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Effect of Eight Weeks of Lycopene Supplementation on Oxidative Stress and Adiponectin Gene Expression in Rats with Fatty Liver Disease

Nastaran Amini; MSc [1], Mandana Gholami; PhD*[2] , Seyyedmostafa Seyyedashour; MSc[1] & Mansour Shoae; MSc[1]

[1] Department of Physical Education, Faculty of Literature, Humanities and Social Sciences, Islamic Azad University Science and Research Branch, Tehran, Iran; [2] Department of Physical Education and Sport Sciences, Faculty of Literature, Humanities and Social Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran.

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Corresponding author
gholami_man@yahoo.com
Department of Physical Education and Sport Sciences, Faculty of Literature, Humanities and Social Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran.

Postal code: 1477893855
Tel: +98 9121491868

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ABSTRACT

Background: Increased consumption of fat and sugar has been linked to obesity and diseases like non-alcoholic fatty liver disease (NAFLD). Lycopene (LYC), an antioxidant, has been studied for its potential in protecting against fatty liver damage. This study aims to investigate how lycopene affects the antioxidant system and the expression of the adiponectin gene in rats with fatty liver disease. **Methods:** Wistar rats were divided into three groups: control, n=8), high fat diet (HFD, n=8), and lycopene (HFD+LYC, n=8). The lycopene group received a solution containing 100 mg/kg of lycopene three days a week, while the other groups received standard food for eight weeks via gavage. The levels of adiponectin gene expression in the liver were assessed using the real time PCR method. Additionally, the levels of antioxidant enzymes in the serum were measured using ELISA. **Results:** Although lycopene did not have a significant therapeutic effect on malondialdehyde (MDA) compared HFD group (P=0.6103), it improved the levels of the SOD enzyme and the expression of the adiponectin gene compared with HFD group (P=0.0002, P=0.0001). This was a significant decrease in collagen deposition in liver tissue of HFD+LYC group compared to HFD group (P<0.0001). **Conclusion:** Lycopene demonstrates the potential as a therapeutic option for NAFLD. However, more trials are needed to support this idea.

Introduction

Nonalcoholic fatty liver disease is a chronic liver condition characterized by excessive fat accumulation in the liver without secondary causes (Brunner *et al.*, 2019). Over the past four decades, non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disorder (with a global prevalence of around 25% of the adult population) which is recognized to have a close, bidirectional association with components of metabolic syndrome (Powell *et al.*, 2021). A

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previous study showed that particle matter exposure via induction of oxidative stress, induced liver inflammation that has a critical role in liver pathogenesis (Fanaei *et al.*, 2021). Human research have shown that high-fat diets (≥30% of energy from fats) can without difficulty induce obesity. Intake of a high-fat (HF) weight loss plan has long been recognized to increase one's chance for some clinical conditions together with obesity, diabetes, and metabolic syndrome. (Cordner and Tamashiro, 2015, Hariri and Thibault, 2010)

Adiponectin (also known as AdipoQ, apM1 or Acrp30) is a tissue-specific protein of 247 amino acids that shares significant similarity with collagen VIII and X and complements protein C1q. The reduction of this protein plays a key role in obesity-related diseases, including diabetes and cardiovascular diseases (Howlader *et al.*, 2021). Adiponectin is one of the maximum critical adipocytokines, involved in the regulation of insulin sensitivity, glucose metabolism, and lipid metabolism. In addition, adiponectin has effective anti-inflammatory and antiatherogenic traits (Zhang *et al.*, 2019). In this place, there is increasing evidence for the function of adiponectin in NAFLD. Adiponectin is the most considerable and adipose-specific adipocytokine. Contrary to other adipocytokines, adiponectin is sarcastically increased with decreasing fat mass (Polyzos *et al.*, 2011). A complex interaction among adipokines and cytokines produced via adipocytes and/or inflammatory cells infiltrating adipose tissue seems to play an essential role in the pathogenesis of NAFLD, as they will alter insulin sensitivity in insulin targeted organs, such as the liver (Polyzos *et al.*, 2010). Improved adipokine degrees, more specifically, adiponectin concentrations, can exert favorable effects, leading to amelioration of NAFLD and its connected complications (Shabalala *et al.*, 2020).

Oxidative stress is defined as an imbalance between antioxidant defenses and free radical production (Martínez-Martínez and Cachofeiro, 2022). When there is an imbalance between the production of reactive species derived from oxygen and nitrogen, known as oxidative stress, it can lead to pathological signaling and damage to proteins, lipids, and DNA. This imbalance can occur due to either an excessive production of reactive oxygen species (ROS) or a failure of antioxidant defenses in certain subcellular compartments or the entire tissue (Forman and Zhang, 2021, Griendling *et al.*, 2021). The initial line of defense in antioxidants consists of superoxide dismutase (SOD), catalase, and glutathione peroxidase. These antioxidants play a crucial role in the overall defense strategy against oxidative damage (Mao *et al.*, 2019). When the levels of free radicals increase, the production of malondialdehyde (MDA), a well-known byproduct of lipid peroxidation, also increases. Thus, the concentration of MDA serves as a marker for oxidative stress (Alizadeh and Kheirouri, 2019).

Lycopene (LYC) is considered a potent natural antioxidant due to its molecular structure containing thirteen conjugated double bonds. The trans isomer of lycopene is primarily present in tomatoes, but it can also be found in varying concentrations in other red fruits and vegetables like red carrots, watermelons, grapefruits, and papayas (Kapała *et al.*, 2022, Zhao *et al.*, 2023). Numerous biological activities of LYC were identified, such as antioxidant, anticancer, anti-inflammation, cardiovascular, neural protective effects and treatment of NAFLD (Elvira-Torales *et al.*, 2019, Gao *et al.*, 2023). Moreover, lycopene also reduces the development of hepatic steatosis induced by an HF diet and oral administration of lycopene lowered MDA level while increasing SOD activity in the rat liver with HFD-induced NAFLD (Ferramosca *et al.*, 2017, Lee *et al.*, 2019).

The aim of this study was to examine the potential of lycopene to prevent oxidative damage. The authors conducted an investigation to determine the impact of lycopene supplementation on the antioxidant status of rats with fatty liver disease and assess whether lycopene supplementation could offer hepatoprotection for rats with NAFLD.

Materials and Methods

Animals, diets, and experiment design

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In this experimental study which was authorized by the Islamic Azad University Science and Research Branch (IR.IAU.SRB.REC.1402.026), the number of samples was determined after statistical analysis and considering ethical issues. 24 male Wistar rats (body weight 220±20g) were obtained from the Pasture Iran Institute animal house. Three rats were kept in each single polyacrylic cage and were quarantined. All animals were housed under standard controlled conditions (temperature: 23±3 ℃, humidity: 50±10% and 12 hours light/dark cycle). After one week of adaptation, the animals were divided into three experimental groups, eight per group (control, high fat diet, high fat diet+lycopene). For the induction of fatty liver, the fat groups and the lycopene+high fat group were fed with a high-fat diet for 45 days. To prepare a high-fat diet, 15% animal fat and 4% cholesterol were added to 81% of normal diets (**Table 1**) (Efati *et al.*, 2016). Then, the lycopene group received a lycopene supplement at a dose of 100 mg/kg (Aydemir *et al.*, 2012), and the fat groups were administered normal saline for 8 weeks (Control: standard diet, HFD: High-fat diet and gavaged with normal saline, Lycopene group: High-fat diet plus 100 mg/kg lycopene per body weight of rat). They were gavaged three times a week. During this period, all groups had free access to water and food. The animals were provided with compassionate care in accordance with the National Institutes of Health Guidelines of the United States (National Research Council of United States, 1996) and the ethical regulations of Harbin Medical University.

Table 1. Percentage of normal diet and high fat diet materials.

Nutrients	Normal diet (%)	High fat diet (%)
Fat	12	22
Carbohydrate	57	50
Protein	28	24
Others	3	4

Blood and tissue samples

Material sampling was conducted after a 12-hour fasting period for the animals. Rats were euthanized by cervical dislocation at the end of the experiment with CO2, and blood samples were immediately withdrawn from the heart for the measurement of blood and serum parameters and biochemical markers assay. Serum was collected from the blood after centrifugation at 3500 rpm for 15 min at 4 ℃. The right liver lobe was fixed in 10% formalin to prepare paraffin sections, and the rest was stored at -80 ℃ for the other assays. For histological processing, the sectioned tissues were stained with hematoxylin and eosin (H&E) and examined for morphological and histological parameters by light microscopy.

Biochemical measurements

The levels of malondialdehyde (MDA) and superoxide dismutase (SOD) indicated the presence of oxidative and antioxidant activities, respectively. The MDA Assay Kit (Zellbio, Germany) and SOD assay kit (Zellbio, Germany) were used to detect these two indicators according to the manufacturer's instructions.

Real-time quantitative PCR analysis

In order to extract total RNA from liver tissues and assess their quantity and purity, the authors employed TRIzol reagent and a NanoDrop spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA), respectively. Subsequently, approximately 1 µg of RNA was converted into cDNA through reverse transcription using a PrimeScript RT Master Mix (TaKaRa, Beijing, China). The SYBR Premix Ex Taq fluorescent quantitative PCR (Eppendorf, Framingham, MA, USA) was used to perform real-time quantitative PCR. The conditions for qPCR were as follows: initial denaturation at 95 °C for 30 s, followed by 40 cycles at 95 °C for 5 s and 60 °C for 32 s. The primers are shown in **Table 2**.

Table 2. Adiponectin and GAPDH primers.

Gene name	Primer sequence
r-GAPDH-F	AGGTCGGTGTGAACGGATTTG
r-GAPDH-R	TGTAGACCATGTAGTTGAGGTCA
r-Adiponectin-F	AACATTCCGGGGCTCTACTAC
r-Adiponectin-R	AGGCCTGGTCCACATTTTTTT

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Histological examinations

Liver tissue was settled in 10% formalin and inserted in paraffin wax; then, they were cut into 5 µm thick serial segments, mounted on slides, and recolored with H&E. The nearness of liver hemorage determined utilizing an optical light magnifying lens. Then, Image J software was used for image analysis at a cross section of 100 micrometers at that point. It was deciphered with the assistance of a histopathologist.

Data analysis

All data were presented as means±SD. The mean of all findings among the different groups was compared using the One-Way ANOVA: Post Hoc-Tukey's test. Data were analyzed using GraphPad Prism version 9 for Windows, and a probability of less than 0.05 was considered significant.

Result

Effects of LYC on serum SOD and MDA levels

The serum levels of MDA were significantly different among the groups based on the results of a one-way ANOVA. Tukey's HSD test revealed that MDA levels were significantly higher in HFD rats compared to the control group (P<0.0001). However, there was no significant difference in MDA levels between the HFD+LYC group and the HFD group (P=0.610) although HFD+LYC was still significantly higher than the control group (P=0.0002, **Figure 1**).

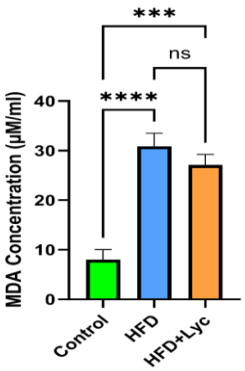

Figure 1. The ANOVA test results for MDA concentration in research groups.
NS: Not significant; *: P≤0.05; **: P≤0.01; ***: P≤0.001; ****: P≤0.0001; **HDF**: High fat diet; **Lyc:** lycopene.

Similarly, the serum levels of SOD were significantly different among the groups (P<0.005) based on the results of a one-way ANOVA. Tukey's HSD test revealed that SOD levels were significantly lower in HFD rats compared to the control and HFD+LYC (P<0.0001, P=0.0002) although HFD+LYC was still significantly lower than the control group (P=0.022, **Figure 2**).

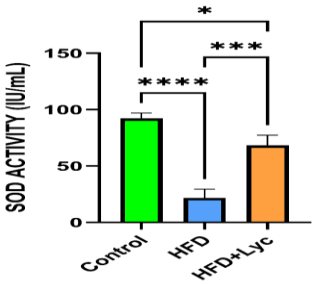

Figure 2. The ANOVA test results for SOD concentration in research groups.
NS: Not significant; *: P≤0.05; **: P≤0.01; ***: P≤0.001; ****: P≤0.0001; **HDF**: High fat diet; **Lyc**: lycopene.

Adiponectin expression in liver tissue of NAFLD rats

The mRNA levels of adiponectin in the liver tissue of NAFLD rats were analyzed. Significant differences were observed among the groups (P<0.005) using a one-way ANOVA. Tukey's HSD test revealed that the levels were significantly lower in HFD rats compared to the control group and HFD+LYC group (P<0.0001, P=0.0001). However, the levels were significantly higher in the HFD+LYC group compared to the HFD group (P=0.037, **Figure 3**).

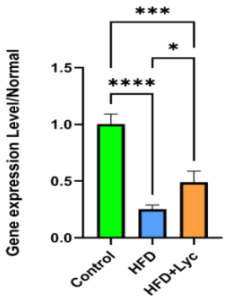

Figure 3. The ANOVA test results for Adiponectin expression in research groups,
NS: Not significant; *: P≤0.05; **: P≤0.01; ***: P≤0.001; ****: P≤0.0001; **HDF:** High fat diet; **Lyc**: lycopene.

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Collagen deposition in liver tissue of NAFLD rats

Tukey's post hoc test showed the amount of liver collagen deposition increased significantly in both HFD and HFD+LYC groups compared to the control group (P<0.0001, P<0.0001), but in the HFD+LYC group, this amount was significantly improved compared to the HFD group (P=0.005, **Figure 4**).

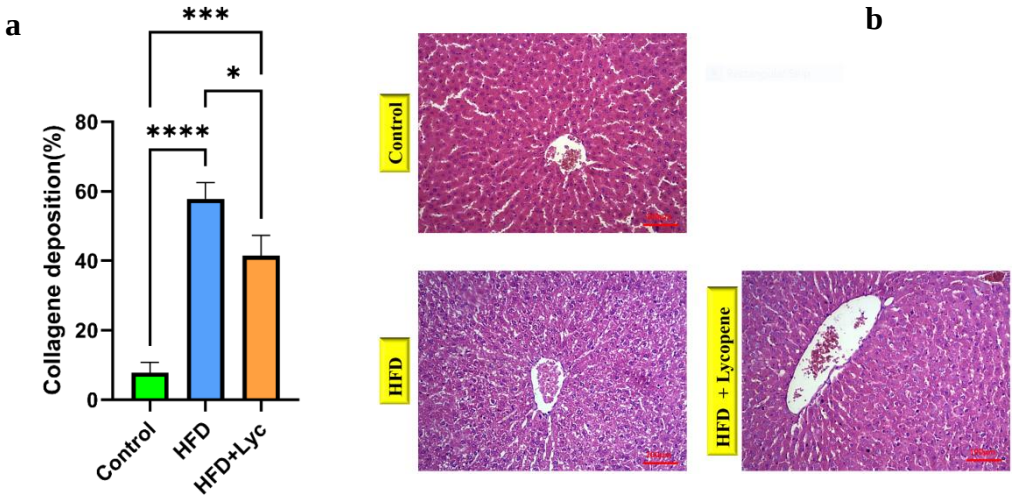

Figure 4. (a) The ANOVA test results for liver collagen deposition (%) in research groups; (b) Representative histological images of liver tissues (H&E staining); **NS**: Not significant; *: P≤0.05; **: P≤0.01; ***: P≤0.001;****: P≤0.0001; **HDF**: High fat diet; **Lyc**: lycopene,

Discussion

The present study aimed to investigate the effects of lycopene supplementation on adiponectin gene expression and collagen deposition in the liver, and the levels of anti-oxidant parameters (i.e., SOD, MDA) in the serum of male rats with NAFLD. However, lycopene increased the levels of adiponectin gene expression in the liver tissue, and serum SOD of NAFLD rats, but the levels of serum MDA and liver collagen deposition decreased.

NAFLD also known as "Fatty liver," is characterized by the presence of macrovesicular changes (steatosis) without inflammation and lobular inflammation in individuals who do not consume significant amounts of alcohol (Antunes *et al.*, 2023). The disease can manifest as either silent liver disease or non-alcoholic steatohepatitis (NASH) (Milić *et al.*, 2014). Both hepatic steatosis and NASH are strongly associated with obesity, including metabolically healthy obese individuals (Tsankof *et al.*, 2022). NAFLD is closely linked to metabolic disorders such as insulin resistance, chronic low-grade inflammation, and oxidative stress (Morais *et al.*, 2017). Oxidative stress occurs when the balance between prooxidative and antioxidant factors favors the former (Jakubiak *et al.*, 2021). Oxidative stress by ROS increases the danger of numerous disorders, such as inflammatory illnesses, cardiovascular disorder, diabetes, cancer, Alzheimer's disorder, cataracts, autism and aging. Antioxidants can immediately have interaction with the reactive radicals to damage them with the aid of receiving or giving an electron(s) to put off the unpaired radical situations, or they will indirectly lower the generation of free radicals by way of restricting the activities or proscribing free radical producing enzymes or intensifying both expressions activities and of different antioxidant enzymes (Abdulrahman *et al.*, 2023). Adiponectin, a biologically active polypeptide, has been found to reduce oxidative stress, inflammation, and apoptosis (Tu *et al.*, 2019). The body contains a

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substantial amount of SOD, which plays a crucial role in eliminating free radicals and protects against the damage caused by reactive oxygen species (Yin *et al.*, 2019). ROS can harm macromolecules like proteins, lipids, and DNA (Jakubiak *et al.*, 2021). MDA is the main end product of lipid peroxidation (Pudi *et al.*, 2022). In the present study, patients with NAFLD were exhibited to have higher MDA and NO metabolites, as well as lower total thiol status (tSH) values and SOD interest than control subjects (Arya *et al.*, 2021) .

The current study observed that lycopene exhibited antioxidant properties. Although there was a decrease in MDA, it was not statistically significant, while the antioxidant molecule SOD increased. These findings align with previous studies. One study demonstrated that lycopene supplementation at a dosage of 10 mg/kg/day increased MDA and improved hepatic antioxidant capacity (Róvero Costa *et al.*, 2019). Another study showed that lycopene supplementation at varying dosages (0, 5, 10, and 15 mg/kg) decreased serum oxidative stress biomarkers such as GHb, ox-LDL, and MDA, while it increased total antioxidative capacity, SOD, and GPx (Zheng *et al.*, 2019). Also, some studies suggested that the beneficial effects of LYC on obese animals may be related to the attenuation of abnormal lipid metabolism within which induces a reduction in serum levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), alanine transaminase (ALT) and aspartate transferase (AST) in obese mice (Zhu *et al.*, 2020) .

Moreover, this study found that lycopene increased adiponectin expression, which was consistent with previous findings. One research reported that lycopene supplementation at a dosage of 10 mg/kg increased both plasma concentration and mRNA expression of adiponectin in adipose tissue (Luvizotto *et al.*, 2015). Numerous projects have proven that the upregulation of adiponectinhas antiobesity results (Huang *et al.*, 2008) and lycopene can lower inflammatory markers and decrease obesity related complications, consisting of nonalcoholic steat ohepatitis (Luvizotto Rde *et al.*, 2013).

While adiponectin performs a critical role within the regulation of glucose and lipid homeostasis. Adiponectin additionally has a strong anti-inflammatory activity. Also, it dampens the early levels of macrophage inflammatory responses, inhibiting the increase of myelomonocytic progenitor cells and reducing the ability of mature macrophages to respond to activation. Adiponectin suppresses phagocytic interest in addition to lipopolysaccharide (LPS)-stimulated cytokine manufacturing in macrophages (Huang *et al.*, 2008). Even as the mechanisms for the long term anti-inflammatory outcomes of adiponectin are not properly understood, recent statistics recommend that adiponectin acts, at least in component, to increase the expression of anti-inflammatory mediators, which includes interleukin (IL)-10 (Park *et al.*, 2007).

In conclusion, the administration of LYC (100 mg/kg) orally resulted in increased SOD activities and reduced MDA in the livers of obese model rats. Additionally, the LYC treated group exhibited an increase in adiponectin mRNA expression. These findings suggest that LYC may play a crucial role in preventing liver damage induced by HFD by enhancing antioxidant enzyme levels and reducing lipid peroxides.

Throughout the pathogenesis of liver fibrosis, collagen is collecting in hepatocytes. Hydroxyproline (HYP) is a function of amino acid in collagen. Its content material can circuitously reflect the level of collagen accumulation in the liver and consequently becomes an indicator to evaluate the degree of liver fibrosis (Ren *et al.*, 2020). Collagen-producing cells are activated via fibrous cytokines, TGF-β1, and angiotensin (Yun *et al.*, 2021).

In this study, the authors examined a higher dose of lycopene compared to other studies, but on fewer days per week. Not observing the toxicity of lycopene in this concentration can help researchers in the future for further studies. Since only the real-time PCR method was used due to financial constraints, it is recommended that researchers use

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other methods such as western blotting, immunofluorescence, and immunohistochemistry for more detailed examinations in the future. In addition, due to the close relationship between adiponectin and leptin, it is recommended to measure these two together in future studies.

Conclusions

Lycopene decreases MDA levels and increases SOD levels and adiponectin gene expression, according to these results; it may be concluded that lycopene has a therapeutic potential to control obesity and oxidative stress.

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Authors' contributions

N Amini and S Seyyedashour and M Shoae involved in Study concept and design. Data acquisition was done by N Amini and analysis and interpretation of data were done by M Shoae and S Seyyedashour. N Amini contributed to writing the draft of the manuscript. M Gholami and N Amini involved in critical revision of the manuscript. The statistical analysis of the data was done by S Seyyedashour. All authors read the final revised manuscript and approved it for publication.

Conflict of interest

The authors declare no conflicts of interest related to this study

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