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Vang, Ole

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What is new for resveratrol? Is a new set of recommendations necessary?

Ole Vang

Department of Science, System, and Models, Roskilde University, Roskilde, Denmark

Address for correspondence: Ole Vang, Department of Science, System and Models, Roskilde University, Universitetsvej 1, DK-4000 Roskilde, Denmark. ov@ruc.dk

Numerous scientific papers have suggested health-promoting effects of resveratrol, including claims in the prevention of diseases such as coronary heart disease, diabetes, and cancer. Therefore, it was proposed that the scientific community needed to express recommendations on the human use of resveratrol. Such recommendations were formulated after the first international resveratrol conference in Denmark, Resveratrol2010. The working group stated that the evidence was "not sufficiently strong to justify recommendation for the chronic administration of resveratrol to human beings, beyond the dose which can be obtained from dietary sources." It was a disappointing conclusion relative to the positive claims about the therapeutic potential of resveratrol made by the media. However, since 2010, results from the first clinical trials on resveratrol have been made available. Because of these emerging results, it is necessary to formulate updated versions of the recommendations.

Keywords: resveratrol; clinical trials; human use; human health

Introduction

Resveratrol is a naturally occurring stilbene, colloquially known as "red wine medicine." Resveratrol is a chemically simple compound, but various resveratrol derivatives, as well as dimeric, trimeric, and tetrameric forms, are found in nature. Although recent studies have explored these resveratrol derivatives, the present review is focusing on resveratrol only.

Resveratrol has received much attention in public and scientific communities, and a set of recommendations in relation to human consumption was formulated at Resveratrol2010, the 1st International Conference on Resveratrol and Health (Helsingør, Denmark). The aim of the present review is to show the relevance of these recommendations in 2010 and to discuss the necessity of formulating a new set of recommendations at the Resveratrol2012 meeting in Leicester, December 2012.

When Takaoka first published the existence of resveratrol in *Veratrum grandiflorum,*[1] very few noticed this observation, until some biological effects observed from extracts of *Polygonum cuspidatum* were linked to its high content of resveratrol[2] and resveratrol was found in edible sources such as grapes and wine.[3] The major findings of biological responses to resveratrol (Fig. 1) can be characterized as (1) Frankel *et al.* found in 1993 that resveratrol modulates LDL levels, indicating a potential reduced risk for development of coronary heart disease;[4] (2) the chemo-preventive effect of reseveratrol in a mouse skin cancer model was shown by Jang *et al.*[5] in 1997; (3) a major focus was prompted by the observation that resveratrol extends the life span of yeast;[6] (4) the effect of resveratrol on obesity and diabetes was identified by two groups in 2006.[7,8] A few phase I clinical trials focusing on the pharmacokinetics of resveratrol were published before 2010, but since then, the number of clinical trials exploring the biological effects of resveratrol has increased significantly.

Scientific focus on resveratrol

The scientific focus on resveratrol has followed the profile of curcumin and, to a lesser extent quercetin (Fig. 1), whereas several other naturally

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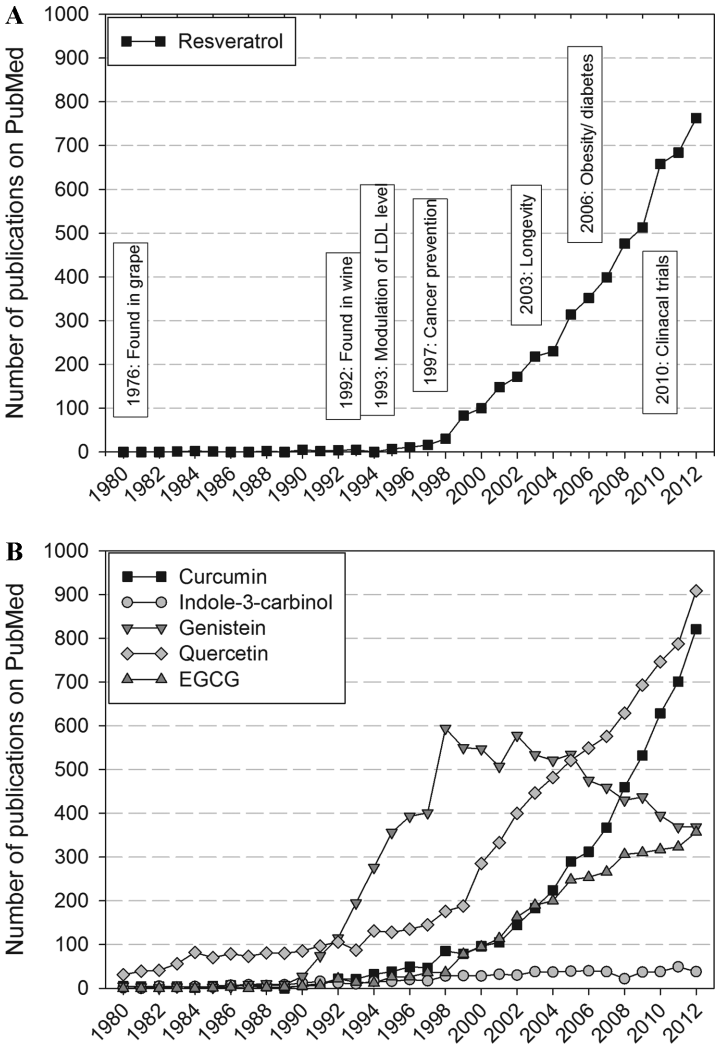

Figure 1. Increasing scientific interest on the biological effects of resveratrol and other naturally occurring bioactive substances. The number of hits obtained by searching (A) "resveratrol" and (B) "curcumin," "indole-3-carbinol," "genistein," "quercetin," or "epigallocatechin-3-gallate" (EGCG) for each year from 1980 to 2012 on PubMed (http://www.ncbi.nlm.nih.gov/pubmed?db=pubmed) is shown.

occurring bioactive substances, such as indole-3-carbinol (from cruciferous vegetables) or genistein (mainly from soybeans) have shown quite different profiles of interest. The chemopreventive effect of indole-3-carbinol was proposed in animal models in 1978 by Wattenberg *et al.*,[9] but the annual number of scientific publications has been quite constant over the years. The scientific interest in the flavonoid quercetin was also significant in the 1980s and 1990s, with an increased interest during the first decade of 2000. Comparisons of publication frequency indicate a more specific increased scientific interest in resveratrol and curcumin relative to many other potentially health-promoting naturally occurring compounds. Further, the interest for resveratrol and curcumin has not yet reached a plateau, as observed for genistein.

The total number of scientific publications indexed in PubMed has increased in the period analyzed (from about 280,000 in 1980 to about 910,000 in 2012). Even when taking this total increase of publications into consideration, the increase in publications focusing on resveratrol or curcumin is very significant. The scientific focus on

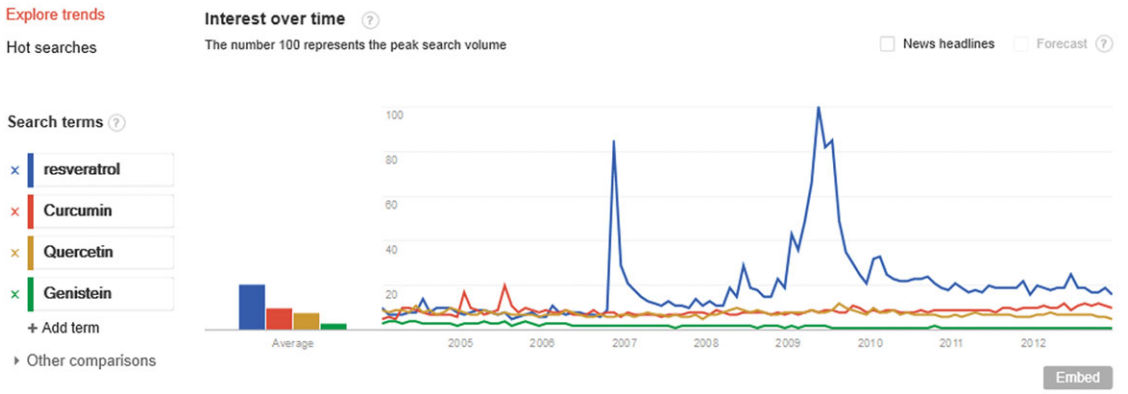

Figure 2. Relative search activity on the Internet using Google. The search activity is displayed by using Google Trends (http://www.google.com/trends/explore) in the period of January 2004–December 2012. The search words were "resveratrol," "curcumin," "genistein," and "quercetin."

resveratrol is high relative to other naturally occurring compounds. By December 2012, the accumulated number of PubMed-identified publications focused on resveratrol was comparable with curcumin (both around 5400 publications), nearly half as many as genistein or quercetin (both around 9600 publications), and significantly more than well-known bioactive compounds like apigenin, epigallocatechin-3-gallate, lycopene, ellagic acid, naringin, sulforaphane, and dialylsulfide (ranging between 300 and 3000 publications).

Resveratrol claims

Nearly all data concerning the biological effects of resveratrol up to 2010 were generated *in vitro* or in animal models. Therefore, the health significance of resveratrol in humans has been unclear, even though the substance has been popularly claimed as a treatment agent for a range of cancers and as an antiaging compound. Such claims are not supported by strong scientific evidence. Translating specific scientific messages from experimental laboratories to the general public is a very difficult and complex task. It is in general a major challenge that most of the statements concerning the health effects of resveratrol are based on animal studies and mechanistic studies (*in vitro*), and details relevant to experimental setup and models are often lost in translation from the scientific literature to the mass media.

In addition, there are a number of examples where the outcome from *in vitro* experiments differs from the response in experimental animals or from the effects observed in humans. As one recent example, resveratrol inhibited cell proliferation and invasiveness of ovarian cancer cells *in vitro,* but did not exhibit this effect on the same cancer cells *in vivo.*[10] Therefore, one has to be careful when translating data from *in vitro* experiments or animal experiments to humans. On the other hand, as will be discussed later, the options for performing the optimal or correct experiments in humans to prove the effect of substances like resveratrol are rather limited.

The focus on resveratrol in the public domain

Scanning Internet search activities can provide a relevant parameter of interest in the public domain. A search using Google Trends (http://www.google.com/trends/) provides the relative search activities using Google search machinery since 2004 (Fig. 2). In the public domain as well as in the scientific community, there is a large interest for information on resveratrol, which peaked in late 2006 and during 2009. The peak in interest in 2006 can be related to the scientific breakthroughs that year by Baur *et al.*[7] and Lagouge *et al.*,[8] whereas the peak in 2009 was likely because of a high public focus on resveratrol by trendsetters like Oprah Winfrey. The interest has, since 2009, generally been at a much higher level compared to curcumin, genistein, or quercetin. In the same time period, the number of websites dedicated to resveratrol has increased exponentially, with significantly more sites focusing on resveratrol than curcumin.

Overall conclusions from the working group at Resveratrol 2010

By 2010, in light of the increasingly large number of publications, the growing hype around resveratrol, and the large number of unsupported claims about its health benefits propagated by the media, there was a need to sum up all the available scientific data on resveratrol and to formulate recommendations for the human use of resveratrol and for research in the coming years. As a follow-up from Resveratrol2010, the 1st International Conference on Resveratrol and Health (Helsingør, Denmark), such recommendations were formulated and published in *PLoS One* in 2011.[11] By considering the knowledge gained as a result of the formulation of these recommendations, we can evaluate their significance and consider whether the recommendations need to be updated.

The overall conclusion from the Resveratrol2010 working group was presented as a double statement: "The published evidence is not sufficiently strong to justify a recommendation for the administration of resveratrol to humans, beyond the dose which can be obtained from dietary sources," but "animal data are promising in prevention of various cancer types, coronary heart diseases, and diabetes, which strongly indicate the need for human clinical trials."[11] The major challenge at the time of formulation of the recommendations was that no human clinical trials were available, even though a few were published in the few months after the conference. On the basis of the animal data alone, the working group could not support recommendations for resveratrol use in humans at higher concentrations than those obtained through the diet. The translation from animal to human is not straightforward because of potential differences between experimental animals (rodents) and humans in the bioavailability and mechanisms of action of resveratrol. A careful statement was chosen, which was supported by the animal experiments completed and published at that time.

The evaluation was based on the following five test questions:[11]

1. Can resveratrol be recommended in the prevention or treatment of human diseases?
2. Are there observed side effects caused by the intake of resveratrol in humans?
3. What is the relevant dose of resveratrol?
4. What valid data are available regarding an effect in various species of experimental animals?
5. Which relevant (overall) mechanisms of action of resveratrol have been documented?

Questions 1–3 focus on the effects of resveratrol in humans, whereas question 4 concerns the effects of resveratrol in animal models. The first part of the overall conclusion addressed 1–3, stating that administration of extended levels of resveratrol to humans cannot be recommended. As long-term exposure trials with resveratrol had not been performed at that time; there were neither direct data on side effects nor data from humans that could support an estimated dose of resveratrol for human use. No-observed-adverse-effect levels for maternal toxicity and embryo–fetal development are around 750 mg resveratrol/kg/day in rats, which has been translated to a safe daily dose of 450 mg for a 60 kg person.[12] This estimate was based on one long-term study in one species and a study in a second species is necessary.

Although the working group could not recommend a specific dose of resveratrol for human intake because health-promoting effects had not been investigated in humans, it was also necessary to state that no significant side effects have been observed in animal studies or in short-term human studies when very high doses of resveratrol were used (e.g., 2.5–5 g/day).

Advantages and challenges of the recommendations

These formal recommendations on the human use of resveratrol summarize the existing body of knowledge in a few lines, assuming that the members of the working group have done their best to compile the most valid data in the recommendations. The conclusions may be used directly by medical doctors to address questions from their patients about whether dietary supplementation with resveratrol may prevent lifestyle diseases. The recommendations may be used also by a well-oriented layperson, relevant target person, or member of the media who needs a source for presenting valid scientific information on resveratrol. The recommendations also provide goals for the future of research needed in the field of resveratrol to answer the question of human use.

Ann. N.Y. Acad. Sci. 1290 (2013) 1–11

On the other hand, such short brief statements may well be too simple to express the nuances relevant to the diversity of biological effects of resveratrol. Resveratrol seems to have numerous cellular targets. Not all of these targets are likely to be equally relevant to any one disease. Problems relevant to issues like resveratrol administration may also be masked by such brevity. In the attempt to make clear recommendations, the working group may have made the same error of oversimplification of which we accuse the media in relation to the effects of resveratrol.

How was the message received in the scientific and general societies?

Scientific relevance can be measured by the number of citations of the publication in *PLoS One*.[11] Using the metric analysis at the *PLoS One* article homepage (http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0019881), where the paper was ranked among the top five resveratrol papers published in *PLoS One* (December 2012) in relation to number of citations and the usage of the article (number of downloads), $1^{1}/_{2}$ years after publication. In contrast, the recommendations have only rarely been cited on the Internet outside of scientific publications. However, claims found on the Internet in relation to the health effects of resveratrol appear to be much more balanced at present, indicating that the formulation of the recommendations has had an effect on the delivery of the information on resveratrol.

Clinical trials testing the health-promoting effect of resveratrol: what has happened since September 2010?

One of the central recommendations from the working group at the Resveratrol2010 conference was to initiate clinical trials to evaluate the health effects of resveratrol in humans, and many such trials have been published since September 2010. Table 1 lists the published trials up to the end of 2012 testing the effect of pure resveratrol, whereas Table 2 lists trials of resveratrol as part of a mixture with other potentially bioactive compounds. Translating the effects of resveratrol from studies using a mixture containing resveratrol is not possible without data from experiments where resveratrol is used in a pure form. On the other hand, exclusively evaluating trials with pure resveratrol will not reveal relevant combinatory effects of resveratrol with other bioactive compounds.

The specific doses of resveratrol used in the various experiments differ dramatically. Using pure resveratrol, daily doses as low as 5 mg twice daily for four weeks showed an effect on insulin sensitivity,[13] and 10 mg/day for three months produced increased flow-mediated dilation.[14] Daily doses up to 2.5 or 5 g resveratrol have been used in several trials for up to 29 days with effects on the relevant biochemical parameters.[15,16] Adverse effects have been observed using such high resveratrol levels: therefore the daily dose during long-term exposure to pure resveratrol should be kept below 1–1.5 g.

Both sexes have been included in the trials. Only a few trials have included young healthy subjects,[17] as most trials have focused on subjects with a disease or increased risk for the development of the disease. Designing trials using subjects with pre-disease status introduces difficulties in demonstrating preventive effects, as several disease stages may have already initiated even though the disease is not manifest. Therefore, long-term clinical trials including young subjects will need to be performed to assess preventive effects, but it will be challenging to demonstrate relevant effects of resveratrol in such low-risk cohorts.

The duration of the trials varies from acute exposure,[18,19] to a few days (5–8) of exposure,[20,21] to up to one year.[22] Most trials expose the subjects to resveratrol in time frames of 1–3 months. The relatively short duration of the trials is a challenge, as they permit analysis of therapeutic but not preventive potential. Without taking the practical and economical aspects of such studies into consideration, a trial to show a preventive effect of resveratrol should run for a minimum of one year. It is obvious that such trials are expensive and not easily funded, but they will be necessary to obtain relevant information about the preventive potential of resveratrol.

Most of the clinical trials, particularly the larger ones, have focused on the effects of resveratrol on cardiovascular disease and diabetes and on inflammation status. The strongest effects were observed in subjects with enhanced levels of disease-related markers,[13,14,19,23–25] but some trials did not show any effect of resveratrol,[26] even though study participants had high-risk profiles.[27] Trials examining resveratrol in relation to cancer have been small in

Table 1. Clinical trials analyzing biological effects of resveratrol. The biological effects of resveratrol (Resv) alone have been studied in the trials shown in the table. The various effects are divided into groups depending on the major scope of the trial

Number of subjects	Type of study	Dose and duration	Effect of Resv	Reference
		Cognitive/brain function/emotional		
22	Double-blind, placebo-controlled, crossover study	250 or 500 mg Resv in a single dose	Cerebral blood flow ↑ Oxygen extraction ↑	18
		Cancer		
20 colorectal cancer patients	Open-label study	0.5 or 1.0 g daily doses of Resv for 8 days	Tumor cell proliferation ↓	21
40: 18♀, 22♂	Open-label study	0.5, 1, 2.5, or 5 g Resv/day for 29 days	IGF-I ↓ IGF-binding protein-3 ↓	15
42: 31 ♀, 11 ♂	Open-label study	1 g Resv/day for 4 weeks	Level of specific cytochrome P450 enzymes ↓ GST activity and GST-π →	28
9 subjects, stage IV colo-rectal cancer, w. hepatic metastases	Randomized (2:1) double-blind study	5 g Resv/day for 10–21 days	Hepatic apoptosis ↑	16
		Metabolic syndrome/insulin sensitivity/NAFLD/diabetes		
11 overweight ♂	Randomized, double-blinded crossover study	150 mg Resv/day in 30 days	Sleeping and metabolic rate ↓ Fat in liver ↓ Circulating glucose ↓ Triglycerides ↓ Inflam. markers ↓ Systolic blood press. ↓ Lipolysis in adipose tissue ↓ Plasma fatty acids ↓ Glycerol in the postprandial state ↓	23
Nonobese, postmenopausal ♀	Randomized, double-blind, placebo-controlled study	75 mg Resv/day for 12 weeks	Body composition → Resting metabolic rate → Plasma lipids → Inflammatory markers → Adipose tissue insulin sensitivity →	26
24 obese, healthy ♂	Randomized, double-blinded, placebo-controlled, and parallel-group design	3 × 500 mg Resv/day for 4 weeks	Insulin sensitivity → Endogenous glucose production → Turnover and oxidation rates of glucose → No effect on blood pressure → Resting energy expenditure → Oxidation rates of lipid → Ectopic or visceral fat content → Inflammatory and metabolic biomarkers →	27

Continued

Ann. N.Y. Acad. Sci. 1290 (2013) 1–11

Table 1. *Continued*

Number of subjects	Type of study	Dose and duration	Effect of Resv	Reference
19 type 2 diabetic patients	Randomized, double-blinded, and placebo-controlled study	5 mg Resv b.i.d. for 4 weeks	Insulin sensitivity ↑ Oxidative stress ↓	13
10 older people w/ moderately insulin resistance	Randomized, open-label study	Daily dose of 1, 1.5, or 2 g Resv for 4 weeks	Peak post-meal glucose ↓ 3 hour glucose ↓ Post-meal insulin ↓ Insulin sensitivity ↑	24
		Cardiovascular		
40	Randomized, double-blinded and placebo-controlled study	10 mg Resv/day in 3 months	Flow-mediated dilation ↑ Left ventricular diastolic function ↑ LDLc ↓	14
19	Randomized, double-blinded, placebo-controlled, and crossover study	A single acute dose of 0, 30, 90, and 270 mg Resv	Flow-mediated dilation ↑, dose dependent	19
87 in three groups	Randomized, double-blinded, active-controlled,	20 mg Resv/day ± calcium fructoborate for 60 days	Inflam. markers ↓ LDLc ↓ HDLc ↑ Triacylglycerols ↓ Quality of life ↑	25
		Skin		
20 patients (8♀, 12♂) with facial acne vulgaris	Single-blinded, placebo-controlled study	10 μg/g of gel. Applied daily for 60 days	GAGS score: ↓	29

GAGS, global acne grading system; GST, glutathione S-transferase; HDLc, high-density lipoprotein-cholesterol; IGF-I, insulin-like growth factor-1; LDLc, low-density lipoprotein-cholesterol; ↑, increased response; ↓, decreased response; →, no significant effect.

size and have focused on the therapeutic effect of resveratrol in relation to cancer markers. Ironically, such therapeutic studies have not really been performed in experimental animals, where studies have focused on the preventive effect of resveratrol.

To some extent, is it more meaningful to estimate the effect of resveratrol when it is part of a dietary matrix. It is likely also easier to get such trials accepted, as supplementations are more natural and the exposure to resveratrol is generally lower in these trials. Among the published trials where resveratrol is part of a matrix, medium-high levels of resveratrol have been used, but these have not shown statistically significant effects: in one trial, a 100–400 mg resveratrol exposure reduced inflammation[30] and increased flow-mediated dilation,[31] but these parameters were not found changed in other trials using the same levels of resveratrol.[20,31] However, a set of trials where the subjects were exposed to low amounts of resveratrol for six months and one year did show significant effects on cardiovascular biochemical markers.[22,32]

Beyond these major diseases, the effect of resveratrol on cognitive or brain function has been only marginally investigated,[17,18] while a significant effect of resveratrol on skin was found in two studies.[29,33]

Do we need a new set of recommendations for the use of resveratrol?

On the basis of the human trials focused on the health-promoting effects of resveratrol conducted during the last two years, the set of recommendations formulated in September 2010 have to be updated. The clinical trials are still small relative to

Table 2. Clinical trials analyzing biological effects of resveratrol as part of a mix. The biological effects of resveratrol (Resv) as part of a mixture have been studied in the trials shown in the table. The various effects are divided into the major groups depending on the major scope of the trial

Number of subjects	Type of study	Dose and duration	Effect of Resv	Reference
Cognitive/brain function/emotional				
40 subjects in two groups	Randomized, double blinded, placebo-controlled study	Daily 46 g grape powder with 1.75 mg Resv/kg (0.08 mg/day) for 45 days	Mood →	17
Cancer				
8 colon cancer patients	Open-label study	3.9 or 15.6 mg/day Resv with quercetin	Wnt signaling in colon cancer cells →	34
8 colon cancer patients	Open-label study	Freeze-dried grape powder with Resv (corresponding to 0.073 and 0.114 mg Resv/day)	Wnt signaling in colon cancer cells → In normal cells ↓	34
12: 7 ♀, 5 ♂	Open-label study	Food supplement containing 2 mg Resv + 100 mg grape extract 3 times daily for 5 days	DNA stability → Redox status → Inflammation →	20
36 ♀	Randomized crossover study	237 mL red or white wine for 21 days. The level of Resv is not shown	Red relative to white wine: Testosterone ↑ Sex hormone binding globulin ↑ Luteinizing hormone ↑	35
30 healthy subjects	Open-label study	1/3, 2/3, or 1 lb of red grapes per day for 2 weeks, but the level of Resv was not shown	Colonic mucosal cell proliferation ↓ Cyclin D1 and CD133 ↓	36
Inflammation				
20	Randomized, placebo controlled study	*Polygonum cuspidatum* extract containing 40 mg Resv/day for 6 weeks	ROS ↓ Inflammatory markers ↓ HDL, LDL → Insulin, glucose →	37
10 subjects (31 ♀, 11 ♂) given a high-fat, high-carbohydrate diet	Crossover and placebo-controlled study	100 mg of Resv + 75 mg polyphenols from a grape extract/single administration	TLR4 ↓, CD14 ↓, SOCS3 ↓, IL-1β ↓, Keap-1 ↓ Nrf-2 binding activity ↑, expression of NQO-1 and GST-P1 ↑	30
36 ♂, with BMI between 25.5 and 35.0 and a low-grade inflammation	Randomized, double-blind, placebo-controlled, crossover study	Anti-inflammatory dietary mix (AIDM) containing Resv (25.2 mg/day for 5 weeks	Inflammatory markers → Adiponectin ↑ Adipose tissue inflammation ↓ Endothelial function ↓ Liver fatty acid Oxidation ↑	38

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Ann. N.Y. Acad. Sci. 1290 (2013) 1–11

Table 2. *Continued*

Number of subjects	Type of study	Dose and duration	Effect of Resv	Reference
Metabolic syndrome/insulin sensitivity/NAFLD/diabetes				
34 people with metabolic syndrome	Randomized	100 mg Resv (Longevinex®) daily for 0–3 or 3–6 months	Insulin resistance → Lipid profile → Inflamm. markers →	31
32 obese in 3 groups (17♀, 15♂)	Randomized, single-blinded, with sequential design	1 capsule/day of 150 mg Resv, 400 mg catechin-rich grape seed extract (CGSE), or 300 mg RTP for 28 days	GSH ↓ Anti-oxid. enzymes → Lipid perxid → oxLDL → 8-OH-dG →	39
Cardiovascular				
75 in 3 groups	Triple-blinded randomized study	Placebo, 350 mg grape extract (GE), 350 Resv-enriched GE (8 mg Resv) for 6 months	LDLc ↓, ApoB ↓, oxLDL ↓ oxLDL/ApoB; ↓ non-HDLc /ApoB ↑	32
150 in 3 groups	Randomized double-blinded placebo-controlled study	Placebo, 350 mg grape extract (GE), 350 Resv-enriched GE (8 mg Resv) for 6 months + double amount for next 6 months	Inflamm. markers ↓ Adiponectin ↑	22
34 subjects with metabolic syndrome	Randomized	100 mg Resv (Longevinex) daily for 0–3 or 3– 6 months	Flow-mediated dilatation ↑ Blood pressure →	31
67 subjects w/ high risk for atherosclerosis	Randomized, placebo-controlled crossover study	272 mL red wine/day (0.82 mg Resv) for 4 weeks	ICAM-1 ↓, E-selectin ↓, IL-6 ↓ Lymphocyte function-associated antigen 1 ↓ Macrophage-1 Receptor ↓ Sialyl-Lewis X ↓ C-C chemokine receptor type 2 ↓	40
Skin				
50: 35♀, 15♂	Randomized, placebo-controlled study	133 mg grape extract (8 mg Resv) /day for 60 days	Moisturization index ↑ Skin elasticity ↑ Skin roughness ↓ Wrinkle depth ↓	33
Fitness and muscle injury				
40 active young adults in two groups	Randomized, double blinded, placebo-controlled study	Daily 46 g grape powder with 1.75 mg Resv/kg (0.08 mg/day) for 45 days	VO_2max → Work capacity → Perceived health status → Inflammation → Pain → Physical function responses →	17

8-OH-dG, 8-deoxy-guanine; ApoB, apolipoprotein B; GSH, glutathione; GST, glutathion S-transferase; HDL, high density lipoprotein; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; oxLDL, oxidized LDL; LDL, low density lipoprotein; ROS, reactive oxygen species; TLR4, Toll-like receptor 4; SOCS3, suppressor of cytokine signaling 3; ↑, increased response; ↓, decreased response; →, no significant effect.

the sample sizes used for testing drugs, and analysis of the possible disease-preventive effect is facing several challenges. To determine potential preventive effects of a dietary compound like resveratrol, long-term exposures of large cohorts of participants in stages of low risk of disease development are needed. The dietary bioactive compounds do not work like typically man-made drugs that have a single high-affinity target, but rather modulate a range of cellular targets with only low affinity. Therefore, the effects of a single compound at low levels are rather small, and one may expect that the biological effects are caused by combined effects of several (or many) dietary bioactive compounds ingested simultaneously. Therefore, the effect of resveratrol may be underestimated when analyzed as a single compound under investigation.

Conclusions: what has been learned from working with the recommendations?

Resveratrol has been the focus of considerable hype in both the general and scientific communities. This hype has propelled research on the compound, but it has also stimulated the propagation of many unsupported claims concerning the putative health benefits of the compound. Therefore, it was necessary in 2010 to formulate a set of recommendations on the use of resveratrol. These have, in general, been accepted well and have contributed to the establishment of a series of clinical trials focusing on the health effects of resveratrol. This high number of clinical trials analyzing the effect of resveratrol demand a new set of recommendations.

Most of these clinical trials have been designed to evaluate the therapeutic effect of resveratrol rather than the disease-preventive effect of the compound. A preventive study needs to expose test subjects before they show any sign of the disease, and then the cohort members have to be treated for a sufficiently long time that a significant amount of subjects in the control group will develop the disease. To get substantial power in the analysis, the number of participants has to be high. Therefore, these trials will be very expensive, and the number of such studies in the future will be low: other models for prevention studies have to be included. The use of the pig as a reliable model will support the prevention experiments in rodents and provide us with necessary knowledge that may not be available in humans.

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Conflicts of interest

The author declares no conflicts of interest.

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