REPUBLIC OF TURKEY
VAN YUZUNCU YIL UNIVERSITY
INSTITUTE OF HEALTH SCIENCE

# A HISTOPATHOLOGICAL, IMMUNOHISTOCHEMICAL AND BIOCHEMICAL INVESTIGATION ON THE ANTIDIABETIC EFFECTS OF THE *PISTACIA TEREBINTHUS* IN DIABETIC RATS

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MASTER THESIS

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III

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## LIST OF ABBREVIATION

**ADA** : American Diabetes Association

**ALP** : Alkaline phosphatase

**ALT** : Alanine aminotransferase

**APCs** : antigen-presenting cells

**AST** : Aspartate transaminase

**BHT** : butylated hydroxytoluene

**CK** : Creatine Kinase

**cm** : Centimeter

**DM** : Diabetes Mellitus

**GD** : Gestational Diabetes

**IDF** : International Diabetes Federation

**IU** : International Units

**LDL** : Low-Density Lipoprotein (Cholesterol)

**mg** : milligram

**Mg** : Magnesium

**ml** : millilitre

**P. terebinthus** : *Pistacia terebinthus*

**RBCs** : Red blood cells

**SC** : Subcutaneous

**STZ** : Streptozotocin

**T1D** : Type 1 Diabetes

**T2D** : Type 2 Diabetes

**WHO** : World Health Organization

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# 1. INTRODUCTION

The term diabetes mellitus (DM) portrays a metabolic issue of numerous etiology described by chronic hyperglycemia with unsettling influences of carbohydrate, fat and protein metabolism coming about because of deformities in insulin discharge, insulin activity, or both. The impacts of diabetes mellitus incorporate long term harm, brokenness, and disappointment of different organs particularly the eyes, kidneys, nerves, heart, furthermore blood vessels (Alberti and Zimmet, 1998).

The clinical hugeness of diabetes will be frequently shown by the presences of manifestations for example, moderate recuperating of wounds or injuries (Chawla et al., 2013), dyslipidemia (Tan et al., 2011), Polyphagia, polyuria, polydipsia furthermore unexplained weight passing and will be affirmed by estimation about abnormal hyperglycemia (Luka and Mohammed, 2012; Beidokhti and Jäger, 2017). In its most extreme forms, ketoacidosis or a non-ketotic hyperosmolar state (HHS) might create and prompt stupor, unconsciousness and, Previously without compelling treatment, demise (Alberti and Zimmet, 1998).

Around the world, 382 million individuals have diabetes and the assessed figure to 2035 will be 592 million (Beidokhti and Jäger, 2017). Diabetes caused death of 1.5 million people in 2012, higher-than-ideal blood glucose caused an extra 2.2 million deaths by expanding the dangers of cardiovascular and different illnesses. 43% of deaths happen before the age of 70 years. The rate of deaths attributable from high blood glucose or diabetes that happens preceding age 70 is higher in low- also middle-income nations than in high-income nations. Generally speaking, 1 in 12 of worldwide all-cause deaths was evaluated to be attributable to diabetes in grown-ups. WHO undertakings that diabetes will be the seventh driving reason for death in 2030 (American Diabetes Association, 2016).

The two most widespread types of diabetes are type 1 diabetes (T1D) is described by penetration of the pancreas via autoreactive T cells and autoimmune devastation of pancreatic beta cells (β-cell), prompting a totally decreased secretion of insulin and type 2 diabetes (T2D) is related with impeded reaction to insulin and β-cell

brokenness causing hyperglycemia owing to disorder in carbohydrate, fat and also lipid metabolism (Yeghiazaryan et al., 2012).

Insulin resistance has long been considered the hallmark of T2D, but the natural history of diabetes depends, in large part, on the adaptation of pancreatic ß-cells to meet the increased demand for insulin that results from insulin resistance. In fact, ß-cell failure has been described as the primary determinant of whether an insulin resistant individual will progress to diabetes (Prentki et al., 2006). The long term impact on the danger of diabetes, diabetes-related macrovascular and microvascular complexities, the morbidity, and mortality of diabetes is due to the development of both macrovascular and microvascular complications (Brownlee, 2001). Macrovascular encompasses myocardial infarction, stroke, and peripheral artery disease; it is caused by atherosclerosis. Beside retinopathy, nephropathy, and neuropathy are three main microvascular complications (Blonde, 2012).

Conventional plants were utilized from antiquated circumstances as of not long ago a day to treat hypoglycemic and hyperglycemic conditions (Huxtable, 1990). There are various plants that have been demonstrated overall valuable for treatment of DM infection and known to have hypoglycemic activities (Sharma et al., 2003; Kar et al., 2006; Kumar et al., 2006). Furthermore, the quantity of these plants is more than 400 plants. Before finding of anti-diabetic medications, patients utilized therapeutic and conventional plants for the treatment of DM disease (Day et al., 1988; Rafieian-Kopaei et al., 2014). The benefits of these plants is that their items are safe in contrast to the synthetic drugs that are regarded as unsafe to human and environment (Das et al., 1999).

Plants influence glucose by means of different systems. These incorporate anticipation of insulinase action, insulin kinase exercises, and capacity of repairing pancreatic β cells (Chakravarthy et al., 1980; Bailey et al., 1989; Abdel-Moneim et al., 1999). Fibers of plants may rival the retention of starches and in this way, decrease glucose levels. (Bever et al., 1979).

*Pistacia terebinthus* known as "menengiç" in Turkey is a plant from Anacardiaceae family and used as an herbal medicine because it has a therapeutic

advantages and used for treatment of many diseases such as eczema, paralysis, renal stones, and also jaundice (Tastekin et al., 2014).

*Pistacia terebinthus* has many pharmacological activities including such as antioxidant, antimicrobial, antiviral, anticholinesterase, anti-inflammatory, antinociceptive, antidiabetic, antitumor, antihyperlipidemic, antiatherosclerotic, and hepatoprotective activities and also their beneficial effects in gastrointestinal disorders (Bozorgi et al., 2013).

This study aimed to determine the antidiabetic activity of *Pistacia terebinthus* leave extracts on histopathological and immunohistochemical changes in β-cells of streptozotocin (STZ)-induced diabetic rats and to correlate these effects with plasma glucose and insulin levels.

# 2. GENERAL INFORMATION

## 2.1. Diabetes Mellitus

Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insülin action or both (Wild et al., 2004). This disease is portrayed by chronic hyperglycemia and disorder in the digestion of proteins, lipids, and carbohydrates and coming about because of it is possible that either of insufficiency in insulin secretion and resistance to insulin (Alberti and Zimmet, 1998). The mechanism for interpreting of the cooperation between these variables is that pancreatic beta cells fail in reparations of insulin resistance, and in this manner the activity of insulin diminishes (Cavaghan et al., 2000; Nyenwe et al., 2011; Ryden et al, 2013).

Insulin is a peptide hormone produced by the pancreatic β-cells. The primary part of insulin is to control blood glucose concentrations through its anabolic activities advancing take-up and storage of glucose into peripheral tissues. Although the signs are not severe or sometimes absent in many cases they comprise recurrent urination, blurred vision, thirsty and decrease weight (American Diabetes Association, 2010). Patients with diabetes additionally display, in the hazardous example, manifestations like ketoacidosis and coma (Ryden et al., 2013).

Diabetes Mellitus was related with secondary life threatening inconveniences that in 2013 killed 5.1 million people groups around the world, and 2.8% of the populace experienced this illness all through the world. Likewise, this may increment to 5.4% by the time of 2025 (Shukla et al., 2011; Aguiree et al., 2013).

The correct reason for DM is hard to see, yet it is beginning has been consolidated to gestation, sedentary lifestyles, unwell diets, urbanization, weight, and genetic predisposition (Marieb et al., 2010; Sue Kirkman et al., 2012). DM may bring about a wide range of sicknesses, since hyperglycemia make harm eyes, nerves, kidney, veins, and commonly, renal end-arrange ailment, which is caused by acquired and hereditary deficiency in production of insulin (Modak et al., 2007).

### 2.2. History of Diabetes Mellitus

Diabetes mellitus as an illness, for example a group of symptoms, however not its pathogenesis, has been known by doctors for about 3,500 years in Egypt (Ebbell, 1937). From ancient Greek (Siphon) mean diabetes which is refers too much urination, mellitus is additionally from Greek and it signifies "honey" and it was developed from "mel" (Sodeman, 1992).

Until 1921, when Sir Frederick Grant Banting, and Charles Herbert Best repeated the work of Minkowski and Von Mering, the endocrine role of the pancreas in metabolism, and indeed the existence of insulin, was not further clarified, and went further to show they could switch prompted diabetes in dogs by giving them a concentrate from the pancreatic islets of Langerhans of healthy dog. They infuse the insulin into dogs whose pancreases have been extracted, and the dogs glucose levels go down. James Collip purifies the extract so that it can be used in humans (Banting et al., 1991).

In 1922 isolating of insulin succeeded by the Banting, Collip, and Macleod, and it was used the first time for treatment, famously saving the life of a 14-year-old patient, Leonard Thompson, who survived for a further 13 years courtesy of his insulin injections (Banting et al., 1991). Close to at 1949 Rachmiel Levine, finds that insulin works like a key, transporting glucose into cells. In 1959 Utilizing radioimmunoassay innovation, Solomon Berson, and Rosalyn Yalow, build up a technique for measuring insulin in the blood. They see that some people with diabetes still make their own insulin, and they recognize "insulin-dependent" (type 1) and "non-insulin-dependent" (type 2) diabetes (Straus and Yallow, 1977). Metformin is a biguanide that prevents glucose generation in the liver. The medication metformin becomes available in the U.S In 1995 (Bailey et al., 1996).

### 2.3. Epidemiology

DM is an ailment that is found in all societies, the range of DM is low in some areas of the world, while in some different areas the range is high, for example, in Greenland and Alaska and some other places. The most predominance of type 2

diabetes mellitus (NIDDM) is in America and India. In these nations, the predominance of DM is higher than %55 and it is the highest range on the world planet (Warron et al., 1994).

171 million from the People in 2010 suffered from diabetes in the world (Wild et al., 2004) and by 2013 increased to 382 million. This number is estimated high to 55 % by 2035 (Guariguata, 2013). As a result of the physical inactivity of people, an increase in obesity ratio and population growth and other causes that lead to DM. Environmental and genetic factors play an important role in the development of this disease in populations (Wild et al., 2004).

As per International Diabetes Federation data, the DM caused 5.1 million deaths as well as costing 548 billion (USD) in health spending only in 2013 (Guariguata, 2013). Data's from some studies revealed that the highest degree of diabetes prevalence in 2010 was in North America followed by Eastern Mediterranean and Middle East (EMME) and South Asia. India, China, USA, Russian Federation, and Brazil were in the top countries for diabetes prevalence in 2010. It is estimated that diabetes will be more prevalent in developing countries compared with developed countries in the future (Shaw et al., 2010). In the Turkish population, according to Turkish Diabetes Epidemiology Study (TURDEP) in 2002 revealed that Impaired glucose tolerance (IGT) was 6.7%, and the degree of diabetes prevalence was 7.2 % (Satman et al., 2002). While in 2011 newer data are dealing with increasing this ratio to about 8 % IGT and 13.37 % for diabetes (Buyukbese and Bakar, 2012).

### 2.4. Pathogenesis of DM

#### 2.4.1. Pathogenesis of T1DM

Recent studies estimate the evaluation of T1D associated autoimmunity in the months to years before the onset of symptomatic, also show a degree of synchronization, therefore autoimmunity plays a critical role in the evaluation of Type 1 diabetes (Kukko et al., 2005).

The disease presents to be a result of a complex interaction between the immune system, genetic predisposition, and environmental factors.T-cells are present in the

inflammatory lesion (insulitis) (Bottazzo et al., 1985). The first identified inflammatory infiltrates in pancreatic islets, which have since then become a hallmark of T1D termed ‘insulitis' (Gepts, 1965; Van-Belle et al., 2011). Patients with T1D shows the presence of immunological activity of the pancreas by histological analysis (Foulis and Stewart 1987). Current evidence suggests that initiation of type 1 diabetes requires both CD4+ and CD8+ T-cells; that auto reactive T-cells differentiate into effectors by engaging β-cell antigens on local antigen-presenting cells (APCs); that initiating CD4+ T-cells are insulin-reactive; and that CD8+ T-cells play a important role as β-cell killers (Santamaria, 2010). The immune response and the immune regulation are involved in the pathogenesis of T1D, in which cellular immunity plays a important role for the infiltration of CD4+ and CD8+ T lymphocyte, natural killer cells, B lymphocytes, dendritic cells and other immune cells take part in the harm of pancreatic β-cells, which ultimately lead to T1D (Li et al., 2014).

### 2.4.2. Pathogenesis of type 2 diabetes

The main characteristics of type 2 diabetes mellitus are insufficiency and resistance of Insulin (DeFronzo, 1999).

**Insulin insufficiency**

Reduced mass and dysfunction of beta cells are causes of insulin insufficiency (Sone and Kagawa, 2004). Pancreatic beta cell dysfunction is resulting from both glucotoxicity and lipotoxicity which mediated by hyperglycemia and lipidemia respectively (Poitout and Robertson, 2002). On the other hand, beta cell mass reduction which noticed in T2DM (Sakuraba et al., 2002) is caused by hypoglycemia-induced beta cellular apoptosis without sufficient compensatory regeneration (Koyama et al., 1998).

**Insulin resistance**

Insulin resistance is a disease that cells, tissues and systems of the body don't have the reaction to the typical amount of insulin. Type 2 diabetes comes about because of a deficient compensatory function of beta cells in insulin resistance (Bonner-Weir, 2000). In insulin safe patients, insulin is unable to attenuate hepatic glucose and to

stimulate target organs to uptake glucose from plasma for either storage or oxidation purposes (Ferrannini, 2009).

In spite of the distinctions in mechanisms of insulin resistance in various organs, the general underlying causes are fatty acid-mediated inflammation (Sears and Perry, 2015). The Most factors that adversely affect the action of Insulin are secreted in adipose tissues by free fatty acids and adipokines, which are some proteins (Pereira and Maahs, 2008). Free unsaturated fats are the primary giver, since it was realized that palmitate caused a decrease in cell insulin receptor by means of repressing quality articulation of insulin receptor proteins (Bhattacharya et al., 2007). Macrophages emit proinflammatory cytokines through inflammation. These cytokines can disturb insulin marking pathway in organs that are focused by insulin (de Luca and Olefsky, 2007; Sears and Perry, 2015). Notwithstanding cytokines, excretion of fat tissue including leptins and adiponectin contribute to impairment action of insulin (McArdle et al., 2013).

High-hazard ethnic groups for diabetes also insulin resistance and variability in risk level due to ethnicity are pieces of evidence for a genetic basis of diabetes while the exact genetic mechanism (such as gene defect ) is under study (Leahy, 2005). Moderate hereditary impacts once insulin response imperviousness need been approved, Also extreme manifestations of this illness might effect from defects for insulin response receptor because of capable gene change (Mercado et al., 2002). Notwithstanding these facts, genotype best yields An predisposition to diabetes, Furthermore natural elements assume a elementary part in the plausibility about diabetes improvement (Leahy, 2005). Relationship is posative between T2DM and some environmental factors such as physical inactivity, fatten, and smoking have been observed (Hu et al., 2001; Ferrannini, 2009).

### 2.5. Classification of Diabetes Mellitus

DM mainly are classified in to four types. They comprise (IDDM) insulin dependent diabetes mellitus which is type 1 DM, and (NIDDM) non-insulin dependent diabetes mellitus which is type 2 DM, these two types are the most popular types while

another two types are less popular, comprise gestational diabetes and genetically modified diabetes mellitus (Deopa et al., 2013).

### 2.5.1. Type 1 diabetes mellitus (insulin-dependent diabetes)

Type 1 diabetes is an immune system malady recognized by loss of insulin-delivering pancreatic β cells and this causes to β cell pulverization which is prompting finished insulin inadequacy. This kind of diabetes is generally found in kids and teenagers and at some point named by "adolescent diabetes" (Petlevski et al., 2001).

The rate of the destruction of β cells of this kind of diabetes might be transformed from a man to someone else, in a few people the destruction is fast and moderate in others, the quick destruction is mainly occurring in kids and at some point in grown-ups. The tardy destruction may happen in grown-ups and at some point may demonstrate to latest autoimmune diabetes in adults (LADA). The primary appearance of this illness in some of patients in kids and grown-ups is ketoacidosis (Ziegler et al., 1989; Zimmet et al., 1994; Humphrey et al., 1998).

In type 1 diabetes, due to metabolic acidosis, the patient’s body will fail to control of hyperglycemia and the ketoacids amassed. In these cases, diabetic may prompt unconsciousness, and even demise. Insulin is imperative for people with type 1 diabetes to avert ketoacidosis, coma and death (Norris et al., 2001; Guyton et al., 2001). An investigation in 2002 demonstrated that, conceivable reasons for insulin resistance in diabetes type 1 inciude severe metabolic decompensation, growth hormone counter regulatory during adulthood, and harm in glucose metabolism (Gortmaher et al., 1990).

The most spread condition in type 1 diabetes patients are gloom and sadness (Northam et al., 2005; Gendelman. et al., 2009). According to researchers, they discussed that there are a bigger number of patient with diabetes encounter sub-clinical diabetes-related distress than experience above-threshold psychological disorders, and this trouble may influence glycemic control more than clinical disorders (Gonzalez et al., 2011; Esbitt et al., 2013).

In 1923 Macleod and Banting received a Nobel Prize for the detection of a peptide hormone, insulin able to restore blood glucose homeostasis in persons with type

1 diabetes. What's more, they demonstrated that insulin is discharged by the ß-cells of the pancreatic islets of Langerhans which are a group of pancreatic cells, in response to increase blood glucose, and adjust tissue development, growth and entire body glucose homeostasis by adjusting protein, lipid and carbohydrate metabolism (Rosenfeld, 2002).

### 2.5.2. Type 2 diabetes mellitus (non-insulin dependent diabetes)

NIDDM is usually found in adults and its name is ‘adult diabetes’’ and it represents over 90% of all diabetes cases around the world, It is the most common type of diabetes and depends on the specific genetic factors (West, 2000; Abate et al., 2001).

Resistance to the action of insulin and disorder of insulin secretion, are the main characteristics of T2D, which is the most popular type, is mainly a result of obesity and physical inactivity in genetically predisposed people (Shojania et al., 2006). In people with this type of diabetes, blood sugar must be controlled either by diet, or with oral hypoglycemic medications or in acute cases with exogenous insulin (Brancati et al., 1996; Winkleby et al., 1998).

Type 2 diabetes creates when insulin resistance is joined by pancreatic β-cell dysfunction, which causes corresponding insulin insufficiency and hyperglycemia. Investigation of pancreatic tissue from patients with T2D explains diminished ß-cell mass and capacity (Sakuraba. et al., 2002; Butler. et al., 2003; Del Guerra. et al., 2005).

### 2.5.3. Gestational diabetes mellitus

This is the third kind of diabetes mellitus, which can cause pregnant ladies, particularly in the second trimester of pregnancy. In this type, insulin resistance is expanding bit by bit until delivery and in the most cases it vanishes quickly (Ryan et al., 1985; Ben-Haroush et al., 2003). Gestational diabetes is a carbohydrate intolerance causing hyperglycemia with a variable severity in the principal acknowledgment of pregnancy (ADA, 2007). Additionally gestational diabetes is related with both insulin resistance and harm in insulin discharge (Kuhl, 1991).

### 2.5.4. Other specific types

Other specific types of diabetes mellitus include genetic diseases of β cells, endocrinopathies, endocrine pancreatic diseases, chemical effects, infections and medicines, the immune mechanisms, and diabetic genetic syndrome (Kuzuya et al., 2001).

## 2.6. Diabetes Complications

Absence or dysfunction of insulin-creating β-cells brings about the advancement of type 1 and type 2 diabetes mellitus, individually. Diabetes can influence various organ systems in the body and after some time can prompt serious confusions (Deshpande et al., 2008). The cost per patient exponentially increments with the quantity or number of complications from 4 to 20 time the cost of a patient without complications when 1 to 4 complications are present (Kitabchi et al., 2009). Diabetes complications can be categorized to microvascular complications, which is coming about because of harm to small blood vessels and macrovascular complications which is because of harm to bigger blood vessels (Forbes et al., 2013).

Damage of the eye (retinopathy), renal system (nephropathy) and nervous system (neuropathy) are the microvascular complications. stroke, peripheral vascular disease, and cardiovascular disease are the Macrovascular complications. Peripheral vascular disease may lead to bruises or wounds that don't recuperate, gangrene, and at last to removal. These can fundamentally decrease future and personal satisfaction for patients with diabetes (ADA, 2006).

## 2.7. Role of Plants in Diabetes Mellitus

Utilization of natural drugs for the treatment of DM has been known for quite a long time (Yeh et al., 2003). for treat diabetes, more than 1200 kind of plants that have been used in the worldwide. The oral antidiabetic drugs have many side effects, for example, hypoglycemia, congestive heart failure, weight pick up and anemia (Zimmet et al., 2001; Nesto et al., 2003). Along these lines, the scan for more successful and more secure antidiabetic drugs is a critical stride towards the administration of diabetes and its complications.

The number of plants has been considered as useful for the treatment of DM everywhere throughout the world are more than about 400 plants. (Day et al., 1988). Traditional antidiabetic plants can enhance blood glucose control, and they totally could be indicated for treatment of disorders that identified with diabetes, additionally they were used to adjust the diabetes before identification of insulin. Plants that are utilized for treatment of diabetes successfully avert insulin resistance and oxidative anxiety (Gray et al., 1997; Perez-Gutierrez et al., 2012).

Many investigations have clarified the best plants that have antidiabetic action. They showed that the water solvent of plant components were able to increase transportation of glucose and metabolism in muscle and to empower discharge of insulin (Gallagher et al., 2003).

Generally, traditional herbal medications have been appeared to have fruitful pharmacological activity, for example, for the situation with metformin, detached from Galega officinalis (Bailey, 1988). Customary plants have been utilized as a cure for diabetes for quite a while before the presentation of current medication. The hypoglycemic impact of some herbal extracts has been confirmed in human and animal models of diabetes. As of late, consideration has been centered around regular items particularly food plants, as a possible source of more potent and more secure antidiabetic medication (Cheng, 2005).

### 2.8. Pistacia Terebinthus

*Pistacia terebinthus* known as "menengic" in Turkey is one of the 20 species of Pistacia belonging to the family Anacardiaceae, is widely known as terebinth and turpentine tree. Being an indigenous tree in the Canary Islands, and the Mediterranean district, PT generally spreads from Morocco, Portugal to Greece and Turkey (Tastekin et al., 2014). It's additionally been recorded in the Northern Africa, Arabian Peninsula, and Western Asia. *Pistacia terebinthus* likewise develops in a few habitats in southern Kosovo (Pulaj et al., 2016).

This species of plant is widely grown in the southern and western regions of Turkey (Davis, 1967). The turpentine tree is a perennial, found to grow on dry rock

slopes and hillsides or in pine forests, especially in the Taurus mountains, from just above sea level to 1600 m (Baytop, 1984; Baytop, 1994; Kavak et al., 2010).

**Figure 1**. *Pistacia terebinthus* indigenous deciduous tree in the Siirt province.

The *Pistacia terebinthus* is dioecious tree, with female and male flowers on separate plants and deciduous tree which is manually shedding its leaves, Ranging in size of the large shrub growing of 5 to 10 m tall (Pulaj et al., 2016), and of the shrub to a small tree (about 2–6 m) (Aydın and Özcan, 2002).

The leaves are compound, the lengthy are 10–20 cm, the odd pinnate are five to eleven opposite glossy oval leaflets, the leaflets 2–6 cm tall and 1–3 cm broad. The fruit comprises of small, globular drupes five to seven mm long, red to black when mature. The flowers are ruddy purple, showing up with the new leaves in early spring. All parts of the plant have a strong resinous smell and when the fat extracted from its fruits is used for soap production (called bıttım sabunu ) as well as for the cooking oil in some area in Turkey (Topçu et al,. 2007).

*Pistacia terebinthus* has pulled in the consideration of analysts due to of its cell antioxidant (Topçu et al., 2007), antipyretic, antiseptic and anti-inflammatory (Baytop, 1984) properties and in the its seeds have oil substance (Marcopoulos, 1965; Matthäus and Özcan, 2006). There are many reports of the composition of P. terebinthus volatiles,

which obtained from the entire fruits, leaves, or from its flowers and twigs (Gogus et al., 2011).

The products of this tree in Turkey are known a çitlenbik, sakızagacı, çedene, çıtlak, yabanifıstık, melengiç and menengiç (terebinth) among individuals. (Yüksel et al., 2015). P. terebinthus fruits have been mainly use for preparation of coffee which is mixed with milk which called 'menengic kahvesi' (Hacıbekiroğlu et al., 2015). PTF coffee or "Menengiç" coffee is the most traditional and famous herbal coffee (Secilmis et al., 2015).

### 2.8.4. Chemical constituents of pistacia terebinthus

The chemical contents of PT include fatty acids, sterols, and tocopherols. The main fatty acid is oleic acid, accounting for 43-51% of the fatty acids. In the content of *Pistacia terebinthus* Active vitamin E was determined to be 396.8-517.7 mg/kg and α and γ tocopherol, which are among predominant isomers, content was determined to be 110-150 mg/kg. It is known that β sitosterol is the major sterol, representing for 80% (1341-1802 mg/kg) of the sterols (Bahcecioglu et al., 2015).

*Pistacia terebinthus* produces a rich blend of substances, including organic acids, sugars, fundamental oils, resin, proteins, tannins and flavonoids (Pulaj et al,. 2016; Álvarez et al.,2009; Durmaz and Gokmen, 2011). The essential oil is fluid with yellowish color and trademark smell (Özcan et al., 2009). According to the organs of the plant which essential oil are obtained and the geographical origin of the plant populations of PT change chemical composition of essential oil, the compound structure of the essential oil of *Pistacia terebinthus* developing wild in Turkey varied based on the organs from which the essential oils are acquired (e.g., flowers, youthful shoots, unripe and ripe fruits). The primary mixes included α-pinene (5, 12.4, 15 and 5 %), β-pinene (1.4, 8, 11.5 and 22.5 %), limonene (3, 9.4, 34 and 32.8 %), and germacrene D (follow, 19.9, 3.5 and 4.6 %), separately. while leaf essential oil in the Turkey was ruled by α-terpineol (5 %), αcadinol (7 %), trailed by phytol (5 %), δ-cadinene (5 %), and bornyl acetic acid derivation (4 %) (Pulaj et al., 2016).

A sum of 14 segments has been recognized in the EO of PT seed. The significant composition was β-pinene with a level of 38.28 %. It was trailed by α-pinene, p-cymene and α-terpinene accounting respectively for 15.73, 15.62 and 12.83 % (Dhifi et al., 2012).

The galls contain a blend of EO 4 %, resin 60 % and tannins 36 % (Pulaj et al., 2016). And furthermore the fruits are rich in terms of organic nutrients. The 100 g of terebinth organic products contain around kcal 594, 2 g rough fiber, 7.3 mg Fe, 136 mg Ca, 20.8 g protein, 500 mg P, 16.4 g starch, 51.6 g fat, 158mg Mg, 1.02mg K, 66IU vitamin, 0.4 mg vitamin B60, 1.45 mg vitamin B2, 62mg vitaminB1, 5.2mg vitamin E and 7 mg vitamin C. In this way ,they are assessed as a contrasting option to modern medicine in different ways (Yüksel et al., 2015).

### 2.8.2. Folk medicine of pistacia terebinthus

*Pistacia terebinthus* is generally used in traditional Turkish folk medicine to treat peptic ulcer, asthma, gastralgia, rheumatism, sunstroke, cough (externally), skin inflammation, looseness of the bowels, and throat inflammation (Tuzlaci and Aymaz, 2001). Furthermore, Pistacia species have stimulant, astringent, diuretic, antipyretic, antibacterial, anti-inflammatory antitussive, and antiviral impacts. They are utilized as a part of the treatment of renal stones, loss of motion, dermatitis and furthermore icterus. Crude extracts, essential oils and some triterpenoid substances of Pistacia species have anti-inflammatory and antifungal exercises. Moreover, alpha-tocopherol (vitamin E), a characteristic antioxidant, is present abundantly in Pistacia leaves (Tastekin et al., 2014).

In traditional medicine various parts of these species have been used for different purposes like tonic, antihypertensive, sterile, aphrodisiac and management of gastrointestinal, respiratory tract, dental, liver and urinary tract disorders (Bozorgi et al., 2013).

Various organs of turpentine tree are gathered for some purposes in different locales of the world. Its new shoots and fruits are utilized for human nourishment. In Turkey, the leaves of *Pistacia terebinthus* ssp. terebinthus (known as menengic) are

utilized as a part of the burntreatment. The gum (terebinthus = Terebenthina chia, T. cypria), privately called menengic sakizi, collected from *Pistacia terebinthus* branches, is utilized as a antiseptic for bronchitis and other respiratory and urinary system illnesses, and is given orally in 0.2-0.5g measurements three times day by day. It cures asthma, and it additionally has antipyretic and hostile to inflammatory properties (Dhifi et al., 2012).

In South Turkey the fruits have been used as appetizers in the diet for several thousand years and also used in baking of specialty village bread. The plant is rich in tannin and resinous substances and has been known for its sweet-smelling properties (Aydın and Özcan, 2002). Furthermore, in some region of Turkey when the fat extracted from its fruits is used for soap production (called bıttım sabunu ) as well as for the cooking oil (Topçu et al., 2007). *Pistacia terebinthus* soap seemed to be used safely and effectively in the management or treatment of skin toxicity induced by Cetuximab (Tastekin et al., 2014). P. terebinthus fruits also mixed with milk for preparation of caffee known as ‘menengic kahvesi (Hacıbekiroğlu et al., 2015).

Masticadienolic acid, masticadienonic acid, and morolic acid, three triterpene isolated from P. terebinthus gall, seem to be responsible for its anti-inflammatory activity. Furthermore, oleanonic corrosive from the nerves of *P. terebinthus* decreased the creation of leukotriene B4 from rodent peritoneal leukocytes and demonstrated hostile to edematous action in mice (Bozorgi et al., 2013).

The extracts of the kernel and seed appear significant antiviral and anti-inflammatory action was found in triterpenic compounds (Topçu et al., 2007). turpentine derived from PT in different countries used as a traditional medicine such as, in Iran, the smoke is used as an air purifier and disinfectant (Pulaj et al., 2016).

### 2.8.3. Pistacia terebinthus fruit (PTF) coffee

Coffee is consumed in high amounts around the world and differs in terms of brewing and roasting conditions with respect to different regions. also, herbal coffee has been used to reduce side effects, for example high caffeine content of excessive coffee

consumption. This permitted getting home grown items which are created and expended like espresso beans (Secilmis et al., 2015).

PTF coffee or “Menengiç” coffee is the famous and traditional herbal coffee in Turkey. The fruits have been acquired from *P.terebinthus* which is a member of the family Anacardiaceae. The PTF has been used in folk medicine for gastralgia (internally), rheumatism and cough (externally) and also as stimulant, diuretic and antitussive. In different areas of the world, diverse organs of this tree are used for several purposes due to its antioxidant effect. PTF contains similar flavor compounds to coffee beans, proposing that PTF may give a contrasting option to use in the coffee industry. Therefore, PTF have a high potential as an alternative to coffee beans because of its unique flavor and aroma (Çiftçi et al., 2009). The PTF espresso was observed to be rich in Vitamins, unsaturated fats and follow components, proposing that they might be significant for drink utilizes (Secilmis et al., 2015).

Roasting is a critical procedure for the coffee industry because of improvement of fragrance and flavor mixes. The broiling strategies and conditions importantly affect the development of the roasted coffee flavors. The consistently broiled coffee bean with full fragrance could be acquired by utilizing microwave roasting. Conventional pan roasting is the most well-known technique for PTF coffee preparing. As opposed to Arabica coffee, PTF coffee has an oily structure like sludge due to its high oil content. This needs to diminish oil substance to acquire an item in powder shape with a more eligible flavor (Secilmis et al., 2015).

In city of Elazig (East Anatolia range of Turkey), it is customarily arranged and drunk, and is known as 'Çedene coffee', which is sold like other coffee as simmered and squashed frame in the market (Bahcecioglu et al., 2015).

### 2.8.4. Medical properties of pistacia terebinthus

Medical findigs additionally detect the wide pharmacological action from different parts of these species, for example, antioxidant, anticholinesterase, antihyperlipidemic, antiviral, antinociceptive, antidiabetic antiatherosclerotic, antitumor,

antimicrobial, anti-inflammatory, and hepatoprotective activities and furthermore their positive effect in gastrointestinal disease (Bozorgi et al., 2013).

*P. terebinthus* has pulled in the consideration of analysts due to of its cell antioxidant (Topçu et al., 2007), cytotoxic, antipyretic, antiseptic and anti-inflammatory activities (Baytop, 1984), especially due to flavonoids and other phenolic contents (Topçu et al., 2007), and in the its seeds have oil substance (Dhifi et al., 2012).

In the Turkey, terebinthus is utilized as an antiseptic for bronchitis and many urinary and respiratory system illnesses, and is given orally in 0.2-0.5g measurements three times day by day. It treat asthma, and it additionally has hostile to inflammatory and antipyretic properties (Dhifi et al., 2012). Also when the fat extracted from its fruits is used for soap production (called bıttım sabunu ) as well as for the cooking oil in the some area of Turkey (Topçu et al., 2007).The extracts of the kernel and seed appear significant antiviral and anti-inflammatory action was found in triterpenic compounds (Topçu et al., 2007).

**Antioxidant properties of *pistacia terebinthus***

Oxidation is caused by the mix of free radicals and oxygen and can harm biomolecules, advancing atherosclerosis, maturing, disease and a few other human wellbeing issue and advance lipid peroxidation in nourishments, in this manner diminishing the nutritious esteem and nature of the sustenance. Around the world, the food industry depends on synthetic antioxidant compounds to repress sustenance oxidation. However late study have demonstrated that synthetic antioxidants usually utilized by the nourishment industry, for example, butylated hydroxyanisole, butylated hydroxytoluene (BHT) and tert-butylhydro-quinone, are gathered in the body and cause or advance a some diseases (Kıvçak and Akay, 2005).

Natural antimicrobial and antioxidant compounds have gotten more consideration and research lately as another option to synthetic substances for nourishment conservation. Many investigations have been focused on different extracts (EX) and essential oils (EO) of sweet-smelling plants, which are considered to elevate human health and to have a huge potential as food preservatives (Kavak et al., 2010).

Pistacia leaves naturally occurring α-Tocopherol (vitamin E). The pharmacological Properties of this vitamin, broadly used as a natural antioxidant, are are notable. Besides, a-tocopherol was utilized as a part of cosmetology (Kıvçak and Akay, 2005). The investigations on Pistacia species proposed that they may be utilized as vital characteristic antioxidant sources. Since, they contain phenolics and flavonoids, for example, a-tocopherol and quercetin which are utilized standard antioxidant mixes (Topçu et al,. 2007). Plant leaves indicated higher antioxidant capacity as 85 TEAC (trolox equivalent antioxidant capacity) esteem and higher antimicrobial movement towards Staphylococcus aureus (Kavak et al., 2010). Some examination demonstrated some hypolipidemic impact of the dried fruit extract of *P. terebinthus* on the rabbits without dangerous effect. In like manner, another investigation demonstrated some lessening of artheriosclerosis and revision of lipid profile. Late investigations demonstrated that a diminishing in blood cholesterol level of around 1% will lessen artheriosclerosis' frequency by around 2%, and antioxidants pley a vital part to decrase cholesterol level (Topçu et al., 2007).

The extracts of *P. terebinthus* has 12 times higher antioxidant capacity when contrasted with ascorbic acid and butyl-ated hydroxyanisole. This, likely, is a result of phenol and high flavonoid parts. Membrane stabilizing effect of alpha tocopherol is outstanding (Bahcecioglu et al.) *P. terebinthus* resins were effective in protecting human Low-density lipoprotein (LDL) from oxidation in vitro (Bozorgi et al., 2013). P. terebinthus had a high antioxidant capacity showing a conceivable preventive role in tumor chances by wiping out the free radicals attack (Kavak et al., 2010).

*P. terebinthus* has a preventive impact against exploratory hepatic fibrosis. This impact is by all accounts related with strong antioxidant and anti-inflammatory efficacy (Bahcecioglu et al., 2015).

**Anti-inflammatoris properties of Pistacia terebinthus**

Masticadienolic acid, masticadienonic acid, and morolic acid, three triterpene isolated from the gall of *P. terebinthus*, seem to be responsible for its anti-inflammatory activity. Furthermore, oleanonic corrosive from the galls of *P. terebinthus* decreased the

creation of leukotriene B4 from rodent peritoneal leukocytes and demonstrated hostile to edematous action in mice (Bozorgi et al., 2013).

The extracts of the kernel and seed appear significant antiviral and anti-inflammatory action (Topçu et al., 2007). *P. terebinthus* gave a huge reduction in necrosis, inflammation and fibrosis scores. (Bahcecioglu et al., 2015).

**Anticholinesterase properties of Pistacia terebinthus**

Enzymes that catalyzes the hydrolysis of the neurotransmitter acetylcholine in to choline and acidic acid, called Cholinesterase. While, any agent or substance that restrains a cholinesterase by combination with it called anticholinesterase.

*P.terebinthus* fruits had hard anticholinesterase activity, they could be new origin of anticholinesterase compounds and phytochemical studies are needed to characterize their active constituents, also significant anticholinesterase activity of these plants are n-hexane and dichloromethane which extracts from it, The outcome of the anticholinesterase assay showed that the ethanol and ethanol-water extracts of. *Pistacia terebinthus* fruits has strong anticholinesterase ability ( Hacıbekiroğlu et al., 2015).

**Antibacterial properties of terebinthus**

Antimicrobials are various substances or chemicals used in food products to diminish or slow down the growth rate of microbial pathogens, in order to prevent or reduce foodborne diseases. Antimicrobials are primarily classified into two categories: synthetic and natural. Natural antimicrobials are a potential alternative to chemical preservatives in terms of consumer acceptability and their health concerns about chemical preservatives. food can be contaminated with pathogenic microorganisms (e.g. Salmonella sp., Listeria monocytogenes and Escherichia coli), which represent a great concern to public health. The antibacterial action of *Pistacia terebinthus* EO against Staphylococcus aureus underpins the utilization of this species in different customary therapeutic applications, particularly concerning its utilization as an anti-inflammatory agent and disinfectant. Additionally look into is important to analyze the safe of its utilization for topical or oral applications (Pulaj et al., 2016). Antibacterial activity was more active against Gram positive than Gram negative microbes. This antibacterial

activity is slow due to the important amount of hydrocarbon monoterpenes. In fact, it is reported that EOs containing oxygenated monoterpenes in high proportions exhibit antibacterial and antifungal activities (Dhifi et al., 2012).

*P. terebinthus* leaf extract indicated antimicrobial action against S. aureus with a base restraint centralization of ≤1.56 mgml-1. Then again, there was no antimicrobial impact of crude concentrate on E. coli. Since E. coli is gram negative microscopic organisms and has a lipopolysaccharide external layer, exchange of molecules is accomplished through the cell layer with porins. Antimicrobial protection in gram (-) organism being is as often as possible intervened by means of modifications in an external layer porin, which essentially diminishes the capacity of antimicrobial to infiltrate the external plasma layer and reach its site of activity. Consequently capacity of molecules to go through these channels was influenced by their size and shape. Flavonoids found in leaf extract likely couldn't pass through the cell membrane (Kavak et al., 2010).

**Antifungal properties of Pistacia terebinthus**

Antifungal activity was established in *P. terebinthus* against an agricultural pathogenic fungi (Topçu et al., 2007). In Pistacia species, E oils and some triterpenoid components have antifungal and anti-inflammatory activities (Tastekin et al., 2014).

**Antidiabetic activity of Pistacia terebinthus**

DM is a chronic glucose metabolism disorder coming from insulin resistance and pancreatic beta cells dysfunction. The level of cardiovascular diseases is increased 2-4 fold in people with T2D. Traditional plants have been used as a cure for diabetes for a long time before the introduction of modern medicine. A few examples of plants that are commonly known for their hypoglycemic activity one of them *Pistacia terebinthus*. The society today does not aware the ability of these plants to prevent diabetes. In Turkey, its Leaf used for Stomach ache, mycosis, and anti-diabetic (Bozorgi et al., 2013).

# 3. MATERIALS AND METHOD

## 3.1. Experimental Animals

Experiments were performed on 40 male Wistar rats, weighting 160–200 g and aging six-eight weeks. All animals were housed under safe research center conditions in a temperature controlled room (22-24$^{o}$C) and kept on a 12 h light/dark cycle. All rats had access to nourishment and water advertisement libitium. The animals were provided by the Experimental Animal Center of Van Yuzuncu Yil University, Turkey. Blood glucose and body weight were checked before treatment once every week all through a month of test period.

## 3.2. Equipment and Apparatus

Automatic micropipette (Socorex)
Nikon digital camera (DXM-1200F)
Biochemical analyzer (Mindray, BS-120, Shanghai, China)
Automatic tissue processor (LEICA TP 1020 Semi-enclosed Benchtop)
Centrifuge ( Hettich TD4, Shanghai, China)
Sensitive Balance, Bosch S2000
Jelly tubes
Normal syringe 10 ml
Eppendorf tubes
Insulin injector syringe
Glucometer (Accu-Chek, Taiwan)
Falcon tube 50 ml
Blue pipette tips
Biochemical auto analyzer (HITACHI-911, Japan)
Microscope (LECLI DSe E 400)
Water bath
Tissue imbedded paraffin (LEICA Eg115o H Shanghai, China)
Refrigerator
Microtome (LEICA RM 2135 Shanghai, China)

### 3.3. Preparation of Diet and Plant Material

Fruit's oil of *Pistacia terebinthus* were purchased from Siirt region from Turkey were used in the experiments.

### 3.4. Diabetes Model with Streptozotocin (STZ)

#### 3.4.1. Streptozotocin structure and mechanism of action

STZ has closed equation ($C_8H_{15}N_{30}$) and molecular weight of 265.2 dalton. It is anhydrous type of STZ in 115$^oC$ a powder which has white to light-yellow colure. It was carcinogenic properties (Arison and Fendale, 1967). This substance a poisonous characteristic, it can be saved in the frozen faraway from air and humidity without changes in several months. It's dissolvable in each water or ketones and it must be utilized directly after preparing the solution because f precariousness. STZ is cytotoxic chemical that is particularly poisonous to the pancreatic, insulinproducing beta cells in mammals, leads to the degeneration of the Langerhans islets βcells and has been broadly used as a technique for inducing DM in experimental animals and for treatment of malignant β-cells tumors and other neoplasms (Rakieten et al., 1963). The STZ injections trigger a cell-mediated autoimmune reaction directed against the pancreatic β-cells. Moreover, the specificity of the reaction to STZ was evaluated by comparison with another betacytotoxic diabetogenic agent, alloxan. Inaddition alloxan has also same effect, but various kinds of animals show different level of sensitivity against alloxan while STZ is effective in every animal (Szkudelski, 2001).

#### 3.4.2. Inducing of diabetes

Diabetes mellitus was induced by single intraperitoneal (IP) injection of freshly prepared STZ (Sigma-aldrich, Saint Louis, MO) at dose of 55 mg/kg b.w. dissolved in 0.01 M citrate buffer, pH 4.5. After 72 h of STZ injection, and overnight fast, blood was taken from tail artery of the rats. Accu-Chek monitoring used to rapidly changing blood glucose level, when rats with blood glucose higher than 200 mg/dl were selected for the diabetic groups and involved to the examination. Rats those diabetes were not induced, same dose of STZ again injected to them. Injection of STZ and attack on pancreas cause

hypersecretion of insulin and this lead to intensive hypoglycemia and this may cause death to many animals, to avoid this, drinking water containing 10% dextrose were given to rats directly after I.P of STZ. In addition for taken care about rats, blood glucose were measured at 3rd, 15th and 28th days of throughout experimental model in blood taken from tail puncture.

### 3.5. Experimental Protocols

Experimental animals were randomly divided into 5 groups; each group was included 8 animals. The examination period was continuous for four weeks as below:

1. Control group (C): Did not receive any other kind of co-supplementation. Rats were given normal water and standard diet.
2. Diabetes group (D): In this group diabetes was induced by administered 55 ml/kg single dose of STZ IP injection and given standard diet with normal water.
3. Diabetes treated with *Pistacia terebinthus* fruit oil group (DPT): This group after administration a single dose of 55 mg/kg bw ip streptozotocin after 3 days (blood glucose values of rats will be 200 mg/dL). Menengic (*Pistacia terebinthus*) oil, every days will be given by intragastric tube 2 ml/kg/rat per day. And the standard pellet will be fed with feed.
4. Menengiç (*Pistacia terebinthus*) (PT): The rats in this group, Menengic (*Pistacia terebinthus*) oil, will be given orally by using intragastric tube as 2 ml/kg/rat every day with standard diet.
5. Diabetes with drug (Acarbose) group (DA): The rats of this group were exposed to STZ injection I.P for diabetes development after that 20 mg/kg, per day dose of Acarbose tablet (Glucobay), (Bayer Türk Kimya San) has been administered at a daily oral dose intragastrically.

### 3.6. Blood Sample Collection and Biochemical Analysis

At the end of the treatment period, all rats were fasted for 18 h, weighed and then anaesthetized with an IP injection of ketamine hydrochloride 50 mg/kg with 10 mg/kg dose of xylazine. The animals were continually monitored until total loss of

consciousness was reached, as indicated by a total lack of response after a foot pinch. Blood samples were collected from the heart puncture of rats and transferred to suitable tubes for biochemical analysis such as ALT, AST, ALP, LDH, Triglyceride, Cholesterol, Urea and Creatinine levels were examined by chemistry analyzer (BS-120, Shenzhen Mindray High-Tech Co, Ltd China).

### 3.7. Histopathological Investigations

Tissue samples were taken from the liver, kidney and pancreas and fixated in 10% buffered formalin solution solution. After routine tissue follow-up, the samples were embedded into paraffin blocks; 4 μm-sections were taken using microtome (Leica RM 2135); stained with hematoxylin-eosin and examined under light microscope (Nikon 80i-DS-RI2).

### 3.8. Immunohistochemically Investigations

Immunohistochemistry was performed to investigate insulin expressions. The streptavidin-peroxidase method (ABC) was used to stain the sections. Commercial antibodies were visualized on 4-μm-thick paraffin sections using an indirect streptavidin/biotin immunoperoxidase kit (Histostain Plus Bulk Kit, Zymed, South San Francisco, CA, USA). All steps were carried out following the procedure described by Sağsöz and Saruhan (2011). Tissue sections were incubated with the insulin (abcam ab-181547) (1:1000) primary antibodys overnight at 4° C. Finally, to visualize the reactions, the sections were reacted for 5-15 min with diaminobenzidine (DAB) for insulin staining. After the development of the DAB reactions, the sections were counterstained with Gill's Hematoxylin. The sections then were passed through alcohol and xylene and mounted directly with Entellan mounting medium. We used negative controls to verify staining. The slides were reacted with PBS instead of primer antibodies as negative controls. The slides were examined and photographed using a light microscope (E-400; Nikon, Tokyo, Japan) equipped with a video camera (DXM1200F, Nikon, Tokyo, Japan).

### 3.9. Statistical Analysis

All data were expressed as mean ± standard deviation. The statistical analyses were made using the Minitab 13 (Minitab, State College, PA) for windows packet program. One-way analysis of variance (ANOVA) statistical test was used to determine the differences between means of the experimental groups accepting the significance level at $p \leq 0.05$.

## 4. RESULTS

### 4.1 Effect on Body Weight

The diabetic rats exhibited profound body weight loss as compared to normal rats. The initial, half-way and final body weights of the rats are shown in Table 1. The final body weights in diabetic group (D), diabetes *Pistacia terebinthus* group (DPT), and diabetic acarbose group (DA) were significantly decreased when they compared with measuring at 14 days and also higher decreased compared with baseline weight at the start of the investigation. In contrast, body weights in control group (C) was significantly higher in comparison to other groups during experimental period while *Pistacia terebinthus* group (PT) was not significantly changed in body weight. Diabetes seemed to be more effective in decreasing body weight (Figure 2).

**Table 1**. Mean±Standard Deviation of mean body weight in different groups.

| Groups | 1st day Body Weights (g) Mean ± Std. Dev | 14 th day Body Weights(g) Mean ± Std. Dev | 28 th day Body Weights(g) Mean ± Std. Dev |
|---|---|---|---|
| C (n=8) | 191.18 ± 10.21 | 242.42 ± 23.18 | 283.12 ± 15.41 |
| D (n=8) | 227.42 ± 09.45 | 213.43 ± 15.28 [a] | 191.47 ± 18.42 [a] |
| DPT (n=8) | 202.43 ± 14.35 | 224.41 ± 12.24 [ab] | 241.33 ± 11.24 [ab] |
| PT (n=8) | 201.33 ± 13.10 | 238.47 ± 26.14 [b] | 292.48 ± 27.41 [b] |
| DA (n=8) | 205.58 ± 14.46 | 223.43 ± 13.41 [ab] | 234.46 19.26 [ab] |

Differences between groups were considered to be significant when ($p \leq 0.05$).
[a]Different from the control group.
[b]Different from the diabetes mellitus group.

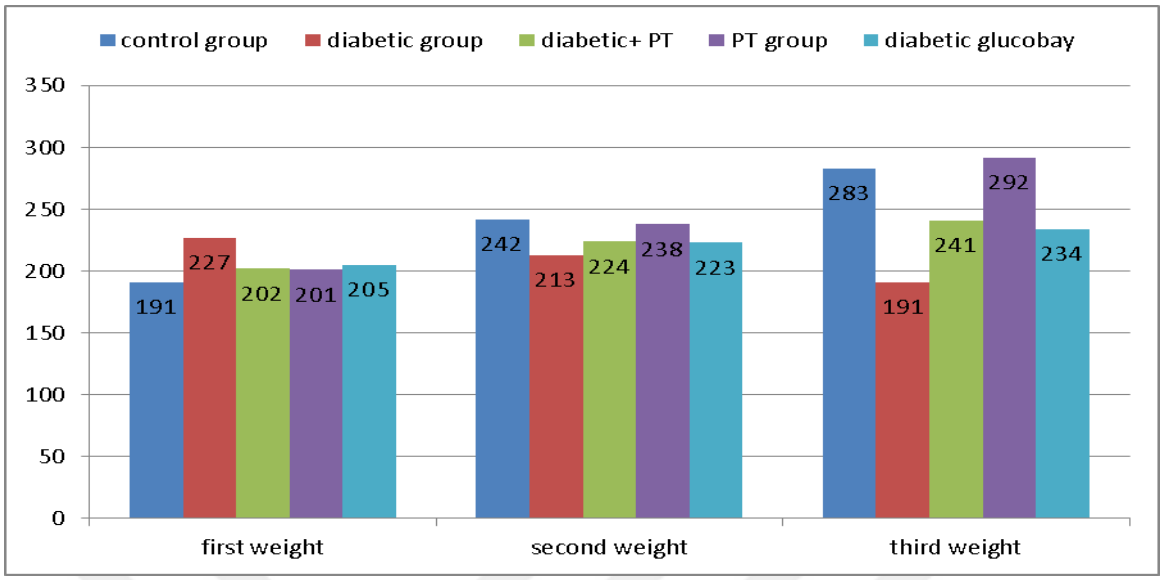


**Figure 2**. Changes in body weight in different groups of rats.

### 4.2. Effect on serum glucose

The serum glucose concentration (mg/dl) in the Group C was significantly ($p \leq 0.05$) lower, whereas Group D showed significantly ($p \leq 0.05$) higher concentration as compared to other groups throughout the experiment (Table 2). On the other hand, *Pistacia terebinthus*-fed group rats showed relative to control (C) rats during the first, second and fourth week, respectively.

**Table 2**. Mean±Standard Deviation of mean blood glucose in different groups**.**

| Groups | Period | | |
|---|---|---|---|
| | 3st day blood glucose (mg/dl) Mean ± Std. Dev | 14th day blood glucose (mg/dl) Mean ± Std. Dev | 28th day blood glucose (mg/dl) Mean ± Std. Dev |
| C (n=8) | 106.16 ± 10.87 | 112.50 ± 12.73 | 109.33± 14.23 |
| D (n=8) | 591.24 ± 8.10 [a] | 582.50 ± 11.37 [a] | 486.46 ± 17.42 [a] |
| DPT (n=8) | 563.16 ± 23.21 [a] | 379.26 ± 64.36 [ab] | 243.43 ± 19.23 [ab] |
| PT (n=8) | 102.12 ± 6.92 [b] | 107.33 ± 15.61 [b] | 104.10 ± 816 [b] |
| DA (n=8) | 572.66 ± 14.26 [a] | 546.33 ± 18.61 [a] | 306.46 ± 25.02 [ab] |

Differences between groups were considered to be significant when ($p \leq 0.05$).
[a]Different from the control group.

[b]Different from the diabetes mellitus group.

The two diabetic treated Groups (DPT and DA) showed significant ($p \leq 0.05$) decrease in glucose concentration on last week and as compared to Group D; the decrease was the highest in Groups C and PT. All Higher blood glucose concentrations were observed in group D, DPT and DA group after 72 hours of STZ injection, and gradually decreased on day 14th and 28th also significant difference between group D and treated diabetes groups (DPT, DA). *Pistacia terebinthus* inhibited the development of diabetes induced by STZ treatment (Figure 3).

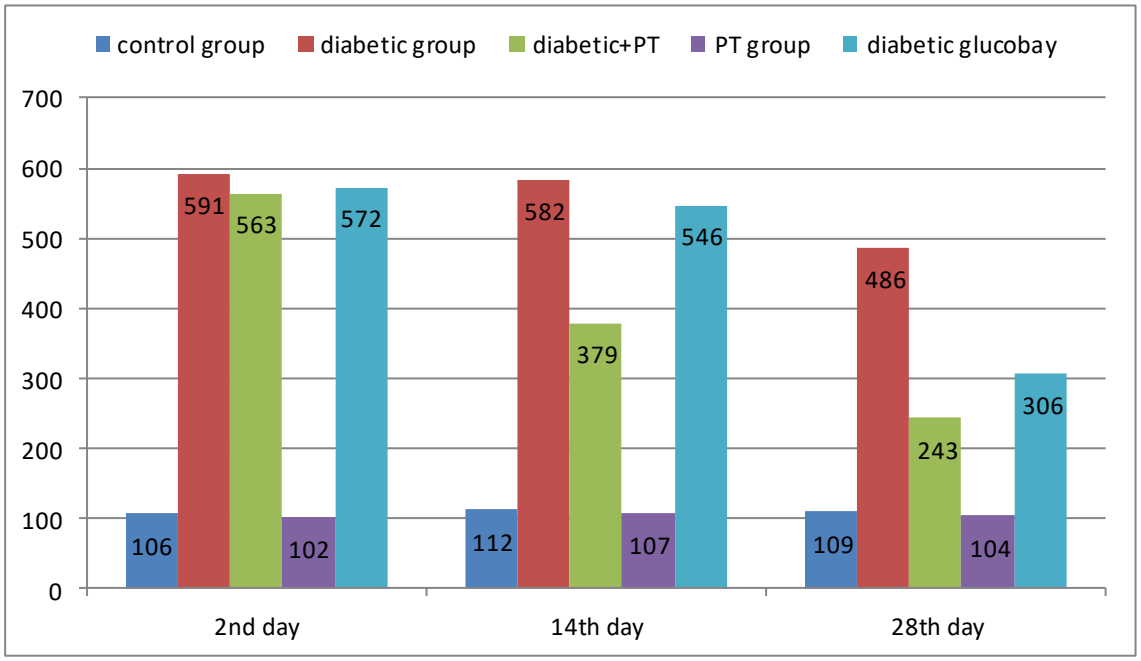


**Figure 3.** Blood glucose changes in different groups of rats.

### 4.3. Histopathological Findings

#### 4.3.1. Liver

**a) Control group:** The normal histological structure of the liver was observed in the this group. (Figure 4).

**b) Diabetic group:** Vacuolization and hydropic degeneration in hepatocytes and necrosis as a single component were observed in liver sections of DM group rats. Slight fibrosis and inflammatory cell infiltration were detected in portal areas. The normal arrangement of hepatocyte cords was observed to be impaired and became an irregular

cell community. The sinusoidal structure was sharply decreased and lost its continuity in several areas due to the formation of these lesions (dissociation) (Figure 5).

**c) Diabetic + P. terebinthus treated group:** In diabetic rats treated *P. terebinthus* with extracts revealed that the structure is preserved, showed slight vacuolations of sporadic hepatocytes. In this group histopathological findings of liver that had no significant differences comparison with control group (Figure 6).

**d) P. terebinthus-fed group**: The normal histological structure of the liver was observed. In this group histopathological analysis of liver that had no significant differences comparison with control group (Figure 7).

**e) Diabetic + drug treated group**: Liver of diabetic rat treated with Acarbose revealed vacuolations of sporadic hepatocytes (Figure 8).

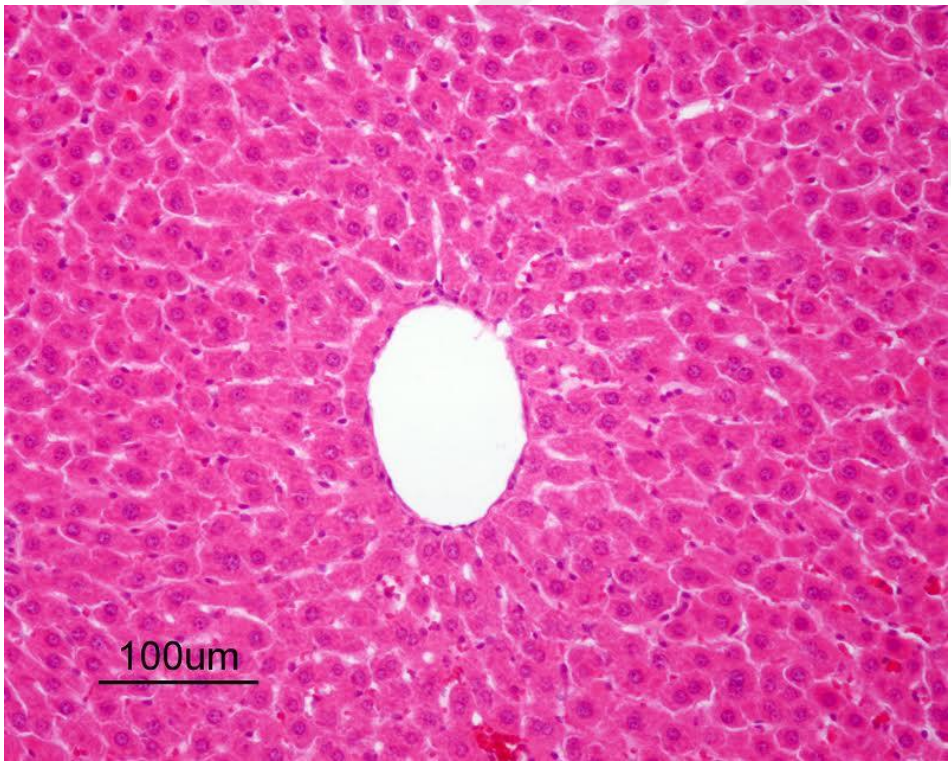


**Figure 4.** (Control group): Normal histological appearence of the liver. H.E.

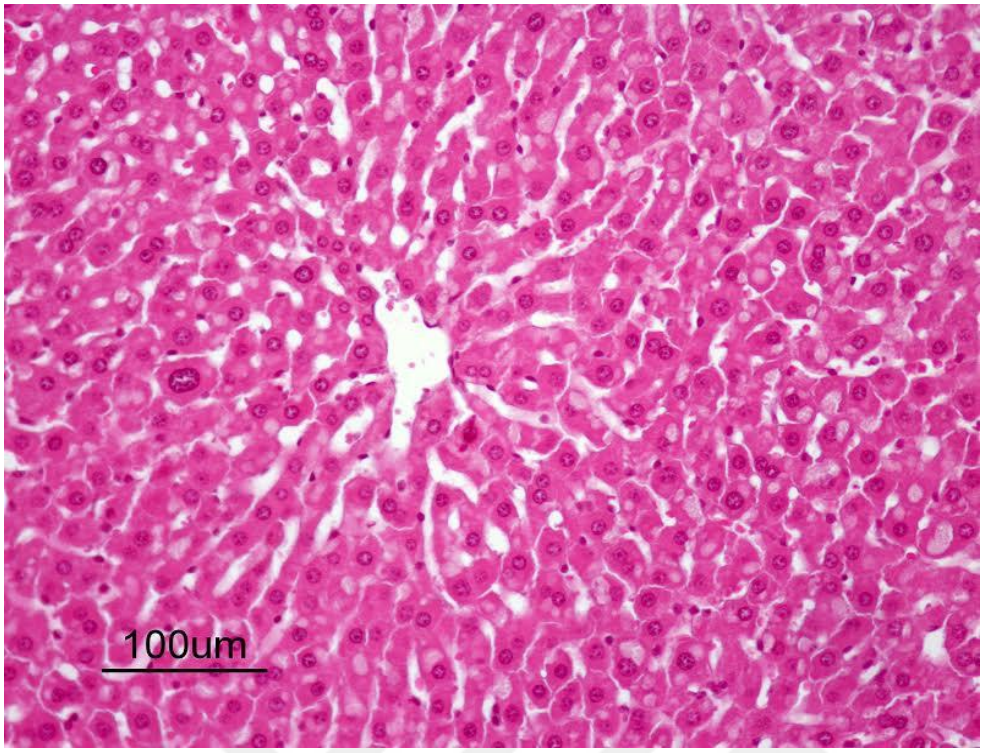


**Figure 5**. (Diabetic group): Vacuolization and hydropic degeneration in hepatocytes and sinusoidal dilatation. H.E.

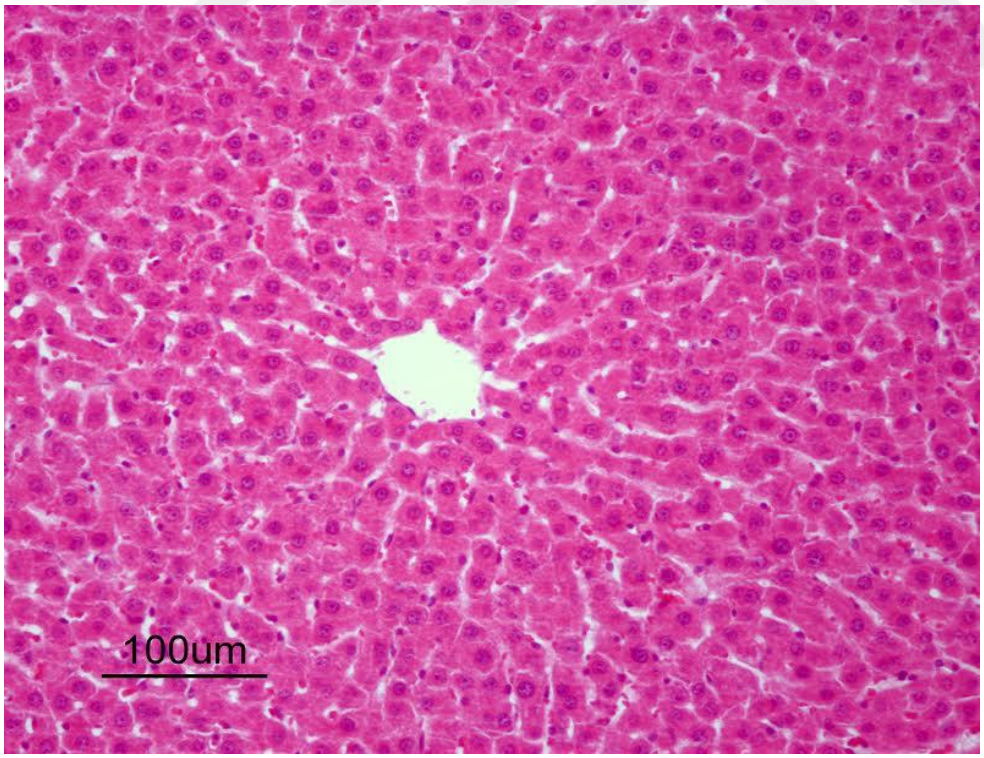


**Figure 6**. (Diabetic+ *P. terebinthus* treated group): Nearly normal histological appearence of the liver. H.E.

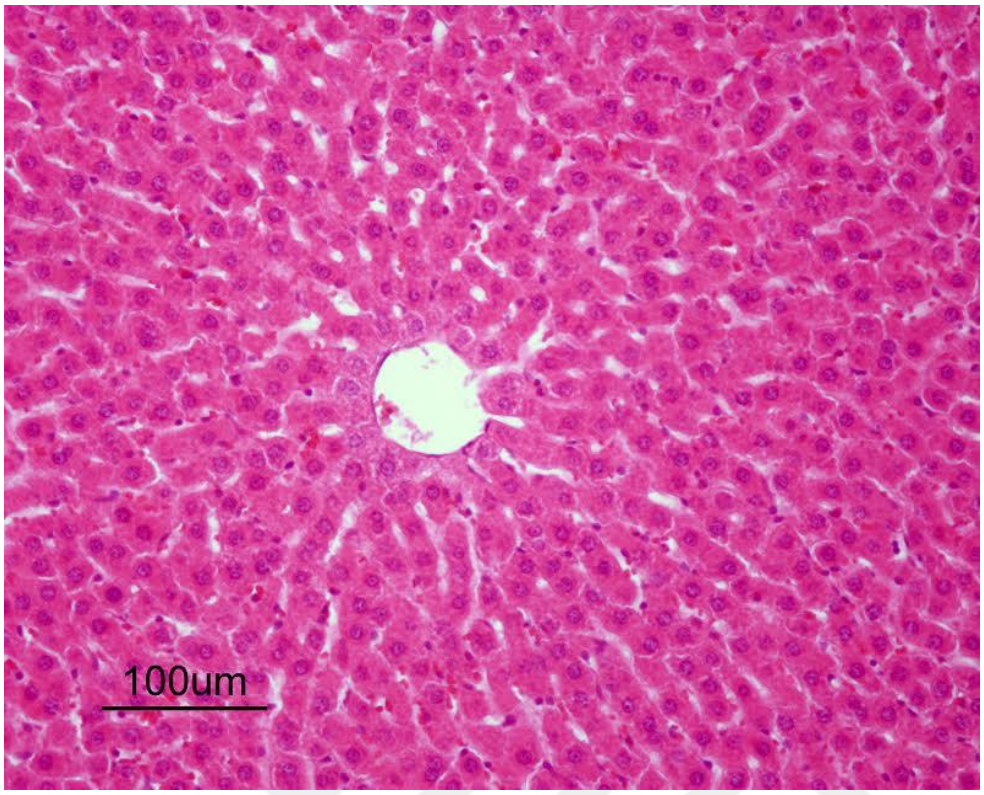


**Figure 7**. (*P. terebinthus* -fed group): Normal histological appearence of the liver. H.E.

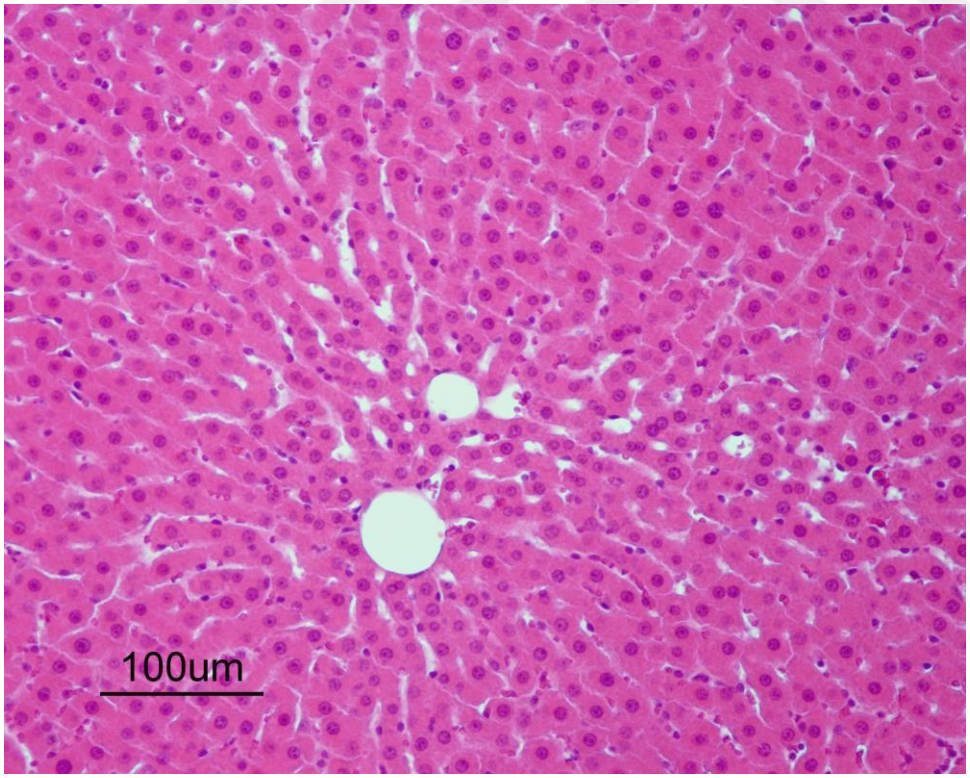


**Figure 8**. (Diabetic+drug treated group): Hydropic degeneration in some hepatocytes and slight sinusoidal dilatation. H.E.

### 4.3.2. Pancreas

**a) Control group:** Microscopic examination after hematoxylin and eosin (H&E) staining of the pancreas of control rats showed normal pancreatic parenchyma cells and islet structure. Many adjusted normal proportions of islet of langerhans were discovered all around the pancreatic acini. Prominent nuclei with well-arranged lobules with surrounding islet cells were found among normal control rats (Figure 9).

**b) Diabetic group:** The most significant findings in the group with DM were degenerative and necrotic changes in the islet cells of Langerhans. As a result, significant cell loss was observed in the islets as well as the cellular order was disrupted, the islets were atrophied and the structure was deteriorated. Hydropic degeneration and degranulation were observed in the cytoplasm of degenerative cells, and nucleus and cytoplasm were observed to be stained with a dark color. (Figure 10).

**c) Diabetic + P. terebinthus treated group:** A significant recovery was observed in the islet of Langerhans of rats in DM+*P. terebinthus* treatment groups, and the islets of Langerhans was found to be preserved against the toxic effects of STZ. The islet of Langerhans was found to have same characteristics with control group in DM+*P. terebinthus* group. The Pancreatic tissue damage caused by STZ was reversed and the normalization of pancreatic architecture was observed when diabetic rats were treated with *P. terebinthus* leave extractions revealed vacuolations of β-cells (Figure 11).

**d) P. terebinthus-fed group**: Examined sections of *P. terebinthus* -fed rats showed normal histological structure of pancreatic tissue, which had no significant differences comparison with control rats (Figure 12).

***e)*** **Diabetic + drug treated group**: The islet of Langerhans were observed to be preserved partially in rats in DM + Acarbose treatment group whereas degenerative and necrotic changes were formed in several cells (Figure 13).

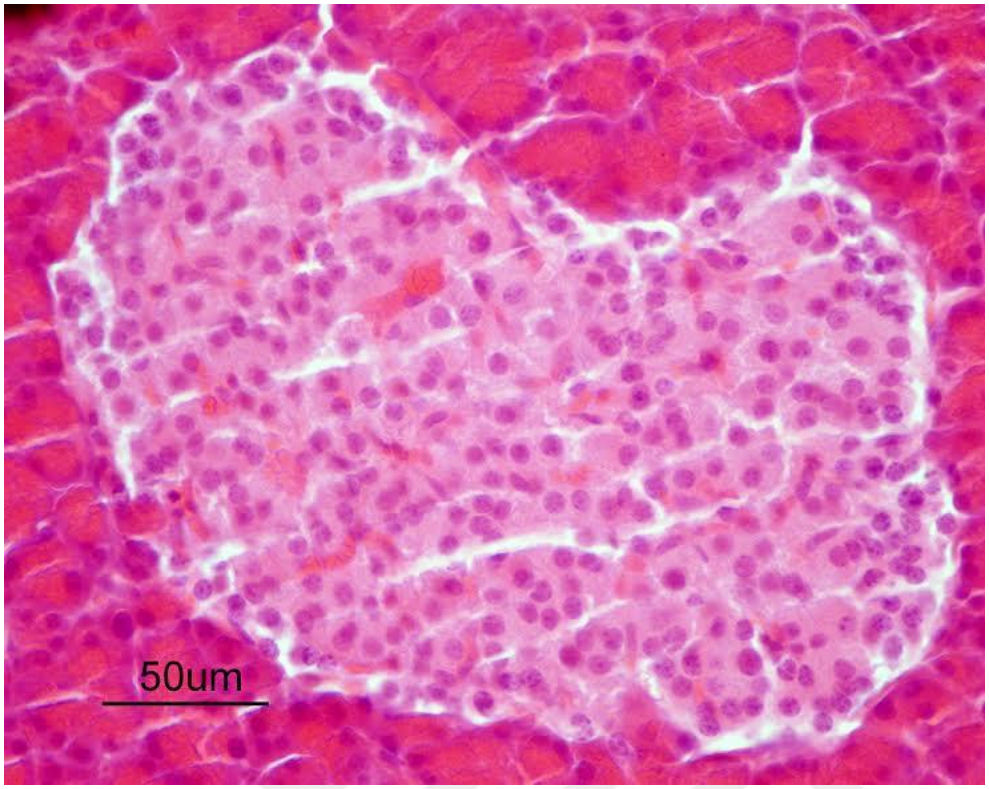


**Figure 9**. (Control group): Normal histological appearence of the islets of Langerhans of pancreas. H.E.

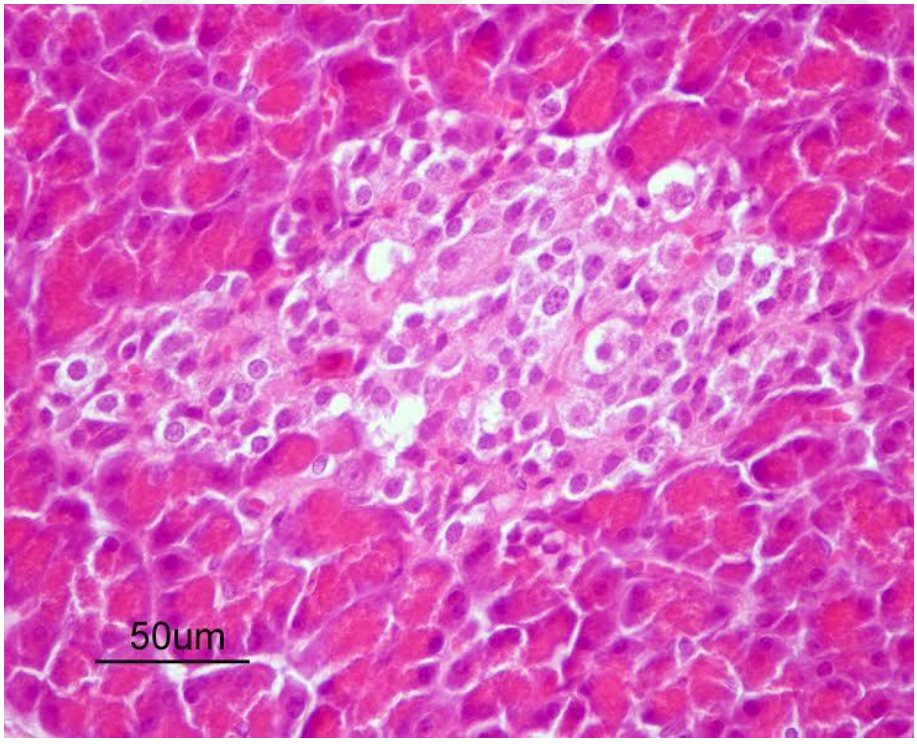


**Figure 10**. (Diabetic group): Showing hydropic degenaration and necrosis of some cells of islets of Langerhans. H.E.

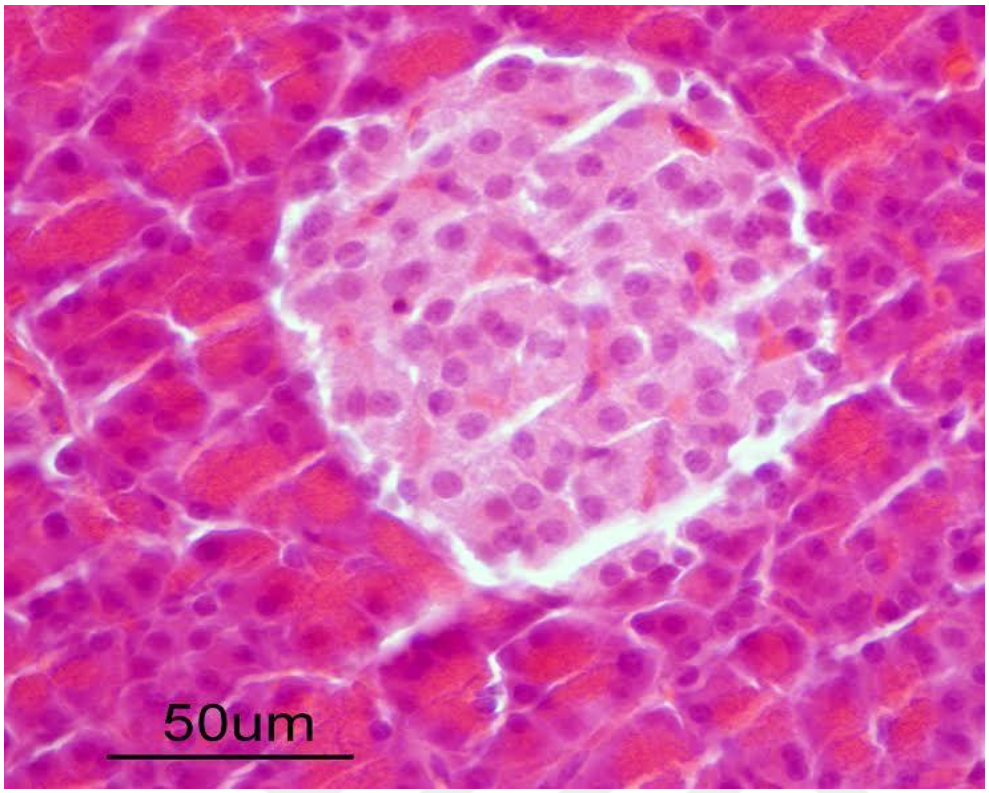


**Figure 11**. (Diabetic+ P. terebinthus treated group): Almost normal histological appearence of the islets of Langerhans of pancreas. H.E.

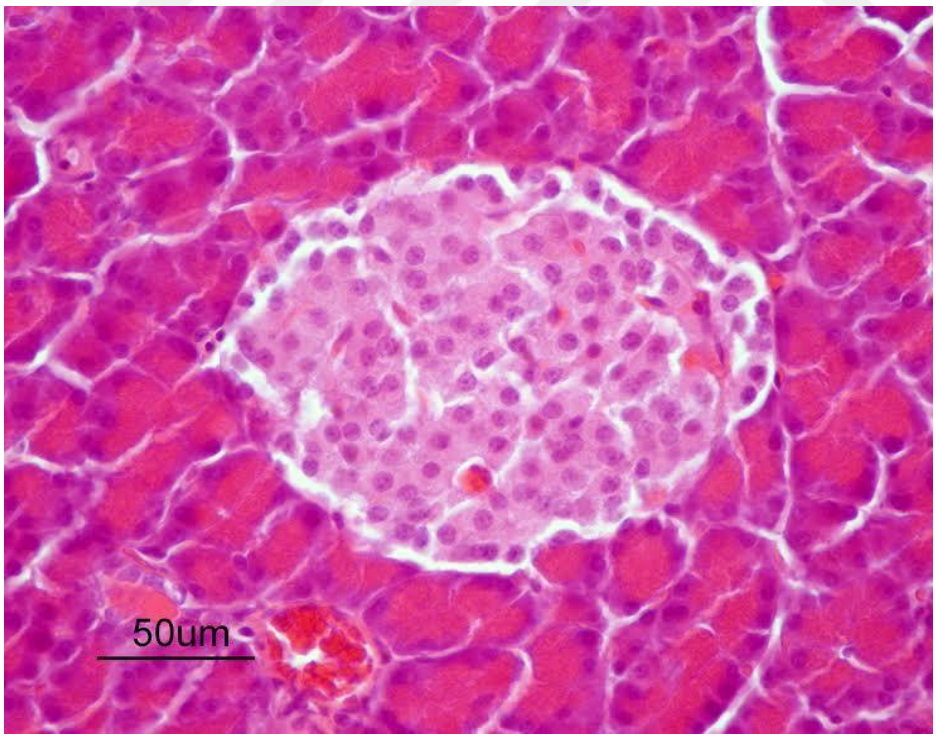


**Figure 12**. (P. terebinthus-fed group): Normal histological appearence of the islets of Langerhans of pancreas. H.E.

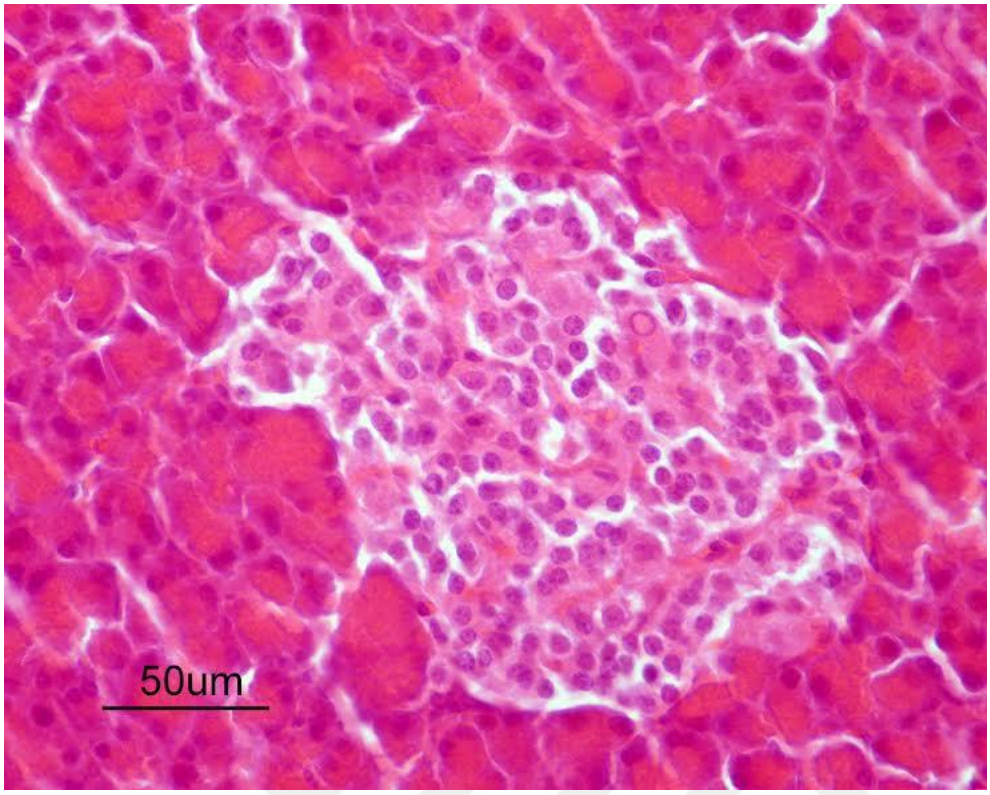


**Figure 13**. (Diabetic+drug treated group): Appearence of pancreas of diabetic rat showing slight hydropic degeneration and a few necrotic cells of islets of Langerhans of pancreas. H.E.

### 4.3.3. Kidney

**a) Control group:** Morphological properties of kidney stayed normal in the control like glomeruli, tubuli and ascending and descending loops (Figure 14).

**b) Diabetic group:** In the kidneys of rats in DM group, tubular dilatation, vacuolization, degeneration and necrosis were observed significantly in tubulus epithelial cells and glomerular mesengial cells. Focal inflammatory cells were seen in the intertubular areas. Glomeruli, which were narrowed in bowman capsule, were observed to create adhesion with the basal membrane (Figure 15).

**c) Diabetic + P. terebinthus treated group:** The findings, which were formed as a result of DM, were observed to be significantly reduced in the kidney of rats in DM+ *P. terebinthus* group, and slight degeneration and necrosis were observed in the tubulus epithelial cells as well. However, tubulus and glomerulus of the kidney of rats in

DM+*P. terebinthus* group were found to be in an approximate status as control group in general (Figure 16).

**d) *P.* terebinthus -fed group**: The *P. terebinthus* -fed rats was no significant difference when comparison with normal control rats (Figure 17).

**e) Diabetic + drug treated group**: Slight hydropic degeneration and necrosis were detected in some parts of the tubular epithelial cells in the kidney of rats in DM + Acarbose treatment group. Additionally, adhesions were observed in bowman capsule of some glomerulus (Figure 18).

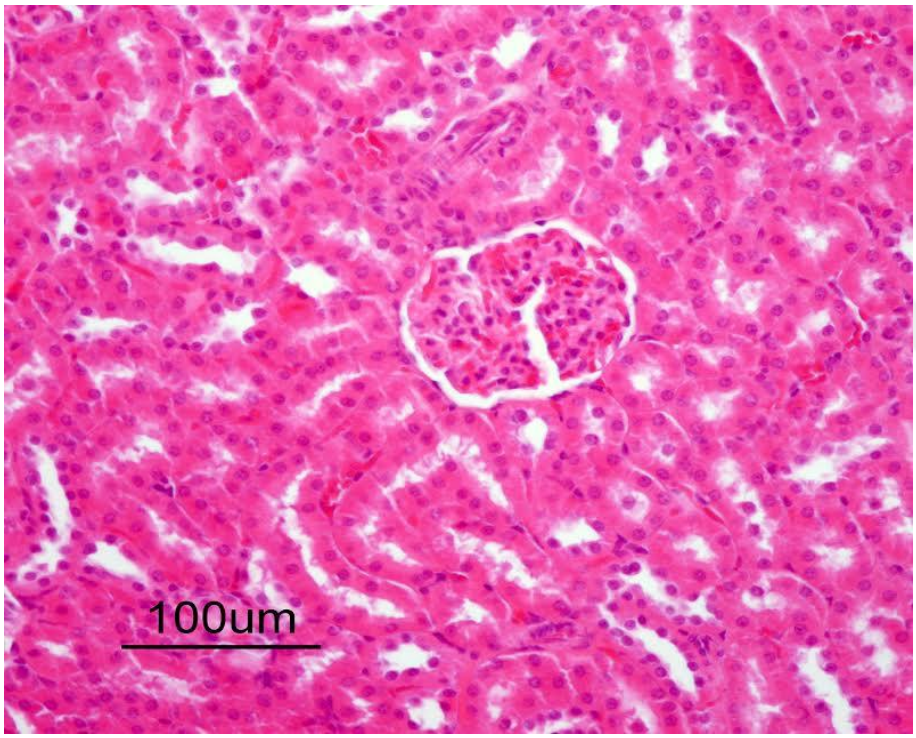


**Figure 14.** (Control group). Normal histological appearence of kidney. H.E

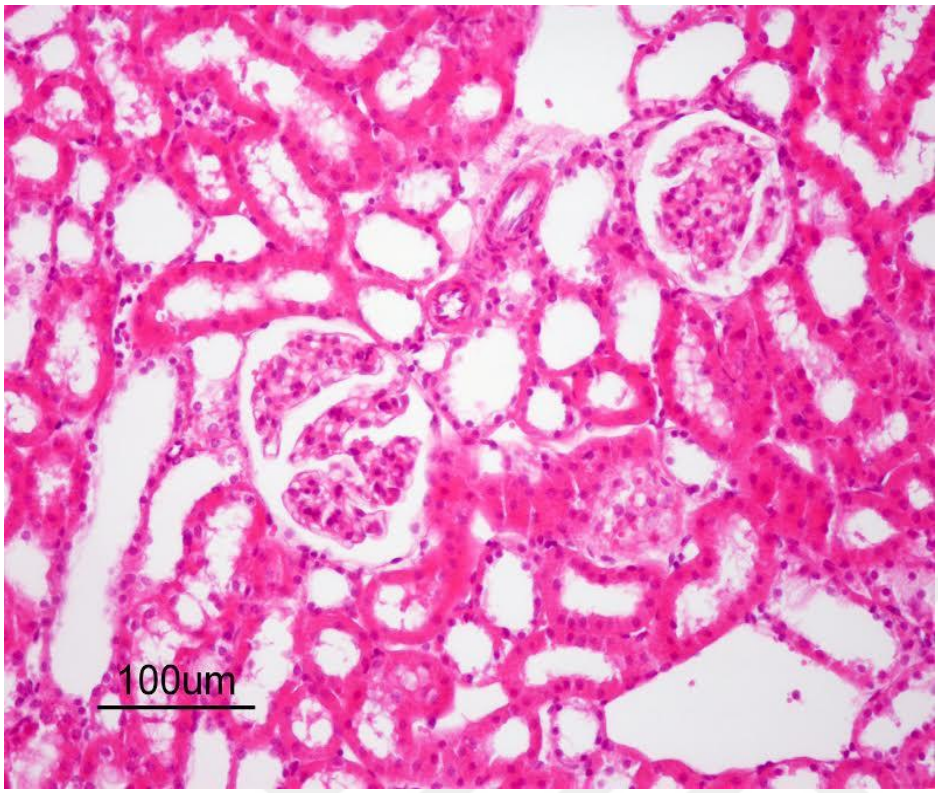


**Figure 15**. (Diabetic group): Tubular dilatation, degeneration, necrosis and vacuolization of podocyte of glomeruli and epithel cell of tubuli. H. E.

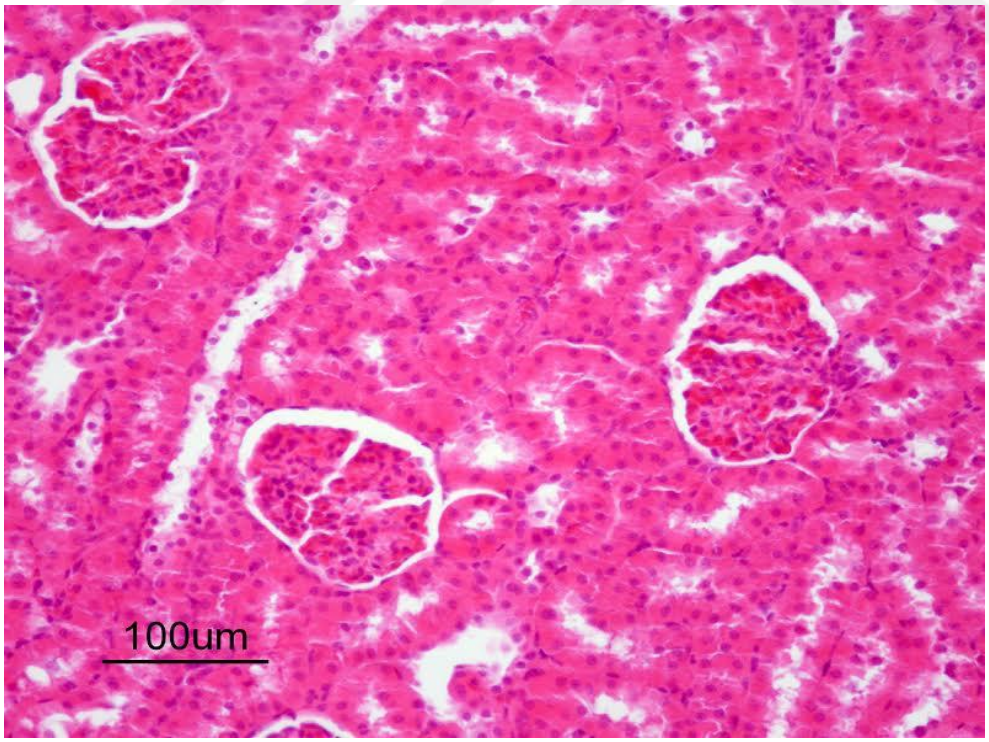


**Figure 16**. (Diabetic+ P. terebinthus treated group): Slight hydropic degeneration in tubular epithelium of kidney. H.E.

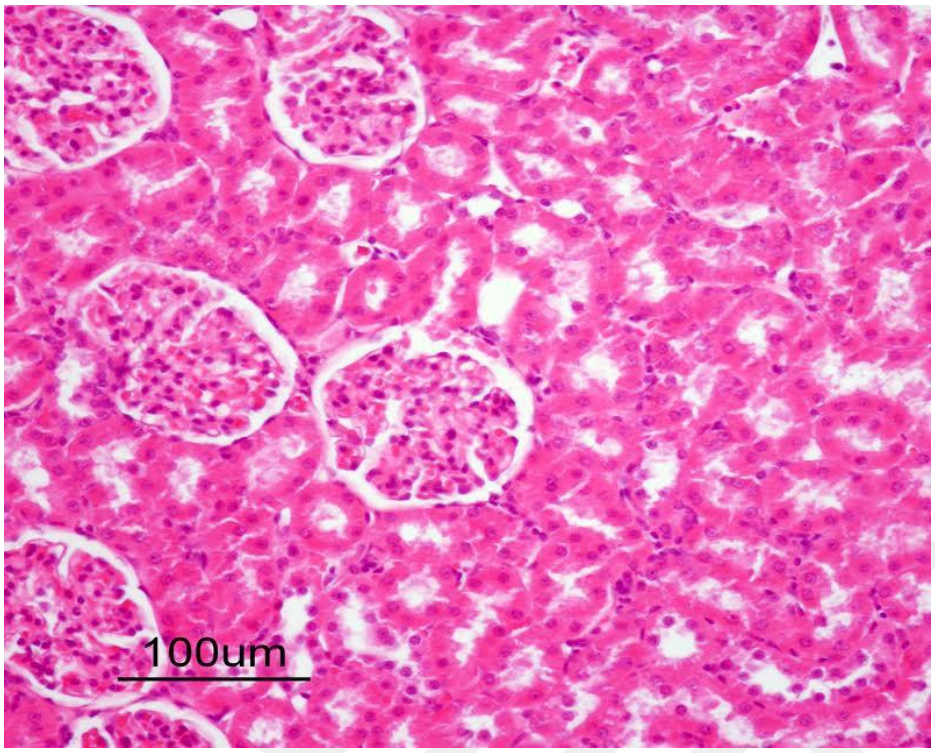


**Figure 17**. (P. terebinthus -fed group): Normal histological appearence of kidney. H. E.

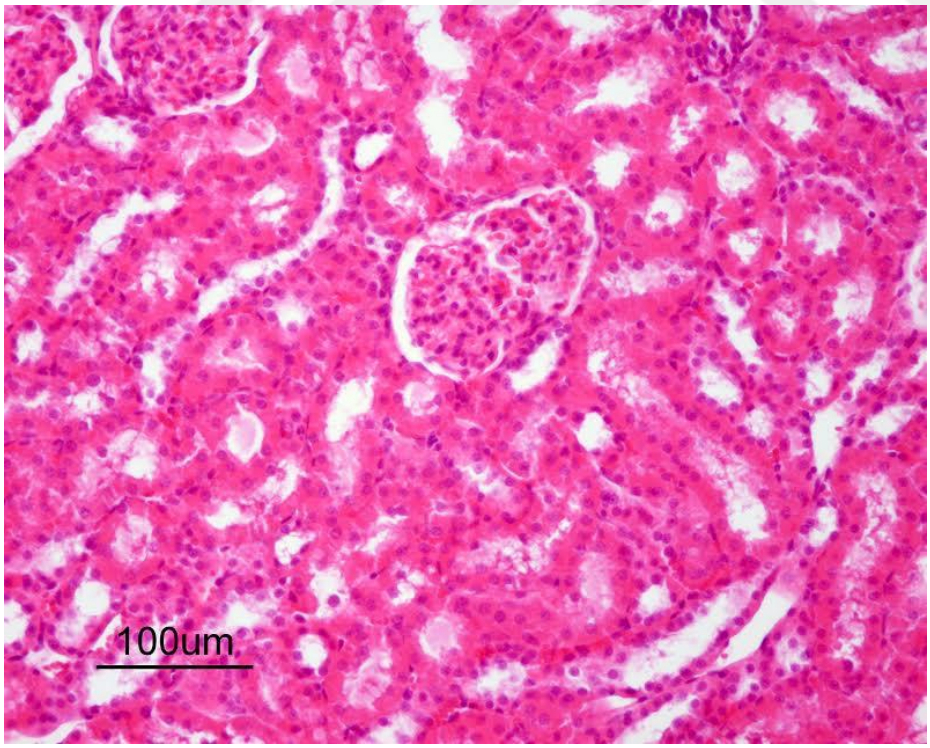


**Figure 18**. (Diabetic + drug treated group): Slight hydropic degeneration in tubular epithelium of kidney. H.E.

**Table 3.** Histopathological findings in liver, kidney and pancreas tissues.

| Changes/Lesions | Groups | | | | |
|---|---|---|---|---|---|
| | Control group | Diabetic group | Diabetic + *P. terebinthus* treated group | Diabetic + drug treated group | *P. terebinthus* group |
| Dissociation of remarc cordons | -/8 | 8/8 | 4/8 | 4/8 | -/8 |
| *Slight* | - | 1 | 2 | 1 | - |
| *Moderate* | - | 1 | 1 | 2 | - |
| *Severe* | - | 6 | 1 | 1 | - |
| Vacoulation in hepatocytes | -/8 | 8/8 | 4/8 | 4/8 | -/8 |
| *Slight* | - | - | 2 | 2 | - |
| *Moderate* | - | 1 | 2 | 1 | - |
| *Severe* | - | 7 | - | 1 | - |
| Bile-duct proliferation | -/8 | 7/8 | 3/8 | 4/8 | -/8 |
| *Slight* | - | 1 | 1 | 2 | - |
| *Moderate* | - | 2 | 2 | 1 | - |
| *Severe* | - | 4 | - | 1 | - |
| Periportal fibrosis | -/8 | 7/8 | 2/8 | 3/8 | -/8 |
| *Slight* | - | 2 | 1 | 1 | - |
| *Moderate* | - | 1 | 1 | 2 | - |
| *Severe* | - | 4 | - | - | - |
| Degeneration and necrosis in tubuli epithelial cells | -/8 | 8/8 | 3/8 | 4/8 | -/8 |
| *Slight* | - | 2 | 1 | 2 | - |
| *Moderate* | - | 3 | 2 | 2 | - |
| *Severe* | - | 3 | - | - | - |
| Disorder of glomerular structure | -/8 | 8/8 | 3/8 | 4/8 | -/8 |
| *Slight* | - | 2 | 2 | 1 | - |
| *Moderate* | - | 3 | 1 | 3 | - |
| *Severe* | - | 3 | - | - | - |
| Disorder of islets of Langerhans structure | /8 | 8/8 | 2/8 | 3/8 | /8 |
| *Slight* | - | - | 1 | 1 | - |
| *Moderate* | - | 2 | 1 | 2 | - |
| *Severe* | - | 6 | - | - | - |
| Degeneration of β-cells | /8 | 8/8 | 2/8 | 3/8 | /8 |
| *Slight* | - | - | 1 | 1 | - |
| *Moderate* | - | 2 | 1 | 2 | - |
| *Severe* | - | 6 | - | - | - |

### 4.4. Immunohistochemical evaluation

**a) Control group:** Strong insulin immunopositive reaction were observed in pancreatic tissue sections and the islets of Langerhans of the control group rats (Figure 19).

**b) Diabetic group:** The diabetic group showed a marked destraction in β-cells number. Immunohistochemical reactions revealed marked reduction in

immunoreactivity for insulin antibody inside islet β-cells and only a few β-cells displayed minimal insulin immunoreaction (Figure 20).

**c) Diabetic + *P.* terebinthus treated group:** In diabetic rats treated *P. terebinthus* extracts was increased in the number and percentage area of reactive β-cells an apparent founded as compared with the control diabetic group. Some islets of the rats presented increased β-cells populations; mean insulin concentration of the diabetic rats that received *P. terebinthus* increased (Figure 21).

**d) Diabetic + drug treated group:** Almost normal immunohistochemical appearence were seen having moderate immunoreactivity of insulin in β-cells, which occupy most of the işlet (Figure 22).

**e) P. terebinthus -fed group**: Serum insulin concentration of the diabetic rats that received *P. terebinthus* extracts was significantly higher than in the diabetic rat (Figure 23).

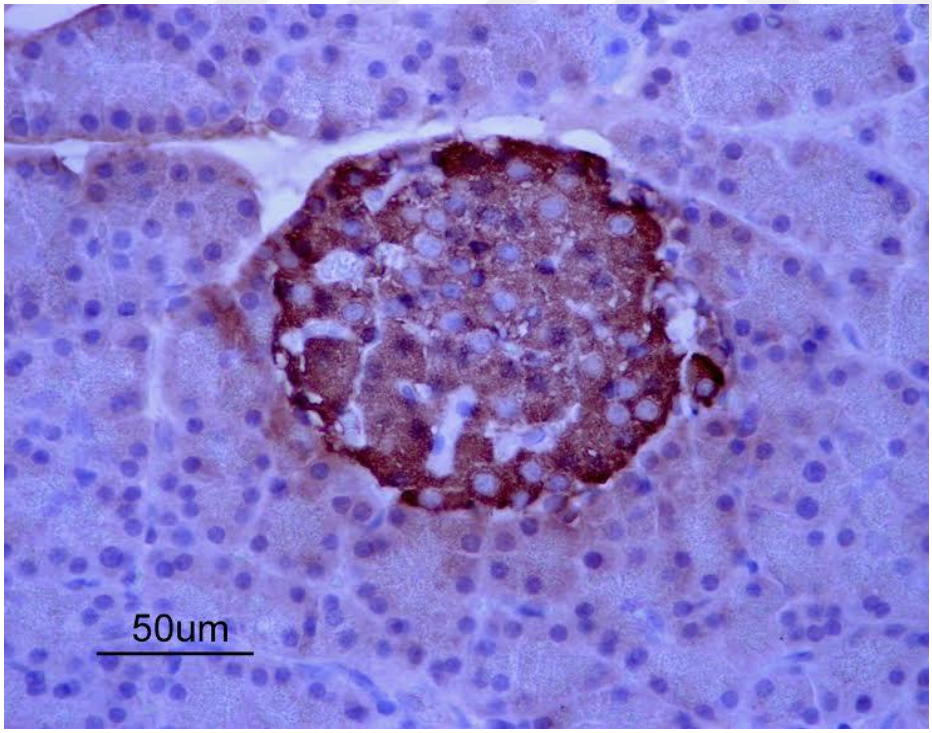


**Figure 19**. (Control group): Insulin immunohistochemical staining of islets of langerhans of pancreas demonstrating strong immunoreactivity of insulin in β-cells, which occupy most of the islet. Immunperoxidase (ABC method).

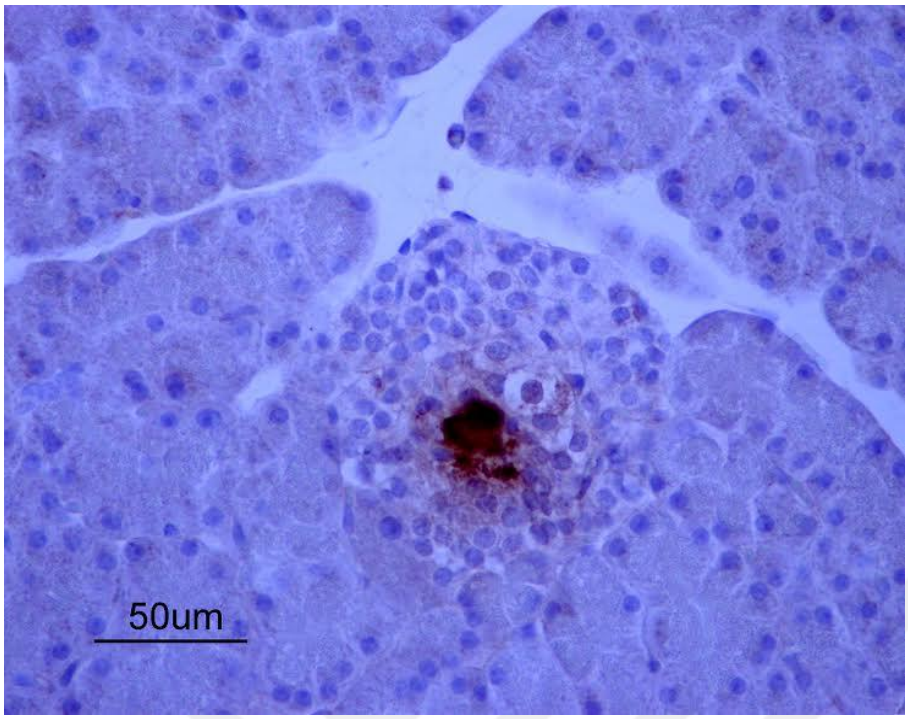


**Figure 20.** (Diabetic group): A photomicrograph of insulin immunohistochemical staining of islets of Langerhans of pancreas showing very weak immunoreactivity of insulin in β-cells. Immunperoxidase (ABC method).

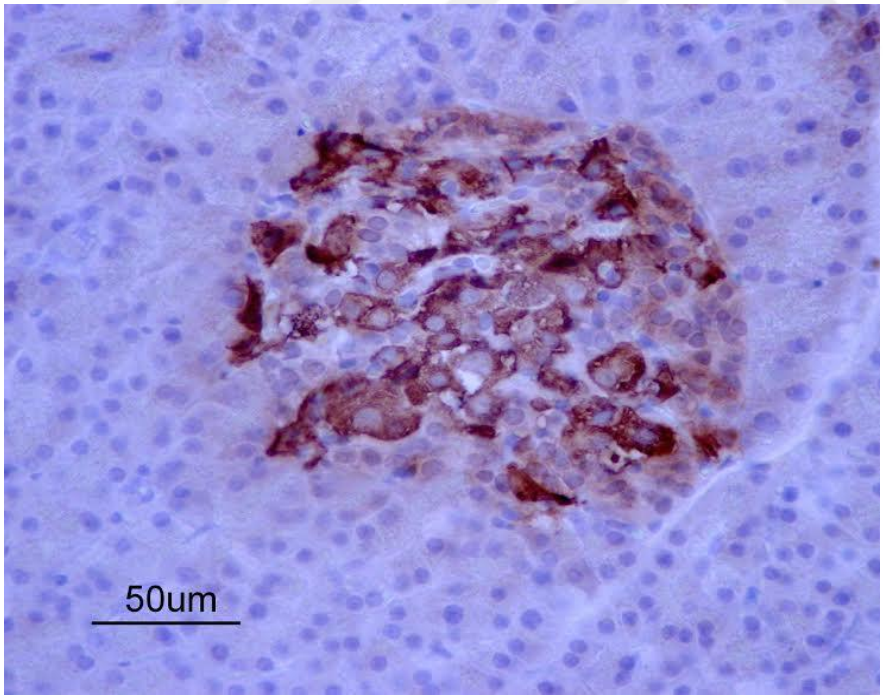


**Figure 21.** (Diabetic+ P. terebinthus treated group): Almost normal immunohistochemical appearence of pancreas. A photomicrograph showing moderate insulin immunoreactivity in islet β-cells with increasing insulin immunoreactivity. Immunperoxidase (ABC method).

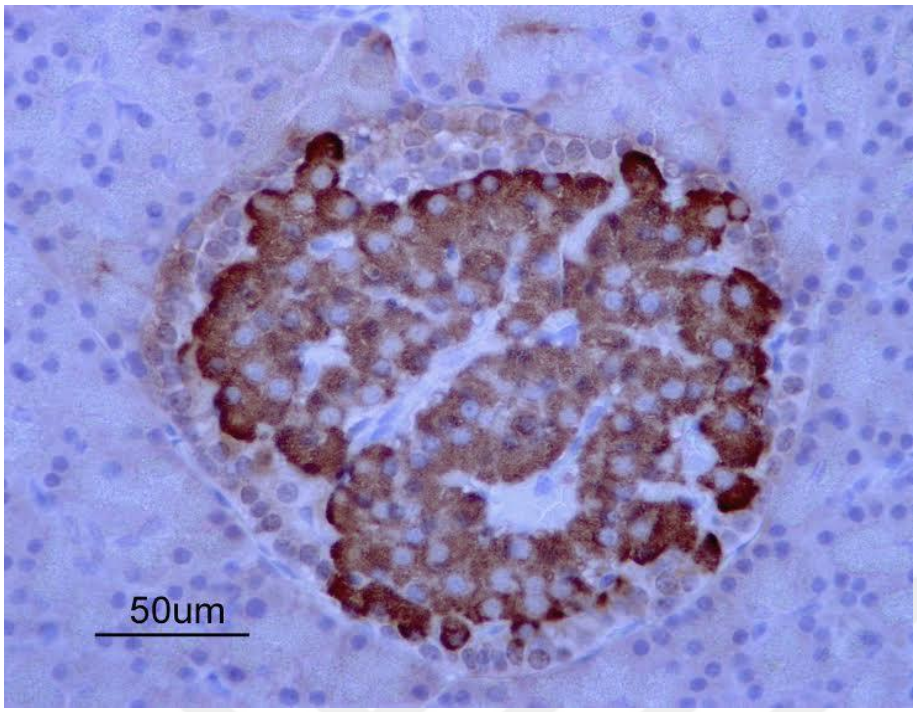


**Figure 22**. (P. terebinthus -fed group): Showing normal immunohistochemical appearence of pancreas. Immunoreactivity of insulin in β-cells, which occupy most of the islet. Immunperoxidase (ABC method).

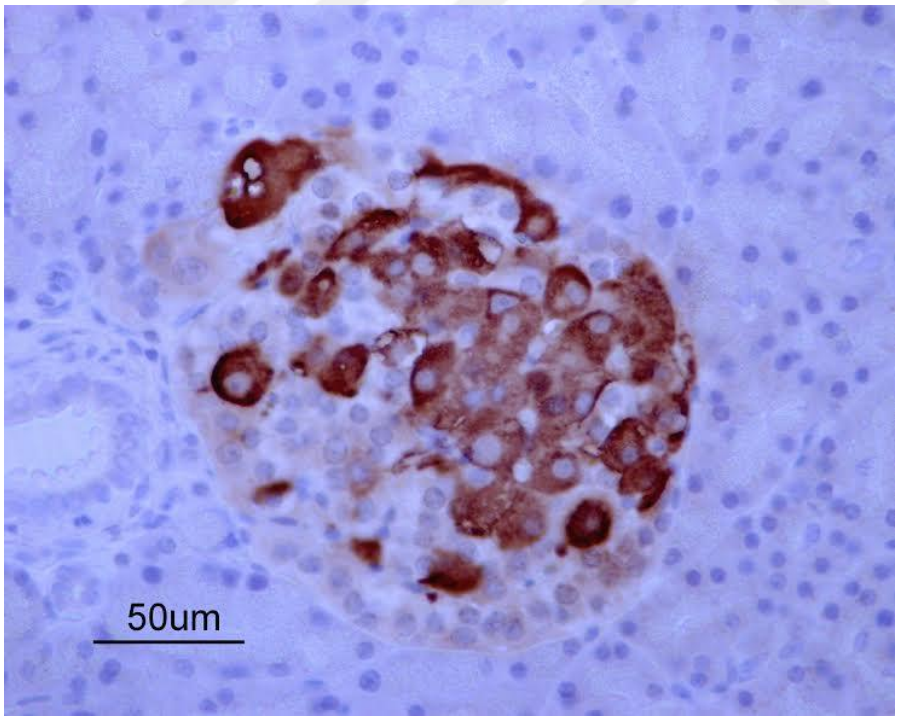


**Figure 23**. (Diabetic+drug treated group): Almost normal immunohistochemical appearence of pancreas, howing moderate immunoreactivity of insulin in β-cells, which occupy most of the islet. Immunperoxidase staining (ABC method).

### 4.5. Biochemical Results

**Table 4.** Changes in the serum of ALT, AST, ALP, LDH, Triglyceride, Cholesterol, Urea and Creatinine levels in different groups under study.

| Biochemical tests | Groups | | | | |
|---|---|---|---|---|---|
| | Control group | Diabetic group | Diabetic + *P. terebinthus* treated group | Diabetic + drug treated group | *P. terebinthus* group |
| ALT | 46.54±3.35 | 782.83±132.74[a] | 83.47±34.17[ab] | 94.16±3.76[ab] | 57.47±17.36[b] |
| AST | 105.40±28.71 | 624.74±47.78[a] | 167.72±34.45[ab] | 189.43±31.27[ab] | 96.73±10.42[b] |
| ALP | 134.16±32.15 | 798.57±97.45[a] | 206.03±57.46[ab] | 237.16±51.65[ab] | 108.50±16.14[b] |
| LDH | 342.5±52.18 | 986.61±161.05[a] | 551.84±31.43[ab] | 612.50±57.15[ab] | 321.25±30.19[b] |
| Cholesterol | 52.41±1.26 | 93.21±3.47[a] | 62.10±3.14[ab] | 63.52±3.76[ab] | 49,75±1,45[b] |
| Triglyceride | 61.26±21.47 | 251.15±73.14[a] | 94.40±14.42[ab] | 112.45±15.34[ab] | 58.75±14.43[b] |
| CRE | 0.45.6±0.08 | 2.37.1±0.48[a] | 0.71.4±0.24[a] | 0.89.8±0.47[a] | 0.39.6±0.8[b] |
| Urea | 35.47±3.21 | 114.16±7.45[a] | 52.15±3.71[ab] | 64.15±2.46[ab] | 36.72±2.54[b] |

Differences between groups were considered to be significant when ($p \leq 0.05$).
[a]Different from the control group.
[b]Different from the diabetes mellitus group.

The levels of alanine aminotransferase (ALT) enzyme were insignificantly ($P > 0.05$) decreased in *P. terebinthus* diabetic treated rats according to the diabetic groups. Also ALT level was significantly ($P \leq 0.05$) lower in P. terebinthus treated groups and acarbose diabetic treated group as compared to that of diabetes group (Table 3 and Figure 24).

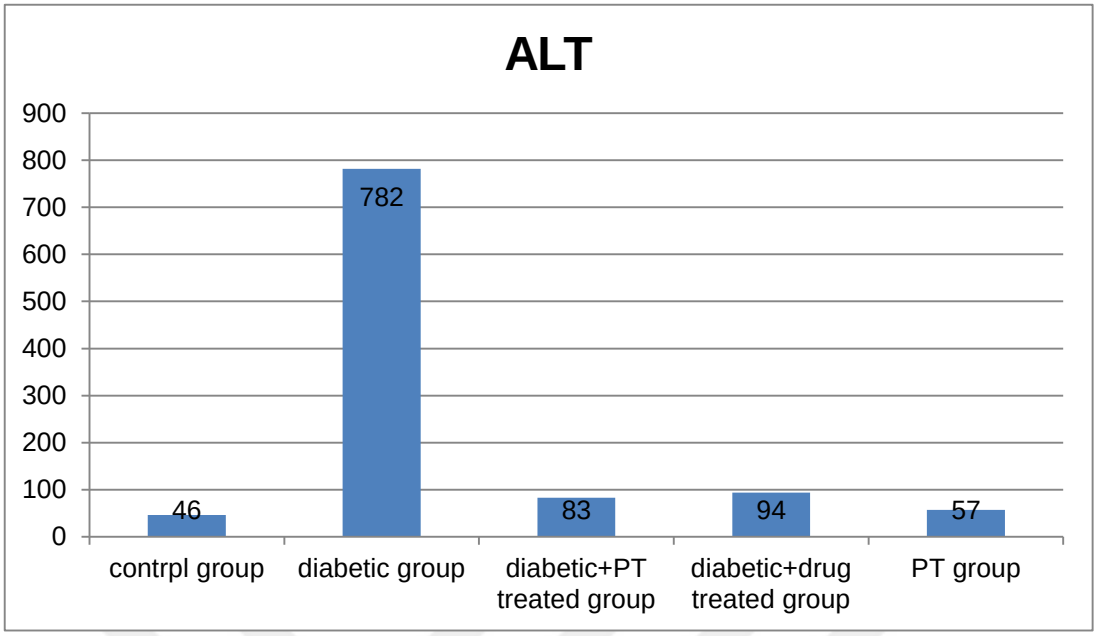


**Figure 24**. The levels of serum ALT (U/L) averages in experimental groups.

The mean values of aspartate aminotransferase (AST) activities were significantly decreased in diabetes treated groups and undiabetes groups vs. diabetes group ($P \leq 0.05$). However, the level of AST was lower in P. terebinthus treated rats as comparison other rat goups (Table 3 and Figure 25).

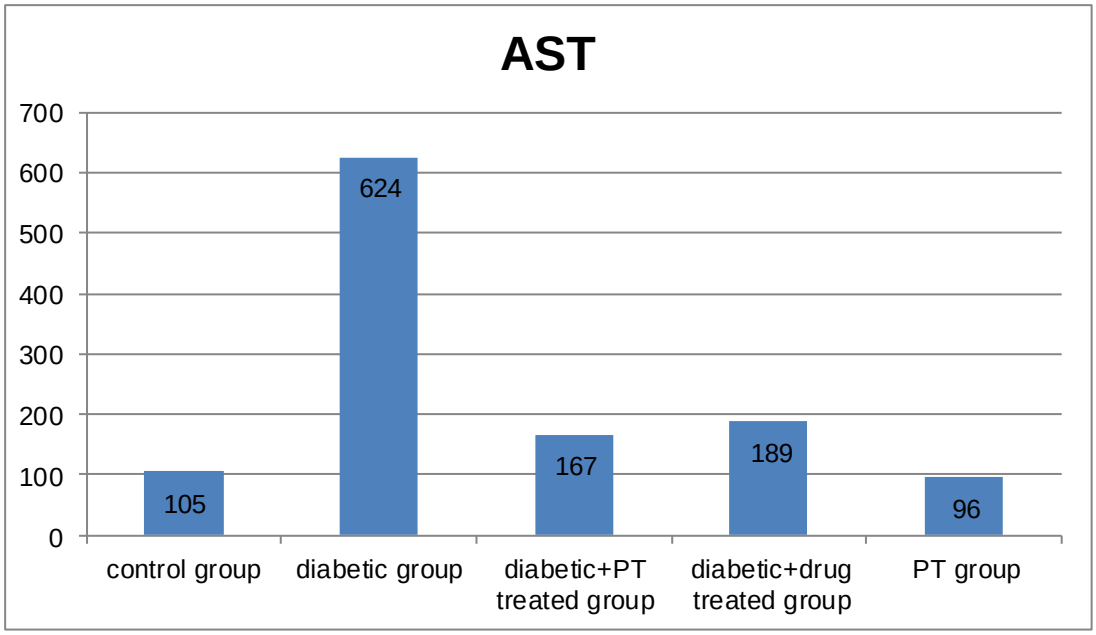


**Figure 25**. The levels of serum AST (U/L) averages in experimental groups.

A statistically non-significant decrease ($P > 0.05$) found in alkaline phosphatase (ALP) level *P. terebinthus* diabetes treartment group in comparison with diabetes groups. In addition, statistically significant decrease ($P \leq 0.05$) can be seen in both diabetes drug treatment acarbose and undiabetes treatment of *P. terebinthus* extracts as compared with diabetes group (Table 3 and Figure 26).

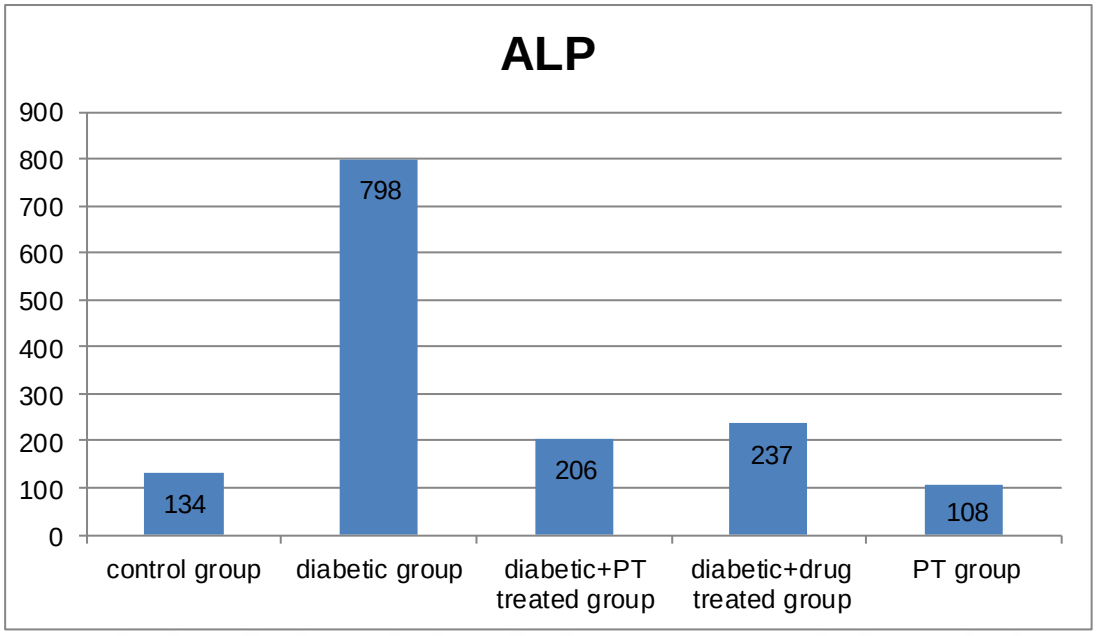


**Figure 26.** The serum levels of ALP % (U/L) averages in experimental groups.

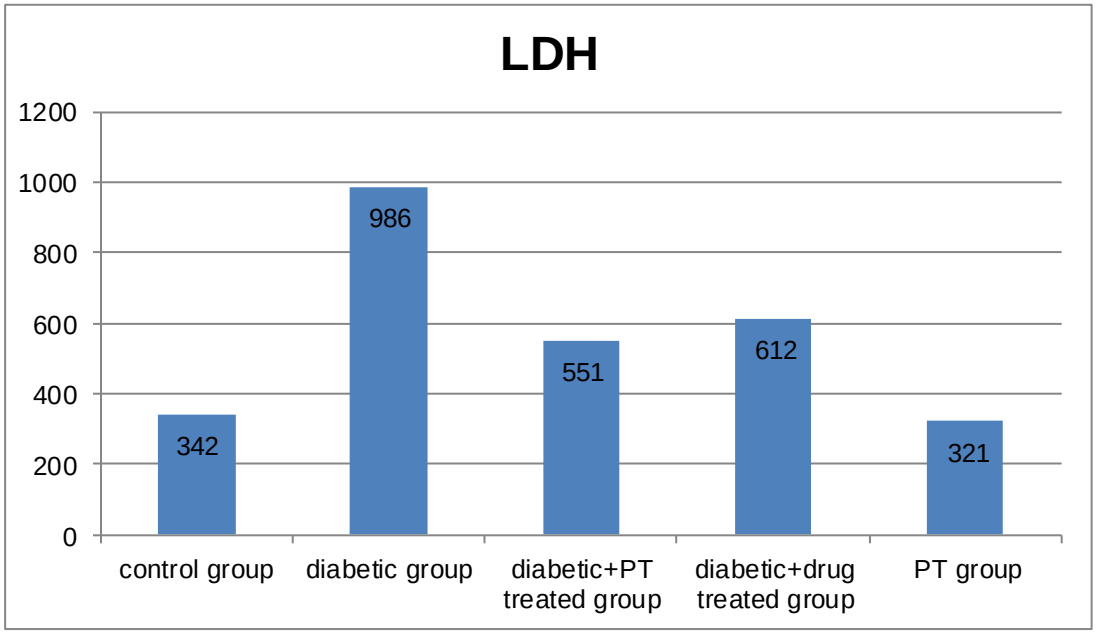


**Figure 27**. The levels of serum LDH in experimental groups.

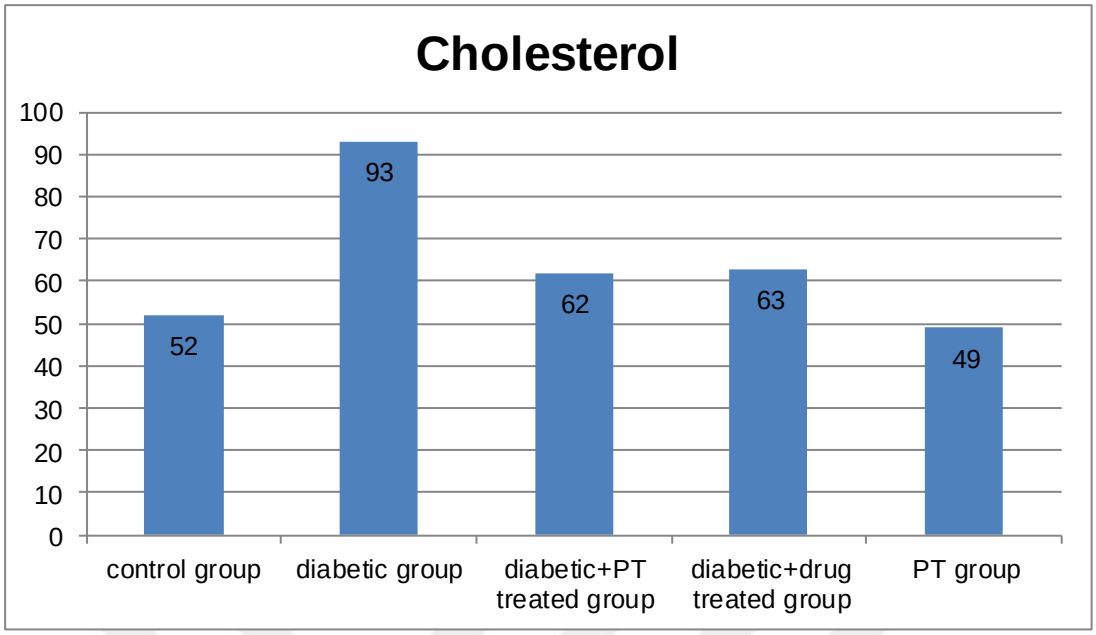


**Figure 28**. The levels of serum cholesterol in experimental groups.

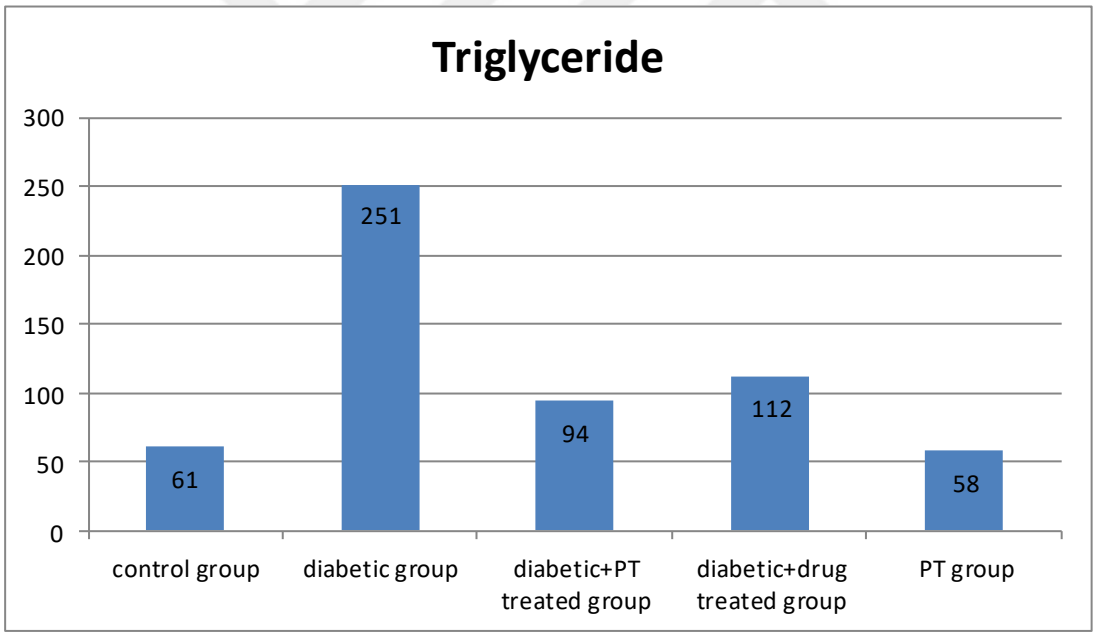


**Figure 29**. The levels of serum Triglyceride in experimental groups.

The mean values of Urea level were significantly decreased in diabetes P. terebinthus extracts group as compared with diabetic groups ($P \leq 0.05$). However, the alterations of urea level were significantly improved of all diabetic groups and P. terebinthus extracts as compared with diabetic groups ($P \leq 0.05$), (Table 3 and Figure 30).

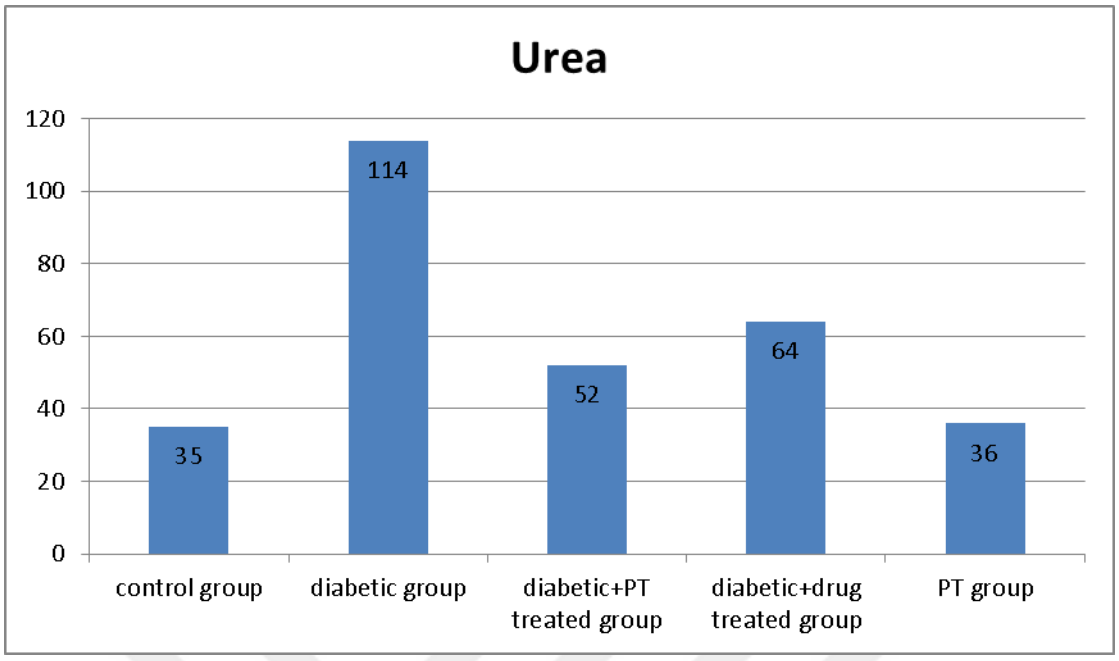


**Figure 30**. The levels of serum UREA (mg/dL) averages in experimental groups.

The level of creatinine kinase (CK) was decreased significantly ($P \leq 0.05$) in the diabetic *P. terebinthus* group in comparison with the diabetic group (Table 3 and Figure 31).

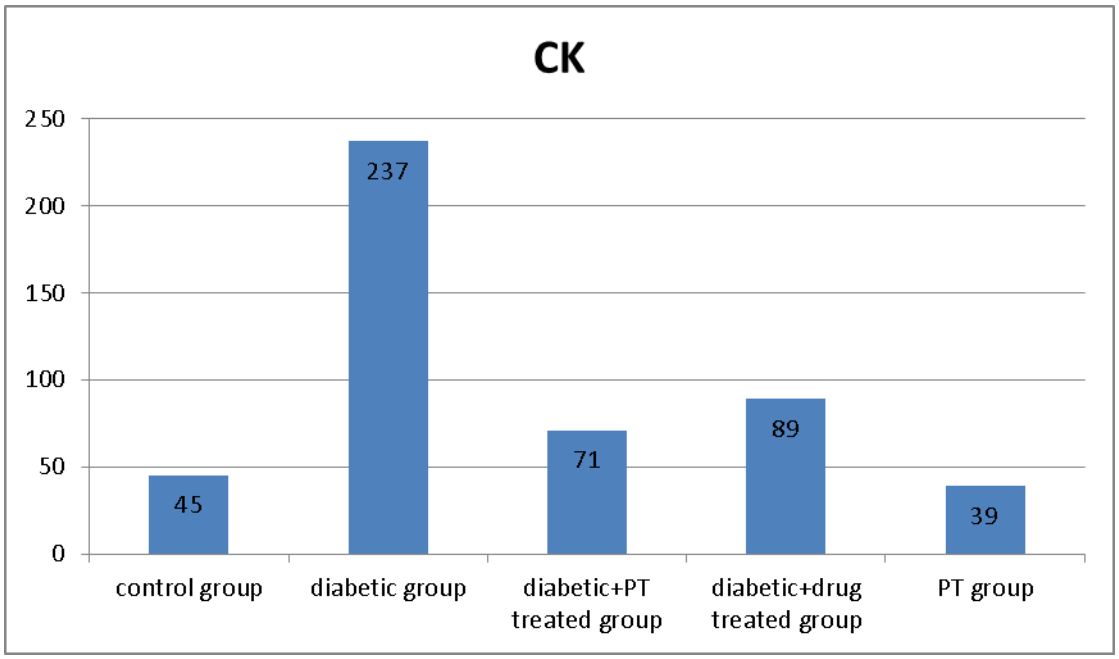


**Figure 31.** The serum levels of CK (U/L) averages in experimental groups.

## 5. DISCUSSION AND CONCLUSION

Diabetes mellitus is a group of metabolic diseases characterized by a serious, chronic metabolic disorder that occurs either when the pancreas does not generate enough insulin, or when the body cannot effectively use the produced insulin (WHO, 1999). When diabetes is not well managed, may lead to many serious health and life-threatening complications such as the heart attack, stroke, kidney failure, leg amputation, vision loss and nerve damage (WHO, 2016). Diabetes and its complications contribute harshly to mortality, costs and poor quality of life. Oral antidiabetic drugs have high costs and potentially hazardous side effects such as hypoglycemia, weight gain, anemia and congestive heart failure (Zimmet et al., 2001; Nesto et al., 2003). Hence, DM has been cured with herbs for centuries and there are lots of herbs that have been reported to exert antidiabetic activity (Afolayan and Sunmonu, 2010). Many studies are underway to find new effective agents that can increase or preserve islet β-cell mass and function, providing a plant to lower the burden of morbidity from DM and it is complications (Tarabra et al., 2012). Herbal treatments are widely used around the world for treatment of diabetes, but medical research is inadequate to explore their effectiveness (Afolayan and Sunmonu, 2010). Among these herbal medicines P. terebinthus is used in the herbal treatment. In this study was performed to testify the potential antidiabetic/ameliorative effect of P. terebinthus by against STZ-induced severe diabetic disorders like hepatopathy, nephropathy, oxidative stress, hyperlipidemia.

Diabetes mellitus is accompanied with elevated glycogenolysis, lipolysis, gluconeogenesis. Additionally, the insulin failure is also known to reduce the protein content in muscular tissue by promoting proteolysis. Diabetes diabetes is closely related to live weight loss (Chatterjee and Shinde, 2002). It may also be reported that induction of hyperglycaemia and hypoinsulinemia using streptozotocin or alloxan by triggering trigger catabolism of fats and proteins causes loss in the body weight of diabet-induced animals (Zafar and Naeem-ul-Hassan Naqvi, 2010; Ewenighi et al., 2015). Therefore, weight loss is a very common condition in diabetes. As summarized in Table 1 of this study, there was notable the loss of body weight in the DM group, while on the *P. terebinthus* extract group was not detected any changes. Declined in body weight seen

in diabetes mellitus could be due to use of metabolic fuels other than glucose such as fats and body proteins, as diabetic animals could not use glucose due to lack of insulin and/or its action. Findings of this experiment are in agreement with the findings of previous studies. Treatment of *P. terebinthus* extract in diabetic rats was resulted with major improvement in the body weight gain. Inhibition of body weight loss is also thought a positive effect of *P. terebinthus* extract on energy metabolism.

Long-period damages of he chronic hyperglycemia and hyperlipidemia result in dysfunction and failure of various organs, especially the kidneys, liver, eyes, heart, blood vessels, and nerves (American Diabetes Association, 2008). The liver has been stated to be a central metabolic organ and its normal cell architecture is very affected when exposed to diabetic agents (Zhang et al., 2012). STZ administration in diabetic studies may elicite severe injury of hepatocytes and the other hepatic cells and architecture as histopathological findings including necrosis in hepatocytes, inflammatory cell infiltration, lipidosis (Rathinam et al., 2014; Uyar et al., 2017) severe vacuolization with picnotic nucleus and impairment in portal area (Gargouri et al., 2016). In this study, similar findings were detected in the DM group rats. There were notably reduced of histopathological damages in DM+ *P. terebinthus* group. Diabetic nephropathy is one of the most severe complication of DM including essential histopathological findings such as thickening of basal membranes, tubular degeneration and necrosis, glomerular cell (podocyte) loss (Forbes et al., 2008), inflamatuar cell infiltration, dilatation of tubuli, glomerular deterioration and atrophy (Yaman et al., 2017). This findings is in agreement with the results of present studies in DM group rats. The findings of the *P. terebinthus* treatment groups were found to be declined noteworthy; moreover, the similar appearance of the kidneys of control group rats was detected. It is reported that STZ-induced pancreatic β-cells was investigated in lots of studies, and β-cells were thought to be damaged due to production of ROS (Kanter et al., 2004). In histopathological study, small and shrunken islets and destruction of beta cells like hydropic degeneration and picnotic nucleus formation were seen in the diabetic rats (Ilango and Chitra., 2009). In this study, the structures of the islets of Langerhans was determined deteriorated and atrophied in DM group rats, and endocrine cells showed significant hydropic degeneration and picnotic nucleus formation as a result of STZ induced. These histological findings were observed to be consistent with

the previous studies (Talchai et al., 2012; Uyar et al., 2017). The findings was determined to be notably declined as a result of *P. terebinthus* administration, and the islets of Langerhans of DM + *P. terebinthus* administration group consisted of well-formed islets were found to be in a similar histological appearance with the control group. These results indicated that *P. terebinthus* extract may substantially ameliorated hepatorenal and pancreatic damages associated with diabetes.

Some parameters such as AST, ALT, ALP, GGT, LDH, CRE, BUN and Urea are considered sensitive indicators of the hepatorenal damage or dysfunction indicating inflammation, lesions or obstruction (Doğan and Celik., 2016). Hepatotoxic effects of STZ cause AST, ALT, GGT and ALP enzymes leaking out from the liver cytosol into the blood circulation (Navarro et al., 1993). When the cellular degeneration or destruction occured in tissue these enzyme levels elevate in serum (Hassoun and Stohs, 1995). Additionally, LDH activity increases due to liver, muscle and heart damage (Aldrich, 2003). Raised ALP activity indicates bone and liver diseases or bile duct obstruction (Mayne, 1994). Raising in serum CRE, BUN and Urea parameters reflects active renal damages or disfonction. BUN and CRE are major biomarkers for assessment of glomerular filtration rate (He et al., 2006). Previous studies showed the increases in AST, ALT, ALP (Daisy et al., 2009), LDH, CRE and Urea activity in the serum of diabetic rats (Ozkol et al., 2013). In this study, STZ administration caused severe hepatorenal damage, as evidenced by the noteworthy increase in serum AST, ALT, ALP, LDH, GGT, CRE, BUN and urea levels in diabetic rats compared to control rats. On the other hand, *P. terebinthus* treatment showed a tissue regeneration and notably decline this parameters in serum, indicating a ameliorative role for against hepatorenal damages.

Diabetes mellitus may also be related to other metabolic failure as hypercholesterolemia (El-Sabbagh et al., 2014). Therefore, the levels of serum lipids like TG, TC, LDL and HDL are increased in diabetes mellitus and the abnormal high levels of serum lipids in diabetes mellitus due to elevate in the mobilization of free fatty acids from fat deposits (Rhoads, et al., 1976) is an important risk for complications such as coronary heart disease in particular (Goodman and Gilman, 1985). The lowering of lipid concentration levels through dietary or drugs treatment seems to be associated with

a decline in the risk of vascular disease (Betteridge, 1997). High levels concentration of TC and, more importantly, LDL are essential coronary risk factors, and low plasma levels of HDL is associated with cardiovascular risk factor (Gordon and Rifkind, 1989). In diabetic rats, the rise in TC and TG is associated with the increase in LDL and decrease in HDL. Diabetic rats with FE treated brought TC and TG back to near normal levels, which could be due to an increase in insulin secretion, which, in turn, inhibits hormone sensitive lipase and increases the utilization of glucose and thereby decreasing the mobilization of free fatty acids from the fat depots. The diabetic rats treated with FE extract showed an elevation in HDL and reduction in LDL as evidenced by decreased levels of TC and TG. Lowering of serum and tissue lipids through diet or drug seems to be associated with a decline in the risk of vascular disease (Al-Shamaony et al., 1994). In this study, levels of lipid profile showed that the *P. terebinthus* extract might have positive effects on lipid metabolism.

Many studies of STZ-induced diabetes have been shown that the immune reaction was decreased against the insulin antibodies in the β-cells of Langerhans islets of diabetic animals (El-Kordy et al., 2015, Uyar et al., 2017). Langerhans islets were determined to be protected morphologically thanks to the supplemantation with plant extracts, and the immune reaction was reported to be enhanced for the insulin antibodies (Wang et al., 2017). In this study, diabetic rats had a very weak insulin positive immunreaction in the Langerhans islets compared to the control group. The immunohistochemical findings against the insulin antibodies in the β-cells presented in this experiment confirm the results reported by above mentioned researchers who detected a decreased insulin immunoreactive β-cells in the Langerhans islets of diabetic rats. In PTY groups, insulin positive immunestaining areas were found to be elevated significantly. These results showed that *P. terebinthus* could be induce notably prevention in the functioning of β-cells from oxidative stress as evidenced by the elevated serum insulin level.

These results showed that *P. terebinthus* have a ameliorative impact on liver, kidney and pancreas injury in STZ-induced diabetic animals probably due to its antidiabetic and antihyperglycemic effect and provides a novel therapeutic strategy for

the diabetic damages. Therefore, *P. terebinthus* administration is thought to be helpful in the treatment of diabetes related complications.

## SUMMARY

**Abdulrahman NT, A Histopathological, Immunohistochemical and Biochemical Investigation on the Antidiabetic Effects of the *Pistacia terebinthus* in Diabetic Rats. Van Yuzuncu Yil University, Institute of Health Science, Veterinary Faculty, Department of Pathology, Master Science Thesis, Van, 2017**. This investigation aimed to determine the antidiabetic activity of *P. terebinthus* extracts on histopathological and immunohistochemical alters in β-cells of streptozotocin (STZ)-induced diabetic rats. A total of forty healthy adult Wistar albino male rats were divided randomly into five groups as Control group (C), Diabetic group (D), Diabetes + Acarbose (DA) Diabetes + *Pistacia terebinthus* (DPT), *Pistacia terebinthus* (PT). Diabetes was established by STZ intraperitoneally (IP) a single-dose STZ injection in a dose of 55 mg/kg body weight. DPT and PT groups received in addition *Pistacia terebinthus* for 28d via orogastric gavage and Diabetic Acarbose (DA) group at 20 mg/kg bw was used as a reference drug. Blood glucose levels were recorded throughout the all experiment period. Hepatorenal and pancreatic protection by FE extracts was further supported by the almost normal histology in diabetic ratlarda with PT supplemented-treated as compared to histopathological changes such as inflammatory cell infiltration, hydropic degeneration and necrosis in the STZ-treated rats. Insulin immunoreactivity in β-cells of pancreas decreased in the DM group, whereas administration of supplementary *Pistacia terebinthus* helped restore the degenerative effects of STZ in the DPY group. Declined levels of blood glucose AST, ALT, ALP, GGT, LDH, CRE, BUN, Urea and lipid profile levels including TG, TC, HDL and LDL were detected in plant extract supplemented diabetic group. In sum up, *Pistacia terebinthus* has a protective impact on liver, kidney and pancreas tissues damage probably due to its antidiabetic effect in STZ-induced diabetic rats.



**Key words:** Diabetes, Histopathology, Immunohistochemistry, *Pistacia terebinthus*, Rat.

## ÖZET

**Abdulrahaman NT, Menengiç'in (*Pistacia terebinthus*) Diabetik Ratlar Üzerindeki Antidiabetik Etkisinin Histopatolojik, İmmunohistokimyasal ve Biyokimyasal Olarak Araştırılması. Van Yüzüncü Yıl Üniversitesi, Sağlık Bilimleri Enstitüsü Veteriner Fakültesi, Patoloji Anabilimdalı, Yüksek Lisans Tezi, Van, 2017.** Bu çalışmada, streptozotosin (STZ) ile oluşturulan diyabetik rat modelinde, karaciğer, böbrek ve pankreasta meydana gelen histopatolojik ve immunohistokimyasal değişiklikler ile biyokimyasal parametreler üzerine Menengiç'in (*Pistacia terebinthus*) koruyucu etkinliği araştırıldı. Kırk adet Wistar albino cinsi rat; Kontrol (K); Diyabet (D); Diyabet + Akarboz (DA); Diyabet + Menengiç yağı (DPT); Menengiç yağı (PT) olmak üzere 5 gruba ayrıldı. Deneysel diyabet 55 mg/kg streptozotosinin intraperitoneal (i.p.) olarak tek enjeksiyonu ile gerçekleştirildi. Menengiç yağı günlük 2 ml dozda 28 gün boyunca gavaj olarak verildi. Sıçanların kan glukoz düzeyleri ve canlı ağırlıkları deney süresince kaydedildi. Karaciğer kesitlerinin histopatolojik incelenmesinde, diyabetik sıçanlarda hepatositlerde dejenerasyon ve nekroz, portal alanlarda yangısal hücre infiltrasyonu, fibrozis ve safra kanalı hiperplazisi görüldü. Böbrek kesitlerinde tubulus epitel hücrelerinde dejenerasyon ve nekrozlara rastlandı. Pankreas kesitlerinde Langerhans adacıklarının belirgin hücre kaybı sonucu normal görünümünü kaybettiği gözlendi. Bu histopatolojik değişiklikler STZ ile birlikte Menengiç yağı verilen grupta önemli derecede azalmıştı. Pankreasın immunohistokimyasal incelenmesinde sadece STZ verilen diyabet grubunun Langerhans adacıklarında İnsulin boyaması negative yakın bir görünüm arzederken STZ ile birlikte Menengiç yağı verilen grupta insülin boyanması kontrol grubuyla benzerdi. Biyokimyasal incelemelerde diyabet grubuna göre DPT grubunda, Glucose, ALT, AST, ALP, LDH, Triglyceride, Cholesterol, Urea and Creatinine parametrelerinde düzelmeler görüldü. Sonuç olarak, Menengiçin karaciğer, böbrek ve pankreasta diyabet ve diyabet komplikasyonlarına bağlı olarak gelişen olumsuzluklara karşı koruyucu etkiye sahip olduğu sonucuna varılmıştır.



**Anahtar Kelimeler:** Diyabet, Histoptoloji, İmmunohistokimya, Menengiç (*Pistacia terebinthus*), Rat.

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## CARRICULUM VITAE

Nabaz Taher ABDULRAHAMN, I am from Rwanduz city in the North Iraq. I was born on April 10, 1992 in Rwanduz. I was completed elementary, and High Schools in Rwanduz, after that I went to Duhok city to begin the undergraduate admission process at the University of Duhok in the College of Veterinary Medicine during the years (2010-2015), and I was awarded a Bachelor's degree in Veterinary Medicine and Surgery (BVM&S). I got admission in Van Yuzuncu Yil University in Turkey at February of 2016 and began postgraduate studies at Institute of Health Science in Faculty of Veterinary Medicine in the Department of Pathology during the years (2016-2018).

# ATTACHMENTS

**Attachemnt 1.** Ethics committee project permission form

**T.C.**
**YÜZÜNCÜ YIL ÜNİVERSİTESİ**
**HAYVAN DENEYLERİ YEREL ETİK KURULU**

**ARAŞTIRMA BAŞVURU ONAY BELGESİ**

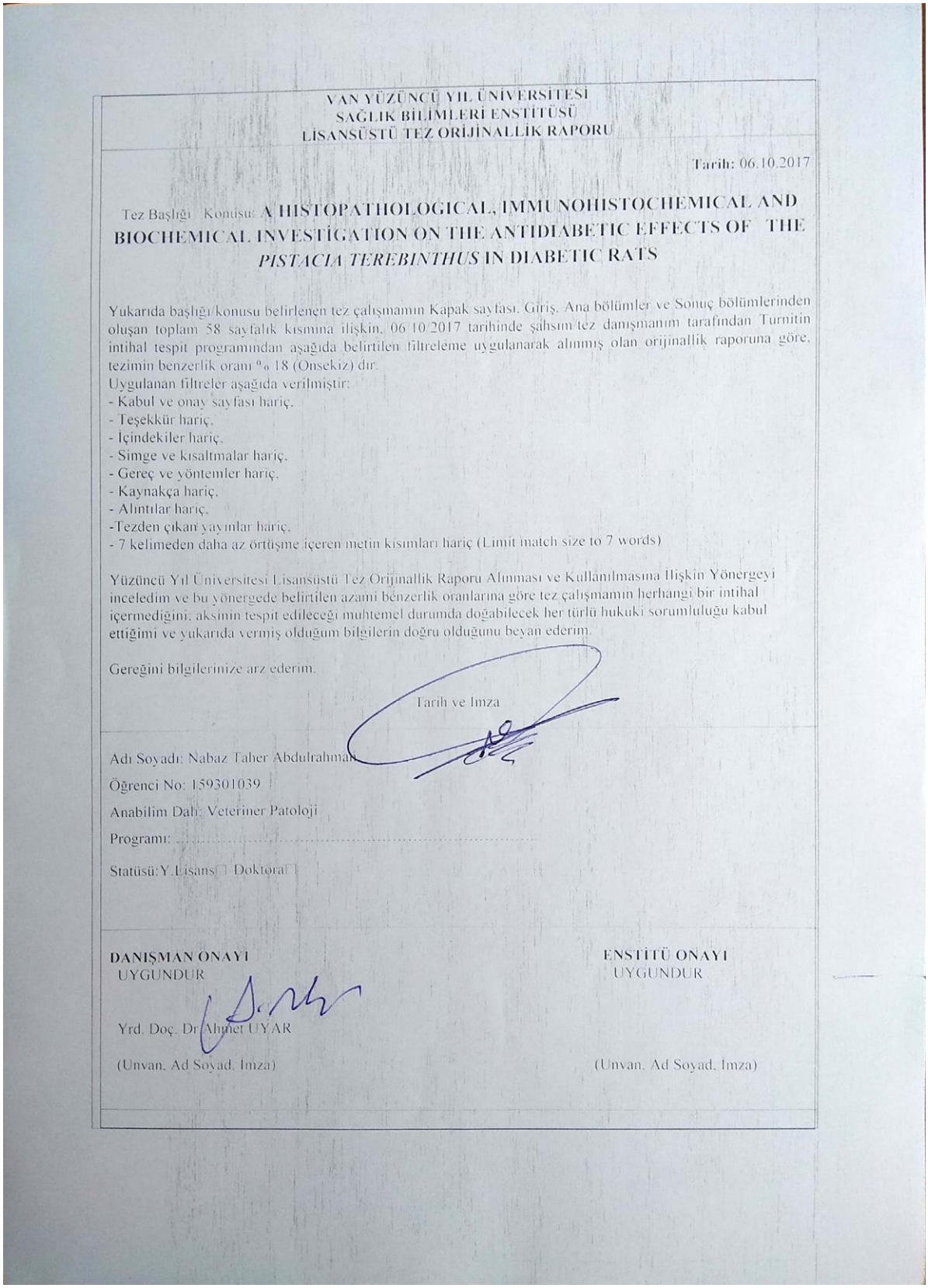
| | | |
|---|---|---|
| | Araştırmanın Adı | Menengiç'in (*Pistacia terebinthus*) Diabetik Ratlar Üzerindeki Antidiabetik Etkisinin Histopatolojik, İmmunohistokimyasal ve Biyokimyasal Olarak Araştırılması |
| | Araştırmanın Yürütücüsü | Yrd. Doç. Dr. Ahmet UYAR |
| | Yardımcı Araştırıcılar | Yük. Lis. Öğr. Nabaz Taher ABDULRAHMAN |
| | Kurumu | Veteriner Fakültesi |
| | Araştırmanın Tahmini Süresi | 12 Ay |
| | Kullanılacak Hayvan Türü ve Sayısı | Sıçan 40 Adet |
| | Destekleyecek Kuruluş (lar) | YYÜ Bilimsel Araştırma Proje Başkanlığı |
| | Başvuru Tarihi | 24.01.2017 |

| | | |
|---|---|---|
| **KARAR BİLGİLERİ** | **Karar No:2017/01** | **Tarih:26.01.2017** |
| | Yüzüncü Yıl Üniversitesi Veteriner Fakültesi öğretim üyesi/elemanı Yrd. Doç. Dr. Ahmet UYAR sorumluluğunda yürütülmesi planlanan ve yukarıda başvuru bilgileri verilen yüksek lisans projesi gerekçe, amaç ve yöntemler dikkate alınarak ilgi başvuru belgeleri incelendi. Çalışmanın etik açıdan uygun olduğuna, projenin aşağıdaki hususlar dikkate alınarak yürütülmesine ve proje yürütücüsüne iletilmesine oy birliği / oy çokluğu ile karar verildi.<br>1) Projede herhangi bir değişiklik gerektiğinde kurulumuzdan onay alınması.<br>2) Projede çalışacağı bildirilen araştırıcılarda değişiklik olduğunda kurulumuzdan onay alınması.<br>3) Deney hayvanları üzerinde yapılacak girişimin başlangıç ve bitiş tarihlerinin bildirilmesi.<br>4) Çalışma süresinde tamamlanamaz ise ek süre talebinde bulunulması.<br>5) Çalışma tamamlandığında sonuç raporunun gönderilmesi. | |

| | | |
|---|---|---|
| | **BAŞKAN/CHAİR**<br>Prof. Dr. Semiha DEDE | |
| **ÜYE**<br>Prof. Dr. Fazıl ŞEN | **ÜYE**<br>Prof. Dr. Sıddık KESKİN | **ÜYE**<br>Prof. Dr. Suphi DENİZ |
| **ÜYE**<br>Prof. Dr. N. Tuğba BİNGÖL | **ÜYE**<br>Doç. Dr. Atilla DURMUŞ | **ÜYE**<br>Doç. Dr. Abdulbaki AKSAKAL |
| **ÜYE**<br>Doç. Dr. Nalan ÖZDAL | **ÜYE**<br>Yrd. Doç. Dr. Özer ALKAN | **ÜYE**<br>Yrd. Doç. Dr. Ferda KARAKUŞ |
| **ÜYE**<br>Yrd. Doç. Dr. Canser Yılmaz DEMİR | **ÜYE**<br>Yrd. Doç. Dr. Yıldıray BAŞBUĞAN | **ÜYE**<br>Zir. Müh. Kenan YILDIRIMOĞLU |
| **ÜYE**<br>Vet. Hek. İsmail Hakkı BEHÇET | | |

***Bu form YÜHADYEK tarafından doldurulacaktır.**

**Attachment 2**. Intihal Raporu



VAN YÜZÜNCÜ YIL ÜNİVERSİTESİ
SAĞLIK BİLİMLERİ ENSTİTÜSÜ
LİSANSÜSTÜ TEZ ORİJİNALLİK RAPORU

Tarih: 06.10.2017

Tez Başlığı / Konusu: A HISTOPATHOLOGICAL, IMMUNOHISTOCHEMICAL AND BIOCHEMICAL INVESTİGATION ON THE ANTIDIABETIC EFFECTS OF THE *PISTACIA TEREBINTHUS* IN DIABETIC RATS

Yukarıda başlığı/konusu belirlenen tez çalışmamın Kapak sayfası, Giriş, Ana bölümler ve Sonuç bölümlerinden oluşan toplam 58 sayfalık kısmına ilişkin, 06/10/2017 tarihinde şahsım/tez danışmanım tarafından Turnitin intihal tespit programından aşağıda belirtilen filtreleme uygulanarak alınmış olan orijinallik raporuna göre, tezimin benzerlik oranı % 18 (Onsekiz) dir.
Uygulanan filtreler aşağıda verilmiştir:
- Kabul ve onay sayfası hariç,
- Teşekkür hariç,
- İçindekiler hariç,
- Simge ve kısaltmalar hariç,
- Gereç ve yöntemler hariç,
- Kaynakça hariç,
- Alıntılar hariç,
-Tezden çıkan yayınlar hariç,
- 7 kelimeden daha az örtüşme içeren metin kısımları hariç (Limit match size to 7 words)

Yüzüncü Yıl Üniversitesi Lisansüstü Tez Orijinallik Raporu Alınması ve Kullanılmasına İlişkin Yönergeyi inceledim ve bu yönergede belirtilen azami benzerlik oranlarına göre tez çalışmamın herhangi bir intihal içermediğini; aksinin tespit edileceği muhtemel durumda doğabilecek her türlü hukuki sorumluluğu kabul ettiğimi ve yukarıda vermiş olduğum bilgilerin doğru olduğunu beyan ederim.

Gereğini bilgilerinize arz ederim.

Tarih ve İmza

Adı Soyadı: Nabaz Taher Abdulrahman
Öğrenci No: 159301039
Anabilim Dalı: Veteriner Patoloji
Programı: .....
Statüsü: Y.Lisans ☐ Doktora ☐

**DANIŞMAN ONAYI**
UYGUNDUR

Yrd. Doç. Dr. Ahmet UYAR

(Unvan, Ad Soyad, İmza)

**ENSTİTÜ ONAYI**
UYGUNDUR

(Unvan, Ad Soyad, İmza)