin resistance.

Hyperlipidaemia is the major metabolic complication of both clinical and experimental diabetes (Albirink and Man, 1958; Bierman *et al.*, 1975). It has been demonstrated that insulin deficiency in diabetes leads to a variety of

**Table 1.** Changes in the levels of plasma glucose in normal and experimental rats

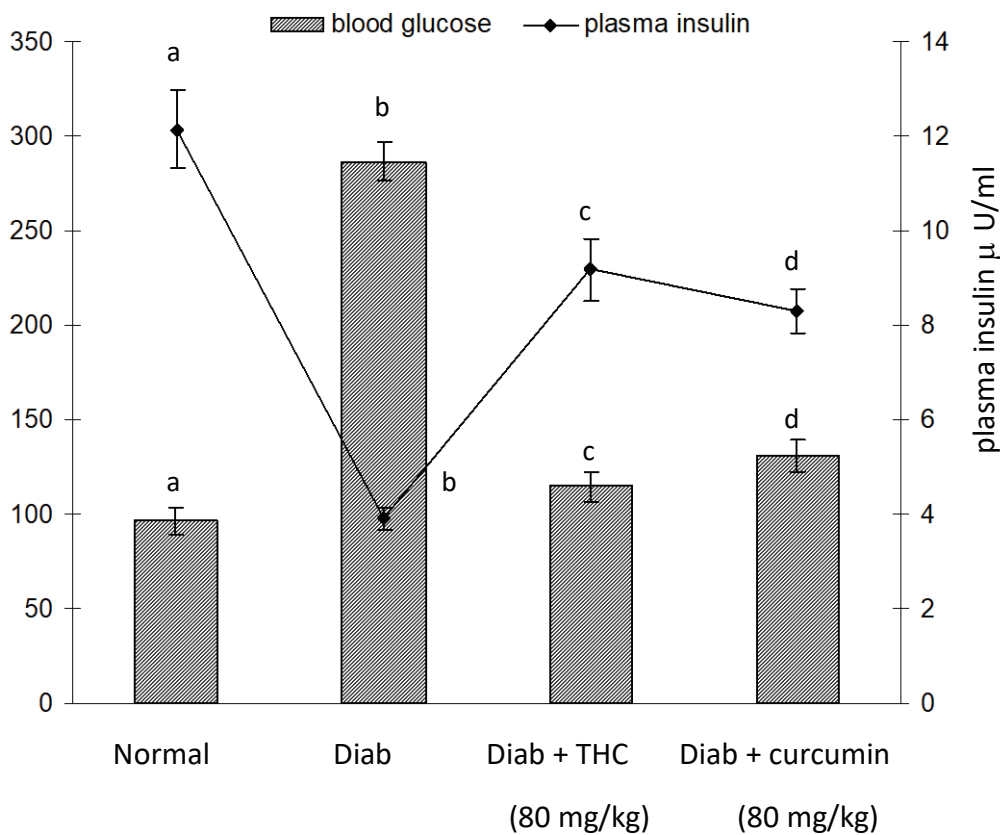
Groups	Glucose (mg/dl)	
	Initial	Final
Normal control	79.70±4.32	82.67±5.03a
Normal + THC (80mg/kg)	80.68±5.54	78.51±5.08a
Diabetic control	295.59±18.78	389.47±25.62b
Diabetic THC (80mg/kg)	289.57±12.68	111.41±9.63c
Diabetic + curcumin (80mg/kg)	287.58±17.41	128.17±11.89d

Values are given as mean  $\pm$ SD from 6 rats in each group. Values not sharing a common superscript letter differ significantly at (DMRT).

**Table 2.** Effect of THC on changes in the levels of lipoproteins and cholesterol in normal and experimental rats

Groups	Normal	Normal + THC	Diabetic control	Diabetic + THC	Diabetic + curcumin
Serum					
Total cholesterol (mg/dl)	94.31 ± 7.49a	93.11 ± 5.82 a	172.41 ± 15.34b	110.71 ± 8.71c	122.51 ± 9.41d
HDL-C (mg/dl)	53.71 ± 4.30a	55.22 ± 6.53a	27.41 ± 2.15b	49.51 ± 3.73c	42.55 ± 3.66d
LDL-C (mg/dl)	30.71 ± 2.52a	29.75 ± 2.26a	129.18 ± 9.62b	44.51 ± 4.51c	59.32 ± 5.18d
VLDL-C (mg/dl)	10.21 ± 1.22a	10.30 ± 1.15a	20.13 ± 1.71b	13.22 ± 1.01c	15.27 ± 1.30d
Liver (mg/100g tissue)	319.51 ± 15.77a	322.55 ± 14.41a	527.43 ± 27.85b	395.41 ± 17.31c	428.41 ± 19.41d
Kidney (mg/100g tissue)	369.89 ± 16.51a	377.41 ± 15.33a	529.81 ± 24.19b	412.41 ± 19.11c	438.25 ± 18.41d
Hepatic HMG-CoA ReductaseA	1.63 ± 0.1a	1.79 ± 0.1a	1.05 ± 0.1b	1.57 ± 0.1c	1.51 ± 0.1d

A – HMG-CoA / Mevalonate ratio Values are given as mean  $\pm$ SD from 6 rats in each group. Values not sharing a common superscript letter differ significantly at (DMRT).



**Figure 1.** Effect of the on the levels of blood glucose and plasma insulin in normal and experimental rats  
Diab - Diabetic control, THC - Tetrahydrocurcumin.

Values are given as mean  $\pm$ S.D for 6 rats in each group.

Values not sharing a common superscript letter differ significantly at  $p < 0.05$  (Duncan’s Multiple Range Test).

dearrangements in metabolic and regulatory process, which in turn leads to accumulation of lipids such as TC and TGs in diabetic patients (Jaiprakash *et al.*, 1993). Changes in the concentration of plasma lipids including cholesterol are complications frequently observed in patients with diabetes and certainly contribute to the development of vascular disease (Nikkila and Kekki, 1973).

Hypercholesterolemia and hypertriglyceridemia are independent major risk factors that alone or together can accelerate the development of coronary artery disease (CAD) (McKenney, 2001). The cause of hyperlipidemia has been related to increased lipid synthesis, decreased lipid clearance from the blood or a combination of these two processes.

In this experiment, diabetes mellitus characterized by hyperglycaemia and hyperlipidemia, which indicate the increased risk for the complications of atherosclerosis. Lowering of serum lipid levels through dietary or drug therapy seems to be associated with a decrease in the risk of vascular disease and related complications (Rhoads *et al.*, 1976; Brown *et al.*, 1993).

The results of this study indicate that lipid and lipoprotein abnormalities developed in diabetic condition were significantly counteracted by administration of THC. Excess of fatty acid in serum promotes the conversion of some liver and kidney fatty acids into PLs and cholesterol. These two substances along with excess TGs formed at the same time in the liver and may be discharged into the blood in the form of lipoproteins (Bopanna *et al.*, 1997). It was observed by Krauss-Friedman that the plasma lipoproteins increase as much as 3-fold in diabetic rats giving a total concentration of serum lipids of several percent rather than normal. This high lipid concentration may lead to the rapid development of atherosclerosis in diabetic patients (Pushparaj *et al.*, 2000). Besides serum cholesterol, the elevated levels of TGs and PLs are also reduced counteracted by THC.

Increased triglyceride and reduced HDL-C cholesterol levels are the key characteristics of dyslipidemia in type 2 diabetes (Lehto *et al.*, 1997). Hypertriglyceridemia in type 2 diabetes can result from an increased hepatic VLDL over production and impaired catabolism of triglyceride-rich particles. The function of lipoprotein lipase (Lpl), a key enzyme in removal and degradation of TGs from circulation is attenuated by both insulin deprivation and insulin resistance. Dysfunction of Lpl contributes to hypertriglyceridemia in the fasting and postprandial state. It has been postulated that high plasma triglyceride influences LDL size and density through a cycle of lipid exchange (Taskinen *et al.*, 1996). Low-density lipoprotein oxidation is a potential atherogenic agent and protecting LDL from oxidation prevents atherogenesis. A decrease in serum TCs level with an increase in the HDL-C level in diabetic rats treated with THC can be ascribed to the reduction of LDL-C and VLDL-C. Low VLDL levels in blood are possibly induced by THC may be due to repression of hepatic synthesis of VLDL elevation of fatty

acid oxidation inhibition of VLDL secretion from the liver. hydroxy--methylglutamyl coenzyme HMG-CoA) reductase catalyses the rate-limiting step in cholesterol biosynthesis and its activity correlates closely with the rate of tissue cholesterol synthesis. As reported earlier, the activity of HMG-CoA reductase was found to be increased significantly in diabetic rats (Lehto *et al.*, 1997). The increase in the liver and kidney cholesterol in diabetic rats observed in our study could be due to increased cholesterogenesis. The significant increase in the level of extra hepatic cholesterol could be due to decreased removal of cholesterol from extra hepatic tissues by HDL-C. The increased concentration of FFAs in tissues may be due to lipid breakdown and this may cause increased generation of NADPH, which results in the activation of NADPH dependent microsomal lipid peroxidation.

Diabetic rats treated with THC and curcumin shown significant decrease in serum and tissue lipids, THC produced a better effect than the curcumin. The abnormal high concentration of serum lipids in diabetes is mainly due to the increase in the mobilization of FFAs from the peripheral depots, since insulin inhibits the hormone sensitive lipase. The increased level of cholesterol in liver and kidney is due to the decreased level of HDL-C. This in turn results in decreased removal of cholesterol from extra-hepatic tissues by the HDL-C (Prince *et al.*, 1999). Oral administration of THC and curcumin to diabetic rats reversed all the above changes.

## CONCLUSION

It can be concluded from the data that THC significantly reduces the level of serum and tissue lipids, which are actively raised in streptozotocin diabetic rats. THC has beneficial effect on plasma insulin and blood glucose level. Moreover it was a prevention of lipid metabolism defects could represent a protective mechanism against the development of atherosclerosis.

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