CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2022.2101428

Taylor & Francis
Taylor & Francis Group

REVIEW

Effects and mechanisms of resveratrol for prevention and management of cancers: An updated review

Si-Xia Wu[a], Ruo-Gu Xiong[a], Si-Yu Huang[a], Dan-Dan Zhou[a], Adila Saimaiti[a], Cai-Ning Zhao[b], Ao Shang[c], Yun-Jian Zhang[d], Ren-You Gan[e] and Hua-Bin Li[a]

[a]Guangdong Provincial Key Laboratory of Food, Nutrition and Health, Department of Nutrition, School of Public Health, Sun Yat-Sen University, Guangzhou, China; [b]Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; [c]School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; [d]Department of Thyroid and Breast Surgery, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; [e]Research Center for Plants and Human Health, Institute of Urban Agriculture, Chinese Academy of Agricultural Sciences, Chengdu, China

ABSTRACT

Cancer is a severe public health problem. Resveratrol is a famous natural compound that has various bioactivities, such as antioxidant, anti-inflammatory, antidiabetic and antiaging activities. Especially, resveratrol could prevent and treat various cancers, such as oral, thyroid, breast, lung, liver, pancreatic, gastric, colorectal, bladder, prostate and ovarian cancers. The underlying mechanisms have been widely studied, such as inhibiting cell proliferation, suppressing metastasis, inducing apoptosis, stimulating autophagy, modulating immune system, attenuating inflammation, regulating gut microbiota and enhancing effects of other anticancer drugs. In this review, we summarize effects and mechanisms of resveratrol on different cancers. This paper is helpful to develop resveratrol, crude extract containing resveratrol, or foods containing resveratrol into functional food, dietary supplements or auxiliary agents for prevention and management of cancers.

KEYWORDS

Resveratrol; anticancer; mechanism; proliferation; apoptosis; metastasis

Introduction

Cancer has caused severe disease burdens in the world. There are nearly 19.3 million newly-diagnosed cancer cases and almost 10 million deaths caused by cancer according to Global Cancer Statistics 2020 (Sung et al. 2021). Surgery, chemotherapy and radiotherapy are three main therapies for cancers, but their efficiencies are limited with some adverse effect. Therefore, it is significant to search novel strategies for the prevention and treatment of cancers. The anticancer effects of natural compounds have attracted more and more attention of researchers. Increasing studies showed that bioactive compounds from vegetables, fruits, spices, tea and medicinal plants could play a vital role in the prevention and management of cancers through different mechanisms (Farha et al. 2022; Mao et al. 2020; Tao et al. 2020; Tao et al. 2018; Xu et al. 2020c).

Polyphenols are bioactive compounds that have many beneficial effects via different mechanisms, such as anti-inflammation, antioxidation, anti-obesity, modulation of gut microbiota and cardiovascular protection (Cao et al. 2019b; Shang et al. 2021). Resveratrol is a natural phenolic compound and widely exists in many foods, such as grapes, peanuts, pistachios, bilberries and blueberries (Mukherjee, Dudley, and Das 2010). Many studies have shown that resveratrol has various bioactivities, such as antioxidant, anti-inflammatory, antidiabetic, antiaging, immunomodulatory and neuroprotective activities (Meng et al. 2020; Yeung et al. 2019; Zhou et al. 2021). In addition, anticancer effects and mechanisms of resveratrol have been widely studied since its anticancer activity was first reported in a famous journal Science in 1997 (Jang et al. 1997), and the results showed that it could be a promising agent for the prevention and treatment of various cancers, such as breast, cervical, uterine, skin, gastric, kidney and liver cancers (Elshaer et al. 2018; Rauf et al. 2018; Ren et al. 2021). In this review, we summarize effects and mechanisms of resveratrol on various cancers and a special attention is paid to the underlying mechanisms of action.

Effects of resveratrol on cancers

Breast cancer

Breast cancer is one of the most dangerous cancers worldwide, and seriously threatens health of women (Li et al. 2017). Resveratrol could suppress breast cancer cell proliferation (Table 1). For example, resveratrol inhibited proliferation of 4T1 breast cancer cells through inducing cell cycle arrest in the S phase (Wu et al. 2019). In addition, resveratrol suppressed proliferation of estrogen receptor-positive breast cancer cells by downregulating expression of enhancer of zeste homolog 2 (EZH2), and

CONTACT Hua-Bin Li lihuabin@mail.sysu.edu.cn; Ren-You Gan ganrenyou@caas.cn

Table 1. The anticancer effects and related mechanisms of resveratrol.

Cancers	Study types	Models	Dosages	Effects and mechanisms	Ref.
Breast cancer					
	In vitro	MCF-10A and MDA-MB-231 cells	0, 3.125, 6.25, 12.5, 25, 50, 100, 200 μM	Promoting apoptosis; Reducing mRNA expression of POLD1 Inhibiting anti-apoptotic index PARP1, PCNA, BCL-2 Increasing apoptosis index Cleaved-Caspase3;	(Liang et al. 2021)
	In vitro	MDA-MB-231 cells	10 mM	Inhibiting Na^+-dependent Pi transporter Restraining adhesion or migration;	(Lacerda-Abreu, Russo-Abrahao, and Meyer-Fernandes 2021)
	In vitro	4T1 cells	0, 50, 100, 150, 200, 250 μM	Suppressing proliferation Inducing apoptosis;	(Wu et al. 2019)
	In vitro	MDA-MB-231, MDA-MB-453, MDA-MB-436, BT549 cells	12.5, 25, 50, 100 μM	Inhibiting migration Raising expression of E-cadherin Reducing expression of MMP-2, MMP-9, vimentin;	(Sun et al. 2019)
	In vivo	Athymic nude mice	40 mg/kg	Inhibiting lung metastasis;	
	In vitro	ER-positive MCF-7 and T47D cells	0, 20, 40, 80 μM	Inhibiting proliferation and migration of ER-positive breast cancer cells Downregulating the expression of EZH2;	(Hu et al. 2019)
	In vitro	BT549 and Cal51 cells	0, 20, 50, 100 μM	Reducing cell survival in the Cal51 TNBC cells with piceatannol Upregulating expression of gamma H2AX and cleaved caspase 3 Downregulating expression of p38-MAPK Inducing G1-to-S cell cycle arrest;	(Lucas et al. 2018)
	In vitro	MCF-7 cell	0, 10, 30, 100 μM	Increasing cell apoptosis and suppressing cell proliferative with 3 Gy ionizing radiation Decreasing Bax/Bcl-2 ratio;	(da Costa Araldi et al. 2018)
	In vitro	MCF-7, T47-D and MDA-MB-231 cells	0, 30, 50, 100, 150, 250 μM	Enhancing the anti-proliferative effects of cisplatin Inhibiting the protein level of Rad51 and the relative transcript levels of homologous recombination initiation complex components Maintaining phosphorylation of H2AX histone at serine 139;	(Leon-Galicia et al. 2018)
	In vitro	ER-, PR-, HER2- MDA-MB-231, ER+, PR+, HER2MCF-7 cells	10, 15, 20 μM	Promoting apoptosis in MDA-MB-231 cells with proanthocyanidins Increasing Bax expression and decreasing Bcl-2 expression Reducing DNA methyltransferase activity and HDAC activity;	(Gao and Tollefsbol 2018)
Colorectal Cancer					
	In vitro	CL187, Colo205, HCT-8, SW480, and HCT-116 cells	0, 10, 20, 50, 80, 100 μM	Suppressing the proliferation of various colorectal cancer cells Decreasing Top1 and Tdp1 contents and mRNA expression in wild-type;	(Zhang et al. 2021)
	In vitro	Colo-320 and Colo-741 cells	5, 10, 25, 50, 100 μg/ml	Reducing cell viability Inducing mitochondrial-mediated apoptosis of primary colon cancer cells;	(Madencioglu et al. 2021)
	In vitro	SW 620 and HCT 116 cells	0, 2, 4, 8,16, 32, 64, 125, 250, 500 μg/ml	Inhibiting colorectal cancer cell viability Modulating an ROS-mediated mitochondrial apoptotic pathway Upregulating the protein expression levels of cytochrome c, cleaved caspase-9 and cleaved caspase-3 Downregulating the protein expression levels of Bcl-2;	(Fu et al. 2020)
	In vitro	HT-29 and HCT 116 cells	100 μM	Increasing the protein expression levels of RKIP Suppressing the migration of colorectal cancer cell;	(Dariya et al. 2020)
	In vitro	SW480 and SW620 cells	7.5, 15, 30, 60, 120, 240 μM	uppressing the invasion and metastasis of colon cancer	(Yuan et al. 2019)
	In vivo	Nude mice	150 mg/kg	Enhancing E-cadherin expression; Reducing expression of N-cadherin, phosphor (p)-AKT1, p-GSK-3-β, and snail;	
	In vitro	HCT116, CO115 and SW48 cells	0, 12.5, 25, 37.5, 50 μM	Inducing the activation of p53-mediated apoptosis in colon cancer Upregulating the expression of tumor protein p53 and p53 target genes Enhancing SET domain containing lysine methyltransferase 7/9 expression;	(Liu, Z.L. et al., 2019)

(*Continued*)

Table 1. (Continued).

Cancers	Study types	Models	Dosages	Effects and mechanisms	Ref.
	In vitro	DLD1 and HCT15 cells	0, 10, 20, 30, 40 μM	Inhibiting cell proliferation and colony growth in DLD1 and HCT15 colon cancer cells Mediating the AKT/STAT3 signaling pathway Downregulating the expression of cyclin D1, cyclin E2 and BCL2 apoptosis regulator Upregulating BCL2 associated X and tumor protein p53;	(Li et al. 2019a)
	In vitro	SW620 cells	5, 10, 20, 40, 80, 160 μM	Promoting the oxygen consumption of mitochondrial biogenesis Inducing fatty acid oxidation Increasing hyperpolarization of mitochondrial membrane and ROS production;	(Blanquer-Rossello et al. 2017)
	In vitro	HCT116 cells	5 μM	Blocking the TNF-β-induced proliferation and invasion of HCT116 colorectal cancer cells Inhibiting TNF-β/TNF-β R-induced activation of NF-κ B Modulating gene products, and caspase-3 cleavage;	(Buhrmann et al. 2019b)
	In vitro	HCT116 and SW620 cells	0, 2, 4, 8, 16, 32, 64, 125, 250, 500 μg/ml	Inducing the apoptosis of CRC cells through ROS-mediated mitochondrial apoptotic pathway Increasing ROS levels and the protein expression levels of cytochrome c, cleaved caspase-9 and cleaved caspase-3 Decreasing the expression levels of Bcl-2;	(Fu et al. 2020)
	In vitro	HCT116 and CT26 cells	5 μg/ml	Enhancing the sensitivity of colorectal cancer cells to cetuximab Upregulating the expression and phosphorylation of connexin 43 Promoting gap junction function;	(Wang et al. 2020b)
	In vivo	C57BL/6 mice	100 mg/kg	Changing the gut microbiome and short chain fatty acid composition Suppressing histone deacetylases Downregulating pro-inflammatory Th1 and Th17 cells Upregulating anti-inflammatory CD4+ FOXP3+ (Tregs) and CD4+ IL10+ cells;	(Alrafas et al. 2020)
	In vitro	HCT116 and SW480 cells	5 μM	Reversing TNF-β/TNF-β R-induced EMT in CRC cells Inhibiting NF-κB and focal adhesion kinase;	(Buhrmann et al. 2019a)
	In vitro	HCT-116 cell	0, 25, 50, 100, 200, 400 μM	Suppressing the invasion and apoptosis of CRC cells Promoting EMT to MET Upregulating the expression of miR-200c;	(Dermani et al. 2017)
Pancreatic Cancer					
	In vitro	EPP85-181P, EPP85-181RNOV, AsPC-1 and H6c7 cells	0, 5, 10, 25, 50, 100, 150, 200 μM	Reversing human pancreatic cancer cell proliferation Increasing the expression levels of Bcl-2 pro-apoptotic proteins Decreasing the expression levels of anti-apoptotic proteins;	(Ratajczak et al. 2021)
	In vitro	Panc-1 and Mia Paca-2 cells	50 μM	Weakening the malignant progression of pancreatic cancer Inhibiting hypoxia-induced pancreatic stellate cell activation Restraining the interplay between pancreatic stellate cells and pancreatic cancer cells;	(Xiao et al. 2020)
	In vivo	KPC mice, LSL-$Kras^{G12D}$ mice, and $Trp53^{fl/fl}$ mice	50 mg/kg	Suppressing VEGF-A, SDF-1, IL-6, α-SMA, and HIF-1α expression Suppressing stromal desmoplastic reaction on pancreatic cancer cells;	
	In vivo	*LSL-Kras*$^{G12D/+}$ (K) and *Pdx1-Cre* (C) mice	50 mg/kg	Preventing the progression of pancreatic precancerous lesions Suppressing the activation of NF-κB signaling pathway related molecules;	(Qian et al. 2020)
	In vitro	PANC-1, Mia-PaCa, Capan-2 cells	0, 50, 100, 150 μM	Promoting ROS production and mitochondrial-dependent apoptosis;	(Luo et al. 2021)
	In vitro	MiaPaCa- 2 and Panc- 1 cells	50 μmol/L	Reversing the gemcitabine-induced chemo-resistance and enhance the sensitivity of gemcitabine;	(Zhou et al. 2019)
	In vivo	LSL- KrasG12D/+; Trp53fl/+; Pdx1- Cre (KPC) mice	50 mg/kg	Inhibiting the expression of sterol regulatory element binding protein 1 Repressing the sphere formation ability Downregulating the expression of CSC markers;	

(*Continued*)

Table 1. (Continued).

Cancers	Study types	Models	Dosages	Effects and mechanisms	Ref.
	In vitro	Panc-1, Mia paca-2, CF pac-1, and BxPC-3 cell lines	0, 50, 100, 150, 200 μM	Improving the sensitivity of pancreatic cancer cells to gemcitabine Promoting cellular ROS accumulation Inducing Nrf2 signaling pathway Inhibiting the expression of NAF-1;	(Cheng et al. 2018a)
	In vitro	BXPC-3, CAPAN2, MiaPaCa-2 and PANC-1 cell lines	0, 100, 200, 300 μM	Inhibiting the cell growth and induced the apoptosis of pancreatic cancer cells with capsaicin	(Vendrely et al. 2017)
	In vivo	NOD/Shi-SCID IL2Rγnull mice	150 mg/kg	Increasing ROS production to stimulate the activation of the stress response MAP kinase p38;	
	In vitro	PANC-1 and SW1990 cell lines	200 μM	Repressing proliferation, migration, and invasion in pancreatic cancer cells Inhibiting the expression of RYR2 Increasing the PTEN expression;	(Jiang et al. 2022)
Prostate Cancer					
	In vitro	LNCaP and RWPE-1 cells	0, 25, 50, 100, 200 μM	Suppressing the proliferation of prostate cancer cells Promoting the apoptosis of prostate cancer cells Reducing the expression of AR mRNA and protein levels;	(Ye et al. 2020)
	In vitro	DU145 and PC3 cell lines	0, 10, 25, 50, 75 μM	Weakening the proliferation and migration of prostate cancer cells Mediating the degradation of TRAF6 Facilitating the repression of the NF-κB pathway;	(Khusbu et al. 2020)
	In vitro	DU145 and PC-3 cells	0, 10, 25,50 μM	Decreasing HGF-mediated interaction between the stroma and epithelium Restraining epithelial prostate cancer cell migration Attenuating EMT;	(Hsieh and Wu 2020)
	In vitro	Androgen-independent DU145 and PC3 cells, and androgen-dependent LNCaP cells	0, 0.1, 1, 5, 25,50, 100 μM	Ameliorating the apoptosis of androgen-independent prostate cancer cells Enhancing DUSP1 expression Repressing the NF-κB pathway and Cox-2 expression;	(Martinez-Martinez et al. 2019)
	In vitro	LNCaP cells	50, 100 μM	Suppressing DHT-induced prostate cancer metastasis Downregulating the expression of AR, CXCR4, p-PI3K, p-AKT and the downstream genes related with cell cycle progression Upregulating the expression of the apoptosis-related genes;	(Jang et al. 2019)
	In vitro	PC3, LNCaP, C2C12, and SHSY5Y cell lines	0, 1, 5, 10 μM	Attenuating PC3 prostate cancer cell metabolic and growth Interfering with glucose fermentation and boosting respiration;	(Fonseca et al. 2019)
	In vitro	TRAMP cells	50 μM	Promoting the apoptosis in prostate cancer cells Increasing ROS concentration and expression of Bax, HIF-1α and p53 Inhibiting the expression of Bcl2;	(Wang, Gao, and Zhang 2018)
	In vitro	LNCaP cells	0, 5, 10, 20, 50 μM	Increasing the accumulation of nuclear COX-2 Inducing the phosphorylation and nuclear translocation of mitogen-activated protein kinase;	(Cheng et al. 2018b)
	In vitro	DU145 (androgen-insensitive), LNCaP(androgen-sensitive); RWPE-1 cells	25 μM	Inhibiting cell viability and proliferation in prostate cancer DU145 and LNCaP cells Upregulating the expression of PCAT29 Interfering with the STAT3 and miR-21 signaling;	(Al Aameri et al. 2017)
	In vitro	DU145 and C42B cells	5, 10, 15, 20, 25, 50 μM	Improving the efficacy of docetaxel treatment Increasing the pro-apoptotic genes Bax, BID, and BAK Decreasing the anti-apoptotic genes MCL-1, BCL-2, BCL-XL Suppressing the expression of CDK4, cyclin D1, cyclin E1;	(Singh et al. 2017)
	In vitro	DAB2IP knockdown cell lines LAPC4-KD and PC3-KD	25 μg/ml	Increasing the apoptosis of radio-resistant prostate cancer cells Inhibiting the repair of radiation-induced DNA double-strand break Inducing the G2/M arrest;	(Chen et al. 2017)
Lung Cancer					
	In vitro	A549 and H1299 cell lines	0, 1, 5, 10, 20, 30 μM	Inhibiting PD-L1 expression in lung cancer cells through Wnt pathway Suppressing the T-cell-mediated immune response;	(Yang et al., 2021c)

(*Continued*)

Table 1. (Continued).

Cancers	Study types	Models	Dosages	Effects and mechanisms	Ref.
	In vitro	A549 and NCI-H292 cells	12.5, 25, 50, 75 μM	Inhibiting the proliferation and metastasis of malignant mucinous lung tumor cells Reducing the expression of SPDEF and MUC5AC Suppressing the ERK and AKT signaling pathway;	(Lin et al. 2021)
	In vivo	Male Rowett nude rats	250 mg/kg	Inhibiting NSCLC progression Downregulating the expressions of STAT3, HIF-1α, and VEGF;	(Wang et al. 2020a)
	In vitro	Human SCLC H446 cell line	40 μM	Restraining the viability and promoting the apoptosis of human SCLC H446 cells Upregulating cytochrome c expression Boosting the translocation of AIF from the cytoplasm to the nucleus;	(Li et al. 2020b)
	In vitro	SCLC H446 cell line	40 μg/mL	Suppressing the viability and increasing the apoptosis of human SCLC H446 cells Upregulating the expression of cytochrome c Downregulating the expression of PI3K/AKT/c-Myc signaling pathway components;	(Li et al. 2020b)
	In vitro	ASTC-a-1 and A549 cells; primary human fetal lung fibroblast cells PC14, H69, and IMR90	100 μM	Inhibiting the expression of PRMT5 Decreasing AKT/GSK-3 β phosphorylation and the downstream targets cyclin D1 and E1 expression;	(Li et al. 2019c)
	In vitro	A549 and H23 cells	20, 50, 100 μM	Upregulating the expression of ZFP36 Reducing the expression of DNA (cytosine-5)-methyltransferase 1 Promoting demethylation of the ZFP36 promoter;	(Fudhaili et al. 2019)
	In vitro	SCLC H446 cells	0, 20, 30, 35, 40 μg/ml	Enhancing the anticancer effect of cisplatin Inducing mitochondrial depolarization Increasing cytochrome c release and AIF translocation Regulating the protein levels of Bcl-2, Bcl-xL and Bax;	(Li et al. 2018)
	In vitro	A549 and HCC-15 cells	0, 12.5, 25, 50 μM	Enhancing TRAIL-mediated apoptosis Palliating TRAIL resistance Downregulating the expression of anti-apoptotic factors (Bcl-2, Bcl-xl) Suppressing the AKT/NF-κB signaling pathway;	(Rasheduzzaman, Jeong, and Park 2018)
Gastric Cancer					
	In vitro	SNU-216, SNU-484, SNU-601, SNU-638, and SNU-668 cells	0, 25, 50, 100 μM	Binding to the PIM-1 at the ATP-binding pocket Inhibiting PIM-1 kinase activity;	(Kim, S. et al., 2020)
	In vitro	BGC823 cell	0, 5, 10, 25, 50, 100, 200, 400 μM	Suppressing metastasis-associated MALAT1 expression Inhibiting MALAT1-mediated EMT;	(Yang et al. 2019)
	In vitro	HGC-27 cell	20 μM	Downregulating the expression of IL-6, IL-8, MCP-1, VEGF and related protein secretion Restraining the activation of Wnt/β-catenin signaling Suppressing the progress of GC-MSC-induced EMT;	(Yin et al. 2020)
	In vitro	SGC-7901 cell line	50 μM	Inhibiting the proliferation, migration and invasive of SGC-7901 cells Downregulating HIF-1α protein levels induced by hypoxia; Suppressing the activation of the Hedgehog pathway	(Xu et al. 2020b)
	In vitro	SGC7901 and HSC-39 cells	0, 10, 20, 30, 40, 50, 100 μM	Suppressing IL-6 induced gastric cancer metastasis and matrix metalloproteinases activation Decreasing the Raf/MAPK signaling pathway activation;	(Yang et al. 2018)
	In vitro	SGC-7901 cells	0, 10, 50, 100, 200 and 400 μM	Increasing the levels of the pro-apoptotic proteins Bax, cleaved caspase-3 and cleaved caspase-8 Decreasing the level of the anti-apoptotic protein Bcl-2 Inhibiting the activation of NF-κB;	(Wu et al. 2018)
	In vitro	MGC-803 cells	0, 50, 75, 100 μM	Suppressing the growth of MGC-803 cell Downregulating- the mRNA and protein levels of β-catenin, c-myc, and cyclin D1 Inhibiting the Wnt signaling pathway;	(Dai et al. 2018)
	In vitro	EPG85-257RDB, EPG85-257RNOV, EPG85-257P cells	30, 50 μM	Decreasing the resistance of gastric cancer cells Downregulating the mRNA and protein levels of ABCB1, ANXA1 and TXN;	(Mieszala et al. 2018)

(*Continued*)

Table 1. (Continued).

Cancers	Study types	Models	Dosages	Effects and mechanisms	Ref.
	In vitro	AGS, KATO III, MKN-45 and NCI-N87 cells	0, 5, 10, 20, 30, 40, 50, 60, 70, 80 μM	Sensitizing AGS gastric cancer cells to cisplatin Upregulating the levels of Bax, cleaved PARP, GRP78, PERK, p-eIF2α and cleaved caspase-12 Decreasing the expression level of Bcl-2;	(Ren et al. 2020)
	In vitro	SGC7901 and MGC803 cells	0, 10, 20, 50, 100 mg/L	eversing the DOX resistance of gastric cancer, attenuate the aggressive biological features, and induce cell apoptosis Suppressing EMT Inhibiting the activation of PTEN/AKT signaling pathway;	(Xu et al. 2017)
Oral Cancer					
	In vitro	OEC-M1 cells	40 μM	Increasing the expression of pro-apoptotic BAD Decreasing the expression of PD-L1, BTLA and cyclin D1 Reversing the stimulatory effects of thyroid hormone;	(Lin et al. 2019)
	In vitro	YD-9 and YD-38 cells	25 μM	Repressing the invasion of RCP-induced OSCC Inhibiting the expression of RCP-induced Zeb1 Blocking β1 integrin endosome recycling and EGFR activation Downregulating the expression of MT1-MMP;	(Kim, J.Y. et al., 2020)
	In vitro	Human oral epidermoid carcinoma cell line, OEC-M1 cells; human squamous carcinoma of the tongue, SCC-25 cells	10 μM	Inhibited the expression of pro-inflammatory IL-1β and TNF-α and the activity of the PD-1/PD-L1 checkpoint Inhibiting SATA3 signal transduction pathway;	(Ho et al. 2020)
	In vitro	Squamous cell carcinomas SCC-15 and Cal-33 cells; normal human embryonic kidney HEK-293 cells	10, 25, 50 μM	Leading to cell growth inhibition, DNA damage, and S-phase cell cycle arrest in oral cancer cells but not in normal cells Inducing apoptosis in oral cancer cells Inducing the cleavage of PARP1 Increasing the expression level of Bax;	(Singh et al. 2020)
	In vitro	Human tongue squamous cell carcinoma CAL 27 cell line	0, 25, 50, 75, 100, 200 μM	Promote autophagy and apoptosis Increasing phosphorylation of AMPK Upregulating the autophagic mRNA gene expression Atg5, Atg12, Beclin-1 and LC3-II;	(Chang et al. 2017)
	In vitro	Human oral epidermoid carcinoma cell line, OEC-M1;Human squamous carcinoma of the tongue cell line, SCC-25	10, 40 μM	Reestablishing expression of COX-2/p53-dependent genes and anti-proliferation in oral cancer cells Suppressing the T-4-activated STAT3 signal transduction axis with the STAT3 inhibitor S31-201;	(Chen et al., 2019)
Thyroid Cancer					
	In vitro	Nthy-ori 3-1 and FTC133 cells	50, 100, 150, 200, 250, 300, 350, 400 μM	Reducing tumorigenesis of Follicular Thyroid Cancer Upregulating expression of ST6GAL2;	(Xu et al. 2020a)
	In vivo	Athymic nude mice	40 mg/kg	Stimulating the Hippo pathway;	
	In vitro	THJ-16T and 21T cells	100 μM	Suppressing Anaplastic thyroid cancer cells growth Increasing PTEN levels Changing sodium/iodide symporter intracellular distribution;	(Xiong et al. 2020)
	In vitro	KTC-1 and TPC-1 cells	10, 50, 100, 150 μM	Sensitizing the antitumor effects of rapamycin in papillary thyroid cancer treatment Suppressing AKT activation caused by rapamycin Repressing the important target of mTOR;	(Bian et al. 2020)
	In vivo	Nude BALB/c mice	30 mg/kg	Decreasing tumor size in xenograft mice Decreasing phosphorylation of AKT and p70S6K in tumors;	
	In vitro	ATC cell lines THJ-16T; medulloblastoma cell lines UW228-2	100 μM	Increasing the sensitivity of retinoic acid in anaplastic thyroid cancer cell line THJ-11T and UW228-2 cells Upregulating the expression CRABP2 Inducing CRABP2 demethylation;	(Liu, X. et al., 2019)

(*Continued*)

Table 1. (Continued).

Cancers	Study types	Models	Dosages	Effects and mechanisms	Ref.
Bladder Cancer					
	In vitro	5637 cells	25, 50, 100, 200 μmol/l.	Upregulating the expression level of PTEN mRNA and protein Downregulating the expression of p-AKT mRNA and protein;	(Li et al. 2019b)
	In vitro	RT4, 5637, and T24 cells	12.5, 25, 50, 100, 150, 200, 250 μM	Inhibiting the proliferative of bladder tumor cells Downregulating the gene expression of AKT, mTOR and SRC in the TP53 wild type cells Decreasing the gene expression of PLK1 In the TP53 mutated cells;	(Almeida et al. 2019)
	In vitro	T24 cell	0, 10, 25, 50, 100 μM	Reducing the expression and secretion of MMP-2 and MMP-9 Inhibiting the phosphorylation of extracellular signal-regulated protein kinase;	(Bai et al. 2017)
	In vitro	pumc-91/ADM cell line	0, 50, 100, 150, 200, 250, 300, 350 μM	Weakening ADM resistance and enhance the cytotoxicity of ADM in ADM-resistant pumc-91 cells Downregulating the expression level of MRP1, LRP, GST, BCL-2 Upregulating the expression level of Topo-II;	(Wang et al. 2017)
	In vitro	WTMEFs, TSC1-null MEFS, HCV29, 639V, and MGHU1 cells	100 μM	Promoting the apoptosis of human bladder cancer cell lines Suppressing rapamycin-induced AKT activation Inhibiting mTOR pathway;	(Alayev et al. 2017)
	In vitro	T24 T24-GCB cells	0, 75, 150 μM	Decreasing the drug resistance of T24-GCB cells to GCB Inducing the expression of ABCC2 and cleaved-PARP Reducing the expression of DCK, TK1 and TK2;	(Cho et al. 2019)
Ovarian Cancer					
	In vitro	SKOV-3 and OV-90 cell lines	0, 5, 10, 100, 200, 400 μM	Attenuating the proliferation and migration of OV-90 and SKOV-3 cells Decreasing the expression of Bcl-2 Increasing the expression of microRNA-34a;	(Yao et al. 2021)
	In vitro	A2780 and SKOV3 cells	0, 10, 20, 50, 100, 200 μM	Promoting the apoptosis of caspase-dependent cell Inhibiting Notch1 and PTEN/AKT signaling pathway Upregulating ROS generation;	(Kim, Park, and Woo 2019)
	In vitro	SKOV3 and OVCAR-3 cell lines	25, 50, 100 μM	Boosting the apoptosis of ovarian cancer cells Downregulating the expression levels of galectin-3 Upregulating the expression levels of miR-424-3p;	(El-kott et al. 2019)
	In vitro	A2780, SKOV3 cell lines	25, 50, 100, 200, 400, 800 μM	Suppressing the proliferation and induce the apoptosis Restricting the glycolysis Upregulating the expression and activation of AMPK and Caspase 3 Downregulating the expression and activation of mTOR;	(Liu et al. 2018)
	In vivo	BALB/c nude mice	100 mg/kg	Inhibited ovarian cancer growth and liver metastasis in xenograft mouse model;	
	In vitro	NIH-OVCAR3 cells	100 μM	Increasing the expression of ARH-I Decreasing the expression of STAT3 Inducing cells autophagy at the migration front;	(Ferraresi et al. 2017)
Cervical Cancer					
	In vitro	HeLa and Ca Ski cells	0, 5, 10, 20, 40 μM	Repressing the transcription and translation of HPV E6 and E7 genes Promoting G1/S phase transition arrest;	(Sun et al. 2021b)
	In vitro	HPV18-positive HeLa cells and HPV16-positive SiHa cells	0, 5, 10, 20, 40 μM	Inhibiting the proliferation and metastatic potential of cervical cancer cells; Reducing phosphorylation of STAT3 at Tyr705 but not Ser727;	(Sun et al. 2020)
	In vivo	Athymic BALB/C nude mice	30 mg/kg		
	In vitro	HeLa cell line	0, 20, 40, 60, 80 μmol/L	Enhancing the activation and nuclear translocation promotion of FOXO3a Upregulating the expression of Bcl-2 interacting mediator of cell death;	(Liu et al. 2020)
	In vitro	HeLa cell line	0, 10, 20, 50, 100 μM	Decreasing the expression level of PLSCR1;	(Zhao et al. 2019)
Gallbladder Cancer					
	In vitro	SK-ChA-1 and MZ-ChA-1 cells	32, 64 μM	Having a cytotoxic effect on human gallbladder cancer cells Decreasing the inhibition of Transglutaminase 2;	(Roncoroni et al. 2018)

(*Continued*)

Table 1. (Continued).

Cancers	Study types	Models	Dosages	Effects and mechanisms	Ref.
Head and Neck Cancer					
	In vitro	Squamous tongue carcinoma cell line PE/CA-PJ49; squamous pharyngeal carcinoma cell line FaDu	50 μM	Promoting cell apoptosis in FaDu cells with cisplatin-resveratrol combination treatment Upregulating c-MYC and TP53 expression Downregulating BCL-2 expression;	(Bostan et al. 2021)
	In vivo	BALB/c nude male mice	100 mg/kg	Inhibiting the migration of head and neck cancer cells Stimulating the mRNA expression of REG III Enhancing chemo- and radio-sensitivity in head and neck cancer;	(Mikami et al. 2019)
Liver Cancer					
	In vitro	Human normal liver cell lines L02 and HepG2 human hepatoma cells	5 μg/mL	Increasing caspase-3, caspase-8, caspase-9, p53 and p21 expressions Decreasing mRNA and protein expressions of NF-κB, COX-2, MMP-2;	(Jiang et al. 2017)

Abbreviation: ADM, adriamycin; AKT, protein kinase B; AMP, adenosine monophosphate; AMPK, AMP-activated kinase; AIF, apoptosis inducing factor; AR, androgen receptor; ATP, adenosine triphosphate; ATC, anaplastic thyroid cancer; Bcl-2, B-cell lymphoma-2; BTLA, B- and T-lymphocyte attenuator; CD133, Cancer stem cells; Cox-2, cyclooxygenase-2; CRABP2, cellular retinoic acid binding protein 2; CRC, colorectal cancer; CXCR4, C-X-C chemokine receptor type 4; DHT, dihydrotestosterone; DOX, doxorubicin; DUSP1, dual specificity phosphatase 1; EMT, epithelial-mesenchymal transition; ER-positive, estrogen receptor-positive; EZH2, enhancer of zeste homolog 2; FOXO, forkhead box O; GRP78, glucose-regulated protein 78; GC, gastric cancer; GST, glutathione S-transferase; GSK, glycogen synthase kinase; HDAC, histone deacetylase; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor 1 alpha; HPV, human papillomavirus; IL-6, interleukin 6; LC3-II, microtubule-associated protein 1 light chain 3 type II; MALAT1, lung adenocarcinoma transcript 1; MMP, mitochondrial membrane potential; MRP1, multidrug resistance protein 1; mTOR, mammalian target of rapamycin; MUC5AC, Mucin 5, including subtypes A and C; NF-κB, nuclear factor kappa B; NSCLC, non-small-cell lung cancer; Nrf2, nuclear factor erythroid 2-related factor 2; OC, ovarian cancer; OSCC, oral squamous cell carcinoma; PARP, poly ADP-ribose polymerase; p-AKT, phospho-AKT; PCNA, proliferating cell nuclear antigen; PDH, pyruvate dehydrogenase; PD-L1, programmed death-ligand 1; p-eIF2α, p-eukaryotic translation initiation factor 2 alpha; PERK, PRKR-like ER kinase; PIM-1, proviral integration site for Moloney murine leukemia virus; PI3K, phosphatidylinositol 3 kinase; PLSCR1, phospholipid scramblase 1; POLD1, polymerase delta 1; PRMT5, protein arginine methyltransferase 5; PTEN, phosphatase and tensin homolog; RCP, rab coupling protein; REG III, regenerating gene III; RKIP, Raf-1 kinase inhibitory protein; ROS, reactive oxygen species; SCLC, small-cell lung cancer; SDF-1, stromal cell-derived factor 1; α-SMA, alpha-smooth muscle actin; STAT3, signal transduction and transcription activator 3; ST6GAL2, alpha-2,6-sialyltransferase 2; STZ, streptozotocin; TNF-α, tumor necrosis factor-alpha; TNBC, triple negative breast cancer; TNF-β, tumor necrosis factor-beta; TNF-β R, tumor necrosis factor-beta receptor; Topo-II, topoisomerase-II; TRAF6, TNF-receptor associated factor 6; VEGF-A, vascular endothelial growth factor A.

further modulating the extracellular signal-regulated kinase (ERK) 1/2 signaling pathway (Hu et al. 2019).

Breast cancer cells are prone to migrate, and resveratrol could inhibit their metastasis via different mechanisms. For instance, resveratrol inhibited metastasis of transforming growth factor-1-induced MDA-MB-231 cells by raising expression of E-cadherin, and reducing expression of matrix metalloproteinase (MMP)-2, MMP-9, and vimentin (Sun et al. 2019). An in vivo study showed that resveratrol also kept down lung metastasis in an athymic nude mouse model bearing MDA231 human breast cancer xenografts without impairing body weight or liver and kidney functions (Sun et al. 2019). In addition, resveratrol inhibited the Na^+-dependent Pi transporter non-competitively to restrain the adhesion or migration of MDA-MB-231 cells, which prevented the metastatic processes of breast cancer cells (Lacerda-Abreu, Russo-Abrahao, and Meyer-Fernandes 2021).

Cancer cells always loss apoptotic control, hence inducing apoptosis plays an important role in the treatment of cancers. Several studies showed that resveratrol could induce apoptosis of breast cancer cells. For example, resveratrol promoted apoptosis of triple negative breast cancer (TNBC) cells by reducing the mRNA expression of polymerase delta 1 (POLD1). Moreover, resveratrol inhibited expression of poly ADP-ribose polymerase, proliferating cell nuclear antigen, and B-cell lymphoma-2 (Bcl-2), and increased cleaved caspase-3 expression, which were associated with inducement of TNBC cell apoptosis (Liang et al. 2021).

Resveratrol could combine with other natural compounds to synergistically treat breast cancer. For example, the combination of resveratrol and piceatannol reduced cell survival in the Cal51 TNBC cells through upregulating expression of phosphorylated histone H2AX (γ-H2AX) and cleaved caspase-3, downregulating expression of p38 mitogen-activated protein kinase (p38-MAPK), and inducing G1-to-S cell cycle arrest (Lucas et al. 2018). In addition, the combination of resveratrol and proanthocyanidins synergistically promoted apoptosis of MDA-MB-231 cells by increasing Bax expression and decreasing Bcl-2 expression. Moreover, the co-treatment also reduced activity of DNA methyltransferase and histone deacetylase, which could further inhibit breast cancer development (Gao and Tollefsbol 2018).

Resveratrol could enhance the anticancer effects when combined with other chemotherapeutic drugs. Cisplatin is used to treat many cancers in clinic. One study found that resveratrol effectively elevated the anti-proliferative effect of cisplatin on breast cancer MCF-7 and MCF-7R cells through inhibiting the protein level of Rad51 and the relative transcript levels of homologous recombination initiation complex components, and maintaining γ-H2AX at serine 139 (Leon-Galicia et al. 2018). Another study showed that compared with treatment of cisplatin alone, its combination with resveratrol led to more cytotoxicity in breast cancer MDA-MB-231 cell line, including early apoptosis, depolarization, and DNA fragmentation (Yang et al. 2021a). Additionally, doxorubicin is an effective chemotherapeutic drug for breast cancer therapy, but it is common to induce breast cancer drug resistance. Resveratrol was found to increase the long-term toxicity of doxorubicin in breast cancer by modulating expression of genes that were involved in doxorubicin-treated resistance, including CCND1, CDH1, ESR1, PTPN11, HSP90AA1 and MAPK3 (Vargas et al. 2020).

Radiation therapy is commonly used in breast cancer, and resveratrol could enhance the sensitivity of breast cancer cells to radiation therapy. Specifically, the combination of 10 μM resveratrol and 3 Gy ionizing radiation induced the apoptosis of MCF-7 breast cancer cells by decreasing the Bax/Bcl-2 ratio, and suppressed cell proliferation via increasing the expression of p53 and cell cycle arrest at S phase (da Costa Araldi et al. 2018).

In short, resveratrol plays a significant role in breast cancer treatment through different mechanisms, including inhibition of breast cancer cell proliferation, suppression of metastasis, inducement of apoptosis. Moreover, the combination of resveratrol and other natural compounds, including piceatannol and proanthocyanidins, could synergistically prevent and treat breast cancer. In addition, resveratrol could enhance the anticancer effects of other anticancer agents, such as cisplatin and doxorubicin, and increase the sensitivity of breast cancer cells to radiation therapy.

Colorectal cancer

Colorectal cancer is a common cancer (Davidson et al. 2021; Tao et al. 2018). Resveratrol could inhibit colorectal cancer cell proliferation through different mechanisms. For instance, resveratrol suppressed proliferation of colorectal cancer cells through modulating expression of topoisomerase 1 (Top1) and tyrosyl-DNA phosphodiesterase 1 (Tdp1) (Zhang et al. 2021). Additionally, resveratrol reduced cell viability both in Colo-320 and Colo-741 colon cancer cells, and it might be more effective to induce mitochondrial-mediated apoptosis rather than enhance senescence of primary colon cancer cells (Madencioglu et al. 2021).

Resveratrol could suppress invasion and metastasis of colorectal cancer cells. Raf kinase inhibitor protein acts as a tumor cell metastasis suppressor and prognostic indicator for colorectal cancer, and resveratrol increased its expression levels (Dariya et al. 2020). In addition, resveratrol reduced the tumor necrosis factor (TNF)-β-induced proliferation and invasion of HCT116 colorectal cancer cells through suppression of TNF-β-stimulated nuclear factor-kappa B (NF-κB) signaling pathway (Buhrmann et al. 2019b). Additionally, resveratrol could suppress the invasion and metastasis of colon cancer through reversal of epithelial-to-mesenchymal transition (EMT) by several mechanisms. For example, resveratrol reversed EMT by upregulating expression of miR-200c in HCT-116 colorectal cancer cells (Dermani et al. 2017). Moreover, another study showed that resveratrol reversed TNF-β/TNF-β R-induced EMT in colorectal cancer cells via inhibition of NF-κB and focal adhesion kinase (Buhrmann et al. 2019a). Additionally, an in vivo study found that resveratrol markedly suppressed EMT in colon cancer cells through protein kinase B (AKT)/glycogen synthase kinase (GSK)-3-β/Snail signaling pathway (Yuan et al. 2019).

Resveratrol could prevent and treat colorectal cancer by inducement of cell apoptosis. For example, resveratrol promoted apoptosis of colorectal cancer cells through ROS-mediated mitochondrial apoptotic pathway, by increasing ROS levels and expression of cytochrome c, cleaved caspase-9 and cleaved caspase-3, and decreasing expression of Bcl-2 (Fu et al. 2020). In addition, metabolism of cancer cells primarily depends on glycolysis for ATP production rather than mitochondrial oxidative phosphorylation (Warburg effect). Resveratrol enhanced the oxygen consumption of mitochondrial biogenesis and induced fatty acid oxidation, and further increased hyperpolarization of mitochondrial membrane and ROS production, which resulted in apoptosis of SW620 colon cancer cells (Blanquer-Rossello et al. 2017).

Resveratrol could regulate expression of circulating inflammatory biomarkers and gut microbiota to inhibit development of colorectal cancer. For example, in an azoxymethane and dextran sodium sulphate-induced colorectal cancer murine model, resveratrol increased genus level of *Ruminococcus*, *Akkermansia*, *Dehalobacterium* and *Anerostipes*, and changed short chain fatty acid composition (Alrafas et al. 2020). Furthermore, resveratrol inhibited the inflammatory T-cell response via decreasing pro-inflammatory Th1 and Th17 cells, and increasing anti-inflammatory CD4+ FOXP3+ Treg cells and CD4+ IL10+ cells, which was related to alleviate the colonic inflammation and prevent inflammation-driven colorectal cancer (Alrafas et al. 2020).

Resveratrol was able to enhance the sensitivity of colorectal cancer cells to other anticancer drugs. For instance, cetuximab is a recombinant chimeric human–mouse monoclonal antibody that can suppress the activation and phosphorylation of epidermal growth factor receptor, and is widely used to treat many cancers (Li et al. 2020a). One study pointed out that resveratrol enhanced the sensitivity of colorectal cancer cells to cetuximab by increasing the expression and phosphorylation of connexin 43 and promoting gap junction function, which was involved in the inhibition of AKT pathway (Wang et al. 2020b).

In a word, resveratrol could be a potent compound for prevention and treatment of colorectal cancer. Resveratrol could inhibit colorectal cancer cell proliferation, suppress metastasis, induce apoptosis, regulate gut microbiota, modulate expression of circulating inflammatory biomarkers, and enhance the sensitivity of colorectal cancer cells to cetuximab.

Pancreatic cancer

Pancreatic cancer is a threatening cancer worldwide, and the conventional treatment methods, such as chemotherapy or radiotherapy, often cannot bring desired therapeutic effects (Bray et al. 2018; Chauhan et al. 2020). Many studies showed that resveratrol could effectively inhibit pancreatic cancer cell proliferation and attenuate malignant progression. For example, resveratrol suppressed human pancreatic cancer cell proliferation by downregulating expression level of Bcl-2 (Ratajczak et al. 2021). Another study showed that resveratrol repressed proliferation and metastasis of pancreatic cancer cells through inhibiting expression of ryanodine receptor type 2 (RYR2) and increasing phosphatase and tensin homolog (PTEN) expression (Jiang et al. 2022). In addition, resveratrol also showed an anti-proliferative effect on pancreatic cancer cells by promoting ROS production and mitochondrial-dependent apoptosis (Luo et al. 2021). Moreover, resveratrol weakened the malignant progression of pancreatic cancer via inhibiting hypoxia-induced pancreatic stellate cells activation and restraining interplay between pancreatic stellate cells and pancreatic cancer cells (Xiao et al. 2020). An in vivo study showed that resveratrol suppressed vascular endothelial growth factor A (VEGF-A), stromal cell-derived factor 1 (SDF-1), interleukin (IL)-6, alpha-smooth muscle actin (α-SMA) and hypoxia-inducible factor (HIF)-1α expression and stromal desmoplastic reaction on pancreatic cancer cells (Xiao et al. 2020).

Resveratrol also could prevent progression of pancreatic cancer by modulating immune system. For instance, resveratrol inhibited immunoreactivity of N-cadherin and TNF-α in CD133+ pancreatic cancer cells (Hoca et al. 2020). In addition, resveratrol prevented the progression of pancreatic precancerous lesions via suppressing the activation of NF-κB signaling pathway (Qian et al. 2020).

Resveratrol could decrease chemo-resistance of pancreatic cancer cells to gemcitabine, which is commonly used for pancreatic cancer chemotherapy. For example, resveratrol enhanced the sensitivity of gemcitabine in pancreatic cancer cells through inhibiting the expression of sterol regulatory element binding protein 1, which in turn repressed the sphere formation ability and downregulated expression of cancer stem cell (CSC) markers (Zhou et al. 2019). Another study showed that resveratrol improved the sensitivity of pancreatic cancer cells to gemcitabine by promoting cellular ROS accumulation, inducing nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway and inhibiting the expression of nutrient-deprivation autophagy factor 1 (NAF-1) (Cheng et al. 2018a).

The combination of resveratrol and other bioactive compounds could enhance the anticancer effects on pancreatic cancer. For instance, capsaicin is an alkaloid which widely exists in hot peppers, and it is commonly used to treat pain and inflammation (Zhang et al. 2020). The combination of resveratrol and capsaicin inhibited cell growth and induced apoptosis of pancreatic cancer cells through increasing ROS production to stimulate the activation of the stress response p38-MAPK (Vendrely et al. 2017).

In short, resveratrol has anticancer effects on pancreatic cancer by inhibiting pancreatic cancer cell proliferation, suppressing metastasis, modulating immune system, and decreasing chemo-resistance of pancreatic cancer cells to gemcitabine. In addition, the combination of resveratrol and capsaicin could enhance the anticancer effects on pancreatic cancer.

Prostate cancer

Prostate cancer is a common cancer of male genitourinary system, and its incidence increases with age (Zaffaroni and

Beretta 2021). Several studies showed that resveratrol could inhibit the prostate cancer cell proliferation through different mechanisms. For instance, resveratrol had anti-proliferation effect in human prostate cancer LNCaP cells via increasing accumulation of nuclear COX-2 and inducing phosphorylation and nuclear translocation of mitogen-activated protein kinase (Cheng et al. 2018b). Furthermore, resveratrol attenuated PC3 prostate cancer cell proliferation by interfering with glucose fermentation and boosting respiration. In addition, resveratrol was observed to inhibit cell viability and proliferation in prostate cancer DU145 and LNCaP cells through upregulating expression of prostate cancer associated transcript 29 (PCAT29) (Al Aameri et al. 2017).

Resveratrol could suppress prostate cancer cell metastasis. For example, resveratrol decreased hepatocyte growth factor (HGF)-mediated interaction between the stroma and epithelium, and suppressed epithelial prostate cancer cell migration via attenuating EMT (Hsieh and Wu 2020). Besides, resveratrol inhibited dihydrotestosterone (DHT)-induced prostate cancer cell metastasis through downregulating expression of androgen receptor (AR), C-X-C chemokine receptor type 4 (CXCR4), p-PI3K, p-AKT and related downstream genes, and upregulating expression of apoptosis-related genes, which was involved in the AR and CXCR4 pathway (Jang et al. 2019). Additionally, resveratrol suppressed proliferation and migration of prostate cancer DU145 and PC3 cells by mediating degradation of TRAF6, and inhibiting of NF-κ B pathway to repress EMT (Khusbu et al. 2020).

Several studies showed that resveratrol could induce apoptosis of prostate cancer cell. For example, resveratrol stimulated apoptosis of androgen-independent prostate cancer cells by enhancing dual specificity phosphatase 1 (DUSP1) expression, and inhibiting NF-κB pathway and Cox-2 expression (Martinez-Martinez et al. 2019). Another study showed that resveratrol promoted prostate cancer cell apoptosis through increasing ROS concentration and expression of Bax, hypoxia-inducible factor (HIF)-1α and p53, and inhibiting expression of Bcl-2 (Wang, Gao, and Zhang 2018). Furthermore, resveratrol reduced expression of AR mRNA and protein to suppress prostate cancer cell proliferation and promote apoptosis through PI3K/AKT signaling pathway (Ye et al. 2020).

Resveratrol could enhance the sensitivity of prostate cancer cells to docetaxel, which is a microtubule-stabilizing agent widely used for treatment of hormonerefractory prostate cancer. However, frequent acquisition of docetaxel resistance is the limitation of docetaxel in long-term treatment of prostate cancer (Barata and Sartor 2019). Resveratrol improved the efficacy of docetaxel on prostate cancer cells through increasing expression of Bax, BID and BAK, and decreasing expression of MCL-1, Bcl-2 and Bcl-xL (Singh et al. 2017). Furthermore, combination of resveratrol and docetaxel induced cell cycle arrest in prostate cancer C4-2B cells via stimulating expression of p53 and suppressing expression of CDK4, cyclin D1, cyclin E1 (Singh et al. 2017).

Resveratrol could weaken resistance of radiotherapy in prostate cancer. For example, resveratrol increased apoptosis of radio-resistant prostate cancer cells via inhibiting repair of radiation-induced DNA double-strand break and inducing the G2/M arrest (Chen et al. 2017).

In a word, resveratrol could inhibit prostate cancer cell proliferation, suppress prostate cancer cell metastasis, induce apoptosis of prostate cancer cells, and enhance the sensitivity of prostate cancer cells to docetaxel and radiation therapy.

Lung cancer

Lung cancer is the most cause of cancer deaths (Cao et al. 2019a). Several studies showed that resveratrol could inhibit lung cancer cell proliferation, suppress metastasis and induce apoptosis. For example, resveratrol inhibited proliferation and metastasis of malignant mucinous lung tumor cells by reducing expression of SAM pointed domain containing Ets transcription factor (SPDEF) and mucin 5, including subtypes A and C (MUC5AC) via suppression of ERK and AKT signaling pathways (Lin et al. 2021). Furthermore, resveratrol inhibited non-small-cell lung cancer progression by downregulating expressions of signal transduction and transcription activator 3 (STAT3), HIF-1α, and VEGF (Wang et al. 2020a). In addition, resveratrol suppressed viability of human small-cell lung cancer (SCLC) H446 cells and induced apoptosis by upregulating cytochrome c expression and downregulating expression of PI3K/AKT/c-Myc signaling pathway components (Li et al. 2020b). Additionally, resveratrol inhibited expression of protein arginine methyltransferase 5 (PRMT5), and decreased AKT/GSK-3-β phosphorylation and downstream targets cyclin D1 and E1 expression, which induced apoptosis of human lung cancer cells (Li et al. 2019c).

The other mechanisms of resveratrol against lung cancer have been widely studied. For instance, a clinical trial showed that inhibitory effect of resveratrol on lung cancer was involved in the immune signaling pathway and regulation of *ANPEP*, *CD69*, *ITGAL*, and *PTPRC* expression (Gao and Ren 2021). Another study showed that resveratrol inhibited PD-L1 expression in lung cancer cells through Wnt pathway to suppress T-cell-mediated immune response (Yang et al. 2021b). In addition, resveratrol epigenetically upregulated expression of zinc finger protein 36 (ZFP36) in A549 lung cancer cells by reducing expression of DNA (cytosine-5)-methyltransferase 1 and promoting demethylation of ZFP36 promoter (Fudhaili et al. 2019).

Resveratrol could enhance the sensitivity of lung cancer cells to other chemotherapeutic agents. For example, resveratrol increased anticancer effect of cisplatin in SCLC H446 cells through inducing mitochondrial depolarization, increasing cytochrome c release and apoptosis-inducing factor (AIF) translocation, and regulating the protein levels of Bcl-2, Bcl-xL and Bax (Li et al. 2018). Additionally, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is an effective anticancer agent for various cancers and resveratrol enhanced TRAIL-mediated apoptosis and palliated TRAIL resistance in NSCLC by downregulating expression of Bcl-2 and Bcl-xl, and suppressing AKT/NF-κ B signaling pathway (Rasheduzzaman, Jeong, and Park 2018).

In brief, resveratrol has anticancer effects on lung cancer and the mechanisms of action mainly include inhibition of lung cancer cell proliferation, suppression of metastasis and inducement of apoptosis. Furthermore, resveratrol could enhance the sensitivity of lung cancer cells to other chemotherapeutic agents, such as cisplatin and TRAIL.

Gastric cancer

Gastric cancer is one of the most common cancers worldwide (Mao et al. 2020). Some studies showed that resveratrol could prevent and treat gastric cancer via different pathways. For example, resveratrol repressed proliferation of human gastric cancer SNU-601 cells by inhibiting proviral integration site for moloney murine leukemia virus (PIM)-1 kinase activity (Kim et al. 2020b). Additionally, resveratrol suppressed growth of MGC-803 cells through downregulating mRNA and protein levels of β-catenin, c-myc, and cyclin D1, and inhibiting the Wnt signaling pathway (Dai et al. 2018). Moreover, resveratrol weakened invasion and migration of human gastric cancer cell line BGC823 by suppressing metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) expression, and inhibiting MALAT1-mediated EMT (Yang et al. 2019). In addition, mesenchymal stem cells (MSCs) were closely related to cancer metastasis and resveratrol reversed the pro-metastatic effect of GC-MSCs on gastric cancer cells, through downregulating IL-6, IL-8, MCP-1 and VEGF expression, and inhibiting activation of GC-MSC-induced Wnt/β-catenin signaling pathway (Yin et al. 2020). Resveratrol inhibited proliferation, migration and invasive of SGC-7901 cells through downregulation of HIF-1α protein levels, and suppressed EMT by inhibiting activation of the Hedgehog pathway (Xu et al. 2020b). Moreover, resveratrol suppressed IL-6 induced gastric cancer metastasis and matrix metalloproteinases activation through decreasing Raf/MAPK signaling activation (Yang et al. 2018). Besides, resveratrol induced apoptosis of SGC-7901 cells via increasing levels of cleaved caspase-3 and cleaved caspase-8, decreasing level of Bcl-2, and inhibiting activation of NF-κB signaling pathway (Wu et al. 2018).

Resveratrol could decrease the resistance of gastric cancer cells to other anticancer drugs. For instance, resveratrol enhanced anticancer effects of cisplatin in AGS gastric cancer cells by upregulating levels of cleaved poly-ADP-ribose polymerase (PARP), glucose-regulated protein 78, PRKR-like ER kinase and p-eukaryotic translation initiation factor-2-α (Ren et al. 2020). Additionally, resveratrol reversed the doxorubicin resistance of gastric cancer through suppression of EMT by inhibiting activation of PTEN/AKT signaling pathway (Xu et al. 2017). In addition, resveratrol decreased the multidrug resistance of gastric cancer cells through downregulating mRNA and protein levels of ATP binding cassette subfamily B member 1, Annexin A1 and thioredoxin (Mieszala et al. 2018).

In short, resveratrol could prevent and treat gastric cancer, and the underlying mechanisms mainly involved inhibiting gastric cancer cell proliferation, suppressing metastasis and inducing apoptosis. Moreover, resveratrol could decrease the resistance of gastric cancer cells to other anticancer drugs, such as cisplatin and doxorubicin.

Oral cancer

Oral cancer is a common malignant tumor, and a public health problem (Almeida et al. 2021). Resveratrol could prevent and treat oral cancer through inhibition of oral cancer cell proliferation and suppression of metastasis. For example, resveratrol reversed thyroid hormone-induced oral cancer cell proliferation by downregulating expression of cyclin D1, PD-L1 and BTLA, and upregulating expression of BAD in SSC-25 cells and OEC-M1 cells (Lin et al. 2019). In addition, rab coupling protein (RCP) was correlated with cancers cell proliferation and invasion, and resveratrol repressed invasion of RCP-induced oral squamous cell carcinoma (OSCC) by inhibiting expression of RCP-induced Zeb1, and suppressing β1 integrin endosome recycling and EGFR activation (Kim et al. 2020a). Furthermore, resveratrol inhibited metastasis of OSCC through suppression of EMT by downregulating expression of MT1-MMP (Kim et al. 2020a).

Resveratrol could enhance anticancer effects of other agents in oral cancer treatment. For instance, nano-diamino-tetrac (NDAT) is a tetraiodothyroxine deaminated nano-particulated analog, and resveratrol-NDAT combination treatment synergistically inhibited expression of pro-inflammatory IL-1β and TNF-α, and suppressing activity of PD-1/PD-L1 checkpoint in oral cancer cells (Ho et al. 2020). Furthermore, in the presence of thyroxine, NDAT enhanced anti-proliferation effect of resveratrol in oral cancer cells by inhibiting SATA3 signal transduction pathway (Ho et al. 2020). Additionally, the combination of resveratrol and quercetin led to cell growth inhibition, DNA damage, and S-phase cell cycle arrest in oral cancer cells but not in normal cells (Singh et al. 2020). Moreover, this combination treatment induced apoptosis in oral cancer cells through inducing cleavage of PARP1 and increasing expression of Bax (Singh et al. 2020). In addition, resveratrol promoted autophagy and apoptosis in cisplatin-resistant oral cancer cells through increasing phosphorylation of AMP-activated kinase (AMPK), inhibiting AKT signaling pathway, and upregulating autophagic mRNA gene expression, including Atg5, Atg12, Beclin-1 and LC3-II (Chang et al. 2017).

In a word, resveratrol has anticancer effects on oral cancer, and the related mechanisms mainly include inhibition of oral cancer cell proliferation and suppression of metastasis. In addition, resveratrol could enhance anticancer effects of other agents, such as NDAT, quercetin and cisplatin.

Thyroid cancer

Thyroid cancer is the most common endocrine malignancy tumor worldwide (Sharifi-Rad et al. 2020). Several studies showed that resveratrol could have an anticancer effect on thyroid cancer through different pathway. For example, resveratrol inhibited the tumorigenesis of follicular thyroid

cancer via upregulating expression of ST6GAL2, and stimulating the Hippo pathway (Xu et al. 2020a). For anaplastic thyroid cancer cells, resveratrol suppressed cell proliferation by increasing PTEN levels and changing sodium/iodide symporter intracellular distribution (Xiong et al. 2020). Additionally, resveratrol inhibited proliferation of anaplastic thyroid cancer cells through decreasing expression level of LIF, and repressing p-STAT3 nuclear translocation (Wu, J. et al., 2020).

Resveratrol could increase the sensitivity of thyroid cancer cells to other anticancer agents. A study showed that resveratrol enhanced the sensitivity of retinoic acid in anaplastic thyroid cancer THJ-11T and UW228-2 cells through upregulating expression of cellular retinoic acid binding protein 2 (CRABP2) and inducing CRABP2 demethylation (Liu, X. et al., 2019). Another study pointed out that resveratrol increased antitumor effect of rapamycin in papillary thyroid cancer by suppressing AKT activation caused by rapamycin, and inhibiting activation of mTOR (Bian et al. 2020).

In short, resveratrol could prevent and treat thyroid cancer, and the mechanisms of action mainly include inhibition of tumorigenesis and thyroid cancer cell proliferation. Moreover, resveratrol could increase the sensitivity of thyroid cancer cells to other anticancer agents, such as retinoic acid and rapamycin.

Bladder cancer

Bladder cancer is a common cancer worldwide (Wu, Q. et al., 2020). Several studies showed resveratrol could prevent and treat bladder cancer through suppression of bladder cancer cell proliferation, inhibition of metastasis and inducement of apoptosis. For example, resveratrol suppressed bladder cancer cell proliferation and promoted apoptosis by upregulating mRNA and protein level of PTEN, and downregulating expression of p-AKT (Li et al. 2019b). Additionally, resveratrol inhibited proliferation of bladder cancer cells and induced apoptosis via downregulating genes expression of AKT, mTOR and SRC (Almeida et al. 2019). In addition, resveratrol suppressed migration and invasion of bladder cancer cells by reducing expression and secretion of MMP-2 and MMP-9, and inhibiting phosphorylation of extracellular signal-regulated protein kinase (Bai et al. 2017).

Several studies showed that resveratrol could sensitize bladder cancer cells to anticancer agents, such as adriamycin, rapamycin, gemcitabine. For example, resveratrol decreased adriamycin (ADM) resistance and enhanced cytotoxicity of ADM in ADM-resistant pumc-91 cells through downregulating expression level of multidrug resistance protein 1 (MRP1), LRP, glutathione S-transferase (GST) and Bcl-2, and upregulating expression level of Topo-II (Wang et al. 2017). Additionally, resveratrol induced apoptosis of rapamycin on human bladder cancer cell lines through suppressing rapamycin-induced AKT activation, and inhibiting mTOR pathway (Alayev et al. 2017). Furthermore, resveratrol reduced the drug resistance of T24-GCB cells to gemcitabine (GCB), enhanced cytotoxicity of GCB and suppressed migration of T24-GCB cells through increasing expression of ABCC2 and cleaved-PARP, and decreasing expression of deoxycytidine kinase (DCK), TK1 and TK2 (Cho et al. 2019).

In short, resveratrol has anticancer effects on bladder cancer, and the mechanisms of action mainly include inhibition of bladder cancer cell proliferation, suppression of metastasis and inducement of apoptosis. In addition, resveratrol could enhance the sensitivity of bladder cancer cells to anticancer agents, such as adriamycin, rapamycin and gemcitabine.

Ovarian cancer

Ovarian cancer is a common cancer in women, and a global public health problem (Wu et al. 2021). Resveratrol could play an important role in prevention and treatment of ovarian cancer through several pathways. For example, resveratrol attenuated proliferation and migration of OV-90 and SKOV-3 cells by decreasing Bcl-2 expression and increasing microRNA-34 expression (Yao et al. 2021). Moreover, resveratrol boosted apoptosis of ovarian cancer cells via downregulating expression levels of galectin-3 and upregulating expression levels of miR-424-3p (El-kott et al. 2019). In addition, IL-6-induced ovarian cancer cell migration was weakened by resveratrol through increasing expression of ARH-I and decreasing expression of STAT3, which was linked to induce cell autophagy at the cell migration front (Ferraresi et al. 2017). Another study showed that resveratrol suppressed ovarian cancer cell proliferation and induced apoptosis in A2780 and SKOV3 ovarian cancer cells via restricting the glycolysis, upregulating expression and activation of AMPK and caspase-3, and downregulating expression and activation of mTOR (Liu et al. 2018). Furthermore, the in vivo study showed that resveratrol inhibited ovarian cancer cell growth and liver metastasis in xenograft mouse model (Liu et al. 2018). Additionally, resveratrol promoted apoptosis of caspase-dependent cells via inhibiting the Notch1 and PTEN/AKT signaling pathway and upregulating ROS generation in human ovarian cancer cells (Kim, Park, and Woo 2019).

In a word, resveratrol could prevent and treat ovarian cancer, and the mechanisms mainly include inhibiting ovarian cancer cell proliferation, suppressing metastasis, inducing apoptosis and stimulating autophagy.

Cervical cancer

Cervical cancer is one of the most dangerous malignant tumors in women (He, Xia, and Li 2021). Several studies showed that resveratrol could have anticancer effects against cervical cancer through different pathways. For example, resveratrol inhibited growth of HeLa cells through decreasing expression level of phospholipid scramblase 1 (PLSCR1) (Zhao et al. 2019). Furthermore, resveratrol suppressed proliferation and metastasis of cervical cancer cells via reducing phosphorylation of STAT3 (Sun et al. 2020). Another study showed that resveratrol suppressed cervical cancer HeLa cells proliferation and enhanced apoptosis via activation and

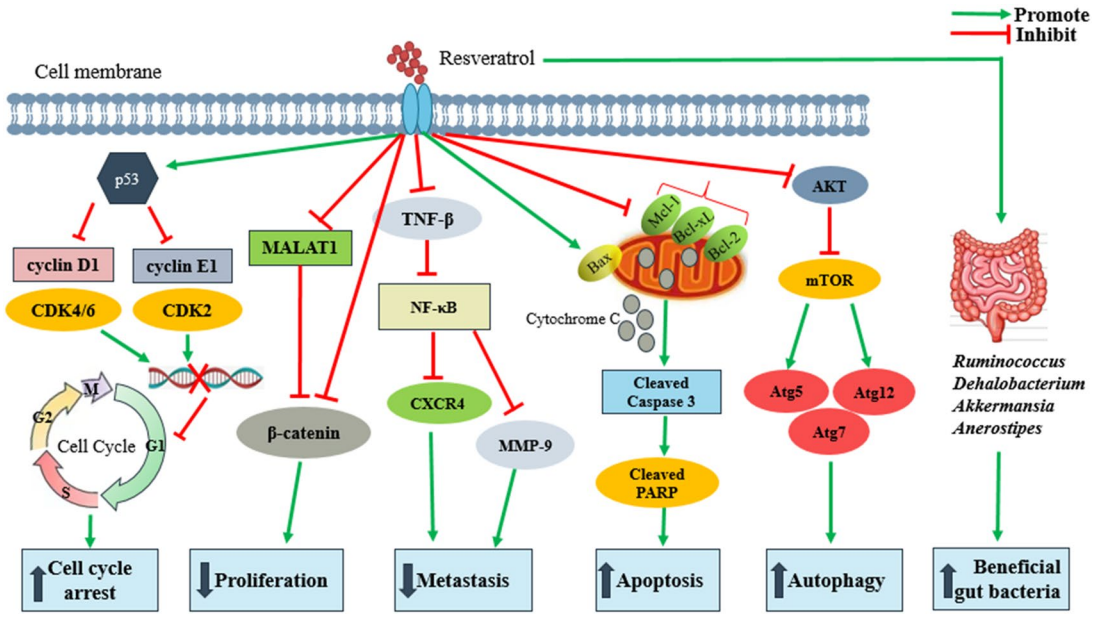

Figure 1. The effects and mechanisms of resveratrol on cancers. Resveratrol could stimulate cancer cells arrest by increasing expression of p53, decreasing expression of cyclin D1, cyclin E1, CDK2 and CDK4, inhibiting specific DNA sequences, and then blocking the G/S transition of the cells. Furthermore, resveratrol inhibited cancer cells proliferation through suppressing expression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and β-catenin. Moreover, resveratrol suppressed cancer cells metastasis via inhibiting the tumor necrosis factor (TNF)-β and nuclear factor-kappa B (NF-κB) signaling pathways, and futher decreasing expression of C-X-C chemokine receptor type 4 (CXCR4) and matrix metalloproteinase (MMP)-9. Additionally, resveratrol induced canccer cells apoptosis by upregulating expression of Bax, downregulating expression of Mcl-1, Bcl-xL and Bcl-2, enhancing cytochrome c release, and then increasing expression of cleaved caspase-3 and cleaved poly-ADP-ribose polymerase (PARP). Resveratrol also stimulated cancer cells autophagy by inhibting activation of protein kinase B (AKT) and mammalian target of rapamycin (mTOR) signaling pathways, increasing expression of Atg 5, Atg 7, Atg 12. In addition, resveratrol regulated gut microbiota to exert anticancer effects, such as increaseing genus level of *Ruminococcus*, *Akkermansia*, *Dehalobacterium* and *Anerostipes*.

nuclear translocation promotion of forkhead box O 3a, which further upregulated expression of Bcl-2 interacting mediator of cell death (Liu et al. 2020). In addition, resveratrol repressed cervical cancer development and induced apoptosis through inhibiting transcription and translation of HPV E6 and E7 genes, and promoting G1/S phase transition arrest (Sun et al. 2021b).

In a word, resveratrol has anticancer effects on cervical cancer, and the underlying mechanisms mainly include suppression of cervical cancer cell proliferation, inhibition of metastasis and inducement of apoptosis.

Other cancers

In addition to the cancers mentioned above, resveratrol also has the potential to treat other cancers, such as renal, liver, gallbladder, and head and neck cancers. For instance, resveratrol suppressed renal cancer cell proliferation, induced cell apoptosis, and arrested cell cycle via increasing expression of miR-30a-5p (Zhu et al. 2021). Furthermore, resveratrol inhibited proliferation of renal cancer stem cells and promoted apoptosis through decreasing expression of the Sonic hedgehog pathway-related proteins (Sun et al. 2021a). Another study showed that resveratrol had a cytotoxic effect on human gallbladder cancer cells and inhibited cells growth through increasing activation of transglutaminase 2 (Roncoroni et al. 2018). Additionally, an in vivo study showed that resveratrol inhibited migration of head and neck cancer cells by stimulating mRNA expression of regenerating gene III (Mikami et al. 2019). Moreover, resveratrol enhanced head and neck cancer cells response to cisplatin by inducing apoptosis, upregulating expression of c-MYC and TP53, and downregulating Bcl-2 expression (Bostan et al. 2021). In addition, resveratrol enhanced anticancer effect of paclitaxel on liver cancer HepG2 cells by increasing caspase-3, caspase-8, caspase-9, p53 and p21 expressions, and decreasing mRNA and protein expressions of NF-κB, COX-2 and MMP-2 (Jiang et al. 2017). In conclusion, resveratrol has shown anticancer effects on various cancers, such as breast, colorectal, pancreatic, prostate, lung, gastric, oral, thyroid, bladder and ovarian cancers.

Anticancer mechanisms of resveratrol

Resveratrol showed anticancer activity against different cancers, and the anticancer mechanisms were summarized below (Figure 1). (1) Resveratrol could arrest cancer cell cycle through increasing expression of p53 and suppressing expression of CDK4, cyclin D1 and cyclin E1. (2) Resveratrol could inhibit cancer cell proliferation by upregulating expression of PCAT29, BAD and PTEN, increasing ROS production, promoting accumulation of nuclear COX-2, inducing phosphorylation and nuclear translocation of mitogen-activated protein kinase, downregulating expression of cyclin D1, PD-L1, BTLA, EZH2 and LIF, inhibiting

p-STAT3 nuclear translocation and PIM-1 kinase activity. (3) Resveratrol could suppress metastasis of cancer cells via increasing expression of E-cadherin, RKIP and regenerating gene III, reducing expression of CXCR4, SPDEF, MALAT1, MCP-1, MMP-2 and MMP-9, reversing the EMT, and modulating AKT/GSK-3-β/snail, Wnt/β-catenin and Raf/MAPK signaling pathways. (4) Resveratrol could induce cancer cell apoptosis through decreasing expression of Bcl-2, Bcl-xL, MCL-1, Cox-2, PRMT5 and galectin-3, increasing expression of Bax, BID, BAK, cytochrome c, cleaved caspase-3, cleaved caspase-9 and p53, enhancing ROS production, as well as inhibiting NF-κB, AKT/GSK-3-β and mTOR signaling pathways. (5) Resveratrol could stimulate cancer cell autophagy by increasing expression of ARH-I, decreasing expression of STAT3, upregulating autophagic mRNA gene expression Atg5, Atg7, Atg12, Beclin-1 and LC3-II, and modulating AMPK and AKT signaling pathways. (6) Resveratrol could prevent cancers through modulating immune system via inhibiting immunoreactivity of N-cadherin and TNF-α, as well as suppressing PD-L1 expression through Wnt pathway to inhibit T-cell-mediated immune response. (7) Resveratrol could attenuate inflammation through downregulating pro-inflammatory Th1 and Th17 cells, and upregulating anti-inflammatory CD4+ FOXP3+ (Tregs) and CD4+ IL10+ cells. (8) Resveratrol also could regulate gut microbiota to exert anticancer effects, such as increasing genus levels of *Ruminococcus*, *Akkermansia*, *Dehalobacterium* and *Anerostipes*. (9) Resveratrol could enhance sensitivity of chemotherapeutic drugs, such as cisplatin, gemcitabine, cetuximab and doxorubicin, and increase sensitivity of radiotherapy.

Conclusions and perspectives

Cancer is a severe public health problem in the world. Resveratrol showed anticancer activities against various cancers, such as breast, colorectal, pancreatic, prostate, lung, gastric, oral, thyroid, bladder and ovarian cancers. The potential mechanisms of action mainly include arresting cell cycle, inhibiting cell proliferation, suppressing metastasis, inducing apoptosis, stimulating autophagy, modulating immune system, attenuating inflammation, regulating gut microbiota as well as enhancing the effects of other cancer therapies. Therefore, foods containing resveratrol (such as grape), resveratrol extract (such as the extract from grape skin and seeds), and resveratrol could be developed as the functional food, dietary supplements or auxiliary agents for prevention and management of cancers. In the future, effects of resveratrol on more cancers should be evaluated, and the potential mechanisms should be studied. Additionally, more clinical trials should be carried out to confirm effects of resveratrol on human beings, and the adverse effects should also be observed.

Author contributions

Conceptualization, S.-X.W., Y.-J.Z., R.-Y.G., and H.-B.L.; Writing—original draft preparation, S.-X.W., R.-G.X., S.-Y.H., D.-D.Z., A.S. (Adila Saimaiti), C.-N.Z., and A.S. (Ao Shang); Writing—review and editing, Y.-J.Z., R.-Y.G. and H.-B.L.; Supervision, Y.-J.Z., R.-Y.G. and H.-B.L.; Funding acquisition, R.-Y.G. and H.-B.L.

Disclosure statement

The authors declare no conflict of interest.

Funding

This research was funded by Local Financial Funds of National Agricultural Science and Technology Center, Chengdu (No. NASC2021KR01), and the Key Project of Guangdong Provincial Science and Technology Program (No. 2014B020205002).

ORCID

Adila Saimaiti http://orcid.org/0000-0003-2377-0908
Ren-You Gan http://orcid.org/0000-0002-4162-1511
Hua-Bin Li http://orcid.org/0000-0003-2332-8554

References

Al Aameri, R. F. H., S. Sheth, E. M. A. Alanisi, V. Borse, D. Mukherjea, L. P. Rybak, and V. Ramkumar. 2017. Tonic suppression of PCAT29 by the IL-6 signaling pathway in prostate cancer: Reversal by resveratrol. *Plos One* 12 (5):e0177198. doi: 10.1371/journal.pone.0177198.

Alayev, A., R. S. Salamon, N. S. Schwartz, A. Y. Berman, S. L. Wiener, and M. K. Holz. 2017. Combination of rapamycin and resveratrol for treatment of bladder cancer. *Journal of Cellular Physiology* 232 (2):436–46. doi: 10.1002/jcp.25443.

Almeida, T. C., G. N. da Silva, D. V. de Souza, A. C. de Moraes Malinverni, O. Aguiar, Jr, D. Estadella, and D. A. Ribeiro. 2021. Resveratrol effects in oral cancer cells: A comprehensive review. *Medical Oncology* 38 (8):97. doi: 10.1007/s12032-021-01548-0.

Almeida, T. C., C. C. C. Guerra, B. L. G. De Assis, R. Soares, C. C. M. Garcia, A. A. Lima, and G. N. da Silva. 2019. Antiproliferative and toxicogenomic effects of resveratrol in bladder cancer cells with different TP53 status. *Environmental and Molecular Mutagenesis* 60 (8):740–51. doi: 10.1002/em.22297.

Alrafas, H. R., P. B. Busbee, K. N. Chitrala, M. Nagarkatti, and P. Nagarkatti. 2020. Alterations in the gut microbiome and suppression of histone deacetylases by resveratrol are associated with attenuation of colonic inflammation and protection against colorectal cancer. *Journal of Clinical Medicine* 9 (6):1796. doi: 10.3390/jcm9061796.

da Costa Araldi, I. C., F. P. R. Bordin, F. C. Cadoná, F. Barbisan, V. F. Azzolin, C. F. Teixeira, T. Baumhardt, I. B. M. da Cruz, M. M. M. F. Duarte, L. d F. Bauermann, et al. 2018. The in vitro radiosensitizer potential of resveratrol on MCF-7 breast cancer cells. *Chemico-Biological Interactions* 282:85–92. doi: 10.1016/j.cbi.2018.01.013.

Bai, Y., H. Yang, G. Zhang, L. Hu, Y. Lei, Y. Qin, Y. Yang, Q. Wang, R. Li, Q. Mao, et al. 2017. Inhibitory effects of resveratrol on the adhesion, migration and invasion of human bladder cancer cells. *Molecular Medicine Reports* 15 (2):885–9. doi: 10.3892/mmr.2016.6051.

Barata, P. C, and A. O. Sartor. 2019. Metastatic castration-sensitive prostate cancer: Abiraterone, docetaxel, or. *Cancer* 125 (11):1777–88. doi: 10.1002/cncr.32039.

Bian, P., W. Hu, C. Liu, and L. Li. 2020. Resveratrol potentiates the anti-tumor effects of rapamycin in papillary thyroid cancer: PI3K/AKT/mTOR pathway involved. *Archives of Biochemistry and Biophysics* 689:108461. doi: 10.1016/j.abb.2020.108461.

Blanquer-Rossello, M. D., R. Hernandez-Lopez, P. Roca, J. Oliver, and A. Valle. 2017. Resveratrol induces mitochondrial respiration and apoptosis in SW620 colon cancer cells. *Biochimica et Biophysica*

Acta. General Subjects 1861 (2):431–40. doi: 10.1016/j.bbagen.2016.10.009.

Bostan, M., M. Mihaila, G. G. Petrica-Matei, N. Radu, R. Hainarosie, C. D. Stefanescu, V. Roman, and C. C. Diaconu. 2021. Resveratrol modulation of apoptosis and cell cycle response to cisplatin in head and neck cancer cell lines. *International Journal of Molecular Sciences* 22 (12):6322. doi: 10.3390/ijms22126322.

Bray, F., J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal. 2018. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 68 (6):394–13. doi: 10.3322/caac.21609.

Buhrmann, C., M. Yazdi, B. Popper, A. B. Kunnumakkara, B. B. Aggarwal, and M. Shakibaei. 2019a. Induction of the epithelial-to-mesenchymal transition of human colorectal cancer by human TNF-beta (lymphotoxin) and its reversal by resveratrol. *Nutrients* 11 (3):704. doi: 10.3390/nu11030704.

Buhrmann, C., M. Yazdi, B. Popper, P. Shayan, A. Goel, B. B. Aggarwal, and M. Shakibaei. 2019b. Evidence that TNF-beta induces proliferation in colorectal cancer cells and resveratrol can down-modulate it. *Experimental Biology and Medicine (Maywood, N.J.)* 244 (1):1–12. doi: 10.1177/1535370218824538.

Cao, S.-Y., Y. Li, X. Meng, C.-N. Zhao, S. Li, R.-Y. Gan, and H.-B. Li. 2019a. Dietary natural products and lung cancer: Effects and mechanisms of action. *Journal of Functional Foods* 52:316–31. doi: 10.1016/j.jff.2018.11.004.

Cao, S.-Y., C.-N. Zhao, R.-Y. Gan, X.-Y. Xu, X.-L. Wei, H. Corke, A. G. Atanasov, and H.-B. Li. 2019b. Effects and mechanisms of tea and its bioactive compounds for the prevention and treatment of cardiovascular diseases: An updated review. *Antioxidants* 8 (6):166. doi: 10.3390/antiox8060166.

Chang, C.-H., C.-Y. Lee, C.-C. Lu, F.-J. Tsai, Y.-M. Hsu, J.-W. Tsao, Y.-N. Juan, H.-Y. Chiu, J.-S. Yang, C.-C. Wang, et al. 2017. Resveratrol-induced autophagy and apoptosis in cisplatin-resistant human oral cancer car cells: A key role of AMPK and AKT/mTOR signaling. *International Journal of Oncology* 50 (3):873–82. doi: 10.3892/ijo.2017.3866.

Chauhan, S. S., A. B. Shetty, E. Hatami, P. Chowdhury, and M. M. Yallapu. 2020. Pectin-tannic acid nano-complexes promote the delivery and bioactivity of drugs in pancreatic cancer cells. *Pharmaceutics* 12 (3):285. doi: 10.3390/pharmaceutics12030285.

Chen, Y.-A., H.-M. Lien, M.-C. Kao, U.-G. Lo, L.-C. Lin, C.-J. Lin, S.-J. Chang, C.-C. Chen, J.-T. Hsieh, H. Lin, et al. 2017. Sensitization of radioresistant prostate cancer cells by resveratrol isolated from arachis hypogaea stems. *Plos One* 12 (1):e0169204. doi: 10.1371/journal.pone.0169204.

Chen, Y.-R., Y.-S. Chen, Y.-T. Chin, Z.-L. Li, Y.-J. Shih, Y.-C S. H. Yang, C. A. ChangOu, P.-Y. Su, S.-H. Wang, Y.-H. Wu, et al. 2019. Thyroid hormone-induced expression of inflammatory cytokines interfere with resveratrol-induced anti-proliferation of oral cancer cells. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 132:110693. doi: 10.1016/j.fct.2019.110693.

Cheng, L., B. Yan, K. Chen, Z. Jiang, C. Zhou, J. Cao, W. Qian, J. Li, L. Sun, J. Ma, et al. 2018a. Resveratrol-induced downregulation of NAF-1 enhances the sensitivity of pancreatic cancer cells to gemcitabine via the ROS/Nrf2 signaling pathways. *Oxidative Medicine and Cellular Longevity* 2018:9482018. doi: 10.1155/2018/9482018.

Cheng, T.-M., Y.-T. Chin, Y. Ho, Y.-R. Chen, Y.-N. Yang, Y.-C. Yang, Y.-J. Shih, T.-I. Lin, H.-Y. Lin, P. J. Davis, et al. 2018b. Resveratrol induces sumoylated COX-2-dependent anti-proliferation in human prostate cancer LNCaP cells. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 112:67–75. doi: 10.1016/j.fct.2017.12.011.

Cho, C. J., C. W. Yang, C. L. Wu, J. Y. Ho, C. P. Yu, S. T. Wu, and D. S. Yu. 2019. The modulation study of multiple drug resistance in bladder cancer by curcumin and resveratrol. *Oncology Letters* 18 (6):6869–76. doi: 10.3892/ol.2019.11023.

Dai, H., H. B. Deng, Y. H. Wang, and J. J. Guo. 2018. Resveratrol inhibits the growth of gastric cancer via the Wnt/-catenin pathway. *Oncology Letters* 16 (2):1579–83. doi: 10.3892/ol.2018.8772.

Dariya, B., S. K. Behera, G. Srivani, S. Aliya, A. Alam, and G. P. Nagaraju. 2020. Resveratrol binds and activates RKIP protein in colorectal cancer. *Amino Acids* 52 (9):1299–306. doi: 10.1007/s00726-020-02889-2.

Davidson, K. W., M. J. Barry, C. M. Mangione, M. Cabana, A. B. Caughey, E. M. Davis, K. E. Donahue, C. A. Doubeni, A. H. Krist, M. Kubik, et al. 2021. Screening for colorectal cancer: Us preventive services task force recommendation statement. *Jama* 325 (19):1965–77. doi: 10.1001/jama.2021.6238.

Dermani, F. K., M. Saidijam, R. Amini, A. Mahdavinezhad, K. Heydari, and R. Najafi. 2017. Resveratrol inhibits proliferation, invasion, and epithelial-mesenchymal transition by increasing miR-200c expression in HCT-116 colorectal cancer cells. *Journal of Cellular Biochemistry* 118 (6):1547–55. doi: 10.1002/jcb.25816.

El-kott, A. F., A. A. Shati, M. A. Al-Kahtani, and S. A. Alharbi. 2019. The apoptotic effect of resveratrol in ovarian cancer cells is associated with downregulation of galectin-3 and stimulating Mir-424-3p transcription. *Journal of Food Biochemistry* 43 (12):e13072. doi: 10.1111/jfbc.13072.

Elshaer, M., Y. R. Chen, X. J. Wang, and X. W. Tang. 2018. Resveratrol: An overview of its anti-cancer mechanisms. *Life Sciences* 207:340–9. doi: 10.1016/j.lfs.2018.06.028.

Farha, A. K., R.-Y. Gan, H.-B. Li, D.-T. Wu, A. G. Atanasov, K. Gul, J.-R. Zhang, Q.-Q. Yang, and H. Corke. 2022. The anticancer potential of the dietary polyphenol rutin: Current status, challenges, and perspectives. *Critical Reviews in Food Science and Nutrition* 62 (3):832–59. doi: 10.1080/10408398.2020.1829541.

Ferraresi, A., S. Phadngam, F. Morani, A. Galetto, O. Alabiso, G. Chiorino, and C. Isidoro. 2017. Resveratrol inhibits IL-6-induced ovarian cancer cell migration through epigenetic up-regulation of autophagy. *Molecular Carcinogenesis* 56 (3):1164–81. doi: 10.1002/mc.22582.

Fonseca, J., F. Moradi, L. A. Maddalena, B. Ferreira-Tollstadius, S. Selim, and J. A. Stuart. 2019. Resveratrol integrates metabolic and growth effects in PC3 prostate cancer cells-involvement of prolyl hydroxylase and hypoxia inducible factor-1. *Oncology Letters* 17 (1):697–705. doi: 10.3892/ol.2018.9526.

Fu, Y., Y. Ye, G. Zhu, Y. Xu, J. Sun, H. Wu, F. Feng, Z. Wen, S. Jiang, Y. Li, et al. 2020. Resveratrol induces human colorectal cancer cell apoptosis by activating the mitochondrial pathway via increasing reactive oxygen species. *Molecular Medicine Reports* 23 (3):170. doi: 10.3892/mmr.2020.11809.

Fudhaili, A., N. A. Yoon, S. Kang, J. Ryu, J. Y. Jeong, D. H. Lee, and S. S. Kang. 2019. Resveratrol epigenetically regulates the expression of zinc finger protein 36 in non-small cell lung cancer cell lines. *Oncology Reports* 41 (2):1377–86. doi: 10.3892/or.2018.6898.

Gao, P, and G. H. Ren. 2021. Identification of potential target genes of non-small cell lung cancer in response to resveratrol treatment by bioinformatics analysis. *Aging* 13 (19):23245–61. doi: 10.18632/aging.203616.

Gao, Y. F, and T. O. Tollefsbol. 2018. Combinational proanthocyanidins and resveratrol synergistically inhibit human breast cancer cells and impact epigenetic-mediating machinery. *International Journal of Molecular Sciences* 19 (8):2204. doi: 10.3390/ijms19082204.

He, M., L. Xia, and J. Li. 2021. Potential mechanisms of plant-derived natural products in the treatment of cervical cancer. *Biomolecules* 11 (10):1539. doi: 10.3390/biom11101539.

Ho, Y., C.-Y. Wu, Y.-T. Chin, Z.-L. Li, Y.-S. Pan, T.-Y. Huang, P.-Y. Su, S.-Y. Lee, D. R. Crawford, K.-W. Su, et al. 2020. Ndat suppresses pro-inflammatory gene expression to enhance resveratrol-induced anti-proliferation in oral cancer cells. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association* 136:111092. doi: 10.1016/j.fct.2019.111092.

Hoca, M., E. Becer, H. Kabadayi, S. Yucecan, and H. S. Vatansever. 2020. The effect of resveratrol and quercetin on epithelial-mesenchymal transition in pancreatic cancer stem cell. *Nutrition and Cancer* 72 (7):1231–42. doi: 10.1080/01635581.2019.1670853.

Hsieh, T. C, and J. M. Wu. 2020. Resveratrol suppresses prostate cancer epithelial cell scatter/invasion by targeting inhibition of hepato-

cyte growth factor (HGF) secretion by prostate stromal cells and upregulation of e-cadherin by prostate cancer epithelial cells. *International Journal of Molecular Sciences* 21 (5):1760. doi: 10.3390/ijms21051760.

Hu, C. Y., Y. Liu, M. Y. Teng, K. L. Jiao, J. Zhen, M. X. Wu, and Z. Li. 2019. Resveratrol inhibits the proliferation of estrogen receptor-positive breast cancer cells by suppressing EZH2 through the modulation of ERK1/2 signaling. *Cell Biology and Toxicology* 35 (5):445–56. doi: 10.1007/s10565-019-09471-x.

Jang, M., L. Cai, G. O. Udeani, K. V. Slowing, C. F. Thomas, C. W. Beecher, H. H. Fong, N. R. Farnsworth, A. D. Kinghorn, R. G. Mehta, et al. 1997. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science (New York, N.Y.)* 275 (5297):218–20. doi: 10.1126/science.275.5297.218.

Jang, Y. G., R. E. Go, K. A. Hwang, and K. C. Choi. 2019. Resveratrol inhibits DHT-induced progression of prostate cancer cell line through interfering with the AR and CXCR4 pathway. *The Journal of Steroid Biochemistry and Molecular Biology* 192:105406. doi: 10.1016/j.jsbmb.2019.105406.

Jiang, H., G. T. Wang, J. T. Gu, Y. Xiao, P. L. Wang, X. Huang, H. C. Sha, Z. Wang, and Q. Y. Ma. 2022. Resveratrol inhibits the expression of RYR2 and is a potential treatment for pancreatic cancer. *Naunyn-Schmiedeberg's Archives of Pharmacology* 395 (3):315–24. doi: 10.1007/s00210-022-02203-9.

Jiang, Q., M. Y. Yang, Z. Qu, J. X. Zhou, and Q. Zhang. 2017. Resveratrol enhances anticancer effects of paclitaxel in HEPG2 human liver cancer cells. *BMC Complementary and Alternative Medicine* 17 (1):477. doi: 10.1186/s12906-017-1956-0.

Khusbu, F. Y., X. Zhou, M. Roy, F. Z. Chen, Q. Cao, and H. C. Chen. 2020. Resveratrol induces depletion of TRAF6 and suppresses prostate cancer cell proliferation and migration. *The International Journal of Biochemistry & Cell Biology* 118:105644. doi: 10.1016/j.biocel.2019.105644.

Kim, J. Y., K. H. Cho, B. Y. Jeong, C. G. Park, and H. Y. Lee. 2020a. Zeb1 for RCP-induced oral cancer cell invasion and its suppression by resveratrol. *Experimental & Molecular Medicine* 52 (7):1152–63. doi: 10.1038/s12276-020-0474-1.

Kim, S., W. Kim, D.-H. Kim, J.-H. Jang, S.-J. Kim, S.-A. Park, H. Hahn, B. W. Han, H.-K. Na, K.-S. Chun, et al. 2020b. Resveratrol suppresses gastric cancer cell proliferation and survival through inhibition of PIM-1 kinase activity. *Archives of Biochemistry and Biophysics* 689:108413. doi: 10.1016/j.abb.2020.108413.

Kim, T. H., J. H. Park, and J. S. Woo. 2019. Resveratrol induces cell death through ros-dependent downregulation of Notch1/PTEN/Akt signaling in ovarian cancer cells. *Molecular Medicine Reports* 19 (4):3353–60. doi: 10.3892/mmr.2019.9962.

Lacerda-Abreu, M. A., T. Russo-Abrahao, and J. R. Meyer-Fernandes. 2021. Resveratrol is an inhibitor of sodium-dependent inorganic phosphate transport in triple-negative MDA-MB-231 breast cancer cells. *Cell Biology International* 45 (8):1768–75. doi: 10.1002/cbin.11616.

Leon-Galicia, I., J. Diaz-Chavez, M. E. Albino-Sanchez, E. Garcia-Villa, R. Bermudez-Cruz, J. Garcia-Mena, L. A. Herrera, A. Garcia-Carranca, and P. Gariglio. 2018. Resveratrol decreases Rad51 expression and sensitizes cisplatin-resistant MCF-7 breast cancer cells. *Oncology Reports* 39 (6):3025–33. doi: 10.3892/or.2018.6336.

Li, D., G. Wang, G. Jin, K. Yao, Z. Zhao, L. Bie, Y. Guo, N. Li, W. Deng, X. Chen, et al. 2019a. Resveratrol suppresses colon cancer growth by targeting the AKT/STAT3 signaling pathway. *International Journal of Molecular Medicine* 43 (1):630–40. doi: 10.3892/ijmm.2018.3969.

Li, L. J., D. K. Chen, J. L. Zhu, J. Ouyang, B. L. Song, S. L. Zhao, K. S. Luo, W. Li, and Y. Liu. 2019b. Inhibition of resveratrol on bladder cancer and its molecular mechanism. *Acta Medica Mediterranea* 35 (2):797–802. doi: 10.19193/0393-6384_2019_2_120.

Li, R., M. Liang, X. Liang, L. Yang, M. Su, and K. P. Lai. 2020a. Chemotherapeutic effectiveness of combining cetuximab for metastatic colorectal cancer treatment: A system review and meta-analysis. *Frontiers in Oncology* 10:868. doi: 10.3389/fonc.2020.00868.

Li, W. P., C. M. Li, L. J. Ma, and F. G. Jin. 2020b. Resveratrol inhibits its viability and induces apoptosis in the small-cell lung cancer H446 cell line via the PI3K/Akt/c-Myc pathway. *Oncology Reports* 44 (5):1821–30. doi: 10.3892/or.2020.7747.

Li, W. P., Y. Shi, R. X. Wang, L. Pan, L. J. Ma, and F. G. Jin. 2018. Resveratrol promotes the sensitivity of small-cell lung cancer H446 cells to cisplatin by regulating intrinsic apoptosis. *International Journal of Oncology* 53 (5):2123–30. doi: 10.3892/ijo.2018.4533.

Li, Y., S. Li, X. Meng, R.-Y. Gan, J.-J. Zhang, and H.-B. Li. 2017. Dietary natural products for prevention and treatment of breast cancer. *Nutrients* 9 (7):728. doi: 10.3390/nu9070728.

Li, Y., Y. X. Yang, X. P. Liu, Y. W. Long, and Y. H. Zheng. 2019c. Prmt5 promotes human lung cancer cell apoptosis via AKT/GSK3 beta signaling induced by resveratrol. *Cell Transplantation* 28 (12):1664–73. doi: 10.1177/0963689719885083.

Liang, Z.-J., Y. Wan, D.-D. Zhu, M.-X. Wang, H.-M. Jiang, D.-L. Huang, L.-F. Luo, M.-J. Chen, W.-P. Yang, H.-M. Li, et al. 2021. Resveratrol mediates the apoptosis of triple negative breast cancer cells by reducing pold1 expression. *Frontiers in Oncology* 11:569295. doi: 10.3389/fonc.2021.569295.

Lin, C.-C., Y.-T. Chin, Y.-J. Shih, Y.-R. Chen, Y.-Y. Chung, C.-Y. Lin, C.-N. Hsiung, J. Whang-Peng, S.-Y. Lee, H.-Y. Lin, et al. 2019. Resveratrol antagonizes thyroid hormone-induced expression of checkpoint and proliferative genes in oral cancer cells. *Journal of Dental Sciences* 14 (3):255–62. doi: 10.1016/j.jds.2019.01.013.

Lin, Y.-H., L.-Y. Zhu, Y.-Q. Yang, Z.-H. Zhang, Q.-G. Chen, Y.-P. Sun, J.-J. Bi, X.-M. Luo, Z.-H. Ni, X.-B. Wang, et al. 2021. Resveratrol inhibits MUC5AC expression by regulating SPDEF in lung cancer cells. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 89:153601. doi: 10.1016/j.phymed.2021.153601.

Liu, X., H. Li, M. L. Wu, J. Wu, Y. Sun, K. L. Zhang, and J. Liu. 2019. Resveratrol reverses retinoic acid resistance of anaplastic thyroid cancer cells via demethylating CRABP2 gene. *Frontiers in Endocrinology* 10:734. doi: 10.3389/fendo.2019.00734.

Liu, Y., L. Tong, Y. Luo, X. Li, G. W. Chen, and Y. F. Wang. 2018. Resveratrol inhibits the proliferation and induces the apoptosis in ovarian cancer cells via inhibiting glycolysis and targeting AMPK/mTOR signaling pathway. *Journal of Cellular Biochemistry* 119 (7):6162–72. doi: 10.1002/jcb.26822.

Liu, Z. L., X. H. Wu, J. J. Lv, H. Sun, and F. Q. Zhou. 2019. Resveratrol induces p53 in colorectal cancer through SET7/9. *Oncology Letters* 17 (4):3783–9. doi: 10.3892/ol.2019.10034.

Liu, Z. X., Y. J. Li, G. H. She, X. F. Zheng, L. Y. Shao, P. Y. Wang, M. Pang, S. Y. Xie, and Y. X. Sun. 2020. Resveratrol induces cervical cancer hela cell apoptosis through the activation and nuclear translocation promotion of foxo3a. *Die Pharmazie* 75 (6):250–4. doi: 10.1691/ph.2020.0386.

Lucas, J., T. C. Hsieh, H. D. Halicka, Z. Darzynkiewicz, and J. M. Wu. 2018. Upregulation of PD-l1 expression by resveratrol and piceatannol in breast and colorectal cancer cells occurs via HDAC3/p300-mediated NF-kappa B signaling. *International Journal of Oncology* 53 (4):1469–80. doi: 10.3892/ijo.2018.4512.

Luo, Y. Y., D. Liu, X. Q. Wang, X. P. Ye, N. Li, Y. Zhang, J. J. Song, and Q. Wang. 2021. Resveratrol exerts an antiproliferative effect in pancreatic cancer cells by inducing mitochondrial-mediated apoptosis. *Acta Poloniae Pharmaceutica - Drug Research* 77 (6):871–9. doi: 10.32383/appdr/130296.

Madencioglu, S., E. Becer, H. Kabadayi, H. S. Vatansever, and S. Yucecan. 2021. Resveratrol triggers apoptosis in colon cancer cells rather than senescence. *Progress in Nutrition* 23 (1):e2021018. doi: 10.23751/pn.v23i1.9571.

Mao, Q.-Q., X.-Y. Xu, A. Shang, R.-Y. Gan, D.-T. Wu, A. G. Atanasov, and H.-B. Li. 2020. Phytochemicals for the prevention and treatment of gastric cancer: Effects and mechanisms. *International Journal of Molecular Sciences* 21 (2):570. doi: 10.3390/ijms21020570.

Martinez-Martinez, D., A. Soto, B. Gil-Araujo, B. Gallego, A. Chiloeches, and M. Lasa. 2019. Resveratrol promotes apoptosis through the induction of dual specificity phosphatase 1 and sensitizes prostate cancer cells to cisplatin. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association* 124:273–9. doi: 10.1016/j.fct.2018.12.014.

Meng, X., J. Zhou, C.-N. Zhao, R.-Y. Gan, and H.-B. Li. 2020. Health benefits and molecular mechanisms of resveratrol: A narrative review. *Foods* 9 (3):340. doi: 10.3390/foods9030340.

Mieszala, K., M. Rudewicz, A. Gomulkiewicz, K. Ratajczak-Wielgomas, J. Grzegrzolka, P. Dziegiel, and S. Borska. 2018. Expression of genes and proteins of multidrug resistance in gastric cancer cells treated with resveratrol. *Oncology Letters* 15 (4):5825–32. doi: 10.3892/ol.2018.8022.

Mikami, S., I. Ota, T. Masui, T. Uchiyama, H. Okamoto, T. Kimura, S. Takasawa, and T. Kitahara. 2019. Resveratrol-induced REG iii expression enhances chemo- and radiosensitivity in head and neck cancer in xenograft mice. *Oncology Reports* 42 (1):436–42. doi: 10.3892/or.2019.7137.

Mukherjee, S., J. I. Dudley, and D. K. Das. 2010. Dose-dependency of resveratrol in providing health benefits. *Dose-Response* 8 (4):dose-response.0. doi: 10.2203/dose-response.09-015.Mukherjee.

Qian, W., Q. Xiao, L. Wang, T. Qin, Y. Xiao, J. Li, Y. Yue, C. Zhou, W. Duan, Q. Ma, et al. 2020. Resveratrol slows the tumourigenesis of pancreatic cancer by inhibiting NF kappa B activation. *Biomedicine & Pharmacotherapy* 127:110116. doi: 10.1016/j.biopha.2020.110116.

Rasheduzzaman, M., J. K. Jeong, and S. Y. Park. 2018. Resveratrol sensitizes lung cancer cell to TRAIL by p53 independent and suppression of Akt/NF-kappa B signaling. *Life Sciences* 208:208–20. doi: 10.1016/j.lfs.2018.07.035.

Ratajczak, K., N. Glatzel-Plucińska, K. Ratajczak-Wielgomas, K. Nowińska, and S. Borska. 2021. Effect of resveratrol treatment on human pancreatic cancer cells through alterations of Bcl-2 family members. *Molecules* 26 (21):6560. doi: 10.3390/molecules26216560.

Rauf, A., M. Imran, M. S. Butt, M. Nadeem, D. G. Peters, and M. S. Mubarak. 2018. Resveratrol as an anti-cancer agent: A review. *Critical Reviews in Food Science and Nutrition* 58 (9):1428–47. doi: 10.1080/10408398.2016.1263597.

Ren, B., M. X.-Y. Kwah, C. Liu, Z. Ma, M. K. Shanmugam, L. Ding, X. Xiang, P. C.-L. Ho, L. Wang, P. S. Ong, et al. 2021. Resveratrol for cancer therapy: Challenges and future perspectives. *Cancer Letters* 515:63–72. doi: 10.1016/j.canlet.2021.05.001.

Ren, M. T., X. X. Zhou, M. L. Gu, W. R. Jiao, M. S. Yu, Y. M. Wang, S. Liu, J. P. Yang, and F. Ji. 2020. Resveratrol synergizes with cisplatin in antineoplastic effects against AGS gastric cancer cells by inducing endoplasmic reticulum stress-mediated apoptosis and G2/M phase arrest. *Oncology Reports* 44 (4):1605–15. doi: 10.3892/or.2020.7708.

Roncoroni, L., L. Elli, P. Braidotti, D. Tosi, V. Vaira, L. Tacchini, V. Lombardo, F. Branchi, A. Scricciolo, L. Doneda, et al. 2018. Transglutaminase 2 mediates the cytotoxicity of resveratrol in a human cholangiocarcinoma and gallbladder cancer cell lines. *Nutrition and Cancer* 70 (5):761–9. doi: 10.1080/01635581.2018.1470648.

Shang, A., J. Li, D.-D. Zhou, R.-Y. Gan, and H.-B. Li. 2021. Molecular mechanisms underlying health benefits of tea compounds. *Free Radical Biology & Medicine* 172:181–200. doi: 10.1016/j.freeradbiomed.2021.06.006.

Sharifi-Rad, J., S. Rajabi, M. Martorell, M. D. López, M. T. Toro, S. Barollo, D. Armanini, P. V. T. Fokou, G. Zagotto, G. Ribaudo, et al. 2020. Plant natural products with anti-thyroid cancer activity. *Fitoterapia* 146:104640. doi: 10.1016/j.fitote.2020.104640.

Singh, S. K., S. Banerjee, E. P. Acosta, J. W. Lillard, and R. Singh. 2017. Resveratrol induces cell cycle arrest and apoptosis with docetaxel in prostate cancer cells via a p53/p21(WAF1/CIP1) and p27(KIP1) pathway. *Oncotarget* 8 (10):17216–28. doi: 10.18632/oncotarget.15303.

Singh, V., R. Singh, P. K. Kujur, and R. P. Singh. 2020. Combination of resveratrol and quercetin causes cell growth inhibition, DNA damage, cell cycle arrest, and apoptosis in oral cancer cells. *Assay and Drug Development Technologies* 18 (5):226–38. doi: 10.1089/adt.2020.972.

Sun, H., T. Zhang, R. Liu, W. Cao, Z. Zhang, Z. Liu, W. Qian, D. Wang, D. Yu, C. Zhong, et al. 2021a. Resveratrol inhibition of renal cancer stem cell characteristics and modulation of the sonic hedgehog pathway. *Nutrition and Cancer* 73 (7):1157–67. doi: 10.1080/01635581.2020.1784966.

Sun, X. D., P. Fu, L. X. Xie, S. M. Chai, Q. Q. Xu, L. Zeng, X. B. Wang, N. Jiang, and M. Sang. 2021b. Resveratrol inhibits the progression of cervical cancer by suppressing the transcription and expression of HPV E6 and E7 genes. *International Journal of Molecular Medicine* 47 (1):335–45. doi: 10.3892/ijmm.2020.4789.

Sun, X., Q. Xu, L. Zeng, L. Xie, Q. Zhao, H. Xu, X. Wang, N. Jiang, P. Fu, M. Sang, et al. 2020. Resveratrol suppresses the growth and metastatic potential of cervical cancer by inhibiting STAT3(Tyr705) phosphorylation. *Cancer Medicine* 9 (22):8685–700. doi: 10.1002/cam4.3510.

Sun, Y., Q. M. Zhou, Y. Y. Lu, H. Zhang, Q. L. Chen, M. Zhao, and S. B. Su. 2019. Resveratrol inhibits the migration and metastasis of MDA-MB-231 human breast cancer by reversing TGF-beta 1-induced epithelial-mesenchymal transition. *Molecules* 24 (6):1131. doi: 10.3390/molecules24061131.

Sung, H., J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, and F. Bray. 2021. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 71 (3):209–49. doi: 10.3322/caac.21660.

Tao, J., S. Li, R.-Y. Gan, C.-N. Zhao, X. Meng, and H.-B. Li. 2020. Targeting gut microbiota with dietary components on cancer: Effects and potential mechanisms of action. *Critical Reviews in Food Science and Nutrition* 60 (6):1025–37. doi: 10.1080/10408398.2018.1555789.

Tao, J., Y. Li, S. Li, and H.-B. Li. 2018. Plant foods for the prevention and management of colon cancer. *Journal of Functional Foods* 42:95–110. doi: 10.1016/j.jff.2017.12.064.

Vargas, J. E., R. Puga, G. Lenz, C. Trindade, and E. Filippi-Chiela. 2020. Cellular mechanisms triggered by the cotreatment of resveratrol and doxorubicin in breast cancer: A translational in vitro-in silico model. *Oxidative Medicine and Cellular Longevity* 2020:5432651. doi: 10.1155/2020/5432651.

Vendrely, V., E. Peuchant, E. Buscail, I. Moranvillier, B. Rousseau, A. Bedel, A. Brillac, H. de Verneuil, F. Moreau-Gaudry, S. Dabernat, et al. 2017. Resveratrol and capsaicin used together as food complements reduce tumor growth and rescue full efficiency of low dose gemcitabine in a pancreatic cancer model. *Cancer Letters* 390:91–102. doi: 10.1016/j.canlet.2017.01.002.

Wang, D. L., Z. F. Gao, and X. Zhang. 2018. Resveratrol induces apoptosis in murine prostate cancer cells via hypoxia-inducible factor 1-alpha (HIF-1 alpha)/reactive oxygen species (ROS)/P53 signaling. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* 24:8970–6. doi: 10.12659/msm.913290.

Wang, H. X., R. Z. Jia, T. L. Lv, M. Wang, S. W. He, and X. Zhang. 2020a. Resveratrol suppresses tumor progression via inhibiting STAT3/HIF-1 alpha/VEGF pathway in an orthotopic rat model of non-small-cell lung cancer (NSCLC). *OncoTargets and Therapy* ume 13:7057–63. doi: 10.2147/OTT.S259016.

Wang, S. S., Q. Meng, Q. Xie, and M. Zhang. 2017. Effect and mechanism of resveratrol on drug resistance in human bladder cancer cells. *Molecular Medicine Reports* 15 (3):1179–87. doi: 10.3892/mmr.2017.6111.

Wang, Y. J., W. H. Wang, X. J. Wu, C. J. Li, Y. P. Huang, H. Y. Zhou, and Y. Cui. 2020b. Resveratrol sensitizes colorectal cancer cells to cetuximab by connexin 43 upregulation-induced Akt inhibition. *Frontiers in Oncology* 10:383. doi: 10.3389/fonc.2020.00383.

Wu, H., L. Chen, F. F. Zhu, X. Han, L. D. Sun, and K. P. Chen. 2019. The cytotoxicity effect of resveratrol: Cell cycle arrest and induced apoptosis of breast cancer 4T1 cells. *Toxins* 11 (12):731. doi: 10.3390/toxins11120731.

Wu, J., Y. T. Li, X. T. Tian, Y. S. Liu, M. L. Wu, P. N. Li, and J. Liu. 2020. STAT3 signaling statuses determine the fate of resveratrol-treated anaplastic thyroid cancer cells. *Cancer Biomarkers* 27 (4):461–9. doi: 10.3233/CBM-191010.

Wu, J., T. Zhou, Y. Wang, Y. Jiang, and Y. Wang. 2021. Mechanisms and advances in anti-ovarian cancer with natural plants component. *Molecules* 26 (19):5949. doi: 10.3390/molecules26195949.

Wu, Q., J. P. C. Wong, and H. F. Kwok. 2020. Putting the brakes on tumorigenesis with natural products of plant origin: Insights into

the molecular mechanisms of actions and immune targets for bladder cancer treatment. *Cells* 9 (5):1213. doi: 10.3390/cells9051213.

Wu, X. X., Y. D. Xu, B. R. Zhu, Q. Liu, Q. F. Yao, and G. Zhao. 2018. Resveratrol induces apoptosis in SGC-7901 gastric cancer cells. *Oncology Letters* 16 (3):2949–56. doi: 10.3892/ol.2018.9045.

Xiao, Y., T. Qin, L. Sun, W. Qian, J. Li, W. Duan, J. Lei, Z. Wang, J. Ma, X. Li, et al. 2020. Resveratrol ameliorates the malignant progression of pancreatic cancer by inhibiting hypoxia-induced pancreatic stellate cell activation. *Cell Transplantation* 29:963689720929987. doi: 10.1177/0963689720929987.

Xiong, L., J. H. Nie, X. M. Lin, J. B. Wu, Z. Chen, B. Xu, and J. Liu. 2020. Biological implications of PTEN upregulation and altered sodium/iodide symporter intracellular distribution in resveratrol-suppressed anaplastic thyroid cancer cells. *Journal of Cancer* 11 (23):6883–91. doi: 10.7150/jca.48180.

Xu, G. R., J. Z. Chen, G. R. Wang, J. H. Xiao, N. Zhang, Y. Y. Chen, H. R. Yu, G. Z. Wang, and Y. F. Zhao. 2020a. Resveratrol inhibits the tumorigenesis of follicular thyroid cancer via ST6GAL2-regulated activation of the hippo signaling pathway. *Molecular Therapy Oncolytics* 16:124–33. doi: 10.1016/j.omto.2019.12.010.

Xu, J. H., D. Y. Liu, H. L. Niu, G. F. Zhu, Y. W. Xu, D. L. Ye, J. Li, and Q. L. Zhang. 2017. Resveratrol reverses doxorubicin resistance by inhibiting epithelial-mesenchymal transition (EMT) through modulating PTEN/Akt signaling pathway in gastric cancer. *Journal of Experimental & Clinical Cancer Research* 36 (1):19. doi: 10.1186/s13046-016-0487-8.

Xu, Q. H., Y. Xiao, X. Q. Li, L. Fan, C. C. Zhou, L. Cheng, Z. D. Jiang, and G. H. Wang. 2020b. Resveratrol counteracts hypoxia-induced gastric cancer invasion and EMT through hedgehog pathway suppression. *Anti-Cancer Agents in Medicinal Chemistry* 20 (9):1105–14. doi: 10.2174/1871520620666200402080034.

Xu, X.-Y., C.-N. Zhao, S.-Y. Cao, G.-Y. Tang, R.-Y. Gan, and H.-B. Li. 2020c. Effects and mechanisms of tea for the prevention and management of cancers: An updated review. *Critical Reviews in Food Science and Nutrition* 60 (10):1693–705. doi: 10.1080/10408398.2019.1588223.

Yang, M. D., Y. Sun, W. J. Zhou, X. Z. Xie, Q. M. Zhou, Y. Y. Lu, and S. B. Su. 2021a. Resveratrol enhances inhibition effects of cisplatin on cell migration and invasion and tumor growth in breast cancer MDA-MB-231 cell models in vivo and in vitro. *Molecules* 26 (8):2204. doi: 10.3390/molecules26082204.

Yang, M., Z. Li, J. Tao, H. Hu, Z. Li, Z. Zhang, F. Cheng, Y. Sun, Y. Zhang, J. Yang, et al. 2021b. Resveratrol induces PD-L1 expression through snail-driven activation of wnt pathway in lung cancer cells. *Journal of Cancer Research and Clinical Oncology* 147 (4):1101–13. doi: 10.1007/s00432-021-03510-z.

Yang, T. T., J. M. Zhang, J. T. Zhou, M. X. Zhu, L. Wang, and L. H. Yan. 2018. Resveratrol inhibits interleukin-6 induced invasion of human gastric cancer cells. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 99:766–73. doi: 10.1016/j.biopha.2018.01.153.

Yang, Z. Y., Q. G. Xie, Z. L. Chen, H. B. Ni, L. Xia, Q. F. Zhao, Z. Y. Chen, and P. F. Chen. 2019. Resveratrol suppresses the invasion and migration of human gastric cancer cells via inhibition of malat1-mediated epithelial-to-mesenchymal transition. *Experimental and Therapeutic Medicine* 17 (3):1569–78. doi: 10.3892/etm.2018.7142.

Yao, S. L., M. Gao, Z. J. Wang, W. Y. Wang, L. Zhan, and B. Wei. 2021. Upregulation of microRNA-34a sensitizes ovarian cancer cells to resveratrol by targeting Bcl-2. *Yonsei Medical Journal* 62 (8):691–701. doi: 10.3349/ymj.2021.62.8.691.

Ye, M., H. S. Tian, S. H. Lin, J. R. Mo, Z. Li, X. J. Chen, and J. J. Liu. 2020. Resveratrol inhibits proliferation and promotes apoptosis via the androgen receptor splicing variant 7 and PI3K/AKT signaling pathway in LNCaP prostate cancer cells. *Oncology Letters* 20 (5):1– doi: 10.3892/ol.2020.12032.

Yeung, A. W. K., B. B. Aggarwal, I. E. Orhan, D. Barreca, M. Battino, T. Belwal, A. Bishayee, M. Daglia, H. P. Devkota, et al. 2019. Resveratrol, a popular dietary supplement for human and animal health: Quantitative research literature analysis – A review. *Animal Science Papers and Reports* 37 (2):103–18.

Yin, L., R. Zhang, Y. Hu, W. Li, M. Wang, Z. Liang, Z. Sun, R. Ji, W. Xu, H. Qian, et al. 2020. Gastric-cancer-derived mesenchymal stem cells: A promising target for resveratrol in the suppression of gastric cancer metastasis. *Human Cell* 33 (3):652–62. doi: 10.1007/s13577-020-00339-5.

Yuan, L., M. Zhou, D. Huang, H. S. Wasan, K. Zhang, L. Sun, H. Huang, S. Ma, M. Shen, S. Ruan, et al. 2019. Resveratrol inhibits the invasion and metastasis of colon cancer through reversal of epithelial-mesenchymal transition via the AKT/GSK-3 beta/snail signaling pathway. *Molecular Medicine Reports* 20 (3):2783–95. doi: 10.3892/mmr.2019.10528.

Zaffaroni, N, and G. L. Beretta. 2021. Resveratrol and prostate cancer: The power of phytochemicals. *Current Medicinal Chemistry* 28 (24):4845–62. doi: 10.2174/0929867328666201228124038.

Zhang, S., D. Wang, J. Huang, Y. Hu, and Y. Xu. 2020. Application of capsaicin as a potential new therapeutic drug in human cancers. *Journal of Clinical Pharmacy and Therapeutics* 45 (1):16–28. doi: 10.1111/jcpt.13039.

Zhang, Y. T., Y. Li, C. C. Sun, X. Chen, L. Y. Han, T. Q. Wang, J. F. Liu, X. J. Chen, and D. Zhao. 2021. Effect of pterostilbene, a natural derivative of resveratrol, in the treatment of colorectal cancer through Top1/Tdp1-mediated DNA repair pathway. *Cancers* 13 (16):4002. doi: 10.3390/cancers13164002.

Zhao, Y. H., X. Y. Yuan, X. Li, and Y. Zhang. 2019. Resveratrol significantly inhibits the occurrence and development of cervical cancer by regulating phospholipid scramblase 1. *Journal of Cellular Biochemistry* 120 (2):1527–31. doi: 10.1002/jcb.27335.

Zhou, C., W. Qian, J. Ma, L. Cheng, Z. Jiang, B. Yan, J. Li, W. Duan, L. Sun, J. Cao, et al. 2019. Resveratrol enhances the chemotherapeutic response and reverses the stemness induced by gemcitabine in pancreatic cancer cells via targeting srebp1. *Cell Proliferation* 52 (1):e12514. doi: 10.1111/cpr.12514.

Zhou, D.-D., M. Luo, S.-Y. Huang, A. Saimaiti, A. Shang, R.-Y. Gan, and H.-B. Li. 2021. Effects and mechanisms of resveratrol on aging and age-related diseases. *Oxidative Medicine and Cellular Longevity* 2021:9932218. doi: 10.1155/2021/9932218.

Zhu, Z. W., J. G. Wu, L. Y. Xu, Y. Wan, H. C. Chao, and T. Sun. 2021. Chinese herb resveratrol inhibits renal pelvic cancer cell proliferation via regulating miR-30a-5p. *Journal of Biobased Materials and Bioenergy* 15 (2):253–9. doi: 10.1166/jbmb.2021.2063.