Absorption and metabolism of red wine polyphenols and their potential health benefits in cardiovascular function

Dear Sir:

In a recent issue of the Journal, Chiva-Blanch et al (1) reported the differential effects of the polyphenols and alcohol in red wine (RW) on the expression of adhesion molecules and inflammatory cytokines related to atherosclerosis in subjects at high risk of cardiovascular disease. We appreciate the authors’ cautious deduction that both ethanol and nonalcoholic compounds contribute to the antiinflammatory effects of RW on the basis of a randomized clinical trial of RW and dealcoholized RW (DRW).

Although we have little doubt about the alcohol-independent cardiovascular effects of the phenolic compounds of RW, we were concerned about the actual concentrations of urinary polyphenols and their metabolites reported in the study. The authors reported that 24-h urinary excretion of total resveratrol metabolites increased in relation to baseline amounts from 1.24 μmol (95% CI: 0.91, 1.65 μmol) to 4.69 μmol (95% CI: 3.86, 5.53 μmol) and 8.33 μmol (95% CI: 6.86, 10.19 μmol) after ingestion of RW and DRW, respectively. The authors suggested that resveratrol metabolite concentrations were statistically higher after the DRW compared with RW intervention (P = 0.002). However, it seems clear from a great number of recent studies that the cardiovascular effects of polyphenols are dependent on their bioavailability, and alcohol in RW may improve polyphenol availability by increasing its intestinal absorption or by delaying its excretion (2, 3), indicating that RW intake should produce higher concentrations of urinary resveratrol metabolites than DRW ingestion. It is, therefore, reasonable to assume that the consumption of RW and DRW also should, at least, lead to similar concentrations of urinary resveratrol metabolites, despite the fact that the resveratrol content of RW is slightly higher than that of DRW as depicted in Table 1 of their article. More important, we also recognized that the observed significant increase (P = 0.002) in urinary resveratrol metabolites after DRW intake was not paralleled by the increase in the tested biomarkers related to atherosclerosis in comparison with RW ingestion (Tables 4 and 5 of their article). Therefore, the present data make sense if RW polyphenols, including resveratrol, are associated with the tested vascular health benefits.

One of the main limitations of Chiva-Blanch et al’s study (1) is that it does not report the circulating metabolite concentrations after the consumption of RW and DRW. To elucidate the finding that polyphenols are responsible for the alcohol-independent cardiovascular effect of RW, plasma analysis for polyphenols and their metabolites is determinant. Several causality criteria for the assessment of any compound as a potential mediator of vascular function have been established previously, and these have to meet the condition that the test compound should be absorbed from a food matrix by humans and should be transported to the appropriate site or tissue (as quantifiable in circulation), and its circulating amounts temporally parallel the hypothesized vascular effects (4, 5). Although the study conducted by Chiva-Blanch et al (1) showed consistent effects of both RW and DRW on several intermediate markers for vascular function, it is still not fully known whether their action could be specifically related to RW polyphenols.

Another limitation of this study was that although the authors measured total urinary resveratrol metabolites as an indicator of polyphenolic absorption, 24-h urinary excretion results of total resveratrol metabolites were not corrected for creatinine (eg, nmol/g creatinine). It also must be noted that the authors omitted a necessary explanation as to whether the analysis of total resveratrol metabolites was to measure total resveratrol concentrations, which are calculated as the sum of resveratrol and its sulfated or glucuronidated metabolites after enzymatic hydrolysis with glucuronidase and sulfatase, as well as methylated resveratrol. It is well known that, in humans, ingested polyphenols are extensively metabolized and excreted as sulfated, glucuronidated, or methylated phase II conjugates (5–7), and authentic standards of resveratrol metabolites are not generally commercially available. It is also surprising that the study design was to elucidate whether the cardioprotective effects of RW intake are attributed to alcohol, polyphenols, or the synergistic effect of both, although the concentration-dependent effects of resveratrol metabolites and ethylglucuronide as the indicators of polyphenolic and alcohol absorption from RW, DRW, and gin were not adequately discussed in the article. The observed results did not well support the hypothesis raised by authors that the ethanol and polyphenols in RW were responsible for the regulation of soluble inflammatory mediators in high-risk patients.

Epidemiologic studies have shown that moderate intake of RW protects against cardiovascular diseases, and this effect has been attributed to polyphenols (2, 3, 8, 9). However, Chiva-Blanch et al (1) noted that there was inadequate experimental evidence to implicate specific polyphenols in RW. Data on the intestinal absorption of polyphenols from RW intake are sparse, and it is not yet known to what extent these components are bioavailable and whether alcohol plays a role in their absorption. Dietary intake of polyphenols is not guaranteed to equate with exposure at the tissue level, because polyphenols from food, including RW, are poorly absorbed in humans (8). Given this, the possibility that RW polyphenols affect vascular function is intriguing and deserves attention in future studies.

XY has received research funding from the National Natural Science Foundation of China (C30972054 and C31171678). None of the authors declared a financial or personal conflict of interest.

Xingbin Yang

College of Food Engineering and Nutritional Science
Shaanxi Normal University
LETTERS TO THE EDITOR

Reply to X Yang and Y Zhao

Dear Sir:

We thank Yang et al for their interest in our work and appreciate the opportunity to respond to a number of the issues raised in their letter. The aim of our study (1) was to evaluate and compare the effects of moderate consumption of red wine (RW), gin, and deacoholized RW (DRW) on the expression of soluble and leukocyte adhesion molecules as well as of proinflammatory cytokines related to the early stages of atherosclerosis in subjects at high risk of coronary heart disease. One of the concerns raised in the letter by Yang et al was the actual concentrations of urinary polyphenols and their metabolites. We reported 24-h urinary excretion of total resveratrol metabolites only as a measure of intervention compliance because resveratrol metabolites have been previously described as a marker of wine consumption by our research group (2). After our study was published, an error was identified in the calculation of total resveratrol metabolites in 24-h urinary excretion. Consequently, the results of the statistical analysis have been updated, and nonsignificant differences were observed after RW and DRW interventions. (The corrected values appear in an erratum in this issue.)

The comments by Yang et al with regard to the role of alcohol in RW on the availability of polyphenols raise important questions. In vitro studies cited by Yang et al found that alcohol from RW increased the absorption of quercetin and its 3-O-glucoside (3) and seems to contribute indirectly to the antioxidant capacity of wine by increasing the bioavailability of its phenolic compounds (4). However, the in vivo evidence supports similar bioavailability for catechins, malvidin-3-glucoside, and caffeic acid and production of 4-O-methylgallic acid after consumption of RW and DRW (5, 6). Nevertheless, the alcohol in RW delayed the elimination of (+)-catechin from the plasma compartment (6). Urinary catechin concentration after consumption of RW tended to be higher (20%) compared with that after the consumption of DRW (P = 0.06) (6). Other in vivo intervention studies that administered pure polyphenols (ie, resveratrol, catechin, or quercetin) in different matrices have shown contradictory results. For example, alcohol did not improve the bioavailability of total resveratrol and catechin when comparing white wine (11.5% ethanol content) with grape juice or vegetable juice/homogenate matrices but increased the absorption and excretion of quercetin (6). In addition, 5% alcohol did not improve the bioavailability of resveratrol when coadministered with quercetin (7). Therefore, the effect of alcohol on polyphenol absorption remains unclear, and further studies in this field are required.

We agree that the cardiovascular effects of RW polyphenols depend on their bioavailability. Total resveratrol represents 4.4% of total phenolics in the RW and DRW used in the study (our article’s Table 1), and the resveratrol concentration of RW was not significantly higher than that of DRW. In terms of bioavailability, resveratrol is well absorbed but scarcely bioavailable because it is rapidly metabolized (7). Poorly absorbed proanthocyanidins and anthocyanins from wine reach the colon, where they are metabolized to phenolic acids by the microbiota (6). Therefore, knowledge of the whole profile of RW polyphenol metabolites as well as the effect of microbiota on bioavailability is key to understanding its health impact in further studies (6).

Yang et al highlighted 2 limitations of our study (1). In this long-term study, fasting blood samples were collected only at baseline and on the day after the last day of each intervention. When only fasting blood is sampled, care should be taken when interpreting data on biomarker intake (8). The relation between intake of a polyphenolic food constituent and the appearance of a metabolite in plasma depends on the elimination rate of this metabolite. Half-lives of polyphenols are ~2 h for anthocyanins and flavanones, 2–3 h for flavanols, and 11–28 h for flavonols such as quercetin (8). The 24-h urine accurately reflects the total polyphenol absorption, is a quantitative measure of the total amounts of polyphenol metabolites over a 24-h period, and monitors the daily intake more robustly than does a single plasma measurement (8). Therefore, we provided the urinary measurement of biomarkers of wine consumption [sum of total resveratrol metabolites previously described by Zamora-Ros et al (2)] and ethylglucuronide as the biomarker of alcohol consumption in 24-h urine samples as an objective measure of adherence with the interventions.

The other limitation mentioned by Yang et al was that the 24-h urinary excretion of total resveratrol metabolites was not creatinine adjusted. The 24-h urinary excretion of polyphenols is considered to

Yan Zhao

REFERENCES


E-mail: xingbinyang@hotmail.com
Xi’an 710062
China

School of Pharmacy
Fourth Military Medical University
Xi’an 710032
China

Xi’an 710062
China

Yan Zhao

REFERENCES
