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A Review on Antidiabetic Effect of Tetrahydrocurcumin in Type 2 Diabetes

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Abstract

Diabetes mellitus is possibly the world's largest growing metabolic disease and as the knowledge on the heterogeneity of this disorder is advanced, the need for more appropriate therapy increases. Currently available drug regimes for management of diabetes mellitus have certain drawbacks and, therefore, there is a need for safer and more effective antidiabetic drugs. Natural products from medicinal plants continue to form a common platform for the discovery of new chemical entities in the modern drug discovery programmes. The belief that natural medicines are much safer than synthetic drugs has gained popularity in recent years and lead to tremendous growth of phytopharmaceutical usage. A wide array of plant derived active principles (phytochemicals) for possible use in the treatment of type 2 diabetes mellitus has been reported. Curcuma longa 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 antihyperglycemic activity, hypolipidemic action and anti - renal lesion effect. The use of curcumin is recommended for prevention of advanced glycated end products (AGE) accumulation and the associated complications of diabetes. Tetrahydrocurcumin (THC), one of the active metabolites of curcumin on antioxidants status in streptozotocin (STZ) - nicotinamide induced diabetic rats. THC is used in the treatment of several diseases such as prevents cancer, protects against inflammation, atherosclerotic lesions, hepatotoxicity and nephrotoxicity and diabetes. THC has been reported to exhibit the same physiological and pharmacological properties of curcumin. Curcumin is rapidly metabolized during absorption from the intestine, yielding THC, which has shown the strongest antioxidant activity among all curcuminoids. Curcuma longa has been used medically for many years to treat chronic disorders. The whole plants are used for treating diabetes. Curcumin has been reported to produce significant atihyperglycemic effect. Administration of THC has significant antidiabetic effect in STZ - nicotinamide induced diabetes. The THC exhibited its antidiabetic effect by influencing the carbohydrate metabolism, lipid metabolism, oxidative stress induced lipid peroxidation, membrane bound enzymes, insulin binding to erythrocyte receptor and collagen content and its characteristics. The antidiabetic effect of THC provides sufficient documentation to define its role and action for its potential and promising use in treating diabetes.

Keywords: *Tetrahydrocurcumin, Curcumin, Streptozotocin, Nicotinamide, Diabetes, Antioxidants, Lipids.*

Introduction

Diabetes mellitus is a non-communicable disease, which is considered as one of the five leading causes of death in the world (Ugochukwu and Babady, 2003). The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both (Zimmet et al. 2001). The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs (American Diabetes Association, 2002). The latest World Health Organization (WHO) estimate for the number of people with diabetes, worldwide to be 370 million by 2030 (WHO, 2003).

Insulin resistance in peripheral target tissues and impaired insulin secretory capacity of pancreatic β-cells contribute to the pathogenesis of type 2 diabetes (Poitout and Robertson, 2002). The pancreatic islets in type 2 diabetes retains cells in ratio to cells that are not consistently altered and normal cell mass appears to be preserved in most patients (Polonsky et al. 1996). Pancreatic islet amyloid, resulting from a deposition of amylin, is found in a high percentage in type 2 diabetic patients (Kahn, 1999).

Genetic factors appear to be the major determinants for the development of type 2 diabetes mellitus. Genetically determined post-receptor intracellular defects likely play a key role. The resulting hyperinsulinemia may lead to other common conditions such as obesity, hypertension, hyperlipidemia and coronary artery disease (Froguel and Velho, 2001). Patients generally loose the early insulin secretory response to glucose and may secrete relatively large amounts of proinsulin (Cavaghan et al. 2000). In established diabetes, although fasting plasma insulin levels may be normal or even increased in type 2 diabetic patients, glucose stimulated insulin secretion is decreased. The decreased insulin levels reduce insulin mediated glucose uptake and fail to restrainhepatic glucose production (Hansen, 2002).

Phytochemicals

Currently available drug regimens for management of diabetes mellitus have certain drawbacks and, therefore, there is a need for safer and more effective antidiabetic drugs. Natural products from medicinal plants continue to form a common platform for the discovery of new chemical entities in the modern drug discovery programmes. The belief that natural medicines are much safer than synthetic drugs has gained popularity in recent years and lead to tremendous growth of phytopharmaceutical usage (Bhattaram et al. 2002). A wide array of plant derived active principles (phytochemicals) for possible use in the treatment of type 2 diabetes mellitus has been reported (Bailey and Day, 1989).

Turmeric

The turmeric (*Curcuma longa*) plant, a perennial herb belonging to the ginger family, is cultivated extensively in south and southeast tropical Asia. The rhizome of this plant is also referred to as the “root” and is the most useful part of the plant for culinary and medicinal purposes.
The rhizome of turmeric is highly aromatic and antiseptic. The medicinal properties of turmeric have been expounded in Ayurvedic and traditional Chinese medicine (TCM) texts. Turmeric is traditionally known as a stomachic, blood purifier and is useful for the common cold, leprosy, intermittent fevers, afflictions of the liver, indolent ulcer, pyogenic (forming pus) afflictions, wound-healing and inflammation. In recent years, the medicinal properties of turmeric have increasingly been recognized. It is being researched systematically even in the Western world. (Bharat et al. 2007). The most active component of turmeric is curcumin, which makes up 2 to 5% of the spice (Aggarwal et al. 2003).

Curcumin

Curcumin is an orange-yellow component of turmeric (*Curcuma longa*), a spice often found in curry powder. In recent years, considerable interest has been focused on curcumin due to treat a wide variety of disorders without any side effects. The structure of curcumin ($C_{21}H_{20}O_6$) was first described in 1913 by Lampe and Milobedeska and shown to be diferuloylmethane (Aggarwal et al. 2003). Turmeric is used as a dietary spice, coloring agent in foods and textiles and a treatment for a wide variety of ailments. 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 disease (Aggarwal et al. 2003).

Curcumin is one of the compounds undergoing clinical trials for the prevention of human cancers at National Cancer Institute, Bethesda, USA (Kelloff et al. 1999). Curcumin shows remarkable pharmacological activity: it is a very strong but safe anti-inflammatory agent (Duke, 2002), it displays some inhibition of the HIV proteases (Tohda et al. 2006) and it seems to have anti-cancer activity (Mohamad et al. 2005). Curcumin acts as a lipoxygenase substrate (Dechatowongse, 1976) and also inhibitor of cyclooxygenase enzymes (Ahsan et al. 1999). The main action of curcumin is due to its ability to inhibit the formation of ROS such as hydroxy radicals and superoxide anion (Thapliyal and Maru, 2001).

In experimental studies to examine the potential beneficial effects of curcumin against diabetes, curcumin has been shown to reduce the hyperlipidemia (Babu and Srinivasan, 1997), delay the development of cataract (Suryanarayana et al. 2005), ameliorate the renal lesions (Babu and Srinivasan, 1998), and reduce the cross-linking of collagen (Sajithlal et al. 1998) in a 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 the wound healing in STZ-treated diabetic rats

and genetically diabetic mice (Sidhu et al. 1999) and attenuated the phenylephrin-induced increase in vascular reactivity of aorta in STZ treated diabetic rats.

Tetrahydrocurcumin

THC, produced from curcumin by hydrogenation, are colorless which render these products useful in non-colored food and cosmetic applications that currently employ synthetic antioxidants (Majeed et al. 1995). THC is one of the major metabolites of curcumin, with potential bioactivity. This metabolite was identified in intestinal and hepatic cytosol from humans and rats (Naito et al. 2002). 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). Final reduction of THC to hexahydrocurcuminol may occur in microsomes (possibly by cytochrome P450 reductase) (Iresonet 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 (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 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 (Lim et al. 2001). Furthermore, Okada et al. (2001) have claimed that THC has more potent antioxidant activity than curcumin. Several independent studies reported the significant antioxidant effects of the THC obtained from turmeric (Osawa et al. 1995; Sugiyama et al. 1996; Nakamura et al. 1998).

The phenolic group of curcumin plays the major role in their antioxidant and free radical scavenging activities. Priyadarsini et al. (2003) studied a series of curcumin and THC, bearing various hydroxy and methoxy groups on their benzene subunits. Priyadarsini et al. (2003) described the syntheses and a systematic determination of their antioxidant and hydrogen donating capabilities using the 2,2′-diphenyl-1-picrylhydrazyl (DPPH) method at 25°C in methanol. The results showed that the THC were in general much more efficient than their curcumin analogs, if they include both a phenol group in meta or para of the linking chain and a phenol or methoxy group as neighbor. This efficiency gain of THC by comparison to curcumin was not attributed to the presence of the β-diketone moiety in the chain, as it was already proposed (Sugiyama et al. 1996), but to the presence of benzylic hydrogens, which are involved in the oxidation process of these compounds and not in curcumin.

Pharmacological properties of THC

THC is used in the treatment of several diseases such as prevents cancer (Lin and Lin-Shiau, 2001), protects against inflammation (Nakamura, 1998), atherosclerotic lesions (Naito et al. 2002), hepatotoxicity (Pari and Murugan, 2004) and nephrotoxicity (Pari and Murugan, 2006).

Physical and chemical characteristics

THC are polyphenolic compounds with para-hydroxyl functional groups and keto functional groups that participate in antioxidant and chemopreventive action (Sugiyama et al. 1996). THC is a hydrogenation product of curcumin produced by reducing curcumin in an organic solvent using a metal catalyst. The superior antioxidant property of this analogue continued with its lack of yellow colour, render it useful in achromatic food and cosmetic application that currently empty conventional synthetic antioxidant.

Metabolism of THC

Curcumin was first biotransformed to dihydrocurcumin and THC and these compounds were subsequently converted to monoglucuronide conjugates, which also possesses antioxidant activity (Pan et al. 1999). THC is metabolized to monoglucuronide and sulfate conjugate, which are excreted primarily in bile and lesser extent in urine.

Antioxidant effect of THC

THC is a potent antioxidant than the commonly used synthetic antioxidants, butylated hydroxytoluene. THC generally has stronger inhibitory effect than curcumin *in vivo* system (Osawa et al. 1995; Sugiyama et al. 1996). Curcuminoids and THC were shown to be effective antioxidant (Okada et al. 2001). Their efficacy is concentration dependent, THC being effective even at lower concentration.

- THC play a major role in scavenging or neutralizing of free radicals
- Interacting with oxidative cascade and preventing its outcome

- Oxygen quenching, and making it less available for oxidative reaction
- Inhibition of oxidative enzyme like cytochrome P450 and chelating or disarming oxidative properties of metal ion such as iron (Fe).

The turmeric and its active constituent curcumin or curcuminoids and water-soluble peptide of turmeric have antioxidant properties and effectively inhibit the free radical damage to biomolecules both *in vitro* and *in vivo* conditions. The fact that curcuminoids act as antioxidant by prevention and intervention process makes them very unique natural antioxidants.

THC dose dependent study on diabetes

Liver is an insulin dependent tissue, which plays a pivotal role in glucose and lipid homeostasis and is severely affected during diabetes (Seifter and England, 1982). The activities of the regulatory enzymes like hexokinase, glucose-6-phosphate dehydrogenase and gluconeogenic enzymes such as fructose-1,6-bisphosphatase and glucose-6-phosphatase are markedly altered during diabetes (Hers et al. 1987).

Different doses of THC (20, 40 and 80 mg\kg body weight) were orally administered to diabetic rats for 45 days, after which activities of hexokinase, glucose-6-phosphate dehydrogenase, glucose-6-phosphatase, fructose-1,6-bisphosphatase, sorbitol dehydrogenase in liver and glycogen content in liver and muscle were assayed. The activities of gluconeogeneic enzymes were significantly increased, whereas the activities of hexokinase, glucose-6-phosphate dehydrogenase and glycogen were significantly decreased in diabetic control rats. Both THC and Curcumin were able to restore the altered enzyme activities to almost near normal levels. THC was more effective than Curcumin. Our results indicate that administration of THC to diabetic animals normalizes blood glucose and causes marked improvement of altered carbohydrate metabolic enzymes during diabetes (Pari and Murugan, 2005). We conclude that THC has beneficial effects on glucose concentration as well as sequential metabolic correlation between increased glycolysis, decreased gluconeogenesis, increased hydrogen shuttle reactions. It suggests the possible biochemical mechanisms through which THC regulates glucose homeostasis in diabetic condition.

Influence of THC on changes in glycoprotein components

Glycation is a nonenzymatic reaction of glucose and other saccharide derivatives with proteins, nucleotides and lipids (Brownlee, 2001). Several workers have suggested that elevated levels of plasma glycoprotein components in diabetic rats could be a consequence of abnormal carbohydrate metabolism. Insulin deficiency and high levels of plasma glucose in diabetic condition may result in an increase of glycoproteins synthesis (Patti et al. 1999). Oral administration of THC to diabetic rats showed a decrease in the level of blood glucose and plasma glycoproteins. The levels of plasma insulin and tissue sialic acid were increased whereas the levels of tissue hexose, hexosamine and fucose were near normal in diabetic rats treated with THC and curcumin. THC possesses a significant beneficial effect on glycoprotein moiety in addition to its antidiabetic effect. The effect of THC is more prominent than curcumin (Pari and Murugan, 2007b). In conclusion THC reversed the abnormalities in the levels of glycoprotein components. THC may have beneficial effects in diabetes mellitus, by the enhancement of insulin action, as evident by the increased level of insulin in diabetic rats treated with THC and curcumin, which may be responsible for the reversal of glycoprotein changes.

Effect of THC on serum and tissue lipid peroxidation and lipids

Hyperlipdaemia is the major metabolic complication of both clinical and experimental diabetes (Bierman et al. 1975). It has been demonstrated that insulin deficiency in diabetes leads to a variety of dearangements in metabolic and regulatory process, which in turn leads to accumulation of lipids such as Total cholesterol (TC) and triglycerides (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).

Hyperlipidemia is an associated complication of diabetes mellitus. THC 80mg/kg body weight was orally administered to diabetic rats for 45 days, resulted a significant reduction in blood glucose and significant increase in plasma insulin in diabetic rats, which proved its antidiabetic effect. THC also caused a significant reduction in lipid peroxidation (thiobarbituric acid reactive substances and hydroperoxides) and lipids (cholesterol, triglycerides, free fatty acids and phospholipids) in serum and tissues, suggesting its role in protection against lipid peroxidation and its antihyperlipidemic effect. THC showed a better effect when compared with curcumin. Results that THC showed antihyperlipidemic effect in addtion to its antidiabetic effect in type 2 diabetic rats (Murugan and Pari, 2006). It can be concluded from the data that THC significantly reduces the level of serum and tissue lipids and lipid peroxidation marker, which are actively raised in STZ 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.

Preventive effects of THC on brain lipid peroxidation

The neurological consequences of diabetes mellitus in the central nervous system (CNS) are now receiving greater attention. Cognitive deficits, along with morphological and neurochemical alterations illustrate that the neurological complications of diabetes were not limited to peripheral neuropathies (Pari and Murugan, 2007a). The central complications of hyperglycemia also include the potentiation of neuronal damage observed following hypoxic/ischemic events, as well as stroke. Glucose utilization was decreased in the brain during diabetes (McCall, 1992), providing a potential mechanism for increased vulnerability to acute pathological events.

Oxidative damage has been suggested to be a contributory factor in development and complication of diabetes. To investigate the effect of THC on the occurrence of oxidative stress in the brain of rats during diabetes by measuring the extent of oxidative damage as well as the status of the antioxidant defense system. Oral administration of THC at 80 mg/kg body weight of diabetic rats for 45 days resulted in significant reduction in blood glucose and significant increase in plasma insulin levels. In addition, THC caused significant increase in the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione in brain of diabetic rats with significant decrease in thiobarbituric acid reactive substances (TBARS) and hydroperoxides formation in brain, suggesting its role in protection against lipid peroxidation induced membrane damage. The effect of THC was better when compared with curcumin. Resultsthat THC showed antioxidant effect in addition to its antidiabetic effect in type 2 diabetic rats (Pari and Murugan, 2007a). Concluded that in diabetes, brain tissue was more vulnerable to oxidative stress and showed increased lipid peroxidation. The above observations showed that THC possesses antioxidant effect that may contribute to its protective action against lipid peroxidation and enhancement of cellular antioxidant defense. This activity contributes to the protection against oxidative damage in STZ induced diabetes.

Antihyperlipidemic effect of curcumin and THC

A marked increase in serum TG, FFA and fluctuations in serum TC was observed in uncontrolled diabetic rats. Excess fatty acids in serum produced by the STZ-induced diabetes promote the conversion of some liver fatty acids into PL and TC. These two substances along with excess TG formed at the same time in the liver may be discharged into the blood in the form of lipoproteins (Bopanna et al. 1997). It has been reported that the plasma lipoproteins increase as much as 3-fold in STZ-induced diabetes 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 TC, the elevated levels of TG and PL were also significantly counteracted by SPEt.

HMG-CoA reductase catalyzes the rate-limiting step in cholesterol biosynthesis and its activity correlates closely with the rate of tissue TC synthesis. Increased activity of HMG-CoA reductase activity was observed in our study. Decreased HMG-CoA/Mevalonate ratio indicates increased activity of the enzyme (Murugan, 2021). The increase in the liver TC in diabetic control rats observed in our study could be due to increased cholesterogenesis. The significant increase in the level of extrahepatic TC could be due to decreased removal of TC from extrahepatic tissues by HDL-C.

THC caused a significant reduction serum and liver cholesterol, triglycerides, free fatty acids, phospholipids, HMG CoA reductase activity, very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) – cholesterol levels. The decreased serum high-density lipoprotein (HDL)-cholesterol in diabetic rats was also reversed towards normalization after the treatment. These biochemical observations were supplemented by histopathological examination of liver section. The effect was compared with curcumin (80 mg/kg body weight). The results showed that THC had antihyperlipidaemic action in control and experimental diabetic rats. The antidiabetic and antihyperlipidaemic effects of THC are more potent than those of curcumin at the same dose (Pari and Murugan, 2007c). Thus, concludes that THC and curcumin significantly reduces the levels of serum and liver lipids, which are actively raised in STZ and nicotinamide diabetes rats. The mode of action of our compound having an additional lipid-lowering properties and it is considered to be a possible therapeutic value. THC suggests that having a possible biochemical mechanism through which the regulation of glucose and lipid homeostasis.

Effect of THC on serum and tissue antioxidant

Chronic hyperglycemia is the primer of a series of cascade reactions causing the over production of free radicals and increasing evidences indicate that these contributes to the development of diabetic complications (Baynes and Thrope, 1999). Defense system against oxidative attacks is usually able to buffer most ROS

produced during physiological and pathological metabolism. However, the imbalance in scavenging of free radicals, due to an increase in oxidative flux or a decrease in the antioxidant ability is responsible for cellular and tissue damage in diabetes mellitus (Cakatay et al. 1995).

Oxidative stress has been suggested to be a contributory factor in development and complication of diabetes. THC at 80mg/kg body weight of diabetic rats for 45 days resulted in significant increase in the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, reduced glutathione, vitamin C and vitamin E in serum, liver and kidney of diabetic rats with significant decrease in thiobarbituric acid reactive substances (TBARS) and hydroperoxides formation in liver and kidney, suggesting its role in protection against lipid peroxidation induced membrane damage. These biochemical observations were supplemented by histopathological examination of liver and kidney section. The antidiabetic and antioxidant effects of THC are more potent than those of curcumin at the same dose. Results that THC showed antioxidant effect in addition to its antidiabetic effect in type 2 diabetic rats (Murugan and Pari, 2006a; Murugan P and Pari, 2006b). In conclusion, THC possesses antioxidant effect that may contribute to its protective action against lipid peroxidation and enhancing effect on cellular antioxidant defense. This activity contributes to the protection against oxidative damage in STZ induced diabetes.

Influence of THC on erythrocyte membrane bound enzymes and antioxidant status

Free radicals react with lipids and causes peroxidative changes that result in enhanced lipid peroxidation (Girotti, 1985). The increase in lipid peroxidation might be a reflection of decrease in enzymatic and nonenzymatic antioxidants of defense systems. Increased lipid peroxidation under diabetic conditions can be due to increased oxidative stress in the cell as a result of depletion of antioxidant scavenger systems. The decreased levels of erythrocyte GSH in diabetes may be due to increased utilization in trapping the oxyradicals.

`The effect of THC and curcumin on glucose, insulin, haemoglobin, glycosylated haemoglobin, thiobarbituric acid reactive substances (TBARS), superoxide dismutase (SOD), catalase (CAT), glutathione peroxide (Gpx), glutathione-S-transferase (GST), reduced glutathione (GSH) and membrane bound enzymes were studied. The effect of THC was compared with curcumin. The levels of blood glucose, glycosylated haemoglobin, erythrocyte TBARS, were increased significantly whereas the level of plasma insulin and haemoglobin, erythrocyte antioxidants (SOD, CAT, GPx, GST and GSH), membrane bound total ATPase, Na+/K+-ATPase, Ca2+- ATPase, Mg2+- ATPase were decreased significantly in diabetic rats. Administration of THC and curcumin to diabetic rats showed decreased level of blood glucose, glycosylated haemoglobin and erythrocyte TBARS. In addition, the levels of plasma insulin, haemoglobin, erythrocyte antioxidants and the activities of membrane bound enzymes also were increased in THC and curcumin treated diabetic rats. These biochemical observations were supplemented by histopathological examination of pancreas section. THC possesses a significant beneficial effect on erythrocyte membrane bound enzymes and antioxidants defense in addition to its antidiabetic effect (Murugan and Pari, 2007c). In conclusion lipid peroxidation and glycosylation of proteins can cause reduction in the activities of enzymes and alteration in the structure and function of membranes (Flecha et al., 1990). A reduction in the lipid peroxidation and glycosylation of proteins can prevent diminution in the activities of ATPases, which is beneficial because any reduction in ATPases activity can affect the intracellular concentrations of Na+, K+ and Ca2+, alter the signal transduction pathway, and affect contractility, which in turn leads to cellular dysfunction. Administration of THC and curcumin to diabetic rats showed significant elevation in the activities of total ATPase, Na+/K+-ATPase, Ca2+- ATPase and Mg2+-ATPase in erythrocyte membrane when compared with diabetic control rats. The reversal of erythrocyte membrane bound ATPases activity in diabetic rats by THC and curcumin could be due to increase in metabolism of glucose, and thus the lowering of the glucose concentration in diabetic rats, would result in the activate antioxidant defense, reduction of free radical production, lipid peroxidation and the glycosylation of haemoglobin observed.

Protective role of THC on changes in the fatty acid composition

Fatty acid is required for both the structure and function of every cell in the body and they form an important component of cell membranes. They undergo changes during the process of injury, repair and cell growth (Cameron and Cotter, 1999). Several studies found that there is a significant alteration in the fatty acid composition of serum and variety of tissues in both experimental and human diabetes (Murugan and Pari, 2007a; Murugan, 2023b). Effect of THC on blood glucose, plasma insulin and fatty acid composition of total lipids in liver, kidney and brain of control and 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) acid in 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 antihyperlipidaemic effects of THC are more potent than those of curcumin at the same dose. Results that THC showed antihyperlipidemic effect in addtion to its antidiabetic effect in type 2 diabetic rats (Murugan and Pari, 2007a). In conclusion, THC and curcumin to STZ - nicotinamide diabetic rats decrease tissue lipids and maintains the fatty acid composition in normal level. The THC administration showed more effective than curcumin.

Influence of THC on hepatic and renal functional markers and protein levels

The liver and kidney play a major role in the pathogenesis of type 2 diabetes. It contributes to insulin resistance, along with muscle and adipose tissues, and it has a major impact on the incidence of hyperglycaemia. Hepatic diseases such as cirrhosis, viral hepatitis and nonalcoholic fatty liver disease are associated with altered glucose metabolism and a higher prevalence of diabetes mellitus (DeFronzo et al., 1992). Diabetic nephropathy is a serious complication of type 1 diabetes and type 2 diabetes. It's also called diabetic kidney disease. In the United States, about 1 in 3 people living with diabetes have diabetic nephropathy. Diabetic nephropathy affects the kidneys' usual work of removing waste products and extra fluid from the body. The best way to prevent or delay diabetic nephropathy is by living a healthy lifestyle and keeping diabetes and high blood pressure managed. Over years, diabetic nephropathy slowly damages the kidneys' filtering system. Early treatment may prevent this condition or slow it and lower the chance of complications (Koya et al., 2009).

Oral administration of THC at 80 mg/kg body weight to diabetic rats for 45 days resulted in a significant decreased the levels of plasma total protein, albumin, globulin and albumin/globulin ratio as compared to control rats. After treatment with THC and curcumin total protein, albumin, globulin and albumin/globulin ratio were brought back to near normal levels. The activities of hepatic and renal markers were significantly elevated in diabetic rats as compared to control rats, and treatment with THC and curcumin have reversed these parameters to near normal levels. In diabetic rats, the decreased levels of urea, uric acid and creatinine with increased levels of was observed, and treatment with THC and curcumin have reversed these parameters to near normal levels.THC had a better protective effect when compared with curcumin (Murugan and Pari, 2007b). In conclusion, our study suggests that the liver and kidney functions are highly altered in diabetic state. Treatment with THC and curcumin reversed these changes in diabetic rats, which indicates that THC and curcumin protect the hepatic and renal function in diabetic condition.

Influence of THC on tail tendon collagen contents and its properties

Collagen is an important constituent of most of the tissues that are affected during diabetes. Modifications of this protein may play a critical role in the complications of diabetes (Paul and Bailey, 1996). In diabetic rats collagen content was increased significantly with extensive modifications in the characteristics such as extent of glycation, cross-linking and collagen linked fluorescence. The extent of glycation and collagen linked fluorescence were significantly increased in tail tendon of diabetic rats. This could be due to ambient exposure of the tissue to glucose in diabetic state. In addition to glucose, free radicals and lipid peroxides generated during diabetes play an important role in the development of collagen-linked fluorescence (Odetti et al. 1994).

Changes in the structural and functional properties of collagen caused by advanced glycation might be of importance for the etiology of late complications in diabetes. Curcumin is the most active component of turmeric. It is believed that curcumin is a potent antioxidant and anti-inflammatory agent. THC is one of the major metabolites of curcumin, exhibits many of the same physiologic and pharmacological activities as curcumin and in some systems may exert greater antioxidant activity than curcumin. In diabetic rats, hydroxyproline and collagen content as well as its degree of cross-linking were increased, as shown by increased extent of glycation, collagen-linked fluorescence, neutral salt collagen, decreased acid and pepsin solubility. Administration of THC for 45 days to diabetic rats significantly reduced the accumulation and cross-linking of collagen. The effects of THC were comparable with those of curcumin. In conclusion, administration of THC had a positive influence on the content of collagen and its STZ and nicotinamide diabetic rats. The THC administration showed more effective than curcumin (Pari and Murugan, 2006d).

Effect of THC on insulin receptors status in type 2 diabetic rats: Studies on insulin binding to erythrocytes

A number of studies have shown that human erythrocytes can be used as a cellular model for assessing the status of insulin receptors in diabetes (Gambhir et al. 1978; Pari and Murugan, 2007). Since erythrocytes can be easily obtained in sufficient number of serial studies, they have been used as a model for insulin binding studies (Pollet et al. 1981; Grigorescu et al. 1983; Susheela et al. 1987).

Erythrocytes should therefore be useful to reflect other tissues in terms of change in insulin receptor affinity and long-term changes in receptor concentration (Ward and Harrison, 1986). Ligand-receptor binding studies are widely used for receptor characterization and in high throughput drug screening. Receptor binding is used to characterize receptors and to evaluate potential pharmaceutical agents by assessing their ability to interfere with specific binding of a radiolabelled ligand to its receptors. Using the radioreceptor assay of Gambhir et al. (1978), we have investigated the effect of THC and curcumin on 125I-insulin binding to erythrocyte receptor of normal and experimental rats and to determine whether the plasma insulin concentration could affect the number and/or affinity of insulin receptor sites according to the down and up regulation theory.

Using circulating erythrocytes as the cellular mode, insulin-binding effect of THC and curcumin was investigated. STZ - nicotinamide induced male Wistar rats were used as experimental models. THC (80 mg/kg body weight) was administered orally for 45 days. Effect of THC on blood glucose, plasma insulin and insulin binding to its receptor on the cell membrane of erythrocytes were studied. Mean specific binding of insulin was significantly lowered in diabetic rats with decrease in plasma insulin. This was due to a significant decrease in mean insulin receptor. Erythrocytes from diabetic rats showed decreased ability of insulin binding with receptor when compared with THC treated diabetic rats. Scatchard analysis demonstrated that the decrease in insulin binding was accounted by a decrease in insulin receptor sites per cell with erythrocytes of diabetic rats having less insulin receptor sites per cell with THC treated rats. High affinity (Kd1), low affinity (Kd2) and kinetic analysis revealed an increase in the average receptor affinity with erythrocytes from THC treated rats when compared with diabetic rats. These results suggest that acute alteration of the insulin receptor on the membranes of erythrocytes occurred in diabetic rats. Treatment with THC significantly improved specific insulin binding to receptors, with receptor number and affinity binding to near normal levels. Our study suggests that how THC increases the total cellular insulin binding sites with significant increase in plasma insulin. The effect of THC is more prominent than curcumin (Murugan et al., 2008). In conclusion, oral treatment with the THC and curcumin improved the erythrocyte membrane insulin binding sites with concomitant increase of plasma insulin. The molecular basis for each event that occurs after the binding of insulin to its receptor remains to be examined.

Conclusion

Administration of THC and curcumin has significant antidiabetic effect in STZ-nicotinamide induced type 2 diabetes. The THC and curcumin exhibited its antidiabetic effect by influencing the carbohydrate metabolism, lipid metabolism, oxidative stress induced lipid peroxidation, membrane bound enzymes, histopathological changes, insulin binding to erythrocyte receptor and collagen content and its characteristics. The antidiabetic effect of THC provides sufficient documentation to define its role and action for its potential and promising use in treating diabetes. The THC administration showed more effective than curcumin.

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