



# Kiwifruit Supplementation Increases the Activity of the Paraoxonase Enzyme and decreases Oxidized Low-Density Lipoprotein in High-Fat Diet Fed Hamsters

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## Abstract

**Background:** It is shown that kiwifruit elevates serum high-density lipoprotein cholesterol (HDL-C) levels and exhibits beneficial effects on human health due to its antioxidant potential.

**Objectives:** This study aimed to investigate the impact of kiwifruit on the activity of the paraoxonase 1 (PON1) enzyme, as a main antioxidant enzyme in HDL functionality, in a high-fat diet (HFD).

**Methods:** To this end, 42 male Syrian hamsters were divided into 6 groups including hamsters receiving a normal diet (the control normal group), a regular diet supplemented with kiwifruit at two concentrations (i.e., 1.86 g/kg and 3.73 g/kg), a HFD comprised of 15% butterfat + 0.05% cholesterol (the control high-fat group), and a HFD supplemented with kiwifruit at two concentrations (i.e., 1.86 and 3.73 g/kg) for 8 weeks.

**Results:** The results showed that supplementation of kiwifruit to the HFD increased the levels of HDL-C and remarkably reduced the concentrations of oxidized low-density lipoprotein (ox-LDL) and malondialdehyde (MDA) compared with the control-HF group. In addition, the paraoxonase activity of PON1 significantly increased in HFD supplemented with kiwifruit (1.86 g/kg), and finally, arylesterase (ARE) activity increased in all treated groups when compared with untreated groups.

**Conclusion:** Our findings suggested that kiwifruit can improve the lipid profile and prevent oxidative stress-induced by lipid peroxidation in hamsters receiving HFD, thus increasing the ARE and paraoxonase activities of PON1.

**Keywords:** Kiwifruit, Paraoxonase 1, Liver tissue, High-density lipoprotein, High-fat diet

## Background

Oxidative stress can cause physical and chemical modifications in low-density lipoprotein (LDL) through the peroxidation of polyunsaturated fatty acids and the changes in apolipoprotein B by which LDL is converted into an oxidized form (ox-LDL) which is unrecognizable by the LDL receptor (1). Ox-LDL binds to its cognate receptors expressed on endothelial cells, macrophages, and smooth muscle cells, developing foam-cell formation and atherosclerosis and thus plays a crucial role in the expansion of atherosclerotic lesions (2,3). It has been shown that the activity of some antioxidant enzymes, including paraoxonase-1 (PON1), inhibits the oxidation process of LDL (4). On the other hand, the protective role of high-density lipoprotein cholesterol (HDL) against atherogenesis is mediated via reversing the cholesterol transport system in which excess cholesterol is removed from the systemic vasculature and then delivered to the

liver (5). According to Shih et al (6), HDL is capable of protecting LDL from oxidation due to its antioxidant properties. It is thought that the antioxidant potential of HDL is ascribed to enzymes associated with HDL, including PON1 which is mostly secreted by the liver and mainly located on HDL particles (7). PON can prevent atherosclerosis through multiple mechanisms such as the prevention of the cellular uptake of oxidized LDL mediated by a scavenger receptor CD36, the inhibition of cholesterol biosynthesis, and the promotion of cholesterol efflux from macrophages (8). PON1 can also be regarded as an antioxidant enzyme that can prevent the oxidation process in LDL, HDL, and macrophages, thus hydrolytic activity, leading to the hindrance of atherosclerosis development (9,10). It has been implicated that both genetic and environmental factors cooperatively influence the activity of PON1 and the expression level of the gene encoding the PON1 enzyme (11). Further, diet is considered to be

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one of the environmental factors affecting the expression of the PON1 enzyme since malnutrition or healthy foods can change the expression of PON1 (12). Furthermore, fruits could be used to mitigate oxidative stress due to having a high amount of antioxidant agents and thus can increase the activity and mRNA expression of PON1 (13). Particularly, kiwifruit is one of the most abundantly grown fruits containing various phytonutrient compounds such as vitamin C, flavonoids, carotenoids, and minerals. The *Actinidia deliciosa* 'Hayward' (green kiwifruit) is one of the most popular members of the kiwifruit family, possessing a rich source of antioxidant agents such as ascorbic acid and vitamin E (14). Moreover, green kiwifruit is well-known for its significant levels of soluble fibers, potassium, folate, and other phytochemicals including polyphenols and carotenoids (15,16). There are a few studies about the impact of green kiwifruit consumption on the lipid profile in individuals with hyperlipidemia. These studies have highlighted a significant increase in plasma HDL-C and a remarkable decrease in the ratio of the total cholesterol (TC) to HDL-C in response to kiwifruit consumption (16,17). Considering the beneficial effect of kiwifruit on the redox system and the HDL-C profile, it is hypothesized that the supplementation of kiwifruit could enhance the activity of PON1. Therefore, this study evaluated the lipid profile, oxidative stress, and the serum levels of the PON1 enzyme in the Syrian hamster submitted to HFD.

### Methods

#### Animal Procedures

Forty-two male golden Syrian hamsters (*Mesocricetus auratus*) with an age spectrum of 6-8 weeks and a weight range between 120 g and 150 g were obtained from the animal facility of Hamadan University of Medical Sciences (Hamadan-Iran). The animals were kept under standard conditions at a temperature of 20-22°C, the relative humidity of 45%-55%, and a 12-hour light/dark cycle with *ad libitum* access to standard chow and tap water.

To induce hyperlipidemia, male hamsters were fed with HFD containing a standard chow diet supplemented with 0.05% cholesterol (Sigma Chemical Company) and 15% butter, as previously described (18). The regular diet consisted of commercial standard chow although the amount of kiwi consumption was adjusted to the weight of hamsters and was equivalent to the consumption of 1 or 2 kiwifruit(s) per day by a human weighing 70 kg (1.86 or 3.73 g/kg, respectively).

Moreover, kiwifruit was obtained from local markets, washed with tap water, cut into appropriate sizes, and finally, mixed using a blender for 5 minutes. The same amounts (1.86 g/kg) of homogenates were dissolved in 1 mL of water and orally administered to hamsters at two doses of 1.86 and 3.73 mg/kg/d for eight weeks.

The animals were then randomly assigned to six groups (7

hamsters per group):

*Control normal group (CN)*: Hamsters received a regular diet plus normal saline.

*Control normal + 1.86 g/kg kiwi (Nd1)*: Animals received a standard diet plus kiwifruit at a dose of 1.86 g/kg.

*Control normal + 3.73 g/kg kiwi (Nd2)*: Hamsters were fed with a normal diet plus kiwifruit at a dose of 3.73 g/kg.

*Control-HF group*: Animals were submitted to the HFD, along with normal saline.

*HFD + 1.86 g/kg kiwi (Hfd1)*: Hamsters were subjected to the HFD plus kiwifruit at a dose of 1.86 g/kg.

*HFD + 3.73 g/kg kiwi*: Animals received the HFD plus kiwifruit at a dose of 3.73 g/kg.

At the end of the experiment, all hamsters were anesthetized with diethyl ether and sacrificed by cervical dislocation. Next, the blood samples were obtained from the inferior vena cava to isolate sera. The collected serum samples were then stored at -80°C until further analyses. To collect liver specimens, a longitudinal incision was made in the abdominal region of hamsters, minced into proper sections, and stored at -80°C until use.

#### Serum Lipid Profile

The serum TC was measured by the enzymatic method using a commercial kit (Pars Azmun Company, Tehran, Iran) based on photometric detection. The levels of serum LDL-C and HDL-C were directly determined with the commercial kits (Paad Company, Tehran, Iran) based on enzymatic reactions.

#### Serum Malondialdehyde

The reaction of thiobarbituric acid with lipid peroxides was performed, and the pink-colored product was detected by fluorometric assay at a wavelength of 553 nm with excitation at 515 nm, and the results were expressed as the  $\mu\text{mol/L}$  of tetraethoxypropane as a standard solution (19).

#### Total Antioxidant Capacity

The principle of the ferric reducing ability of plasma assay is based on the reduction of the ferric tripyridyltriazine ( $\text{Fe}^{3+}$ -TPTZ) complex to ferrous tripyridyltriazine ( $\text{Fe}^{2+}$ -TPTZ) by available antioxidants in samples at low pH, and the results were expressed as  $\mu\text{mol/L}$  of  $\text{FeSO}_4$  (20).

#### Paraoxonase Activity

A fresh mixture of the Tris-HCl buffer (pH=8.0, 100 mM) containing 3.3 mM paraoxon (diethyl p-nitrophenyl phosphate), as an enzyme substrate, 1 mM  $\text{CaCl}_2$ , and 15  $\mu\text{L}$  samples was used to determine paraoxonase activity (21,22). The paraoxonase activity was expressed as U/mL considering that 1 unit of the enzyme produces 1 nmol of 4-nitrophenol per minute at 20 °C under the standard assay condition (The  $E_{405\text{M}} = 17600 \text{ M}^{-1} \text{ cm}^{-1}$ ) according to (21).

## Archive of SID Arylesterase Activity

Arylesterase (ARE) activity was measured in serum specimens spectrophotometrically at a wavelength of 270 nm using phenylacetate (Merck Schuchardt, Hohenbrunn, Germany) as an enzyme substrate (22) and was expressed as U/L. According to Javadzadeh et al (23), one unit of ARE is equal to 1 mmol of phenylacetate hydrolyzed per minute at 20°C under standard conditions (The E270 =1310 M<sup>-1</sup> cm<sup>-1</sup>).

### Oxidized LDL

The levels of serum ox-LDL were calculated using the Hamster-specific commercial quantitative sandwich enzyme-linked immunosorbent assay kit (MyBioSource, Cat. No: MBS006916).

### Statistical Analysis

The obtained data were statistically analyzed using the SPSS package program, version 19.0. The Shapiro-Wilk test was employed to examine data normality. If the obtained data were normally distributed, the difference among the groups was evaluated by one-way ANOVA, followed by Tukey post hoc test. If the data were not normally distributed, the differences between the groups were calculated by the Kruskal-Wallis and Mann-Whitney tests if appropriate. The values were represented as the mean and standard deviation (mean ± SD), and the level of significance was set at  $P < 0.05$ .

## Results

### Effect of Kiwifruit Consumption on the Serum Lipid Profile

At the end of the experiment (8 weeks), HFD caused a significant increase in the levels of TC ( $P < 0.05$ ), HDL-C ( $P < 0.01$ ), and LDL-C ( $P < 0.05$ ) in the control-HF group as compared with the control normal group (Table 1).

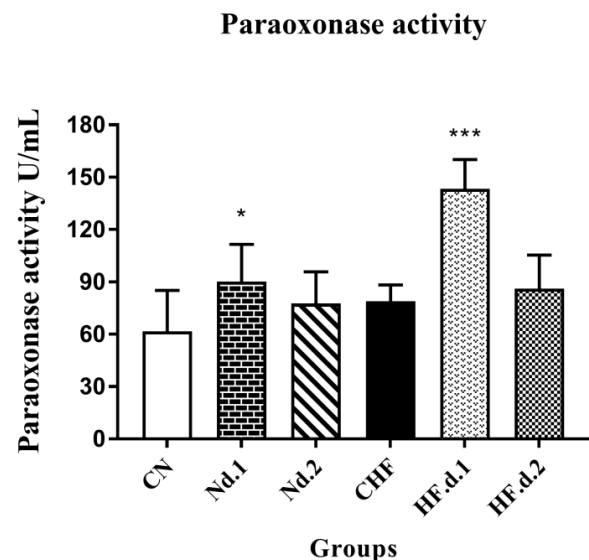
The results showed that there was no significant difference in the concentration of TC when all experimental groups were individually compared with each control group ( $P > 0.05$ ). Although the levels of HDL-C increased in the HFD +1.86 g/kg kiwi and HFD +3.73 g/kg groups compared with the control-HFD group, such an increase was statistically significant only in the HFD +3.73 g/kg kiwi group ( $P < 0.01$ ). The results further revealed that the level of LDL-C was lower in the HFD +1.86 kiwi

and HFD +3.73 kiwi groups compared to the control-HF group although the decrease in LDL-C was not significant ( $P > 0.05$ ). It should be noted that the concentrations of HDL-C and LDL-C remained unchanged in hamsters which were fed with a normal diet and treated with kiwifruit ( $P > 0.05$ ).

### Effect of Kiwifruit Consumption on Paraoxonase and ARE Activities

As shown in Figure 1, the serum activity of PON1 increased in all experimental groups after an 8-week period of kiwifruit consumption although such an increase was statistically meaningful only in a lower dose of kiwifruit (1.86 g/kg); the control N group compared to Nd.1 (61.68±23.47 vs. 90.20±21.39 U/mL,  $P < 0.05$ ) and control, as well as the HF group compared to the HFd.1 (78.90±9.31 vs. 143.38±16.68 U/mL,  $P < 0.001$ ).

The impact of kiwifruit consumption on ARE activity is shown in Figure 2. Eight weeks of kiwifruit

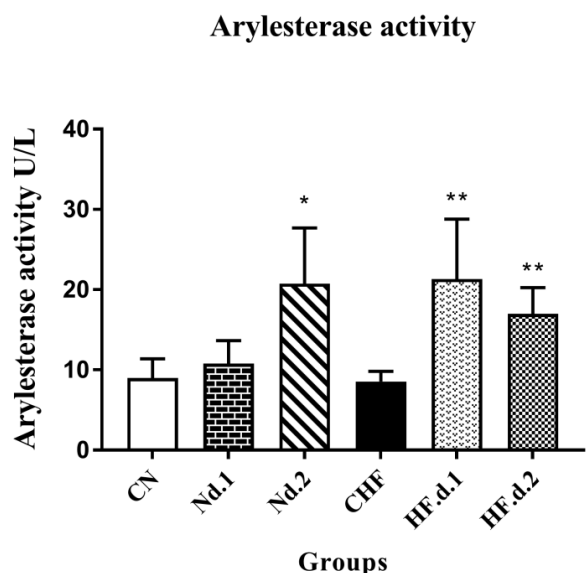


**Figure 1.** Paraoxonase1 Activity (U/mL) in the Serum of High-fat Diet Fed Hamsters (n=7 in each group) Supplemented With Kiwifruit. Note. ; \* $P < 0.05$  N.treatment group versus control.N group, \*\*\* $P < 0.001$  HF.treatment groups versus control.HF. Control-N: Control normal; control.HF: Control high-fat; HFd.1: High-fat dose 1 kiwi (1.86 g/kg); HFd.2: High-fat dose 2 kiwi (3.73 g/kg); Nd.1: Normal dose 1 kiwi (1.86 g/kg); Nd.2: Normal dose 2 kiwi (3.73 g/kg). The data are expressed as mean ± standard deviation.

**Table 1.** Concentration of Serum LDL-C, HDL-C, and TC in Control and High-Fat Diet Fed Hamsters (n=7 in Each Group) Supplemented With Kiwifruit

	Control Normal	Normal Dose 1 Kiwi (1.86 g/kg)	Normal Dose 2 Kiwi (3.73 g/kg)	Control High Fat	High Fat Dose 1 Kiwi (1.86 g/kg)	High Fat Dose 2 Kiwi (3.73 g/kg)
LDL-C mg/dL	10.28±2.24	10.16±3.33	9.85±1.88	27.6±13.06 <sup>f</sup>	17.4±6.8	23.83±15.62
HDL-C mg/dL	24.57±4.30	24.83±5.01	24.85±4.29	36.33±7.80 <sup>ff</sup>	43.42±3.77	49±9.59 <sup>fff</sup>
TC mg/dL	82.85±14.84	67.33±14.92	69.42±14.52	280.66±123.86 <sup>f</sup>	272±127.17	280.71±133.71

Note. LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol; SD: Standard deviation. <sup>f</sup> $P < 0.01$  HF.treatment groups versus control.HF and N.treatment group versus control.N group. <sup>ff</sup> $P < 0.05$ , <sup>fff</sup> $P < 0.001$  control.HF versus the control.N group. The data are expressed as mean ± standard deviation.



**Figure 2.** Arylesterase activity (U/L) in the Serum of High-fat Diet Fed Hamsters (n=7 in each group) Supplemented With Kiwifruit  
 Note. \* $P < 0.05$  N.treatment group versus control.N group; \*\* $P < 0.01$  HF.treatment groups versus control.HF. Control-N: Control normal; Control.HF: Control high-fat; HFd.1: High-fat dose 1 kiwi (1.86 g/kg); HFd.2: High-fat dose 2 kiwi (3.73 g/kg); Nd.1: Normal dose 1 kiwi (1.86 g/kg); Nd.2: Normal dose 2 kiwi (3.73 g/kg). The data are expressed as mean  $\pm$  standard deviation.

supplementation led to a significant elevation in the serum ARE activity in all experimental groups except for hamsters fed with a normal diet + 1.86 g/kg kiwi. Moreover, the consumption of the lower dose of kiwi (1.86 g/kg) raised the ARE activity more effectively than the higher dose of kiwifruit in HFD groups (HFd.1,  $21.31 \pm 7.46$  and HFd.2,  $16.96 \pm 3.26$  compared to  $8.59 \pm 1.26$  U/mL of the control-HF group).

#### Effect of Kiwifruit Consumption on Oxidative Stress and Antioxidant Status

After 8 weeks of kiwi supplementation, there was a moderate increase in the serum level of antioxidants in all groups receiving kiwifruit when compared with each control group although such an increment was not statistically significant ( $P > 0.05$ ). Additionally, the level of malondialdehyde (MDA) remarkably ( $P < 0.05$ ) decreased in all groups treated with kiwifruit (except for the group that received a normal diet +1.86 g/kg kiwi) when compared with each control group (Table 2).

Based on the results, the levels of serum ox-LDL were significantly higher in the control-HF group

( $0.73 \pm 0.09$ ) compared with the control normal group ( $0.58 \pm 0.09$  ng/mL,  $P < 0.05$ ). The results indicated that the supplementation of kiwifruit remarkably ( $P < 0.01$ ) diminished the serum levels of ox-LDL in the HFD +1.86 g/kg kiwi ( $0.48 \pm 0.04$  ng/mL) and HFD +3.73 g/kg kiwi ( $0.56 \pm 0.08$  ng/mL) groups in comparison with the control-HF group.

#### Discussion

PON1 is one of the most important endogenous antioxidant enzymes protecting humans against several disorders such as atherosclerosis (4). Although increased oxidative stress and the production of lipid peroxides lead to a reduction in the activity of PON1, the consumption of diets containing antioxidant compounds may compensate for the decrease of PON1 activity and the enzyme activity to the baseline (24).

In the present study, an increment was observed in the ARE activity in all hamsters receiving kiwifruit in comparison with the controls. Both doses of kiwifruit (i.e., 1.86 g/kg and 3.73 g/kg) significantly elevated the ARE activity in hamsters receiving HFD. ARE activity is considered a reliable index for the levels of the PON1 enzyme (25). It seems that kiwifruit, as a rich source of antioxidants, has stimulatory effects on ARE activity. In our previous study, we determined the levels of pyrogallol, vitamin C, as well as the total phenolic and flavonoid contents represented as gallic acid and quercetin equivalents (14). It was reported that an increase in the rate of oxidative stress may result in a reduction in PON1 activity in diabetic patients (24). Thus, it would be plausible that kiwifruit could lead to an increase in PON1 activity in hamsters fed with HFD, thus reducing the rate of oxidative stress. This idea was also supported by a decrease in the concentrations of MDA and ox-LDL in hamsters fed with HFD supplemented with the kiwifruit for eight weeks.

In our study, paraoxonase activity significantly increased in hamsters receiving a regular diet or the HFD supplemented with kiwifruit at a concentration of 1.86 g/kg. This is an important observation indicating that the consumption of kiwifruit, especially in HFD, could raise PON1 activity. This is in line with the results of previous studies, showing the effect of antioxidant consumption on PON1 activity. Jarvik et al reported that the intake of vitamins C and E is associated with the increment in PON1 activity (26). Besides, the results of our previous study showed that kiwifruit possesses high levels of vitamin

**Table 2.** The Concentration of Serum FRAP and MDA in Control and High-fat Diet Fed Hamsters (n=7 in Each Group) Supplemented With Kiwifruit

	Control Normal	Normal Dose 1 Kiwi (1.86 g/kg)	Normal Dose 2 Kiwi (3.73 g/kg)	Control High Fat	High Fat Dose 1 Kiwi (1.86 g/kg)	High Fat Dose 2 Kiwi (3.73 g/kg)
FRAP $\mu$ mol/L	742 $\pm$ 79.42	781.7 $\pm$ 105.65	827.8 $\pm$ 193.73	1208 $\pm$ 171.61	1279.4 $\pm$ 201.49	1263 $\pm$ 431.26
MDA $\mu$ mol/L	0.25 $\pm$ 0.05	0.28 $\pm$ 0.07	0.11 $\pm$ 0.02*	0.44 $\pm$ 0.1	0.18 $\pm$ 0.06***	0.18 $\pm$ 0.04***

Note. FRAP: Ferric reducing the ability of plasma; MDA: Malondialdehyde; SD: Standard deviation. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$  HF.treatment groups versus control.HF and N.treatment group versus the control.N group. The data are expressed as mean  $\pm$  standard deviation.

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C, pyrogallol, flavonoid, and phenolic content (14). Based on the findings of another study, PON1 activity increased in hypercholesterolemic Syrian hamsters receiving some juices containing high levels of polyphenols and other antioxidants (27).

PON1 is an HDL-bound antioxidant enzyme and thus its serum concentration is positively correlated with the levels of HDL. In addition, HDL is the primary acceptor of PON1, stimulates enzyme secretion, and increases the serum activity of the PON1 enzyme. It has also been reported that HDL stabilizes the enzyme after release, and therefore, maintains enzyme activity (28). Our results demonstrated the increased level of HDL-C and PON1 activity in hamsters subjected to HFD that were treated with kiwifruit. A significant reduction was also observed in the levels of ox-LDL and MDA (a final product of lipid peroxidation) in hamsters nourished with HFD supplemented with kiwifruit. Our findings confirm the result of Chang and Liu, suggesting that four and eight weeks of kiwifruit consumption could lead to a decrease in the oxidation rate of LDL particles and the concentration of lipid peroxides (i.e., MDA and 4-HNE) in hyperlipidemic individuals (17). In addition, the normal group receiving +3.73 g/kg kiwi exhibited a significant reduction in the level of MDA. Our findings represent that PON1 activity can reduce LDL oxidation, and consequently, MDA production in HFD, which is in agreement with the results of Kumar and Rizvi, confirming an inverse correlation between serum ARE activity and ox-LDL or MDA (3).

### Conclusion

Kiwifruit supplementation alleviated the complications of HFD, thereby preventing lipid oxidation-induced oxidative stress and increasing the activity of the PON1 enzyme. Our findings suggested that the consumption of kiwifruit could improve the lipid profile in animals subjected to HFD while decreasing the rate of lipid peroxidation.

### Authors' Contributions

Designed the study and wrote the paper: HT, IK, SM, NR; Contributed in sample collection and performing experiments: NR, ZZ, MS, EAO. All authors have contributed in the critical revision of the manuscript.

### Conflict of Interest Disclosures

The authors declare no potential conflicts of interest relevant to this article.

### Ethical Issues

The animal experiments were approved by the Ethics Committee of the Hamadan University of Medical Sciences.

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