Chapter 4

Histopathology
The architectural dynamics of a tissue are very essential for maintaining the tissue integrity and for effective physiological, biochemical functions. The cellular and sub-cellular constituents of tissue in terms of size, shape and number play an important role in the physiological and metabolic functions. Under physiological conditions the diversified structural and biophysicochemical components of the cell act and maintain a dynamic synergistic equilibrium (anatomophysiological synergism) determined and regulated in an orderly manner by intrinsic mechanism in conjunction with the environmental condition of the cell. In abnormal condition of a structural, metabolic or functional character, reversible changes (histometabolic dysergia) take place. However, if such endogenous or exogenous phenomena are repeated or perpetuated with out control and exceed the physiologic endurance, then eventually disorganization or dissolution of the integrated anatomophysiological synergistic equilibrium follows with consequent irreversible changes of structural (degeneration), metabolic (histometabolic pathergia) and functional (dysfunction or paralysis) character (Minckler, 1971) takes place in cell. Therefore, the histological structure of tissue in an animal has a profound influence on its function.
Histopathology

Histology, the study of microanatomy of specific tissues, has been successfully employed as a diagnostic tool in medical and veterinary sciences since the first cellular investigations carried out in nineteenth century (Virchow, 1858). Histology is a structural science and serves to compliment the knowledge gained from the anatomy, physiology and pathology and it gives insight into the functioning of tissues and organs. The knowledge of the histology is useful to distinguish normal cells from abnormal or diseased ones, which helps in diagnosis of many diseases (Majumdar, 1980).

Liver pathology

The liver is the target organ in the body, ordinarily weighing about 3.5 lbs and measuring about 8-9 inches in length and 4-5 inches in width. It is located in the abdominal area of the body, just beneath the diaphragm of the stomach. The liver is connected to the diaphragm and to the anterior walls of the abdomen by five ligaments, one of which is a fibrous cord resulting from the atrophy of the umbilical vein of intrauterine life (Kilmer and Diana). Blood vessels connected to the liver include the hepatic artery, the portal vein, and the hepatic veins, as well as many capillaries. The liver is composed of lobules, chains of hepatic cells held together by connective tissues. Each lobule contains blood vessels in close connection with secretary cells and ducts by which secretions are carried away. Blood comes to the liver from the stomach, spleen, pancreas and the intestines. Flow of blood through the liver is estimated to be about 800-1000 ml/min. The greater portion of which comes from the portal vein. The liver can hold up to a pint of blood at a time, an amount equivalent to about 13% of the body’s total blood supply.

Liver is metabolically the most complex organ in the body and serves numerous vital functions. These include energy balance regulation, blood protein synthesis and immune modulation. Efficient liver function is
necessary for the processing and excretion of endotoxic and exotoxic chemicals (hormones, drugs, chemicals etc.) which are commonly referred to as “xenobiotic” chemicals. Inefficient liver function can lead to “metabolic poisoning” which a nondescript term is referring to the build up within cells, tissues and organs of metabolites which have not been processed by the liver and excreted. These metabolites alter the pH gradient and electrolyte profile within cells and can serve as competitive enzyme inhibitors that ultimately interrupt effective bioenergetics within the cell. The symptoms of metabolic poisoning at the elevated level are reflective of poor energy dynamics and include fatigue, hypotonia and brain biochemical disturbances. Recent studies have reported a relation between impaired detoxification capability, mitochondrial dysfunctions and chronic fatigue syndrome (CFS). These reports suggest that oxidative damage due to mitochondria and the detoxification process is itself a fundamental mechanism in the development of CFS.

The major metabolic functions of the liver can be summarized into several major categories:

**Carbohydrate Metabolism**

It is critical for all animals to maintain concentration of glucose in blood within a narrow, normal range. Maintenance of normal blood glucose levels over both short (hours) and long (days to week) periods of time is one particularly important function of the liver. Hepatocytes house many different metabolic pathways and employ dozens of enzymes that are alternatively turned on or off depending on whether blood levels of glucose are rising or falling out of the normal range. Two important examples of these abilities are:

- Excess glucose entering the blood after a meal is rapidly taken up by the liver and sequestered as the large polymer, glycogen (a process
called glycogenesis). Later, when blood concentration of glucose begin to decline, the liver activates other pathways which lead to depolymerization of glycogen (glycogenolysis) and export of glucose back into the blood for transport to all other tissues.

➢ When hepatic glycogen reserves become exhausted, as occurs when an animal has not eaten for several hours, the hepatocytes don’t give up. They first recognize the problem and activate additional groups of enzymes that begin synthesizing glucose out of such things as amino acids and non-hexose carbohydrates (gluconeogenesis). The ability of the liver to synthesize this “new” glucose is of monumental importance to carnivores, which at least in the wild, have diets virtually devoid of starch.

**Lipid metabolism**

Few aspects of lipid metabolism are unique to the liver, but many are carried out predominantly by the liver. Major examples of the role of the liver in lipid metabolism include:

➢ The liver is extremely active in oxidizing triglycerides to produce energy. The liver breaks down many more fatty acids that the hepatocytes need, and export large quantities of acetoacetate into blood where it can be picked up and readily metabolized by other tissues.

➢ Bulks of the lipoproteins are synthesized in the liver.

➢ The liver is the major site for converting excess carbohydrates and proteins into fatty acids and triglyceride, which are then exported and stored in adipose tissue.

➢ The liver synthesizes large quantities of cholesterol and phospholipids. Some of this is packaged with lipoproteins and made available to the rest of the body. The remainder is excreted in bile as cholesterol or after conversion to bile acids.
Protein metabolism

The most critical aspects of protein metabolism that occur in the liver are:

- Deamination and transamination of amino acids, followed by conversion of the non-nitrogenous part of those molecules to glucose or lipids.
- Several of the enzymes used in these pathways (for example, alanine and Aspartate aminotransferases) are commonly assayed in serum to assess liver damage.
- Removal of ammonia from the body by synthesis of urea. Ammonia is very toxic and if not rapidly and efficiently removed from the circulation, will result in central nervous system disease. A frequent cause of such hepatic encephalopathy in dogs and cats are malformations of the blood supply to the liver called portosystemic shunts.
- Synthesis of non-essential amino acids.
- Hepatocytes are responsible for synthesis of most of the plasma proteins. Albumin, the major plasma protein, is synthesized almost exclusively by the liver. Also, the liver synthesizes many of the clotting factors necessary for blood coagulation.

Alcohol-induced oxidative stress in the liver cells plays a major role in the development of alcoholic liver disease. This condition results from several processes related to alcohol metabolism: (1). Changes in the NAD/NADH ratio resulting from alcohol breakdown by alcohol dehydrogenase. (2). Production of ROS during alcohol metabolism by the microsomal ethanol-oxidizing system. (3). Depletion of GSH and (4). Decreased activity of antioxidant enzymes (Nordmann, 1994). Increased ROS production and decreased antioxidant potential, among other harmful effects, cause lipid peroxidation which leads to damage to liver cells.
Alcoholism is a serious problem for any age group that can have pathological effect on several important systems of the body, eg: CNS, CVS, Liver, Kidney function and Cognitive function.

Insulin dependent diabetes mellitus (IDDM) and Noninsulin dependent diabetes mellitus is characterized by a series of complications that affects many organs. Diabetes is known to produce substantial changes in intracellular metabolism in most tissues, including liver (Satav and katyare, 2004; Sajad et al., 2008). Our histological findings (See slide: 4) are in agreement with the degenerative structural changes reported to occur in liver tissue as a result of insulin depletion (Das et al., 1996). Because of the importance of the liver in carbohydrate, protein and lipid metabolism, the present study is designed to investigate liver histopathological changes possibly occurring in diabetic rats.

Histological Changes, Results and Discussion:

The liver tissue of the saline control, ginger treatment, diabetic, ethanol treated, ethanol treated diabetic and ethanol treated diabetic condition with ginger treatment rats were examined for structural changes under the light microscope using hemotoxylin and eosin staining.

Histological examinations of the liver by light microscope are figured in plate 1, 2, 3, 4, 5, 6.

Control rat livers had normal histology with normal hepatocellular architecture with central vein (CV). Normal hepatocytes (NH) have pink eosinophilic cytoplasm without any inclusions and with mostly central single nuclei (N). These cells have well-defined cell borders, are polygonal, and are arranged in sheets. Hepatic sinusoids (HS) were not dilated; there were no areas of hemorrhage or fibrosis.
In ginger treated rats, normal hepatocytes (NH), with prominent nucleus (N) were observed and normal central vein (CV), Dilatation hepatic Sinusoids (DHS) was also seen.

In ethanol treated rats, Mild degeneration of hepatic cytes (MDH). Dilatation hepatic Sinusoids (DHS) was observed. Mild congestion central vein (MCCV) and disturbed architecture of hepatic cards was also observed.

In Diabetic (STZ-induced) rats, Dilatation hepatic Sinusoids (DHS), degenerated hepatocytes (DGH) and Loss of Architecture of hepatic cards was observed. Congestion central vein (CCV) and have seen severe damage compare to alcohol treatment.

In ethanol treated diabetic rats Necrosis of hepatosytes (NH), Zigzag of hepatic cards (ZHC), and destruction of central vein (DCV), complete disruption of hepatic parenchyma were observed. Dilatation hepatic Sinusoids (DHS) was also observed.

In ethanol treated diabetic rats with ginger treatment, Mild degeneration of hepatic cytes (MDH), Savior Dilatation of Central Vain (SDCV) and the arrangement of hepatic cards in normal way and hepatic Sinusoids (HS) appears to be restored.

From the results obtained 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; Oba et al., 2005). The damage to the liver after ethanol ingestion is a well known phenomenon, and the obvious sign of hepatic injury is the leakage of cellular enzymes into plasma (Baldi et al., 1993). The increased levels of serum enzymes such as AAT and ALAT have been observed in alcohol-administered rats, which indicate the increased permeability, damage and/or necrosis of hepatocytes (Goldberg and Watts, 1965).
These results indicate that diabetes mellitus produces degenerative changes in liver, probably, due to increased lipid peroxidation. It has been suggested that lipid peroxidation of biological membranes is often associated with the development of liver damage (Casini et al., 1997). It also has been suggested that the rabbit liver microsomes, particularly the xenobiotic transforming enzyme system, are very sensitive to lipid peroxidation (Mezes et al., 1996). Thus, the oxidative decompositions of liver occurring because of the increased lipid peroxidation could be the reason for the hepatocellular degeneration (Turkdogan et al., 2001). Therefore we thought that liver degeneration of diabetic rats was probably due to increased lipid peroxidation.

Itoh et al., (1979) have considered that fatty infiltration of liver as a precursor of cirrhosis in diabetic patients. Falchuk et al., (1980) showed hepatic fatty steatosis and pericentral fibrosis in diabetic patients. They recognized hepatocytes were markedly swollen and suggested that these abnormalities may represent an intermediate lesion between fatty steatosis and cirrhosis. Nanji et al., (1986) mentioned that the damage was mainly to the plasma membrane of the hepatocytes and could be attributed to the elevation in aspartate aminotransferases in patients with fatty infiltrations. The activities of alkaline phosphatase, aspartate aminotransferases, alanine aminotransferases were increased significantly in STZ-diabetic rats.

Satav and Katyara, (2004) studied the effect of STZ-induced diabetes on the oxidative energy metabolism in rat liver mitochondria and found reduction in respiratory activity. Lukivskaya et al., (2007) related the liver pathological changes in alloxan diabetic rats to the mitochondrial abnormalities. Many authors suggested that liver mitochondrial dysfunction in diabetes is related to the oxidative stress enhanced in diabetic animals (Kucharska, 2007) and patients (Bukker et al., 2000).
The results showed that ginger can able to do scavenging free radical by its potent antioxidants. These results were also clearly established from the data how the ginger reduced the level of malondialdehyde acting as lipid peroxidation marker and increased the activity of antioxidant enzyme, Superoxide dismutase. Similarly Siddaraju and Dharmesh (2007) reported that ginger – free phenolic and ginger hydrolysed phenolic fractions exhibited strong antioxidant properties. Amin and Hamza, (2006) demonstrated that Zingiber officinale increased the activities of testicular antioxidant enzymes such as, Superoxide dismutase, glutathione and catalase and reduced level of malondialdehyde.

Histopathological changes in ethanol treated diabetic rat liver shows dilation of blood vessels, congestion in the lobules, some hemorrhagic coagulative foci in hepatic parenchyma, and infiltration of mixed inflammatory cells around the necrotic hepatocytes. In this study, there was a pronounced restoration of the normal hepatic architecture after the treatment of ethanol treated diabetic rats with ginger extract.
Plate 1:

Fig (A): Photo micro graph of Normal control (NC) rat liver showing (H&E, 10X)

1. Normal architecture with central vein (CV),
2. Normal hepatocytes (NH) with
3. Mostly central single nuclei (N) and
4. Hepatic sinusoids (HS) were not dilated.

Fig (B): Photo micro graph of Ginger treated (Gt) rat liver showing (H&E, 10X)

1. Normal hepatocytes (NH)
2. Prominent nucleus (N)
3. Normal central vein (CV)
4. Dilatation hepatic Sinusoids (DHS) was also seen.
Plate 2:

Fig (A): Photo micro graph of Ethanol treated (Et) rat liver showing (H&E, 10X)

1. Mild degeneration of hepatic cytes (MDH)
2. Dilatation hepatic Sinusoids (DHS)
3. Mild congestion central vein (MCCV) was observed.

Fig (B): Photo micro graph of Diabetic (Di) liver showing (H&E, 10X)

1. Dilatation hepatic Sinusoids (DHS)
2. Degenerated hepatocytes (DGH)
3. Congestion central vein (CCV)
Plate 3:

Fig (A): Photo micro graph of Ethanol treated diabetic (Di + Et) rat liver showing (H&E, 10X)

1. Necrosis of hepatocytes (NH)
2. Zigzag of hepatic cards (ZHC)
3. Destruction of central vein (DCV)
4. Dilatation hepatic Sinusoids (DHS) was also observed

Fig (B): Photo micro graph of Diabetic + Ethanol + Ginger treated (Di + Et + Gt) rat liver showing (H&E, 10X)

1. Mild degeneration of hepatic cytes (MDH)
2. Savior Dilatation of Central Vain (SDCV)
3. Hepatic Sinusoids (HS).
Plate – 3:

Fig: (A)

Fig: (B)
In the present investigation the antioxidant properties of *Gingiber officinale* and Hepatoprotective role of ginger against ethanol treated oxidative stress under STZ induced diabetes has been studied by selecting albino rat as an experimental model.

The survey of literature revealed that the reports regarding the effects of Ethanol, STZ induced Diabetes and ginger on the antioxidant defense system, oxidative metabolic enzyme system, lipid peroxidation levels and amino transferases activities in the liver tissue of male albino rat are inconclusive and inadequate, particularly the interative effect of Ethanol, Diabetes and effect of ginger in ethanol treated diabetic rats. This field of research has to be explored in view of the beneficial aspects of ginger to alcoholic diabetic patients. In the World around 6-8% of the people who are having diabetes are alcoholics. Low percent of alcohol to diabetic patients are beneficial, where as high percent of alcohol is dangerous and harmful. Diabetic patients are taking alcohol every day and they are eating spicy foods. However the role of ginger in alcoholic-diabetic condition is not reported. Hence, in the present investigation the impact of ginger in ethanol treated diabetic rat has been studied with selected antioxidant enzymes, lipid peroxidation levels, oxidative enzymes, amino transferases enzyme activities and Histopathology.
Wistar strain male albino rats (6 months) were maintained in the animal house at 27°C with photoperiod of 12 hours light and 12 hours darkness, were used in the present study. They were maintained in clean polypropylene cages and fed with standard rat pellet diet (Hindustan lever Ltd., Mumbai) and water ad libitum.

Diabetes was induced by the method of Rakieten et al. (1963) and ethanol administration was followed as per the protocols given by Somani and Husain (1997b). The animals were divided into 6 groups. Each group consists of six animals and the division of groups is as follows.

- **Group I**: Normal Control (NC)
- **Group II**: Ginger treatment (Gt)
- **Group III**: Ethanol treatment (Et)
- **Group IV**: Diabetic Control (Di)
- **Group V**: Diabetic+Ethanol (Di+Et)
- **Group VI**: Diabetic+Ethanol+Ginger treatment (Di+Et+Gt)

All the animals received the treatment for a period of one month. The animals were sacrificed after 24 hours of the last day treatment by cervical dislocation. The liver tissue was excised, the tissue was washed with ice-cold saline, and immediately stored in deep freezer at -80°C for biochemical analysis. A part of the tissue was processed for histopathological studies.

The studies on selected antioxidant enzyme system, oxidative metabolic enzyme system, lipid peroxidation levels, amino transferases and histopathological changes were observed in this study as follows.

1. Blood glucose levels were increased in ethanol treated, diabetic condition and in ethanol treated diabetic rats. But in ginger treated and in ginger supplementation to ethanol treated diabetic group, blood glucose levels were decreased. This may be due to the anitdiabetic compounds present in ginger.
2. We observed body weight changes in the current investigation. In ethanol treated, ginger treated and ginger treatment in ethanol treated diabetic rats the body weight were increased. But in diabetic condition and in ethanol treated diabetic condition body weights were decreased. This may be due to mobilization of body reserves like adipose tissue or fat to meet the extra energy demands.

3. The elevated level of total protein content was observed in the liver tissue of ginger and ethanol treated diabetic rats with ginger treatment. Which may be due to decreased proteolysis and increased generation of energy by ATPases where ginger treatment enhances the ability to release energy by effective utilization of various metabolic fuels including stored ones, due to improved oxidative capacity, and enhances the oxidative phosphorylation leading to the elevation of high energy phosphate reserves, such increase in energy availability may stimulate the free amino acids for the synthesis of protein. Hence elevated level of protein content was observed.

Total protein content was decreased in the liver tissue of ethanol treated, ethanol treated diabetic rats. The diminishment of proteins suggest that ethanol toxicity in diabetic condition induces rapid degradation of proteins (which may be decreased due to protein synthesis (or) increased proteolysis) may be explained in terms of accelerated proteolytic activity. In the combination of alcohol treated diabetic rats with ginger treatment showed slight elevated total protein content, suggesting the beneficial effect of ginger under ethanol treated diabetic conditions.

4. Increased free amino acid content was observed in the liver tissue of ethanol, diabetic and ethanol treated diabetic rats which may be due to decreased rate of amino acid utilization for protein synthesis. Elevated levels of free amino acids were observed in ethanol treated diabetic rats.
which may be due to increased proteolysis (or) decreased uptake of amino acids into protein synthesis and enhanced catabolism during ethanol toxicity in diabetic condition, might be the factors responsible for elevated amino acid content in the present study. In the combination of alcohol treated diabetic rats with ginger treatment showed decreasing the total free amino acids content, suggesting the beneficial effect of ginger under ethanol treated diabetic conditions.

5. The data obtained in the current investigation on G-6-PDH showed a low activity in ethanol treated, diabetic and ethanol treatment in diabetic condition rats, which could be attributed to the reduced availability of NADPH. With ginger treatment G-6-PDH was significantly elevated indicating the active operation of HMP pathway in meeting the energy crisis and generation of reduced NADP for the detoxification of oxidative free radicals in rats. In the combination treatment i.e. ginger treatment in ethanol treated diabetic rats an up regulation of G-6-PDH activity was observed which indicate the ginger treatment may decrease the ethanol toxicity and free radicals which are produced and ethanol treated diabetic rats.

6. The decrement in NADP dependent ICDH indicates lesser involvement of TCA cycle in the oxidative reactions in ethanol treated diabetic rats. The possible reason for an increase in NADP-ICDH activity during ginger treatment is to step up energy production to meet energy demands.

7. The citric acid cycle enzyme MDH was assayed as markers of mitochondrial oxidative capacity. A disturbed oxidative metabolism was reported due to ethanol toxicity, diabetic condition and in ethanol treated diabetic condition suggests that deceleration of TCA cycle. An increase in this enzyme activity in ginger treated and in ginger treatment in ethanol treated diabetic rats reveal increased mitochondrial oxidative
potential and energy synthesis utilizing fats as substrates by ginger. However, this was restored with combination treatment i.e. ginger treatment in ethanol treated diabetic rats. Thus, it seems ginger is beneficial to restore the lost MDH activity in the combination treatment it also indicate high utilization of malate which was diminished with ethanol toxicity in diabetic condition. Thus, the up regulation of oxidative metabolism with high turn over of energy substances leads to high energy out put which is required during ginger treatment.

8. The data for the specific activity of GDH was observed significantly elevated in ginger treated group and in ginger treatment in ethanol treated diabetic condition. This elevation in activity may help in supply of more amount of a-ketoglutarate to TCA cycle to meet the energy demand due to crisis followed by ethanol treatment, diabetic condition and ethanol treatment in diabetic condition.

To be precise, the present findings on oxidative metabolic enzymes in the liver tissue showed an over all increase in all the dehydrogenase activities with ginger treatment in one month period. The data obtained clearly demonstrated that ginger treatment increases the mitochondrial activity and possible shift from anaerobic to aerobic metabolism. The elevated G-6-PDH indicates active participation of HMP pathway in meeting the energy crisis and generating NADP for detoxification of free radicals which were frequently produced by ethanol intoxication, diabetic condition and ethanol treatment in diabetic condition. The increased GDH activity with ginger treatment indicates the increased levels of GSH in liver tissue.

9. In the present study a significant decrease in the activity of SOD was observed in ethanol treatment, diabetic condition and ethanol treatment in diabetic condition. Elevation of SOD activity was observed with ginger treatment. The treatment with ginger ethanolic extract could able to elevate the SOD activity in the experimental rats suggesting that Gingiber
officinale treatment is beneficial to the animals. The elevation of SOD might be aimed at removal of superoxide anions radicals generated in ethanol treated diabetic condition.

10. Catalase, a major antioxidant enzyme, containing iron as the prosthetic group, reduces the toxic hydrogen peroxide into water and protects the cell from possible oxidative damage. Increased CAT activity in ethanol treated diabetic rats might be related to its active involvement in decomposition of hydrogen peroxide generated during dismutation of superoxide anion radicals by SOD. The up regulation of CAT activity was found with response to ginger supplementation. The combined action of SOD and CAT worked as an efficient mechanism for the removal of ROS and also enhancement of antioxidant enzyme system efficiently.

11. The ginger treatment increased the GPx activity, where as in ethanol treatment, diabetic condition and ethanol treatment in diabetic condition GPx activity was decreased. However, the combination treatment up regulated both GSH Px activities a significant manner. This indicates an active participation of the enzyme in scavenging of the hydro peroxides that are generated due to ethanol, diabetic condition and ethanol treatment in diabetic condition.

12. We observed a significant decrease in GR activity under ethanol treated diabetic condition. Up regulation of GR activity in contemporary investigation with response to ginger treatment was observed. This elevation may be due to increased Se-GPx activity.

13. GST which is known to play a central role in the biotransformation of xenobiotics including oxidative stress was observed a significant increment in all the experimental rats except ginger treated and ginger treatment in ethanol treated diabetic rats. This may be due to incline in cellular repair capacity or antioxidant status. Ginger treatment in ethanol
treated diabetic rats down regulated GST activity indicates deactivation of the enzyme in response to ginger. Since GST is an inducible enzyme, Decreased availability of GSH or the stimulation of enzyme may result in Decreased activity of GST.

14. GSH is involved in a number of cell functions such as antioxidant defense. When GSH was measured, a decrease in its concentration observed in ethanol treated, diabetic and ethanol treatment in diabetic condition. This confirms increased susceptibility to oxidative stress to toxic compounds. Elevated levels of GSH with ginger treatment is a beneficial phenomenon to counter oxidative stress by either synthesizing more GSH or increasing its uptake from extra liver tissue sources.

15. In the present study we observed the Lipid peroxidation which is an index of oxidative stress condition of the animal was measured by assaying the MDA content. We observed increased levels of MDA in ethanol, diabetic and in ethanol treated diabetic condition. This observation reveals that the hydroxyl radicals that are released may reacted with PUFAs which reflect the membrane derangement, loss of membrane fluidity and permeability that ultimately leads to tissue damage. With ginger treatment MDA levels were decreased and reversed the tissue damage to normal stage. This suggests the efficient use of antioxidants which are present in ginger by the rats, in ethanol treated diabetic condition.

In precise, the data obtained in the present investigation revealed that there is a significant elevation of all major antioxidant enzyme activities in the liver tissue with response to ginger treatment.

16. The activities of transaminases (AAT & ALAT) are increased with ethanol, diabetic and ethanol treated diabetic rats, it reflects high utilization of aspartate and alanine in oxidative pathways during ethanol treated diabetic condition. The greater increase of transaminases in the
liver result in decreased production of ammonia and urea and other consequent metabolic effects on mitochondrial structural and functional integrity which is restored and improved with ginger treatment. Hence ginger treatment countered the ethanol treated diabetics in the aminotransferases and demonstrated greater transmitting role of transaminases by reducing protein catabolism.

17. Leucine (LAT), isoleucine (ILAT) and valin (VAT) transaminase activities were high in ethanol, diabetic and ethanol treated diabetic rats, enunciating that oxidation of Leucine, isoleucine and valin was enhanced during ethanol toxicity in diabetic condition. The elevated activity levels of BCATs indicate the possible impairment in the conservation of essential amino acids and also suggest the augmented recycling of carbon skeleton of these FAAs through respective ketoacids. The elevated BCATs may also be responsible for the generation of a series of products essential for fatty acid bio-synthesis and cycle operation. Hence, with ginger treatment in ethanol treated diabetic rats all these parameters were decreased. This suggests the efficient use of antioxidants which are present in ginger by the rats, in ethanol treated diabetic condition.

18. Histopathological observations were made to elucidate relationship between lipid peroxidation and tissue damage in ethanol treated, diabetic, and in ethanol treated diabetic condition. Necrosis of hepatocytes, destruction of central vein, complete disruption of hepatic parenchyma and disturbed architecture of hepatic cards were observed in these groups. The changes noticed are quite prominent. The pathological changes in liver might be due to increased free radicals production and elevated lipid peroxidation. Where as, in ginger treated and in ginger treatment in ethanol treated diabetic rats the damages which are caused by ethanol in diabetic rats was recovered. In these groups, Savior Dilatation of Central Vain, arrangement of hepatic cards in normal way and hepatic Sinusoids appears to be restored.
19. To conclude the present findings reveals that one month treatment with selected dosage of ginger that was adopted is beneficial in countering the alterations in antioxidant enzyme system, oxidative enzymes, lipid peroxidation, and aminotransferases activities in wistar strain rats. The antioxidant defense system which plays a major role in countering the free radicals in ethanol treated diabetic rats were reversed back to normal levels when ginger is given. The oxidative enzymes also reversed back to normal control values. The changes in markers of oxidative stress which include lipid peroxidation, aminotransferases and antioxidant enzymes indicating efficient adaptative machinery of hepatic tissue in detoxification of oxygen species that are produced due to diabetes and ethanol. From this study we could draw a conclusion stating that ginger treatment to ethanol treated diabetic rats may be beneficial to improve the metabolic efficiency and thereby improve the health status. Thus ginger may be used in the formulation of herbal drugs which can be used in the treatment of diabetes. Since ginger exhibited antioxidant and antidiabetic activity, it may be clinically useful in the control of human diabetes. Thus, finally we conclude that successive studies are mandatory to establish the precise nature of ginger active constituents as well as their mechanism of action.