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THE EFFECTS OF GRIND - DRY OLIVE LEAVES SUPPLEMENTS IN DIETS OF DIABETIC LOCAL MALE RABBITS INDUCE BY ALLOXAN ON SOME PRODUCTIVE AND, PHYSIOLOGICAL TRAITS

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Abstract

Present study was conducted to determine the antidiabetic, antioxidant effects of dry grind olive leafs and its protective effects on feed intake, total protein, globulin, Albumin, ALT, ALP enzyme activity of domestic male rabbits, induced diabetic by Alloxan injected, experiment was done in the Animal House, College of Veterinary Medicine, University of Baghdad, from 20 November to 30 January, including 10 days as an adaptation period, animals were divided randomly and body weights were consider, into four groups, the first group was treated with normal physiologic solution and kept as control negative group while and provide with standard rabbits diets, The three groups were treated with150 mg/kg BW of Alloxan I/P and added to their diets grind OL in (0%, 4%, 8%) percentage respectively and, blood sample were obtained directly from heart every biweekly, blood serum store for biochemical tests. The results showed that there was a significant increase ($P \leq 0.05$) in the feed intake, total protein albumin, globulin, the ALT enzyme activities of positive control (diabetic) group in comparative with healthy rabbits while there was an clear improvements and significant ($P \leq 0.05$) decrease in both groups those received 4% and 8% OL (diabetic animals compared to positive control group.

Key words: total protein, improvements, healthy rabbits, ALT enzyme, physiologic.

Introduction

Olive leaf (OL) is one of the potent source of plant polyphenols having antioxidant, antimicrobial, antiviral properties due to its rich phenolic contents. The most phenolic component of this content is oleuropein, which gives high palatability to olive or its olive oil. In order to utilize oleuropein and other bioactive components within OL effectively enough, they should be extracted from olive leaf. Olive leaf (OLE) contains compounds with potent antioxidant and antimicrobial activities against bacteria, fungi, and mycoplasma (Huang *et al.,* 2003: Aliabadi *et al*., 2012: Baraa. N. and Ellaf H., 2019) Diabetes mellitus (DM) is a common disorder associated with increased morbidity and mortality and can be defined as a group of metabolic diseases characterized by chronic hyperglycemia due to defective insulin secretion, insulin action, or both, resulting in impaired carbohydrate, lipid, and protein metabolism (Lebovitz, 1994). Pharmacological treatment of DM is based on oral hypoglycemic agents and insulin which have so many side effects (Andreoli *et al*., 1990) Diabetes is a combination of varying metabolic disorders and a high blood sugar concentration due to insulin deficiency or hypersensitivity to insulin tissues or both (Lebovitz, 1994). Which leads to disturbances in the systematic metabolism of carbohydrates, fat and protein. Diabetes is associated with high blood cholesterol concentration, triglycerides, low-density lipoprotein, therefore the main objective of this research is to determine the effects of grind of dry olive leaves in diabetic local rabbits induce by Alloxan injected on some productive and physiological tarts.

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Material and Methods

About 28 physical healthy domestic male rabbits, 2-3 month of age and 1200-1500 gm weight was used obtained from different local markets. Animals were divided randomly into to four groups of seven animals each; body weight was considered and housed individually in cages of (50cmn× 50cm × 40cm) along the study period of 70 days (from 15 November to January 25 of 2019) including 14 days as an adaptation period.

Experimental Design

Animals were divided into 4 groups 7 to each, Group

1: that getting basal diet free from feed additives and kept as negative control, Group 2: Control group, Diabetic rabbits (Alloxan treated) fed with slandered rabbits diets and kept as positive controls. Group 3: (injected by 150mg /km- Alloxan) Diabetic rabbits fed standard diet ad with added with 4% grinding dry olive leaves, Group 4: (treated with 150mg/km by Alloxan) Diabetic rabbits fed slandered diet added with 8% of grinding dry olive leaf all group were provided with water and feed ad libitum. Along the experimental period.

Olive Leaves Processing

OL will collect from some areas of local olive trees clean and dried by oven at 80°C for 48 hours, then Ground by use a milled electric grinding machine, the powder mixed with wet pellets (macerated in water) to form pasty material which pass from electric meat warp machine to form a new pellets included OL constitution. The new feed pellets were mixed with powder of OL as following formula: 40 gm of Ground OL plus 960 gm of basal diet (pellets)/group of (8% Olive leaves/diet) and 80 gm of Grind olive leaves plus 920 gm of basal diet (Pellets)/ group of (8% OL/diet). Animals were weighted at each twice week end in the morning before diet supplement.

Induce Diabetic

Diabetes was induced in overnight fasted rabbits by injection of Alloxan dissolved in normal saline (0.9% NaCl) at a dose of 150 mg/kg body weight. Whereas the animals of control group received normal saline . Alloxan can prompt fatal hypoglycemia as a result of massive pancreatic insulin release and to antagonist this hypoglycemic effect, the animals were supplied with dextrose solution 5% after 12 hours. of Alloxan treatment for next 24h. Induction of diabetes was tested after 48h. and the animals were permitted one week for the stabilization of blood glucose level. At five day, animal having a blood glucose level higher than 200 mg/dL and above consider diabetic and used for the study Keys, (Al- Bert *et al*., 2014).

The Study Sample and Parameters

Feed intakes of all animals was taken biweekly along the period of experiment. Blood samples were taken biweekly to study some blood parameters and included Total serum protein concentration, albumin globulin concentrations. And, Alanine transferase enzyme Alkaline Phosphatase enzyme.

Blood Sampling

Samples of Blood of all groups were takin directly from the heart by sterile syringe while the animals at alive into sterile vials biweekly, from starting of experiment period. The region of puncture was sterilized. 5 ml of blood samples were taken and kept in sterilized gel tube free of anticoagulant substances, to isolated the serum for measuring liver enzymes (ALT and ALP), albumin, serum total proteins, globulin, Immediately after collection the Sera separation samples of all animals were done by using centrifuge (3000 rpm) for 10 minutes and preserved in freezing at (-16°C -20°C) for later use. The most biochemical tests and blood testing were done at the Public Health Laboratory, College of Veterinary Medicine (ªahin *et al*., 2001).

Results and Discussion

The Feed intake g/day

As it is shown that daily feed of animals the positive control group as well as the both treated 4% and 8% olive leaves supplemented group diabetic –Alloxant injected were recorded significantly ($P<0.05$) low values in comparative with negative group or (healthy animals) from started to end of experimental period and the both

Table 1: Composition and chemical analyses of the basal diet.

Ingredients %	Basal diet
Yellow corn	15.3
Soybean meal (44% CP)	19.0
Wheat bran	10.0
Alfalfa hay meal	39.2
Barley	12.0
Dicalcium phosphate	0.7
Limestone	1.0
Common salt	0.5
Vit. & Min. Premix*	0.3
Molasses	2.0
Total	100
*Calculated analysis (air-dry basis NRC, 1977)*DE kcal/kg - 2501	
CP %	18.65
EE%	2.42
CF %	13.97
Ca %	1.17
P %	0.56
Lysine %	0.93
Methionine %	0.25
Methionine + Cysteine	0.59
Cost of 1kg diet; L.E.	2.45

Note. * Each 3 kg Vit. & Min. Premix contains: Vit.A, 12,000,000IU; Vit.D3, 2,500,000IU; Vit.E, 10g; Vit.K, 2.5g; Vit.B2, 5 g; Vit.B6, 1.5 g; Vit.B12, 10 mg; Biotin, 50 mg; Folic acid, 1.0 g; Nicotinic acid, 30 mg; Pantothenic acid, 10 g; Antioxidant, 10 g; Mn, 60 g; Cu, 10 g; Zn, 55 g; Fe, 35 g; I, 1.0 g; Co, 250 mg and Se, 150 mg.

4%, 8% treated group is still with parallel levels of feed consuming compare with feed intake ranges of diabetic that received 0% olive leaves, present results of current study was full agreement with results were obtained by some investigators whom reported, that before injection of alloxan, the ewes consumed c. 2.2 kg day-I feed. During the first days after alloxan, when ewes were being 'stabilized', feed intakes were suppressed. Thereafter, once ewes had been 'stabilized' with exogenous insulin, feed intake returned to normal levels before increasing to be significantly higher ,these may have been attributed to the mild hyperglycemias occurring during this period when doses of exogenous insulin were being adjusted to control plasma glucose and similar observations have been made in sheep where good control of plasma glucose has been achieved after alloxan Accordingly, it is suggested that the suppressions in feed intake and milk yield were attributable to reversible effects of alloxan on the kidney (Leenanuruksa *et al.,* 1988) these kidney defects explain that the recovery effects of olive leaves supplementation wasn't appear obviously, in such parameter, moreover, Olive leaf-derived polyphenols have been identified as therapeutic agents delaying the progression of advanced glycation end products-mediated inflammatory diseases such as diabetes. (Chandler *et al.,* 2010) Additionally, oleuropein and tannins in olive leaves are reported to act as a-glucosidase inhibitors, reducing the absorption of carbohydrates in the gut (Jemai *et al.,* 2009) in same trend decrease in feed intake in treated groups suffer from diabetic my attributed to that oleuropein in olive leaves has been shown to accelerate the cellular uptake of glucose, leading to reduced plasma glucose. (Gonzalez *et al.,* 1992) Since oleuropein is a glycoside, it could potentially access a glucose transporter such as a sodium-dependent glucose transporter (SGLT1) found in the epithelial cells of the small intestine, thereby permitting its entry into the cells. (Wolffram *et al.,* 2002).

Total blood serum protein

-Albumin

-Globulin

From results illustrated in table 2, 3, 4. The mean values of total serum protein, Albumin, Globulin of negative (healthy animals) groups had been recorded a significant

Table 1: Effect of 4% and 8% olive leaves supplementation in diet of diabetic male rabbit induced by Alloxan injected on feed intake g/day.

Period	After two week		After four week	After six weeks	After eight weeks
Groups	n	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Con.Gr	7	A 509.0± 39.79	A 518.0± 1.73	A 491.14± 30.05	A 511.14± 15.37
0% Gr.	7	B 325.25± 12.04	C 315.75± 6.01	B 322.50± 9.35	B 327.75± 25.56
4%Gr.	7	B 322.50± 8.41	C 329.50± 16.97	B 320.75± 8.02	B 326.50± 33.0
8%Gr.	7	B 323.0± 17.09	B 362.50± 23.18	B 320.0± 5.77	B 328.75± 10.94

(P<0.05), Means with the different capital letters in same column differed significantly.

Table 2: Effect of grind dry olive leaves on total serum protein gm\L levels gm\L in diabetic male rabbits induced by Alloxan.

Period	After two week		After four week	After six weeks	After eight weeks
Groups	n	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Con. Gr	7	A 7.85± 0.36	A 8.14± 0.13	A 7.51± 0.29	A 7.64± 0.31
0% Gr.	7	C 5.04± 0.26	C 5.07± 0.54	D 5.04± 0.18	D 4.52± 0.38
4% Gr.	7	B 7.0± 0.17	B 7.29± 0.53	C 6.13± 0.16	C 5.74± 0.32
8% Gr.	7	A 7.92± 0.30	AB 7.68± 0.44	B 7.20± 0.29	B 6.24± 0.28

(P<0.05), Means with the different capital letters in same column differed significant.

Table 3: Effect of grind dry olive leaves on Albumin levels gm\L in diabetic male rabbits induced by Alloxan.

Period	After two week		After four week	After six weeks	After eight weeks
Groups	n	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Con. Gr	7	A 4.42 ± 0.33	A 5.09 ± 0.59	A 4.54 ± 0.42	A 4.29 ± 0.21
0% Gr.	7	B 3.06 ± 0.32	B 3.14 ± 0.50	C 2.99 ± 0.34	C 2.60 ± 0.35
4% Gr.	7	A 4.02 ± 0.33	A 4.49 ± 0.54	B 4.05 ± 0.33	B 3.65 ± 0.54
8% Gr.	7	A 4.55 ± 0.80	A 4.99 ± 0.71	A 4.71 ± 0.34	B 3.60 ± 0.44

(P<0.05), Means with the different capital letters in same column differed significant.

Table 4: Effect of grind dry olive leaves on Globulin levels gm\L in diabetic male rabbits induced by Alloxan.

Period	After two week		After four week	After six weeks	After eight weeks
Groups	n	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Con. Gr	7	A 3.43± 0.40	A 3.14± 0.54	A 3.19± 0.17	A 3.30± 0.26
0% Gr.	7	C 1.97± 0.13	C 1.94± 0.59	B 2.04± 0.25	C 1.87± 0.27
4% Gr.	7	B 2.93± 0.34	B 2.51± 0.55	B 2.07± 0.32	C 1.94± 0.44
8% Gr.	7	AB 3.37±0.53	AB 2.70± 0.32	B 2.30± 0.51	B 2.64± 0.58

(P<0.05), Means with the different capital letters in same column differed significant.

(P<0.05) high levels in comparative with other 4%, 8% olive leaves treated as well as positive (0% olive leaves) which recorded significant (P<0.05) high the lowest levels among all group, during all periods of experiment, this decline in total protein levels in positive control group may be attributed to free radicals productions as a results of Alloxan treated such results in good agreements with (Albendea *et al*., 2007), who described that Free radicals may also be involvement in the observed reduce in protein content whereas subjected to the free radicals leads to protein fragmentation, protein peroxides generation, enzymatic oxidation and degradation of proteins and some investigators revealed that decrease in serum protein as a results of elevate blood glucose lead to formation of advanced glycosylated products with subsequent hyper-filtration and a potential increase of 5%-10% in glomerular filtration and glomerular hypertrophy caused pathophysiologic components of diabetic nephropathy and internal protein hypertension (RadbillB *et al.,* 2008). In same trend (Mansour *et al*., 2002; Garber, 1980), assured that, the total protein concentration declined seriously in alloxan - diabetic rats or may be referred to a depression in amino acid uptake leads to a extremely reduced the concentration of a variety of essential amino acids (Brosnan *et al*., 1984) and an elevated transformation rate of glycogenic amino acid to CO_2 and H_2O (Mortimore and Manton, 1970). in same line leaf (Meral *et al*., 2001: Abood *et al.,* 2013), referred in his study that diabetes provoked oxidative stress by raised reactive oxygen species, elevated malondialdehyde and by impaired antioxidative defense, as inferred from confused olive leaf, but the improvements in olive leaves treated groups might be suggest that The olive leaf administration leads to improvement the decline in the plasma protein content possibly by scavenging the free radicals and ameliorating the antioxidative status and in turn the process of protein synthesis (Wessam, 2012). However, the improvements in total protein of both olive laves groups groups might be due to The positive impact of treatment with crude oleuropein on these enzymes observed in the present study could be explained with two possible mechanisms. First, the antioxidative effect of oleuropein may prevent further glycosylation and peroxidation of proteins by interacting with free radicals and hence minimizing their noxious effects. Second, oleuropein may induce protein synthesis of these enzymes that explains the observed elevated activity after treatment, (Masella *et al.,* 2004), the obtained results showed an ameliorative effect of both group 4% and 8% on oxidative stress caused by olive leaf where the values returned to normal negative control levels. Such effect may be attributed to the antioxidant effect of flavonoids and Similar results were reported by (Vayalil, 2002); Orabi and Shawky, 2014 and El- Far *et al*., 2016. However it's our opinion that in diabetic the decrease in serum total protein may be due to increase excretion due to nephropathy or decrease in production due to defect in insulin secretion or action or both which must refer that free radicals which produce as a secondary diabetic complication is the major causative agents.

AlanineAminotransferase enzyme (ALT/GPT)

Alkaline Phosphatase enzyme (ALP)

Results obtained from table 5, 6 showed that there were about 2 fold significant (p<0.05) increase () in all liver enzyme activities including the, Alanine amino-transferase (ALT), Alkaline Phosphotransferases (ALP) enzymes in blood serum of studied animals were receiving, 0%, Olive leaves as well as the both of 4% and 8% Olive leaves receiving groups which induce diabetic by injected with 150m/gm Body Weights of Alloxan and the animals received 8% Olive Leaves were shown better decreasing (improving) than 4% Olive leaves group, in comparative with normal rabbits or negative groups which recorded the lowest values in all test during all studying periods, its worthy to mention that, the ALT was dependent on the amino acid groups of alanine and glutamine are taken up by the liver and any elevation in their levels of concentration were reflect the changes in the liver metabolism associated with glucose synthesis (El-Maghawry *et al.,* 2000), such trend also suggested there were cells damage in one or more of tissues present in liver, heart, skeletal muscle, kidney and pancreas, caused increased plasma activity of these enzymes

Table 5: Effect of grind dry olive leaves on ALT enzyme U\L in diabetic male rabbits induced by Alloxan.

Period	After two week		After four week	After six weeks	After eight weeks
Groups	n	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Con. Gr	7	D 42.41 ± 10.31	D 52.17 ± 12.13	C 50.38 ± 9.50	C 52.99 ± 7.42
0% Gr.	7	A 124.86 ± 9.95	A 123.71 ± 4.44	A 119.70 ± 5.97	A 121.74 ± 3.53
4% Gr.	7	B 80.67 ± 6.40	B 74.0 ± 5.24	B 77.01 ± 7.26	B 70.04 ± 16.76
8% Gr.	7	C 65.72 ± 3.33	C 65.49 ± 3.62	C 56.24 ± 10.73	B 65.61 ± 5.04

(P<0.05), Means with the different capital letters in same column differed significant.

Table 6: Effect of grind dry olive leaves on ALP enzyme U\L in diabetic male rabbits induced by Alloxan.

Period	After two week		After four week	After six weeks	After eight weeks
Groups	n	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Con. Gr	7	C 75.50 ± 4.63	C 83.18 ± 5.06	C 77.64 ± 8.19	D 80.37 ± 8.2
0% Gr.	7	A 157.91 ± 20.14	A 166.90 ± 3.64	A 160.10 ± 20.83	A 169.47 ± 3.71
4% Gr.	7	B 115.92 ± 20.41	B 123.63 ± 4.10	B 118.13 ± 3.70	B 122.42 ± 2.55
8% Gr.	7	C 79.13 ± 7.34	C 89.42 ± 20.82	C 86.70 ± 4.45	C 91.50 ± 7.51

(P<0.05), Means with the different capital letters in same column differed significant.

(kaneko *et al.,* 2008 : Ali., 2018) 23 and Davis *et al*., (2017), also indicated that diabetes may be induced hepatic dysfunction. Supporting our finding it has been found by Larcan *et al.,* 1979, that liver was necrotized in diabetic patients. Therefore, the increment of the activities, ALT in plasma may be mainly due to the leakage of these enzymes from the liver cytosol into the bloodstream (Navarro *et al.,* 1993) In the present study, the administration of alloxan induces hepatocellular damage, which is one of the characteristic changes in diabetes as evidenced by high serum activity of ALT and ALP in positive control group (T2). Therefore, the significant elevation (P<0.05) in the activity of AST in the serum as observed in the diabetic positive control group when compared to 4%, 8% treated group indicates possible damage to the liver or muscle. However, all the induced treated groups are significantly (p<0.05) lowered the serum activity of AST, when compared to the positive group. Elevated activity of serum enzymes is indicative of cellular leakage and loss of functional integrity of cell membrane in liver (Watkins & Seef, 2006), ALT was cytosolic enzymes. These results indicate that the olive leaf have impacted positively to the liver and reduced hepatic damage. In medicine, the presence of increased activity of AST in serum is an indicator of liver damage (Giboney, 2005), similar result were showed with a different plant extracts by (Chavan Sandeep, *et al.,* 2012) the reverse of this enzyme to normal by the extracts may be due to the prevention of the leakage of intracellular enzymes by the presence of polyphenol in the extracts and their membrane stabilizing activity, the commonly accepted view that serum levels of transaminases return to normal with the healing of hepatic parenchyma and the regeneration of hepatocytes (Chavan Sandeep, *et al.,* 2012).

On the other hand, treatment of the diabetic Rabbit with either Olive leaf caused reduction in the activity of these enzymes in plasma compared to the mean values of Alloxan group. Moreover some investigators, Ohaeri, 2001; 30 Mehar and Asija, 2015), in a study that, in diabetic patients, the normal level of ALT may be greater than the chance of liver disease, thus, In liver disease patients, the normal level of ALT and AST may be greater than the risk of diabetes (Govind and Rajesh, 2015: Lateef *et al.,* 2015). The beneficial effect of olive leafs to controlling and decreased the deleterious effects of diabetic mellitus lead to improve liver enzyme in both treated groups that receiving 4%, 8% grind dry olive leafs , especially the last one. This result also closely agreement with results reaching by some researchers, (Moran *et al.,* 2011; Nannipieri, 2005; Ramnanan *et al.,* 2011) whom were reported that there were obvious significantly Increased in activities of liver enzymes such as ALT and ALP are associated with hepatocellular injury accompanied with insulin resistance, metabolic syndrome and type II diabetes from the start to the end of the studying periods in the diabetic rabbits treated with olive leaves.in same line ,there were significant decreasing or improvement in the all liver enzymes levels that olive leaves treated groups and this might be attributed to the presence of some active constituent like flavonoids and terpenoids in the Olive leaves which had have hepatoprotective effect against hepatotoxins (Miles *et al.,* 2005), which are studied to evaluate the hepatic profile, and an increase

in these enzyme activities reflected liver damage ,where High transaminases levels are caused by hepatocellular inflammation (Pratt and Kaplan, 2000). Thus, Some drugs such as Alloxan or Streptozotocin induce diabetic treatments, have been caused a significant important role in the alteration of liver functions since the activity of ALT were significantly ($p<0.05$) higher than those of normal values. In the present study, a reduction in ALT levels were found in diabetic rats treated with Olive leaves might be due to effects of the olive leaves, polyphenols antiinflammatory activity, which allowed to regulate and improve the transaminases levels [Laaboudi *et al.,* 2016; Ghanam *et al.,* 2015). However, The present results indicated that, treatment with Olive Leaves didn't permit the, ALT or ALP activity from rising in the plasma of diabetic treated group compared to diabetic control group, moreover approximately all levels of means of enzymes activity in treated group was very close to normal group. At the same time, In diabetes mellitus, a significant decrease in levels of total protein and albumin and increases of levels of ALT and ALP indicated the damage happen to liver cells in diabetic group (Kamel *et al.,* 2011), (Sakr *et al.,* 2016), reported that, diabetic caused structural alterations in the liver, these alterations include leucocytic infiltrations, congestion of blood vessels, and cytoplasmic vacuolization of hepatocytes, Of these liver enzymes, ALT is most closely related to liver fat accumulation and consequently ALT has been used as a marker of non-alcoholic fatty liver disease (NAFLD) (Clark *et al.*, 2003; 42 Abdel-Rahim, 2010). Regarding to the liver enzymes activities, the Olive Leaves treated groups improved the activities of ALP, and ALT table 5, 6 . The obtained results of Hamad (Hamad, 2015), showed that, olive leaf have very high phenol content and possess a strong antioxidant activity and significant effect on liver damages induced by CCl4 administration, which result in improved serum ALT and AST and increased serum total antioxidant capacity in comparison with CCl_4 treated group. So, the improving effect of olive may related to its antioxidant activity.

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