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Resveratrol-related compounds: Potential for cancer and beyond

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Abstract: The nutraceutical resveratrol is associated with a range of biological effects, from antibiotic to anti-inflammatory activities. One major axis of research has sought to harness its anti-tumour potential, with promising preclinical results and early clinical trials. A second strong interest relies on the anti-ageing effects ascribed to the compound and its application to stem cell research. It is becoming clear however that these possible favourable effects are conditioned by a set concentration range not easily controllable *in vivo*. Here we evoke novel developments in the field that could lead to more reliable conditions for the translational use of resveratrol-based compounds.

Introduction

Resveratrol (RV) is a stilbenoid first isolated in 1939 from the traditional medicine plant *Veratrum grandiflorum* and also present in various foods such as grapes, apples, pistachios, plums and peanuts, earning it a place of choice among nutraceuticals (Zhang *et al.*, 2021). From the two isomeric forms of RV, the trans-version is considered more biologically active (Kuršvietienė *et al.*, 2016). Despite its low natural solubility in water, RV shows relatively high absorption (over 70%) after oral consumption (Vitrac *et al.*, 2003; Walle *et al.*, 2004), however its bioavailability is considered to be below 1% (Walle, 2011). RV is among the most actively studied natural compounds, as underlined by the number of RV-related entries recorded in the international clinical trial database (www.clinicaltrials.gov) covering a wide range of applications. This variety of biological effects can be linked to the diverse cellular pathways activated by RV, as the compound interacts with different cellular components and exerts multiple biological activities, including antioxidant (de la Lastra and Villegas, 2007; Xia *et al.*, 2017), anti-inflammatory (Meng *et al.*, 2021; Magrone *et al.*, 2019), anti-microbial (Bostanghadiri *et al.*, 2017), anti-proliferative (Stivala *et al.*, 2001; Savio *et al.*, 2016; Maccario *et al.*, 2012) properties. RV is predominantly associated with antioxidant activity, an effect linked to the presence in its structure of three hydroxyl groups (Kuršvietienė *et al.*, 2016; Stivala *et al.*, 2001), as the molecule acts as scavenger of free radicals by increasing the intracellular concentration of antioxidant enzymes including SOD (superoxide dismutase), catalase, glutathione reductase and glutathione peroxidase (Yen *et al.*, 2003; Ramprasath and Jones, 2010). It has however been proposed that RV could display a pro-oxidant activity, which could be responsible for lipid peroxidation and DNA damage (de la Lastra and Villegas, 2007). RV is also able to modulate several signalling pathways involved in inflammation, including AP-1, COX and NF-κB leading to an anti-inflammatory response (Meng *et al.*, 2021). Crucially, RV is considered a potent activator of the NAD-dependent deacetylase enzyme Sirtuin 1 (SIRT1), a pleiotropic regulator of gene expression and silencing with particular relevance to cancer development (Yi and Luo, 2010; Choupani *et al.*, 2018).

Possible Anti-Cancer Applications

RV has been taken up as anti-cancer molecule following numerous studies demonstrating its anti-tumoral profile, through combined effects on cancer cell proliferation, tumour microenvironment and angiogenesis (reviewed in (Naujokat and McKee, 2020)). RV is considered a chemopreventive agent, acting in the three major stages of carcinogenesis (Fig. 1).

In particular, RV is involved in the regulation of phase I and II enzymes and in the scavenging of ROS, blocking the initiation stage of carcinogenesis (Ko *et al.*, 2017). RV has been observed to inhibit cell proliferation, arrest the replication cycle, and induce apoptosis and autophagy (Salehi *et al.*, 2018) in several *in vitro* cancer models such as HT1080 fibrosarcoma and MCF7 breast adenocarcinoma (Stivala *et al.*, 2001; Savio *et al.*, 2016; Maccario *et al.*, 2012).

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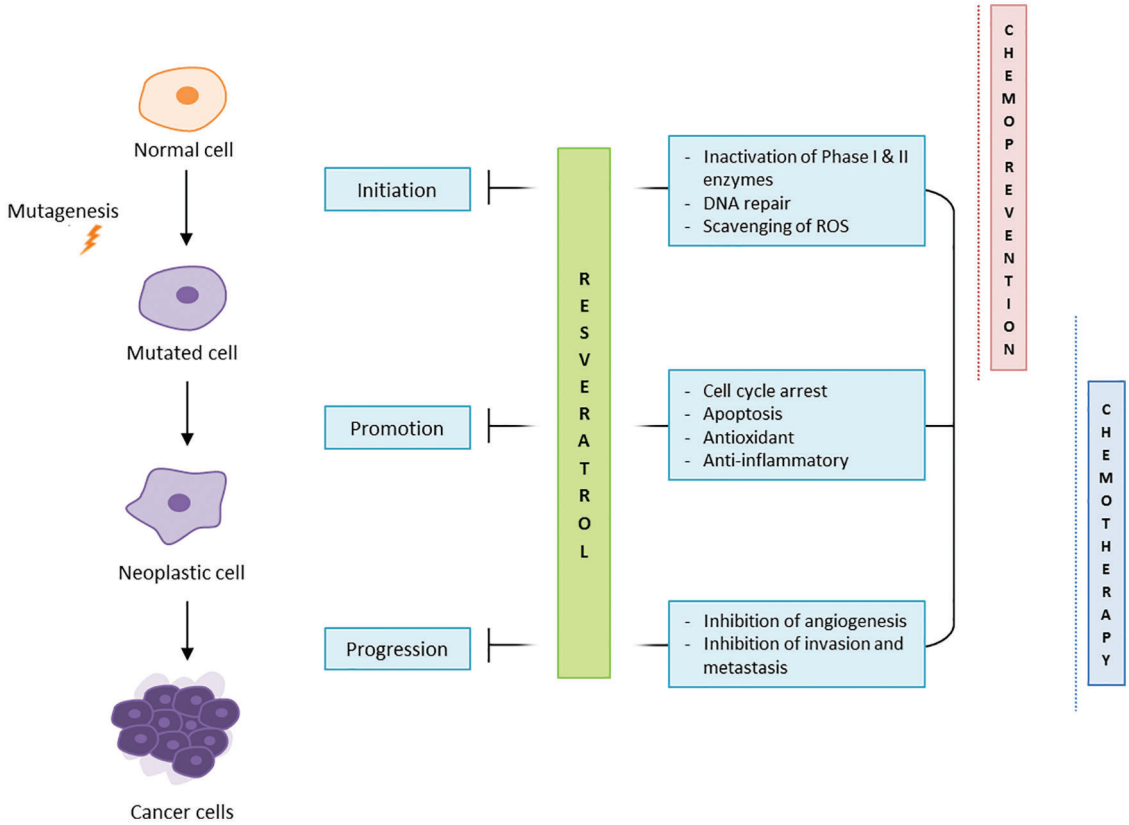

FIGURE 1. RV anti-cancer effects.

SIRT1 being a major mediator of RV effects, the ability of RV to upregulate SIRT1 in cancer cells is thought to induce in turn the degradation of β-catenin, supporting anti-cancer activities (Jung *et al.*, 2013; Firestein *et al.*, 2008). The ability of RV to inhibit the growth of cancerous cells is associated with well-documented therapeutic effects on the tumour environment including inhibition of angiogenesis and matrix metalloproteases (MMPs), modulation of epithelial-to-mesenchymal transition (EMT), and inhibition of invasion and metastasis (Belleri *et al.*, 2008; Rauf *et al.*, 2018). The compound was also shown to downregulate the phosphorylation and acetylation of NF-κB, impairing tumour proliferation, invasion and metastasis. In ovarian cancer cell lines, Tino *et al.* (2016) demonstrated that RV treatment inhibited cell growth by decreasing NF-κB levels and its downstream gene vascular endothelial growth factor (VEGF), which contributes to angiogenesis.

Its direct and indirect anti-tumour properties, combined with the aforementioned antioxidant and anti-inflammatory effects, hold clear potential for the use of RV in the clinic. Although clinical evaluation of the molecule is not without challenges (Ren *et al.*, 2021), some clinical trials have investigated the use of RV in cancer patients, in multiple myeloma, breast and colorectal cancer (Berman *et al.*, 2017). While treatment of colorectal cancer patients with RV or grape powder showed partly reduced tumour proliferation and increased cleaved caspase-3 levels in malignant hepatic metastases (Howells *et al.*, 2011), results to date are not fully consistent across models, as it did yield adverse effects in the multiple myeloma trial (Berman *et al.*, 2017). Preclinical observations have shown steadier benefits using RV, proposed as a chemosensitizer in complement to conventional chemotherapy (Harikumar *et al.*, 2010). This approach trialled by applying RV in combination with doxorubicin (DOX) in breast (Jin *et al.*, 2019), ovarian (Tino *et al.*, 2016) and colorectal (Buhrmann *et al.*, 2016) cancer cell models, was observed to inhibit proliferation, metastasis and chemoresistance. RV could thus potentiate chemotherapy and lower the necessary drug doses, consequently reducing the detrimental effects in patients from oxidative stress, lipid peroxidation, inflammation, apoptosis and autophagy (Yang *et al.*, 2022).

Diverse Effects on Stem Cell Populations

Beside this possible role in cancer, RV have been linked to increased longevity and resistance to age-induced degeneration (Bonkowski and Sinclair, 2016), contributing to its promotion as a multifaceted anti-ageing compound attracting much commercial interest. The effect of RV on stem cell populations, responsible for the long term maintenance of organs and tissue throughout the lifetime, has been investigated in a range of cellular models and linked to its ability to activate Sirtuins (Stefani *et al.*, 2007; Catalgol *et al.*, 2012).

RV was reported to promote self-renewal in undifferentiated embryonic stem cell (ESC) cultures, in both mouse and human models, and reduce apoptotic markers (Li *et al.*, 2017; Safaeinejad *et al.*, 2017, 2018). Consequently, RV is among the additives trialled to facilitate cellular reprogramming for the production of induced pluripotent stem cells (iPSC) (Chen *et al.*, 2011; Ding *et al.*, 2013), presumed to act on the SIRT1-SOX2 axis. Application of RV at various concentrations yielded diverse outcomes on adult stem cell populations, in particular lower concentrations were reported to increase the proliferative

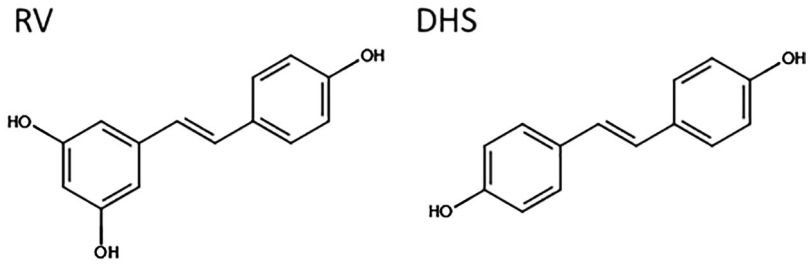

FIGURE 2. Chemical structure of RV (trans-3,5,4'-trihydroxystilbene) and DHS (trans-4,4'-dihydroxystilbene). Image created using the design tool from https://chem-space.com.

ability of mesenchymal progenitors (Yoon *et al.*, 2014; Yuan *et al.*, 2012), with a similar effect on neuroprogenitor also limited to lower doses (Kumar *et al.*, 2016). With regards to differentiation response, low dose RV applied to pancreatic stem cells improved β-cell formation (Xu *et al.*, 2017), while RV added to endothelial progenitors at 20 μM supported their differentiation (Campagnolo *et al.*, 2015). In differentiating mesenchymal stem cell (MSC) cultures, RV was consistently observed to promote osteogenesis (Moon *et al.*, 2020; Dai *et al.*, 2007; Wang *et al.*, 2019; Song *et al.*, 2022) at doses up to 1 μM (reviewed in (Safaeinejad *et al.*, 2018)), warranting its incorporation in tissue engineering products for localised release to promote bone repair (Wei *et al.*, 2021). RV added to mouse mesenchymal progenitors also caused inhibition of the adipogenic response (Zhou *et al.*, 2015; Li *et al.*, 2016) through Sirt1 (Jang *et al.*, 2017), although some conflicting reports have observed the opposite effect in some mouse (Hu *et al.*, 2015) and in human progenitors (Caldarelli *et al.*, 2015). The publication of such discordant results further underlines the likelihood of RV acting in a dose-, time- and species-dependent manner, already evidenced in certain stem cell models (Safaeinejad *et al.*, 2018; Peltz *et al.*, 2012).

Outstanding Issues & Perspectives

The basis of this apparent discrepancy in the differentiation response to RV has been linked to a biphasic dose-response profile (Borriello *et al.*, 2013; reviewed in (Calabrese *et al.*, 2010)), which might hinder general comparisons across models and studies. The fact that RV's beneficial effects may depend on reaching a specific *in vivo* concentration, points to the need for a better controlled pharmacological profile to achieve the desired effects (Scott *et al.*, 2012; Cai *et al.*, 2015). Better RV bioavailability is under active investigation (Chimento *et al.*, 2019), including via alternative formulations (Howells *et al.*, 2011; Tripathi *et al.*, 2018), nano-encapsulation to assist the delivery and release (Santos *et al.*, 2019) and chemical analogues including hydroxylated (Piotrowska *et al.*, 2012) or methylated (Kapetanovic *et al.*, 2011) derivatives such as pterostilbene showing superior bioavailability *in vivo*. One derivative in particular, trans-4,4′-dihydroxystilbene or DHS has shown promising biological characteristics. Produced as a synthetic new compound, its chemical structure (Fig. 2) was originally optimised to replicate the trans bicyclic/phenolic stilbene backbone of RV, based on the correlation previously observed between structure and activity (Stivala *et al.*, 2001). DHS was subsequently also identified as a natural derivative (Torres *et al.*, 2003), and found to be a potent antioxidant and anti-proliferative stilbene, superior to RV *in vitro* (Maccario *et al.*, 2012; Savio *et al.*, 2009).

DHS is active at a lower concentration compared to RV, and shows a different mechanism of action. In particular, DHS modified the cell cycle in the G1 phase, whereas RV induces a block at the beginning of the S phase, involving different DNA polymerases (Savio *et al.*, 2009). Strictly related to its structure, DHS is more potent than RV in inhibiting neoplastic transformation of murine fibroblasts, as well as the proliferation and invasion of breast cancer cells (Maccario *et al.*, 2012). *In vivo*, a murine lung cancer model was used to show that tumour volume and cell proliferation were significantly inhibited by DHS, and this is related to the reduction of angiogenesis (Savio *et al.*, 2016). In addition, liver metastatic lesions were significantly reduced by DHS treatment, an observation that was confirmed in a zebrafish tumour model (Savio *et al.*, 2016) and in a separate colon cancer model (Kimura *et al.*, 2020). These early results underline the potential of DHS as an alternative RV derivative for treatment of cancer and metastasis. More work is underway to explore its biological effects on other cell types and broader therapeutic applications.

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References

Belleri M, Ribatti D, Savio M, Stivala LA, Forti L et al. (2008). $\alpha_v\beta_3$ integrin-dependent antiangiogenic activity of resveratrol

stereoisomers. *Molecular Cancer Therapeutics* **7**: 3761–3770. DOI 10.1158/1535-7163.MCT-07-2351.

Berman AY, Motechin RA, Wiesenfeld MY, Holz MK (2017). The therapeutic potential of resveratrol: A review of clinical trials. *npj Precision Oncology* **1**: 35. DOI 10.1038/s41698-017-0038-6.

Bonkowski MS, Sinclair DA (2016). Slowing ageing by design: The rise of NAD^+ and sirtuin-activating compounds. *Nature Reviews Molecular Cell Biology* **17**: 679–690. DOI 10.1038/nrm.2016.93.

Borriello A, Bencivenga D, Caldarelli I, Tramontano A, Borgia A et al. (2013). Resveratrol and cancer treatment: Is hormesis a yet unsolved matter? *Current Pharmaceutical Design* **19**: 5384–5393. DOI 10.2174/1381612811319300007.

Bostanghadiri N, Pormohammad A, Chirani AS, Pouriran R, Erfanimanesh S et al. (2017). Comprehensive review on the antimicrobial potency of the plant polyphenol resveratrol. *Biomedicine & Pharmacotherapy* **95**: 1588–1595. DOI 10.1016/j.biopha.2017.09.084.

Buhrmann C, Shayan P, Popper B, Goel A, Shakibaei M (2016). Sirt1 is required for resveratrol-mediated chemopreventive effects in colorectal cancer cells. *Nutrients* **8**: 145. DOI 10.3390/nu8030145.

Cai H, Scott E, Kholghi A, Andreadi C, Rufini A et al. (2015). Cancer chemoprevention: Evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice. *Science Traslational Medicine* **7**: 298ra117. DOI 10.1126/scitranslmed.aaa7619.

Calabrese EJ, Mattson MP, Calabrese V (2010). Resveratrol commonly displays hormesis: Occurrence and biomedical significance. *Human & Experimental Toxicology* **29**: 980–1015. DOI 10.1177/0960327110383625.

Caldarelli I, Speranza MC, Bencivenga D, Tramontano A, Borgia A et al. (2015). Resveratrol mimics insulin activity in the adipogenic commitment of human bone marrow mesenchymal stromal cells. *The International Journal of Biochemistry & Cell Biology* **60**: 60–72. DOI 10.1016/j.biocel.2014.12.011.

Campagnolo P, Hong X, Di Bernardini E, Smyrnias I, Hu Y et al. (2015). Resveratrol-induced vascular progenitor differentiation towards endothelial lineage via MiR-21/Akt/β-catenin is protective in vessel graft models. *PLoS One* **10**: e0125122. DOI 10.1371/journal.pone.0125122.

Catalgol B, Saime B, Taga Y, Ozer NK (2012). Resveratrol: French paradox revisited. *Frontiers in Pharmacology* **3**: 141. DOI 10.3389/fphar.2012.00141.

Chen T, She L, Yu J, Wan H, Guo A et al. (2011). Rapamycin and other longevity-promoting compounds enhance the generation of mouse induced pluripotent stem cells: Longevity-promoting agents enhance reprogramming. *Aging Cell* **10**: 908–911. DOI 10.1111/j.1474-9726.2011.00722.x.

Chimento A, De Amicis F, Sirianni R, Sinicropi MS, Puoci F et al. (2019). Progress to improve oral bioavailability and beneficial effects of resveratrol. *International Journal of Molecular Sciences* **20**: 1381. DOI 10.3390/ijms20061381.

Choupani J, Derakhshan SM, Bayat S, Alivand MR, Khaniani MS (2018). Narrower insight to SIRT1 role in cancer: A potential therapeutic target to control epithelial-mesenchymal transition in cancer cells. *Journal of Cellular Physiology* **233**: 4443–4457. DOI 10.1002/jcp.26302.

Dai Z, Li Y, Quarles LD, Song T, Pan W et al. (2007). Resveratrol enhances proliferation and osteoblastic differentiation in human mesenchymal stem cells via ER-dependent ERK1/2 activation. *Phytomedicine* **14**: 806–814. DOI 10.1016/j.phymed.2007.04.003.

de la Lastra C, Villegas I (2007). Resveratrol as an antioxidant and pro-oxidant agent: Mechanisms and clinical implications. *Biochemical Society Transactions* **35**: 1156–1160. DOI 10.1042/BST0351156.

Ding DF, Li X, Xu H, Wang Z, Liang Q et al. (2013). Mechanism of resveratrol on the promotion of induced pluripotent stem cells. *Journal of Integrative Medicine* **11**: 389–396. DOI 10.3736/jintegrmed2013039.

Firestein R, Blander G, Michan S, Oberdoerffer P, Ogino S et al. (2008). The SIRT1 deacetylase suppresses intestinal tumorigenesis and colon cancer growth. *PLoS One* **3**: e2020.

Harikumar KB, Kunnumakkara AB, Sethi G, Diagaradjane P, Anand P et al. (2010). Resveratrol, a multitargeted agent, can enhance antitumor activity of gemcitabine *in vitro* and in orthotopic mouse model of human pancreatic cancer. *International Journal of Cancer* **127**: 257–268.

Howells LM, Berry DP, Elliott PJ, Jacobson EW, Hoffmann E et al. (2011). Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases—safety, pharmacokinetics, and pharmacodynamics. *Cancer Prevention Research* **4**: 1419–1425. DOI 10.1158/1940-6207.CAPR-11-0148.

Hu P, Zhao L, Chen J (2015). Physiologically achievable doses of resveratrol enhance 3T3-L1 adipocyte differentiation. *European Journal of Nutrition* **54**: 569–579. DOI 10.1007/s00394-014-0738-4.

Jang MJ, Park UH, Kim JW, Choi H, Um SJ et al. (2017). CACUL1 reciprocally regulates SIRT1 and LSD1 to repress PPARγ and inhibit adipogenesis. *Cell Death & Disease* **8**: 3201. DOI 10.1038/s41419-017-0070-z.

Jin X, Wei Y, Liu Y, Lu X, Ding F et al. (2019). Resveratrol promotes sensitization to doxorubicin by inhibiting epithelial-mesenchymal transition and modulating SIRT1/B-catenin signaling pathway in breast cancer. *Cancer Medicine* **8**: 1246–1257. DOI 10.1002/cam4.1993.

Jung W, Hong KD, Jung WY, Lee E, Shin BK et al. (2013). SIRT1 expression is associated with good prognosis in colorectal cancer. *Korean Journal of Pathology* **47**: 332. DOI 10.4132/KoreanJPathol.2013.47.4.332.

Kapetanovic IM, Muzzio M, Huang Z, Thompson TN, McCormick DL (2011). Pharmacokinetics, oral bioavailability, and metabolic profile of resveratrol and its dimethylether analog, pterostilbene, in rats. *Cancer Chemother Pharmacol* **68**: 593–601. DOI 10.1007/s00280-010-1525-4.

Kimura Y, Sumiyoshi M, Kiyoi T, Baba K (2020). Dihydroxystilbenes prevent azoxymethane/dextran sulfate sodium-induced colon cancer by inhibiting colon cytokines, a chemokine, and programmed cell death-1 in C57BL/6J mice. *European Journal of Pharmacology* **886**: 173445. DOI 10.1016/j.ejphar.2020.173445.

Ko JH, Sethi G, Um JY, Shanmugam MK, Arfuso F et al. (2017). The role of resveratrol in cancer therapy. *International Journal of Molecular Sciences* **18**: 2589. DOI 10.3390/ijms18122589.

Kumar V, Pandey A, Jahan S, Shukla RK, Kumar D et al. (2016). Differential responses of trans-resveratrol on proliferation of neural progenitor cells and aged rat hippocampal neurogenesis. *Scientific Reports* **6**: 28142. DOI 10.1038/srep28142.

Kuršvietienė L, Stanevičienė I, Mongirdienė A, Bernatonienė J (2016). Multiplicity of effects and health benefits of resveratrol. *Medicina* **52**: 148–155. DOI 10.1016/j.medici.2016.03.003.

Li N, Du Z, Shen Q, Lei Q, Zhang Y et al. (2017). Resveratrol enhances self-renewal of mouse embryonic stem cells. *Journal of Cellular Biochemistry* **118**: 1928–1935. DOI 10.1002/jcb.25942.

Li S, Bouzar C, Cottet-Rousselle C, Zagotta I, Lamarche F et al. (2016). Resveratrol inhibits lipogenesis of 3T3-L1 and SGBS cells by inhibition of insulin signaling and mitochondrial mass increase. *Biochimica et Biophysica Acta (BBA)-Bioenergetics* **1857**: 643–652. DOI 10.1016/j.bbabio.2016.03.009.

Maccario C, Savio M, Ferraro D, Bianchi L, Pizzala R et al. (2012). The resveratrol analog 4,4′-dihydroxy-trans-stilbene suppresses transformation in normal mouse fibroblasts and inhibits proliferation and invasion of human breast cancer cells. *Carcinogenesis* **33**: 2172–2180. DOI 10.1093/carcin/bgs244.

Magrone T, Magrone M, Russo MA, Jirillo E (2019). Recent advances on the anti-inflammatory and antioxidant properties of red grape polyphenols: *In vitro* and *in vivo* studies. *Antioxidants* **9**: 35. DOI 10.3390/antiox9010035.

Meng T, Xiao D, Muhammed A, Deng J, Chen L et al. (2021). Anti-inflammatory action and mechanisms of resveratrol. *Molecules* **26**: 229. DOI 10.3390/molecules26010229.

Moon DK, Kim BG, Lee AR, Choe YI, Khan I et al. (2020). Resveratrol can enhance osteogenic differentiation and mitochondrial biogenesis from human periosteum-derived mesenchymal stem cells. *Journal of Orthopaedic Surgery and Research* **15**: 203. DOI 10.1186/s13018-020-01684-9.

Naujokat C, McKee DL (2020). The big five phytochemicals targeting cancer stem cells: Curcumin, EGCG, sulforaphane, resveratrol and genistei. *Current Medicinal Chemistry* **22**: 4321–4342.

Peltz L, Gomez J, Marquez M, Alencastro F, Atashpanjeh N et al. (2012). Resveratrol exerts dosage and duration dependent effect on human mesenchymal stem cell development. *PLoS One* **7**: e37162. DOI 10.1371/journal.pone.0037162.

Piotrowska H, Kucinska M, Murias M (2012). Biological activity of piceatannol: Leaving the shadow of resveratrol. *Mutation Research* **750**: 60–82. DOI 10.1016/j.mrrev.2011.11.001.

Ramprasath VR, Jones PJH (2010). Anti-atherogenic effects of resveratrol. *European Journal of Clinical Nutrition* **64**: 660–668. DOI 10.1038/ejcn.2010.77.

Rauf A, Imran M, Butt MS, Nadeem M, Peters DG et al. (2018). Resveratrol as an anti-cancer agent: A review. *Critical Reviews in Food Science and Nutrition* **58**: 1428–1447. DOI 10.1080/10408398.2016.1263597.

Ren B, Kwah MXY, Liu C, Ma Z, Shanmugam MK et al. (2021). Resveratrol for cancer therapy: Challenges and future perspectives. *Cancer Letters* **515**: 63–72. DOI 10.1016/j.canlet.2021.05.001.

Safaeinejad Z, Kazeminasab F, Kiani-Esfahani A, Ghaedi K, Nasr-Esfahani MH (2018). Multi-effects of resveratrol on stem cell characteristics: Effective dose, time, cell culture conditions and cell type-specific responses of stem cells to resveratrol. *European Journal of Medicinal Chemistry* **155**: 651–657. DOI 10.1016/j.ejmech.2018.06.037.

Safaeinejad Z, Nabiuni M, Peymani M, Ghaedi K, Nasr-Esfahani MH et al. (2017). Resveratrol promotes human embryonic stem cells self-renewal by targeting SIRT1-ERK signaling pathway. *European Journal of Cell Biology* **96**: 665–672. DOI 10.1016/j.ejcb.2017.08.002.

Salehi B, Mishra A, Nigam M, Sener B, Kilic M et al. (2018). Resveratrol: A double-edged sword in health benefits. *Biomedicines* **6**: 91. DOI 10.3390/biomedicines6030091.

Santos AC, Pereira I, Pereira-Silva M, Ferreira L, Caldas M et al. (2019). Nanotechnology-based formulations for resveratrol delivery: Effects on resveratrol *in vivo* bioavailability and bioactivity. *Colloids and Surfaces B: Biointerfaces* **180**: 127–140. DOI 10.1016/j.colsurfb.2019.04.030.

Savio M, Coppa T, Bianchi L, Vannini V, Maga G et al. (2009). The resveratrol analogue 4,4′-Dihydroxy-trans-stilbene inhibits cell proliferation with higher efficiency but different mechanism from resveratrol. *The International Journal of Biochemistry & Cell Biology* **41**: 2493–2502. DOI 10.1016/j.biocel.2009.08.005.

Savio M, Ferraro D, Maccario C, Vaccarone R, Jensen LD et al. (2016). Resveratrol analogue 4,4′-dihydroxy-trans-stilbene potently inhibits cancer invasion and metastasis. *Scientific Reports* **6**: 19973. DOI 10.1038/srep19973.

Scott E, Steward WP, Gescher AJ, Brown K (2012). Resveratrol in human cancer chemoprevention choosing the right dose. *Moecular Nutrition & Food Research* **56**: 7–13. DOI 10.1002/mnfr.201100400.

Song CY, Guo Y, Chen FY, Liu WG (2022). Resveratrol promotes osteogenic differentiation of bone marrow-derived mesenchymal stem cells through MiR-193a/SIRT7 axis. *Calcified Tissue International* **110**: 117–130. DOI 10.1007/s00223-021-00892-7.

Stefani M, Markus MA, Lin RCY, Pinese M, Dawes IW et al. (2007). The effect of resveratrol on a cell model of human aging. *Annals of the New York Academy of Sciences* **1114**: 407–418. DOI 10.1196/annals.1396.001.

Stivala LA, Savio M, Carafoli F, Perucca P, Bianchi L et al. (2001). Specific structural determinants are responsible for the antioxidant activity and the cell cycle effects of resveratrol. *Journal of Biological Chemistry* **276**: 22586–22594. DOI 10.1074/jbc.M101846200.

Tino AB, Chitcholtan K, Sykes PH, Garrill A (2016). Resveratrol and acetyl-resveratrol modulate activity of VEGF and IL-8 in ovarian cancer cell aggregates via attenuation of the NF-κB protein. *Journal of Ovarian Research* **9**: 84. DOI 10.1186/s13048-016-0293-0.

Torres P, Avila JG, Romo de Vivar A, García AM, Marín JC et al. (2003). Antioxidant and insect growth regulatory activities of stilbenes and extracts from yucca periculosa. *Phytochemistry* **64**: 463–473. DOI 10.1016/S0031-9422(03)00348-0.

Tripathi V, Chhabria S, Jadhav V, Bhartiya D, Tripathi A (2018). Stem cells and progenitors in human peripheral blood get activated by extremely active resveratrol (XARTM). *Stem Cell Reviews and Reports* **14**: 213–222. DOI 10.1007/s12015-017-9784-7.

Vitrac X, Desmoulière A, Brouillaud B, Krisa S, Deffieux G et al. (2003). Distribution of [14C]-trans-resveratrol, a cancer chemopreventive polyphenol, in mouse tissues after oral administration. *Life Sciences* **72**: 2219–2233. DOI 10.1016/S0024-3205(03)00096-1.

Walle T (2011). Bioavailability of resveratrol: Resveratrol bioavailability. *Annals of the New York Academy of Sciences* **1215**: 9–15. DOI 10.1111/j.1749-6632.2010.05842.x.

Walle T, Hsieh F, DeLegge MH, Oatis JE, Walle UK (2004). High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metabolism and Disposition* **32**: 1377–1382. DOI 10.1124/dmd.104.000885.

Wang H, Hu Z, Wu J, Mei Y, Zhang Q et al. (2019). Sirt1 promotes osteogenic differentiation and increases alveolar bone mass via Bmi1 activation in mice. *Journal of Bone and Mineral Research* **34**: 1169–1181.

Wei B, Wang W, Liu X, Xu C, Wang Y et al. (2021). Gelatin methacrylate hydrogel scaffold carrying resveratrol-loaded solid lipid nanoparticles for enhancement of osteogenic differentiation of BMSCs and effective bone regeneration. *Regenerative Biomaterials* **8**: rbab044.

Xia N, Daiber A, Förstermann U, Li H (2017). Antioxidant effects of resveratrol in the cardiovascular system. *British Journal of Pharmacology* **174**: 1633–1646.

Xu S, Sun F, Ren L, Yang H, Tian N et al. (2017). Resveratrol controlled the fate of porcine pancreatic stem cells through the Wnt/β-Catenin signaling pathway mediated by Sirt1. *PLoS One* **12**: e0187159.

Yang R, Dong H, Jia S, Yang Z (2022). Resveratrol as a modulatory of apoptosis and autophagy in cancer therapy. *Clinical and Translational Oncology* **24**: 1219–1230. DOI 10.1007/s12094-021-02770-y.

Yen GC, Duh PD, Lin CW (2003). Effects of resveratrol and 4-hexylresorcinol on hydrogen peroxide-induced oxidative DNA damage in human lymphocytes. *Free Radical Research* **37**: 509–514.

Yi J, Luo J (2010). SIRT1 and P53, effect on cancer, senescence and beyond. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics* **1804**: 1684–1689. DOI 10.1016/j.bbapap.2010.05.002.

Yoon DS, Choi Y, Jang Y, Lee M, Choi WJ et al. (2014). SIRT1 directly regulates SOX2 to maintain self-renewal and multipotency in bone marrow-derived mesenchymal stem cells. *Stem Cells* **32**: 3219–3231. DOI 10.1002/stem.1811.

Yuan HF, Zhai C, Yan XL, Zhao DD, Wang JX et al. (2012). SIRT1 is required for long-term growth of human mesenchymal stem cells. *Journal of Molecular Medicine* **90**: 389–400. DOI 10.1007/s00109-011-0825-4.

Zhang LX, Li CX, Kakar MU, Khan MS, Wu PF et al. (2021). Resveratrol (RV): A pharmacological review and call for further research. *Biomedicine & Pharmacotherapy* **143**: 112164. DOI 10.1016/j.biopha.2021.112164.

Zhou Y, Zhou Z, Zhang W, Hu X, Wei H et al. (2015). SIRT1 inhibits adipogenesis and promotes myogenic differentiation in C3H10T1/2 pluripotent cells by regulating wnt signaling. *Cell & Bioscience* **5**: 61. DOI 10.1186/s13578-015-0055-5.