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Potential Effects of Olive Oil and Thyme Powder on Oxidative Stress and Liver Functions of Cirrhotic Rats

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Abstract:

This study was designed to determine the effects of olive oil and thyme powder on liver functions and oxidative stress of cirrhotic rats. Thirty-five male rats were divided into two main groups: the negative control group (n=7) and fed on a basal diet. The second group (n= 27) was intraperitoneally injected with carbon tetrachloride (CCl₄) for six weeks to induce liver cirrhosis, then divided into four sub-groups; first group (group 2) was positive control; groups (3 and 4) were fed on a basal diet supplemented with olive oil (5%) and thyme powder (10%), respectively. The last group (group 5) was fed on a basal diet supplemented with a mixture of olive oil (5%) and thyme powder (10%). The results indicated that olive oil, thyme, and their mixture significantly increased (P<0.05) the level of IgM, IgG, albumin, and globulin in cirrhotic rats compared to the positive control group. Also, the level of antioxidant indicators (glutathione, GSH, and superoxide dismutase, SOD) were significantly (P<0.05) increased, while the level of malonaldehyde (MDA) was significantly decreased. Furthermore, liver functions (ALT, AST, ALP, and T.bilirubin) of cirrhotic rats were significantly (P<0.05) improved in treated groups. The synergistic protection effect was recorded for the mixture group (i.e., olive oil and thyme powder), which could be attributed to their high total phenolic content and high antioxidant activity. It could be concluded that olive oil and thyme powder could be promising foods for controlling liver cirrhosis.

Keywords: Antioxidant, Malonaldehyde, Carbon Tetrachloride, Immunity, Phenolics.

Introduction

Liver cirrhosis is designated by the replacement of normal liver tissue by fibrotic scar tissue and by regeneration of hepatocytes which progressively leads to loss of liver

functions⁽¹⁾. It is a final common pathway of all chronic liver diseases, estimated as one of the ten most common causes of mortality globally^(2,3). Also, the growing disease may result in liver failure with portal hypertension and an increased prospect of liver cancer⁽⁴⁾. The complications of cirrhosis of human beings contained oxidative damage and resulted in a decline of glutathione reductase level, an increase in malonaldehyde (MDA) level, and a decrease in the activity of superoxide dismutase⁽⁵⁻⁸⁾.

Therapeutic plant extracts/parts showed an increasing interest as a non-drug cure for many diseases⁽⁹⁻¹¹⁾; this may be due to its flavonoids and other polyphenols constituents that contribute to the modulation of many biological processes, especially in vivo oxidative balances, inflammatory, and damage of cells and tissues⁽¹²⁾. Thyme (*Thymus vulgaris*) was a sweet-smelling indigenous herb in the Mediterranean area⁽¹³⁾, known locally as "Zaatar." It has been suggested as a natural alternative to synthetic antioxidants. Thyme also serves as a liver cleansing tonic, ameliorates blood circulation, and stimulates the overall system, according to Höferl et al.⁽¹⁴⁾. Flavonoids, thymol, carvacrol, eugenol, aliphatic phenols, and luteolin and saponins contribute to the potency of the thymus⁽¹⁵⁾. The antioxidants thymol and carvacrol are detected in thyme⁽¹⁶⁾. Accordingly, You and Deans⁽¹⁷⁾ assess whether dietary supplementation of thyme oil could address the negative antioxidant-pro-oxidant balance with age .

Virgin olive (*Olea europaea* L.) oil has been widely produced and used throughout history in all parts of the world and is appreciated for its delectable flavor and scent, as well as its nutritional properties⁽¹⁸⁾. It has been proven to contain a higher level of unsaturated fatty acids and is widely regarded as superior to other oils in health maintenance⁽¹⁹⁾. Olive intake has been demonstrated to have anti-inflammatory, antithrombotic, antihypertensive, and vasodilator properties⁽²⁰⁾. Therefore, the present study was carried out to evaluate the potential effects of olive oil and thyme powder on oxidative stress and liver functions of cirrhotic rats

Materials and methods

Materials:

Olive oil and thyme powder were obtained and confirmed by Agriculture Research Center, Ministry of Agriculture, Cairo, Egypt, in January 2020.

Rats:

Thirty-five adult male albino rats of Sprague Dawley strain, weighing (200±5g) were purchased from Helwan Farm for Experimental Animals, Cairo, Egypt. The experiment was conducted at the Laboratory of Agriculture Research Center, Regional Center of Food and Feed, Biology Department, Giza, Egypt.

Chemicals:

Kits for biochemical analysis were purchased from Gama Trade Company for Pharmaceutical and chemicals, Dokki, Egypt. Carbon tetrachloride (CCl₄), Casein, vitamins, minerals, cellulose, and choline were obtained from Morgan Chemical Factory, Cairo, Egypt. All other chemicals and solvents used were of analytical grade were purchased from El-Ghomorya Company for Trading Drugs, Chemicals, and Medical Suppliers, Cairo, Egypt.

Methods :

Total phenolics and flavonoids content determination

Total phenolics and total flavonoids content in olive oil and thyme powder were determined according to Zilic et al. ⁽²¹⁾. Total phenolics and total flavonoids of olive oil and thyme samples were expressed as mg of gallic acid equivalent (GAE) and rutin equivalent (RE) per g, respectively.

Experimental Design

Thirty-five rats were housed in well-aerated cages under hygienic conditions and fed on a basal diet for one week for adaptation. After this week, the rats were divided into two groups: the first group (n=7) was kept as a negative control/normal group and fed on a basal diet. The second main group (n=27) was intraperitoneally injected with CCl₄ at 0.5ml/100 g. body weight for the first time, then 0.3 ml/100g BW twice a week for six weeks to cause cirrhosis of the liver ⁽²²⁾. Four rats from the injected rats were chosen randomly and killed for pathological examination to determine liver cirrhosis. Then, the infected rats were classified into four sub-groups. One group of them (group 2) served as a positive control group; groups (3 and 4) were fed on a basal diet supplemented with olive oil (5%) and thyme powder (10%), respectively. At the same time, the last group (group 5) was fed on a basal diet supplemented with a mixture of olive oil (5%) and thyme powder (10%). At the end of the experiment (8 weeks), the rats fasted for 12 hours and were sacrificed under ether anesthesia. Blood samples were collected from medial canthus of the eyes of rats using fine capillary glass tubes into a centrifuge tube without any anticoagulant and centrifuged for 15 minutes at 3000 r.p.m. to obtain serum which was stored at -20°C until used for subsequent analysis.

Biochemical analysis

According to Ziva and Pannall ⁽²³⁾, immunoglobulin M (IgM) and immunoglobulin G (IgG) were determined. Reitman and Frankel's ⁽²⁴⁾ approach was used to assess serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), whereas Roy's ⁽²⁵⁾ method was used to determine alkaline phosphatase (ALP). Total serum protein, albumin, and globulin were estimated according to Weissman et al. ⁽²⁶⁾. Total bilirubin was measured according to Kaplan's guidelines ⁽²⁷⁾. Glutathione (GSH), Superoxide

Dismutase (SOD), and malondialdehyde (MDA) were measured using the procedures outlined by Beutler et al. ⁽²⁸⁾; Kakkar et al. ⁽²⁹⁾; and Draper and Hadly ⁽³⁰⁾.

Statistical analysis

The data were presented as a mean with standard deviation (SE). The statistical analysis was carried out using SPSS-PC statistical software (Version 18.0 SPSS Inc., Chicago, USA) using the Dunk 'test multiple range post-hoc test. Data were analyzed by one-way analysis variance (ANOVA). The values were considered significantly different at $P < 0.05$.

Ethical approval

Biological experiments for this study were ethically approved by the Scientific Research Ethics Committee (Animal Care and Use), Faculty of Home Economics, Helwan University, Cairo, Egypt.

Results

Total phenolics and flavonoids of olive oil and thyme were illustrated in Table (1). The total phenolic content in olive oil and thyme powder are 154.3 and 205.34 mg as GAE/g, respectively. In comparison, the total flavonoids content in olive oil and thyme powder are 115.8 and 42.17 mg RUE/g, respectively. Such data indicated that thyme is higher in total phenols than olive oil, while total flavonoids are higher in olive oil than thyme.

Table (1): Total phenols and flavonoids of thyme and olive oil

Parameters	Thyme	Olive oil
Total phenols (mg GAE/g)	205.34±10.45 ^a	154.3 ±9.77 ^b
Total flavonoids (mg RUE/g)	42.17±8.31 ^b	115.8 ±11.71 ^a

Each value represents the mean value of three replicates ±SD. Means with the different superscript letters in the same row are significantly different at $p < 0.05$.

The effect of thyme and olive oil on the immune functions of cirrhotic rats is illustrated in Table (2). Rats injected with CCl₄ had a significant ($P < 0.05$) decrease in IgM and IgG compared to the negative control group. The concentrations of both IgM and IgG were significantly increased ($P < 0.05$) at the groups treated with the tested materials compared to the positive control group. The supplementation with thyme caused a significant ($P < 0.05$) increase in the level of IgM and IgG as compared to olive oil supplementation. The highest increase in IgM (89.71%) and IgG (93.33%) are found in the mixture group. Table (3) shows the effect of thyme and olive oil on liver functions of cirrhotic rats. Injection with CCL₄ caused a significant ($P < 0.05$) decrease in liver functions (ALT, AST, ALP, and T. bilirubin) as compared to the normal control group. The supplementation with either olive oil, thyme, or their mixture is significantly lowered ($P < 0.05$) the elevated

level of liver functions compared to the positive control group. The best improvement in liver functions is recorded in the group fed the mixture.

Table (2): Effect of thyme and olive oil on immune functions of cirrhotic rats.

Parameters	IgM (g/L)	% of increasing	IgG (g/L)	% of increasing
Groups				
Control (-ve)	245.67±2.13 ^d	-	125.82±1.17 ^d	-
Control (+ve)	184.22±2.26 ^e	-	80.52±1.67 ^e	-
Olive oil	290.80±2.38 ^c	57.87	131.75±2.25 ^c	63.62
Thyme	322.90±6.76 ^b	75.29	140.07±1.60 ^b	73.95
Mixture (Olive oil + Thyme)	349.45±4.50 ^a	89.71	155.67±1.79 ^a	93.33

Values are expressed as means ± SE. Values at the same column with different letters are significantly different at $P < 0.05$.

Table (3): Effect of thyme and olive oil on liver functions of cirrhotic rats

Parameters	ALT	AST (U/L)	ALP	T. bilirubin mg/dl
Groups				
Control (-ve)	27.15±1.38 ^d	70.10±1.05 ^e	202.75±2.56 ^c	4.87±0.35 ^c
Control (+ve)	52.65±2.50 ^a	104.10±2.16 ^a	235.52±2.37 ^a	8.00±0.14 ^a
Olive oil	41.20±1.29 ^b	91.25±1.79 ^b	223.47±2.40 ^b	6.17±0.27 ^b
Thyme	35.12±0.82 ^c	82.25±1.25 ^c	218.05±1.99 ^b	5.82±0.35 ^b
Mixture (Olive oil + Thyme)	36.50±1.57 ^{bc}	75.70±1.63 ^d	208.80±1.19 ^c	4.95±0.09 ^c

Values are expressed as means ± SE. Values at the same column with different letters are significantly different at $P < 0.05$.

The level of serum total protein, albumin, and globulin are significantly ($P < 0.05$) decreased at the positive control group as compared to the normal control group, as shown in Table (4). The treatment with the tested materials caused a higher improvement ($P < 0.05$) of total protein, albumin, and globulin than the positive control group. The highest increase for all of such parameters was recorded for the mixture group.

Rats of the positive control group had a significant ($P < 0.05$) increase in serum MDA level while the levels of GSH and SOD are significantly ($P < 0.05$) increased as compared to the normal control group (Table 5). On the other hand, the levels of MDA are significantly ($P < 0.05$) decreased in the groups fed on olive oil, thyme, and their combination compared to the positive control group. The levels of GSH and SOD are statistically ($P < 0.05$) increased at the same tested materials compared to the positive control group. The greatest improvement for all oxidative stress parameter was recorded for the mixture group

Table (4): Effect of thyme and olive oil on total protein, albumin, and globulin of cirrhotic rats.

Parameters	Total protein	Albumin (g/dl)	Globulin
Groups			
Control (-ve)	7.82±0.22 ^a	4.30±0.12 ^a	3.07±0.08 ^a
Control (+ve)	5.45±0.25 ^d	2.22±0.12 ^e	1.60±0.10 ^d
Olive oil	6.10±0.12 ^c	2.77±0.11 ^d	1.99±0.04 ^c
Thyme	6.95±0.17 ^b	3.30±0.20 ^c	2.27±0.11 ^c
Mixture (Olive oil + Thyme)	7.32±0.17 ^{ab}	3.82±0.17 ^b	2.66±0.17 ^b

Values are expressed as means ± SE. Values at the same column with different letters are significantly different at $P < 0.05$.

Table (5): Effect of thyme and olive oil on oxidative stress in cirrhotic rats

Parameters	MDA (n mol/ml)	GSH (μ mol/dl)	SOD (μ/dl)
Groups			
Control (-ve)	40.11±1.31 ^e	14.02±0.01 ^b	88.33±2.20 ^a
Control (+ve)	86.32±1.78 ^a	8.72±0.26 ^d	50.00±1.24 ^d
Olive oil	57.31±2.87 ^{cd}	11.52±0.35 ^c	72.70±2.90 ^b
Thyme	62.22±1.09 ^{bc}	12.10±0.54 ^c	68.25±2.32 ^b
Mixture (Olive oil + Thyme)	51.22±1.10 ^d	17.14±0.34 ^a	81.61±1.01 ^a

Values are expressed as means ± SE. Values at the same column with different letters are significantly different at $P < 0.05$.

Discussion

Flavored olive oils with herbs or species have been more popular in recent years due to the further health benefits they provide to customers beyond that of olive oil. Thyme has long been used in traditional medicine to cure several illnesses, and it is still used today. Therefore, this trial was conducted to evaluate the effect of olive oil, thyme, and their mixture on oxidative stress and liver functions in cirrhotic rats.

Many essential vitamins are found in thyme, including B-complex, folic acid, -carotene, A, K, E, and C^(31,32). Vitamin C help in the body's development of immunity to infectious agents and the scavenging of damaging pro-inflammatory free radicals. Vitamin A is an antioxidant that is needed to keep mucous membranes and skin healthy and for vision. Natural foods high in flavonoids, such as vitamin A and beta-carotene, can help defend against lung and oral cavity malignancies⁽³³⁾. The antibacterial activities of thyme essential oil have been discovered to be the strongest⁽³⁴⁾. In another study, rats were given 1000 mg of thyme /kg of body weight had a significant ($P < 0.05$) rise in RBCs, WBCs, lymphocyte, neutrophil, and monocyte counts, as well as a decrease in eosinophil counts⁽³⁵⁾. Diets including olive oil have some favorable benefits on immune system activities, which is most likely attributable to the action of oleic acid rather than other compounds

found in this fat. Epidemiological, clinical, and experimental studies in the last few years have demonstrated the potential of certain dietary lipids (containing polyunsaturated or monounsaturated fatty acids) as immune system modulators due to their ability to suppress several immune system functions in both humans and animals ^(36,37).

Treatment of rats with thyme, olive oil, or their combination enhanced liver functions. Thyme extracts have been used in traditional medicine to treat a variety of respiratory disorders such as asthma and bronchitis and other pathologies due to qualities such as antiseptic, antispasmodic, and antitussive antibacterial, antifungal, antioxidative, and antiviral ⁽³⁸⁾. According to Shanon ⁽³⁹⁾, adding a 10% aqueous extract of thyme to the drinking water of broiler chicken moms produces a decrease in liver enzymes, which could be attributed to thyme components that boost antioxidant status. Total phenols in thyme lower ALP levels by obstructing ALP production in the liver and bones ⁽⁴⁰⁾. The properties of the thyme constituents as polyphenols (Thymol and Carvacrol) and flavonoids (caffeic acid, rosmarinic acid, apigenin, thymine, and luteolin) protect the cellular membranes' integrity from AlCl₃-induced oxidative damage and repair the antioxidant system ⁽⁴¹⁾. According to other authors, thymol was reported to reduce reactive oxygen species (ROS) production in male Swiss albino mice and suppress CCl₄-induced hepatotoxicity as measured by lipid peroxidation and histological analysis ⁽⁴²⁾. On the other hand, Bars-Cortina et al. ⁽⁴³⁾ indicate a protective effect of olive and thyme phenols supplemented in the diet on α -tocopherol, resulting in a higher concentration of endogenous α -tocopherol in the rat liver. Vitamin E acts as a potent antioxidant in biological systems ⁽⁴⁴⁾.

Treatment with olive oil (10 ml/kg) reduced hepatic MDA and hydroxyproline levels. Olive oil was found to reduce CCl₄-induced liver fibrosis, necrosis, and expression of smooth muscle alpha-actinin histological studies ⁽⁴⁵⁾. Compared to the positive CCl₄ control group, treating the hepatotoxic rats with olive oil (1 ml/kg body weight) resulted in significant improvements in all biochemical tests. Olive oil's physiologically active components may be responsible for its hepatoprotective properties ⁽⁴⁶⁾.

Regarding protein parameters, the supplementation with thyme, olive oil, and their mixture significantly increased ($P < 0.05$) the mean level of serum protein compared to the positive control group. Mansour et al., ⁽⁴⁷⁾ for example, obtained similar results in 2002. Furthermore, according to Seung et al. ⁽⁴⁸⁾, thyme has a successful defensive instrument due to reactive oxygen species, which may be linked to reduced oxidative stress. Accordingly, El-Ghousein and Al-Beitowi ⁽⁴⁹⁾ reported that dietary thyme in the chicken diet on serum glucose, total protein, and globulins was significantly increased. Also, Hassanen and Ahmed ⁽⁵⁰⁾ showed that treatment with olive oil exhibited improvement in liver functions and reduced the severity of the liver injury. In addition, several studies ^(37,51,52) found that olive oil enhanced liver function. Meanwhile, triglycerides and

cholesterol levels in the blood were much lower. Finally, H. Negm⁽⁵³⁾ found that using olive oil supplements improved liver and renal function. In the case of thyme, Shanon⁽³⁹⁾ found that adding a 10% aqueous extract of thyme to the drinking water of broiler chicken moms caused a decrease in liver enzymes. This effect could be related to thyme components that boost antioxidant status. Thyme includes flavonoids, which help to reduce ALP levels after a liver and bone blockage procedure⁽⁴⁰⁾. Thymol suppressed cytochrome P450 mediated metabolic activation of CCl₄⁽⁵⁴⁾. Furthermore, carvacrol exerted antioxidant and hepatoprotective effects in rats⁽⁵⁵⁾. Also, Esmail⁽⁵⁶⁾ showed that supplementation with thyme significantly ($P < 0.05$) enhanced liver functions and also serum protein parameters (albumin, globulin, and total protein), serum CAT, SOD, and decreased MDA significantly compared to the positive control.

The supplementation with either thyme or olive oil significantly increased the antioxidant enzymes of cirrhotic rats. This result follows Abd El Kader and Mohamed⁽⁵⁷⁾, who reported that thyme enhances the antioxidant defense enzymes SOD, CAT and replenishes GSH storage. Moreover, thyme extract has an inhibitory effect on lipid peroxidation, which could decrease the strength of inflammatory response⁽⁵⁸⁾. The same results were obtained by Rubió et al.⁽⁵⁹⁾. Also, Rana and Soni⁽⁶⁰⁾ noted in a rat study that a diet containing thyme diminished the impact of a stress-induced reduction in the activities of SOD, glutathione (GPx), and catalase (CAT) as compared to the normal control diet. This result is due to flavonoids (tymusin, eriodictyol, xanthomycol, 7-methylsudachitin), phenolic acids (the conjugated form of caffeic acid, rosmarinic acid), and monoterpenes (thymol and carvacrol) content of thyme⁽⁶¹⁾. Phenolics in virgin olive oil were found to modulate oxidative stress *in vitro* and *in vivo*, mainly by acting as a free radical scavenger via their hydrogen donation and electron transferability, as well as metal chelating activity⁽⁶²⁾. Since olive oil is normally consumed with other foods, phytochemicals in olive oil could work with phytochemicals in other foods in the diet to modulate antioxidant defenses in an additive/synergistic manner⁽⁶¹⁾. Also, Amamou et al.⁽⁶³⁾ suggest that olive oil or colocynth oil consumption could protect the rat liver against Cd-induced injury by increasing the activities of antioxidant enzymes and reducing oxidative stress. Antioxidant protection by phenolics from olive and thyme against oxidative stress occurs primarily through a direct antioxidant effect and may be related to the phenolic plasmatic metabolites⁽⁵⁹⁾.

Conclusion

Olive oil, thyme powder, and their mixture were effective in protecting against CCl₄-induced liver cirrhosis. These results supported our hypothesis that the tested materials contain several classes of phytochemicals, principally phenolics, and flavonoids, with other compounds that can prevent or inhibit CCl₄ hepatotoxicity. Therefore, we

recommended that olive oil, thyme powder, and mixture be included in our daily diets, drinks, and food supplementation, especially for cirrhotic patients.

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التأثيرات المحتملة لزيت الزيتون والزعتر على الإجهاد التأكسدي ووظائف الكبد في الفئران المصابة بتليف الكبد

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الملخص العربي

تم تصميم هذه الدراسة لتحديد آثار زيت الزيتون ومسحوق الزعتر على وظائف الكبد والإجهاد التأكسدي للفئران المصابة بالتليف الكبدي. تم تقسيم ٣٥ فأرا ذكرا إلى مجموعتين رئيسيتين: مجموعة ضابطة سالبة (N=٧) وتم تغذيتها على الوجبة النموذجية فقط. المجموعة الرئيسية الثانية (N=٢٨) تم حقنها بمادة رابع كلوريد الكربون على مدار ستة أسابيع من أجل أحداث تليف الكبد ثم بعد ذلك تم تقسيمها إلى أربعة مجاميع فرعية متساوية على النحو التالي: مجموعة واحدة منهم (المجموعة ٢) كانت مجموعة ضابطة موجبة، المجموعات (٣ و٤) تم تغذيتها على الوجبة النموذجية مضاف إليه زيت الزيتون بنسبة ٥ ٪ ومسحوق الزعتر بنسبة ١٠ ٪ على التوالي، المجموعة (٥) تم تغذيتها على الوجبة النموذجية مضاف إليه خليط من زيت الزيتون بنسبة ٥ ٪ ومسحوق الزعتر بنسبة ١٠ ٪. أوضحت النتائج أن التغذية على زيت الزيتون والزعتر ومخلوطين أدى إلى زيادة معنوية ($P < 0.05$) في مستوى الاجسام المناعية IgG ، IgM وكذلك الألبومين والجلوبيولين في الفئران المصابة بالتليف الكبدي مقارنة بالمجموعة الضابطة الموجبة. بالإضافة إلى ذلك، ارتفع مستوى مركب الجلوتاثيون GSH ، ونشاط انزيم سوبر اكسيد دسميوتيز SOD المضادان للاكسدة بشكل كبير بينما انخفض مستوى الشقوق الحرة (مركب المالونالدهيد MDA) بشكل كبير بسبب تناول زيت الزيتون ومسحوق الزعتر. علاوة على ذلك تحسنت وظائف الكبد في الفئران بشكل ملحوظ في المجموعات المعالجة. كما أرجعت الدراسة الحماية التآزرية لزيت الزيتون ومسحوق الزعتر إلى التأثير المضاد للاكسدة المباشر لمحتوياتهما من الفينولات. لذا خلصت الدراسة إلى ان كلا من زيت الزيتون ومسحوق الزعتر من الأغذية الوظيفية التي قد يكون لها اثار جيدة في الوقاية من والمساعدة في علاج مرض التليف الكبدي.

الكلمات المفتاحية: مضادات الاكسدة، الشقوق الحرة، رباعي كلوريد الكربون، المناعة، الانين ترانزامينز، الفينولات