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The effect of resveratrol on longevity across species: a meta-analysis

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Resveratrol has shown evidence of decreasing cancer incidence, heart disease, metabolic syndrome and neural degeneration in animal studies. However, the effects on longevity are mixed. We aimed to quantify the current knowledge of life extension from resveratrol. We used meta-analytic techniques to assess the effect resveratrol has on survival, using data from 19 published papers, including six species: yeast, nematodes, mice, fruitflies, Mexican fruitflies and turquoise killifish. Overall, our results indicate that resveratrol acts as a life-extending agent. The effect is most potent in yeast and nematodes, with diminished reliability in most higher-order species. Turquoise killifish were especially sensitive to life-extending effects of resveratrol but showed much variation. Much of the considerable heterogeneity in our analysis was owing to unexplained variation between studies. In summary, we can report that few species conclusively show life extension in response to resveratrol. As such, we question the practice of the substance being marketed as a life-extending health supplement for humans.

Keywords: caloric restriction; MCMC; meta-regression; life extension; phytoalexin; red wine

1. INTRODUCTION

Dietary restriction has long been believed to be the most reliable and effective means of promoting longer lifespans [1,2]. This relatively simple dietary intervention has tapped into a complex network of biological systems controlling ageing and has generated much information on the nutrient signalling pathways that contribute to the rate of senescence [3]. Researchers noted that resveratrol, a phytoalexin most abundant in red wine, acted upon some of the same ageing mechanisms as dietary restriction, namely Sirt1 signalling [4] (although see Pacholec *et al.* [5]). Such an effect could account for the so-called French Paradox, explaining how the health risks of rich diets could be mitigated by moderate consumption of red wine [6].

The potential for resveratrol to confer the longevity benefits of dietary restriction has generated enormous interest in the scientific community. Resveratrol is mentioned in over 50 reviews published in scientific journals (electronic supplementary material, table S1), although the body of empirical research is considerably smaller owing to the protracted and expensive nature of longevity research. Resveratrol has shown evidence of decreasing cancer incidence, heart disease, metabolic syndrome and neural degeneration in animal studies [7]. As human clinical trials of resveratrol are now underway [7], it is high time to review the current state of knowledge regarding the life-extending properties of resveratrol. To our knowledge, this is the first quantitative review of resveratrol using rigorous meta-analytic methods.

2. MATERIAL AND METHODS

In brief, papers were collected from searches of ISI Web of Science. This yielded 19 papers that fit our requirements, with additional unpublished survival data provided by the authors of Bass *et al.* [8] (electronic supplementary material, table S2). We calculated the log hazard ratio (ln(HR), i.e. risk of death) from comparisons between control and resveratrol treatment group survival curves at nine points throughout each experiment (at 90, 80 . . . 20% and 10% of control group survival; electronic supplementary material, figure S1). This procedure allows for a more comprehensive effect size estimate than taking data from one point measurement, such as using the average longevity of the longest-lived 10 per cent of subjects (a common maximum longevity proxy). Our approach takes into consideration the overall shape of the survival curve [9] and allows for direct comparisons of species with varying lifespans. In total, we collected 187 data points from six animal species in 19 studies.

We analysed these effect sizes using Bayesian meta-analytic statistical techniques implemented in the R package MCMCglmm [10,11] in R v. 2.13.1 [12]. Both study and species identities were included as random factors in one meta-analytic model (i.e. traditional meta-analysis; electronic supplementary material, table S3 and S4); we also note that residual (within-study) variance was modelled in addition to sampling error (measurement) variance. To see species-specific effects, we used species as a fixed factor with study as a random factor in an alternative meta-analytic model (i.e. meta-regression; electronic supplementary material, table S3 and S4). Additional study factors, including sex, resveratrol dose per body mass, diet, reproductive status, and year of publication, were also considered as possible moderators in further meta-regression analyses (electronic supplementary material, table S3 and S4). Moderators were *z*-transformed, so that continuous variables could be compared based on average values. Reference variables for factor moderators were as follows: sex = hermaphrodite/asexual group, diet = standard and reproductive status = virgin. The 'best' model was selected for the moderators resulting in the lowest deviance information criterion (DIC) value (electronic supplementary material, table S3 and S4). We tested for heterogeneity by assessing the I^2 value of the random effects, i.e. the percentage contribution of random effects to the sum of all variance components including sampling error variance (see the electronic supplementary material). We tested for publication bias (positive life-extension results being more likely to be published) by visual inspection of the funnel plot (figure 1*a*) and by performing Egger's regression on data points consisting of the residuals and sampling errors [13] (figure 1*b*; see also electronic supplementary material). For interpretability, we report our results in hazard ratio (HR) rather than ln(HR), so that 1 indicates no difference in risk of death.

3. RESULTS

Overall, resveratrol decreased the risk of death (Bayesian mixed-effects meta-analysis: ($\beta_{\text{meta-analytic mean}} = 0.629$, 95% highest posterior density (HPD) = 0.487–0.910; figure 2*a*). Nematode worms (*Caenorhabditis elegans*), yeast (*Saccharomyces cerevisiae*) and turquoise killifish (*Nothobranchius furzeri*) showed a moderate decrease in risk of death ($\beta_{C.elegans} = 0.510$, 95% HPD = 0.392–0.647; $\beta_{S.\ cerevisiae} = 0.574$, 95% HPD = 0.376–0.834; $\beta_{N.\ furzeri} = 0.401$, 95% HPD = 0.197–0.887; figure 2*a*). *Drosophila melanogaster* tended towards a decreased risk of death owing to resveratrol treatment ($\beta_{D.melanogaster} = 0.796$, 95% HPD = 0.623–1.058; figure 2*a*). By contrast, mice (*Mus musculus*) and Mexican fruitflies (*Anastrepha ludens*) appeared largely unaffected

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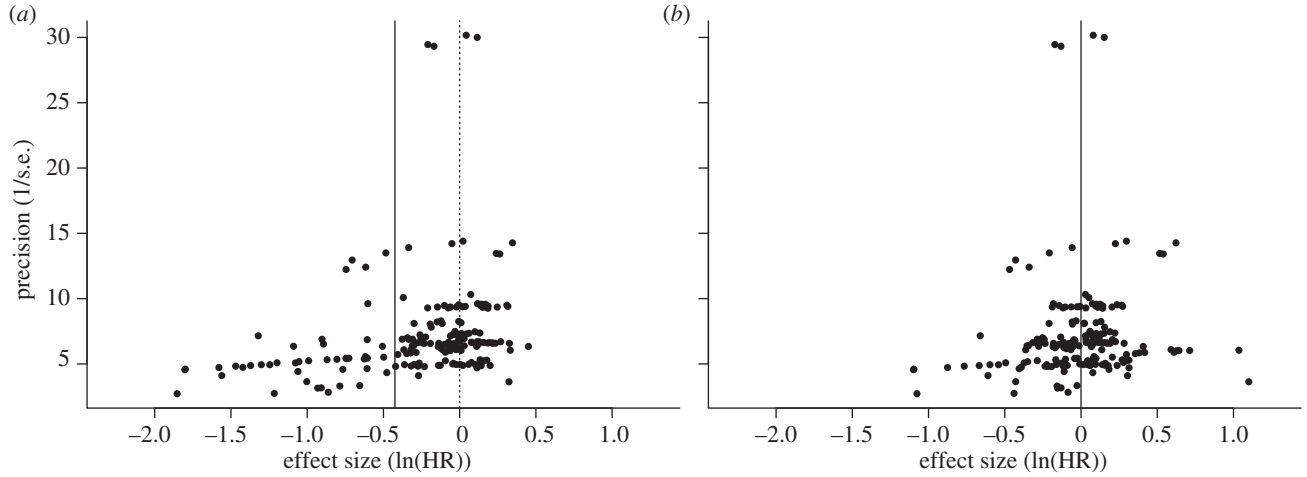

Figure 1. Funnel plots of (*a*) the effect size estimates (ln(HR)) from each control-resveratrol treatment group comparison; and (*b*) the residual effect sizes plotted against their precision (1/s.e.). In Cohen's scale, the ln(HR) effect size values of approximately 0.2, 0.6 and 1.1 correspond to 'small', 'moderate' and 'large' effects, respectively [2]. The solid line indicates the overall meta-analytic mean, and the dashed line indicates zero effect size. Symmetry in (*b*), the funnel plot of the combined values of the residuals from the intercept model and the sampling errors, indicates little evidence for publication bias.

by resveratrol treatment ($\beta_{M.musculus} = 0.865$, 95% HPD = 0.501–1.445; $\beta_{A.\ ludens} = 0.998$, 95% HPD = 0.501–2.205; figure 2*a*).

Despite these varying species outcomes, we observed higher heterogeneity owing to between-study as well as within-study variation ($I^2_{\text{study}} = 53.1\%$; $I^2_{\text{residual}} = 31.1\%$) than between-species variation ($I^2_{\text{species}} = 13.7\%$; electronic supplementary material, table S3) in the best-fit model (note also, however, that species variance estimate was based on only six species). Animals on specialized diets were less likely to show a life-extension response to resveratrol treatment, although the effect was small ($\beta_{\text{diet}} = 1.172$, 95% HPD = 0.986–1.353; figure 2*b*). Mixed-sex (both males and females included) experiments were less likely to result in increased longevity than hermaphrodite/asexual studies, however there was a wide range of effects ($\beta_{\text{mixed-sex}} = 1.770$, 95% HPD = 0.965–2.746; figure 2*b*). There was little difference between the single sex studies and hermaphrodites/asexual studies ($\beta_{\text{males-only}} = 1.236$, 95% HPD=0.757–1.967; $\beta_{\text{females-only}} = 1.256$, 95% HPD=0.775–2.020; figure 2*b*). Dose and reproductive status were not included in the best-fit model (electronic supplementary material, table S4). Egger's regression test indicated little evidence for publication bias ($\beta_{\text{intercept}} = -0.332$, 95% HPD = −1.007–0.305); however, there was a small effect indicating that more recent papers were less likely to detect a benefit from resveratrol ($\beta_{\text{year}} = 1.124$, 95% HPD = 0.950–1.342; figure 2*b*).

4. DISCUSSION

The high heterogeneity between and within papers could not be fully attributed to any of the moderators we analysed. The effects of diet and sex were small and inconclusive. The tendency towards smaller effect sizes being reported in more recent studies does not suggest publication bias, as supported by the analysis of the Egger's regression. Observing the between-species differences, we noted that *N. furzeri* (turquoise killifish) stand out as a contradiction to the trend of decreasing resveratrol benefits in higher-order animals. More research is required to confirm that these fish truly are exceptionally receptive to resveratrol (one experimental group saw a 500% decrease in risk of death). *Nothobranchius furzeri* were selected for age research because of their conveniently short lifespan [14], and this suggests that resveratrol may be acting on the naturally evolved mechanism that causes their condensed life history. *Nothobranchius furzeri* are known to have a high incidence of age-dependent neoplasias in the liver and kidney, which could be a potential target for the health benefits of resveratrol, thus extending their overall lifespan [15].

At a glance, our results confirm the claims that resveratrol extends longevity. However, the analytical method we have used allows us to observe where this statement is unable to be supported. Both the species model and our 'best'-fit meta-analytic model show a stark contrast between our hermaphrodite/asexual reference group (yeast and nematodes) and the higher-order animals, excepting *N. furzeri*. Importantly, this divide is not observed in dietary restriction research, where flies and mice show robust life-extension responses [1,2]. Clearly, dietary restriction in higher-order animals involves more complex interactions than those upon which resveratrol acts. New research into different compounds may be more promising, with interest mounting in the anti-ageing effects of downregulating the target of rapamycin pathway [16].

In summary, we have found resveratrol to have a robust life-extension effect in yeast, nematodes and killifish, but we have no explanation for how and why this effect is not nearly so reliable in flies and mice. Our moderators were unable to describe the origin of this heterogeneity, perhaps because minor experimental factors may make animals more or less sensitive to resveratrol depending on their condition. Resveratrol has shown some indication of positive effects on insulin and metabolic function in humans [17,18]. However, at a time when human trials testing for health benefits from resveratrol are in their early days, we believe it is

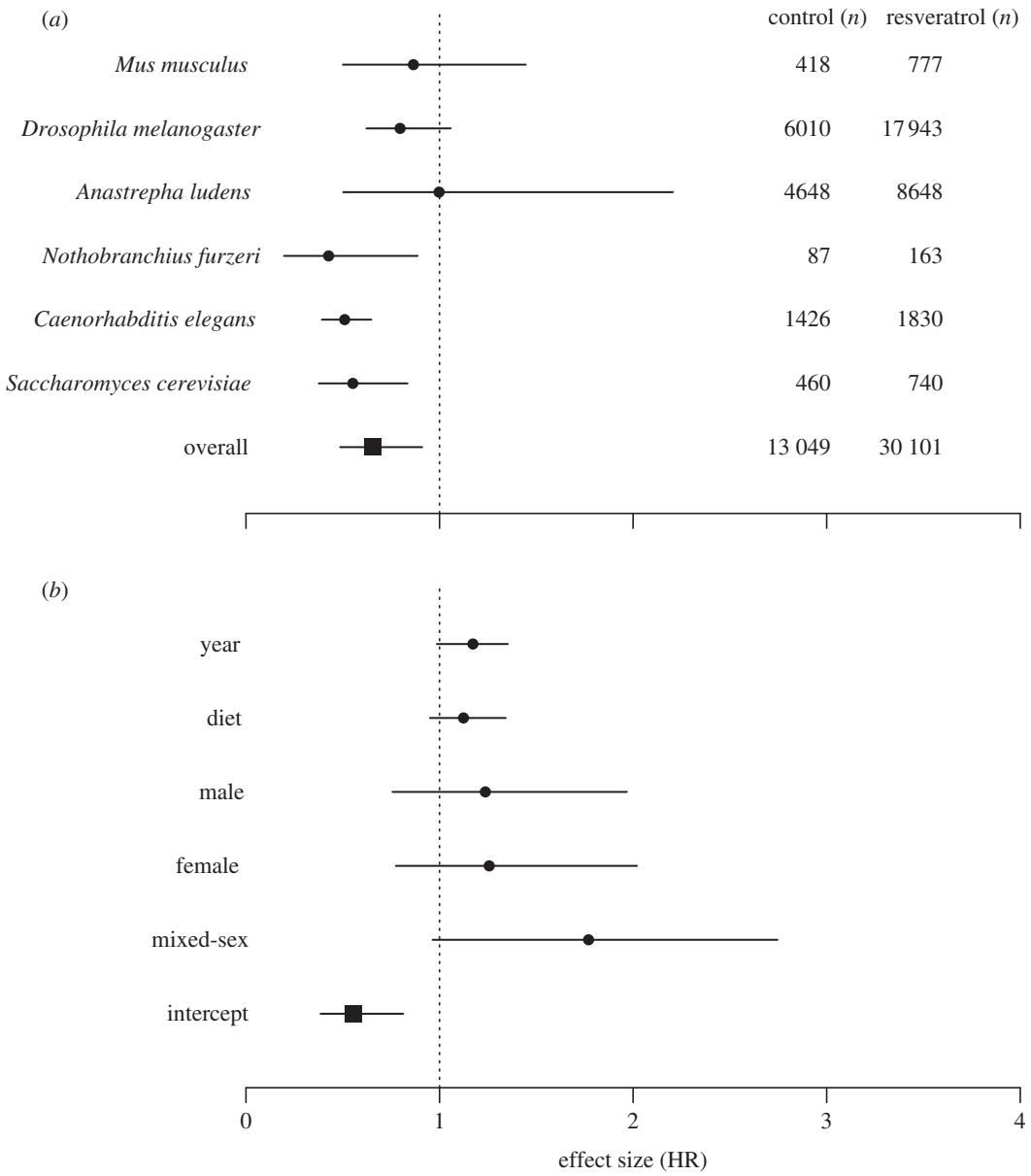

Figure 2. Both the overall meta-analysis (the intercept model; (*a*)) and meta-regression (the 'best' model; (*b*))—controlling for study and species as random factors—show that resveratrol treatment increases longevity, as indicated by 1 being excluded from the 95% highest posterior density (HPD) interval of the intercepts. When species effect was tested as a fixed factor, with study as a random factor, the species effect size estimates and associated HPD intervals depicted were observed (*a*). Numbers in the right columns indicate the number of individuals per treatment group in the original experiments. Hazard ratio (HR) values of less than 1 mean that the control group died out earlier than the resveratrol treatment group, and therefore a negative point estimate with a 95% HPD interval not spanning 1 means resveratrol increased longevity. The effects of the moderators depicted in (*b*) are based upon average values for year, abnormal compared with standard diets, and sex groups when compared with the hermaphrodite/asexual group. In Cohen's scale, the HR effect size values of approximately 1.2, 1.9 and 3 over 1 and 0.8, 0.5 or 0.3 below 1 corresponds to 'small', 'moderate' and 'large' effects, respectively [2].

inappropriate for resveratrol to be marketed as a life-extending health supplement when our analysis of the current knowledge provides such varied results.

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