Introduction
1. DIABETES

Diabetes mellitus is a syndrome characterized by disordered metabolism and inappropriately high blood sugar (hyperglycaemia) resulting from either low levels of the hormone insulin or from abnormal resistance to insulin's effects coupled with inadequate levels of insulin secretion to compensate (Tierney et al., 2002). The characteristic symptoms are excessive urine production (polyuria), excessive thirst and increased fluid intake (polydipsia).

Diabetes takes 2 main forms- The first is diabetes insipidus (Insipidus = Insipid, tasteless) and second form is diabetes mellitus (Mellitus = Honey). Diabetes insipidus characterized by choking thrust and large volumes of pale, dilute urine with no abnormal constituents, it occurs due to inadequate secretion of the pituitary hormone, anti-diuretic hormone in the body. Diabetes mellitus is a constitutional disorder caused by the malfunctioning of the pancreas, a gland that produces insulin. Insulin is an "anaerobic hormone" that helps in assimilation of glucose in the human body.
The chemical imbalance of insulin leads to:

(a). **Hyperglycemia** (High blood glucose level): It occurs when pancreas fail to produce adequate insulin, the hormone needed to convert glucose into energy.

(b). **Polyuria** (excessive urination): Hyperglycemia may exceed renal threshold and result in Polyuria.

(c). **Polydypsia** (excessive drinking): Polyuria results in water loss leading to dehydration of the body leading to polydypsia

(d). **Polyphagia** (excessive eating): Lose of glucose via urine causes a demand of more fuel in the body. As a result, a diabetic gets a voracious appetite, i.e., Polyphagia.

(e). **Wasting**: To meet the rising demands of the fuel in the body, endogenous proteins and fats are catabolized. As a result, a diabetic loses weight (i.e., wasting) despite of hearty meals.

Long term complication of diabetes can lead to degenerative changes in the blood vessels, atherosclerosis (hardening of the arteries); it may also result in microangiopathy (thickening of the capillary walls), paralysis, tiredness, recurrent infections, problems with visions, peripheral neuritis, heart attacks and gangrene are complications that commonly diabetics face.

### 1.1 PATHOPHYSIOLOGY

Mechanism of insulin release in normal pancreatic beta (β) cells. Insulin production is more or less constant within the β cells, irrespective of blood glucose levels. It is stored within vacuoles pending release, via exocytosis, which is triggered by increased blood glucose levels.

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 deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus.
Insulin is released into the blood by $\beta$-cells, found in the Islets of Langerhans in the pancreas, in response to rising levels of blood glucose 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. Lowered 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. Glucose thus recovered by the liver re-enters the bloodstream; muscle cells lack the necessary export mechanism.

Higher insulin levels increase many 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, 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.

1.2 COMPLICATIONS OF DIABETES

Diabetes 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 (doubled risk), chronic renal failure, retinal damage (which can lead to blindness), nerve damage (of several kinds), and
microvascular damage, which may cause impotence and poor healing. Poor healing of wounds, particularly of the feet, can lead to gangrene, which may require amputation. Adequate treatment of diabetes, as well as increased emphasis on blood pressure control and lifestyle factors (such as not smoking and keeping a healthy body weight), may improve the risk profile of most afore mentioned complications. In the developed world, diabetes is the most significant cause of adult blindness in the non-elderly, the leading cause of non-traumatic amputation in adults, and diabetic nephropathy is the main illness requiring renal dialysis.

I. Acute complications

(a) Hyperglycemia

Too high blood glucose is called 'hyperglycemia'. If very high, it can cause acute complications. In Type 1 diabetics, one of these is diabetic ketoacidosis which is always a medical emergency, and can often be noticed by a kind of fruity smell on the breath. Another acute complication, more common in Type 2 diabetics, is non-ketotic hyperosmolar coma which is also very dangerous.

(b) Hypoglycemia

Too low blood glucose is called hypoglycemia. It can also cause acute complications. If too low, diabetics can have many symptoms such as sweating, trembling, anger (or feeling passive), etc. possibly even passing out. But diabetics with hypoglycemia may be confused or even unconscious. They may even appear to have had too much alcohol. Severe hypoglycemia is very dangerous and can cause death.

In patients with diabetes, this can be caused by several factors, such as too much or incorrectly timed insulin, too much or incorrectly timed exercise (exercise decreases insulin requirements) or not enough food (specifically glucose-producing carbohydrates). In most cases, hypoglycemia is treated
with sugary drinks or food. In severe cases, an injection of glucagon (a hormone with the opposite effects of insulin) or an intravenous infusion of glucose is used for treatment, but usually only if the person is unconscious. In hospital, intravenous dextrose is often used.

(c) Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is an acute and dangerous complication that is always a medical emergency. Lack of insulin causes the liver to turn fat into ketone bodies, a fuel mainly used by the brain. Elevated levels of ketone bodies in the blood decrease the blood's pH, leading to most of the symptoms of DKA. On presentation at hospital, the patient in DKA is typically dehydrated and is breathing rapidly and deeply. Abdominal pain is common and may be severe. The level of consciousness is typically normal until late in the process, when lethargy may progress to coma. Ketoacidosis can become severe enough to cause hypotension, shock, and death. Prompt proper treatment usually results in full recovery, though death can result from inadequate or delayed treatment, or from complications. Ketoacidosis is much more common in type 1 diabetes than type 2.

(d) Nonketotic hyperosmolar coma

The hyperosmolar nonketotic state (HNS) is an acute complication with many symptoms in common with DKA, but an entirely different cause and different treatment. In a person with very high blood glucose levels (usually considered to be above 300 mg/dL (16 mmol/l)), water is drawn out of cells into the blood by osmosis and the kidneys dump glucose into the urine. This results in loss of water and an increase in blood osmolality. If fluid is not replaced (by mouth or intravenously), the osmotic effect of high glucose levels combined with the loss of water will eventually lead to dehydration. The body's cells become progressively dehydrated as water is taken from them and excreted. Electrolyte imbalances are also common and
dangerous. As with DKA, urgent medical treatment is necessary, especially volume replacement. Lethargy may ultimately progress to a coma, which is more common in type 2 diabetes than type 1.

II. Chronic complications

(a) Hyperglycemia

Chronic complications are mostly caused by hyperglycemia (but not high enough to always cause acute complications). It causes damage to blood vessels and nerves. Damage to blood vessels can eventually cause strokes, heart attacks, kidney failure, blindness, slow healing of skin breaks, and so more infections, and even amputations from poor circulation (decreased blood flow, usually to the feet and toes). Damage to nerves can make diabetics not feel pain (when this happens, it's usually in their feet). This causes them to have more injuries and not realize they have hurt themselves. Damage to nerves can also cause pain even when there's no real injury. It's a kind of phantom pain or ghost pain. This can be so bad that people need strong pain medicines.

(b) Vascular disease

Chronic elevation of blood glucose level leads to damage of blood vessels (angiopathy). The endothelial cells lining the blood vessels take in more glucose than normal, since they don't depend on insulin. They then form more surface glycoproteins than normal, and cause the basement membrane to grow thicker and weaker. In diabetes, the resulting problems are grouped under "microvascular disease" (due to damage to small blood vessels) and "macrovascular disease" (due to damage to the arteries).

(c) Image of fundus showing scatter laser surgery for diabetic retinopathy

The damage to small blood vessels leads to a microangiopathy, which can cause one or more of the following:
Diabetic retinopathy: Growth of friable and poor-quality new blood vessels in the retina as well as macular edema (swelling of the macula), which can lead to severe vision loss or blindness. Retinal damage (from microangiopathy) makes it the most common cause of blindness among non-elderly adults in the US.

Diabetic neuropathy: Abnormal and decreased sensation, usually in a 'glove and stocking' distribution starting with the feet but potentially in other nerves, later often fingers and hands. When combined with damaged blood vessels this can lead to diabetic foot. Other forms of diabetic neuropathy may present as mononeuritis or autonomic neuropathy. Diabetic amyotrophy is muscle weakness due to neuropathy.

Diabetic nephropathy: Damage to the kidney which can lead to chronic renal failure, eventually requiring dialysis. Diabetes mellitus is the most common cause of adult kidney failure worldwide in the developed world.

Macrovascular disease leads to cardiovascular disease, to which accelerated atherosclerosis is a contributor. Coronary artery disease, leading to angina or myocardial infarction ("heart attack") stroke (mainly the ischemic type) and peripheral vascular disease, which contributes to intermittent claudication (exertion-related leg and foot pain) as well as diabetic foot.

(d) Diabetic myonecrosis (muscle wasting)

Diabetic foot, often due to a combination of neuropathy and arterial disease, may cause skin ulcer and infection and, in serious cases, necrosis and gangrene. It is the most common cause of adult amputation, usually of toes and or feet, in the developed world.

Carotid artery stenosis does not occur more often in diabetes, and there appears to be a lower prevalence of abdominal aortic aneurysm. However, diabetes does cause higher morbidity, mortality and operative risks with these conditions (Weiss and Sumpio, 2006).
1.3 TYPES OF DIABETES

The World Health Organization recognizes three main forms of diabetes mellitus: type 1, type 2, and gestational diabetes (occurring during pregnancy) (World Health Organisation, 1999) which have similar signs, symptoms, and consequences, but different causes and population distributions. Ultimately, all forms are due to the β cells of the pancreas being unable to produce sufficient insulin to prevent hyperglycemia (Rother, 2007).

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 (Other "types" of diabetes, 2005), 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 (Diseases: Johns Hopkins Autoimmune Disease Research Center, 2007). There is also maturity onset diabetes of the young (MODY) which is a single gene disorder with strong family history that presents as type 2 diabetes before 30 years of age.

I. 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. The main cause of this β cell loss is a T-cell mediated autoimmune attack (Rother, 2007). There is no known preventative measure that can be taken against type 1 diabetes, which comprises up to 10% of diabetes mellitus cases in North America and Europe (though this varies by
geographical location). Most affected people are otherwise healthy and of a healthy weight when 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 cases of diabetes affecting children.

The principal treatment of type 1 diabetes, even from the earliest stages, is replacement of insulin combined with careful monitoring of blood glucose levels using blood testing monitors. Without insulin, ketosis and diabetic ketoacidosis can develop and coma or death will result. Emphasis is also placed on lifestyle adjustments (diet and exercise) though these cannot reverse the loss. 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.

Type 1 treatment must be continued indefinitely. Treatment does not impair normal activities, if sufficient awareness, appropriate care, and discipline in testing and medication is taken. The average glucose level for the type 1 patient should be as close to normal (80–120 mg/dL, 4–6 mmol/l) as 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 200 mg/dL (10 mmol/l) are often accompanied by discomfort and frequent urination leading to dehydration. Values above 300 mg/dL (15 mmol/l) usually require immediate treatment and may lead to ketoacidosis.

II. Type 2 - diabetes mellitus

Type 2 diabetes mellitus is due to insulin resistance or reduced insulin sensitivity, combined with reduced insulin secretion. The defective responsiveness of body tissues to insulin almost certainly involves the insulin
receptor in cell membranes. In the early stage, 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 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 for 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 (Eberhart et al., 2004). 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 (Arlan and Janet, 2003).

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 diabetic nephropathy, vascular disease (including coronary artery disease), vision damage due to diabetic retinopathy, loss of sensation or pain due to diabetes neuropathy, and liver damage from non-alcoholic steatohepatitis.

Type 2 diabetes is usually first treated by increasing physical activity, decreasing carbohydrate intake, and losing 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 usual next step, if necessary, is treatment with oral antidiabetic 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 cause mortality and stroke (UK Prospective Diabetes Study Group, 1998). 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.

III. Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of 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 profusion 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.

IV. Other types

There are several rare causes of diabetes mellitus that do not fit into type 1, type 2, or gestational diabetes; attempts to classify them remain controversial. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also be 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. The ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in (1999).

1.4 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 (weeks or months) in type 1 diabetes, particularly in children. However, in type 2 diabetes the symptoms develop much more slowly and may be subtle or completely absent. Type 1 diabetes may also cause weight loss (despite normal or increased eating) and irreducible fatigue. These symptoms can also manifest in type 2 diabetes in patients whose diabetes is poorly controlled.
When the glucose concentration in the blood is raised beyond the 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 the reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells, 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. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change whereas type 2 is generally more gradual, but should still be suspected.

Patients (usually with type 1 diabetes) may also present with diabetic 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 Diabetic ketoacidosis, coma may follow, progressing to death. DKA is a medical emergency and requires hospital admission.

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.

1.5 DIAGNOSIS

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following (World Health Organisation, 1999).
- Fasting plasma glucose level at or above 126 mg/dL (7.0 mmol/l).
- Plasma glucose at or above 200 mg/dL (11.1 mmol/l) two hours after a 75 g oral glucose load as in a glucose tolerance test.
- Random plasma glucose at or above 200 mg/dL (11.1 mmol/l).

A positive result, in the absence of clinical symptoms of diabetes, should be confirmed by another of the above-listed methods on a different day. Most physicians prefer to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete. According to the current definition, two fasting glucose measurements above 126 mg/dL (7.0 mmol/l) is considered diagnostic for diabetes mellitus.

Patients with fasting glucose levels between 110 and 125 mg/dL (6.1 and 7.0 mmol/l) are considered to have impaired fasting glycemia. Patients with plasma glucose at or above 140 mg/dL or 7.8 mmol/l two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these, two pre-diabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.

While not used for diagnosis, an elevated level of glucose irreversibly bound to hemoglobin (termed glycosylated hemoglobin or HbA1c) of 6.0% or higher (the 2003 revised U.S. standard) is considered abnormal by most labs; HbA1c is primarily used as a treatment-tracking test reflecting average blood glucose levels over the preceding 90 days (approximately). However, some physicians may order this test at the time of diagnosis to track changes over time. The current recommended goal for HbA1c in patients with diabetes is (<7.0%), which is considered good glycemic control, although some guidelines are stricter (<6.5%). People with diabetes who have HbA1c levels within this range have a significantly lower incidence of complications from diabetes, including retinopathy and diabetic nephropathy (Genuth, 2006; Sniderman et al., 2007).
1.6 SCREENING

Diabetes screening is recommended for many people at various stages of life, and for those with any of several risk factors. The screening test varies according to circumstances and local policy, and may be a random blood glucose test, a fasting blood glucose test, a blood glucose test two hours after 75 g of glucose, or an even more formal glucose tolerance test. Many healthcare providers recommend universal screening for adults at age 40 or 50, and often periodically thereafter. Earlier screening is typically recommended for those with risk factors such as obesity, family history of diabetes, high-risk ethnicity (Mestizo/Hispanic, Native American, Afro-Caribbean, Pacific Island, and South Asian ancestry) (Seidell, 2000; Lee et al., 2007).

1.7 TREATMENT OF DIABETES

The most important goal in diabetes is to keep blood glucose as normal as possible. Since it usually goes up after eating, and down after exercise, coping with it sensibly is often complex, and usually takes care and thought. And treatment differs between Type 1 and Type 2. People with Type 1 are treated with insulin. People with Type 2 usually begin with diet, exercise, and weight loss, perhaps moving to pills (and sometimes insulin).

Education is important for both types of diabetes. Diabetics must learn about diet. They learn how to estimate and keep track of how much carbohydrate, protein, and fat are in different foods. They plan their meals to have the right amount of carbohydrates, proteins, and fats. Patients with Type 1 may decide how much insulin to take before a meal based on how much they will eat.

Diabetics must also be careful about exercise. Exercise is important to stay healthy. But too hard or too long exercise may cause hypoglycemia. So diabetics must also carefully plan exercise like they plan meals.
In addition to controlling blood glucose other treatments may be needed. Diabetics often have blood vessel diseases, so it is important to pay attention to other diseases which may affect blood vessels. In people with diabetes, treating high blood pressure (hypertension) and high cholesterol is even more important than usually. Both of these diseases damage blood vessels. The treatment goals can change for diabetics. For instance, in people without diabetes, blood pressure should be 140/90 or less. In diabetics it should be 130/80 or less.

1.8 TREATMENT AND MANAGEMENT

Diabetes mellitus is currently a chronic disease, without a cure, and medical emphasis must necessarily be on managing/avoiding possible short-term as well as long-term diabetes-related problems. There is an exceptionally important role for patient education, dietetic support, sensible exercise, self glucose monitoring, with the goal of keeping both short-term blood glucose levels, and long term levels as well, within acceptable bounds. Careful control is needed to reduce the risk of long term complications. This can be achieved with combinations of diet, exercise and weight loss (type 2), various oral diabetic drugs (type 2 only), and insulin use (type 1 and increasingly for type 2 not responding to oral medication). In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications should be undertaken to control blood pressure (Adler, 2000) and cholesterol by exercising more, smoking cessation, consuming an appropriate diet, wearing diabetic socks, and if necessary, taking any of several drugs to reduced pressure.

1.9 DIET AN IMPORTANT FACTOR

A person suffering from diabetes should follow a prudent diet to help keep their blood sugar levels under control. Diet recommended for diabetes is based on foods high in complex carbohydrates, rich in fibers and low in sugar and fat. A diabetic should eat meals regularly. Eat more of starchy, fibrous foods such as beans, peas, whole meal bread, lentils, etc.
Eat plenty of fruits and vegetables as these are a natural source of fibers and vitamins. Fruits like rose apple and jamun are recommended for diabetics. Vegetables like bitter gourd's (Karela / Momordica charantia) anti-diabetic properties have already been practiced in Ayurveda; some other vegetables recommended are drumstick and bimbi. The curry-leaf tree (Murraya koenigii) is one of the traditional Indian plants with reputed benefit in diabetes.

1.10. HERBAL FORMULATION: Tribals in Madhya Pradesh use many kinds of herbs to cure Shakkar Ki Bimari (Diabetes). Tribals perform various healing methods to cure several disorders. A common formulation for curing diabetes is mentioned below.

1.11. COMBINATION OF HERBS: Annona squamosa, Gymnema sylvestre, Tinospora cordifolia, Azadirachta indica, Emblica officinalis, Curcuma longa, Trigonella foenum-graecum and Aegle marmelos.

Tiwari and Rao (2002) have reviewed the state of research in this field in a recent issue of Current Science. The phytochemicals identified from traditional medicinal plants are presenting an exciting opportunity for the development of new types of therapeutics. This has accelerated the global effort to harness and harvest those medicinal plants that bear a substantial amount of potential phytochemicals showing multiple beneficial effects in combating diabetes and diabetes-related complications.

2. ALCOHOL

Alcohol use is related to wide range of physical, mental and social harms (Abel, 1997). Most health Professionals agrees that alcohol affects practically every organ in the human body. Alcohol consumption was linked to more than 60 disease conditions in a series of recent meta-analyses (Single et al., 1999; Ridolfo and Stevenson, 2001). Alcoholism is a serious problem for any age group that can have pathological effect on several important
systems of the body, eg: Central vascular system, Central nervous system, Liver, Kidney function and Cognitive function. It is generally accepted that excessive alcohol consumption can induce dramatic changes in the physiological and biochemical processes of the whole organism and in the cells (Clemens and Jerrells, 2004; Poschl and Seitz, 2004; Oba et al., 2005).

Alcohol has been implicated in the genesis of liver disease. Both its consumption and metabolism promote the production of inflammatory mediators that result in hepatotoxicity and fibrogenesis. With time, this leads to progressively severe liver injury and, eventually, causes cirrhosis (Diehl, 1998). Toxic substances generated during the metabolism of alcohol in the liver may contribute to the development of alcoholic liver disease (ALD). These substances include highly reactive molecules that can damage vital cell components through oxidation (Fernandez-Checha et al., 1997; Ishii et al., 1997). Oxidative stress is well recognized to be a key step in the pathogenesis of ethanol-associated liver injury (Fernandez-Checha et al., 1997).

2.1 METABOLISM OF ALCOHOL (Metabolic pathways of Alcohol)

Most of the alcohol that people drink is metabolized in the liver. The metabolism of ethanol within the body has been investigated and identification of the pathway is useful for the purpose of further investigation. Alcohol induced oxidative stress is linked to the metabolism of ethanol. More than 90% of ingested ethanol is metabolized in the body to acetaldehyde and acetate. Three metabolic pathways of ethanol have been described in the human body so far (Zima et al., 2001). These three distinct enzymatic pathways of ethanol in the hepatocyte are located in different subcellular compartments (Jelski et al., 1999; Temel et al., 2002).

Enzymatic Pathways

i) Alcohol dehydrogenase (ADH) pathway of cytosol or the soluble fraction of the cell.
ii) The Microsomal Ethanol Oxidizing System (MEOS) located in the endoplasmic reticulum and

iii) Catalase (CAT) located in the peroxisomes.

i) Alcohol Dehydrogenase (ADH)

The major pathway for alcohol metabolism involves the enzyme alcohol dehydrogenase (ADH). This enzyme converts alcohol to acetaldehyde with NAD as a hydrogen acceptor through a chemical process called oxidation in the cell cytosol of the liver. In this reaction hydrogen is transferred from substrate to the co-factor NAD, converting it to its reduced form NADH (Lieber, 1996). Acetaldehyde is highly toxic to the body, even in low concentrations. Normally, however, acetaldehyde is rapidly metabolized to acetate by the enzyme aldehyde dehydrogenase (ALDH). Most of the acetate travels through the blood stream to other parts of the body, where it can enter other metabolic cycles that produce energy for useful molecules. The useful biological role of both ADH and ALDH is to metabolize vitamin A (Cunningham and Bailey, 2001).

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\text{CH}_3\text{CH}_2\text{OH} + \text{NAD} \rightarrow \text{CH}_3\text{CHO} + \text{NADH}^+ + \text{H}^+
\]

ii) Microsomal Ethanol Oxidizing System (MEOS)

The Microsomal Ethanol Oxidizing system (MEOS) is an alternate pathway for alcohol metabolism in the liver. Microsomal enzymes belong to a family of proteins called cytochromes. Some cytochromes, located in a cellular substructure called the endoplasmic reticulum, detoxify harmful substances that enter the body.

The MEOS oxidizes alcohol to acetaldehyde by means of a cytochrome called P450 2E1, or CYP2E1, which is found in the endoplasmic reticulum of liver cells. Normally functioning at a low level, CYP2E1 is stimulated to a higher by the presence of alcohol. Thus, the MEOS becomes
increasingly important as alcohol consumption becomes heavier and more chronic (Maher, 1997). Ethanol can increase liver concentration of CYP2E1 up to ten folds. The induction of CYP2E1 by ethanol may be a significant contribution to alcohol induced liver disease. This induction is associated with proliferation of endoplasmic reticulum, which is accompanied by increased oxidation of NADPH with resulting H$_2$O$_2$ generation. The activated CYP2E1 by ethanol is one of the main metabolic pathway for ethanol which is responsible for the production of oxidative damage in hepatocytes (Tanaka et al., 2000).

Increased generation of oxygen and ethanol derived free radicals occurs at the microsomal levels, especially during the action of the ethanol inducible cytochrome P450 2E1. In addition, the 2E1 induction contributes to the well known lipid peroxidation associated with alcohol liver injury (Lieber, 1996). Lipid peroxidation and superoxide production correlate with the amount of cytochrome P450 2E1. MEOS aggravates the oxidative stress directly as well as indirectly by impairing the defense systems (Temel et al., 2002).

$$\text{CH}_3\text{CH}_2\text{OH} + \text{NADPH} + \text{H}^+ \xrightarrow{\text{Catalase (CAT)}} \text{CH}_3\text{CHO} + \text{NADP}^+ + 2\text{H}_2\text{O}$$

As a third route of ethanol metabolism, catalase plays a role. Catalase located in the peroxisomes of liver and in other cells. Catalase metabolizes a small amount of ethanol when sufficient hydrogen peroxide (H$_2$O$_2$) is available without requiring NAD as a cofactor (Husain and Somani, 1997a; Jelski et al., 1999). The catalase contribute might be enhanced if sufficient amount of H$_2$O$_2$ becomes available through the β-oxidation of fatty acids in the peroxisomes. Peroxisomal β-oxidation was observed only in the absence of ADH activity (Lieber, 1996 and Temel et al., 2002). All three of these pathways produce specific metabolites and toxic substances, and all three,
results in production of acetaldehyde, a highly reactive metabolite and disrupts the antioxidant system.

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\text{CH}_3\text{CH}_2\text{OH} + \text{H}_2\text{O}_2 \rightarrow \text{CH}_3\text{CHO} + 2\text{H}_2\text{O}
\]

2.2 ACETALDEHYDE (CH\textsubscript{3}CHO) AND ITS TOXICITY

Acetaldehyde, the primary metabolic product of alcohol in the liver, appears to be a key generator of free radicals. Acetaldehyde is then further metabolized in mitochondria by the enzyme aldehyde dehydrogenase (ALDH) to acetic acid (CH\textsubscript{3}COOH), which can be metabolized into carbon dioxide (CO\textsubscript{2}) and water (H\textsubscript{2}O) with a release of energy. The mitochondrial form of acetaldehyde dehydrogenase plays an important role in maintaining the low concentration of acetaldehyde in the hepatic tissue (Cunningham and Bailey, 2001; Das et al., 2005). But acetaldehyde is not always rapidly metabolized into less toxic compounds. Acetaldehyde can promote membrane damage and can stimulate the synthesis of collagen to form scar tissue, because of its reactivity. The alcoholics find the flushing, headache, nausea, vomiting and other side effects to be strong disincentive for further ethanol ingestion.

\[
\text{CH}_3\text{CHO} + \text{NAD} \rightarrow \text{CH}_3\text{CHOH} + \text{NAD}^+ + \text{H}^+
\]

The toxicity of acetaldehyde is due, in part, to its capacity to form protein adducts, resulting in antibody production, enzyme inactivation and DNA repair. It is also associated with a sticking impairment of the capacity of the liver to utilize oxygen (Lieber, 1996). Acetaldehyde, which escapes immediate conversion to acetic acid, can bind to cystein, a constituent of the antioxidant peptide glutathione (GSH), further compromising liver mitochondrial function with oxidative damage. Acetaldehyde released into the bloodstream can drift to other organs notably the brain where it can damage protein and DNA as well as cause lipid peroxidation in membranes.
2.3 ADDUCTS FORMATION

Chronic alcoholism is associated with degenerative and inflammatory changes in many organs, including the liver, brain, kidney, heart, skeletal muscle, stomach and pancreas (Brooks, 1997). The toxic effects have been shown to be directly due to ethanol and its oxidation products. One among the various cellular mechanisms of ethanol toxicity is the alteration in membrane structure and function. Ethanol interacts with the cellular constituents causing profound changes in their structure, organization and functions. Alteration in lipid components and ion-channels by ethanol can cause changes in membrane function by altering its fluidity (Rubin and Rottenberg, 1982).
Introduction

Most of the alcohol a person ingests is eliminated from the body via a series of chemical reactions in the liver that are collectively referred to as oxidative metabolism. Because the liver is one of the organs that most commonly exhibits alcohol-induced damage, researchers have attributed many of the disturbances in liver structure and function frequently seen in alcoholics to the products of alcohol metabolism (Lieber, 1988; Tuma and Sorrell, 1995). The most important enzyme involved in the breakdown of alcohol is called alcohol dehydrogenase, which converts alcohol into acetaldehyde, a highly reactive and toxic molecule that may play a crucial role in alcohol-related liver damage.

Another enzyme that can mediate the initial step of alcohol metabolism is cytochrome P450 2E1. The chemical reaction promoted by this enzyme also results in the formation of acetaldehyde, as well as in the production of highly reactive oxygen-containing molecules called oxygen radicals, including the hydroxyethyl radical (HER). Excessive production of oxygen radicals and/or a concurrent deficiency of molecules that can eliminate these radicals (i.e., antioxidants) creates a condition in the cell known as oxidative stress, which can lead to cell death. Furthermore, oxygen radicals can interact with fat (i.e., lipid) molecules in the cell membranes in a process called lipid peroxidation, which in turn results in the generation of additional reactive molecules similar to acetaldehyde, especially malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) (Niemela, 1999; Cederbaum, 2001).

Because acetaldehyde and the lipid peroxide-derived aldehydes (i.e., MDA and HNE) are chemically reactive, they can interact with proteins and other complex molecules to form modified molecules known as adducts. The formation of these aldehyde-protein adducts is believed to be a key event in the development of alcohol-induced liver injury (Tuma and Sorrell, 1995; Niemela, 2001; Tuma, 2002).
As mentioned above, alcohol degradation using both alcohol dehydrogenase and cytochrome P450 2E1 generates reactive compounds that can bind to proteins and form adducts (see the figure: 2). Numerous studies have reported that a variety of protein adducts are formed in the liver as a result of alcohol consumption and degradation. The major reactive molecules participating in adduct formation appear to be those that are chemically known as aldehydes, specifically acetaldehyde, MDA, and HNE (Tuma and Sorrell, 1995; Niemela, 2001).
The formation of acetaldehyde–protein adducts has received the most attention from researchers to date (Tuma and Sorrell, 1995; Worrall and Thiele, 2001). Acetaldehyde can react with proteins in the body to form both unstable adducts, which are immediately converted into other compounds, and stable adducts, which remain in the cell for a certain length of time. Proteins are made up of approximately 20 different building blocks (i.e., amino acids). Researchers have found that acetaldehyde interacts with specific amino acids, particularly lysine, during adduct formation. Although investigators also have identified the chemical group – a, so called amino group1– with, which acetaldehyde interacts, the exact chemical structures of the stable adducts have not yet been resolved. (1 An amino group is a structural characteristic of all amino acids.)

The lipid peroxide–derived aldehyde, MDA and HNE, also can react with proteins, generating a variety of adducts (Esterbauer et al., 1991; Worrall and Thiele, 2001). MDA, like acetaldehyde, reacts mainly with amino groups found in proteins and forms a variety of diverse adducts, complicating the analysis of the exact processes occurring during MDA–protein adduct formation. 4-hydroxy-2-nonenal (HNE) can react with various amino acids in proteins but appears to interact primarily with the amino acids lysine, cysteine, and histidine to form relatively stable HNE–protein adducts.

(ii) Formation of Mixed (Hybrid) Adducts

Each of the aldehydes discussed here can form adducts with proteins on its own. During alcohol metabolism in the liver, however, the aldehydes coexist in the cells and may influence each other’s reactivity with proteins. For example, researchers have found that MDA and acetaldehyde react with proteins in a synergistic manner (Tuma et al., 1996; Tuma, 2002). This means that the presence of both aldehydes strikingly increases each aldehyde’s binding to proteins, generating mixed (i.e., hybrid) adducts that clearly differ from the adducts formed by either aldehyde alone. These composite MDA–acetaldehyde–protein adducts, called mixed MDA–acetaldehyde–protein
adducts (MAA), consist of two major components whose structures have been determined and that contain the amino acid lysine: (1) a relatively stable compound containing two molecules of MDA and one molecule of acetaldehyde; and (2) a compound containing one molecule of MDA and one molecule of acetaldehyde, which appears to serve as a precursor for the more stable adduct.

(iii) Adduct Formation and Its Role in Liver Injury

Although the formation of adducts in the liver during alcohol consumption has been well established, more information is needed concerning the effects of these adducts on liver cell function and the role they play in liver injury. Recent research in this area has provided some interesting and exciting information on the link between adduct formation and liver dysfunction and injury. These findings may represent a first step in the development of therapeutic interventions that can interfere with adduct formation and its consequences and thereby help reduce the risk of ALD.

One line of evidence concerns the locations of adduct formation and alcohol-related tissue damage in the liver. As mentioned in the previous section, acetaldehyde adducts form primarily in the perivenous region of the liver, which is also the region where alcoholic liver injury starts and predominates, thus supporting the hypothesis that acetaldehyde adducts may contribute to alcoholic liver disease. Moreover, acetaldehyde adducts are evident in the early phase of ALD, and in advanced liver disease they are found in the same areas that show evidence of inflammation and scar tissue formation (i.e., fibrosis). MDA adducts are found at the same sites as (i.e., colocalize with) acetaldehyde adducts in areas where changes in tissue structure (i.e., histological changes) occur in alcoholic liver disease (Niemela, 1999; 2001). Additional studies using a specially bred type of small pig (i.e., micropigs) as a model system for the development of alcoholic liver disease reported a progressive accumulation of acetaldehyde, MDA, and HNE adducts after prolonged alcohol intake, which coincided with progressive liver
injury (Halsted et al., 1993; Niemela et al., 1995). Moreover, acetaldehyde and MDA adducts, which increased after alcohol feeding, colocalized with the sites of collagen deposits, a characteristic step in scar tissue formation that occurs prior to fibrosis. Thus, these findings indicate a link between acetaldehyde and MDA adducts and the subsequent development of fibrosis in the perivenous region.

Researchers have identified several mechanisms through which various adducts could contribute to liver damage. As mentioned earlier, aldehydes interact primarily with the amino acid lysine. Thus, aldehydes particularly interfere with the functions of those proteins that carry a lysine residue at a location in the protein that is critical to the protein's function (Tuma and Sorrell, 1995). Examples of such proteins include the lysine-dependent enzymes, the regulatory protein calmodulin, and the cytoskeletal protein tubulin. Acetaldehyde–tubulin adducts appear to be especially important and relevant to alcohol–induced liver injury. Studies have shown that modification of only 5 percent of the individual molecules of a certain type of tubulin (i.e., α–tubulin) by acetaldehyde leads to complete inhibition of tubulin assembly into microtubules (Tuma et al., 1991; Tuma and Sorrell, 1995). Impaired microtubule function likely accounts for the observed defects in protein secretion and other protein transport pathways in the liver that result from chronic alcohol consumption (Tuma et al., 1991; Tuma and Sorrell, 1995). This altered microtubule function also could lead to a considerable disorganization of the hepatocytes that is characterized by various structural changes and which could progress to more severe liver damage in alcohol abusers. Investigators have described impaired function of numerous proteins other than tubulin by adduct formation; however, the role of these adducts in liver dysfunction and injury remains to be established.

2.4 ALCOHOL INDUCED LIVER

A substantial amount of evidence indicates that alcoholic liver disease develops when alcohol alters the cellular environment of the liver, thereby
initiating abnormal interactions among various types of liver cells. According to one prominent hypothesis, alcohol causes changes to the walls of the intestine, which allows a harmful bacterial product called endotoxin to pass into the blood more readily (Tsukamoto and Kaplowitz, 1996). As a result, endotoxin levels in the blood and tissues rise. The body responds to this increase in endotoxin by launching a coordinated immune response. For example, high endotoxin levels in the liver cause immune cells residing in the liver (Kupffer cells) to release signaling molecules (i.e. cytokines) as well as other compounds (e.g., prostaglandins) that result in a stepped-up inflammatory response. Cytokines and prostaglandins, in turn, increase the metabolic activities of liver cells, especially the hepatocytes, which account for approximately 90 percent of the liver cell mass. When their metabolism increases, the cells require more oxygen and fuel (nutrients) to keep pace with this increased metabolic demand. Oxygen is required for many biochemical reactions in the cell, and the breakdown of nutrients provides the energy needed for these reactions. In addition, the breakdown of alcohol itself, which occurs primarily in the hepatocytes, increases the liver’s need for oxygen.

Under normal circumstances the blood supplies enough oxygen to the liver, but if hepatocytes use up more oxygen because of the breakdown of alcohol, oxygen deficits (i.e., hypoxia) can develop in some liver areas. Hypoxia, in turn, may impede the liver cells’ ability to produce an energy-rich molecule called adenosine triphosphate (ATP), which is generated during the breakdown of nutrients and supplies energy needed for numerous biochemical reactions. Sufficiently high levels of ATP are essential to the survival of all cells; reduced ATP levels in the liver are one factor contributing to liver cell death and may contribute to development of alcoholic cirrhosis.

(i). Effects of Alcohol Consumption on Oxygen Use in the Liver

Alcohol consumption can increase the liver cell’s use of oxygen both indirectly and directly. The indirect pathway is associated with the alcohol—
induced activation of immune cells (Kupffer cells) that reside in the liver. When Kupffer cells become activated, they release various signaling and stimulatory molecules, including prostaglandin E2. This molecule can stimulate the metabolic activity of the hepatocytes. This metabolic activity consists of breaking down and synthesizing many essential molecules and cell components, and the chemical reactions involved in these processes frequently involve oxygen molecules (i.e., oxidation and reduction reactions). Thus, more active metabolism in the liver increases the need for oxygen. Animal studies have yielded results consistent with this scenario, showing that oxygen use in the liver increases after both acute and chronic alcohol administration (Videla et al., 1973; Yuki and Thurman, 1980; Arteel et al., 1996).

In addition to these indirect effects, alcohol directly enhances the liver’s oxygen use through its own breakdown in the hepatocytes. Alcohol can be broken down with the help of several enzyme systems, including alcohol dehydrogenase, the cytochrome P450 system, and the fatty acid–catalase system (Cunningham and Bailey, 2001). [Alcohol dehydrogenase is located in the fluid filling the cell (i.e., the cytosol), the cytochrome P450 system is sequestered within tubular structures in the cell called the endoplasmic reticulum, and the fatty acid–catalase system is located in cell structures called peroxisomes]. Each of these systems oxidizes alcohol - that is, the chemical reaction involved uses oxygen (O₂), or removes electrons from the alcohol molecule or its degradation products, or both (see figure 1) of these three systems, the alcohol dehydrogenase system breaks down most of the alcohol, particularly after moderate alcohol use.

The alcohol–related increase in the liver’s use of oxygen exacerbates the normal differences in oxygen levels found within each of the basic structures, or lobules, of the liver (Junqueira et al., 1998). The entire liver consists of many thousands of these lobules, each of which is made up of
hundreds of hepatocytes and other types of cells (see figure 3). Each lobule exhibits the same pattern of blood flow: Nutrient- and oxygen-rich blood enters the liver from the portal vein and hepatic artery and is distributed to all the lobules. Within each lobule, the blood flows past the hepatocytes through small channels called sinusoids before exiting the lobule through the hepatic venule, a small vein located in the center of each lobule. As a result, hepatocytes located near where the blood enters the lobule—that is, close to the portal vein and hepatic artery (i.e., the periportal hepatocytes)—are exposed to the most nutrient- and oxygen-rich blood. Liver cells closer to where the blood exits the lobule at the hepatic venule (i.e., perivenous hepatocytes) are exposed to blood containing less oxygen because much of the oxygen and nutrients already has been extracted from the blood by other hepatocytes. Thus, even under normal metabolic conditions—that is, in the absence of alcohol—oxygen levels vary in different regions of the liver lobule, with high concentrations in the periportal cells and lower levels in the perivenous hepatocytes (see figure 4).

**Figure 3:** The structure of the liver's functional units, or lobules. Blood enters the lobules through branches of the portal vein and hepatic artery, then flows through small channels called sinusoids that are lined with primary liver cells (i.e., hepatocytes). The hepatocytes remove toxic substances, including alcohol, from the blood, which then exits the lobule through the central vein (i.e., the hepatic venule).

**SOURCE:** Adapted from Ross et al. 1995.
When alcohol is consumed and subsequently broken down in the liver, the oxidation reactions involved lead to even lower concentrations than normal in the perivenous region of the lobule (Sato et al., 1983; Arkel et al., 1996). The same region also is the first to show liver cell death after chronic alcohol consumption (Ishak et al., 1991), suggesting that an oxygen deficit in this region may be a risk factor for the development of alcoholic liver disease.

3. DIABETES – ALCOHOL

Chronic excessive consumption of alcohol (Ethanol) may lead to deleterious upon many organs and metabolism (Gatti et al., 1993; Xu et al., 1998; Farren and tipton, 1999). However, moderate intake of alcohol was reported to be beneficial in many diseases, including diabetes mellitus (Klastsky et al., 1992; Goldberg et al., 1977). Alcohol enhances insulin
sensitivity in type 2 diabetes (Eagles and Martin, 1998; Weil, 1998). Numerous studies have demonstrated a J-shaped relationship between alcohol consumption and mortality in the general population, with the lowest risks for mortality observed with light to moderate alcohol consumption (Camargo et al., 1997; Hoffmeister et al., 1999; Dawson, 2000).

Consumption of alcoholic beverages is the leading cause of severe hypoglycemic coma and deaths (White et al., 1993; Criqui and Golomb, 1999; Koppes et al., 2005). It has been established that alcohol interferes with glycemic control primarily by inhibiting glucogenesis through an effect of redox state of the liver and hepatic glucose production, and reducing the mobilization of carbohydrates during hypoglycemia (Yki-Jarvien et al., 1988; Avogaro et al., 1993). The diabetogenic effects of alcohol include its contribution to excess intake and obesity, induction of Pancreatitis, disturbance of carbohydrate and glucose metabolism and impairment of liver function (Manolio et al., 1990; Perry et al., 1998). The complications include diabetic ketoacidosis, hyperosmolar coma, infection and diabetic retinopathy, amputation, chronic micro vascular complications, including, peripheral neuropathy, nephropathy, and erectile dysfunction, and chronic macro vascular complications, including coronary heart disease, cerebral vascular disease, and peripheral vascular disease (Moss et al., 1992; Andrea et al., 2004).

This most likely takes place in the liver, as fasting triglycerides levels reflect endogenous hepatic triglyceride synthesis (Anonymous, 2000). Fatty deposition of liver cells from alcohol, caused by increased lipogenesis and decreased oxidation of free fatty acids, is thought to proceed the development of hepatic fibrosis and subsequent cirrhosis among heavy alcohol drinkers (Balkau et al., 1991). Steatosis (Fatty liver) correlates with liver enzymes increased by alcohol consumption (e.g. aspartate aminotransferase) and also with fasting blood glucose and serum triglycerides.
It has been reported previously that large amounts of alcohol decrease insulin mediated glucose uptake and that is the reason alcoholics have decreased glucose tolerance (Yki-Jarvinen and Nikkila, 1985). This finding may be due to toxic effect of alcohol acting directly on pancreatic islet cells, or to inhibition of insulin secretion and increase in insulin resistance (Shelmet et al., 1988). Ethanol 2, 3-butanediol and 1, 2-propanediol, the metabolites of ethanol, are potent inhibitors of basal and insulin-stimulated adipocyte metabolism in vitro (Lomeo et al., 1988). This effect may be relevant to the pathogenesis of high incidence of type 2 diabetes in heavy drinkers. Moderate or trivial alcohol consumption was associated with a significant risk reduction for the prevalence of Proteinuria, peripheral neuropathy, stroke, angina, hypertension and amputation.

I. Free radicals or Reactive Oxygen Species (ROS)

One factor that has been suggested as playing a central role in many pathways of alcohol-induced damage, and which has been the focus of much research, is the excessive generation of molecules called free radicals, which can result in a state called oxidative stress. Particularly important are the actions of a class of oxygen-containing free radicals known as reactive oxygen species (ROS). ROS can damage or cause complete degradation (i.e., peroxidation) of essential complex molecules in the cells, including fat molecules (i.e., lipids), proteins, and DNA.

A free radical is an atom, molecule, or compound that is highly unstable because of its atomic or molecular structure (i.e., the distribution of electrons within the molecule). As a result, free radicals are very reactive as they attempt to pair up with other molecules, atoms, or even individual electrons to create a stable compound.

One chemical element frequently involved in free radical formation is oxygen. Molecular oxygen (O₂) is essential for cell function because it plays a
pivotal role in a series of biochemical reactions occurring in the respiratory chain, which is responsible for most of the production of adenosine triphosphate (ATP), which provides the energy required for a multitude of cellular reactions and functions.

The respiratory chain, which takes place in membrane-enclosed cell structures called mitochondria, an electron and a proton ($H^+$) are removed from a helper molecule (i.e., cofactor) called reduced nicotinamide adenine dinucleotide (NADH). The electron is transferred to the first component of the respiratory chain, and the proton is released into the surrounding fluid. Chemically speaking, NADH is oxidized to NAD$^+$ in this reaction, whereas the respiratory chain, component that accepts the electron is reduced. The NAD$^+$ subsequently can be used again to accept new hydrogen atoms that are generated during the metabolism of sugars (e.g., glucose) and other nutrients. The reduced respiratory chain component, in turn, passes the electron on to other molecules in the respiratory chain until it is finally transferred to O$_2$, which then interacts with protons in cells to generate water. This series of electron transfer reactions generates sufficient energy to produce several molecules of ATP for each electron that passes through the respiratory chain.

Molecular oxygen can accept a total of four electrons, one at a time, and the corresponding number of protons to generate two molecules of water. During this process, different oxygen radicals are successively formed as intermediate products, including superoxide anion ($O_2^-$); peroxide ($O_2$), which normally exists in cells as hydrogen peroxide (H$_2$O$_2$); and the hydroxyl radical ($OH^-$). Superoxide, peroxide, and the hydroxyl radical are considered the primary ROS and have sparked major research on the role of free radicals in biology and medicine. However, because they are unstable and rapidly react with additional electrons and protons, most of these ROS are converted to water before they can damage cells. It has been estimated that only about 2
to 3 percent of the O₂ consumed by the respiratory chain is converted to ROS (Chance et al., 1979). Nevertheless, the toxic effects of oxygen in biological systems - such as the breakdown (i.e., oxidation) of lipids, inactivation of enzymes, introduction of changes (i.e., mutations) in the DNA, and destruction of cell membranes and, ultimately, cells - are attributable to the reduction of O₂ to ROS (De Groot, 1994; Nakazawa et al., 1996; Toykuni, 1999).

Table. 1. Different types of free radicals and their defence system

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Type of free radical or oxidants</th>
<th>Defence systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Superoxide anion (O₂⁻⁻)</td>
<td>Superoxide dismutase</td>
</tr>
<tr>
<td>2.</td>
<td>Hydroxide radical (OH)</td>
<td>(SOD), Mn-SOD, Cu, Zn- SOD</td>
</tr>
<tr>
<td>3.</td>
<td>Peroxy radical (ROO)</td>
<td>Tocopherols, Ubiquinone Carotenoids</td>
</tr>
<tr>
<td>4.</td>
<td>Singlet oxygen (O₂)</td>
<td>Catalase, Se-gluthione peroxidase (GPx)</td>
</tr>
<tr>
<td>5.</td>
<td>Hydrogen peroxide (H₂O₂)</td>
<td>Se-gluthione peroxide (GPx), Glutathione</td>
</tr>
<tr>
<td>6.</td>
<td>Hydro peroxides (ROO)</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Transition metals (Fe²⁺, Cu⁺⁺)</td>
<td>Reductase (GR chelators)</td>
</tr>
</tbody>
</table>

II. Protection against ROS Toxicity

Because ROS production is a naturally occurring process, a variety of enzymatic and nonenzymatic mechanisms have evolved to protect cells against ROS (Yu, 1994). At least some of these mechanisms are impaired after long-term alcohol consumption and may therefore contribute to damage to the liver and other organs.

Reactive oxygen species (ROS) are generated spontaneously in the living cell during metabolism. Antioxidants act as a major defense against ROS mediated toxicity by protecting membrane and cytosolic compounds. These compounds exhibit a wide spectrum of activity against toxicants/carcinogens and have the capacity to intervene in carcinogen metabolism. The
antioxidant defenses include natural and synthetic antioxidants and the antioxidant enzymes present in the biological system (Sies, 1991). Plant products exert their antioxidant effect by quenching free radicals. By reducing exposure to free radicals and by increasing intake of antioxidant nutrients it is possible to reduce the risk due to free radical health problems associated with the aging process, cancer and atherosclerosis (Ames et al., 1993).

4. ANTIOXIDANT DEFENSE MECHANISM

About a decade ago, Scientists from various countries signed in Saas Fee (Switzerland), a declaration on the significance of antioxidants in preventive medicine. This declaration stated that antioxidant nutrients may have major significance in the prevention of number of diseases. These include cardiovascular and cerebro-vascular diseases, some forms of cancer, and several other disorders, many of which may be age-related (Nordmann, 1994).

Animal tissues are constantly coping with high reactive oxygen species, such as super oxide anion, hydroxyl radicals, hydrogen peroxides and other radicals generating during numerous metabolic reactions (Castillo et al., 1992; Cabre et al., 2000). The generation of small amount of free radicals appears to have an important biological function, but oxidative stress is caused by excess production of reactive oxygen species (Halliwell, 1997; Giordano, 2005). To protect the cell and organ system of the body against reactive oxygen species, mammal cells are well equipped with highly sophisticated and complex defense mechanisms known as antioxidant defense mechanism. Antioxidant defense systems protect cellular homeostasis from oxidative disruption by reactive molecules generated through the reduction of molecular oxygen. The efficient functionality of these mechanisms requires the concerted action of the individual systems. These defense systems also have to be in concert with the components responsible for the repair processes of oxidatively damaged molecules in order in the cell integrity (Inmaculada Bando et al., 2005).
The term antioxidant has been defined by Halliwell and Gutteridge (1989) as "any substance that delays or inhibits oxidative damage to a target molecule". Antioxidant enzymes, together with the substance that are capable of either reducing ROMs (Reactive oxygen intermediates) or preventing their formation, form a powerful reducing buffer which affects the ability of the cell to counteract the action of oxygen metabolites. All reducing agents thereby form the protective mechanisms, which maintain the lowest possible levels of Reactive oxygen intermediates (ROM) inside the cell (Helmut Sies, 1997).

Antioxidant defenses, present in all aerobic organisms include antioxidant enzymes and free radical scavengers whose function is to remove reactive oxygen species (ROS), thus protecting the functions of organisms from oxidative stress (Regoli and Principato, 1995). The sensitivity of cell to oxidants is attenuated by antioxidant defense system such as Super oxide dismutase (SOD), Catalase (CAT), Glutathione Reductase (GR), Glutathione Peroxidase (GPx), Glutathione-S-transferase (GST), Glutathione (GSH). The antioxidant defense system maintains a relatively low rate of the reactive and harmful 'OH (Ismail Celik et al., 2006).

i). Superoxide Dismutase (SOD)

SOD is the most important antioxidant enzyme because it is found virtually in all aerobic organisms. SODs are a family of metalloenzymes that converts $O_2^-$ to $H_2O_2$ according to the following reaction. The transition metal of the enzyme reacts with $O_2^-$ taking its electron. $O_2^-$ is the only known substrate for SOD (Ray and Husain, 2002; Smith et al., 2003).

$$2H_2O_2 + O_2 \rightarrow H_2O_2 + O_2$$
The superoxide dismutase (SOD) catalyzes the dismutation of two superoxide radicals into hydrogen peroxide and oxygen. The hydrogen peroxide is further oxidized by other enzymes. These enzymes obey first order reaction kinetics and the forward rate constants are almost diffusion limited. These results in a steady state concentration of superoxide in tissue that varies directly with the rate of superoxide generation and inversely with the tissue concentration of scavenging enzymes (Enghild et al., 1999). In humans, three forms of superoxide dismutases are present. SOD1 is located in the cytoplasm, SOD2 in the mitochondria and SOD3 is in extra cellular. The first is a dimer (consists of two units), while the others are tetramers (four subunits). SOD1 and SOD3 contain copper and zinc, while SOD2 has manganese in its reactive centre. The genes are located on chromosomes 21, 6 and 4, respectively (21q22.1, 6q25.3 and 4p15.3-p15.1). Simply-stated, SOD out competes damaging reactions of superoxide anion, thus protecting the cell from superoxide toxicity. The reaction of superoxide with non-radicals is spin forbidden. In biological systems, this means its main reactions are with itself (dismutation) or with another biological radical such as nitric oxide (NO).

SOD is biologically necessary because superoxide reacts even faster with certain targets such as NO radical, which makes peroxynitrite. Similarly, the dismutation rate is second order with respect to initial superoxide concentration. In contrast, the reaction of superoxide with SOD is first order with respect to superoxide concentration. Superoxide is one of the main reactive oxygen species in the cell and as such, SOD serves a key antioxidant role. The physiological importance of SODs is illustrated by the severe pathologies evident in mice genetically engineered to lack these enzymes. Mice lacking SOD2 die several days after birth, amidst massive oxidative stress (Li et al., 1995). Mice lacking SOD1 develop a wide range of pathologies, including hepatocellular carcinoma, an acceleration of age-related muscle mass loss, and an earlier incidence of cataracts and a reduced lifespan (Elchuri et al., 2005; Muller et al., 2006).
(ii) Catalase

Catalase was first noticed by Louis Jacques Thénard in 1811. In 1900 Oscar Loew was the first to give it the name catalase. Catalase is a heme containing redox enzyme. Although the tissue distribution of catalase is widespread, the level of activity varies not only between tissues but within the cell itself. Catalase is present predominantly in the peroxisomes (Microbodies) in liver and kidney and also in the micro peroxisomes of other tissues. It has 240,000 molecular weight in yeast, 220,000 in human blood. Catalase is a tetramer of four polypeptide chains, each over 500 amino acids long, (Boon et al., 2007). It contains four porphyrin heme (iron) groups which allow the enzyme to react with the hydrogen peroxide. Most of the in vitro studies suggested that this antioxidant function as promotion/ transformation inhibitor carcinogenesis.

Catalase catalyses the decomposition of hydrogen peroxide to water (H₂O) and oxygen (O₂).

\[ 2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2 \]

H₂O₂ is a powerful oxidizing agent and is potentially damaging to the cells. By preventing excessive H₂O₂ build up, catalase allows important cellular processes which produce H₂O₂ as a byproduct to take place safely.

Catalase performs a very elegant 'reshuffling' of toxic compounds, i.e. peroxidative reaction, a second family of reactions catalysed by catalase, possibilities for the compound RH₂ include phenols, formic acid, formaldehyde and alcohols.

\[ \text{H}_2\text{O}_2 + \text{RH}_2 \rightarrow 2\text{H}_2\text{O} + \text{R} \]
(iii) Glutathione peroxidase

Glutathione peroxidase is the general name of an enzyme family with peroxidase activity whose main biological role is to protect the organism from oxidative damage. The biochemical function of glutathione peroxidase is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water. Based on selenium (Se) dependency, GSH-Px can be divided into two forms: Se dependent GSH-Px (Se-GSH-Px) and Se-independent GSH-Px (Non-Se GSH-Px). GSH-Px is a molecule with four selenocysteine amino acid residues. The enzyme is located in both the cytosol (70%) and mitochondria (30%) of various tissues. As the integrity of the cellular and subcellular membranes depends heavily on glutathione peroxidase, the antioxidative protective system of glutathione peroxidase itself depends heavily on the presence of selenium.

Glutathione peroxidase enzyme is a well-known first line of defense against oxidative stress, which in turn requires glutathione as a cofactor. Glutathione peroxidase is considered the major detoxification enzyme for \( \text{H}_2\text{O}_2 \). Among the many functions of glutathione, one main function is it involves in the generation of the nucleotide precursors of DNA via the reduction of ribonucleotides to deoxyribonucleotides (Meister and Anderson, 1991).

(iv) Glutathione Reductase

Although glutathione reductase (GR) is not directly involved in removing ROS, it serves an important role in converting GSSG to GSH, thereby maintaining GSH-Px catalytic function and a reduced intracellular redox status (Halliwell and Gutteridge, 1989). Glutathione reductase is an ancillary enzyme to limit the amounts of ROS via its reduction of GSSG in the presence of an adequate supply of NADPH thus, the ration of GSH/GSSG is maintained at a high level so that the cell maintains the capacity to combat oxidative stress.
(v) Glutathione-S-transferase

The mammalian GST super-family comprises cytosolic dimeric isoenzymes of 45–55 kDa size which have been assigned to at least four generic classes: \( \alpha, \mu, \phi \) and \( \theta \). (Beckett and Hayes, 1992) Glutathione-S-transferase (GST) family of enzymes comprises a long list of cytosolic, mitochondrial, and microsomal proteins which are capable of multiple reactions with a multitude of substrates, both endogenous and xenobiotic. These enzymes catalyze the conjugation of a molecule of GSH to an electrophilic or other reactive species (Jakoby and Habig, 1980; Kodavanti, 1999). This activity is useful in the detoxification of endogenous compounds such as peroxidised lipids as well as the metabolism of xenobiotics. As well as their enzymatic activities, GSTs may also bind toxins and function as transport proteins. Because of this, an early term for GSTs was “ligandin” (Litwack et al., 1971). GST catalyzes the conjugation of GSH with a wide variety of organic compounds, including certain species of hydroperoxides thereby shares peroxidase activity with GSH-Px (Habig et al., 1974). Unlike GSH-Px, GST activity is not affected by selenium deficiency, however GSH concentration is critical for the enzyme’s catalytic function (Ji and Leeuwenburgh, 1996).

(vi) Glutathione

Glutathione (GSH) is a naturally occurring protein that protects every cell, tissue, and organ from toxic free radicals and disease. It is a tripeptide of three amino acids - glycine, glutamate (glutamic acid), and cysteine. These precursors are necessary for the manufacture of glutathione within the cells. Glutathione is a tripeptide (\( \gamma \)-glutamyl cysteinyl glycine) the most abundant thiol present in all mammalian cells. Glutathione is the major cellular reductant (Chance et al., 1979) present in milli molar quantities in many cell
types. Under normal conditions, the ratio of GSH to GSSG is high, and a drop in this ratio is considered indicative of oxidative stress. Glutathione is generally considered an intracellular antioxidant, but recent studies indicate that it may be released into the circulation, presumably as a defense against ROS generated by inflammatory cells, or during ischemia reperfusion (Liu et al., 1994). GSH reduces hydrogen and organic peroxides via a reaction catalyzed by GPx; it serves as a scavenger of OH· and singlet oxygen (O₂⁻) (Halliwell and Gutteridge, 1989); and GSH is believed to reduce tocopherol radicals, either directly or indirectly by reducing DHA radical there by prevent lipid peroxidation (Niki et al., 1985). By donating its proton, GSH is oxidized to GSSG, which can be reduced back to GSH by glutathione reductase (GR), a flavon-containing enzyme using NADPH as the reducing power.

Antioxidants such as certain enzymes, vitamins, and other substances protect cells against oxidation (Fernandez-Checha et al., 1997; Ishii et al., 1997; Das et al., 2005) and an imbalance between oxidants and antioxidants can lead to oxidative stress, characterized by escalating cell damage (Fernandez-Checha et al., 1997). Oxidative stress and associated cellular injury promote inflammation. Antioxidants could have beneficial effects in reducing the incidence of ethanol-induced changes in cellular lipids, proteins and nucleic acids. They could act by reducing free radical production (e.g. chelators of redox-active iron derivatives), trapping free radicals themselves, interrupting the peroxidation process or reinforcing the natural antioxidant defence (Nordman, 1994; Das et al., 2005).

5. GINGER

The antioxidant enzymes in the tissues can effectively scavenge free radicals that are generated during xenobiotic metabolism (Percival, 1998). Since ancient times spices have been added to different types of food to improve the flavour. Natural products and their active principles as sources
for new drug discovery and treatment of diseases have attracted attention in recent years. Herbs and spices are generally considered safe and proved to be effective against various human ailments and their medicinal uses have been gradually increasing in developed countries. Now it is well known that spices possess antioxidant activity and prevent oxidation of lipids in foodstuffs. Kikusaki and Nakatani, (1993) reported that chemical constituents like gingerols and shogaols present in ginger exhibited strong antioxidative activity. Sekiwa Kubota and Kobayashi, (2000) reported that novel glucosides related to gingerdiol from ginger has antioxidative activity using the linoleic acid model system and by their DPPH radical scavenging ability. Gingerol, the pungent factor in ginger oleoresin, inhibited phospholipid peroxidation induced by the FeCl₃ ascorbate system (Aeschbach et al., 1994). These in vitro observations prompted us to investigate if ginger consumption through diet can improve the in vivo antioxidant status.

*Zingiber officinale* (Roscoe; Zingiberaceae) is widely used around the world in foods as a spice. For centuries, it has been an important ingredient in Chinese, Ayurvedic and Tibb-Unani herbal medicines for the treatment of cataract, rheumatism, nervous diseases, gingivitis, toothache, asthma, stroke, constipation and diabetes (Awang, 1992; Wang and Wang, 2005; Tapsell et al., 2006). Ginger also used to treat a number of diseased conditions including headache, cold, arthritis, postoperative nausea and vomiting, motion sickness, and reduces symptoms in patients with nausea of pregnancy (Phillips et al., 1993; Arfeen et al., 1995; Grant and Lutz, 2000; Vutyavanich et al., 2001).

Several reviews have appeared in the literature about this plant, and this may reflect the popularity of the subject and its common use as a spice and a medicinal plant (Afzal et al., 2001; Chrubasik et al., 2005). Many reviews have been devoted to specific aspects of ginger’s actions. For example, the review of Grzanna et al., (2005) was on the use of ginger as an
anti-inflammatory agent, while that of Shukla and Singh (2007) dealt with the cancer prevention properties of the crude drug. The actions of ginger as a post-operative antiemetic substance were the subject of a review by Chaiyakunapruk et al., (2006). Here, the aim was to summarize the hepatoprotective activity of the ethanol extract of *Zingiber officinale* was assessed by changes in several liver biochemical parameters, using ethanol treated oxidative stress against STZ-Induced diabetic rats.

Currently there is a strong interest in the study of natural compounds with free radical scavenging capacity. Dietary antioxidants reduce free radical formation and as a consequence oxidative stress in general, by way of countering LDL oxidation and platelet aggregation and by inhibition of the synthesis of proinflammatory cytokines (Kushi et al., 1996). Lipid peroxidation in tissues results in the production and propagation of free radical reactions primarily involving membrane polyunsaturated fatty acids (PUFAs). This has been implicated in the pathogenesis of numerous diseases including atherosclerosis, diabetes, cancer and rheumatoid arthritis as well as in drug associated toxicity and aging (Halliwell and Gutteridge, 1989).

### 5.1 GINGER CHEMICAL PROPERTIES

The constituents of ginger are numerous and vary depending on the place of origin and whether the rhizomes are fresh or dry. The pungency of fresh ginger is due to primarily the gingerols, which are a homologous series of phenols. The most abundant is [6]-gingerol, although smaller quantities of other gingerols with different chain lengths are also present. The pungency of dry ginger mainly results from shogaols (for example, [6]-shogaol), which are dehydrated forms of gingerols. Shogaols are formed from the corresponding gingerol during thermal processing (Wohlmuth et al., 2005).

Jolad et al., (2004) examined organically-grown fresh ginger and identified 63 compounds, of which 31 had been previously reported as constituents of ginger and 20 were hitherto unknown compounds. The
identified components included gingerols, shogaols, 3-dihydroshogaols, paradols, dihydroparadols, acetyl derivatives of gingerols, gingerdiols, mono- and diacetyl derivatives of gingerdiols, 1-dehydrogingerdiones, diarylheptanoids, and methyl ether derivatives of some of these compounds.

In addition to [6]-gingerol, [4]-, [7]-, [8]-, and [10]-gingerol were identified, as well as methyl [4]-gingerol and methyl [8]-gingerol. [4]-, [6]-, [8]-, [10] - and [12]-Shogaol were characterized, as were methyl [4]-, methyl [6] - and methyl [8]-shogaol. Paradols are 5-deoxygingerols. [6]-Paradol, along with [7]-, [8]-, [9]-, [10]-, [11]-, and [13] - paradols were detected in the fresh ginger, as was methyl [6]-paradol.

**Structures of Gingerol, Shogaol and Zingerone**

Ma et al., (2004) reported the isolation of seven previously unknown diarylheptanoids from the ethanol extract of Chinese ginger, along with 25 known compounds, including 8 diarylheptanoids. An example of one of the novel compounds reported is (3S, 5S)-3,5-diacetoxy-1,7-bis (4-hydroxyl-3-ethoxyphenyl) heptane. In a later paper, Wei et al., (2005) reported significant cytotoxic and apoptotic activities against human promyelocytic leukemia cells of several ginger constituents, including some diarylheptanoids and gingerol-related compounds.

1. Acetoxyl groups at the 3- and/or 5 positions of the side chain.
2. The appropriate longer alkyl side-chain length.
3. The ortho-diphenoxyl functionality on the aromatic ring.
4. The α, β-unsaturated ketone moiety in the side chain.
Introduction

For the analysis of the major constituents of ginger ([6]-, [8]-, [10]-gingerol and [6]-shogaol) in dietary supplements, spices, teas and beverages containing the crude drug, a high-performance liquid chromatographic procedure has recently been published by Schwertner and Rios (2007).

(i) Anti-oxidant actions of ginger

Several authors have shown that ginger is endowed with strong in vitro and in vivo antioxidant properties. The antioxidant action of ginger has been proposed as one of the major possible mechanisms for the protective actions of the plant against toxicity and lethality of radiation (Jagetia et al., 2003; Haksar et al., 2006) and a number of toxic agents such as carbon tetrachloride and cisplatin (Amin and Hamza, 2006; Yemitan and Izegbu, 2006), and as an anti-ulcer drug (Siddaraju and Dharmesh, 2007).

Recently, it has been shown that [6]-gingerol is endowed with strong antioxidant action both in vivo and in vitro, in addition to strong anti-inflammatory and anti-apoptotic actions (Kim et al., 2007).

6. OBJECTIVES OF THE PRESENT STUDY

The reviewed literature reveals the state of diabetes, alcohol (ethanol) and their effect on antioxidant, oxidative enzymes systems. The people in the world in general who consume alcohol inspite of having diabetes. When we study such alcoholic diabetic patients, the production of free radicals and to counter these free radicals antioxidant enzymes systems alterations would be expected in the study. The therapeutic role of ginger on alcoholic condition and also on diabetic condition independently with reference to antioxidant, lipid peroxidation have been reported extensively. However the role of ginger in alcoholic-diabetic combined condition has not been reported so far.

Hence in the present investigation the therapeutic role of ginger on carbohydrates metabolic profiles, energy metabolic and antioxidant enzymes in alcohol treated diabetic rats has taken for study.
7. PROGRAM OF THE PRESENT STUDY

Several authors reported that STZ-induced diabetic rats showed reduced activities of antioxidant enzymes, oxidative enzymes and enhanced the lipid peroxidation levels. Alcohol itself induced decreased antioxidant, oxidative and increased the amino transferases activities and lipid peroxidation levels. Keeping in view of this above literature and background, the author has planned the following program of work to elucidate the role of ginger in combined alcoholic-diabetic condition employing rat as an animal model.

1. The activities of SOD, CAT, GPx, GR, GST and level of GSH were assayed to know the impact of diabetes alcoholic conditions.

2. To elucidate the energy metabolic enzymes regulation due to the effect of ethanol, diabetic (STZ), Diabetic + Ethanol, and Diabetic + ethanol + ginger, the oxidative enzymes such as GDH, MDH, G6PDH and ICDH were assayed to understand how they are regulated the body system.

3. The extent of lipid peroxidation was assessed by measuring the fate of free radical production with reference to ethanol intoxication, diabetic condition, alcohol treatment in diabetic condition and ginger treatment in alcohol treated diabetic condition.

4. The enzyme activities of AAT, ALAT were estimated in ethanol treated, diabetic, and ethanol treated diabetic rats with ginger treatment and also branched chain amino transferases like LAT, ILAT and VAT were estimated, in the present study to know the alterations in aminotransferases under the above stress condition.

5. Blood glucose and body weight levels were also measured to know the state of regulation of diabetes under treated and untreated condition.
6. Histopathological studies were also carried out studied in all the above experimental groups to assess pathological situation of the liver.

The results obtained in the current investigation have been described in detail in the light of available recent reports to understand the response of antioxidant system and related oxidative enzyme system in liver tissue of male albino rats during ethanol, ethanol treatment in diabetic condition and ginger treatment in ethanol treated diabetic rats.