Original Article

TJVR 2019; 3(1): 13-20

Turkish Journal of Veterinary Research

http://www.dergipark.gov.tr/tjvr

e-ISSN: 2602-3695

The effects of *Juniperus communis* (Cupressaceae) oil application on the serum paraoxonase and pancreatic enzymes activities and lipid levels in experimental diabetic rats

Evan Abdulkarim Mahmood[1] Tahir Kahraman[2]

[1] *Department of Pharmacy, Institute of Technology, Sulaimaniah, Iraq*
[2] *Department of Biochemistry, Faculty of Medicine, Karabuk University, Karabuk, Turkey,*

Correspondence: *Tahir Kahraman (drtahirkahraman@hotmail.com)*

Received: 11.03.2019 Accepted: 22.03.2019

ABSTRACT

Objective: The oil of *Juniperus communis* (JC) which is among medicinal plants, has many pharmacological activities. In this study, the effects of JC oil on serum paraoxonase (PON_1), pancreatic enzymes levels and lipid levels in experimental diabetic rats were investigated.

Materials and Methods: Thirty-two male Wistar-Albino rats (250-300g) were used. The rats were divided equally into four groups, control (C), diabetes (D), *JC* oil (J), and diabetes + *JC* oil (DJ). D and DJ groups were intraperitoneally (IP) injected with 45 mg/kg streptozotocin (STZ). *JC* oil was administered as 200 mg/kg/21 days by oral gavage in J and DJ groups.

Results: Total cholesterol (TC) and triglyceride (TG) levels were significantly decreased in the J and DJ groups when compared to C and D groups ($p \leq 0.001$). There was no difference in TG levels between D and control group ($p \geq 0.05$). Lipoprotein levels were not statistically significant between any group ($p \geq 0.05$). Comparing to the control group in the diabetes and DJ groups; significant decreased amylase levels and increased lipase levels ($p \leq 0.001$) was observed. Paraoxonase activity in D group was statistically lower than in the other groups ($p \leq 0.05$). There is no significant difference between the C group and the *J* group ($p > 0.05$). PON_1 level has a significant elevation in the DJ in comparison with the D group ($p \leq 0.05$).

Discussion: As a result, JC oil caused an increase in antioxidant PON_1 enzyme level and a decrease in lipid levels in diabetes. The data obtained are supportive that *JC* oil may be a potential protective effect against diabetes-associated complications.

Keywords: *Diabetes, Juniperus communis oil, Paraoxonase, Lipoproteins, Lipids, Pancreatic enzymes*

INTRODUCTION

Diabetes mellitus (DM) is a diverse group of metabolic diseases that is characterized by chronic hyperglycaemia and abnormalities in carbohydrate, lipid and protein metabolism. Chronic and postprandial hyperglycaemia is mainly responsible for the acute, short term, and late complications that affect all organs and systems in the body (Benjamin et. al. 2016).

Diabetes and its complications is a leading cause of death and paralysis, reducing total and healthy life expectancy (Alberti and Zimmet, 1998). DM increases the risk of microvascular damage (eg, retinopathy, nephropathy and neuropathy) (Alexandru et al., 2016). Hyperglycaemia in the course of diabetes contributes to the oxidative stress, causing the redox balance of the body to change into excessive production of reactive oxygen species (Prasath et al. 2013).

There are a number of plants that have been proved worldwide to be useful for treatment of DM disease and known to have hypoglycaemic activities (Akdogan et al., 2012; Yegin et al. 2013; Çiftçi et al. 2017). The mechanisms, by which the herbs generally act, are not fully established, but most of medicinal plants possess antioxidant activities. These plants have been shown to be effective by this property is various conditions including diabetes, cancer, memory deficit, Alzheimer's disease, atherosclerosis, diabetes and cardiovascular diseases. Antioxidant activities of herbal medicines are also effective in reducing the toxicities of toxic agents or other drugs (Karimi et al., 2015).

JC oil is used as a herbal medicine because it has therapeutic advantages and used for treatment of many diseases such as arthritis, diabetes, cancer and kidney disorders. *JC* oil has many pharmacological activities including hepatoprotective, antibacterial, anti-inflammatory and antidiabetic activities (Seca and Silva, 2005). Oil obtained from *JC* fruit by means of hydroxylation method was found to be composed of monoterpene hydrocarbon (22.97%), oxygenated monoterpene (14.86%), sesquiterpene hydrocarbon (32.43%), oxygenated sesquiterpene (6.75%), diterpene (1.35%), and others (21.62%) (Tuzmen and Hafizoğlu 2004).

Paraoxonase (PON_1) is a serum esterase that synthesized in the liver and associated with the "good" cholesterol high density lipoprotein (HDL). Population diabetes mellitus was shown to have marked reductions in serum paraoxonase activity without having a significantly lower HDL cholesterol concentration and this shows that serum paraoxonase activity is low in insulin-dependent diabetics (Mackness et al., 2002; Çiftçi et al., 2017). PON_1 is a potent anti-diabetic enzyme that exerts this protection against diabetes through its antioxidative characteristics and by its insulin stimulation properties on β-cells. The PON_1 activity and concentration are highly variable in humans. Both quality and quantity of the enzyme in serum are important in an individual for risk of developing cardiovascular disease (Koren-Gluzer et al., 2011).

The aim of this study is to investigate the effect of *JC* oil with antioxidant/oxidant status, and antidiabetic properties (hiperglisemia, hyperlipidaemia) on serum paraoxonase and pancreatic enzymes activity, lipid and lipoprotein levels in rats with experimentally diabetes induced rats.

MATERIALS and METHODS

JC oil

The cold infiltration form which was produced by *JC* oil, was purchased from Nature Derman Food, Drugs Firm, Bursa, Turkey. *JC* oil was dissolved in distilled water containing 0.5% sodium carboxyl methyl cellulose (CMC).

Animals

In this study, 32 male Wistar-Albino rats weighing 250-300 g were acquired from the Experimental Animal Unit of Van Yuzuncu Yil University, Faculty of Medicine. Subjects were divided equally into four experimental groups, control (C), diabetes generated (D), *JC* oil given (J), diabetes induced, and *JC* oil given (DJ). The rats were accommodated in cages, in which feed and fresh water were present all the time, in the rooms adjusted for a temperature of 22±2 °C, applied for 12 hours in darkness / light during the three weeks trial period. Experiments conducted according to ethical rules and carried out under the supervision of Van Yuzuncu Yil University Animal Experiments Local Ethics Committee (2016-04).

Experimental animal design

Diabetes was induced in D and DJ groups by injecting 45 mg/kg single dose of streptozotocin (Sigma, Germany) dissolved in citrate buffer PH: 4.5 intraperitoneally (IP) (Vardi et al. 2005). 200 mg/kg of *JC* oil extract was administered to the rats of J group, DJ group with intragastric gavage (Petlevski et al., 2001). Experimental animal desing were given in Table 1.

Control group (C): Eight rats were randomly selected as the control group. 45mg/kg single dose of physiological serum was injected intraperitoneally (IP). The feed was collected at 8^{oo} AM daily, and removed from rats of this group and rats were given distilled water with 0.5% of carboxymethyl cellulose (CMC) orally by gavage at 10^{oo} AM.

Diabetes group (D): It contains eight male rats which exposed to single dose of 45 mg/kg of streptozotocin in citrate buffer intraperitoneally. After 72 hour of injection, blood glucose was measured using glucometer (eBsensor, Taiwan), and rats with more than 300 mg/dl blood glucose were considered diabetic. Also, this group was feed only standard diet. The feed was collected at 8^{oo} AM daily, and removed from rats of this group and every rat were given distilled water (contents 0.5% of CMC) orally by gavage at 10^{oo} AM.

Table 1. Preparation of the experimental animal

Control group (C)	Diabetes group (D)	*Juniperus communis* oil (J)	Diabetes+ *J. communis* oil (DJ)
Distilled water (contents 0.5% of CMC)	STZ (45mg/kg) Distilled water (contents 0.5% of CMC)	(200 mg/kg of *JC* oil and dissolved in distilled water (contents 0.5% of CMC)	STZ (45mg/kg) + (*JC* oil and dissolved in distilled water (contents 0.5% of CMC)

***JC* oil group (J):** Every day, the feed of rats was collected at 8^{00} AM. *Juniperus communis* oil was given dissolved distilled water (contents 0.5% of CMC) and eight rats were applied orally by gavage for 21 days as 200 mg/kg/day at 10^{00} AM.

Diabetes and *JC* oil group (DJ): Diabetes was induced in this group by injecting single dose of 45 mg/kg Streptozotocin (Sigma, Germany) dissolved in citrate buffer intraperitoneally given. After 72 hours, blood glucose has been examined using glucometer using strips and glucometer (eBsensor, Taiwan) and rats with more than 300 mg/kg blood glucose were considered diabetic. Every day, the feed of rats was collected at 8^{00} AM. *Juniperus communis* oil was given dissolved distilled water (contents 0.5% of CMC) was applied orally by gavage to those rats with blood glucose levels of 300 mg/dL and above, at 21 days as 200 mg/kg/day at 10^{00} AM.

Sample collection

After 21 days of the experimental regime, blood was withdrawn from heart puncture into both jell tubes and EDTA tubes under ketamine anesthesia. Blood collected in jell tubes were centrifuged (3000 rpm at 4^{o}C) for 10 minutes. Then the separated serum was transferred to eppendorf tubes. Blood glucose in serum and Hb1Ac levels in total blood were measured on the same day. The serum was stored at -20 ° C until analysis of other parameters.

Biochemical analysis

At the end of the study, biochemical parameters of serum glucose, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein- cholesterol (LDL-C), total cholesterol (TC), total triglycerides (TG), amylase and lipase were determined using commercial kits (Roche, Germany) and biochemical autoanalyzer model HITACHI/P800 supplied by (Roche, Germany). HbA1c was also determined from EDTA tubes blood at the same day using commercial kits and COBAS Integra 800 auto analyser supplied by Roche, Germany. Spectrophotometric method was used in the determination of paraoxonase activity in serum. This enzyme was examined using commercial kit from Rel assay, Gaziantep, Turkey (Catalog Number 1027010).

Statistical analysis

At the end of the study, all data from groups for every biochemical parameter were analyzed using SPSS program pack 13.0. Comparisons among groups were done using nonparametric Kruskal-Wallis test first and then the Mann-Whitney U-test as the post hoc test correction was used. Data were given as mean ± SD (standard deviation) and *p*-values≤0.001 and ≤0.05 were considered statistically significant, respectively.

RESULTS

The levels of serum glucose, HbA1c, total cholesterol, total triglycerides, lipoproteins (HDL-C, LDL-C and VLDL-C), exocrine pancreatic functions (amylase and lipase), and paraoxonase in all experimental groups were shown in Table 2.

There is a significant increase in serum glucose level in the D group when compared to control group (p≤0.001). No significant difference can be seen in glucose level between control group and *JC* group (J) (p≥0.05). Glucose level was decreased significantly in the DJ group when compared to D group (p≤0.001) (Table 2).

Level of HbA1c in Table 2 were significantly increased only in the D group and decreased significantly in DJ group when compared to the C group (p≤0.001). There is no significant difference between the C group and *JC* oil group (p≥0.05). In comparison between both the D and the DJ groups, a significant decrease can be seen in the DJ group (p≤0.001).

Serum total cholesterol level was considerably increased in the D group comparison with C group (p≤0.001). Level of total cholesterol in the *J* group is significantly elevated when compared to the C group (p≤0.001). A significant decrease in total cholesterol level can be seen in the DJ group compared to the D group (p≤0.001) (Table 2).

Serum triglyceride levels between the C group and the D group showed no significant difference (p≥0.05). Serum triglyceride level was decreased significantly in the *JC* group (J), when compared with the C group (p≤0.001). It is also significantly

decreased in the DJ group and the *J* group in comparison with the D group (p≤0.001) (Table 2).

Serum levels of lipoprotein (HDL-C, LDL-C, VLDL-C) showed no significant difference between the C group and both the D group and *J* groups. Also, no significant difference can be seen between D group and DJ group (p≥0.05) (Table 2).

Serum levels of amylase enzyme showed statistically significant lowering in the D group when it is compared to the C group (p≤0.001). No significant difference has been detected between the C group and *J* group (p≥0.05). Also, there is no significant difference between the D group and the DJ in amylase activity (p≥0.05) (Table 2).

Serum lipase enzyme level showed statistically significant elevation in diabetes group (D), when compared to control group (C) (p≤0.05). But there is no significant difference between the C group (C) and the *J g*roup and between the D group and the DJ in lipase activity (p≥0.05) (Table 2).

Serum paraoxonase-1 (PON_1) enzyme activity was significantly lower in the D group than in the C group (p≤0.05). There is no significant difference between the C group and the *J* group (p>0.05). PON_1 level has a significant elevation in the DJ in comparison with the D group (p≤0.05) (Table 2).

Table 2. Serum glucose, hemoglobin A1c, total cholesterol, total triglyceride, lipoprotein, lipase, amylase and paraoxonase levels of rats in groups.

	Control (C)	Diabetes (D)	*JC oil* (J)	Diabetes+*JC oil* (DJ)	*P*
Glucose (mg/dL)	156±37 a	636±83 c	206±33 a	497±118 b	0.001
HbA1c (%)	3.78±0.13 a	8.04±0.76 c	3.80±0.12 a	6.89±1.59 b	0.001
TC (mg/dL)	56±9 a	76±10 c	65±6 b	60±3 ab	0.001
TG (mg/dL)	88±1 b	100±3 b	55±2 a	46±5 a	0.001
HDL-C (mg/dL)	52±13 a	58±4 a	57±7 a	57±6 a	0.455
LDL-C (mg/dL)	20±7 a	25±4 ac	30±6 c	25±4 ac	0.019
VLDL-C (mg/dL)	18±2 b	20±6 b	12±5 a	10±1 a	0.001
Amylase U/L	1073±75 b	692±253 a	1074±71 b	676±91 a	0.001
Lipase (U/L)	7.63±1.30 a	20.88±7.77 b	8.87±2.80 a	23.00±7.67 b	0.001
PON_1 (U/L)	33.07±31.94 b	3.17±4.94 a	54.13±26.43 b	36.45±18.73 b	0.05

Differences between mean values with different letters are significant (P≤0.001-0,05).

HbA1c , Hemoglobin A1c; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; PON_1, paraoxonase. Data were expressed as mean±SD

DISCUSSION

Diabetes mellitus and its complications are among today's most common diseases and the incidence is increasing. Among the complications high blood cholesterol and triglyceride levels are two of the fundamental reasons underlying serious health problems, primarily atherosclerosis and heart diseases, of people today. For this reason, retaining the blood cholesterol levels at normal levels is important to stop the progression of numerous diseases. Many traditional plant treatments for diabetes have been used all over the world; in this study we used *JC* plant oil as anti-diabetic plant that used to prevent diabetes mellitus disease. Moreover, Swanston-Flatt et al. (1990) studied the effect of several plants including *JC* on glucose homeostasis. These plants have been used as traditional treatments for diabetes mellitus.

Several studies showed that plants may cause an increase in beta cells in the pancreas by activating regeneration of insulin secreting cells (Abdel-Moneim et al., 1997). Additionally, fibre content of plants is known to interfere with the carbohydrate content in the process of intestinal absorption lowering blood glucose levels (Nelson et al., 1991). *JC* has a strong antioxidant activity among traditional plants. This activity might have preventive effects against protein glycation. This activity has also roles in alleviating diabetic macro vascular and micro vascular complications (Asgary et al., 2014).

In addition to *JC* oil, another critical reason, behind the inhibitory effect of *JC* plant on glucose and HbA1c, is that this plant contains flavonoids which are a group of polyphenolic compounds ubiquitously found in plants including fruits and vegetables. Natural flavonoids can be used as alternative blockers of cellular glucose uptake in vitro (Jae, 1999).

Antioxidant phytoconstituents are the secondary constituents or metabolites naturally found in plants such as fruits and vegetables. Plants produce a various types of antioxidant compounds such as carotenoids, flavonoids, cinnamic acids, benzoic acids, folic acid, ascorbic acid, tocopherols and tocotrienols. Several synthetic antidiabetic drugs like glipalamide, metformin, and repaglinide also possess antioxidant activity, so this shows a similarity–between natural–antioxidant substances and synthetic drugs (Venkatesh and Sood, 2011).

In the current study, cholesterol, triglyceride, were significantly decreased after the treatment of diabetic rats with the *JC* plant oil. The inhibitory effects of this plant are consistent with many other studies.

Another study showed that *JC* oil also decreased the cholesterol levels in diabetic rats but in that study, cholesterol containing diet was used to induce hypercholesterolemia, then they used different doses of the plant oil detecting different hypocholesterolemic activities (Akdogan et al., 2012).

Constituents in *JC* are important in cholesterol reducing activity. Several mechanisms were suggested to clarify the inhibitory effect of plant sterols and stanols against cholesterol levels. First, plant sterol competes with cholesterol to unite with micelle thus leading to lower cholesterol absorption. Second, plant sterol competes with cholesterol to enter through the cell membrane in the intestines, thus leading to low cholesterol absorption. Finally, by the action of these substances, the soluble cholesterol transforms into non-soluble cholesterol, which prevents absorption. Thus, cholesterol is excreted through feces (Williams and Gokool, 2005).

In this study, the level of serum triglycerides was decreased significantly in diabetic rats after using the plant. Diabetic dyslipidaemia is regarded as a major risk factor for diabetic complications and has been widely investigated. Macro and micro angiopathies in diabetic dyslipidaemia are characterized by nephropathy, neuropathy, retinopathy, and complications belonging to cardiovascular, cerebrovascular and peripheral vascular systems (Habib and Aslam, 2003).

In the present study, the level amylase was decreased in the diabetes in comparison to control group. The same conclusion was reported by other previous researchers and it was suggested that low serum amylase in diabetes was associated with increased risk of metabolic abnormalities (Nakajima et al., 2011). The reduction in the serum pancreatic amylase was recorded in both types of diabetes, which amounted to 71% for type 1 diabetics and 49% for type 2 diabetics. On the other hand, the reduction in serum amylase in type 2 diabetes was higher in patients with longer duration of illness (59%) and in patients with low serum insulin value (79%), while reduction in serum lipase was only detected in patients with very low serum insulin (34%) (Augsteen et al., 2005).

In the current study, a slight decrease in the levels of amylase can be seen in diabetic rats after the treatment *JC* oil; however, this decrease was not statistically significant. Other previous studies showed that *JC* oil exhibited a strong inhibitory effect on amylase enzyme (Najafian et al., 2011; Jumepaeng et al., 2013).

Substances that are inhibitors for α-amylase enzyme are available in plants such as polyphenolic compounds and glycoproteins (Babu et al., 2013). The inhibition of amylase enzyme by *JC* may be due to the presence of some secondary metabolites such as lignans, coumarins, sterols, aliphatic compounds, and other terpenes in the hydro alcoholic extract. Leaves and fruits of *JC* also contain relatively high amounts of monoterpene hydrocarbons such as α-pinene, limonene and β-myrcene which they result in lowering amylase enzyme (Lohani et al., 2013).

The natural bioactive compound available in *JC* including luteolin, β-pinene, and myrcene may also be inhibiting amylase enzyme activity. It was known that luteolin can cause a reduction in amylase enzyme activity (Kim et al., 2000). Steroids that are found in *JC* may also cause inhibition of amylase activity because of their effect on pancreatic secretion (Barzilai et al., 1986; Jelenković et al., 2014).

In the current study, the level of lipase was increased significantly in diabetes. The same results were found in some previous studies. It was known that nearly 25% of diabetic subjects showed an

increase in the pancreatic level to an extent that, the authors suggest that pancreas levels should be regarded as a parameter for diabetic diagnosis (Steinberg et al., 2014). Despite these findings occasional diabetic lipase reduction can be seen. In type 2 diabetes, the reduction in lipase activity was only detected in patients with very low serum insulin level (Augsteen et al, 2005).

In this study, the treatment of diabetic rats showed no considerable effect on lipase activity; however, this result disagrees with some studies that deal with the activity of anti-diabetic plant on lipase activity. A large study concluded that most of anti-diabetic plants have also anti-lipase activities. The study suggested using those plants for the treatment of obesity and diabetic dyslipidaemia due to their inhibitory effects on lipase activity. Further studies about the effect of *JC* on lipase activity may clarify the exact effect of this plant (Young and Hui, 2005).

The present study showed that diabetes was associated with a significant reduction in serum paraoxonase activity, this result has been shown also by other researchers (Gupta et al., 2011; Kota et al., 2013; Yegin et al., 2013; Çiftçi et al. 2017). Serum Paraoxonase-1 (PON_1) is an antioxidant enzyme that associated with high-density lipoproteins. Low PON_1 activity has been found in oxidative stress-associated processes as dyslipidaemia, advancing age, diabetes mellitus, and smoking. In diabetes, oxidative stress is related to the degree of insulin resistance, a key component of the metabolic syndrome (Senti et al., 2003). The decreased activities of serum Paraoxonase-1 (PON_1), an antioxidant enzyme has been shown to be related with dyslipidemia, diabetes mellitus, advanced age, hypertension, low HDL and increased oxidative stress (Turkoglu et al. 2008; Yegin et al., 2013).

In the current study, there is a significant decrease of PON_1 activity in the diabetes group compared to control group. After giving *JC* oil to the diabetic rats, PON_1 activity was increased significantly. This stimulatory effect on paraoxonase enzyme activity is shown for the first time and regarded as the main discovery for this study. Decreased serum PON_1 activity in diabetes may play an important role the in development of premature atherosclerosis and thereby cardiovascular diseases (Ferretti et al., 2001).

Strong antioxidant property of *JC* is regarded as a common cause of increasing activity of PON levels (Hoferl et al., 2014). Phytochemicals with antioxidant activity such as coumarins, phenylpropanoids, cinnamic acids, diterpenes, flavonoids, monoterpenes, lignans, tannins and triterpenes also are beneficial in protecting diabetes or diabetic complications (Montonen et al., 2004). Among the antioxidant substances, activities of radical scavenging of flavonoids are well understood (Lohani et al., 2013).

PON_1 levels have clinical significance, it was known that high-density lipoproteins (HDL) reduce the accumulation of lipid peroxides in LDL mainly due to paraoxonase enzyme activity proven via in vitro studies. PON_1 is responsible for the most of antioxidant properties of HDL, and because PON_1 is antioxidant and anti-inflammatory enzyme so deficiency of this enzyme results in inflammation and oxidative stress (Litvinov et al., 2012).

CONCLUSION

In conclusion, this study showed that JC oil enhances anti-diabetic activity by reducing both glucose and glycosylated hemoglobin levels. High blood cholesterol and triglyceride level are one of the fundamental reasons underlying serious health problems, primarily atherosclerosis and heart diseases, of people now a days. The oil of this plant showed that it could play a role in alleviating diabetic dyslipidemia as it reduced plasma lipid levels. Finally, the plant caused an increase in the paraoxonase activity in diabetic rats leading to increase in antioxidant activities in diabetic subjects.

The increase of antioxidant PON_1 enzyme level and a decrease in lipid levels in diabetes make of *JC* oil a potentially protective against the complications of diabetes.

ACKNOWLEDGMENTS

In this work, a piece of Evan Abdulkarim Mahmood's master thesis was utilized. Some of the data given in this article were presented as a poster presentation in "1st International Congress on Medicinal and Aromatic Plants" Konya/Turkey, 9-12/MAY/ 2017.

Ethical approval: The study was approved by judgement with 05.05.2016-2016-04 reference number of Van Yuzuncu Yil University Animal Experiments Local Ethics Committee.

Conflict of Interests: The authors declared that there is no conflict of interests.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

Abdel-Moneim A, El-Feki M, Salah E. Effect of Nigella sativa, fish oil and gliclazide on alloxan diabetic rats 1-biochemical and histopathological studies. *J Egy Ger Soci Zool* 1997; 23: 237-266.

Akdogan M, Koyu A, Ciris M, Yildiz K. Anti-hypercholesterolemic activity of *J. communis L* oil in rats: A biochemical and histopathological investigation. *J Biomed Res* 2012; 23(3): 321-328.

Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO Consultation. *Diabetic Med* 1998; 15(7): 539-553.

Alexandru N, Badila E, Weiss E, Cochior D, Stępień E, Georgescu A. Vascular complications in diabetes: Microparticles and microparticle associated MicroRNAs as active players. *Biochem Biophys Res Commun* 2016; 472(1):1-10.

Asgary S, Naderi GA, Shams Ardekani MR, et al. Inhibition of protein glycation by essential oils of branchlets and fruits of *J. communis* subsp. hemisphaerica. *Res Pharm Sci* 2014; 9(3): 179–185.

Augsteen AA, Abu-Umair MS, Mahmoud SA. Biochemical analysis of serum pancreatic amylase and lipase enzymes in patients with type 1 and type 2 diabetes mellitus. *Saudi Med* 2005; 26(1): 73-77.

Babu PV, Liu D, Gilbert ER. Recent advances in understanding the anti-diabetic actions of dietary flavonoids. *J Nutr Biochem* 2013; 24(11): 1777-1789.

Barzilai A, Medina JA, Toth L, Dreiling DA. The effect of steroid administration on pancreatic secretion during and after hypovolemic shock. *Int J Pancreatol* 1986; 1(5-6): 381-388.

Benjamin IJ, Griggs RC, Wing EJ, Gregory F. Andreoli and Carpenters Cecil essentials of medicine, 9th Edition, Elsevier /Saunders Philadelphia. 2016.

Çiftçi İN, Yur F, Yegin SÇ. Deneysel diyabet oluşturulan ve likopen uygulanan ratların karaciğer dokusunda paraoksonaz aktivitesinin incelenmesi. *Cum Univ Sağ Bil Enst Derg* 2017; 1: 01-08.

Ferretti G, Bacchetti T, Marchionni C, Caldarelli L, Curatola G. Effect of glycation of high-density lipoproteins on their physicochemical properties and on paraoxonase activity. *Acta Diabetol* 2001; 38(4): 163-169.

Gupta N, Binukumar BK, Singh S, et al. Serum paraoxonase-1 (PON_1) activities (PONase/AREarease) and polymorphisms in patients with type 2 diabetes mellitus In A North-West Indian Population. *Gene* 2011; 487: 88-95.

Habib SS, Aslam M. Risk factors, knowledge and health status in diabetic patients. *Saudi Med J* 2003; 24(11): 1219-1224.

Hoferl M, Stoilova I, Schmidt E. et al. Chemical composition and antioxidant properties of Juniper berry (J. communis l.) essential oil. Action of the essential oil on the antioxidant protection of Saccharomyces cerevisiae model organism. *Antioxidants* 2014; 3(1): 81-98.

Jae BP. Flavonoids are potential inhibitors of glucose uptake in U937 cells. *Biochem Biophys Res Commun* 1999; 260(2): 568–574.

Jelenković L, Jovanović VS, Palić I, Mitić V, Radulović M. In vitro screening of α-amylase inhibition by selected terpenes from essential oils. *Trop J Pharmac Res* 2014; 13(9): 1421-1428.

Jumepaeng T, Prachakool S, Luthria DL, Chanthai S. Determination of antioxidant capacity and α-amylase inhibitory activity of the essential oils from citronella grass and lemongrass. *Int Food Res J* 2013; 20(1): 481-485.

Karimi A, Majlesi M, Rafieian-Kopaei M. Herbal versus synthetic drugs; Beliefs and facts, *J Nephropharmacol* 2015; 4(1): 27–30.

Kim JS, Kwon CS, Son KH. Inhibition of alpha-glucosidase and amylase by luteolin, a flavonoid. *Bioscience Biotechnol Biochem* 2000; 64(11): 2458-2461.

Koren-Gluzer M, Aviram M, Meilin E, Hayek T. The antioxidant HDL-associated paraoxonase-1 (PON1) attenuates diabetes development and stimulates β-cell insulin release. *Atherosclerosis* 2011; 219(2): 510–518.

Kota SK, Meher LK, Kota SK, Jammula S, Krishna SV, Modi KD. Implications of serum paraoxonase activity in obesity, diabetes mellitus, and dyslipidemia. *Ind J Endoc Metab* 2013; 17(3): 402-412.

Litvinov D, Mahini H, Garelnabi M. Antioxidant and anti-inflammatory role of paraoxonase 1; implication in arteriosclerosis diseases. *N Am Med Sci* 2012; 4(11): 523-532.

Lohani H, Haider SZ, Chauhan NK, Sah S, Andola HC. Aroma profile of two Juniperus species from Alpine region in Uttarakhand. *J Nat Prod* 2013; 6: 38-43.

Mackness B, Durrington PN, Boulton AJ, Hine D, Mackness MI. Serum paraoxonase activity in patients with type 1 diabetes compared to healthy controls. *Eur J Clin Invest* 2002; 32(4): 259–264.

Najafian M, Ebrahim-Habibi A, Yaghmaei P, Parivar K, Larijani B. Citral AS. A Potential Antihyperlipidemic Medicine In Diabetes: A Study On Streptozotocin Induced Diabetic Rats. *Diabet Metab Disord* 2011; 10: 1- 8.

Nakajima K, Nemoto T, Muneyuki T, Kakei M, Fuchigami H, Munakata H. Low serum amylase in association with metabolic syndrome and diabetes: A community-based study. *Cardiovas Diabetol* 2011; 10: 34.

Nelson RW, Ihle SL, Lewis LD, et al. Effects of dietary fiber supplementation on glycemic control in dogs with alloxan-induced diabetes mellitus. *Am Vet Res* 1991; 52(12): 2060-2066.

Petlevski R, Hadzija M, Slijepcevic M, Juretic D. Effect of 'Antidiabetis' herbal preparation on serum glucose and fructosamine in NOD mice. *J Ethnopharmacol* 2001; 75(2-3): 181-184.

Prasath GS, Subramanian SP. Fisetin, a tetra hydroxy flavone recuperates antioxidant status and protects hepatocellular ultrastructure from hyperglycemia mediated oxidative stress in streptozotocin induced experimental diabetes in rats. *Food Chem Toxicol* 2013; 59: 249-255.

Seca AML, Silva AMS. Recent Progress in Medicinal Plants, Volume 16: Phytomedicines, Chapter: The chemical composition of the Juniperus genus (1970-2004), Publisher: Studium Press (India) Pvt. Ltd., Editors: Govil JN, Sing VK, Bhardwaj R. pp.401-522. 2005.

Senti M, Tomás M, Fito M, et al. antioxidant paraoxonase 1 activity in the metabolic syndrome. *J Clin Endocrinol Metab* 2003; 88(11): 5422-5426.

Steinberg WM, Nauck MA, Zinman B, et al. Lipase and amylase activity in subjects with type 2 diabetes: Baseline data from over 9000 subjects in the LEADER Trial. *Pancreas* 2014; 43(8): 1223-1231.

Swanston-Flatt SK, Day C, Bailey CJ, Flatt PR. Traditional plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice. *Diabetologia* 1990; 33(8): 462-464.

Turkoglu S, Bulmus FG, Parmaksız F, Özkan Y, Gursu F. Paraoxonase 1 and arylesterase activity levels in patients with metabolic sendrome. *Fırat Tıp Derg* 2008; (13(2): 110-115.

Tuzmen I, Hafizoglu H. Terpene groups in essential oils of Juniperus L. cones and leaves of grown in Turkey. *ZKU Bartin Faculty of Forestry Journal* 2004; 6(6): 88-95.

Vardi N, Iraz M, Öztürk F, et al. Deneysel diyabetin sıçan böbreklerinde meydana getirdiği histolojik değişiklikler üzerine melatoninin iyileştirici etkileri. *Inönü Üniv Tıp Fak Derg* 2005; 12(3): 145-152.

Venkatesh R, Sood D. A review of the physiological implications of antioxidants in food. bachelor of science interactive qualifying project. *Worcester Polytechnic Institute* 2011; 1(1083): 1-37.

Williams E, Gokool N. An update on the role of plant sterols and stanols in the management of hypercholesterolaemia. *CNmag* 2005; 5: 36-38.

Yegin SC, Yur F, Ceylan E. Effect of lycopene application in rats with experimental diabetes using lipoprotein, paraoxonase and cytokines. *J Membr Biol* 2013; 246(8): 621-626.

Young KH, Hui KM. Screening of Korean medicinal plants for lipase inhibitory activity. *Phytother Res* 2005; 19(4): 359-360.