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Resveratrol as an Anticancer Agent: A Review

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ABSTRACT

Owing to their antimicrobial, antioxidant, and anti-inflammatory activity, grapes (*Vitis vinifera* L.) are the archetypal paradigms of fruits used not only for nutritional purposes but also for exclusive therapeutics. Grapes are a prominent and promising source of phytochemicals, especially resveratrol, a phytoalexin antioxidant found in red grapes which has both chemopreventive and therapeutic effects against various ailments. Resveratrol's role in reducing different human cancers, including breast, cervical, uterine, blood, kidney, liver, eye, bladder, thyroid, esophageal, prostate, brain, lung, skin, gastric, colon, head and neck, bone, ovarian, and cervical, has been reviewed. This review covers the literature that deals with the anticancer mechanism of resveratrol with special reference to antioxidant potential. Furthermore, this article summarizes the literature pertaining to resveratrol as an anticancer agent.

KEYWORDS: Resveratrol, chemopreventive agent, human cancers

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INTRODUCTION

Resveratrol (3,5,4′-trihydroxystilbene, Figure 1), a naturally occurring polyphenolic compound, is a stilbene found in significant amounts in grapes, berries, peanuts, and other plant sources as well as in red wine (Bielsalski, 2007). Concentrations of resveratrol in red and white wines are between 14 and 0.1 mg/L, respectively (Baur and Sinclair, 2006). Similarly, concentrations of resveratrol in grape juice and whole grapes have been found to range from 0.05 to 0.5 mg/L, and up to 3.54 mg/L. This compound has become very popular due to its anticancer potential, first reported in 1997 (Jang et al., 1997). Since then, researchers have paid attention to this compound owing to its promising role in mediating inflammation, tumerogenesis, and cardioprotective effects, among other things (Baur and Sinclair, 2006). Resveratrol also lowers the Michaelis constant of SIRT1 (sirtuin 1, a protein encoded by SIRT1) for both the acetylated substrate and NAD(+) and it increases cell survival by stimulating SIRT1-dependent deacetylation of p53. In yeast, it mimics calorie restriction by stimulating Sir2, increasing DNA stability, and extending lifespan by 70% (Howitz et al., 2003). Grapes, as effective remedial agents against cardiovascular disorders, are part of the French Paradox. Similarly, researchers discovered that large doses of resveratrol significantly extend the lifespan of mammals (Baur and Sinclair, 2006).

Antioxidant and anti-inflammatory effects of dietary polyphenols such as curcumin (diferuloylmethane, a principal component of turmeric) and resveratrol have been reported to control undesired effects of oxidative stress achieved by modulatory activation of NF-κB (Rahman et al., 2006). In addition, resveratrol suppresses enzymes, such as cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2) (Das and Das, 2007).

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Cancer continues to be a global burden, despite the advent of technological and pharmaceutical improvements over the past two decades (Seyed et al., 2016). Methods of cancer treatment include surgery, radiotherapy, anticancer drugs (chemotherapy) in addition to other specialized techniques. Published reports indicated that approximately 90−95% of all cancers is attributed to lifestyle, such as alcohol consumption, obesity, outdoor pollution, food additives, among other things, and the remaining 5−10% to defective genes (de Martel et al., 2012; Irigaray et al., 2007). Herbs have been used for years either as complementary therapy or dietary agents to influence cellular signaling (Martin, 2006). For example, resveratrol extracted from grapes has been employed as an alternative drug to treat different cancers. Many reports have indicated that resveratrol provides a wide range of preventive and therapeutic options against different types of cancer. Moreover, resveratrol has been widely envisioned as potentially useful for anticancer therapy when combined with other chemotherapeutic drugs, and it has received considerable attention for its potential as a chemopreventive agent against human cancers. Along these lines, the action of resveratrol against cancer cells has been the subject of other research. Aluyen et al. evaluated three ways to explain the effects of resveratrol on different types of cancer cells; these are cell apoptosis, antiproliferation, and anti-inflammation (Aluyen et al., 2012). In a similar fashion, a very recent review by Varoni and colleagues focused on various mechanisms of action by which resveratrol acts, such as signaling pathways related to growth factors and receptor tyrosine kinases, signal transduction by the growth factor β, and appoptosis and inflammation (Varoni et al., 2016). These two reviews focus on the mechanisms of action of resveratrol against a limited number of cancers, whereas other publications emphasize individual in vitro or in vivo investigations. The present review offers a more comprehensive account (including the inclusion

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of more references) of the effect of resveratrol and its mechanism of action on a much larger body of cancers.

Accordingly, and owing to the wide range of preventive and therapeutic options of resveratrol against different types of cancer, this review focuses on the chemopreventive and therapeutic ability of this natural compound, with emphasis on the mechanism of its action. Table 1 is a compilation of different types of cancer, the mechanism of action of resveratrol on those cancers, and a list of pertinent references, whereas shown in Figure 2 is the anticancer role of resveratrol.

ANTICANCER POTENTIAL OF RESVERATROL

COLORECTAL CANCER

Resveratrol has been found to be an effective anticancer agent against LoVo cells *in vitro* and *in vivo*. This anticancer effect is induced by TGF-β through multiple approaches such as (a) suppressing the TGF-β-induced epithelial mesenchymal transition (EMT), (b) decreasing the rate of lung metastases and hepatic metastases, and (c) preventing TGF-β1, promoting the invasion and metastasis of CRC, decreasing the E-cadherin expression, elevating vimentin expression, and activating the TGF-β1/Smads signaling pathway. Resveratrol also suppresses the invasive and migratory ability of LoVo cells, enhances the expression of E-cadherin, and represses the expression of vimentin along with inhibition of the TGF-β1/Smads signaling pathway. In addition, it lowers the level of EMT-inducing transcription of E-cadherin and transcription factors Snail during the initiation of TGF-β1-induced EMT. It also suppresses the EMT in CRC

via TGF-β1/Smads signaling pathway-mediated Snail/E-cadherin expression (Ji et al., 2015). Saud et al. (2014) investigated the effects of resveratrol administration (105 and 210 mg) and found a 60% inhibition rate in tumor production and tumor size in mice. These researchers concluded that resveratrol enhances the expression of miR-96, and can prevent the formation and growth of colorectal tumors by down-regulating Kras expression (Saud et al., 2014). In addition, resveratrol was found to exert a modulatory role on mitomycin C (MMC)-mediated effects of colorectal cancer via inhibiting cell growth, modulating genes, upregulating p21 (WAF1/CIP1) that suppresses the cell cycle at G0/G1 and G2/M phases (Ali et al., 2014). Moreover, resveratrol has anticancer effects in colon cancer cell lines, particularly in relation to the DNA-damage response (DDR; PIKKs-Chks-p53 signaling cascade) and its cellular consequences. These responses were studied for the first time and correlated with activation of DDR, apoptosis, and senescence. Low concentrations of resveratrol have no significant effect on induction of apoptosis but do delay the S-phase cycle, whereas higher concentrations for longer periods effectively lead to transient micronucleations and senescence phenotypes associated with polyploidisation. However, resistance towards resveratrol was reported, which was reflected through higher degrees of ploidy and macronucleation as compared to parental cells. These transient effects and emergence of resistance are linked to the abilities of cells to escape progressively resveratrol-induced DNA damage (Colin et al., 2014).

For HT-29 colon carcinoma cells, Schroeter et al. reported that resveratrol (≥100 and 250 μM) counteracted DOX-induced formation of DNA-TOP-intermediates for TOP IIα and TOP IIβ. It also modulated the DNA-strand breaking potential of DOX by mediating protective effects and diminishing the intracellular concentrations of DOX (Schroeter et al., 2014). With

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oxaliplatin (L-OHP)-resistant colorectal cancer cells (HCT116/L-OHP), it down-regulated the expression levels of mRNA and P-glycoprotein/multidrug resistance protein 1 (P-gp/MDR1) and lowered MDR1 promoter activity. By enhancing the intracellular accumulation of rhodamine 123, resveratrol can reverse multidrug resistance by reducing drug efflux and down-regulating MDR1 expression. Additionally, resveratrol lowers the phosphorylation levels of IκBα and the activity of nuclear factor-κB (NF-κB), and reduces nuclear translocation of the NF-κB subunit p65. Furthermore, promoter activity and down-regulation of MDR1 expression were mediated by resveratrol-induced AMP-activated protein kinase (AMPK) phosphorylation. The AMPKα siRNA transfection reversed the suppressive effects of resveratrol on cAMP-responsive element-binding protein (CREB) phosphorylation and MDR1 expression (Wang et al., 2015).

Treatment with resveratrol (12.5--200 μmol/L) for 48 h significantly inhibited colorectal cancer stem cell (CCSCs HCT116) proliferation by increasing the proportion of cells in the G0/G1 phase and by decreasing those in the S phase in a dose-dependent manner. On the other hand, higher concentrations of resveratrol enhanced the rate of apoptosis and expression of MICA/B in CCSCs (Yang et al., 2015). Additionally, it induces apoptotic cell death as indicated by the cleavage of PARP-1 and chromatin condensation and also activates the tumor suppressor p53 which promotes the apoptosis process. At a concentration of 25 μM, resveratrol induced DNA damage such as double-strand breaks. Further exposure to HCT-116 cells which activate the Ataxia Telangiectasia Mutated (ATM) kinase, and p53 expression (Demoulin et al., 2015). In parental CRC cell lines (SW480, HCT116) and their corresponding isogenic 5-FU-chemoresistant derived clones (SW480R, HCT116R), resveratrol blocked the growth of all four CRC cell lines and synergized invasion inhibitory effects of 5-FU. Resveratrol also prompts a

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transition from 5-fluorouracil-induced formation of microvilli to a planar cell surface along with up-regulation of gap- and tight junctions (claudin-2), desmosomes, and adhesion molecules (E-cadherin) expression in HCT116R and HCT116 cells. Furthermore, it attenuates drug resistance via suppression of epithelial-mesenchymal transition (EMT) factors (increased E-cadherin, decreased vimentin and slug) and down-regulation of NF-κB activation and its translocation to the nucleus and abolished NF-κB-regulated gene end products (MMP-9, caspase-3). This inhibition was mediated via suppression of IκBα phosphorylation and IκBα kinase and degradation (Buhrmann et al., 2015; Wang et al., 2015).

Effects of cisplatin (CIS) on cytotoxicity, apoptosis, cell cycle, and cisplatin cellular uptake were examined in the presence and absence of resveratrol. Results revealed that resveratrol (15 μg/mL) increases the cytotoxic effects of cisplatin against the growth of both parent and CIS-resistant HCT-116 CRC cells, with a half maximal inhibitory concentration of 4.20 and 4.72 μg/mL, respectively. Resveratrol also led to a significant increase in the early apoptosis fraction and enhanced subsequent apoptotic effects of CIS. Cellular uptake of CIS was significantly increased in the presence of resveratrol, as compared with CIS treatment alone, and resveratrol treatment sensitized the CIS-resistant HCT-116 cells (Osman et al., 2015). In a similar fashion, Wong and coworkers discovered that resveratrol increases nitric oxide (NO) production via increased expression and activation of endothelial-form-NO-synthase (eNOS) in endothelial cells. The endogenous NO/cGMP/PKG pathway, as well as downstream cell-survival proteins (Inhibitor of Apoptosis Proteins (IAPs)), were studied in relation to pro- and anti-angiogenic effects of resveratrol in human umbilical vein endothelial cells (HUVECs). Resveratrol, at higher/anti-angiogenic concentrations, inhibits HUVEC tube formation and cell

migration/invasion (indices of angiogenesis), whereas at lower concentrations stimulates proliferation and protects HUVECs against spontaneous apoptosis. On the other hand, 8-Br-cGMP, a direct activator of PKG, protects against pro-apoptotic effects of high concentrations of resveratrol. It suppresses endogenous PKG kinase activity and decreases the expression of four cell-survival proteins, c-IAP2, c-IAP1, XIAP, and livin. In addition, resveratrol-induced anti-angiogenesis induced the suppression of PKG signaling and decreased the expression of the cell-survival proteins c-IAP1, c-IAP2, livin, and XIAP (Wong et al., 2015).

BREAST CANCER

Breast cancer is one of the leading causes of mortality among women worldwide. In the USA, breast cancer represents the most common neoplasm and the second leading cause of cancer death in women (DeSantis et al., 2014). Herceptin, chemically known as trastuzumab, is considered an effective treatment option for patients with HER-2 receptor positive breast cancer; it reduces the risk of cancer recurrence after surgery. On the other hand, resveratrol and didox are chemopreventive agents with potential anticancer properties. A recent study by Abdel-Latif and coworkers (Abdel-Latif et al., 2015) focused on the effect of resveratrol and didox on the cytotoxicity profile of herceptin in T47D and MCF-7 cell lines which are HER-2 receptor positive and HER-2 receptor negative breast cancer cell lines, respectively. These researchers found that a combination of herceptin with resveratrol promoted a remarkable reduction of the HER-2 receptor expression compared to single treatments. They concluded that this combination, in addition to herceptin/didox, improved the cytotoxic profile of herceptin in both

studied breast cancer cell lines. Mitani et al. (2014a) similarly investigated the effect of resveratrol on hypoxia-induced resistance to doxorubicin in the MCF-7 cancer cell line. They found that resveratrol inhibits the hypoxia-induced expression of carbonyl reductase 1 (CBR1) and hypoxia-inducible factor (HIF)-1α protein at mRNA and protein levels. Suppression of HIF-1α protein occurs even in the presence of the proteasome inhibitor MG132 in hypoxia. HIF-1α increases CBR1 expression in MCF-7 cells, whereas resveratrol decreases CBR1 expression by lowering HIF-1α protein expression, perhaps through a proteasome-independent pathway, and consequently repressed hypoxia-induced resistance to doxorubicin.

On the other hand, administration of resveratrol (3 μM) caused apoptotic death by increasing cytochrome C release, Bax/Bcl-xL ratio, and the cleaved product of caspase 3 and PARP in cells. Interestingly, this combination did not alter the protein expressions of WNT-TCF and Notch signaling components, *β*-catenin and cleaved notch-1 val1744, respectively. Furthermore, the combination also significantly decreased the intermediates of Hedgehog-Gli cascade including SMO, SHH, Gli-1, c-MYC, Cyclin-D1, etc., and increased the level of p21(Waf/Cip1) *in vitro* and *in vivo*. That the expression of the above proteins and Gli1 promoter activity in p21(Waf/Cip1) knockout cells was unaltered is suggestive of the fact that this combination causes apoptosis through p21(Waf/Cip1). Conclusively, resveratrol induces apoptotic death significantly in cigarette smoke-induced breast cancer cell lines via p2(Waf/Cip1) and mediated suppression of Hedgehog-Gli cascade (Mohapatra et al., 2015). In a previous study, Mohapatra et al. (2014) evaluated resveratrol-induced apoptosis in cigarette- smoke-condensate (CSC) transformed (MCF-10A-Tr) cells via enhancing p21 protein expression, reducing the tumor size(s) and expression of anti-apoptotic proteins (e.g., AKT, PI3K, NFκB). Results from this

investigation revealed that expressions of cell cycle regulatory (CDC-2, Cyclins, CDC-6), BER linked (Pol-δ, Pol-β, Pol-η, Pol-ε, RPA, DNA-Ligase-I, Fen-1) proteins and LP-BER activity were lowered in MCF-10A-Tr cells, but remain significantly unaltered in isogenic p21 null MCF-10A-Tr cells after resveratrol treatment. Furthermore, resveratrol enhanced the p21 that blocked LP-BER in MCF-10A-Tr cells by increasing its interaction with PCNA in competition with Fen-1 (Mohapatra et al., 2014).

Singh and colleagues examined the effect of resveratrol on inhibition in addition to mechanisms of resveratrol-mediated protection against estrogen-induced breast cancer. Their results suggested that treatment with resveratrol induced apoptosis and lowered 17β-estradiol (E2)-resveratrol mediated DNA damage in mammary tissues (Singh et al., 2014). Furthermore, it induces p53/p21WAF1/CIP1-dependent apoptosis in MCF-7 cells and exhibits p53-independent apoptosis in MDA-MB-231 cells (Kim et al., 2014). Khan and coworkers recently examined the effect of resveratrol on the growth of breast cancer cells by means of cytotoxicity-based MTT assay. These researchers found that resveratrol-mediated down-regulation of fatty acid synthase (FASN) and human epidermal growth factor receptor 2 (HER2) genes synergistically induced apoptotic death in SKBR-3 cells. In addition, they concluded that resveratrol inhibits proliferation of breast cancer cells via inhibition of the fatty-acid-synthase signaling pathway (Khan et al., 2014). An investigation by Alayev et al. revealed that a combination of rapamycin and resveratrol inhibits the mechanistic target of rapamycin complex 1 (mTORC1) signaling and at the same time prevents Akt activation and autophagy, leading to apoptosis; these results are promising in breast cancer treatment (Alayev et al., 2015). With the aid of a mixed micelle system composed of methoxy poly(ethylene glycol)-b-polycaprolactone (mPEG-PCL) and d-α-

tocopherol polyethylene glycol succinate, Wang and coworkers prepared resveratrol-loaded mixed micelles. They used micelles to examine the antitumor activity against doxorubicin (Dox)-resistant breast cancer MCF-7/ADR cells and found that these mixed micelles have promise for the treatment of drug-resistant breast cancer (Wang et al., 2015).

OVARIAN CANCER

Ovarian cancer (OC), one of the most common female malignancies, accounts for the leading death rate among the gynecologic cancers. Surgical treatment is the first choice to remove ovarian cancer if the tumor is well differentiated, in relatively small size, or confined to the ovary; however, chemotherapy can also be used in many cases (Zhong, et al., 2015). Zhong et al. employed two ovarian cell lines (CAOV-3 and OVCAR-3) to study the inhibitory effect of resveratrol on ovarian cancer cells. Through this investigation they showed that resveratrol suppresses the growth of CAOV-3 and OVCAR-3 cells in dose- and time-related fashions. In addition, they found that this suppression is attributable to inhibition of STAT3 signaling, and they concluded that resveratrol could be a promising candidate for the treatment of ovarian cancer, especially when there is resistance to conventional therapeutic agents. A recent study by Seino and colleagues revealed that resveratrol effectively kills ovarian cancer stem cells independently of reactive oxygen species (ROS), whereas ROS dependently reduced ovarian CSCs that survived resveratrol treatment (Seino et al., 2015).

Resveratrol also regulates glucose metabolism and modulates GLUT1 in ovarian cancer cell lines. It also suppresses glucose uptake, induces apoptosis, and inhibits the plasma membrane GLUT1 localization linked with the inhibition of Akt activity (Gwak et al., 2015). Guo et al. (2015) investigated the caspase-independent cell-death pathway induced by

resveratrol-bovine serum albumin nanoparticles (RES-BSANP) in human ovarian cancer SKOV3 cells. Translocation of AIF from the mitochondria to the cytoplasm occurred earlier than that of Cyto c. In addition, binding of Bax was required for the release of AIF and Cyto c from the mitochondria. These researchers showed that RES-BSANP induced apoptosis in SKOV3 is mediated by activation of caspase. Resveratrol also (a) suppresses the epithelial-to-mesenchymal transition with concomitant recovery of E-cadherin expression, (b) down-regulates NE-induced human telomerase reverse transcriptase (hTERT) expression, (c) inhibits Src phosphorylation and HIF-1α expression, and (d) lowers NE-induced Slug expression and subsequent ovarian cancer invasion (Kim et al., 2015). Similarly, a recent study that dealt with ovarian cancer cells revealed that resveratrol inhibits cisplatin-induced epithelial-to-mesenchymal transition (EMT) which is a key process in cancer progression (Baribeau et al., 2014).

Lang and colleagues employed various molecular biology techniques (flow cytometry, western blotting, and RNA interference) to investigate the mechanism concerning the anti-cancer effect of resveratrol on human ovarian cancer cells (OVCAR-3 and Caov-3); their major focus was on the potential role of autophagy in resveratrol-induced apoptotic cell death (Lang et al., 2015). These researchers demonstrated that resveratrol causes the generation of reactive oxygen species (ROS), triggering autophagy and subsequent apoptotic cell death. Furthermore, they found that resveratrol induced ATG5 expression and promoted LC3 cleavage. In another study by Mikuła-Pietrasik et al. (2014), different concentrations of resveratrol (10, 50, and 100 μM) exhibited inhibitory effects on ovarian cancer cells (OVCAR-3, A2780, SKOV-3) by lowering cellular α5β1 integrin level and by enhancing the secretion of HA to the environment. Resveratrol also attenuates the proliferation of serum-starved PA-1 cells stimulated with insulin

and, in addition, it activates caspase-3, -7, and -9 and induces apoptosis in PA-1 cells. Lee and coworkers investigated the inhibitory effect of resveratrol on the growth of human ovarian cancer PA-1 cells; they found that resveratrol inhibits insulin- or serum-induced growth of ovarian cancer PA-1 by decreasing eEF1A expression (Lee et al., 2009). Moreover, reveratrol significantly lowers glucose uptake, lactate production, and the levels of phosphorylated Akt and mTOR in epithelial ovarian cancer cells (Kueck et al., 2007).

CERVICAL CANCER

Cervical cancers (CC) are leading causes of cancer-related death among women in developing countries (Schiller and Davies 2004; Ojesina 2014). Although surgery is still the first choice of CC treatments, chemotherapy has been widely used to prevent recurrence in post-operative management of CCs (Liu and Zheng 2013). Owing to drug resistance and severe toxicities, there is a need to explore more reliable and less toxic therapeutic approaches to treat cervical cancers. Zhang et al. examined the effect of resveratrol on STAT3-, Notch-, and Wnt-mediated signaling pathways in different cervical cancer cell lines (Zhang et al., 2014). They discovered that treating HeLa and SiHa cells with 100 μM resveratrol led to extensive apoptosis along with inhibition of the three signaling pathways (STAT3, Notch, and Wnt**).** Li and coworkers similarly investigated the effects of resveratrol on GRIM-19-Stat3 signaling in HeLa cells derived from a cervical tumor. These researchers discovered that resveratrol inhibits cell proliferation via suppression of Stat3 phosphorylation (Li et al., 2015). Similar results were obtained by other researchers (Tomoaia et al., 2015).

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In an investigation performed by García-Zepeda and coworkers, it was found that resveratrol induces cell death in cervical cancer cells via apoptosis and autophagy. It enhanced lysosomal permeability (autophagy), and decreased the expression of p53. Treatment with resveratrol resulted in a decrease in the expression of p65, which is an NF-κB subunit in all cell lines except SiHa; these results indicate that resveratrol acts through different mechanisms to induce cell death in cell lines derived from cervical cancer (García-Zepeda et al., 2013). In addition, it inhibits phorbol 12-myristate 13-acetate (PMA)-induced invasion and migration in both A549 and HeLa cells. Resveratrol also lowers the expression and enzymatic activity of matrix metalloproteinase-9 (MMP-9), and inhibits promoter activity of PMA-stimulated MMP-9. Moreover, it inhibits transcription of MMP-9 by suppressing the NF-κB and AP-1 transactivation in human metastatic lung and cervical cancer cells (Kim et al., 2012).

Resveratrol induces GFP-LC3 aggregation, and it enhances the presence of LC3-II and autophagosomes. Furthermore, resveratrol induces cytosolic translocation of cytochrome c, activation of caspase-3, and cell apoptosis. Resveratrol induces dissipation of lysosomal membrane permeability (LMP), as well as increased cytosolic expression and activity of Cathepsin L (cat L). Inhibition of cat L by small interference RNA (siRNA) protects cells from RSV-induced cytotoxicity. In contrast, inhibition of SCCA 1 by siRNA promotes RSV-induced cytotoxicity. On the contrary, inhibition of autophagic response by wortmannin (WT) or asparagine (ASP) results in decreased early LC3-II formation, reduced LMP, and abolishment of RSV-induced cell death (Hsu et al., 2009). Resveratrol exerts apoptosis by increasing the activities of caspase-9 and caspase-3 while concurrently lowering mitochondrial membrane

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potential in HeLa cells. It also exhibits DNA fragmentation and decreases the level of HDM2 gene expression (Dhandayuthapani et al., 2013).

LIVER CANCER

Dai et al. explored the effect of resveratrol on hexokinase 2 (HK2) expressions and hepatocellular carcinoma (HCC) cell glycolysis. These researchers found that resveratrol treatment significantly inhibits cell proliferation in HCC cell lines in a dose-dependent manner, due partly to inhibition of glycolysis in aerobic HCC cells. It also sensitizes aerobic glycolytic HCC cells. Furthermore, mitochondrial apoptosis was linked to a significant reduction in HK2 expression after resveratrol treatment (Dai et al., 2015). Peng et al. showed that resveratrol (at a dose of 40 μmol/L) down-regulates phosphorylated liver kinase B1 (pLKB1) on the senescence of acute myeloid leukemia (AML) stem cells via activation of SIRT1 and induces apoptosis of CD34(+)CD38(--) KG1a cells (Peng et al., 2015). It also activates caspase-3 and 9, up-regulates the Bax/Bcl-2 ratio, and induces p53 expression via apoptosis in HepG2 cells. Furthermore, resveratrol (when given in combination with matrine) exhibits significant antiproliferative effects by (a) inducing apoptosis, by activating caspase-3 and caspase-9, (b) down-regulating survivin, (c) inducing reactive oxygen species, and (d) producting and disrupting the mitochondrial membrane potential (Ou et al., 2014). Similarly, in a dose-dependent manner, it inhibits the activities of eleven human HDACs enzymes of class I, II, and IV and displays anticancer activity on hepatoma cell lines HepG2, Hep3B, and HuH7 (Venturelli et al., 2013).

In liver cancer cells, resveratrol induces expression of methionine adenosyltransferase 2B (MAT2B) V1 and V2 in a time- and dose-dependent manner by enhancing transcription, protein

and mRNA stabilization. First, HuR expression enhances SIRT1 and MAT2B after treatment with resveratrol. Similarly, expression of the RNA-binding protein HuR enhances MAT2B mRNA stability, whereas SIRT1 increases the MAT2B transcription. Resveratrol also increases the interaction of MATβ with HuR and SIRT1 and lowers the interaction between MATβ and MATα2. On the other hand, MATβ reduces the K_i of MATα2 for S-adenosylmethionine (AdoMet), whereas the interaction among SIRT1, MATβ, and HuR enhances the stability of these proteins. Resveratrol has pro-apoptotic and growth suppressive effects via inducing MAT2B and knocking down MAT2BV1. In addition, it shows the same effect on the growth of MAT2BV2 (Yang et al., 2013). Administration of resveratrol (50 mg/kg BW/day) significantly down-regulates the expressions of MLCK and induces apoptotic death and suppresses liver tumorigenesis in hepatocellular carcinoma (HCC) rats induced by DENA (Zhang et al., 2013). Additionally, researchers have found that treatment with resveratrol (20--80 μmol/L for 24 h, 48 h, or 72 h) suppresses cell growth and induces apoptotic cell death in murine hepatocarcinoma Hepa 1-6 cells by activating caspase-3 and producing ROS (Du et al., 2012). Resveratrol treatment (50, 100 and 300 mg/kg) reverses the DENA-induced alteration of the level and expression of IL-1β, hepatic TNF-α, and IL-6. These results suggest that resveratrol-mediated chemoprevention of rat liver carcinogenesis is related to alteration of proinflammatory cytokines (Mbimba et al., 2012). In Previous work, Yu and colleagues concluded that resveratrol significantly lowers expressions of VEGF protein and mRNA, inhibits NF-kappa B activation, and decreases microvessel density (Yu et al., 2010).

HEAD AND NECK CANCER

Numerous researchers have investigated the effect of resveratrol alone or in combination with other drugs on head and neck squamous cell carcinomas (HNSCC) (Masuelli et al., 2014; Shrotriya et al., 2015). These workers found that resveratrol enhances the apoptotic effect and increases the activity of curcumin on HNSCC cell lines. A resveratrol-curcumin combination induces apoptosis by (a) enhancing PARP-1 cleavage, (b) increasing the Bax/Bcl-2 ratio, (c) suppressing ERK1 and ERK2 phosphorylation, (d) increasing LC3 II expression, (e) forming autophagic vacuoles, and (f) inducing cytoplasmic NF-κB accumulation as seen with transplanted salivary gland cancer cells (SALTO) in BALB/c mice. On the other hand, Cai and others discovered that resveratrol suppresses cell viability and promotes apoptosis in the human nasopharyngeal carcinoma (NPC) cell line C666-1 by (a) activating caspase-3, (b) altering Bax/Bcl-2 apoptotic signaling, and (c) activating AMPK activity (Cai et al., 2015). Similarly, administration of resveratrol at various concentrations (0--100 μM) exhibits anti-invasive activity seen in a human oral cancer cell line (SCC-9). Also, it inhibits matrix metalloproteinase-9 (MMP-9) expression, and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced migration capacities of SCC-9 cells. Moreover, phosphorylation of c-Jun N-terminal kinase (JNK)1/2 and extracellular-signal-regulated kinase (ERK)1/2, which participate both in down-regulating protein expression and in transcription of MMP-9, were suppressed by resveratrol (Lin et al., 2014). Recently, researchers demonstrated that resveratrol inhibits cell growth and induces cell death in head and neck squamous cells (HNSCC) by targeting cell survival and cell death regulatory pathways (Shrotriya et al., 2015).

In OC2 human oral cancer cells, resveratrol affects cytosolic free Ca^{2+} concentrations $[Ca^{2+}]i$ and viability. Resveratrol (20--40 μM) induces apoptosis and increases $[Ca^{2+}]i$ by

evoking PLC-dependent Ca^{2+} release from the endoplasmic reticulum and by causing Ca^{2+} entry via nifedipine-sensitive, PKC-regulated mechanisms in a dose-dependent fashion (Chang et al., 2015). Shan et al. reported that resveratrol (100 μmol) treatment significantly lowers the migratory and invasive abilities of KB cells. Migratory and invasive abilities were decreased for 1 or 2 h by 49.92 and 58.21%, respectively, in the Transwell assay. These researchers concluded that resveratrol has the potential to act as a chemopreventive agent to lower the invasion and metastasis of OSCC (Shan et al., 2014). Oral tumorigenesis was induced in C57BL/6 mice by administration of 4-nitroquinoline-1-oxide (4NQO) (100 μg/mL in drinking water) for 8 weeks. Resveratrol (0.25%) in the diet significantly reduced the incidence of and prevented the multiplicity and severity of 4NQO-induced preneoplastic and neoplastic lesions. In comparison to 4NQO-treated mice, resveratrol enhanced apoptotic death (TUNEL-positive cells) and lowered proliferation (BrdU labeling index), increased activated metabolic regulator phospho-AMPK (Thr172), and reduced the autophagy flux marker p62. In addition, it considerably protected cells from the 4NQO-induced oral tumorigenesis by inhibiting proliferation, modulating AMPK activation, and inducing apoptosis and autophagy (Shrotriya et al., 2015). In addition, it was also effective in the chemoprevention of 7,12-dimethylbenz[a]anthracene (DMBA)-induced oral carcinogenesis, especially when it is complexed with 2-hydroxypropyl-beta-cyclodextrin (Berta et al., 2010). A good review was recently published that focuses on the effect of green tea extracts and resveratrol in the treatment of oral cancer (Zlotogorski et al., 2013).

Baek and coworkers recently studied the effect of resveratrol on signal transducer and activator of transcription 3 (STAT3) signaling cascade and its regulated functional responses in

squamous-cell carcinoma of the head and neck (SCCHN) cells (Baek et al., 2016). This study was undertaken due to the fact that STAT3 is persistently activated in SCCHN and can cause uncontrolled cellular proliferation and division; therefore, targeted abrogation of STAT3 could be an effective strategy to lower the risk of SCCHN. This investigation revealed that resveratrol down-regulates various STAT3-regulated gene products and that it inhibits proliferation, induces cell accumulation in the sub-G1 phase, and causes apoptosis. Results also showed that resveratrol blocks the STAT3 signaling pathway by suppressing cytokine signaling-1 (SOCS-1), thereby attenuating STAT3 phosphorylation and proliferation in SCCHN cells.

GASTRIC OR STOMACH CANCER

Epithelial-mesenchymal transition (EMT) is a cellular process that is associated with cancer metastasis and invasion. Resveratrol suppresses EMT and the hedgehog (Hh) signaling pathway and also decreases the viability of SGC-7901 cells in a dose-dependent fashion (Gao et al., 2015). Similarly, resveratrol inhibits the growth of human gastric cancer (SGC7901) cells through multiple mechanisms such as (a) inducing cell apoptosis, (b) down-regulating survivin expression, (c) enhancing the proportion of cells in the G0/G1 phase, and (d) decreasing the proportion of cells in the S and G2/M phases, respectively (Liu and Zhang, 2014).

Resveratrol lowers the protein expression of cyclin D1, phospho-glycogen synthase kinase 3β (p-GSK3β), tensin homologue (p-PTEN) and phospho-phosphatasephospho-protein kinase B (p-PKB/Akt), and phospho-phosphatidylinositol 3′-OH kinase (p-PI3K). Furthermore, it suppresses the progression of the cell cycle in MGC803 cells by inhibiting p-Akt and p-PI3K expression. Collectively, resveratrol exerts cell cycle arrest in human gastric cancer MGC803 cells via regulation of the PTEN/PI3K/Akt signaling pathway (Jing et al., 2016). Ko and

colleagues investigated the protective effects of whole grape juice (with skin and seeds) on cisplatin-induced acute gastrointestinal tract disorders and nephrotoxicity in Wistar rats. These workers found that grape juice induces beneficial effects in preventing cisplatin-mediated dyspepsia, but does not offer protection against cisplatin-induced acute renal toxicity (Ko et al., 2016). Earlier findings by Yang et al. revealed that resveratrol inhibits the proliferation of gastric cancer cells in a dose-dependent manner. Treatment with different concentrations of resveratrol, at levels of 25 and 50 μM, (a) suppressed cell viability, (b) diminished the clonogenic potential, (c) arrested the cell cycle at the G1 phase, and (d) led to senescence instead of apoptosis in gastric cancer cell lines. Resveratrol also down-regulated the senescence pathways such as cyclin D1, cyclin-dependent kinase (6 and CDK4), and cyclin D1, p16, and p21. On the other hand, at a concentration of 40 mg/kg/d, resveratrol lowers the fraction of Ki67-positive cells in tumor specimens from nude mice. Senescence and changes in the expression of regulators are involved in the cell cycle and senescence pathways (Yang et al., 2013). In a paper published in 2002, researchers found that resveratrol-induced inhibition of SNU-1 proliferation may depend on NO formation; they concluded that resveratrol can be used as a chemopreventive agent against gastric cancer (Holian et al., 2002). Furthermore, treatment of gastric cell lines (SNU-1) with resveratrol (100 μM) for 24 h caused significant cell death and cell cycle arrest, and suppressed the DHCer desaturase activity as compared to the specific inhibitor GT-11. Additionally, it induced p53 expression, which is associated with enhancement of cytotoxicity (Shin et al., 2012).

Administration of resveratrol at concentrations up to 200 μmol/L for 48 h significantly induced apoptosis and DNA damage in human gastric adenocarcinoma SGC7901 cells, as found

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by Wang and coworkers, who attributed this effect to increased generation of reactive oxygen species (ROS) (Wang et al., 2012). Similarly, resveratrol at 5 and 10 μg/mL concentrations increased the frequency of micronuclei in gastric adenocarcinoma in a dose-dependent manner (Mitrut et al., 2009). On the other hand, it was found that *trans*-resveratrol inhibits proliferation of hydrogen peroxide-induced adenocarcinoma gastric cells by inactivating the MEK1/2-ERK1/2-c-Jun signaling axis (Aquilano et al., 2009). Zheng and colleagues concluded that garlic oil combined with resveratrol causes significant apoptosis, elevates levels of mRNA and Bax, and lowers mRNA expression of bcl-2 in the gastric cancer cell line MGC-803. This combination also enhances Fas protein expression (Zheng and Li, 2008). Riles et al. discovered that resveratrol causes fragmentation of DNA and cleavage of nuclear lamins A and B and PARP of gastric cancer cells. It also induces apoptotic death, up-regulates the p53 protein in SNU-1 and AGS cells, down-regulates survival in SNU-1 cells, while concurrently stimulating caspase 3 and cytochrome C oxidase activities in AGS and KATO-III cells (Riles et al., 2006).

Resveratrol exhibits anticancer effects on gastric adenocarcinoma cells (SNU-1 cells) by suppressing DNA synthesis, activating nitric oxide synthase, inducing apoptosis, and inhibiting total PKC and PKC alpha activity. Treatment of gastric adenocarcinoma with resveratrol resulted in (a) time- and concentration-dependent accumulation of tumor suppressors p21 (cip1/WAF-1) and p53, (b) loss of membrane-associated PKC delta protein, and (c) a concomitant increase in cytosolic PKC alpha. Arrest of the cell cycle at the transition of S to G(2)/M phases correlates with the profile of (3)H-thymidine incorporation and accumulation of p21(cip1/WAF-1); this was temporally dependent on an increase of p53. SNU-1 cells responded to resveratrol treatment with up-regulation of both Fas and Fas-L proteins, whereas in KATO-III cells, with deleted p53,

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only Fas-L increased after resveratrol treatment. Although Fas and Fas-L proteins in SNU-1 cells and Fas-L in KATO-III cells were elevated within 24 h of cell treatment with low concentrations of resveratrol, significant apoptotic responses at these concentrations were observed only after 48 h. These findings indicate that resveratrol engages PKC alpha and delta signals in gastric adenocarcinoma SNU-1 cells prior to up-regulation of antiproliferative and pro-apoptotic signals (Atten et al., 2005).

A good review pertaining to the therapeutic potential of resveratrol against gastric cancer initiation and progression has recently been published (Zulueta et al., 2015). That review revealed one of the major causes of gastric cancer to be infections caused by *Helicobacter pylori* (*H. pylori*). Accordingly, resveratrol exerts bactericidal activity against *H. pylori* and is a powerful antioxidant, thus acting as a tumor preventive agent. In addition, resveratrol intracellular signaling results in growth arrest and apoptosis, so that it can be directed against tumor progression.

LUNG CANCER

Lung cancer, also known as lung carcinoma, is a malignant tumor characterized by uncontrolled cell growth (Tsao, 2007). Approximately 85% of cases of lung cancer are due to long-term tobacco smoking; however, 10--15% of such cases occur in individuals who never smoked (Thun et al., 2008). These cases are often caused by a combination of genetic factors and exposure to radon gas, asbestos, second-hand smoke, or other forms of air pollution (O'Reilly, 2007). Lung cancer is the number one cause of cancer deaths in men and second most common in women after breast cancer. Globally in 2012, lung cancer occurred in 1.8 million people and

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resulted in 1.6 million deaths (WHO, 2014). Treatment includes surgery, chemotherapy, and radiotherapy.

In a recent study by Yang and coworkers, it was found that treatment with 25 μmol/L of resveratrol up-regulated the 21 long-noncoding RNAs (lncRNAs) and down-regulated the 19 lncRNAs in lung cancer A549 cells. In addition, these researchers found that AK001796, the lncRNA with the most clearly altered expression, was overexpressed in lung cancer tissues and cell lines, but its expression was down-regulated in resveratrol-treated lung cancer cells (Yang et al., 2015a). Research published by Ko et al. showed that treatment of two non-small-cell lung cancer (NSCLC) cells, H1703 and H1975, with etoposide (VP-16, a topoisomerase II inhibitor) enhanced XRCC1 mRNA and protein expression through AKT and ERK1/2 activation. This has been achieved by enhancement of the cytotoxicity and inhibition of cell growth via knocking down XRCC1 in NSCLC cells by transfection of XRCC1 siRNA and inactivation of ERK1/2 and AKT. On the other hand, treatment with resveratrol suppressed the expression of XRCC1 and increased the etoposide-induced cell death of these cells. Combination treatment of etoposide with resveratrol inhibited the transfection with constitutive active MKK1 or AKT vectors and XRCC1 protein level (Ko et al., 2015).

In an attempt to establish a novel treatment for NSCLC by creating a suicide gene therapy that expresses GADD45α protein under the control of resveratrol-responsive CArG elements, scientists recently discovered that resveratrol, at doses ranging from 25 to 100 μM, can induce Egr-1 expression rapidly and transiently when lung cancer cells of type A549 are incubated (Shi et al., 2015). They concluded that resveratrol is able to activate Egr-1 expression in several cancers (including lung cancer) and is a promoter of GADD45α expression. Gu and

coworkers discovered that treatment with a combination of resveratrol and arsenic trioxide (As_2O_3, a potent anticancer drug) resulted in a synergistic increase of cytotoxicity and apoptosis in cells at the tested concentration. This therapy caused more genotoxicity and serious oxidative stress in A549 cells than a single-agent treatment, and could also increase the release of cytochrome c and the expressions of death receptors Fas and FasL (Gu et al., 2015).

Lucas and coworkers studied the effect of resveratrol as an anticancer agent on A549 human lung adenocarcinoma epithelial cells. They found that treatment with increasing concentrations (0--175 μM) of resveratrol for 24 h results in a decrease in cell viability and apoptosis through mitochondrial pathway alignment in A549 human lung adenocarcinoma epithelial cells (Lucas and Kolodziej, 2015). Similarly, treatment of NSCLC with resveratrol was found to inhibit the epidermal growth factor receptor (EGFR), to lower cell viability and colony formation, and to induce cell apoptosis in non-small-cell lung cancer cells (A549, H460, H1975, and PC-9). Additionally, a combination of resveratrol with erlotinib (used to treat, among other cancers, non-small-cell lung cancer cells) did not repress expression of Mcl-1 and survivin (apoptisis proteins), whereas it promoted PUMA and p53 expressions and caspase 3 activity. Furthermore, this resveratrol-erlotinib combination also suppressed the AKT/mTOR/S6 kinase pathway. Subsequently, small interfering RNA (siRNA) depletion of PUMA and overexpression of survivin significantly attenuated apoptosis of human non-small-cell lung cancer (NSCLC) cells induced by the combination of the two drugs (Nie et al., 2015).

In a recent study, Ma and colleagues investigated the effects of resveratrol on the cell viability and apoptosis in human non-small-cell lung cancer against H838 and H520 cell lines. These researchers showed that resveratrol inhibits the proliferation of H838 and H520 cells in a

dose- and time-dependent manner. In addition, they found that resveratrol increases apoptosis by depolarization of the mitochondrial membrane potential, by release of cytochrome c from mitochondria to cytosol, and by abnormal expression of Bcl-2 and Bax proteins. Furthermore, resveratrol was shown to enhance the effects of cisplatin on inhibition of cancer cell proliferation (Ma et al., 2015). In a similar fashion, Lee et al. designed a study to ascertain whether inhibition of Bcl-xL (a key antiapoptotic protein of the Bcl-2 family) can influence cell growth and apoptosis against simultaneous treatment of resveratrol and clofarabine in the human malignant mesothelioma H-2452 cells. They discovered that this treatment decreases Mcl-1 protein levels in the cells. Furthermore, they concluded that the efficacy of resveratrol and clofarabine for apoptosis induction is significantly boosted via a Bcl-xL-lowering strategy in which the simultaneous targeting of Mcl-1 and Bcl-xL could be a more effective approach for treatment of malignant mesothelioma (Lee et al., 2014).

PROSTATE CANCER

This cancer occurs in a man’s prostate----a small walnut-shaped gland that produces the seminal fluid that nourishes and transports sperm. After skin cancer, it is the most common cancer among men in the United States and is more common in men older than age 50. Treatment involves surgery, radiotherapy, and chemotherapy in addition to more specialized techniques depending, among other variables, on the progress of the cancer.

Several research papers have appeared in the literature that deal with resveratrol as a chemotherapeutic agent against prostate cancer. Lee and coworkers examined the effect of resveratrol on the reporter gene activity of the androgen receptor (AR) and signal transducer and

activator of transcription-3 (STAT3) in human prostate cancer (LNCaP-FGC) cells stimulated with interleukin-6 (IL-6) and/or dihydrotestosterone (DHT). These researchers found that resveratrol suppresses the growth of LNCaP-FGC cells in a time- and concentration-dependent manner. In addition, they proposed that the inhibitory effects of resveratrol on IL-6- and/or DHT-induced AR transcriptional activity in LNCaP prostate cancer cells are partly mediated through suppression of STAT3 reporter-gene activity. These findings suggest that resveratrol can be a promising therapy for the treatment of prostate cancer (Lee et al., 2014a). In a recent investigation, Mitani and colleagues showed that resveratrol exhibits antiproliferative activity against the growth of human prostate cancer LNCaP in castrated male BALB/cSlc-nu/nu mice (5 weeks old). A resveratrol diet (4 g/kg diet) for 40 days decreased the protein level of hypoxia-inducible factor (HIF)-1α, and reduced the mRNA levels of androgen-responsive genes. Additionally, it inhibited the nuclear accumulation of β-catenin. Similarly, the castration-resistant stage and the hypoxia-induced nuclear accumulation of β-catenin were suppressed by administration of resveratrol. Furthermore, resveratrol inhibits the expression level of HIF-1α, even in the presence of a proteasome inhibitor, and it suppresses hypoxia-enhanced AR transactivation. These findings indicate that dietary resveratrol represses nuclear localization of β-catenin by decreasing the HIF-1α expression, perhaps in a proteasome-independent manner, and that it inhibits β-catenin-mediated AR signaling, which contributes to suppression of tumor growth of CRPC (Mitani et al., 2014).

Resveratrol exerts its anticancer activity in prostate cancer, at least in part, through epigenetic mechanisms, including post-translational modification and reactivation of PTEN tumor suppressor; this finding emerged in a recent investigation (Dhar et al., 2015). These

researchers found that resveratrol promotes acetylation and reactivation of PTEN via inhibition of the metastasis-associated protein 1 (MTA1)/HDAC complex, resulting in inhibition of the Akt pathway. These findings highlight the importance of resveratrol and other MTA1/HDAC inhibitors for prostate cancer chemoprevention and treatment. In an attempt to understand the mechanism of action by which resveratrol exerts its anti-proliferative effect in androgen-independent prostate cancer cells, Selvaraj et al. discovered that resveratrol activates autophagic cell death in PC3 and DU145 cells, which is dependent on stromal interaction molecule 1 (STIM1) expression (Selvaraj et al., 2016). These researchers demonstrated that treatment with resveratrol causes a decrease in STIM1 expression in a time-dependent manner and it attenuates STIM1 association with TRPC1 and Orai1. Additionally, they suggested that resveratrol induces autophagy-mediated cell death in PC3 and DU145 cells through regulation of sore-operated calcium entry (SOCE) mechanisms that involve down-regulating STIM1 expression and that trigger endoplasmic reticulum (ER) stress by depleting the ER calcium pool.

In their work on the cytotoxic properties of resveratrol tetramer r-viniferin on the prostate cancer cell line LNCaP, Empl and associates demonstrated that r-viniferin is significantly more potent than resveratrol in the inhibition of cell growth. Therefore, that it could be employed as a chemopreventive agent in prostate cancer therapy (Empl et al., 2015). As suggested by some researchers, resveratrol exhibits its anticancer effects through regulation of chromatin modifier metastasis-associated protein 1 (MTA1) and microRNAs (miRNAs), and highlights the anticancer effects of these compounds in preclinical models of prostate cancer (Kumar et al., 2015). On the other hand, resveratrol down-regulates PTEN-targeting members of the oncogenic miR-17 family, which is overexpressed in prostate cancer; these are results of a recent study by

Dhar and coworkers. Through down-regulation of miR-17-5p and miR-106a-5p expression, in both tumors and systemic circulation, resveratrol preserved PTEN mRNA and protein levels leading to reduced tumor growth *in vivo*. These researchers concluded that resveratrol can be employed as an attractive miRNA-mediated chemopreventive and therapeutic agent in the treatment of prostate cancer (Dhar et al., 2015a).

SKIN CANCER

Skin cancer is by far the most common type of cancer. It includes melanoma, basal and squamous cell, Merkel cell carcinoma, and lymphoma of the skin. Treatment generally involves surgery, radiotherapy, and chemotherapy, in addition to other specialized techniques. One of the agents that has been used as a chemotherapeutic drug for various types of cancer, including skin cancer, is 5-fluorouracil. In this context, Karla et al. reported that treatment with resveratrol causes induced apoptosis in TPA- and DMBA-promoted skin tumors in mice (Kalra et al., 2008). This regression of skin cancer was evidenced by the appearance of a sub-G1 fraction along with an increase in the number of apoptotic cells. Additionally, treatment with resveratrol prompted p53 expression and pro-apoptotic Bax with a decrease in anti-apoptotic protein Bcl-2. Those researchers concluded that the chemopreventive activity of resveratrol can be ascribed to modulation of proteins involved in the mitochondrial pathway of apoptosis (Kalra et al., 2008). In an investigation by Reagan-Shaw and coworkers, it was demonstrated that treatment with resveratrol causes further stimulation of UVB-mediated increases in cyclin kinase inhibitor WAF1/p21 and tumor suppressor p53. On the basis of their observations, these researchers suggested that the antiproliferative effects of resveratrol might be mediated via modulation in the expression and function of cell-cycle regulatory proteins cyclin-D1 and -D2, cdk-2, -4 and -6,

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and WAF1/p21 (Reagan-Shaw et al., 2004). In subsequent work, Aziz and colleagues showed that pre-treatment of mice with resveratrol (10 μmol in 200 μL acetone/mouse) resulted in significant inhibition of UV-B exposure-mediated increase in cellular proliferations (Ki-67 immunostaining) accompanied by an increase in protein levels of epidermal cyclooxygenase-2 and ornithine decarboxylase, which are established markers of tumor promotion. In addition, resveratrol causes an increase in protein and messenger RNA levels of survivin, and an increase in phosphorylation of survivin in the skin of SKH-1 hairless mice. These chemopreventive effects of resveratrol against UV-B exposure-mediated damage in the skins of SKH-1 hairless mice are believed to have been exerted via inhibition of survivin and the associated events (Aziz et al., 2005).

Lee and colleagues investigated the anti-angiogenic effects of resveratrol and 5-fluorouracil either alone or in combination in a B16 murine melanoma model. They found that co-treatment inhibits cell proliferation more efficiently than either drug alone. In addition, it was discovered that resveratrol exerts its anticancer and antiproliferative effect by altering the expression levels of cyclooxygenase-2, AMP-activated protein kinase (AMPK), vascular endothelial growth factor (VEGF), and vasodilator-stimulated phosphoprotein (Lee et al., 2015). In addition, other researchers discovered that a combination of ursolic acid and resveratrol is more effective in the inhibition of TPA-induced epidermal hyperproliferation than individual compounds. This combination also inhibits TPA-induced signaling pathways, including EGFR, STAT3, Src, Akt, Cox-2, Fas, NF-κB, p38 MAPK, c-Jun, and JNK1/2 and increases the levels of tumor suppressors, such as p21 and PDCD4 (Cho et al., 2015). Similarly, resveratrol and *p*-glycoprotein inhibitors were found to enhance antiskin cancer effects of ursolic acid;

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resveratrol and ursolic acid interact synergistically, but not through inhibition of P-gp (Junco et al., 2013).

Other researchers have shown that resveratrol targets survivin in skin-cancer cell lines by inhibiting β-catenin and STAT3 and by inducing apoptosis (Habibie et al., 2014). In their evaluation of the inhibitory effects of resveratrol on melanin synthesis in ultraviolet B-induced pigmentation in Guinea pig skin, Lee and coworkers showed that it inhibits melanin synthesis and thus prevents skin cancer through reduction in tyrosinase-related protein 2 among the melanogenic enzymes (Lee et al., 2014a). On the other hand, resveratrol was found to be cytotoxic in Merkel cell carcinoma (MCC) cell lines where cell growth was inhibited by induction of apoptosis, and its combination with cisplatin and etoposide led to a partial synergistic inhibition of cell proliferation. In addition, resveratrol and irradiation led to a synergistic reduction in colony formation compared to irradiation alone; this may suggest that resveratrol is a promising agent in combination with radiation therapy (Heiduschka et al., 2014). Moreover, resveratrol inhibits the growth of human skin squamous cell carcinoma A431 by inducing apoptosis and by suppressing survivin and the activation of caspase-3 (Hao et al., 2013). Furthermore, resveratrol (a) inhibits the expression of apoptosis-related factors, ERK, p53, survivin, (b) up-regulates protein and mRNA expression of p53, (c) down-regulates protein and mRNA expression of SVVS, and (d) induces apoptosis (Hao et al., 2013a).

Chen and coworkers evaluated the antitumor effects of resveratrol in an experimental mouse metastasis tumor model. These researchers demonstrated that resveratrol inhibits LPS-induced tumor migration and markers of EMT and that it significantly extends animal survival in addition to reducing the tumor size (Chen et al., 2012). Furthermore, resveratrol was found to

down-regulate the level of Rictor which leads to a decrease in the RhoA-GTPase and alters actin cytoskeleton organization, restores RhoA-GTPase activity and actin cytoskeleton network, and reduces β-gal activity. This would suggest that resveratrol suppresses UV-induced skin carcinogenesis through a mechanism that involves down-regulation of Rictor (Back et al., 2012). Jagdeo et al. studied the ability of resveratrol to modulate the hydrogen peroxide-induced up-regulation of reactive oxygen species (ROS) in normal human skin fibroblast cells *in vitro*. These researchers discovered that resveratrol significantly reduces intracellular hydrogen peroxide-upregulated ROS in a dose-dependent manner in human skin fibroblasts *in vitro* (Jagdeo et al., 2010). In a similar fashion, George and coworkers examined the combination effects of resveratrol and black tea in suppressing a two-stage mouse skin carcinogenesis induced by 7,12-dimethylbenz[a]anthracene (DMBA) and 12-*O*-tetradecanoylphorbol 13-acetate (TPA). Results revealed that resveratrol significantly reduces tumor incidence by ∼67% and ∼75% in both stages of carcinogenesis. However, combination of both at low doses was more effective and reduced tumor incidence by 89%. In addition, this combination also reduced tumor volume and number. This effect was due to lower expression of phosphorylated mitogen-activated protein kinase (MAPKs) family proteins such as c-Jun N-terminal kinase 1/2, extracellular signal-regulated kinase 1/2, and p38 and enhanced total p53 and phospho p53 (Ser 15) (George et al., 2011).

The combined effect of ultraviolet (UVB) (30 mJ/cm^2) and resveratrol (60 μM) on A431 carcinoma cells was explored by Roy and his team. Results from their investigation showed that exposure of A431 carcinoma cells to either UV-B radiation or resveratrol can inhibit cell proliferation and induce apoptosis. However, this combination was more effective, and it

disrupted the nuclear factor-kappaB (NF-kappaB) pathway by blocking phosphorylation of serine 536 and inactivating NF-kappaB and subsequent degradation of IκBα, which regulates the expression of survivin (Roy et al., 2009). Moreover, resveratrol and UVB treatment decreased the phosphorylation of tyrosine 701 of the important transcription factor, signal transducer activator of transcription (STAT1), which inhibits translocation of phospho-STAT1 to the nucleus. In another study, Roy and coworkers discovered that resveratrol increases DMBA, suppresses p53 and Bax, and decreases the expression of Bcl-2 and survivin. In addition, supplementation with resveratrol caused release of cytochrome c, activation of caspases, and an increase in apoptotic protease-activating factor-1 (Apaf-1) as a mechanism of apoptosis induction. It was suggested that inhibition of skin tumorigenesis by resveratrol occurs via regulation of phosphatidylinositol-3-kinase (PI3K)/ and AKT proteins involved in cancer progression (Roy et al., 2009a).

The effect of resveratrol on oral squamous cancer cell (OSCC) lines (SCC-VII, SCC-25, and YD-38) has been recently investigated (Yu et al., 2016). MTS assay and flow cytometry have been employed to study inhibition of cell proliferation and apoptosis. In addition, western blot analysis was performed to explore the effect of resveratrol on the expression of proteins associated with cell cycle regulation. Results revealed that treatment with resveratrol results in a concentration- and time-dependent inhibition of proliferation in all three tested cell lines with IC_{50} values of 0.5, 0.7, and 1.0 μg/mL for SCC-VII, SCC-25, and YD-38 cell lines, respectively. Furthermore, results indicated that resveratrol inhibits the proliferation of OSCC oral cancer cells through induction of apoptosis and G2/M phase cell cycle arrest.

ESOPHAGEAL CANCER

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Surgery is commonly used to treat esophageal cancer that has not spread beyond the esophagus and its surrounding lymph nodes. Other options to treat cancer cells include radiotherapy and chemotherapy. In a publication by Zhou et al., it was found that resveratrol inhibites the growth of esophageal cancer cells in a dose- and time-dependent manner when the cancer cell line EC-9706 was employed. These researchers believed that induced apoptosis may be mediated via down-regulating the apoptosis-regulated gene Bcl-2 and up-regulating the expression of apoptosis-regulated gene bax (Zhou et al., 2003). On the other hand, Woodall and coworkers examined the effects of resveratrol on the transition from reflux esophagitis to Barrett's metaplasia to dysplasia to esophageal adenocarcinoma in male Sprague-Dawley rats. They found that resveratrol significantly lowers the severity of esophagitis incidence of carcinoma and intestinal metaplasia (Woodall et al., 2009).

Recently, it was demostarted that intake of lignans, quercetin, and resveratrol may play a protective role in the development of esophageal cancer in the Swedish population (Lin et al., 2014). In addition, Tang et al., who studied the anti-cancer activity of resveratrol in human esophageal squamous-cell carcinoma (ESCC), found that resveratrol inhibits the growth of human esophageal squamous-cell carcinoma (ESCC) in a dose-dependent manner by inducing cell-cycle arrest at the sub-G1 phase (Tang et al., 2013). Similarly, a recent investigation by Fan and cowrkers revealed that treatment of esophageal adenocarcinoma cells (OAC) with resveratrol suppresses cell proliferation and reduces the level of p27Kip1 (a cyclin-dependent kinase inhibitor). Additionally, it resulted in an increase in the levels of S-phase kinase-associated protein 2 (Skp2) of p27Kip1-E3 ubiquitin ligase and 26S proteasome activity. Their findings suggest that resveratrol inhibits Skp2-mediated ubiquitylation and 26S proteasome-

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dependent degradation of p27Kip1 via AMPK activation to suppress OAC proliferation (Fan et al., 2014).

THYROID CANCER

The recommended and widely used treatment for patients with thyroid diseases, including thyroid cancer and Graves' disease, is radioactive iodine (best known as ^{131}I). However, side effects of this regime include DNA damage and chromosomal breaks which could lead to cell damage and death (Robbins and Schlumberger, 2005). In addition, studies have shown that ^{131}I therapy is associated with increased genetic damage. Furthermore, the occurrence of secondary malignancies and leukemia might increase with higher doses of radioiodine (Chow 2005). Accordingly, there is a pressing need for protection of normal cells which may mitigate side effects induced by ^{131}I. Resveratrol has been shown to protect genotoxicity induced by ^{131}I on normal human lymphocytes and to lower significantly DNA damage induced by ^{131}I *in vitro* (Hedayati et al., 2013). In recent research, Hosseinimehr and Husseini investigated the therapeutic effects of resveratrol on cell death induced by ^{131}I in thyroid human cancer and human nonmalignant fibroblast cells *in vitro* (Hosseinimehr et al., 2014). Results from this study showed that resveratrol enhances ^{131}I-induced cell death of thyroid cancer cells as well as exerting a protective effect on normal cells against ^{131}I toxicity. Additionally, other researchers found that treatment with resveratrol causes growth suppression, probably through apoptosis, along with an increase in the cleavage of caspase-3 and PARP (Truong et al., 2011). Data from a study conducted by Yu et al. showed that resveratrol inhibits ATC cell growth via apoptosis and S phase cell-cycle arrest at a relatively low concentration (Yu et al., 2013). Moreover, it

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enhances redifferentiation in ATC cells, which is dependent upon the activation of Notch1 signaling. This Notch1 pathway has been suggested as being important in the regulation of thyroid cancer cell growth and expression of thyrocyte differentiation markers. In another study, resveratrol administration (1--10 μM) exhibited activation and nuclear translocation of MAPK (extracellular signal-regulated kinase 1/2) in two follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC) cell lines. It also enhanced the serine phosphorylation of p53, cellular abundance of the oncogene suppressor protein p53, and abundance of c-jun, c-fos, and p21 mRNAs (Shih et al., 2002).

A patent pertaining to treatment of thyroid cancer has been recently published. This anti-cancer agent contains curcumin, lentinan, resveratrol, filler, disintegrating agents, and surfactants. The disintegrating agent is crosslinked sodium CM-cellulose and sodium carboxymethyl starch; the surfactant is soybean lecithin and SDS, and the filler is lactose, starch, dextrin, mannitol. This medicine also includes lubricant and corrective. It is claimed by the authors that this medicine has rapid dissolution, good bioavailability, stability, significant treatment effect on thyroid cancer, no toxic side effects, and a simple preparation process (Zhang et al., 2016). Furthermore, an antitumor medicine was recently formulated by Chinese researchers (Wang et al., 2016). This medicine consists of resveratrol 60--200 parts, pterostilbene 30--150 parts, green-tea extract 50--220 parts, and Semen Coicis extract 100--280 parts. This medicine is intended to treat different types of cancer including, but not limited to, colon cancer, lung cancer, melanoma cancer, prostate cancer, liver cancer, renal cancer, gastric cancer, sarcoma, neural glial cancer, pancreatic cancer, ovarian cancer, and breast cancer. Inventers of this medicine claim that it fully plays the synergistic effect of the components and has good

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stability, long action time, and improved curative effect---in addition to being safe and with no toxic side effect.

UTERINE OR ENDOMETRIAL CANCER

As an anticancer agent, resveratrol exerts antiproliferative and pro-apoptotic activity in various cancer cell types; however, its effect on uterine cancer cells has been poorly understood. Sexton and colleagues explored the effect of resveratrol for its anti-proliferative and pro-apoptotic activity against uterine cancer cells via inhibition of COX-2 expression and/or activity (Sexton et al., 2006). These researchers employed six different human uterine cancer cell lines (HeLa, Hec-1A, KLE, RL95-2, Ishikawa, and EN-1078D) as models, and they discovered that high doses of resveratrol trigger apoptosis in five out of six uterine cancer cell lines and decrease uterine cancer cell proliferation. They also found that resveratrol reduces cellular levels of the phosphorylated active form of anti-apoptotic kinase AKT. In addition, results from their investigation revealed that resveratrol decreases endogenous COX-2 protein levels associated with a decrease in the production of cyclooxygenase (COX) metabolites PGE2 and PGF2α in each uterine cancer cell line. They concluded that high doses of resveratrol exhibit antitumor activity against uterine cancer cells and regulate COX expression.

Rezk and coworkers examined the use of resveratrol to improve the effectiveness of cisplatin and doxorubicin in ovarian and uterine cancer cells (Rezk et al., 2006). They found that resveratrol, combined with either cisplatin or doxorubicin, showed an additive growth-inhibitory anticancer effect. Additionally, they found an increase in the viability of neonatal rat ventricular myocytes treated with doxorubicin as well as a reduction of doxorubicin-induced bradycardia and QTc interval prolongation in mice in the presence of resveratrol. Research by Bhat and Pezzuto

revealed that treatment of cultured human endometrial adenocarcinoma (Ishikawa) cells with resveratrol at concentrations as high as 10 μM does not significantly increase the levels of an estrogen-inducible marker enzyme, alkaline phosphatase (Bhat and Pezzuto, 2001). In addition, these researchers found that resveratrol inhibits Ishikawa cell proliferation with cells accumulating in the S phase of the cycle ≤48 h in a time-dependent manner. They suggested that resveratrol exhibits an antiproliferative effect in these cells, which may be mediated by both estrogen-dependent and estrogen-independent mechanisms. Furthermore, other researchers confirmed that resveratrol at concentrations of 1, 10, 50 and 100 μM administered for 1, 3, 5, and 7 days showed an antiproliferative activity against endometrial cancer cells in the Ishikawa cell line by (a) significantly lowering epidermal growth factor (EGF), (b) up-regulating the vascular endothelial growth factor (VEGF), and (c) decreasing Bax and p21` expression (Kaneuchi et al., 2003).

BLADDER CANCER

Different concentrations of resveratrol administered for specific time intervals (100 μM for 1 h, 150 μM and 200 μM for 2 h) exhibited a remarkable effect on human bladder transitional cell carcinomas (TCCs). These dosages (a) caused a significant cell cycle-arrest in S phase, (b) induced apoptosis, (c) attenuated the nuclear translocation, phosphorylation, and transcription of STAT3, (d) down-regulated the STAT3 downstream genes (cyclinD1, c-Myc, survivin, and VEGF) and nuclear translocations of p53 and Sirt1 (Wu et al., 2014). Additionally, treatment with resveratrol exerts cytotoxicity and apoptotic cell death in T24 and 5637 cancer cell lines via down-regulating the miR-21 accompanied with suppression of phospho-Akt and Bcl‑2 protein expression in a dose-dependent manner. It also inhibits Akt activity, down-regulates Bcl‑2

expression, and induces apoptosis. Furthermore, it adjusts the miR‑21 regulation of the Akt/Bcl‑2 signaling pathway in bladder cancer cells (Zhou et al., 2014). Moreover, resveratrol exerts a cytotoxic effect against BTT739 and T24 bladder cancer cell lines by (a) decreasing cell viability and inducing apoptosis, (b) disrupting considerably the mitochondrial membrane potential, (c) enhancing the ROS production, and (d) lowering adenosine 5′-triphosphate concentrations in a concentration- and time-dependent manner. It also releases cytochrome c from mitochondria to the cytosol, and promotes activation of caspase-9 and caspase-3 (Lin et al., 2012). Similarly, it was found that administration of resveratrol (2.5 μM) offers protection from oxidative damage, whereas a concentration of 50 μM considerably induced apoptosis, enhanced the Bad/Bcl-2 ratio (proapoptotic/antiapoptotic proteins), modulated NO and PGE(2) secretion, and exhibited an anti-adhesion activity of neutrophils on PMA-activated ECV304 cells (Stocco et al., 2012).

Resveratrol causes apoptosis in bladder cancer cell (T24) lines by multiple mechanisms such as (a) induction of apoptosis, (b) modulation of Bcl-2 family proteins, (c) activation of caspase 3 and caspase 9 followed by poly(ADP-ribose) polymerase degradation, (d) G(1) phase cell cycle arrest, (e) activation of p21, (f) down-regulation of cyclin D1, cyclin-dependent kinase 4, and phosphorylated Rb, (g) inhibition of phosphorylation of Akt, (h) enhancement of phosphorylation of p38 MAPK, and (i) diminution of the expression of vascular endothelial growth factor and fibroblast growth factor-2 (Bai et al., 2010). On the other hand, Wu et al. showed that exposure to resveratrol results in growth inhibition and apoptosis of bladder cancer cells; these were results from an *in vitro* and *in vivo* investigation. Resveratrol acted via

inhibition of STAT3 activiation and induction of Sirt1 and p53 nuclear translation (Wu et al., 2014).

Alayev and associates recently examined the effect of combining rapamycin and resveratrol for the treatment of bladder cancer in cell lines with increasd mTORCi signaling, including those caused by TSC1. They concluded that, when combined with rapamycin, resveratrol is able to (a) block rapamycin-induced Akt activation, while maintaining mammalian target of rapamycin (mTOR) pathway inhibition and (b) induce cancer cell death. Thus, this combination can be a promising therapeutic option for treatment of bladder cancer (Alayev et al., 2016).

KIDNEY AND EYE CANCER

Results from a study undertaken by Raghubeer and coworkers (Raghubeer et al., 2015) revealed that administration of resveratrol (25 µM) significantly increases mRNA expression of the DNA repair enzyme OGG1. These researchers showed that treatment with ochratoxin A (OTA) and a combination of OTA with resveratrol considerably lowers OGG1 expression. They concluded from their investigations that resveratrol alone, as well as in conjunction with OTA, considerably lowers the mRNA expression of Nrf2 (Raghubeer et al., 2015). Other workers discovered that administration of different concentrations of resveratrol (0, 10, 20 and 40 µmol/L) for various time intervals (24, 48 and 72 h) causes anticancer effects on human renal cancer (786-0) cells by (a) suppressing the expression of the vascular endothelial growth factor (VEGF) gene and (b) inhibiting the proliferation of 786-0 cells in a concentration-dependent manner (Yang et al., 2011). In addition, resveratrol induces differential expression of genes that

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are directly or indirectly related to RCC cell growth suppression and induction of RCC cell death (Shi et al., 2004).

Similarly, resveratrol lowers cell viability, suppresses cell growth, induces S-phase cell cycle arrest, and causes apoptotic cell death in a dose- and time-dependent manner in Y79 cells. It evokes rapid dissipation of DeltaPsim, release of cytochrome c into the cytoplasm, and enhances the activities of caspase-3 and caspase-9. Furthermore, it directly induces depolarization of isolated mitochondria in a cell-free system, and it suppresses Y79 cell growth and induces apoptosis by activating the mitochondrial (intrinsic) apoptotic pathway (Sareen et al., 2006).

BRAIN CANCER

Firouzi and coworkers recently evaluated the combined effect of resveratrol and methoxyamine on radiosensitivity of iododeoxyuridine in the spheroid culture of U87MG glioblastoma cell line by means of colony formation and alkaline comet assays. These researchers found that methoxyamine and resveratrol can significantly reduce colony number and induce DNA damage of glioblastoma spheroid cells treated with iododeoxyuridine in combination with gamma-rays. Therefore, resveratrol at a 20-μM concentration shows promise as a cancer-treatment therapy when used in conjunction with radiation coupled with the radiosensitizer iododeoxyuridine (IUdR) (Firouzi et al., 2015). In addition, other investigators discovered that resveratrol (a) lowers the expression and activity of the POK erythroid ontogenic factor (Pokemon) in glioma cells, (b) suppresses the Sp1 DNA binding activity to the Pokemon promoter, (c) enhances the recruitment of HDAC1, and (d) lowers the p300 to the Pokemon promoter (Yang et al., 2016).

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BONE CANCER

Chondrosarcoma is becoming the most significant primary bone cancer that forms in cartilage cells. In a recent investigation by Dai and colleagues, it was concluded that resveratrol induces apoptosis and inhibits matrix metalloproteinase (MMP)-induced differentiation in chondrosarcoma cells in a dose-dependent manner by inhibiting MMP2 and MMP9 protein expression. It also inhibits the activity of phosphoinositide 3-kinase/AKT and p38 mitogen-activated protein kinase signaling pathways (Dai et al., 2015). Moreover, it (a) induces cell apoptosis in murine 3T3-L1 adipocytes, (b) activates the mitochondrial apoptotic signaling pathway, (c) decreases the mitochondrial membrane potential (MMP), and (d) activates caspase 3, in addition to elevating phosphorylation of AMP-activated protein kinase α (AMPKα) which is accompanied with lowering of phosphorylation of protein kinase B (AKT) level. Furthermore, AMPKα activation suppresses the downstream of p-AKT, and then activates the mitochondrion-mediated apoptotic pathway (Chen et al., 2015).

BLOOD CANCER

Tsan and colleagues published a review about the anti-leukemia effect of resveratrol. Results from early work published in the review indicated that resveratrol inhibits the growth of leukemia cells, possibly via different mechanisms that include (a) induction of leukemia cell differentiation, (b) apoptosis and cell cycle arrest at S-phase, and (c) inhibition of DNA synthesis by inhibiting ribonucleotide reductase or DNA polymerase (Tsan et al., 2002). On the other hand, Peng et al. (2015) and others examined the effect of resveratrol down-regulated phosphorylated liver kinase B1 (pLKB1) on the senescence of acute myeloid leukemia (AML)

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stem cells. These researchers found that resveratrol at a concentration of 40 μmol/L down-regulated the expression of pLKB1 via activation of SIRT1, which induces senescence and apoptosis of CD34(+)CD38(-) KG1a cells (Zunino and Storms, 2015). Similarly, it was indicated that resveratrol induces apoptosis of human chronic myelogenous leukemia cells in vitro through p38- and JNK-regulated H2AX phosphorylation. They found that treatment of k562 cells with resveratrol induces apoptosis and phosphorylation of H2AX at Ser139 in a time- and dose-dependent manner (Wu et al., 2015).

CONCLUSIONS

At present, dependence on intrinsic foodstuffs is gaining popularity in the fight against diseases such as cardiovascular disorders, cancer insurgence, and immune dysfunction. Due to their lesser side effects and cost, conventional therapies such as natural products, particularly in the treatment of cancer, have attracted the attention of the scientific and medical communities. Grapes hold a unique place in history, and are renowned for their medicinal properties. Current progress in the field of immuno-nutrition, pharmacology, and physiology have enhanced the significance of grapes as a nutritional food against various ailments. Much research has been carried out on the health-promoting potential of grapes, often in reference to their bioactive component resveratrol, which can scavenge free radicals, protect membranes from damage, and maintain cell integrity. Antiplatelet aggregation, antithrombosis, decreasing homocysteine level, and cholesterol lowering are also possible modes of action that result in reduced risks of atherosclerosis and related cardiovascular disorders. Certainly, evidence has been presented in its favor, but some vague reports demand that further scientific research is needed. One way to

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increase absorption of resveratrol in the intestine is to synthesize or extract derivatives that will be more soluble than the parent compound. Another approach is to use solid lipid nanoparticles (SLN) that would act as vehicles to carry resveratrol across cell walls. Since most findings cited in the present review are based on in vitro and in vivo studies, which do not necessarily represent the effect on humans of resveratrol or its extracts, alone or in combination with other drugs, more investigations which could involve different pharmacokinetic parameters are recommended before this substance hits the market as a prescribed drug. In addition, development of a standardized extract or dosage could also be pursued in clinical trials.

In this review, we have demonstrated that resveratrol provides a wide range of preventive and therapeutic options against different types of cancer, and has been widely envisioned as an agent in anticancer therapy. In conclusion, resveratrol can be a useful complementary medicine for the prevention and treatment of different types of cancers due to its natural origin, safety, and low cost relative to cancer drugs. However, further studies are needed on this natural compound.

CONFLICT OF INTEREST

The authors declare no conflicts of interest

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REFERENCES

Abdel-Latif, G. A., Al-Abd, A. M., Tadros, M. G., Al-Abbasi, F. A., Khalifa, A. E., and Abdel-Naim, A. B. (2015). The chemomodulatory effects of resveratrol and didox on herceptin cytotoxicity in breast cancer cell lines. *Sci. Rep*. **5**:12054.

Alayev, A., Berger, S. M., Kramer, M. Y., Schwartz, N. S., and Holz, M. K. (2015). The combination of rapamycin and resveratrol blocks autophagy and induces apoptosis in breast cancer cells. *J. Cell Biochem.* **116(3)**: 450-457.

Alayev, A., Salamon, R. S., Schwartz, N. S., Berman, A. Y., Wiener, S. L., and Holz, M. K. (2016). Combination of Rapamycin and Resveratrol for Treatment of Bladder Cancer. *J. Cell Physiol*. doi: 10.1002/jcp.25443.

Ali, I., and Braun, D. P. (2014). Resveratrol enhances mitomycin C-mediated suppression of human colorectal cancer cell proliferation by up-regulation of p21WAF1/CIP1. *Anticancer Res*. **34(10)**: 5439-46.

Aluyen, J. K., Ton, Q. N., Tran, T., Yang, A. E., Gottlieb, H. B., and Bellanger, R. A. (2012). Resveratrol: Potential as Anicancer Agent. *J. Diet. Suppl.* **9(1)**: 45-56.

Aquilano, K., Baldelli, S., Rotilio, G., and Ciriolo, M. R. (2009). Trans-Resveratrol inhibits H_2O_2-induced adenocarcinoma gastric cells proliferation via inactivation of MEK1/2-ERK1/2-c-Jun signalling axis. *Biochem. Pharmacol*. **77(3)**: 337-47.

 ACCEPTED MANUSCRIPT

Atten, M. J., Godoy-Romero, E., Attar, B. M., Milson, T., Zopel, M., and Holian, O. (2005). Resveratrol regulates cellular PKC alpha and delta to inhibit growth and induce apoptosis in gastric cancer cells. *Invest. New Drugs*. **23(2**): 111-19.

Aziz, M. H., Afaq, F., and Ahmad, N. (2005). Prevention of ultraviolet-B radiation damage by resveratrol in mouse skin is mediated via modulation in survivin. *Photochem. Photobiol.* **81(1)**: 25-31.

Back, J. H., Zhu, Y., Calabro, A., Queenan, C., Kim, A. S., Arbesman, J., and Kim, A. L. (2012). Resveratrol-mediated downregulation of Rictor attenuates autophagic process and suppresses UV-induced skin carcinogenesis. *Photochem. Photobiol*. **88(5)**: 1165-72.

Baek, S. H., Ko, J. H., Lee, H., Jung, J., Kong, M., Lee, J. W., Lee, J., Chinnathambi, A., Zayed, M. E., Alharbi, S. A., et al. (2016). Resveratrol inhibits STAT3 signaling pathway through the induction of SOCS-1: Role in apoptosis induction and radiosensitization in head and neck tumor cells. *Phytomedicine* **23(5)**: 566-77.

Bai, Y., Mao, Q. Q., Qin, J., Zheng, X. Y., Wang, Y. B., Yang, K., Shen, H. F., and Xie, L. P. (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(2)**: 488-93.

Baribeau, S., Chaudhry, P., Parent, S., and Asselin, É. (2014). Resveratrol inhibits cisplatin-induced epithelial-to-mesenchymal transition in ovarian cancer cell lines. *PLoS One*. **9(1)**: e86987.

Baur, J. A., and Sinclair, D. A. (2006). Therapeutic potential of resveratrol: the in vivo evidence. *Nat. Rev. Drug Discov*. **5**: 493-506.

Berta, G. N., Salamone, P., Sprio, A. E., Di Scipio, F., Marinos, L. M., Sapino, S., Carlotti, M. E., Cavalli, R., and Di Carlo, F. (2010). Chemoprevention of 7,12-dimethylbenz[a]anthracene (DMBA)-induced oral carcinogenesis in hamster cheek pouch by topical application of resveratrol complexed with 2-hydroxypropyl-beta-cyclodextrin. *Oral Oncol*. **46(1)**: 42-48.

Bhat, K. P., and Pezzuto, J. M. (2001). Resveratrol exhibits cytostatic and antiestrogenic properties with human endometrial adenocarcinoma (Ishikawa) cells. *Cancer Res*. **61(16)**: 6137-44.

Bielsalski, H. K. (2007). Polyphenols and inflammation: basic interactions. Curr. Opin. Clin. Nutr. Metab. Care **10**: 724-728.

Buhrmann, C., Shayan, P., Kraehe, P, Popper, B., Goel, A., and Shakibaei, M. (2015). Resveratrol induces chemosensitization to 5-fluorouracil through up-regulation of intercellular junctions, Epithelial-to-mesenchymal transition and apoptosis in colorectal cancer. *Biochem. Pharmacol*. **98(1)**: 51-68.

Cai, Y., Zhao, L., Qin, Y., Zhang, M., and He, Y. (2015). Resveratrol inhibits proliferation and induces apoptosis of nasopharyngeal carcinoma cell line C666-1 through AMPK activation. *Pharmazie*. **70(6)**: 399-403.

Chang, H. J., Chou, C. T., Chang, H. T., Liang, W. Z., Hung, T. Y., Li, Y. D., Fang, Y. C., Kuo, C. C., Kuo, D. H., Shieh, P., and Jan, C. R.. (2015). Mechanisms of resveratrol-induced changes

in cytosolic free calcium ion concentrations and cell viability in OC2 human oral cancer cells. *Hum. Exp. Toxicol*. **34(3)**: 289-99.

Chen, M. C., Chang, W. W., Kuan, Y. D., Lin, S. T., Hsu, H. C., and Lee, C. H. (2012). Resveratrol inhibits LPS-induced epithelial-mesenchymal transition in mouse melanoma model. *Innate Immun*. **18(5)**: 685-93.

Chen, S., Zhou, N., Zhang, Z., Li, W., and Zhu, W. (2015). Resveratrol induces cell apoptosis in adipocytes via AMPK activation. *Biochem. Biophys. Res. Commun*. **457(4)**: 608-13.

Cho, J., Rho, O., Junco, J., Carbajal, S., Siegel, D., Slaga, T. J., and DiGiovanni, J. (2015). Effect of Combined Treatment with Ursolic Acid and Resveratrol on Skin Tumor Promotion by 12-O-Tetradecanoylphorbol-13-Acetate. *Cancer Prev. Res*. **8(9)**: 817-25.

Chow, S. M. (2005). Side effects of high-dose radioactive iodine for ablation or treatment of differentiated thyroid carcinoma. *Hong Kong J. Radiol*. **8(3)**: 127–135.

Colin, D. J., Limagne, E., Ragot, K., Lizard, G., Ghiringhelli, F., Solary, É., Chauffert, B., Latruffe, N., and Delmas, D. (2014). The role of reactive oxygen species and subsequent DNA-damage response in the emergence of resistance towards resveratrol in colon cancer models. *Cell Death Dis.* **5**: e1533.

Dai, Z., Lei, P., Xie, J., and Hu, Y. (2015). Antitumor effect of resveratrol on chondrosarcoma cells via phosphoinositide 3-kinase/AKT and p38 mitogen-activated protein kinase pathways. *Mol. Med. Rep*. **12(2)**: 3151-5.

ACCEPTED MANUSCRIPT

Das, S., and Das, D. K. (2007). Anti-inflammatory responses of resveratrol. *Inflamm. Allergy. Drug Targets.* **6(3)**: 168-173.

de Martel, C., Ferlay, J., Franceschi, S., Vignat, J., Bray, F., Forman, D., and Plummer, M. (2012). Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol*. **13(6)**: 607-15.

Demoulin, B., Hermant, M., Castrogiovanni, C., Staudt, C., and Dumont, P. (2015). Resveratrol induces DNA damage in colon cancer cells by poisoning topoisomerase II and activates the ATM kinase to trigger p53-dependent apoptosis. *Toxicol. In Vitro*. **29(5)**: 1156-65.

DeSantis, C., Ma, J., Bryan, L., and Jemal, A. (2013). Breast cancer statistics. *CA Cancer J. Clin*. **64**: 52–62.

Dhandayuthapani, S., Marimuthu, P., Hörmann, V., Kumi-Diaka, J., and Rathinavelu, A. (2013). Induction of apoptosis in HeLa cells via caspase activation by resveratrol and genistein. *J. Med. Food.* **16(2)**: 139-46.

Dhar, S., Kumar, A., Li, K., Tzivion, G., and Levenson, A. S. (2015). Resveratrol regulates PTEN/Akt pathway through inhibition of MTA1/HDAC unit of the NuRD complex in prostate cancer. *Biochim. Biophys. Acta*. **1853(2)**: 265-75.

Dhar, S., Kumar, A., Rimando, A. M., Zhang, X., and Levenson, A. S. (2015a). Resveratrol and pterostilbene epigenetically restore PTEN expression by targeting oncomiRs of the miR-17 family in prostate cancer. *Oncotarget*. 6(29): 27214–26.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Du, Q., Shen, K. P., Hu, B., and Deng, S. (2012). Effects of resveratrol on apoptosis and ROS production in Hepa 1-6 hepatocarcinoma cells. *Zhong Yao Cai*. **35(3)**: 443-48.

Empl, M. T., Albers, M., Wang, S., and Steinberg, P. (2015). The Resveratrol Tetramer r-Viniferin Induces a Cell Cycle Arrest Followed by Apoptosis in the Prostate Cancer Cell Line LNCaP. *Phytother. Res*. **29(10)**: 1640-45.

Fan, G. H., Wang, Z. M., Yang, X., Xu, L. P., Qin, Q., Zhang, C., Ma, J. X., Cheng, H. Y., and Sun, X. C. (2014). Resveratrol inhibits oesophageal adenocarcinoma cell proliferation via AMP-activated protein kinase signaling. *Asian Pac. J. Cancer Prev*. **15(2)**: 677-82.

Firouzi, F., Khoei, S., and Mirzaei, H. R. (2015). Role of resveratrol on the cytotoxic effects and DNA damages of iododeoxyuridine and megavoltage radiation in spheroid culture of U87MG glioblastoma cell line. *Gen. Physiol. Biophys*. **34(1)**: 43-50.

Gao, Q., Yuan, Y., Gan, H. Z, and Peng, Q. (2015). Resveratrol inhibits the hedgehog signaling pathway and epithelial-mesenchymal transition and suppresses gastric cancer invasion and metastasis. *Oncol. Lett*. **9(5)**: 2381-87.

García-Zepeda, S. P., García-Villa, E., Díaz-Chávez, J., Hernández-Pando, R., and Gariglio, P. (2013). Resveratrol induces cell death in cervical cancer cells through apoptosis and autophagy. *Eur. J. Cancer Prev*. **22(6)**: 577-84.

George, J., Singh, M., Srivastava, A. K., Bhui, K., Roy, P., Chaturvedi, P. K., and 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(8)**: e23395.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Gu, S., Chen, C., Jiang, X., and Zhang, Z. (2015). Resveratrol synergistically triggers apoptotic cell death with arsenic trioxide via oxidative stress in human lung adenocarcinoma A549 cells. *Biol. Trace Elem. Res*. **163(1-2)**: 112-23.

Guo, L., Peng, Y., Li Y, Yao J, Zhang G, Chen J, Wang, J., and Sui, L. (2015). Cell death pathway induced by resveratrol-bovine serum albumin nanoparticles in a human ovarian cell line. *Oncol. Lett*. **9(3)**: 1359-63.

Gwak, H., Haegeman, G., Tsang, B. K., and Song, Y. S. (2015). Cancer-specific interruption of glucose metabolism by resveratrol is mediated through inhibition of Akt/GLUT1 axis in ovarian cancer cells. *Mol Carcinog*. **54(12)**: 1529-40.

Habibie, Yokoyama, S., Abdelhamed, S., Awale, S., Sakurai, H., Hayakawa, Y., and Saiki, I. (2014). Survivin suppression through STAT3/β-catenin is essential for resveratrol-induced melanoma apoptosis. *Int. J. Oncol*. **45(2)**: 895-901.

Hao, Y. Q., Huang, W. X., Feng, H. X., Zhang, G. H., Ning, X. H., Li, H. G., Hao, C. G., and Li, Z. H. (2013). Study of apoptosis related factors regulatory mechanism of resveratrol to human skin squamous cell carcinoma A431 xenograft in nude mice. *Zhonghua Yi Xue Za Zhi*. **93(6)**: 464-68.

Hao, Y., Huang, W., Liao, M., Zhu, Y., Liu, H., Hao, C., Liu, G., Zhang, G., Feng, H., Ning, X., Li, H., and Li, Z. (2013a). The inhibition of resveratrol to human skin squamous cell carcinoma A431 xenografts in nude mice. *Fitoterapia*. **86**: 84-91.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Hedayati, M., Shafaghati, N., and Hosseinimehr, S. J. (2013). Resveratrol mitigates genotoxicity induced by iodine-131 in primary human lymphocytes. *Radiat. Environ. Biophys*. **52(2)**: 287–91.

Heiduschka, G., Lill, C., Seemann, R., Brunner, M., Schmid, R., Houben, R., Bigenzahn, J., and Thurnher, D. (2014). The effect of resveratrol in combination with irradiation and chemotherapy: study using Merkel cell carcinoma cell lines. *Strahlenther Onkol*. **190(1)**: 75-80.

Holian, O., Wahid, S., Atten, M. J., and Attar, B. M. (2002). Inhibition of gastric cancer cell proliferation by resveratrol: role of nitric oxide. Am J Physiol Gastrointest *Liver Physiol*. **282(5)**: G809-16.

Hosseinimehr, S. J., and Hosseini, S. A. H. (2014). Resveratrol sensitizes selectively thyroid cancer cell to 131-iodine toxicity. *J. Toxicol*. **2014**: Article ID 839597. doi.org/10.1155/2014/839597.

Howitz, K. T., Bitterman, K. J., Cohen, H. Y., Lamming, D. W. et al. (2003). Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. *Nature*. **425**: 191-196.

Hsu, K. F., Wu, C. L., Huang, S. C., Wu, C. M., Hsiao, J. R., Yo, Y. T., Chen, Y. H., Shiau, A. L., and Chou, C. Y. (2009). Cathepsin L mediates resveratrol-induced autophagy and apoptotic cell death in cervical cancer cells. *Autophagy*. **5(4)**: 451-60.

Irigaray, P., Newby, J. A., Clapp, R., Hardell, L., Howard, V., Montagnier, L., Epstein, S., and Belpomme, D. (2007). Lifestyle-related factors and environmental agents causing cancer: an overview. Biomed. Pharmacother. **61**: 640–58.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Jagdeo, J., Adams, L., Lev-Tov, H., Sieminska, J., Michl, J., and Brody, N. (2010). Dose-dependent antioxidant function of resveratrol demonstrated via modulation of reactive oxygen species in normal human skin fibroblasts in vitro. *J. Drugs Dermatol*. **9(12**): 1523-26.

Jang, M., Cai, L., Udeani, G. O., Slowing, K. V., Thomas, C. F., Beecher, C. W. et al. (1997). Cancer chemoprotective activity of resveratrol, a natural product derived from grapes. *Science*. **275**: 218-220.

Ji, Q., Liu, X., Han, Z., Zhou, L., Sui, H., Yan, L., Jiang, H., Ren, J., Cai, J., and Li, Q. (2015). Resveratrol suppresses epithelial-to-mesenchymal transition in colorectal cancer through TGF-β1/Smads signaling pathway mediated Snail/E-cadherin expression. *BMC Cancer*. **15**: 97.

Jing, X., Cheng, W., Wang, S., Li, P., and He, L. (2016). Resveratrol induces cell cycle arrest in human gastric cancer MGC803 cells via the PTEN regulated PI3K/Akt signaling pathway. *Oncol. Rep*. **5(1)**: 472-8.

Junco, J. J., Mancha, A., Malik, G., Wei, S. J., Kim, D. J., Liang, H., and Slaga, T. J. (2013). Resveratrol and P-glycoprotein inhibitors enhance the anti-skin cancer effects of ursolic acid. *Mol. Cancer Res*. **11(12)**: 1521-29.

Kalra, N., Roy, P., Prasad, S., and Shukla, Y. (2008). Resveratrol induces apoptosis involving mitochondrial pathways in mouse skin tumorigenesis. *Life Sci*. **82(7-8)**:348-58.

Kaneuchi, M., Sasaki, M., Tanaka, Y., Yamamoto, R., Sakuragi, N., and Dahiya, R. (2003). Resveratrol suppresses growth of Ishikawa cells through down-regulation of EGF. *Int. J. Oncol*. **23(4)**: 1167-72.

 ACCEPTED MANUSCRIPT

Khan, A., Aljarbou, A. N., Aldebasi, Y. H., Faisal, S. M., and Khan, M. A. (2014). Resveratrol suppresses the proliferation of breast cancer cells by inhibiting fatty acid synthase signaling pathway. *Cancer Epidemiol*. **38(6)**: 765-72.

Kim, J. A., Kim, D. H., Hossain, M. A., Kim, M. Y., Sung, B., Yoon, J. H., Suh, H., Jeong, T. C., Chung, H. Y., and Kim, N. D. (2014). HS-1793, a resveratrol analogue, induces cell cycle arrest and apoptotic cell death in human breast cancer cells. *Int. J. Oncol*. **44(2)**: 473-80.

Kim, S. H., Cho, K. H., Kim, Y. N., Jeong, B. Y., Park, C. G., Hur, G. M, and Lee, H. Y. (2016). Resveratrol attenuates norepinephrine-induced ovarian cancer invasiveness through downregulating hTERT expression. *Arch. Pharm. Res*. **39(2)**: 240-48.

Kim, Y. S., Sull, J. W., and Sung, H. J. (2012). Suppressing effect of resveratrol on the migration and invasion of human metastatic lung and cervical cancer cells. *Mol. Biol. Rep*. **39(9)**: 8709-16.

Ko, J. C., Syu, J. J., Chen, J. C., Wang, T. J., Chang, P. Y., Chen, C. Y., Jian, Y. T., Jian, Y. J., and Lin, Y. W. (2015). Resveratrol Enhances Etoposide-Induced Cytotoxicity through Down-Regulating ERK1/2 and AKT-Mediated X-ray Repair Cross-Complement Group 1 (XRCC1) Protein Expression in Human Non-Small-Cell Lung Cancer Cells. *Basic Clin. Pharmacol. Toxicol.* **7(6)**: 383-91.

Ko, J. L., Tsai, C. H., Liu, T. C., Lin, M. Y., Lin, H. L., and Ou, C. C. (2016). Differential effects of grape juice on gastric emptying and renal function from cisplatin-induced acute adverse toxicity. *Hum. Exp. Toxicol*. **5(8)**: 808-17.

ACCEPTED MANUSCRIPT

Kueck, A., Opipari, A. W. Jr, Griffith, K. A., Tan, L., Choi, M., Huang, J., Wahl, H., and Liu, J. R. (2007). Resveratrol inhibits glucose metabolism in human ovarian cancer cells. *Gynecol. Oncol*. **107(3)**: 450-7.

Kumar, A., Dhar, S., Rimando, A. M., Lage, J. M., Lewin, J. R., Zhang, X., and Levenson A. S. (2015). Epigenetic potential of resveratrol and analogs in preclinical models of prostate cancer. *Ann. N. Y. Acad. Sci*. **1348(1)**: 1-9.

Lang, F., Qin, Z., Li, F., Zhang, H., Fang, Z., and Hao E. (2015). Apoptotic Cell Death Induced by Resveratrol Is Partially Mediated by the Autophagy Pathway in Human Ovarian Cancer Cells. *PLoS One*. **10(6)**: eo129196/1-eo129196/17.

Lee, M. H., Choi, B. Y., Kundu, J. K., Shin, Y. K., Na, H. K., and Surh, Y. J. (2009). Resveratrol suppresses growth of human ovarian cancer cells in culture and in a murine xenograft model: eukaryotic elongation factor 1A2 as a potential target. *Cancer Res*. **69(18)**: 7449-58.

Lee, M. H., Kundu, J. K., Keum, Y. S., Cho, Y. Y., Surh, Y. J., and Choi, B. Y. (2014a). Resveratrol Inhibits IL-6-Induced Transcriptional Activity of AR and STAT3 in Human Prostate Cancer LNCaP-FGC Cells. *Biomol. Ther. (Seoul)*. **22(5)**: 426-30.

Lee, S. H., Koo, B. S., Park, S. Y., and Kim, Y. M. (2015). Anti-angiogenic effects of resveratrol in combination with 5-fluorouracil on B16 murine melanoma cells. *Mol. Med. Rep*. **12(2)**: 2777-83.

 ACCEPTED MANUSCRIPT

Lee, T. H., Seo, J. O., Baek, S. H., and Kim, S. Y. (2014a). Inhibitory effects of resveratrol on melanin synthesis in ultraviolet B-induced pigmentation in Guinea pig skin. *Biomol. Ther. (Seoul)*. **22(1)**: 35-40.

Lee, Y. J., Hwang, I. S., Lee, Y. J., Lee, C. H., Kim, S. H., Nam, H. S., Choi, Y. J., and Lee S. H. (2014). Knockdown of Bcl-xL enhances growth-inhibiting and apoptosis-inducing effects of resveratrol and clofarabine in malignant mesothelioma H-2452 cells. *J. Korean Med. Sci*. **29(11)**: 1464-72.

Li, Y.-G., Xia, H.-J., Tao, J.-P., Xin, P., Liu, M.-Y., Li, J.-B., Zhu, W., and Wei, M. (2015). GRIM‐19‐mediated Stat3 activation is a determinant for resveratrol‐induced proliferation and cytotoxicity in cervical tumor-derived cell lines. *Mol. Med. Rep.* **11(2)**: 1272-77.

Lin, F. Y., Hsieh, Y. H., Yang, S. F., Chen, C. T., Tang, C. H., et al. (2015). Resveratrol suppresses TPA-induced matrix metalloproteinase-9 expression through the inhibition of MAPK pathways in oral cancer cells. *J. Oral. Pathol. Med*. **44(9)**: 699-706.

Lin, X., Wu, G., Huo, W. Q., Zhang, Y., and Jin, F. S. (2012). Resveratrol induces apoptosis associated with mitochondrial dysfunction in bladder carcinoma cells. *Int. J. Urol*. **19(8)**: 757-64.

Lin, Y., Yngve, A., Lagergren, J., and Lu, Y. (2014). A dietary pattern rich in lignans, quercetin and resveratrol decreases the risk of oesophageal cancer. *Br. J. Nutr*. **112(12)**: 2002-9.

Liu, M. L., and Zhang, S. J. (2014). Effects of resveratrol on the protein expression of survivin and cell apoptosis in human gastric cancer cells. *J. BUON*. **19(3)**: 713-7.

Liu, S. Y., and Zheng, P. S. (2013). High aldehyde dehydrogenase activity identifies cancer stem cells in human cervical cancer. *Oncotarget*. **4(12)**: 2462-75.

Lucas, I. K., and Kolodziej, H. (2015). Trans-Resveratrol Induces Apoptosis through ROS-Triggered Mitochondria-Dependent Pathways in A549 Human Lung Adenocarcinoma Epithelial Cells. *Planta Med*. **81**: 1038-44.

Ma, L., Li, W., Wang, R., Nan, Y., Wang, Q., Liu, W., and Jin, F. (2015). Resveratrol enhanced anticancer effects of cisplatin on non-small cell lung cancer cell lines by inducing mitochondrial dysfunction and cell apoptosis. *Int. J. Oncol*. **47(4)**: 1460-68.

Martin, K. R. (2006). Targeting apoptosis with dietary bioactive agents. *Exp. Biol. Med*. **231**: 117−29.

Masuelli, L., Di Stefano, E., Fantini, M., Mattera, R., Benvenuto, M., et al. (2014). Resveratrol potentiates the in vitro and in vivo anti-tumoral effects of curcumin in head and neck carcinomas. *Oncotarget*. **5(21)**: 10745-62.

Mbimba, T., Awale, P., Bhatia, D., Geldenhuys, W. J., Darvesh, A. S., Carroll, R. T., and Bishayee, A. (2012). Alteration of hepatic proinflammatory cytokines is involved in the resveratrol-mediated chemoprevention of chemically-induced hepatocarcinogenesis. *Curr. Pharm. Biotechnol*. **13(1)**: 229-34.

Mikuła-Pietrasik, J., Sosińska, P., and Książek, K. (2014). Resveratrol inhibits ovarian cancer cell adhesion to peritoneal mesothelium in vitro by modulating the production of α5β1 integrins and hyaluronic acid. *Gynecol. Oncol*. **134(3)**: 624-30.

Mitani, T., Harada, N., Tanimori, S., Nakano, Y., Inui, H., and Yamaji, R. (2014). Resveratrol inhibits hypoxia-inducible factor-1α-mediated androgen receptor signaling and represses tumor progression in castration-resistant prostate cancer. *J. Nutr. Sci. Vitaminol (Tokyo)*. **60(4)**: 276-82.

Mitani, T., Ito, Y., Harada, N., Nakano, Y., Inui, H., Ashida, H., and Yamaji, R. (2014a). Resveratrol reduces the hypoxia-induced resistance to doxorubicin in breast cancer cells. *J. Nutr. Sci. Vitaminol (Tokyo)*. **60(2)**: 122-8.

Mitruţ, P., Burada, F., Enescu, A., Scorei, R., Badea, D., Genunche-Dumitrescu, A., Rogoz, I., and Manea M. (2009). The genotoxicity study of resveratrol in primary gastric adenocarcinoma cell cultures. *Rom. J. Morphol. Embryol*. **50(3)**: 429-33.

Mohapatra, P., Satapathy, S. R., Siddharth, S., Das, D., Nayak, A., and Kundu, C. N. (2015). Resveratrol and curcumin synergistically induces apoptosis in cigarette smoke condensate transformed breast epithelial cells through a p21(Waf1/Cip1) mediated inhibition of Hh-Gli signaling. *Int. J. Biochem. Cell. Biol*. **66**: 75-84.

Mohapatra, P., Satapathy, S. R., Das, D., Siddharth, S., Choudhuri, T., and Kundu, C. N. (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(3)**: 221-31.

Nie, P., Hu, W., Zhang, T., Yang, Y., Hou, B., and Zou, Z. (2015). Synergistic induction of erlotinib-mediated apoptosis by resveratrol in human non-small-cell lung cancer cells by down-regulating survivin and up-regulating PUMA. *Cell. Physiol. Biochem*. **35(6)**: 2255-71.

ACCEPTED MANUSCRIPT

Ojesina, A. I., Lichtenstein, L., Freeman, S. S., Pedamallu, C. S., Imaz-Rosshandler, I., et al. (2014). Landscape of genomic alterations in cervical carcinomas. *Nature*. **506(7488)**: 371-75.

O'Reilly, K. M., Mclaughlin, A. M., Beckett, W. S., and Sime, P. J. (2007). Asbestos-related lung disease. *Am. Fam. Physician*. **75(5)**: 683–688.

Osman, A. M., Al-Malki, H. S., Al-Harthi, S. E., El-Hanafy, A. A., Elashmaoui, H. M., and Elshal, M. F. (2015). Modulatory role of resveratrol on cytotoxic activity of cisplatin, sensitization and modification of cisplatin resistance in colorectal cancer cells. *Mol. Med. Rep*. **12(1)**: 1368-74.

Ou, X., Chen, Y., Cheng, X., Zhang, X., and He, Q. (2014). Potentiation of resveratrol-induced apoptosis by matrine in human hepatoma HepG2 cells. *Oncol. Rep*. **32(6)**: 2803-9.

Peng, D. Y., Song, H., and Liu, L. B. (2015). Resveratrol-downregulated phosphorylated liver kinase B1 is involved in senescence of acute myeloid leukemia stem cells. *J. Huazhong Univ. Sci. Technolog. Med. Sci*. **35(4)**: 485-89.

Raghubeer, S., Nagiah, S., Phulukdaree, A., and Chuturgoon, A. (2015). The phytoalexin resveratrol ameliorates ochratoxin A toxicity in human embryonic kidney (HEK293) Cells. *J. Cell Biochem*. **116(12)**: 2947-55.

Rahman, I., Biswas, S. K., and Kirkham, P. A. (2006). Regulation of inflammation and redox signaling by dietary polyphenols. *Biochem. Pharmacol*. **72**: 1439-52.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Reagan-Shaw, S., Afaq, F., Aziz, M. H., Ahmad, N. (2004). Modulations of critical cell cycle regulatory events during chemoprevention of ultraviolet B-mediated responses by resveratrol in SKH-1 hairless mouse skin. *Oncogene*. **23(30)**: 5151-60.

Rezk, Y. A., Balulad, S. S., Keller, R. S., and Bennett, J. A. (2006). Use of resveratrol to improve the effectiveness of cisplatin and doxorubicin: study in human gynecologic cancer cell lines and in rodent heart. *Am. J. Obstet. Gynecol*. **194(5)**: e23-6.

Riles, W. L., Erickson, J., Nayyar, S., Atten, M. J., Attar, B. M., and Holian, O. (2006). Resveratrol engages selective apoptotic signals in gastric adenocarcinoma cells. *World J. Gastroenterol*. **12(35)**: 5628-34.

Robbins, R. J., and Schlumberger, M. J. (2005). The evolving role of ^{131}I for the treatment of differentiated thyroid carcinoma. *J. Nucl. Med*. **46**: 28S–37S.

Roy, P., Madan, E., Kalra, N., Nigam, N., George, J., Ray, R. S., Hans, R. K., Prasad, S., and Shukla, Y. (2009). Resveratrol enhances ultraviolet B-induced cell death through nuclear factor-kappaB pathway in human epidermoid carcinoma A431 cells. *Biochem. Biophys. Res. Commun*. **384(2)**: 215-20.

Roy, P., Kalra, N., Prasad, S., George, J., and Shukla, Y. (2009a). Chemopreventive potential of resveratrol in mouse skin tumors through regulation of mitochondrial and PI3K/AKT signaling pathways. *Pharm. Res*. **26(1)**: 211-17.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Sareen, D., van Ginkel, P. R., Takach, J. C., Mohiuddin, A., Darjatmoko, S. R., Albert, D. M., and Polans, A. S. (2006). Mitochondria as the primary target of resveratrol-induced apoptosis in human retinoblastoma cells. *Invest. Ophthalmol. Vis. Sci*. **47(9)**: 3708-16.

Saud, S. M., Li, W., Morris, N. L., Matter, M. S., Colburn, N. H., Kim, Y. S., and Young, M. R. (2014). Resveratrol prevents tumorigenesis in mouse model of Kras activated sporadic colorectal cancer by suppressing oncogenic Kras expression. *Carcinogenesis*. **35(12)**: 2778-86.

Schiller, J. T., and Davies, P. (2004). Delivering on the promise: HPV vaccines and cervical cancer. *Nat. Rev. Microbiol***. 2(4)**: 343-47.

Schroeter, A., and Marko, D. (2014). Resveratrol modulates the topoisomerase inhibitory potential of doxorubicin in human colon carcinoma cells. *Molecules*. **19(12)**: 20054-72.

Seino, M., Okada, M., Shibuya, K., Seino, S., Suzuki, S., Takeda, H., Ohta, T., Kurachi, H., and Kitanaka, C. (2015). Differential contribution of ROS to resveratrol-induced cell death and loss of self-renewal capacity of ovarian cancer stem cells. *Anticancer Res*. **35(1)**: 85-96.

Selvaraj, S., Sun, Y., Sukumaran, P., Singh, B. B. (2016). Resveratrol activates autophagic cell death in prostate cancer cells via downregulation of STIM1 and the mTOR pathway. *Mol. Carcinog*. 2016: **55(5)**: 818-31.

Seyed, M. A., Jantan, I., Bukhari, S. N. A., and Vijayaraghavan, K. (2016). A Comprehensive Review on the Chemotherapeutic Potential of Piceatannol for Cancer Treatment, with Mechanistic Insights. *J. Agric. Food Chem*. **64**: 725−37.

 ACCEPTED MANUSCRIPT

Sexton, E., Van Themsche, C., LeBlanc, K., Parent, S., Lemoine, P., and Asselin, E. (2006). Resveratrol interferes with AKT activity and triggers apoptosis in human uterine cancer cells. *Mol. Cancer*. **5**: 45.

Shan, Z., Yang, G., Xiang, W., Pei-jun, W., and Bin, Z. (2014). Effects of resveratrol on oral squamous cell carcinoma (OSCC) cells in vitro. *J. Cancer Res. Clin. Oncol*. **140(3)**: 371-4.

Shi, Q., Geldenhuys, W., Sutariya, V., Bishayee, A., Patel, I., and Bhatia, D. (2015). CArG-driven GADD45α activated by resveratrol inhibits lung cancer cells. *Genes Cancer*. **6**: 220-30.

Shi, T., Liou, L. S., Sadhukhan, P., Duan, Z. H., Novick, A. C., Hissong, J. G., Almasan, A., and DiDonato, J. A. (2004). Effects of resveratrol on gene expression in renal cell carcinoma. *Cancer Biol. Ther*. **3(9)**: 882-8.

Shih, A., Davis, F. B., Lin, H. Y., and Davis, P. J. (2002). Resveratrol induces apoptosis in thyroid cancer cell lines via a MAPK- and p53-dependent mechanism. *J. Clin. Endocrinol. Metab*. **87(3)**: 1223-32.

Shin, K. O., Park, N. Y., Seo, C. H., Hong, S. P., Oh, K. W., Hong, J. T., Han, S. K., and Lee, Y. M. (2012). Inhibition of sphingolipid metabolism enhances resveratrol chemotherapy in human gastric cancer cells. *Biomol. Ther. (Seoul)*. **20(5)**: 470-6.

Shrotriya, S., Agarwal, R., and Sclafani, R. A. (2015). A perspective on chemoprevention by resveratrol in head and neck squamous cell carcinoma. *Adv. Exp. Med. Biol*. **815**: 333-48.

ACCEPTED MANUSCRIPT

Shrotriya, S., Tyagi, A., Deep, G., Orlicky, D. J., Wisell, J., Wang, X. J., Sclafani, R. A., Agarwal, R., and Agarwal, C. (2015). Grape seed extract and resveratrol prevent 4-nitroquinoline 1-oxide induced oral tumorigenesis in mice by modulating AMPK activation and associated biological responses. *Mol. Carcinog*. **54(4)**: 291-300.

Singh, B., Shoulson, R., Chatterjee, A., Ronghe A, Bhat, N. K., Dim, D. C., and Bhat, H. K. (2014). Resveratrol inhibits estrogen-induced breast carcinogenesis through induction of NRF2-mediated protective pathways. *Carcinogenesis*. **35(8)**: 1872-80.

Stocco, B., Toledo, K., Salvador, M., Paulo, M., Koyama, N., and Torqueti Toloi, M. R. (2012). Dose-dependent effect of resveratrol on bladder cancer cells: chemoprevention and oxidative stress. *Maturitas*. **72(1)**: 72-8.

Tang, Q., Li, G., Wei, X., Zhang, J., Chiu, J. F., Hasenmayer, D., Zhang, D., and Zhang, H. (2013). Resveratrol-induced apoptosis is enhanced by inhibition of autophagy in esophageal squamous cell carcinoma. *Cancer Lett*. **336(2)**: 325-37.

Thun, M. J., Hannan, L. M., Adams-Campbell, L. L., et al. (2008). Lung cancer occurrence in never-smokers: an analysis of 13 cohorts and 22 cancer registry studies. *PLoS Medicine*. **5 (9)**: e185.

Tomoaia, G., Horovitz, O., Mocanu, A., Nita, A., Avram, A., Racz CP2, Soritau, O., Cenariu, M., and Tomoaia-Cotisel, M. (2015). Effects of doxorubicin mediated by gold nanoparticles and resveratrol in two human cervical tumor cell lines. *Colloids Surf. B Biointerfaces*. **135**: 726-34.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Truong, M., Cook, M. R., Pinchot, S. N., Kunnimalaiyaan, M., and Chen, H. (2011). Resveratrol induces Notch2-mediated apoptosis and suppression of neuroendocrine markers in medullary thyroid cancer. *Ann. Surg. Oncol*. **18(5)**:1506-11.

Tsao, A. S. Lung Carcinoma: Tumors of the Lungs. Merck Manual Professional Edition, Online edition. Retrieved 15 August 2007.

Tsan, M.-F., White, J. E., Maheshwari, J. G., and Chikkappa, G. (2002). Anti-leukemia effect of resveratrol. *Leuk. Lymphoma*. **43(5)**: 983-87.

Varoni, E. M., Lo Faro, A. F., Sharifi-Rad, J., Iriti, M. (2016). Anticancer molecular mechanisms of resveratrol. *Front. Nutr*. **3**: 8. doi: 10.3389/fnut.2016.00008.

Venturelli, S., Berger, A., Böcker, A., Busch, C. et al. (2013). Resveratrol as a pan-HDAC inhibitor alters the acetylation status of histone [corrected] proteins in human-derived hepatoblastoma cells. *PLoS One*. **8(8)**: e73097.

Wang, L., Li, H., and Zhang, D. (2016). Anti-tumor composition of resveratrol and its preparation method. Yibei (Tianjin) Biotechnology Co., Ltd., Peop. Rep. China. From Faming Zhuanli Shenqing, CN 105596889 A 20160525.

Wang, S., Chen, R., Morott, J., Repka, M. A., Wang, Y., and Chen, M. (2015). mPEG-b-PCL/TPGS mixed micelles for delivery of resveratrol in overcoming resistant breast cancer. *Expert Opin. Drug Deliv*. **12(3)**: 361-73.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Wang, Z., Li, W., Meng, X., and Jia, B. (2012). Resveratrol induces gastric cancer cell apoptosis via reactive oxygen species, but independent of sirtuin1. *Clin. Exp. Pharmacol. Physiol*. **39(3)**: 227-32.

Wang, Z., Zhang, L., Ni, Z., Sun, J., Gao, H., Cheng, Z., Xu, J., and Yin, P. (2015). Resveratrol induces AMPK-dependent MDR1 inhibition in colorectal cancer HCT116/L-OHP cells by preventing activation of NF-κB signaling and suppressing cAMP-responsive element transcriptional activity. *Tumour Biol*. **36(12)**: 9499-510.

Wang, Z., Li, W., Meng, X., and Jia, B. (2012). Resveratrol induces gastric cancer cell apoptosis via reactive oxygen species, but independent of sirtuin1. *Clin. Exp. Pharmacol. Physiol*. **39(3)**: 227-32.

WHO. World Cancer Report 2014. Chapter 1.1. ISBN 9283204298.

WHO. World Cancer Report 2014. Chapter 5.1. ISBN 9283204298.

Wong, J. C., and Fiscus, R. R. (2015). Resveratrol at anti-angiogenesis/anticancer concentrations suppresses protein kinase G signaling and decreases IAPs expression in HUVECs. *Anticancer Res*. **35(1)**: 273-81.

Woodall, C. E., Li, Y., Liu, Q-H., Wo, J., and Martin, R. C. (2009). Chemoprevention of metaplasia initiation and carcinogenic progression to esophageal adenocarcinoma by resveratrol supplementation. *Anticancer Drugs*. **20(6)**: 437-43.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Wu, M-L., Li, H., Yu, L-J., Chen, X-Y., Kong, Q-Y., Song, X., Shu, X-H., and Liu, J. (2014). Short-term resveratrol exposure causes in vitro and in vivo growth inhibition and apoptosis of bladder cancer cells. *PLoS One*. **9(2)**: e89806.

Wu, X. P., Xiong, M., Xu, C. S., Duan, L. N., Dong, Y. Q., Luo, Y., Niu, T. H., and Lu, C. R. (2015). Resveratrol induces apoptosis of human chronic myelogenous leukemia cells in vitro through p38 and JNK-regulated H2AX phosphorylation. *Acta Pharmacol. Sin*. **36(3)**: 353-61.

Yang, H., Zheng, Y., Li, T. W., Peng, H., Fernandez-Ramos, D., Martínez-Chantar, M. L., Rojas, A. L., Mato, J. M., and Lu, S. C. (2013). Methionine adenosyltransferase 2B, HuR, and sirtuin 1 protein cross-talk impacts on the effect of resveratrol on apoptosis and growth in liver cancer cells. *J. Biol. Chem*. **288(32)**: 23161-70.

Yang, J., Liu, J., Lyu, X., and Fei, S. (2015). Resveratrol inhibits cell proliferation and up-regulates MICA/B expression in human colon cancer stem cells. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi*. **31(7)**: 889-93.

Yang, Q., Xu, E., Dai, J., Liu, B., Han, Z., Wu, J., Zhang, S., Peng, B., Zhang, Y., and Jiang, Y. (2015a). A novel long noncoding RNA AK001796 acts as an oncogene and is involved in cell growth inhibition by resveratrol in lung cancer. *Toxicol. Appl. Pharmacol*. **285(2)**: 79-88.

Yang, R., Zhang, H., and Zhu, L. (2011). Inhibitory effect of resveratrol on the expression of the VEGF gene and proliferation in renal cancer cells. *Mol. Med. Rep*. **4(5)**: 981-83.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Yang, Y., Cui, J., Xue, F., Overstreet, A. M., Zhan, Y., Shan, D., Li, H., Li, H., Wang, Y., Zhang, M., Yu, C., and Xu, Z. D. (2016). Resveratrol represses pokemon expression in human glioma cells. *Mol. Neurobiol*. **53(2)**: 1266-78.

Yu, X. M., Jaskula-Sztul, R., Ahmed, K., and Harrison, A. D, (2013). Kunnimalaiyaan M, Chen H. Resveratrol induces differentiation markers expression in anaplastic thyroid carcinoma via activation of Notch1 signaling and suppresses cell growth. *Mol. Cancer Ther*. **12(7)**: 1276-87.

Yu, X.-D., Yang, J.-l., Zhang, W.-L., and Liu, D.-X. (2016). Resveratrol inhibits oral squamous cell carcinoma through induction of apoptosis and G2/M phase cell cycle arrest. *Tumor Biology*. **37(3)**: 2871-77.

Yu, H. B., Zhang, H. F., Zhang, X., Li, D. Y., Xue, H. Z., Pan, C. E., and Zhao, S. H. (2010). Resveratrol inhibits VEGF expression of human hepatocellular carcinoma cells through a NF-kappa B-mediated mechanism. *Hepatogastroenterology*. **57**: 1241-46.

Zhang, L., Li, J., Duan, J., and Yuan, X. (2016). Medicine for treating thyroid cancer. Faming Zhuanli Shenqing. 2016, CN 105748504 A 20160713.Zhang, P., Li, H., Yang, B., Yang, F.,

Zhang L. L., Kong, Q. Y. , Chen, X. Y., Wu, ML., and Liu, J. (2014). Biological significance and therapeutic implication of resveratrol-inhibited Wnt, Notch and STAT3 signaling in cervical cancer cells. *Genes Cancer*. **5(5-6)**: 154-64.

 ACCEPTED MANUSCRIPT

Zhang, X. L., Yu, H., Xiong, Y. Y., Ma, S. T., Zhao, L., and She, S. F. (2013). Resveratrol down-regulates Myosin light chain kinase, induces apoptosis and inhibits diethylnitrosamine-induced liver tumorigenesis in rats. *Int. J. Mol. Sci*. **14(1)**: 1940-51.

Zheng, G. H., Li, H. Q. (2008). Effects of garlic oil combined with resveratrol on inducting of apoptosis and expression of Fas, bcl-2 and bax in human gastric cancer cell line. *Zhonghua Yu Fang Yi Xue Za Zhi*. **42(1)**: 39-42.

Zhong, L.-X., Li, H., Wu, M.-L., Liu, X.-Y., Zhong, M.-J., Chen, X.-Y., Liu., J., and Zhang, Y. (2015). Inhibition of STAT3 signaling as critical molecular event in resveratrol-suppressed ovarian cancer cells. *J. Ovarian Res*. 8: 25.

Zhou, C., Ding, J., and Wu, Y. (2014). Resveratrol induces apoptosis of bladder cancer cells via miR‐21 regulation of the Akt/Bcl‐2 signaling pathway. *Mol. Med. Rep*. **9(4)**: 1467-73.

Zhou, H. B., Yan, Y., Sun, Y. N., and Zhu, J. R. (2003). Resveratrol induces apoptosis in human esophageal carcinoma cells. *World J. Gastroenterol*. **9(3)**: 408-11.

Zlotogorski, A., Dayan, A., Dayan, D., Chaushu, G., Salo, T., and Vered, M. Nutraceuticals as new treatment approaches for oral cancer: II. Green tea extracts and resveratrol. *Oral Oncol*. **49(6)**: 502-6.

Zulueta, A., Caretti, A., Signorelli, P., and Ghidoni, R. (2015). Resveratrol: a potential challenger against gastric cancer. *World J. Gastroenterol*. **21(37)**: 10636-43.

Zunino, S. J., and Storms, D. H. (2015). Physiological levels of resveratrol metabolites are ineffective as anti-leukemia agents against Jurkat leukemia cells. *Nutr. Cancer*. **67(2)**: 266-74.

Table 1. Types of Cancer Treated by Resveratrol, Mechanisms of Action, and Pertinent References.

Cancer Types	Mechanisms	References
Colorectal	Suppresses the TGF-β-induced epithelial mesenchymal transition (EMT)	(Ji et al., 2015)
	Decreases the E-cadherin expression and elevating Vimentin expression	
	Activates the TGF-β1/Smads signaling pathway	
	Enhances the expression of E-cadherin, and represses the expression of Vimentin	
	Lowers the level of EMT-inducing transcription of E-cadherin and transcription factors Snail during the initiation of TGF-β1-induced EMT	
	Enhances the expression of miR-96, and down-regulates the Kras	(Saud et al. 2014)
	Up-regulates p21 (WAF1/CIP1)	(Ali et al., 2014)
	Modulates the DNA-strand breaking potential of DOX	(Schroeter et al., 2014)
	Down-regulates the expression levels of mRNA and P-glycoprotein/multi-drug resistance protein 1 (P-gp/MDR1) protein	(Wang et al., 2015)
	Lowers the phosphorylation levels of IκBα, and nuclear factor-κB (NF-κB) activity	
	Induces apoptotic cell death and activates the tumor suppressor p53	(Demoulin et al., 2015)
	Suppresses epithelial-mesenchymal transition (EMT) factors (increases E-cadherin and decreases vimentin and slug)	(Buhrmann et al., 2015; Wang et al., 2015)
	Sensitizes the CIS-resistant HCT-116 cells	(Osman et al., 2015)
	Inhibites HUVEC tube formation and cell migration/invasion	(Wong et al., 2015)
	Suppresses endogenous PKG kinase activity and decreases the expression of four cell-survival proteins, c-IAP2, c-IAP1, XIAP, and livin	
BREAST	Decreases the gene expression of BCL-xl in HER-2 receptor negative and HER-2 receptor positive breast cancer cell lines (MCF-7 and T47D cell lines).	(Abdel-Latif et al., 2015)
	Represses the expression of hypoxia-induced expression of carbonyl reductase 1 (CBR1) and hypoxia-inducible factor	(Mitani et al., 2014a)

	(HIF)-1α protein	
	Suppresses Hedgehog-Gli cascade	(Mohapatra et al., 2015)
	Reduces the expression of anti-apoptotic proteins (e.g. AKT, PI3K, NFκB).	(Mohapatra et al., 2014)
	Lowers expressions of cell cycle regulatory (CDC-2, Cyclins, CDC-6), BER linkes (Pol-δ, Pol-β, Pol-η, Pol-ε, RPA, DNA-Ligase-I, Fen-1) proteins	
	Enhances the NQO1, SOD3 and OGG1 genes	(Singh et al., 2014)
	Preventes E2-mediated inhibition of detoxification genes AOX1 and FMO1	
	Inhibits E2-mediated alterations in NRF2 promoter methylation and expression of NRF2 targeting miR-93 during E2-induced breast carcinogenesis	
	Suppresses cell growth, induces apoptotic cell death and G2/M arrest in MCF-7 and MDA-MB-231 cells	(Kim et al., 2014)
	Induces p53/p21WAF1/CIP1-dependent apoptosis	
Ovarian	Suppresses glucose uptake and induces apoptosis	(Gwak et al., 2015)
	Inhibits plasma membrane GLUT1 localization linked with the inhibition of Akt activity	
	Inhibits OVCAR-3 and CAOV-3 cells	(Zhong et al., 2015)
	Suppresses the epithelial-to-mesenchymal transition with concomitant recovery of E-cadherin expression	(Kim et al., 2016)
	Down-regulates NE-induced human telomerase reverse transcriptase (hTERT) expression	
	Inhibits Src phosphorylation and HIF-1α expression	
	Lowers cellular α5β1 integrin level and enhanced the secretion of HA to the environment	(Mikuła-Pietrasik et al., 2014)
	Attenuates the proliferation of serum-starved PA-1 cells stimulated with insulin	
	Activates caspase-3, -7, and -9 and induces apoptosis in PA-1 cells	
	Lowers bromodeoxyuridine positivity, decreases cell nuclear antigen, and enhances terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling	(Lee et al., 2009).
	Lowers lactate production levels of phosphorylated Akt and mTOR	(Kueck et al., 2007)
Cervical	Suppresses Stat3 phosphorylation in HeLa cells	(Tomoaia et al. 2015)
	Inhibits activation of STAT3, Notch, and Wnt	(Kim et al., 2015)
	Causes cell cycle arrest at the G1 phase, induced apoptosis	

	Lowers mitochondrial membrane potential	
	Enhances lysosomal permeability (autophagy) and decreases the expression of p53	(García-Zepeda et al., 2013)
	Lowers the expression of p65 (an NF-κB subunit)	
	Inhibits phorbol 12-myristate 13-acetate (PMA)-induced invasion and migration	(Kim et al., 2012)
	Lowers the enzymatic activity of matrix metalloproteinase-9 (MMP-9)	
	Suppresses the NF-κB and AP-1 transactivation	
	Induces cytosolic translocation of cytochrome c, caspase 3activation and apoptotic cell death	(Hsu et al., 2009)
	Induces dissipation of lysosomal membrane permeability (LMP) leakage and increases cytosolic expression and activity of cat L	
	Enhances the activities of caspase-9 and caspase-3	(Dhandayuthapani et al., 2013)
	Lowers the level of HDM2 gene expression	
Liver	Sensitizes aerobic glycolytic HCC cells	(Dai et al., 2015)
	Increases sorafenib-induced cell growth inhibition in aerobic glycolytic HCC cells	
	Up-regulates the Bax/Bcl-2 ratio	(Ou et al., 2014)
	Disruptes mitochondrial membrane potential (Δψm)	
	Down-regulates phosphorylated liver kinase B1 (pLKB1)	(Peng et al., 2015)
	Suppresses the activities of eleven human HDACs enzymes of class I, II and IV	(Venturelli et al., 2013)
	Increases the interaction of MATβ with HuR and SIRT1 as well as loweres the interaction between MATβ and MATα2	(Yang et al., 2013)
Head and neck	Enhances PARP-1 cleavage	(Masuelli et al., 2014; Shrotriya et al., 2015)
	Increases the Bax/Bcl-2 ratio	
	Suppresses ERK1 and ERK2 phosphorylation	
	Activates AMPK activity and blockes the s6 activities and p70S6K	(Cai et al., 2015)
	Inhibits matrix metalloproteinase-9 (MMP-9) expression, and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced migration capacities	(Lin et al., 2014)
	Significantly loweres the migratory and invasive abilities of KB cells	(Shan et al., 2014)
	Preventes the multiplicity and severity of 4NQO-induced preneoplastic and neoplastic lesions	(Shrotriya et al., 2015; Zlotogorski et al., 2013)
	Lowers proliferation (BrdU labeling index) and increases activated metabolic regulator phospho-AMPK (Thr172)	
Stomach	Suppresses EMT and the hedgehog (Hh) signaling pathway	(Gao et al., 2015)

	Down-regulates survivin expression Causes cell-cycle arrest in the G0/G1 phase	(Liu and Zhang, 2014)
	Up-regulates both Fas and Fas-L proteins	(Atten et al., 2005)
	Lowers the protein expression of cyclin D1, phospho-glycogen synthase kinase 3β (p-GSK3β), and tensin homologue (p-PTEN) Represses p-Akt and p-PI3K expression	(Jing et al., 2015; Ko et al., 2015)
	Down-regulates the senescence pathways such as cyclin D1, cyclin-dependent kinase (6 and CDK4), cyclin D1, p16, and p21 Reduces the fractions of Ki67-positive cells	(Yang et al., 2013)
	Suppresses the DHCer desaturase activity	(Shin et al., 2012)
	Inhibits ERK1/2 phosphorylation by MEK1/2	(Aquilano et al., 2009)
	Lowers the mRNA expression of bcl-2	(Zheng et al., 2008)
	Stimulates caspase 3 and cytochrome C oxidase activities	(Riles et al., 2006)
Lung	Up-regulates the 21 long noncoding RNAs (lncRNAs) Down-regulates the 19 lncRNAs	(Yang et al., 2015)
	Suppresses the expression of XRCC1 and increases the etoposide-induced cell death	(Ko et al., 2015)
	Activates MAPK family members JNK and p38, and blockes the activation of ERK	(Wu et al., 2015)
	Transiently induces Egr-1 through ERK/JNK-ElK-1	(Shi et al., 2015)
	Inhibits the proliferation of H838 and H520 cells Releases of cytochrome c from mitochondria to cytosol	(Ma et al., 2015)
	Suppresses the Bcl-xL influences cell growth and apoptosis Decreases Mcl-1 protein levels	(Lee et al., 2014)
	Inhibits the epidermal growth factor receptor (EGFR) Lowers cell viability and colony formation Suppresses the AKT/mTOR/S6 kinase pathway	(Nie et al., 2015)
Prostate	Blocks up regulation of autophagy Restores inhibition of Akt	(Alayev et al., 2015).
	Promotes acetylation and reactivation of PTEN	(Dhar et al., 2015).
	Enhances the AR transcriptional activity Suppresses the IL-6-induced STAT3 transcriptional activity Reduces the prostate-specific antigen (PSA) production	(Lee et al., 2014a)
	Decreases the levels of endogenous as well as exogenously expressed miR-17, miR-20a and miR-106b	(Dhar et al., 2015)

	Decreases the protein level of hypoxia-inducible factor (HIF)-1α, and reduces the mRNA levels of androgen-responsive genes	(Mitani et al., 2014)
	Inhibits the nuclear accumulation of β-catenin Represses the nuclear localization of β-catenin	
	Decreases stromal interaction molecule 1 (STIM1) expression Lowers ER calcium storage and store operated calcium entry (SOCE)	(Selvaraj et al., 2015; Empl et al., 2015)
	Down-regulates STIM1 expression and triggers ER stress by depleting ER calcium pool	
	Regulates chromatin modifier metastasis-associated protein 1 (MTA1) and microRNAs (miRNAs)	(Kumar et al., 2015)
Skin	Alteres the expression levels of cyclooxygenase-2, AMP-activated protein kinase (AMPK), and vascular endothelial growth factor (VEGF)	(Lee et al., 2015; Cho et al., 2015)
	Inhibits β-catenin and STAT3 and inducing apoptosis	(Habibie et al., 2014)
	Suppresses α-melanocyte-stimulating hormone signaling, viability, migration, Lowers the expression of tyrosinase-related proteins 1 and 2, melanogenesis-related proteins tyrosinase	(Lee et al., 2014; Heiduschka et al., 2014)
	Decreases Smac/DIABLO Enhances UV-B-mediated induction of apoptosis	(Aziz et al., 2005)
	Mediates via modulation in the expression and function of cell cycle regulatory proteins cyclin-D1 and -D2, cdk-2, -4 and -6, and WAF1/p21 Inhibits MAPK pathway	(Reagan-Shaw et al., 2004)
	Inhibits the expression of apoptosis-related factors, ERK Down-regulates the mRNA expression of SVVS	(Hao et al., 2013; Tsai et al., 2012)
	Down-regulates the level of Rictor Lowers the RhoA-GTPase and altered actin cytoskeleton organization, restored RhoA-GTPase activity and actin cytoskeleton network, and reduced the β-gal activity	(Back et al., 2012)
	Reduces expressions of c-Jun N-terminal kinase 1/2, extracellular signal-regulates kinase 1/2, and p38 and enhanced total p53 and phospho p53 (Ser 15)	(George et al.,2011)
	Disrupts the nuclear factor-kappaB (NF-kappaB) pathway Decreases phosphorylation of tyrosine 701 Inhibits the metastatic protein LIMK1	(Roy et al., 2009)
	Reduces intracellular hydrogen peroxide-up regulated ROS	(Jagdeo et al., 2010)
	Regulates Phosphatidylinositol-3-kinase (PI3K)/ and AKT proteins	(Roy et al., 2009)

	Up-regulates survivin (both at protein- and mRNA- levels) and phospho-Survivin protein Down-regulates proapoptotic Smac/DIABLO protein	(Aziz et al., 2005a)
Esophageal	Lowers the severity of esophagitis, incidences of carcinoma and intestinal metaplasia	(Woodall et al., 2009)
	Reduces the level of p27Kip1, a cyclin-dependent kinase inhibitor, and increases the levels of S-phase kinase-associated protein 2 (Skp2)	(Fan et al., 2014; Lin et al., 2014)
	Suppresses the N-nitrosomethylbenzylamine (NMBA)-induced	(Li et al., 2002)
	Enhances the production of prostaglandin E(2) (PGE(2)) Decreases the higher expression of COX-1, & up-regulated COX-2 expression	
	Exhibits activation and nuclear translocation of MAPK (extracellular signal-regulates kinase 1/2)	(Shih et al., 2002)
	Enhances the serine phosphorylation of p53, cellular abundance of the oncogene suppresses protein p53, and abundance of c-jun, c-fos, and p21 mRNAs	
Uterine	Reduces cellular levels of the phosphorylated active form of anti-apoptotic kinase AKT	Sexton et al. (2006)
	Decreases the production of cyclooxygenase (COX) metabolites PGE2 and PGF2α	
	Lowers epidermal growth factor (EGF)	(Kaneuchi et al., 2003)
	Up-regulates the vascular endothelial growth factor (VEGF)	
Bladder	Attenuates the nuclear translocation, phosphorylation, transcription of STAT3	(Wu et al., 2014)
	Down-regulates the STAT3 downstream genes (cyclinD1, c-Myc, survivin, and VEGF) and nuclear translocations of p53 and Sirt1	
	Enhances the Bad/Bcl-2 ratio (proapoptotic/antiapoptotic proteins)	(Stocco et al., 2012)
	Modulates NO and PGE(2) secretion	
	Lowers adenosine 5'-triphosphate	(Lin et al., 2012)
	Releases cytochrome c from mitochondria to the cytosol	
	Down-regulates the miR-21 accompanied	(Zhou et al., 2014)
	Modulates Bcl-2 family proteins	(Bai et al., 2010)
	Activates caspase 3 and caspase 9	
	Causes G(1) phase cell cycle arrest	
	Down-regulates cyclin D1, cyclin-dependent kinase 4, and phosphorylated Rbx	

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Kidney and eye	Increases mRNA expression of the DNA repair enzyme OGG1	(Raghubeer et al., 2015)
	Suppresses expression of the vascular endothelial growth factor (VEGF) gene	(Yang et al., 2011)
	Suppresses the Y79 cell growth	(Sareen et al., 2006)
	Activates mitochondrial (intrinsic) apoptotic pathway	
Brain	Reduces colony number and induces DNA damage of glioblastoma spheroid cells	Firouzi et al. (2015)
	Lowers the expression and activity of POK erythroid ontogenic factor (Pokemon)	(Yang et al., 2016)
Bone	Inhibits matrix metalloproteinase (MMP)-induced differentiation	(Dai et al., 2015)
	Suppresses the activity of phosphoinositide 3-kinase/AKT and p38 mitogen-activated protein kinase signaling pathways	
	Activates the mitochondrial apoptotic signaling pathway	(Chen et al., 2015)
	Decreases the mitochondrial membrane potential (MMP)	
Blood	Down-regulates phosphorylated liver kinase B1 (pLKB1)	(Peng et al., 2015)
	Activates SIRT1 and induces apoptosis	(Zunino et al., 2015)

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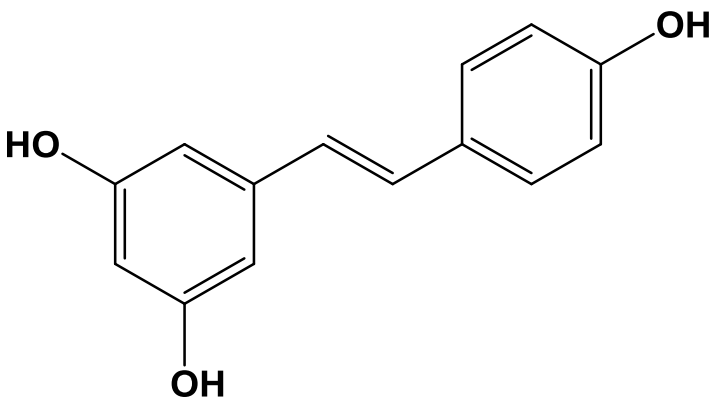

FIGURE 1: RESVERATROL

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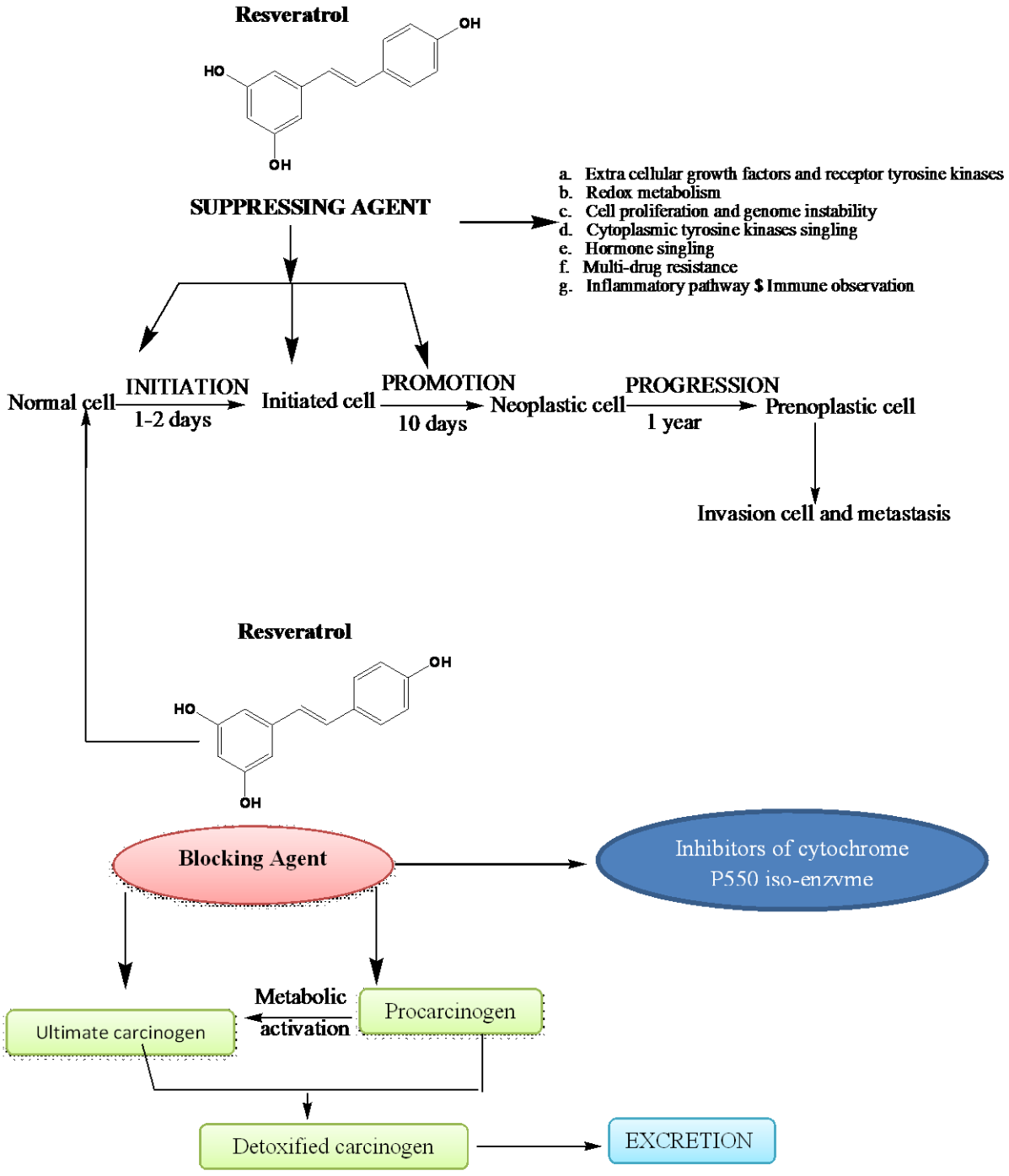

FIGURE 2. ANTICANCER ROLE OF RESVERATROL

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