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Effect of Tetrahydrocurcumin and Pterostilbene Dose Dependent Study and Oral Glucose Tolerance Test in Streptozotocin-Nicotinamide induced Type 2 Diabetic Rats

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Abstract: Diabetes mellitus is probably 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. Management 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 oral hypoglycemic drugs are having undesirable side effects. Medicinal plants with hypoglycemic activity were used for many centuries and sometimes as regular constituents of the diet, it is assumed that they do not have many side effects. Tetrahydrocurcumin (THC) is one of the major metabolites of curcumin which exhibits many of the same physiologic and pharmacological activities as curcumin and in some systems may exert greater antioxidant activity than curcumin. *Pterocarpus marsupium* has also been used in the treatment of toothache, diarrhoea, heartburn, urinary tract infections, boils, sores and skin diseases. *Pterocarpus marsupium* has been used for many years in the treatment of diabetes mellitus. Pterostilbene (PTS) was found to be one of the active constituents in the extracts of the heartwood of *Pterocarpus marsupium*. PTS is a useful bioactive compound in preventing type 1 diabetes, insulin resistance and type 2 diabetes in animal models. Plants play a major role in the introduction of new therapeutic agents and have received much attention as sources of biologically active substances. In this study different doses of THC (20, 40 and 80 mg/kg body weight) and PTS (10, 20 and 40 mg/kg body weight) were orally administered to diabetic rats for 45 days, and after the treatment glucose levels were assayed.

Keywords: Blood glucose, Plasma insulin, Pancreas, Tetrahydrocurcumin, Pterostilbene, Metformin

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Introduction

Diabetes mellitus (DM) is a major public health issue affecting more than 400 million people worldwide (Khursheed *et al.*, 2019). This

metabolic disorder progressively leads to chronic microvascular, macrovascular and neuropathic life threatening complications. DM is caused either by

deficiency of insulin secretion, damage of pancreatic β cell or insulin resistance related to non-use of insulin. Inclination to sedentary lifestyle may be the major reason for the continual rise in the number of diabetic patients globally which is expected to strike 366 million in 2030 in the elderly population (>65 years) (Wild *et al.*, 2004).

Currently available drug regimes for management of DM 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 DM has been reported (Bailey and Day, 1989).

Pterocarpus marsupium Roxb (family: Leguminosae) is a large tree commonly known as Vijayasar in Hindi and Indian Kino in English. *P. marsupium* has been used in the treatment of toothache, diarrhoea, heartburn, urinary tract infections, boils, sores and skin diseases. Several experimental studies in chemically induced diabetes conducted with whole extracts of bark or heartwood of *P. marsupium* have shown its efficacy in reducing blood sugar levels (Joglekar *et al.*, 1959; Ahmad *et al.*, 1991; Manickam *et al.*, 1997).

PTS is a phenolic compound, which is reported to be the only stilbene found in the genus *Pterocarpus*, and it was first isolated from *P. santalinus* (red sandalwood) (Seshadri, 1972). Together with resveratrol, it has also been identified in *Vitis vinifera* leaves (Langcake *et al.*, 1979), in infected grape berries and in healthy and immature berries (Pezet and Pont, 1988).

PTS has been demonstrated to have a Chemo-

preventive activity similar to that of resveratrol and it is cytotoxic for a number of *in vitro* cancer cell lines (Rimando *et al.*, 2002). PTS and its natural 3 hydroxy derivative both possess interesting antileukemic properties and they may constitute effective and powerful drugs in multidrug resistance (MDR) and apoptosis resistant hematological malignancies (Manlio *et al.*, 2005).

PTS was found to be one of the active constituents in the extracts of the heartwood of *P. marsupium* (Maurya *et al.*, 1984). The water stored in tumblers made out of the heartwood of *P. marsupium* is used as a traditional therapy for patients with DM (Maheswari *et al.*, 1980). An aqueous extract of heartwood of *P. marsupium* has been tested clinically and found to be effective in NIDDM patients (ICMR, 1998). When administered to STZ induced hyperglycemic rats, PTS and marsupin two of the major phenolic constituents in aqueous decoction of the heartwood of *P. marsupium*, significantly decreased plasma glucose (Manickam *et al.*, 1997).

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 (Holder *et al.*, 1978; 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) (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 (Murugan and Pari, 2006a; Murugan and Pari, 2007a; Murugan *et al.*, 2008).

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 (Murugan, 2022; Murugan, 2023 a,b).

The phenolic group of curcumin plays the major role in their antioxidant and free radical scavenging activities. Murugan and Pari (2005) studied a series of curcumin and THC, bearing various hydroxy and methoxy groups on their benzene subunits. Murugan and Pari (2005) 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.

THC is used in the treatment of several diseases such as -- prevents cancer, protects

against inflammation, atherosclerotic lesions (Murugan and Pari, 2007b; Pari and Murugan, 2007), hepatotoxicity (Pari and Murugan, 2004) and nephrotoxicity (Murugan and Pari, 2006b).

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 (Murugan and Pari, 2006c).

In this study different doses of THC (20, 40 and 80 mg/kg body weight) and PTS (10, 20 and 40 mg/kg body weight) were orally administered to diabetic rats for 45 days, and after the treatment glucose levels were assayed.

Materials and Methods

Drugs and chemicals:

THC and PTS were a gift provided by Sabinsa Corporation, USA. All other chemicals and biochemicals were of analytical grade.

Induction of diabetes:

Non-Insulin dependent DM was induced (Masiello *et al.*, 1998) in overnight fasted rats by a single intraperitoneal injection of 65 mg/kg streptozotocin (STZ), 15 min after the intraperitoneal administration of 110 mg/kg of nicotinamide. STZ 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 54 rats (48 diabetic surviving rats, 6 normal rats) were used. The rats

were divided into nine groups of 6 each, after the induction of STZ diabetes. The duration of experiment was 45 days.

Group 1: Normal rats.

Group 2: Diabetic control rats.

Group 3: Diabetic rats given THC (20 mg/kg body weight) in aqueous suspension daily using an intragastric tube for 45 days.

Group 4: Diabetic rats given THC (40 mg/kg body weight) in aqueous suspension daily using an intragastric tube for 45 days.

Group 5: Diabetic rats given THC (80 mg/kg body weight) in aqueous suspension daily using an intragastric tube for 45 days.

Group 6: Diabetic rats given PTS (10 mg/kg body weight) in aqueous suspension daily using an intragastric tube for 45 days.

Group 7: Diabetic rats given PTS (20 mg/kg body weight) in aqueous suspension daily using an intragastric tube for 45 days.

Group 8: Diabetic rats given PTS (40 mg/kg body weight) in aqueous suspension daily using an intragastric tube for 45 days.

Group 9: Diabetic rats given metformin (500 mg/kg body weight) in aqueous suspension daily using an intragastric tube for 45 days.

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.

Analytical procedure:

Estimation of blood glucose:

Blood glucose was estimated by the method of O-toluidine using the modified reagent of Sasaki *et al.* (1972).

Oral glucose tolerance test (OGTT):

OGTT was performed according to the method of du Vigneaud and Karr (1925). After overnight fasting, '0' min blood sample (0.2 ml) was taken

from the rats in normal and experimental rats. Without delay, a glucose solution (2 g/kg body weight) was administered by gavage. Four more samples were taken at 30, 60, 90 and 120 min after glucose administration. All the blood samples were collected with potassium oxalate and sodium fluoride for the estimation of blood glucose and the glucose present in the different samples were estimated by the method of O-toluidine (Sasaki *et al.*, 1972) as described previously.

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

Table 1 shows the effect of treatment with various doses of THC and PTS on blood glucose levels. In all the THC (20, 40 and 80 mg/kg body weight) and PTS (10, 20 and 40 mg/kg body weight) treated groups, although a significant antihyperglycemic ($p < 0.01$) effect was evident from first week onwards, decrease in blood sugar was maximum on completion of the third week (66.5%) ($p < 0.001$) in the group receiving 80 mg/kg body weight of THC. On the other hand, PTS treated groups showed an antihyperglycemic effect much later in groups receiving 40 mg/kg body weight (60.5 and 56.3% respectively). THC at a dose of 80 mg/kg body weight showed a highly significant effect compared to 20 and 40 mg/kg body weight. PTS at a dose of 40 mg/kg body weight showed a highly significant effect compared to 10 and 20 mg/kg body weight. The THC administration showed more effective than curcumin.

Oral Glucose Tolerance Test (OGTT):

Table 2 shows the blood glucose levels of normal and experimental rats after oral administration of glucose (2 g/kg body weight). In diabetic rats, the blood glucose levels reached peak at 60 min.

Table 1: Effect of 6-weeks treatment with various doses of THC and PTS on glucose levels in normal and experimental rats

<i>Groups</i>	'0' day	48 h after STZ injection	I week (after treatment)	II week	<i>III week</i>	<i>IV week</i>	<i>V week</i>	<i>VI week</i>
<i>Blood Glucose (mg/dl)</i>								
Normal	87.24 ± 5.41	85.63 ± 6.52	84.73 ± 6.65	85.21 ± 3.73	84.25 ± 6.54	83.47 ± 5.54	84.45 ± 5.25	84.25 ± 5.65
Diabetic control	78.45 ± 4.65	259.35 ± 14.65**	261.62 ± 0.65**	276.41 ± 16.62**	305.65 ± 16.45**	324.87 ± 22.41**	325.54 ± 18.74**	332.56 ± 25.54**
Diabetic+ THC (20 mg)	76.47 ± 4.54	240.35 ± 19.45**	219.32 ± 14.19* (9.02)	198.41 ± 10.35** (17.58)	179.21 ± 11.98** (25.65)	158.30 ± 7.21** (35.02)	131.59 ± 6.39** (40.25)	107.21 ± 6.24** (50.10)
Diabetic+ THC (40 mg)	78.32 ± 4.28	245.21 ± 13.20**	222.54 ± 10.45* (11.54)	197.45 ± 9.87** (21.35)	165.53 ± 7.82** (33.40)	140.31 ± 5.31** (40.40)	115.15 ± 7.03** (50.36)	98.01 ± 4.21** (61.20)
Diabetic+ THC (80 mg)	79.41 ± 3.20	253.61 ± 15.41**	214.40 ± 10.39** (16.47)	178.90 ± 6.25** (30.35)	113.05 ± 8.36** (53.90)	106.32 ± 6.47** (57.60)	91.21 ± 6.30** (61.50)	86.18 ± 5.42** (64.60)
Diabetic+ PTS (10 mg)	76.50 ± 4.91	240.35 ± 19.52**	216.46 ± 12.29* (9.22)	198.41 ± 10.31** (17.32)	179.21 ± 11.41** (24.70)	157.30 ± 7.10** (33.17)	132.51 ± 6.36** (40.42)	107.12 ± 6.48** (54.18)
Diabetic+ PTS (20 mg)	79.41 ± 4.35	246.02 ± 13.20**	220.30 ± 10.64* (11.20)	195.42 ± 9.72** (20.47)	164.59 ± 7.79** (32.25)	141.49 ± 5.48** (42.48)	118.68 ± 7.21** (50.15)	98.21 ± 4.69** (59.18)
Diabetic+ PTS (40 mg)	78.36 ± 3.43	258.60 ± 15.39**	215.41 ± 10.35** (15.20)	175.90 ± 6.25** (30.40)	113.25 ± 8.48** (50.76)	106.31 ± 6.21** (57.51)	91.25 ± 6.55** (62.41)	86.36 ± 5.42** (65.60)
Diabetic + Metformin (500 mg/kg)	76.41 ± 4.28	244.51 ± 13.68**	215.30 ± 7.34* (10.50)	190.66 ± 9.1** (20.15)	117.30 ± 4.0** (50.80)	110.51 ± 5.20** (50.52)	97.51 ± 5.11** (59.15)	88.87 ± 6.50** (60.40)

Values are given as mean ± S.D for 6 rats in each group. Values in parentheses indicated the percentage lowering of blood glucose in comparison to basal reading after streptozotocin (STZ) administration at 48 h. Diabetic control was compared with normal. Experimental groups were compared with corresponding values after streptozotocin injection (48 h). * - p< 0.01, ** - p<0.001.

Table 2: Oral glucose tolerance test in normal and experimental rats

<i>Groups</i>	Blood Glucose Levels (mg/dl)				
	0 min	30 min	60 min	90 min	120 min
Normal	89.36 ± 5.54 ^a	176.70 ± 6.45 ^a	157.40 ± 9.72 ^a	104.73 ± 5.15 ^a	98.16 ± 5.40 ^a
Diabetic control	265.36 ± 8.15 ^b	331.50 ± 14.15 ^b	370.39 ± 9.55 ^b	340.65 ± 8.45 ^b	311.30 ± 9.30 ^b
Diabetic + THC (80 mg/kg)	102.30 ± 4.80 ^c	196.80 ± 8.80 ^c	175.59 ± 5.29 ^c	129.21 ± 5.54 ^c	113.15 ± 5.45 ^c
Diabetic + PTS (40 mg/kg)	113.43 ± 4.75 ^d	210.73 ± 8.76 ^d	185.51 ± 5.25 ^d	138.09 ± 5.54 ^d	126.15 ± 5.45 ^d
Diabetic + Metformin (500 mg/kg)	118.01 ± 6.19 ^d	214.03 ± 7.64 ^d	192.83 ± 4.20 ^d	139.15 ± 6.17 ^d	129.67 ± 5.25 ^d

Values are given as mean ± S.D for 6 rats in each group.

Values not sharing a common superscript letter differ significantly at p<0.05 (DMRT).

Although the glucose levels started to decline in THC and PTS treated rats (90 and 120 min), the levels of glucose remained higher even after 120 min intervals in diabetic control rats. Normal rats treated with THC and PTS showed a significant decrease in the glucose level at 120 min when compared to its 30 and 60 min blood glucose levels.

Discussion

Diabetes is a metabolic disease and its incidence is considered to be high all over the world (Devendra and Eisenbarth, 2004). Epidemiological studies and clinical studies strongly support the notion that hyperglycemia is the principal cause of complications. Effective blood glucose control is the key for preventing or reversing diabetic complications and improving quality of life in patients with diabetes (Zimmet *et al.*, 2001). Thus, sustained reduction in hyperglycemia will decrease the risk of developing microvascular and macrovascular complications (Brownlee, 2001). Throughout the world many traditional plant treatments for diabetes exist. However, few have received scientific or medical scrutiny and the WHO has recommended accordingly that traditional plant treatment for diabetes warrant further evaluation (WHO, 1999).

Masiello *et al.* (1998) described a new experimental diabetic model in adult rats administered STZ and partially protected with a suitable dose of nicotinamide. This syndrome 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) suggest that following STZ and nicotinamide administration a partial loss of β -cell mass occurs by necrosis and/or apoptosis, induced by the relatively specific cytotoxic effect of STZ only partially counteracted by nicotinamide. The residual β -cells (about 60% of the original mass) are most likely those, which escaped from irreversible damage and maintained the differentiation of

mature β cells. Hence the potentiation of insulin secretion by THC may be from the residual β -cell mass.

The possible mechanism by which THC and PTS brings about its antihyperglycemic action may be by stimulation of surviving β -cells to release more insulin. This was clearly evidenced by the increased level of insulin in diabetic rats treated with THC.

The administration of THC and PTS to decrease the increased blood glucose concentration to normal glycemic concentration is an essential trigger for the brain to revert its normal homeostasis during experimental diabetes. THC has the ability to trigger the proinsulin synthesis and also insulin release, which might be helpful to reduce the plasma glucose and increase insulin during diabetes.

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 (Murugan and Pari, 2006a; Murugan and Pari, 2007c). 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 ROS and inhibit peroxidation of lipids could be useful as preventive agents against DM (Halim Eshart, 2002). The ability of THC increases 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) implied 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 prevent 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 investigation, treatment with THC and PTS showed significant antihyperglycaemic activity. The maximum reduction in glucose levels was seen in groups receiving 80 mg/kg of the THC and 40 mg/kg of PTS. Moreover, it indirectly indicates that part of the antihyperglycaemic activity of this phytochemicals is due to release of insulin from the existing β cells of pancreas. The possible mechanism of action of THC and PTS could be correlated with the reminiscent effect of the hypoglycaemic sulphonylureas which promote insulin secretion by closure of K^+ - ATP channels, membrane depolarization and stimulation of Ca^{2+} influx, an initial key step in insulin secretion. In this context a number of other plants have also been reported to have antihyperglycaemic and insulin-release stimulatory effects (Murugan and Pari, 2007b).

Administration of THC and PTS has significant antidiabetic effect in STZ-nicotinamide induced diabetes. The antidiabetic effect of THC and PTS provide sufficient documentation to define its role and action for its potential and promising use in treating diabetes. The THC administration showed more effective than PTS and metformin.

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