REVIEW

Resveratrol and health – A comprehensive review of human clinical trials

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In the past decade, the small polyphenol resveratrol has received widespread attention as either a potential therapy or as a preventive agent for numerous diseases. Studies using purified enzymes, cultured cells, and laboratory animals have suggested that resveratrol has anti-aging, anti-carcinogenic, anti-inflammatory, and anti-oxidant properties that might be relevant to chronic diseases and/or longevity in humans. Although the supporting research in laboratory models is quite substantial, only recently data has emerged to describe the effects of resveratrol supplementation on physiological responses in humans. The limited number of human clinical trials that are available has largely described various aspects of resveratrol's safety and bioavailability, reaching a consensus that it is generally well-tolerated, but have poor bioavailability. Very few published human studies have explored the ability of resveratrol to achieve the physiological benefits that have been observed in laboratory models, although many clinical trials have recently been initiated. This review aims to examine the current state of knowledge on the effects of resveratrol on humans and to utilize this information to develop further guidelines for the implementation of human clinical trials.

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1 Introduction

From the years 2000 to 2030, the number of individuals in the United States aged 65 y and older is projected to more than double from 35 million to 71.1 million, increasing from 12.4% to about 19% of the population [1]. This rapid demographic shift will markedly increase the prevalence of age-related disorders including diabetes mellitus, cardiovascular and neurodegenerative diseases, and cancer. Unsurprisingly, the search for interventions that can prevent and alleviate age-related health problems is rapidly accelerating. Traditionally, chronic diseases have been treated through pharmaceutical interventions following a medical diagnosis. Over the past few decades, there has been an increasing emphasis on using lifestyle changes and nutritional modifications to prevent and treat chronic diseases [2, 3]. Caloric restriction is an effective means of preventing chronic disease and ultimately increasing lifespan in laboratory animals [4]. However, it is difficult to employ in actual practice, especially considering the cultural emphasis on eating that is a major contributor to many chronic diseases. As such, considerable research has been directed toward identifying substances that mimic the physiological effects of caloric restriction, and resveratrol has emerged as a leading candidate in this realm [4].

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenol found in grapes (*Vitis vinifera*), a variety of berries, peanuts, and medicinal plants, such as Japanese knotweed (*Polygonum cuspidatum*) [5]. The most important dietary source of

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Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; **FMD,** flow-mediated vasodilation; **GP,** grape powder; **ROS,** reactive oxygen species; **SIRT1,** sirtuin 1; **TLR4,** toll-like receptor 4

resveratrol is red wine, and it is often postulated to be an important factor in the French Paradox, a term coined to describe the observation that the French population has a very low incidence of cardiovascular disease, despite a diet high in saturated fats [6]. Scientific interest in resveratrol has continually gained momentum since 1997, when it was first demonstrated to prevent carcinogenesis in mice [7]. In the intervening years, this molecule has received considerable attention for its anti-inflammatory, anti-tumorigenic, and anti-oxidant properties, as well as its ability to increase lifespan in lower organisms and improve general health in mammals [8]. Recent data suggest that resveratrol does not extend lifespan in healthy mice or in a model of premature aging [9], but does appear to delay or attenuate many age-related changes and prevent early mortality in obese animals [10–12]. Reports of significant life extension in simpler laboratory organisms, combined with thousands of in vitro and in vivo studies supporting a role for resveratrol in either the prevention or treatment of chronic diseases, suggest that resveratrol and similar nutraceuticals may have the potential to make an unprecedented impact on human health.

Resveratrol has multiple mechanisms of action that may be related to its health benefits [5]. Similar to most polyphenols, resveratrol has intrinsic anti-oxidant capacity, but it also induces the expression of a number of anti-oxidant enzymes, making it difficult to decipher the precise contribution of each mechanism to an overall reduction in oxidative stress [13]. Resveratrol further interacts with a large number of receptors, kinases, and other enzymes that could plausibly make major contributions to its biological effects. In vivo, resveratrol treatment stimulates the activities of sirtuin 1 (SIRT1) and adenosine monophosphate-activated protein kinase (AMPK), both of which influence the regulation of metabolism in multiple tissues [8, 14, 15]. Intriguingly, some of the beneficial effects of resveratrol appear to be replicated by overexpression of SIRT1 [16], or by treatment with a structurally unrelated SIRT1 activator [17], and animals that lack AMPK fail to exhibit many of the normal responses to resveratrol [18]. Resveratrol further inhibits cyclooxygenases [19], and could therefore act through some of the same mechanisms as aspirin. An unbiased approach to select resveratrol-binding proteins revealed quinone reductase 2, which is inhibited by resveratrol, as one of the highest affinity targets, although the significance of this observation is not yet known [20]. Fully defining the targets of resveratrol that are biologically relevant is an enormous task, made more difficult by questions of whether effects are either direct or indirect, and often conflicting results in different systems. A full discussion of these issues is beyond the scope of this review, and has been attempted elsewhere (e.g. [21–23]). The complexity of resveratrol's effects in cells and in animals presents a major challenge in moving forward with human studies.

Although almost all the nearly 4000 published studies on resveratrol were performed in vitro or in animal models (see Fig. 1), intense media coverage highlighting its potential applications in the prevention and treatment of age-related diseases has inspired many individuals to try resveratrol supplements, and many companies to develop either resveratrol-based drugs or nutraceuticals. Indeed, a 2007 cross-sectional study found that supplemental resveratrol is taken by 2/3 of people who routinely consume multiple dietary supplements [24], and this number may have increased as studies describing resveratrol's health benefits have reached the mainstream media. Because of the continued public interest and the explosion of resveratrol supplements on the market, an urgent need exists to summarize the available clinical literature, which is the overarching goal of the present review. We will consider research related to resveratrol's bioavailability (both from

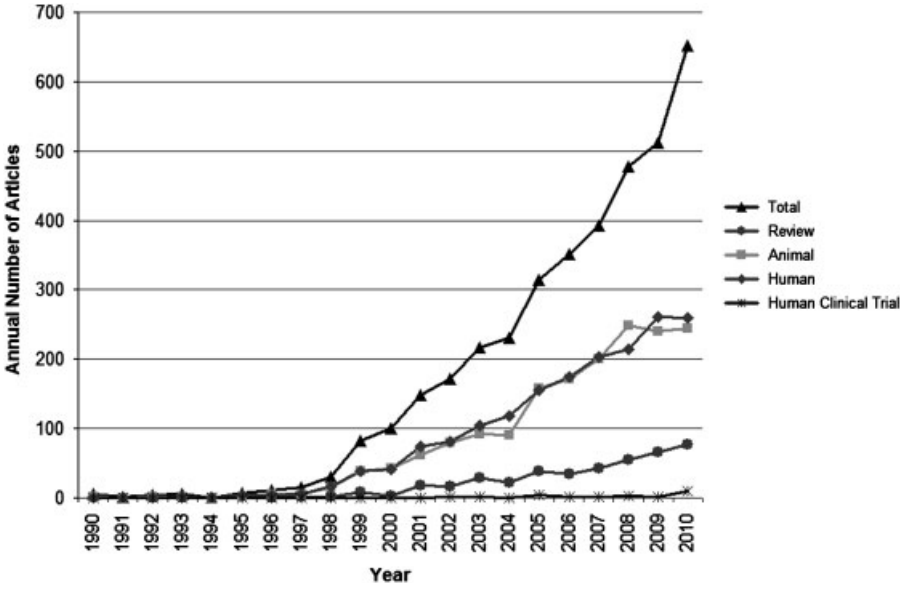

Figure 1. Annual count of resveratrol articles indexed on PubMed. The results include articles with the term ''resveratrol'' in found in the title, abstract, or keywords. Note that ''human'' studies includes cell culture studies. Some studies which were not resveratrol specific (i.e. general red wine and polyphenol studies) were indexed as ''human clinical trial.''

red wine and resveratrol supplementation), as well as its effects on oxidative stress, inflammation, obesity, diabetes, and cardiovascular health, and how it interacts with drug-metabolizing enzymes. Finally, we will discuss theoretical, methodological, and statistical limitations of the literature, and explore promising directions for future research in light of the current findings.

2 Bioavailability

A number of studies have demonstrated that resveratrol and other polyphenols have very low bioavailability, leading to concern that many of the beneficial effects observed in either cells or biochemical assays may not be achievable in humans due to rapid metabolism [25]. The absorption and metabolism of resveratrol appear to be broadly similar to that of other polyphenols such as quercetin and catechin [25], although a number of factors may influence the pharmacokinetics of each. Further studies are needed to compare maximum or average concentrations of resveratrol (C_{max} or C_{avg}, respectively) in human plasma or tissue with the concentrations necessary for achieving physiological benefit in animal and in vitro models. Although this provides researchers with a starting point, little is known about how time-dependent bioavailability variables relate to resveratrol's mechanisms of action (e.g. whether short-term C_{max} or long-term C_{avg} is most important), the bioactivity of resveratrol's metabolites [26, 27], or the degree to which this varies between either target tissues or species. A recent review by Patel et al. [28] details pharmacokinetic and metabolic aspects of resveratrol's bioavailability, as well as the safety of resveratrol. Herein, we have focused on the plasma C_{max} resulting from resveratrol supplementation, as this is the most easily translated variable in relating data from laboratory animals and in vitro models to humans. For the purposes of this review, all plasma concentrations have been converted to μg/L (228.24 g resveratrol = 1 mole).

3 Bioavailability from resveratrol supplements

There is a dose-dependent response between resveratrol intake and C_{max}. The greatest plasma *trans*-resveratrol concentrations have been reported by Boocock et al. [29] and Brown et al. [30], both of whom supplemented humans with up to 5 g *trans*-resveratrol. 5 g *trans*-resveratrol as a single dose resulted in a 24 h mean plasma concentration of 51.9 μg/L 24 h after administration, with a C_{max} of 538.8 μg/L attained 1.5 h after administration. The lowest dose used in the study (0.5 g) resulted in a 24-h mean plasma concentration of 8.36 μg/L, with a C_{max} of 72.6 μg/L at 0.83 h following administration [29]. Coefficient of variation (CV) for C_{max} for the dosages used ranged from 48.9 to 73.1%, indicating substantial variation in metabolism between subjects. Similarly, Chow et al. found plasma resveratrol concentration to range from 8.3 to 404.4 μg/L 1 h following 1 g resveratrol supplementation [31]. C_{max} can be increased through multiple days of supplementation [32]. Almeida et al. [32] administered 13 doses of 25, 50, 100, and 150 mg *trans*-resveratrol at 4-h intervals to 4 respective groups of 8 healthy subjects and compared plasma resveratrol concentration following the first and last (13th) dose. C_{max} more than doubled in the 25 and 150 mg group between the first and thirteenth dose, although this was not observed with the 50 and 100 mg groups. Regardless, C_{max} of the 150 mg group was 63.8 μg/L following 13 days of administration, far lower than the C_{max} for 5 g dosage used by Boocock [29, 31], but similar to C_{max} Boocock achieved following a single 0.5 g dosage. The CV for C_{max} was large, similar to that reported by Boocock et al., ranging from 40 to 113%. Although C_{max} was not reported following initial dose, data from Brown et al. [30] demonstrate that this occurs at higher dosages as well. Following 29 days of 5 g *trans*-resveratrol administration, Brown et al. [30] found plasma C_{max} to be 958.6 μg/L. This C_{max} is higher than that reported by Boocock et al. [29] following a single 5 g dose.

There is evidence that resveratrol and its metabolites accumulate within human cells in vivo in a tissue-specific manner and this is highly dependent on the dosage. Following either 0.5 or 1 g/day of resveratrol administration to 20 prostate and colon cancer patients for 8 days, normal prostate tissue contained resveratrol metabolites but no free resveratrol. Conversely, normal colonic tissue had considerably more *trans*-resveratrol (674 ± 1303 nmol/g) than metabolites for the 1 g/day group, whereas the 0.5 g/day had much lower concentrations (18.6 ± 17.4 nmol/g) [33]. Despite these differences, it is uncertain if the optimal resveratrol concentration and metabolite profile differs in other tissues and further research is needed in this area. The wide variability in tissue concentration observed is consistent with that of the plasma, further emphasizing inter-individual differences in bioavailability.

4 Bioavailability from wine and juice consumption

In considering studies using wine as a means of resveratrol administration, it is important to note that the resveratrol concentrations in wine vary widely, even within a given variety of grape or growing region [34]. Gresele et al. [35] found 15 days of 300 mL wine consumption to increase plasma resveratrol concentration (total, including metabolites, precluding accurate conversion to μg/L) from 0.72 ± 0.3 to 1.33 ± 0.3 μmol/L for white wine (0.25 g polyphenols/L) and from 0.71 ± 0.2 to 1.72 ± 0.1 μmol/L for red wine (1.8 g polyphenols/ L). Red wine increased plasma resveratrol by 1.0 μmol/L, whereas white wine increased plasma resveratrol concentration by 0.6 μmol/L. Interestingly, subjects in this study had moderate levels of resveratrol (0.71–0.72 μmol/L)

present in their plasma at the beginning of the experiment, despite being asked to refrain from wine consumption for the preceding week. The plasma $t_{1/2}$ of *trans*-resveratrol [29] is inconsistent with retention of these plasma concentrations over the course of 1 wk, raising the possibility that other dietary sources of resveratrol may be contributing to the plasma level, or that metabolites may be stored in various tissues and released into the bloodstream.

Dietary factors may influence plasma resveratrol concentrations and this may vary considerably between individuals [36]. Vitaglione et al. [36] found that free *trans*-resveratrol was not detectable in serum when 300 mL of red wine was consumed concurrently with a high-fat meal, although glucuronidated metabolites were present in four of the ten subjects. Similarly, detectable levels of free *trans*-resveratrol were found in the serum of only four of ten subjects following a different meal, and three of five subjects who consumed 600 mL of red wine on an empty stomach. Of the 25 subjects tested under these various conditions, only 11 subjects showed any evidence of either resveratrol or its metabolites in their serum during a 4-h period. The authors concluded the wide variation in subject responses combined with the low bioavailability suggests the combination of polyphenols, rather than resveratrol itself, may account for the French Paradox [36]. The suggestion of the importance of a synergistic effect of grapeskin polyphenols, rather than a single polyphenol, has been advanced elsewhere [37–40].

There is an additional evidence that the matrix in which resveratrol is provided influences its bioavailability. Goldberg et al. [25] provided twelve (three groups of four) healthy male subjects with 25 mg *trans*-resveratrol per 70 kg/body weight dissolved in 100 mL of V8 vegetable juice, white wine, or white grape juice and measured serum concentration of free and conjugated resveratrol at baseline, 30, 60, 120, and 240 min after administration. There were significant differences in bioavailability patterns between matrices, with plasma resveratrol concentration decreasing most rapidly with V8 vegetable juice and least rapidly using grape juice. Peak plasma concentrations were highest at the 30 min mark for all three matrices, with the lowest concentration for wine (416 μg/L) and the greatest for V8 (471 μg/L). Four hours after administration, serum concentrations remained elevated over 50 μg/L for all three matrices. Although these results indicated the matrix of resveratrol administration does influence bioavailability, it should be emphasized that this is the only study to carefully evaluate this aspect of bioavailability, and results may differ with a larger sample size. As free resveratrol was not measured separately, it is difficult to compare these results with other bioavailability studies.

5 Limitations to bioavailability research

Overall, the aforementioned studies suggest that the plasma concentrations of resveratrol achievable through high-dose supplementation are considerably greater than those derived from wine alone, and that there is considerable inter-individual variation in resveratrol bioavailability [29, 41]. The activities of various resveratrol metabolites remain an open question. Reporting of plasma resveratrol measurements has been inconsistent, with researchers employing a variety of analytical chemistry techniques, and with some reporting concentrations of resveratrol and its metabolites separately [29] and others reporting combined measurements [35]. Animal models have suggested that metabolites of resveratrol may be converted back into resveratrol at the tissue level, although this has not been rigorously demonstrated [29, 42]. Finally, there is limited and sometimes conflicting information available from basic science research regarding the plasma concentrations necessary for a given physiological effect. If a specific threshold C_{max} is necessary to achieve a physiological effect, timing of doses, as well as the matrix in which resveratrol is delivered, may prevent the necessary C_{max} from being reached even if absorption (i.e. measured by area under curve) remains unchanged. On a similar note, it is unclear if small doses of resveratrol on a regular basis (i.e. years of wine consumption) would have the same physiological effect as the high C_{max} observed from supplementation.

6 Oxidative stress and inflammation

Resveratrol has been reported to decrease oxidative stress and attenuate inflammation, and these mechanisms may account for many of its health benefits. Oxidative stress occurs when an excess of reactive oxygen species (ROS) are generated from any of a variety of sources, including the mitochondrial electron transport chain and reduced nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidases. ROS can damage macromolecules and activate signaling pathways that include a number of inflammatory mediators [43, 44]. Inflammation, in turn, can lead to further oxidative stress in a cycle that contributes to the progression of many diseases. Atherosclerosis, diabetes mellitus, chronic obstructive pulmonary disease, and cancer are examples of diseases associated with ROS-induced chronic inflammation [43, 45, 46]. Laboratory models suggest these diseases can either be prevented, treated, or cured through attenuating ROS, which may be achieved through treatment with resveratrol [22, 47, 48]. To date, human trials in this area have been very limited. The antioxidant activity of resveratrol may inhibit oxidation of low-density lipoproteins (LDL), and therefore decrease endothelial damage associated with cardiovascular disease [49]. This has been observed following red wine consumption [37, 49, 50], but has not yet been directly measured following resveratrol supplementation in humans. Ghanim et al. [51] found that 6 wk of supplementation with 200 mg of *P. cuspidatum* extract containing 40 mg of resveratrol did not alter fasting plasma concentrations of cholesterol (total, LDL, and HDL), triglycerides, or leptin compared with placebo in 20 healthy individuals. However, mononuclear cells from the

resveratrol group demonstrated suppressed nuclear factor kappa B (NFκB) binding, decreased ROS generation, and decreased tumor necrosis factor alpha (TNFα) and IL-6. Additionally, plasma TNFα and C-reactive protein (CRP) were significantly reduced. These findings reveal that resveratrol's actions on the cellular level can indeed influence plasma biomarker measurements associated with inflammation and risk for various diseases.

In a separate study, Ghanim et al. [52] provided 10 healthy humans with a high-fat high-carbohydrate meal on two occasions; once with a placebo and the other with a supplement containing 100 mg resveratrol and 75 mg grapeskin polyphenols. The resveratrol supplementation significantly increased nuclear factor (erythroid-derived 2)-like 2 (Nrf-2)-binding activity following the meal, and significantly increased messenger RNA (mRNA) expression of the NAD(P)H dehydrogenase [quinone] 1 (NQO-1) and glutathione *S*-transferase pi 1 (GST-π1) genes, suggesting a strong anti-oxidant effect. The resveratrol supplement also attenuated the postprandial rise in cluster of differentiation 14 (CD14) and IL-1β mRNA and toll-like receptor 4 (TLR4) protein in mononuclear cells, while also decreasing plasma endotoxin. These data strongly suggest that resveratrol reduces the oxidative and inflammatory responses of a high-fat high-carbohydrate meal and has potential to reduce the risk of atherosclerosis and diabetes through these mechanisms. It is also noteworthy that these results were achieved using a relatively small dosage of resveratrol compared with other studies.

7 Obesity and diabetes

In rodent models of diet-induced obesity, resveratrol improves insulin sensitivity and lowers body weight [14], which has lead to much speculation about its potential as an anti-diabetic in humans. Contrary to popular assumption, these effects do not seem to be tightly linked, because doses of resveratrol that are too low to produce weight loss still improve glucose tolerance [8]. In fact, low doses that are still sufficient to prolong survival in obese mice may even cause weight gain [11]. Animals treated with high doses of resveratrol lose weight, and are capable of expending more energy, based on their ability to either run farther or tolerate cold longer than their untreated counterparts [14]. However, it is not clear that either of these observations is relevant to the weight loss, because voluntary exercise is actually lower in the resveratrol-treated group and body temperature is not detectably changed under normal conditions. Recently, 1 year of treatment with resveratrol at 200 mg kg^{-1} day^{-1} was found to increase basal metabolic rate and total daily energy expenditure in the nonhuman primate *Microcebus murinus* [53, 54], providing further suggestive evidence for the possibility that resveratrol might be an effective way to enhance energy expenditure and/or promote weight loss. To our knowledge, there has been no controlled study of resveratrol's effects on weight loss in humans, despite this being one of the most frequent claims touted by supplement manufacturers. Body composition and body weight have not been specifically addressed as outcome measures in any of the chronic supplementation studies, and changes in weight have not been reported as a side effect.

Multiple mechanisms have been proposed to account for the insulin-sensitizing effects of resveratrol, including anti-inflammatory effects [55], SIRT1-dependent suppression of protein-tyrosine phosphatase 1B (PTP1B, the phosphatase that acts on the insulin receptor) [56], and prevention of ectopic lipid accumulation in muscle and liver by increased mitochondrial content [8, 14], which is thought to be mediated by an SIRT1-dependent pathway, and has recently been shown to require AMPK [18]. To date, there is only one peer-reviewed human clinical trial that addresses the effects of resveratrol on insulin sensitivity [57], and none on obesity. In early 2008, Sirtris Pharmaceuticals announced that their proprietary formulation of resveratrol, SRT501, had improved glucose tolerance in type II diabetics in a Phase 1b clinical trial, in the absence of serious adverse events [58]. In mid-2010, Crandall et al. presented preliminary findings supporting an insulin-sensitizing effect of resveratrol in humans [59]. Ten patients, aged 60–80 with impaired glucose tolerance, were treated with resveratrol for 4 wk. Fasting glucose was unchanged, but postprandial glucose levels were lowered without an increase in insulin production, indicating improved insulin sensitivity [59]. Notably, the doses in the Sirtris trials (2.5–5 g/day) were in the range where gastrointestinal side effects have been reported [30], and the doses in the Crandall trial (1–2 g/day) were very close, meaning that a thorough evaluation of both the efficacy and the side effects is needed to determine the potential of resveratrol as an anti-diabetic in humans. The full data sets from each of these studies have not yet been made public or subjected to peer review, making it difficult to accurately judge the importance of the findings at present.

Most recently, Brasnyo et al. [57] found that 4 wk of twice daily 5 mg of *trans*-resveratrol supplementation significantly improved insulin sensitivity, computed using homeostatic model assessment of insulin resistance (HOMA-IR), lowered blood glucose levels, and delayed glucose peak following a standardized meal in type II diabetic men ($n = 10$) compared with placebo ($n = 9$). The authors suggested that decreased oxidative stress, as indicated by significant reductions in 24 h urinary creatinine-normalized *ortho*-tyrosine concentrations, and significantly increased Akt phosphorylation may have contributed to these effects. None of the reported changes were observed after the first 2 wk of resveratrol supplementation. It is also noteworthy that Ghanim et al. [51] found that fasting glucose, insulin, or HOMA-IR scores remained unchanged following 6 wk of 40 mg resveratrol supplementation (in *P. cuspidatum* extract) in healthy individuals. Given that symptoms of hypoglycemia have not been reported in any of the bioavailability and safety studies, it appears that resveratrol is likely to be free from one of the major risks associated with many anti-diabetic agents, making it an attractive choice if efficacy can be more thoroughly demonstrated.

8 Cardiovascular effects

The suggested link between resveratrol and the French Paradox has created considerable interest in studying resveratrol's potential to improve cardiovascular health. A number of published reviews have summarized the relationship between red wine, grape juice, and other grape product consumption and physiological factors which reduce the risk of cardiovascular disease, including increased blood flow, decreased oxidative stress, and decreased inflammation [60–63]. One of the key cardioprotective mechanisms of resveratrol stems from its ability to upregulate endothelial nitric oxide synthase (eNOS) [38–40], which ultimately increases nitric oxide (NO) mediated vasodilation and increases blood flow. Additionally, human platelets exposed to physiologically attainable concentrations of resveratrol have been shown to increase eNOS activation, leading to greater NO production and decreased platelet activation [35]. While there is evidence that resveratrol is the most potent of the grapeskin polyphenols in upregulating eNOS, it cannot account for all of the eNOS upregulation which follows red wine consumption [38–40], further supporting the role of synergism in optimizing resveratrol's physiologic effects.

Arterial responsiveness to NO is often measured using flow-mediated vasodilation (FMD) of the brachial artery. FMD is widely used in evaluating endothelial function and decreased FMD is a risk factor for cardiovascular disease in older adults [64] and low risk populations [65]. Wong et al. [66] found FMD increased 45 min following 30 mg, 90 mg, and 270 mg dosages of *trans*-resveratrol in 19 overweight/obese individuals with unmedicated borderline hypertension. FMD significantly increased compared to placebo following each of the three dosages, while baseline arterial diameter remained unchanged. Though there was no difference in FMD between the three dosages, there was a significant ($p < 0.01$) though weak ($r^2 = 0.08$) linear relationship between plasma resveratrol concentration and FMD. The authors do not thoroughly discuss this relationship (presented in Fig. 2 of their manuscript), but it appears that most individuals experienced a similar increase in FMD across multiple plasma concentrations, while a few individuals exhibited a much stronger dose-dependent response. This further emphasizes the wide between-subject variability in response to resveratrol supplementation.

Kennedy (2010) found that 500 mg *trans*-resveratrol supplementation increased cerebral blood flow and hemoglobin status using near infrared spectroscopy in healthy young adults during a series of mental tasks. This increase remained significant over placebo for nearly the entire period of 45 to 81 minutes following administration. Similarly, Kennedy also found 250 mg *trans*-resveratrol to increase cerebral blood flow compared to placebo, though less dramatically and at fewer time points than the higher dose, suggesting a dose-dependent action of resveratrol for improving cerebral blood flow. Despite increased blood flow in both groups, resveratrol did not enhance cognitive function. Discrepancy in the existence of dose-dependent effects between Kennedy and Wong may be attributed to differences in dependent variables and/or dosage. Wong's highest dosage (270 mg) was similar to Kennedy's lowest dosage (250 mg), and it is possible that a higher dosage would have produced a greater FMD response in Wong's data set.

9 Hepatic metabolism

Previous research has suggested resveratrol can alter cytochrome p450 (CYP) enzyme activity, which can theoretically alter the metabolism of other drugs, as well as the activation and detoxification of carcinogens. To date, there has only been one published study that has investigated this in human subjects. Chow et al. [31] observed that 1 g of resveratrol taken daily for 4 weeks induced CYP1A2 activity and inhibited CYP3A4, CYP2D6, and CYP2C9 activity (measured through validated indices using probe drugs) in 42 healthy adults. It is uncertain how the induction of CYP1A2 would ultimately affect health, as it is responsible for both activating and detoxifying carcinogens. Inhibition of the three other CYP's may affect drug metabolism and therefore alter efficacy. While CYP2C9 activity was inhibited across the spectrum of subjects, CYP3A4 and CYP2D6 activity were only significantly reduced in those with the greatest baselines values and CYP1A2 was induced in those with the lowest baseline values. Likewise, lymphocyte GST-π did not show any significant changes in the group as a whole, but it was significantly increased in individuals with low baseline values. These data demonstrate resveratrol's effects are not necessarily universal, but rather dependent on the physiologic status of an individual, which may also depend on genotype.

10 Current limitations to human clinical trial data

Given the thousands of publications investigating resveratrol in laboratory models, it is rather surprising so few studies have evaluated the efficacy of resveratrol in humans. In part, this may be attributable to the pharmaceutical industry's reluctance to promote resveratrol, or any natural compound, in combating chronic diseases which may be otherwise targeted through more profitable proprietary drugs [67]. Though limited data are available on resveratrol's efficacy in treating many chronic diseases in humans, clinical trials evaluating the effects of resveratrol on cancer are conspicuously absent from the published literature. Resveratrol has shown much promise in treating cancer in laboratory animals and in vitro human cell studies [68–70], yet there is still a large void in human research. This may soon change, as six of the clinical trials currently listed for resveratrol on www.clinicaltrials.gov (Table 2 in Supporting Information) include cancer patients as a target population. While data on cancer treatment from laboratory animal data

Table 1. Summary of peer review published clinical trials

Authors	Participants (*N*)	Objective	Form of Resveratrol	Dose	Outcome
Almeida et al. [32]	Healthy men (20) and women (20)	Bioavailability from resveratrol supplement	25, 50, 100, or 150 mg capsules	Multiple; 6 x/day at 4 h intervals for 13 doses	C_{max} more than doubled in 25 and 150 mg between 1st and 13th doses. C_{max} of 150 mg grp was 63.8 μg/L following 13 days of administration. Bioavailability was higher after morning administration
Boocock et al. [29]	Healthy men (18) and women (22)	Bioavailability from resveratrol supplement	0.5, 1, 2.5 or 5 g capsules	Single	0.5 g dose resulted in 24-h mean plasma concentration of 8.36 μg/L, with a C_{max} of 72.6 μg/L at 0.83 h following administration
Brasnyo et al. [57]	Diabetic men (19)	Diabetes and oxidative stress	5 mg	Twice daily for 4 wk	Decreased glucose, increased time to glucose peak, and decreased insulin resistance following a meal. Increased Akt phosphorylation and decreased urinary *ortho*-tyrosine
Brown et al. [30]	Healthy men (22) and women (18)	Bioavailability from resveratrol supplement	0.5, 1, 2.5, or 5 g caplets	Multiple, once daily for 29 days	Plasma C_{max} was 958.6 μg/L following 29 days of 5 g. 2.5 and 5.0 g caused mild to moderate gastrointestinal symptoms
Chow et al. [31]	Healthy men (11) and women (31)	Bioavailability from resveratrol supplement	1 g caplets	Multiple (500 mg caplets); once daily for 28 days	Plasma resveratrol concentration range: 8.3–404.4 μg/L 1 h following supplementation. Resveratrol was well-tolerated
Ghanim et al. [51]	Healthy adults (20)	Oxidative stress and inflammation	Randomized, placebo controlled 40 mg	Daily for 6 wk	Resveratrol's actions on cellular level can influence plasma biomarker measurements associated with inflammation and risk for various diseases
Ghanim et al. [52]	Healthy men (4) and women (6)	Oxidative stress and inflammation	Crossover, placebo controlled. (i) High-fat high-carbohydrate meal with placebo (ii) High-fat high-carbohydrate meal with 100 mg resveratrol and 75 mg grapeskin polyphenols	2 visits, 1 wk apart	Resveratrol increased Nrf-2 binding activity following the meal and increased in mRNA expression of the NQO-1 and GST-π1 genes. Resveratrol attenuated postprandial rise in CD14 and IL-1β mRNA and TLR4 protein in mononuclear cells, while also decreasing plasma endotoxin
Goldberg et al. [25]	Healthy men (12)	Bioavailability from wine consumption	25 mg/70 kg body weight dissolved in 100 mL of white wine, white grape juice, or V8 vegetable juice	Single	Significant differences in bioavailability patterns between matrices, with plasma resveratrol concentration decreasing most rapidly with V8 and least rapidly using grape juice
Gresele et al. [35]	Healthy men (9) and women (11)	Bioavailability from wine consumption	Total polyphenolic concentration: Red wine = 1.8 g/L; white wine = 0.25 g/L	15 d of 300 mL/d white or red wine	Red wine increased plasma resveratrol by 1.0 μg/L, whereas white wine increased plasma resveratrol concentration by 0.6 μg/L
Kennedy et al. [85]	Young healthy men (4) and women (20)	Cardiovascular effects	Double-blind, placebo-controlled, crossover 250 or 500 mg capsules	Single; once daily on 3 separate days	Resveratrol increased cerebral blood flow and hemoglobin but did not enhance cognitive function. Effects were dose-dependent

Table 1. Continued.

Authors	Participants (*N*)	Objective	Form of Resveratrol	Dose	Outcome
Nguyen et al. [95]	Eight colorectal cancer patients	A phase-I pilot study in patients with colon cancer was performed to evaluate the effects of a low dose of plant-derived resveratrol formulation and resveratrol-containing freeze-dried grape powder (GP) on Wnt signaling in the colon	4 grps. (i) $N = 3$: 80 g of grape powder (ii) $N = 2$ 120 g of grape powder (iii) $N = 2$ 20 mg of R+ quercetin (iv) $N = 1$ 80 mg of R+ quercetin (for 2 wk)		These data suggest that GP, which contains low dosages of resveratrol in combination with other bioactive components, can inhibit the Wnt pathway in vivo and that this effect is confined to the normal colonic mucosa
Patel et al. [33]	Prostate and colon cancer patients	Bioavailability from resveratrol supplementation	1 g/day		Prostate tissue contained resveratrol metabolites but no free resveratrol, whereas colonic tissue had considerably more *trans*-resveratrol (674 nmol/g) than metabolites (86 nmol/g)
Vitaglione et al. [36]	Healthy men (14) and women (11)	Bioavailability from wine consumption	300 or 600 mL red wine, consumed after fasting or with meals of varying lipid contents	3.4, 7.5, 33 μg/kg Single	Wide variation in subject responses combined with low bioavailability suggests the combination of polyphenols may account for French Paradox
Walle et al. [41]	Healthy men (3), women (3)	Bioavailability from resveratrol supplementation	25 mg taken orally and intravenously	Single	Absorption is 70% with plasma half-life of 9.2 h. Mostly excreted in urine
Wong et al. [66]	Overweight/obese men (14) and post-menopausal women (5) with borderline hypertension	Cardiovascular effects	Double-blind, randomized, crossover 30 mg, 90 mg, and 270 mg capsules at weekly intervals	Each dose for 1 wk	FMD increased 45 min following 30, 90, and 270 mg dosages of resveratrol

are largely positive, it is noteworthy that one recent study demonstrated resveratrol to decrease liver tumors, while increasing lymphoma and possibly solid tumors [9]. This is consistent with the concern that resveratrol can have pro-oxidant effects, especially in the presence of copper, which is elevated in certain tumors, and that this may exacerbate the effects of cancer. Therefore, resveratrol should be vigorously pursued as a therapeutic agent for cancer patients, but careful consideration should be given to the characteristics of the tumors to be treated.

Resveratrol's ability to combat aging at the cellular level [71–73] may ultimately lead to breakthroughs in geriatric and anti-aging medicine, but the data supporting this in humans are scant. The benefits of resveratrol for memory and prevention of neurodegenerative diseases is well documented in laboratory animals [74–76], and this aspect is only beginning to be explored through a number of ongoing human clinical trials (Table 2 in Supporting Information). Resveratrol has been demonstrated to modulate mitochondrial biogenesis through activating PGC-1α [77, 78], which may ultimately slow the aging process and prevent a number of chronic diseases [79] and improve muscular endurance [80]. Laboratory models have found resveratrol reduces oxidative stress in skeletal muscle following exercise [81] and disuse [82], and suppresses aging-associated decrements in physical performance [83], but does not attenuate sarcopenia [84]. Together, these data demonstrate the importance of examining both physiologic effects and functional outcomes as endpoints in human clinical trials. Unfortunately, it will take years to determine resveratrol's efficacy for improving long-term quality of life in the geriatric population and even longer to establish whether resveratrol can slow the aging process and lower the incidence of chronic disease in humans.

Though initial results for resveratrol clinical trials are promising, the extent of publication bias, if any, is unknown. It is possible that either neutral or negative findings from human clinical trials may be withheld from publication if they could have negative financial consequences to a corporation providing funding for the data. This is exemplified by the termination of Sirtris's clinical trial using a resveratrol formulation, SRT501, whereby adverse events were reported in the mainstream media, but further details have not been made available to the scientific community. A positive result, on the other hand, would likely have been published in detail. As a whole, the current literature suggests that resveratrol is safe and may promote beneficial changes in health, although further research is necessary. This review identified six peer-reviewed publications [31, 51, 52, 57, 66, 85], one research announcement [58] and one major professional presentation [59] (that has not yet been published in a peer-reviewed form) that measured end points beyond bioavailability and safety, with the longest study being 6 wk in duration. While findings of improved insulin resistance, blood flow, and decreased oxidative stress and inflammation combined with excellent short-term safety point to a promising future, there is no way of knowing if these will translate into long-term health benefits until well-controlled studies are performed.

One of the most challenging aspects of evaluating resveratrol's efficacy in human clinical trials is the wide variety of formulations used. The human trials that examine specific health benefits include doses ranging from 5 mg to 5 g, with some supplements containing additional compounds with putative synergistic effects, and others using pure resveratrol (Table 1). In many cases, the other compounds present in the matrix used to deliver resveratrol may enhance its action, or produce their own effects [86]. For instance, 270 mg *trans*-resveratrol [66] and 600 mg of grapeskin extract containing < 50 mg *trans*-resveratrol [87] have been found to comparably increase FMD of the brachial artery one hour following consumption, whereas 90 mg *trans*-resveratrol [66] tends to have a smaller effect. Ghanim's two studies illustrate this point in that six weeks of *P. cuspidatum* supplementation did not significantly alter either TLR4 mRNA or protein expression [51], whereas one meal with a resveratrol and grapeskin polyphenol supplement significantly increased TLR4 protein expression [52]. The differing dosages of resveratrol, synergistic compounds, and timing and duration of supplementation could have all influenced the results, but the relative contributions of these factors are unknown.

Additionally, human clinical trials currently focus on resveratrol's ability to induce physiologic benefits. While this is extremely important, it is also necessary to evaluate comparative efficacy between resveratrol and other compounds. For instance, Ghanim et al.'s report that resveratrol reduces postprandial plasma concentrations of endotoxin is an exciting finding, but the authors also show that orange juice has the same effect [52]. For these reasons, human clinical trials with any natural product should have a major focus on comparative efficacy, once the optimal dosage and synergistic formulation have been determined for a given physiological outcome. It is important to note that studies using healthy subjects may not fully demonstrate resveratrol's true potential. This is most notable from Chow et al.'s study [31], which demonstrated that those towards the unhealthy end of the spectrum showed improvement for many variables, in contrast to individuals with healthy baseline values, who did not show any change. Therefore, resveratrol may be particularly useful for improving individuals with certain pathologies, and it may also prove beneficial in preventing a number of chronic conditions, even if it falls short of producing the superhuman changes that some advertisements might suggest.

11 Research in progress

Several clinical trials of either supplemented or dietary (e.g. grapes, grape juice, peanut butter) resveratrol are currently at various stages of completion. For example, a key term search using "resveratrol" in www.clinicaltrials.gov revealed 30 studies at different stages, involving various

forms and dosages of resveratrol (retrieved April 19, 2011). More specifically, 7 studies were active but not yet recruiting 8 studies were active and recruiting, 10 studies were completed, 1 study terminated, and 4 studies with unknown status (i.e. information has not been updated recently) (see Table 2 in Supporting Information for a more detailed description of these studies). It is worthy to note that 4 trials classified as resveratrol studies are not specifically examining the effects of a supplement, but rather a resveratrol containing product, such as grape juice, grapes, and peanuts. We also identified six published research abstracts [59, 88–92] which report preliminary findings from additional human clinical trials with resveratrol, though these have not yet undergone peer review.

Similar to the published research described in the sections above, the study designs for upcoming trials (e.g. dosages/formulations of resveratrol, length of trial) vary greatly, with doses as high as 7.5 g in healthy adults [93]. A main limitation and criticism of the clinical resveratrol research is a lack of trials examining the longer-term health effects of resveratrol. It is our hope that the recently announced one-year randomized double-blind clinical study sponsored by the Danish Council for Strategic Research to investigate resveratrol supplementation on the management of metabolic syndrome, osteoporosis, and chronic inflammation will begin to address this important research question [94]. In summary, as we anxiously await the results of these trials, further controlled clinical trials are required to determine the preventive and therapeutic efficacy of either dietary or supplemented resveratrol.

12 Summary and recommendations

The emerging data from human clinical trials confirms what the past decade of in vitro and laboratory animal models have suggested; resveratrol has considerable potential to improve health and prevent chronic disease in humans. We believe the evidence is sufficiently strong to conclude that a single dose of resveratrol is able to induce beneficial physiologic responses, and that either weeks or months of resveratrol supplementation produces physiologic changes that are predictive of improved health, especially in clinical populations with compromised health. However, it is not yet certain if long-term resveratrol supplementation will maintain these physiologic benefits to ultimately impact the incidence of chronic disease or extend lifespan, and the small number of human clinical trials remains dwarfed by the thousands of basic science experiments. Nonetheless, we believe it is possible that healthy individuals may still benefit from resveratrol's potential to delay or prevent age and lifestyle induced decrements in health, though considerable research is needed on this front. To further evaluate resveratrol's potential for widespread use in human medicine, we recommend continued research exploring a gamut of physiologic responses in humans, ranging from gene expression through clinical measurements and health outcomes. Future research should aim to:

(i) Compare different dosages and/or formulations of resveratrol, in terms of both efficacy and bioavailability. The use of a single dosage or formulation does not readily help to identify the optimal dosage or synergistic combination to achieve a given outcome, or the target plasma concentration required to achieve this outcome in humans.

(ii) Examine comparative efficacy of resveratrol to alternatives for a given outcome/treatment. For resveratrol to be considered a serious option in the prevention and treatment of chronic disease, it is critical to determine if resveratrol is superior to existing therapies in terms of cost, safety, and/or efficacy.

(iii) Determine if resveratrol can have either additive or synergistic effects in combination with other therapies. Much of the current research has focused on resveratrol as a stand-alone therapeutic agent, however, it is possible that resveratrol supplementation may synergistically enhance existing therapeutic devices or compounds.

(iv) Study the effects of long-term resveratrol supplementation. The acute effects of resveratrol are evident, but it is not yet clear how this relates to long-term health. Additionally, it is unknown how long it takes for the effects of resveratrol to plateau and if tachyphalaxis (a rapid decrease in responsiveness after chronic exposure) occurs.

(v) Further determine the activity of resveratrol's metabolites. Human clinical trials have generally concentrated on attaining targeted concentrations of free resveratrol, but the possibility that resveratrol's metabolites are bioactive warrants further consideration.

(vi) Determine what genetic factors account for differences in bioavailability and physiologic responses to resveratrol between individuals. As medicine moves to more individualized approaches, it will be increasingly valuable to know whether an individual is likely to respond to resveratrol favorably or not.

Conflict of interest statement: *James M. Smoliga and Joseph A. Baur have no conflicts of interests to declare. Heather A. Hausenblas is a scientific advisor for ResVitale, Inc., which is a nutraceutical company that manufactures resveratrol supplements.*

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