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Effect of red wine on urinary protein, 8-hydroxydeoxyguanosine, and liver-type fatty acid–binding protein excretion in patients with diabetic nephropathy

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Abstract

The aim of the present study was to determine whether red or white wine affects urinary protein, 8-hydroxydeoxyguanosine (8-OHdG), and liver-type fatty acid–binding protein (L-FABP) excretion in type 2 diabetic nephropathy patients. Twenty-four type 2 diabetes mellitus patients with nephropathy were randomly allocated to drink a 118-mL (4-oz) glass of red wine (n = 12, group A) or white wine (n = 12, group B) daily for 6 months. Twelve type 2 diabetes mellitus patients with nephropathy who did not drink any wines served as control subjects (group C). Serum creatinine, 24-hour creatinine clearance, hemoglobin A_{1c}, urinary protein, urinary 8-OHdG, and urinary L-FABP were measured before and 3 and 6 months after the start of the study. In groups A, B, and C, serum creatinine, 24-hour creatinine clearance, and hemoglobin A_{1c} changed little during the experimental period. However, urinary protein, 8-OHdG, and L-FABP excretions were significantly decreased at 3 ($P < .05$) and 6 months ($P < .01$) compared with the baseline values in group A. In contrast, these markers changed little during the experimental period in groups B and C. Thus, these urinary markers were significantly lower in group A than in groups B and C at 3 and 6 months. These results suggest that red wine is renoprotective whereas white wine has no such effect in type 2 diabetes mellitus patients with nephropathy. The renoprotective effect of red wine may be due in part to its ability to reduce oxidative stress.

1. Introduction

Oxidative stress is a central pathogenic mechanism underlying ischemic heart disease, atherosclerosis, and other chronic diseases [1]. The kidney is particularly vulnerable to damage caused by reactive oxygen species, probably because of the abundance of polyunsaturated fatty acids contained in renal lipids [2]. Reactive oxygen species are involved in the pathogenesis of glomerulosclerosis and tubulointerstitial fibrosis [2]. Epidemiologic studies have suggested beneficial effects of dietary polyphenols in reducing the risk of chronic diseases by reducing oxidative stress [3]. The beneficial effects of red wine polyphenols include prevention and/or attenuation of myocardial fibrosis, reduction in aortic wall thickening, and improvement in vascular function [4].

Diabetic nephropathy is a serious microvascular complication of diabetes and one of the main causes of end-stage renal disease. Many studies have revealed that increased oxidative stress is a major pathophysiologic mechanism underlying development of diabetic nephropathy. Treatment with a polyphenolic phytoalexin present in red wine significantly attenuated renal dysfunction and oxidative stress in diabetic rats [5]. Consumption of a moderate amount of red wine may have beneficial effects toward prevention of cardiovascular disease in diabetes patients [6]. In healthy persons, red wine has more antioxidant activity than white wine by virtue of its higher content of polyphenol [7]. However, little is known about the effect of white wine on renal function.

Liver-type fatty acid–binding protein (L-FABP) of 14.4 kd is expressed in proximal tubules of the human

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kidney [8]. Various pathophysiologic stresses on the proximal tubules such as significant proteinuria induce up-regulation of human L-FABP gene expression, resulting in increased urinary L-FABP excretion [8]. Urinary L-FABP levels reflect the clinical progression of chronic kidney disease. Urinary 8-hydroxydeoxyguanosine (8-OHdG) has been reported to serve as a sensitive biomarker of oxidative DNA damage [9], and its excretion is significantly correlated with the severity of tubulointerstitial lesions in patients with diabetic nephropathy [10]. The aim of the present study was to determine whether consumption of red wine or white wine affects urinary protein, 8-OHdG, and L-FABP excretion in type 2 diabetic nephropathy patients.

2. Subjects and methods

Thirty-six patients with type 2 diabetic nephropathy (23 men and 13 women; age, 55 ± 11 years) were enrolled in the study. Diagnosis was based on clinical symptoms including chronic diabetes, increased urinary albumin excretion and retinopathy, laboratory data, or histologic findings according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [11]. *Diabetic nephropathy* was defined as at least 2 of 3 measurements of the albumin-creatinine ratio done before the present study. All patients showed overt proteinuria (>0.5g/d). All patients were treated with antidiabetic drugs and by diet, and each had a hemoglobin A_{1c} (HbA_{1c}) level of less than 7.0%. In addition, many patients were treated with antiplatelet drugs, statins, and/or antihypertensive drugs (Table 1). The doses of these medications were not altered during the study periods. Patients with nondiabetic or obstructive kidney disease and those with macroscopic hematuria, abnormal urinary sediment, or a history of glomerulonephritis or nephroureterolithiasis were excluded. No patient had a serum creatinine level in excess of 1.5 mg/dL or 24-hour creatinine clearance (Ccr) rate of less than 80 mL/min. The study protocol was approved by the local ethics committee, and informed consent was obtained from each participant.

Twenty-four diabetic nephropathy patients were randomly allocated to drink a 118-mL (4-oz) glass of red wine (alcohol, 12.8% ± 1.4%) (n = 12, group A) or white wine (alcohol, 12.6% ± 1.3%) (n = 12, group B) daily for 6 months. Twenty-four patients including groups A and B had alcohol history before the study. Before drinking the red or white wine, patients were asked to abstain from consuming any alcohol, grapes, or grape products for 2 weeks. Marfella et al [12] reported that, before drinking the red wine, subjects were asked to abstain from consuming any alcohol for 1 week to determine the effects of red wine on oxidative stress. From their results, we considered that a 2-week washout period is enough for this study. The patients were required to record intake of alcoholic beverages and agreed not to consume other alcoholic beverages during the study period. Twelve diabetic nephropathy patients who did not drink either red wine or white wine served as the control group (group C). They were specifically chosen as abstainers or alcohol allergy who would not drink alcohol in any circumstance. A placebo such as alcohol-free wine was not used because of difficulty to obtain informed consent from 12 patients in group C. Patients in the 3 groups were required to avoid all foods/beverages rich in polyphenols over the study period. All patients submitted a diary of foods and beverages consumed. The food diaries were given to the dietician, who reviewed the contents. The study protocol was adopted from Marfella et al [6]. The mean recommended caloric intake was 1600 kcal/d, protein was 50 to 60 g/d, and NaCl was 7 g/d. Serum creatinine, 24-hour Ccr, HbA_{1c}, urinary protein, urinary 8-OHdG, and urinary L-FABP were measured before and 3 and 6 months after the start of the study. These urinary markers were measured in the total 24-hour urine sample. The urinary L-FABP concentration was measured with human monoclonal antibodies, as reported previously [8,13], and expressed as the ratio of the urinary L-FABP level to the urinary creatinine level [8,13]. Urinary 8-OHdG was measured by enzyme-linked immunosorbent assay with a highly sensitive monoclonal antibody, as described previously (8-OHdG Check; Nikken Foods, Fukuroi, Shizuoka, Japan) [14,15].

Table 1
Clinical and laboratory data upon patients' entry into the study

	Group A (n = 12)	Group B (n = 12)	Group C (n = 12)
Sex ratio (male/female)	8/4	8/4	7/5
Age (y)	54 ± 12	53 ± 10	56 ± 11
BMI (kg/m^2)	24.0 ± 4.0	23.6 ± 3.8	23.8 ± 4.2
T-chol (mg/dL)	200 ± 22	194 ± 18	202 ± 16
TG (mg/dL)	122 ± 12	128 ± 14	130 ± 16
Serum creatinine (mg/dL)	1.0 ± 0.1	0.9 ± 0.1	1.0 ± 0.1
24-h Ccr (mL/min)	99 ± 11	103 ± 13	103 ± 15
HbA_{1c} (%)	6.2 ± 0.5	6.3 ± 0.6	6.4 ± 0.5
SBP (mm Hg)	136 ± 8	132 ± 6	138 ± 10
DBP (mm Hg)	82 ± 4	86 ± 6	84 ± 6
Urinary protein (g/d)	1.5 ± 0.5	1.4 ± 0.6	1.6 ± 0.6
Urinary 8-OHdG (ng/mg Cr)	21.0 ± 4.6	22.5 ± 6.0	22.5 ± 5.8
Urinary L-FABP (mg/g Cr)	62.0 ± 28.5	59.5 ± 25.5	60.5 ± 28.0
Drugs used			
Antihypertensive			
ARB	8	9	9
ACEI	6	7	6
Ca antagonist	6	7	6
α-Blocker	6	4	5
Antidiabetic			
Insulin	4	5	4
Glibenclamide	10	10	9
Voglibose	3	4	3
Pioglitazone	2	2	2
Statin	8	8	8
Antiplatelet	5	5	5

Diabetic nephropathy patients consumed 118 mL of red wine daily (group A), 118 mL of white wine daily (group B), or no wine (group C). Number of patients is shown unless otherwise indicated. T-chol indicates total cholesterol; TG, triglyceride; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Table 2
Changes in serum creatinine, 24-hour Ccr, HbA_{1c}, and systolic and diastolic blood pressure per group

	Group A			Group B			Group C		
	Before	3 mo	6 mo	Before	3 mo	6 mo	Before	3 mo	6 mo
sCr (mg/dL)	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.2
24-h Ccr (mL/min)	99 ± 11	98 ± 11	99 ± 12	103 ± 13	101 ± 12	102 ± 13	103 ± 15	102 ± 14	101 ± 13
HbA_{1c} (%)	6.2 ± 0.5	6.1 ± 0.4	6.1 ± 0.5	6.3 ± 0.6	6.2 ± 0.5	6.2 ± 0.6	6.4 ± 0.5	6.3 ± 0.5	6.3 ± 0.6
SBP (mm Hg)	136 ± 8	134 ± 6*	132 ± 6*	132 ± 6	133 ± 7	132 ± 8	138 ± 10	137 ± 9	137 ± 8
DBP (mm Hg)	82 ± 4	80 ± 4*	80 ± 5*	86 ± 6	85 ± 7	85 ± 5	84 ± 6	84 ± 7	85 ± 6

Data are expressed as mean ± SD. sCr indicates serum creatinine.
* $P < .05$ vs before.

Data are expressed as mean ± SD. Multiple comparisons were subjected to analysis of variance, which was followed by the Tukey posttest for pairwise comparisons. The Mann-Whitney *U* test for unpaired data and the Wilcoxon rank-sum test for paired data were used for analysis of differences between groups. Regression analysis was used to examine changes in urinary protein, urinary 8-OHdG, and urinary L-FABP in the red wine group (group A). A *P* value of less than .05 was considered statistically significant.

3. Results

There were no adverse effects including hypoglycemia during 6 months in all subjects. Clinical and laboratory baseline data of each group are shown in Table 1. After 6 months, the intake of fruit, vegetables, fish, meat, and polyunsaturated fatty acids was similar in the 3 groups (statistically not significant). We found a similar intake of total calories between the 3 groups (A, 1660 ± 140 kcal/d; B, 1640 ± 120 kcal/d; C, 1680 ± 130 kcal/d) (statistically not significant). There were no differences in body mass index (BMI) among the 3 groups after 6 months. In group C, analysis of the food diaries did not show any evidence of alcohol intake during the experimental periods. Systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine, 24-hour Ccr, HbA_{1c}, urinary protein, urinary 8-OHdG, and urinary L-FABP differed little between the 3 groups before the experimental period. Serum creatinine, 24-hour Ccr, and HbA_{1c} changed little during the experimental period in any of the 3 groups (Table 2). No significant differences occurred among 3 groups. In group A, SBP was significantly decreased at 3 months ($P < .05$) and at 6 months ($P < .05$); and DBP was also significantly decreased at 3 months ($P < .05$) and at 6 months ($P < .05$) in comparison with the baseline value. The changes in urinary protein and the Δ difference between the baseline value and values at 3 and 6 months are shown for the 3 groups in Fig. 1. In group A, urinary protein excretion was significantly decreased at 3 months (1.5 ± 0.5 vs 1.2 ± 0.4 g/d, $P < .05$) and at 6 months (1.5 ± 0.5 vs 0.9 ± 0.3 g/d, $P < .01$). However, urinary protein levels changed little during the experimental period in groups B and C. There was a significant difference in urinary protein levels between group A and group B or group C at 6 months,

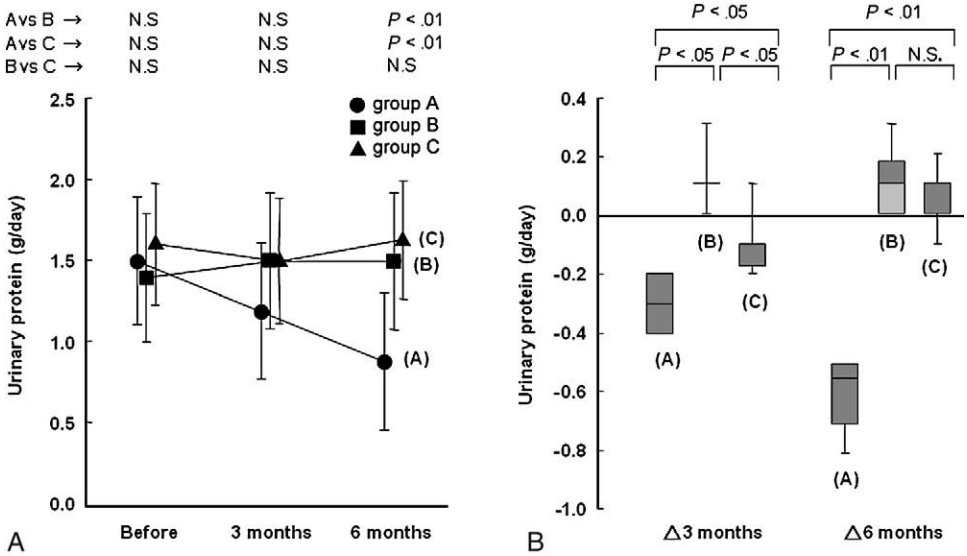

Fig. 1. Changes in urinary protein (A) and the Δ difference (B) between the baseline value and values at 3 and 6 months for the 3 groups. NS indicates not significant.

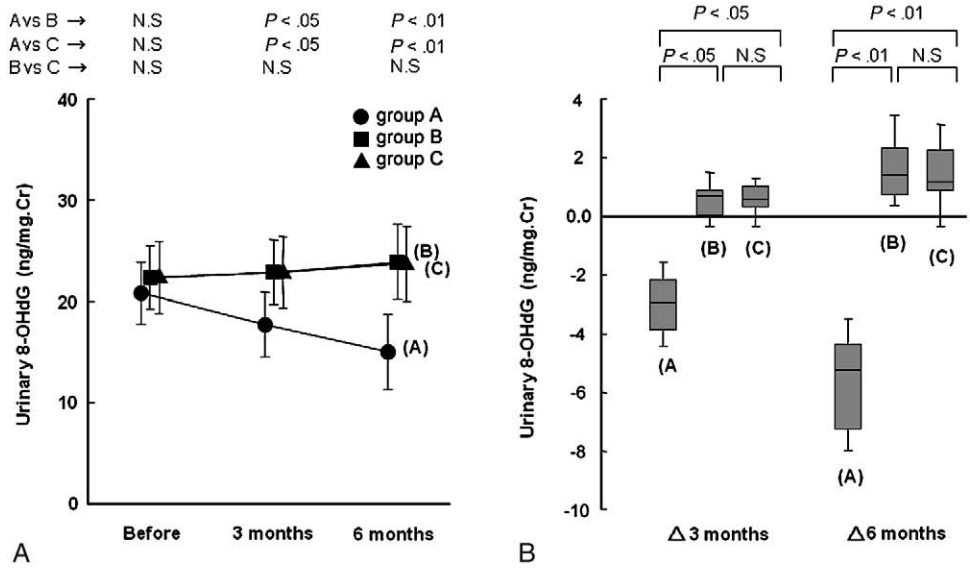

Fig. 2. Changes in urinary 8-OHdG levels (A) and the Δ difference (B) between baseline values and values at 3 and 6 months for the 3 groups.

whereas there was no significant difference between A and group B or group C at 3 months. The changes in urinary 8-OHdG and the Δ difference between the baseline value and values at 3 and 6 months are shown for the 3 groups in Fig. 2. Urinary 8-OHdG excretion was significantly decreased at 3 months (21.0 ± 406 vs 18.0 ± 3.8 ng/mg Cr, $P < .05$) and at 6 months (21.0 ± 406 vs 15.4 ± 3.2 ng/mg Cr, $P < .01$) in group A in comparison with the baseline value. However, urinary 8-OHdG levels changed little during the experimental period in groups B and C. There was a significant difference in urinary 8-OHdG levels between group A and group B or group C at 3 and 6 months. The changes in urinary L-FABP and the Δ difference between the baseline value and values at 3 and 6 months for 3 groups are shown in Fig. 3. In group A, urinary L-FABP excretion was significantly decreased in comparison with baseline values at 3 months (62.0 ± 28.5 vs 50.8 ± 24.0 μg/g Cr, $P < .05$) and 6 months (62.0 ± 28.5 vs 42.0 ± 20.0 μg/g Cr, $P < .01$). In contrast, urinary L-FABP levels changed little during the experimental period in groups B and C. There was a significant difference in urinary L-FABP levels between group A and group B or group C at 6 months, whereas there was no significant difference between group A and group B or group C at 3 months. Thus, urinary protein, urinary 8-OHdG, and urinary L-FABP levels were significantly lower in group A than in groups B and C at 6 months ($P < .01$).

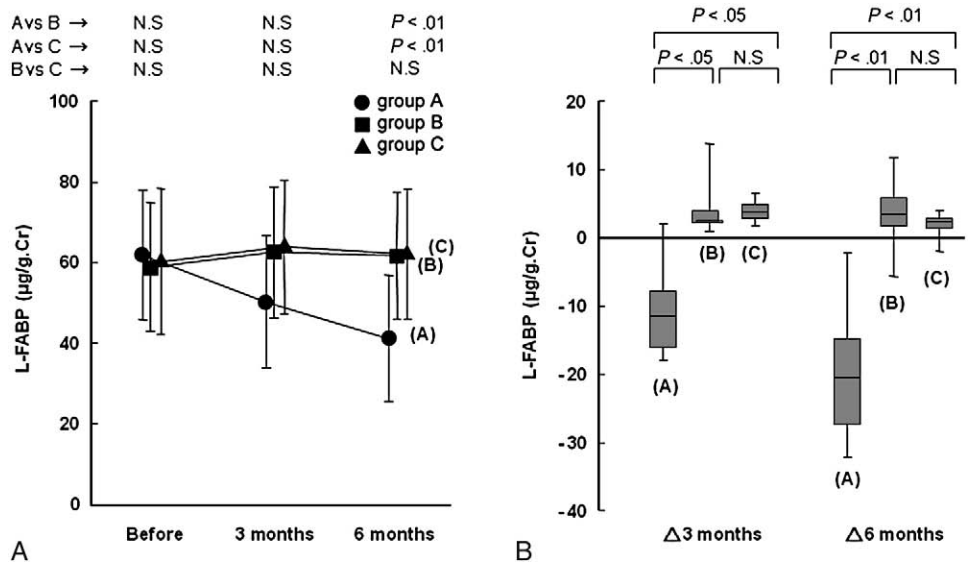

Fig. 3. Changes in urinary L-FABP levels (A) and the Δ difference (B) between baseline values and values at 3 and 6 months for the 3 groups.

4. Discussion

In the present study, we first observed that red, but not white, wine reduced urinary protein, urinary 8-OHdG, and urinary L-FABP levels in patients with diabetic nephropathy. Previous studies of tubulointerstitial injury as well as glomerular injury in diabetes may provide additional insight into the pathogenesis of diabetic nephropathy and lead to the identification of targets for therapeutic intervention [16]. We reported previously that urinary L-FABP appears to be associated with the progression of diabetic nephropathy [15]. Increased oxidative stress may play an important role in the progression of diabetic nephropathy [10]. Urinary 8-OHdG is reported to be a sensitive biomarker of oxidative DNA damage in diabetic nephropathy, and increased urinary 8-OHdG and the risk of vascular complication may be present at early stages of diabetes [10]. Oxidative stress appears to increase as chronic kidney disease progresses, and it probably correlates with the degree of renal dysfunction [17]. In addition, proteinuria is pathogenic to proximal tubular cells and is linked with progression to renal failure [18]. Tubulointerstitial damage may be provoked not only by proteinuria but also by other stresses including oxidative stress and the presence of toxins [8,13]. In healthy volunteers, daily consumption of red wine resulted in a marked decrease in 8-OHdG [1]. The health benefits of moderate consumption of red wine are attributed in part to its antioxidant properties [2]. The antioxidant defense system of the kidney is enhanced after chronic exposure to a moderate amount of red wine, a response that arises from the combined effects of ethanol and the nonalcoholic components, mainly polyphenols. Rodrigo and Rivera [2] suggested a protective effect of moderate wine consumption against the development and progression of renal diseases based on the existing concepts of the pathophysiology of kidney damage mediated by oxidative stress. They also reported that chronic exposure to moderate amounts of ethanol results in increased activity of the renal antioxidant enzymes, supporting a renoprotective effect of red wine based on its antioxidant properties [19]. In the present study, red wine reduced urinary 8-OHdG levels in diabetic nephropathy patients. Our data suggest that red wine reduced the urinary L-FABP levels, in part, by reducing the 8-OHdG level. However, other mechanism may be also considered for the reduction of proteinuria and urinary L-FABP by red wine intake. There is considerable evidence that red wine exhibits anti-inflammatory activity, including inhibition of reactive oxygen species in neutrophils, monocytes, and macrophages [20]. The release of various cytokines from macrophages and lymphocytes is also inhibited by red wine [21]. It may be hypothesized that red wine would prevent oxidant-dependent inflammatory responses in patients with diabetic nephropathy. Cigarette smoking may be associated with tubulointerstitial injury in diabetic nephropathy patients [22], and it is associated with oxidative stress. The number of smokers in each of our 3 study groups was similar (7 in group A, 6 in group B, and 6 in group C). We believe that smoking had little effect on the present data including urinary 8-OHdG and urinary L-FABP excretion in group A. Angiotensin receptor antagonist, pioglitazone, statin, and antiplatelet drugs have been reported to exert renoprotective effects against tubulointerstitial injury [15,23,24]. In the present study, the number of patients who used these drugs was similar in the 3 groups.

Little is known about whether white wine has a renoprotective effect. In the present study, white wine showed little renoprotection. Pignatelli et al [7] reported that a urinary oxidative stress marker decreased significantly in subjects who consumed wine, with a greater percentage decrease in subjects given red wine than in those given white wine. They showed that red wine has more antioxidant activity than white wine by virtue of its higher polyphenol content, an effect that may be dependent upon a synergism among polyphenols. In contrast, Cui et al [25] reported that white wine has a cardioprotective effect, in part, due to antioxidant activity. Results of the present study suggest that red wine is superior to white wine in terms of renoprotection. Most recently, Dudley et al [26] reported that white wine can provide cardioprotection similar to red wine. However, the mechanisms responsible for the effect of white wine on renal function remain unclear. The reduction in proteinuria seen after 6 months of red wine ingestion might be, in part, due to lower blood pressure. However, the intake of red wine polyphenols was reported to prevent angiotensin II–induced hypertension and endothelial dysfunction [27]. Some investigators have reported that the vasodilator effect of red wine is dependent on nitric oxide in the cardio- and renovascular systems [28,29]. Mozaffrieh et al [30] reported that red wine polyphenols exert vasoprotection by inhibiting the synthesis of endothelin-1. Recently, Lopez-Sepulveda et al [31] reported that red wine polyphenol reduces hypertension and vascular dysfunction through reduction in vascular oxidative stress in animal models. Further studies of the relation between nitric oxide/endothelin and urinary biomarkers in diabetic nephropathy and the effects of red wine on these markers are needed. In the present study, BMIs in the 3 groups were slightly decreased; but the decrease was statistically not significant. This may be due to the effect of diet but not due to the effect of wine itself.

In summary, results of the present study suggest that red wine, not white wine, reduces urinary protein, urinary 8-OHdG, and urinary L-FABP levels in patients with diabetic nephropathy and that the renoprotective effect of red wine may be due in part to its ability to reduce oxidative stress.

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