

ORIGINAL ARTICLE

Protective role of tetrahydrocurcumin on changes in the fatty acid composition in streptozotocin-nicotinamide induced type 2 diabetic rats

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Summary

Curcumin is the most active component of turmeric. It is believed that curcumin is a potent antioxidant and anti-inflammatory agent. Tetrahydrocurcumin (THC), one of the major metabolites of curcumin, exhibits many of the same physiological and pharmacological activities as curcumin and in some systems may exert greater antioxidant activity than curcumin. The aim of this study was to evaluate the effect of THC on the blood glucose, plasma insulin and fatty acid composition of the total lipids in the liver, kidney and brain of control and streptozotocin (STZ)-nicotinamide diabetic rats. The analysis of fatty acids showed that there was a significant increase in the concentrations of palmitic acid (16:1), stearic acid (18:0) and oleic acid (18:1) in the liver, kidney and brain, whereas the concentrations of linolenic acid (18:3) and arachidonic acid (20:4) were significantly decreased. Oral administration of the THC (80 mg/kg body weight) for 45 days to diabetic rats decreased the concentrations of fatty acids, viz., palmitic, stearic, and oleic acid, whereas linolenic and arachidonic acid were elevated. These results suggest that THC exhibits antidiabetic and antihyperlipidemic effects in STZ-nicotinamide induced diabetic rats. It also prevents the fatty acid changes produced during diabetes. The antidiabetic and antihyperlipidemic effects of THC are more potent than those of curcumin at the same dose. The results of the present study indicate that THC showed an antihyperlipidemic effect in addition to its antidiabetic effect in type 2 diabetic rats.

Keywords: diabetes – tetrahydrocurcumin – curcumin – blood glucose – insulin – fatty acids

INTRODUCTION

Diabetes is the fastest growing metabolic disorder in the world and a major cause of morbidity in developed countries. However, it is predicted that in the future the developing world will be hit the hardest by the escalating diabetes epidemic. According to recent reports, by the year 2025 there will be 84–224 million diabetic subjects in the developing countries and the highest number will

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be in India (King 2001). Chronic hyperglycaemia due to uncontrolled diabetes causes a number of secondary complications like cardiovascular, renal, neurological and ocular disorders. Though various mechanisms have been proposed, several studies suggest that oxidative stress is a major determinant in the pathogenesis of various vascular and non-vascular diabetic complications (Baynes 1999, Brownlee 2001).

Fatty acids form an important component of cell membranes, are eicosanoid precursors and are therefore required for both the structure and function of every cell in the body. Fatty acids in the ester form are generally present as triglycerides, phospholipids and cholesterol esters. As esters of phospholipids they form an important part of the cell membrane, while as triglycerides they constitute an important source of stored energy.

During the process of injury, repair and cell growth, the fatty acids in phospholipids undergo severe modification (Cameron and Cottter 1997). An earlier report showed that there is an alteration in the fatty acid composition in the plasma and erythrocyte membrane of diabetic patients (Faas et al. 1988). Seigneur et al. (1994) reported that there is a significant alteration in the fatty acid composition of serum and a variety of tissues in experimental diabetes (Seigneur et al. 1994). Previous studies have also reported that the extent of hepatic regeneration was higher in the phospholipid fraction of the long chain triglyceride groups (Folsom et al. 1996, Pelikanova et al. 1991). The fatty acid composition of cell membranes can influence membrane-associated phenomena such as the interaction between insulin and its receptor (Stubbs and Smith 1984).

For various reasons in recent years the popularity of complementary medicine has increased. Dietary measures and traditional plant therapies as prescribed by ayurvedic and other indigenous systems of medicine are commonly being used in India (Warier 1995). The beneficial actions of diets on the amelioration of diabetic symptoms are well documented.

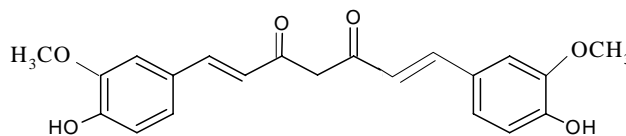
Curcumin (Fig.1) is the substance that gives the spice turmeric, which is extensively used in Indian cuisine as a component of curry powder, its yellow color (Aggarwal et al. 2003). Curcumin is extracted from the roots of the *Curcuma longa* plant (Turmeric) (Aggarwal et al. 2003). Curcumin (diferuloylmethane) is the most active component of turmeric. It is believed that curcumin is a potent antioxidant and anti-inflammatory agent. Practitioners of traditional Indian medicine believe that curcumin powder is beneficial against many diseases including biliary disorders, anorexia, coughs, diabetes, hepatic disorders, rheumatism, sinusitis, cancer, and Alzheimer's disease (Aggarwal et al. 2003). In experimental studies to examine the potential beneficial effects of

curcumin against diabetes, curcumin has been shown to reduce hyperlipidaemia (Babu and Srinivasan 1997), delay the development of cataract (Suryanarayana et al. 2005), ameliorate renal lesions (Babu and Srinivasan 1998), and reduce the cross-linking of collagen (Sajithlal et al. 1998) in a streptozotocin (STZ)-treated diabetic animal model. Curcumin has also been shown to lower blood glucose levels in type 2 diabetic KK-Ay mice (Nishiyama et al. 2005) and STZ-treated rats (Mahesh et al. 2005). Curcumin supplementation promotes wound healing in STZ-treated diabetic rats and genetically diabetic mice (Sidhu et al. 1999) and attenuates the phenylephrin-induced increase in vascular reactivity of the aorta in STZ-treated diabetic rats.

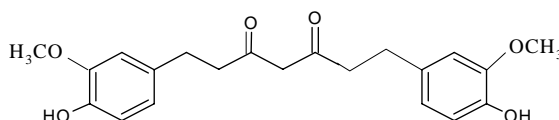
Tetrahydrocurcumin (THC) (Fig.1) is one of the major metabolites of curcumin, with potential potent bioactivity. This metabolite was identified in intestinal and hepatic cytosol from humans and rats (Holder et al. 1978, Naito et al. 2002), and similarly to curcumin, THC possesses hydroxyl groups that make it a typical substrate for glucuronide conjugation. The reduction of curcumin to THC seems to occur primarily in a cytosolic compartment (intestinal or hepatic, possibly via a reductase enzyme) (Ireson et al. 2002). The final reduction of THC to hexahydrocurcuminol may occur in microsomes, possibly by cytochrome P450 reductase (Ireson et al. 2002). Recently, attention has focused on THC, as one of the major metabolites of curcumin, because this compound appears to exert greater antioxidant activity in both *in vitro* and *in vivo* systems (Okada et al. 2001, Pari and Murugan 2004). Structurally, THC and curcumin have identical β -diketone structures and phenolic groups, but differ in that THC lacks the double bonds (Sugiyama et al. 1996, Okada et al. 2001). Sugiyama et al. (1996) demonstrated that THC exhibited similar physiological and pharmacological properties as the active form of curcumin *in vivo*. Naito et al. (2002) showed a clear involvement of THC in biochemical and molecular actions at the cellular level in ameliorating oxidative stress in cholesterol-fed rabbits. Some researchers also have focused on the neuroprotective role of curcumin in amyloid neurotoxicity and amyloid fibril formation in Alzheimer's models and other possible neurodegenerative diseases (Yang et al. 2006). Furthermore, Okada et al. (2001) have claimed that THC has more potent antioxidant activity than curcumin. Curcuminoids induce antioxidant enzymes, such as glutathione peroxidase, glutathione S-transferase and NADPH:quinone reductase, but THC was found to be more active than curcumin and scavenged Fe-NTA-induced free radicals more effectively than curcumin *in vitro*. A role for curcumin in the prevention of cancer and other chronic diseases, due to various biological

activities, has also been suggested (Lin and Lin-Shiau 2001). In our previous study, we have demonstrated the antidiabetic effect of THC in

STZ-induced diabetic rats (Pari and Murugan 2005).



Structure of curcumin



Structure of tetrahydrocurcumin

Fig. 1. Chemical structures of curcumin and its major metabolite, tetrahydrocurcumin (THC). Curcumin and THC have similar β -diketone structures and phenolic groups. The circle shows the major difference in their H-bonding side, which may make THC less polar than curcumin.

To our knowledge, no other biochemical investigations have been carried out on the effect of THC in control and STZ-nicotinamide induced diabetic rats. So, the present investigation was carried out to study the effect of THC on fatty acid composition and lipids in control and diabetic rats.

MATERIALS AND METHODS

Animals

Adult male albino Wistar rats (8 weeks), weighing 180 to 200 g bred in the Central Animal House, Rajah Muthiah Medical College, Annamalai University, were used. All animal experiments were approved by the ethical committee (Vide. No: 284, 2005), Annamalai University and were in accordance with the guidelines of the National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India. The animals were housed in polycarbonate cages in a room with a 12 h day-night cycle, temperature of 24 ± 2 °C, humidity of 45 to 64 %. During the whole experimental period, animals were fed with a balanced commercial diet (Hindustan Lever Ltd., Mumbai, India) 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 (i.p.) of 65 mg/kg body weight STZ, 15 min after the i.p. administration of 110 mg/kg body weight of nicotinamide. STZ was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal saline. Hyperglycaemia was confirmed by elevated glucose levels in plasma, determined at 72 h and then on day 7 after injection. 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 STZ diabetes. The experimental period was 45 days.

Group I: Normal untreated rats. Group II: Diabetic control rats. Group III: Diabetic rats given THC (80 mg/kg body weight) in aqueous suspension daily using an intragastric tube for 45 days. Group IV: Diabetic rats given curcumin (80 mg/kg body weight) 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 a tube containing potassium oxalate and sodium fluoride for the estimation of blood glucose and the plasma was separated for the estimation of insulin. Liver, kidney and brain were dissected out, patted dry and weighed.

Analytical Methods

Blood glucose was estimated colorimetrically using commercial diagnostic kits (Sigma Diagnostics (I) Pvt Ltd., Baroda, India) (Lott and Turner, 1975).

Plasma insulin was assayed by ELISA using a Boehringer-Mannheim kit with an ES300 Boehringer analyzer (Mannheim, Germany).

Fatty acid composition was performed according to the method of Morrison and Smith (1964). Fatty acid analysis was performed using a Tracer 540 gas chromatograph equipped with a column 2 cm long \times 2 mm internal diameter, packed with 10% Cilar on chromosorb W, 80/100 mesh. Fatty acids separated were identified by the comparison of retention times with those obtained by the separation of a mixture of standard fatty acids. Measurements of peak areas and data

processing were carried out by electronic integrator. Individual fatty acids were expressed as a percentage of total fatty acids in 100 mg tissue.

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 at the significance level $2\alpha=0.05$ (Duncan 1957).

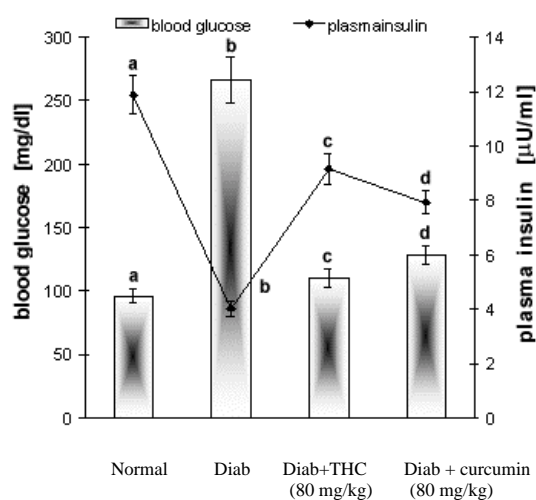


Fig. 2. Effect of THC on the levels of blood glucose and plasma insulin in normal and experimental rats. Values are given as mean \pm S.D for 6 rats in each group. Values not sharing a common superscript letter differ significantly (DMRT). Diab – diabetes, THC – tetrahydrocurcumin

RESULTS

Fig. 2 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 a 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 reported that THC at 80 mg/kg body weight showed a 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 proved to be more effective than curcumin.

Tables 1, 2 and 3 show the changes in the fatty acid composition in liver, kidney and brain of control and experimental rats. There was a significant increase in the palmitic acid (16:0), stearic acid (18:0) and oleic acid (18:1) in liver, kidney and brain of STZ diabetic rats. In contrast

there was a significant decrease in the concentration of linolenic acid (18:3) and arachidonic acid (20:4) in tissues of diabetic rats. In diabetic rats treated with THC and curcumin, the concentration of palmitic acid, stearic acid and oleic acid decreased, whereas linolenic acid and arachidonic acid were increased. The THC administration proved to be more effective than curcumin.

DISCUSSION

Diabetes mellitus comprises a group of chronic diseases characterized by hyperglycaemia or diminished insulin secretion or both (Baynes and Thorpe 1999, Robertson 2004) and profound effects on lipid metabolism. Hyperlipidaemia has an association with atherosclerosis and the incidence of atherosclerosis is vastly increased in diabetics (Farva et al. 1986, Bopanna et al. 1997). The capacity of THC to decrease the elevated blood sugar to normal level is an essential trigger for the

liver to revert to its normal homeostasis during experimental diabetes. The possible mechanism by which THC exerts its hypoglycaemic action in diabetic rats may be by potentiating the plasma insulin effect by increasing the pancreatic secretion of insulin from the existing β -cells as evidenced by a significant increase in the level of insulin by THC in diabetic rats. The STZ-induced diabetic animal is considered as an animal model of hyperlipidaemia (Pushparaj et al. 2000). STZ induces oxygen free radicals and also lipid peroxidation by generating peroxynitrate, which is spontaneously formed when nitric oxide and superoxide co-exists (Bassirat and Khalil 2000).

Fatty acid is required for both the structure and function of every cell in the body and forms an important component of cell membranes. It undergoes changes during the process of injury, repair and cell growth (Cameron and Cotter 1997). Tilvis et al. 1986, Seigneur et al. (1994) have reported that there is a significant alteration in the fatty acid composition of serum and a variety of tissues in both experimental and human diabetes (Pelikanova et al. 1991, Folsom et al. 1996).

Administration of THC increased the activity of antioxidants and may help to control free radical, as THC and curcumin offered protection to cells against oxidative stress by scavenging free radicals (Khopde et al. 2000, Okada et al. 2001) generated during diabetes (Anusuya and Menon 2003, Mahesh et al. 2005). The increased levels of free radical scavenging enzymes may act as an added compensation mechanism to maintain the cell integrity and protection against free radical damage.

An improvement of the antioxidant status might result from the above-mentioned effects of curcumin on AGE formation, (Sajithlal et al. 1998) but also direct inhibition of free radicals. Curcumin that can scavenge the reactive oxygen species (ROS) and inhibit peroxidation of lipids could be useful as a preventive agent against diabetes mellitus (Halim Eshart 2002). The ability of THC to increase the activities of antioxidant enzymes in STZ-treated rats implies that THC reactivates the antioxidant defense system, thereby increasing the capacity of anti-diabetic activity through the enhanced scavenging of oxy- radicals. The results of Sugiyama et al. (1996) imply that the β -diketone moiety of THC exhibits its antioxidative activity by cleaving the C-C bond at the active methylene carbon between two carbonyls in the β -diketone moiety. In addition, THC and curcumin maintain the blood glucose homeostasis, which in turn prevents the autoxidation of glucose by the presence of insulin secretion from the pancreatic β -cells in drug treated diabetic rats. Thus, findings related to THC suggest that it may safely be implicated as an antioxidant agent in addition to its antidiabetic effect.

In the present study, we have observed a marked alteration in the fatty acid composition of total lipids in the liver, kidney and brain tissues. There was an increase in palmitic acid (16:0) and stearic acid (18:0) in the tissues of diabetic rats. This observation coincides with the previous report, which showed that there is a preferential synthesis of stearic acid and total saturated fatty acids in type I diabetic patients (Tilvis et al. 1986, Vessby 2000).

Administration of THC to diabetic rats significantly decreased the concentration of stearic acid and palmitic acid in various tissues. This may represent an attempt by THC to minimize the toxicity of fatty acid ethyl esters formed from saturated fatty and ethyl ester species.

In the diabetic rats, the concentration of oleic acid was also observed to increase significantly. This observation was correlated with an earlier study that showed an increase in the concentration of oleic acid in the membrane of both type I and type II diabetic patients (Seigneur et al. 1994). Similarly, an increase in the concentration of oleic acid in liver and kidneys has been reported (Ravi et al 2005).

In our study we have also observed a significant decrease in linolenic acid and arachidonic acid in diabetic rat tissues. Since these are rich in polyunsaturated fatty acids, they are the major targets for ROS damage. The polyunsaturated fatty acids include n-6 and n-3 essential fatty acids, which are necessary for normal membrane structure and fluidity, and eicosanoid production.

The common dietary sources are linoleic acid (n-6) and/ or α -linolenic acid (n-3) which are further metabolized by a series of desaturation and elongation steps to produce several polyunsaturated fatty acids, including arachidonic acid (n-6) and eicosapentaenoic acid which are major precursors of prostanoids, leukotrienes and other mediators. Diabetes reduces the rate of limiting desaturation steps, particularly delta-6 desaturation that converts linoleic acid to γ -linolenic acid and α -linolenic acid to stearidonic acid. Thus, the reduced availability of essential fatty acid intermediates in diabetes is further exacerbated by increased destruction due to elevated ROS (Cameron and Cotter 1997).

Treatment by THC provides a significant protection against changes in the fatty acid composition in diabetic rats. n-6 and n-3 polyunsaturated fatty acids are known to decrease thrombosis and atherosclerosis, which lower the incidence of cardiovascular disease (Demaision et al. 1994). This effect may also be due to improved glycaemic control and increased plasma insulin that allows the diabetes rats treated with THC to maintain the tissue fatty acid composition at a normal level.

Table 1. **Changes in the fatty acid composition of total liver lipids in normal and experimental rats**

Group	Percentage of fatty acid / 100 mg tissue				
	16:0 Palmitic acid	18:0 Stearic acid	18:1 Oleic acid	18:3 Linolenic acid	20:4 Arachidonic acid
Normal	20.78 ± 1.24 ^a	11.80 ± 0.70 ^a	7.97 ± 0.45 ^a	6.76 ± 0.40 ^a	20.05 ± 1.19 ^a
Diabetic Control	27.73 ± 1.90 ^b	17.51 ± 1.20 ^b	13.78 ± 0.94 ^b	2.52 ± 0.17 ^b	12.12 ± 0.83 ^b
Diabetic + THC	22.58 ± 1.54 ^{ac}	13.22 ± 0.75 ^c	9.88 ± 0.63 ^c	4.83 ± 0.34 ^c	18.01 ± 1.24 ^c
Diabetic + Curcumin	24.30 ± 1.32 ^c	14.31 ± 0.77 ^d	11.20 ± 0.61 ^d	3.50 ± 0.19 ^d	16.48 ± 0.89 ^d

Values are given as mean ± S.D from ten rats in each group. Values not sharing a common superscript letter differ significantly (DMRT).

Table 2. **Changes in the fatty acid composition of total kidney lipids in normal and experimental rats**

Group	Percentage of fatty acid / 100 mg tissue				
	16:0 Palmitic acid	18:0 Stearic acid	18:1 Oleic acid	18:3 Linolenic acid	20:4 Arachidonic acid
Normal	22.32 ± 1.33 ^a	13.01 ± 0.77 ^a	5.75 ± 0.34 ^a	6.76 ± 0.40 ^a	12.91 ± 0.76 ^a
Diabetic Control	31.86 ± 2.19 ^b	22.43 ± 1.54 ^b	11.57 ± 0.79 ^b	2.52 ± 0.17 ^b	5.43 ± 0.37 ^b
Diabetic + THC	25.41 ± 1.61 ^c	15.83 ± 1.02 ^c	7.66 ± 0.48 ^c	4.83 ± 0.34 ^c	10.46 ± 0.72 ^c
Diabetic + Curcumin	27.81 ± 1.51 ^d	17.40 ± 0.93 ^d	9.20 ± 0.50 ^d	3.50 ± 0.19 ^d	9.30 ± 0.51 ^d

Symbols as in Table 1.

Table 3. Changes in the fatty acid composition of total brain lipids in normal and experimental rats

Group	Percentage of fatty acid / 100 mg tissue				
	16:0 Palmitic acid	18:0 Stearic acid	18:1 Oleic acid	18:3 Linolenic acid	20:4 Arachidonic acid
Normal	22.97 ± 1.02 ^a	12.89 ± 1.08 ^a	9.59 ± 0.57 ^a	8.37 ± 0.49 ^a	16.04 ± 0.95 ^a
Diabetic Control	36.22 ± 2.49 ^b	21.43 ± 1.47 ^b	16.50 ± 1.13 ^b	3.82 ± 0.26 ^b	7.55 ± 0.52 ^b
Diabetic + THC	26.09 ± 1.50 ^c	14.62 ± 0.93 ^c	11.57 ± 0.79 ^c	6.24 ± 0.43 ^c	14.28 ± 0.98 ^c
Diabetic + Curcumin	29.41 ± 1.60 ^d	16.30 ± 0.78 ^d	13.01 ± 0.71 ^d	5.20 ± 0.14 ^d	12.60 ± 0.69 ^d

Symbols as in Table 1.

In conclusion, the present investigation shows that the administration of THC and curcumin to STZ-nicotinamide diabetic rats decreases tissue lipids and maintains fatty acid composition at a normal level.

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