Dried plums (prunes) reduce atherosclerosis lesion area in apolipoprotein E-deficient mice

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Dried plums are a fruit high in pectin with substantial antioxidant activity. Previous studies in rats and man indicate that dried plums or plum fibre lower liver and plasma cholesterol, respectively. The apoE-deficient mouse, which develops atherosclerotic lesions rapidly when fed cholesterol, was used to determine the ability of dried plums to reduce atherosclerosis. Diets containing 0·15 % cholesterol and either 0 (B + C), 4·75 % (Lo DP) or 9·5 % (Hi DP) dried plum powder were fed for 5 months. An additional group fed the basal diet without cholesterol (B – C) was included as a negative control. Arterial trees were dissected, stained to visualize lesions, and lesion area was quantitated by imaging software. Urinary thiobarbituric acid-reactive substances (TBARS) excretion and serum amyloid P-component (SAP) were measured as indicators of oxidative stress and inflammation, respectively. Final serum cholesterol was significantly increased and serum TAG decreased in the B + C group and dried plum groups relative to the B – C group. Percentage arterial tree atherosclerotic lesion area was significantly lower in the B – C and Lo DP groups compared to the B + C group (P<0·05), with a trend for a difference between the B + C and Hi DP groups (P=0·075). SAP concentration was significantly lower in the B – C and Lo DP groups with the Hi DP group trending lower than the B + C group. Urinary TBARS excretion did not differ among the groups. These results suggest that consuming dried plums may help slow the development of atherosclerosis.

Dried plums: Atherosclerosis: Cholesterol: Inflammation: ApoE-deficient mouse

Atherosclerosis is an inflammatory disease of the arteries that is the primary cause of CVD and stroke, the leading causes of morbidity and mortality in Western societies. Many years of research have established the multifactorial nature of atherosclerosis. In developed countries, unhealthy diets represent one of the major modifiable risk factors. Among dietary factors that may influence development of CVD, there is considerable epidemiological support for a protective effect of fruit and vegetables. Indeed, the WHO has estimated that low fruit and vegetable intake contributes to 31 % of the risk for CHD and 11 % of ischaemic stroke in developed countries.

Fruit and vegetable consumption may lower risk of CVD by several mechanisms. Elevated serum concentrations of total and LDL-cholesterol have long been recognized as risk factors. Isolated viscous dietary fibres such as pectins and mucilages, present in fruits and vegetables, have a well-established hypocholesterolaemic effect. Further, pectin-rich foods such as a mixture of vegetables or apples and guava fruit have demonstrated cholesterol lowering in man. Considerable evidence indicates an association between elevated oxidative stress and the development of atherosclerosis. Many fruits and vegetables are concentrated sources of antioxidants due to the presence of a variety of secondary plant metabolites that may act to reduce oxidative stress. For example, pomegranate juice, a rich source of antioxidants, increased plasma antioxidant activity and reduced plasma lipid peroxides in man and reduced atherosclerotic lesion size in apoE-deficient mice. Inflammation also plays a prominent role in both the initiation and progression of atherosclerosis. Serum C-reactive protein, a non-specific systemic marker of inflammation, has been shown to be moderately predictive of CHD. The serum concentration of C-reactive protein is positively associated with a Western pattern diet and, in elderly subjects, a significant inverse association between frequency of intake of fruits and vegetables and serum C-reactive protein has been found. Increasing fruit and vegetable consumption in healthy men for 4 weeks significantly reduced C-reactive protein. Thus, fruits and vegetables may be effective in reducing the risk of atherosclerosis by reducing serum cholesterol, oxidative stress and inflammation.

Dried plums, also known as prunes, are cultivar fruits of Prunus domestica L. native to the Caucasus region in Western Asia. Dried plums are a good source of the cholesterol-lowering fibre pectin, and have been shown to lower serum cholesterol in both rats and man. Tinker et al. found that mildly hypercholesterolaemic men experienced a reduction in both total and LDL-cholesterol after consuming 100 g dried plums/d. Tinker et al. further demonstrated that dried plum fibre significantly reduced plasma and liver cholesterol in cholesterol-fed rats. Dried plums are also a good source of the cholesterol-lowering fibre pectin. Further, pectin-rich foods such as a mixture of vegetables or apples and guava fruit have demonstrated cholesterol lowering in man. Considerable evidence indicates an association between elevated oxidative stress and the development of atherosclerosis. Many fruits and vegetables are concentrated sources of antioxidants due to the presence of a variety of secondary plant metabolites that may act to reduce oxidative stress. For example, pomegranate juice, a rich source of antioxidants, increased plasma antioxidant activity and reduced plasma lipid peroxides in man and reduced atherosclerotic lesion size in apoE-deficient mice. Inflammation also plays a prominent role in both the initiation and progression of atherosclerosis. Serum C-reactive protein, a non-specific systemic marker of inflammation, has been shown to be moderately predictive of CHD. The serum concentration of C-reactive protein is positively associated with a Western pattern diet and, in elderly subjects, a significant inverse association between frequency of intake of fruits and vegetables and serum C-reactive protein has been found. Increasing fruit and vegetable consumption in healthy men for 4 weeks significantly reduced C-reactive protein. Thus, fruits and vegetables may be effective in reducing the risk of atherosclerosis by reducing serum cholesterol, oxidative stress and inflammation.

Abbreviations: ORAC, oxygen radical absorbance capacity; SAP, serum amyloid P-component; TBARS, thiobarbituric acid-reactive substances.

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rich source of antioxidants with an antioxidant content similar to blueberries and similar to or much greater than raisins, depending on the method of assay. Dried plum extracts and prune juice extracts contain significant amounts of antioxidant phenolic compounds that have been found to inhibit LDL oxidation in vitro. Neochlorogenic acid and chlorogenic acid, the two major polyphenols in dried plums, have been shown to function as potent superoxide scavengers. Thus, dried plum consumption may have utility in reducing the development of atherosclerosis.

The apoE-deficient mouse is a useful animal model for studying the development of atherosclerosis directly. The animals develop severe hypercholesterolaemia and develop atherosclerotic lesions similar in appearance and distribution to those observed in man consuming a Western-type diet. In addition, the histological appearance of the atherosclerotic lesions in apoE-deficient mice is similar to those observed in man. Proteomic and metabolomic analyses of atherosclerotic lesions in apoE-deficient mice indicate increased oxidative stress and inflammatory changes as lesions become more severe. Thus, the apoE-deficient mouse appears to be an excellent model to investigate the effect of dietary components on atherosclerotic lesion development.

The objectives of the current study were to determine whether a diet containing dried plums, in the form of a powder, could alter the progression of atherosclerosis in the apoE-deficient mouse, influence blood lipid levels, and alter markers of oxidative stress and inflammation.

**Methods and materials**

**Animals and diets**

Male C57BL/6J apoE-deficient mice (5 weeks old; Jackson Laboratory, Bar Harbor, ME, USA) with an initial body weight of between 14 and 17 g were divided into four dietary groups of twelve animals each. Three to four animals were housed per box in a temperature-controlled animal facility with a daily photoperiod of 12 h of light. The experimental protocol for animal use was approved by the University of Minnesota Animal Care Committee. Mice were fed one of the four experimental diets modified from the AIN-93G rodent diet. The composition of the diets is shown in Table 1. Dried plums were incorporated into the basal diet and prune juice extracts contain significant amounts of antioxidant polyphenols, similar to blueberries and similar to or much greater than raisins. Phenolic compounds in dried plum powder were extracted as previously described. An aliquot of the extract was diluted with an equal volume of distilled deionized water, the mixture centrifuged at 4°C at 12,000 g for 20 min and the supernatant stored at −20°C until analysis of total phenolic compounds.

**Characterization of dried plum powder**

Phenolic compounds in dried plum powder were extracted as previously described. An aliquot of the extract was diluted with an equal volume of distilled deionized water, the mixture centrifuged at 4°C at 12,000 g for 20 min and the supernatant stored at −20°C until analysis of total phenolic compounds. Another aliquot of extract solution was evaporated with nitrogen gas, reconstituted with deionized water, and used for analysis of neochlorogenic, chlorogenic, cryptochlorogenic and caffeic acids by HPLC, as described later.

**Lipids**

Blood was collected from non-fasted animals at weeks 4 and 15 by tail-nick. At the end of the feeding trial, animals were
fasted for 6–8 h, anaesthetized with Isoflurane (USP, Phoenix Pharmaceutical Inc.) and blood was collected by cardiac puncture through the right ventricle, the serum was obtained and stored at −70°C. Serum cholesterol and TAG concentrations were determined enzymatically using commercial kits (Sigma Diagnostics Catalog #352-100 and TRO100, respectively; St. Louis, MO, USA). Liver lipids were extracted from a sample of perfused tissue using chloroform–methanol[30]. Chloroform–methanol was evaporated under nitrogen gas and total liver cholesterol was determined by enzymatic assay after samples were solubilized in Triton X-100–acetone.

Arterial preparation for visualization of atherosclerotic lesions
The arterial system was perfused through the left ventricle (exiting via the right atria) with 3 ml PBS, followed by 3 ml 10 % formalin in PBS at a flow of approximately 1 ml/min. The arterial tree was dissected with the aid of a stereo microscope and stored in 70 % ethanol. Atherosclerotic lesions were visualized by staining with 0·2 % Oil Red O in 78 % methanol and 22 % 1M-NaOH for 50 min. The arterial tree was then pinned on to black wax, water added to the pan to prevent drying, and the tree photographed using a digital camera with a polarizing filter. Areas of the arterial tree and aortic arch and the atherosclerotic lesion area within the tree and arch were calculated using computer-assisted morphometry (Image Pro Plus; Media Cybernetics, Silver Spring, MD, USA) by an investigator blinded to the treatment groups. Lesion areas of the aortic arch or arterial tree were expressed as a percentage of the respective areas.

Urinary thiobarbituric acid-reactive substances
Total body oxidative stress was estimated by measure of urinary thiobarbituric acid-reactive substances (TBARS) following the method of Lee et al. (31). Each TBARS measurement was based on a pooled collection from animals housed together by box.

Table 2. Effect of dried plum diets on plasma and serum lipid levels in the apoE mouse*

<table>
<thead>
<tr>
<th>Diet</th>
<th>4 weeks</th>
<th></th>
<th></th>
<th>15 weeks</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
<td>SEM</td>
</tr>
<tr>
<td>B−C</td>
<td>10.9a</td>
<td>0.2</td>
<td>12.3a</td>
<td>0.8</td>
<td>10.1a</td>
<td>0.6</td>
</tr>
<tr>
<td>B+C</td>
<td>25.1a</td>
<td>1.5</td>
<td>24.7a</td>
<td>1.2</td>
<td>12.9a</td>
<td>0.8</td>
</tr>
<tr>
<td>Lo DP</td>
<td>24.6a</td>
<td>0.9</td>
<td>24.7a</td>
<td>1.4</td>
<td>13.8a</td>
<td>0.8</td>
</tr>
<tr>
<td>Hi DP</td>
<td>25.1a</td>
<td>1.0</td>
<td>22.7a</td>
<td>1.6</td>
<td>14.6a</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* For details of procedures and diets, see the methods and materials section and Table 1.

Statistical analysis
Data were examined by one-way ANOVA using Statistical Analysis Systems statistical software package version 9.1 (SAS Institute, Cary, NC, USA). Values for SAP were analysed as ranks, due to a lack of equal variance among the groups for this variable. Differences among group means were inspected using Duncan’s multiple comparison test. A probability of P<0.05 was used as the critical level of significance. Pearson correlation analysis was used to determine associations between measurements, except for SAP, in which case Spearman correlations were calculated.

Results
Characterization of dried plum powder
The dried plum powder was found to contain by HPLC analysis (mg/kg): 83.1, neochlorogenic acid; 40.0, chlorogenic acid; 108.1, cryptochlorogenic acid; 7.5, caffeic acid. The total phenolics concentration, determined spectrophotometrically, was 13.8 g/kg. The ORAC value of the dried plum powder was 4.22 Trolox equivalents/mg.

Body weights
There were no significant differences in either initial (14.3–16.4 g) or final body weights (26.0–28.2 g) among the dietary groups.

Blood lipids
After 4 weeks of feeding, plasma cholesterol concentration in the B+C group was more than double that of the B−C group (Table 2). Neither diet containing dried plum powder affected plasma cholesterol at 4 weeks; however, there was

Serum amyloid P-component
Inflammation was estimated by measurement of serum amyloid P-component (SAP) concentration by ELISA as previously described[32].

* Downloaded from https://www.cambridge.org/core, IP address: 54.70.40.11, on 25 Sep 2018 at 15:16:58, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms . https://doi.org/10.1017/S0007114508995684
a trend towards lower plasma cholesterol concentration at 15 weeks in the Hi DP group. No significant differences were found in fasting serum cholesterol at 20 weeks with the addition of dried plum powder at either level. Final serum cholesterol concentrations were greater in the mice of all cholesterol-containing diets (12.9–14.6 mmol/l) compared to those fed the cholesterol-free diet (10.1 mmol/l). Overall, fasting serum cholesterol values were significantly lower than levels from fed animals, regardless of diet group.

Fasting final serum TAG concentrations were significantly greater in mice fed the B + C diet (0.76 mmol/l) compared to the B + C diet (0.37 mmol/l). There were no significant differences in serum TAG levels between the dried plum-containing diets and the B + C group.

Atherosclerotic lesions

Lesion area in the aortic arch and the entire arterial tree is shown quantitatively in Table 3, and representative images of the arterial trees are shown in Fig. 1. As can be seen, mice fed the cholesterol-free B – C diet had a small lesion area. However, addition of 0.15% cholesterol to the diet (B + C group) dramatically increased lesion area in the arterial tree. Cholesterol addition to the diet resulted in a significant increase in lesion area from 1.85 to 19.6% in the aortic arch and from 1.2 to 8% in the arterial tree. The addition of 4.75% dried plums, an amount approximately equivalent to consuming ten to twelve dried plums per day in man, resulted in a significant reduction (P < 0.05) of atherosclerotic lesion occurrence in both the aortic arch and arterial tree. Mice fed twice this amount, 9.5% dried plum, showed a trend towards a reduction in lesion area in both the aortic arch and the entire arterial tree, but the differences did not achieve statistical significance.

Oxidative stress and inflammation

The 24 h urinary excretion of TBARS did not differ among the groups. However, there was a trend for a difference between animals in the B + C diet compared to the B – C diet (P = 0.058 by Student’s t test) (Table 4).

Table 3. Atherosclerotic lesion area in the aortic arch and arterial trees of apoE-deficient mice fed dried plum diets for 20 weeks* (Mean values with their standard errors)

<table>
<thead>
<tr>
<th>Diet</th>
<th>Area of aortic arch with lesions (%)</th>
<th>Area of arterial tree with lesions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
</tr>
<tr>
<td>B – C</td>
<td>2.0±</td>
<td>0.6±</td>
</tr>
<tr>
<td>B + C</td>
<td>19.6±</td>
<td>2.7±</td>
</tr>
<tr>
<td>Lo DP</td>
<td>11.5±</td>
<td>0.8±</td>
</tr>
<tr>
<td>Hi DP</td>
<td>16.0±</td>
<td>1.5±</td>
</tr>
</tbody>
</table>

B = C, basal group with no added cholesterol; B + C, basal group with added cholesterol; Hi DP, 9.5% dried plum powder with added cholesterol group; Lo DP, 4.75% dried plum powder with added cholesterol group.

* Mean values within a column with unlike superscript letters were significantly different (P < 0.05).

* For details of procedures and diets, see the methods and materials section and Table 1.

Table 4. Effect of dried plum diets on markers of oxidative stress and inflammation* (Mean values with their standard errors)

<table>
<thead>
<tr>
<th>Diet</th>
<th>Urinary TBARS (μg/24h) (n 3–4)</th>
<th>SAP (μg/ml) (n 8–10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
</tr>
<tr>
<td>B – C</td>
<td>0.58</td>
<td>0.08</td>
</tr>
<tr>
<td>B + C</td>
<td>1.05</td>
<td>0.18</td>
</tr>
<tr>
<td>Lo DP</td>
<td>0.69</td>
<td>0.14</td>
</tr>
<tr>
<td>Hi DP</td>
<td>0.55</td>
<td>0.28</td>
</tr>
</tbody>
</table>

B = C, basal group with no added cholesterol; B + C, basal group with added cholesterol; Hi DP, 9.5% dried plum powder with added cholesterol group; Lo DP, 4.75% dried plum powder with added cholesterol group; SAP, serum amyloid P-component; TBARS, thiobarbituric acid-reactive substances.

* Mean values within a column with unlike superscript letters were significantly different (P < 0.05).

* For details of procedures and diets, see the methods and materials section and Table 1.
the entire arterial tree ($r=0.22$, $r=0.19$), the correlation between SAP and lesions in the aortic arch approached statistical significance ($r=0.31$, $P=0.065$). Further, there was no significant correlation between the group means of the 24 h urinary excretion of TBARS and SAP ($r=0.768$, $P=0.23$). However, there was a high correlation between the group means for 24 h urinary excretion of TBARS and lesion area of the aortic arch ($r=0.945$, $P=0.055$) or the total arterial tree ($r=0.965$, $P=0.035$).

Discussion

In the present study we have used an animal model of atherosclerosis development, the apoE-deficient mouse, to examine directly the effect of a fruit, dried plums, on development of the disease. The present findings indicate that dried plums, fed in the form of a dried powder, significantly reduced the area of atherosclerotic lesion in the entire arterial tree as well as the aortic arch, when incorporated into the diet at 4.75 %. At 9.5 % of the diet, there was a trend for reduction in lesion area in the aortic arch. It is not clear why the higher concentration of dried plum powder was less effective than the lower concentration at reducing atherosclerotic lesion area.

The drying used to create the powder would likely have created some Maillard reaction products. It may be that these products, at the concentration found in the 9.5 % dried plum powder diet, attenuated the effect of dried plums on reducing lesion area. However, this is speculative, since there appear to be no studies of the effects of Maillard reaction products on atherosclerosis.

Although there are numerous studies of the effects of fruits and vegetables on serum cholesterol, few studies exist on the effect of fruits or vegetables on atherosclerosis itself. A mixture of green vegetables, fed at 30 % of the diet to LDL receptor−/− mice for 16 weeks, resulted in a significant decrease in aortic atherosclerosis (ester$^{(33)}$). In contrast to the present study, in which the Lo DP group showed reduced concentrations of the acute-phase protein SAP, no reduction was seen in the acute-phase protein serum amyloid A. Pomegranate juice, given in the drinking water to apoE-deficient mice has been shown to reduce aortic lesion size$^{(11,12)}$. Deacetalized red wine, also administered in the drinking water, reduced both aortic arch lesion area and wall thickness$^{(34)}$. However, neither red wine nor red wine powder altered plaque area in the aortic bulb or the brachiocephalic trunk in apoE-deficient mice$^{(35)}$.

No vegetables appear to have been examined for their ability to retard development of atherosclerosis in apoE-deficient mice. However, large decreases in aortic arch lesion area (44 %) were found in apoE-deficient mice administered ginger extracts in their drinking water$^{(36)}$. Thus, the present study using dried plums, fed in the form of a powder, appears to be the first examining the effect of a fruit in a relatively intact form (i.e. not a juice or extract) on the development of atherosclerosis.

In the present study, apoE-deficient mice fed a diet containing 0.15 % cholesterol experienced a large and significant increase in serum cholesterol compared to those fed the cholesterol-free diet, by 4 weeks of feeding. This elevation in serum cholesterol persisted through to the end of the experiment, although in the final blood sample, collected as a fasting sample, the difference relative to mice fed the cholesterol-free diet was not as large as in unfasted animals (weeks 4 and 15). It is well established that the apoE-deficient mouse shows an elevation in serum cholesterol when fed an atherogenic diet, e.g. a diet high in saturated fat and cholesterol$^{(37)}$. However, studies that have examined the effect of only cholesterol, without the addition of other atherogenic agents such as saturated fats or bile acids, are few. ApoE-deficient mice fed a chow diet containing 2 % cholesterol also showed elevated serum cholesterol compared to those fed a cholesterol-free chow diet$^{(38)}$, whereas apoE-deficient mice fed 0.02 % cholesterol did not$^{(39)}$. It appears that a modest dietary cholesterol concentration of 0.15 % is sufficient to elevate serum cholesterol in this animal model.

Interestingly, a lack of change in total plasma cholesterol concentrations did not seem to preclude a reduction in development of atherosclerosis. The dried plum diets had no influence on plasma cholesterol, except for a modest but statistically significant decrease in the Hi DP group at 15 weeks relative to the B + C group. Although apoE-deficient mice fed black rice pigment exhibited both a lower total serum cholesterol and reduced plaque area in the aortic sinus$^{(40)}$, other studies have not found an association between plasma cholesterol and lesion area$^{(41,42)}$. This inconsistent association clearly suggests that other factors play a major role in determining lesion development.

ApoE-deficient mice are well known to exhibit elevated serum TAG concentrations, due to accumulation of VLDL and chylomicron remnants, as apoE is necessary for efficient catabolism of lipoprotein remnants via the LDL receptor$^{(23)}$. The addition of cholesterol to the diet reduced fasting serum TAG concentration by half, with no further significant reduction by the dried plum diets. This dramatic effect of dietary cholesterol on serum TAG concentration in apoE-deficient mice does not appear to have been previously documented. There does not seem to be an obvious explanation for this unexpected result.

It is now acknowledged that atherosclerosis is an inflammatory condition and that the degree of inflammation, as measured by the acute-phase protein C-reactive protein, is positively associated with the incidence of coronary events$^{(43)}$. Dried plums contain small amounts of flavonoids, predominately rutin$^{(24)}$. Flavonoids have been shown to affect the immune response and the generation of inflammatory processes. In the present study, the major acute-phase protein of mice, SAP, was measured as an indicator of inflammation$^{(44)}$. Mice from both dried plum diets had SAP concentrations numerically lower than the B + C diet and approximately equal to the B − C diet, only the B − C and Lo DP groups were statistically significantly different from the B + C group. There was a strong trend for a correlation between aortic lesion area and SAP concentration, suggesting a connection between inflammation and lesion area in this model of atherosclerosis.

The role of oxidative events in the development of atherosclerosis has been intensively studied but remains unclear. Considerable evidence has accumulated demonstrating the oxidative modification of LDL particles, which are suggested to lead to endothelial injury and foam cell formation. However, the general lack of effect of dietary antioxidants on CVD in human trials and the dissociation of the development of atherosclerosis from lipoprotein lipid oxidation in animal models$^{(34,45)}$ raises...
questions about the role of dietary antioxidants in reducing atherosclerosis development. Although we found no statistically significant differences among the groups in a well-accepted marker of oxidative stress, urinary TBARS excretion, likely due to the small sample size, it is interesting that a high correlation was found between the group means of urinary TBARS and lesion areas. Dried plums are concentrated sources of chlorogenic and neochlorogenic acids, which are potent antioxidants in vitro\(^\text{21}\). However, chlorogenic acid is poorly absorbed within the small intestine, and largely passes into the large intestine where it is metabolized by gut microflora. This is consistent with the recent finding that neither dried plums or dried plum juice consumption raised plasma ORAC in man\(^\text{26}\). In the present study, the dried plum powder contained \(<5\%\) neochlorogenic acid and \(<10\%\) chlorogenic acid of that reported for dried plums, depending on variety and drying conditions of the dried plums\(^\text{24}\). Given the low concentration of neochlorogenic and chlorogenic acid in the dried plum powder and their demonstrated poor intestinal absorption, it seems unlikely that the dried plum diets in this experiment produced a significant biological antioxidant effect.

The present results, which demonstrate a reduction in atherosclerosis by dried plum powder, reinforce the idea that consumption of fruits in general and dried plums in particular may be useful for reducing the risk of heart disease and stroke. This benefit may be mediated by reducing inflammatory events within the arterial wall. Further studies examining the anti-inflammatory effects of fruits seem warranted.

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References


