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Resveratrol and cancer treatment: updates

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Cancer, a growing health problem worldwide, affects millions of people every year. The overall survival rates of most cancers have been prolonged owing to the efforts of clinicians and scientists. However, some tumors develop resistance to chemoradiotherapeutic agents, and the cancer research community continues to search for effective sensitizers. Resveratrol, a natural polyphenolic phytoalexin, has shown promising effects in inhibiting proliferation and cancer progression in several tumor models. However, its molecular mechanisms and applications in chemotherapy and radiotherapy have yet to be fully determined. In this concise review, we highlight the role and related molecular mechanisms of resveratrol in cancer treatment. In particular, we focus on the role of resveratrol in the tumor microenvironment and the sensitization of cancer cells for chemotherapy and radiotherapy. Resveratrol shows promising efficacies in cancer treatment and may be applied in clinical therapy, but it requires further clinical study.

Keywords: resveratrol; cancer therapy; tumor microenvironment; cancer stem cells; chemoradiosensitization

Introduction

Cancer is a major worldwide public health problem, and it has become the second leading cause of death in America. The American National Center for Health Statistics estimates that there will be more than 1.6 million new cancer diagnoses and more than 600,000 cancer-related deaths in 2017.[1] Surgery, chemotherapy, and radiotherapy are the most common therapies for cancer. Chemotherapy and radiotherapy are used as the primary treatment regimens in most cancer patients and play vital roles in cancer treatment, because many patients are diagnosed at advanced stages past the window for surgery. However, more and more tumors become resistant to chemotherapy (chemoresistance) and radiotherapy (radioresistance), which has become a major hurdle in cancer therapy. Furthermore, complications emerge when cancer cells develop chemoresistance and radioresistance via multiple mechanisms, and the chemotherapeutic agents and radiotherapy often cause adverse events. Therefore, we need to identify a new strategy or new therapeutic agent that can overcome chemoresistance and radioresistance.

Over the past years, more and more natural products have been discovered to be effective anticancer drugs owing to advantages like multitargeting properties, immediate availability, low cost, and low toxicity. Polyphenols, commonly found in fruits and vegetables, have been demonstrated to have multiple effects in several chronic diseases treatment as well as cancers. Resveratrol (*trans*-3,4′,5-trihydroxystilbene), a classical natural polyphenolic phytoalexin, is found in a number of plants and traditional Chinese medicines (e.g., white hellebore, grape skin, red wine, *Rheum officinale* Baill, berries, peanuts, and *Polygonum cuspidatum*).[2] Many studies have demonstrated the antioxidant, anti-inflammatory, and protective activity of resveratrol against metabolic disorders and cardiac diseases.[3] However, the specific molecular mechanisms of resveratrol in cancer treatment are not very clear and need to be further investigated.

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Over the past several years, numerous studies have demonstrated that resveratrol can directly inhibit the proliferation and viability of cancer cells in a dose- and time-dependent manner *in vitro,* and many reports have demonstrated that resveratrol could be used as a cancer chemopreventive agent owing to its ability to induce growth inhibition, cell cycle arrest, and apoptosis in several human cancer cell lines.[4,5] Although resveratrol has shown many anticancer effects, the mechanisms by which it exerts these effects are not yet fully understood. In this paper, we will review recent advances in the use of resveratrol and its analogs in cancer treatment, focusing on the role of resveratrol in the tumor microenvironment and in sensitization of cancer cells for chemotherapy and radiotherapy and its relative mechanisms and future applications.

Resveratrol regulates the level of reactive oxygen species

Reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and free radicals (e.g., hydroxyl radical ($^{\bullet}OH$), superoxide anion ($^{\bullet}O^{2-}$), and lipid peroxides), can damage nucleic acids, lipids, and proteins.[6] It has been demonstrated that most malignant tumor cells have increased levels of ROS, which play an important role in the initiation and progression of cancer by promoting cell proliferation, survival, invasion, and metastasis.[5,7] Resveratrol has antioxidant properties through modulating antioxidant enzyme activity, which likely contributes to its anticancer effects. Mechanistically, resveratrol can upregulate superoxide dismutase (SOD), catalase, and glutathione peroxidase expression and their enzymatic activity in tumor cells, which leads to mitochondrial accumulation of H_2O_2 and ultimately induced cancer cell apoptosis. On the other hand, slight upregulation of antioxidative enzymes and reducing oxidative stress could explain the protective effect of resveratrol on normal cells. Jung *et al.* demonstrated that resveratrol can inhibit the level of intracellular ROS and downregulate hypoxia-inducible factor-1α (HIF-1α) accumulation, thus suppressing lung cancer, colon cancer, and breast cancer cell ^{18}F-FDG uptake and glycolytic metabolism.[8] Kong *et al.* found that pterostilbene, a natural dimethylated analog of resveratrol, could increase ROS levels via suppression of ERK1/2 and activation of p38 mitogen-activated protein kinase (MAPK) signaling pathways to induce human diffuse large B cell lymphoma cell apoptosis *in vivo* and *in vitro.*[9] This may explain why combinations of resveratrol and other chemotherapy drugs showed better anticancer effects. Vendrely *et al.* reported that ROS production was exacerbated after treatment with resveratrol analogues and capsaicin in pancreatic adenocarcinoma, which resulted in activation of the p38 MAPK pathway and disrupted the balance of Bcl-2 and BAX expression, leading to apoptosis.[5] Kim *et al.* also found that capsaicin and resveratrol, alone or in combination, induced cell apoptosis and inhibited cell growth through upregulating NO production and Bax expression, accompanied by a reduction of MDM2, Bcl-2, *cytochrome* c expression and activation of caspase-9, caspase-3, caspase-8, death receptor 4, and Fas (CD95), suggesting that capsaicin and resveratrol induce cell apoptosis through activation of the mitochondrial and death receptor pathways together.[10]

The main molecular mechanisms of resveratrol in killing tumor cells

The antitumor effect of resveratrol depends on the type and status of cancer cells, and this effect depends on the dose of resveratrol. For most tumor cells, resveratrol can induce apoptosis and cell cycle arrest. However, for neuronal cells or endothelial cells suffering severe oxidative stress, resveratrol can also help them avoid radiation damage and cytotoxic drug stimulation by reducing oxidative stress and upregulating the expression of survival proteins.[11] As a result, resveratrol can be used in chemotherapy to protect normal cells to reduce adverse effects owing to this property. In general, the specific molecular mechanisms and signaling pathways involved in the antitumor effect of resveratrol include (1) regulation of mitochondrial and caspase cascade enzymatic system activation; (2) upregulation of cyclin-dependent kinase inhibitors, tumor suppressor genes, death-induced cytokines, and their receptors; (3) downregulation of the expression of survival proteins associated with the development of chemoresistance, including survivin, cFLIP, cIAPs, and antiapoptotic proteins (Bcl-2 and Bcl-XL);[12] (4) activation of adenosine 5′-monophosphate–activated protein kinase (AMPK), and (5) inhibition of MAPK, phosphoinositide 3-kinase (PI3K)/Akt,[13] hedgehog (HH),[14] hippo–YAP,[15] PKC, EGFR kinase, nuclear

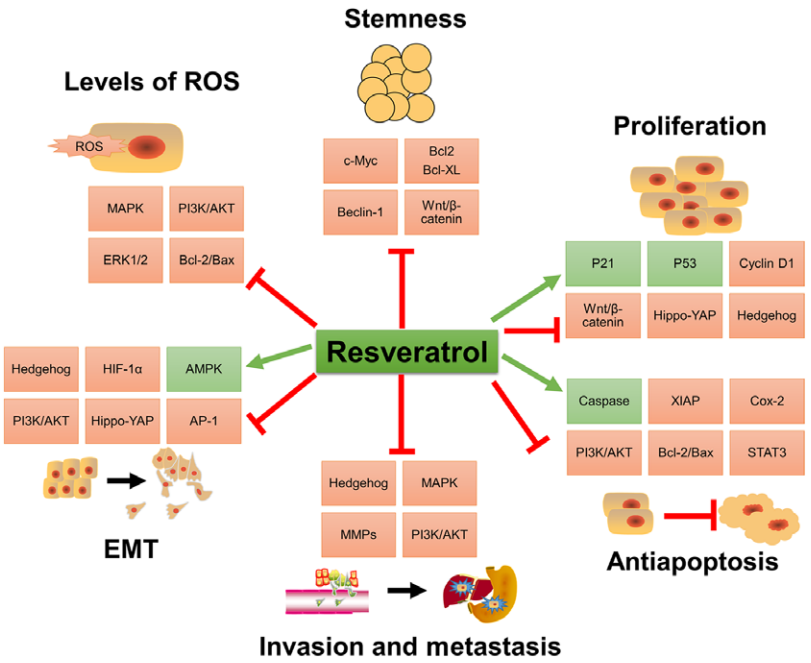

Figure 1. The signaling pathways by which resveratrol suppresses the malignant biological behaviors of cancer cells, including proliferation, antiapoptosis, invasion, migration, EMT progress, levels of ROS, and stemness.

factor κB (NF-κB), activating protein-1 (AP-1),[16] HIF-1α,[17] and signal transducer and activator of transcription 3 (STAT3).[18] However, the exact molecular mechanisms need further investigation.

The role of resveratrol in the tumor microenvironment

The tumor microenvironment is a complex environment containing various cellular components (e.g., stromal cells, immune cells, and vascular endothelial cells), multitudinous factors (e.g., cytokines), abundant extracellular matrix (ECM), and their various cross talk networks; in other words, intercellular or extracellular interaction networks in the tumor microenvironment usually play vital roles in both tumor initiation and progression. Specifically, the formation and progression of the cancer cell, as well as metastasis and chemoresistance, are related to the tumor microenvironment. For example, tumor cells and inflammatory cells can produce some cytokines, like tumor necrosis factor (TNF)-α, which can promote tumor malignant progression through the induction of NF-κB–dependent antiapoptotic molecules.[19] In other words, effective methods of modulating the tumor microenvironment could be a new mode of cancer therapy. Therefore, as an effective antitumor bioactive substance, resveratrol can modulate the tumor microenvironment via multiple pathways (Fig. 1).

Desmoplasia, a dominant characteristic of the pancreatic ductal adenocarcinoma (PDAC) tumor microenvironment, is induced by activation of pancreatic stellate cells (PSCs), which synthesize and secrete large amounts of ECM, as well as other factors, such as cytokines and growth factors, which can promote fibrosis and accelerate tumor growth.[20] Tsang *et al.*[21] and Lin *et al.*[22] demonstrated that resveratrol can suppress the activation of PSCs, and the suppressive effects are associated with a decrease in NF-κB activation and Akt phosphorylation. The activated PSCs exhibit tumor-promoting effects via complicated interactions with pancreatic cancer cells and other cellular or noncellular components, as well as the fibrosis in PDAC tumor microenvironments. We speculated that PSCs or other cancer-associated fibroblasts (CAFs) may have a marked influence on promoting cancer cell proliferation and invasion through PDGF/PDGFR, stromal-derived factor-1/CXCR4, the IGF-1/IGF1R signaling pathway, and MMP-2/9 secretion, and these promotion effects could be reversed by resveratrol treatment.[23–25]

In addition, another prominent characteristic of the tumor microenvironment is increased levels of immune or inflammation-related cells and factors, such as lymph cells, granulocytes, macrophages, cytokines, and adhesion molecules. For instance, it has been proved clearly that at least 25% of malignant tumors are induced or worsened by an inflammatory environment. Inflammation, in particular chronic inflammation, has been shown to play a crucial role in infection, diabetes mellitus, and cancer.[26] Although the mechanisms of these are still not yet clear, we can hypothesize that intricate inflammatory or immunological reaction in local tumor microenvironments, as well as throughout the body, has key roles in tumor development. During these processes, inflammation or immunity results from complex responses that involve many molecular and cellular events and the intricate interactions among innate and adaptive cells, such as lymphocytes, dendritic cells, and macrophages, as well as cytokines secreted by them or other nonimmune cells (e.g., cancer cells or vascular endothelial cells) in the tumor microenvironment as a consequence of cell–cell interactions.[27] Accumulating evidence indicates that resveratrol may play an important anti-inflammatory role in the tumor microenvironment. One of the possible mechanisms for its protective activities is downregulation of inflammatory responses, including inhibition of synthesis and release of proinflammatory mediators, such as IL-1β, IL-6, and TNF-α,[28] and increased expression of anti-inflammatory factors like IL-10,[29] modification of eicosanoid synthesis, or inhibition of enzymes, such as cyclooxygenase-1 (COX-1) or COX-2, which are responsible for the synthesis of proinflammatory mediators through the inhibitory effects of resveratrol on transcription factors like NF-κB or AP-1. Moreover, resveratrol also showed an ability to inhibit some activated immune cells, such as T cells, B cells, and macrophages through the CD28/CTLA-4 and CD80 costimulatory pathway.[30] CD28 is expressed on resting T cells and can be engaged by either CD80 or CD86 on antigen-presenting cells (APCs), leading to the activation of resting T cells. This costimulation leads T cells to increase the production of growth factor and increase cell survival signals. CD28 and CTLA-4 are both expressed on activated T cells. Engagement of CTLA-4 on CD80 or CD86 on APCs decreases T cell proliferation, growth factor production, and cell cycle progression. Resveratrol suppressed the activity of T and B cells and macrophages via the following mechanisms: inhibition of proliferation of T cells and secretion of IFN-γ and IL-4, suppression of proliferation of B cells and production of IgG1 and IgG2a isotypes, suppression of proinflammatory cytokines (IL-1, IL-6, and TNF-α) but upregulation of anti-inflammatory cytokine IL-10, and downregulation of expression of CD28 on $CD4^+$ T cells and CD80 on macrophages.[30] Taken together, these data suggest that resveratrol may be used to modulate the immunological reaction in tumor microenvironment.

Tang *et al.*[31] demonstrated that resveratrol induced nuclear accumulation of COX-2 and facilitates p53-dependent apoptosis in human breast cancer cells. Additionally, tumor vessels and vascular endothelial cells are one of the most essential parts of tumor microenvironment. Folkman[32] first presented the hypothesis that tumor growth depends on angiogenesis in 1971. From then on, accumulating data have revealed that angiogenesis facilitates tumor progression via delivering oxygen and nutrients to cancer cells and other cells in the tumor microenvironment, exacerbating tumor local invasion or metastasis and increasing various immune or inflammatory elements (e.g., cytokines, IL-1, VEGF, and MMPs), CAFs, and other cellular or noncellular elements, which further contribute to tumor progression, metastasis, and chemoresistance when they infiltrate into the tumor microenvironment.[33–35] Hence, angiogenesis in the tumor microenvironment is becoming a promising therapeutic target in cancer therapy, and Garvin *et al.*[36] demonstrated that resveratrol can inhibit tumor angiogenesis in breast cancer xenografts. Furthermore, Bishayee *et al.*[37] showed that resveratrol impaired VEGF expression through downregulation of HIF-1α, which may reduce angiogenesis during hepatocarcinogenesis. More directly, resveratrol can play an efficient role in antiangiogenesis by affecting the growth of capillary endothelial cells *in vitro* and new blood vessels growth *in vivo*.[38]

In conclusion, resveratrol plays a significant role in the treatment of cancer through modulating the tumor microenvironment via several modes (Fig. 2) for which the specific mechanisms still need to be determined. Well-designed clinical trials are urgently needed as well.

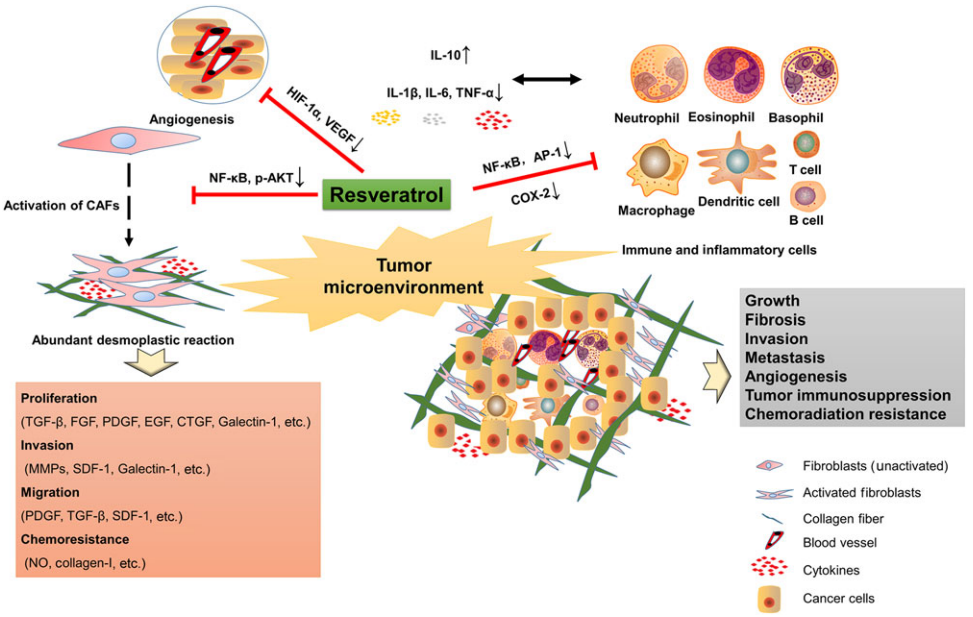

Figure 2. The effects of resveratrol on the tumor microenvironment. The tumor microenvironment consists of various cellular components (e.g., fibroblasts, immune cells, and vascular endothelial cells), multitudinous factors (e.g., cytokines), and abundant ECM. Resveratrol suppresses the activation of cancer-associated fibroblasts by inhibiting the NF-κB and AKT pathway to inhibit the proliferation, invasion, migration, and chemoresistance of cancer cells. Resveratrol exhibits anti-inflammatory activity by inhibiting COX-2, the core of inflammation, and decreasing the secretion of proinflammatory factors, such as IL-1β, IL-6, and TNF-α, and increasing anti-inflammatory factors like IL-10, inhibition of transcriptional factor NF-κB or AP-1, and inhibition of activated immune cells, such as T cells, B cells, and macrophages. Resveratrol impairs VEGF expression through downregulation of HIF-1α, and this may cause a reduction of angiogenesis.

Resveratrol sensitizes cancer cells to chemotherapy

To date, tumor therapy resistance has become a serious problem worldwide. The search for more effective treatments is still ongoing. Researchers have tried to determine the mechanisms responsible for drug resistance, which may include tumor cell-intrinsic mechanisms, such as modulation of tumor angiogenesis, proliferation, metastasis, and invasion and activation of antiapoptotic signaling pathways; and cell-extrinsic mechanisms, such as the tumor microenvironment, the mesenchyme compartment, and tumor immunology.

The effects of many herbal medicines against drug resistance have been reported in multiple cancer types. Resveratrol was assessed on various types of cancers as a chemotherapy sensitizer, including pancreatic cancer,[39] breast cancer,[40] and colon cancer.[41] The mechanisms by which resveratrol chemosensitizes cancer cells include inhibition of tumor cell proliferation, metastasis, and angiogenesis and induction of tumor cell apoptosis through the inhibition of related signaling pathways, such as SIRT1, the STAT3 signaling pathway, the Hh signaling pathway, the AMPK/YAP pathway, and the PTEN/PI3K/AKT and NF-κB signaling pathway.[15,42–45] Resveratrol enhanced the cytotoxicity of anticancer agents through promoting S phase cell cycle arrest accompanied by a significant decrease in levels of proteins involved in drug resistance, such as MRP1, LRP, GST, and BCL-2, as well as topoisomerase II, in resveratrol treatment groups compared with controls in bladder cancer cells.[46] Sun *et al.* found that resveratrol induced cancer cell apoptosis, which was associated with mitochondrial dysfunction, ROS elevation, and intracellular drug accumulation via inhibition of chemoresistance-related proteins. Overexpression of HER2, a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family, has been shown to play a significant role in breast cancer, and HER2 has become an important biomarker and a potential target of breast cancer therapy. Single-agent docetaxel can induce HER-2–mediated

resistance to cell death via phosphorylation of Akt and activation of Bad; MAPK signaling pathway (ERK, JNK, and P38) phosphorylation; and AP-1, Bcl-2, and XIAP upregulation, which can be significantly inhibited by resveratrol. These results demonstrate that resveratrol could serve as a chemosensitizer in docetaxel chemotherapy by targeting HER2 and blocking its downstream signaling pathways, such as the Akt and MAPK pathways.[47] Resveratrol prevents epithelial–mesenchymal transition (EMT) of gastric cancer and functions as a novel sensitizer to reverse docetaxel resistance via the PTEN/Akt signaling pathway. Docetaxel–resveratrol combined treatment provides a promising future for gastric cancer patients to postpone drug resistance and prolong survival.[45] Resveratrol can induce S phase arrest, and the combination of 5-fluorouracil and resveratrol can induce cell apoptosis significantly through elevation of levels of cleaved poly(ADP-ribose) polymerase (PARP), activated caspase-3, and p53 proteins and the Bax/Bcl-2 ratio.[48]

In many cancers, the cytotoxicity of chemotherapeutic agents is largely attributed to induction of cell apoptosis. However, it has been widely acknowledged that aberrant NF-κB activation could induce cell proliferation, angiogenesis, and invasion/metastasis and is closely associated with chemoresistance.[49] Moreover, NF-κB activation could upregulate the levels of some antiapoptotic genes, including TNF receptor–associated factor 1(TRAF1), TRAF2, Bcl-2 family members, c-IAP1, and c-IAP.[50] Elevated NF-κB activity has also been demonstrated to play a vital role in Kras-induced pancreatic cancer progression and to help tumor cells survive gemcitabine treatment.[51,52] Resveratrol–temozolomide combined treatment reverses the chemoresistance of glioblastoma cells by reducing NF-κB activity and nuclear translocation, which can be abolished by recombinant NF-κB subunit p65, suggesting that the underlying mechanisms of NF-κB are regulated by resveratrol in chemosensitization.[43]

Effects of resveratrol on cancer stem cell–induced chemoresistance

Cancer stem cells (CSCs) are a subgroup of cancer cells that have characteristics associated with normal stem cells. CSCs may generate tumors through the stem cell processes of self-renewal and differentiation into multiple cell types, cause relapse and metastasis by giving rise to new tumors, and add a new level of complexity to therapeutic failure. Conventional chemotherapies usually kill differentiated or differentiating cells that constitute most of the tumor and do not generate new cells, while a population of CSCs could survive and cause relapse. CSCs play an important role in various prosurvival mechanisms against chemotherapy, such as elevated apoptosis resistance, DNA repair efficiency, drug-efflux pumps, detoxification enzyme expression, and quiescence.[53] Therefore, development of specific therapies targeting CSCs could improve cancer patients' survival time and quality of life, especially for patients with distant metastasis. Resveratrol may sensitize CSCs to chemotherapy via suppressing CSC self-renewal pathways, including the Wnt/β-catenin, notch, and HH signaling pathway.[54] Cell viability, proliferation, and motility of glioma stem cells are inhibited after resveratrol treatment, which may function through modulating the Wnt signaling pathway and its downstream molecules, such as c-Myc and β-catenin. In the meantime, TWIST1 and SNAIL1, two EMT markers, are downregulated.[55] A combination of resveratrol and grape seed extract induces apoptosis in colon CSCs via elevated p53, cleaved PARP, and altered Bax/Bcl-2 ratio.[56] In breast CSCs, resveratrol significantly reduced cell viability and mammosphere formation, followed by induction of apoptosis in cancer stem-like cells. This inhibitory effect of resveratrol is accompanied by a significant reduction in lipid synthesis,which is caused by downregulation of the fatty acid synthase gene followed by upregulation of proapoptotic genes *DAPK2* and *BNIP3*.[57]

Resveratrol sensitizes cancer cells to radiotherapy

Resveratrol enhances radiosensitivity and has synergistic antitumor effects both *in vitro* and *in vivo*. In general, combined resveratrol and ionizing radiation cancer treatment significantly increases tumor cell autophagy and apoptosis,[58] reduces the repair of DNA damage,[59] causes premature senescence partly via increasing DNA double-strand breaks, and markedly upregulates ROS production, which can be attenuated by the ROS scavenger *N*-acetylcysteine.[60] Resveratrol functions as a radiation sensitizer in melanoma via decreasing cyclin B, cyclin D, Cdk2, and Cdk4 expression and inducing proapoptosis effects mediated by FLIP, Bcl-2, and survivin

downregulation,[61] and sensitizes nasopharyngeal cancer cells to ionizing radiation by inhibiting E2F1 and p-AKT *in vitro*. Furthermore, resveratrol combined with radiation therapy significantly reduces tumor volume and weight compared with single treatment *in vivo*[62] and increases apoptosis and autophagy in glioma xenografts of a nude mouse model.[59] However, the combination therapy has little effect on p-AKT expression in prostate cancer, whereas the expression of p-H2A.X, a marker for senescence, is increased,[63] indicating that different mechanisms are involved, despite similar synergistic tumor-killing effects among numerous cancer types.

Apart from inducing the death of several cancer cell lines synergistically with radiation, resveratrol may be used as a radioprotective agent to reduce the adverse effects induced by radiotherapy. Radiation damages cells via direct ionization of the atoms within DNA and other cellular molecules and by indirect effects mediated through free oxygen radicals. Irradiation-associated ROS production, however, occurs not only in cancer cells, but also in healthy tissues. Irradiation of healthy tissues during the course of therapeutic radiation can result in a range of side effects, including self-limited acute toxicities, mild chronic symptoms, and severe organ dysfunction, including xerostomia (dry mouth), mucositis, dental carries, difficulty swallowing, and eventually inadequate feeding. An animal study was carried out in rats that were exposed to total-body irradiation 24 h after the resveratrol treatment. The results showed that antioxidant glutathione levels were significantly increased, and the tissue activities of malondialdehyde (MDA) in both the parotid and submandibular glands were significantly reduced by high doses of resveratrol treatment (100 mg/kg).[64] Adhami *et al.*[65] examined the mechanisms of resveratrol-mediated protection of human skin keratinocytes from the adverse effects of UVB radiation. This study demonstrated that UVB (40 mJ/cm^2) exposure led to a significant activation of NF-κB in normal human epidermal keratinocytes, whereas pretreatment with resveratrol resulted in a significant dose- and time-dependent downmodulation of UVB-induced inhibitory κB kinase/IκBα–mediated NF-κB activation. Resveratrol counteracts γ-irradiation radiotherapy-induced premature ovarian failure via activation of PPAR-γ and SIRT1, attenuating radiation-triggered inflammatory process through decreasing NF-κB and PARP-1 expression, which led to the expression of inflammatory markers, including IL-6, IL-8, and visfatin mRNA levels, as well as inducible nitric oxide synthase and COX-2 protein expression with a concomitant reduction in IL-10 mRNA levels.[66] Another animal study showed that radiation caused a reduction of saliva secretion, salivary amylase activity, and SOD expression and an elevation of MDA in mice. Administration of resveratrol reversed the reduction of saliva secretion induced by irradiation and restored salivary amylase and SOD activity. In addition, resveratrol inhibited increases in transforming growth factor β1 expression induced by radiation.[67] This result showed that resveratrol may be used as a radioprotective agent to reduce the adverse effects, including xerostomia and mucositis, induced by radiotherapy. Furthermore, resveratrol reduced radiation-induced chromosome aberration frequencies in mouse bone marrow cells.[68] These results showed that resveratrol may be used as a radioprotective agent before radiotherapy. However, for therapy of radioresistant malignant cells, the dose and content of resveratrol and ionizing radiation should be applied meticulously in order to achieve an appropriate therapeutic effect with less toxicity to normal cells.

Taken together, these data demonstrate that resveratrol can be used as an anticancer drug for patients that increases sensitivity to chemotherapy and radiotherapy and reduces adverse effects.

The clinical applications of resveratrol require further investigation

Safety of resveratrol

In order to investigate the safety and pharmacokinetics of resveratrol before its application in cancer prevention and therapy, 40 healthy volunteers were recruited and divided into four groups that ingested resveratrol at a dose of 0.5, 1.0, 2.5, or 5.0 g, respectively, for 4 weeks (Table 1).[69] Resveratrol was rapidly absorbed, and it yielded peak concentration at nearly 1 h postingestion. The plasma elimination half-life of resveratrol varied between 4.77 and 9.70 hours.[69] The majority of adverse events were mild gastrointestinal discomfort, including diarrhea, nausea, flatulence, and abdominal discomfort, and were mainly reported in participants with higher doses of resveratrol (2.5 and 5.0 g).[69] Weight loss was not observed in any of the participants, and

Table 1. Clinical trials of resveratrol in healthy volunteers or patients with malignant disease

Author	Purpose	Participants	Dose	Results
Brown *et al.*[69]	To assess its safety and pharmacokinetics	40 healthy volunteers	0.5, 1.0, 2.5, or 5.0 g	Resveratrol was safe, but the 2.5 and 5 g doses caused mild-to-moderate gastrointestinal symptoms
Patel *et al.*[70]	To measure concentrations of resveratrol and its metabolites in colorectal tissue of humans who ingested resveratrol	20 patients with histologically confirmed colorectal cancer	0.5 or 1.0 g	Daily oral doses of resveratrol at 0.5 or 1.0 g produce levels in the human gastrointestinal tract of an order of magnitude sufficient to elicit anticarcinogenic effects
Howells *et al.*[74]	To assess the safety, pharmacokinetics, and pharmacodynamics of micronized resveratrol (SRT501)	9 patients presenting with confirmed stage IV colorectal cancer and hepatic metastases	5.0 g	SRT501 was found to be well tolerated, and it increased apoptosis in malignant hepatic tissues
Zhu *et al.*[71]	To assess the effect of resveratrol on DNA methylation and prostaglandin expression in humans	39 adult women at increased breast cancer risk	5 or 50 mg	Resveratrol decreased the methylation of the tumor suppressor gene *RASSF-1*α
Chow *et al.*[73]	To determine the effect of resveratrol on drug and carcinogen metabolizing enzymes	42 healthy volunteers	1.0 g	Resveratrol can modulate enzyme systems involved in carcinogen activation and detoxification, which may be one mechanism by which resveratrol inhibits carcinogenesis
Popat *et al.*[75]	Phase II study of resveratrol (SRT501) with bortezomib for patients with relapsed and/or refractory multiple myeloma	24 patients who had relapsed or were refractory to at least one prior therapy	5.0 g	Resveratrol showed an unacceptable safety profile and minimal efficacy in patients with relapsed or refractory multiple myeloma

all of them presented normal performance status during the study period.[69] In order to investigate the safety of resveratrol, it was verified in patients with resectable colorectal cancer.[70] Patients ingested 0.5 or 1.0 g resveratrol daily for 8 days before surgery. Similar to the previous report,[69] it was well tolerated in patients at doses of 0.5 or 1.0 g, and there were no reported resveratrol-related adverse events.[70] These data suggest that intake of resveratrol is relatively safe, despite the incidence of mild-to-moderate gastrointestinal discomfort.

Resveratrol showed promising effects in cancer prevention and treatment

In order to verify the role of resveratrol in cancer prevention and treatment, 39 adult women with increased breast cancer risk were recruited to investigate the cancer-preventive effects of resveratrol (Table 1). After intake of resveratrol or placebo daily for 12 weeks, mammary ductoscopy specimens from all of the participants were collected and analyzed for methylation of p16, CCND2, RASSF-1α, and APC. This study revealed that ingestion of resveratrol decreased methylation of RASSF-1α,[71] which is implicated in cell cycle regulation, apoptosis, and tumorigenesis.[72] A previous clinical study suggested that resveratrol can modulate enzymes involved in carcinogen activation and detoxification, and this may be one of the mechanisms by which resveratrol inhibits carcinogenesis.[73] In colorectal cancer, resveratrol reduced immunostaining of Ki-67, which is exclusively expressed in proliferating cells and used as a maker of cell growth,[70] and it promoted apoptosis, which was reflected by increased

immunostaining of cleaved caspase 3.[74] However, whether intake of resveratrol can inhibit cancer progression or prolong overall survival of patients remains to be determined. A phase II study was performed to evaluate the therapeutic effect of resveratrol in patients with relapsed and/or refractory multiple myeloma (MM).[75] Twenty-four patients who had relapsed MM or were refractory to at least one prior therapy were enrolled in the phase II clinical trial of SRT501, a micronized form of resveratrol, with or without bortezomib.[75] However, this phase II study showed minimal efficacy and an unacceptable safety profile of SRT501 (5.0 g) in patients with relapsed/refractory MM.[75] We conclude that resveratrol requires further clinical evaluation.

Conclusions and therapeutic perspectives

On the basis of previous experimental and clinical trials of resveratrol and the molecular characteristics of resveratrol, we propose that resveratrol could be applied under the following possible therapeutic strategies. First, resveratrol could be used as a neoadjuvant chemotherapy agent before surgery to decrease tumor volume owing to its ability to inhibit cancer cell proliferation and induce apoptosis. Second, resveratrol could be used as an adjuvant chemotherapy drug to inhibit the early invasion and metastasis of cancer after surgery. Third, resveratrol could be used as a radiotherapy or chemotherapy sensitization agent with chemotherapy agents, such as capsaicin, docetaxel, DOX, gemcitabine, and temozolomide, because resveratrol may improve their anticancer effects. Fourth, resveratrol could be used in cancer prevention for people at high risk of cancer. Fifth, resveratrol could be used as a radioprotective agent to reduce adverse effects, including xerostomia and mucositis, induced by radiotherapy. Moreover, the tumor microenvironment plays a key role in tumor progression. Tumor cells, CAFs, and inflammatory cells are novel and important members of the tumor microenvironment and have close interactions via cellular or noncellular components. Resveratrol could be used as a therapy agent targeting the complicated interactions in the tumor microenvironment to improve cancer treatment. Although resveratrol has showed some promising effect in cancer treatment *in vitro* and *in vivo*, we still need more clinical trials to prove its safety and efficacy in cancer treatment.

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Competing interests

The authors disclose no potential competing interests.

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