

Biochemical effects of oleuropein in gentamicin-induced nephrotoxicity in rats  
Hassan Ahmadvand<sup>(1)</sup>, Shahrokh Bagheri<sup>(2)</sup>, Ahmad Tamjidi-Poor<sup>(3)</sup>, Mostafa Cheraghi<sup>(4)</sup>,  
Mozhgan Azadpour<sup>(3)</sup>, Behrouz Ezatpour<sup>(3)</sup>, Sanaz Moghadam<sup>(3)</sup>,  
Gholamreza Shahsavari<sup>(2)</sup>, Masumeh Jalalvand<sup>(5)</sup>

Original Article

Abstract

**BACKGROUND:** Oleuropein is a natural antioxidant and scavenging free radicals. In the present study, we examined effect of oleuropein on the paraoxonase 1 (PON1) activity, lipid peroxidation, lipid profile, atherogenic indexes, and relationship of PON1 activity by high-density lipoprotein-cholesterol (HDL-C) and atherogenic indices in gentamicin (GM)-induced nephrotoxicity in rats.

**METHODS:** This is a lab trial study in Khorramabad, Lorestan province of Iran (2013). 30 Sprague-Dawley rats were divided into three groups to receive saline; GM, 100 mg/kg/day; and GM plus oleuropein by 15 mg/kg intraperitoneal daily, respectively. After 12 days, animals were anesthetized, blood samples were also collected before killing to measure the levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and very LDL (VLDL), HDL-C, atherogenic index, lipid peroxidation, and the activities of PON1 of all groups were analyzed. Data were analyzed, and  $P < 0.050$  was considered significant.

**RESULTS:** Oleuropein significantly decreased lipid peroxidation, TG, TC, LDL, VLDL, atherogenic index, atherogenic coefficient (AC), and cardiac risk ratio (CRR). HDL-C level was significantly increased when treated with oleuropein. The activity of PON1 in treated animals was  $(62.64 \pm 8.68)$  that it was significantly higher than untreated animals  $(47.06 \pm 4.10)$  ( $P = 0.047$ ). The activity of PON1 in the untreated nephrotoxic rats was significantly lower than that of control animals  $(77.84 \pm 9.43)$  ( $P = 0.030$ ). Furthermore, the activity of PON1 correlated positively with HDL-C and negatively with AC, CRR 1, and CRR 2 in the treated group with oleuropein.

**CONCLUSION:** This study showed that oleuropein improves PON1 activity, lipid profile, and atherogenic index and can probably decrease the risk of cardiovascular death in nephrotoxic patients.

**Keywords:** Gentamicin; Paraoxonase 1; Lipid Peroxidation; Nephrotoxicity; Lipid; Rat; Atherogenic Index; Oleuropein

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Introduction

Human serum paraoxonase 1 (PON1) is an antioxidant enzyme in high-density lipoprotein-cholesterol (HDL-C) and is considered the major determinant of the antioxidant action of HDLC.<sup>1</sup> Major part of this enzyme in the serum is associated with HDL-C particles, but a low level of PON1 was also observed in very low-density lipoprotein (VLDL) and postprandial chylomicrons. PON1

inhibits LDL oxidation in vitro, and other studies have shown that PON1 prevents the formation of oxidatively LDL, inactivates LDL-derived oxidized phospholipids, and protects phospholipids in HDL from oxidation.<sup>1,2</sup> PON1 has antiatherogenic properties because PON1 has the ability to protect lipoprotein particles from free radical oxidation, and it can hydrolyze oxidized cholesteryl esters, phosphatidylcholine core aldehydes, and degrade

1- Razi Herbal Medicine Research Center AND Department of Biochemistry, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

2- Department of Biochemistry, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

3- Razi Herbal Medicine Research Center, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

4- Department of Cardiology, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

5- Department of Immunology, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

Correspondence to: Shahrokh Bagheri, Email: sbg1660@yahoo.com

hydrogen peroxide.<sup>1-3</sup>

Gentamicin (GM) is a common antibiotic that is used against most of the Gram-negative microorganisms.<sup>4</sup> Therapeutic GM can cause nephrotoxicity and acute kidney injury.<sup>5,6</sup> GM generates reactive oxygen species (ROS) in the kidney.<sup>7</sup> ROS cause of injury and death cells in more tissue such as renal, liver, and lung in pathological conditions.<sup>8</sup> After using GM lipid peroxidation increases and antioxidant such as glutathione, Vitamin E decrease.<sup>9</sup> The most of the researchers recommend the using of natural various antioxidants as supplement or drug against nephrotoxicity and chronic diseases.<sup>10</sup> Natural antioxidant such as rosmarinic acid and coenzyme Q10 and flavonoid compounds such as quercetin have protective effects on various tissue injury such as renal injury and nephrotoxicity.<sup>11-13</sup> Synthetic and chemical antioxidant are not safe, but natural antioxidants are safe and do not side effects; therefore, natural antioxidants are good alternative for prevention of nephrotoxicity induced by GM.<sup>14</sup>

Oleuropein is derived from olive oil and olive leaf.<sup>12</sup> Researchers have reported that oleuropein is a good antioxidant.<sup>15</sup> Previous our study showed that oleuropein has a protective effect on oxidative stress in spinal cord injury.<sup>16</sup> Therefore, oleuropein as antioxidative supplements is good for the prevention of nephrotoxic complications such as hyperlipemia.<sup>17</sup>

Since the effects of oleuropein on lipid profile, atherogenic indexes, PON1 activity and its association with atherogenic indexes in nephrotoxicity induced by GM in rats have not previously been reported; the aims of this lab trial study were to evaluate biochemical effects of oleuropein in GM-induced nephrotoxicity in rats in Khorramabad, Lorestan province of Iran.

## Materials and Methods

About 30 male Sprague Dawley rats (180-200 g) were prepared from Pasteur Institute of Tehran, Iran. The animals were divided into three groups randomly including 10 rats each as follows: Group 1 intraperitoneal (i.p.) saline injection, 0.25 ml/day for 12 days; Group 2, GM injection for 12 days; and Group 3, oleuropein, 15 mg/kg/day injection. One hour before, GM injection,<sup>18</sup> 100 mg/kg/day, was injected i.p. for 12 days.<sup>19</sup> After the last injection of GM, blood samples were obtained from animals and serum was separated.

### *Determination of lipid profile and atherogenic indexes*

The serum levels of triglyceride (TG), total cholesterol

(TC), LDL, VLDL, HDL-C, and atherogenic index of all groups were measured. TC and TG concentrations were measured by biochemical analyzer using commercial kits (Olympus AU-600, Tokyo, Japan). HDL-C was analyzed by a Pars Azmoon kit from Iran. LDL and VLDL were calculated by Friedewald et al.<sup>20</sup> equation.

The atherogenic index-[log (TG/HDL-C)], the atherogenic coefficient (AC)-[(TC-HDL-C)/HDL-C], cardiac risk ratio (CRR): (TC/HDL-C), and CRR: (LDL/HDL-C) were calculated by Ikewuchi and Ikewuchi<sup>21</sup> equation.

### *Measurement of lipid peroxidation*

Serum levels of lipid peroxidation were measured in accordance with previous our study.<sup>22</sup>

### *Measurement of PON1 activity*

PON1 activity was determined using paraoxon as a substrate in accordance with previous our study.<sup>23</sup>

Data between groups were first tested Kruskal–Wallis one-way and then between two groups were analyzed by Mann–Whitney U-test. The Spearman's correlation analysis was used for statistical calculations. Statistical analysis were performed using the SPSS software (version 13, SPSS Inc., Chicago, IL, USA).

## Results

The level of FBG, TG, and TC in the untreated nephrotoxic rats was significantly higher than that of control animals. The nephrotoxic rats treated with oleuropein could significantly inhibit the increase of FBG, TG, and TC in comparison with the untreated nephrotoxic animals ( $P = 0.001$ ,  $P = 0.001$ ). The level of TG and TC in the untreated nephrotoxic rats was significantly higher than that of control animals ( $P = 0.002$ ,  $P = 0.006$ ,  $P = 0.001$ ) (Table 1).

The level of HDL in the nephrotoxic rats untreated was not significantly against control animals ( $P = 0.615$ ). The treatment of nephrotoxic rats with oleuropein could not significantly (26.32%) inhibit the decrease of HDL-C in comparison with the nephrotoxic animals ( $P = 0.233$ ) (Table 1). The level of LDL and VLDL in the untreated nephrotoxic rats was higher than that of rats significantly ( $P = 0.020$ ,  $P = 0.006$ ). The treatment of a nephrotoxic animal with oleuropein could significantly inhibit the increase of LDL and in comparison with the untreated nephrotoxic animals ( $P = 0.010$ ).

The level of the atherogenic index and AC in the untreated nephrotoxic rats was significantly higher than that of control animals ( $P = 0.044$ ,  $P = 0.003$ ).

**Table 1.** Effect of oleuropein on total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein-cholesterol, very-LDL atherogenic index, atherogenic coefficient, cardiac risk ratio 1, CRR 2, level of lipid peroxidation and paraoxonase 1 activity in nephrotoxic rats

Parameter	Control	Nephrotoxic	Nephrotoxic + OLE	P
	Mean ± SD	Mean ± SD	Mean ± SD	
FBG	111.17 ± 18.90*	143.00 ± 21.27	110.00 ± 13.91*	0.009
TG (mg/dl)	62.00 ± 14.38*	79.71 ± 10.70	83.60 ± 8.08**	0.013
TC (mg/dl)	108.50 ± 13.08*	159.00 ± 39.16	116.00 ± 13.08*	0.009
HDL-C (mg/dl)	47.47 ± 18.48	42.97 ± 12.56	54.28 ± 14.05	0.463
LDL (mg/dl)	48.63 ± 19.78*	100.08 ± 44.85	45.00 ± 25.64*	0.017
VLDL (mg/dl)	12.40 ± 2.87*	15.94 ± 2.14	16.72 ± 1.62**	0.036
Atherogenic index [(units) (log (TG/HDL-C))]	0.13 ± 0.05*	0.29 ± 0.01	0.19 ± 0.02*	0.021
AC [(TC-HDL-C)/HDL-C]	1.51 ± 0.75*	3.06 ± 1.66	1.28 ± 0.68*	0.036
CRR 1 (TC/HDL-C)	2.51 ± 0.75	4.05 ± 1.66	2.28 ± 0.69	0.360
CRR 2 (LDL/HDL-C)	1.23 ± 0.68*	2.65 ± 1.55	2.28 ± 0.69*	0.033
Lipid peroxidation (nmol/mg protein)	82.48 ± 20.40*	128.18 ± 7.36	95.52 ± 38.39*	0.029
PON1 activity (nmol/min/ml)	77.84 ± 9.43*	47.06 ± 4.10	62.64 ± 8.68*	0.039

\*Significant change in comparison with nephrotoxic without treatment at  $P < 0.050$ , \*\*Significant change in comparison with control at  $P < 0.050$ ; OLE: Oleuropein; FBG: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; PON1: Paraoxonase 1; AC: Atherogenic coefficient; CRR: Cardiac risk ratio

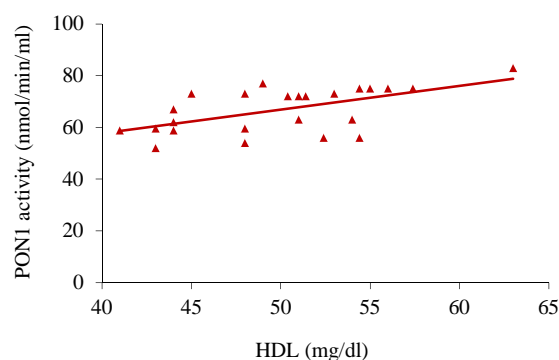
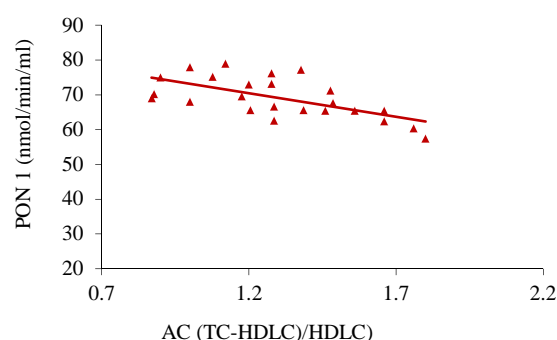
Oleuropein decreases significantly atherogenic index and AC in comparison with the untreated nephrotoxic animals ( $P = 0.032$ ). The level of AC in the untreated rats was significantly (2.02-fold) higher than that of control animals ( $P = 0.003$ ,  $P = 0.002$ ) (Table 1). The level of CRR 1 and CRR 2 in the untreated rats was significantly higher than that of control animals ( $P = 0.003$ ,  $P = 0.003$ ). Oleuropein decrease significantly (43.71%) inhibit CRR 1 and CRR 2 in comparison with the untreated animals ( $P = 0.001$ ,  $P = 0.001$ ) (Table 1).

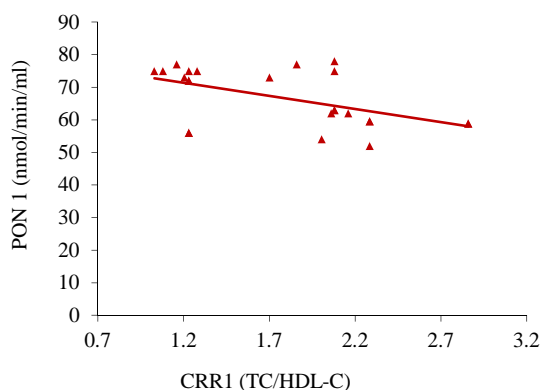
The level of lipid peroxidation in the untreated nephrotoxic rats was significantly (1.55-fold) higher than that of control rats ( $P = 0.032$ ). Oleuropein decrease significantly (25.48%) level of lipid peroxidation in with the untreated nephrotoxic animals ( $P = 0.050$ ). The treatment of a nephrotoxic animal with oleuropein could significantly (33.11%) elevate the decrease of PON1 activity (Table 1) ( $P = 0.047$ ).

The activity of PON1 correlated positively with HDL-C ( $r = 0.291$ ,  $P = 0.006$ ) (Figure 1). The activity of PON1 correlated coefficient ( $r = -0.404$ ,  $P = 0.001$ ) (Figure 2), CRR 1 ( $r = -0.273$ ,  $P = 0.009$ ) (Figure 3) and CRR 2 ( $r = -0.228$ ,  $P = 0.018$ ) (Figure 4).

## Discussion

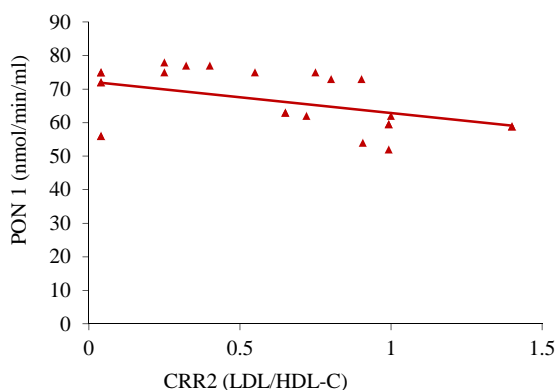
Effect of oleuropein on serum level of malondialdehyde (MDA) and PON1 activity and its correlation with HDL and atherogenic index nephrotoxicity significantly increased serum lipid peroxidation concentrations and decreased PON1 activity in comparison with the control group.

**Figure 1.** Correlation between maternal serum paraoxonase 1 (PON1) activity and levels of high-density lipoprotein (HDL) cholesterol in nephrotoxic rats treated with oleuropein**Figure 2.** Correlation between maternal serum paraoxonase 1 (PON1) activity and levels of the atherogenic coefficient (AC) [TC (TC-HDL-C)/HDL-C] in nephrotoxic rats treated with oleuropein  
TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol



**Figure 3.** Correlation between maternal serum paraoxonase 1 (PON1) activity and levels of cardiac risk ratio 1 (CRR 1) [CRR (TC/HDL-C)] in nephrotoxic rats treated with oleuropein  
TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol

Treatment of nephrotoxic animals with oleuropein significantly inhibited the increase of serum lipid peroxidation concentrations. Furthermore, the treatment of nephrotoxic animals with oleuropein significantly inhibited of serum PON1 activity in comparison with the untreated animals. The most relevant finding of this study is that activity of PON1 correlated positively with HDL and negatively with AC CRR 1 and CRR 2 in treated nephrotoxic animals. Researchers showed that PON1 as the antioxidant enzyme inhibit the oxidative modification of LDL and contribute to most of the antioxidative activity that has been attributed to HDL.<sup>24</sup> PON1 activity was positively correlated with HDL-C level.<sup>25</sup>



**Figure 4.** Correlation between maternal serum paraoxonase 1 (PON1) activity and levels of cardiac risk ratio 2 (CRR 2) [CRR (LDL/HDL-C)] in nephrotoxic rats treated with oleuropein  
LDL: Low-density lipoprotein; HDL-C: High-density lipoprotein-cholesterol

This study showed that the level of HDL correlated positively with PON1 activity. Furthermore, CRR 1, CRR 2, and AC correlated negatively with PON1 activity in treated animals. Researchers showed that PON1 has good effects on lipid and lipoprotein metabolism.<sup>26</sup> Furthermore; many studies showed that PON1 as the antioxidant enzyme decrease formation of different types modified LDL such as oxidized LDL. Modified LDL such as oxidized LDL and glycosylated LDL are risk factors for atherogenesis. Therefore, PON1 as the antioxidant enzyme inhibit atherogenesis.<sup>25-28</sup> Many studies showed that oxidative stress case creation of nephrotoxic complications such as liver and renal injury and hyperlipemia.<sup>28-30</sup> Therefore, numerous reports and our results indicated that the using of natural antioxidants such as Vitamin E, coenzyme Q10, rosmarinic acid, phenol and flavonoid compounds as supplementary prevent nephrotoxic complications including of liver and renal injury and hyperlipemia.<sup>12,13,31-34</sup>

#### **Effect of oleuropein on serum lipid profile and atherogenic index**

Nephrotoxicity significantly increased serum level of FBG, TG, TC, VLDL, and LDL in untreated animals. Treatment of nephrotoxic animals with oleuropein significantly inhibited the increase of serum level of FBG, TG, TC, VLDL and LDL, CRR, AC, and atherogenic index in treated nephrotoxic animals. Moreover, oleuropein significantly inhibited decrease of serum HDL-C concentrations in treated nephrotoxic animals. There are reports that natural antioxidant such as alpha lipoic acid, Vitamin C, Vitamin E, coenzyme Q10, selenium and natural phenolic compounds have hypolipidemic effects.<sup>35,36</sup> In addition, Andreadou et al.<sup>37</sup> showed oleuropein could reduce serum levels of TC and TG in hypercholesterolemic rabbits.

Therefore, numerous reports and our results indicated that the using of oleuropein similarity to natural antioxidants such as Vitamin E, coenzyme Q10, phenol and flavonoid compounds decrease cholesterol, TG, and lipoproteins. As supplementary prevent nephrotoxic complications including of liver and renal injury and hyperlipemia.<sup>35-37</sup>

Therefore, natural antioxidant such as oleuropein has hypolipidemic and antioxidative, and it prevent nephrotoxic complications including of liver and renal injury and hyperlipemia. The mechanisms hypolipidemic effects of oleuropein by which oleuropein is not well known. The



mechanism of hypolipidemic and antiatherogenic action of oleuropein and others natural antioxidant may be due to the inhibition of dietary lipid digestion and absorption and lipid and lipoprotein metabolism pathways.<sup>38-40</sup> Furthermore, oleuropein and anthers antioxidants have antioxidant activities and prevent glycation lipoproteins, enzymes, and proteins that involve lipid and lipoprotein metabolism pathways.<sup>39-42</sup>

Although the detailed molecular protective mechanisms of oleuropein cannot be fully explained by our results, our results are satisfactory oleuropein as a natural antioxidant with multi-beneficial properties can be introduced for inhibition of stress oxidative in patients.

### Conclusion

This study showed that oleuropein has beneficial effects in increasing the reduced serum level of HDL and PON1 activity in nephrotoxic rats.

This study showed that level of HDL was correlated positively with PON1 activity HDL, and the atherogenic index was correlated negatively with PON1 activity. Moreover, this study showed oleuropein has hypolipidemic and antiatherogenic effects and protective effects on lipid peroxidation and PON1 activity in nephrotoxic rats. Hence, oleuropein is a good antioxidant, and it introduces as the antiatherogenic compound that can decrease the risk of cardiovascular death in nephrotoxic.

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### Conflict of Interests

Authors have no conflict of interests.

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