Synergism Among Flavonoids in Inhibiting Platelet Aggregation and H$_2$O$_2$ Production

To the Editor:

In vitro and in vivo studies carried out by Freedman et al demonstrated that purple grape juice inhibits platelet aggregation and production of superoxide anion and increases the platelet formation of nitric oxide. These findings are of potential relevance for explaining the cardioprotective effect of grape juice and red wine. The authors sought also to investigate the mechanism by which grape juice inhibits platelet function and observed a consistent difference in terms of platelet inhibition among the 5 fractions of grape twice containing flavonoids. We agree with the authors that flavonoids, which are constituent of both red wine and grape juice, contribute to inhibiting platelet activity, but there are some issues that merit consideration.

The first point is to determine whether one or more flavonoids contribute to the antiplatelet effect of red wine or grape juice. Assuming that only one flavonoid inhibits platelet function is not realistic because the concentration of flavonoids in human circulation is low. Surprisingly, there are no data of flavonoids concentration in human circulation after assumption of red wine, but taking into account other sources, such as onions or tea, the plasma concentration would range from 0.6 to 13 μmol/L. Assuming a similar range of concentration after ingestion of red wine or grape juice, it is difficult to imagine that one flavonoid contributes to platelet inhibition. Indeed, Freedman’s study and others demonstrated in vitro that much higher concentrations, for instance of quercetin or resveratrol, are necessary for inhibiting platelet function.

On the basis of these considerations, we combined in vitro 2 flavonoids, namely quercetin and catechin, and demonstrated that they are synergistic in reducing platelet formation of H$_2$O$_2$ and inhibiting platelet function by interfering with the activation of phospholipase C pathway. As this effect was observed with concentrations of quercetin and catechin (5 μmol/L and 25 μmol/L, respectively) close to those potentially achievable in vivo, it is difficult to believe that the concept of synergism among the flavonoids could help explain the antiplatelet activity of red wine and grape juice in vivo. In this regard, it is crucial that future studies with red wine or grape juice provide information on flavonoid bioavailability and its relationship with antioxidant activity and platelet function.

Response

The findings from our study are in agreement with the main comments of Violi and colleagues. A central message of this study is that one isolated flavonoid is not responsible for the antioxidant and platelet inhibitory effects that we reported. This is clear from the failure of any single flavonoid group to cause the same effects as the purple grape juice either in vitro or ex vivo. As we were not sure what the relevant flavonoids were, it was difficult to measure specific flavonoids from the subjects who drank the juice. However, we do not believe that the quercetin or resveratrol are the main substances responsible for the platelet inhibitory or nitric oxide–releasing effects. Although previous studies have shown that, in vitro, flavonoids including quercetin, resveratrol, and catechin inhibit platelet aggregation, the physiological relevance of these findings has been questioned in humans because oral supplementation with quercetin causes markedly increased plasma levels but does not alter total, LDL, or HDL cholesterol levels or change thrombogenic markers including platelet aggregation and platelet thromboxane B$_2$ production. However, Violi and colleagues are correct that flavonoid levels would have provided useful information especially as a point of comparison with the antioxidant levels measured from the plasma of subjects who consumed purple grape juice.

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