JOURNAL OF MEDICINAL FOOD
J Med Food 00 (0) 2021, 1–8

DOI: 10.1089/jmf.2020.0142

Dried Plum Consumption Improves Total Cholesterol and Antioxidant Capacity and Reduces Inflammation in Healthy Postmenopausal Women

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ABSTRACT Dried plums contain bioactive components that have demonstrated antioxidant and anti-inflammatory effects. The objective of this study was to determine if dried plum consumption reduces the risk factors for cardiovascular disease (CVD) in postmenopausal women, specifically examining lipid profiles, oxidative stress, antioxidant capacity, and inflammation in a dose-dependent manner. We conducted a 6-month, parallel-design controlled clinical trial, where 48 postmenopausal women were randomly assigned to consume 0, 50, or 100 g of dried plum each day. After 6 months of intervention, total cholesterol (TC) in the 100 g/day treatment group ($P = .002$) and high-density lipoprotein cholesterol in the 50 g/day treatment group ($P = .005$) improved significantly compared to baseline. Inflammatory biomarkers interleukin-6 ($P = .044$) and tumor necrosis factor-α ($P = .040$) were significantly lower after 6 months within the 50 g/day dried plum group compared to baseline. Moreover, total antioxidant capacity increased significantly within the 50 g/day group ($P = .046$), and superoxide dismutase activity increased significantly within both 50 and 100 g/day groups ($P = .044$ and $P = .027$, respectively) after 6 months compared to baseline. In addition, plasma activities of alanine transaminase ($P = .046$), lactate dehydrogenase ($P = .039$), and creatine kinase ($P = .030$) were significantly lower after 6 months in the 50 g/day dried plum group. These findings suggest that daily consumption of 50–100 g dried plum improves CVD risk factors in postmenopausal women as exhibited by lower TC, oxidative stress, and inflammatory markers with no clear dose dependence.

KEYWORDS: • ***antioxidants*** • ***cardiovascular disease*** • ***clinical trial*** • ***dose dependency*** • ***dried plum*** • ***inflammation*** • ***lipid profile***

INTRODUCTION

CARDIOVASCULAR DISEASE (CVD) is the leading cause of death worldwide.[1] Approximately 17.9 million people died globally from CVD in 2016,[1] and it has been predicted that by 2030, about 116 million people in the United States will suffer from a heart disease-related illness.[2] In 2012, total costs related to CVD were estimated to be ~$316.6 billion in the United States and are expected to increase to $818 billion by 2030.[2,3]

A decline in estrogen levels in postmenopausal women significantly increases their risk for CVD.[4,5] Reduced estrogen levels are associated with alterations in lipid metabolism, blood pressure, and vascular function. In addition, it increases the production of pro-inflammatory molecules[6,7] and oxidative stress.[8,9] While CVD attenuating drugs are used widely, there are detrimental side effects and high costs associated with them.[10] As alternative therapeutic approaches to drug therapy, animal and human studies have shown that high polyphenol and the fiber content of dried plums may mitigate the risk factors for heart disease.[11–13]

Considerable research has demonstrated the cardiovascular benefits of individual components of dried plum. However, a limited number of studies have examined the effects of dried plum as a whole on CVD risk factors, and even fewer studies have examined their dose-dependent effects. Animal and *in vitro* studies have indicated that dried plums and extracts have anti-inflammatory effects,[11,14,15] decrease oxidative stress,[11,15] and lower the risk of hypertension[16] and hypercholesterolemia.[17] In human studies, the consumption of 100 g of dried plums per day reduced lipid peroxidation, lowered total and low-density lipoprotein cholesterol (LDL-C), and decreased systemic inflammatory biomarkers.[12,18,19] Furthermore, a lower dose of 200 kcal/day (equivalent to 83–84 g/day) of dried plums increased plasma antioxidant capacity.[12] The latter suggests that quantities under 100 g/day may improve risk factors related to CVD.

Although dried plums produce positive effects on CVD risk factors, there are insufficient data to determine if their effect is dose dependent. Furthermore, very few studies have

Manuscript received 14 July 2020. Revision accepted 17 March 2020.

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examined the effect of dried plum consumption on multiple CVD risk factors in the postmenopausal population. Therefore, the objectives of this study were to determine the impacts of daily consumption of dried plums on lipid profiles, oxidative stress, and inflammation in postmenopausal women and whether a higher dose (100 g/day) is more effective than a lower dose (50 g/day). We hypothesized that daily consumption of dried plums would improve CVD risk factors of postmenopausal women in a dose-dependent manner.

MATERIALS AND METHODS

Study population

Forty-eight postmenopausal women aged 65–79 years old were recruited from a study designed to address the impact of dried plum on bone health. Menopausal status was defined as not having menstruation for at least an entire year. According to Table 1, the length of time between the participants' age at last menopausal period and their current age was well over 1 year.

Participants were excluded if they were currently on parathyroid hormone, growth hormone, steroids, or any other prescription medications. Those having a metabolic bone disease, renal disease, gastrointestinal disease, liver disease, respiratory disease, CVD, diabetes mellitus, or any other chronic inflammatory diseases were also excluded from the study. In addition, heavy smokers (>20 cigarettes/day), as well as subjects who regularly consumed dried plum or prune juice, were excluded from the study. Regular dried plum consumption was defined as consuming 4 dried plums per day, 4 times a week. However, the study population was consuming less than 1–2 plums per week.

All research methods in this study were approved by the Institutional Review Board. A completed written consent form was provided to and obtained from all participants (ClinicalTrials.gov, No. NCT02325895).

Anthropometric, dietary, and physical activity assessment

Before intervention, a brief medical history, as well as the height and weight measurements, was obtained from each participant. Body mass index (BMI) was calculated as weight in kilograms/height in meters squared (kg/m^2). Three-day food records were collected through interviews and analyzed at baseline and 6 months using Food Processor software version 7.50 (ESHA Research, Salem, OR). Current physical activities, including leisure, occupational, and home activities, were evaluated using the Community Health Activities Model Program for Seniors questionnaire.[20]

Experimental design

A parallel-arm, randomized controlled trial was conducted with participants randomly assigned to one of three groups: 0 g/day ($n=16$), 50 g/day ($n=16$), and 100 g/day ($n=16$) of dried plum for 6 months. The composition of dried plums per 100 g obtained from Food Processor version 7.50 (ESHA Research) included 239 kcal energy, 2.61 g protein, 0.52 g fat, 7.10 g total fiber, 51 mg calcium, 79 mg phosphorus, and 62.7 g total carbohydrates.[21] The participants were instructed to maintain their regular diet and physical activity during the study. Overnight fasting venous blood samples were collected at baseline and after 6 months. The blood samples were centrifuged at 1200 *g* at 4°C for 10 min, and the plasma was separated into aliquots and stored at −80°C until analysis. More details on the experimental design are provided in the previous article.[21]

Biochemical analysis

Lipid profile was determined by measuring plasma triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) by kits from Stanbio Laboratory (Boerne, TX). The LDL-C was calculated using the equation: LDL-C = TC – HDL-C – TG/5.

Tumor necrosis factor-α (TNF-α) was determined using an ELISA Kit (Cayman Chemical, Ann Arbor, MI). Thiobarbituric acid reactive substances (TBARS) were measured using a commercial assay kit (Cayman Chemical) to indicate oxidative stress. Total antioxidant capacity was measured using the Sigma Antioxidant Assay Kit (Sigma, St. Louis, MO). Activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S transferase (GST) were determined using Cayman

Table 1. Characteristics of the Study Population at Baseline and After 6 Months for the Control (0 g/day Dried Plum) and Treatment Groups (50 and 100 g/day Dried Plum)

	0 g/day dried plum		*50 g/day dried plum*		*100 g/day dried plum*	
Measures	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*
Age (years)	71.0 ± 2.9	—	68.5 ± 4.3	—	70.4 ± 3.7	—
LMP age (years)	49.2 ± 6.6	—	49.3 ± 7.6	—	49.3 ± 7.7	—
Height (cm)	161.2 ± 7.0	—	161.7 ± 6.0	—	162.0 ± 7.2	—
Weight (kg)	65.0 ± 10.6	65.7 ± 9.6	64.5 ± 12.1	62.8 ± 11.6	65.5 ± 8.9	65.9 ± 9.6
BMI (kg/m^2)	25.0 ± 4.3	25.3 ± 4.7	24.8 ± 3.9	24.2 ± 3.8	24.9 ± 4.0	25.1 ± 3.6

Values are expressed as mean ± standard deviation. The baseline characteristics of the participants were not significantly different between groups. There were no significant mean characteristic differences observed within or between each treatment group.

BMI, body mass index; LMP, last menstrual period.

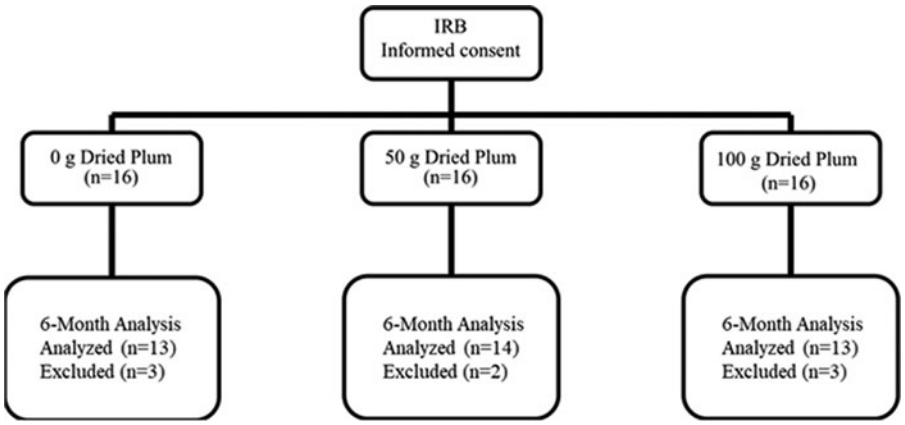

FIG. 1. Experimental design and study participation. IRB, Institutional Review Board.

assay kits (Cayman Chemical). Interleukin-6 (IL-6) was measured using an Immunometric Enzyme Immunoassay Kit (Cayman Chemical).

The activities of plasma aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and creatine kinase (CK) were determined using commercial assay kits (Stanbio Laboratory) as indices of liver function.

Statistical analysis

A sample size determination of 48 was calculated using G*Power 3.1.9.2[22] based on a previous human trial of 100 g of dried plum consumption on C-reactive protein[18] with a power of 0.7 and α value of 0.05. Statistical analysis was performed using a mixed design in SPSS Statistics 24 (IBM, Armonk, NY) to determine the main and interaction effects of dose intervention (0, 50, or 100 g/day dried plum) and time (baseline and 6 months). A split-plot model of repeated measures was used for statistical analysis within treatment groups. Paired t-tests were used within groups, and an independent *t*-test was used between groups as *post hoc* tests where appropriate. Baseline differences between trials were tested using a one-way analysis of variance. In the case of a significant difference, analysis of covariance (ANCOVA) with baseline as a covariate was performed. Data are reported as mean ± standard deviation. In all statistical comparisons, differences with $P \leq .05$ were considered statistically significant.

RESULTS

Forty of the 48 participants completed the study and were included in the final analysis (Fig. 1); 13 of which were in the control group, 14 in the 50 g/day dried plum group, and 13 in the 100 g/day dried plum group. Participant attrition was due to noncompliance or personal and health-related issues. A summary of the participants' characteristics is presented in Table 1. There were no statistically significant differences in mean age, height, and age of the last menstrual period among groups at baseline (Table 1). Weight and BMI did not change over time across all groups. No differences in dietary intake and physical activity were observed. The diet analysis of the 3-day food records did not show any significant differences among baseline values of control, 50 g/day, and 100 g/day dried plums and between baseline and 6-month values for each group (for complete data, please refer to Hooshmand *et al.*[21]).

Lipid profile

While consuming 50 g/day dried plums for 6 months resulted in a nonsignificant decrease in TC levels ($P = .085$), consuming 100 g/day significantly reduced TC compared to baseline ($P = .002$) (Table 2). HDL-C levels were raised significantly by consuming 50 g/day dried plum compared to baseline ($P = .005$), resulting in a lower TC to HDL-C ratio ($P = .014$). The trend of reduction of LDL-C and TG in those consuming 100 g/day dried plum was shown compared to their baseline values ($P = .076$ and $P = .088$, respectively).

Table 2. Lipid Profiles of Postmenopausal Women Consuming 0, 50, and 100 g/Day of Dried Plum at Baseline and After 6 Months

	0 g/day dried plum		*50 g/day dried plum*		*100 g/day dried plum*	
Measures	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*
TC (mg/dL)	153.6 ± 40.8	149.8 ± 42.6	152.7 ± 48.7	128.1 ± 64.7	149.6 ± 39.6	90.7 ± 33.1*
HDL-C (mg/dL)	41.2 ± 7.7	40.1 ± 17.5	38.6 ± 16.2	48.6 ± 17.6*	40.2 ± 27.3	43.9 ± 16.3
LDL-C (mg/dL)	86.9 ± 39.2	86.6 ± 25.3	88.4 ± 26.5	70.6 ± 58.3	103.9 ± 42.7	85.0 ± 46.4
TG (mg/dL)	91.3 ± 46.1	89.2 ± 53.1	92.4 ± 49.5	85.0 ± 26.9	102.8 ± 41.3	90.8 ± 33.0
TC:HDL-C	3.77 ± 1.4	4.25 ± 1.9	4.52 ± 1.2	2.81 ± 1.1*	4.67 ± 2.1	3.93 ± 1.0

Values are expressed as mean ± standard deviation.

Values that have * are significantly different at $P < .05$ in comparison to the corresponding baseline value.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

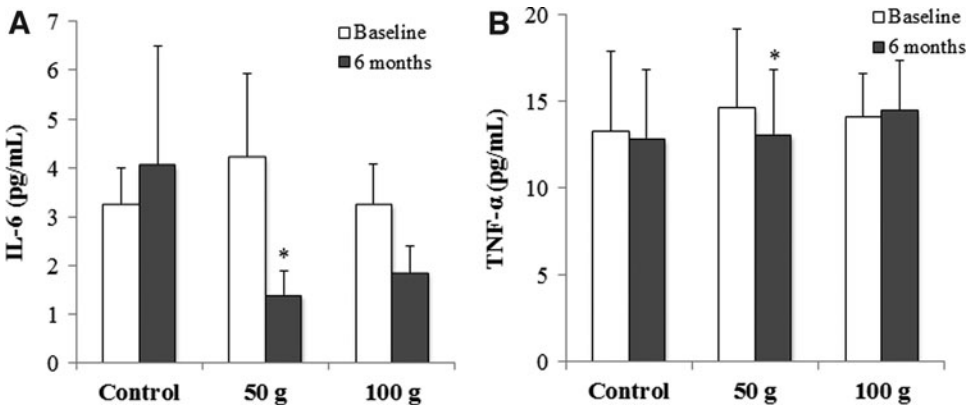

FIG. 2. **(A)** IL-6 concentration. **(B)** TNF-α concentration. Bars with * are significantly different from baseline ($P < .05$). IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

Inflammatory biomarkers

Although there was a nonsignificant decrease in IL-6 levels after consuming 100 g/day dried plum for 6 months ($P = .075$), a significant reduction was detected after 6-month consumption of the lower dose ($P = .044$; Fig. 2A). Similar results were found for TNF-α, where only the 50 g/day consumption resulted in a significant reduction compared to baseline ($P = .040$; Fig. 2B).

Oxidative stress, antioxidant capacity, and antioxidant enzymes

Both treatment groups also experienced significantly lower TBARS than their basline levels ($P = .046$ for 50 g/day, and $P = .044$ for 100 g/day) (Table 3). Moreover, consumption of 50 g/day dried plum resulted in a significant increase in total antioxidant capacity ($P = .046$) for this group (Table 3). The SOD activity increased significantly within both 50 g/day ($P = .044$) and 100 g/day ($P = .027$) dried plum groups after 6 months compared to their corresponding baseline values. Consumption of 50 g/day dried plum resulted in a significant increase in GST activity compared to baseline ($P = .031$). No statistical differences were detected for CAT and GPx activities after 6 months for either dose of dried plums (Table 3). No significant differences were found among the three treatment groups at baseline regarding the biochemical indicators, except for GPx. However, after running ANCOVA with baseline as a covariate, no significant differences were detected in GPx.

Liver function enzyme activity

The 50 g/day consumption of dried plum showed significant changes in liver function enzyme activities, where ALT ($P = .046$), LDH ($P = .039$), and CK ($P = .030$) decreased significantly at 6 months compared to the baseline (Table 4). Both treatment groups showed a trend of lower AST than their baseline levels ($P = .085$ for 50 g/day, and $P = .068$ for 100 g/day). Eating 100 g/day dried plum showed a trend of lower LDH ($P = .093$). ALP activities did not change in either group over time.

DISCUSSION

It has been well documented that postmenopausal women are at higher risk of developing CVD associated with reduced ovarian hormones.[5,23] Endogenous estrogen has cardioprotective effects related to estrogen-mediated vasodilation and reductions in oxidative stress and inflammatory biomarkers.[5,24,25] Moreover, menopause has been shown to have unfavorable consequences on lipid metabolism, including LDL-C, TG, and TC.[6,26–29] A diet composed of 25% dried plum powder was shown to significantly lower

Table 3. Oxidative Stress, Antioxidant Capacity, and Antioxidant Enzyme Activities of Postmenopausal Women Consuming 0, 50, and 100 g/Day of Dried Plum at Baseline and After 6 Months

	0 g/day dried plum		*50 g/day dried plum*		*100 g/day dried plum*	
Measures	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*
TBARS (μM/L)	0.45 ± 0.2	0.43 ± 0.2	0.42 ± 0.2	0.34 ± 0.3*	0.40 ± 0.1	0.31 ± 0.1*
TAC (mM/L)	0.87 ± 0.2	0.81 ± 0.2	0.87 ± 0.3	1.02 ± 0.2*	0.91 ± 0.2	0.93 ± 0.3
SOD (U/mL)	10.4 ± 5.6	11.6 ± 4.6	9.90 ± 4.6	13.9 ± 5.0*	9.88 ± 2.8	12.5 ± 3.3*
CAT [nM/(min·mL)]	80.9 ± 25.3	85.9 ± 30.5	90.2 ± 32.7	97.8 ± 32.8	97.8 ± 66.5	104.5 ± 48
GST [nM/min·mL)]	5.69 ± 4.5	4.43 ± 4.2	4.14 ± 3.0	6.54 ± 5.0*	4.34 ± 5.1	6.16 ± 3.0
GPx [nM/min·mL)]	402 ± 121	359 ± 130	295 ± 119	359 ± 112	337 ± 191	401 ± 152

Values are expressed as mean ± standard deviation.

Values that have * are significantly different at $P < .05$ in comparison to the corresponding baseline value.

CAT, catalase; GPx, glutathione peroxidase; GST, glutathione S transferase; SOD, superoxide dismutase; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances.

Table 4. Liver Function Enzyme Activity of Postmenopausal Women Consuming 0, 50, and 100 g/Day of Dried Plum at Baseline and After 6 Months

	0 g/day dried plum		*50 g/day dried plum*		*100 g/day dried plum*	
Measures	*Baseline*	*6 months*	*Baseline*	*6 months*	*Baseline*	*6 months*
AST (U/L)	17.4 ± 7.6	20.9 ± 9.3	22.7 ± 11.6	17.4 ± 8.2	24.2 ± 7.8	18.6 ± 7.9
ALT (U/L)	12.0 ± 4.0	13.7 ± 5.4	12.2 ± 5.4	10.4 ± 4.1*	12.7 ± 8.4	10.1 ± 4.9
ALP (U/L)	22.8 ± 7.1	25.0 ± 10.4	24.0 ± 9.8	18.2 ± 9.0	23.0 ± 9.2	17.7 ± 9.9
LDH (U/L)	46.5 ± 29.7	44.6 ± 15.3	50.8 ± 24.0	36.5 ± 19.0*	54.8 ± 38.5	36.5 ± 18.0
CK (U/L)	36.9 ± 14.3	30.5 ± 25.4	35.8 ± 21.3	23.3 ± 14.6*	47.9 ± 49.7	40.7 ± 18.6

Values are expressed as mean ± standard deviation.

Values that have * are significantly different at $P < .05$ in comparison to the corresponding baseline value.

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; LDH, lactate dehydrogenase.

total and non-HDL cholesterol levels in ovariectomy-induced hypercholesterolemic rats than ovariectomized rats fed no dried plum.[17] A human study using prune essence concentrate showed that consuming both 50 and 100 mL/day significantly decreased TC and LDL-C compared to baseline and placebo in healthy subjects with mild hypercholesterolemia after 4 weeks.[30]

In the present study with postmenopausal women, supplementation with 100 g/day dried plum resulted in significantly lower TC concentrations. Besides, consumption of 50 g/day dried plum led to significantly higher HDL-C levels and, therefore, significantly lower TC to HDL ratios. Chai *et al.*[18] also found that daily consumption of 100 g dried plum reduced TC and LDL-C levels at 12 months compared to baseline in postmenopausal women. Researchers of a recent 2-week study that evaluated the impacts of feeding 6 (42 g) and 2 (14 g) dried plums daily found no favorable impact on vascular function or plasma lipids in 27 postmenopausal women.[31] However, as suggested by the researchers, the absence of a control group and the short-term nature of the study may have negated the potential to detect positive effects.

In another study,[32] significant reductions of TC and LDL-C were detected in prehypertensive middle-aged men and women after 8 weeks of eating either 11.5 or 23 g/day of dried plum compared to a control group. This suggests that doses even lower than 50 g/day may improve blood lipid concentrations in the presence of CVD risk factors. The significant increase in HDL-C after consumption of 50 g/day dried plums found in the present study demonstrates the potential of the lower dose to improve lipid profile.

Dried plum is high in soluble and insoluble fiber, primarily pectin and cellulose.[31,33] Soluble fiber intake has been established as having a role in improving cholesterol concentrations by increasing bile excretion and reducing dietary cholesterol absorption. It has also been demonstrated that a dose–response relationship exists between increased dietary fiber intake and increased HDL-C, as well as decreased TC to HDL-C ratio in both males and females.[34] This may at least partially account for the similar positive effects on blood lipids reported here.

Oxidative stress has been established as having a vital role in the initiation and development of CVD, leading to recent research focusing on antioxidant therapeutic approaches.[35–37] Dried plums have a high antioxidant capacity, in part, due to their high polyphenol content.[16,38–40] Several clinical trials have studied the effect of daily consumption of dried plum, as well as dried plum (prunes) extracts or concentrates on oxidative stress, antioxidant capacity, and antioxidant enzyme activity. In the present study, both 50 and 100 g/day of dried plum consumption decreased production of TBARS, indicating its effectiveness in reducing oxidative stress. A significant increase in SOD enzyme activity after consuming both doses of dried plums further supports dried plum's antioxidant benefits.

These results are consistent with a previous study,[12] where an 8-week period of consuming 200 kcal/day of dried plum consumption produced an increase in antioxidant capacity in healthy overweight adults. In another study,[18] a significant reduction in lipid hydroperoxide levels in postmenopausal women was observed after 12 months of 100 g/day dried plum consumption. In addition, dried plum extracts have been shown *in vitro* to reduce superoxide anion (O_2^-) levels in vascular smooth muscle cells isolated from rats.[16] Further lending support to the potential for dried plums to reduce oxidative stress, prune essence concentrate at both 50 mL/day and 100 mL/day doses decreased TBARS levels significantly relative to placebo and baseline.[30]

Chlorogenic acid isomers have been identified as the principal phenolic compound found in dried plums and demonstrate high antioxidant capacity.[41] In an animal study,[42] dietary chlorogenic acid supplementation reduced hydrogen peroxide (H_2O_2) and O_2^- concentrations and decreased NADPH-dependent O_2^- production in the vascular wall of spontaneously hypertensive rats. As the primary function of NADPH oxidase activity is the production of reactive oxygen species, the inhibitory effects of chlorogenic acid on NADPH oxidase activity suggest a possible mechanism for the antioxidant properties of dried plums.[43] High performance liquid chromatography analysis has indicated that chlorogenic acid only accounts for $\sim$28% of dried plum's oxygen radical absorbance capacity, suggesting that antioxidant activity may result from other components of dried plum as well.[41,44]

Pectin polysaccharides extracted from plums decrease O_2^- production by inhibiting xanthine oxidase activity *in vitro*.[45] Xanthine oxidase is expressed throughout the cardiovascular system and is a significant source of O_2^- and

H_2O_2.[37] Furthermore, xanthine oxidase and O_2^- production are modulated by NADPH oxidase, indicating that the inhibitory effect on NADPH oxidase from chlorogenic acid in dried plum may also influence xanthine oxidase activity.[37] Epicatechin and catechin compounds present in dried plum have also been demonstrated to produce antioxidant and anti-inflammatory effects.[46,47]

Inflammation has been classified as a risk factor for CVD because of its significant role in CVD development and progression.[48] The current study yielded significantly lower IL-6 and TNF-α concentrations resulting from 6 months of consuming 50 g/day dried plum consumption. Previous research[15] has demonstrated that polyphenolic extracts of fresh plum significantly decreased IL-6 and IL-8 in human umbilical vein endothelial cells by 4.4 and 7.4-fold, respectively. As inflammation within the endothelium is directly related to atherosclerosis development, a reduction in IL-6 and IL-8 in human endothelial cells indicates that plum polyphenols may lower the inflammatory risk associated with CVD.

Anti-inflammatory effects of dried plum consumption may be explained by its ability to downregulate the expression of pro-inflammatory mediators. Dried plum extracts have been shown to reduce TNF-α and cyclooxygenase-2 expression in H_2O_2 and lipopolysaccharides (LPS) stimulated RAW264.7 macrophage cells.[14,49] Specifically, chlorogenic acid in dried plum has been shown to decrease the expression of TNF-α, IL-1β, and IL-6 in LPS treated RAW264.7 macrophage cells.[50]

In addition to the potential mechanisms mentioned previously, a systematic review by Lever *et al.*[51] suggested that intake of plums may improve the intestinal microbiota and hence exhibit several health-promoting effects such as antioxidant, anti-inflammatory, and hypocholesterolemic properties. Other researchers have also reported the beneficial effects of consuming prune essence concentrate on intestinal microbiota.[30] This has been attributed to the nutritional composition of plums containing fiber, especially the insoluble fiber pectin, sorbitol, and phenolic compounds, which may act as prebiotics and feed the healthy intestinal bacteria.[30,51]

Impaired hepatic function is clinically classified by elevations in liver enzymes and has been suggested to be associated with increased risk for CVD.[52–54] Accumulation of fat in the liver and elevated liver enzymes are associated with type 2 diabetes[55] and hypertension,[56] both of which are representative risk factors for CVD. In the present study, liver function enzyme activities of ALT, LDH, and CK significantly decreased in response to 50 g/day of dried plum consumption. These findings are in agreement with a previous study[57] that found a significant reduction in ALT in healthy adults after daily consumption of 3 dried plums for 8 weeks.

The current study included only healthy participants with no clinical elevations in any biomarkers relating to CVD risk factors. Perhaps the beneficial effects of dried plum would have been more discernible in a population with higher risk for CVD. Moreover, the sample size was relatively small. Hence, studies using a larger sample size are warranted to verify these findings and better evaluate the effect of dried plum consumption on CVD risk factors in postmenopausal women.

CONCLUSION

The findings of the present study suggest that daily consumption of 50–100 g dried plums may improve CVD risk factors in healthy postmenopausal women by increasing total antioxidant capacity and antioxidant enzyme activity, lowering lipid peroxidation, and lowering IL-6. Moreover, the lower dose of 50 g/day of dried plum not only produced beneficial effects similar to those of the higher dose (100 g/day) but also additionally improved the lipid profile by increasing HDL-C, the inflammatory markers by decreasing TNF-α, and markers of liver enzyme activity and heart function by reducing ALT, LDH, and CK. Moreover, a lower dose of dried plum is better tolerated due to reduced digestive side effects and, therefore, may be a more practical option than the higher amount. Of the many bioactive components of dried plum, identification of the specific ones, as well as their biological action that contributes to its attenuating effects on CVD risk, remains to be determined.

ACKNOWLEDGMENTS

The authors thank the California Dried Plum Board for providing the dried plums used in the study. The study was funded by the San Diego State University Grant Program, California Dried Plum Board, and the Kasch-Boyer Endowed Scholarship in the School of Exercise and Nutritional Sciences.

AUTHOR DISCLOSURE STATEMENT

The authors declare that there is no conflict of interest.

FUNDING INFORMATION

This study was funded by the San Diego State University Grant Program, the California Dried Plum Board (No. 57114A; ClinicalTrials.gov, No. NCT02325895), and the Kasch-Boyer Endowed Scholarship in Exercise and Nutritional Sciences in San Diego State University.

REFERENCES

1. World Health Organization (WHO): Cardiovascular Diseases (CVDs) Fact Sheet 2017. www.who.int/mediacentre/factsheets/fs317/en (accessed February 2020).
2. ScienceDaily: Cost to Treat Heart Disease in United States Will Triple by 2030. Science News, 2011. www.sciencedaily.com/releases/2011/01/110124121545.htm (accessed February 2020).
3. Mozaffarian D, Benjamin EK, Go AS, *et al.*: Heart Disease and Stroke Statistics—2016 Update: A Report From the American Heart Association. *Circulation* 2016;133:e39–e316.
4. Sathyapalan T, Aye M, Rigby AS, *et al.*: Soy isoflavones improve cardiovascular disease risk markers in women during the early menopause. *Nutr Metab Cardiovas* 2018;28:691–697.

5. Yang XP, Reckelhoff JF: Estrogen, hormonal replacement therapy and cardiovascular disease. *Curr Opin in Nephrol Hy* 2011; 20:133–138.
6. Gencel VB, Benjamin MM, Bahou SN, Khalil RA: Vascular effects of phytoestrogens and alternative menopausal hormone therapy in cardiovascular disease. *Mini Rev Med Chem* 2012;12: 149–174.
7. Piche ME, Lemieux S, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J: Relation of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. *Am J Cardiol* 2005;96:92–97.
8. Bednarek-Tupikowska G, Tupikowski K, Bidzinska B, Bohdanowicz-Pawlak A, *et al.*: Serum lipid peroxides and total antioxidant status in postmenopausal women on hormone replacement therapy. *Gynecol Endocrinol* 2004;19:57–63.
9. Signorelli SS, Neri S, Sciacchitano S, *et al.*: Duration of menopause and behavior of malondialdehyde, lipids, lipoproteins and carotid wall artery intima-media thickness. *Maturitas* 2001;39: 39–42.
10. Schwartz JB: Gender-specific implications for cardiovascular medication use in the elderly optimizing therapy for older women. *Cardiol Rev* 2003;11:275–298.
11. Gallaher CM, Gallaher DD: Dried plums (prunes) reduce atherosclerosis lesion area in apolipoprotein E-deficient mice. *Br J Nutr* 2009;101:233–239.
12. Clayton Z, Fusco E, Schreiber L, *et al.*: Snack selection influences glucose metabolism, antioxidant capacity and cholesterol in healthy overweight adults: A randomized parallel arm trial. *Nutr Res* 2019;65:89–98.
13. Khurana S, Venkataraman K., Hollingsworth A, Piche M, Tai TC: Polyphenols: benefits to the cardiovascular system in health and in aging. *Nutrients* 2013;5:3779–3827.
14. Kumar A, Hooshmand S, Arjmandi BH: Dried plum polyphenols decreased markers of inflammation and lipid peroxidation in RAW264.7 macrophage cells. *Faseb J* 2009;23:547.4.
15. Townsley ED, Noratto G, Angel G, Del Follo A, Byrne D, Mertens-Talcott S: Plum polyphenolics decrease oxidative stress and inflammation in vascular endothelial cells. *Faseb J* 2009;23: 717.12.
16. Negishi H, Onobayashi Y, Xu JW, *et al.*: Effects of prune extract on blood pressure elevation in stroke-prone spontaneously hypertensive rats. *Clin Exp Pharmacol P* 2007;34:S47–S48.
17. Lucas EA, Juma S, Stoecker BJ, Arjmandi BH: Prune suppresses ovariectomy-induced hypercholesterolemia in rats. *J Nutr Biochem* 2000;11:255–259.
18. Chai SC, Hooshmand S, Saadat RL, Payton ME, Brummel-Smith K, Arjmandi BH: Daily apple versus dried plum: Impact on cardiovascular disease risk factors in postmenopausal women. *J Acad Nutr Diet* 2012;112:1158–1168.
19. Tinker LF, Schneeman BO, Davis PA, Gallaher DD, Waggoner CR: Consumption of prunes as a source of dietary fiber in men with mild hypercholesterolemia. *Am J Clin Nutr* 1991;53:1259–1265.
20. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL: CHAMPS physical activity questionnaire for older adults: Outcomes for Interventions. *Med Sci Sport Exer* 2001;33:1126–1141.
21. Hooshmand S, Kern M, Metti D, *et al.*: The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic postmenopausal women: A randomized, controlled trial. *Osteoporos Int* 2016;27:2271–2279.
22. Faul F, Erdfelder E, Buchner A, Lang AG: Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods* 2009;41:1149–1160.
23. Huang CH, Li CL, Kor CT, Chang CC: Menopausal symptoms and risk of coronary heart disease in middle-aged women: A nationwide population-based cohort study. *PLoS One* 2018;13: e0206036.
24. Xing DQ, Nozell S, Chen YF, Hage F, Oparil S: Estrogen and mechanisms of vascular protection. *Arterioscl Throm Vas* 2009; 29:289–295.
25. Lagranha CJ, Deschamps A, Aponte A, Steenbergen C, Murphy E: Sex differences in the phosphorylation of mitochondrial proteins result in reduced production of reactive oxygen species and cardioprotection in females. *Circ Res* 2010;106:1681–1691.
26. Matthews KA, Kuller LH, Sutton-Tyrrell K, Chang YF: Changes in cardiovascular risk factors during the perimenopause and postmenopause and carotid artery atherosclerosis in healthy women. *Stroke* 2001;32:1104–1110.
27. Matthews KA, Crawford SL, Chae CU, *et al.*: Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol* 2009;54:2366–2373.
28. Kozakowski J, Gietka-Czernel M, Leszczyńska D, Majos A: Obesity in menopause—our negligence or an unfortunate inevitability? *Menopause Rev* 2017;16:61–65.
29. Chae CU, Derby CA: The menopausal transition and cardiovascular risk. *Obstet Gynecol Clin North Am* 2011;38:477–488.
30. Chiua H-F, Huangb Y-C, Luc Y-Y, *et al.*: Regulatory/modulatory effect of prune essence concentrate on intestinal function and blood lipids. *Pharm Biol* 2017;55:974–979.
31. Al-Dashti YA, Holt RR, Carson JG, Keen CL, Hackman RM: Effects of Short-term dried plum (prune) intake on markers of bone resorption and vascular function in healthy postmenopausal women: A randomized crossover trial. *J Med Food* 2019;22:982–992.
32. Ahmed T, Sadia H, Batool S, Janjua A, Shuja F: Use of prunes as a control of hypertension. *J Ayub Med Coll Abbottabad* 2010;22: 28–31.
33. Stacewicz-Sapuntzakis M: Dried plums and their products: Composition and health effects-an updated review. *Crit Rev Food Sci* 2013;53:1277–1302.
34. Zhou Q, Wu J, Tang J, Wang JJ, Lu CH, Wang PX: Beneficial effect of higher dietary fiber intake on plasma HDL-C and TC/HDL-C ratio among Chinese rural-to-urban migrant workers. *Int J Environ Res Public Health* 2015;12:4726–4738.
35. Miletić N, Mitrović O, Popović B, Mašković P, Mitić M, Petković M: Chemical changes caused by air drying of fresh plum fruits. *Int Food Res J* 2019;26:1191–1200.
36. Csanyi G, Miller FJ Jr.: Oxidative stress in cardiovascular disease. *Int J Mol Sci* 2014;15:6002–6008.
37. Sugamura K, Keaney JF: Reactive oxygen species in cardiovascular disease. *Free Radic Biol Med* 2011;51:978–992.
38. Li Y, Lai P, Chen J, *et al.*: Extraction optimization of polyphenols, antioxidant and xanthine oxidase inhibitory activities from Prunus salicina Lindl. *Food Sci Technol* 2016;36:520–525.

39. Kayano S, Kikuzaki H, Fukutsuka N, Mitani T, Nakatani N: Antioxidant activity of prune (Prunus domestica L.) constituents and a new synergist. *J Agr Food Chem* 2002;50:3708–3712.
40. Donovan JL, Meyer AS, Waterhouse AL: Phenolic composition and antioxidant activity of prunes and prune juice (Prunus domestica). *J Agr Food Chem* 1998;46:1247–1252.
41. Kayano SI, Kikuzaki H, Yamada NF, *et al.*: Antioxidant properties of prunes (*Prunus domestica* L.) and their constituents. *Biofactors* 2004;21:309–313.
42. Suzuki A, Yamamoto N, Jokura H, *et al.*: Chlorogenic acid attenuates hypertension and improves endothelial function in spontaneously hypertensive rats. *J Hypertens* 2006;24:1065–1073.
43. Drummond GR, Selemidis S, Griendling KK, Sobey CG: Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets. *Nat Rev Drug Discov* 2011;10:453–471.
44. Kayano S, Yamada NF, Suzuki T, *et al.*: Quantitative evaluation of antioxidant components in prunes (*Prunus domestica* L.). *J Agr Food Chem* 2003;51:1480–1485.
45. Popov SV, Ovodova RG, Golovchenko VV, *et al.*: Pectic polysaccharides of the fresh plum *Prunus domestica* L. isolated with a simulated gastric fluid and their anti-inflammatory and antioxidant activities. *Food Chem* 2014;143:106–113.
46. Kimura Y, Ito H, Kawaji M, Ikami T, Hatano T: Characterization and antioxidative properties of oligomeric proanthocyanidin from prunes, dried fruit of *Prunus domestica* L. *Biosci Biotech Biochem* 2008;72:1615–1618.
47. Abd El-Aziz TA, Mohamed RH, Pasha HF, Abdel-Aziz HR: Catechin protects against oxidative stress and inflammatory-mediated cardiotoxicity in adriamycin-treated rats. *Clin Exp Med* 2012;12:233–240.
48. Libby P: Inflammation and cardiovascular disease mechanisms. *Am J Clin Nutr* 2006;83:456S–460S.
49. Bu SY, Lerner M, Stoecker BJ, *et al.*: Dried plum polyphenols inhibit osteoclastogenesis by downregulating NFATc1 and inflammatory mediators. *Calcified Tissue Int* 2008;82:475–488.
50. Hwang SJ, Kim Y-W, Park Y, Lee H-J, Kim K-W: Anti-inflammatory effects of chlorogenic acid in lipopolysaccharide-stimulated RAW 264.7 cells. *Inflamm Res* 2014;63:81–90.
51. Lever E, Cole J, Scott SM, Emery PW, Whelan K: Systematic review: The effect of prunes on gastrointestinal function. *Aliment Pharmacol Ther* 2014;40:750–758.
52. Targher G, Day CP, Bonora E: Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *New Engl J Med* 2010;363:1341–1350.
53. Kunutsor SK, Apekey TA, Khan H: Liver enzymes and risk of cardiovascular disease in the general population: A meta-analysis of prospective cohort studies. *Atherosclerosis* 2014;236:7–17.
54. Choi KM, Han K, Park S, *et al.*: Implication of liver enzymes on incident cardiovascular diseases and mortality: A nationwide population-based cohort study. *Sci Rep* 2018;8:3764–3773.
55. Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA: Alanine aminotransferase, gamma-glutamyltransferase, and incident diabetes: The British Women's Heart and Health Study and meta-analysis. *Diabetes Care* 2009;32:741–750.
56. Stranges S, Trevisan M, Dorn JM, Dmochowski J, Donahue RP: Body fat distribution, liver enzymes, and risk of hypertension: Evidence from the Western New York Study. *Hypertension* 2005;46:1186–1193.
57. Ahmed T, Sadia H, Khalid A, Batool S, Janjua A: Report: prunes and liver function: A clinical trial. *Pak J Pharm Sci* 2010;23:463–466.