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ORIGINAL ARTICLE

OLIVE OILS IMMUNOMODULATORY EFFECT IN PROTECTION THE LIVER AND HEART TISSUES IN RATS FED WITH HIGH CHOLESTEROL DIETS

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Abstract:

Due to our busy lives and rely on the consumption of junk food, leading to increase cholesterol levels in blood, that causes heart diseases. And according to the global trend in reduction of using medications that cause imbalance in the body's functions and the trend to use natural materials in the treatment of diseases, as they have no side effects on human health if used as doctor describe. The question is: Does the quality of olive oil have a role in its hypocholesterolamic effect? The present study aimed to determine the protective role of tow types olive oils on heart and liver tissues in rats fed on high cholesterol diet. Hypercholesterolaemia induced in male albino rats, by feeding on high cholesterol diets. Hypercholesterolaemia characterized by significant increase in the averages of total cholesterol and triglycerides, LDL and decreased levels of HDL. The study includes histological, histopathological and immunological studies, which delineated increase of fat droplets, degenerated hepatocytes, and increase in CD45RO expression in the hepatic tissue. Treatment with olive oils reduced the serum levels of cholesterol, triglycerides, LDL and increased the HDL levels. The histological picture of liver and heart reported improvents, and decrease in CD45RO expression in liver tissue.

KEYWORDS:

Olive oils, Hypercholesterolaemia, Liver, Heart, CD45RO.

INTRODUCTION

Hypercholesterolaemia (HPC) is a common disease in the developed countries and is considered as one of the life style diseases recognized as the main risk factor for atherosclerosis and heart diseases (Robertson *et al*., 2004). Beside the negative effects on the general immune responsiveness (Ludewig *et al.*, 2001), HPC clearly affects antibody production both the autoantigen and exogenous antibody, through changes in the spleen and liver functions and causes the cerebral microvasculature to undergo oxidative stress due to the circulating soluble mediators e.g. cytokines (Ishikawa *et al*., 2004). Hypercholesterolaemic low density lipoprotein (LDL) mice have higher net production of reactive oxygen species (ROS) and higher susceptibility to develop membrane permeability transition. Increased ROS production was observed in mitochondria isolated from intact spleen mononuclear cells (Oliveira et al.,

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2005). Besides HPC affects (directly or indirectly) the production of leucocytes in the bone marrow and/or the circulation (Feldman *et al*., 1991), and its strong inflammatory component which is characterized by the penetration of monocytes and T-cells into the developing lesions (Steinberg, 2005).

Olive oil is a nutritious complex compound made of fatty acids, vitamins, volatile components, and water-soluble components. Oleic and linoleic acids are the most important primary fatty acids. The levels of these acids and other fatty acids change with the progress of maturity of fruits, the cultivar, and the growing conditions (Tous and Romero 1993). Olive oil has recently become more valued for its health benefits. It is very high in monounsaturated (oleic acid), polyunsaturated (linoleic acid) and saturated fats (palmitic and stearic acids) (Sacks, 1995). It is good for prevention heart diseases (UNCTD, 1993).

Vegetable oils such as coconut oil or palm oil, which are used in confectionery, contain saturated fatty acids, similar to those of dairy origin in butter for example. Olive oil, on the other hand, is rich in monounsaturated fatty acids (more than 79%) – mainly oleic acid. Oleic acid is responsible for the cardiovascular benefits of olive oil. Elevated levels of cholesterol associated with low-density lipoproteins (LDL) in the blood are an important risk factor for heart disease. The substitution of saturated fats with monounsaturated fat lowers blood LDL cholesterol, thus reducing cardiovascular risk (Tuck and Hayball, 2002).

Olives and olive oil are both food and medicine. It is the healthiest of vegetable oils than other sources of alimentary fat because of its high content of monounsaturated fat (mainly oleic acid) and polyphenols and very low in the bad saturated fats. Furthermore, it is very rich in other health-promoting micronutrients like squalene, terpenoids and tocopherols (Owen *et al*., 2000). These types of fatty acids are low risk fats as shown in animal models and though the observation that the incidence of specific diseases is lower in the Mediterranean region where such oils are customarily used (Weisburger, 2000; Farooqui, 2012). In addition, they are much more resistant to peroxidation than polyunsaturated, and it has heart friendly properties (Grootveld *et al*., 1998).

Several studies (Tuck and Hayball, 2002) confirmed that virgin olive oil helped to lower LDL (bad) cholesterol and, perhaps more importantly, stimulated an increase in HDL (good) cholesterol. This is all very good for those concerned about their cholesterol levels, especially the good HDL cholesterol, and the effects on the human circulatory system. Virgin olive oil has no trans fatty acids because it has not been partially hydrogenated in a factory to make it solid at room temperature.

Al-Rawi and Ali (2011), studied the antioxidant effect of olive oil against the histopathological alterations induced by high cholesterol diet on the aorta and liver of rat. Gorinstein et al., (2002), delineated the effect of olive oils on lipid metabolism and antioxidant activity on male hypercholesterolaemic rats. The authors found that virgin olive oil possess hypolipidemic and antioxidant properties. It is more evident when this oil is added to the diets of rats fed cholesterol. These positive properties are attributed mostly to the phenolic compounds of the studied oils.

The aim of the present study is to evaluate the immunomodulatory effect of tow types of olive oils on the liver and heart tissues of rats fed on high cholesterol diet.

MATERIAL AND METHODS

Animals and diets:

The study conducted on rats as follows, group 1: control group fed on normal diet, group 2&3: rats received 0.75 ml/kg/day olive oil (Mohaghegi *et al.*, 2010) from Al-Jouf and Gurayate samples. Rats belonging to the 4th group fed on hypercholesterolaemic diet, and animals in group 5&6 fed on high cholesterol diet plus the two types of olive oils.

Biochemical analysis:

After 2 weeks of high fat diet intake and at the end of the study i.e after the 4 weeks after the intake of high fat diet and olive oils, all rats were sacrificed and blood samples were collected in clean dry tubes for serum assessment of total cholesterol (Trinder & Ann 1969), triglycerides (Wahlefield, 1974) and lipoproteins concentrations in serum (Richmond, 1973). Liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP)] were measured in this study.

Histopathological studies:

Liver and heart specimens were collected from all dissected animals, immersed in saline, put in

10% neutral buffered formalin and stained with heamatoxylin and eosin for histopathological studies.

Immunohistochemical investigation:

Fresh sample pieces of liver tissue were fixed in 10% neutral buffered formalin, then post-fixed in B5 before embedding in paraffin. Slides were then put in 30% hydrogen peroxide, and washed in 10mM phosphate-buffered saline (PBS) pH 7.4. Sections were incubated with 10%goat non-immune serum, and then incubated with anti-CD45RO antibodies (Zymed). The color was developed using an AEC kit according to the manufacturer's directions.

Statistical analysis:

The data were presented as mean ± SE. one way Analysis of Variance (ANOVA) followed by post hoc-least significant difference analysis (LSD) was performed using the statistical package for social science (SPSS, Chicago, IL) version 16 to compare all the treated groups. Values of $p < 0.05$ were considered significant.

RESULTS

Biochemical Analysis:

Serum results (Table 1) of the hypercholesterolaemic rats revealed that feeding on high cholesterol diet for 2 weeks caused a highly significant increase in total cholesterol (TC), triglycerides (TG), low density lipid cholesterol fraction (LDL) and total lipids (TL) levels. On the other hand, significant decrease in high density lipid cholesterol fraction (HDL) reached to 22.00 mg/dl as compared to normal control. Liver profile analysis reported significant increase in HCD as compared with control levels. These levels recorded 32.00 u/l for , aspartate aminotransferase (AST), 40.00 u/l for alanine aminotransferase (ALT) and 206.67 u/l for alkaline phosphatase (ALP).

Table 1. Averages of serum lipid and liver profile of control and hypercholesterolaemic rats after 2 weeks of feeding high cholesterol diet.

PARAMETERS	GROUPS	
	C	HCD
TC (mg/dl)	102.00±1.15	111.67±0.88 [a]
T.G (mg/dl)	94.66±0.88	107.00±0.57 [a]
HDL (mg/dl)	28.00±0.57	22.00±1.15 [a]
LDL (mg/dl)	61.33±0.88	71.33±0.88 [a]
TL (mg/dl)	315.00±0.57	325.33±0.88 [a]
AST (u/l)	25.66±0.88	32.00±0.57 [a]
ALT (u/l)	34.00±0.57	40.00±1.15 [a]
ALP (u/l)	201.33±0.88	206.67±0.88[a]

Each value represents the Mean±SE of 3 determinations.
Superscript letters denote the significant difference at ($P<0.05$).
a: values are significantly different from control group.

The serum data for lipid profile revealed non-significant differences between the control group and Al-Jouf (JF) and Gurayat (GT) olive oils treated groups, as tabulated in Table 2. Increase in TC (129.0 mg/dl), TG (120.33 mg/dl), LDL (72.33mg/dl), TL (317.33mg/dl) and the decrease in HDL (27.33 mg/dl) were reported as a result of feeding on cholesterol diet. Hypercholesterolaemic rats treated with JF and GT olive oils showed decreases in TC, TG, LDL and TL levels but increase values in HDL fraction as compared to the control group. These values were significantly as compared with HCD group. Consistent with liver histopathological findings, the activity of the injury marker AST increased significantly (60.66 u/l) in hypercholesterolaemic rats. The liver-specific marker ALT and ALP were increased and reached 54.66 and 233.0 u/l respectively, as compared with normal control. It could be concluded from this results, that feeding on high cholesterol diet abolished the liver injury and dysfunction. On the other hand,

administration of JF and GT diminishes these damages by preventing the increase of AST, ALT and ALP.

Table 2. Averages of serum lipid and liver profile of control and different experimental groups.

PARAMETRES	GROUPS					
	C	JF	GT	HCD	HCD+JF	HCD+GT
TC (mg/dl)	111.67±0.88	107.33±1.20	108.00±1.15	129.00±1.73 [abc]	116.00±0.57 [d]	121.67±0.88 [d]
T.G (mg/dl)	105.33±0.88	101.00±0.57	103.67±0.88	120.33±0.88 [abc]	110.00±1.15 [d]	115.33±0.88 [d]
HDL (mg/dl)	26.00±1.73	33.66±0.88	30.33±0.88	20.33±0.88 [abc]	27.33±1.20 [d]	27.66±0.88 [d]
LDL (mg/dl)	67.00±0.57	62.66 ±1.45	66.66±0.88	83.66±2.96 [abc]	72.33±1.20 [d]	76.66±0.88 [d]
TL (mg/dl)	316.00±1.73	307.33±3.71	313.67±0.88	335.33±0.88 [abc]	317.33±0.88 [d]	321.67±0.88 [d]
AST (u/l)	32.66±1.45	32.00±1.15	34.66±1.45	60.66±1.76 [abc]	39.33±0.88 [d]	41.00±1.52 [d]
ALT (u/l)	35.33±1.20	33.66±0.88	34.33±1.20	54.66±1.45 [abc]	46.00±0.57 [d]	49.33±1.45 [d]
ALP (u/l)	202.33±0.88	203.00±1.15	205.33±2.02	233.00±1.73 [abc]	220.33±0.88 [d]	222.67±1.20 [d]

Each value represents the Mean±SE of 3 determinations. Superscript letters denote the significant difference at ($P<0.05$).
a: values are significantly different from control group. b: values are significantly different from JF group.
c: values are significantly different from GT group. d: values are significantly different from HCD group.

Histopathological Studies of Liver:

Liver sections from rats of the control group showed normal architecture of the hepatic tissue with hepatocytes radiating from the central vein (Fig.1). Sections of liver from rats treated with JF and GT olive oils also revealed normal architecture (Fig.2 & 3).

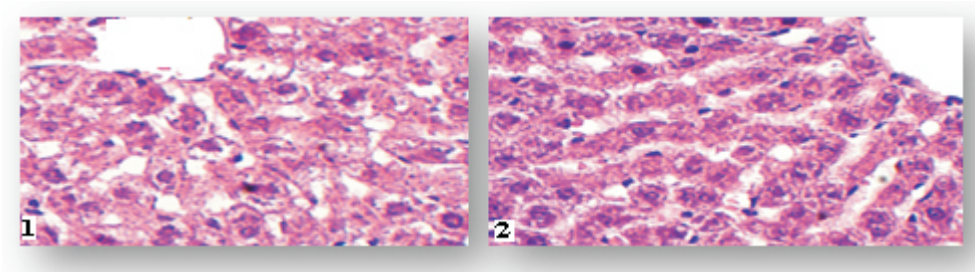

Fig. 1. Photomicrograph of liver section from control rat showing normal hepatic tissue with hepatocytes radiating from central vein. (H-E, X400).

Fig. 2. Photomicrograph of liver section from JF treated rat showing normal hepatic architecture. (H-E, X400).

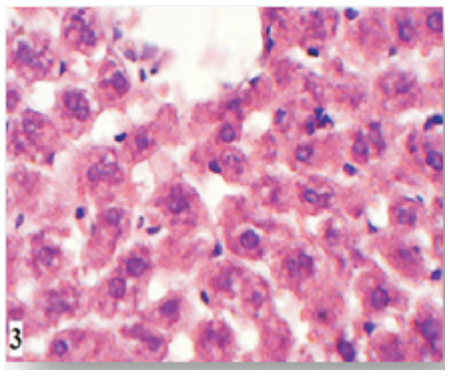

Fig. 3. Photomicrograph of liver section from GT treated rat showing normal hepatic architecture. (H-E, X400).

Histological changes in liver tissues were first manifested as a result of HCD intake. This was characterized by early degenerative changes of the hepatocytes around the dilated central vein which filled with RBCs and the endothelium is absent (Fig.4), Degenerated and vacuolated hepatocytes, the chromatin material is dispersed and many cells showed different stages of apoptosis (Fig.5), increase of fat droplets infiltration (Fig.6), fat droplets between hepatocytes, RBCs scattered in the central vein and lymphocytes in the hepatic tissue (Fig.7), degenerative hepatocytes and some hepatocytes contain vacuoles (Fig.8).

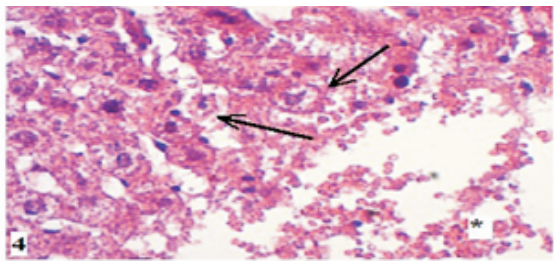

Fig. 4. Photomicrograph of liver section from HCD rat showing degenerative hepatocytes (arrows) around the dilated central vein which stuffed with RBCs (*) and its endothelial epithelium is absent. (H-E, X400).

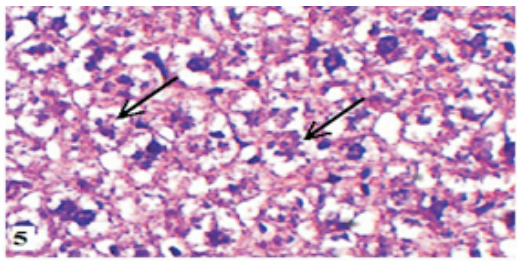

Fig. 5. Photomicrograph of liver section from HCD feeding rat showing degenerated and vacuolated hepatocytes. The chromatin material is dispersed and many cells showed different stages of apoptosis (arrows) (H-E, X400).

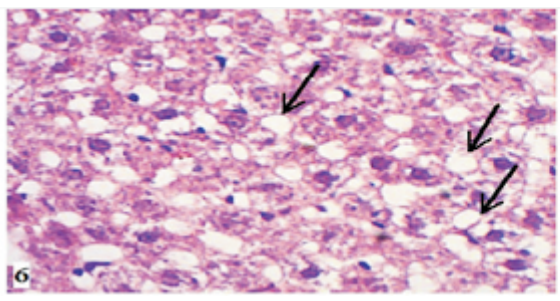

Fig. 6. Photomicrograph of liver section from HCD rat showing increase of fat droplets infiltration (arrows) in the hepatic tissue (H-E, X400).

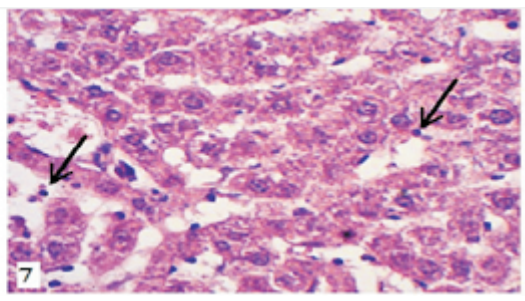

Fig. 7. Photomicrograph of liver section from HCD feeding rat showing fat droplets between hepatocytes RBCs scattered in the central vein and lymphocytes in the hepatic tissue (arrows). (H-E, X400).

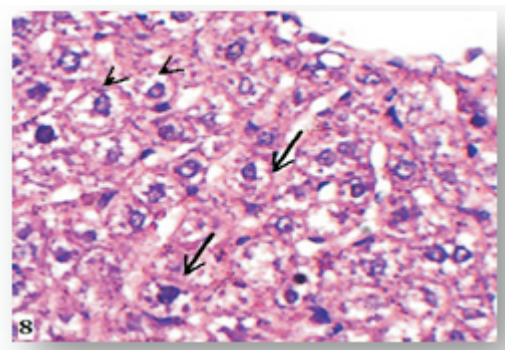

Fig. 8. Photomicrograph of liver section from HCD rat showing degenerative hepatocytes (head arrows) and some hepatocytes contain vacuoles (arrows) (H-E, X400).

After the administration of olive oils to hypercholestrolaemic rats, liver sections revealed near to normal appearance of the hepatic cells around the central vein, with regenerative hepatocytes contain double nuclei (Fig.9 & 10).

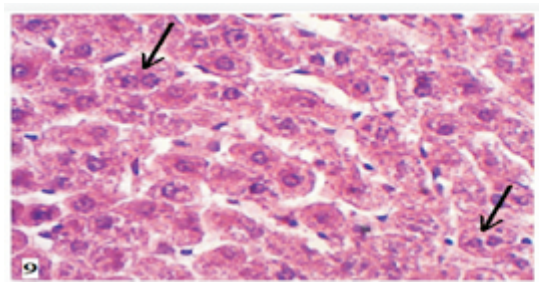

Fig. 9. Photomicrograph of liver section from HCD+JF showing binucleated (arrows) regenerated hepatocytes. (H-E, X400).

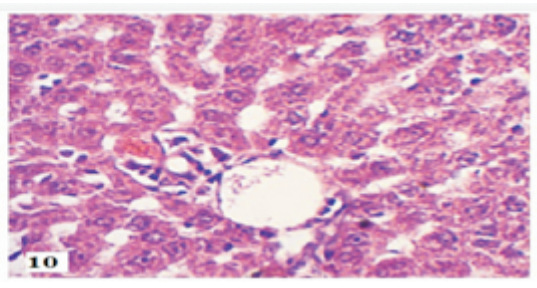

Fig. 10. Photomicrograph of liver section from HCD+GT rat showing near to normal arrangement of the hepatic cells around the central vein. (H-E, X400).

Immunohistochemical Investigation of Liver:

Liver sections from rats fed on HCD revealed an increase in expression of CD45RO which was more pronounced around the hepatocytes as shown in figure 13 as compared with normal control, JF and GT olive oils treated rats in figure11 & 12. On the other hand, liver sections from hypercholesterolaemic rats treated with olive oils expressed few CD45RO cells subsets (Fig.14) only around the degenerative areas as compared with high cholesterol diet fed rats.

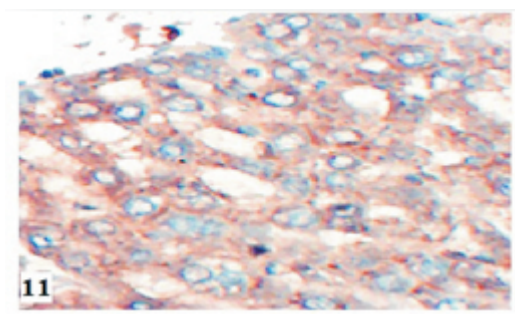

Fig. 11. Photomicrograph of liver section from control rat showing no CD_{45RO} cells distribution (Immunohistochemical stain, X400).

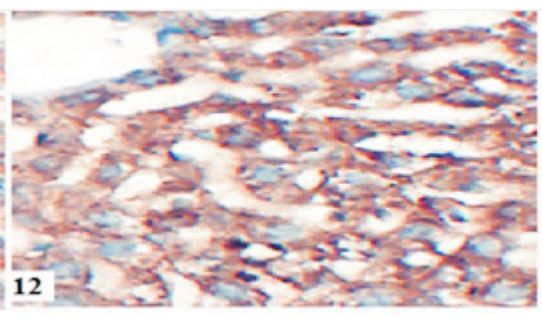

Fig. 12. Photomicrograph of liver section from GT treated rat showing no CD_{45RO} cells distribution (Immunohistochemical stain, X400).

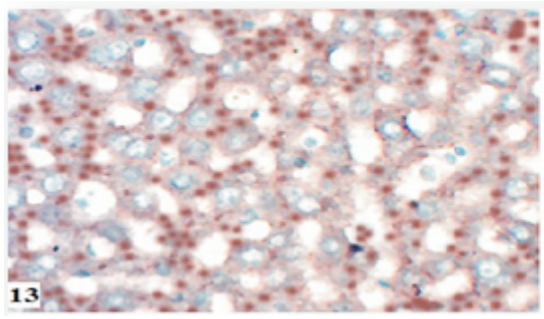

Fig. 13. Photomicrograph of liver section from HCD rat showing increase in CD_{45RO} cells distribution in the hepatic tissue (Immunohistochemical stain, X400).

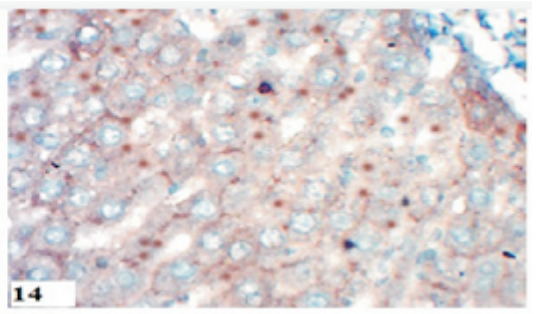

Fig. 14. Photomicrograph of liver section from HCD+JF treated rat showing decrease in CD_{45RO} cells distribution as compared with HCD rat (Immunohistochemical stain, X400).

Histopathological Studies of Heart:

Cardiac muscles from control rats section revealed the normal packed branching of the myocardiocytes with central nuclei (Fig. 15). No histological differences were found in JF or GT olive oils treated group (Fig. 16), where heart section showed normal histological profile of the cardiac tissue.

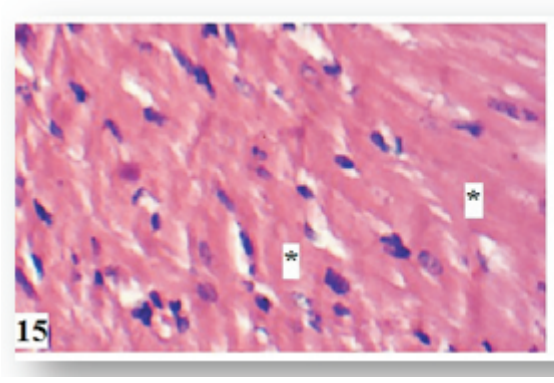

Fig. 15. Photomicrograph from heart section from control rat showing normal packed branching of the myocardiocytes (*) with central nuclei (H-E, X400).

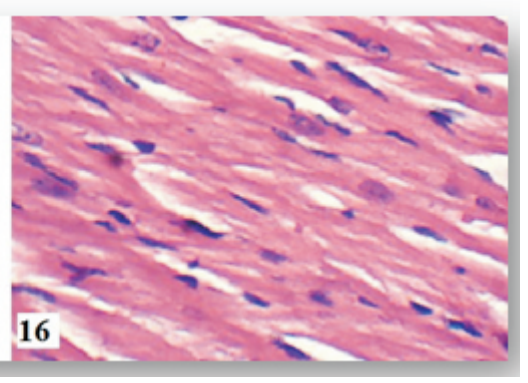

Fig. 16. Photomicrograph from heart section from JF olive oil treated rat showing normal histological profile of the cardiac tissue (H-E, X400).

Regarding to the influence of high cholesterol diet on cardiac muscles of rats, investigated sections delineated detached myofibrils, which showing cytoplasmic vacuolization and nuclei disarrangement and appeared as peripheral nuclei (Fig.17), myodegeneration and disarrangement of the nuclei and presence of macrophages (Fig. 18), dilated blood vessel with thickened walls and its lumen filled with RBCs (Fig. 19), disarrangement of myofibrils and the presence of lymphocytic infiltration (Fig. 20).

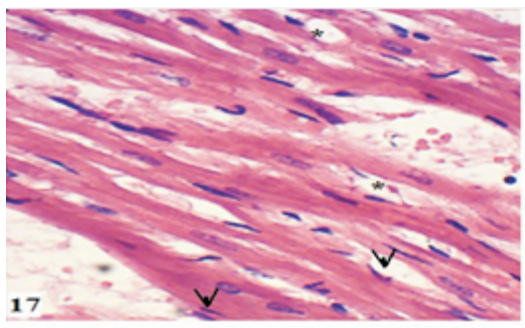

Fig. 17. Photomicrograph of heart section from HCD treated rat showing detached myofibrils, which showing cytoplasmic vacuolization (*) and nuclei disarrangement and appeared as peripheral nuclei (head arrows) (H-E, X400).

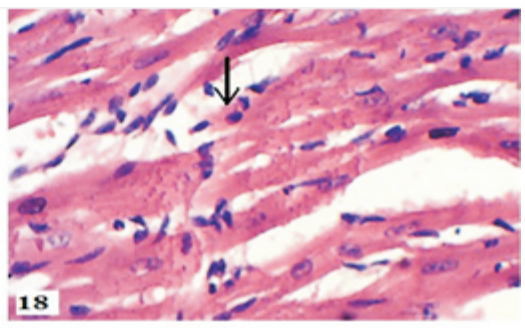

Fig. 18. Photomicrograph of heart section from HCD treated rat showing myodegeneration and disarrangement of the nuclei and presence of macrophages (arrows) (H-E, X400).

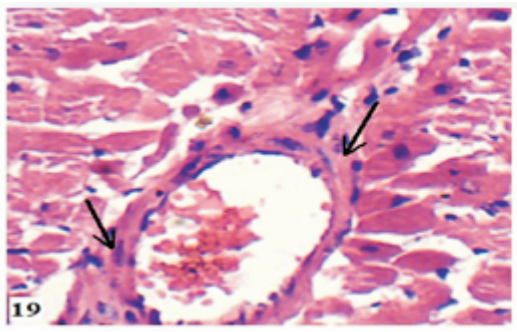

Fig. 19. Photomicrograph of heart section from HCD treated rat showing dilated blood vessel with thickened walls (arrows) and its lumen filled with RBCs (H-E, X400).

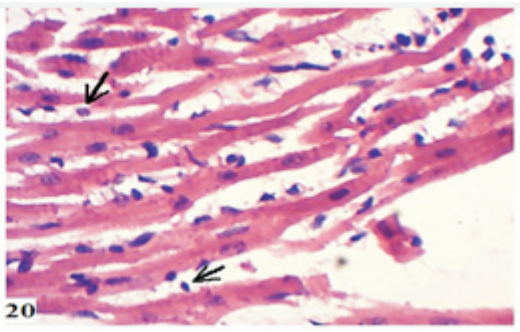

Fig. 20. Photomicrograph of heart section from HCD treated rat showing disarrangement of myofibrils and the presence of lymphocytic infiltration (arrows) (H-E, X400).

As olive oils was given together with HCD, limited lesions were encountered. This was represented by its anti-inflammatory action and improving the cardiac muscles architecture. Heart sections from HCD+JF treated rats showed near to normal arrangement of the myofibrils with prominent nuclei (Fig. 21) and heart section from rat treated with showing near to normal arrangement of the myofibrils from rats treated with HCD+GT as compared with HCD feeding rats (Fig. 22). The improvement was more pronounced in JF treated group.

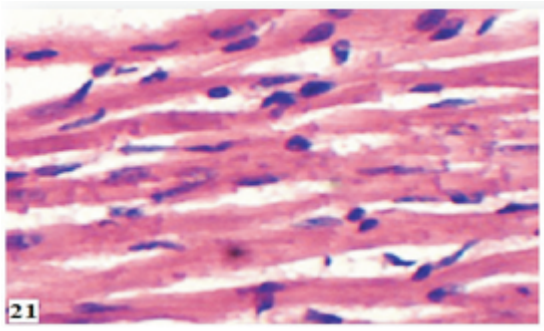

Fig. 21. Photomicrograph of heart section from rat treated with HCD+JF showing near to normal arrangement of the myofibrils with prominent nuclei as compared with HCD feeding rat (H-E, X400).

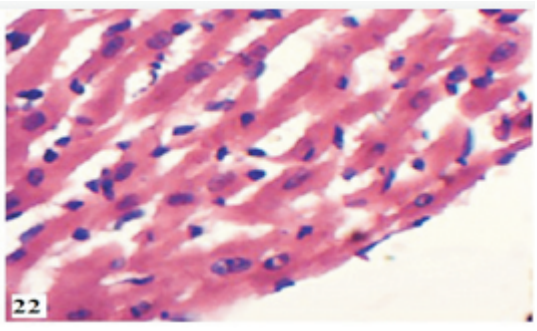

Fig. 22. Photomicrograph of heart section from rat treated with HCD+GT showing near to normal arrangement of the myofibrils as compared with HCD feeding rat (H-E, X400).

DISCUSSION

The present study delineated that Al-Jouf and Gurayat olive oils have a protective effect against the increase in lipid profile in hypercholesterolaemic rats. This come in accordance with the results of Gorinstein et al., (2002), who studied the effect of olive oils on lipid metabolism and antioxidant activity on male rats adapted to 1% cholesterol diets. The oil-supplemented diets significantly lessened the increase in plasma TC, TG and LDL due to dietary cholesterol. In the hypercholesterolaemic rats fed with olive oil groups the added oils significantly hindered the decrease in the plasma antioxidant activity, lipid profile and increase in HDL levels. These results demonstrate that virgin olive oil possess hypolipidemic and antioxidant properties. It is more evident when these oils are added to the diets of rats fed cholesterol. These positive properties are attributed mostly to the phenolic compounds of the studied oils. Also Mohaghegi et al., (2010) found that virgin olive oil reduced the LDL/HDL ratio in doses of 0.25, 0.5, and 0.75 mL/kg/day. The HCD group showed abnormal liver function tests as reported in this study. ALT, AST, and ALP serum levels were increased significantly as compared with the normal control levels. This come in agreements with Lu et al. (2007). In the present study JF and GT olive oils ameliorate the damage caused by HCD, by

returing the serum levels of liver enzymes to normal values. This in harmony with Nakbi et al. (2010), who that the increase of AST, ALT and ALP activities were markedly reduced in the presence of olive oil ($p < 0.05$).

The histological picture of liver showed many disturbances according to the feeding on high cholesterol diet. Which, leading to the increase of liver function enzymes (Wang, et al., 2012). Hepatocyte apoptosis in addition to oxidative stress could be a key component in the pathogenesis of feeding on high fat diet as reported by Wang et al., (2008). The key histological features of inflammatory cell infiltration, and degeneration of hepatocytes, were induced by HFD feeding, with increased hepatic TNF-alpha mRNA expression. HFD-fed rats had elevated lipid peroxidation products and CYP2E1 protein in the liver. The apoptotic hepatocytes were significantly greater in livers of rats fed HFD, and these were associated with a higher level of cleaved caspase-3. These data indicate that the increased oxidative stress and its associated JNK activation as well as an imbalance of pro- and anti-apoptotic proteins in the Bcl-2 family all contribute to high hepatocyte apoptosis.

This damage were counteracting by olive oil administration. This come in harmony with the result of Al-Rawi and Ali (2011), who studied the antioxidant effect of olive oil against the histopathological alterations induced by high cholesterol diet on the aorta and Liver of rat. The results demonstrated that treating rat with high cholesterol diet induced sever histopathological changes in the liver, these changes included distribution of liver architecture as it lost the normal radiating pattern, cellular infiltration and cells turned into large foam cells contained numerous internal cytoplasmic vesicles. This indicated that olive oil showed antioxidant effects and improvement in the structure of the aorta and liver of rats. Nakbi et al. (2010) showed that the extra virgin olive oil and hydrophilic fraction intake induced a significant increase in antioxidant enzyme activity and a decrease in markers of liver damage. The hydrophilic fraction of olive oil seems to be the effective one in reducing toxin-induced oxidative stress, indicating that hydrophilic extract may exert a direct antioxidant effect on hepatic cells.

Liver sections from hypercholesterolaemic rats reported an increase in the expression of CD45RO cells as compared with those from hypercholesterolaemic rats treated with olive oils this may be related to the immunologic effect of olive oil. CD45, the leucocytes common antigen, is a haemopoietic cell-specific tyrosine phosphatase. Many isoforms are generated by alternative splicing, but their functions remains obscure. The extracellular domain of CD45 is highly polymorphic in all vertebrates. Importantly, human polymorphic variants that alter CD45 isoform expression are associated with autoimmune and infectious diseases, establishing CD45 as an important immunomodulator with a significant influence on disease burden, where the alteration in CD45 expression has major effects on immune function (Tchilian and Beverley, 2006; Ward et al., 2006). Furthermore, the high expression of CD45 showed a negative correlation with serum HDLc levels and a positive correlation with plasma LDL levels, therefore probably enhance monocytes adhesion to the endothelium and increase proliferation of smooth muscle cells (Stemme et al. 1992; Rothe et al., 1996; Behr-Roussel et al., 2000; Cao et al. 2006). Hence, neointimal rat smooth muscle cells can also recruit memory T-cells in flow; which supported a significantly enhanced arrest of CD4 and CD45RO T-cells, the main components of atherosclerotic lesions (Pauletto et al., 2000; Artese et al., 2005; Baker et al., 2006). The presence of these cells is because of a direct response to the oxidized LDL (OxLDL) accumulation in the arterial wall. High concentrations of OxLDL in the vessels phagocytosed by macrophages, thereby contribute to a cascade of events characterized as immunoinflammatory reactions of atherosclerosis (Shoenfeld et al., 2004).The present study reported many disorder in hypercholesterolaemic rat heart sections. This damage involved disturbance in myofiblis arrangement, fat deposition, presence of RBCs inside the cardiac tissue and inflammatory cells infiltration. Ma et al., (2013) reported that inflammatory stress exacerbates the progression of cardiac fibrosis in high-fat-fed mice, suggesting that hyperlipidaemia and inflammation act synergistically to redistribute plasma lipids to cardiac tissues and accelerate the progression of cardiac fibrosis. Again, Tilellis et al. (2008) showed that high fat diet induces cardiac hypertrophy, inflammation, intramyocardial lipid accumulation and oxidative stress.

Olive oil is an integral ingredient of the Mediterranean diet, and it has proven effects in preventing the development of cardiovascular disease (CVD) as mentioned by Esstruch (2010). and colon and breast cancer, among other illnesses (Waterman & Lockwood, 2007). Olive oil has been found to counteract inflammation by significantly decreasing the levels of (soluble) intercellular adhesion molecule-1 (ICAM-1) and tumour necrosis factor alpha (TNFα) (Papageorgiou et al., 2011); vascular cell adhesion molecule (VCAM-1), ICAM-1, and TNFα have all been implicated in atherogenesis. Despite its anti-inflammatory qualities, the effect of olive oil in arthritis has not been widely tested but oleuropein aglycone, a major component of olive oil, ameliorated the clinical signs and histological changes in the joints and paws of mice with collagen induced arthritis (Impellizzeri et al., 2011).

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