REVIEW

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Properties and molecular mechanisms of resveratrol: a review

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Resveratrol, for example widely present in the Chinese herbal medicine *Polygonum cuspidatum*, it is a natural phytoalexin, and has many biochemical activities, such as anti-tumor, anti-cardiovascular diseases, anti-bacterial, anti-inflammatory, anti-aging and other effects. This article will concentrate on the physical and chemical properties of resveratrol, the biological and pharmacological effects for its anticancer activities. An outlook is given to the development and application prospects in this drug.

1. Introduction

With the recognition of traditional Chinese Medicine as well as the rapid advances made in biomedical research, an unprecedented interest in researching the properties of Chinese herbals or natural products arose. As a group of most interesting compounds, phytoalexins have been studied widely (Soleas et al. 1997). A remarkable compound is resveratrol (RSV), a major phytoalexin isolated from the roots of the oriental medicinal plant *Polygonum Cuspidatum* (Bate-Smith 1962). Later studies showed that red wine also contains resveratrol in considerable concentrations (Barron et al. 2014; Siemann and Creasy 1992), which seems to be related to the wine's cardioprotective effect (Naumenko et al. 2013; Sato et al. 2002) known as "French paradox" (Kopp 1998). Since the first reports on cancer chemopreventive activity of RSV in animal models of carcinogenesis (Jang et al. 1997), investigations have been directed at understanding the molecular mechanisms of its biological effects. These include suppression of cellular proliferation *via* inhibition of key steps in the signal transduction pathways (Pozo-Guisado et al. 2002; Qin et al. 2014; Szaefer et al. 2014) and cyclin-dependent kinases (Liu et al. 2014a; Mohapatra et al. 2014), promotion of cellular differentiation (Dai et al. 2007), scavenging/suppression of intracellular reactive oxygen species (ROS) (Csiszar et al. 2006), induction of apoptotic cell death through activation of mitochondria-dependent or -independent pathways (Dörrie et al. 2001; Su et al. 2005), as well as regulate autophagy to decide cell fate (Zhang et al. 2013). This review is intended to provide an overview of the properties and the biological effects of this remarkable compound, which could have potential as a chemopreventive and chemotherapeutic agent.

2. Characteristics of resveratrol

Root extracts from *Polygonum cuspidatum* have been used extensively in oriental folk medicine (Bate-Smith 1962). They are containing RSV as eucalyptus and spruce, flowering plants, peanuts, and grapevines do (Soleas et al., 1997). Since the first reported detection methods of *trans*-RSV (Langcake and Pryce 1976) and the recognition as a compound in red wine (Siemann and Creasy 1992), more and more studies reported beneficial effects of RVS on human health. Oxidative dimerization of RSV leads to the formation of viniferins that could be reproduced by exposure of the parent compound to horseradish peroxidase-hydrogen peroxide system *in vitro* (Pezet et al. 2004). The synthetic ability is highest before the grapes reach maturity, and is low in buds, flowers, and mature fruits (Chong et al. 2009; Jeandet et al. 2010).

The detection the RSV content has not just concentrated to plant components but also involved the products of plants, such as wines and grape juices. HPLC combined with GC-MS to determine RSV concentration has shown that both *cis*- and *trans*-isomers are present in wine, with the *trans*-isomer in significantly higher concentration (Cai et al. 2009; Sun et al. 2007). The chemical structure of RSV is similar to that of the estrogen diethylstilbestrol. Two phenol rings are linked by a styrene double bond to generate 3,4,5-trihydroxystilbene. The *trans*-isomer can be transformed to the *cis*-form under UV exposure. *Trans*-RSV is commercially available and is relatively stable if protected from high pH and light (Soleas et al. 1997). Absorbance of the *trans*-isomer is located at 307 nm and that of the *cis*-isomer at 288 nm, which allows separation and detection of the two isomers by HPLC using a C18 reverse phase column (Roldán et al. 2003). Gas chromatography has also been used to determine concentrations of *trans*- and *cis*-isomers (Soleas et al. 2001). The potential of plants to synthesize RSV may be useful to provide resistance against a variety of plant diseases.

3. The main molecular mechanisms of RSV

Regarding cancer chemopreventive activity of carcinogenesis, there has been a big amount of studies reporting the effects of RSV on critical events that regulate cellular proliferation and growth. The potential molecular function of RSV are related to aspects of differentiation, transformation, cell cycle regulation, and cell death induction (Delmas et al. 2011; Ko et al. 2011; Lopez-Lluch et al. 2012; Zhang et al. 2013). Those functions affect cancer cell survival mainly including intracellular ROS generation, protein kinases activation, induction of enzymes

which induce inflammatory mediators such as COX and lipoxygenase, transcription factors such as NF-kB and p53 activation.

3.1. Resveratrol regulates cell cycle, apoptosis and autophagy

Carcinogenesis is a process that involves dysregulated growth, an outcome of enhanced proliferation triggers cell cycle, apoptosis and autophagy initiation to balance the cell fate. Regulation of growth and proliferation in untransformed cells is maintained *via* regulation of the cell cycle by the cell cycle checkpoint proteins, such as p53, p16, and the CDK inhibitor $p21^{Waf1/Cip1}$. Any changes in the normal functioning of these proteins allow the cells to undergo unabated cycling resulting in accumulation of DNA mutations, a prerequisite for carcinogenesis. A number of studies have now established that RSV inhibits cellular proliferation by inducing cell cycle arrest in the G1/S phase (Casanova et al. 2012; Khan et al. 2013; Li et al. 2011). Cancer cell exposure to RSV resulted in accumulation in the S phase (Aires et al. 2014; Joe et al. 2002; Larrosa et al. 2003). Exposure to RSV also resulted in a transient increase in the expression of G1/S regulators, such as cyclin D1, cdk4, and cyclin E (Das and Vasanthi 2013; Pozo-Guisado et al. 2002); cyclins D1 and E are responsible for S phase entry. These cells ultimately undergo apoptotic death, unlike the breast cancer cell line MDA-MB-231, where cell cycle activation or up-regulation of p21, p53, or p27 did not occur and the mode of inhibition of cell proliferation was attributed to nonapoptotic death of the cell (Pozo-Guisado et al. 2002). The compound was extremely effective against a highly invasive breast carcinoma cell line (Bai et al. 2010). Other studies also showed that RSV treatment induced cell cycle arrest at the S/G2 phase transition, and increase in the G1/S phase in HL60 cells, which lead to an increase in cyclins A and E and inactivation of cdc2 (Filippi-Chiela et al. 2013). In another study, RSV decreased the levels of cyclins D1, D2, E, and cdk2 and cdk4/6 (Ahmad et al. 2001). Suppression of cell cycle progression through the S and G2 phases and a concomitant increase in the expression of p53 and $p2^{Waf1/Cip1}$ have also been demonstrated in pulmonary epithelial cells upon exposure to RSV (Simão et al. 2012). Collectively, the effect of RSV on growth and cell cycle control proteins seems to vary between cell types. The involvement of p53 and p21 has also been reported in the apoptotic response elicited by RSV. As p53 controls the transcription of a number of essential mediators of apoptosis such as CD95/Fas, Bax, p21, etc., the p53 dependence of RSV-induced apoptosis is of particular importance. Publications about suppression of DMBA-induced mammary carcinogenesis by RSV in rats was linked to inhibition of COX-2 and MMP9 expression and the blocking of NF-kB activation (Kundu et al. 2004; Shishodia and Aggarwal 2004). There are also reports indicating that RSV interfered with H_2O_2 -induced apoptotic signals (Guo et al. 2013; Schneider and Pozzi 2011; Singh and Chopra 2014). A slight increase in intracellular O^{2-} can inhibit receptor or drug-induced apoptosis *via* direct or indirect effects on caspase activation pathways (Cheng et al. 2014; Clement and Stamenkovic 1996; Guo et al. 2013).

Autophagy is a catabolic process for the degradation and recycling of macromolecules and organelles, which is activated during stress conditions. As a type of programmed cell death (type II), autophagy is morphologically distinct from apoptosis. Autophagic cell death is identified by extensive inclusion of cytoplasm and organelles within autophagosomes and the localization of microtubule-associated light chain 3 (LC3) protein into autophagosomal membranes (Kroemer and Jäättelä 2005). There is little, if any, caspase activation and DNA fragmentation, and the cytoskeleton initially remains intact. This is in contrast to apoptosis during which there is chromosome condensation, DNA fragmentation, usually caspase activation, and membrane rearrangement and blebbing. Research has shown RSV to induce autophagy in different cancer cell line models such as ovarian (Kueck et al. 2007; Opipari et al. 2004), leukemia cells (Puissant and Auberger 2010; Puissant et al. 2010), lung (Zhang et al. 2013) and esophageal cells (Tang et al. 2013), and breast cancer cells (Scarlatti et al. 2008). The signaling pathways by which RSV mediates autophagy induction involve several mechanisms, such as: inhibition of mTOR pathway and stimulation of AMPK pathway (Puissant et al. 2010; Zhang et al. 2013); falls in glucose uptake and lactate production limiting steps in glycolysis (Kueck et al. 2007); accumulation of the PELP-1, a novel estrogen receptor coactivator, in autophagosomes (Ohshiro et al. 2007); activation of the Vps34 kinase, a class III PI3K (Trincheri et al. 2008); and an increase in dihydroceramide levels by the inhibition of dihydroceramide desaturase activity (Signorelli et al. 2009). It is possible that RSV induced mitochondrial dysfunctions would be the common starting point, since mitochondrial dysfunction may be a point of overlap between apoptotic and autophagocytic processes (Kimmelman 2011; Kondo et al. 2005).

3.2. Resveratrol regulates the ROS production

Normal cellular metabolism generates reactive oxygen species (ROS) such as superoxide (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-) (Devasagayam et al. 2004). Excessive accumulation of ROS by the cellular antioxidant defenses contains a number of intracellular enzymes, such as glutathione (GSH), superoxide dismutase (SOD), and catalase (Halliwell 2012; Halliwell and Gutteridge 1999; Sen et al. 2010). The lack of inherent ability to neutralize the accumulation of ROS results in their abnormal accumulation intracellular is commonly known as "oxidative stress." Phenolic compounds present in red wine elicit antioxidant activity and prevent LDL oxidation convinced the health protection of red wine (Lionetto et al. 2011; Whitehead et al. 1995). In accordance to that, epidemiological studies have focused on moderate intake of wine particularly in regions of European where the diet is rich in fat (Baba et al. 2007; Lapointe et al. 2006). Some research supports the suggestion that RSV is a potent inhibitor for oxidation of polyunsaturated fatty acids (PUFA) which play a major role in atherosclerosis (Macedo et al. 2013; Petrovski et al. 2011). As a matter of fact, RSV was shown to be more helpful than flavonoids in preventing copper-catalyzed oxidation, and as LDL has high affinity for copper chelating activity prevents oxidative modification of LDL (Aviram and Fuhrman 2002; Baur and Sinclair 2006). Addition of RSV to the culture medium resulted in a dose-dependent decrease in the intracellular concentration of ApoB and a significant reduction in the rate of secretion of cholesterol esters and triglycerides. The latter is an indication of fewer VLDL and therefore lower LDL production (Penumathsa et al. 2007; Wilson et al. 1996).

Through its inhibitory effect on membrane lipid peroxidation, RSV has also been shown to reduce the toxic effects of ROS in living cells. For example, rat adrenal pheochromocytoma cells (PC12) exposed to ethanol-induced oxidative death was remarkably protected in the presence of RSV (Sun et al. 1997). In similar experiments the death inhibitory activity was attributed to the ability of RSV to block internalization of oxidized lipoproteins (Draczynska-Lusiak et al. 1998; Sato et al. 2014).

The antioxidant activity of RSV has also been shown to inhibit proliferation of hepatic stellate cells (Shiozaki et al. 2011), a major player in the development of liver fibrosis, suggesting a hepatoprotective effect. Further corroborating the antioxidant

activity of RSV are data demonstrating significant inhibition of phorbol ester (PMA)-induced intracellular ROS production (Martinez and Moreno 2000). As phorbol esters are potent tumor promoters, this inhibitory activity of RSV could prevent the development of a pro-oxidant surroundings that favors carcinogenesis (Kensler and Trush 1984).

In addition to the antioxidant properties of RSV, two other biological effects of RSV support its cardioprotective effects. First, RSV has been shown to modulate the production of nitric oxide (NO) from vascular endothelium, a nitrogen species involved in inflammatory responses (Bradamante et al. 2004; Hung et al. 2000). Increased levels of NO can cause vascular damage, thereby contributing to the development of athermanous plaques. Second, RSV has been shown to inhibit platelet aggregation, another major contributor in the process of atherosclerosis (Brandolini et al. 2002; Orsini et al. 1997). Platelets stick to the endothelial surface of blood vessels, can activate the process of thrombus formation and their aggregation could set into motion the process of vascular occlusion. Platelets have also been linked to the synthesis of eicosanoids from arachidonic acid that contributes to platelet adhesion (Bhat et al. 2001). A dose-dependent decrease in platelet aggregation has been demonstrated with RSV, lending further support to its preventive activity against coronary artery disease. This has been linked to the ability of RSV to inhibit eicosanoid synthesis (Soleas et al. 1997).

3.3. RSV regulates the key cancer related genes expression

The biological effects of RSV on a variety of critical biochemical pathways include a direct or indirect effect on gene expression, a process controlled by a class of proteins called transcription factors. The upstream signals to trigger nuclear localization and DNA binding of these transcription factors vary depending on the stimulus, cell type, and the potential response. One of the most striking biological activities of RSV is their remarkable anti-inflammatory potential (Liu et al. 2014b; Orsu et al. 2013). Due to this association, there has been a lot of interest in investigating the effects of RSV and its derivatives on transcription factors that regulate the expression of inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin 1(IL-1), IL-6, and especially NF-kB activity (Bharti and Aggarwal 2002; Estrov et al. 2003).

Most agents that activate NF-kB also activate the activator protein 1 (AP1) (Angel et al. 2001; Shaulian and Karin 2002). Studies have shown that RSV can inhibit TNF-induced activation of AP-1 (Bharti and Aggarwal 2002; Liu et al. 2014b). The activation of AP-1 is mediated by JNK (c-Jun N-terminal protein kinase) and upstream kinases, such as MEK and MEKK (Karin and Delhase 1998). Since previous studies have shown that TNF-induced activities of JNK and MEK were inhibited by RSV, this may provide a possible mechanism for AP-1 inhibition (Bharti and Aggarwal 2002). Among the proteins induced upon activation of NF-kB and AP-1 which correlated with inflammation is COX-2 and iNOS (Brune and von Knethen 2002; Li et al. 2013), two enzymes are inhibited by RSV. Thus, it is possible that RSV inhibits iNOS and COX-2 *via* its inhibitory effect on these transcription factors. It is also possible that the expression of other genes regulated by NF-kB or AP-1, which have been implicated in carcinogenesis, may also be down-regulated after exposure to RSV. Consistent with this, recent reports have demonstrated that RSV suppresses carcinogenesis *via* down-regulation of MMP2 and 9. RSV inhibits NF-kB activity, which consequently reduces the transcription level of MMPs (Shishodia and Aggarwal 2004; Yar et al. 2011).

P53 serves as the guardian of the genome by regulating the cell cycle (prevents progression through S phase) and activating the transcription of DNA repair enzymes such as GADD45, thereby preventing damaged DNA from being replicated (Bieging et al. 2014; Luo et al. 2014). In addition, p53 can activate the gene transcription involved in the apoptotic and autophagic pathways, thus ensuring and balancing the physiological and unwanted cells (Flatt et al. 2000). Loss of function such as mutation of p53 is associated with an increased incidence of tumor progression (Hussain et al. 2000; Sørlie et al. 2014). Studies indicated that RSV can induce accumulation of p53 leading to an increase in transcription of the cyclin-dependent kinase inhibitor $p21^{Waf1/Cip1}$ and cell cycle arrest (Hsieh et al. 1999; Liu et al. 2014a). In a different model using a mouse epidermal cell line, RSV was shown to increase the transactivation of p53 activity by specifically activating phosphorylation at serine 15, mutation of which abrogates the apoptotic activity of p53 (She et al. 2001). This was linked to an upstream activation of the MAP kinases, particularly ERK and p38 kinase. Similarly, gene knockout of p53 (p53-/-) in mouse fibroblasts resulted in resistance to RSV-induced death, further supporting involvement of p53 in the biological activity of RSV (Hsieh et al. 2011).

4. Prospect

Knowledge presented here highlights the clinical potential of RSV. Its relatively simple chemical structure enables RSV to interact with receptors and enzymes, giving rise to biological effects such as suppression of growth, induction of differentiation, inhibition of ROS production, cell cycle regulation, regulation of gene expression by affecting transcription factor activity, and up-regulation of death-inducing factors. These *in vitro* effects have been corroborated in some studies demonstrating the beneficial effects on cardiovascular, neurological, and hepatic systems; however, the most exciting findings are the cancer chemopreventive and chemotherapeutic activities of RSV. Being a natural constituent of wine, fruits, and nuts and the fact that it has no untoward effects on normal cells or tissues, RSV is under preclinical scrutiny. Owning to all these properties, RSV seems to be a good natural inducer or chemosensitizer of cell death against many tumor cell types and the development of RSV analogs with better *in vivo* efficacy appears to be a promising route towards new therapeutic strategies.

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References

Ahmad N, Adhami VM, Afaq F, Feyes DK, Mukhtar H (2001) Resveratrol causes WAF-1/p21-mediated G1-phase arrest of cell cycle and induction of apoptosis in human epidermoid carcinoma A431 cells. Clin Cancer Res 7: 1466–1473.

Aires V, Brassart B, Carlier A, Scagliarini A, Mandard S, Limagne E, Solary E, Martiny L, Tarpin M, Delmas D (2014) A role for peroxisome proliferator-activated receptor gamma in resveratrol-induced colon cancer cell apoptosis. Mol Nutr Food Res 58: 1785–1794.

Angel P, Szabowski A, Schorpp-Kistner M (2001) Function and regulation of AP-1 subunits in skin physiology and pathology. Oncogene 20: 2413–2423.

Aviram M, Fuhrman B (2002) Wine flavonoids protect against LDL oxidation and atherosclerosis. Ann N Y Acad Sci 957: 146–161.

Baba S, Osakabe N, Kato Y, Natsume M, Yasuda A, Kido T, Fukuda K, Muto Y, Kondo K (2007) Continuous intake of polyphenolic compounds containing cocoa powder reduces LDL oxidative susceptibility and has beneficial effects on plasma HDL-cholesterol concentrations in humans. Am J Clin Nutr 85: 709–717.

Bai Y, Mao QQ, Qin J, Zheng XY, Wang YB, Yang K, Shen HF, Xie LP (2010) Resveratrol induces apoptosis and cell cycle arrest of human T24 bladder cancer cells *in vitro* and inhibits tumor growth *in vivo*. Cancer Sci 101: 488–493.

Barron CC, Moore J, Tsakiridis T, Pickering G, Tsiani E (2014) Inhibition of human lung cancer cell proliferation and survival by wine. Cancer Cell Int 14: 6.

Bate-Smith E (1962) The phenolic constituents of plants and their taxonomic significance. I. Dicotyledons. J Linnean Soc London, Botany 58: 95–173.

Baur JA, Sinclair DA (2006) Therapeutic potential of resveratrol: the *in vivo* evidence. Nature Rev Drug Discov 5: 493–506.

Bharti AC, Aggarwal BB (2002) Nuclear factor-kappa B and cancer: its role in prevention and therapy. Biochem Pharmacol 64: 883–888.

Bhat KP, Kosmeder JW, Pezzuto JM (2001) Biological effects of resveratrol. Antiox Redox Signal 3: 1041–1064.

Bieging KT, Mello SS, Attardi LD (2014) Unravelling mechanisms of p53-mediated tumour suppression. Nature Rev Cancer 14: 359–370.

Bradamante S, Barenghi L, Villa A (2004) Cardiovascular protective effects of resveratrol. Cardiovasc Drug Rev 22: 169–188.

Brandolini V, Maietti A, Tedeschi P, Durini E, Vertuani S, Manfredini S (2002) Capillary electrophoresis determination, synthesis, and stability of resveratrol and related 3-O-β-D-glucopyranosides. J Agricult Food Chem 50: 7407–7411.

Brune B, von Knethen A (2002) The role of nitric oxide and cyclooxygenase-2 in attenuating apoptosis. J Environ Pathol Toxicol Oncol 21: 103–121.

Cai L, Koziel JA, Dharmadhikari M, van Leeuwen J (2009) Rapid determination of *trans*-resveratrol in red wine by solid-phase microextraction with on-fiber derivatization and multidimensional gas chromatography–mass spectrometry. J Chromatogr A 1216: 281–287.

Casanova F, Quarti J, da Costa DCF, Ramos CA, da Silva JL, Fialho E (2012) Resveratrol chemosensitizes breast cancer cells to melphalan by cell cycle arrest. J Cell Biochem 113: 2586–2596.

Cheng W, Zhang R, Yao C, He L, Jia K, Yang B, Du P, Zhuang H, Chen J, Liu Z (2014) A critical role of FADD (Ffs-associated protein with death domain) phosphorylation in intracellular reactive oxygen species (ROS) homeostasis and aging. Antiox Redox Signal 21: 33–45.

Chong J, Poutaraud A, Hugueney P (2009) Metabolism and roles of stilbenes in plants. Plant Sci 177: 143–155.

Clement M.-V, Stamenkovic I (1996) Superoxide anion is a natural inhibitor of FAS-mediated cell death. EMBO J 15: 216–225.

Csiszar A, Smith K, Labinskyy N, Orosz Z, Rivera A, Ungvari Z (2006) Resveratrol attenuates TNF-α-induced activation of coronary arterial endothelial cells: role of NF-κB inhibition. Am J Physiol Heart Circul Physiol 291: H1694-H1699.

Dörrie J, Gerauer H, Wachter Y, Zunino SJ (2001) Resveratrol induces extensive apoptosis by depolarizing mitochondrial membranes and activating caspase-9 in acute lymphoblastic leukemia cells. Cancer Res 61: 4731–4739.

Dai Z, Li Y, Quarles L, Song T, Pan W, Zhou H, Xiao Z (2007) Resveratrol enhances proliferation and osteoblastic differentiation in human mesenchymal stem cells via ER-dependent ERK1/2 activation. Phytomedicine 14: 806–814.

Das DK, Vasanthi H (2013) Resveratrol in dermal health. In Bioactive Dietary Factors and Plant Extracts in Dermatology (Springer), pp. 177–187.

Delmas D, Solary E, Latruffe N (2011) Resveratrol, a phytochemical inducer of multiple cell death pathways: apoptosis, autophagy and mitotic catastrophe. Curr Med Chem 18: 1100–1121.

Devasagayam T, Tilak J, Boloor K, Sane K, Ghaskadbi SS, Lele R (2004) Free radicals and antioxidants in human health: current status and future prospects. J Assoc Physicians India 52: 794–804.

Draczynska-Lusiak B, Doung A, Sun AY (1998) Oxidized lipoproteins may play a role in neuronal cell death in Alzheimer disease. Mol Chem Neuropathol 33: 139–148.

Estrov Z, Shishodia S, Faderl S, Harris D, Van Q, Kantarjian HM, Talpaz M, Aggarwal BB (2003) Resveratrol blocks interleukin-1β–induced activation of the nuclear transcription factor NF-κB, inhibits proliferation, causes S-phase arrest, and induces apoptosis of acute myeloid leukemia cells. Blood 102: 987–995.

Filippi-Chiela EC, Thomé MP, Bueno e Silva, MM, Pelegrini AL, Ledur PF, Garicochea B, Zamin LL, Lenz G (2013) Resveratrol abrogates the temozolomide-induced G2 arrest leading to mitotic catastrophe and reinforces the temozolomide-induced senescence in glioma cells. BMC Cancer 13: 147.

Flatt PM, Polyak K, Tang LJ, Scatena CD, Westfall MD, Rubinstein LA, Yu J, Kinzler KW, Vogelstein B, Hill DE (2000) p53-Dependent expression of PIG3 during proliferation, genotoxic stress, and reversible growth arrest. Cancer Lett 156: 63–72.

Guo R, Su Y, Liu B, Li S, Zhou S, Xu Y (2013) Resveratrol suppresses oxidised low-density lipoprotein-induced macrophage apoptosis through inhibition of intracellular reactive oxygen species generation, LOX-1, and the p38 MAPK pathway. Cell Physiol Biochem 34: 603–616.

Halliwell B (2012) Free radicals and antioxidants: updating a personal view. Nutr Rev 70: 257–265.

Halliwell B, Gutteridge JM (1999) Free radicals in biology and medicine, 1999 (Clarendon Press, Oxford).

Hsieh T-C, Juan G, Darzynkiewicz Z, Wu JM (1999) Resveratrol increases nitric oxide synthase, induces accumulation of p53 and p21WAF1/CIP1, and suppresses cultured bovine pulmonary artery endothelial cell proliferation by perturbing progression through S and G2. Cancer Res 59: 2596–2601.

Hsieh TC, Wong C, Bennett JD, Wu JM (2011) Regulation of p53 and cell proliferation by resveratrol and its derivatives in breast cancer cells: an in silico and biochemical approach targeting integrin αvβ3. Int J Cancer 129: 2732–2743.

Hung LM, Chen JK, Huang SS, Lee RS, Su MJ (2000) Cardioprotective effect of resveratrol, a natural antioxidant derived from grapes. Cardiovasc Res 18: 549–555.

Hussain SP, Hollstein MH, Harris CC (2000) p53 tumor suppressor gene: at the crossroads of molecular carcinogenesis, molecular epidemiology, and human risk assessment. Ann N Y Acad Sci 919: 79–85.

Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG (1997). Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 275: 218–220.

Jeandet P, Delaunois B, Conreux A, Donnez D, Nuzzo V, Cordelier S, Clément C, Courot E (2010) Biosynthesis, metabolism, molecular engineering, and biological functions of stilbene phytoalexins in plants. Biofactors 36: 331–341.

Joe AK, Liu H, Suzui M, Vural ME, Xiao D, Weinstein IB (2002) Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines. Clin Cancer Res 8: 893–903.

Karin M, Delhase M (1998) JNK or IKK, AP-1 or NF-κB, which are the targets for MEK kinase 1 action? Proc Nat Acad Sci 95: 9067–9069.

Kensler TW, Trush MA (1984) Role of oxygen radicals in tumor promotion. Environ Mutagen 6: 593–616.

Khan MA, Chen H-C, Wan X-X, Tania M, Xu A-H., Chen F-Z,. Zhang D-Z (2013) Regulatory effects of resveratrol on antioxidant enzymes: a mechanism of growth inhibition and apoptosis induction in cancer cells. Mol Cells 35: 219–225.

Kimmelman AC (2011) The dynamic nature of autophagy in cancer. Genes Dev 25: 1999–2010.

Ko Y-C, Chang C-L, Chien H-F, Wu C-H, Lin L-I (2011) Resveratrol enhances the expression of death receptor Fas/CD95 and induces differentiation and apoptosis in anaplastic large-cell lymphoma cells. Cancer Lett 309: 46–53.

Kondo Y, Kanzawa T, Sawaya R, Kondo S (2005) The role of autophagy in cancer development and response to therapy. Nature Rev Cancer 5: 726–734.

Kopp P (1998) Resveratrol, a phytoestrogen found in red wine. A possible explanation for the conundrum of the 'French paradox'? Eur J Endocrinol 138: 619–620.

Kroemer G, Jäättelä M (2005) Lysosomes and autophagy in cell death control. Nature Rev Cancer 5: 886–897.

Kueck A, Opipari Jr, AW, Griffith KA, Tan L, Choi M, Huang J, Wahl H, Liu JR (2007) Resveratrol inhibits glucose metabolism in human ovarian cancer cells. Gynecol Oncol 107: 450–457.

Kundu JK, Chun KS, Kim SO, Surh YJ (2004) Resveratrol inhibits phorbol ester - induced cyclooxygenase - 2 expression in mouse skin: MAPKs and AP-1 as potential molecular targets. Biofactors 21: 33–39.

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

Lapointe A, Couillard C, Lemieux S (2006) Effects of dietary factors on oxidation of low-density lipoprotein particles. J Nutr Biochem 17: 645–658.

Larrosa M, Tomás-Barberán FA, Espín JC (2003) Grape polyphenol resveratrol and the related molecule 4-hydroxystilbene induce growth inhibition, apoptosis, S-phase arrest, and upregulation of cyclins A, E, and B1

in human SK-Mel-28 melanoma cells. J Agricult Food Chem 51: 4576–4584.
Li G, He S, Chang L, Lu H, Zhang H, Zhang H, Chiu J (2011) GADD45α and annexin A1 are involved in the apoptosis of HL-60 induced by resveratrol. Phytomedicine 18: 704–709.
Li X-H, McGrath KC, Tran VH, Li Y-M, Duke CC, Roufogalis BD, Heather AK (2013) Attenuation of proinflammatory responses by S-[6]-gingerol via inhibition of ROS/NF-Kappa B/COX2 activation in HuH7 cells. Evid Based Complement Alt Med 2013: 146142.
Lionetto M, Giordano M, Calisi A, Erroi E, De Nuccio F, Schettino T (2011) Effect of the daily ingestion of a purified anthocyanin extract from grape skin on rat serum antioxidant capacity. Physiol Res 60: 637–645.
Liu B, Zhou Z, Zhou W, Liu J, Zhang Q, Xia J, Liu J, Chen N, Li M, Zhu R (2014a) Resveratrol inhibits proliferation in human colorectal carcinoma cells by inducing G1/S-phase cell cycle arrest and apoptosis through caspase/cyclin-CDK pathways. Mol Med Rep 10: 1697–1702.
Liu T, Zang N, Zhou N, Li W, Xie X, Deng Y, Ren L, Long X, Li S, Zhou L (2014b) Resveratrol inhibits the TRIF dependent pathway by up-regulating SARM, contributing to anti-inflammatory effects after respiratory syncytial virus infection. J Virol 63: 4229–4236.
Lopez-Lluch G, Santa Cruz-Calvo S, Navas P (2012) Resveratrol in cancer: cellular and mitochondrial consequences of proton transport inhibition. Curr Pharm Des 18: 1338–1344.
Luo Y, Hartford SA, Zeng R, Southard TL, Shima N, Schimenti JC (2014) Hypersensitivity of Primordial Germ Cells to Compromised Replication-Associated DNA Repair Involves ATM-p53-p21 Signaling. PLoS Genet 10: e1004471.
Macedo LFL, Rogero MM, Guimaraes JP, Granato D, Lobato LP, Castro IA (2013) Effect of red wines with different *in vitro* antioxidant activity on oxidative stress of high-fat diet rats. Food Chem 137: 122–129.
Martinez J, Moreno JJ (2000) Effect of resveratrol, a natural polyphenolic compound, on reactive oxygen species and prostaglandin production. Biochem Pharmacol 59: 865–870.
Mohapatra P, Satapathy SR, Das D, Siddharth S, Choudhuri T, Kundu CN (2014) Resveratrol mediated cell death in cigarette smoke transformed breast epithelial cells is through induction of p21Waf1/Cip1 and inhibition of long patch base excision repair pathway. Toxicol Appl Pharmacol 275: 221–231.
Naumenko SE, Latysheva TV, Gilinsky MA, Rogachev AD, Komarova NI, Salakhutdinov NF, Tolstikov GA (2013). Cardioprotective effect of resveratrol and resveratroloside. Cardiovasc Hematol Agents Med Chem 11: 207–210.
Ohshiro K, Rayala SK, Kondo S, Gaur A, Vadlamudi RK, El-Naggar AK, Kumar R (2007) Identifying the estrogen receptor coactivator PELP1 in autophagosomes. Cancer Res 67: 8164–8171.
Opipari AW, Tan L, Boitano AE, Sorenson DR, Aurora A, Liu JR (2004) Resveratrol-induced autophagocytosis in ovarian cancer cells. Cancer Res 64: 696–703.
Orsini F, Pelizzoni F, Verotta L, Aburjai T, Rogers CB (1997) Isolation, synthesis, and antiplatelet aggregation activity of resveratrol 3-O-β-D-glucopyranoside and related compounds. J Nat Prod 60: 1082–1087.
Orsu P, Murthy B, Akula A (2013) Cerebroprotective potential of resveratrol through anti-oxidant and anti-inflammatory mechanisms in rats. J Neural Transm 120: 1217–1223.
Penumathsa SV, Thirunavukkarasu M, Koneru S, Juhasz B, Zhan L, Pant R, Menon VP, Otani H, Maulik N (2007) Statin and resveratrol in combination induces cardioprotection against myocardial infarction in hypercholesterolemic rat. J Mol Cell Cardiol 42: 508–516.
Petrovski G, Gurusamy N, Das DK (2011) Resveratrol in cardiovascular health and disease. Ann NY Acad Sci 1215: 22–33.
Pezet R, Gindro K, Viret O, Spring J-L (2004) Glycosylation and oxidative dimerization of resveratrol are respectively associated to sensitivity and resistance of grapevine cultivars to downy mildew. Physiol Mol Plant Pathol 65: 297–303.
Pozo-Guisado E, Alvarez-Barrientos A, Mulero-Navarro S, Santiago-Josefat B, Fernandez-Salguero PM (2002) The antiproliferative activity of resveratrol results in apoptosis in MCF-7 but not in MDA-MB-231 human breast cancer cells: cell-specific alteration of the cell cycle. Biochem Pharmacol 64: 1375–1386.
Puissant A, Auberger P (2010) AMPK-and p62/SQSTM1-dependent autophagy mediate Resveratrol-induced cell death in chronic myelogenous leukemia. Autophagy 6: 655–657.
Puissant A, Robert G, Fenouille N, Luciano F, Cassuto J-P, Raynaud S, Auberger P (2010) Resveratrol promotes autophagic cell death in chronic myelogenous leukemia cells via JNK-mediated p62/SQSTM1 expression and AMPK activation. Cancer Res 70: 1042–1052.
Qin Y, Ma Z, Dang X, Li W, Ma Q (2014) Effect of resveratrol on proliferation and apoptosis of human pancreatic cancer MIA PaCa-2 cells may involve inhibition of the Hedgehog signaling pathway. Mol Med Rep 10: 2563–2567.
Roldán A, Palacios V, Caro I, Pérez L (2003) Resveratrol content of Palomino fino grapes: influence of vintage and fungal infection. J Agricult Food Chem 51: 1464–1468.
Sørlie T, Johnsen H, Vu P, Lind GE, Lothe R, Børresen-Dale A-L (2014) Mutation screening of the TP53 gene by temporal temperature gel electrophoresis (TTGE). In Molecular Toxicology Protocols (Springer), pp. 315–324.
Sato K, Tobo M, Mogi C, Murata N, Kotake M, Kuwabara A, Im D-S, Okajima F (2014). Lipoprotein-associated lysolipids are differentially involved in high-density lipoprotein-and its oxidized form-induced neurite remodeling in PC12 cells. Neurochem Int 68: 38–47.
Sato M, Maulik N, Das DK (2002) Cardioprotection with alcohol. Ann N Y Acad Sci 957: 122–135.
Scarlatti F, Maffei R, Beau I, Codogno P, Ghidoni R (2008) Role of non-canonical Beclin 1-independent autophagy in cell death induced by resveratrol in human breast cancer cells. Cell Death Differ 15: 1318–1329.
Schneider C, Pozzi A (2011) Cyclooxygenases and lipoxygenases in cancer. Cancer Metastasis Rev 30: 277–294.
Sen S, Chakraborty R, Sridhar C, Reddy Y, De B (2010). Free Radicals, antioxidants, diseases and phytomedicines: current status and future prospect. Int J Pharm Sci Rev Res 3: 91.
Shaulian E, Karin M (2002) AP-1 as a regulator of cell life and death. Nature Cell Biol 4: E131-E136.
She Q-B, Bode AM, Ma W-Y, Chen N-Y, Dong Z (2001). Resveratrol-induced activation of p53 and apoptosis is mediated by extracellular-signal-regulated protein kinases and p38 kinase. Cancer Res 61: 1604–1610.
Shiozaki M, Hayakawa N, Shibata M, Koike M, Uchiyama Y, Gotow T (2011) Closer association of mitochondria with lipid droplets in hepatocytes and activation of Kupffer cells in resveratrol-treated senescence-accelerated mice. Histochem Cell Biol 136: 475–489.
Shishodia S, Aggarwal BB (2004) Cyclooxygenase (COX)-2 inhibitor celecoxib abrogates activation of cigarette smoke-induced nuclear factor (NF)-κB by suppressing activation of I-κB α kinase in human non-small cell lung carcinoma correlation with suppression of cyclin D1, COX-2, and matrix metalloproteinase-9. Cancer Res 64: 5004–5012.
Siemann E, Creasy L (1992) Concentration of the phytoalexin resveratrol in wine. Am J Enol Viticult 43: 49–52.
Signorelli P, Munoz-Olaya JM, Gagliostro V, Casas J, Ghidoni R, Fabriàs G (2009) Dihydroceramide intracellular increase in response to resveratrol treatment mediates autophagy in gastric cancer cells. Cancer Lett 282: 238–243.
Simão F, Pagnussat AS, Seo JH, Navaratna D, Leung W, Lok J, Guo S, Waeber C, Salbego CG, Lo EH (2012) Pro-angiogenic effects of resveratrol in brain endothelial cells: nitric oxide-mediated regulation of vascular endothelial growth factor and metalloproteinases. J Cereb Blood Flow Metab 32: 884–895.
Singh DP, Chopra K (2014) Flavocoxid, dual inhibitor of cyclooxygenase-2 and 5-lipoxygenase, exhibits neuroprotection in rat model of ischaemic stroke. Pharmacol Biochem Behavior 120: 33–42.
Soleas GJ, Diamandis EP, Goldberg DM (1997) Resveratrol: a molecule whose time has come? And gone? Clin Biochem 30: 91–113.
Soleas GJ, Yan J, Goldberg DM (2001) Measurement of trans-resveratrol,(+)-catechin, and quercetin in rat and human blood and urine by gas chromatography with mass selective detection. Methods Enzymol 335: 130.
Su J-L, Lin M-T, Hong C-C, Chang C-C, Shiah S-G, Wu C-W, Chen S-T, Chau Y-P, Kuo M-L (2005) Resveratrol induces FasL-related apoptosis through Cdc42 activation of ASK1/JNK-dependent signaling pathway in human leukemia HL-60 cells. Carcinogenesis 26: 1–10.
Sun AY, Chen Y-M, James-Kracke M, Wixom P, Cheng Y (1997) Ethanol-induced cell death by lipid peroxidation in PC12 cells. Neurochem Res 22: 1187–1192.
Sun J, Liang F, Bin Y, Li P, Duan C (2007) Screening non-colored phenolics in red wines using liquid chromatography/ultraviolet and mass spectrometry/mass spectrometry libraries. Molecules 12: 679–693.
Szaefer H, Cichocki M, Krajka-Kuźniak V, Stefański T, Sobiak S, Liczn-erska B, Baer-Dubowska W (2014) The effect of resveratrol and its

methylthio-derivatives on NF-κB and AP-1 signaling pathways in HaCaT keratinocytes. Pharmacol Rep 66: 732–740.

Tang Q, Li G, Wei X, Zhang J, Chiu J-F, Hasenmayer D, Zhang D, Zhang H (2013) Resveratrol-induced apoptosis is enhanced by inhibition of autophagy in esophageal squamous cell carcinoma. Cancer Lett 336: 325–337.

Trincheri NF, Follo C, Nicotra G, Peracchio C, Castino R, Isidoro C (2008) Resveratrol-induced apoptosis depends on the lipid kinase activity of Vps34 and on the formation of autophagolysosomes. Carcinogenesis 29: 381–389.

Whitehead TP, Robinson D, Allaway S, Syms J, Hale A (1995) Effect of red wine ingestion on the antioxidant capacity of serum. Clin Chem 41: 32–35.

Wilson T, Knight TJ, Beitz DC, Lewis DS, Engen RL (1996). Resveratrol promotes atherosclerosis in hypercholesterolemic rabbits. Life Sci 59: PL15-PL21.

Yar A, Menevse S, Alp E (2011) The effects of resveratrol on cyclooxygenase-1 and-2, nuclear factor kappa beta, matrix metalloproteinase-9, and sirtuin 1 mRNA expression in hearts of streptozotocin-induced diabetic rats. Genet Mol Res 10: 2962–2975.

Zhang J, Chiu J, Zhang H, Qi T, Tang Q, Ma K, Lu H, Li G (2013) Autophagic cell death induced by resveratrol depends on the Ca^{2+}/AMPK/mTOR pathway in A549 cells. Biochem Pharmacol 86: 317–328.