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Therapeutic Effects of Olive Oil in Diabetic Rat

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Abstract--- *The current study conducted for evaluation the therapeutic effects on diabetic rats. Forty male rats were used in this study which divided into 4 groups, 10 rats were in each group, Group A serve as control group, Group B given alloxan monohydrate at dose of (150 mg/ kg), Group C given alloxan monohydrate at dose of (150 mg/ kg) then received orally (0.5 ml/kg B.W) of olive oil for 4 weeks, Group D received orally (0.5 ml/kg B.W) of olive oil for 4 weeks (control positive). blood samples were aspirated at zero, 15 and 30 days of experiment to estimate the blood glucose, cholesterol and HDL. Pancreas and liver were taken for histopathology. The results showed an increase in blood glucose, cholesterol in group B and decreasing in HDL levels. Group C showed significant ($P<0.05$) decreased in serum glucose and cholesterol concentration at days 15 and 30 compared with Group A and D, while the HDL showed significant increase as compared with control group. Group D showed only significant increase in HDL concentration. Histopathology of pancreas showed in group B at all period showed no difference in histopathological changes, which characterized by moderate atrophy with reduced number of islet cells to severe atrophy ,shrunken in size, severe destruction of the islets of Langerhans. Islet cells showed vaculations. Also, liver of Group B showed severe fatty change with acute cellular degeneration with congestion of sinosoides with inflammatory cell infiltration mostly lymphocytic cuffing, while pancreas of treated rats with olive oil at day 30 showed mild to moderate reduction in the size and number of the islets in this group. In Group C, the liver architecture appears more or less like control group with the exception of some congestion areas in the blood sinusoids. In conclusion, Olive oil can alleviate the adverse effects of diabetes in rats.*

Keywords--- *Rat, Diabetes, Olive Oil, Histopathology.*

I. INTRODUCTION

Diabetes mellitus are groups of metabolic disease where an individual has a higher sugar in blood, either due to insufficient pancreatic secretion of insulin or may be due to improper response of the cells to the insulin (insulin resistance) (Shoback, 2011).

Diabetes mellitus regarded as one of the greatest challenging problems in the current century (Jia, 2014), Diabetes is a main problem to the public health in all countries of the world, Among the diseases that leading to death, diabetes is graded as a seventh and when the fatal fate are occupied into the account, it is graded as third

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(Shaw et al., 2010), The increasing occurrence of the diabetes in most developing countries continued the tendency of urbanization and changes in lifestyle, maybe most prominently a "Western-style" food (Deguchi and Miyazaki, 2010). Diabetes is recognized also in cats, dogs, mice and rats and it is possibly happens in most mammals (Zheng and Kern, 2010; Jarad et al., 2020).

Type I diabetes mellitus (IDDM) comprise about 10% of all diabetes cases (Paschou et al., 2018). Current studies reported that Type I diabetes incidence increasing by percent of 3% annually of the world (Borchers, 2010). This type of diabetes formerly encompassed by the IDDM consequences from destruction of cells by autoimmune manner of pancreatic β cells (American Diabetes Association, 2010).

Non-insulin dependent diabetes mellitus (NIDDM) is a long-lasting metabolic condition in which the incidence has been rising gradually world widely (Olokoba et al., 2012).

Olive is a good source of edible oil and is also used for table particularly for pickles. In addition to its nutritional and medicinal value, its fat content is also free from cholesterol (Morello et al.,2004). It is an integral part of the Mediterranean diet. In general, its action on the human immune system has allowed its application in the resolution or attenuation of diseases characterized by inflammative disturbances, since it contains various elements which contain some biological activities. (Kremer et al., 1990; Linos et al., 1991), and in clinical nutrition (Sala-Vila et al.,2007).

As a common outcome in patients with chronic metabolic syndrome, the medeterian diet can be fairly believed to prevent diabetes from progressing (Giugliano and Esposito ,2008). Two retrospective research from Southern European samples indicated a lower diabetes in previously stable people with improved adherence to the Medeterian diet (Garcia-Gonzalez et al., 2008), or survivors with an infarction of myocardium (Mozaffarian et al., 2007).

A clinical and survey studies were done by some these contributor authors (Hasan et al., 2018; Hasan et al., 2018; Abdulgafor et al., 2018; Hussein et al., 2019; Mohammed et al., 2019; SABEEH et al., 2019; Suleiman et al., 2020; AL-Kubaisi et al., 2020; ALHTHEAL et al., 2020; Younis et al., 2020; Kareem et al., 2020; Bedn et al., 2020; Bdewi et al., 2020; Jarad et al., 2020).

The aims of this study was to assess the efficacy of olive oil in alleviate signs of diabetes.

II. MATERIALS AND METHODS

A total number of 40 male Albino Wister rats were used in this investigation. Their age range between 3-4 months, their weights ranged between 150 - 170 gm. They were divided into 4 groups, each group contain 10 rats,

Group A: control negative group

Group B: Diabetes mellitus induced experimentally by alloxan monohydrate at dose of (150 mg/ kg) injected in the marginal vein (Weekers *et al.,* 2002). Diabetes will checked upon by monitering the level of plasma glucose once a week following alloxan treatment. When plasma glucose concentration reached 9.4 mmol / Liter rats were considered to be diabetics (Weekers, 2003), the normal plasma glucose level were between 3.3 – 6.1 mmol/ L.

Group C: Diabetes mellitus induced experimentally by alloxan monohydrate at dose of (150 mg/ kg) injected in

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the marginal vein (Weekers *et al*., 2002). Diabetes will checked upon by monitering the level of plasma glucose once a week following alloxan treatment. When plasma glucose concentration reached 9.4 mmol / Liter rats were considered to be diabetics (Weekers, 2003), the normal plasma glucose level were between 3.3 – 6.1 mmol/ L. then received orally (0.5 ml/kg B.W) of olive oil for 4 weeks (AL- Gaborry , 2010).

Group D: control positive group which received orally (0.5 ml/kg B.W) of olive oil for 4 weeks (AL-Gaboory , 2010).

Blood were collected at 0, 15 and 30 days of the experiment from all experimental groups for measuring Glucose, Cholesterol, HDL by using commercial kits obtained from Biolabo company.

For histological studies, rats were anesthetized, then sacrificed. Immediately, after scarification, pancreas and liver were excised and preserved in 10% formalin for histological study (Suvarna *et al*., 2018).

III. RESULTS AND DISCUSSION

After 5 days of Alloxan injection, animals in diabetic groups were showed diabetic signs including: polyuria, polydipsia , polyphagia, and skin dryness when compared with Group A and Group D, these signs disappear gradually in group C after day 21.

The statistical analysis for Serum Glucose concentration (mg/dl) revealed that the Group B showed a significant increase ($P<0.05$) in serum glucose concentration at the 15 and 30 days compared with Group A and D in the same period.

Meanwhile Group C was showed significant ($P<0.05$) decreased in serum glucose concentration at days 15 and 30 compared with Group A and D in the same period Table (1).

Table 1: Effect of Olive Oil on Serum Glucose (mg/dl) Concentration in Normal and Diabetes Rats Groups at different Periods

DAYS / GROUPS	0 Day	15 Days	30 Days
A	180.70±11.41 A a	185.30±5.52 B a	194.61±9.30 A a
B	193.00±11.76 A b	246.20±18.31 A a	233.00±3.62 B a
C	196.21±5.73 A a	126.00±0.40 B b	120.00±3.57 B b
D	199.00±12.27 A a	192.00±5.73 B a	188.5±2.56 B a

- Capital letters denote significant difference ($P<0.05$) within a column
- Small letters denote significant differences ($P<0.05$) within a row.

These results occur in diabetic rats due to destroy of the ß-cells in pancreas by Alloxan and absent of insulin secretion (Lenzen and Patent, 1988; Elsner et al.,2006).

Effects on the insulin content and β-cell insulin mRNA by numerous natural antioxidants have previously seen

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by other researchers (Kaneto et al., 2007; Sato et al.,2007). Leaves of Olea europea L. extracts contain a compounds of polyphenol, principally oleuropein that may keep the insulin-secreting cells against the oxidative stress (Cumaoğlu et al.,2011). Dried extract of olive leaves delayed appearance of sustained hyperglycemia and preventing type 1 diabetes(Saksida et al.,2011; Cvjetićanin et al., 2010). Besides, olive leave polyphenol as therapeutic agent delayed the Advanced glycemia-mediated inflammatory disorders such as diabetes development (Chandler et al., 2010).

The existing results displayed a significant increase (P<0.05) in total serum cholesterol (mg/dl) in diabetic group at days 15 and 30 compared with Groups A and D at the same period. Meanwhile Group C showed significant decrease (P<0.05) in total serum cholesterol at days 15 and 30 compared with Groups A and D in the same time Table (2).

Table 2: Effect of Olive Oil on Serum Cholesterol (mg/dl) Concentration in Normal and Diabetes Rats Groups in different Periods

DAYS / GROUP	0 Day	15 Days	30 Days
A	98.22±12.18 A a	96.21±11.63 B a	101.2±12.3 C a
B	86.31±9.98 A b	138.0±6.72 A a	136.5±2.23 A a
C	102.0±4.38 A b	128.35±1.31 A a	111.25±1.75 B ab
D	92.32±3.51 A a	95.18±16.2 B a	93.1±2.93 C a

- Capital letters denote significant difference (P<0.05) within a column.
- Small letters denote significant differences (P<0.05) within a row.

It was clear that the Group B result revealed significant decrease (P<0.05) in serum HDL-C concentration at days 15 and 30 as compared with Groups A and D at the same time. Also there is no significant (P<0.05) in Group B during days 15 and 30. Moreover the Group C results showed increase in HDL-C concentration at days 30 compared with Group B at the same time, but these results are non significant (P<0.05). Meanwhile Group C showed significant increase (P<0.05) in serum HDL-C concentration at day 30 compared with it at day 15, as shown in table (3).

Table 3: Effect of Olive Oil on Serum HDL-C (mg/dl) Concentration in Normal and Diabetes Rats Groups at different Periods

DAYS / GROUP	0 Day	15 Days	30 Days
A	45.75±4.58 A a	41.22±3.21 C a	48.64±1.47 B a
B	47.16±3.16 A b	31.75±2.59 D a	33.14±2.63 C a
C	46.14±2.82 A b	54.13±3.73 A a	53.25±2.21 A a
D	44.17±2.36 A b	48.13±2.73 B ab	57.36±1.62 A a

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In the diabetic state insufficiency of insulin leads to lipogenesis inhibition, increased lipolysis which lead to elevate the efflux of free tissue fatty acids and insulin-mediated muscle skeletal dysfunction contributing to elevated concentrations of free fatty acids (Kelley and Simoneau, 1994). In response, the liver will increase VLDL production and cholesteryl ester synthesis (Cummings et al., 1995). Free fatty acids combine with a cholesterol molecule to form a cholesteryl ester. Cholesteryl ester concentrations may regulate VLDL production, with increased concentrations of cholesterol ester that lead to elevated the VLDL synthesis (Sniderman et al., 2001; Goldstein and Brawn, 1977).The increase of T.G, LDL-C particles results from increased VLDL secretion (Reaven et al., 1993;Tan et al., 1995). Also the elevation of TG may be due to impaired of lipoprotein lipase (Sniderman et al., 2001). The lipoprotein lipase activity is markedly impaired due to insulin deficiency (Kanters et al., 2001).While Insulin raises LDL receptor numbers so a persistent shortage in insulin could be linked to reduced LDL receptor concentration (Goldstein and brawn, 1977).

The hepatic TG lipase become more active and catabolizes the TG resulting a reduction in HDL particle size and an increase in HDL-C clearance, which leads to decreased HDL-C concentration in diabetic case (Suckling et al., 1993; Sniderman et al., 2001). These results agree with the studies of Chow and Hong (2002) and Idogun et al. (2007) these studies reported that diabetic rats had marked elevated concentration of plasma T.G, total cholesterol and LDL-C but decreased concentration of plasma HDL-C.

Increased triglycerides (TG) and decreased high-density lipoprotein (HDL-C) are considered to be major risk factors for the development of Insulin resistance and metabolic syndrome. The abnormal The enhanced transport of free fatty acids from peripheral depots is largely a result of a high degree of serum lipids in diabetes, since insulin inhibits hormone-sensitive lipase. On the other side, lipolysis is stimulated by glucagons, catecholamines and other hormones. Therefore, pronounced hyperlipemia characterizing the diabetic state can be seen as a consequence of the uninhibited actions of lipolytic hormones in fat deposition (Venkateswaran et al.,2002; Suryawanshi et al.,2006). In both regular and hyperlipidimic subjects, serum level HDL-C has been documented to be reversely associated with plasma level VLDL-C, TG (Gaziano et al., 1997).

There are usually high concentrations of sequalene in olive oil as compared with other common fats and oils consumed by humans. Its inhibition to farnesylation by inactivation of β –hydroxyl –β methylglutary –CoA reductase leading to a significant decrease in serum cholesterol concentration (Fabini et al., 2006) could be claimed.

Histopathological results there have been no significant changes in pancreatic histology and liver during different periods in Group A and D (Figure 1). Pancreas lesion in group B at all period showed no difference in histopathological changes, which characterized by moderate atrophy with reduced number of islet cells to severe atrophy ,shrunken in size, severe destruction of the islets of Langerhans. Islet cells showed vaculations (Figure 2). Also, liver of Group B showed severe fatty change with acute cellular degeneration with congestion of sinosoides with inflammatory cell infiltration mostly lymphocytic cuffing (Figure 3).

Histopathological changes observed in pancreas of treated rats with olive oil at day 30 showed mild to moderate

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reduction in the size and number of the islets in this group (Figure 4). In Group C, the liver architecture appears more or less like control group with the exception of some congestion areas in the blood sinusoids (Figure 5).

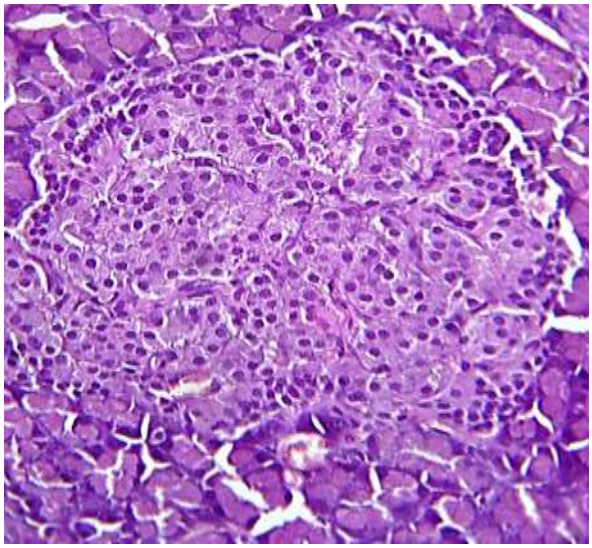

Figure 1: Histopathological Section in the Pancreas of Group a Show Normal Structure of Islets of Langerhans (H and E, X40)

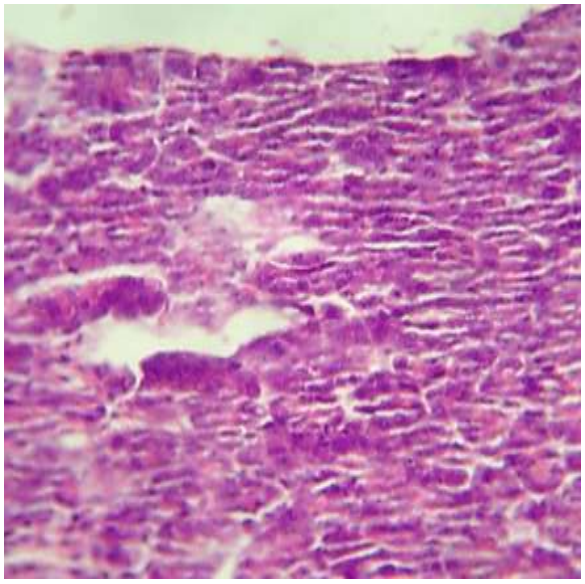

Figure 2: Histopathological Section in the Pancreas of Group B Showed Vacuolation and Shrinkage in Size in Islets of Langerhans and Marked Atrophy

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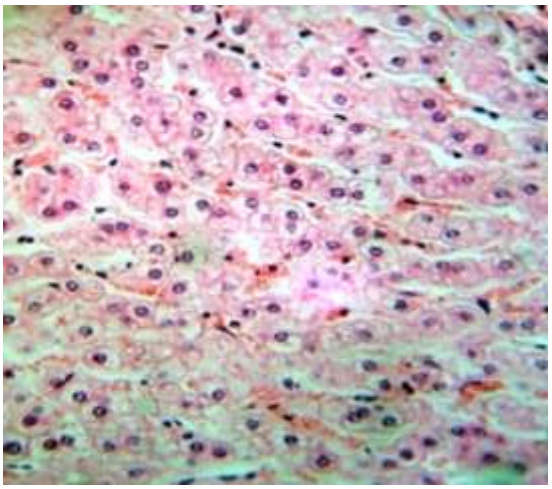

Figure 3: Histopathological Section in the Liver of Group B at Days 60 Showed Severe Fatty Change and Hemorrhage in Sinusoid (H and E,X40)

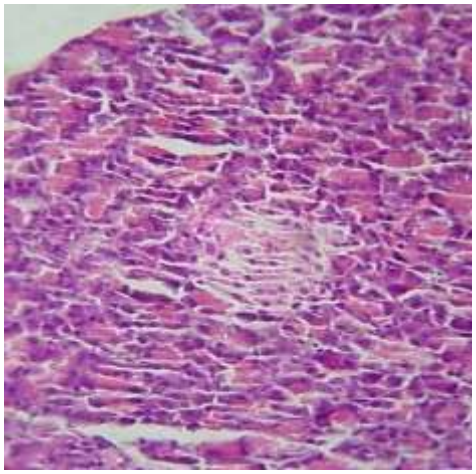

Figure 4: Histopathological Section in the Pancreas Group C Showed Limited Vacuolation in Islets of LANGERHANS (H and E, X40)

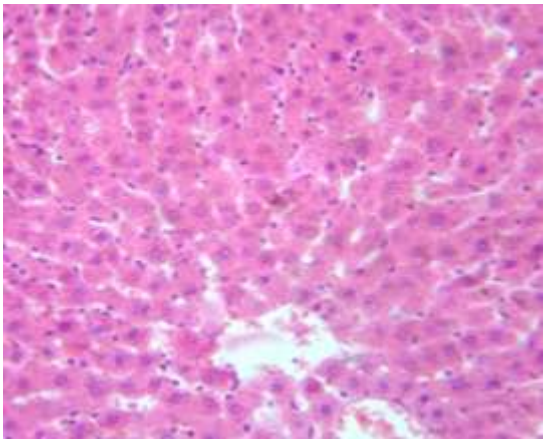

Figure 5: Histopathological Section in the Liver of Group C Showed Normal Liver Architecture (H and E, X40)

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In diabetic group, the cytotoxic action of Alloxan is mediated by reactive oxygen species (Lenzen and Panten, 1988). The redox cycle with the creation of superoxide radicals is established by alloxan and its dialuric acid reduction drug. The radicals undergo hydrogen peroxide dispersion. The reaction of Fenton is consequently extremely reactive hydroxyl radicals. The activity of reactive oxygen species with the concentration of cytosolic calcium raise at the same time causes rapid degradation and necrosis of β -cells and thus lead to reduce the size of islets of Langerhanse in pancreatic tissue and increase the blood sugar level (Lenzen and Pantan, 1988; Oberley, 1988; Lenzen, 2008).

These damages that occured in the liver of diabetic rats may be due to oxygen free radicals (Meerson et al., 1982). Stated that the cytotoxic effect of oxygen-free radicals by peroxidation of membrane pH contributes to a decrease in permeability and the loss of membrane integrity (Tesfamariam, 1994).The persistent of hyperglycaemia causes increased production of Oxygen Free Radicals from glucose oxidation and protein glycosylation (Wolff and Dean, 1987;Wautier et al.,1994). Cells and tissues are shielded from oxidative damage through cellular pathways such as antioxidant enzymes (Freeman and Crapo, 1982). The disparity in development of Oxygen Free Radicals and mobile protection systems may be crucial to impact vascular injury (Kakkar et al., 1996).

The excessive fatty change in liver was due to the glycogenolysis, lipolysis and proteolysis that may occur as a result to hyperglycemia and insulin insufficiency and defect in lipid metabolism (Buko et al., 1996).

Olive oil produces a variety of safe fat antioxidants that reduce the danger of cell injury olive oil (Owen et al., 2004) by free radicals scavenging (Alarcon de la Lastra et al., 2001). It was shown that, supplementation of mice with extra-virgin Olive oil potentially has a direct protective effect against oxidation of islet Langerhans (Oliveras-Lopez et al.,2008).This would be related to the free radicals scavenging, anti-inflammatory and antioxidant activities of active polyphenol (HT) of olive oil (Masella et al.,2004; Quiles et al.,2002), that protect pancreatic "cells from damage and death induced by oxidative stress (Nivitabishekam et al.,2009) .As Well As , These antioxidants may inactivate free circulating radicals which quench NO before reaching pancreatic β-cells, where their harm and/or death have been caused. (Vina et al.,2006).

In conclusion, olive oil can alleviate the pathological effects of diabetes in rats.

REFERENCES

[1] AL- Gaborry, W.B. (2010). Protective And Therapeutic Role Of Olive Oil And Folic Acid In Some Biochemical Parameters And Histological Changes In Male Rabbits Exposed To Methionine Over Load . *MSC .,thesis ,collage of veterinary medicine /University of Baghdad* .

[2] Alarcon de la Lastra, C.; Barranco, M.D.; Motilva,V. and Herrerías, J. M.(2001).Mediterranean diet and health. *Curr. Pharm. Des.,*7:933-950.

[3] American Diabetes Association. (2010). Diagnosis and classification of diabetes mellitus. *Diabetes care*, 33(Supplement 1), S62-S69.

[4] Borchers, A. T., Uibo, R., & Gershwin, M. E. (2010). The geoepidemiology of type 1 diabetes. *Autoimmunity reviews*, 9(5), A355-A365.

DOI: 10.37200/IJPR/V24I4/PR2020441
Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020

[5] Buko, V.; Lukivskaya, O. ;Nikitin, V.; Tarasov, Y.; Zavodnik, L.; Borodinsky, A. ; Gorenshtein, B.; Janz, B.; Gundermann K.J. and Schumacher, R. (1996). Hepatic and pancreatic effects of polyenoylphosphatidyl choline in rats with alloxan induced diabetes. Cell. *Biochem. Funct.; Jun.,* 14: 131-137.

[6] Chandler ,D.; Woldu, A.; Rahmadi, A.; Shanmugam, K.; Steiner, N.; Wright, E.; Benavente-García , O.; Schulz, O.; Castillo, J.and Münch, G. (2010). Effects of plant-derived polyphenols on TNF-alpha and nitric oxide production induced by advanced glycation endproducts. Mol. *Nutr. Food Res* .,54 (2): S141–S150.

[7] Chow, C. K. and Hong, C. B. (2002). Dietary vitamin E and selenium and toxicity of nitrite and nitrate. *Toxicology.*,180: 195-207.

[8] Cumaoğlu, A.; Rackova, L.; Stefek, M.; Kartal,M.; Maechler, P and Cimen Karasu,C.(2011). Effects of olive leaf polyphenols against H2O2 toxicity in insulin secreting β-cells . *J.Bioch.polonica.*,58,(1): 45–50.

[9] Cummings, M.H.;Watts ,G.F.and Umpleby, A.M.(1995). Increased hepatic secretion of very-low-density lipoprotein apolipoprotein B-100 in NIDDM. *Diabetologia.*,38:959-967.

[10] Cvjetićanin, T.; Miljković, D.; Stojanović, I.; Dekanski, D and Stosić-Grujicić, S. (2010). Dried leaf extract of Olea europaea ameliorates islet-directed autoimmunity in mice. *Br. J. Nutr.,* 103: 1413-1424.

[11] Deguchi, Y., & Miyazaki, K. (2010). Anti-hyperglycemic and anti-hyperlipidemic effects of guava leaf extract. *Nutrition & metabolism*, 7(1), 9.

[12] Elsner, M. ; Gurgul-Convey, E. and Lenzen, S. (2006). Free Radical Biology. *Medicine.*,41: 825.

[13] Fabini, R.; Bartolomeo, A.; Rosignoli, D.;Servili P.;Selvaggini, M. R.; Montedoro, G. F.; Saverio, C.; and Morozzi, G. (2006).Virgin Olive Oil Phenols Inhibit Proliferation of Human Promyelocytic LeukemiaCells (HL60) by Inducing Apoptosis and Differentiation. *Nutrition*, 136(3): 614 – 619.

[14] Freeman, B.A. and Crapo J.D. (1982). Biology of disease. Free radicals and tissue injury. *Lab. Invest.,* 47: 412-426.

[15] Garcia-Gonzalez, D.L.; Aparicio-Ruiz, R. and Aparicio, R. (2008). Virgin olive oil-chemical implications on quality and health. *Europ. J. Lipid Sci. and Tech.,* 110:1-6.

[16] Gaziano, J.M.; Hennekens, C.H. and O.Donnell, C.J.(1997).Fasting triglycerides , high density lipoprotein and risk of myocardial infarction. *circulation*, 96:2520-2525.

[17] Giugliano, D. and Esposito, K. (2008).Mediterranean Diet and metabolic diseases. *Curr .Opin .Lipidol* .,19:63-8.

[18] Goldstein, J.L. and Brown, M.S. (1977). The low-density lipoprotein pathway and its relation to atherosclerosis. *Ann .Rev.Biochem.,* 46:897-930.

[19] Hasan M S, Hussein M A and Yousif A A & Alwan M J, Confirmatory Detection of Escherichia Coli O157:H7 in Diarrheic and Non-Diarrheic Calves by using Real Time PCR with Studying the Antimicrobial Susceptibility of these Bacteria. *Journal of Global Pharma Technology*, 2018: 10(08):90-96.

[20] Idogun, E.S.; Unuigbe, E.I.;Ogunro, P.S.; Akinola, O.T.and Famodu, A.A .(2007). Assessment of serum lipids in Nigerians with type 2 diabetes mellitus complications. *Pak. J. Med. Sci.(Part 1).,* 23(5): 708 – 712.

DOI: 10.37200/IJPR/V24I4/PR2020441
Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020

[21] JARAD, A. S., JUMAA, A. HASAN, M.S. et al., (2020). Diabetic Wound Healing Enhancement by Tadalafil. *International Journal of Pharmaceutical Research* , Vol 12, Issue 3: 841-847.

[22] Jia, W. (2014). Diabetes: a challenge for China in the 21st century. *The Lancet Diabetes & Endocrinology,* 2(4), e6-e7.

[23] Kakkar, R.; Mantha, S.V. ; Kalra, J. and Prasad K.(1996). Time course study of oxidative stress in aorta and heart of diabetic rats. *Clin. Sci*.,9l (4): 441-448.

[24] Kaneto, H.; Matsuoka ,T.A.; Katakami ,N.; Kawamori, D.; Miyatsuka, T.; Yoshiuchi, K.; Yasuda, T.; Sakamoto, K.; Yamasaki, Y. and Matsuhisa, M .(2007). Oxidative stress and the JNK pathway are involved in the development of type 1 and type 2 diabetes. *Curr. Mol. Med .,7*: 674– 686.

[25] Kanters, S.D.; Banga, J.D.and Erkelens, D.W(2001). Lipidlowering therapy in diabetes mellitus. *Neth. J.Med.* ,58:214–222.

[26] KAREEM, M. H., KHALAF, J. M., HASAN, M. S., SALEH, E. N., & D SALIH, N. O. M. A. N. (2020). Effects of Eucalyptus Alcoholic Extracts on Pathogenic E. coli, Invitro Study. *International Journal of Pharmaceutical Research,* 12(1):1033-1034.

[27] Kelley, D.E. and Simoneau, J.A.(1994). Impaired free fatty acid utilization by skeletal muscle in non-insulindependent diabetes mellitus. *J. Clin. Invest.*,94:2349-2356.

[28] Kremer, J.; Lawrence, D.L.; Jubiz, W.; DiGiacomo, R.; Rynes, R.; Bartholomew, L.E. A and Sherman, M. (1990) . Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis: clinical and immunologic effects. *Arthritis Rheum* .,33:810–820.

[29] Lenzen, S. and Panten, U. (1988). Alloxan: history and mechanism of action. *Diabetologia.,* 31: 337-342.

[30] Lenzen, S.(2008). The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia.,* 51:216-226.

[31] Lenzen, S.; Brand, F.H. and Panten, U. (1988). Structural requirementsof alloxan and ninhydrin for glucokinase inhibition and of glucosefor protection against inhibition. Br J Pharmacol (in pressMalaisse, W.J .(1982) .Alloxan toxicity to the pancreatic B-cell. *Biochem. Pharmacol* .,31:3527-3534.

[32] Linos, A.; Kaklamanis , E.; Kontomerkos, A.; Koumantaki, Y.; Gazi, S.; Vaiopoulos, G.; Tsokos, G.C. and Kaklamanis, P. (1991) .The effect of olive oil and fish consumption on rheumatoid arthritis: a case control study. *Scand J. Rheumatol.,* 20:419–426.

[33] Masella, R.; Vari, R.; D'Archivio, M.; Di Benedetto, R.; Matarrese, P.; Malorni , W.; Scazzochio, B. and Giovannini, C.(2004). Extra virgin olive oil biophenols inhibit cellmediated oxidation of LDL by increasing the mRNA transcription of glutathione-related enzymes. *J .Nutr.,* 134:785-791.

[34] Meerson, F.Z.; Kagan, V.E. ; Kozlov, Y.P. ; Belkina ,L.M. and Arklipenko, Y.V. (1982). The role of lipid peroxidation in pathogenesis of ischemica damage and antioxidant protection of the heart. *Basic Res. Cardiol.,* 77: 465-46 8.

[35] Morello, J.R.; Motilva, M.J.; Tovar, M.J.and Romero, M.P.(2004). Changes in commercial virgin olive oil during storage, with special emphasis on the phenolic fraction. *Food Chem.,* 85: 357-364.

DOI: 10.37200/IJPR/V24I4/PR2020441
Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020

[36] Mozaffarian, D.; Marfisi , R.; Levantesi, G.; Silletta, M.G. Tavazzi, L.; Tognoni , G, Valagussa , F. and Marchioli, R .(2007). Incidence of new-onset diabetes and impaired fasting glucose in patients with recent myocardial infarction and the effect of clinical and lifestyle risk factors. *Lancet* ,370:667e75.

[37] Nivitabishekam, S.N. ; Asad, M. and Prasad, V.S. (2009). Pharmacodynamic interaction of Momordica charantia with rosiglitazone in rats. Chem. *Biol. Interact.*, 177 : 247–253.

[38] Oberley, L.W.(1988). Free radicals and diabetes.Free Rad. *Biol. Med.*, 5: 113-124.

[39] Oliveras-Lopez,M.; Berna,G.; Carneiro,E.M.; Serrana,H.L.; Martin,F.and Lopez, M.C.(2008). An Extra-Virgin Olive Oil Rich in Polyphenolic Compounds Has Antioxidant Effects in of Mice . *J. Nutr. and Dis.*, 1074- 1078.

[40] Olokoba, A. B., Obateru, O. A., & Olokoba, L. B. (2012). Type 2 diabetes mellitus: a review of current trends. *Oman medical journal*, 27(4), 269.

[41] Owen, R.W.; Haubner, R.; Wurtele ,G, Hull, W. E.; Spiegelhalder, B and Bartsch, H.(2004). Olives and olive oil in cancer prevention. *Europ. J .Cancer.Prev* ., 13:319-326.

[42] Paschou, S. , Nektaria Papadopoulou-Marketou, George P Chrousos and Christina Kanaka-Gantenbein. (2018). On type 1 diabetes mellitus pathogenesis. *Endocrine Connections* 7, R38–R46.

[43] Quiles, J.L.; Farquharson, A.J. ; Simpson, D.K. ; Grant, I. and Wahle, K.W.J.(2002). Olive oil phenolics: effects on DNA oxidation and redox enzyme mRNA in prostate cells. *Br. J. Nutr.*, 88 :225–234.

[44] Reaven ,G.M.; Chen, Y.D. and Jeppesen, J.(1993). Insulin resistance and hyperinsulinemia in individuals with small, dense low density lipoprotein particles. *J. Clin. Invest.*, 92:141-146.

[45] Saksida, T.; Miljković, D.; Dekanski, D.; Stojanović, I and Stošić-Grujičić, S.(2011). Dry Olive Leaf Extract (Dole) Down-Regulates The Progression Of Experimental Immune-Mediated Diabetes By Modulation Of Cytokine Profile In The Draining Lymph Nodes. *Arch. Biol. Sci.*, 63 (2): 289-297.

[46] Sala-Vila, A.; Barbosa, V.M and Calder , P.C. (2007). Olive oil in parenteral nutrition. Curr. Opin. Clinic. *Nutr. Metab. Care*, 10: 165–174.

[47] Sato, H.; Genet, C.; Strehle, A.; Thomas, C.; Lobstein, A.; Wagner, A.; Mioskowski, C.; Auwerx, J.and Saladin, R. (2007). Anti-hyperglycemic activity of a TGR5 agonist isolated from Olea europaea. Biochem Biophys . *Res Commun.*, 362: 793–798.

[48] Shaw, J. E., Sicree, R. A., & Zimmet, P. Z. (2010). Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes research and clinical practice*, 87(1), 4-14.

[49] Shoback D, Gardner DG, Dolores K (2011). Greenspan's basic and clinical diabetes mellitus. *Trends In Neuroscience* 14:452-57.

[50] Sniderman, A.D.;Scantlebury, T. and Cianflone,K.(2001) . Hypertriglyceridemic hyperapob: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. *Ann. Intern. Med.*, 135:447-459 .

[51] Suckling, K. E. and Brian, J. (1993). Animal Models of Human lipid Metabolism. *Prog lipid. Res.*, 32: 124.

[52] Suryawanshi, N.P.; Bhutey, A.K. ; Nagdeote, A.N. ; Jadhav, A.A. and Manoorkar, G.S.(2006). Study of lipid peroxide and lipid profile in diabetes mellitus. *Indi. J. Clinic. Biochem.*, 21: 126-130.

DOI: 10.37200/IJPR/V24I4/PR2020441
Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020

[53] Suvarna, K. S., Layton, C., & Bancroft, J. D. (Eds.). (2018). Bancroft's Theory and Practice of Histological Techniques E-Book. *Elsevier Health Sciences.*

[54] Tan, K.C.; Cooper, M.B.and Ling, K.L.(1995). Fasting and postprandial determinants for the occurrence of small dense LDL species in non-insulin-dependent diabetic patients with and without hypertriglyceridaemia. *Atherosclerosis.*,113:273-287.

[55] Tesfamariam, B.(1994). Free radicals in diabetic endothelial cell dysfunction. *Free Rad. Biol. Med.,* 16: 383-91.

[56] Venkateswaran, S.; Pari , L. and Saravanan, G.(2002). Effect of Phaseolus vulgaris on circulatory antioxidants and lipids in rats with streptozotocininduced diabetes. *J.Med.Food.*, 5: 97-103.

[57] Vina, J.; Borras, C.; Gomez-Cabrera, M. C. and Orr, W. C. (2006). Role of reactive oxygen species and (phyto) oestrogens in the modula- tion of adaptive response to stress. Free Radic. Res., 40: 111– 119.

[58] Wautier, J.L.; Wautier, M.P. and Schmidt, A.M.(1994). Advanced glycation end products (AGES) on the surface of diabetic erythrocytes bind to the vessel wall via a specific receptor inducing oxidant stress in the vasculature: a link between surface association AGEs and diabetic complications. *Proc. Natl. Acad. Sci. USA.*, 91: 7742-6.

[59] Weekers, F. (2003). Metabolic, endocrine and immune effects of stress hyperglycemia in rabbit model of prolonged critical illness. *Endocrinology.* 144: 5329-5338.

[60] Weekers, F. Van, HE.; Coopans, W. and Michalaki, M. (2002). A novel in vivo rabbit model of hypercatabolic critical illness reveals a bi-phasic neurendocrine stress response. *Endocrinology.* 143:764-774.

[61] Wolff, S.P. and Dean, R.T. (1987). Glucose autoxidation and protein modification: The potential role of autoxidative glycosylation in diabetes. *Biochem. J.*, 245: 243-50.

[62] Zheng, L., & Kern, T. S. (2010). In vivo models of diabetic retinopathy. In Experimental Approaches to Diabetic Retinopathy(Vol. 20, pp. 42-60). *Karger Publishers.*

[63] Suleiman , J. M., Omar-Althani Shareef Saed, SMA AL-Kubaisi, Hasan, M.S., Maher Saber Owain , Mohammed Ali Hussein , Ahmed Sami Jarad (2020). Molecular characterization of eae and Stxs genes for *E. coli O157:H7 isolates from calves. Medico-legal update*, 20 (10).

[64] Hasan M S, Hussein M A and Yousif A A & Alwan M J, Confirmatory Detection of Escherichia Coli O157:H7 in Diarrheic and Non-Diarrheic Calves by using Real Time PCR with Studying the Antimicrobial Susceptibility of these Bacteria. *Journal of Global Pharma Technology*, 2018: 10(08):90-96.

[65] Jarad, A. S., SMA AL-Kubaisi, Roua Jamal Abdulkhaliq and Hasan, M.S. (2020). Bacteriological and Pathological study on kidneys of Slaughtered sheep in Fallujah city. *Indian journal of forensic medicine and toxicology*, 14(1): 665-671.

[66] Abdulgafor, A. B., Owain, M. S., Hasan, M. S., Hussein, M. A., Aboud, Q. M., & Al-Zobaie, A. J. (2018). Liver, kidney function tests and oxidative damage during and after treatment of Salmonella typhimurium infection in experimental local rabbits. *International Journal of Pharmaceutical Quality Assurance*, 9.(6-5)

DOI: 10.37200/IJPR/V24I4/PR2020441
Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020

[67] Bdewi, S. Y., Kareem, M. H., Shwaish, M. M., & Hasan, M. S. (2020). Isolation of MRSA from Drinking water Supplies in Al-Anbar Province, Iraq. *Medico-legal Update*, 20(1), 715.

[68] Bedn, A. A., Hammoodi, O. T., Hasan, M. S., Saleh, E. N., & Salih, N. D. (2020). In-vitro Effects of Tribulusterrestris Extracts on S. aureus. *International Journal of Psychosocial Rehabilitation*, 24.(02)

[69] Kareem, M. H., Obaid, A. H., Radhy, A. M., & Hasan, M. S. (2020). Clinical treatment of rabbits experimentally infected with Staphylococcus. *Aureus by using different antibiotics. Drug invention today*, 12, 12.

[70] Hasan, M. S., Abdulgafor, A. B., Hussein, M. A., Owain, M. S., Aboud, Q. M., & Al-Zobaie, A. J. (2018). In-vitro and in-vivo therapeutic study the effect of Ca-EDTA against Salmonella typhimurium infection in experimental local rabbits. *Journal of Pharmaceutical Sciences and Research*, 10(7), 1765-1767.

[71] Hussein, M. A., Owain, M. S., Abdulgafor, A. B., Hasan, M. S., Jarad, A. S., Aboud, Q. M., & Al-Zobaie, A. J. (2019). Study the pathological changes in the intestine of rabbits infected experimentally with Salmonella typhimurium. *International Journal of Veterinary Science*, 8(2), 79-83.

[72] Mohammed, A. J., AL-Ameri, M. H., Saleh, I. D., Salih, N. D., Majeed, A. F., & Hasan, M. S. (2019). EFFECT OF AGE ON SEMEN PARAMETERS AND SPERM DNA FRAGMENTATION IN IRAQI AWASSI RAMS. *Biochemical and cellular archive*, 19(2):3787-3691.

[73] SABEEH, S. I., SALIH, R. A., BDEWI, S. Y., & HASAN, M. S. (2019). Effects of ciprofloxacin on liver and kidney functions and histopathological features in rats. *International Journal of Pharmaceutical Research*, 11.(1)

[74] Younis, L. S., Rasheed, S. T., Aboud, Q. M., Hasan, M. S., & Abid, A. A. (2020). Identification the Effect of Inhibin βA/Activin A Genes Polymorphism on Superovulation (Calving Rate) in Holstein Friesian Cows. *Systematic Reviews in Pharmacy*, 11(2), 471-481.

[75] ALHTHEAL, E. D., RADHY, A. M., HASAN, M. S., KAREEM, M. H., & SALEH, E. N. (2020). Therapeutic Effects of Olive Oil on Rabbit with Lead Toxicity. *International Journal of Pharmaceutical Research*, 12.(1)

[76] AL-Kubaisi SMA, Saed OAS, Suleiman JM, Hasan MS, Owain MS and Jarad AS. Isolation and Identification of Facultative Anaerobic Bacteria from Feces of Pet Dogs. *Medico-legal Update*, 2020; 20(1): 785.

DOI: 10.37200/IJPR/V24I4/PR2020441
Received: 12 Mar 2020 | Revised: 25 Mar 2020 | Accepted: 10 Apr 2020