



Resveratrol as a modulatory of apoptosis and autophagy in cancer therapy

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Abstract

Cancer is one of the leading causes of death, with a heavy socio-economical burden for countries. Despite the great advances that have been made in the treatment of cancer, chemotherapy is still the most common method of treatment. However, many side effects, including hepatotoxicity, renal toxicity, and cardiotoxicity, limit the efficacy of conventional chemotherapy. Over recent years, natural products have attracted attention as therapeutic agents against various diseases, such as cancer. Resveratrol (RES), a natural polyphenol occurring in grapes, nuts, wine, and berries, exhibited potential for preventing and treating various cancer types. RES also ameliorates chemotherapy-induced detrimental effects. Furthermore, RES could modulate apoptosis and autophagy as the main forms of cancer cell deaths by targeting various signaling pathways and up/downregulation of apoptotic and autophagic genes. This review will summarize the anti-cancer effects of RES and focus on the fundamental mechanisms and targets for modulating apoptosis and autophagy by RES.

Keywords Cancer · Resveratrol · Apoptosis · Autophagy · Cancer cell death

Introduction

Besides cardiovascular diseases, cancer is the leading cause of death worldwide [1]. The global incidence and mortality of cancer are increasing, leading to a heavy economic burden to both families and society. It is reported that the incidence of cancer was increased from 18.1 to 19.3 million between 2018 and 2020, and cancer deaths reached 10.0 million from 9.6 million in this period [2, 3]. Despite remarkable efforts to develop novel and more effective approaches, including surgery, radiotherapy, immunotherapy, and suicide genes, chemotherapy as cytotoxic agents are still predominantly used in clinical practices. However, the resistance of tumors to chemotherapeutic agents and their side effects, such as hepatotoxicity and cardiotoxicity, limit their efficiency [4].

Different natural products, including berberine, curcumin, ginsenosides, artemisinins, (-)-epigallocatechin-3-gallate (EGCG), indole-3-carbinol (I3C), triptolide, ursolic acid (UA), oridonin, wogonin, cepharanthine, tanshinones, silibinin, and cucurbitacins, were identified with potent anti-cancer properties, such as anti-angiogenic, anti-metastatic, immune regulatory, multidrug resistance (MDR) reversal, pro-apoptotic, and autophagy regulatory [5]. The natural products attracted attention owing to their low costs, low toxicity, affordability, and multi-targeting properties that modulate several signaling pathways [6, 7]. Resveratrol (RES), a natural polyphenol, is presented in various plants, such as grapes, nuts, wine, and berries [8]. Indeed, RES is a phytoalexin that plants produce in response to environmental stress, such as metallic salts and UV irradiation, or pathogenic attacks, such as bacterial and fungi infections [9]. It has gained extensive attention owing to numerous biological activities in controlling heart diseases, autoimmune disorders, arthritis, and cancer. The chief anti-cancer activity of RES is due to its chemopreventive effect as well as interfering with signaling pathways regulating cell proliferation, inflammation, metastasis, apoptosis, and autophagy [10]. Owing to the preventive and therapeutic effects of RES against various cancers, this review will focus on the beneficial effects of this natural product, with emphasis on its

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modulatory effects on two vital processes during cancer development and treatment, apoptosis and autophagy.

Resveratrol and its anti-cancer effects

Although RES or 3,5,4-trihydroxystilbene firstly was isolated from *Veratrum grandiflorum* root in 1939 [11], it was also identified as one of the active constituents of *Polygonum cuspidatum*, a plant in Japanese and Chinese traditional medicine, in 1963 [12]. Structurally, due to a double “bridge”, RES has cis and trans isomers which the trans form is more stable than the cis one [13]. Although the half-life of RES in the plasma is 8–14 min, its metabolites circulate in the plasma for about 9.2 h [14]. RES could bind to some proteins in the plasma, such as serum albumin and lipoproteins. Following oral administration of RES, it could accumulate in various tissues, such as the liver, intestine, stomach, and organs with diseases, such as cancers [15]. The oral uptake of RES leads to its metabolization into sulfate and glucuronide conjugates, resulting in its low concentration in the plasma [16]. To pass the cell membrane and its intracellular functions, RES could be absorbed via passive diffusion or transport by ion channels [17, 18].

In 1997, Jang et al. found that RES could inhibit carcinogens at three stages: initiation, promotion, and progression [19]. It has been shown that RES has a synergistic effect in combination with chemotherapy agents. For instance, Bostan et al. demonstrated that RES could act as an adjuvant of cisplatin against head and neck cancer (HNSCC) cells and enhance the cytotoxicity effects of cisplatin on induction of apoptosis and cell-cycle arrest [20]. RES could also reverse cancer cells' resistance to chemotherapy agents

[21]. Yang et al. found that RES could resensitize glioma cells to temozolomide (TMZ) by inhibiting the activation of the Wnt pathway and downregulation of *O*⁶-methylguanine-DNA methyltransferase (MGMT) expression [22]. Mechanistically, MGMT determines the resistance of tumor cells to TMZ by removing the added methyl group by TMZ from O-6 positions of guanine [23]. In another study, Jin et al. investigated the effect of RES and doxorubicin (DOX) on the epithelial-mesenchymal transitions (EMTs) and chemoresistance in adriamycin (ADR)-resistant MCF-7/ADR breast cancer cells. They demonstrated that the combination of RES with DOX remarkably inhibited the proliferation and metastasis of MCF-7/ADR cells. RES could reverse the EMT process in MCF-7/ADR cells by promoting the expression of silent mating type information regulation 2 homologue 1 (SIRT1) and modulating the SIRT1/ β -catenin pathway. The upregulated SIRT1 induced the degradation of β -catenin through the promotion of ubiquitin-mediated proteolysis [24]. Many studies have demonstrated that the SIRT1 is a major target of RES and its upregulation is essential for anti-cancer activities of RES [25]. Moreover, RES could downregulate the phosphorylation and acetylation of NF- κ B, resulting in impairments in elements that contribute to tumor proliferation, invasion, and metastasis [25, 26]. For instance, Tino et al. indicated that treating ovarian cancer cell lines with RES and acetyl-RES could inhibit cell growth by decreasing NF- κ B levels and its downstream gene, vascular endothelial growth factor (VEGF) [27]. VEGF is a major growth factor involved in the angiogenesis process that provides nutrients and oxygen to tumor cells for supporting their growth [28]. Table 1 summarizes the effect of RES on the anti-cancer efficacy of other therapeutic agents.

Table 1 The combination of resveratrol and other therapeutic agents in cancer therapy

Resveratrol (dose) (μ M)	Therapeutic agent	Cancer	Pathway	Ref
10	TMZ (100 μ M)	Glioblastoma	MPK-TSC-mTOR	[29]
25	5-FU (10 μ M)	CRC	STAT3/Akt	[30]
15	DTX (1 nM)	Breast	HER-2–Akt	[31]
20	DDP (1 μ g/ml)	Gastric	PERK/eIF2 α /ATF4/CHOP	[32]
20–22	DTX (10 nM)	Prostate	p53/ p21 ^{WAF1/CIP1} and p27 ^{KIP1}	[33]
50	Rapamycin (100 nM)	Thyroid	PI3K/Akt/mTOR	[34]
0.1–10	Pacl (1–100 nM)	Breast	E2/ER α /NGB	[35]
100	MET (20 mM)	Pancreatic	VEGF-B	[36]
100	Rapamycin (20 nM)	Bladder	Akt/mTOR	[37]
100	5-FU (10 μ M)	Colon	STAT3/Akt	[38]
50	DHA (25 μ M)	Liver, Breast	DLC1/TCTP/Cdc42	[39]
50	SAL (2.5)	Breast	JNK-p38-MAPK	[40]

TMZ temozolomide; 5-FU 5-fluorouracil; CRC colorectal cancer; DTX docetaxel; DDP cisplatin; PERK PRKR-like ER kinase; ATF4 activating transcription factor 4; CHOP CCAAT/enhancer binding protein homologous protein (CHOP); Pacl paclitaxel; E2/ER α /NGB 17 β -estradiol/estrogen receptor α /neuroglobin; MET metformin; VEGF vascular endothelial growth factor; DHA dihydroartemisinin; SAL salinomycin

In addition to synergistic effects with chemotherapy agents, RES also reduces the side effects related to chemotherapy. It has been shown that RES could attenuate chemotherapy-induced cardiotoxicity through various pathways. For instance, Tian et al. demonstrated that treatment of rats with DOX impaired cardiac function and increased the levels of creatine kinase isoenzyme (CK-MB) and lactate dehydrogenase (LDH) in the serum. DOX treatment also led to an increase in apoptosis and cell death in cardiomyocytes and a decrease in the expression of VEGFB- compared to the control group, whereas the combination of RES with DOX notably attenuated the cardiotoxicity effects of DOX [41]. In another study, Zhang et al. encapsulated RES into a solid lipid nanoparticle (SLN) to investigate its inhibitory effects on DOX-induced cardiotoxicity. They concluded that the RES-loaded SLN with 271.13 nm particle size not only solved the poor solubility of RES, but also improved heart functions, such as heart rate, and reduced cardiotoxicity induced by DOX administration [42]. RES also can attenuate chemotherapy-induced hepatotoxicity. Recently, Alhusaini et al. showed that twice-weekly administration of DOX for 5 weeks could induce hepatotoxicity in rats, which was demonstrated through the elevation of the levels of alanine aminotransferase (ALT), hepatic malondialdehyde (MDA), transforming growth factor- β 1 (TGF- β 1), and inflammatory cytokines, as well as the structural changes in the liver and downregulation of SIRT1 and endogenous glutathione (GSH). The liposomal RES prevented liver injury via controlling inflammation, oxidative stress, and fibrosis [43]. The other study revealed that pre-treatment of rats with RES or RES + coenzyme Q₁₀ could remarkably mitigate paclitaxel-induced hepatotoxicity [44]. In addition to the mentioned protective effects, RES also ameliorates other detrimental effects induced by chemotherapy (Table 2).

Apoptosis

Cancer development and progression stem from uncontrolled cell differentiation and growth and impairment in the apoptosis process. Apoptosis is an organized process involving cellular proteins and signals transduction cascades. Based on their role, apoptotic proteins are classified into two groups: pro-apoptotic, including caspases and Bcl2 family, and anti-apoptotic proteins. Caspases belong to the cysteine proteases family with 14 proteins which are divided into three subtyped according to their function and structure: (1) inflammatory caspases, including caspases-1, -4, -5, -11, -12, -13, and -14; (2) initiator caspases in apoptotic pathways, including caspases -2, -8, -9, and -10; and (3) effector caspases, including caspases -3, 6-, and -7 [56, 57]. The Bcl2 family proteins, which are localized in the outer membrane of the mitochondria, act as both pro-apoptotic (BAX, BAK, BID, BAD, BIM, BIK, HRK, BMF, PUMA, NOXA, etc.) and anti-apoptotic (BCL-2, MCL-1, BCL-X_L, BFL-1/A1, and BCL-W) proteins [58].

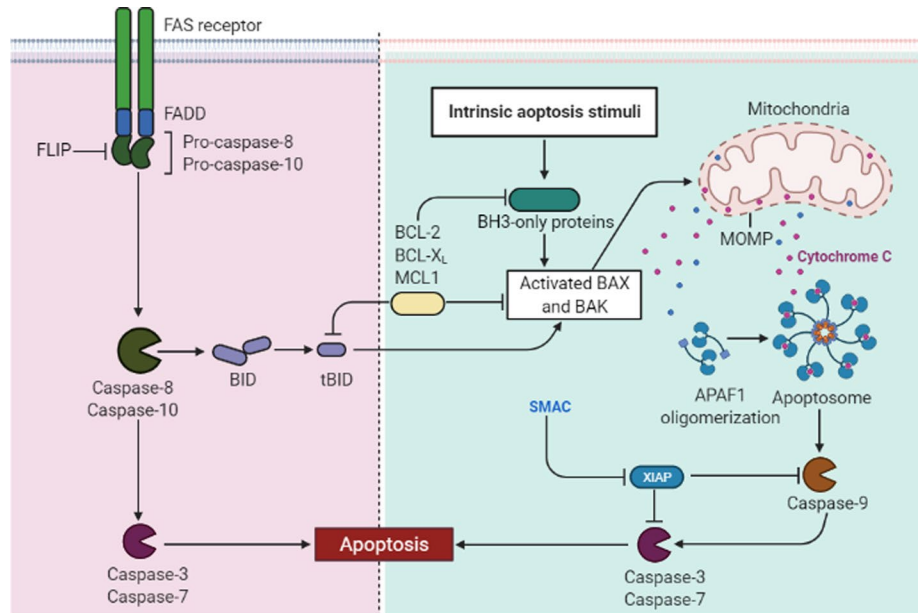
Apoptosis occurs through two main pathways: intrinsic and extrinsic pathways (Fig. 1). The intrinsic pathway begins with mitochondrial outer membrane permeabilization (MOMP) and the release of cytochrome *c* into the cytoplasm, which is activated with pro-apoptotic proteins of the Bcl2 family. The released cytochrome *c* binds to apoptotic protease activating factor 1 (Apaf-1) and procaspase-9 to form the apoptosome complex. The cleavage and activation of procaspase-9 in the apoptosome complex lead to the activation of caspase-3 and subsequently apoptosis [59]. Following cytochrome *c* release from the mitochondria, the inhibitors of apoptosis proteins (IAP), such as IAP1, IAP2, and XIAP, negatively regulate caspase-3 activation [60]. On the other hand, proteins that release together with

Table 2 The effects of resveratrol on the toxicities induced by chemotherapeutic agents

Chemotherapeutic agent	Cytotoxic effect	RES effect	Ref
DDP	Ovarian and uterine toxicity	↓Oxidative stress, apoptosis inflammation	[45]
DDP	Testicular damage	↓Oxidative stress, apoptosis inflammation	[46]
Pacl	Neuropathic pain	↓Apoptosis, inflammation	[47]
DDP	Ovarian damage	↓Inflammation, apoptosis	[48]
CyP	Multi-organ toxicity	↓Oxidative stress, inflammation	[49]
MTX	Liver damage	↓Oxidative stress	[50]
DDP	Ototoxicity	↓Apoptosis	[51]
CyP	Ovarian granulosa cell injury	↓Apoptosis, autophagy, oxidative stress	[52]
DOX	Cardiotoxicity	↓Oxidative stress	[53]
DAC	Cognitive impairment	↓Inflammation	[54]
MTX	Hepatotoxicity	↓Lipid peroxidation	[55]

DDP cisplatin; CyP cyclophosphamide; MTX methotrexate; DOX doxorubicin; DAC docetaxel adriamycin and cyclophosphamide

Fig. 1 The intrinsic and extrinsic pathways of apoptosis



cytochrome *c* from the mitochondria, such as Smac/DIABLO and Omi/HtrA2, can facilitate caspase activity and apoptosis by blocking IAPs function [61]. The extrinsic pathway of apoptosis triggers following the binding of death signals to and the activation of death receptors located on the cell membrane. The binding of TNF, FasL, and TRAIL to their cognate receptors, including TNFR, Fas, DR4, and DR5, results in the recruitment of adaptor proteins, such as adaptor molecule Fas-associated death domain (FADD), and caspase-8 and caspase-10, which form the death-inducing signaling complex (DISC) [62]. The activation of initiator caspases, -8 and -10, leads to the activation of effector caspases and cleavage of the pro-apoptotic protein BID, which

is myristoylated and translocated to the mitochondria to contribute to cytochrome *c* release [63]. Due to homology to caspase-8 and -10, FLIP is recruited to the DISC and blocks caspase activation [64] (Fig. 2).

Autophagy

Autophagy is a conserved process from yeast to the man that maintains cellular homeostasis by eliminating dysfunctional proteins and aged or damaged organelles. For his outstanding works on autophagy mechanisms and their impact on health and disease, the Nobel Prize in Physiology or Medicine was

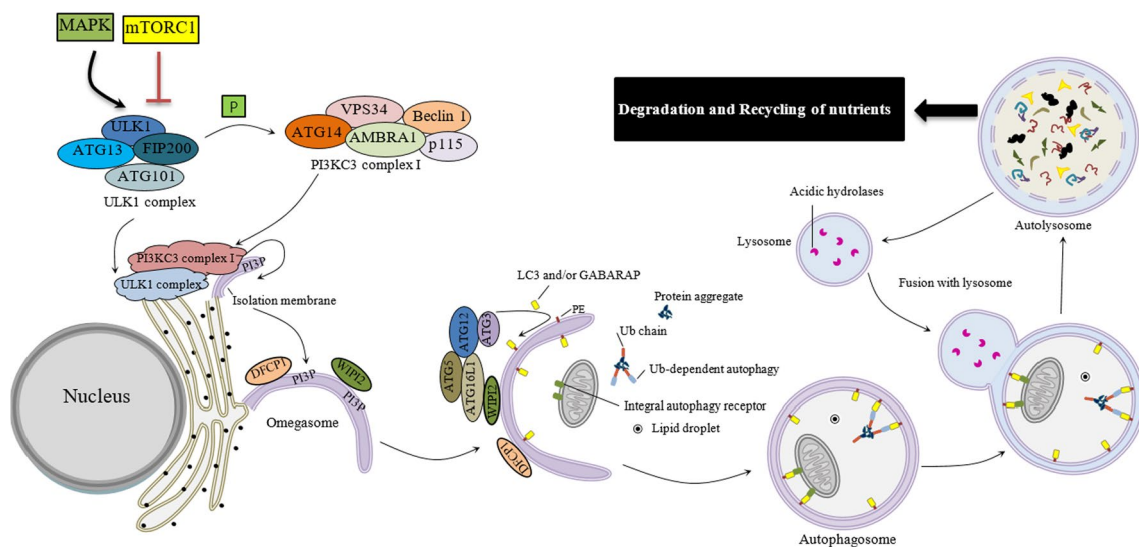


Fig. 2 The molecular mechanism of autophagy

awarded to Yoshinori Ohsumi in 2016 [65]. Three types of autophagy occur in the cell according to their morphology and mechanism: chaperone-mediated autophagy, microautophagy, and macroautophagy, which autophagy usually refers to as macroautophagy [66].

Under nutrient-rich conditions, the mechanistic target of rapamycin complex 1 (mTORC1) in the activated form inhibits autophagy initiation by phosphorylating of autophagy-related protein 13 (ATG13) and blocking its interaction with FIP200 and ULK1. In response to stressful conditions, such as oxidative stress, hypoxia, starvation, and protein aggregation, the ULK1 complex, composed of ULK1, FIP200, ATG13, and ATG101, is activated through dissociation of mTORC1, leading to the phosphorylation of the class III PI3K (PI3KC3) complex and production of phosphatidylinositol-3-phosphate (PI3P) at a characteristic endoplasmic reticulum structure, called the omegasome [67]. PI3P recruits proteins containing the PI3P-binding domain, including DFCP1 and WIPIs, to the omegasome. WIPI2 binds to ATG16L1 and recruits the ATG12~ATG5-ATG16L1 complex, which catalyzes the conjugation of ATG8 proteins, such as LC3 and GABARAPs, to phosphatidylethanolamine (PE). These interactions result in the recruitment of components containing an LC3-interacting region (LIR), and finally, the lipidation, elongation, and closing of the phagophore membrane to form an autophagosome, a double-layered vesicle [68]. After the maturation, the fusion of the autophagosome with the lysosome leads to the degradation of autophagic cargo due to the lysosomal acidic hydrolases. The degraded components are released to the cytoplasm for re-using by cells [69].

It has been shown that autophagy is a dichotomous player in cancer. Autophagy can act as tumorigenesis or tumor-inhibitory element, depending on the cancer type and its stage and genetic context [70]. It can control the quality of organelles and proteins, maintain the stability of the cellular genome, prevent cell injury, inflammation, chronic tissue damage, and inhibit the aggregation and accumulation of oncogenic proteins. These functions of autophagy could suppress tumor initiation, development, proliferation, migration, invasion, and metastases, mainly in the early stages of cancer [71–73]. On the other hand, autophagy could act as a cellular survival, defense, and protective mechanism, reduce DNA damage, maintain mitochondrial function, and sustain tumor growth and survival, leading to tumorigenesis promotion and resistance to therapeutic agents, especially in the late stage of cancer [71, 74].

Resveratrol and apoptosis

It has been shown that the induction of apoptosis and cell-cycle arrest is one of the tumoricidal effects of RES. To induce apoptosis, RES could alter the expression of both

pro-apoptotic and anti-apoptotic proteins. Depending on the RES concentration and cancer cell type, the signaling pathway and the target of RES could be different. In the below, we will discuss the main targets of RES in the induction of apoptosis and its effects on chemosensitization of tumor cells by promoting apoptosis.

Survivin

Survivin, the product of baculoviral inhibitor of apoptosis repeat-containing 5 (*BIRC5*) gene, is the smallest member of the IAP family with a chain of 142 amino acids and a molecular weight of 16.5 kDa [75, 76]. It plays a pivotal role in controlling and regulating cell proliferation, division, and cell cycle. Due to its upregulation in embryos and tumors and weak expression in normal cells, it has been concluded that survivin contributes to rapid cell proliferation and growth [75]. There is evidence that survivin can act as an inhibitory element in apoptosis, both intrinsic and extrinsic pathways. Mechanistically, survivin interacts with the activated form of effector caspases, -3, -7, and -9, and suppresses their cascade and function [77]. In another mechanism, survivin can prevent the activation of caspases by binding to and inactivating Smac/DIABLO [78]. Various therapeutic agents have been developed to target survivin in cancer, such as YM155, LLP3, LY2181308, and shepherdin [79]. The inhibitory effect of RES on survivin also have been demonstrated in various studies. Habibie et al. indicated that RES has cytotoxicity effects on murine and human melanoma cells via inducing apoptosis. The stimulatory effect of RES on apoptosis was due to the inhibition of survivin. Mechanistically, RES diminished survivin expression at the transcriptional level by regulating the STAT3/β-catenin pathway. Furthermore, oral administration of RES (100 mg/kg/day) in a mice model for melanoma showed that RES significantly inhibited tumor growth by reducing survivin expression [80]. In another study, Saha et al. investigated the effect of *trans*-4,4'-dihydroxystilbene (DHS), a RES analog, on melanoma. They showed that DHS could reduce the survival of melanoma cell lines by inducing apoptosis and cell-cycle arrest at G1-phase. RES could also inhibit the metastasis of melanoma cells both in vitro and in vivo, which was demonstrated by repressing the expression of N-cadherin, matrix metalloproteinases-2 (MMP-2), MMP-9, and survivin, as well as reducing melanoma nodules in the lungs [81]. The negative effect of RES on survivin also was reported in gastric cancer cells, which led to induction of apoptosis and cell-cycle arrest at the G0/G1 phase [82]. Moreover, there is evidence that the chemoprotective effects of RES against ultraviolet radiation (UVR)-mediated skin carcinogenesis and its ability to enhance chemosensitivity of tumor cells to chemotherapeutic agents may be associated with the modulation of survivin [83, 84].

p53

It has been shown that the *TP53* gene, a tumor suppressor, is mutated in almost 50% of cancer cells. Under the unstressed conditions, there are very low levels of wild-type p53 in non-transformed cells due to its ubiquitination by the MDM2 and directed for proteasomal degradation. In response to DNA damage, oncogene activation, or other stress stimuli, the activated signaling pathways inhibit MDM2, which leads to an increase in the p53 levels [85]. Although p53 mediates apoptosis through both intrinsic and extrinsic pathways, p53-dependent apoptosis normally follows the intrinsic pathway. Furthermore, most studies revealed that the main contribution of p53 to induction apoptosis is chiefly dependent on transcriptional activity. In this regard, p53 can activate the transcription of pro-apoptotic genes, including PUMA, NOXA, and BAX [86]. In turn, PUMA disassociates p53 from its inactive form, p53-Bcl-X_L complex, by binding to Bcl-X_L in the cytoplasm. The cytosolic p53 can induce BAX oligomerization and then mitochondrial translocation. In addition, mitochondrial p53 promotes BAX and BAK oligomerization, binds to and antagonizes the Bcl-X_L and Bcl-2 anti-apoptotic functions, and forms a complex with cyclophilin D in the inner membrane of mitochondria, resulting in disruption of mitochondrial structure and release of apoptotic factors, such as cytochrome *c* [87, 88]. Targeting and restoring the p53 pathway utilizing peptides and small molecules has been applied in cancer therapy with successful clinical trials [89]. Similarly, RES could induce apoptosis by targeting the p53-mediated pathway [90, 91]. For instance, Li et al. demonstrated that RES could suppress HeLa cell proliferation and enhance apoptosis through the intrinsic and p53 pathways. They showed that treatment of HeLa cells with RES (20 μmol/l) activated caspase – 3 and – 9, upregulated BAX, and downregulated the expression of Bcl-X_L and Bcl-2 proteins. In addition, RES-treated cells exhibited higher levels of p53 protein [92]. In another study, Liu et al. showed that RES could suppress the viability of colorectal cancer cells and enhance the expression of p53 and its target genes, including BAX and PUMA, that play a crucial role in p53-dependent apoptosis. They also indicated that treated cells with RES exhibited upregulation of SET domain-containing lysine methyltransferase 7/9 (SET7/9) [93]. SET7/9 is a positive regulator of p53 that methylates p53 at lysine 372 and increases its stabilization [94]. Wang et al. demonstrated that RES could enhance apoptosis by targeting the HIF-1α/ROS/p53 pathway. They demonstrated that the treatment of prostate cancer cells with RES (50 μM) elevates reactive oxygen species (ROS) concentration, downregulates Bcl2, and upregulates BAX. RES treatment also significantly increased the expression of α-subunit of hypoxia-inducible factor-1 (HIF-1α) and p53 [95]. It has been shown that HIF-1α inhibits p53 degradation

and increases its stability via binding to MDM2 [96, 97]. Another upstream protein in the induction of p53 dependent apoptosis with RES is cyclooxygenase (COX)-2. RES treatment results in phosphorylation and nuclear translocation of ERK1/2 and accumulation of COX-2 in the nuclear, leading to its ability to form complex with p53 and ERK1/2. Subsequently, the phosphorylation of p53 at the Ser-15 (pSer15-p53) induces the expression of anti-proliferation genes of cancer cells. To unveil the mechanism of action, Cheng et al. indicated that sumoylation is pivotal for nuclear accumulation of RES-induced COX-2. Further analyses exhibited that inhibition of COX-2 accumulation in the nuclear as well as sumoylation blockade suppresses RES-induced apoptosis in cancer cells [98].

RES and other therapeutic agents

Moreover, RES could be combined with other therapeutic agents, such as chemotherapy, and enhance their anti-cancer effect by inducing apoptosis. For example, Singh et al. reported that RES enhances the effects of docetaxel (DTX) on prostate cancer cells. The combination of RES and DTX promoted apoptosis via upregulating pro-apoptotic genes, including BAX, BAK, and BID, and downregulating anti-apoptotic genes, including Bcl-X_L, Bcl-2, and MCL-1. The combination regimen also, in turn, induced cell-cycle arrest at the G0/G1 phase by inhibiting the expression of cyclin D1, cyclin E1, CDK4, and inducing Rb hypo-phosphorylation [33]. Rasheduzzaman et al. found that RES could sensitize lung cancer cells to treatment with TRAIL by promoting apoptosis in the p53-independent pathway. They revealed that RES attenuates the resistance to TRAIL via suppressing NF-κB (p65) and enhances TRAIL-mediated apoptosis by inhibiting anti-apoptotic signals [99]. RES can resensitize cisplatin-resistant MCF-7 cells to cisplatin through induction of apoptosis in a p53-dependent pathway. RES induces the phosphorylation of p53 at the Ser-20 in chemoresistant cells and activates the target genes of p53, including BAX and PUMA, leading to apoptosis restoring. Phosphorylation of Ser-15 and -20 enables p53 protein to escape from MDM2-mediated degradation, its stabilization, and apoptosis induction [100]. The other mechanism that RES sensitizes cancer cells to cisplatin stems from its ability to promote apoptosis by inducing the expression of dual-specificity phosphatase 1 (DUSP1) [101]. Mechanistically, the pro-apoptosis property of DUSP1 is associated with its inhibitory effect on p38 MAPK [102]. Furthermore, DUSP1 acts as a mediator of the anti-inflammatory effect of RES and reduces the activation of NF-κB [101]. The synergistic pro-apoptotic effects of RES in combination with cisplatin can be related to its ability to induce apoptosis's intrinsic pathway [103].

Resveratrol and autophagy

The regulatory effect of RES on autophagy has been demonstrated in cancer prevention and treatment [104]. Moreover, RES could induce apoptosis by autophagy. For instance, Miki et al. revealed that the treatment of colon cancer cells with RES could increase both apoptosis and autophagy. Inhibition of RES-induced autophagy with 3-methyladenine reduced apoptosis levels, whereas inhibition of apoptosis increased LC3-II levels did not reduce autophagy. Further analyses exhibited that RES could increase the intracellular levels of ROS, which was correlated to the LC3-II elevation and induction of cleavage of caspase-8 and -3. Thus, the effect of RES treatment on apoptosis induction by autophagy is mediated with ROS in colon cancer cells [105]. Also, RES in combination with cisplatin activated autophagy, whereas autophagy inhibition with 3-methyladenine significantly reduced cisplatin-induced apoptosis [106]. RES can exert its regulatory effects on autophagy through various signaling pathways, transcriptional factors, and cellular targets.

The PI3K/AKT/mTOR pathway

There is accumulating evidence that RES could suppress tumor development and growth by promoting autophagy through the inhibition of the PI3K/AKT/mTOR pathway. For example, Wang et al. indicated the tumoricidal effects of RES on non-small-cell lung cancer (NSCLC) cells. Besides the inhibitory effects on cell proliferation and inducing apoptosis, RES treatment also induced autophagy via upregulating SIRT1. RES increased the expression of LC3 II/I and Beclin1 and reduced p62 expression, an autophagic cargo adaptor protein that recruits organelles and ubiquitinated proteins to the autophagosome. Mechanistically, RES-induced protective autophagy by activating p38-MAPK and inhibiting AKT/mTOR [107]. In another study, Gong and Xia found that RES (100 μ M) could inhibit cell viability, migration, and invasion of melanoma cells, whereas autophagy inhibition reversed the anti-tumor functions of RES. RES treatment also promoted the expression of LC3 II/I and Beclin1 and downregulated p62 expression. They demonstrated that the autophagy induction effect of RES was due to its ability to inhibit the PI3K/AKT/mTOR pathway [108]. Chang et al. studied the anti-tumor activity of RES and its mechanism of action in cisplatin-resistant oral cancer cells. They found that RES treatment (50 μ M) provoked both autophagic and apoptotic cell death of the cancer cell, identified by the formation of autophagic vacuoles, acidic vesicular organelles, and DNA condensation or fragmentation. The

treated cells with RES increased the levels of autophagy proteins, including Atg proteins, LC3-II, PI3K class III, Beclin1, and apoptosis proteins, including caspase-9 and caspase-3. RES treatment decreased the phosphorylation of mTOR on Ser2448 and AKT on Ser473, but increased the levels of AMPK α and its phosphorylation on Thr172 [109]. Similarly, Ma et al. concluded that RES promotes autophagy and apoptosis in a manner dependent on the PI3K/AKT/mTOR signaling pathway in multiple myeloma cells [110]. The inhibitory effect of RES on mTOR also could be owing to its ability to compete with ATP to dock onto the ATP-binding site of mTOR [111].

p62

p62 or sequestosome 1 (SQSTM1) is a multifunctional protein because it consists of different domains, including the ZZ zinc finger domain, Phox-BEM1 (PB1) domain, nuclear export signal (NES) motif, nuclear localization signal (NLS), Keap1-interacting region (KIR), LC3-interaction region (LIR), and C-terminal ubiquitin-associated (UBA) domain [112]. It has been demonstrated that p62 delivers ubiquitinated proteins to the proteasome, and there is evidence that lack of autophagy results in p62 accumulation, whereas p62 impairment induces autophagy [113, 114]. Puissant et al. reported that RES triggers autophagic cell death of chronic myelogenous leukemia (CML) cells via AMPK activation and JNK-mediated accumulation of p62. These results also were demonstrated in RES-treated CD34+ stem cells isolated from CML patients. In contrast, p62 knockdown or JNK inhibition suppressed RES-mediated autophagy and anti-cancer effects. Thus, AMPK-dependent inhibition of mTOR promotes phagophore formation, while JNK activation provokes elongation by inducing p62 expression and promoting its binding to LC3 [115]. In another study, Zhang et al. found that the treatment of A549 cells with RES-induced autophagy and promoted degradation of p62 in an autophagy-mediated manner. They also indicated that p62 downregulation could enhance the formation of the Fas/Cav-1 (caveolin-1) complex, an inducer of apoptosis. The Fas/Cav-1 complex promotes the activation of caspase-8 and cleavage of Beclin1, leading to the release of a C-terminal Beclin1 peptide which triggers apoptosis by translocating to the mitochondria. Furthermore, knockdown of p62 increased caspase-8 activation and apoptosis initiation, whereas knockdown of Cav-1 suppressed apoptosis but enhanced autophagy. They concluded that p62 regulates the transition from autophagy to apoptosis [116]. Also, it has been reported that RES could activate non-canonical autophagy in an Atg-5- and Beclin1-independent manner alongside apoptosis activation in A549 cells. RES-induced autophagy led to attenuated apoptosis, proposing that autophagy may work as a protective pathway in A549 cells. Accordingly,

it was found that RES induces mitophagy, degradation of damaged mitochondria by autophagy, and p62 acts as an adaptor in A549 cells [117].

p53

In addition to apoptosis, p53 also is involved in autophagy. It has been shown that there is an important correlation between p53 and autophagy, in which p53 induces autophagy and autophagy inhibits p53. Autophagy activation by p53 implies that autophagy acts as a part of the p53 protective function, whereas p53 suppression by autophagy participates in tumor development and promotion [118]. The effect of RES on autophagy in a p53-dependent manner has been studied in some studies. For instance, Zhang et al. studied the anti-tumor effects of RES on hepatocellular carcinoma cells and its potential mechanisms of action. They found that RES treatment inhibited the proliferation, viability, and migration of the cancer cells. Also, the treatment of MHCC-97H cells with RES-induced autophagy, characterized by upregulation of LC3 II/I ratio and Beclin1 and downregulation of p62. Furthermore, inhibition of autophagy by treatment with 3-methyladenine reversed RES effects on cancer cell proliferation, viability, and migration, suggesting that autophagy suppression could hamper anti-tumor functions of RES. They indicated that RES increased p53 expression while decreasing the phosphorylated protein kinase B (p-Akt)/Akt ratio, whereas treatment with pifithrin- α and insulin-like growth factor-1 as p53 inhibitor and Akt activator, respectively, downregulated Beclin1 expression while stimulating cancer cell proliferation and migration. Thus, RES could inhibit the proliferation and metastasis of cancer cells by inducing autophagy through activation of p53 and inhibition of PI3K/AKT [119]. In another study, Fan et al. demonstrated 1,031 differentially expressed genes, 680 upregulated and 351 downregulated, in the RES-treated A549 cells, including the p53 pathway. They found that RES treatment could induce apoptosis and autophagy, and it affects apoptosis and autophagic cell death through a p53-dependent pathway in A549 cells. RES treatment upregulated p53 expression, inhibited MDM2 phosphorylation at Ser-166, and decreased AKT phosphorylation at Ser-473, suggesting that RES-induced the triggering of the p53 pathway [120].

Nrf2

The intracellular abundance of nuclear factor (erythroid-derived-2)-like 2 (Nrf2), a protein that regulates oxidative stress responses, is regulated by Kelch-like ECH-associated protein 1 (Keap1) [104]. Under normal conditions, the interaction of Nrf2 with Keap1 directs it toward proteasomal degradation. Under oxidative conditions, the oxidation

and inactivation of Keap1 lead to Nrf2 stabilization and its translocation into the nucleus, resulting in Nrf2 binding to anti-oxidant response elements (AREs) and activation of genes containing AREs [121]. There is evidence that the Nrf2-Keap1-ARE signaling axis has crosstalk with autophagy [122, 123]. For instance, it has been shown that p62 sequesters Keap1 into the autophagosomes through direct interaction with Keap1, which impairs Nrf2 ubiquitylation, leading to triggering the Nrf2 pathway [124]. Kabel et al. indicated that RES in combination with sitagliptin, a dipeptidyl peptidase-4 inhibitor with cytotoxicity activity on tumor cells by inhibiting autophagy, exerted anti-oxidant and anti-inflammatory effects via modulating STAT3/NF- κ B and Nrf2/HO-1 pathway on a renal carcinoma model in rats [125]. In another study, Rai et al. demonstrated that RES could decrease the growth of MCF-7 cells exposed to DOX by stimulating Nrf2, resulting in a reduction in apoptosis (Bax: Bcl-2 ratio and caspase-9), inflammation (NF- κ B and COX-2), and autophagy (LC3 and Beclin1) [126]. In addition, Cheng et al. reported that RES enhanced anti-tumor efficacy of gemcitabine through the inhibition of nutrient-deprivation autophagy factor-1 (NAF-1) via activating the ROS/Nrf2 pathway [127]. NAF-1 is a key regulator of autophagy that could inhibit autophagy by interacting with Beclin1 [128].

Conclusions

In conclusion, RES can modulate cancer treatment and cancer cell death by targeting multiple signaling and molecular pathways. It can reduce side effects associated with conventional chemotherapy and improve results when combined with chemotherapeutic agents and sensitize cells to them. Due to the promising impacts on apoptosis and autophagy, researchers will be motivated to develop RES-based studies for combating cancer, specifically in clinical trials. However, some concerns could be addressed in using RES. One of the concerns is its low solubility that using nanoparticles can increase RES solubility in water. Nanoparticles also can increase the specificity of RES by targeting tumor tissues. Tailoring nanoformulations responsive to external cues (such as ultrasound and magnetic field) and biological cues (such as redox status and pH) could enhance RES delivery and targeting precision. Also, reprogramming the tumor microenvironment to increase the accumulation of RES-loaded nanoformulations besides developing nanoformulations containing transcytosis capability to simplify deep tumor penetration may enhance RES efficacy in fighting cancer. Another consideration in developing RES-loaded nanoformulations is their preparation cost, ensuring the feasibility of their development. Furthermore, the minimal side effects of RES could be due to low or medium doses and

its rapid metabolization into safe analogs. To verify these promising results, investigating RES anti-cancer effects at high doses in similar experiments is imperative to translate into clinical studies.

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Declarations

Conflict of interest All the authors declare that they have no conflict of interest.

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