Letters to the Editor

The Antiinflammatory Effects of Purple Grape Juice Consumption in Subjects with Stable Coronary Artery Disease

To the Editor:

Moderate consumption of red wine is associated with a reduction in cardiovascular disease,1-4 and some of the cardioprotective effects have been attributed to the distinct polyphenolic compounds present in red wine and purple grape products. These polyphenols possess multiple biological effects, including antioxidant and free radical-scavenging properties,5,6 as well as inhibition of platelet activation.7 The growing interest in the presumed benefits of wine in protecting against coronary heart disease coupled with the inherent limitations in promoting alcohol consumption8,9 has led to the examination of the potential beneficial vascular properties of alternative purple grape products. The effect of these flavonoid-rich substances in subjects with cardiovascular disease taking aspirin is unknown. In addition, their impact on the inflammatory properties of platelets has not been studied.

A double blind crossover study was conducted, in which 20 subjects with previously diagnosed coronary disease on standard medications were randomly assigned to drink either placebo or purple grape juice (PGJ; Welch’s Concord) for 14 days separated by a 2-week washout period. All patients maintained aspirin treatment (8 of 20 81 mg/d; 12 of 20 325 mg/d). Mean age was 63 (range 42 to 76) with 17 male and 3 female participants. 10 of 20 had hypertension, and 4 of 20 were active tobacco users. Medications included ACE inhibitor (8 of 20), diuretic therapy (2 of 20), calcium channel blocker (4 of 20), statin (18 of 20), warfarin (2 of 20), and clopidogrel (2 of 20).

Venous blood was obtained from subjects in the fasting state at visits 1 to 4. Washed platelets were used to measure aggregation using ADP, thrombin receptor activating peptide (TRAP), or phorbol ester (PMA) as the platelet agonist. To quantitate markers of platelet activation, plasma thrombin receptor activating peptide (TRAP), or phorbol ester (PMA) as the platelet agonist. To quantitate markers of platelet activation, plasma thrombin receptor activating peptide (TRAP), or phorbol ester (PMA) as the platelet agonist. To quantitate markers of platelet activation, plasma thrombin receptor activating peptide (TRAP), or phorbol ester (PMA) as the platelet agonist. To quantitate markers of platelet activation, plasma thrombin receptor activating peptide (TRAP), or phorbol ester (PMA) as the platelet agonist. To quantitate markers of platelet activation, plasma thrombin receptor activating peptide (TRAP), or phorbol ester (PMA) as the platelet agonist.

Indices of platelet function included aggregation, nitric oxide (NO) production, superoxide release, and soluble CD40L release. The platelet agonist ADP (5 μM) was used. Aggregation with lucigenin detection was used to detect platelet derived nitric oxide (NO) production, a microelectrode was used to measure aggregation using ADP, TRAP, or PMA as the platelet agonist. Indices of platelet thrombotic function and aggregation did not change with PGJ or placebo juice intake (P-selectin, platelet-derived NO, or TXB₂, levels). General inflammatory markers (CRP, IL-8) were unaffected; however, platelet-dependent inflammatory markers were significantly decreased after consumption of PGJ with significantly lower superoxide release (Table 1). Platelet activation leads to surface expression and shedding of the inflammatory mediator CD40L, and a significant decrease in the mean value of sCD40L levels was observed with PGJ versus placebo consumption (Table 1). HDL also significantly increased with PGJ consumption (Table 2).

Consumption of red wine and purple grape juice have previously been shown to have antithrombotic and vasodilatory properties due to antioxidant effects as well as enhanced bioactive NO.5,7 The relevance of the antithrombotic properties in subjects with cardiovascular disease taking aspirin was unknown. Findings from this study indicate that consumption of PGJ fails to add to the platelet inhibitory effects of aspirin as measured by markers of platelet function including aggregation, thromboxane B₂, and P-selectin. However, the role of platelets in inflammatory-dependent vascular processes is of growing interest, and consumption of PGJ appears to attenuate some of these effects, specifically sCD40L release, despite aspirin intake. It is established that CD40–CD40L interactions are central in immune responses and inflammation, but more recently ligation of CD40 on vascular cells and platelets has been shown to contribute to the pathogenesis of atherosclerotic, thrombotic, and inflammatory processes.12,13

In summary, PGJ contains specific flavonoids that may attenuate cardiovascular disease and, specifically, inhibit thrombosis. However, there has been a paucity of clinical studies directly examining this question. In this study, consumption of PGJ did not alter clinical variables or platelet activation in subjects with cardiovascular disease, but did suppress levels of platelet-dependent superoxide and sCD40L release. These findings suggest that consumption of purple grape juice, although not providing an additive antithrombotic effect for patients already on aspirin, may suppress platelet-dependent inflammatory indicators that have been recently linked to cardiovascular disease.

Acknowledgments

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**TABLE 1. Platelet and Inflammatory Function after Consumption of PGJ or Placebo Control**

<table>
<thead>
<tr>
<th></th>
<th>PGJ (n=20)</th>
<th>Placebo (n=20)</th>
<th>Overall P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelet Function</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aggregation, %</td>
<td>58.79±2.06</td>
<td>61.5±2.15</td>
<td>0.144</td>
</tr>
<tr>
<td>(ADP 5 μM/L)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NO, au (median, IQR)</td>
<td>28.41 (9.54, 52.8)</td>
<td>34.36 (19.6, 50.4)</td>
<td>0.839</td>
</tr>
<tr>
<td>P Selectin, ng/ml (median, IQR)</td>
<td>47.9 (21.84, 4.88)</td>
<td>43.8 (17.9, 4.02)</td>
<td>0.518</td>
</tr>
<tr>
<td>Thromboxane B₂, pg/ml (median, IQR)</td>
<td>50.3 (47.5, 51.8)</td>
<td>50.95 (49.05, 53.5)</td>
<td>0.468</td>
</tr>
<tr>
<td><strong>Inflammatory Markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-8, pg/ml</td>
<td>148.5±12.6</td>
<td>159.9±13.62</td>
<td>0.403</td>
</tr>
<tr>
<td>sCD40L, ng/ml</td>
<td>3.7±0.78</td>
<td>6.0±0.58</td>
<td>0.03**</td>
</tr>
<tr>
<td>Superoxide, au</td>
<td>34.5 (IQR: 18.9, 67.2)</td>
<td>50.0 (IQR: 36.9, 84.4)</td>
<td>0.02**</td>
</tr>
<tr>
<td>CRP, ug/ml</td>
<td>2.12±0.227</td>
<td>2.11±0.228</td>
<td>0.982</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*A one-way repeated measure ANOVA with a Holm–Sidak posthoc procedure was used to assess pairwise comparisons.

**Statistical significance determined by Friedman Repeated Measures Analysis of Variance on Ranks.*
TABLE 2. Clinical Laboratory Data after Consumption of PGJ or Placebo Control

<table>
<thead>
<tr>
<th>Clinical Markers</th>
<th>PGJ (n=20)</th>
<th>Placebo (n=20)</th>
<th>Overall P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mg/dl</td>
<td>183.8±9.1</td>
<td>175.3±7.5</td>
<td>0.1</td>
</tr>
<tr>
<td>LDL, mg/dl (median, IQR)</td>
<td>78.0 (62.0, 98.0)</td>
<td>85.0 (71.5, 103.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>50.0±3.2</td>
<td>44.9±2.4</td>
<td>0.02*</td>
</tr>
<tr>
<td>TG, mg/dl</td>
<td>210.9±29.1</td>
<td>237.5±32.0</td>
<td>0.053</td>
</tr>
<tr>
<td>Glucose (median, IQR)</td>
<td>101.0 (92.0, 107.5)</td>
<td>102.0 (95.0, 110)</td>
<td>0.784</td>
</tr>
<tr>
<td>Insulin</td>
<td>15.05±1.89</td>
<td>16.250±1.90</td>
<td>0.475</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Interquartile Range (IQR) represents the 25th and 75th percentile.

*Statistical significance determined by paired t test or Wilcoxon rank-sum data

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