

## LETTER

**Resveratrol as a supplement to exercise training: friend or foe?**

We recently read with great interest the manuscript by Gliemann *et al.* (2013) entitled 'Resveratrol blunts the positive effects of exercise training on cardiovascular health in aged men' as well as the Editorial response by Smoliga & Blanchard (2013). In the study by Gliemann *et al.* (2013), the authors implemented an 8 week exercise-training intervention among sedentary, but otherwise healthy older men [ $n = 27$ ;  $65 \pm 1$  year old (mean  $\pm$  SEM)] in concert with 250 mg day<sup>-1</sup> of oral *trans*-resveratrol supplementation ( $n = 14$ ) or placebo ( $n = 13$ ). The authors noted statistically significant improvements in several cardiovascular outcomes (e.g. mean arterial blood pressure, cholesterol and maximal oxygen uptake) among the placebo group that were not observed among the resveratrol group. Based on these findings, it was concluded that 'resveratrol blunts the positive effects of exercise'. This conclusion has generated much controversy and press, because it is in direct contrast to what would be predicted based on the beneficial effects of resveratrol supplementation during exercise training repeatedly shown in preclinical models (Murase *et al.* 2009; Dolinsky *et al.* 2012; Hart *et al.* 2013; Menzies *et al.* 2013).

We commend Gliemann and colleagues for their significant effort in completing this important work. Similar to Smoliga & Blanchard (2013), however, we were quite surprised by the strong conclusions made based on their study findings. The Editorial by Smoliga & Blanchard (2013) aptly describes several valid concerns about the interpretation of study data and highlights key instances in which inappropriate conclusions may have been drawn. We agree with the points raised by Smoliga & Blanchard (2013) but also believe that additional issues warrant discussion. Thus, the purpose of the present Letter is to highlight key aspects of the study design, interpretation of data and presentation of findings by Gliemann *et al.* (2013) that were not mentioned by Smoliga & Blanchard (2013).

Based on a careful review of the data presented by Gliemann *et al.* (2013), we believe that their conclusion that 'resveratrol might induce a strong adverse effect on

cardiovascular responses to exercise' is too strong and is an overinterpretation of the data. For example, for several variables [i.e. low-density lipoprotein (LDL) cholesterol, mean arterial blood pressure and resting heart rate], the reported discrepancy in statistical significance between the resveratrol and placebo groups appears to be an artifact of relatively small group sizes ( $n \leq 14$ ) and is unlikely to be meaningful clinically. For instance, LDL cholesterol was significantly reduced from 3.3 (mean) to 3.0 mmol l<sup>-1</sup> in the placebo group. In contrast, the reduction in LDL cholesterol in the resveratrol group was of an almost similar magnitude (from 3.6 to 3.4 mmol l<sup>-1</sup>) but described as non-significant. In our opinion, the difference between groups is not clinically relevant and thus should be interpreted more cautiously. Moreover, a litany of intramuscular outcomes related to vascular function and inflammation were evaluated, and none seems to indicate any adverse effect of resveratrol supplementation, further detracting from the conclusion that exercise-derived benefits were abolished.

Several other issues raise concerns about potential overinterpretation of data and the broad-sweeping conclusions drawn therein. First, only healthy men were included in this study, which could have limited the potential range of improvement in many dependent outcomes. Second, given the controlled nature of the study, it is unclear why the use of antihypercholesterolaemia medications was not an exclusionary criterion, because these drugs are known to influence cardiovascular parameters and skeletal muscle function (Ceriello *et al.* 2005; Baer & Wortmann, 2007). Two participants (randomization group unreported) were taking these medications, which could have influenced outcomes and subsequent conclusions, given the small sample size. Third, information is extremely limited regarding participant adherence to the interventions, as well as any controls for diet and outside physical activity. These issues are critical for proper interpretation of laboratory-based studies with small sample sizes, particularly given that even minor lifestyle changes could influence many of the selected outcomes. Additionally, there was no mention of potential dose issues. Given that the optimal dose of

resveratrol for humans, and for 'at risk' populations in particular, is not currently known, this is an important consideration. These issues certainly do not discount the importance of the study, but we would argue that they are cause for more cautious interpretation of the study's findings.

Perhaps the most surprising aspect of the presentation of findings by Gliemann *et al.* (2013) was the lack of reference to the fact that resveratrol improved performance on the step test to a significantly greater degree than placebo. This is a surprising omission, given that this test was described as a 'test of maximum functional capacity'. Notably, this result can only be found within a supplementary table (Table S2 of Gliemann *et al.* 2013). Within the text, the authors stated that performance on this test improved among participants in both the resveratrol and placebo groups, yet there is no statement indicating that resveratrol improved performance to a greater extent than placebo. This is rather surprising, because both groups also improved significantly on the primary outcome of maximal oxygen uptake, but for this outcome the differential improvement between groups is highlighted throughout the manuscript. We can only speculate on the rationale behind the decision not to report this important finding in the main document, but this omission raises some questions regarding the objectivity of the data interpretation.

As a result of the points raised above, we believe that the strongly worded statements that resveratrol 'blunted' or 'abolished' the beneficial effects of exercise are likely to be inappropriate. Such conclusions could potentially discourage future investigations in this area. In our opinion, this would be a detrimental outcome, given the widespread and growing use of resveratrol among the public (Nutrition Business Journal, 2009). Although the findings of Gliemann *et al.* (2013) contribute to the growing body of literature on the effects of resveratrol on exercise performance, several critical questions are left unanswered based on reported findings. Thus, the need remains for future clinical trials to answer such questions and inform public health recommendations related to resveratrol use.

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## Additional Information

### Competing interests

S.D.A. serves as a scientific advisor and as a consultant for the company ReBody, LLC, which is an affiliate of Reserve Life Organics, LLC d/b/a Reserveage Organics, the developer and marketer of health products containing resveratrol. T.W.B. has no competing interests to report.

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