Therapeutic potential of resveratrol: the *in vivo* evidence

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Abstract | Resveratrol, a constituent of red wine, has long been suspected to have cardioprotective effects. Interest in this compound has been renewed in recent years, first from its identification as a chemopreventive agent for skin cancer, and subsequently from reports that it activates sirtuin deacetylases and extends the lifespans of lower organisms. Despite scepticism concerning its bioavailability, a growing body of *in vivo* evidence indicates that resveratrol has protective effects in rodent models of stress and disease. Here, we provide a comprehensive and critical review of the *in vivo* data on resveratrol, and consider its potential as a therapeutic for humans.

Phytoalexin
A toxic compound produced by higher plants in response to infection or other stresses, such as nutrient deprivation.

Caloric restriction
A reduction of calorie intake (typically by 30–40% in rodents) to a level that does not cause malnutrition and that has been shown to increase lifespan and stress-resistance in multiple species.

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Resveratrol (3,5,4′-trihydroxystilbene; FIG. 1) was first isolated from the roots of white hellebore (*Veratrum grandiflorum O. Loes*) in 1940 (REF. 1), and later, in 1963, from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine[2]. Initially characterized as a phytoalexin[3], resveratrol attracted little interest until 1992, when it was postulated to explain some of the cardioprotective effects of red wine[4]. Since then, dozens of reports (FIG. 2) have shown that resveratrol can prevent or slow the progression of a wide variety of illnesses, including cancer[5], cardiovascular disease[6] and ischaemic injuries[7,8], as well as enhance stress resistance and extend the lifespans of various organisms from yeast[9] to vertebrates[10].

The mechanism by which resveratrol exerts such a range of beneficial effects across species and disease models is not yet clear. Attempts to show favourable effects *in vitro* have met with almost universal success, and have led to the identification of multiple direct targets for this compound. However, results from pharmacokinetic studies indicate that circulating resveratrol is rapidly metabolized, and cast doubt on the physiological relevance of the high concentrations typically used for *in vitro* experiments. Further experiments are needed to show whether resveratrol or its metabolites accumulate sufficiently in tissues to recapitulate *in vitro* observations, or whether alternative higher-affinity targets, such as quinone reductase 2 (QR2; also known as NQO2)[11], have the key roles in its protective effects. *In vivo* results have therefore become increasingly important in our attempts to understand how resveratrol is effective in the treatment of disparate diseases.

It is also unclear what conclusion should be drawn from the studies described so far. Are the benefits of resveratrol merely the results of fortuitous interactions with dozens of mammalian proteins? Or is resveratrol acting through a specific genetic pathway that has evolved to increase disease- and stress-resistance? With regard to the latter proposal, there is already ample evidence for the existence of health-promoting pathways that are activated by caloric restriction (BOX 1). It has been known since the 1930s that a severe lowering of caloric intake dramatically slows the rate of ageing in mammals and delays the onset of numerous diseases of ageing, including cancer, cardiovascular disease, diabetes and neurodegeneration[12,13]. It is an attractive hypothesis that resveratrol might use the same pathways activated by caloric restriction in mammals, as it appears to do in lower organisms[9,14]; however, proving this hypothesis will require a better understanding of both processes. This review discusses the effects of resveratrol that have been observed *in vivo* and possible evolutionary explanations, as they relate to the development of human therapeutics, based on either resveratrol itself or new, more potent compounds that mimic its effects.

Resveratrol and cancer

In 1997, Jang[5] and colleagues published a seminal paper reporting the ability of resveratrol to inhibit carcinogenesis at multiple stages. Their finding that topical application of resveratrol reduced the number of skin tumours per mouse by up to 98% triggered research on resveratrol around the world. Systemic administration of resveratrol has since been shown to inhibit the initiation and growth of tumours in a wide variety of rodent cancer models (see Supplementary information S1 (table)). The efficacy of low doses (for example, 200 μg per kg (body weight) daily in a rat model of colon carcinogenesis[15]) suggests

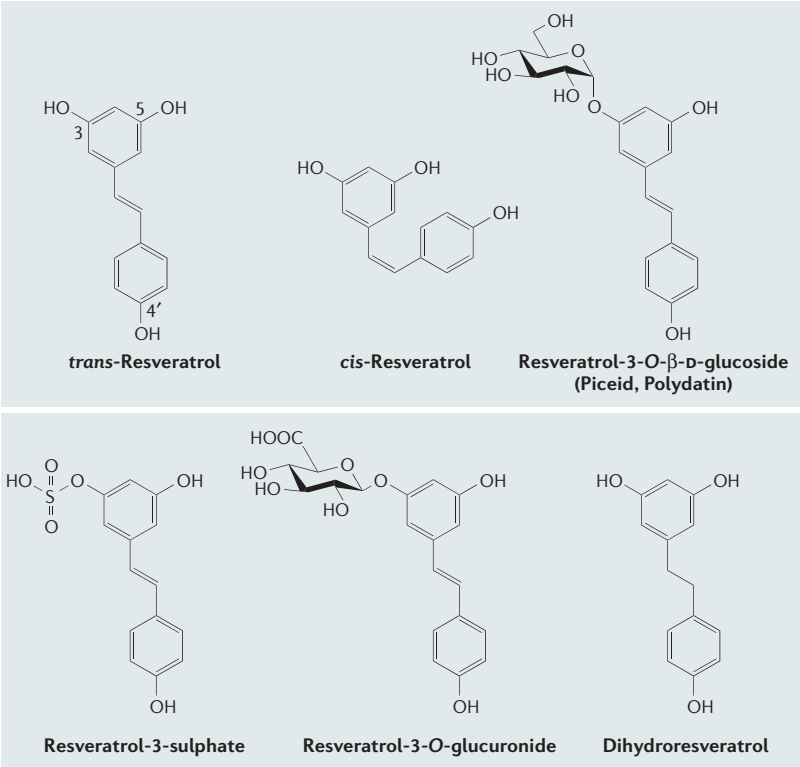

Figure 1 | ***trans*-Resveratrol and related structures.** Piceid is found in grapes and other natural sources of resveratrol. Resveratrol-3-sulphate, resveratrol-3-*O*-glucuronide and dihydroresveratrol are metabolites of resveratrol. The positions of hydroxyl groups are indicated on the parent molecule.

that even the concentration of resveratrol obtained from dietary sources, such as red wine, could be therapeutic in some cases. At higher, but pharmacologically achievable doses, protective effects of resveratrol are more frequently observed, and the results are more dramatic. For example, a daily dose of 40 mg per kg (body weight) increased the survival of mice with subcutaneous neuroblastomas from 0% to 70%[16]. Although most *in vivo* studies strongly support a chemopreventive effect of resveratrol, there are notable exceptions in which no benefit has been observed. For example, administration of 1–5 mg per kg (body weight) daily of resveratrol failed to affect the growth or metastasis of breast cancer in mice, despite promising *in vitro* results[17]. Dosage, delivery method, tumour origin and other components of the diet could all contribute to the efficacy of resveratrol treatment. Overall, *in vivo* studies clearly show great promise for this molecule in the treatment of cancers. Several Phase I clinical trials are currently underway for oral resveratrol in humans at doses as high as 7.5 g per day, including National Cancer Institute-sponsored studies at the University of Michigan, USA, and the University of Leicester, UK (see Further information).

Inhibition of cyclooxygenase and ornithine decarboxylase. Jang[5] and colleagues originally proposed that resveratrol might be an effective chemopreventive agent because it inhibits the enzymatic activity of both forms of cyclooxygenase. Epidemiological evidence shows that long-term inhibition of cyclooxygenase significantly reduces the risk of developing many cancers and deletion of the gene that encodes cyclooxygenase 2 (COX2) is protective in a mouse model of colorectal cancer[18]. Moreover, constitutive expression of this gene in mammary glands or skin promotes carcinogenesis in mice (although a puzzling protective effect was reported for an independent strain in skin)[19]. Resveratrol reduces the total cyclooxygenase activity of tumours and normal tissue *in vivo*[20–22] through moderately selective inhibition of COX1 activity and/or reduction of COX2 at the mRNA level[21,23,24]. *In vitro* studies indicate that transcriptional inhibition of COX2, as well as another important player in carcinogenesis, ornithine decarboxylase (ODC) could be accomplished through inhibition of protein kinase C (PKC)[23,25]. Resveratrol does not directly inhibit ODC activity[26], but reduces its expression *in vivo* and prevents its induction by carcinogens[20,27,28]. Alleles of ODC have been associated with different risk levels for colon cancer[29], and difluoromethylornithine, a direct inhibitor of ODC, suppresses cancer development in animal models[30]. Interestingly, combining difluoromethylornithine with cyclooxygenase inhibitors has been found to prevent tumour development more effectively than inhibition of ODC alone[29]. This implies that resveratrol could slow tumour development through multiple complementary mechanisms.

Inhibition of angiogenesis. Angiogenesis is required to support the growth of most solid tumours beyond a diameter of 2–3 mm. When delivered systemically at a dose of 2.5–100 mg per kg (body weight), resveratrol inhibits tumour-induced neovascularization[31,32] and wound healing[33]. Moreover, resveratrol inhibits vascularization in the corneal micropocket assay in mice at a dose of only 48 μg per kg (body weight) when administered daily[33]. Both cyclooxygenase and ODC promote angiogenesis, and their suppression by resveratrol could have a role in its inhibitory effects on vascularization and tumour growth.

Effects on drug metabolism. Drug metabolism is divided into two phases that involve different enzyme classes. In general, Phase I enzymes, consisting primarily of cytochrome P450s (CYPs) and flavin monooxygenases, are expressed constitutively, although their expression can be induced further. These enzymes oxidize, reduce or hydrolyze foreign molecules to render them more polar and facilitate their excretion. Phase II enzymes include conjugating and antioxidant enzymes that are induced in a coordinated manner to detoxify harmful molecules, including toxic products of Phase I enzymes. Many known chemopreventive agents upregulate Phase II enzymes, and induction of this pathway is considered a promising strategy for cancer prevention, whereas Phase I enzymes, and CYPs in particular, have consistently been implicated in the activation of procarcinogens[34].

Resveratrol modulates the expression and activity of multiple drug-metabolizing enzymes. *In vitro*, resveratrol inhibits the enzymatic activity of various CYPs[35–38] and blocks their transcription through antagonism of

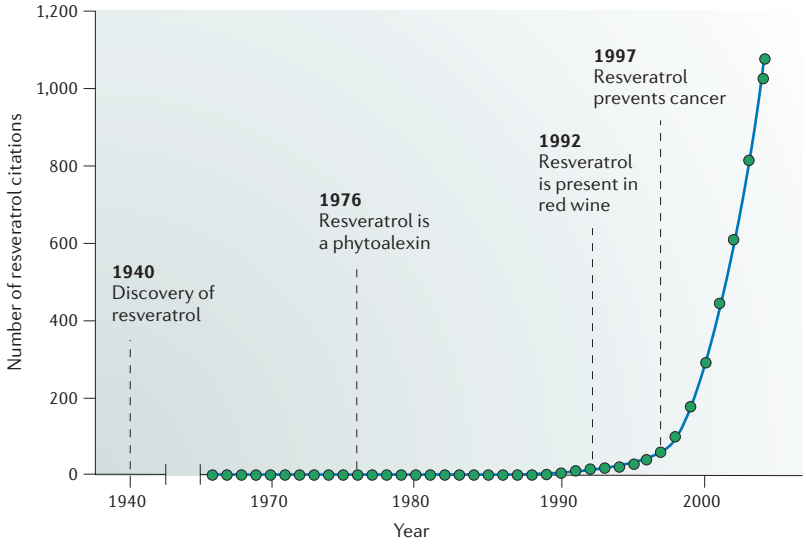

Figure 2 | **Resveratrol citations appearing on PubMed as a function of year.** The PubMed database was searched using the key word 'resveratrol'. The plot shows the cumulative number of hits identified for each year after the creation of Medline in 1963.

the aryl hydrocarbon receptor (AHR)[39,40], suggesting that resveratrol could cause a reduction in the exposure of cells to carcinogens. However, this same activity could make the development of resveratrol as a potential therapeutic problematic because the inhibition of CYPs could alter the pharmacokinetics of other drugs. For example, coadministration of CYP3A4 inhibitors with terfenadine, cisapride or astemizole (all known substrates) can lead to life-threatening ventricular arrhythmia[41]. Nevertheless, coadministration of resveratrol with the carcinogen benzo[a]pyrene, which is activated by the CYP isoform CYP1A1, was shown to reduce expression of this enzyme and significantly abrogate the damaging effects of benzo[a]pyrene in lung tissue *in vivo*[42]. A second study failed to recapitulate these effects, or reduce tumorigenesis, which the authors speculated might be because an insufficient dose of resveratrol was administered[43]. Further studies will be required to confirm antagonism of the AHR *in vivo* and to determine whether resveratrol also inhibits CYPs directly.

Resveratrol has been shown to induce expression of Phase II enzymes *in vitro*[44], and haem oxygenase 1 (REF. 45) and quinone reductase 1 (QR1)[46] *in vivo*, resulting in improved tolerance of ischaemia and increased resistance to menadione (vitamin K3) toxicity. In contrast to its induction of QR1, resveratrol inhibits QR2 with a dissociation constant of 35 nM, making it the highest affinity target for resveratrol reported so far[11]. Although the biological function of QR2 is not well understood, it has been postulated that QR2 might function to control endogenous electrophile concentrations and that an increase in the concentration of electrophilic species could induce expression of Phase II enzymes. In support of this, QR2-deficient cells and mice show enhanced resistance to menadione toxicity[46,47], whereas QR1-deficient mice exhibit increased sensitivity to quinone toxicity[48]. A general downregulation of genes that encode Phase I drug-metabolizing enzymes and upregulation of the Phase II response was confirmed by cDNA arrays and reverse transcriptase-PCR using livers from resveratrol-treated rats[49]. So, through its differential effects on drug-metabolizing enzymes, resveratrol may prevent the activation of carcinogens while simultaneously increasing the body's capacity to eliminate harmful molecules.

Alterations in cell cycle and apoptosis. Another mechanism by which resveratrol could combat tumour formation is induction of cell cycle arrest and apoptosis. The anti-proliferative and pro-apoptotic effects of resveratrol in tumour cell lines have been extensively documented *in vitro* (for a review, see REF. 50) and are supported by downregulation of cell cycle proteins[51–53] and increases in apoptosis[54–56] in tumour models *in vivo*. Although resveratrol has been found to target leukaemic cells preferentially *in vitro* in some studies[57], the specificity of these effects remains unclear as others have found that resveratrol inhibits growth and induces apoptosis in normal haematopoietic cells at similar doses[58]. Some level of specificity could arise from the apparent increased susceptibility of cycling cells to the effects of resveratrol[58]. A more precise mechanism by which resveratrol could act is sensitization of tumour cells to other inducers of apoptosis. Resveratrol has been shown to sensitize several tumour lines, but not normal human fibroblasts, to TRAIL (tumour necrosis factor-related apoptosis-inducing ligand)-induced apoptosis[59]. It remains to be seen whether the pro-apoptotic effects of resveratrol *in vivo* are related to these *in vitro* observations, or secondary to other effects, such as inhibition of angiogenesis.

Antioxidant effects. Reactive oxygen species (ROS) have been shown to have a role in the initiation and progression of cancer through directly damaging DNA and other macromolecules[60,61]. In addition to its possible modulation of antioxidant enzymes involved in the Phase II response, resveratrol has an intrinsic antioxidant capacity that could be related to its chemopreventive effects. *In vivo*, resveratrol has been shown to increase plasma antioxidant capacity and decrease lipid peroxidation[62–64]; however, it is difficult to assess whether these effects are direct, or the result of upregulating endogenous antioxidant enzymes. In addition, clinical trials of antioxidant molecules have yielded disappointing results, suggesting that phytochemicals could possess other properties that are more relevant to cancer prevention[65]. Antioxidant effects of resveratrol are discussed further in later sections.

Resveratrol and heart disease

Regular consumption of red wine is often credited as the explanation for the 'French Paradox'[66,67] — a term coined to describe the observation that the French enjoy a relatively low risk of cardiovascular disease despite a diet that is high in saturated fat[68]. Although regular consumption of any alcoholic beverage in moderation seems to be beneficial to cardiovascular health,

Box 1 | **Caloric restriction mimetics**

Caloric restriction is widely considered to be the most robust and reproducible way of extending health and longevity[12]. Key features in mammals include lower circulating insulin and increased insulin-sensitivity, lower core body temperature, decreased incidence or delayed onset of age-associated diseases, including cancer, cardiovascular and cognitive disorders, and slower age-related decline in many functional tests[193]. Although effects on longevity have not yet been documented for primates, ongoing studies have already provided evidence that at least the health-promoting effects of caloric restriction will be conserved[193].

Because of the enormous potential benefits to human health and the relative unlikelihood that many would be willing or able to maintain a calorie-restricted diet, it has been proposed that a key focus of current research should be the development of drugs that mimic caloric restriction. The first candidate caloric restriction mimetic to be tested was the glycolytic inhibitor 2-deoxyglucose, which was intended to mimic energy restriction directly by limiting glucose flux through cells[199]. Although this strategy has had some success in short-term studies, it has fallen out of favour as a potential human therapeutic because of an apparent narrow therapeutic window between efficacy and toxicity[193]. Other molecules and strategies currently being considered include insulin sensitizers, antioxidants, sirtuin activators and enhancers of fatty acid oxidation and autophagy. Further refinement of our understanding of the mechanism(s) by which caloric restriction elicits its effects, combined with direct testing of putative mimetics, will be an important and exciting area for future studies.

Resveratrol has been considered to be a caloric restriction mimetic in lower organisms, primarily on the basis of its activation of sirtuin proteins and its capacity to extend lifespan[9,14]. In mammals, caloric restriction and resveratrol treatment afford protection against a similar spectrum of diseases (TABLE 1), justifying further investigation into the potential overlap in mechanism of action.

epidemiological studies indicate that red wine confers significant additional benefits[69,70]. Wine and grape extracts have been shown to decrease platelet aggregation[71,72], promote vasorelaxation[73,74], suppress atherosclerosis[75], reduce lipid peroxidation[76], and improve serum cholesterol and triglyceride concentrations[77,78]. The discovery that resveratrol is obtained primarily from red wine in most human diets[4] has prompted extensive research into its potential to explain these cardioprotective effects.

Platelet aggregation. Excessive or inappropriate aggregation of platelets can lead to thrombus formation and subsequent blockages in blood vessels that result in transient ischaemia, myocardial infarction or stroke. Interestingly, resveratrol prevents platelet aggregation *in vitro*[79], and systemic administration of resveratrol blocks the increase in platelet aggregation that is induced in rabbits by a hypercholesterolaemic diet[80], and reduces the atherosclerotic area and the size of the thrombus generated by laser-induced damage to the endothelium in mice that are genetically hypercholesterolaemic[81]. The mechanism for this protective effect of resveratrol could involve its preferential inhibition of COX1 over COX2 activity[5] because the balance of prostaglandins synthesized by the two COX isoforms regulates vascular homeostasis. Thromboxane A2 (TxA_2), which is synthesized by COX1 in platelets, is a potent inducer of platelet aggregation and a vasoconstrictor[82,83], whereas prostacyclin, which is synthesized by COX2 in vascular endothelial cells, is an antiplatelet aggregator and a vasodilator[84]. Selective inhibition of COX1 therefore promotes blood flow and decreases clot formation, whereas drugs that selectively inhibit COX2 could create an environment that is conducive to thrombus formation and increase the risk of cardiovascular complications[85,86]. Under some conditions, inactivation of COX1 by resveratrol is irreversible[87], and as platelets are unable to synthesize new proteins, this suggests that even a transient exposure to resveratrol could have lasting effects *in vivo* (the turnover time for human platelets is ~10 days). Interestingly, this is the mechanism by which aspirin is thought to exert its cardioprotective effects[88–90].

Vasodilation. In addition to possible vasorelaxant effects through the inhibition of TxA_2 synthesis, resveratrol is capable of relaxing isolated arteries and rat aortic rings[91,92]. The vasorelaxant activity of resveratrol has been attributed to its ability to stimulate Ca^{2+}-activated K^+ channels[93] and to enhance nitric oxide signalling in the endothelium[94]. The latter was attributed to inhibition of vascular NADH/NADPH oxidase activity, leading to a reduction in basal superoxide production, and, consequently, decreased inactivation of nitric oxide. *In vivo*, resveratrol has been shown to increase expression of both endothelial and inducible nitric oxide synthase (eNOS and iNOS, respectively)[95]. In arteries isolated from humans with coronary heart disease, nitric oxide-dependent vasorelaxation in response to resveratrol is lost, although some dilation is still observed due to nitric oxide-independent mechanisms[96]. Resveratrol could, therefore, promote vasorelaxation through multiple pathways *in vivo*.

Antioxidant activity. Although resveratrol has been shown to exert antioxidant effects, it is not yet clear if this is primarily a direct scavenging effect or the result of the activation of pathways that upregulate cells' natural antioxidant defences. Oxidation of low-density lipoprotein (LDL) particles is strongly associated with the risk of coronary heart disease and myocardial infarction[97]. Resveratrol prevents LDL oxidation *in vitro* by chelating copper, as well as by directly scavenging free radicals[98] (although other components of red wine are superior free radical scavengers[99]). Treatment of normal rats with resveratrol does not affect lipid peroxidation, as reflected by the presence of thiobarbituric acid-reactive substances[100]. However, resveratrol can be detected in LDL particles from humans after consumption of red wine[101], and the pure compound prevents increases in lipid peroxidation that are induced by tumours[63] or UV irradiation[28], in addition to blocking gentamicin-induced nephrotoxicity[102]. In stroke-prone, spontaneously hypertensive rats, resveratrol significantly reduces markers of oxidative stress such as glycated albumin in serum, and 8-hydroxyguanosine in urine[103]. Furthermore, in guinea pigs, resveratrol induces the activities of QR1 and catalase in cardiac tissue, and decreases the concentration of ROS generated by menadione[46]. These results indicate that resveratrol can suppress pathological increases in the peroxidation of lipids and other macromolecules *in vivo*, but whether the mechanism is direct, indirect, or both is not yet clear.

Cholesterol and triglycerides. Resveratrol was shown, in 1982, to inhibit the deposition of cholesterol and triglycerides in the livers of rats, and to decrease the rate of hepatic triglyceride synthesis[104]. However, more recent *in vivo* studies have failed to detect a significant effect of resveratrol on serum cholesterol or triglyceride concentrations[80,100,103,105–107]. In rare exceptions, total cholesterol concentration was lowered by resveratrol treatment in hypercholesterolaemic rats[108], and serum LDL and very-low-density lipoprotein concentrations were decreased in hepatoma-bearing rats[63]. A positive correlation has been shown between serum cholesterol and hepatoma weight[109], and so a reduction in tumour size could have been the primary effect of resveratrol in the latter study. Current *in vivo* data, therefore, do not provide support for a direct effect of resveratrol on circulating cholesterol and lipid concentrations. Despite this, resveratrol has been shown to reduce the formation of atherosclerotic plaques and restore flow-mediated dilation in rabbits fed a high-cholesterol diet[75]. It is also worth noting that the original 1982 study found piceid (also known as resveratrol β-glucoside or polydatin), which is also present in red wine, to be a far more effective regulator of serum lipid concentrations[104].

Phytooestrogenic effects. Oestrogen replacement therapy has been shown to reduce the risk of cardiovascular disease and osteoporosis in postmenopausal women[110]. Resveratrol has been reported to act as a phytooestrogen in some systems[111], and it has been suggested that this property might mediate its cardioprotective effects[112]. However, both the oestrogenic effects of resveratrol *in vivo* and the cardioprotective effects of oestrogen replacement[113,114] have since become subjects of debate, and a firm connection remains to be established.

Resveratrol, inflammation and immunity

Many human ailments have an inflammatory component. Inflammation is central to the pathology of arthritis, Crohn's disease and psoriasis, and can have a role in the development of both cardiovascular disease and cancer. The cyclooxygenase enzymes are crucial in the production of pro-inflammatory molecules by both the cyclooxygenase and 5-lipoxygenase pathways (for a review, see REF. 115) and inhibitors are commonly used as anti-inflammatory drugs. Because resveratrol is an effective inhibitor of cyclooxygenase activity *in vivo*[20,22,28], its anti-inflammatory properties have been investigated. Resveratrol significantly reduces both acute and chronic chemically induced oedema[5,70,116], lipopolysaccharide-induced airway inflammation[117] and osteoarthritis[118], and helps to prevent allograft rejection[119,120]. Intravenously administered resveratrol decreases inflammation induced by ischaemia/reperfusion, oxidants generated by hypoxanthine/xanthine oxidase (HX/XO) or platelet-activating factor, but not leukotriene B_4 in rats[121]. The first three conditions are all associated with superoxide formation, whereas leukotriene B_4 induces inflammation via a superoxide-independent mechanism[122], suggesting that resveratrol treatment could detoxify or slow production of this molecule. Resveratrol could present an attractive alternative to current treatments for chronic inflammation as long-term use of aspirin can damage the stomach lining[123], and selective COX2 inhibitors developed to avoid this problem have been linked to cardiovascular complications[85,86].

In contrast to its suppressive effects on models of inflammation, resveratrol enhances the immune response of mice treated with the arylating agent dinitrofluorobenzene in a delayed type hypersensitivity assay, and prevents immunosuppression by ethanol[124]. Furthermore, resveratrol protects mice from infection by herpes simplex virus-1 (HSV1) and HSV2 (REFS 125,126). This suggests that the regulation of inflammatory responses by resveratrol is more complex than simple suppression and that specific immune responses could even be enhanced.

Myocardial infarction

Resveratrol has proved to be effective at protecting isolated rat hearts against ischaemia/reperfusion injury. Perfusion of the organ with 10 μM resveratrol for 10–15 min before ischaemic insult results in improved recovery of developed pressure and aortic flow, reduction of malondialdehyde concentrations and reduction of infarct size[59,127–129]. This effect could be, at least partially, related to the antioxidant activity of resveratrol because a resveratrol derivative that incorporates an additional hydroxyl group at the 3′ position — astringinin — exhibits greatly enhanced free radical-scavenging ability, and provides better protection from ischaemic injury[130]. Inhibitors of NOS block the protective effects of resveratrol in isolated rat hearts[131] and hearts from iNOS-null-mice are not protected[132]. Increases in the expression of both eNOS and iNOS[95], as well as increases in serum nitric oxide concentrations[133], were observed in wild-type mice treated with resveratrol, demonstrating that this mechanism could be relevant *in vivo*.

Providing resveratrol in drinking water for 15 days (~1 mg per kg body weight) was sufficient to improve the recovery in function and coronary flow of isolated hearts even 24 hours after resveratrol administration was stopped[134]: this effect was dependent on both nitric oxide and adenosine. Adding resveratrol to drinking water for 16 days (~14 mg per kg body weight) significantly increased cardiac QR1 (DT-diaphorase) and catalase levels in guinea pigs, suggesting an increased capacity to eliminate oxidants[46]. Moreover, resveratrol prevented a rise in ROS in response to menadione in cardiac homogenates and isolated atria. Resveratrol could therefore bring about an increase in nitric oxide concentrations through both increasing expression of nitric oxide synthase and decreasing the inactivation of nitric oxide by free radicals. These data strongly suggest that resveratrol might protect against ischaemic damage during myocardial infarction.

Stroke and brain damage

Numerous studies have raised the possibility that resveratrol might be useful in protecting against brain damage following cerebral ischaemia. Rats given intraperitoneal injections of resveratrol for 21 days, showed less motor impairment and significantly smaller infarct volume after middle cerebral artery occlusion[8]. Similar

effects were observed in wild type, but not peroxisome proliferator-activated receptor-$\alpha^{-/-}$ (PPAR$\alpha^{-/-}$), mice[135]. In Mongolian gerbils, an intraperitoneal injection of resveratrol during or immediately after transient global cerebral ischaemia, followed by a second dose at 24 hours, decreased delayed neuronal cell death and glial cell activation in the hippocampus[7]. A third study found that resveratrol administered intravenously significantly decreased ischaemic volume and brain water content at the extremely low doses of 100 ng and 1 μg per kg (body

Table 1 | **Dietary sources of resveratrol**

Source	*trans*-Resveratrol concentration	Comments	Refs
Dietary			
Red wines	0.1–14.3 mg l^{-1}	*cis*-Resveratrol, *trans*-piceid and *cis*-piceid also present, typically at slightly lower concentrations	181,207–213
White wines	<0.1–2.1 mg l^{-1}	Generally resveratrol found at concentrations of <0.1 mg l^{-1}, exceptions include Swiss, Portuguese and German Riesling wines, *cis*-resveratrol, *trans*-piceid and *cis*-piceid also present	181,201,207, 209,210
Ports and sherries	Generally <0.1 mg l^{-1}		207
Grapes*	0.16–3.54 μg g^{-1}	Contents are similar for wine or table grapes, and black or white grapes. *trans*-Piceid is predominant at concentrations of 1.5–7.3 μg g^{-1}	211,214–216
Dry grape skins	24.06 μg g^{-1} (average)	*trans*-Piceid and *cis*-piceid found at concentrations of 42.19 μg g^{-1} and 92.33 μg g^{-1}, respectively	217
Red grape juices	0.50 mg l^{-1} (average)	*trans*-Piceid, *cis*-piceid and *cis*-resveratrol found at concentrations of 3.38 mg l^{-1}, 0.79 mg l^{-1} and 0.06 mg l^{-1}, respectively	218
White grape juices	0.05 mg l^{-1} (average)	*trans*-Piceid and *cis*-piceid found at concentrations of 0.18 mg l^{-1} and 0.26 mg l^{-1}, respectively	218
Cranberry raw juice	~0.2 mg l^{-1}	*cis*-Resveratrol also found at a concentration of ~0.03 mg l^{-1}	219
Blueberries	Up to ~32 ng g^{-1}		220
Bilberries	Up to ~16 ng g^{-1}		220
Other *Vaccinium* berries	7–5,900 ng g^{-1} (dry sample)	Highest concentrations in lingonberries	216
Peanuts	0.02–1.92 μg g^{-1}		221,222
Roasted peanuts	0.055 μg g^{-1}		223
Boiled peanuts	5.1 μg g^{-1}		211,223
Peanut butters	0.3–0.4 μg g^{-1} (average)	*trans*-Piceid also found at a concentration of 0.13 μg g^{-1}	211,223,224
100% Natural peanut butters	0.65 μg g^{-1} (average)	*trans*-Piceid also found at a concentration of 0.14 μg g^{-1}	224
Pistachios	0.09–1.67 μg g^{-1}		222
Groundnuts (*Arachis hypogaea*)	ND		225
Rhubarb	ND		226
Hops	0.5–1 μg g^{-1}	*trans*-Piceid and *cis*-piceid found at concentrations of 2–9 μg g^{-1} and 0.9–6 μg g^{-1}, respectively	227,228
Itadori (*Polygonum cuspidatum*) tea	0.68 mg l^{-1}	*trans*-Piceid also found at a concentration of 9.1 mg l^{-1}	211
Herbal			
Veratrum (Lily)	ND		1
Cassia quinquangulata	ND		5
Gnetum klossii	ND		229
Polygonum cuspidatum	0.524 mg g^{-1}	*trans*-Piceid also found at a concentration of 1.65 mg g^{-1}	211,230
Rhubarb (*Rheum rhaponticum*) dry root	3.9 mg g^{-1}		230
Yucca schidigera bark	ND		231

Resveratrol has also been detected in peanut roots[232], endophyte-infected grasses[233], *Pterolobium hexapetullum*[234], spruce[235], eucalyptus[236], the heartwood of mulberry[237] and *Bauhinia racemosa*[238]. Heating at 190 °C for 18 min destroys 17–46% of *trans*-resveratrol[220]. *Total resveratrol and piceid content of Napoleon grapes increased twofold during 10 days of refrigerated storage, and by 2–11-fold after UV irradiation[239,240]. *In red globe grapes, resveratrol concentrations increased 2,315-fold after UV irradiation[241]. ND, not determined.

Sirtuin
A member of the family of NAD$^+$-dependent deacetylases named after the *Saccharomyces cerevisiae* silent information regulator 2 (Sir2) protein (class III histone deacetylases).

weight) after middle cerebral artery occlusion in rats[136]. Resveratrol administered intraperitoneally also prevented seizures induced by $FeCl_3$ (REF. 137), kainic acid[138] or pentylenetetrazole[139], and partially restored cognition in rats receiving streptozotocin intracerebroventricularly[140]. These results suggest that resveratrol is capable of penetrating the blood–brain barrier and exerts strong neuroprotective effects, even at low doses.

Developmental effects

As a result of its reported oestrogenic activity, as well as general concern about the safety of high doses, the effects of resveratrol on growth, development and gene expression have been studied in weanling rodents. In general, only minor effects were detected. Resveratrol had no significant effect on body weight, serum cholesterol concentration, radial bone growth, epithelial cell height, insulin-like growth factor-1 (IGF1) expression, or other histological parameters, but caused a mild decrease in uterine weight, shortened the latency to vaginal opening and antagonized the cholesterol-lowering effect of oestradiol[106,141,142]. Treating pregnant mothers with resveratrol also had relatively minor effects on their offspring. These included mild changes in the sizes of various organs, delayed or unaffected vaginal opening, a decrease in female sexual behaviour, transient effects on the reproductive tract and mammary glands, and elongated oestrous cycle, but acrosomal integrity, sperm quality and litter size were not affected[143–145]. A 28-day study of the effects of 20 mg per kg (body weight) oral resveratrol in adult rats found no effect on body weight, food or water consumption, haematological or clinical biochemistry variables, or histopathology[146], and no adverse effects were observed at doses of up to 300 mg per kg (body weight)[147]. Although the effects of resveratrol on development are relatively minor compared with other potential phytooestrogens or similar molecules, more extensive studies will be required before high doses can be recommended for children or pregnant mothers.

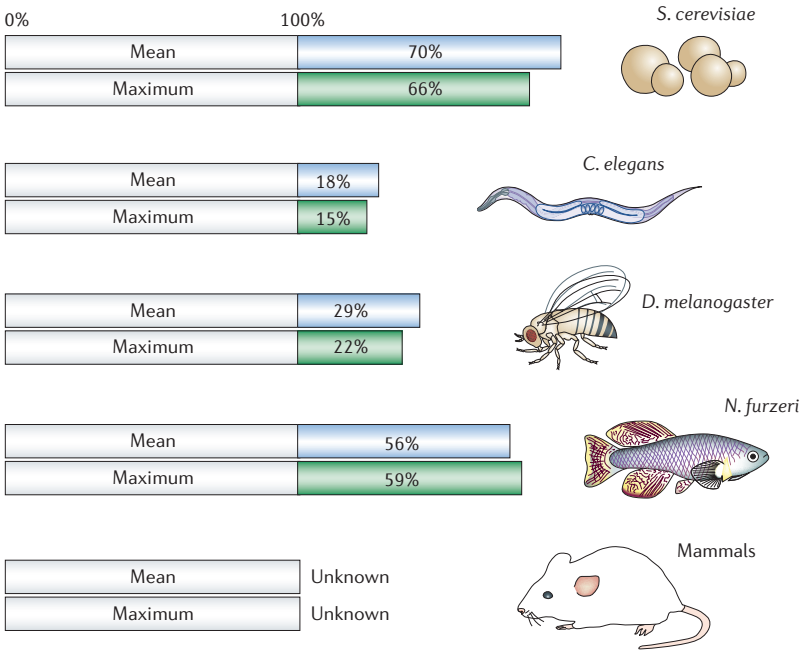

Figure 3 | **The largest reported increases in mean and maximal lifespan for various species treated with resveratrol.** Lifespan extensions in *Saccharomyces cerevisiae*[9], *Caenorhabditis elegans*[14,174], and *Drosophila melanogaster*[14,206] are dependent on sirtuin proteins. However, the role of these proteins in lifespan extension of the short-lived fish *Nothobranchius furzeri*[10] has yet to be investigated.

Other *in vivo* effects of resveratrol

In addition to its other properties, resveratrol is reported to act as an analgesic[148–150], protect against hearing loss[151] and enhance lipopolysaccharide-induced anorexia in rats, although it has no anorexic effect when given alone[152]. Resveratrol has also been shown to reduce injuries to the kidneys[153,154], spinal cord[155,156], liver[157], lungs[158], intestine[159,160] and colon[24]. These additional results indicate that the protective effects of resveratrol are not limited to the heart and brain *in vivo*.

Resveratrol and ageing

Sirtuins are a conserved family of NAD$^+$-dependent deacetylases (class III histone deacetylases) that were named after the founding member, the *Saccharomyces cerevisiae* silent information regulator 2 (Sir2) protein[161]. In yeast, worms and flies, extra copies of the genes that encode sirtuins are associated with extended lifespan[162–164]. Of the seven mammalian sirtuins — SIRT1–7 — SIRT1 is the closest homologue to Sir2, based on amino acid identity. Inbred knockout mice that lack SIRT1 show developmental defects, have a low survival rate and have a significantly shorter lifespan compared with wild-type mice, although outbreeding seems to improve the phenotype significantly[165]. It has been postulated that the main function of sirtuin proteins might be to promote survival and stress resistance in times of adversity[166]. An evolutionary advantage arising from the ability to modify lifespan in response to environmental conditions could have allowed these enzymes to be conserved as species evolved, and to take on new functions in response to new stresses and demands on the organism. This could explain why the same family of enzymes has dramatic effects on lifespan in disparate organisms with seemingly dissimilar causes of ageing[167].

The data from lower organisms have provoked intense research into the function of sirtuin proteins in mammalian systems. An *in vitro* screen for activators of SIRT1 identified resveratrol as the most potent of 18 inducers of deacetylase activity[9]. Subsequent work has shown that resveratrol extends the lifespans of *S. cerevisiae*, *Caenorhabditis elegans* and *Drosophila melanogaster* (FIG. 3), but only if the gene that encodes SIR2 is present in these organisms[9,14]. More recently, resveratrol was shown to extend the maximum lifespan of a species of short-lived fish by up to 59%, concomitant with the maintenance of learning and motor function with age and a dramatic decrease in aggregated proteins in elderly fish brains[10]; however, the extent to which this effect is Sir2-dependent, if at all, is not known.

The *in vitro* activity of SIRT1 against short, unconjugated peptide substrates is not enhanced by resveratrol, leading some to argue that the original observation was

Table 2 | **Peak serum and plasma concentrations of resveratrol and its metabolites after oral dosing**

Species	Dose*	Serum peak		Normalized to 1 mg kg^{-1}		Refs
		Authentic	Derivatives	Authentic	Derivatives	
Single dose as pure resveratrol						
Rat	50	6.6 μM	105 μM (glucuronide)	130 nM	2.1 μM (glucuronide)	175
Rat	2	~2.4 μM		1.2 μM		242
Rat	20	1.2 μM		60 nM		176
Rat	2	0.09 μM	1.2 μM (total)	22 nM	0.6 μM (total)	243
	5	0.11 μM	1.5 μM (total)	45 nM	0.3 μM (total)	
Rat	2	0.77 μM		380 nM		244
Mouse	240	32 μM		46 nM		185
Mouse	20	2.6 μM		130 nM		176
Mouse	20	Trace	~5 μM (sulphate) ~1 μM (glucuronide)	Trace	0.25 μM (sulphate) 0.05 μM (glucuronide)	245
	60	Trace	~300 μM (sulphate) ~170 μM (glucuronide)	Trace	5 μM (sulphate) 2.8 μM (glucuronide)	
Rabbit	20	1.1 μM		55 nM		176
Human	25 mg per 70 kg body weight	~37 nM	~2.1 μM (total)	100 nM	5.9 μM (total)	246
Human	25 mg per person	<22 nM	~2.1 μM (total)	<81 nM	7.7 μM (total)	177
Single dose as red wine						
Rat	80 μg per kg	~88 nM		~1.1 μM		247
Rat	86 μg per kg	~88 nM		~1.0 μM		248
Human	3.4 μg per kg	ND	0–0.11 μM (3-glucuronide) 0–0.42 μM (4′-glucuronide)	ND	0–32 μM (3-glucuronide) 0–120 μM (4′-glucuronide)	178
	32.9 μg per kg	ND	0–0.19 μM (3-glucuronide) 0–2.2 μM (4′-glucuronide)	ND	0–5.8 μM (3-glucuronide) 0–67 μM (4′-glucuronide)	
	7.5 μg per kg	0–26 nM	0–0.16 μM (3-glucuronide) 0–1.3 μM (4′-glucuronide)	0–3.5 μM	0–21 μM (3-glucuronide) 0–170 μM (4′-glucuronide)	

*Quoted as mg per kg body weight unless stated otherwise. ND, none detected.

an artefact of the fluorescent substrate used to monitor the reaction[168,169]. However, activation of SIRT1 by resveratrol is observed in non-fluorescence-based assays when longer peptide substrates are used (A. Sauve, S. Lavu and J. Milne, personal communications) and is abolished in an E230K point mutant of SIRT1 (W. D. Lamming, S. Michan, J.B. and D.A.S., unpublished observations). Moreover, resveratrol consistently recapitulates the protective effects of SIRT1 overexpression in cell culture[9,170], and Sir2/SIRT1 have been shown to be essential mediators of effects on adipogenesis[171], nuclear factor-κB (NF-κB) acetylation[172], protection from mutant huntingtin protein[173], and lifespan extension in lower organisms.

The importance of substrate choice *in vitro* highlights the possibility that resveratrol might alter the substrate specificity of SIRT1 *in vivo*. Indeed, this is the case in *C. elegans* — resveratrol treatment has been shown to have SIR-2-dependent effects that are substantially different from those obtained by simple overexpression[174]. The question of whether enhanced SIRT1 activity and/or resveratrol treatment will increase mammalian lifespan looms large in the ageing-research community.

Pharmacokinetics

It is fair to say that the literature on resveratrol is, in many cases, contradictory and confusing. The wide range of concentrations and doses used to achieve the various effects reported for resveratrol (~32 nM–100 μM *in vitro* and ~100 ng–1,500 mg per kg (body weight) in animals) raises many questions about the concentrations that are achieved or achievable *in vivo*. Furthermore, resveratrol has a short initial half-life (~8–14 min for the primary molecule[175,176]) and is metabolized extensively in the body. As such, calculating the effective *in vivo* concentration of resveratrol or designing new studies based on the current literature can be daunting.

In 2004, Walle[177] and colleagues showed that the bulk of an intravenous dose of resveratrol is converted to sulphate conjugates within ~30 min in humans. A detailed analysis of plasma metabolites after oral dosing was not possible; however, both sulphate and glucuronide conjugates were detected. Five distinct metabolites were present in the urine — resveratrol monosulphate, two isomeric forms of resveratrol monoglucuronide, dihydroresveratrol monosulphate and dihydroresveratrol

Table 3 | **Resveratrol metabolites in plasma after long-term treatment**

Species	Daily dose*	Resveratrol metabolites in plasma	Refs
Rat	40 (as wine)	~33 nM (authentic)	247
Rat	43 (as wine)	~33 nM (authentic)	248
Rat	50 (in diet)	ND	64
	300 (in diet)	ND (authentic), 7.7 μM (3-glucuronide), ND (4′-sulphate), 1.1 μM (3-sulphate), 3.0 μM (3,5-sulphate), 18 μM (3,4′-sulphate), 6.4 μM (3,4′,5-sulphate)	

*Quoted as μg per kg body weight unless stated otherwise. ND, none detected.

monoglucuronide (FIG. 1). Total sulphate conjugates accounted for ~37% of the metabolites in the urine and total glucuronide conjugates ~19%, with the remainder being made up largely by unknown metabolites and only trace amounts of free resveratrol. In addition, Walle *et al.*[177] found that the serum half-life of total resveratrol metabolites was ~9.2 hours, indicating that exposure to modified forms is much higher than that for unchanged resveratrol.

Although modifications such as glucuronidation and sulphation typically reduce the cell permeability of drugs and aid in their excretion, the undeniable *in vivo* efficacy of resveratrol, despite its low bioavailability, has led to speculation that its metabolites could retain some activity. In support of this, several metabolites retain the ability to activate SIRT1 and inhibit cyclooxygenase *in vitro* (A. Mesecar, personal communication). However, resveratrol-3-sulphate fails to inhibit CYPs[35] and there is currently no evidence that any metabolite is able to cross the plasma membrane. Research into the actions of metabolites has been hampered by the lack of commercial sources, but should proceed more readily now that synthetic routes to these molecules have been established by several groups[64,177,178].

The concentrations of *trans*-resveratrol in red wine vary widely (TABLE 1), but a reasonable (if optimistic) estimate is about 5 mg l^{-1} (REFS 179,180). Assuming a consistent daily intake of 375 ml, or about two glasses of wine, a person weighing 70 kg would receive a dose of ~27 μg per kg (body weight) each day. Inclusion of *cis*-resveratrol and polydatin (resveratrol β-glucoside, also known as piceid), depending on the wine, might double this figure[181]. At higher doses, the detrimental effects of alcohol are likely to mask any health benefits. For example, the beneficial effect of alcohol consumption on Alzheimer's disease is maximal at 1–6 drinks per week[182] and consuming more than four drinks per day nullifies the beneficial effect of alcohol on the risk of myocardial infarction[183].

One finding that has often been overlooked is that quercetin, which is also present in red wine, is a picomolar inhibitor of resveratrol sulphation in both the liver and duodenum[184], indicating that the profiles of metabolites obtained after consumption of either red wine or purified resveratrol could be different. Resveratrol , its 3-glucuronide and its 4′-glucuronide were all detected sporadically in the plasma of human participants after ingestion of red wine at concentrations up to 26 nM, 190 nM and 2.2 μM, respectively[178]. Data on the peak serum concentrations of unchanged resveratrol, as well as metabolites, are summarized in TABLES 2,3.

The maximum tolerated dose of resveratrol has not been thoroughly determined, but 300 mg per kg (body weight) showed no detrimental effects in rats[147] and doses up to 100 mg per kg (body weight) have been used routinely in studies on rodents (S1). Although these estimates are subject to change as new data become available, we would currently predict peak serum concentrations of ~2.4 nM unmodified resveratrol and ~180 nM total resveratrol from a dose equivalent to two glasses of red wine, and ~9 μM authentic resveratrol and ~680 μM total resveratrol from a high, but pharmacologically relevant, dose (based on rodent data) of resveratrol of 100 mg per kg (body weight). Insufficient data exist to predict peak concentrations in most tissues, but a ~30-fold enrichment of resveratrol over serum concentrations has been observed in intestinal mucosa[185], as has significant accumulation of resveratrol in the bile, stomach, liver and kidneys[186].

Given that *in vivo* concentrations of individual metabolites can be more than ten times higher than those of the native compound, in the future, there will clearly need to be an emphasis on determining whether the metabolites represent inactivated forms of the drug, act as a pool from which free resveratrol can be released in various tissues or are themselves active in promoting many of the health benefits attributed to resveratrol.

It is also worth considering the potential interactions of resveratrol with other constituents of the diet. Resveratrol has been shown to synergize with both quercetin and ellagic acid in the induction of apoptosis in human leukaemia cells[187], with ethanol in the inhibition of iNOS expression[188], with vitamin E in the prevention of lipid peroxidation[189], with catechin in the protection of PC12 cells from β-amyloid toxicity[190], and with nucleoside analogues in the inhibition of HIV1 replication in cultured T lymphocytes[191]. These effects could help to explain how a relatively low dose of resveratrol obtained from red wine or other dietary sources could produce a measurable health benefit.

Conclusions

In mammals, there is growing evidence that resveratrol can prevent or delay the onset of cancer, heart disease, ischaemic and chemically induced injuries, diabetes, pathological inflammation and viral infection. These effects are observed despite extremely low bioavailability and rapid clearance from the circulation. Administering higher doses to improve efficacy might not be possible as toxic effects have been observed at or above 1 g per kg (body weight)[147]. Moreover, administering a daily dose to a human weighing 75 kg with 100 mg per kg (body weight) of resveratrol would require 2.7 kg of resveratrol a year, at a current cost of about US$6,800. Therefore, blocking the metabolism of resveratrol, developing analogues with improved bioavailability, or finding new, more potent compounds that mimic its effects will become increasingly important.

Box 2 | **The 'xenohormesis hypothesis'**

'Hormesis' describes the phenomenon in which a mild stress (for example, irradiation, heat or toxins) can induce a protective response against subsequent stresses[200]. This hormetic response is credited for the paradoxical result that mildly stressed animals outlive their unstressed counterparts[201], which also possibly applies to humans[202]. It has been suggested that caloric restriction might act as a mild stress to induce a hormetic response[203], which could account for enhanced stress-tolerance and longevity in calorie-restricted mice, as well as the otherwise counterintuitive finding that such animals are better able to resist starvation[204]. In yeast, at least, this contention is strongly supported by the observation that both caloric restriction and mild stresses induce expression of Pnc1, an upstream activator of sirtuin proteins that is necessary and sufficient for lifespan extension[205].

The 'xenohormesis hypothesis' postulates that sensing stress responses, such as resveratrol accumulation, in a food source might be sufficient to induce a hormetic response in animals eating that food[9,197,198]. It can be imagined that throughout evolution, such stress-markers in the surrounding vegetation would have served as strong predictors of a coming famine or direct stress to the animal. Reacting to these molecules would allow the hormetic response to begin ahead of any direct damage or energy deficit, and, more importantly, would not stake the life of the animal on the hope that the initial stress would be mild and/or protective. If the 'xenohormesis hypothesis' is correct, then stressed plants might form an abundant reservoir for medicinal compounds that trigger conserved protective responses in humans. The relatively low amounts of resveratrol in foods belie the possibility that there are numerous potential xenohormetic compounds in a stressed plant that could act additively or even synergistically. Indeed, another potentially xenohormetic compound, quercetin, behaves similarly to resveratrol in many assays and also inhibits sulphation of resveratrol[184], which predicts a greater than additive effect.

It is tempting to view the beneficial effects of resveratrol in mammals as an extension of findings from lower organisms, in which resveratrol acts through Sir2 to mimic caloric restriction. Indeed, caloric restriction is probably the only other treatment for which such a broad array of protective effects is observed in mammals. In addition, resveratrol treatment increases mitochondrial biogenesis (R. de Cabo, personal communication) and, at least under certain conditions, improves insulin sensitivity[192], which is consistent with observations in calorie-restricted animals[193–195]. However, activation of the mammalian Sir2 homologue SIRT1 by resveratrol has yet to be demonstrated *in vivo*, and our current lack of understanding of how caloric restriction brings about its effects precludes a more definitive mechanistic comparison.

Given that many targets for resveratrol have been identified *in vitro*, and effective doses vary over at least three orders of magnitude *in vivo*, it seems likely that resveratrol acts through multiple pathways. Intriguingly, reported effects are overwhelmingly in the direction that would be considered beneficial and in many cases seem to suggest cooperative action. For example, expression of CYP1A1 is downregulated by resveratrol through inhibition of AHR[40], but resveratrol also inhibits the catalytic activity of CYP1A1 directly[36]. The same is true for COX2 — resveratrol interferes with both transcription[23] and catalytic activity[5] of the enzyme. Resveratrol inhibits NF-κB both by blocking the upstream activator PKCδ[196] and by activating the inhibitor SIRT1 (REF. 172). Moreover, resveratrol inhibits inflammation through ostensibly independent effects on NF-κB, cyclooxygenase and interleukin-1β.

One possible explanation for this seemingly coordinated response is that resveratrol resembles an endogenous signalling molecule. Indeed, resveratrol's structure is reminiscent of molecules that stimulate the oestrogen receptors. However, attempts to characterize resveratrol as an *in vivo* oestrogen mimetic have met with limited success[106,142]. Another alternative is the 'xenohormesis hypothesis', which proposes that organisms have evolved to respond to chemical cues in their diets[9,197,198] (BOX 2). Whether resveratrol can stimulate endogenous pathways to promote health and longevity, such as those that are active during caloric restriction, or whether it produces its effects through a series of fortuitous interactions are important issues to address.

It is becoming clear that resveratrol and more potent mimetics show great promise in the treatment of the leading causes of morbidity and mortality in the Western world. So far, little evidence suggests that these health benefits are coupled with deleterious side effects. Even the trade off between individual health and reproductive potential that is characteristic of caloric restriction does not seem to occur in animals with lifespans that have been extended by resveratrol[14]. Could resveratrol and similar molecules form the next class of wonder-drugs? Clinical trials are currently underway in several locations (see Further information) and could soon answer this question. In the meantime, we might all do well to follow the advice of Antonio Todde, once the world's oldest man: "Just love your brother and drink a good glass of red wine every day".

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Competing interests statement

The authors declare competing financial interests: see Web version for details.

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