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Resveratrol – pills to replace a healthy diet?

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Nutrapharmacology, or the use of bioactive food compounds at pharmacological doses is emerging as a therapeutic approach to target the complex metabolic dysregulations in ageing and obesity-related chronic disease. Resveratrol, a polyphenol found in the skin of grapes, and other edible plants and related food products, has received extensive attention through the link with the French paradox, and later with its chemopreventive activity demonstrated *in vitro* and in animal cancer models. A plethora of laboratory investigations has provided evidence for the multi-faceted properties of resveratrol and suggests that resveratrol may target ageing and obesity-related chronic disease by regulating inflammation and oxidative stress. A number of obstacles stand in the path to clinical usage however, not least the lack of clinical evidence to date, and the myriad of doses and formulations available. Further, data on the effects of resveratrol consumption in a capsule *vs*. food form is conflicting, and there are uncertain effects of long term dosing. The review will summarize the human pharmacokinetic and pharmacodynamic published data, and the topics for research if resveratrol is to become a multi-target therapeutic agent addressing chronic disease.

Introduction: nutrapharmacology, the role of food compounds in disease prevention

The use of bioactive food compounds (nutrients and phytochemicals found in fruit, vegetables and spices) at pharmacological doses, is emerging as a therapeutic approach to address the complex metabolic dysregulations in ageing and obesity-related chronic diseases. This is termed nutrapharmacology and the compounds are nutraceuticals. The evidence comes from basic science reports, demonstrating that these compounds can efficiently modulate the oxidative, inflammatory and apoptotic imbalances in chronic disease metabolic pathways [1, 2].

Dietary agents originate from daily food. Therefore they may be more acceptable to consumers who may erroneously perceive them as having fewer side effects than pharmaceutical agents. In contradistinction, people may need to consume large amounts of foods containing these compounds for therapeutic benefit. Whilst it may not be plausible to consume such large amounts, nutraceuticals offer a convenient alternative at a time when, in spite of scientific evidence suggesting their benefits in health and disease prevention, these compounds are poorly represented in our daily menu. However food sources are complex, and are likely to contain combinations of compounds, possibly acting synergistically to enhance/reduce their bioavailability and/or activity [1, 3, 4]. The benefits of dietary constituents may therefore be different from the putative benefits of nutraceutical formulations at pharmacological dose. Additionally, bioactive phytochemicals may have dose-related toxic effects. Thus clinical evidence of both the food and the nutraceutical sources is required before considering these agents in the management of chronic disease.

Resveratrol (RSV) is one compound of interest. It is 13 years since the first paper reported the initial *in vitro* and *in vivo* evidence of cancer chemopreventative activity of RSV [5]. The abundance of research providing promising data brings this phytochemical to the era of clinical testing [6–8]. This review will summarize the pharmacology of RSV, as evidenced in the first published clinical observations, and discuss its clinical relevance.

Resveratrol

History

Since its identification in the 1940s from the white hellebore by Takaoka, and in 1963 in the Japanese knotweed

Polygonum cuspidatum by Nonomura [9] RSV has gained notoriety, helped by media attention in the 1990s when speculated to explain the French paradox [10, 11]. On closer investigation, it appeared that RSV was perhaps the active phytochemical in red wine. The concept of the French paradox has since been challenged, but the apparent cardiovascular protective properties of RSV have been explained by the inhibition of LDL cholesterol peroxidation, free-radical scavenging activity, and modulation of nitric oxide production [12–15]. RSV, as grape and *Polygonum cuspidatum* extracts, is present in Ayur-vedic and traditional Chinese medicine formulae, prescribed for fungal infection, cardiovascular disease, gastrointestinal disorders, diabetes and inflammation [16, 17]. Figure 1 summarizes the last decade of research invested in understanding RSV's biochemical effects, listing genes and products affected by exposure to RSV. Some of the proteins thought to mediate the effects of RSV in the context of multifactorial chronic diseases include AMP-activated protein kinase (AMPK), silent mating type information regulation 2 homolog 1 (SIRT1), N-ribosyldihydronicotinamide:quinone oxidoreductase (NQO2), NFE2-related factor 2 (Nrf2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [18–24]. The extensive range of affected proteins raises the possibility of off-target deleterious effects, further emphasizing the need for formal clinical toxicity and efficacy studies of chronic RSV intake.

Chemical description

RSV is a lipophillic polyphenol. The styrene double-bond allows for *cis* and *trans* conformations [9, 25]. The glucose-bound form of RSV is piceid, dominant in food sources and converted to *trans*-RSV by hydrolysis [26]. Three hydrogen atoms per RSV molecule are available for transfer to reactive species and interrupt oxidative cascades [27]. RSV is produced in response to environmental stress such as UV rays, drought, parasitic or fungal attack [28, 29].

Food sources vs. nutraceuticals

RSV has been found in over 100 plants, often described as abundant in nature. Few edible plants contain RSV however, with minimal amounts provided as shown in Table 1. Cultivars, soil and growing conditions result in large variations in concentrations [30]. Measures are influenced by the inclusion/exclusion of the piceid and *cis*-forms in assays [26]. The nutraceutical form of RSV is usually 99% purified *trans*-RSV, extracted from the rhizome of *Polygonum cuspidatum* or grapes.

A daily menu, including safe wine drinking, could provide 6 to 8 mg of RSV, including numerous other phytochemicals. In contrast, one nutraceutical capsule provides between 20 to 500 mg of pure *trans*-RSV, or 3- to 83-fold the supply of a daily diet. The disparity between the dosages is remarkable, and raises questions on the physiological implications of nutraceutical doses. The scarcity of clinical data and understanding of effects of a dietary *vs*. nutraceutical dose need addressing, considering the wide over the counter availability.

Tolerability and toxicity

Tolerability to nutraceutical RSV has been investigated in healthy lean subjects, from a single up to 29 repeated doses. Tolerability to RSV appears reasonable, with nausea and mild headaches occasionally reported, and mild to moderate diarrhoea reported at larger doses (not always placebo controlled) [31, 32]. These side effects occurred with single daily dosing regimens. If related to peak concentrations, it is possible that split-dosing may improve tolerance. In a study administering 2000 mg twice daily over 1 week [33], there was statistically, but not clinically significant, raised serum bilirubin and potassium concentrations. Daily dosing of 1000 mg for 4 weeks did not change bilirubin concentrations [34]. Data on chronic dosing, e.g. over 90 days, are not available, nor are there data in obese subjects, who are highly represented in the population with chronic disease.

The inhibition and induction by RSV of hepatic P450 isoenzymes involved in phase 1 and 2 detoxification have been observed in subjects receiving 1000 mg RSV nutraceutical daily over 4 weeks. This may be of relevance in patients medicated for co-morbidities due to increased or decreased effect, and drug interactions [34].

Pharmacokinetics

Initial pharmacokinetic (PK) studies used enzymatic hydrolysis to reconvert conjugates to parent RSV for quantification. HPLC with MS/MS is now commonly used to quantify plasma parent and conjugated RSV. Comparison of results is however difficult because different minimal detectable concentrations are used, and the different fractions are not always measured. Definitions of 'total RSV' vary in reports, from unspecified to include parent and/or metabolites detected, or include protein-bound and/or unbound [26, 35]. Table 2 summarizes the PK parameters reported in human studies with administration of nutraceutical forms of RSV.

Absorption

Human absorption seems rapid, via simple intestinal *trans*-epithelial diffusion [36–38]. The rate but not the extent of absorption following a 400 mg RSV nutraceutical dose was significantly impaired when taken with food compared with the fasted state [39]. Similarly, the PK of 2000 mg twice daily showed delayed and decreased absorption with a high fat breakfast [33]. In contrast, RSV absorption when taken as red wine was not reduced by a meal compared with the fasted state [40].

Metabolism and bioavailability

Following ingestion, most RSV undergoes rapid metabolism in enterocytes, resulting in up to a 20-fold higher

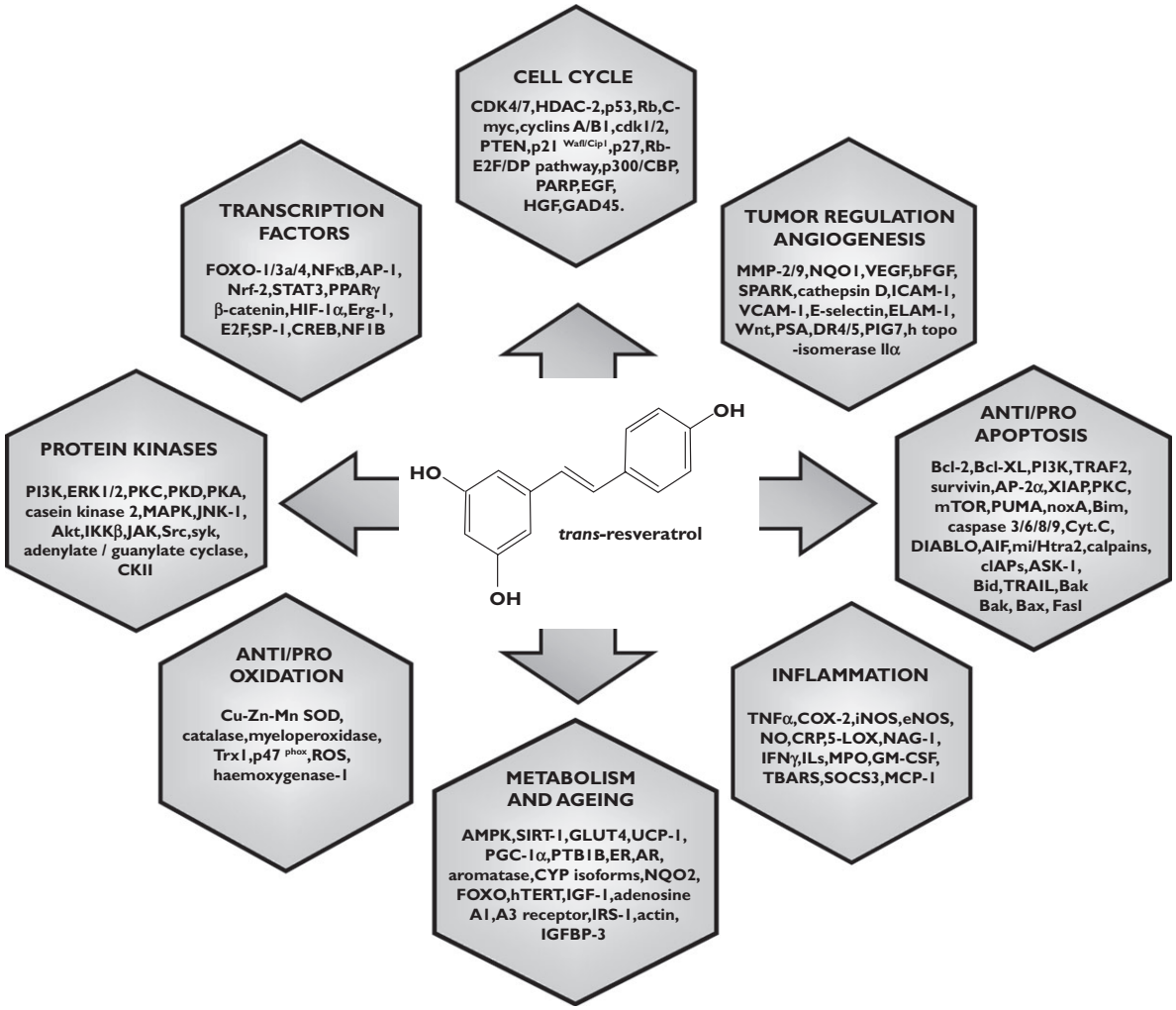

Figure 1

Structure of resveratrol. Genes and products affected by exposure to the compound [7, 17, 25, 56]. CDK – 1/2/4/7, cyclin-dependant kinase 1/2 /4/7; HDAC-2, histone deacetylase 2; P53, tumour protein 53; Rb, retinoblastoma tumour suppressor gene; c-Myc, gene myelocytomatosis; PTEN, phosphatase and tensin homolog; p21$^{Waf1/Cip1}$, cyclin-dependent kinase inhibitor 1A; P27, cyclin dependant kinase inhibitor 27; Rbf-E2F/DP pathway, Retinoblastoma-family protein/ E2F transcription factor/ DP transcription factor; P300/CBP, CREB binding protein; PARP, poly(ADP)-ribose polymerase; EGF, endothelial growth factor; HGF, human growth factor; GAD45, DNA damage inducible gene 45; FOXO-1/3a/4, forkhead transcription factor 1/3a/4; NFκB, nuclear factor kappa B; AP-1, activating protein-1;NRF-2, nuclear respiratory factor-2; STAT3, signal transducer and activator of transcription 3; PPARγ, peroxisome proliferator activated receptor gamma; HIF-1α, hypoxia inducible factor 1-alpha; Erg-1, ets-related gene; E2F, transcription factor E2F; SP-1, Sp1 transcription factor; CREB, cyclic-AMP response element binding proteins; NF1B, neurofibromin 1b; PI3K, phosphoinositide 3 kinases; ERK1/2, extracellular signal regulated kinase 1 /2; PKC, protein kinase C; PKD, protein kinase D; PKA, protein kinase A; MAPK, mitogen activated protein kinase; JNK-1, c-Jun N-terminal kinases; Akt, serine/threonine protein kinase; IKKβ, IkB kinase beta; JAK, Janus kinase; Src, sarcoma pro-oncogenic tyrosine kinase; syk, spleen tyrosine kinase gene; CKII, casein kinase 2; Cu-Zn-Mn SOD, copper-zinc-manganese superoxide dismustase; Trx1, cytosolic thioredoxin; p47 ^{phox}, enzyme for production of superoxide; ROS, reactive oxygen species; AMPK, adenosine monophosphate activated protein kinase; GLUT4, glucose transporter 4; UCP-1, uncoupling protein 1; PGC-1α, PPARgamma coactivator 1 proliferator-activated receptor-gamma; PTB1B, protein tyrosine phosphatase 1 B; ER, eostrogen receptor; AR, andogen receptor; CYP isoforms, cytochrome P450 isoforms; NQO2, NADPH dehydrogease quinone 2; hTERT, human telomerase reverse transcriptase; IGF-1, insulin like growth factor-1; IRS-1, insulin receptor substrate 1; IGFBP-3, Insulin-like growth factor-binding protein 3; TNFα, tumour necrosis factor alpha; COX-2, cyclo-oxygenase 2; iNOS, inducible nitric oxide synthase, eNOS, endothelial nitric oxide synthase; NO, nitric oxide; CRP, C- reactive protein; 5-LOX, 5-lipoxygenase- activating protein; NAG-1, nonsteroidal anti-inflammatory drug-activated gene; IFNγ, interferon gamma; ILs, interleukins; MPO, myeloperoxidase; GM-CSF, granulocyte-macrophage colony stimulating factor; TBARS, thiobarbituric acid reactive substances; SOCS3, Suppressor of cytokine signaling 3; MCP-1, monocyte chemotactic protein-1; TGFβ, transforming growth factor beta; Bcl-2, B-cell lymphoma 2; Bcl-XL, BCL2-like 1; TRAF2, TNF receptor-associated factor 2; AP-2α, activating protein 2; XIAP, X-linked Inhibitor of apoptosis protein; mTOR, mammalian target of rapamycin; PUMA, BCL2 binding component 3; noxA, nitrate reductase, NADH oxidase subunit; Bim, BCL2-like 11 apoptosis facilitator; Cyt. C, cytochrome C; DIABLO, diablo homolog; AIF, apoptosis inducing factor; mi/Htra2, HtrA serine peptidase 2; cIAPs, inhibitor of apoptosis proteins; ASK-1, Apoptosis signal-regulating kinase 1; Bid, BH3 interacting domain death agonist; TRAIL, TNF-related apoptosis-inducing ligand; Bak, BCL2-antagonist/killer 1; Bax, Bcl-2 associated protein; Fasl, Fas antigen ligand; MMP-2/9, matrix metalloproteinases 2/9; NQO1, human NAD(P)H quinone 1; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; ICAM-1, inter-cellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; ELAM-1, endothelium leukocyte adhesion molecule 1; Wnt, wingless-type MMTV integration site family, member; PSA, prostate-specific antigen; DR4/5, tumour necrosis factor receptor superfamily, member 10a/10b; PIG7, p53-induced gene 7.

Table 1

Some sources of resveratrol and amount provided in standard serves

Food sources	Total resveratrol content Average per standard units	 Average equivalent in standard serving	Reference
Red wines	0.1–14.3 mg l^{-1}	150 ml glass: 0.015–2.15 mg	[88, 89]
Pinot noir	10.5 mg l^{-1}	150 ml glass: 1.57 mg	
White wines	<0.1 to 1.2 mg l^{-1}	150 ml glass: 0.015–0.18 mg	
Riesling	up to 1.2 mg l^{-1}	150 ml glass: up to 0.32 mg	
Red grape juice	0.5 mg 100 ml^{-1}	250 ml glass: 1.25 mg	[90, 91]
White grape juice	0.05 mg 100 ml^{-1}	250 ml glass: 0.125 mg	
Cranberry juice	0.2 mg 100 ml^{-1}	250 ml glass: 0.5 mg	
Fresh grape skin	5–10 mg 100 g^{-1}		
Grapes (dry sample)	0.64 mg 100 g^{-1}	250 g (1 cup): 1.6 mg	[30, 92, 93]
Blueberry (dry sample)	0.4 mg 100 g^{-1}	150 g punnet: 0.6 mg	
Strawberries (frozen)	0.375 mg 100 g^{-1}	150 g punnet: 1.56 mg	
Red currant (frozen)	1.5 mg 100 g^{-1}	125 g (1/2 cup): 1.87 mg	
Cranberry (frozen)	1.9 mg 100 g^{-1}	125 g (1/2 cup): 2.41 mg	
Bilberry (frozen)	0.678 mg 100 g^{-1}	125 g (1/2 cup): 1.7 mg	
Raw peanuts	0.15 mg 100 g^{-1}	250 g (1 cup): 0.37 mg	[88, 94, 95]
Roasted peanuts	0.006 mg 100 g^{-1}	250 g (1 cup): 0.015 mg	[96–98]
Boiled peanuts	0.52 mg 100 g^{-1}	250 g (1 cup): 1.3 mg	
100% peanut butter	0.047 mg 100 g^{-1}	1 tablespoon: 0.01 mg	
Cocoa powder	0.185 mg 100 g^{-1}	1 tablespoon: 0.019 mg	
Dark chocolate	0.124 mg 100 g^{-1}	50 g: 0.063 mg	
Milk chocolate	0.001 mg 100 g^{-1}	50 g: 0.0005 mg	
Polygonum cuspidatum	181–350 mg 100 g^{-1}		[88]
Itadori tea	0.97 mg 100 ml^{-1}	200 ml: 1.94 mg	[98]
Nutraceuticals formulae		Capsule: 20 to 500 mg as pure *trans*-RSV, or from 50 μg to 50 mg as part of antioxidant formulae	
Darakchasava (Ayur-vedic formula)	0.36 mg/100 ml^{-1}		[16]

concentration of circulating conjugates, and less than 1% of parent RSV [36, 41]. Seven sulphation and glucuronidation conjugates have been identified [26, 42]. Entero-hepatic recirculation and intestinal de-conjugation of metabolites was evidenced in animals [37, 41]. Extreme inter-individual and inconsistent non-dose-dependent variability were observed in all PK parameters, possibly explained by assay sensitivity, individual enzymatic polymorphism and distinction, or lack of, between parent, *cis*, *trans* and conjugated forms in C_{max} measures. Non-proportional changes in bioavailability were evidenced by non-proportional changes in the C_{max} and AUC with increasing doses (Table 2). Additionally, morning intake demonstrated greater bioavailability, perhaps due to the influence of the circadian rhythm on drug metabolism enzyme activity and the entero-hepatic circulation [43]. These considerations are important when drawing conclusions about RSV bioavailability and correlations with efficacy.

Clinicians are interested in the effects of repeated dosing on bioavailability, especially in the context of chronic disease, where a steady-state concentration of a drug is targeted and intake is chronic. No studies have investigated the benefits of split *vs*. single daily dosing on RSV bioavailability. However repeated intake was observed to increase plasma parent concentration. C_{max} was 2.4 μM after single 5000 mg dose administration [44]. The same investigators reported C_{max} of 4.24 μM with 5000 mg administered daily for 29 days. Surprisingly this increase did not occur at all doses investigated (500 to 5000 mg) [31]. Additionally, clearance appears to decrease with repeated dosing, possibly demonstrating saturable metabolism and altered bioavailability, which is concerning for chronic intake.

Overall, bioavailability of parent RSV is poor due to the rapid metabolism resulting in high concentrations of circulating conjugates. Tissue accumulation of total RSV [45] and activity of conjugates were recently evidenced [46, 47], suggesting that circulating parent concentration may not be the sole mode of exposure. Plasma parent RSV C_{max} was undetectable at 500 mg and 1000 mg doses in colorectal cancer patients after 8 days intake, but total RSV was found in large concentrations in colorectal tumour and nearby healthy tissue, and bioactivity demonstrated [45]. It is unclear whether these concentrations are due to direct absorption of the parent or the absorption of cleaved glucuronide conjugates.

Distribution and excretion

In vitro, 50% to 98% of total RSV was observed non-covalently bound to albumin, LDL and haemoglobin [42, 48, 49]. In humans, close to 50% of total RSV was found to be bound to plasma proteins [26]. Evidence of total RSV

Table 2

Reported nutraceutical RSV pharmacokinetics parameters in humans

99% pure nutraceutical RSV Single dosing Dose	C_{max} of total or [parent] RSV	C_{max} of dominant conj.	t_{max} of total or parent	Half-life of total, parent or [dominant conj.]	AUC of total, parent or [dominant conj.] (ng ml^{-1} h)	Tissue uptake of parent, or [dominant conj.]	CV for C_{max} and AUC	Reference
25 mg labelled RSV/70 kg BW	2 μM [<0.02 μM]	0.9–14 μM (C2 ,C3)	60 min; 2nd peak at 360 min	7.2 to 11.8 h	6240			[41]
500 to 5000 mg	[0.3 to 2.4 μM]	5 to 18.8 μM (C1)	50 to 90 min	2.8 to 8.9 h [3.2 to 11.5 h]	224 to 1319 [4049 to 30 898]		Up to 80%	[44]
400 mg Fed	0.18 μM	Not measured	2 h	–	–		128%	[39]
400 mg Fasting	0.2 μM		30 min					
85.5 mg piceid form equivalent to 50 mg RSV	n.d.	0.94 μM (C3)	360 to 480 min	–	–			[26]
250 mg	[0.024 μM]	1.3 μM	90 min	Not reported	Not reported			[84]
500 mg	[0.062 μM]	3.1 μM (sulphates, unspecified)						
Multiple dosing								
25 mg	**Dose ratio:**	Not measured	50 to 90 min	1–3 h at dose	**AUC ratio:**			[43]
50 mg	50 mg:25 mg = 6			1	150 mg/25 mg = 39			
100 mg	**C_{max} ratio:**			2–5 h at dose				
150 mg	150 mg:25 mg = 25			13				
13 doses over 48 h								
200 mg x 3/day for 3 days	0.15 μM	Not measured	1 to 1.5 h	2.9 to 4.7 h	77 to 116		40%	[99]
2000 mg x2/day								[33]
D7 SDBF	5.6 μM	Not measured	3 h	2.4 h	3558			
D8 HFBF	3 μM		5 h	2.4 h	1966			
D15 SDQ	5.6 μM		4 h	2.2 h	4025			
D16 SDQetoh	5.7 μM		3 h	2.1 h	3800			
500 mg – 8 days	ND	13.4 μM (C6)	Not reported	Not reported	Not reported	18.6 [86 C4] nmol g^{-1}	200%	[45]
1000 mg – 8 days	ND	22.3 μM (C6)				674 [67.2 C1] nmol g^{-1}	200%	
500 mg 29 days	[0.19 to 4.24 μM]	2.5 to 18.3 μM (C1)	60 to 70 min (0.25 to 5 h inter-subject variability)	4.8 to 9.7 h [3.09 to 8.14 h] non dose-dependent	175 to 4097 [3558 to 38 900] non dose-dependent		35 to 107%	[31]
1000 mg 29 days								
2500 mg 29 days								
5000 mg 29 days								
1000 mg 28 days	[0.3 μM]	10.4 μM (C1)	Not reported	Not reported	Not reported		400%	[34]

ND not detected; BW body weight; C_{max}, maximal concentration; t_{max}, time of maximal concentration; AUC, area under the concentration *vs.* time curve; Total RSV, parent and conjugated RSV; CV, coefficient of variability; Conj. conjugates; C1, resverarol-3-O-sulphate; C2, resveratrol- 4′-O-sulphate; C3, resveratrol disulfate, C4; resveratrol 3-O-glucuronide; C5, resveratrol 4′-O- glucuronide; C6, resveratrol sulphate glucuronide; SDBF, standard breakfast; HFBF, high fat breakfast; SDQ, standard breakfast and quercetin; SDQetoh, standard breakfast and quercetin and ethanol.

accumulation in the healthy colon mucosa and tumour tissue demonstrates tissue uptake, identifying the colonic tissue as a target [45]. The kidney is the dominant excretion pathway with urinary and faeces recovery of total RSV between 70 to 98% within 24 h [44].

Pharmacodynamics and clinical evidence

Obesity and ageing related chronic diseases are emerging as a new pandemic, with few solutions [50–52]. At the crossroads of these disorders stands the combination of inflammation and oxidative stress [4, 53]. Through its ability to up-regulate host antioxidant capacity and activity, and inhibit the NFkB and cyclo-oxygenase pro-inflammatory pathways, RSV is potentially in a favourable position to address clinically carcinogenesis, atherogenesis, neurodegeneration, mitochondrial dysfunction and insulin signalling [22, 25, 54–56]. *In vitro*, *ex vivo* and animal model experiments have provided evidence for bioactivity with clinical potential in cancer chemoprevention [57] and therapy [58], cardiovascular disease and obesity [24, 54, 59–61], hepatic alcoholic or metabolic dysregulations [62–67], diabetes [54, 66], arthritis, osteoporosis [68], and neuroprotection [69, 70]. Figure 2 outlines this clinical potential.

It is still the dawn of clinical investigations, because the successful translation in humans of *in vitro* and *in vivo* findings is thought to depend largely on parent RSV plasma bioavailability. Basic science investigations have demonstrated efficacy at parent concentrations physiologically difficult to replicate (>5 μM) [35, 56, 71], considering that daily 5000 mg resulted in plasma parent concentration of 4.24 μM [31].

Animals model experiments have however also shown efficacy at very low concentrations [8], and diametrically opposing activity depending on dose [72]. A possible dose-related target-specific bioactivity allows for anti- or pro-oxidant effects, and apoptotic or survival signalling [71]. This is relevant in the context of multifactorial chronic diseases if this characteristic is confirmed in humans, and if RSV is to become a therapeutic agent.

Table 3 outlines the interventions listed on clinicaltrials.gov and currently underway. The broad range of designs and targeted outcomes reflects the multifaceted potential of RSV, the lack of consensus on adequate dosage, and the debate on the most adequate source: food *vs*. nutraceuticals.

Cardiovascular health

Initial clinical data on cardiovascular protection provides some evidence that low RSV dosages, either through phytochemicals synergy in food sources or at lower nutraceutical doses, are sufficient to induce putative beneficial effects, consistent with animal observations of anti-oxidant, anti-inflammatory and vasorelaxation activity [73, 74].

Red grape polyphenols (containing 0.9 mg RSV) acutely and significantly increased flow mediated dilation (FMD) in males with coronary heart disease, indicating activity on endothelial function [75]. Compared with baseline, powdered mixed grape polyphenols intake (containing 7 μmol kg^{-1} RSV) for 4 weeks significantly decreased triglycerides, LDL cholesterol, apo-lipoproteins B/E, and oxidative stress measured by plasma TNFα and urine isoprostane concentrations, in pre- and post-menopausal women [76]. When compared with water, beer or vodka, red wine intake (100 ml daily) for 3 weeks significantly increased FMD and promoted endothelial progenitor cells level and function, through increased nitric oxide bioavailability [77]. Acute red wine intake (400 ml) with a high fat meal delayed and reduced the peroxidation of post-prandial LDL in healthy subjects when compared with plain ethanol [15]. An acute dose-dependent effect on FMD was also demonstrated in overweight and obese subjects receiving nutraceutical RSV (30, 90 or 270 mg) against placebo [78]. However these dose and intake-dependent benefits remain to be confirmed with chronic intake, and can certainly not be attributed to RSV alone, when whole grape products were administered.

Cancer chemoprevention

Initial oncology trials suggest that both food source RSV as part of a synergy of phytochemicals and large nutraceutical RSV dosages may have chemopreventive activity.

Grape extract (containing 0.073 to 0.114 mg RSV) administered for 14 days pre-surgical resection to colon cancer patients, inhibited the expression of genes implicated in cancer initiation in the healthy mucosa but not cancerous tissue (measured by qRT-PCR) [79, 80]. In contrast, nutraceutical RSV doses of 500 and 1000 mg resulted in a dose-dependent decrease in cell proliferation by up to 5.6% in colorectal tumours after 8 days intake, quantified by immune-histochemical staining of the surrogate marker of cell proliferation Ki-67, in biopsy and surgically removed tissue. This study also provided evidence that the parent and conjugated RSV accumulate in tumour tissue and nearby healthy mucosa, by up to 674 nmol g^{-1}, with a dominance of parent compound [45]. The same investigators explored the effects of repeated dosing (500 mg to 5000 mg) over 29 days in healthy subjects on circulating insulin-like growth factor (IGF)-1 and IGF-binding protein-3 (IGFBP-3), both involved in carcinogenesis pathways [31, 81]. The plasma concentrations of IGF-1 and IGFBP-3, measured by enzyme-linked immunosorbent assay, were significantly decreased from baseline, with the 2500 mg regimen, but interestingly not at lower or higher dosages. The authors suggested the modulation of the IGF axis as a mechanism of action for RSV's chemoprevention activity.

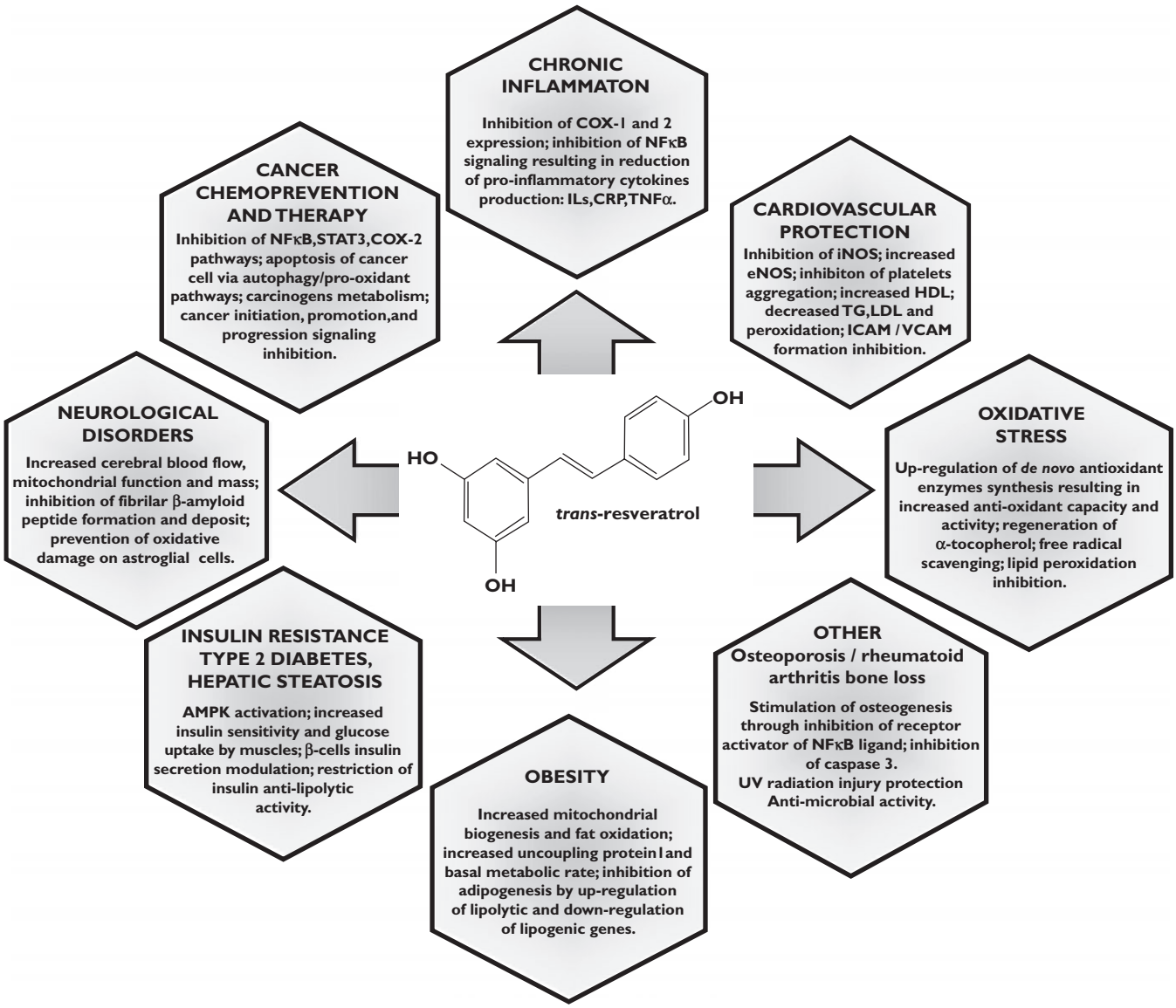

Figure 2

The potential clinical applications of resveratrol and main proposed mechanisms of action [6, 7, 24, 56, 70]. NFκB, nuclear factor kappa B; STAT3, signal transducer and activator of transcription 3; COX-1/2, cyclo-oxygenase 1 /2; IL's, interleukins; CRP, C-reactive protein; AMPK, adenosine monophosphate activated protein kinase; TNFα, tumour necrosis factor alpha; TG, triglycerides; HDL, high density lipoproteins; LDL, low density lipoproteins; ICAM, intercellular adhesion molecule 1; VCAM, vascular cell adhesion molecule 1; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase.

These studies provide some evidence for chemoprevention potential in humans, without clarification on adequate dosages.

Other

Inflammation and oxidative stress were significantly reduced in peripheral blood mononuclear cells of healthy subjects receiving *Polygonum cuspidatum* (containing 40 mg RSV), for 6 weeks against placebo [82]. Reactive oxygen species generation, P47 ^{phox} protein expression (subunit in the enzyme converting O_2 to O_2^- species), and NFκB DNA binding capability were significantly blunted demonstrating modulation of oxidative stress and pro-inflammation signalling. Expression of IL-6, SOCS3, TNFα, plasma C-reactive protein and TNFα concentrations were significantly reduced.

The same group investigated similar biomarkers, endotoxin concentrations and the induction of Nrf2 following a high fat/high carbohydrate meal. Nutraceutical RSV (100 mg) combined with grape extract (75 mg polyphenols) was administered acutely before the meal to healthy individuals. Supplementation significantly blunted

Table 3

Currently recruiting and ongoing clinical trials investigating the effects of RSV (Source: http://www.clinicaltrials.gov)

Investigator	Population	Length and RSV daily dosage	Endpoints
Manini	Aged 65–100 years	12 weeks, 300 mg or 1000 mg	Safety, cognitive and physical performance
Dandona	Obese and type 2 diabetes	12 weeks, 40 mg three times daily or 500 mg	NFκB activity, oxidative stress, GIP, GLP-1 secretions
Poulsen	Obese	5 weeks, daily 500 mg three times daily	Description of the molecular biology underpinning the interplay between calorie restriction, SIRT1, STAT5 and the GH/IGF-I axis
Vita	Overweight, type 2 diabetes	1 week for each 90 and 270 mg	Arterial flow-mediated dilation, inflammation and oxidative stress markers, insulin resistance
Holcombe	Colon cancer, surgery scheduled	4 weeks, 20, 80 or 160 mg	Wnt signaling in cancerous and normal colonic mucosa
Oka	Overweight, ≥50 years, insulin resistant	28 days, 5000 mg	Insulin sensitivity, IGF-1 concentrations, cholesterol, physical activity levels
Kerwin	Clinical diagnosis Alzheimer's disease	52 weeks, 215 mg	Cognition, function and behaviour
Holcombe	Healthy adults	28 days, 1/3, 2/3 or 1 pound fresh grapes	Colonic mucosa cell proliferation. Expression of beta-catenin and Wnt pathway genes. RSV content variation in grapes
Klein	Post-menopausal women	12 weeks, 75 mg or 30% calorie restriction diet	Muscle tissue gene expression, insulin resistance, inflammation, intra-hepatic lipids, body composition
Fu	Malignancy, failed therapies, or no standard care available	28 days cycles, starting at 3000 mg alone or combined with curcumin	Safety-efficacy study, maximum tolerated dose finding
Timmers	Obese, sedentary, 45–65 years	30 days, 150 mg	Fat oxidation, mitochondrial biogenesis and function, adipose and skeletal muscle lipolysis
Hummel	≥50 years, heart failure symptoms	6 weeks 300 mg twice daily dried grape mixed polyphenols	Artery flow-mediated dilation + seven other CVD health markers
Holte	Follicular lymphoma grade I or II	16 weeks, Merlot-grape juice 660 ml or 495 ml	Apoptosis, proliferation of tumour cells, pro- inflammatory cytokines
Sabaté	≥6 months diagnosis of types 2 diabetes with HbA1c >9%	24 weeks, moderate fat diet with or without 32 g peanuts or 2 tablespoons peanut butter	HDL cholesterol, plasma lipids, glucose, HbA1c, anthropometrics, blood pressure

NFκB, nuclear factor kappa B; GIP, gastric inhibitory peptide; GLP-1, glucagon like peptide 1; SIRT1, sirtuin 1; STAT5, signal transducer and activator of transcription 5; GH/IGF-I axis, growth hormone /insulin like growth factor 1 axis; Wnt, wingless-type MMTV integration site family pathway; IGF-1, insulin like growth factor 1; HbA1c, glycosylated haemoglobin A1c; CVD, cardiovascular disease.

the meal-induced inflammatory and oxidative stress, and increased antioxidant capacity compared with placebo (measured by Western blotting and RT-PCR) [83].

Acute nutraceutical RSV dosing (250 or 500 mg) dose-dependently increased cerebral blood flow during cognitive tasking in healthy subjects, indexed by total concentration of haemoglobin and near-infrared-spectroscopy [84].

These studies suggest clinical potential in the modulation of key drivers of chronic diseases. However clinical efficacy remains to be demonstrated with patients in phase 3 trials.

Areas of concern

Poor systemic bioavailability of resveratrol

Enhancing the bioavailability of RSV is the subject of extensive biotechnology research, because poor bioavailability remains a major obstacle to replicate successfully preclinical evidence [85]. Target plasma concentrations, and therefore dosages prescribed, may however differ for different applications, as shown in initial clinical investigations [75, 76].

Exposure to conjugates may play a role in efficacy. In fact, sulphation conjugates were recently reported to modulate inflammation pathways *in vitro* with a similar efficacy to the parent compound in some cases [46, 47], whilst glucuronidation conjugates were reported inactive *in vitro* at concentrations up to 300 μM. Authors have proposed that metabolites may constitute an abundant pool of RSV, via β-glucuronidase and sulphatase deconjugation [36, 86]. Recent evidence of parent RSV tissue accumulation, and bioactivity in spite of undetectable plasma concentrations suggests that efficacy may not necessarily depend on parent RSV circulating concentration alone [45]. It is possible that reaching *in vitro* concentrations may not be necessary, but that the excursion of total RSV (parent and metabolites) under the concentration *vs.* time curve is of importance.

Localization of tissue uptake, what determines target tissues and the target/dose relationship are clearly topics for future research.

Food vs. nutraceutical dose

Dietary intake can reach 6 to 8 mg daily. As such, nutraceutical dosages (20 mg to 500 mg per capsule) may appear disproportionate. In key studies on obesity and ageing dysregulations, the animals received between 20 to 400 mg kg^{-1} body weight [62–65, 67]. Converted to the human equivalent with the body surface area normalization method [87], this equates to 243 to 4875 mg for a

75 kg adult, providing some justification for nutraceutical dosages. In contrast, recent clinical data show bioactivity at µg doses, when provided as part of a synergy of phytochemicals in foods. This fuels the debate on the synergy or antagonism of bioactive dietary compounds, a phenomenon difficult both to ignore and measure.

It is too soon to comment on the most suitable dose and source, or the effects and safety of chronic intake, until further clinical data are available. In the mean time, nutraceutical RSV is easily available commercially, and uncontrolled self-prescribing is encouraged by claims of calorie-restriction mimetic and anti-ageing activity, following initial *in vivo* reports [7].

Conclusions

RSV is an intriguing molecule worth investigating for its multi-target bioactivity, but many questions need answering. These include queries over the long term effects of nutraceutical dosages 100- to 1000-fold higher than dietary sources, the consequences of tissue accumulation and chronically down-regulating inflammatory pathways, the consequences of large circulating concentrations of metabolites which seem bioactive, why there are such large differences in PK between subjects, should disease-prevention and therapeutic doses be different and lastly do apparent saturable kinetics in parent RSV bioavailability and clearance in repeated dosing have toxicity implications?

RSV has encouraging potential to address systemically and at the genomic level inflammation and oxidative stress, two drivers of ageing and chronic diseases [8, 18]. The *in vitro*, *in vivo* and first clinical evidence have certainly confirmed a role for nutrapharmacology in health, and have provided justification for the daily consumption of RSV and other phytochemical containing food products as part of disease prevention, which may ultimately be the reason why these bioactive compounds do exist in nature [3]. Clinical evidence examining the effect of metabolites, the correlation between dose, concentration and effect, especially in the context of chronic disease, is awaited.

Competing Interests

There are no competing interests to declare.

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REFERENCES

1 Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. Annu Rev Nutr 2010; 30: 173–99.

2 Prasad S, Phromnoi K, Yadav VR, Chaturvedi MM, Aggarwal BB. Targeting inflammatory pathways by flavonoids for prevention and treatment of cancer. Planta Med 2010; 76: 1044–63.

3 Anand P, Kunnumakara A, Sundaram C, Harikumar K, Tharakan S, Lai O, Sung B, Aggarwal B. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 2008; 25: 2097–116.

4 Cave M, Hurt R, Frazier T, Matheson P, Garrison R, McClain C, McClave S. Obesity, inflammation, and the potential application of pharmaconutrition. Nutr Clin Pract 2008; 23: 16–34.

5 Jang M, Cai L, Udeani G, Slowing K, Thomas C, Beecher C, Fong H, Farnsworth N, Kinghorn A, Mehta R. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 1997; 275: 218–20.

6 Brown L, Kroon P, Das D, Das S, Tosaki A, Chan V, Singer M, Feick P. The biological responses to resveratrol and other polyphenols from alcoholic beverages. Alcohol Clin Exp Res 2009; 33: 1513–23.

7 Morris B. Calorie restriction mimetics and aging. In: Calorie Restriction, Aging Longevity, eds Everitt AV, Rattan SIS, Couteur DG, de Cabo R. The Netherlands: D Springer Science+Business Media B.V., 2010; 141–75.

8 Kroon A, Iyer A, Chunduri P, Chan V, Brown L. The cardiovascular nutrapharmacology of resveratrol: pharmacokinetics, molecular mechanisms and therapeutic potential. Curr Med Chem 2010; 17: 2442–55.

9 Orallo F. Comparative studies of the antioxidant effects of cis-and trans-resveratrol. Curr Med Chem 2006; 13: 87–98.

10 Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 1992; 339: 1523–26.

11 Criqui M, Ringel B. Does diet or alcohol explain the French paradox? Lancet 1994; 344: 1719–23.

12 Siemann E, Creasy L. Concentration of the phytoalexin resveratrol in wine. Am J Enol Vitic 1992; 43: 49–52.

13 Frankel E, German J, Kinsella J, Parks E, Kanner J. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. Lancet 1993; 341: 454–57.

14 Gresele P, Pignatelli P, Guglielmini G, Carnevale R, Mezzasoma A, Ghiselli A, Momi S, Violi F. Resveratrol, at concentrations attainable with moderate wine consumption, stimulates human platelet nitric oxide production. J Nutr 2008; 138: 1602–08.

15 Natella F, Ghiselli A, Guidi A, Ursini F, Scaccini C. Red wine mitigates the postprandial increase of LDL susceptibility to oxidation. Free Radic Biol Med 2001; 30: 1036–44.

16 Paul B, Masih I, Deopujari J, Charpentier C. Occurrence of resveratrol and pterostilbene in age-old darakchasava, an ayurvedic medicine from India. J Ethnopharmacol 1999; 68: 71–6.

17 Shakibaei M, Harikumar K, Aggarwal B. Resveratrol addiction: to die or not to die. Mol Nutr Food Res 2009; 53: 115–28.

18 Csiszar A. Anti inflammatory effects of resveratrol: possible role in prevention of age related cardiovascular disease. Ann NY Acad Sci 2011; 1215: 117–22.

19 Agarwal B, Baur JA. Resveratrol and life extension. Ann NY Acad Sci 2011; 1215: 138–43.

20 Wu JM, Hsieh T. Resveratrol: a cardioprotective substance. Ann NY Acad Sci 2011; 1215: 16–21.

21 Shukla Y, Singh R. Resveratrol and cellular mechanisms of cancer prevention. Ann NY Acad Sci 2011; 1215: 1–8.

22 Pezzuto J. Resveratrol as an inhibitor of carcinogenesis. Pharm Biol 2008; 46: 443–573.

23 Cantó C, Jiang L, Deshmukh A, Mataki C, Coste A, Lagouge M, Zierath J, Auwerx J. Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle. Cell Metab 2010; 11: 213–19.

24 Um J, Park S, Kang H, Yang S, Foretz M, McBurney M, Kim M, Viollet B, Chung J. AMP-activated protein kinase–deficient mice are resistant to the metabolic effects of resveratrol. Diabetes 2010; 59: 554–63.

25 Pervaiz S, Holme A. Resveratrol: its biologic targets and functional activity. Antioxid Redox Signal 2009; 11: 2851–97.

26 Burkon A, Somoza V. Quantification of free and protein-bound trans-resveratrol metabolites and identification of trans-resveratrol-C/O-conjugated diglucuronides-Two novel resveratrol metabolites in human plasma. Mol Nutr Food Res 2008; 52: 549–57.

27 Caruso F, Tanski J, Villegas-Estrada A, Rossi M. Structural basis for antioxidant activity of trans-resveratrol: ab initio calculations and crystal and molecular structure. J Agric Food Chem 2004; 52: 7279–85.

28 Langcake P, Cornford C, Pryce R. Identification of pterostilbene as a phytoalexin from Vitis vinifera leaves. Phytochemistry 1979; 18: 1025–27.

29 Langcake P, Pryce R. The production of resveratrol by Vitis vinifera and other members of the Vitaceae as a response to infection or injury. Physiol Plant Pathol 1976; 9: 77–86.

30 Lyons M, Yu C, Toma R, Cho S, Reiboldt W, Lee J, van Breemen R. Resveratrol in raw and baked blueberries and bilberries. J Agric Food Chem 2003; 51: 5867–70.

31 Brown V, Patel K, Viskaduraki M, Crowell J, Perloff M, Booth T, Vasilinin G, Sen A, Schinas A, Piccirilli G. Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: safety, pharmacokinetics and effect on the insulin-like growth factor axis. Cancer Res 2010; 70: 9003–11.

32 Cottart C, Nivet Antoine V, Laguillier Morizot C, Beaudeux J. Resveratrol bioavailability and toxicity in humans. Mol Nutr Food Res 2010; 54: 7–16.

33 la Porte C, Voduc N, Zhang G, Seguin I, Tardiff D, Singhal N, Cameron D. Steady-state pharmacokinetics and tolerability of trans-resveratrol 2000mg twice daily with food, quercetin and alcohol (ethanol) in healthy human subjects. Clin Pharmacokinet 2010; 49: 449–54.

34 Chow H, Garland L, Hsu C, Vining D, Chew W, Miller J, Perloff M, Crowell J, Alberts D. Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study. Cancer Prev Res 2010; 3: 1168–75.

35 Gescher A, Steward W. Relationship between mechanisms, bioavailibility, and preclinical chemopreventive efficacy of resveratrol: a conundrum. Cancer Epidemiol Biomarkers Prevent 2003; 12: 953–57.

36 Walle T. Bioavailability of resveratrol. Ann NY Acad Sci 2011; 1215: 9–15.

37 Brisdelli F, D'Andrea G, Bozzi A. Resveratrol: a natural polyphenol with multiple chemopreventive properties (review). Curr Drug Metab 2009; 10: 530–46.

38 Kuhnle G, Spencer J, Chowrimootoo G, Schroeter H, Debnam E, Srai S, Rice-Evans C, Hahn U. Resveratrol is absorbed in the small intestine as resveratrol glucuronide. Biochem Biophys Res Commun 2000; 272: 212–17.

39 Vaz-da-Silva M, Loureiro A, Falcao A, Nunes T, Rocha J, Fernandes-Lopes C, Soares E, Wright L, Almeida L, Soares-da-Silva P. Effect of food on the pharmacokinetic profile of trans-resveratrol. Int J Clin Pharmacol Ther 2008; 46: 564–70.

40 Vitaglione P, Sforza S, Galaverna G, Ghidini C, Caporaso N, Vescovi P, Fogliano V, Marchelli R. Bioavailability of trans resveratrol from red wine in humans. Mol Nutr Food Res 2005; 49: 495–504.

41 Walle T, Hsieh F, DeLegge M, Oatis J, Walle U. High absorption but very low bioavailability of oral resveratrol in humans. Drug Metab Dispos 2004; 32: 1377–82.

42 Wenzel E, Somoza V. Metabolism and bioavailability of trans resveratrol. Mol Nutr Food Res 2005; 49: 472–81.

43 Almeida L, Vaz da Silva M, Falcão A, Soares E, Costa R, Loureiro A, Fernandes Lopes C, Rocha J, Nunes T, Wright L. Pharmacokinetic and safety profile of trans resveratrol in a rising multiple dose study in healthy volunteers. Mol Nutr Food Res 2009; 53: 7–15.

44 Boocock D, Faust G, Patel K, Schinas A, Brown V, Ducharme M, Booth T, Crowell J, Perloff M, Gescher A. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiol Biomarkers Prevent 2007; 16: 1246–52.

45 Patel K, Brown V, Jones D, Britton R, Hemingway D, Miller A, West K, Booth T, Perloff M, Crowell J. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer Res 2010; 70: 7392–99.

46 Calamini B, Ratia K, Malkowski M, Cuendet M, Pezzuto J, Santarsiero B, Mesecar A. Pleiotropic mechanisms facilitated by resveratrol and its metabolites. Biochem J 2010; 429: 273–82.

47 Hoshino J, Park E, Kondratyuk T, Marler L, Pezzuto J, van Breemen R, Mo S, Li Y, Cushman M. Selective synthesis and biological evaluation of sulfate-conjugated resveratrol metabolites. J Med Chem 2010; 53: 5033–43.

48 Jannin B, Menzel M, Berlot J, Delmas D, Lançon A, Latruffe N. Transport of resveratrol, a cancer chemopreventive agent, to cellular targets: plasmatic protein binding and cell uptake. Biochem Pharmacol 2004; 68: 1113–18.

49 Lu Z, Zhang Y, Liu H, Yuan J, Zheng Z, Zou G. Transport of a cancer chemopreventive polyphenol, resveratrol: interaction with serum albumin and hemoglobin. J Fluoresc 2007; 17: 580–87.

50 Christensen K, Doblhammer G, Rau R, Vaupel J. Ageing populations: the challenges ahead. Lancet 2009; 374: 1196–208.

51 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047–53.

52 Dixon J. The effect of obesity on health outcomes. Mol Cell Endocrinol 2010; 316: 104–08.

53 Reuter S, Gupta S, Chaturvedi M, Aggarwal B. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med 2010; 49: 1603–16.

54 Szkudelska K, Szkudelski T. Resveratrol, obesity and diabetes. Eur J Pharmacol 2010; 635: 1–8.

55 Harikumar K, Aggarwal B. A multitargeted agent for age-associated chronic diseases. Cell Cycle 2008; 7: 1020–35.

56 Baur J, Sinclair D. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov 2006; 5: 493–506.

57 Bishayee A. Cancer prevention and treatment with resveratrol: from rodent studies to clinical trials. Cancer Prev Res 2009; 2: 409–18.

58 Harikumar K, Kunnumakkara A, Sethi G, Diagaradjane P, Anand P, Pandey M, Gelovani J, Krishnan S, Guha S, Aggarwal B. Resveratrol, a multitargeted agent, can enhance antitumor activity of gemcitabine in vitro and in orthotopic mouse model of human pancreatic cancer. Int J Cancer 2010; 127: 257–68.

59 Csiszar A, Labinskyy N, Pinto J, Ballabh P, Zhang H, Losonczy G, Pearson K, De Cabo R, Pacher P, Zhang C. Resveratrol induces mitochondrial biogenesis in endothelial cells. Am J Physiol Heart Circ Physiol 2009; 297: H13–20.

60 Csiszar A, Wang M, Lakatta E, Ungvari Z. Inflammation and endothelial dysfunction during aging: role of NF-{kappa} B. J Appl Physiol 2008; 105: 1333–41.

61 Das S, Das D. Resveratrol: a therapeutic promise for cardiovascular diseases. Recent Pat Cardiovas Drug Discov 2007; 2: 133–38.

62 Baur J, Pearson K, Price N, Jamieson H, Lerin C, Kalra A, Prabhu V, Allard J, Lopez-Lluch G, Lewis K. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006; 444: 337–42.

63 Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 [alpha]. Cell 2006; 127: 1109–22.

64 Shang J, Chen LL, Xiao FX, Sun H, Ding HC, Xiao H. Resveratrol improves non-alcoholic fatty liver disease by activating AMP-activated protein kinase. Acta Pharmacol Sin 2008; 29: 698–706.

65 Pearson K, Baur J, Lewis K, Peshkin L, Price N, Labinskyy N, Swindell W, Kamara D, Minor R, Perez E. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. Cell Metab 2008; 8: 157–68.

66 Rivera L, Morón R, Zarzuelo A, Galisteo M. Long-term resveratrol administration reduces metabolic disturbances and lowers blood pressure in obese Zucker rats. Biochem Pharmacol 2009; 77: 1053–63.

67 Dal-Pan A, Blanc S, Aujard F. Resveratrol suppresses body mass gain in a seasonal non-human primate model of obesity. BMC Physiol 2010; 10: 1–10.

68 Shakibaei M, Csaki C, Nebrich S, Mobasheri A. Resveratrol suppresses interleukin-1 [beta]-induced inflammatory signaling and apoptosis in human articular chondrocytes: potential for use as a novel nutraceutical for the treatment of osteoarthritis. Biochem Pharmacol 2008; 76: 1426–39.

69 Rocha-González H, Ambriz-Tututi M, Granados-Soto V. Resveratrol: a natural compound with pharmacological potential in neurodegenerative diseases. CNS Neurosci Ther 2008; 14: 234–47.

70 Markus M, Morris B. Resveratrol in prevention and treatment of common clinical conditions of aging. Clin Interv Aging 2008; 3: 331–39.

71 de la Lastra C, Villegas I. Resveratrol as an antioxidant and pro-oxidant agent: mechanisms and clinical implications. Biochem Soc Trans 2007; 35: 1156–60.

72 Dudley J, Das S, Mukherjee S, Das DK. Resveratrol, a unique phytoalexin present in red wine, delivers either survival signal or death signal to the ischemic myocardium depending on dose. J Nutr Biochem 2009; 20: 443–52.

73 Das M, Das D. Resveratrol and cardiovascular health. Mol Aspects Med 2010; 31: 503–12.

74 Bhat K, Kosmeder J, Pezzuto J. Biological effects of resveratrol. Antioxid Redox Signal 2001; 3: 1041–64.

75 Lekakis J, Rallidis L, Andreadou I, Vamvakou G, Kazantzoglou G, Magiatis P, Skaltsounis A, Kremastinos D. Polyphenolic compounds from red grapes acutely improve endothelial function in patients with coronary heart disease. Eur J Cardiovasc Prev Rehabil 2005; 12: 596–600.

76 Zern T, Wood R, Greene C, West K, Liu Y, Aggarwal D, Shachter N, Fernandez M. Grape polyphenols exert a cardioprotective effect in pre-and postmenopausal women by lowering plasma lipids and reducing oxidative stress. J Nutr 2005; 135: 1911–17.

77 Huang PH, Chen YH, Tsai HY, Chen JS, Wu TC, Lin FY, Sata M, Chen JW, Lin SJ. Intake of red wine increases the number and functional capacity of circulating endothelial progenitor cells by enhancing nitric oxide bioavailability. Arterioscler Thromb Vasc Biol 2010; 30: 869–77.

78 Wong R, Howe P, Buckley J, Coates A, Kunz I, Berry N. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. Nutr Metab Cardiovasc Dis 2010; Epub ahead of print. doi: 10.1016/j.numecd.2010.03.003.

79 Holcombe R. Results of a phase I pilot clinical trial examining the effect of plant-derived resveratrol and grape powder on

Wnt pathway target gene expression in colonic mucosa and colon cancer. Cancer Manag Res 2009; 1: 25–37.

80 Martinez M, Hope C, Planutis K, Planutiene M, Pontello A, Duarte B, Albers C, Holcombe R. Dietary grape-derived resveratrol for colon cancer prevention. J Clin Oncol 28:15s, 2010 (suppl; abstr 3622).

81 Ibrahim Y, Yee D. Insulin-like growth factor-I and cancer risk. Growth Horm IGF Res 2004; 14: 261–69.

82 Ghanim H, Sia C, Abuaysheh S, Korzeniewski K, Patnaik P, Marumganti A, Chaudhuri A, Dandona P. An antiinflammatory and reactive oxygen species suppressive effects of an extract of polygonum cuspidatum containing resveratrol. J Clin Endocrinol Metab 2010; 95: E1–E8.

83 Ghanim H, Sia CL, Korzeniewski K, Lohano T, Abuaysheh S, Marumganti A, Chaudhuri A, Dandona P. A resveratrol and polyphenol preparation suppresses oxidative and inflammatory stress response to a high-fat, high-carbohydrate meal. J Clin Endocrinol Metab 2011; 96: Published online ahead of print.

84 Kennedy D, Wightman E, Reay J, Lietz G, Okello E, Wilde A, Haskell C. Effects of resveratrol on cerebral blood flow variables and cognitive performance in humans: a double-blind, placebo-controlled, crossover investigation. Am J Clin Nutr 2010; 91: 1590–97.

85 Szekeres T, Fritzer-Szekeres M, Saiko P, Jäger W. Resveratrol and resveratrol analogues – structure – activity relationship. Pharm Res 2010; 27: 1042–48.

86 Wang LX, Heredia A, Song H, Zhang Z, Yu B, Davis C, Redfield R. Resveratrol glucuronides as the metabolites of resveratrol in humans: characterization, synthesis, and anti HIV activity. J Pharm Sci 2004; 93: 2448–57.

87 Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. FASEB J 2008; 22: 659–61.

88 Burns J, Yokota T, Ashihara H, Lean M, Crozier A. Plant foods and herbal sources of resveratrol. J Agric Food Chem 2002; 50: 3337–40.

89 Goldberg D, Yan J, Ng E, Diamandis E, Karumanchiri A, Soleas G, Waterhouse A. A global survey of trans-resveratrol concentrations in commercial wines. Am J Enol Vitic 1995; 46: 159–65.

90 Wang Y, Catana F, Yang Y, Roderick R, van Breemen R. An LC-MS method for analyzing total resveratrol in grape juice, cranberry juice, and in wine. J Agric Food Chem 2002; 50: 431–35.

91 Rimando A, Kalt W, Magee J, Dewey J, Ballington J. Resveratrol, pterostilbene, and piceatannol in vaccinium berries. J Agric Food Chem 2004; 52: 4713–19.

92 Wang S, Chen C, Wang C, Chen P. Resveratrol content in strawberry fruit is affected by preharvest conditions. J Agric Food Chem 2007; 55: 8269–74.

93 Wang S, Chen C, Sciarappa W, Wang C, Camp M. Fruit quality, antioxidant capacity, and flavonoid content of organically and conventionally grown blueberries. J Agric Food Chem 2008; 56: 5788–94.

94 Sanders T, McMichael JR, Hendrix K. Occurrence of resveratrol in edible peanuts. J Agric Food Chem 2000; 48: 1243–46.

95 Sobolev V, Cole R. trans-Resveratrol content in commercial peanuts and peanut products. J Agric Food Chem 1999; 47: 1435–39.

96 Hurst W, Glinski J, Miller K, Apgar J, Davey M, Stuart D. Survey of the trans-resveratrol and trans-piceid content of cocoa-containing and chocolate products. J Agric Food Chem 2008; 56: 8374–78.

97 Udenigwe C, Ramprasath V, Aluko R, Jones P. Potential of resveratrol in anticancer and anti inflammatory therapy. Nutr Rev 2008; 66: 445–54.

98 Counet C, Callemien D, Collin S. Chocolate and cocoa: new sources of trans-resveratrol and trans-piceid. Food Chem 2006; 98: 649–57.

99 Nunes T, Almeida L, Rocha J, Falcão A, Fernandes-Lopes C, Loureiro A, Wright L, Vaz-da-Silva M, Soares-da-Silva P. Pharmacokinetics of trans-resveratrol following repeated administration in healthy elderly and young subjects. J Clin Pharmacol 2009; 49: 1477–82.