

Chapter 2

Health Effects of Resveratrol and Its Derivatives

2.1 General Introduction

In this chapter we provide an overview of evidence for and against the putative beneficial effects of resveratrol and its derivatives in human health. Relevant data come from in vitro studies with human cells in culture, in vivo studies using primarily rodent models, and, where available, human clinical studies. While the detailed mechanisms underlying the observed effects are not discussed in detail here, these are the subject of considerable debate and are covered in Chap. 3.

2.2 Resveratrol and Cardiovascular Health

Resveratrol was initially identified as a bioactive component of red wines responsible for the “French Paradox,” i.e., an observation that cardiovascular disease is less common in the French than predicted on the basis of dietary intake of saturated fats (Renaud and de Lorgeril 1992; reviewed in Soleas et al. 1997). Thus, research into the health effects of resveratrol as an isolated compound was initially focused on its interactions with vascular endothelium and platelets to affect aggregation and deposition reactions. The cardioprotective effects that have been ascribed to resveratrol include an ability to reduce the severity of damage incurred following a myocardial infarction, antiatherogenic effects, and positive effects on blood lipid profiles. Although the observed cardiovascular effects were initially attributed to resveratrol’s chemical antioxidant capacity, more current research has focused on its ability to upregulate the expression of endogenous antioxidant enzymes, inhibit the inflammatory activity of cyclo-oxygenases, and promote nitric oxide signalling and vasodilation by activating nitric oxide synthases (reviewed in Ramprasath and Jones 2010). There is a paucity of data describing the cardiovascular effects of the other more abundant stilbenes present in red wines. However, it appears that piceid elicits a very similar range of cardiovascular effects, including protection against ischemia

reperfusion events and vasodilation (reviewed in Long-tao et al. 2012). Few studies have focused on pterostilbene's activities in the cardiovascular system, but the limited data available does support the idea that it may also be cardioprotective (e.g., Park et al. 2010). Understanding the actions of the host of stilbenes found in red wine will be a valuable contribution to the data describing the cardiovascular effects of red wines.

The cardiovascular effects of resveratrol established primarily in rodent models have also been the focus of human clinical trials. In arteries isolated from the adipose tissue of normal human males, resveratrol induces relaxation and thus vasodilation at micromolar concentrations (Cruz et al. 2006). Similar effects have been shown with unpurified red wine polyphenol extract, which causes vasodilation of the brachial artery in males with coronary heart disease (Lekakis et al. 2005). Chronic dietary supplementation with a resveratrol-rich grape supplement attenuates a variety of pro-inflammatory markers in humans with cardiovascular disease (Tomé-Carneiro et al. 2012a, b). In humans, the levels of resveratrol metabolites in urine, indicating relatively high dietary intake, correlate with biomarkers of cardiovascular health (Zamora-Ros et al. 2012).

The molecular mechanisms underlying these cardiovascular effects appear to include interactions with cardiomyocytes and the modulation of nitric oxide signalling in vascular endothelial and smooth muscle cells via regulation of nitric oxide synthase isoforms. These and other mechanisms are discussed in detail in Chap. 3.

2.3 Red Wine Polyphenols and Cancer

In 1997 the first major study of resveratrol's anticancer effects was published by Jang and colleagues, and since that time there have been over a 1,000 publications on this topic. Roles for resveratrol in the inhibition of tumor initiation, promotion, and progression have been reported (e.g., Jang et al. 1997). In vitro, resveratrol effectively slows the growth of a large number of individual cancer cell lines (Table 2.1). In vivo, dietary resveratrol supplementation has been shown to slow the growth of transplanted tumors (Table 2.1). There is far less data on the effects of resveratrol derivatives on cell growth, but the available data suggests that piceid and pterostilbene have similar anticancer activities. For example, piceid inhibited lung tumor growth in mice at oral doses of 300 mg/kg twice daily (Kimura and Okuda 2000). Pterostilbene has recently received considerable attention in this context, and appears to be an effective inhibitor of cell proliferation at low micromolar concentrations (e.g., Lin et al. 2012; Wang et al. 2012a; reviewed by McCormack and McFadden 2012). In our experiments with C2C12 myoblasts, primary myoblasts, PC3 prostate cancer cells, SH-SY5Y neuroblastoma cells, and primary fibroblasts, both pterostilbene and piceid are at least as effective at inhibiting cell growth in vitro as resveratrol (unpublished data). Interestingly, the oligomeric resveratrol derivatives, including α -viniferin, ϵ -viniferin, pallidol, and trans-miyabenol all inhibit

Table 2.1 Resveratrol and wine polyphenols affect cell proliferation in vivo and in vitro (references from within past 5 years)

Cell line	Cancer type	Polyphenol used	Observation	Reference
In Vitro	K562 and K562/IMA-2	Leukemia cell line		
KG-1a	Human promyeloblastic leukemia cells	Resveratrol	Inhibition of cell growth, increased apoptosis	Can et al. (2012)
A375	Melanoma	Resveratrol	Inhibition of cell growth	Hu et al. (2012)
A549	Lung cancer	Pterostilbene	Inhibition of cell growth and increased apoptosis	Mena et al. (2012)
HT29	Colon cancer			
MCF7	Lung cancer			
HT-29 and COLO 201	Human colon cancer cells	Resveratrol	Increased apoptosis	Miki et al. (2012)
Capan-2, Panc-28, and HPDE	Human pancreatic cancer cells	Resveratrol	Inhibition of cell growth and increased apoptosis	Shamim et al. (2012)
SGC7901	Human gastric adenocarcinoma	Resveratrol	Increased apoptosis	Wang et al. (2012b)
HL-1 NB	Tumoral cardiac cell line	Resveratrol	Inhibition of growth, loss of cell adhesion, increased apoptosis	Baarine et al. (2011)
U87 MG and U118 MG	Human glioblastoma cells	Resveratrol	Inhibition of cell proliferation, induction of cellular senescence	Gao et al. (2011)
MCF7	Human breast cancer			
H1299	Non-small-cell lung carcinoma			
PC3	Human prostate cancer cells			
H4-II-E	Rat hepatoma cells	Resveratrol	Inhibition of cell growth	Villa-Cuesta et al. (2011)
PC-3 and C4-2B	Prostate cancer cells	Resveratrol	Cell growth inhibition induction of apoptosis	Brizuela et al. (2010)
PANC-1, BxPC-3 and AsPC-1	Pancreatic cancer cells	Resveratrol	Inhibition of cell growth; cell cycle arrest and apoptosis	Cui et al. (2010)
Mz-ChA-1, HuCC-T1, CCLP1, and SG231	Human cholangiocarcinoma cells	Resveratrol	Decreased cell proliferation, increased apoptosis	Frampton et al. (2010)
MCF7	Breast cancer cell	Resveratrol	*Significant increase in MCF7 tumor cells growth rates	Gakh et al. (2010)

(continued)

Table 2.1 (continued)

Cell line	Cancer type	Polyphenol used	Observation	Reference
B16/DOX	Doxorubicin-resistant B16 melanoma cell subline	Resveratrol	G1 cell cycle arrest and induction of apoptosis	Gatouillat et al. (2010)
Caco-2	Colon cancer cells	Resveratrol	Inhibition of proliferation	Lea et al. (2010)
YUZA26	Melanoma cells	Resveratrol	Dose-dependant decrease in metabolic activity, decreased cell viability	Trapp et al. (2010)
M14				
A375				
MDA-MB-231	Breast cancer cells	Combination of Resveratrol, quercetin, catechin	Induction of apoptosis	Castillo-Pichardo et al. (2012)
CWR22Rv1	Prostate cancer cell line	Resveratrol	Inhibition of proliferation	Hsieh (2009)
HeLa	Cervical cancer cell line	Resveratrol	Inhibition of proliferation, induction of S phase cell cycle arrest	Kramer and Wesierska-Gadek (2009)
MB-CSC	Medulloblastoma cancer stem cells	Resveratrol	Inhibition of proliferation and tumorigenicity	Lu et al. (2009)
A549	Human lung cancer cell lines	Resveratrol	Inhibit cell population growth and induce cell injury	Weng et al. (2009)
CH27				
MDA-MB-435	Breast cancer cell line	Combined resveratrol, quercetin and catechin	Inhibition of proliferation and cell cycle progression	Castillo-Pichardo et al. (2009)
HT29	Human colon adenocarcinoma cancer cell line	Grape seed extract and red wine	Inhibition of proliferation, increased apoptosis	Leifert and Abeywardena (2008)
Caco2	Colon cancer cells			
HepG2	Hepatocarcinoma cells	polyphenolic compounds		
HuTu80	Duodenum adenocarcinoma cells			
HT29	Colorectal cancer cells	Pterostilbene and quercetin	Inhibition of cell growth	Priego et al. (2008)

In vivo	Nude mice, mammary tumor	Combination of grape polyphenols	Decreased tumor growth and metastasis	Castillo-Pichardo and Dharmawardhane (2012)
	Female nude mice injected with U87 MG or U118 MG cells	Resveratrol	Reduced tumorigenicity	Gao et al. (2011)
	Male, Balb/c mice	Resveratrol	Decreased tumor incidence	George et al. (2011)
	Male NMRI/Nu mice implanted with B16/DOX cells	Resveratrol	Decreased tumor growth	Brizuela et al. (2010)
	Nude mice injected with Mz-ChA-1 cells	Resveratrol	Decreased tumor growth	Frampton et al. (2010)
	PC-3 xenograft in nude mice	Resveratrol	Decreased tumor growth	Ganapathy et al. (2010)
	Female B6D2F1 mice	Resveratrol	Decreased tumor growth	Gatouillat et al. (2010)
	Athymic nude mice	Resveratrol	Decreased tumor growth	Oi et al. (2010)
	BALB/c mice injected with C26 colon carcinoma cells	Red wine polyphenols (RWP)	Decreased tumor growth, reduced tumor vascularization, reduced number of lung metastases	Walter et al. (2010)
	Rat hepatocarcinogenesis in Sprague–Dawley rats	Resveratrol	Reduced tumor growth	Bishayee and Dhir (2009)
	Nude mice	Combination of resveratrol, quercetin, and catechin	Decreased primary mammary tumor growth	Castillo-Pichardo et al. (2009)
	Simian Virus-40T-antigen (SV-40 Tag) targeted probasin promoter rat model	Genistein and resveratrol (alone and in combination)	Reduced prostate cancer cell proliferation	Harper et al. (2009)
	Mice with normal and deficient TLR4 function with DMBA-induced skin carcinogenesis	Resveratrol	Fewer tumors, reduced tumor growth, inhibited angiogenesis	Yusuf et al. (2009)
	Euthymic nude mice transplanted with MDA-MB231 cells	Merlot grape polyphenols	Arrest of tumor development	Hakimuddin et al. (2008)

growth at low micromolar concentrations in multiple cell lines including HepG2 liver cells (Colin et al. 2008), colon tumor cells (Marel et al. 2008), and B lymphocytic leukemia cells (Billard et al. 2002).

To date there is limited data available from clinical trials of resveratrol's anticancer effects in humans. However, resveratrol's role as a putative anticancer agent in humans is supported by the results of a recent study in which patients with colorectal cancer were given an oral resveratrol treatment for 8 days. Doses of 0.5 g/day and 1.0 g/day resveratrol significantly reduced cell proliferation in cancerous colon tissue (Patel et al. 2010). Further research involving larger patient cohorts is necessary before resveratrol can be applied to the prevention and treatment of human cancers.

Thus, many of the polyphenolic compounds identified in red wines, including resveratrol, pterostilbene, viniferins, and piceid, can inhibit the growth of cancerous and normal cells in vitro, and tumor grafts in vivo. Since there are no reports of toxicity in humans, there is potential for their use as anticancer agents. However, additional research is required in this area, particularly given the estrogenic properties of these molecules (discussed in further detail in Chap. 3). The structurally related phytoestrogen genistein appears to affect normal development of rodents when dietary supplementation occurs in the neonatal period (reviewed in Jefferson et al. 2007, 2012). A full characterization of resveratrol's physiological effects with an appreciation for its estrogen properties is necessary.

2.4 Red Wine Polyphenols and Neuroprotection

Tredici and colleagues (1999) hypothesized that resveratrol possessed neuroprotective properties in parallel with its better characterized cardioprotective effects. This property of resveratrol was demonstrated in a rat model of in vivo excitotoxic brain damage, where it conferred significant protection against systemic kainic acid injection (Virgili and Contestabile 2000). A similar protective effect of resveratrol against neuronal death in rat models of cerebral ischemia was subsequently shown (Huang et al. 2001; Sinha et al. 2002). There have now been many reports of resveratrol's neuroprotective activities in a variety of contexts (Table 2.2). Although resveratrol's neuroprotection was initially linked to its chemical antioxidant capacity, more recent reports have explored its biological activities, including the modulation of heme oxygenase (Zhuang et al. 2003), matrix metalloproteinase (Gagliano et al. 2005), nitric oxide synthase (Bi et al. 2005), and AMP kinase (Dasgupta and Milbrandt 2007) activities. More recently, the neuroprotective capacity of piceid has been evaluated, with similar outcomes. Acute piceid administration is protective in a similar rat model of brain ischemia/reperfusion injury as investigated with resveratrol (Cheng et al. 2006; Ji et al. 2012). Surprisingly, although the viniferin oligomers of resveratrol show neuroprotective properties in the same rat models of stroke (Kim et al. 2012), there is as yet no data published for pterostilbene.

Table 2.2 Neuroprotection associated with chronic administration of resveratrol and its derivatives

Model	Treatment	Stressor	Effect	Reference
PC12 cells	6–56 h of 5–25 μ M RES	Oxygen–glucose deprivation	Antiapoptotic	Agrawal et al. (2011)
Rat hippocampal slices	75–500 μ M RES	Oxygen–glucose deprivation	Reduced cell death	Raval et al. (2006)
Mice	5 mg/kg RES i.v.	Middle cerebral artery occlusion	Neuroprotective	Shin et al. (2012)
Rats	30 mg/kg RES for 7 days, i.p.	Common carotid and vertebral artery occlusion	Reduced death hippocampal CA1 neurons	Simão et al. (2012a)
Rats	30 mg/kg RES for 7 days, i.p.	Common carotid and vertebral artery occlusion	Reduced astrogial and microglial activation	Simão et al. (2012b)
Rats	10, 50, and 100 mg/kg RES i.p.	Bilateral carotid artery occlusion	Protected mitochondrial function of hippocampal CA1 neurons	Della-Morte et al. (2009)
Rats	10–100 μ M RES by i.p. injection	Asphyxial cardiac arrest	Neuroprotective	Della-Morte et al. (2009)
Mice	50–100 mg/kg/day RES for 1–2 weeks	MPTP	Prevented loss of DA neurons	Blanchet et al. (2008)
Mice	10–40 mg/kg/day RES for 10 weeks	6-OHDA	Reduced neuronal damage	Jin et al. (2008)
HT22 cells	100 mM RES	Glutamate toxicity	Reduced incidence of cell death	Kukui et al. (2010)
SH-SY5Y cells	24–72 h of 1–50 μ M RES	H ₂ O ₂ , paraquat or MMS	Reduced incidence of cell death	Robb and Stuart (2011)
Mice	10 mg/kg/day RES i.p. for 9 weeks	Maneb—and paraquat-induced parkinsonism	Reduced the neurodegenerative and paraquat accumulation	Srivastava et al. (2012)
Rat cortical neuron–glia cultures	2 μ M RES for 12 h	Prion protein peptide PrP (106–126) toxicity	Prevented PrP (106–126)-induced neuronal cell death	Jeong et al. (2012)
Mouse Alzheimer’s model	300 mg/kg/day RES in diet	N.A.	Reduced plaque pathology	Karuppagounder et al. (2009)
Mouse model of multiple sclerosis	100–250 mg/kg/day RES gavage	N.A.	Delay of autoimmune encephalomyelitis, retinal ganglion protection	Fonseca-Kelly et al. (2012)
SAMP8 mouse	120 mg/kg pterostilbene for 8 weeks	N.A.	Neuroprotective	Chang et al. (2012)
Alzheimer’s model				
Striatal precursor cells expressing Mutant Htt	1 μ M trans-e-viniferin for 24–48 h	N.A.	Reduced ROS accumulation, prevented mitochondrial dysfunction	Fu et al. (2012)

Pterostilbene and resveratrol have been investigated for their ability to ameliorate the age-associated decline of cognitive function. In 19-month-old Fisher 344 rats (considered old for this strain) dietary pterostilbene administration for 12–13 weeks improved performance in the Morris water maze test, which is considered a test of working memory (Joseph et al. 2008). Resveratrol similarly preserved working memory in aged mice administered the pro-inflammation agent lipopolysaccharide (Abraham and Johnson 2009), and in aged rats (Zhao et al. 2012). Twenty weeks of dietary resveratrol supplementation also prevented the cognitive deficits caused by high fat feeding in mice, a model of the “cafeteria diet” in humans (Jeon et al. 2012). On the other hand, Park et al. (2012) report a negative effect of dietary resveratrol supplementation on spatial learning and memory in young mice. In the primate *Microcebus murinus* (grey mouse lemur), dietary supplementation with resveratrol for 18 months improved working and spatial memory (Dal-Pan et al. 2011a). The potential for red wine polyphenols to confer protection against acute neuronal insults or to ameliorate the symptoms of chronic neurodegenerative diseases has not been investigated in humans. However, the evidence gathered to date appears promising for the ability of resveratrol and pterostilbene to prevent age-associated cognitive impairments but more work, particularly in humans and with grapevine polyphenols other than resveratrol, is still needed.

2.5 Red Wine Polyphenols and Energy Homeostasis

One of the most publicized health claims for resveratrol in the popular media is its ability to impact body composition and to improve the negative metabolic consequences of high fat diets. In 2006, two high-profile reports provided evidence for a beneficial effect of dietary resveratrol supplementation in male mice fed a high fat diet (Baur et al. 2006; Lagouge et al. 2006). In male mice consuming a high fat diet, resveratrol supplementation at 22.4 mg/kg/day reduced body weight gains and decreased the incidence of spontaneous death over 60 weeks (Baur et al. 2006). Numerous markers of physiological well-being were evaluated and found to be improved with resveratrol supplementation in these mice. In high fat diet fed mice receiving 400 mg/kg/day resveratrol supplementation, the diet-induced body weight gain was reduced significantly, as was overall percentage body fat (Lagouge et al. 2006). In this latter study, body temperature and energy expenditure were increased by resveratrol supplementation, as was apparent mitochondrial abundance in skeletal muscle. Again, a wide variety of indicators of metabolic health were found to be positively altered by resveratrol supplementation in these obese male mice. Generally, resveratrol supplementation in male mice appears to confer protection against many of the negative physiological effects of high fat feeding, including adipogenesis and systemic markers of inflammation (e.g., Kim et al. 2011; Jeon et al. 2012).

Resveratrol supplementation has recently been evaluated in primates. Mouse lemurs (*Microcebus murinus*) given 200 mg resveratrol/kg/day for 4 weeks during

their seasonal body mass gain period (in preparation for winter) showed reduced body mass gain, increased resting metabolic rates, and elevated body temperatures, though no differences in activity were observed (Dal-Pan et al. 2010). Interestingly, in a yearlong study these results, obtained during the winter (short day) season, were different from those found in summer (long day), where no effect on body mass was observed (Dal-Pan et al. 2011b). In this latter study, resveratrol supplementation increased 24 h energy expenditure and resting metabolic rate.

These results from primates were consistent with the notion that resveratrol supplementation could be effective in treating human obesity, and results from a very few human studies have now been reported. In obese (mean body mass index ~ 31.5) human males taking 150 mg/day resveratrol supplements for 30 days (e.g., Timmers et al. 2011) similar changes in muscle mitochondrial metabolic parameters, including apparent increases in mitochondrial abundance, were observed as had been reported in male mice fed a high fat diet (Lagouge et al. 2006; Baur et al. 2006). This result might suggest increased energy expenditure in human males consuming resveratrol supplements; however, no changes in body mass, percentage body fat, or 24 h energy expenditure were observed. In postmenopausal women with normal BMIs taking 75 mg/day resveratrol for 12 weeks (Yoshino et al. 2012), no effects on body mass, percentage body fat, 24 h energy expenditure, or other markers of overall health were observed (Yoshino et al. 2012). Taken together, the few human studies completed to date offer somewhat equivocal support for resveratrol supplementation, though longer-term studies in individuals of unhealthy weight are awaited. Also, at this time we are aware of no reports of the effects of other grapevine polyphenols on obesity and overweight.

2.6 Red Wine Polyphenols and Diabetes

One of the more prominent sequelae of overweight and obesity is type 2 diabetes mellitus, and the potential benefit of dietary resveratrol supplementation in normalizing glucose dyshomeostasis and reducing the side effects of diabetes has been studied (reviewed in Szkudelski and Szkudelska 2011). In rodent models with genetically or chemically induced diabetes, dietary resveratrol reduces many of the cardiovascular side effects of diabetes (Thirunavukkarasu et al. 2007; Silan 2008). There is evidence in the same experimental models that resveratrol can reduce hyperglycemia (Palsamy and Subramanian 2008; Penumathasa et al. 2008). Cellular studies suggest that this anti-hyperglycemic effect could be mediated by a stimulation of glucose transporter activities (e.g., GLUT4; Penumathsa et al. 2008). Other *in vitro* cellular studies indicate effects on the stability and insulin secretion rates of pancreatic beta cells (Palsamy and Subramanian 2010). In a recent clinical trial, patients with type 2 diabetes mellitus were given 150 mg/day resveratrol supplements (Bhatt et al. 2012). This regimen improved a variety of cardiovascular and blood parameters, including mean systolic blood pressure. These data support a beneficial effect of resveratrol on energy homeostasis in humans.

2.7 Resveratrol and Lifespan

In 2003 Howitz et al. reported the ability of resveratrol to extend lifespan in the baker's yeast *Saccharomyces cerevisiae*. These unicellular yeast have been widely used as an experimental model of aging and longevity (reviewed in Kaberlein et al. 2007), despite sharing essentially no physiology with mammals. Interestingly, resveratrol was reported to impact replicative aging (number of daughter cells per mother cell), but not chronological aging (length of time yeast survive in the non-dividing state) (Howitz et al. 2003). This observation motivated a series of studies in invertebrate and vertebrate metazoan species. Wood et al. (2004) reported that resveratrol significantly extended lifespan in two well-studied models of aging, *Drosophila melanogaster* and *Caenorhabditis elegans*. However, subsequent attempts to repeat these results yielded equivocal outcomes (Table 2.3). Bass et al. (2007) were unable to show an effect of resveratrol on longevity in *D. melanogaster*, despite using the same strain and dietary supplementation protocol. Wang et al. (2013) have recently provided data suggesting that, under some specific dietary regimens that differ from that reported by Wood et al. (2004), the lifespan of female *D. melanogaster* can be marginally affected. In this study, no effects were observed in males. In other species of flies, the effects of resveratrol appear to also be quite variable. In another species of fruit fly, *Anastrepha ludens*, dietary resveratrol supplementation had no effect on longevity in males and virtually no effects in females (Zou et al. 2009). In the honeybee, resveratrol increases average lifespan (Rascon et al. 2012). The original lifespan extension result reported for *C. elegans* (Wood et al. 2004) has proven more robust, though the magnitude of the effect reported in most experiments is generally quite small. Bass et al. (2007) showed a very subtle, but positive, effect of resveratrol on *C. elegans* longevity. Subsequently, modest lifespan extensions in *C. elegans* have been demonstrated by other researchers (Gruber et al. 2007; Greer and Brunet 2009; Zarse et al. 2010).

Evidence for effects of resveratrol on aging and longevity in vertebrate species is more limited. The first vertebrate model of aging and longevity in which an effect of resveratrol on lifespan was demonstrated was the short-lived annual fish species *Nothobranchius furzeri*. In this species, a highly significant increase in lifespan of up to 50 % was associated with dietary resveratrol delivery (Valenzano et al. 2006). Lifespan extension has also been reported in the related species *N. guentheri* (Genade and Lang 2013; Yu and Li 2012). Results for mammalian species have been available only relatively recently. In large, multicenter studies of genetically heterogeneous mice, dietary delivery of resveratrol failed to increase lifespan in males or females (Miller et al. 2011; Strong et al. 2013). A long-term study of dietary resveratrol supplementation has been initiated in the primate species *Microcebus murinus* (Dal-Pan et al. 2011b), and this study should provide the best data with which to judge whether there is any potential for resveratrol to affect human longevity.

Table 2.3 Reported effects of resveratrol on lifespan in various metazoan species

Species	Effect on lifespan	Reference
<i>Drosophila melanogaster</i>	Extension	Wood et al. (2004)
<i>D. melanogaster</i>	No effect	Bass et al. (2007)
<i>D. melanogaster</i>	No effect in males	Wang et al. (2013)
	Extension in females	
<i>Anastrepha ludens</i>	No effect	Zou et al. (2009)
<i>Caenorhabditis elegans</i>	Robust extension	Wood et al. (2004)
<i>C. elegans</i>	Marginal effect	Bass et al. (2007)
<i>C. elegans</i>	Extension	Gruber et al. (2007)
<i>C. elegans</i>	Extension	Greer and Brunet (2009)
<i>C. elegans</i>	Extension	Zarse et al. (2010)
<i>Nothobranchius furzeri</i>	Extension	Valenzano et al. (2006)
<i>N. guentheri</i>	Extension	Genade and Lang (2013)
<i>N. guentheri</i>	Extension	Yu and Li (2012)
<i>Mus Musculus</i>	No effect	Miller et al. (2011)
<i>M. Musculus</i>	No effect	Strong et al. (2013)
<i>Microcebus murinus</i>	Study not yet concluded	Dal-Pan et al. (2011b)

2.8 Conclusions: Red Wine Polyphenols and Their Putative Health Effects

In the two decades since the first putative human health effects of resveratrol were hypothesized and reported, a vast wealth of data has accumulated on the subject. Only relatively recently, this literature has expanded to include other grapevine polyphenols. Sufficient data is now available to support clinical trials of resveratrol and other polyphenols, and several of these have been completed or are ongoing. Further development of grapevine polyphenols for human health applications will require continued research into the underlying cellular and molecular mechanisms of these compounds, and details of their bioavailability in vivo. These are the subjects of Chaps. 3 and 4, respectively.

References

Abraham J, Johnson RW (2009) Consuming a diet supplemented with resveratrol reduced infection-related neuroinflammation and deficits in working memory in aged mice. *Rejuvenation Res* 12:445–453

Agrawal M, Kumar V, Kashyap MP, Khanna VK (2011) Ischemic insult induced apoptosis changes in PC12 cells: protection by trans resveratrol. *Eur J Pharmacol* 666:5–11

Baarine M, Thandapilly S, Louis X, Mazue F, Yu L, Delmas D, Neticadan T, Lizard G, Latruffe N (2011) Pro-apoptotic versus anti-apoptotic properties of dietary resveratrol on tumoral and normal cardiac cells. *Genes Nutr* 6:161–169

Bass TM, Weinkove D, Houthoofd K, Gems D, Partridge L (2007) Effects of resveratrol on lifespan in *Drosopholia melanogaster* and *Caenorhabditis elegans*. *Mech Ageing Dev* 128:546–552

- Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, Fishbein KW, Spencer RG, Lakatta EG, Le Couteur D, Shaw RJ, Navas P, Puigserver P, Ingram DK, de Cabo R, Sinclair DA (2006) Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 444:337–342
- Bhatt JK, Thomas S, Nanjan MJ (2012) Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. *Nutr Res* 32:537–541
- Bi XL, Yang JY, Dong YX, Wang JM, Cui YH, Ikeshima T, Zhao YQ, Wu CF (2005) Resveratrol inhibits nitric oxide and TNF-alpha production by lipopolysaccharide-activated microglia. *Int Immunopharmacol* 5:185–193
- Billard C, Izard JC, Roman V, Kern C, Mathiot C, Mentz F, Kolb JP (2002) Comparative antiproliferative and apoptotic effects of resveratrol, epsilon-viniferin and vine-shots derived polyphenols (vineatrols) on chronic B lymphocytic leukemia cells and normal human lymphocytes. *Leuk Lymphoma* 43:1991–2002
- Bishayee S, Dhir N (2009) Resveratrol-mediated chemoprevention of diethylnitrosamine-initiated hepatocarcinogenesis: inhibition of cell proliferation and induction of apoptosis. *Chem Biol Interact* 179:131–144
- Blanchet J, Longpré F, Bureau G, Morissette M, Dipaolo T, Bronchi G, Martinoli MG (2008) Resveratrol, a red wine polyphenol, protects dopaminergic neurons in MPTP-treated mice. *Prog Neuropsychopharmacol Biol Psychiatry* 32:1243–1250
- Brizuela L, Dayon A, Doumerc N, Ader I, Golzio M, Izard J, Hara Y, Malavaud B, Cuvillier O (2010) The sphingosine kinase-1 survival pathway is a molecular target for the tumor-suppressive tea and wine polyphenols in prostate cancer. *FASEB J* 24(10):3882–3894
- Can G, Cakir Z, Kartal M, Gunduz U, Baran Y (2012) Apoptotic effects of resveratrol, a grape polyphenol, on imatinib-sensitive and resistant K562 chronic myeloid leukemia cells. *Anticancer Res* 32:2673–2678
- Castillo-Pichardo L, Dharmawardhane S (2012) Grape polyphenols inhibit akt/mammalian target of rapamycin signaling and potentiate the effects of gefitinib in breast cancer. *Nutr Cancer* 64:1058–1069
- Castillo-Pichardo L, Martínez-Montemayor M, Martínez J, Wall K, Cubano L, Dharmawardhane S (2009) Inhibition of mammary tumor growth and metastases to bone and liver by dietary grape polyphenols. *Clin Exp Metastasis* 26:505–516
- Chang J, Rimando A, Pallas M, Camins A, Porquet D, Reeves J, Shukitt-Hale B, Smith MA, Joseph JA, Casadesus G (2012) Low-dose pterostilbene, but not resveratrol, is a potent neuro-modulator in aging and Alzheimer's disease. *Neurobiol Aging* 33:2062–2071
- Cheng Y, Zhang HT, Sun L, Guo S, Ouyang S, Zhang Y, Xu J (2006) Involvement of cell adhesion molecules in polydatin protection of brain tissues from ischemia-reperfusion injury. *Brain Res* 1110:193–200
- Colin D, Lancon A, Delmas D, Lizard G, Abrossinow J, Kahn E, Jannin B, Latruffe N (2008) Antiproliferative activities of resveratrol and related compounds in human hepatocyte derived HepG2 cells are associated with biochemical cell disturbance revealed by fluorescence analyses. *Biochimie* 90:1674–1684
- Cruz MN, Luksha L, Logman H, Poston L, Agewall S, Kublickiene K (2006) Acute responses to phytoestrogens in small arteries from men with coronary heart disease. *Am J Physiol Heart Circ Physiol* 290:H1969–H1975
- Cui J, Sun R, Yu Y, Gou S, Zhao G, Wang C (2010) Antiproliferative effect of resveratrol in pancreatic cancer cells. *Phytother Res* 24:1637–1644
- Dal-Pan A, Blanc S, Aujard F (2010) Resveratrol suppresses body mass gain in a seasonal non-human primate model of obesity. *BMC Physiol* 10:11
- Dal-Pan A, Pifferi F, Marchal J, Picq JL, Aujard F, RESTRIKAL Consortium (2011a) Cognitive performances are selectively enhanced during chronic caloric restriction or resveratrol supplementation in a primate. *PLoS One* 6:e16581
- Dal-Pan A, Terrien J, Pifferi F, Botalla R, Hardy I, Marchal J, Zahariev A, Chery I, Zizzari P, Perret M, Picq JL, Epelbaum J, Blanc S, Aujard F (2011b) Caloric restriction or resveratrol supple-

- mentation and ageing in a non-human primate: first-year outcome of the RESTRIKAL study in *Microcebus murinus*. *Age* 33:15–31
- Dasgupta B, Milbrandt J (2007) Resveratrol stimulates AMP kinase activity in neurons. *Proc Natl Acad Sci USA* 104:7217–7222
- Della-Morte D, Dave KR, DeFazio RA, Bao YC, Raval AP, Perez-Pinzon MA (2009) Resveratrol pretreatment protects rat brain from cerebral ischemic damage via a sirtuin 1-uncoupling protein 2 pathway. *Neuroscience* 159:993–1002
- Fonseca-Kelly Z, Nassrallah M, Uribe J, Khan RS, Dine K, Dutt M, Shindler KS (2012) Resveratrol neuroprotection in a chronic mouse model of multiple sclerosis. *Front Neurol* 3:84
- Frampton G, Lazcano E, Li H, Mohamad A, DeMorrow S (2010) Resveratrol enhances the sensitivity of cholangiocarcinoma to chemotherapeutic agents. *Lab Invest* 90:1325–1338
- Fu J, Jin J, Cichewicz RH, Hageman SA, Ellis TK, Xiang L, Peng Q, Jiang M, Arbez N, Hotaling K, Ross CA, Duan W (2012) Trans-(ϵ)-viniferin increases mitochondrial sirtuin 3 (SIRT3), activates AMP-activated protein kinase (AMPK), and protects cells in model of huntington disease. *J Biol Chem* 287:24460–24472
- Gagliano N, Moscheni C, Torri C, Magnani I, Bertelli AA, Gioia M (2005) Effect of resveratrol on matrix metalloproteinase-2 (MMP-2) and secreted protein acidic and rich in cysteine (SPARC) on human cultured glioblastoma cells. *Biomed Pharmacother* 59:359–364
- Gakh A, Anisimova N, Kiselevsky M, Sadovnikov S, Stankov I, Yudin M, Rufanov K, Krasavin M, Sosnov A (2010) Dihydro-resveratrol—a potent dietary polyphenol. *Bioorg Med Chem Lett* 20:6149–6151
- Ganapathy S, Chen Q, Singh K, Shankar S, Sriivastava R (2010) Resveratrol enhances antitumor activity of TRAIL in prostate cancer xenografts through activation of FOXO transcription factor. *PLoS One* 5(12):e15627
- Gao Z, Xu M, Barnett T, Xu W (2011) Resveratrol induces cellular senescence with attenuated mono-ubiquitination of histone H2B in glioma cells. *Biochem Biophys Res Commun* 407:271–276
- Gatouillat G, Balasse E, Joseph-Pietras D, Morjani H, Madoulet C (2010) Resveratrol induces cell-cycle disruption and apoptosis in chemoresistant B16 melanoma. *J Cell Biochem* 110:893–902
- Genade T, Lang DM (2013) Resveratrol extends lifespan and preserves glia but not neurons of the *Nothobranchius guentheri* optic tectum. *Exp Gerontol* 48(2):202–212
- George J, Singh M, Srivastava A, Bhui K, Roy P, Chaturvedi P, Shukla Y (2011) Resveratrol and black tea polyphenol combination synergistically suppress mouse skin tumors growth by inhibition of activated MAPKs and p53. *PLoS One* 6:e23395
- Greer EL, Brunet A (2009) Different dietary restriction regimens extend lifespan by both independent and overlapping genetic pathways in *C. elegans*. *Aging Cell* 8:113–127
- Gruber J, Tang SY, Halliwell B (2007) Evidence for a trade-off between survival and fitness caused by resveratrol treatment of *Caenorhabditis elegans*. *Ann N Y Acad Sci* 1100:530–542
- Hakimuddin F, Tiwari K, Paliyath G, Mechling K (2008) Grape and wine polyphenols down-regulate the expression of signal transduction genes and inhibit the growth of estrogen receptor-negative MDA-MB231 tumors in nu/nu mouse xenografts. *Nutr Res* 28:702–713
- Harper C, Cook L, Patel B, Wang J, Altoum I, Arabshahi A, Shiral T, Lamartiniere C (2009) Genistein and resveratrol, alone and in combination, suppress prostate cancer in SV-40 tag rats. *Prostate* 69:1668–1682
- Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisilewski A, Zhang LL, Scherer B, Sinclair DA (2003) Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* 425(6954):191–196
- Hsieh T (2009) Antiproliferative effects of resveratrol and the mediating role of resveratrol targeting protein NQO2 in androgen receptor-positive, hormone-non-responsive CWR22Rv1 cells. *Anticancer Res* 29:3011–3017
- Hu L, Cao D, Li Y, He Y, Guo K (2012) Resveratrol sensitized leukemia stem cell-like KG-1a cells to cytokine-induced killer cells-mediated cytotoxicity through NKG2D ligands and TRAIL receptors. *Cancer Biol Ther* 13:516–526

- Huang SS, Tsai MC, Chih CL, Hung LM, Tsai SK (2001) Resveratrol reduction of infarct size in Long-Evans rats subjected to focal cerebral ischemia. *Life Sci* 69:1057–1065
- Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM (1997) Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* 275:218–220
- Jefferson WN, Padilla-Banks E, Newbold RR (2007) Disruption of the developing female reproductive system by phytoestrogens: genistein as an example. *Mol Nutr Food Res* 51:832–844
- Jefferson WN, Patisaul HB, Williams CJ (2012) Reproductive consequences of developmental phytoestrogen exposure. *Reproduction* 143:247–260
- Jeon BT, Jeong EA, Shin HJ, Lee Y, Lee DH, Kim HJ, Kang SS, Cho GJ, Choi WS, Roh GS (2012) Resveratrol attenuates obesity-associated peripheral and central inflammation and improves memory deficit in mice fed a high-fat diet. *Diabetes* 61:1444–1454
- Jeong JK, Moon MH, Bae BC, Lee YJ, Seol JW, Kang HS, Kim JS, Kang SJ, Park SY (2012) Autophagy induced by resveratrol prevents human prion protein-mediated neurotoxicity. *Neurosci Res* 73:99–105
- Ji H, Zhang X, Du Y, Liu H, Li S, Li L (2012) Polydatin modulates inflammation by decreasing NF- κ B activation and oxidative stress by increasing Gli1, Ptch1, SOD1 expression and ameliorates blood-brain barrier permeability for its neuroprotective effect in pMCAO rat brain. *Brain Res Bull* 87:50–59
- Jin F, Wu Q, Lu YF, Gong QH, Sh JS (2008) Neuroprotective effect of resveratrol on 6-OHDA-induced Parkinson's disease in rats. *Eur J Pharmacol* 600:7882
- Joseph JA, Fisher DR, Cheng V, Rimando AM, Shukitt-Hale B (2008) Cellular and behavioural effects of stilbene resveratrol analogues: implications for reducing the deleterious effects of aging. *J Agric Food Chem* 56:10544–10561
- Kaerberlein M, Burtner CR, Kennedy BK (2007) Recent developments in yeast aging. *PLoS Genet* 3(5):e84
- Karuppagounder SS, Pinto JT, Xu H, Beal MF, Gibson GE (2009) Dietary supplementation with resveratrol reduced plaque pathology in a transgenic model Alzheimer's disease. *Neurochem Int* 54:111–118
- Kim S, Jin Y, Choi Y, Park T (2011) Resveratrol exerts anti-obesity effects via mechanisms involving down-regulation of adipogenic and inflammatory processes in mice. *Biochem Pharmacol* 81:1343–1351
- Kim JY, Jeong HY, Lee HK, Kim S, Hwang BY, Bae K, Seong YH (2012) Neuroprotection of the leaf and stem of *Vitis amurensis* and their active compounds against ischemic brain damage in rats and excitotoxicity in cultured neurons. *Phytomedicine* 19:150–159
- Kimura Y, Okuda H (2000) Effects of naturally occurring stilbene glucosides from medicinal plants and wine, on tumour growth and lung metastasis in Lewis lung carcinoma-bearing mice. *J Pharm Pharmacol* 52:1287–1295
- Kramer M, Wesierska-Gadek J (2009) Monitoring of long-term effects of resveratrol on cell cycle progression of human HeLa cells after administration of a single dose. *Ann N Y Acad Sci* 1171:257–263
- Kukui M, Choi HJ, Zhu BT (2010) Mechanism for the protective effect of resveratrol against oxidative stress-induced neuronal death. *Free Radic Biol Med* 49:800–813
- Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J (2006) Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 α . *Cell* 127:1109–1122
- Lea M, Ibeh C, Han L, Desbordes C (2010) Inhibition of growth and induction of differentiation markers by polyphenolic molecules and histone deacetylase inhibitors in colon cancer cells. *Anticancer Res* 30:311–318
- Leifert W, Abeywardena M (2008) Grape seed and red wine polyphenol extracts inhibit cellular cholesterol uptake, cell proliferation, and 5-lipoxygenase activity. *Nutr Res* 28:842–850
- Lekakis J, Rallidis LS, Andreadou I, Vamvakou G, Kazantzoglou G, Magiatis P, Skaltsounis AL, Kremastinos DT (2005) Polyphenolic compounds from red grapes acutely improve endothe-

- lial function in patients with coronary heart disease. *Eur J Cardiovasc Prev Rehabil* 12: 596–600
- Lin VC, Tsai YC, Lin JN, Fan LL, Pan MH, Ho CT, Wu JY, Way TD (2012) Activation of AMPK by pterostilbene suppresses lipogenesis and cell-cycle progression in p53 positive and negative human prostate cancer cells. *J Agric Food Chem* 60:6399–6407
- Long-tao L, Gang G, Min W, Zhang W (2012) The progress of the research on cardiovascular effects and acting mechanism of polydatin. *Chin J Integr Med* 18:714–719
- Lu K, Chen Y, Tsia P, Tsia M, Lee Y, Chiang C, Kao C, Chiou S, Ku H, Lin C, Chen Y (2009) Evaluation of radiotherapy effect in resveratrol-treated medulloblastoma cancer stem-like cells. *Childs Nerv Syst* 25:543–550
- Marel AK, Lizard G, Izard JC, Latruffe N, Delmas D (2008) Inhibitory effects of trans-resveratrol analogs molecules on the proliferation and the cell cycle progression of human colon tumoral cells. *Mol Nutr Food Res* 52:538–548
- McCormack D, McFadden D (2012) Pterostilbene and cancer: current review. *J Surg Res* 173:e53–e61
- Mena S, Rodriguez M, Ponsoda X, Estrela J, Jäättelä M, Ortega A (2012) Pterostilbene-induced tumor cytotoxicity: a lysosomal membrane permeabilization-dependent mechanism. *PLoS One* 7:e44524
- Miki H, Uehara N, Kimura A, Sasaki T, Yuri T, Yoshizawa K, Tsubura A (2012) Resveratrol induces apoptosis via ROS-triggered autophagy in human colon cancer cells. *Int J Oncol* 40:1020–1028
- Miller RA, Harrison DE, Astle CM, Baur JA, Boyd AR, de Cabo R, Fernandez E, Flurkey K, Javors MA, Nelson JF, Orihuela CJ, Pletcher S, Sharp ZD, Sinclair D, Starnes JW, Wilkinson JE, Nadon NL, Strong R (2011) Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *J Gerontol A Biol Sci Med Sci* 66:191–201
- Oi N, Jeong C, Nadas J, Cho Y, Pugliese A, Bode A, Dong Z (2010) Resveratrol, a red wine polyphenol, suppresses pancreatic cancer by inhibiting leukotriene A₄ hydrolase. *Cancer Res* 70:9755–9764
- Palsamy P, Subramanian S (2008) Resveratrol, a natural phytoalexin, normalizes hyperglycemia in streptozotocin-nicotinamide induced experimental diabetic rats. *Biomed Pharmacother* 62:598–605
- Palsamy P, Subramanian S (2010) Ameliorative potential of resveratrol on proinflammatory cytokines, hyperglycemia mediated oxidative stress, and pancreatic beta-cell dysfunction in streptozotocin-nicotinamide-induced diabetic rats. *J Cell Physiol* 224:423–432
- Park ES, Lim Y, Hong JT, Yoo HS, Lee CK, Pyo MY, Yun YP (2010) Pterostilbene, a natural dimethylated analog of resveratrol, inhibits rat aortic vascular smooth muscle cell proliferation by blocking Akt-dependent pathway. *Vascul Pharmacol* 53:61–67
- Park HR, Kong KH, Yu BP, Mattson MP, Lee J (2012) Resveratrol inhibits the proliferation of neural progenitor cells and hippocampal neurogenesis. *J Biol Chem* 287:42588–42600
- Patel KR, Brown VA, Jones DJ, Britton RG, Hemingway D, Miller AS, West KP, Booth TD, Perloff M, Crowell JA, Brenner DE, Steward WP, Gescher AJ, Brown K (2010) Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. *Cancer Res* 70(19): 7392–7399
- Penumathsa SV, Thirunavukkarasu M, Zhan L, Maulik G, Menon VP, Bagchi D, Maulik N (2008) Resveratrol enhances GLUT-4 translocation to the caveolar lipid raft fractions through AMPK/Akt/eNOS signalling pathway in diabetic myocardium. *J Cell Mol Med* 12:2350–2361
- Priego S, Feddi F, Ferrer P, Mena S, Beniloch M, Ortega A, Carretero J, Obrador E, Asensi M, Astrela J (2008) Natural polyphenols facilitate elimination of HT-29 colorectal cancer xenografts by chemoradiotherapy: a Bcl-2- and superoxide dismutase 2-dependent mechanism. *Mol Cancer Ther* 7:3330–3342
- Ramprasath VR, Jones PJ (2010) Anti-atherogenic effects of resveratrol. *Eur J Clin Nutr* 64: 660–668
- Rascón B, Hubbard BP, Sinclair DA, Amdam GV (2012) The lifespan extension effects of resveratrol are conserved in the honey bee and may be driven by a mechanism related to caloric restriction. *Aging* 4:499–508

- Raval AP, Dave KR, Pérez-Pinzón MA (2006) Resveratrol mimics ischemic preconditioning in the brain. *J Cereb Blood Flow Metab* 26:1141–1147
- Renaud S, de Lorgeril M (1992) Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 339:1523–1526
- Robb EL, Stuart JA (2011) Resveratrol interacts with estrogen receptor- β to inhibit cell replicative growth and enhance stress resistance by upregulating mitochondrial superoxide dismutase. *Free Radic Biol Med* 50(7):821–831
- Shamim U, Hanif S, Albanyan A, Beck F, Bao B, Wang Z, Banerjee S, Sarkar F, Mohammad R, Hadi S, Azmi A (2012) Resveratrol-induced apoptosis is enhanced in low pH environments associated with cancer. *J Cell Physiol* 227:1493–1500
- Shin JA, Lee KE, Kim HS, Park EM (2012) Acute resveratrol treatment modulates multiple signaling pathways in the ischemic brain. *Neurochem Res* 37:2686–2696
- Silan C (2008) The effects of chronic resveratrol treatment on vascular responsiveness of streptozotocin-induced diabetic rats. *Biol Pharm Bull* 31:897–902
- Simão F, Matté A, Pagnussat AS, Netto CA, Salbego CG (2012a) Resveratrol prevents CA1 neurons against ischemic injury by parallel modulation of both GSK-3 β and CREB through PI3-K/Akt pathways. *Eur J Neurosci* 36:2899–2905
- Simão F, Matté A, Pagnussat AS, Netto CA, Salbego CG (2012b) Resveratrol preconditioning modulates inflammatory response in the rat hippocampus following global cerebral ischemia. *Neurochem Int* 61:659–665
- Sinha K, Chaudhary G, Gupta YK (2002) Protective effect of resveratrol against oxidative stress in middle cerebral artery occlusion model of stroke in rats. *Life Sci* 71:655–665
- Soleas GJ, Diamandis EP, Goldberg DM (1997) Resveratrol: a molecule whose time has come? And gone? *Clin Biochem* 30:91–113
- Srivastava G, Dixit A, Yadav S, Patel DK, Prakash O, Singh MP (2012) Resveratrol potentiates cytochrome P450 2 d22-mediated neuroprotection in maneb- and paraquat-induced parkinsonism in the mouse. *Free Radic Biol Med* 52:1294–1306
- Strong R, Miller RA, Astle CM, Baur JA, de Cabo R, Fernandez E, Guo W, Javors M, Kirkland JL, Nelson JF, Sinclair DA, Teter B, Williams D, Zaveri N, Nadon NL, Harrison DE (2013) Evaluation of resveratrol, green tea extract, curcumin, oxaloacetic acid, and medium-chain triglyceride oil on life span of genetically heterogeneous mice. *J Gerontol A Biol Sci Med Sci* 68(1):6–16
- Szkudelski T, Szkudelska K (2011) Anti-diabetic effects of resveratrol. *Ann N Y Acad Sci* 1215:34–39
- Thirunavukkarasu M, Penumathsa SV, Koneru S, Juhasz B, Zhan L, Otani H, Bagchi D, Das DK, Maulik N (2007) Resveratrol alleviates cardiac dysfunction in streptozotocin-induced diabetes: role of nitric oxide, thioredoxin, and heme oxygenase. *Free Radic Biol Med* 43:720–729
- Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, Hoeks J, van der Krieken S, Ryu D, Kersten S, Moonen-Kornips E, Hesselink MK, Kunz I, Schrauwen-Hinderling VB, Blaak EE, Auwerx J, Schrauwen P (2011) Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metab* 14:612–622
- Tomé-Carneiro J, González M, Larrosa M, García-Almagro FJ, Avilés-Plaza F, Parra S, Yáñez-Gascón MJ, Ruiz-Ros JA, García-Conesa MT, Tomás-Barberán FA, Espín JC (2012a) Consumption of a grape extract supplement containing resveratrol decreases oxidized LDL and ApoB in patients undergoing primary prevention of cardiovascular disease: a triple-blind, 6-month follow-up, placebo-controlled, randomized trial. *Mol Nutr Food Res* 56:810–821
- Tomé-Carneiro J, González M, Larrosa M, Yáñez-Gascón MJ, García-Almagro FJ, Ruiz-Ros JA, García-Conesa MT, Tomás-Barberán FA, Espín JC (2012b) One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease. *Am J Cardiol* 110:356–363
- Trapp V, Parmakhtiar B, Papazian V, Willmott L, Fruehauf J (2010) Anti-angiogenic effects of resveratrol mediated by decreased VEGF and increased TSP1 expression in melanoma-endothelial cell co-culture. *Angiogenesis* 13:305–315

- Tredici G, Miloso M, Nicolini G, Galbiati S, Cavaletti G, Bertelli A (1999) Resveratrol, map kinases and neuronal cells: might wine be a neuroprotectant? *Drugs Exp Clin Res* 25:99–103
- Valenzano DR, Terzibasi E, Genade T, Cattaneo A, Domenici L, Cellerino A (2006) Resveratrol prolongs lifespan and retards the onset of age-related markers in a short-lived vertebrate. *Curr Biol* 16:296–300
- Villa-Cuestra E, Boylan J, Tatar M, Gruppuso P (2011) Resveratrol inhibits protein translation in hepatic cells. *PLoS One* 6:e29513
- Virgili M, Contestabile A (2000) Partial neuroprotection of in vivo excitotoxic brain damage by chronic administration of the red wine antioxidant agent, trans-resveratrol in rats. *Neurosci Lett* 281:123–126
- Walter A, Etienne-Selloum N, Brasse D, Khallouf H, Bronner C, Rio M, Beretz A, Schini-Kerth V (2010) Intake of grape-derived polyphenols reduces C26 tumor growth by inhibiting angiogenesis and inducing apoptosis. *FASEB J* 24:3360–3369
- Wang Y, Ding L, Wang X, Zhang J, Han W, Feng L, Sun J, Jin H, Wang XJ (2012a) Pterostilbene simultaneously induces apoptosis, cell cycle arrest and cyto-protective autophagy in breast cancer cells. *Am J Transl Res* 4:44–51
- Wang Z, Li W, Meng X, Jia B (2012b) Resveratrol induces gastric cancer cell apoptosis via reactive oxygen species, but independent of sirtuin1. *Clin Exp Pharmacol Physiol* 39:227–232
- Wang C, Wheeler CT, Alberico T, Sun X, Seeberger J, Laslo M, Spangler E, Kern B, de Cabo R, Zou S (2013) The effect of resveratrol on lifespan depends on both gender and dietary nutrient composition in *Drosophila melanogaster*. *Age (Dordr)* 35(1):69–81
- Weng C, Yang Y, Ho C, Yen G (2009) Mechanisms of apoptotic effects induced by resveratrol, dibenzoylmethane, and their analogues on human lung carcinoma cells. *J Agric Food Chem* 57:5235–5243
- Wood JG, Rogina B, Lavu S, Howitz K, Helfand SL, Tatar M, Sinclair D (2004) Sirtuin activators mimic caloric restriction and delay ageing in metazoans. *Nature* 430:686–689
- Yoshino J, Conte C, Fontana L, Mittendorfer B, Imai S, Schechtman KB, Gu C, Kunz I, Rossi Fanelli F, Patterson BW, Klein S (2012) Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance. *Cell Metab* 16:658–664
- Yu X, Li G (2012) Effects of resveratrol on longevity, cognitive ability and aging-related histological markers in the annual fish *Nothobranchius guentheri*. *Exp Gerontol* 47:940–949
- Yusuf N, Nasti T, Meleth S, Elmets C (2009) Resveratrol enhances cell-mediated immune response to DMBA through TLR4 and prevents DMBA induced cutaneous carcinogenesis. *Mol Carcinog* 48:713–723
- Zamora-Ros R, Urpi-Sarda M, Lamuela-Raventós RM, Martínez-González MÁ, Salas-Salvadó J, Arós F, Fitó M, Lapetra J, Estruch R, Andres-Lacueva C, PREDIMED Study Investigators (2012) High urinary levels of resveratrol metabolites are associated with a reduction in the prevalence of cardiovascular risk factors in high-risk patients. *Pharmacol Res* 65:615–620
- Zarse K, Schmeisser S, Birringer M, Falk E, Schmoll D, Ristow M (2010) Differential effects of resveratrol and SRT1720 on lifespan of adult *Caenorhabditis elegans*. *Horm Metab Res* 42:837–839
- Zhao H, Niu Q, Li X, Liu T, Xu Y, Han H, Wang W, Fan N, Tian Q, Zhang H, Wang Z (2012) Long-term resveratrol consumption protects ovariectomized rats chronically treated with D-galactose from developing memory decline without effects on the uterus. *Brain Res* 1467:67–80
- Zhuang H, Kim YS, Koehler RC, Doré S (2003) Potential mechanism by which resveratrol, a red wine constituent, protects neurons. *Ann N Y Acad Sci* 993:276–286
- Zou S, Carey JR, Liedo P, Ingram DK, Müller HG, Wang JL, Yao F, Yu B, Zhou A (2009) The longevity effect of resveratrol depends on dietary composition and calorie intake in a tephritid fruit fly. *Exp Gerontol* 44:472–476



<http://www.springer.com/978-1-4614-6967-4>

Bioactive Polyphenols from Wine Grapes

Stuart, J.A.; Robb, E.L.

2013, X, 66 p. 10 illus., Softcover

ISBN: 978-1-4614-6967-4