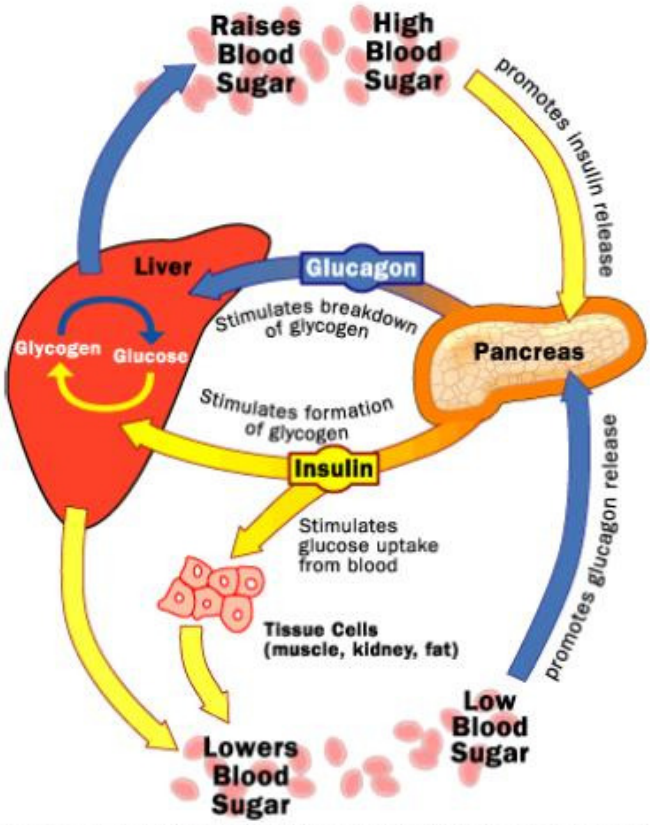
INTRODUCTION

Diabetes mellitus**,** often referred to simply as diabetes, is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia). Blood glucose levels are controlled by a complex interaction of multiple chemicals and hormones in the body, including the hormone insulin made in the beta cells of the pancreas. Diabetes mellitus refers to the group of diseases that lead to high blood glucose levels due to defects in either insulin secretion or insulin action.



Insulin and glucagon have opposite effects on liver and other tissues for controlling blood-glucose levels.

Diabetes develops due to a diminished production of insulin (in *type 1*) or resistance to its effects (in *type 2* and *gestational*). Both lead to hyperglycaemia, which largely causes acute signs of diabetes: excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism. All forms of diabetes are treatable since insulin became medically available in 1921, but there is no cure. The injections by a syringe, insulin pump, or insulin pen deliver insulin, which is a basic treatment of type 1 diabetes. Type 2 is managed with a combination of dietary treatment, exercise, medications and insulin supplementation.

Diabetes and its treatments can cause many complications. Acute complications (hypoglycemia, ketoacidosis, or nonketotic hyperosmolar coma) may occur if the disease is not adequately controlled. Serious long-term complications include cardiovascular disease, chronic renal failure, retinal damage (which can lead to blindness), nerve damage, and microvascular damage, which may cause erectile dysfunction and poor wound healing. Poor healing of wounds, particularly of the feet, can lead to gangrene, and the danger of amputation. Adequate treatment of diabetes, as well as increased emphasis on blood pressure control and lifestyle factors (such as not smoking and maintaining a healthy body weight), may improve the risk profile of most of the chronic complications.

CLASSIFICATION

The term *diabetes*, without qualification, usually refers to diabetes mellitus, which is associated with excessive sweet urine (known as "glycosuria") but there are several rarer conditions also named diabetes.

The most common of these is diabetes insipidus in which the urine is not sweet (insipidus meaning "without taste" in Latin); it can be caused by either kidney (nephrogenic DI) or pituitary gland (central DI) damage.

The term "type 1 diabetes" has universally replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and non-insulin-dependent diabetes (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as, among others, gestational diabetes, insulin-resistant type 1 diabetes (or "double diabetes"), type 2 diabetes which has progressed to require injected insulin, and latent autoimmune diabetes of adults (or LADA or "type 1.5" diabetes. There is also maturity onset diabetes of the young (MODY) which is a group of several single gene (monogenic) disorders with strong family histories that present as type 2 diabetes before 30 years of age.

Type 1 diabetes mellitus

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to a deficiency of insulin. This type of diabetes can be further classified as immune mediated or idiopathic. The majority of type 1 diabetes is of the immune mediated variety, where beta cell loss is a T-cell mediated autoimmune attack. Most affected persons are otherwise healthy and of a healthy weight when the onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

The principal treatment of type 1 diabetes, even in its earliest stages, is the delivery of artificial insulin via injection combined with careful monitoring of blood glucose levels using blood testing monitors. Without insulin, diabetes ketoacidosis often develops which may result in coma or death. Treatment emphasis is now also placed on lifestyle adjustments (diet and exercise) though these cannot reverse the progress of the disease. Apart from the common subcutaneous injections, it is also possible to deliver insulin by a pump, which allows continuous infusion of insulin 24 hours a day at preset levels, and the ability to program doses (a bolus) of insulin as needed at meal times. An inhaled form of insulin was approved by the FDA in January 2006, although it was discontinued for business reasons in October 2007. Non-insulin treatments, such as monoclonal antibodies and

stem-cell based therapies, are effective in animal models but have not yet completed clinical trials in humans.

Type 1 treatment must be continued indefinitely in essentially all cases. Treatment need not significantly impair normal activities, if sufficient patient training, awareness, appropriate care, discipline in testing and dosage of insulin is taken. However, treatment is burdensome for patients; insulin is replaced in a non-physiological manner, and this approach is therefore far from ideal. The average glucose level for the type 1 patient should be as close to normal (80–120 mg/dl, 4–6 mmol/l) as is safely possible. Some physicians suggest up to 140–150 mg/dl (7-7.5 mmol/l) for those having trouble with lower values, such as frequent hypoglycemic events. Values above 400 mg/dl (20 mmol/l) are sometimes accompanied by discomfort and frequent urination leading to dehydration. Values above 600 mg/dl (30 mmol/l) usually require medical treatment and may lead to ketoacidosis, although they are not immediately life-threatening. However, low levels of blood glucose, called hypoglycemia, may lead to seizures or episodes of unconsciousness and must be treated immediately, via emergency high-glucose gel placed in the patient's mouth or an injection of glucagon.

Type 2 diabetes mellitus

Type 2 diabetes mellitus is characterized differently and is due to insulin resistance or reduced insulin sensitivity, combined with relatively reduced insulin secretion which in some cases becomes absolute. The defective responsiveness of body tissues to insulin almost certainly involves

the insulin receptor in cell membranes. However, the specific defects are not known. Diabetes mellitus, due to a known specific defect, are classified separately.

In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity, characterized by elevated levels of insulin in the blood. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver. As the disease progresses, the impairment of insulin secretion worsens, and therapeutic replacement of insulin often becomes necessary.

There are numerous theories as to the exact cause of and mechanism in type 2 diabetes. Central obesity (fat concentrated around the waist in relation to abdominal organs, but not subcutaneous fat) is known to predispose individuals to insulin resistance. Abdominal fat is especially active hormonally, secreting a group of hormones called adipokines that may possibly impair glucose tolerance. Obesity is found in approximately 55% of patients diagnosed with type 2 diabetes. Other factors include aging (about 20% of elderly patients in North America have diabetes) and family history (type 2 is much more common in those with close relatives who have had it). In the last decade, type 2 diabetes has increasingly begun to affect children and adolescents, likely in connection with the increased prevalence of childhood obesity seen in recent decades in some places. Environmental exposures may contribute to recent increases in the rate of type 2 diabetes. A positive correlation has been found between the concentration in the urine of

bisphenol A, a constituent of polycarbonate plastic, and the incidence of type 2 diabetes.

Type 2 diabetes may go unnoticed for years because visible symptoms are typically mild, non-existent or sporadic, and usually there are no ketoacidotic episodes. However, severe long-term complications can result from unnoticed type 2 diabetes, including renal failure due to diabetes nephropathy, vascular disease (including coronary artery disease), vision damage due to diabetes retinopathy, loss of sensation or pain due to diabetes neuropathy, liver damage from non-alcoholic steatohepatitis and heart failure from diabetes cardiomyopathy.

Type 2 diabetes is usually first treated by increasing physical activity, decreasing carbohydrate intake, and loss of weight. These can restore insulin sensitivity even when the weight loss is modest, for example, around 5 kg (10 to 15 lb), most especially when it is in abdominal fat deposits. It is sometimes possible to achieve long-term, satisfactory glucose control with these measures alone. However, the underlying tendency to insulin resistance is not lost, and so attention to diet, exercise, and weight loss must continue. The next usual step, if necessary, is treatment with oral antidiabetes drugs. Insulin production is initially only moderately impaired in type 2 diabetes, so oral medication (often used in various combinations) can be used to improve insulin production (e.g., sulfonylureas), to regulate inappropriate release of glucose by the liver and attenuate insulin resistance to some extent (e.g., metformin), and to substantially attenuate insulin resistance (e.g., thiazolidinediones). According to one study, overweight

patients treated with metformin compared with diet alone, had relative risk reductions of 32% for any diabetes endpoint, 42% for diabetes related death and 36% for all causes of mortality and stroke. Oral medication may eventually fail due to further impairment of beta cell insulin secretion. At this point, insulin therapy is necessary to maintain normal or near normal glucose levels.

Type 3 Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life. Even though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Induction may be indicated with decreased placental function. A cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

Other types of Diabetes

Most cases of diabetes mellitus fall into the two broad etiologic categories of type 1 or type 2 diabetes. However, many types of diabetes mellitus have known specific causes, and thus fall into separate categories as diabetes due to a specific cause. As more research is being done into diabetes, many patients who were previously diagnosed as type 1 or type 2 diabetes will be reclassified as diabetics due to their known specific cause.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells.

SIGNS AND SYMPTOMS

The classical triad of diabetes symptoms is polyuria, polydipsia and polyphagia, which are, respectively, frequent urination, increased thirst and consequent increased fluid intake, and increased appetite. Symptoms may develop quite rapidly (in weeks or months) in type 1 diabetes, particularly in

children. However, in type 2 diabetes, symptoms usually develop much more slowly and may be subtle or completely absent. Type 1 diabetes may also cause a rapid yet significant weight loss (despite normal or even increased eating) and irreducible fatigue. All of these symptoms except weight loss can also manifest in type 2 diabetes in patients whose diabetes is poorly controlled.

When the glucose concentration in the blood rises beyond its renal threshold, reabsorption of glucose in the proximal renal tubuli is incomplete, and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. The lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst.

Prolonged high blood glucose causes glucose absorption, which leads to changes in the shape of the lenses of the eyes, resulting in vision changes; sustained sensible glucose control usually returns the lens to its original shape. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change, whereas, with type 2, change is generally more gradual, but should still be suspected.

Patients (usually with type 1 diabetes) may also initially be found to have diabetes ketoacidosis (DKA), an extreme state of metabolic

dysregulation characterized by the smell of acetone on the patient's breath; a rapid, deep breathing known as Kussmaul breathing; polyuria; nausea; vomiting and abdominal pain; and any of many altered states of consciousness or arousal (such as hostility and mania or, equally, confusion and lethargy). In severe DKA, coma may follow, progressing to death. Diabetes ketoacidosis is a medical emergency and requires immediate hospitalization.

A rarer but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 diabetes and is mainly the result of dehydration due to loss of body water. Often, the patient has been drinking extreme amounts of sugar-containing drinks, leading to a vicious circle in regard to the water loss.

GENETICS

Both type 1 and type 2 diabetes are at least partly inherited. Type 1 diabetes appears to be triggered by some (mainly viral) infections, or less commonly, by stress or environmental exposure (such as exposure to certain chemicals or drugs). There is a genetic element in individual susceptibility to some of these triggers which has been traced to particular HLA genotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility, type 1 diabetes mellitus seems to require an environmental trigger. A small proportion of people with type 1 diabetes carry a mutated gene that causes maturity onset diabetes of the young (MODY).

There is a stronger inheritance pattern for type 2 diabetes. Those with first-degree relatives with type 2 have a much higher risk of developing type 2, increasing with the number of those relatives. Concordance among monozygotic twins is close to 100%, and about 25% of those with the disease have a family history of diabetes. Moreover, obesity (which is an independent risk factor for type 2 diabetes) is strongly inherited.

Various hereditary conditions may feature diabetes, as for example, myotonic dystrophy and Friedreich's ataxia. Wolfram's syndrome is an autosomal recessive neurodegenerative disorder that first becomes evident in childhood.

PATHOPHYSIOLOGY

Insulin production is more or less constant within the beta cells, irrespective of blood glucose levels. It is stored within vacuoles pending release, via exocytosis, which is primarily triggered by food, chiefly food containing absorbable glucose. The chief trigger is a rise in blood glucose levels after eating.

Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells). Therefore, a deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus.

Most of the carbohydrates in food are converted within a few hours to the monosaccharide glucose, the principal carbohydrate found in blood and

used by the body as fuel. The most significant exceptions are fructose, most disaccharides (except sucrose and in some people lactose), and all more complex polysaccharides, with the outstanding exception of starch. Insulin is released into the blood by beta cells (β-cells), found in the Islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage.

Insulin is also the principal control signal for conversion of glucose to glycogen for internal storage in liver and muscle cells. Reduced glucose levels result both in the reduced release of insulin from the beta cells and in the reverse conversion of glycogen to glucose when glucose levels fall. This is mainly controlled by the hormone glucagon which acts in an opposite manner to insulin. Glucose thus recovered by the liver re-enters the bloodstream; muscle cells lack the necessary export mechanism.

Higher insulin levels increase some anabolic ("building up") processes such as cell growth and duplication, protein synthesis, and fat storage. Insulin (or its lack) is the principal signal in converting many of the bidirectional processes of metabolism from a catabolic to an anabolic direction, and vice versa. In particular, a low insulin level is the trigger for entering or leaving ketosis (the fat burning metabolic phase). If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by those body cells that require it

nor will it be stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis. (Encyclopadia Britanicca and National Institute for Health and Clinical Excellence, 2011).

The therapeutic remedies of Diabetes cover a vast region of the healthcare market. Though there are so many hypoglycemic medicines are available in the market but the demand of natural remedies still persists. This is due to the avoidance of side effects posed by these synthetic agents and the price related issues. In India and other countries the herbal treatment of various diseases has a long-long history. Several plants are used for treatment of various diseases. These are natural and do not have any synthetic compounds that may harm the health of the consumer. Due to low cost the herbal medicine are widely used by different commodities. The hypoglycemic nature of *Acacia arabica (*Singh *et al., 2011), Aegle marmelos* (Ayodhya *et al.,* 2010), *Biophytum sensitivum* (Ayodhya *et al.,* 2010), *Ephedra distachya* (Chauhan *et al.,* 2010), *Radix glycyrrhizae* (Ko et al., 2007), *Parinari excelsa* (Rao *et al*., 2010) were well reported in rats. *Tinospora cardifolia* also known as Guduchi, Giloy is well known for its heptoprotective and immunomodulatory activities (Rege *et al.,* 1993). It is a climbing shrub commonly present on the trees of mango and neem. It showed signification reduction in blood sugar level in both normal and Allaxon induced Diabetic mice. In Indian medicine it is widely used for treating diabetes (Stanley and Menon, 2001). The extract of plant parts decreases the blood sugar level (Roman *et al.,* 1992 and Chattopadhyay,

1999). The aim of present study is to investigate hypoglycemic effect of extract of the roots of *Tinospora cordfolia* in normal mice with a fixed dose of 200mg/kg body weight.

MATERIAL AND METHODS

Collection of Plant Material and Extraction

The hanging roots along with the plants of *Tinospora cordifolia* was collected from the trees of Neem from Dept of Botany, University of Rajasthan in the month of April and identified in the herbarium of the deptartment. The stems were washed properly and dried in shade. The methanolic extract of stems was prepared using the standard protocol.

Model Organism

The current study was carried out on inbreed proven fertile mature mice. The healthy mice weighing 20.0-30.0g irrespective of sex were used for the experiment. They were maintained under a controlled day night (12:12h) schedule at 25±1℃. The animals were fed on solid diet and water ad - libitum. The experiments were carried out in between 4 to 5p.m. After a week of acclimatization to laboratory conditions the animals were used for different sets of experiments Approval of Institutional Ethical Committee was sought prior to the commencement of experiment.

Experimental Groups

The experimental animals were divided into two groups.

Group A- Consisting of mice as control. The control animals were fed with distilled water.

Group B- Consisting of normal mice as experimental animals. They were treated with the alcoholic extract of *Tinospora cordifolia* with a dose of 200mg/kg body weight by oral administration.

The blood samples were collected for determination of blood glucose by using BOD-POD with Nelson-Somogyi□s method (Somogyi, 1945).

Statistical analysis

Statistical significance between the different groups was determined using one way analysis of variance (ANOVA) followed by Tukey's multiple comparisons by fixing the P value as <0.05.

RESULTS AND DISCUSSION

The result of experiments has been shown in Table-9.1, where the experimental animals were treated with stem extract of *Tinospora cordifolia* and their blood glucose levels were determined. The blood glucose levels were estimated on various days starting form day 1 to 30th day. The control group revealed blood glucose variations between 120 and 110mg/dl while the

experimental group indicated variations between 90 to 147mg/dl the blood concentrations. The result showed that there was a significant decrease of blood glucose level for all the days (Table 9.1). It is also evident from Table 9.1 that the blood glucose in the experimental mice showed a decreasing trend with gradual decline with respect to time, while during corresponding days the control group exhibited a fairly similar concentration.

The hypoglycemic effect of alcoholic stem extract of *T. cordifolia* with a dose of 200 mg/kg body weight administered orally to the Allaxon treated hyperglycemic mice once in a day for 4-weeks caused significant lowering of blood sugar level. However, there are various plants which show the antidiabetic property such as *Tinospora cripsa* (Noor and Ashroff, 1989). *Momordica charantia, Eugenia jambolina*, (Rathi *et al.,* 2002). The present investigation confirmed the pancreatoprotective, pancreatoregenerative and antidiabetic activity of alcoholic root extracts of *Tinospora cordifolia* in diabetic mice as the extract produced significant decrease in blood sugar concentration with a dose of 200mg/kg body weight of normal mice.

The importance of the liver in the regulation of carbohydrate metabolism is recognized by its ability to store carbohydrates in the form of glycogen (glycogenesis) and to release them in the form of glucose (glycogenolysis) when needed. These processes are regulated by 2 key enzymes: glycogen synthase and glycogen phosphorylase. It is reported that in diabetic animals the glycogen synthase activity was decreased whereas phosphorylase activity increased (Shanmugasundaram *et al.,* 1983). In the present study, the liver glycogen synthase activity decreased and

phosphorylase activity increased substantially (Table 9. 2) in untreated diabetic rats during the study period. The treatment with TC as well as insulin showed effects on the glycogen synthase and phosphorylase activity in these animals. These increased glycogen synthase activities in the liver of TC treated diabetic animals may indicate that the TC decreases blood sugar by increasing the glycogen storage in the liver. It seems that, since the TC treatment could not normalize the phosphorylase activity in the liver, the blood glucose was at elevated levels in TC treated diabetic rats inspite of the enhanced glycogen synthase activity.

Alloxan is well known for its selective beta cell cytotoxicity. It is reported that in alloxan induced diabetic rats the beta cell count/islet and the serum insulin levels decrease considerably (Mitra *et al*., 1996). In the present study, the serum insulin levels also decreased drastically in untreated diabetic rats. Treatment with TC by administration of a single dosage of extract or for 10 and 30 days (Table 9.3) did not increase the serum insulin levels in diabetic animals. In addition, the histological examination of endocrine pancreas in TC treated diabetic rats (Plate 9.1) did not reveal any evidence of regeneration of beta cells of islets of Langerhans. The histological section (Plate 9.1) of the pancreas of the drug treated control rats showed the normal architecture of the islets of Langerhans with the granulated beta cells appearing dark. The histology of the pancreas in diabetic rats showed small and shrunken islets of Langerhans. Destruction of beta-cells was observed in this section. The histology of the pancreas in TC treated diabetic rats showed a similar architecture to that of diabetic rats.

There was no considerable change in the architecture of the islets of Langerhans after the TC treatment. It appears that there was no regeneration of beta cells after the TC treatment; therefore, it appears that the anti-hyperglycemic activity of TC is not through the insulin secretion and is independent of insulin secretion by pancreatic beta cells. Since the present study has some limitations by having limited experimental sample size and methodology, this observation may be suggestive of a need for further research in the future to examine the adverse effects of this drug.

Conclusion

Tinospora cordifolia stem methanolic extract is an effective anti-hyperglycemic drug that can be used in the treatment of DM (Diabetes Mellitus). Although its activity is feeble compared to insulin, it can be used as a supportive drug in the treatment of DM. The anti-diabetic activity of TC is not through the insulin secretion by pancreatic beta cells. It may be due to the increased entry of glucose into the peripheral tissues and organs like the liver. Since TC increased the activity of glycogen synthase in the liver, it may increase the storage of glucose in hepatocytes. It also decreased the activity of phosphorylase in the liver; thereby it may prevent the release of glucose into the blood. The conclusion is that the possible use of these easily available, herbal and non-hazardous natural remedies for the treatment of diabetes mellitus.