

# Biochemical Study of the effect of mixture Fig [*Ficus Carica* L] and Olive oil on liver functions in nonalcoholic fatty liver disease in hyperlipidemic rat model

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## ABSTRACT

Nonalcoholic fatty liver disease (NAFLD), the prevalence of which is rising globally with current upsurge in obesity, is one of the most frequent causes of chronic liver diseases. The aim of the present experimental study was to evaluate the ameliorative effect of chronic oral administration of drenched Fig and Olive oil for 16 weeks on liver function tests of hyperlipidemia rat model. Sixty adult male Wister Albino rats were used. These rats were divided into equal 6 groups [10 rats each] as following: the negative control group, the positive control group [fed on high cholesterol diet at dose 15g/100g B.W. for 16 weeks], statin group [hyperlipidemic treated orally with Statin drug [0.3 mg /100 g] for 16 weeks], Fig treated group [hyperlipidemic treated with drenched Fig [2 ml/kg] for 16 weeks], Olive green treated group [hyperlipidemic treated with Olive green [2 ml/kg] for 16 weeks], Fig & Olive green group Fig treated group [hyperlipidemic treated with drenched Fig [2 ml/kg] and Olive oil [2 ml/kg] for 16 weeks]. At the end of the experiments, they were measured and recorded. Blood was obtained at end of experiment from retro-orbital vein plexus into plain tubes. The serum levels of liver function tests (alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total protein, albumin and globulin) were measured by enzymatic methods. Chronic treatment with Fig, Olive green and both of them orally for 16 weeks decreased hepatic liver enzymes (ALP, AST and ALT), and increased total plasma proteins and albumin. The study findings, therefore suggested the therapeutic potential of Fig and Olive green against nonalcoholic fatty liver disease.

**KEYWORDS:** Fig (*Ficus carica* L); Hyperlipidemia rat model; Liver enzymes; Liver protein; Liver Functions; Olive green.

## INTRODUCTION

Liver is the largest and pivotal gland the main functions of which are metabolism, detoxification, excretion and generation of a variety of coagulation factors [1]. Liver injury is monitored in standard toxicity studies by a range of investigations including clinical biochemistry parameters (enzymes, proteins, lipids, *etc.*). The following endpoints are considered to be mainly related to liver toxicity: its more than or two enzymes indicative of hepatocellular effects such as (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and lactate dehydrogenase [2]. Unfortunately, conventional or synthetic drugs used in the treatment of liver diseases are inadequate and sometimes can have serious side effects. This is one of the reasons for many people in the world over including those in developed countries turning complimentary and alternative medicine. Many traditional remedies employ herbal drugs for the treatment of liver ailments [3]. A number of plants have been shown to possess hepatoprotective property [4, 5].

Herbal medicines have been used traditionally for decades and seem to have lower side effects. Several literature reports report that herbal medicines have shown to reduce fat accumulation, obesity and

hyperlipidemia in animals fed high-fat diets [6, 7, 8]. Fig (*Ficus carica* L) is a deciduous broadleaf shrub belonging to the Moraceae family and is widely known as one of the first edible fruits cultivated by humans in areas with subtropical climate. The Fig originates from Carica in Asia Minor and the primary Fig producers now are America and the Mediterranean [9]. Figs are high in natural and simple sugars, minerals, water, and fiber. They contain substantial levels of potassium, calcium, magnesium, iron, copper, manganese, and sodium, while they are low in fat [10, 11]. They are a good source of flavonoids and polyphenols as well as being rich in the phytosterols lanosterol and stigmasterol [9]. Several reports have shown that the leaf, stem, and woody tissue contain antioxidants and antibiotics [12, 13]. Olive tree (*Olea europaea*), is a species belonging to the family Oleaceae, native to the Mediterranean basin, Asia and parts of Africa [14]. The aqueous extract of Olive leaf contains poly-phenols with an antioxidant potential, the major constituents of the leaf extract are oleuropein and its hydrolysis product, hydroxytyrosol. The antioxidant capacity of Olive leaf contributes to many health benefits. The *in vitro* antioxidant action of Olive has been documented and linked to such benefits as chemoprotection, anti-inflammatory action and prevention of atherosclerotic plaque formation [15]. Olive oil may be helpful in reducing the progression of non-alcoholic fatty liver disease (NAFLD), a pathological condition in which fatty infiltration in the liver exceeds 5%–10% of its weight [16]. Oleuropein administration has hepatoprotective and therapeutic effects on carbon tetrachloride-induced liver damage in mice [17]. Moreover, a diet supplemented with oleuropein reduces induced hepatic steatosis and progression to non-alcoholic steatohepatitis (NASH) in mice fed with a high fat diet [18].

The present experimental study was designed to investigate the possible protective or alleviating effects of oral administration of drenched *Ficus carica* (FC) L. (Moraceae), Olive oil and both for 16 weeks, as well as liver function tests of hyperlipidemia using a chronic high-fat diet rat model. The Fig and Olive green effects were compared to oral treatment with the reference compound statin.

## MATERIALS AND METHODS

### Chemicals:

Cholesterol was obtained from “Technogen”, Cairo, Egypt. It was crashed and mixed with a saturated animal fat [1.5g of cholesterol + 6g of the sheep’s tail fat]. The Turkish dried Figs [*Ficus Carica* L] were bought from the local perfumery centers in Jeddah; they were prepared on daily basis according to Garcia-Salas *et al.* [19] and preserved at room temperature. Extra virgin Olive oil was obtained from a market in Jeddah city. Statin drug was obtained from pharmacy Nahdi in Jeddah, Saudi Arabia.

### Animals:

Sixty adult male Wister Albino rats were used in this experimental study. Their age ranged between 3-4 weeks and their weights ranged from 100-150 grams. The rats obtained under a suitable laboratory conditions from the King Fahd Medical Research Center at King Abdul-Aziz University, Jeddah, Saudi Arabia. The rats were housed in an environmentally controlled room in clean, properly ventilated cages, 3-4 rats in each cage at 22–25°C, relative humidity at [60 ± 10%] and with a 12-h light cycle [05:00–17:00 h]. Diets and tap water were provided *ad libitum*. During the experiment period, care and treatment of rats were in compliance with the Guide for the Care and Use of Laboratory Animals and local institutional guidelines.

### Experimental Design:

After 1-week acclimation, these rats were divided into equal 6 groups [10 rats each]. First group, the negative control group had free access to a normal diet and drinking ordinary tap water. Second group, the positive control group was fed on high cholesterol diet at dose 15g/100g of the total body weight according to Caldwell *et al.* [20] for 16 weeks. Third group, the hyperlipidemic treated with Statin drug group was treated with Statin drug [0.3 mg /100 g] via stomach feeding tube for 16 weeks. Fourth group, the hyperlipidemic treated with drenched Fig [2 ml/kg] orally for 16 weeks through stomach tube. Fifth group, the hyperlipidemic treated with Olive oil [2 ml/kg] orally for 16 weeks through stomach tube. Sixth group, the hyperlipidemic treated with drenched Fig [2 ml/kg] then Olive oil [2 ml/kg] orally for 16 weeks through stomach tube. At the end of the experiments, the final body weight was measured and recorded. The animals were sacrificed by neck dislocation after anesthetized by inhalation of ether anesthesia. The liver was dissected and weighted. The relative liver weight to body weight was calculated and recorded.

### Biochemical studies:

Blood was obtained at end of the experiment from retro-orbital vein plexus into plain tubes. After the bloods were put at room temperature for 1 h, serum was separated by centrifugation at 1500 g for 15 min., then the clear, non-hemolyzed supernatant quickly removed and storage at – 20°C till used. The serum levels of liver function tests (alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT],

total protein, albumin and globulin) were measured by enzymatic methods [Roche, USA] with an automatic analyzer [7170, Hitachi, Japan].

#### Data analysis:

Statistical analysis was made using SPSS software version 20. The levels of measured parameters were expressed as mean  $\pm$  standard deviation. Comparison between the different experimental groups was made using one Way ANOVA test and in the same group in different weeks by paired student "t" test. A *P* value less than 0.05 were considered significance.

## RESULTS AND DISCUSSION

Liver function tests measure the synthetic ability of the liver. They are done by measuring serum levels of total proteins, albumin, globulin, AST, ALT and ALP [21, 22]. Their levels help in early detection of liver dysfunctions before microscopic examination of the liver [23, 24]. Table (1) and Figure (1) showed that there was significant difference between serum levels of alkaline phosphatase between control group and other different studied groups. In hyperlipidemic group, the serum level of ALP was significantly higher than negative control group ( $677.00 \pm 0.55$  versus  $260.00 \pm 0.67$  U/L,  $P = 0.0001$ ) that indicated disturbance in liver functions in hyperlipidemic group. Similar results were reported by Zarei *et al.* [25]. In statin treated group, serum levels of ALP was significantly lowered compared to hyperlipidemic group ( $390.50 \pm 0.67$  versus  $677.00 \pm 0.55$  U/L,  $P = 0.0001$ ). In this respect, Zarei *et al.* [25] reported that statin drug led to decreased in serum level of ALP in rats with hyperlipidemic serum levels. Treatment of rats with Fig, Olive oil and Fig & Olive oil led to lower of ALP serum levels ( $379.00 \pm 0.44$ ,  $372.00 \pm 0.41$  and  $360.00 \pm 0.55$  U/L) compared to hyperlipidemic group ( $677.00 \pm 0.55$  U/L) but still significantly higher than negative control group ( $260.00 \pm 0.67$  U/L). In this respect, El-Shobaki *et al.* [26] reported that a serum level of ALP was higher in group treated with Fig. Bawazir [27] reported that serum ALP was significantly higher in rats treated with Olive green compared with negative control group.

Table (1) and Figure (1) showed that there was significant difference between serum levels of AST between control group and other different studied groups. In hyperlipidemic group, the serum level of AST was significantly higher than negative control group ( $240.00 \pm 0.22$  versus  $72.00 \pm 0.40$  U/L,  $P = 0.0001$ ) that indicated disturbance in liver functions in hyperlipidemic group. Similar results were reported by Zarei *et al.* [25]. In different studied groups, serum level of AST was significantly lower than hyperlipidemic group. In statin treated group, serum levels of AST was significantly lowered compared to hyperlipidemic group ( $128.50 \pm 0.73$  versus  $240.00 \pm 0.22$  U/L,  $P = 0.0001$ ). In this respect, [28, 29] reported increased in serum levels of AST in patients treated with drugs contained statin group than normal levels. Treatment of rats with Fig, Olive oil and Fig & Olive green led to significantly lower of AST serum levels ( $125.00 \pm 0.46$ ,  $108.40 \pm 0.81$  and  $93.90 \pm 0.44$  U/L) compared to hyperlipidemic group ( $240.00 \pm 0.22$  U/L) but still significantly higher than negative control group ( $72.00 \pm 0.40$  U/L). In this respect, El-Shobaki *et al.* [26] reported that in rats, serum level of AST was lower in groups treated with different doses of Fig compared to hyperlipidemic group. Meanwhile, Aghel *et al.* [30] reported that serum level of AST was significantly lower in hyperlipidemic level group compared with negative control after oral administration of Olive green.

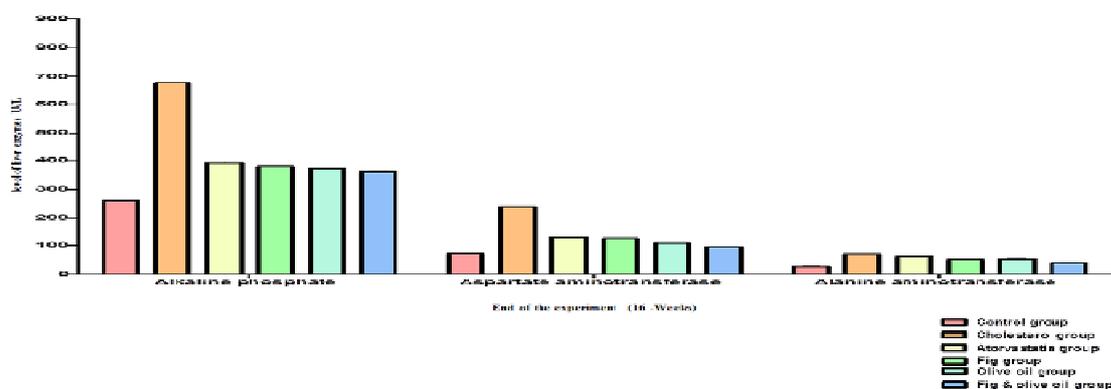
Table (1) and Figure (1) showed that there was significant difference between serum levels of ALT between control group and other different studied groups. In hyperlipidemic group, the serum level of ALT was significantly higher than negative control group ( $70.00 \pm 0.28$  versus  $27.00 \pm 0.50$  U/L,  $P = 0.0001$ ) that indicated disturbance in liver functions in hyperlipidemic group. Similar results were reported by Zarei *et al.* [25]. In different studied groups, serum level of ALT was significantly lower than hyperlipidemic group. In statin treated group, serum levels of ALT was significantly lowered compared to hyperlipidemic group ( $61.30 \pm 0.76$  versus  $70.00 \pm 0.28$  U/L,  $P = 0.0001$ ) but still significantly higher than negative control group. In consistency with the result of the present study [25, 29] reported increased in serum levels of ALT in group treated with statin compared to negative control group. Meanwhile, Pasternal *et al.* [31] reported decreased in serum levels of ALT in patients treated with drugs contained statin group. Treatment of rats with Fig, Olive oil and Fig & Olive green led to significantly lower of ALT serum levels ( $50.00 \pm 0.41$ ,  $52.70 \pm 0.78$  and  $39.99 \pm 0.46$  U/L) compared to hyperlipidemic group ( $70.00 \pm 0.28$  U/L) but still significantly higher than negative control group ( $27.00 \pm 0.50$  U/L). In this respect, Aghel *et al.* [30] reported that in rats, serum level of ALT was lower in groups treated with different doses of Fig compared to hyperlipidemic group. Meanwhile, Necib *et al.* [32] reported that serum level of ALT significantly increased in rats treated with Olive green.

Total proteins are important to maintain the osmotic pressure of the plasma. The serum level of total proteins in rats ranged from 5.6 to 7.6 (grams/ 100 ml) [33].

**Table 1:** Levels of liver Enzyme tests in different groups and different weeks

Groups	Control group	Hyperlipidemic group	Statin treated group	Fig group	Olive oil group	Fig & Olive oil group
Liver Enzyme tests						
Alkaline phosphate (ALP) (U/L)	260.00 ±0.67	677.00 ±0.55	390.50 ±0.67	379.00 ±0.44	372.00 ±0.41	360.00 ±0.55
		P =0.0001	P =0.0001; <sup>1</sup> P=0.0001	P =0.0001; <sup>1</sup> P=0.0001	P =0.0001; <sup>1</sup> P=0.0001	P =0.0001; <sup>1</sup> P=0.0001
Aspartate aminotransferase (AST) (U/L)	72.00 ±0.40	240.00 ±0.22	128.50 ±0.73	125.00 ±0.46	108.40 ±0.81	93.90 ±0.44
		P =0.0001	P =0.0001; <sup>1</sup> P=0.0001	P =0.0001; <sup>1</sup> P=0.0001	P =0.0001; <sup>1</sup> P=0.0001	P =0.0001; <sup>1</sup> P=0.0001
Alanine aminotransferase (ALT) (U/L)	27.00 ±0.50	70.00 ±0.28	61.30 ±0.76	50.00 ±0.41	52.70 ±0.78	39.99 ±0.46
		P =0.0001	P =0.0001; <sup>1</sup> P=0.0001	P =0.0001; <sup>1</sup> P=0.0001	P =0.0001; <sup>1</sup> P=0.0001	P =0.0001; <sup>1</sup> P=0.0001

Data are expressed as mean±/ SD. P: significance versus control group, 1P: significance versus cholesterol group using OneWay Anova test.



**Fig. 1:** Serum levels of different liver enzymes in different groups at week 16th in different groups and final month. Data are expressed as mean±/SD.

Table (2) and Figure (2) showed that there was significant difference between serum levels of total proteins between control group and other different studied groups. In hyperlipidemic group, the serum level of total proteins was significantly lower than negative control group ( $5.00 \pm 0.09$  versus  $7.00 \pm 0.40$  gram/100 mL,  $P = 0.0001$ ) that indicated disturbance in liver functions in hyperlipidemic group. Matos *et al.*, [34] and Gloria *et al.*, [35] reported lower of TP serum level in hyperlipidemic group compared with negative control. In statin treated group, serum levels of TP was insignificantly higher compared to hyperlipidemic group ( $6.34 \pm 0.48$  versus  $5.00 \pm 0.09$  U/L,  $P = 0.167$ ) but still significantly lower than negative control group ( $P = 0.0001$ ). Khasawnah [36] reported lower of serum levels of TP in hyperlipidemic level and statin treated groups compared to negative control group. In Fig treated group, TP serum level ( $6.50 \pm 0.82$ ) was significantly higher than hyperlipidemic group ( $P = 0.044$ ) but still significantly lower than negative control ( $P = 0.044$ ). In consistence with our results, Mujeeb *et al.* [37] reported decreased in TP level in rats fed on Fig. In this study in rats groups treated with Olive green and Fig & Olive green, TP serum levels ( $6.66 \pm 0.42$  and  $6.88 \pm 0.50$ ) were significantly increased compared to hyperlipidemic group ( $P = 0.009$  and  $P = 0.001$ ) and showed insignificant difference than negative control ( $P = 0.170$  and  $P = 0.623$ ). Necib *et al.* [32] reported that serum level of TP in rats group treated with Olive green showed insignificant difference versus negative control group.

The serum level of albumin in rats ranged from 3.8 to 4.8 (grams/ 100 ml) [33].

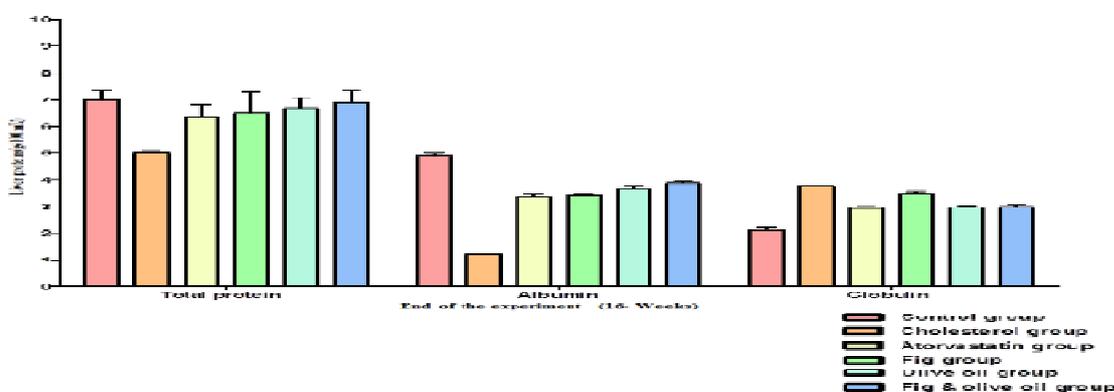
Table (2) and Figure (2) showed that in hyperlipidemic group, the serum level of albumin was significantly lower than negative control group ( $1.23 \pm 0.03$  versus  $4.88 \pm 0.11$  gram/100 mL,  $P = 0.0001$ ). In this respect, Alam *et al.* [38] reported that in White Albino rats, serum level of albumin was significantly decreased in hyperlipidemic group than negative control. The serum levels of albumin in statin treated, Fig, Olive green and Fig & Olive green groups ( $3.39 \pm 0.11$ ,  $3.45 \pm 0.05$ ,  $3.70 \pm 0.08$  and  $3.88 \pm 0.08$ ) were significantly elevated than hyperlipidemic group ( $P = 0.0001$ ) but was still significantly lower than negative control ( $P = 0.0001$ ). In this respect, Yang *et al.* [39] reported decreased in serum level of albumin in statin treated group versus control while [32, 37] reported decreased in serum level of albumin in rats fed on Olive green versus control.

The serum level of globulin in rats ranged from 1.8 to 3.00 (grams/ 100 ml) [33]. Table (2) and Figure (2) showed that in hyperlipidemic group, the serum level of globulin was significantly higher than negative control group ( $3.77 \pm 0.01$  versus  $2.12 \pm 0.08$  gram/100 mL,  $P = 0.0001$ ). The serum levels of globulin in statin treated,

Fig, Olive green and Fig & Olive green groups ( $2.95 \pm 0.05$ ,  $3.50 \pm 0.08$ ,  $2.96 \pm 0.08$  and  $3.00 \pm 0.08$ ) were significantly lowered than hyperlipidemic group ( $P = 0.0001$ ) but was still significantly higher than negative control ( $P = 0.0001$ ).

**Table 2:** Levels of liver protein tests in different groups and different weeks

Groups	Control group	Hyperlipidemic group	Statin treated group	Fig group	Olive oil group	Fig & Olive oil group
Liver protein tests						
Total protein (gram/100 ml)	7.00 $\pm 0.40$	5.00 $\pm 0.09$	6.34 $\pm 0.48$	6.50 $\pm 0.82$	6.66 $\pm 0.42$	6.88 $\pm 0.50$
		$P = 0.0001$	$P = 0.009$ ; $^1P = 0.167$	$P = 0.044$ ; $^1P = 0.044$	$P = 0.170$ ; $^1P = 0.009$	$P = 0.623$ ; $^1P = 0.001$
Albumin (gram/100 ml)	4.88 $\pm 0.11$	1.23 $\pm 0.03$	3.39 $\pm 0.11$	3.45 $\pm 0.05$	3.70 $\pm 0.08$	3.88 $\pm 0.08$
		$P = 0.0001$	$P = 0.0001$ ; $^1P = 0.0001$	$P = 0.0001$ ; $^1P = 0.0001$	$P = 0.0001$ ; $^1P = 0.0001$	$P = 0.0001$ ; $^1P = 0.0001$
Globulin (gram/100 ml)	2.12 $\pm 0.08$	3.77 $\pm 0.01$	2.95 $\pm 0.05$	3.50 $\pm 0.08$	2.96 $\pm 0.08$	3.00 $\pm 0.08$
		$P = 0.0001$	$P = 0.0001$ ; $^1P = 0.0001$	$P = 0.0001$ ; $^1P = 0.0001$	$P = 0.0001$ ; $^1P = 0.0001$	$P = 0.0001$ ; $^1P = 0.0001$



**Fig. 2:** Serum levels of different liver proteins in t groups last month different groups (2 ml). Data are expressed as mean $\pm$  SD

In conclusion, the results of this study revealed that treatment of hyperlipidemic rats with Fig or Olive green or both of them for 16 weeks led to improvement of liver enzymes levels and increased in total proteins and albumin.

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